

MARKERS AND CELLULAR ANTECEDENTS OF RHEUMATOID ARTHRITIS FLARES

CROSS REFERENCE TO RELATED APPLICATION

[001] The present application claims priority to U.S. Application Serial No. 63/283,359, filed November 26, 2021, the entire contents of which is incorporated by reference herein.

STATEMENT OF GOVERNMENT RIGHTS

[002] This invention was made with government support under numbers NS034389, NS081706, NS097404 and 1UM1HG008901 awarded by the National Institutes of Health. The government has certain rights in the present disclosure.

SEQUENCE LISTING

[003] This application contains a Sequence Listing, which was submitted in XML format via EFS-Web, and is hereby incorporated by reference in its entirety. The XML copy, created on November 22, 2022, is named "1119-75-PCT_ST26.xml" and is 37,645 bytes in size.

FIELD

[004] The present disclosure relates generally to the identification and characterization of biological markers which are molecular antecedents of rheumatoid arthritis (RA) flares. The present disclosure further relates to RNA and protein markers that can predict an RA flare one or two weeks prior to the flare. The present disclosure further relates to blood circulating cells, particularly pre-inflammatory mesenchymal cells, which are cellular precursors and indicators of an impending RA flare. The present disclosure relates to methods, kits and markers for the identification and monitoring of flares in RA patients and their application as markers and targets in and for treatment of rheumatoid arthritis and conditions induced or related to rheumatoid arthritis.

BACKGROUND

[005] Rheumatoid arthritis (RA) is a chronic inflammatory disorder and is the most common form of autoimmune arthritis, affecting more than 1.3 million Americans. About 75% of RA patients are women and between 1 and 3% of women may get rheumatoid arthritis in their lifetime. RA is a chronic disease affecting the lining of joints that causes joint pain, stiffness, swelling and decreased movement of the joints and can eventually result in bone erosion and joint deformity.

[006] Treatments for RA can stop joint pain and swelling and prevent joint damage. Early treatment will give better long-term results; patients receiving early treatment are less likely to have the type of joint damage that leads to joint replacement. The main treatment goals with rheumatoid arthritis are to

control inflammation, relieve pain, and reduce disability associated with RA. Treatment usually includes medications, occupational or physical therapy, and regular exercise, although some patients ultimately need surgery, such as synovectomy, tendon repair, joint fusion or total joint replacement to correct joint damage. Nonsteroidal anti-inflammatory drugs (NSAIDs) provide “first-line” RA medicines to relieve pain and reduce inflammation. NSAIDs include non-prescription drugs acetylsalicylate (aspirin), ibuprofen (Advil, Motrin IB) and naproxen sodium (Aleve, Naprosyn) and prescription NSAIDs, such as etodolac (Lodine) and diclofenac (Voltaren). Steroids are anti-inflammatory or immunosuppressants agents and they are prescribed for more severe RA or when RA symptoms flare to ease joint pain and stiffness. Examples of recognized steroids include glucocorticosteroids or corticosteroids, such as prednisone, cortisone and methylprednisolone. Disease-modifying antirheumatic drugs (DMARDs) are prescribed and utilized to slow the progression of RA and save joints and other tissues from permanent damage. Common DMARDs include methotrexate (Trexall, Otrexup), leflunomide (Arava), hydroxychloroquine (Plaquenil) and sulfasalazine (Azulfidine). DMARDs curb the overactive immune system in RA but they are not selective in their targets. Side effects vary but may include liver damage, bone marrow suppression and severe lung infections. Biologics - genetically engineered proteins which target a specific aspect or part of the immune system and act as immunosuppressants - are an increasingly important component in treatment of RA. Tumor necrosis factor (TNF) inhibitors and non-TNF inhibitors (such as cytokine inhibitors, T or B cell inhibitors) are included among the recognized biologics for RA. Biologics include abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), baricitinib (Olumiant), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), rituximab (Rituxan), sarilumab (Kevzara), tocilizumab (Actemra) and tofacitinib (Xeljanz). Adalimumab, etanercept, infliximab, golimumab and certolizumab target TNF (Lis K *et al* (2014) Arch Med Sci 10(6):1175-1185). Rituximab depletes B cells. Anakinra blocks the action of interleukin-1 (IL-1), a master cytokine. Abatacept targets T cells. These types of drugs also increase the risk of infections. Biologic DMARDs are usually most effective when paired with a nonbiologic DMARD, such as methotrexate. New drugs which are specific in their targets but are not biologics include oral small molecule Janus kinase (JAK) inhibitors such as tofacitinib (Xeljanz and Xeljanz XR), baricitinib (Olumiant), and upadacitinib (Rinvoq). The antimetabolite Methotrexate is also often used to treat RA, sometimes in combination with other DMARD drugs including biologic DMARDs.

[007] Recent patient surveys indicate that three-fourths of RA patients are not satisfied with treatments and patients continued to experience bothersome symptoms that impacted their daily activities and life (Radawski C *et al* (2019) Rheumatol Ther 6(3):461-471). RA, like many inflammatory diseases, is characterized by episodes of quiescence and exacerbation (flares). Flares are severe episodes of symptoms and reflect increased disease activity during which joint pain,

swelling, and stiffness are more severe. The duration and intensity of flares vary, the flares are unpredictable, and the molecular events leading to flares are unknown. Such waxing/waning clinical courses are characteristic of many autoimmune diseases, including multiple sclerosis (MS) (Steinman L. (2014) *Annu Rev Immunol* 32:257-81), systemic lupus erythematosus (SLE) (Fava A, Petri M. (2019) *J Autoimmun* 96:1-13), and inflammatory bowel disease (IBD) (Braun J, Wei B (2007) *Annu Rev Pathol* 2:401-29; Braun J *et al* (2007) *Arthritis Rheum* 57:639-47.).

[008] There remains a need for improved disease management among RA and other auto-immune disease patients. The present disclosure addresses such unmet needs in the field and particularly with regard to rheumatoid arthritis (RA).

[009] The citation of references herein shall not be construed as an admission that such is prior art to the present disclosure.

SUMMARY

[0010] In a general aspect, the present disclosure provides antecedents of an RA flare. RNA markers and protein markers have been identified, which are differentially expressed or preferentially expressed prior to an RA flare in an RA patient(s). These RNA transcripts provide markers that can predict an impending flare and the determination and presence of which can be utilized to implement and prescribe treatment and therapy to a patient(s).

[0011] In some embodiments, provided herein is a method for monitoring and/or predicting a rheumatoid arthritis (RA) flare or increased RA disease activity in a patient comprising: (a) detecting in the blood sample increased amounts of a panel of antecedent RA markers, wherein the panel comprises or consists of one or more AC3 markers listed in Table 10; (b) wherein the expression or quantitatively increased amounts of the one or more AC3 markers in the panel predicts an impending RA flare or increased RA disease activity.

[0012] In some embodiments, the panel of antecedent RA markers comprises or consists of one or more or all markers listed in Table 11. In some embodiments, the panel of antecedent RA markers comprises one or more or all markers listed in Table 12. In some embodiments, the panel of antecedent RA markers comprises or consists of one or more or all of the markers listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1).

[0013] In some embodiments, the panel of antecedent RA markers comprises or consists of at least 2 or more markers listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1).

[0014] In some embodiments, the panel of antecedent RA markers comprising or consisting of those listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and

COL5A1) are evaluated to detect increased amounts of one or more of the AC3 markers listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1).

[0015] In some embodiments, the panel of one or more antecedent RA markers comprising or consisting of those listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1) are evaluated utilizing primer pairs provided and listed in Table 13. In some embodiments, the panel of one or more antecedent RA markers comprising or consisting of those listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1) are evaluated utilizing one or more primer pairs selected from SEQ ID Nos: 1-28. In some embodiments, the panel of two or more antecedent RA markers comprising those listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1) are evaluated utilizing two or more primer pairs selected from SEQ ID Nos: 1-28. In some embodiments, the panel of antecedent RA markers comprising or consisting of those listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1) are evaluated utilizing applicable primer pairs selected from SEQ ID Nos: 1-28. In some embodiments, the increased amounts of the panel of AC3 RNA markers or the AC3 protein markers predict an RA flare in about 1 week or about 5-7 days or up to 2 weeks. In some embodiments, the method of any one of the preceding claims, wherein the panel consists of 2 to 283 antecedent markers. In some embodiments, a panel of at least 3, at least 4, at least 5 or at least 6 of the AC3 markers are evaluated in any one of the methods disclosed herein. In some embodiments, the increased amounts of one or more RA antecedent RNA markers (*e.g.*, AC3 RNA markers) are detected using RNAseq or RT-PCR. In some embodiments, the amount of antecedent AC3 markers are decreased in peripheral blood during an RA flare or once a patient exhibits symptoms of an RA flare.

[0016] In some embodiments, the method further comprises administering a therapeutically effective amount of one or more disease-modifying agents for treating RA if the amounts of the panel of the markers in the blood sample is increased relative to the amounts of the panel of the markers in the control blood sample. In some embodiments, this disclosure provides a collection of primer pairs for amplifying the antecedent RA markers in a panel disclosed herein. In some embodiments, the collection comprises one or more primer pairs in Table 13. In some embodiments, the collection of primer pairs comprises one or more of the following: i) a primer pair for amplifying COL14A1, wherein the primer pair comprises oligonucleotides having sequences of SEQ ID NO: 17 and SEQ ID NO: 18; ii) a primer pair for amplifying DCLK1, wherein the primer pair comprises oligonucleotides having sequences of SEQ ID NO: 19 and SEQ ID NO: 20; iii) a primer pair for amplifying FNDC1, wherein the primer pair comprises oligonucleotides having sequences of SEQ ID NO: 21 and SEQ ID NO: 22; iv) a primer pair for amplifying COL16A1, wherein the primer pair comprises oligonucleotides having sequences of SEQ ID NO: 23 and SEQ ID NO: 24; and (v) a

primer pair for amplifying COL1A2, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO: 25 and SEQ ID NO: 26.

[0017] In some embodiments, the collection of primer pairs comprises or consists of one or more of the following: i) a primer pair for amplifying COL14A1, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO: 1 and SEQ ID NO: 2 or of SEQ ID NO: 3 and SEQ ID NO: 4; ii) a primer pair for amplifying DCLK1, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO: 5 and SEQ ID NO: 6 or of SEQ ID NO: 7 and SEQ ID NO: 8; iii) a primer pair for amplifying FNDC1, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO: 9 and SEQ ID NO: 10 or of SEQ ID NO: 11 and SEQ ID NO: 12; iv) a primer pair for amplifying COL16A1, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO: 13 and SEQ ID NO: 14 or of SEQ ID NO: 15 and SEQ ID NO: 16; and v) a primer pair for amplifying COL1A2, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO: 17 and SEQ ID NO: 18 or of SEQ ID NO: 19 and SEQ ID NO: 20.

[0018] In some embodiments, the collection of primer pairs comprise or consists of one or more of the following: i) a primer pair for amplifying COL14A1, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO: 1 and SEQ ID NO: 2 or of SEQ ID NO: 3 and SEQ ID NO: 4; ii) a primer pair for amplifying DCLK1, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO: 5 and SEQ ID NO: 6 or of SEQ ID NO: 7 and SEQ ID NO: 8; iii) a primer pair for amplifying FNDC1, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO: 9 and SEQ ID NO: 10 or of SEQ ID NO: 11 and SEQ ID NO: 12; iv) a primer pair for amplifying COL16A1, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO: 13 and SEQ ID NO: 14 or of SEQ ID NO: 15 and SEQ ID NO: 16; v) a primer pair for amplifying COL1A2, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO: 17 and SEQ ID NO: 18 or of SEQ ID NO: 19 and SEQ ID NO: 20; (vi) a primer pair for amplifying KIAA1755, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO: 21 and SEQ ID NO: 22; (vii) a primer pair for amplifying PXDN, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO: 23 and SEQ ID NO: 24; and (viii) a primer pair for amplifying COL5A1, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO: 25 and SEQ ID NO: 26 or of SEQ ID NO: 27 and SEQ ID NO: 28.

[0019] The present disclosure provides a method for monitoring and/or predicting a rheumatoid arthritis (RA) flare or increased RA disease activity in a patient comprising:

(a) evaluating a blood sample from said patient;

(b) evaluating the blood sample for expression or quantitatively increased amounts of one or more sets of antecedent RNA markers, protein markers or cell markers selected from:

- (i) AC2 markers or proteins as provided in Table 7;
- (ii) AC3 markers or proteins as provided in Table 8, 10, 11 or 12;
- (iii) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 as set out in Table 5;
- (iv) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 as set out in Table 9;
- (v) markers or proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12;

(vi) cell markers CD45- CD31-PDPN+;

(c) wherein the expression or quantitatively increased amounts of the RNA markers or proteins or the presence of the cell markers predicts an impending RA flare.

[0020] In some embodiments, the method does not include the step of collecting the blood from the patient.

[0021] The present disclosure provides a method for monitoring and/or predicting a rheumatoid arthritis (RA) flare in a patient comprising:

(a) isolating a blood sample from said patient;

(b) evaluating the blood sample for expression or quantitatively increased amounts of one or more sets of antecedent RNA markers, protein markers or cell markers selected from:

- (i) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 as set out in Table 5;
- (ii) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 as set out in Table 9;
- (iii) markers or proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12;
- (iv) AC2 markers or proteins as provided in Table 7;
- (v) AC3 markers or proteins as provided in Table 8, 10, 11 or 12; and
- (vi) cell markers CD45- CD31-PDPN+;

(c) wherein the expression or quantitatively increased amounts of the RNA markers or proteins or the presence of the cell markers predicts an impending RA flare.

[0022] In an embodiment of the method, the expression or quantitatively increased amounts of the AC2 RNA markers or proteins predicts an RA flare in about 2 weeks or about 12-14 days. In an embodiment of the method, the expression or quantitatively increased amounts of the AC2 RNA markers or proteins predicts an RA flare in about 2 weeks, with a margin of error of about a week or further 7 days, thus in 7-21 days, or in up or about three weeks, up to 21 days or so.

[0023] In an embodiment of the method, the expression or quantitatively increased amounts of the AC3 RNA markers or proteins predicts an RA flare in about 1 week or about 5-7 days. In an embodiment of the method, the expression or quantitatively increased amounts of the AC3 RNA markers or proteins predicts an RA flare in about 1 week, with a margin of error of about a week or further 7 days, thus in 0-14 days, or in up or about two weeks, up to 14 days or so.

[0024] In an embodiment of the method, a panel of at least 20 of the AC2 or AC3 markers are evaluated. In an embodiment, a panel of at least 10 of the AC2 or AC3 markers are evaluated. At least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50 of the AC2 or AC3 markers may be evaluated.

[0025] In an embodiment of the method, a panel of at least 20 of the AC2 and at least 20 of the AC3 markers are evaluated. In an embodiment, a panel of at least 10 of the AC2 and the AC3 markers are evaluated. At least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50 of the AC2 and the AC3 markers may be evaluated.

[0026] In an embodiment, a panel of at least two, three, four, five, six or seven markers selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12 may be evaluated. In an embodiment, a panel of at least two markers selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12 may be evaluated. In an embodiment, a panel of at least three markers selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12 may be evaluated. In an embodiment, a panel of at least four markers selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12 may be evaluated. In an embodiment, a panel of at least five markers selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12 may be evaluated. In an embodiment, a panel of at least six markers selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12 may be evaluated. In an embodiment, a panel of at least seven markers selected from

COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12 may be evaluated. In an embodiment, a panel of markers COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12 may be evaluated.

[0027] In an embodiment, sublining fibroblast markers selected from the AC3 markers or proteins are evaluated. In an embodiment, AC3 markers or proteins expressed by CD34+, HLADR+ and DKK3+ cells are evaluated. In an embodiment, AC3 markers or proteins expressed by CD45-, CD34+, HLADR+ and DKK3+ cells are evaluated.

[0028] The method includes, wherein the cell marker IL-17RD is also evaluated.

[0029] The present disclosure further provides a method(s) wherein the antecedent RNA markers or protein markers or selected from:

- (a) AC3 markers or proteins as provided in Table 8, 10, 11 or 12;
- (b) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 as set out in Table 5;
- (c) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 as set out in Table 9; and
- (d) markers or proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12;

are decreased in peripheral blood during an RA flare or once a patient exhibits symptoms of an RA flare.

[0030] The present disclosure further provides a method(s) wherein the antecedent RNA markers or protein markers or selected from:

- (a) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 as set out in Table 5;
- (b) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 as set out in Table 9;
- (c) AC3 markers or proteins as provided in Table 8, 10 or 11; and
- (d) AC3 markers or proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12;

are decreased in peripheral blood during an RA flare or once a patient exhibits symptoms of an RA flare.

[0031] The present disclosure provides a method for predicting an impending RA flare and treating a flare in a patient, the method comprising:

(a) contacting a blood sample from the patient with reagents specific for markers selected from a panel of RNA or protein markers to assess expression of the RNA or protein markers, wherein the panel of RNA or protein markers is selected from:

- (i) AC2 markers or proteins as provided in Table 7;
- (ii) AC3 markers or proteins as provided in Table 8, 10 or 11;
- (iii) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 as set out in Table 5;
- (iv) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 as set out in Table 9; and
- (v) markers or proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12;

(b) comparing expression of the markers selected from a panel of RNA or protein markers in the blood sample to expression of the markers in a control blood sample to determine if expression of the markers selected from a panel of RNA or protein markers in the blood sample is increased relative to expression in the control blood sample, wherein detection of increased expression serves to predict an impending RA flare in a patient;

(c) and treating the patient thereby diagnosed with an impending RA flare by administering a therapeutically effective amount of one or more disease-modifying agent for treating RA. As used herein, the term “disease-modifying agent” refers to that an agent that is capable of alleviating the symptoms of RA when administered to a patient who suffers from RA.

[0032] The present disclosure provides a method for predicting an impending RA flare and treating a flare in a patient, the method comprising:

(a) contacting a blood sample from the patient with reagents specific for markers selected from a panel of RNA or protein markers to assess expression of the RNA or protein markers, wherein the panel of RNA or protein markers is selected from:

- (i) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 as set out in Table 5;
- (ii) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 as set out in Table 9;
- (iii) AC2 markers or proteins as provided in Table 7;
- (iv) AC3 markers or proteins as provided in Table 8, 10 or 11; and
- (v) AC3 markers or proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12; and

(b) comparing expression of the markers selected from a panel of RNA or protein markers in the blood sample to expression of the respective markers in a control blood sample to determine if expression of the markers selected from a panel of RNA or protein markers in the blood sample is increased relative to expression in the control blood sample, wherein detection of increased expression serves to predict an impending RA flare in a patient; and treating the patient diagnosed with an impending RA flare by administering a therapeutically effective amount of one or more disease-modifying agent for treating RA.

[0033] In an embodiment of the method, the expression, differential expression, or quantitatively increased amounts of the AC2 RNA markers or proteins predicts an RA flare in about 2 weeks, about 14 days, or about 12-14 days.

[0034] In an embodiment of the method, the expression or quantitatively increased amounts of the AC3 RNA markers or proteins predicts an RA flare in about one week, about 7 days, or about 5-7 days. In an embodiment of the method, the expression, differential expression, or quantitatively increased amounts of the markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 or of the markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 predicts an RA flare in about one week, about 7 days, or about 5-7 days.

[0035] In an embodiment of the method, the expression or quantitatively increased amounts of the AC3 RNA markers or proteins predicts an RA flare in about one week, about 7 days, or about 5-7 days. In an embodiment of the method, the expression, differential expression, or quantitatively increased amounts of the markers or proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12 predicts an RA flare in about one week, about 7 days, or about 5-7 days.

[0036] In an embodiment of the method, the expression or quantitatively increased amounts of RNA or protein markers selected from:

- (a) the AC3 RNA markers or proteins;
- (b) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6;
- (c) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4; and
- (d) markers or proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12;

predicts an RA flare in about 1 week or about 5-7 days.

[0037] In an embodiment of the method, the expression or quantitatively increased amounts of RNA or protein markers selected from:

(a) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6;

(b) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4;

(c) markers or proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12; and

(d) the AC3 RNA markers or proteins;

predicts an RA flare in about 1 week or about 5-7 days.

[0038] Evaluation of RNA or protein expression may be evaluated or assessed using any method known in the art. Thus, in accordance with the methods of the present disclosure, RNA expression may be assessed by RT PCR. In accordance with the method, protein expression may be detected using specific antibodies.

[0039] Cell marker expression or presence on the surface of cells in the blood in accordance with the methods of the present disclosure may be determined using standard and known methods. Cell markers may be evaluated using antibodies. Cell markers may be evaluated using Fluorescent Activated Cell Sorting (FACs) analysis. Cells or cell markers may be evaluated using cell sorting or single-cell assessments.

[0040] In embodiments of the method of the present disclosure, a patient is treated with a disease-modifying agent for treating RA after a patient is diagnosed with an impending RA flare using a method disclosed herein. In some embodiments, the disease-modifying agent may be selected from standard or clinically recognized agents or therapies for RA or arthritic conditions or inflammatory diseases and conditions. In embodiments of the method of the present disclosure, the disease-modifying agent for treating RA may be one or more agent selected from a nonsteroidal anti-inflammatory drug (NSAID), steroid, methotrexate, disease-modifying antirheumatic drug (DMARDs), biologic DMARD, and oral janus kinase (JAK) inhibitor. In an embodiment, the DMARD is selected from methotrexate (Trexall, Otrexup), leflunomide (Arava), hydroxychloroquine (Plaquenil) and sulfasalazine (Azulfidine). There are a variety of known biologic DMARD agents, including various agents being evaluated or with application to RA and/or other arthritic and/or inflammatory conditions. In an aspect, the biologic DMARD may selected from abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), baricitinib (Olmiant), certolizumab (Cimzia), etanercept

(Enbrel), golimumab (Simponi), infliximab (Remicade), rituximab (Rituxan), sarilumab (Kevzara), tocilizumab (Actemra) and tofacitinib (Xeljanz). The biologic DMARD may be a tumor necrosis factor (TNF) inhibitor. In an aspect, the biologic DMARD may be an anti-inflammatory antibody, or an antibody directed to an inflammation or immune modulatory molecule. In an aspect, the antibody may be an interleukin antibody. In some embodiments, the antibody is an IL-17 specific antibody or an IL-17RD specific or IL-17RD blocking or neutralizing antibody. In some embodiments, the IL-17 specific antibody targets one or more members of the IL-17 family selected from the group consisting of IL-17A, IL-17B, IL-17C, IL-17D, IL-17E/IL-25, and IL-17F. In some embodiments, the antibody targets one or more members of the IL-17 receptor family selected from the group consisting of IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE. In one embodiment, the antibody is netakimab.

[0041] In one embodiment, the biologic DMARD is combined with an NSAID and/or with methotrexate. In an embodiment, the JAK inhibitor is selected from tofacitinib (Xeljanz and Xeljanz XR), (Olumiant), and upadacitinib (Rinvoq).

[0042] The present disclosure provides and relates to a circulating pre-inflammatory mesenchymal (PRIME) cell characterized as a CD45-CD31-PDPN⁺ cell, wherein the presence of the cell in peripheral blood is indicative or predictive of an impending RA flare. In an embodiment, the PRIME cell additionally expresses IL-17RD and is IL-17RD⁺. In an embodiment, a plurality of PRIME cells additionally expresses IL-17RD and is IL-17RD⁺.

[0043] The present disclosure further provides a method of predicting an impending RA flare comprising evaluating a blood sample from a patient for the presence of a PRIME cell characterized as a CD45-CD31-PDPN⁺ cell, wherein the presence of detectable PRIME cells in peripheral blood in a patient predicts an impending RA flare in the patient. In an embodiment thereof, the method includes further evaluating for the presence of IL-17RD on a CD45-CD31-PDPN⁺ cell.

[0044] Methods are provided for evaluating and treating an impending flare in an RA patient comprising evaluating the peripheral blood of a patient for the presence of a PRIME cell characterized as a CD45-CD31-PDPN⁺ cell, and treating a patient that is positive for PRIME cells in their peripheral blood with a disease-modifying agent for RA. Methods are provided for evaluating and treating an impending flare in an RA patient comprising evaluating the peripheral blood of a patient for the presence of a PRIME cell characterized as a CD45-CD31-PDPN⁺IL-17RD⁺ cell and treating a patient that is positive for PRIME cells in their peripheral blood with a disease-modifying agent for RA.

[0045] In an additional embodiment of the method, the patient is treated with an IL-17 or IL-17RD antibody. In another embodiment, the patient is further treated with an anti-inflammatory agent and/or an immune modulating agent.

[0046] Methods are provided for evaluating and treating an impending flare in an RA patient comprising evaluating the peripheral blood of a patient for the presence of RNA(s) or protein(s) expressed, specifically expressed or particularly expressed by a PRIME cell characterized as a CD45-CD31-PDPN⁺ cell and treating a patient that is positive for expressing, specifically expressing or particularly expressing RNA(s) or protein(s) of PRIME cells in their peripheral blood with a disease-modifying agent for RA. Methods are provided for evaluating and treating an impending flare in an RA patient comprising evaluating the peripheral blood of a patient for the presence of RNA(s) or protein(s) expressed, specifically expressed or particularly expressed by a cell characterized as a CD45-CD31-PDPN⁺IL-17RD⁺ cell and treating a patient that is positive for the presence of RNA(s) or protein(s) expressed, specifically expressed or particularly expressed by a cell characterized as a CD45-CD31-PDPN⁺IL-17RD⁺ cell in their peripheral blood with a disease-modifying agent for RA.

[0047] The present disclosure includes a set of RNA or protein markers for evaluating and predicting an impending RA flare in a patient comprising or consisting of the markers selected from the group consisting of:

- (i) a panel of at least 20 markers from the AC2 markers provided in Table 7;
- (ii) a panel of at least 20 markers from the AC3 markers provided in Table 8, 10 or 11;
- (iii) markers selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFH4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 as set out in Table 5;
- (iv) markers selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFH4 as set out in Table 9; and
- (v) markers selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12.

[0048] In an aspect of the method, a panel of at least 20 of the AC2 or AC3 markers are provided. In an aspect, a panel of at least 10 of the AC2 or AC3 markers are provided. At least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50 of the AC2 or AC3 markers may be provided.

[0049] In an embodiment, the panel of AC2 markers comprises naïve B cell gene markers and markers of developmental pathways for naïve B cells and leukocytes. In an embodiment, wherein the panel of AC3 markers comprises markers of cartilage morphogenesis, endochondral bone growth, extracellular matrix organization and sublining fibroblasts.

[0050] In another embodiment of the present disclosure a set of one or more markers selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR,

EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 is provided and/or utilized in accordance with the methods hereof. In an aspect, a set of one or more markers selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 is provided and/or utilized in accordance with the methods hereof. In another embodiment, a set of one or markers selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12 is provided and/or utilized in accordance with the methods hereof. In an aspect, a set of two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, ten or more, a dozen, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, a set of 3-5, a set of 5-7, a set of 3-7, a set of 5-8 selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6, a set of 2, 3, 4, 5, 6, 7 of or all of COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12 is provided and/or utilized in accordance with the methods hereof. In an aspect, a set of two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, ten or more, a dozen, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, a set of 3-5, a set of 5-7, a set of 3-7, a set of 5-8 selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 is provided and/or utilized in accordance with the methods hereof. In an aspect, a set of two or more, three or more, four or more, five or more, six or more, seven or more, at least two, at least three, at least four, at least five, at least six, at least seven selected from, or all of COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12 is provided and/or utilized in accordance with the methods hereof.

[0051] The present disclosure also provides a system or kit for predicting an impending RA flare comprising a set of markers as described herein or a set of probes and/or antibodies for evaluating a set of markers as described herein. As an example, a kit or system may include a set of markers or a set of probes and/or antibodies for evaluating a set of markers selected from or for a or any combination of:

- (i) a panel of at least 20 markers from the AC2 markers provided in Table 7;
- (ii) a panel of at least 20 markers from the AC3 markers provided in Table 8, 10 or 11;
- (iii) markers selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 as set out in Table 5;
- (iv) markers selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 as set out in Table 9;

(v) markers selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12.

[0052] In some embodiments, provided herein is a collection of primer pairs for amplifying the AC3 markers in Table 12, wherein the collection of primers comprises or consists of one or more of the primers listed in Table 13. In some embodiments, provided herein is a collection of primer pairs for amplifying the AC3 markers in Table 12, wherein the collection of primers comprise or consists of one or more of the primers SEQ ID Nos: 1-28. In some embodiments, provided herein is a collection of primer pairs for amplifying the AC3 markers in Table 12, wherein the collection of primers comprise or consists of one or more of the forward and reverse primer pairs listed in Table 13. In some embodiments, provided herein is a system or kit for predicting an impending RA flare or increased RA disease activity comprising a panel of markers, wherein the markers are selected from one or more antecedent RA markers listed in Table 10, Table 11, or Table 12.

[0053] In some embodiments, a system or kit disclosed herein further comprises a means for collecting the patient's blood by fingerstick.

[0054] In some embodiments, provided herein is a computer-implemented method for predicting an impending RA flare or increased RA disease activity in a patient comprising:

a) detecting amounts of a panel of AC3 markers, wherein the panel comprises or consists of one or more AC3 markers listed in Table 10, and b) determining, using one or more computer processors, that the patient has an impending RA flare or increased RA disease activity if the amounts of the panel of AC3 markers are higher than the amounts of the panel of AC3 markers in a control blood sample.

[0055] In some embodiments, provided herein is a computer-implemented method for monitoring and/or predicting an impending RA flare or increased RA disease activity in a patient comprising:

a) detecting amounts of a panel of AC3 markers, wherein the panel comprises or consists of one or more or all of the AC3 markers listed in Table 11, and b) determining, using one or more computer processors, that the patient has an impending RA flare or increased RA disease activity if the amounts of the panel of AC3 markers are higher than the amounts of the AC3 markers in a control blood sample.

[0056] In some embodiments, provided herein is a computer-implemented method for monitoring and/or predicting an impending RA flare or increased RA disease activity in a patient comprising:

a) detecting amounts of a panel of AC3 markers, wherein the panel comprises or consists of one or more or all of the AC3 markers listed in Table 12, and b) determining, using one or more computer processors, that the patient has an impending RA flare or increased RA disease activity if the amounts

of the panel of AC3 markers are higher than the amounts of the AC3 markers in a control blood sample.

[0057] In some embodiments, any of the computer-implemented method for monitoring and/or predicting an impending RA flare or increased RA disease activity in a patient as disclosed above further comprises: c) comparing the amounts of the markers in the panel to the amounts of the markers in a control blood sample; and d) administering a therapeutically effective amount of one or more disease-modifying agent for treating RA if the amounts of the markers of the panel in the blood sample is increased relative to the amounts of the markers in the control blood sample, thereby treating the impending flare in the patient comparing the amounts of the markers in the panel to the amounts of the markers in a control blood sample. In some embodiments, step (d) is performed within one (1) week or within 5-7 days from the step (a) of contacting a blood sample from the patient with reagents specific for detecting a panel of AC3 markers of Table 10, 11, or 12.

[0058] In some embodiments, the increased amounts of the AC3 markers predicts an RA flare in about 1 week or about 5-7 days.

[0059] In some embodiments, the markers or marker panels used any one of the methods disclosed herein does not include one or more of Transforming growth factor beta 1 (TGFB1), Tissue inhibitor of metalloproteinase 1 (TIMP1), Interleukin 1 receptor antagonist (IL1RN), COL1A2, COL3A1, and Clusterin (CLU).

[0060] Other objects and advantages will become apparent to those skilled in the art from a review of the ensuing detailed description, which proceeds with reference to the following illustrative drawings, and the attendant claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0061] The patent or patent application contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the U.S. Patent and Trademark Office upon request and payment of the necessary fee.

[0062] **Figure 1** depicts the study overview and validation of in-home assessments of disease activity and gene expression. **A.** Clinical data collection and RNA analysis over time. Study overview of clinical data and sample collection over time. **B.** Clinical and patient reported assessments of disease activity. Correlation between disease activity scores measured in clinic (DAS28) and at home (RAPID3 questionnaire) from the index patient. Locally Weighted Smoothed Scatterplots Showing the Relationship between the Change in RAPID3 scores and DAS28 in the index patient. The solid line represents the point estimates and the gray area represents the 95 percent confidence intervals. **C.** Clinical blood counts and RNASeq-inferred blood counts. Neutrophil, lymphocyte, and monocyte counts measured from paired clinical complete blood counts from venipuncture blood draws and

CIBERSORTx inferred blood counts from RNAseq data from fingerstick blood draws (N=38 paired samples).

[0063] Figure 2 provides clinical and transcriptional characteristics of RA flares in index patient. **A.** Index Patient disease activity over time. Disease activity (RAPID3 questionnaire, N=356), over the course of four years in index patient. Time points are colored according to disease activity category. **B.** Differential expression of genes in flare. Volcano plot of differential gene expression of flare (N=46) versus baseline (N=33), plotting statistical significance ($-\log_{10}(\text{FDR})$) against fold change ($\log_2(\text{FC})$) (gray points are non-significant genes, *i.e.*, $\text{FDR} > 0.1$, red indicates $\text{FDR} < 0.1$ and $\log_2$ fold change > 0 , blue indicates $\text{FDR} < 0.1$ and $\log_2$ fold change < 0). Pathways enriched in significantly increased (**C.**) (Pathways increased in flare) or decreased genes (**D.**) (Pathways decreased in flare) in flare relative to baseline.

[0064] Figure 3 provides transcriptional characteristics of immune activation prior to symptom onset in RA flares. **A.** Disease activity scores over time to flare (measured in days). Box represents disease activity from day -56 to +28 over time to flare. Vertical arrows (in A-D) represent start of flare. **B.** Hierarchical clustering of z scores of 2791 significantly differentially expressed genes over time to flare. Statistically significant clusters are labeled by color. AC2 and AC3 refer to clusters that changed antecedent to flare. **C.** Detailed representation of cluster 1, antecedent cluster 2 (AC2), and antecedent cluster 3 (AC3) genes from Figure 3B over time to flare. **D.** Mean standardized cluster gene expression over time to flare. Light grey lines represent expression of individual genes in the cluster. Dashed horizontal line represents mean baseline gene expression (weeks -8 to -4). Dashed vertical line represents start of flare. **E.** Pathways enriched in clusters 1, AC2, and AC3.

[0065] Figure 4. PRIME cells express AC3 genes. **A.** Synovial cell subtype marker genes in clusters identified in blood (Figure 3A). Enrichment scores of 200 single-cell RNAseq marker genes from 18 synovial panel cell types. Dashed line represents threshold for significance ($\text{FDR} < 0.05$ or $-\log_{10} \text{FDR} > 1.3$). **B.** Mean standardized gene expression and 95% confidence intervals of genes common to synovial sublining fibroblasts (CD34+, DKK+ and HLA-DRA+ fibroblasts) and AC3 in blood over time to flare (dashed vertical line represents start of flare). Error bars represent confidence intervals. **C.** Venn diagram of AC3 genes that decrease during flare in 4 patients. **D.** Flow cytometry of blood samples from 19 RA patients and 18 healthy volunteers (HV). Percent PDPN+/CD45- cells of TOPRO-(live)/CD31- cells is presented. P value represents result of two-sided t-test. **E.** $\log_2$ fold change of AC3 genes expressed in PRIME cells (flow sorted CD45-/CD31-/PDPN+ cells) versus hematopoietic cells (flow sorted CD45+) and $\log_2$ fold change of input cells (stained PBMC but not flow sorted) versus hematopoietic cells (flow sorted CD45+) as technical control for stress of flow sorting.

[0066] **Figure 5** provides a model of blood and synovial gene expression changes antecedent to and during RA flares. Inflammatory signals activate naïve B cells (AC2; Figure 3C-E), which in turn activate PRIME cells (AC3; Figure 3C-E) which harbor the signature of synovial sublining fibroblast genes (Figure 4A). The model proposes that PRIME cells demarginate and are increased in blood prior to flare and then decrease (Figure 4B) just after symptom onset; these cells or their progeny are increased in inflammatory RA synovium where they contribute to and may be sufficient to cause joint inflammation.

[0067] **Figure 6** depicts RNA quality and quantity by volume of fixative. 3 drops of blood harvested with a 21 gauge lancet were added to a microtainer tube prefilled with either 250, 500 or 750ul of PAX gene fixative. Samples were stored at room temperature for 3 days and then RNA was extracted using the PAXgene® RNA kit and RIN scores and quantity of RNA was assessed using the Agilent 2100 Bioanalyzer picochip. Padj= ANOVA, followed by Dunnett's multiple comparisons test, using 250ul as the reference group.

[0068] **Figure 7** depicts RNA quality and quantity by time at room temperature. 100ul of whole blood was added to a microtainer tube prefilled with 250ul PAX gene fixative and frozen after 2 hours, 3 days, or 7 days incubation at room temperature. RNA was extracted using the PAXgene RNA kit with scaled down washes and elutions and RIN scores and quantity of RNA was assessed using the Agilent 2100 BioAnalyzer RNA picochip. Padj= ANOVA, followed by Dunnett's multiple comparisons test, using Day 0 as the reference group.

[0069] **Figure 8** depicts RNA quality and quantity of fresh and mailed samples. 100ul of whole blood was added to a microtainer tube prefilled with 250ul PAXgene fixative and frozen after two-hour incubation at room temperature or mailed. RNA was extracted using the PAXgene RNA kit and RIN scores and quantity of RNA was assessed using the Agilent 2100 BioAnalyzer RNA picochip.

[0070] **Figure 9** depicts RNA quality and quantity by volume of extraction and washes. 3 drops of blood harvested with a 21-gauge lancet were added to a microtainer tube prefilled with 250ul of PAX gene fixative. Samples were stored at room temperature for 3 days and then RNA was extracted using the PAXgene® RNA kit according to manufacturer's directions or with a scaled down version of the PAX protocol, using 25% of the recommended volumes for all washes and elutions. RIN scores and quantity of RNA was assessed using the Agilent 2100 BioAnalyzerRNA picochip. P= unpaired two-sided t test.

[0071] **Figure 10** depicts RNA quality and quantity with and without TriZol reagent extraction step. Mailed patient fingerstick samples were stored in PAXgene® RNA buffer at -80°C. 142 samples had RNA extracted with PAXgene® RNA extraction with low volume washes, 13 samples were thawed and mixed with 700ul Trizol-LS, and 250ul chloroform. After centrifugation, the top layer was precipitated with isopropanol and glycogen and washed with 80% cold ethanol, centrifuged and the

pellet was dried, resuspended in PBS and then purified using the Roche High Pure Isolation kit. P values represent significance of unpaired T tests.

[0072] Figure 11 depicts Cycle Times for HbgA2, 18S RNA, and TNF alpha after GlobinZero depletion. Since ribosomal and hemoglobin RNA represent approximately 98% and 70% of the RNA in whole blood, respectively, we tested standard commercial kits for removing these RNAs prior to RNAseq. 4ml heparinized blood, treated with 1ug/ml LPS for one hour at 37°C and placed 250ul into 250ul PAXgene fixative into replicate microtainer tubes. After RNA extraction samples were either left undepleted or treated with the globin zero depletion kit and then quantitative PCR was performed to test for hemoglobin A2, 18S RNA, or TNF alpha mRNA expression. GlobinZero kits depleted both hemoglobin A2 and 18S ribosomal RNA (increased mean cycle time from 11 to 28 and 10 to 30, respectively) with relative preservation of TNFalpha mRNA. P values represent results of ordinary one-way ANOVA with Tukey's multiple comparisons test.

[0073] Figure 12 provides RNAseq QC metrics of RNA with various quality scores prepared with Illumina TruSeq or Kapa Hyper Prep Kits. **A.** (Left Panel): Distribution of mapping, uniquely mapping, and duplicate reads. **B.** (Right Panel): Distribution of tags assigned to UTR (untranslated region), intergenic, intronic, and CDS (coding sequence) of whole blood RNA samples prepared with Illumina TruSeq or Kapa Hyper Prep Kits with various input RNA quality and quantity. The Illumina TruSeq library Prep demonstrated increased mapping to coding sequence and fewer intergenic reads and was ultimately used for downstream experiments.

[0074] Figure 13 provides comparison of patient reported (RAPID3) and clinical (DAS28) disease activity scores of 4 patients. Paired RAPID3 scores and DAS28-CRP scores were collected from 91 clinic visits of 4 RA patients. The patient reported RAPID3 questionnaire was significantly correlated with clinician generated DAS28 score in all 4 patients.

[0075] Figure 14 depicts clinical features of baseline, flare and on steroid treatment. RAPID3 questionnaire responses from 360 time points and DAS28 ESR, TJC, SJC, ESR, DAS28 CRP, platelet counts and absolute neutrophil counts from 43 clinic visits for one patient over four years. Time points are positioned and colored according to disease activity category: The first (left) set in each graph is baseline, the middle set in each graph is flare, and the third (right) set in each graph is steroid. Steroid treatment was defined as any time point when the patient took any dose of steroid that day, or if the calculated dose, using washout kinetics, was greater than 0.01mg/ml. Samples acquired between two time points that met criteria for flare that did not meet flare criteria were still categorized as flare up until treatment with steroid. TJC indicates tender joint count. SJC indicates swollen joint count. P values represent ANOVA across three disease categories. Flare was associated with significantly increased RAPID3, DAS28 ESR, TJC, SJC, ESR, DAS28CRP, platelets and neutrophils.

[0076] **Figure 15** depicts that differentially expressed flare genes are reproducibly altered in repeated flares. **A.** Index patient disease activity (RAPID3) over time. Top panel dots are colored by disease activity assignment. Bottom panel dots are colored according to clinical flare event number. **B.** Unsupervised hierarchical clustering of genes differentially expressed between baseline and flare. Top bar indicates samples colored according to disease activity assignment. Bottom bar indicates samples colored according to clinical flare event number. Data shows differentially expressed flare genes are represented by multiple clinical events.

[0077] **Figure 16** provides deconvolution of blood cell types over time to flare. Mean cell type trajectories of **A.** ABIS inferred cell types, and **B.** CIBERSORTx inferred cell types over time to flare are plotted (excluding those that were 0 all throughout) showing the mean score with standard error of the mean as a ribbon. These data independently confirm data in main Figure 4A identifying activation of B cells in AC2.

[0078] **Figure 17** depicts that distinct analysis approaches identify activation of naïve B cells in blood 2 weeks prior to flare. **A.** CIBERSORTx inferred naïve B cells by week to flare. **B.** ABIS inferred naïve B cells by week to flare. **C.** Mean expression of 190 synovial single-cell RNAseq naïve B cell marker genes by week to flare. **D.** IGHM (blue/top) and IGHD (red/bottom) gene expression by week to flare. Dashed line indicates first day of symptoms of RA flare, red arrows indicate peak in B cell signature 2 weeks prior to flare.

[0079] **Figure 18** provides mean standardized gene expression of genes common to synovial sublining fibroblasts (CD34+, DKK+, and HLA-DR+ fibroblasts) and AC3 in blood over time to flare. Light gray lines represent the expression of individual genes over time to flare in patient 1 over all flares.

[0080] **Figure 19** depicts gating strategy for quantification of PRIME cells in blood samples. Previously frozen peripheral blood mononuclear cells were thawed and stained with antibodies to CD31, PDPN, and CD45 as well as TOPRO. Live CD31- cells were gated and PDPN +, CD45- cells were enumerated.

[0081] **Figure 20** demonstrates PRIME cells are nucleated. PBMC of RA donor was stained with CD45/CD31/PDPN and either TOPRO (Not Permeabilized) or permeabilization and TOPRO (Permeabilized) and assessed by flow cytometry. PRIME cells were gated as CD45-/CD31-/PDPN+ cells and TOPRO staining of permeabilized and not permeabilized cells is presented. The increased fluorescence of TOPRO in the permeabilized PRIME cells indicates the presence of double stranded nucleic acid.

[0082] **Figure 21** depicts that sorted PRIME cells express synovial fibroblast genes. Log2 fold change of various synovial single-cell RNAseq marker genes in PRIME cells (flow sorted CD45-/CD31-/PDPN+ cells) versus hematopoietic cells (flow sorted CD45+) and Log2 fold change of Input

cells (stained PBMC but not flow sorted) versus hematopoietic cells (flow sorted CD45+) as technical control for stress of flow sorting. These data show that single-cell marker genes of fibroblasts (SC-F1, SC-F2, SC-F3, SC-F4) but not B cells (SC-B1-4), macrophages (SC-M1-4), or T cells (SC-T1-6) are enriched in sorted PRIME cells. Fibroblast genes (as marked) were the only set of synovial cell marker genes enriched in PRIME cells.

[0083] Figure 22 depicts Volcano plot of log₁₀ (-padj) vs Log₂ fold change of PRIME cells (flow sorted DAP-/CD45-/CD31-/PDPN+ cells) versus hematopoietic cells (flow sorted SAP-/CD45+). The results show that classic fibroblast genes are significantly increased in PRIME cells relative to hematopoietic cells.

[0084] Figure 23 illustrates an exemplary process of refining the dataset to identify a panel of a smaller number of markers for prediction of an impending RA flare.

DETAILED DESCRIPTION

[0085] In accordance with the present disclosure there may be employed conventional molecular biology, microbiology, and recombinant DNA techniques within the skill of the art. Such techniques are explained fully in the literature. See, *e.g.*, Sambrook *et al*, “Molecular Cloning: A Laboratory Manual” (1989); “Current Protocols in Molecular Biology” Volumes I-III [Ausubel, R. M., ed. (1994)]; “Cell Biology: A Laboratory Handbook” Volumes I-III [J. E. Celis, ed. (1994)]; “Current Protocols in Immunology” Volumes I-III [Coligan, J. E., ed. (1994)]; “Oligonucleotide Synthesis” (M.J. Gait ed. 1984); “Nucleic Acid Hybridization” [B.D. Hames & S.J. Higgins eds. (1985)]; “Transcription And Translation” [B.D. Hames & S.J. Higgins, eds. (1984)]; “Animal Cell Culture” [R.I. Freshney, ed. (1986)]; “Immobilized Cells And Enzymes” [IRL Press, (1986)]; B. Perbal, “A Practical Guide To Molecular Cloning” (1984).

[0086] Therefore, if appearing herein, the following terms shall have the definitions set out below.

A. TERMINOLOGY

[0087] The term “rheumatoid arthritis” or “RA” refers to a chronic disease, which is immune-mediated and inflammatory and is an autoimmune disorder, affecting the lining of joints that causes joint pain, stiffness, swelling and decreased movement of the joints and can eventually result in bone erosion and joint deformity. RA is a systemic autoimmune disease characterized by the simultaneous inflammation of the synovium of multiple joints.

[0088] An “RA flare” or “flare” refers to a surge in immune-mediated and/or inflammatory activity that is periodically experienced by a patient(s) with RA. During a flare, the level of fatigue and joint symptoms such as pain, swelling, and stiffness temporarily increase. Flares are periods of increased disease activity during which people’s arthritis symptoms, which typically include joint pain, swelling, and stiffness, are more severe. An RA flare can involve an exacerbation of any symptom of the disease, but most commonly includes intense stiffness in the joints. People with RA report these

common symptoms of flares: increased stiffness in joints, pain throughout the entire body, increased difficulty doing everyday tasks, swelling, such as causing shoes not to fit, intense fatigue, flu-like symptoms. The term “increased disease activity,” as used in this application, refers to an increase in disease activity score 28 (DAS28) or RAPID3. DAS28 is a composite score of RA related disease activity encompassing patient global assessment of RA activity, physician assessment of tenderness and swelling from 28 joints, and erythrocyte sedimentation rate (ESR) or C reactive protein (CRP). RAPID3 is a patient reported assessment of function, pain, and global health that correlates with DAS28 (Pincus, *et al.*, *Rheumatology* (Oxford), 2008. 47(3):345-349; Pincus, *et al.*, *Arthritis Care Res* (Hoboken), 2011. 63(8): p. 1142-9; Pincus, T., *et al.*, *J Rheumatol*, 2011. 38(12): p. 2565-71; Pincus, *et al.*, 2008. 35(11): p. 2136-47; Ward *et al.*, *J Rheumatol*, 2019. 46(1): p. 27-30. Increased disease activity is further described in Example 1.

[0089] The term “antibody” describes an immunoglobulin whether natural or partly or wholly synthetically produced. The term also covers any polypeptide or protein having a binding domain which is, or is homologous to, an antibody binding domain. CDR grafted antibodies are also contemplated by this term. An “antibody” is any immunoglobulin, including antibodies and fragments thereof, that binds a specific epitope. The term encompasses polyclonal, monoclonal, and chimeric antibodies. The term “antibody(ies)” includes a wild type immunoglobulin (Ig) molecule, generally comprising four full length polypeptide chains, two heavy (H) chains and two light (L) chains, or an equivalent Ig homologue thereof (*e.g.*, a camelid nanobody, which comprises only a heavy chain); including full length functional mutants, variants, or derivatives thereof, which retain the epitope binding features of an Ig molecule, and including dual specific, bispecific, multispecific, and dual variable domain antibodies; Immunoglobulin molecules can be of any class (*e.g.*, IgG, IgE, IgM, IgD, IgA, and IgY), or subclass (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2). Also included within the meaning of the term “antibody” are any “antibody fragment”.

[0090] An “antibody fragment” means a molecule comprising at least one polypeptide chain that is not full length, including (i) a Fab fragment, which is a monovalent fragment consisting of the variable light (VL), variable heavy (VH), constant light (CL) and constant heavy 1 (CH1) domains; (ii) a F(ab')₂ fragment, which is a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a heavy chain portion of an Fab (Fd) fragment, which consists of the VH and CH1 domains; (iv) a variable fragment (Fv), which consists of the VL and VH domains of a single arm of an antibody, (v) a domain antibody (dAb) fragment, which comprises a single variable domain (Ward, E.S. *et al.*, *Nature* 341, 544-546 (1989)); (vi) a camelid antibody; (vii) an isolated complementarity determining region (CDR); (viii) a Single Chain Fv Fragment wherein a VH domain and a VL domain are linked by a peptide linker which allows the two domains to associate to form an antigen binding site (Bird *et al.*, *Science*, 242, 423-426, 1988; Huston *et al.*,

PNAS USA, 85, 5879-5883, 1988); (ix) a diabody, which is a bivalent, bispecific antibody in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with the complementarity domains of another chain and creating two antigen binding sites (WO94/13804; P. Holliger *et al.* Proc. Natl. Acad. Sci. USA 90 6444-6448, (1993)); and (x) a linear antibody, which comprises a pair of tandem Fv segments (VH-CH1-VH-CH1) which, together with complementarity light chain polypeptides, form a pair of antigen binding regions; (xi) multivalent antibody fragments (scFv dimers, trimers and/or tetramers (Power and Hudson, J Immunol. Methods 242: 193-204 9 (2000)); (xii) a minibody, which is a bivalent molecule comprised of scFv fused to constant immunoglobulin domains, CH3 or CH4, wherein the constant CH3 or CH4 domains serve as dimerization domains (Olafsen T *et al.* (2004) Prot Eng Des Sel 17(4):315-323; Hollinger P and Hudson PJ (2005) Nature Biotech 23(9):1126-1136); and (xiii) other non-full length portions of heavy and/or light chains, or mutants, variants, or derivatives thereof, alone or in any combination.

[0091] As antibodies can be modified in several ways, the term “antibody” should be construed as covering any specific binding member or substance having a binding domain with the required specificity. Thus, this term covers antibody fragments, derivatives, functional equivalents and homologues of antibodies, including any polypeptide comprising an immunoglobulin binding domain, whether natural or wholly or partially synthetic. Chimeric molecules comprising an immunoglobulin binding domain, or equivalent, fused to another polypeptide are therefore included.

[0092] The term “adjuvant(s)” describes a substance, compound, agent or material useful for improving an immune response or immune cell or component stimulation and may in some instances be combined with any particular antigen in an immunological, pharmaceutical or vaccine composition. Adjuvants can be used to increase the amount of antibody and effector T cells produced and to reduce the quantity of antigen or immune stimulant or modulator and the frequency of injection. An adjuvant can serve as a tissue depot that slowly releases the antigen and as a lymphoid system activator that non-specifically enhances the immune response. In a preferred aspect an adjuvant is physiologically and/or pharmaceutically acceptable in a mammal, particularly a human.

[0093] The term “specific” may be used to refer to the situation in which one member of a specific binding pair will not show any significant binding to molecules other than its specific binding partner(s). The term is also applicable where *e.g.*, an antigen binding domain is specific for a particular epitope which is carried by several antigens, in which case the specific binding member carrying the antigen binding domain will be able to bind to the various antigens carrying the epitope.

[0094] The term “comprise” generally used in the sense of include, that is to say permitting the presence of one or more features or components. The term “consist essentially of” refers to a product,

such as a peptide sequence, of a defined number of residues which is not covalently attached to a larger product.

[0095] The term “oligonucleotide,” as used herein in referring to a probe of use the present disclosure, is defined as a molecule comprised of two or more ribonucleotides, preferably more than three. Its exact size will depend upon many factors which, in turn, depend upon the ultimate function and use of the oligonucleotide. The term “primer” as used herein refers to an oligonucleotide, which is capable of acting as a point of initiation of synthesis when placed under conditions in which synthesis of a primer extension product, which is complementary to a nucleic acid strand, is induced, *i.e.*, in the presence of nucleotides and an inducing agent such as a DNA polymerase and at a suitable temperature and pH. The primer may be either single-stranded or double-stranded and must be sufficiently long to prime the synthesis of the desired extension product in the presence of the inducing agent. The exact length of the primer will depend upon many factors, including temperature, source of primer and use of the method. For example, for diagnostic applications, depending on the complexity of the target sequence, the oligonucleotide primer typically contains 15-25 or more nucleotides, although it may contain fewer nucleotides.

[0096] The term “agent” means any molecule, including polypeptides, antibodies, polynucleotides, chemical compounds and small molecules. In particular the term agent includes compounds such as test compounds or drug candidate compounds.

[0097] The term “assay” means any process used to measure a specific property of a compound. A “screening assay” means a process used to characterize or select compounds based upon their activity from a collection of compounds.

[0098] The term “protein” is used herein to mean protein, polypeptide, oligopeptide or peptide. The terms “protein marker”, “biomarker” or “protein marker of impending flare” are used herein to refer to proteins associated with or predictive or which precede specific diseases or conditions or symptoms, including proteins from or associated with aspects, cells or tissues affected by a disease or condition or symptom. In accordance with the present disclosure, the increase in marker expression relative to that detected or characteristic of a subject/s without overt organic RA disease or significant joint or pain symptoms or without an impending flare or a normal, healthy subject/s (control/controls) is positively correlated with, indicative of, or diagnostic for the impending presence or flare or flare-up of a disease or condition or symptoms thereof particularly an exacerbation of disease or symptoms, such as rheumatoid arthritis and particularly an RA flare, in a patient.

[0099] As used herein, the terms “increase” in marker expression or “differential expression” of a marker refer to a statistically significant increase or presence in a test sample (e.g., a sample from an RA patient) relative to a control sample when detected using the same assay under the same assay

conditions. The term “increase” in expression or amounts with respect to a panel of markers refers to a statistically significant increase or presence of each marker in the panel. Typically assays for detecting expression of RNA markers are known, and the exemplary assays include RT-PCR, RNAseq, and the like. Typically assays for detecting the expression of protein markers are well known, and the exemplary assays include Western blot, ELISA, FACS, and the like. In some embodiments, an increase refers to that the amount of a marker detected in a blood sample from a patient is more than 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 200%, or 500% of the amount of the same marker in a control blood sample. In some embodiments, an increase includes an increase from 0 to any amount; for example, if a marker is not detectable in a control sample but is detected in a test sample in the same assay and under the same assay conditions, then the test sample is determined to have increased amount of the marker. The term statistically significant is used in the art to refer to the likelihood that a result or relationship is caused by something other than mere random chance. Statistical hypothesis testing is traditionally employed to determine if a result is statistically significant or not. Such testing provides a “p-value” representing the probability that random chance could explain the result. In general, a 5% or lower p-value is considered to be statistically significant.

[00100] The term “decrease” in marker expression or amount refer to a statistically significant decrease relative to controls when detected using the same assay and under the same assay conditions. A decrease in marker expression refers to that the amount of a marker detected in a blood sample from a patient is less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, less than 10% of the amount of the same marker in a control blood sample. In some embodiments, a decrease also includes a decrease from any amount to 0 (the marker is absent in the test sample); for example, if a marker is detectable in a control sample but not detectable in a test sample in the same assay and under the same assay conditions, then test sample is determined to have decreased amount of the marker.

[00101] The term “a control blood sample” refers to a blood sample from a healthy individual. In some embodiments, the control blood sample can be a baseline sample from the same patient who is evaluated for the RA flare. In some embodiments, the control blood sample can be from a patient with unrelated illness, such as non-RA patients who have osteoarthritis.

[00102] A skilled practitioner would, moreover, appreciate that a relative increase or decrease in a particular protein (a protein marker) or a particular RNA (an RNA marker) in a sample alone may be weakly indicative or predictive of disease, but may not be diagnostic per se, if noted as a single determinant. If, however, a plurality of such single determinants is noted in a biological sample, the combined detection of several, even weakly indicative, determinants may serve to identify a strong

combinatorial diagnostic indicator of impending disease or symptomatic disease aspects, such as impending RA flare. Furthermore, the single protein/determinant need not approach the threshold of weak diagnostic by itself but in combination with the detection of an increase of another protein or proteins or RNA or RNAs (other markers) may serve as a strong combinatorial diagnostic indication of an impending disease state. Accordingly, also encompassed herein are combinatorial diagnostic indicators or combinatorial markers that are associated with a particular disease or an impending disease and not observed in healthy subjects or patients with other diseases. For purpose of this disclosure, unless otherwise noted, a marker can refer to either the RNA transcribed from a gene or protein encoded by the same gene. For example, an AC3 marker (*e.g.*, the KIAA1755 marker) can refer to either the RNA transcribed (*e.g.*, the KIAA1755 RNA) from a gene in the AC3 panel or a protein (*e.g.*, the KIAA1755 protein) encoded by the gene in the AC3 panel.

[0103] Accordingly, selected sets of one, two, three, several, at least 10, about 10, a dozen, 10-15, about 20, at least 20, 25, 30, about 30 and more, etc of the markers of this invention (up to the number equivalent to all of the markers, or all in a set of markers, including any intervening number, in whole number increments, *e.g.*, 1, 2, 3, 4, 5, 6 ...) can be used as diagnostic indicators and predictors of an impending flare for methods and/or in kits described herein. In one embodiment, larger numbers of the markers identified herein are used in methods or kits of the present disclosure, since the accuracy of the method or kit may improve as the number of markers screened increases. With respect to aspects of the present disclosure pertaining to evaluating therapeutic efficacy, the methods and kits of the present disclosure include evaluating whether administration of a therapeutic composition causes a change, either a transient change or a long term change, in expression of one or more of the markers; in expression of two or more of the markers; in expression of three or more of the biomarkers; in expression of four or more of the biomarkers; in expression of five or more of the biomarkers, in expression of six or more of the biomarkers, etc.

[0104] As an example, a straightforward identification of a protein marker or an RNA marker is the presence of a protein or RNA associated with an impending disease or condition and not with other conditions that might be clinically confused with the disease under consideration. Variations to this scenario include the situation wherein a marker is present in an increased quantity compared to other conditions or controls. Although not a protein marker, an example is the presence of glucose in the blood in high quantities in diabetics compared to normal individuals who have glucose present but not in elevated quantities. A variation is where the functional marker is not just one protein but two or more in combination that can be quantitatively different, wherein the ensemble defines its marker potential.

[00105] In some embodiments, a marker of the present disclosure is a member of a biological pathway. As used herein, the term “precursor” or “successor” refers to molecules that precede or follow the marker in the biological pathway. Thus, once a marker is identified as a member of one or more biological pathways, the present disclosure includes additional members of the biological pathway that come before (are upstream of or a precursor of) or follow (are downstream of) the marker. Such identification of biological pathways and their members is within the skill of one in the art.

[00106] Also encompassed herein is the analysis of markers identified and listed in the tables presented herein to identify metabolic pathways implicated in the pathogenesis, maintenance, and/or progression of a disease or an impending disease or system or flare. Such analyses may utilize a variety of software programs or approaches known and available to the skilled artisan. Multiple hits in a particular metabolic pathway underscore the potential importance of the pathway for the disease and direct therapeutic intervention toward appropriate modulation of same. Accordingly, the present methods encompass such analyses and the identification of metabolic pathways of potential significance in a particular disease or impending disease aspect or symptom. Knowing that, for example, activation of a metabolic pathway appears to be linked or associated with a particular disease or impending symptom presents the opportunity to test pharmaceutical modulators of the pathway (*i.e.*, inhibitors) to determine if such modulators could be used as therapeutics for treatment of patients with the disease or impending disease or symptoms. This and these aspects are illustrated and described herein including in the examples.

[00107] In accordance with the present disclosure, the tables present information with which an ordinarily skilled practitioner can access the amino acid sequences of the proteins and RNAs identified herein as markers, as well as nucleic acid sequences encoding same. A stepwise protocol or means for identification of the sequences listed in the tables presented herein may include the artisan accessing one of the publicly available databases and entering the ensembl number or gene name or symbol to identify the sequence and relevant marker information. Such information may be used to design probes for detection of any of the proteins, genes, RNAs listed therein or to identify commercially available probes or antibodies therefore or thereof. Primers for detection of nucleic acid sequences encoding any of the proteins listed in the tables presented herein are also envisioned as primers for PCR including RT PCR. Such primers may be used to detect RNA expression levels (including relative increases or decreases as compared to controls) of a marker relevant to the present disclosure. The design of primers for detecting expression levels of RNA (*e.g.*, mRNA) of a marker or markers listed herein is a matter of routine practice with the nucleic acid sequence in hand as provided by publicly available websites such as those mentioned above. Such probes and primers are useful for the kits described herein.

[00108] The term “preventing” or “prevention” refers to a reduction in risk of acquiring or developing a disease or disorder (*i.e.*, causing at least one of the clinical symptoms of the disease not to develop) in a subject that may be exposed to a disease-causing agent, or predisposed to the disease in advance of disease onset. The term “prophylaxis” is related to and encompassed in the term “prevention” and refers to a measure or procedure the purpose of which is to prevent, rather than to treat or cure a disease. Non-limiting examples of prophylactic measures may include the administration of vaccines; the administration of low molecular weight heparin to hospital patients at risk for thrombosis due, for example, to immobilization; and the administration of an anti-malarial agent such as chloroquine, in advance of a visit to a geographical region where malaria is endemic or the risk of contracting malaria is high.

[00109] “Therapeutically effective amount” means that amount of a drug, compound, antibody, or pharmaceutical agent that will elicit the biological or medical response of a subject that is being sought by a medical doctor or other clinician. In particular, with regard to gram-positive bacterial infections and growth of gram-positive bacteria, the term “effective amount” is intended to include an effective amount of a compound or agent that will bring about a biologically meaningful decrease in the amount of or extent of disease or flare free time period and or increase in length of a subject’s survival or period disease-free or in remission or free of flare(s). The phrase “therapeutically effective amount” is used herein to mean an amount sufficient to prevent, and preferably reduce by at least about 30 percent, more preferably by at least 50 percent, most preferably by at least 90 percent, a clinically significant change, or enhanced survival or disease-free period by at least about 30 percent, more preferably by at least 50 percent, most preferably by at least 90 percent.

[00110] The term “treating” or “treatment” of any disease, condition, or infection refers, in one embodiment, to ameliorating the disease or infection (*i.e.*, arresting the disease or growth of the infectious agent or bacteria or reducing the manifestation, extent or severity of at least one of the clinical symptoms thereof). In another embodiment “treating” or “treatment” refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In another embodiment, “treating” or “treatment” refers to modulating the disease or infection, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. In a further embodiment, “treating” or “treatment” relates to slowing the progression of a disease or reducing an infection. In some embodiments, “treating” a patient having or being diagnosed with an impending RA flare refers to treating the patient to prevent an impending flare or ameliorate symptoms related to the flare, for example, resulting in the patient experiencing a reduced flare, fewer pathologies and/or symptoms associated with a flare, or resulting in a flare and its associated disease exacerbations being reduced, limited in duration, or avoided.

[0011] The phrase “pharmaceutically acceptable” refers to molecular entities and compositions that are physiologically tolerable and do not typically produce an allergic or similar untoward reaction, such as gastric upset, dizziness and the like, when administered to a human.

[0012] As used herein, “pg” means picogram, “ng” means nanogram, “ug” or “μg” mean microgram, “mg” means milligram, “ul” or “μl” mean microliter, “ml” means milliliter, “l” means liter.

B. DETAILED DISCLOSURE.

[0013] The present disclosure relates to and provides previously unidentified and unrecognized markers, particularly RNA markers and protein markers, which are indicators and antecedents of an impending rheumatoid arthritis (RA) flare. The markers are differentially expressed or preferentially expressed prior to an RA flare in an RA patient and the expression profile of which can be used to predict an impending flare and can be utilized to implement and prescribe treatment and therapy to a patient. In some embodiments, an antecedent marker can be an RNA marker (*e.g.*, an AC3 RNA marker) or a protein marker (a AC3 protein marker) so long as they are differentially expressed or preferentially expressed before an RA flare.

[0014] This application incorporates by reference the entire content of the following publication: Orange *et al.*, N. Engl. J. Med. 383: 218-28 (2020), available at DOI: 10.1056/NEJMoa2004114.

RA

[0015] Arthritis is a disease that may cause damage to the healthy cartilage of joints, leading to degenerative changes, loss of function and joint instability. Inflammatory arthritis describes conditions characterized by pain, swelling, tenderness and warmth in the joints, as well as morning stiffness that lasts for more than an hour. An increase of cytokines leads to degradation of articular cartilage and a decrease of growth factors which induce chondrogenesis in inflammatory arthritis. The most common inflammatory arthritis associated disorders rheumatoid arthritis (RA), psoriatic arthritis (PsA), systemic lupus erythematosus (SLE, lupus), ankylosing spondylitis (AS), and gouty arthritis (gout). Arthritis damages the cartilage within joints, resulting in degenerative changes, including loss of function and joint instability. Ankylosing spondylitis (AS) is a chronic inflammatory condition affecting the spine and bone-to-tendon attachment area within the sacroiliac joint leading to back pain and progressive spinal stiffness. Rheumatoid arthritis is a chronic, systemic autoimmune disease characterized by the simultaneous inflammation of the synovium of multiple joints, leading to joint damage (*e.g.*, destruction, deformation and disability). Gout is a chronic inflammatory disease that causes an alteration of joints resulting in severe pain and is associated with an accumulation of uric acid within the body resulting from dysregulated purine metabolism, causing recurrent

paroxysmal inflammation in the joints. Allopurinol and febuxostat are the primary treatment options for individuals with gout.

[00116] Various disease-modifying agents for treating or modifying RA, including for management and alleviation of RA flares, are known and in use clinically. Nonsteroidal anti-inflammatory drugs (NSAIDs) or disease-modifying antirheumatic drug (DMARDs) have been used for the treatment of these inflammatory diseases, particularly RA. More recently, biologic DMARDs have been introduced with excellent results. NSAIDs include non-prescription drugs acetylsalicylate (aspirin), ibuprofen (Advil, Motrin IB) and naproxen sodium (Aleve, Naprosyn) and prescription NSAIDs such as etodolac (Lodine) and diclofenac (Voltaren). Steroids are anti-inflammatory or immunosuppressants agents and are prescribed for more severe RA or when RA symptoms flare to ease joint pain and stiffness. Examples include glucocorticosteroids or corticosteroids such as prednisone, cortisone and methylprednisolone. DMARDs are prescribed and utilized to slow the progression of RA and save joints and other tissues from permanent damage. Common conventional DMARDs include methotrexate (Trexall, Otrexup), leflunomide (Arava), hydroxychloroquine (Plaquenil) and sulfasalazine (Azulfidine). DMARDs curb the overactive immune system in RA but aren't selective in their targets. Biologics - genetically engineered proteins which target a specific aspect or part of the immune system and act as immunosuppressants - are an increasingly important component in treatment of RA and are commonly denoted biologic DMARDs or bDMARDs. Biologics include abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), baricitinib (Olumiant), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), rituximab (Rituxan), sarilumab (Kevzara), tocilizumab (Actemra) and tofacitinib (Xeljanz). Adalimumab, etanercept, infliximab, golimumab and certolizumab target tumor necrosis factor (TNF). Rituximab is effective against B cells. Anakinra blocks the action of interleukin-1 (IL-1), a master cytokine. Abatacept targets T cells. Biologic DMARDs are usually most effective when paired with a nonbiologic DMARD, such as methotrexate. New DMARD drugs which are specific in their targets but are not biologics include oral small molecule Janus kinase (JAK) inhibitors such as tofacitinib (Xeljanz and Xeljanz XR), baricitinib (Olumiant), and upadacitinib (Rinvoq).

[00117] The American College of Rheumatology (ACR) has recommendations for RA patient treatment given various disease parameters (*e.g.*, Singh J *et al.* (2016) *Arthritis Rheumatol* 68:1-26). Disease activity scales are utilized in managing RA patients and choosing appropriate treatment modalities, including the routine assessment of patient index data 3 (RAPID3) and the disease activity score 28 (DAS28) (Fransen, J *et al.* (2003) *Arthritis Rheum* 49 Suppl:S214-24), which incorporates tenderness and swelling from 28 joints, erythrocyte sedimentation rate (ESR) and patient global assessment of disease activity, both of which have been utilized in studies described herein. Additional assessment instruments include Patient Activity Scale (PAS) or PASII (Wolfe, F *et al.*

(2005) *J Rheumatol* 32:2410–5), Clinical Disease Activity Index (CDAI) (Aletaha, D *et al.* (2005) *Arthritis Res Ther* 7: R796–806) and Simplified Disease Activity Index (SDAI) (Smolen, JS *et al.* (2003) *Rheumatology* 42:244–57). Each of these scales and assessments are applicable in treatment once a patient has symptomatic aspects or indicators of a flare or of disease. These scales cannot predict a flare, they are indicators of a flare or of exacerbation of disease.

[00118] RA patients are not able to predict a flare and are therefore subject to unpredictable exacerbations of disease and disease-associated symptoms and continual, progressive joint damage. The availability of dependable markers of impending flare(s), which can be readily and reliably assessed, particularly without significant clinical intervention, would significantly impact the treatment and management of RA patients and reduce the impact and long-term effects of the disease.

AC2 markers

[00119] Toward that end, the present disclosure provides a first set of markers that are expressed two weeks or about two weeks prior to an RA flare. These markers are referred to as the AC2 markers. The timing before flare can have a margin of error of about a week or 7 days. Referring to the studies provided herein, patients symptoms were assessed using a questionnaire that asked about how they were doing over the past week, therefore there is a possible seven-day margin of error in timing. For instance, given the questionnaire, the researchers could not necessarily discriminate between symptoms that started that day (or on day 1) vs 6 days earlier, or about a week or up to 7 days earlier. Therefore, the timing of the first set of markers is about two weeks, with a margin of error up to an additional 7 days, therefore up to 3 weeks or a week up to three weeks or 7-21 days. A first set of markers can be identified and characterized in a patient sample, particularly a blood sample, including a fingerstick sample of blood, two weeks or about two weeks, about 14 days, approximately 14 days, more than one week, more than 12 days, more than 10 days, about 10-14 days, about 12-14 days prior to an RA flare, with a margin of error in each instance of up to about a week or 7 days, therefore, with a margin of error up to three weeks, at least a week, about two or three weeks, two or three weeks, about 7-21 days, up to 21 days, at least 7-10 days, about two to three weeks prior to an RA flare. These antecedent markers, particularly denoted AC2 markers, are provided in Table 7. As shown in Example 2 and Table 7, the RNA analysis of fingerstick blood samples from RA patients indicate that all AC2 RNA markers listed in Table 7 increased the week prior to flare and was then decreased for the duration of the flare.

AC3 markers

[00120] Another and second set of markers are provided that are expressed one week or about one week, or about 7 days, approximately 7 days, prior to an RA flare. These markers are also referred to as the AC3 markers. The timing before flare can have a margin of error of about a week or 7 days.

Referring to the studies provided herein, patients symptoms were assessed using a questionnaire that asked about how they were doing over the past week, therefore there is a possible seven-day margin of error in timing. For instance, given the questionnaire, the researchers could not necessarily discriminate between symptoms that started that day (or on day 1) vs 6 days earlier, or about a week or up to 7 days earlier. The second set of markers can be identified and characterized in a patient sample, particularly a blood sample, including a fingerstick sample of blood, about one week, or about 7 days, approximately 7 days, about 5-7 days prior to an RA flare, with a margin of error in each instance of up to about a week or 7 days, therefore, with a margin of error up to two weeks, up to 14 days, 0-14 days, about one to two weeks, at least a week, about a week to 10 days, 7-14 days, 5-14 days prior to a flare. These antecedent markers, particularly denoted AC3 markers, are provided in Table 8. The set of AC2 markers or the first set of markers are expressed further out from a flare and more than a week before flare, up to three weeks prior to an RA flare, while the set of AC3 markers or the second set of markers are expressed thereafter or closer to a flare and about a week or up to two weeks prior to a flare. See Example 2.

[00121]In an aspect, the AC3 markers, or one or more AC3 marker, or AC3 markers which are sublining fibroblast genes, are decreased during flare or after the commencement of a flare or once a patient experiences physical indicators or symptoms of a flare. Physical indicators or symptoms of a flare may be selected from stiffness in joints, pain throughout the body, increased difficulty doing everyday tasks, swelling, fatigue and flu-like symptoms. In an aspect, synovial cell marker genes or proteins among the AC3 markers and Table 8 are selected. A flare(s) may be evaluated by recognition of the symptoms in a patient and/or utilizing any recognized disease activity scales, including as described and provided herein.

[00122]RNA markers and protein markers of impending flare which are particularly selected for determining and predicting impending RA flares are provided in Table 9. The markers COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4. RNAs or their encoded proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 are expressed one week or about one week, or about 7 days, approximately 7 days, about 5-7 days, at least 5 days prior to an RA flare. Markers selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4. RNAs or their encoded proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 are expressed one week or about one week, or about 7 days, approximately 7 days, about 5-7 days, at least 5 days prior to an RA flare. In particular, the markers are differentially expressed in a patient prior to a flare. Markers selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4. RNAs or their

encoded proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 are differentially expressed, their expression is increased or higher relative to other markers or proteins, or their expression is significantly increased relative to expression in a normal sample or a sample from an individual that does not have RA or any other recognized inflammatory or autoimmune disease, one week or about one week, or about 7 days, approximately 7 days, about 5-7 days, at least 5 days prior to an RA flare. As noted above, the margin of error in timing may be up to a week or 7 days. Therefore expression of these markers selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4. RNAs or their encoded proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 maybe increased one top two weeks or 0-14 days, or about a week or two prior to a flare. Expression of RNAs or their encoded proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 are decreased in peripheral blood during an RA flare. Expression of RNAs or their encoded proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 are decreased in peripheral blood during an RA flare in comparison to their expression prior to a flare, particularly their expression about a week, or up to two weeks, prior to a flare.

[00123]RNA markers and protein markers of impending flare which are particularly selected for determining and predicting impending RA flares are provided in Table 12. The markers COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1. RNAs or their encoded proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 are expressed one week or about one week, or about 7 days, approximately 7 days, about 5-7 days, at least 5 days prior to an RA flare. Markers selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1. RNAs or their encoded proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 are expressed one week or about one week, or about 7 days, approximately 7 days, about 5-7 days, at least 5 days prior to an RA flare. In particular, the markers are differentially expressed in a patient prior to a flare. Markers selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1. RNAs or their encoded proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 are differentially expressed, their expression is increased or higher relative to other markers or proteins, or their expression is significantly increased relative to expression in a normal sample or a sample from an individual that does not have RA or any other recognized inflammatory or autoimmune disease, one week or about one week, or about 7 days, approximately 7 days, about 5-7 days, at least 5 days prior to an RA flare. As noted above, the margin of error in timing may be up to a week or 7 days. Therefore, expression of

these markers selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1. RNAs or their encoded proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 maybe increased one top two weeks or 0-14 days, or about a week or two prior to a flare. Expression of RNAs or their encoded proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 are decreased in peripheral blood during an RA flare. Expression of RNAs or their encoded proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 are decreased in peripheral blood during an RA flare in comparison to their expression prior to a flare, particularly their expression about a week, or up to two weeks, prior to a flare.

[00124] RNA markers and transcripts or protein markers common to synovial sublining fibroblasts which are markers of impending flare and are capable of predicting or determining an impending flare or increased disease activity as set out in Table 5. The markers comprise or consist of COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFH4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6. The markers are COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFH4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6. The markers are selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFH4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6. RNAs or their encoded proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFH4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 are expressed one week or about one week, or about 7 days, approximately 7 days, about 5-7 days, at least 5 days, prior to an RA flare. As noted above, the margin of error in timing may be up to a week or 7 days. Therefore, expression of these markers of impending flare may be found or evident a week or up to two weeks, at least about a week, about 0- 14 days, up to two weeks, 5-14 days prior to a flare. Expression of RNAs or their encoded proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFH4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 are, decreased in peripheral blood during an RA flare.

Refined AC3 markers

[00125] In some embodiments, the method of predicting an impending RA flare includes detecting in the blood sample increased amounts of a panel of AC3 markers, wherein the panel of antecedent AC3 markers comprises or consists of one or more markers listed in Table 10, for example, at least 5, at least 10, at least 50, at least 100 markers. In some embodiments, the panel of antecedent AC3 markers comprise or consist of 2-283 markers, *e.g.*, 8-200, 8-180, or 10-150 markers of the markers listed in

Table 10, including all markers listed in Table 12. In some embodiments, the panel comprise or consist of 65-283 markers of the markers listed in Table 10, including some or all markers listed in Table 11. In some embodiments, the panel comprise or consist of all markers listed in Table 10. As shown in Example 3, genes listed in Table 10 are expressed in high levels (top quartile) in blood samples from RA patients and thus can be used for prediction of an impending RA with high confidence. The detection of increased amounts of these AC3 markers indicates an impending RA flare in about a week or up to two weeks.

[00126] In some embodiments, the panel comprise or consist of one or more markers listed in Table 11, for example, at least 5, at least 10, at least 20, at least 30 markers of the markers listed in Table 11. In some embodiments, the panel comprises or consists of 2-65 markers, *e.g.*, 5-65 markers, 10-60 markers, or 20-55 markers, including some or all markers listed in Table 12. In some embodiments, the panel comprises or consists of all markers listed in Table 11. In some embodiments, the panel comprises or consists of all markers listed in Table 12. As shown in Example 3, markers listed in Table 11 overlap with published synovial marker genes in a published dataset (accession # SDY998). This overlap is useful because it increases the specificity of the gene list by enriching for genes that are not typically expressed in circulating white blood cells, thus more likely be indicators for disease conditions. The detection of significantly increased amounts of these AC3 markers (for example, having a fold change with a P value less than 0.05) indicates an impending RA flare in about a week or up to two weeks.

[00127] In some embodiments, the panel comprises or consist of one or more markers listed in Table 12, for example, at least 5, at least 6, at least 7 markers listed in Table 11. In some embodiments, the panel comprises or consists of 2-8 markers, *e.g.*, 4-8 markers, 5-8 markers, 6-8 markers, or 7-8 markers of those listed in Table 12. In some embodiments, the panel comprises or consists of all markers listed in Table 12, *i.e.*, COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1. As shown in Example 3, genes listed in Table 12 were enriched for synovial sublining genes relative to fibroblast genes. The detection of increased amounts of these AC3 markers indicates an impending RA flare in about a week or up to two weeks.

[00128] In some embodiments, a panel of at least 20 of the AC2 or AC3 markers described above may be evaluated. In an aspect, a panel of at least 10 of the AC2 or AC3 markers are evaluated. At least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50 of the AC2 or AC3 markers are evaluated to determine their amounts in a blood sample from the patient. A panel of at least 20 of the AC2 and at least 20 of the AC3 markers may be evaluated. In an aspect, a panel of at least 10 of the AC2 and the AC3

markers are evaluated. At least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50 of the AC2 and the AC3 markers are evaluated.

Cell markers

[00129]In accordance with the present disclosure herein, the recognition of unique markers in peripheral blood has led to the identification and characterization of a distinctive and specific cell or cell type circulating in the blood of a patient or individual prior to a flare. This unique and specific blood circulating cell is a novel indicator of an impending RA flare. The present disclosure includes a unique blood circulating cell, denoted a Pre-Inflammatory mesenchymal (PRIME) cell, which has been identified and characterized as circulating in peripheral blood in a patient, particularly an RA patient, particularly a human, prior to an RA flare. The presence of this cell in peripheral blood indicates that an RA flare will occur or become evident by way of one or more patient symptom(s). The cell can be identified in patient peripheral blood about one week, one week, about 7 days, about 5-8 days, about 5-7 days, 5-8 days, 5-7 days, about 4-7 days, 4-7 days, about 3-7 days, 3-7 days prior to an RA flare. The cell can be identified in patient peripheral blood about one week, one week, about 7 days, about 5-8 days, about 5-7 days, 5-8 days, 5-7 days, about 4-7 days, 4-7 days, about 3-7 days, 3-7 days prior to inflammation of one or more joints or pain in one or more joints in a patient. As noted above, the margin of error in timing may be up to a week or about 7 days. Therefore, the cell can be identified in patient peripheral blood about one week to about 2 weeks, about 7-14 days, up to 14 days, 0-14 days, about 3-14 days, about 5-14 days prior to an RA flare. In an embodiment, PRIME cell(s) can be identified and characterized as a CD45-CD31-PDPN+ cell, particularly as a CD45-CD31-PDPN+ cell in peripheral blood. In another embodiment, PRIME cell(s) can be identified and characterized as a CD45-CD31-PDPN+IL-17RD+ cell, particularly as a CD45-CD31-PDPN+IL-17RD+ cell in peripheral blood.

[00130]In an embodiment, identifying and characterizing the presence of CD45-CD31-PDPN+cells or CD45-CD31-PDPN+IL-17RD+ cells in peripheral blood provides a diagnostic which is predictive of an impending flare in an RA patient. In an embodiment, identifying and characterizing the presence of CD45-CD31-PDPN+cells or CD45-CD31-PDPN+IL-17RD+ cells in peripheral blood provides a diagnostic which is predictive of an impending flare, or of stiffness in joints, pain throughout the body, increased difficulty doing everyday tasks, swelling, fatigue and/or flu-like symptoms in a patient, including an RA patient, or a patient which is suspected of having RA or an arthritic or inflammatory disease.

[00131]The present disclosure thus provides a method for monitoring and predicting a rheumatoid arthritis (RA) flare in a patient comprising:

- (a) optionally isolating a blood sample from said patient;
- (b) evaluating the blood sample for expression or quantitatively increased amounts of one or more sets of antecedent RNA markers, protein markers or cell markers selected from:
 - (i) AC2 markers or proteins as provided in Table 7;
 - (ii) AC3 markers or proteins as provided in Table 8;
 - (iii) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 as set out in Table 5;
 - (iv) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 as set out in Table 9;
 - (v) markers or proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1;
 - (vi) cell markers CD45- CD31-PDPN+;
- (c) wherein the expression or quantitatively increased amounts of the RNA markers or proteins or the presence of the cell markers predicts an impending RA flare.

[00132]The expression or quantitatively increased amounts of the AC2 RNA markers or proteins predicts an RA flare in about 2 weeks or about 12-14 days, with a margin of error of up to about a week or 7 days, thus in about 7-21 days. Differential expression of AC2 markers has been identified and characterized in RA patients approximately two weeks prior to the presence of symptoms indicative of an RA flare in the patients. The expression or quantitatively increased amounts of the AC3 RNA markers or proteins predicts an RA flare in about 1 week or about 5-7 days, with a margin of error of about a week or 7 days, thus in about a week or up to 2 weeks, or up to 14 days. Differential expression of AC3 markers has been identified and characterized in RA patients approximately one week or about 5-7 days prior to the presence of symptoms indicative of an RA flare in the patients. The period of time prior to recognition of flare symptoms may vary by a day, a few days or several days from either a week before or two weeks before. The variation may be as a result of the timing of blood collection or sample collection for evaluation of the marker(s). The variation may be as a result of the sensitivity of the patient to symptoms of an RA flare or the ability of a patient to identify or recognize the symptoms or any clinical parameter of a flare. In as much as physical indicators or symptoms of a flare may be selected from stiffness in joints, pain throughout the body, increased difficulty doing everyday tasks, swelling, fatigue and flu-like symptoms, these may be recognized immediately or in the short term or may be recognized after a day or two or several days of symptoms in and by a patient.

[00133] Any applicable and sufficient number of markers may be evaluated in a patient to determine or predict an impending flare. Thus, the markers should be sufficient to reliably predict an impending flare. One skilled in the art will be able to utilize the data herein and available to provide a set of markers necessary or sufficient to predict a flare. In particular and for example, markers which are associated with certain pathways or responses may be selected. Pathways involved in myeloid, neutrophil, Fc receptor signaling and platelet activation may be selected. Genes or markers associated with developmental pathways for naïve B cells and leukocytes may be selected from among the AC2 genes. Naïve B cell genes may be selected from among AC2 genes. Pathways related to extracellular matrix, collagen and connective tissue development may be selected, and may be particularly selected from among the AC3 genes. The present disclosure describes that AC3 was enriched for pathways not typical of blood samples, including cartilage morphogenesis, endochondral bone growth, and extracellular matrix organization. Genes for these pathways or associated with these may be selected from the AC3 genes as markers for predicting RA flares. AC3 is described as enriched with sublining fibroblast genes, in a particular aspect the sublining fibroblast genes CD34+, HLA-DR+, and DKK3+. AC3 is described as enriched with sublining fibroblast genes, in a particular aspect the sublining fibroblast genes CD45-CD34+, CD45-HLA-DR+, and CD45-DKK3+. In an aspect, these may be particularly selected from or included in the markers selected from the AC3 genes. In an embodiment, sublining fibroblast markers selected from the AC3 markers or proteins are selected and evaluated. In an embodiment, AC3 RNA markers or protein markers expressed by CD34+, HLADR+ and DKK3+ cells are evaluated. In an embodiment, AC3 markers or proteins expressed by CD45-CD34+, CD45-HLADR+ and CD45-DKK3+ cells are evaluated. The method includes wherein the cell marker IL-17RD is also evaluated. In an embodiment, AC3 RNA markers or protein markers expressed by PRIME cells, CD45-CD31-PDPN+ cells, or CD45-CD31-PDPN+IL-17RD+ cells are evaluated.

[00134] Notably, many of the relevant and most particular markers provided herein are unusual in peripheral blood and/or are not necessarily or particularly associated with inflammation or an inflammatory condition per se. This facilitates their specificity, relevance and significance in particularly or specifically predicting or implying an impending RA flare, and/or exacerbation of joint symptoms. Some prior marker studies have identified inflammatory genes, such as inflammation gene expression panels, wherein the genes are associated with RA or inflammatory type conditions of RA, such as described in US Patent 7,935,482. These inflammatory genes provide a distinct profile and profiling from those provided herein, are particularly skewed and relevant for inflammation, and are not predictive of an impending flare.

Sample collection

[00135] In some embodiments, a method of predicting or preventing an impending RA disclosed herein uses a small volume collected via fingerstick (*e.g.*, using a deep lancet). In some embodiments, the sample volume is less than 500 μL , less than 300 μL , less than 250 μL , less than 200 μL , *e.g.*, about 150 μL . In some embodiments, the sample volume is about 100-300 μL , 50-300 μL , 50-250 μL , or 50-200 μL . In some embodiments, the sample volume is less than 100 μL , less than 50 μL , about 10-50 μL , about 8 -15 μL , about 10-20 μL , or about 10 μL . In some embodiments, the fingerstick sample may comprise blood droplets directly from a fingerstick, *e.g.*, using a 21 gauge x 1.8 mm deep lancet. In some embodiments, the blood droplets are collected via a capillary tube. In some embodiments, the blood droplets are collected in a microtainer tube, *e.g.*, BD Microtainer[®] blood collection tubes, available from Becton, Dickinson and Company, Franklin Lakes, NJ. As compared to conventional methods of collecting blood via, *e.g.*, by venipuncture, collecting blood by fingerstick can be performed by patients at home with ease. The volume is small and does not cause substantial discomfort to patients. After the blood sample is drawn, it can be stored and mailed to a test center to be analyzed. Methods of collecting blood samples are well known and also are described in Example 1. As shown in Example 1, the results of RNAseq analyses of these fingerstick blood samples demonstrate that the data correlate well the results obtained from conventional, gold standard clinical measurement of blood counts. Thus, in some embodiments, the method comprises collecting a blood sample from a patient by fingerstick, and the sample is then analyzed to detect whether there are increased amounts of the antecedent RA markers for determining if the patient will have an impending RA flare or increased disease activity as disclosed herein.

Selecting patients

[00136] In some embodiments, a method of predicting or preventing an impending RA disclosed herein comprises selecting a patient who has been determined to have increased amounts of a panel of antecedent RA markers as disclosed herein, and treating the patient with a therapeutically effective amount of one or more disease-modifying agent. In some embodiments, the panel of antecedent markers comprises or consists of one or more markers listed in Table 10, for example, at least 5, at least 10, at least 50, at least 100 markers. In some embodiments, the panel comprise or consist of 2-283 markers, *e.g.*, 8-200, 8-180, or 10-150 markers of the markers listed in Table 10, including all markers listed in Table 12. In some embodiments, the panel comprise or consist of 65-283 of the markers listed in Table 10, including some or all markers listed in Table 11. In some embodiments, the panel comprise or consist of all markers listed in Table 10. In some embodiments, the panel comprises or consists of one or more markers listed in Table 11, for example, at least 5, at least 10, at least 20, at least 30 markers of the markers listed in Table 11. In some embodiments, the panel

comprise or consists of 2-65 marker, *e.g.*, 5-65 markers, 10-60 markers, or 20-55 markers, including some or all markers listed in Table 12. In some embodiments, the panel comprise or consist of all markers listed in Table 11. In some embodiments, the panel comprise or consist of one or more markers listed in Table 12, for example, at least 5, at least 6, at least 7 markers listed in Table 11. In some embodiments, the panel comprise or consists of 2-8 markers, *e.g.*, 4-8 markers, 5-8 markers, 6-8 markers, or 7-8 markers of those listed in Table 12. In some embodiments, the panel comprise or consists of at least 2, at least 3, at least 4, at least 5, at least 6 at least 7 or all markers of those listed in Table 12. In some embodiments, the panel comprises or consists of all markers listed in Table 12, *i.e.*, COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1.

Methods of determining the amounts of the antecedent RA markers

[00137] Polypeptide or protein markers and RNA(s) or RNA markers may be isolated or evaluated by any suitable method known in the art. Proteins or RNAs can be purified or assayed by standard methods known in the art, such as via immunoassay, ELISA, nucleic acid probes, primers, oligonucleotides, antibody affinity methods, RNA sequencing, and the like. In one embodiment, polypeptide and metabolite markers may be isolated from a biological sample using standard techniques known in the art, for example, affinity purification using substrate-bound antibodies that specifically bind to the marker. As described herein, immunoaffinity depletion of abundant RNA(s) or proteins (with masking potential) enhances coverage and detection of low abundance proteins or RNA(s).

[00138] Antibodies immunospecific for any one of the markers provided herein may be known and available to the public, and they may be accessed via the scientific community or purchased from a commercial vendor. Readily searchable databases or web browsers may be utilized, for example, for identifying potential suppliers for such antibodies.

[00139] In some embodiments, the markers are RNA markers, and increased amounts of the RNA markers in the blood sample can be detected using methods well known, for example, RT-PCR or RNAseq. In some embodiments, RNA is extracted from the blood sample and the isolated RNA is sequenced using any suitable methods and kits. In some embodiments, kits such as Illumina TruSeq or Kapa Hyper Prep Kits are used for sequencing. In some embodiments, the isolated RNA is first converted to cDNA before sequencing. In some embodiments, the cDNAs are amplified and amplification products are sequenced. The expression or amount of the RNA marker is quantified by counting the number of reads that mapped to the marker.

[00140] In some embodiments, the markers are protein markers and increased amounts of the protein markers in the blood sample can be detected using methods well known in the art, for example, ELISA, Westernblots, and the like. The detection of increased amounts of the markers (RNA and/or

protein markers) in a panel disclosed above, for example, a panel comprising one or more or all markers in Table 12, indicates an impending RA flare.

Treating a patient with an impending RA

[00141]The present disclosure particularly relates to predicting an impending RA flare in a patient and treating the patient for the impending flare so that the patient experiences a reduced flare, fewer pathologies and/or symptoms associated with a flare, or such that a flare and its associated disease exacerbations are reduced, limited in duration, or avoided. This a method is provided herein for predicting an impending flare and treating a patient diagnosed with an impending flare, so that prophylaxis may be achieved. This serves to significantly reduce the disease and the associated difficulties for an RA patient and provides a clinically more stable RA scenario.

[00142]In some embodiments, the method for predicting and/or treating an impending RA flare or increased disease activity in a patient comprises: a) contacting a blood sample from the patient with reagents specific for a panel of AC3 markers, wherein the panel comprise one or more, or all AC3 markers listed in Table 10, Table 11, or Table 12, b) detecting amounts of the markers of the panel in the blood sample, c) comparing the amounts of the markers in the panel to the amounts of the markers in a control blood sample, where increased amounts indicates an impending RA flare in a patient, and optionally d) administering a therapeutically effective amount of one or more disease-modifying agent for treating RA if the amounts of the markers of the panel in the blood sample is increased relative to the amounts of the markers in the control blood sample, thereby treating the impending flare in the patient. In some embodiments, the markers are RNA markers and detecting the amounts of the markers comprises reversely transcribing the RNA markers into cDNAs, and amplifying the cDNAs using primers to produce amplification products. In some embodiments, the markers are RNA markers listed in Table 12 and the cDNA reversely transcribed from these markers are amplified before sequencing. In some embodiments, cDNAs of these markers are amplified using the primer sets that are suitable for amplifying these markers, for example those listed in Table 13.

[00143]In some embodiments, methods are provided for predicting an impending RA flare and/or treating a patient to prevent an impending flare in a patient, including comprising:

- a) isolating a blood sample from the patient;
- b) contacting the blood sample with reagents specific for markers selected from a panel of RNA or protein markers to assess expression of the RNA or protein markers, wherein the panel of RNA or protein markers is selected from:
 - (i) AC2 markers or proteins as provided in Table 7;
 - (ii) AC3 markers or proteins as provided in Table 8, 10 or 11;

- (iii) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 as set out in Table 5;
 - (iv) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 as set out in Table 9;
 - (v) markers or proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12; and
- c) comparing expression of the markers selected from a panel of RNA or protein markers in the blood sample to expression of the markers in a control blood sample to determine if expression of the markers selected from a panel of RNA or protein markers in the blood sample is increased relative to expression in the control blood sample, wherein detection of increased expression serves to predict an impending RA flare in a patient;
- and treating the patient thereby diagnosed with an impending RA flare by administering a therapeutically effective amount of one or more disease-modifying agent for treating RA.

[00144] The expression, differential expression, or quantitatively increased amounts of the AC2 RNA markers or proteins may predict or may be utilized to predict an RA flare in about 2 weeks, about 14 days, or about 12-14 days, up to in about 3 weeks or about 21 days, given margin of error. The expression or quantitatively increased amounts of the AC3 RNA markers or proteins may predict or may be utilized to predict an RA flare in about one week, about 7 days, or about 5-7 days, up to or about up to two weeks or about 14 days, given margin of error. In an aspect of the method, the expression, differential expression, or quantitatively increased amounts of the markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 or of the markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 predicts an RA flare in about one week, about 7 days, or about 5-7 days, up to about two weeks or 14 days given margin of error. In an aspect of the method, the expression, differential expression, or quantitatively increased amounts of the markers or proteins selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 predicts an RA flare in about one week, about 7 days, or about 5-7 days, up to about two weeks or 14 days given margin of error.

[00145] Evaluation of RNA or protein expression may be conducted using any method known in the art. Thus, in accordance with the methods of the present disclosure, RNA expression may be assessed by RT PCR. RNA expression may be determined by RNA sequencing. In accordance with the method, protein expression may be assessed using specific antibodies, assessing for protein activity, utilizing protein ligands.

[00146] Cell marker expression or presence on the surface of cells in the blood in accordance with the methods of the present disclosure may be determined using standard and known methods. Cell markers may be evaluated using antibodies. Cell markers may be evaluated using FACs analysis. Cells or cell markers may be evaluated using cell sorting or single-cell assessments. Cells, including the PRIME cells of the present disclosure may be isolated using cell surface marker antibodies. Methods of isolating PRIME cells, characterized as CD45-CD31-PDPN+ cells, using or via cell surface markers are thus provided in an embodiment of the present disclosure.

[00147] The disease-modifying agent for treating RA may be selected from standard or clinically recognized agents or therapies for RA or arthritic conditions or inflammatory diseases and conditions. In aspects, the disease-modifying agent for treating RA may be one or more agent selected from a nonsteroidal anti-inflammatory drug (NSAID), steroid, methotrexate, disease-modifying antirheumatic drug (DMARDs), biologic DMARD, and oral janus kinase (JAK) inhibitor. DMARD may be one or more of methotrexate (Trexall, Otrexup), leflunomide (Arava), hydroxychloroquine (Plaquenil) and sulfasalazine (Azulfidine). Biologic DMARD may be one or more or any of abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), baricitinib (Olmiant), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), rituximab (Rituxan), sarilumab (Kevzara), tocilizumab (Actemra) and tofacitinib (Xeljanz). Exemplary JAK inhibitor include tofacitinib (Xeljanz and Xeljanz XR), baricitinib (Olmiant), and upadacitinib (Rinvoq). The biologic DMARD may be a tumor necrosis factor (TNF) inhibitor. In an aspect, the biologic DMARD may be an anti-inflammatory antibody or an antibody directed to an inflammation or immune modulatory molecule. In an aspect, the antibody may be an interleukin antibody. The antibody may be an IL-17 specific antibody or an IL-17RD specific or IL-17RD blocking or neutralizing antibody. The antibody may be a podoplanin (PDPN) antibody. The antibody may be a bispecific podoplanin (PDPN) antibody, such as a bispecific PDPN IL-17RD antibody.

[00148] A novel and unique circulating cell has been identified as a cellular indicator of an impending flare and which specifically contributes to the impending flare. Thus, a circulating pre-inflammatory mesenchymal (PRIME) cell, characterized as a CD45-CD31-PDPN+ cell, has been identified and is provided herein wherein the presence of the cell in peripheral blood is indicative or predictive of an impending RA flare. In an aspect, the PRIME cell additionally expresses IL-17RD and is IL-17RD+. In an aspect, a panel of PRIME cells additionally expresses IL-17RD and is IL-17RD+. Methods for isolating PRIME cells, CD45-CD31-PDPN+ cells, and additionally IL-17RD+ cells, including for analysis and/or evaluation with potential therapeutics or cell modulators, are provided as an embodiment of the present disclosure. The cells may be selected or isolated via their cell surface markers, including as CD45-CD31-PDPN+, additionally including IL-17RD+. Methods for evaluating

agents that modulate or inhibit CD45-CD31-PDPN+ cells, and additionally IL-17RD+ cells, are provided.

[00149] A method is herein now provided for predicting an impending RA flare comprising evaluating a blood sample from a patient for the presence of a PRIME cell characterized as a CD45-CD31-PDPN+ cell, wherein the presence of detectable PRIME cells in peripheral blood in a patient predicts an impending RA flare in the patient. In an aspect thereof, the method includes further evaluating for the presence of IL-17RD on a CD45-CD31-PDPN+ cell. Methods are provided for evaluating and treating an impending flare in an RA patient comprising evaluating the peripheral blood of a patient for the presence of a PRIME cell characterized as a CD45-CD31-PDPN+ cell and treating a patient that is positive for PRIME cells in their peripheral blood with a disease-modifying agent for RA. Methods are provided for evaluating and treating an impending flare in an RA patient comprising evaluating the peripheral blood of a patient for the presence of a PRIME cell characterized as a CD45-CD31-PDPN+IL-17RD+ cell and treating a patient that is positive for PRIME cells in their peripheral blood with a disease-modifying agent for RA.

[00150] Methods are provided for evaluating and treating an impending flare in an RA patient comprising evaluating the peripheral blood of a patient for the presence of RNA(s) or protein(s) expressed, specifically expressed or particularly expressed by a PRIME cell characterized as a CD45-CD31-PDPN+ cell and treating a patient that is positive for expressing, specifically expressing or particularly expressing RNA(s) or protein(s) of PRIME cells in their peripheral blood with a disease-modifying agent for RA. Methods are provided for evaluating and treating an impending flare in an RA patient comprising evaluating the peripheral blood of a patient for the presence of RNA(s) or protein(s) expressed, specifically expressed or particularly expressed by a cell characterized as a CD45-CD31-PDPN+IL-17RD+ cell and treating a patient that is positive for the presence of RNA(s) or protein(s) expressed, specifically expressed or particularly expressed by a cell characterized as a CD45-CD31-PDPN+IL-17RD+ cell in their peripheral blood with a disease-modifying agent for RA. The specification details the overlapping expression of various and numerous specific AC3 marker genes with gene expression (for example as detected by RNA presence) in PRIME cells characterized as a CD45-CD31-PDPN+ cells.

[00151] The disease-modifying agent may be selected from those as described and provided herein or as known and recognized to a clinician or physician. Antibodies directed to immune modulators or inflammatory modulators may be selected. In an aspect, the patient is treated with an IL-17 or IL-17RD antibody. In another aspect, the patient is further treated with an anti-inflammatory agent and/or an immune modulating agent. In an aspect the patient is treated with a podoplanin (PDPN) antibody. In an aspect the patient is treated with one or more antibody directed to a surface marker on

the PRIME cell, for example a marker from among the AC3 gene markers which is expressed on the cell surface. In an aspect the patient is treated with one or more antibody directed to a surface marker selected from the markers or proteins COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6. In an aspect, the patient is treated with one or more antibody directed to a surface marker selected from the markers or proteins COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1.

[00152]Two monoclonal antibodies targeting IL-17A (Secukinumab (AIN457, Novartis), Ixekizumab (LY2439821, EliLilly) and one against the IL-17 receptor (Brodalumab (KHK4827, AMG827, Kyowa/Amgen) are approved for the treatment of moderate-to-severe plaque psoriasis (Silfvast-Kaiser A *et al.* (2019) Expert Opin Biol Ther 19(1):45-54;doi: 10.1080/14712598.2019.1555235). Other IL-17A antibodies include Remtolumab (ABT-122, Abbvie), ALX-0761 (MSB0010841, Ablynx/Merck), BCD-085 (Biocad), COVA322 (Covagen), LY3114062 (EliLilly), Perakizumab (RG4934, RO5310074, Hoffman-LaRoche), Vunakizumab (SHR-1314, Jiangsu Hengrui), CNTO 6785 (Morphosys/Janssen), CJM112 (Novartis) and Bimekizumab (UCB4940, UCB) (Ibrahim S *et al* (2017) Clin Colorectal Cancer 17(1):e109-13). The IL-17A specific antibody secukinumab and other anti-IL-17 agents have also been reported effective in ankylosing spondylitis (Wendling D *et al* (2019) Expert Opin Biol Ther 19(1):55-64. doi: 10.1080/14712598.2019.1554053). These antibodies are of use and application in accordance with the present disclosure.

[00153]Podoplanin (PDPN) antibodies have also been described. These include the anti-podoplanin antibody clone 8.1.1 (Lax S *et al* (2017) BMJ Open Respiratory Res 4:e000257;doi:10.1136/bmjresp-2017-000257), a chimeric mouse-human podoplanin antibody chLpMab-7 (Kato Y (2015) Oncotarget 6(34):36003-36018) and anti-human podoplanin rat antibody NZ-1 and chimeric rat-human antibody derived therefrom (NZ-8) Abe S *et al* (2013) J Immunol 190(12):6239-6249).

[00154]Immune modulators may be included in a composition with or administered with antibodies or agents, including those targeting the markers or proteins of the present disclosure, and/or administered at a different time to enhance immune modulation and/or RA therapy, including immune therapies directed against RA or RA flares. An immune modulator may be an adjuvant. Applicable immune modulators include IDO, TDO (Platten M (2012) Cancer Research 72(21):5435-40), α -galactosyl ceramide and analogs thereof such as threitolceramide (ThrCer) and ThrCer 6, TLR ligands such as poly I:C (TLR3), MPL (TLR4), imiquimod (TLR7), R848 (TLR8) or CpG (TLR9), iCOSTLA-4, PD1, PD1 ligand, OX40 and OX40 ligand, Lag3, GITR, GITR ligand interleukins, tumor necrosis factor (TNF) or other growth factors, colony stimulating factors, T cell modulators including modulators of CD8⁺ T cells, cytokines or hormones which stimulate the immune response or

reduction or elimination of cancer cells or tumors (Mellman I (2011) Nature (480):480 - 489). Additional immunomodulators are small molecules, antagonist antibodies or agonist antibodies targeting the applicable immune modulators including IDO, TDO, Toll like receptor family or iCOS, CTLA-4, PD1, PD1 ligand, OX40 and OX40 ligand, interleukins, tumor necrosis factor (TNF) or other growth factors, colony stimulating factors, T cell modulators including modulators of CD8⁺ T cells, cytokines which stimulate the immune response or reduction or elimination of cancer cells or tumors. Additional immune modulators, including TLR ligands such as poly I:C (TLR3), MPL (TLR4), imiquimod (TLR7), R848 (TLR8) or CpG (TLR9) can be used, including in combination with other modulators, agents or antibodies.

[00155] The unique specificity of the markers of the present disclosure provides diagnostic and therapeutic uses to identify, characterize and target RA flares or conditions and symptoms associated with an arthritis and/or inflammatory condition, particularly prior to the appearance of clinical symptoms. In particular, markers of the present disclosure are useful in modulating arthritic or inflammatory disease, particularly RA. Markers of the present disclosure are useful in inflammatory arthritis associated disorders, particularly rheumatoid arthritis (RA). Markers may further be useful in other conditions of inflammatory arthritis, particularly psoriatic arthritis (PsA), systemic lupus erythematosus (SLE, lupus), ankylosing spondylitis (AS), and gouty arthritis (gout). In an aspect thereof, antibodies or agents targeting the RNA markers or protein markers are useful in modulating an RA flare or joint inflammation or other physical indicators and symptoms of an RA flare. The antibodies or agents have applicability in therapeutic treatment or management of RA. The antibodies or agents may further have applicability in other common inflammatory arthritis associated disorders, particularly and such as psoriatic arthritis (PsA), systemic lupus erythematosus (SLE, lupus), ankylosing spondylitis (AS), and gouty arthritis (gout). The antibodies or agents targeting the RNA markers or proteins have applicability in enhancing the therapeutic effect including the anti-rheumatic effect of traditional RA disease-modifying agents or therapy(ies).

[00156] In some embodiments, the disclosure includes a set of RNA or protein markers for evaluating and predicting an impending RA flare in a patient comprising the markers selected from:

- (i) a panel of at least 20 markers from the AC2 markers provided in Table 7;
- (ii) a panel of at least 20 markers from the AC3 markers provided in Table 8, 10 or 11;
- (iii) markers selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 as set out in Table 5;
- (iv) markers selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 as set out in Table 9;

(v) markers selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12.

[00157] The markers may be a panel of at least 20 of the AC2 or AC3 markers, a panel of at least 10 of the AC2 or AC3 markers. At least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50 of the AC2 or AC3 markers may be included. Particular markers may be selected and utilized. An AC2 marker panel may comprise naïve B cell gene markers and markers of developmental pathways for naïve B cells and leukocytes. A panel of AC3 markers may comprise markers of cartilage morphogenesis, endochondral bone growth, extracellular matrix organization and sublining fibroblasts. A panel of AC3 markers may comprise markers which are expressed or differentially expressed by PRIME cells, CD45-CD31-PDPN+ or are CD45-CD31-PDPN+IL-17RD+ cells, cells precursors to sublining fibroblasts, particularly RA sublining fibroblasts.

[00158] The set of markers provided and/or utilized in accordance with the methods hereof may be one or more markers selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6. In an aspect, a set of one or more markers selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 is provided and/or utilized in accordance with the methods hereof. In an aspect, a set of one or more markers selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 is provided and/or utilized in accordance with the methods hereof. A set of, or one or more sets of, two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, ten or more, a dozen, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, a set of 5-10, a set of 3-5, a set of 5-7, a set of 3-7, a set of 5-8 selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFHX4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 is provided and/or utilized in accordance with the methods hereof. A set of, or one or more sets of, two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, ten or more, a dozen, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, a set of 5-10, a set of 3-5, a set of 5-7, a set of 3-7, a set of 5-8 selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFHX4 is provided and/or utilized in accordance with the methods hereof. A set of one, two, three, four, five, six, seven, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7 or all of COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 is provided and/or utilized in accordance with the methods hereof. Multiple sets

may be utilized, for example a set of markers of one type or metabolic pathway, combined with a distinct set of another type or metabolic or cellular pathway or cell.

[00159] In some embodiments, the disclosure includes a set of RNA or protein markers for evaluating and predicting an impending RA flare in a patient comprising one or more markers listed in Table 10, for example, at least 5, at least 10, at least 50, at least 100 markers. In some embodiments, the panel of antecedent AC3 markers comprise or consist of 2-283 markers, *e.g.*, 8-200, 8-180, or 10-150 markers of the markers listed in Table 10, including all markers listed in Table 12. In some embodiments, the panel comprise or consist of 65-283 markers of the markers listed in Table 10, including some or all markers listed in Table 11. In some embodiments, the panel comprise or consist of all markers listed in Table 10. In some embodiments, the panel comprise or consist of one or more markers listed in Table 11, for example, at least 5, at least 10, at least 20, at least 30 markers of the markers listed in Table 11. In some embodiments, the panel comprise or consist of one or more markers listed in Table 12. In some embodiments, the panel comprise or consist of two or more markers listed in Table 12. In some embodiments, the panel comprise or consist of three or more markers listed in Table 12. In some embodiments, the panel comprise or consist of four or more markers listed in Table 12. In some embodiments, the panel comprise or consist of five or more markers listed in Table 12. In some embodiments, the panel comprise or consist of six or more markers listed in Table 12. In some embodiments, the panel comprise or consist of seven or more markers listed in Table 12. In some embodiments, the panel comprise or consist of all markers listed in Table 12, *i.e.*, COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1.

[00160] The present disclosure also relates to a variety of diagnostic applications, including methods for detecting the expression of or elevated presence of any of the markers of the present disclosure, particularly the RNA markers or protein markers described and provided herein. Thus, the presence or amount of RNA or protein is evaluated. Protein may be evaluated by reference to their ability to be recognized by a specific antibody directed thereto. Peptide complexes can be identified, targeted, labeled, and/or quantitated on cells, including cell(s) in peripheral blood. Diagnostic applications include *in vitro* and *in vivo* applications well known and standard to the skilled artisan and based on the present description. Diagnostic assays and kits for *in vitro* assessment and evaluation of marker status or marker amounts may be utilized to diagnose, evaluate and monitor patient samples including those known to have or suspected of having arthritis, inflammatory arthritis, or RA. The assessment and evaluation of RA disease status is useful in determining the suitability of a patient for a clinical trial of a drug or for the administration of a particular therapy or disease-modifying agent, including a DMARD or an antibody, including as described herein, including combinations thereof, versus a different agent or therapy. This type of diagnostic monitoring and assessment is already in practice

utilizing antibodies against the HER2 protein in breast cancer (Hercep Test, Dako Corporation), where the assay is also used to evaluate patients for antibody therapy using Herceptin. *In vivo* applications may include imaging of joints, including radioimaging.

Primers sets and markers

[00161] In some embodiments, this disclosure provides a collection of primer pairs for amplifying the cDNAs reversely transcribed from the RA markers in a panel disclosed herein. In some embodiments, the collection comprise one or more prime pairs in Table 13.

[00162] In a further embodiment, test kits suitable for use by a medical specialist may be prepared to determine the presence or absence of aberrant, differential or increased expression of one or more or of a panel of markers described herein. One class of kits will contain at least the labeled marker or its binding partner, for instance an antibody specific thereto, and directions, of course, depending upon the method selected. In some embodiments, a kit disclosed herein comprises a collection of primer pairs for amplifying the cDNAs reversely transcribed from the RA markers in a panel disclosed herein. In some embodiments, the kit comprise one or more prime pairs in Table 13. The kit may also contain peripheral reagents such as buffers, stabilizers, etc.

[00163] Accordingly, a test kit may be prepared for the demonstration of the presence of or elevated levels of one or more marker or protein marker of an impending RA flare, comprising:

- (a) a predetermined amount of at least one labeled immunochemically reactive component obtained by the direct or indirect attachment of the protein marker or a specific binding partner or antibody thereto, to a detectable label;
- (b) other reagents; and
- (c) directions for use of said kit.

[00164] In accordance with the above, an assay system for screening potential drugs effective to modulate an RA flare or prevent an RA flare and/or the activity of a marker or protein marker of the present disclosure may be prepared. The marker peptide or antibody thereto may be introduced into a test system, and the prospective drug may also be introduced into the resulting system cell culture, and the culture thereafter examined to observe any changes in the activity of the cells, binding of the antibody, or amount and extent of the marker due either to the addition of the prospective drug alone, or due to the effect of added quantities of a known agent(s).

[00165] The present disclosure provides a system or kit for predicting an impending RA flare comprising a set of markers as described and provided herein or a set of probes and/or antibodies for evaluating a set of markers as described and provided herein.

[00166] As an example, a kit or system may include a set of markers or a set of, primers, and/or antibodies for evaluating a set of markers selected from or for a or any combination of:

- (i) a panel of at least 20 markers from the AC2 markers provided in Table 7;
- (ii) a panel of at least 20 markers from the AC3 markers provided in Table 8, 10 or 11;
- (iii) markers selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1, ZFH4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 as set out in Table 5;
- (iv) markers selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFH4 as set out in Table 9;
- (v) markers selected from COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1 as set out in Table 12.

[00167] The system or kit may further comprise a means for collection of the patient's blood by fingerstick, for example, a transdermal puncture tool, microtainer blood collection tubes, a lancet (*e.g.*, a 21 gauge x 1.8 mm deep lancet), and the like. In some embodiments, the system or kit may further comprise one or more controls, *e.g.*, samples that contain one or more markers in amounts similar to those in healthy individuals. In some embodiments, the system or kit may further comprise enzymes and buffers for nucleic acid extraction and amplification.

[00168] In some embodiments, the system or kit comprises a receptacle for receiving the blood sample, for example, the fingerstick blood sample. The receptacle may be configured to hold a volume of a blood sample between 1 μ l and 1 ml, for example, between 10 μ l and 500 μ l, between 10 μ l and 300 μ l, or between 20 μ l and 300 μ l. The receptacle may have a defined volume that is the same as a suitable volume of sample for processing and analysis by the rest of the system components.

[00169] In some embodiments, a system, or kit disclosed herein comprise one or more additional components. Non-limiting examples of an additional component include a sample transportation compartment, a sample storage compartment, a sample and/or reagent receptacle, a temperature indicator, an electronic port, a communication connection, a communication component, a sample collection component, and a housing component.

[00170] In some embodiments, systems and kits disclosed herein are handheld or tabletop, and may be conveniently employed at the point of care, for example, at home, in a school, on a battlefield, on a farm, or any other site where it would be impractical or inconvenient to visit a laboratory or clinical setting. In some instances, some, a majority of, or all components of the system or kit are housed in a single device (for example, a single handheld device) having a length, a width, and a height. In some instances the length of the single device is between 1 to 20 inches, for example, 2 to 12 inches, or 2 to

8 inches, or 3 to 6 inches. In some instances the width of single unit is between 1 to 20 inches, for example, 2 to 12 inches, or 2 to 8 inches, or 3 to 6 inches. In some instances the height of single device is between 1 to 20 inches, for example, 2 to 12 inches, or 2 to 8 inches, or 3 to 6 inches.

[00171] In some instances, a method of monitoring and predicting a rheumatoid arthritis (RA) flare or increased RA disease activity comprises obtaining a fingerstick blood sample and detecting increased amounts of a panel of antecedent RA markers with the single handheld device disclosed above. In some instances, the subject performs the obtaining by pressing his or her skin against a transdermal puncture tool of the handheld device. In some embodiments, the method further comprises detecting the amount of a panel of markers with the handheld device, comparing the amounts of the markers in the panel to the amounts of the markers in the panel in a control blood sample, wherein increased amounts indicate an impending RA flare in a patient.

[00172] Computer implemented methods and systems

[00173] This invention also provides a non-transitory computer-readable medium having computer-executable instructions, which when executed, causes a processor to access data attributed to a sample from a patient, the data comprising measurements of amounts of a panel of antecedent RA markers. In some embodiments, the markers are AC3 markers. In some embodiments, the markers are AC2 markers. In some embodiments, the AC3 markers comprise one or more or all markers provided in Tables 6, 8, 9, 10, 11, or 12. In some embodiments, the panel of antecedent AC3 markers comprise or consist of 2-283 markers, *e.g.*, 8-200, 8-180, or 10-150 markers of the markers listed in Table 10, including all markers listed in Table 12. In some embodiments, the panel comprise or consist of 65-283 markers of the markers listed in Table 10, including some or all markers listed in Table 11. In some embodiments, the panel comprise or consist of all markers listed in Table 10. In some embodiments, the panel comprise or consist of all markers listed in Table 12.

[00174] The processor, executing the instructions embodied in the computer-readable medium, determined that the patient will have an impending RA flare in about one week, about 7 days, or about 5-7 days, up to or about up to two weeks or about 14 days, given margin of error.

[00175] The non-transitory computer-readable medium may be, but is not limited to, an electronic, magnetic, optical, electromagnetic, infrared, or semiconductor system, apparatus, device, or propagation medium. More specific examples (a non-exhaustive list) of the computer-readable medium would include the following: an electrical connection having one or more wires, a portable computer diskette, a random access memory (RAM), a read-only memory (ROM), an erasable programmable read-only memory (EPROM or Flash memory), an optical fiber, and a portable compact disc read-only memory (CD-ROM). Note that the non-transitory computer-readable medium any be any suitable medium, upon which the program is printed, as the program can be electronically

captured, via, for instance, optical scanning of the paper or other medium, then compiled, interpreted or otherwise processed in a suitable manner if necessary, and then stored in a computer memory.

[00176] Also provided herein is a computer system for predicting, monitoring, or preventing an impending RA flare. The system may comprise a detection device that is configured to detect amounts of the antecedent RA marker panels as disclosed above. The system further comprises an analyzing device in communication with the detection device, the analyzing device comprising a variety of typical computer components, including a non-transitory computer-readable medium. The analyzing device may also comprise a database storing reference values for each of the markers used in the panel. These reference values may be the average amounts of the markers from the control blood samples. In some embodiments, the control samples may be from a population of healthy individuals. As stated above, the non-transitory computer-readable medium also hosts computer-executable instructions, when executed, causes a computer processor to access data attributed to a sample from a patient, *e.g.*, to obtain measurements of detected amounts of the antecedent RA markers in the panel and to compare the detected amounts of the antecedent RA markers in the panel with the reference values, to determine the patient will have an impending RA flare if the detected amounts are higher than the respective reference values for the markers.

[00177] In some embodiments, the results of determination are communicated to a patient, for example, an RA patient, or a patient which is suspected of having RA or an arthritic or inflammatory disease. In some embodiments, the results of determination are communicated to a physician, who will then prescribe one or more disease-modifying agent for treating RA or inflammatory diseases and conditions as disclosed herein. In some embodiments, the results of the determination are communicated on a mobile device, computer, notepad, or other electronic device in communication with a device of the system disclosed herein. In some embodiments, the results of determination and data are communicated to a mobile application via a computer network, and the mobile application is configured to locate, encrypt, index, and/or processing information. Optionally, the mobile application provides a personalized, tailored user experience based on personal information and experience. The mobile application may also provide interactive instructions to inform user how to use the system and kits, and how to interpret, prepare for, and treat the impending RA flares. The mobile application may also provide tools for sharing and tracking information, test results, and events.

[00178] This invention thus also provides a computer-implemented method for determining an impending RA flare or increased disease activity. The method comprises detecting the amounts of one or more antecedent markers in a blood sample from a patient; comparing the detected amounts with the reference values for the markers (amounts of the markers in a control sample or control samples); and determining the patient will have an impending RA flare if detected amounts are higher than the

reference values for the markers. In preferred embodiments, the method steps of comparing the amounts of the markers with the reference values and/or determining the patient will have an impending RA flare are conducted with one or more computer processors.

[00179]As will be apparent to those skilled in the art to which the present disclosure pertains, the present disclosure may be embodied in forms other than those specifically disclosed above without departing from the spirit or essential characteristics of the present disclosure. The particular embodiments of the present disclosure described above, are, therefore, to be considered as illustrative and not restrictive. The scope of the present disclosure is as set forth in the appended claims rather than being limited to the examples contained in the forgoing description

EXEMPLARY EMBODIMENTS

[00180]This disclosure provides the following non-limiting embodiments.

[00181]Embodiment 1. A method for monitoring and predicting a rheumatoid arthritis (RA) flare in a patient comprising:

- (a) isolating a blood sample from said patient;
- (b) evaluating the blood sample for expression or quantitatively increased amounts of one or more sets of antecedent RNA markers, protein markers or cell markers selected from:
 - (i) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGRI, ZFH4, COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 as set out in Table 5;
 - (ii) markers or proteins selected from COL1A2, COL5A1, COL16A1,
 - (iii) COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGRI and ZFH4 as set out in Table 9;
 - (iv) AC2 markers or proteins as provided in Table 7;
 - (v) AC3 markers or proteins as provided in Table 8, 10, 11, or 12; and
 - (vi) cell markers CD45- CD31-PDPN+;
- (c) wherein the expression or quantitatively increased amounts of the RNA markers or proteins or the presence of the cell markers predicts an impending RA flare.

[00182]Embodiment 2. The method of embodiment 1, wherein the expression or quantitatively increased amounts of the AC2 RNA markers or proteins predicts an RA flare in about 2 weeks or about 12-14 days or up to 3 weeks.

[00183]Embodiment 3. The method of embodiment 1, wherein the expression or quantitatively increased amounts of the AC3 RNA markers or proteins predicts an RA flare in about 1 week or about 5-7 days or up to 2 weeks.

[00184]Embodiment 4. The method of embodiment 1, wherein a panel of at least 20 of the AC2 or AC3 markers are evaluated.

[00185]Embodiment 5. The method of embodiment 1, wherein a panel of at least 20 of the AC2 and at least 20 of the AC3 markers are evaluated.

[00186]Embodiment 6. The method of embodiment 1, wherein a panel of at least 10 of the AC2 or AC3 markers are evaluated.

[00187]Embodiment 7. The method of embodiment 1, wherein a panel of at least 10 of the AC2 and at least 10 of the AC3 markers are evaluated.

[00188]Embodiment 8. The method of embodiment 1, wherein sublining fibroblast markers selected from the AC3 markers or proteins are evaluated.

[00189]Embodiment 9. The method of embodiment 1, wherein AC3 markers or proteins expressed by CD34+, HLADR+ and DKK3+ cells are evaluated.

[00190]Embodiment 10. The method of embodiment 1, wherein the cell marker IL1 7RD is also evaluated.

[00191]Embodiment 11. The method of embodiment 1, wherein RNA expression is assessed by RT PCR.

[00192]Embodiment 12. The method of embodiment 1 wherein protein expression is assessed using specific antibodies.

[00193]Embodiment 13. The method of embodiment 1 wherein cell markers are evaluated using FACs analysis.

[00194]Embodiment 14. The method of embodiment 1 wherein the antecedent RNA markers or protein markers or selected from:

(a) markers or proteins selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK 1, SCARA5, EGFR, EGR 1, ZFHX4, COL3A 1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6 as set out in Table 5;

(b) markers or proteins selected from COL1A2, COL5A 1, COL16A 1, COL14A 1, COL4A2, PXDN, ST5, DCLK 1, SCARA5, EGFR, EGR 1 and ZFHX4 as set out in Table 9; and

(c) AC3 markers or proteins as provided in Tables 8, 10, 11, or 12;

are decreased in peripheral blood during an RA flare or once a patient exhibits symptoms of an RA flare.

[00195]Embodiment 15. A method for predicting an impending RA flare and treating a flare in a patient, the method comprising:

- (a) isolating a blood sample from the patient;
 - (b) contacting the blood sample with reagents specific for markers selected from a panel of RNA or protein markers to assess expression of the RNA or protein markers, wherein the panel of RNA or protein markers is selected from:
 - (i) markers or proteins selected from COL1A2, COL5A 1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK 1, SCARA5, EGFR, EGR1 , ZFH4, COL3A1, COMP, FNDC1, GALNT15, SULF1 , GPX8 and IGFBP6 as set out in Table 5;
 - (ii) markers or proteins selected from COL1A2, COL5A 1 , COL16A 1 , COL14A 1, COL4A2, PXDN, ST5, DCLK 1 , SCARA5, EGFR, EGR1 and ZFH4 as set out in Table 9;
 - (iii) AC2 markers or proteins as provided in Table 7; and
 - (iv) AC3 markers or proteins as provided in Table 8;
 - (a) comparing expression of the markers selected from a panel of RNA or protein markers in the blood sample to expression of the markers in a control blood sample to determine if expression of the markers selected from a panel of RNA or protein markers in the blood sample is increased relative to expression in the control blood sample, wherein detection of increased expression serves to predict an impending RA flare in the patient;
- and treating the patient thereby diagnosed with an impending RA flare by administering a therapeutically effective amount of one or more disease-modifying agent for treating RA.

[00196] Embodiment 16. The method of embodiment 15, wherein RNA expression is assessed by RT PCR.

[00197] Embodiment 17. The method of embodiment 15, wherein protein expression is assessed using specific antibodies.

[00198] Embodiment 18. The method of embodiment 15, wherein the expression or quantitatively increased amounts of the AC2 RNA markers or proteins predicts an RA flare in about 2 weeks or about 12-14 days or about 3 weeks.

[00199] Embodiment 19. The method of embodiment 15, wherein the expression or quantitatively increased amounts of RNA or protein markers selected from:

- (a) markers or proteins selected from COL1A2, COL5A1, COL16A 1, COL14A1, COL4A2, PXDN, ST5, DCLK 1 , SCARA5, EGFR, EGR 1, ZFH4, COL3A1 , COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6;
- (b) markers or proteins selected from COL1A2, COL5A 1 , COL16A 1, COL14A 1 , COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR 1 and ZFH4; and
- (c) the AC3 RNA markers or proteins;

wherein the method predicts an RA flare will occur in about 1 week, about 5-7 days, or about 2 weeks.

[00200] Embodiment 20. The method of embodiment 15, wherein the disease-modifying agent for treating RA is one or more agent selected from a nonsteroidal anti-inflammatory drug (NSAID), steroid, methotrexate, disease-modifying antirheumatic drug (DMARDs), biologic DMARD, and oral janus kinase (JAK) inhibitor.

[00201] Embodiment 21. The method of embodiment 20, wherein the DMARD is selected from methotrexate (Trexall, Otrexup), leflunomide (Arava), hydroxychloroquine (Plaquenil) and sulfasalazine (Azulfidine).

[00202] Embodiment 22. The method of embodiment 20, wherein the biologic DMARD is selected from abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), baricitinib (Olmiant), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), rituximab (Rituxan), sarilumab (Kevzara), tocilizumab (Actemra) and tofacitinib (Xeljanz).

[00203] Embodiment 23. The method of embodiment 20, wherein the biologic DMARD is a tumor necrosis factor (TNF) inhibitor.

[00204] Embodiment 24. The method of embodiment 20, wherein the biologic DMARD is combined with an NSAID and/or with methotrexate.

[00205] Embodiment 25. The method of embodiment 20, wherein the JAK inhibitor is selected from tofacitinib (Xeljanz and Xeljanz XR), baricitinib (Olmiant), and upadacitinib (Rinvoq).

[00206] Embodiment 26. The method of embodiment 15, wherein the disease-modifying agent for treating RA is an IL-17 antibody or an IL1 7RD blocking antibody.

[00207] Embodiment 27. A circulating pre-inflammatory mesenchymal (PRIME) cell characterized as a CD45-CD31- PDPN+ cell, wherein the presence of the cell in peripheral blood is indicative or predictive of an impending RA flare.

[00208] Embodiment 28. The PRIME cell of embodiment 27, which additionally expresses IL1 7RD and is IL1 7RD+.

[00209] Embodiment 29. A method of predicting an impending RA flare comprising evaluating a blood sample from a patient for the presence of a PRIME cell characterized as a CD45-CD31-PDPN+ cell, wherein the presence of detectable PRIME cells in peripheral blood in a patient predicts an impending RA flare in the patient.

[00210] Embodiment 30. The method of embodiment 29, further evaluating for the presence of IL-17RD on a CD45-CD31- PDPN+ cell.

[00211]Embodiment 31. A method for evaluating and treating an impending flare in an RA patient comprising evaluating the peripheral blood of a patient for the presence of a PRIME cell characterized as a CD45- CD3 I-PDPN+IL1 7RD+ cell and treating a patient that is positive for PRIME cells in their peripheral blood with a disease-modifying agent for RA.

[00212]Embodiment 32. The method of embodiment 31, wherein the patient is treated with an IL-17 or IL-17RD antibody.

[00213]Embodiment 33. The method of embodiment 32, wherein the patient is further treated with an anti-inflammatory agent and/or an immune modulating agent.

[00214]Embodiment 34. A set of RNA or protein markers for evaluating and predicting an impending RA flare in a patient comprising the markers selected from:

- (i) markers selected from COL1A2, COL5A1, COL16A 1, COL14A1, COL4A2, PXDN, ST5, DCLK I , SCARA5, EGFR, EGR I, ZFH4, COL3A I , COMP, FNDC1, GALNT15, SULF1 , GPX8 and IGFBP6 as set out in Table 5;
- (ii) markers selected from COL1 A2, COL5A 1, COL16A1, COL14A 1 , COL4A2, PXDN, ST5, DCLKI, SCARA5, EGFR, EGR I and ZFH4 as set out in Table 9;
- (iii) a panel of at least 20 markers from the AC2 markers provided in Table 7; and
- (iv) a panel of at least 20 markers from the AC3 markers provided in Table 8.

[00215]Embodiment 35. The marker set of embodiment 34, wherein the panel of AC2 markers comprises naïve B cell gene markers and markers of developmental pathways for naïve B cells and leukocytes.

[00216]Embodiment 36. The marker set of embodiment 34, wherein the panel of AC3 markers comprises markers of cartilage morphogenesis, endochondral bone growth, extracellular matrix organization and sublining fibroblasts.

[00217]Embodiment 37. A system or kit for predicting an impending RA flare comprising a set of markers of embodiment 34 or a set of probes and/or antibodies for evaluating a set of markers of embodiment 34.

[00218]Embodiment 38. The system or kit of embodiment 37, which further comprises a means for collection of the patient's blood by fingerstick.

[00219]Embodiment 2.1. A method for monitoring and predicting a rheumatoid arthritis (RA) flare or increased RA disease activity in a patient comprising:

[00220](a) detecting in the blood sample increased amounts of a panel of antecedent RA markers, wherein the panel comprise one or more AC3 markers listed in Table 10;

[00221](b) wherein the expression or quantitatively increased amounts of the AC3 markers predicts an impending RA flare or increased RA disease activity.

[00222]Embodiment 2.2. The method of embodiment 2.1, wherein the panel comprise one or more AC3 markers listed in Table 11.

[00223]Embodiment 2.3. The method of embodiment 2.1, wherein the one or more or all AC3 markers are selected from those listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1).

[00224]Embodiment 2.3.1 The method of claim 2.1, wherein a panel of antecedent RA markers comprising at least 2 or more markers listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1) are evaluated to detect increased amounts of one or more of the AC3 markers evaluated.

[00225]Embodiment 2.3.2 The method of Embodiment 2.1, wherein a panel of antecedent RA markers comprising those listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1) are evaluated to detect increased amounts of one or more of the AC3 markers listed in Table 12.

[00226]Embodiment 2.4. The method of any of the preceding embodiments, wherein the increased amounts of the AC3 RNA markers or the AC3 protein markers predicts an RA flare in about 1 week or about 5-7 days or up to 2 weeks.

[00227]Embodiment 2.5. The method of any one of the preceding embodiments, wherein the panel consists of 2 to 283 antecedent markers.

[00228]Embodiment 2.6. The method of any one of the preceding embodiments, wherein a panel of at least 3, at least 4, at least 5 at least 6 of the AC3 markers are evaluated.

[00229]Embodiment 2.7. The method of any one of the preceding embodiments, wherein the method further comprises detecting increased amounts of one or more AC2 markers listed in Table 7.

[00230]Embodiment 2.8. The method of any one of the preceding embodiments, wherein the increased amounts of one or more AC3 markers predicts an RA flare in about 1 week or about 5-7 days or up to 2 weeks.

[00231]Embodiment 2.9. The method of any of the preceding embodiments, wherein the increased amounts of one or more AC3 RNA markers in are detected using RNAseq or RT-PCR.

[00232]Embodiment 2.10. The method of any of Embodiment 2.1- Embodiment 2.9, wherein the detecting the increased amounts of the one or more AC3 RNA markers comprises amplifying the one or more AC3 RNA markers in Table 12 using primer listed in Table 13.

[00233] Embodiment 2.11. The method of any one of Embodiment 2.1- Embodiment 2.10, the increased amount of the one or more AC3 protein markers is detected using antibodies specific for the AC3 protein markers.

[00234] Embodiment 2.12. The method of any of Embodiment 2.1- Embodiment 2.11, wherein the amount of AC3 markers are decreased in peripheral blood during an RA flare or once a patient exhibits symptoms of an RA flare.

[00235] Embodiment 2.13. A computer implemented method for predicting an impending RA flare or increased RA disease activity in a patient comprising:

- a) detecting amounts of a panel of AC3 markers, wherein the panel comprise one or more AC3 markers listed in Table 10, and
- b) determining, using one or more computer processors, that the patient has an impending RA flare or increased RA disease activity if the amounts of the panel of AC3 markers are higher than the amounts of the AC3 markers in a control blood sample.

[00236] Embodiment 2.14. A method for predicting or treating an impending RA flare in a patient, the method comprising:

- a) contacting a blood sample from the patient with reagents specific for a panel of AC3 markers, wherein the panel comprise one or more AC3 markers listed in Table 10,
- b) detecting amounts of the markers of the panel in the blood sample, wherein detection of increased amounts serves to predict an impending RA flare in a patient,
- c) comparing the amounts of the markers in the panel to the amounts of the markers in a control blood sample, and
- d) administering a therapeutically effective amount of one or more disease-modifying agent for treating RA if the amounts of the markers of the panel in the blood sample is increased relative to the amounts of the markers in the control blood sample, thereby treating the impending flare in the patient.

[00237] Embodiment 2.15. The method of any of the preceding embodiments, wherein the one or more AC3 markers are selected from those listed in Table 11.

[00238] Embodiment 2.16. The method of embodiment 2.1, wherein the one or more or all AC3 markers are selected from those listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1).

[0001] Embodiment 2.16.1 The method of claim 2.14, wherein a panel of antecedent RA markers comprising at least 2 or more markers listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1) are evaluated to detect increased amounts of one or more of the AC3 markers evaluated.

[002] Embodiment 2.16.2 The method of Embodiment 2.14, wherein a panel of antecedent RA markers comprising those listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1) are evaluated to detect increased amounts of one or more of the AC3 markers listed in Table 12.

[003] Embodiment 2.17. The method of any of the preceding embodiments, wherein the increased amounts of the AC3 markers predicts an RA flare in about 1 week or about 5-7 days.

[004] Embodiment 2.18. The method of embodiment 2.14, wherein step (d) is performed within one (1) week or within 5-7 days from the step (a).

[005] Embodiment 2.19. The method of embodiment 2.14, wherein the disease-modifying agent for treating RA is one or more agent selected from a nonsteroidal anti-inflammatory drug (NSAID), steroid, methotrexate, disease-modifying antirheumatic drug (DMARDs), biologic DMARD, and oral janus kinase (JAK) inhibitor.

[006] Embodiment 2.20. The method of embodiment 2.19, wherein the DMARD is selected from methotrexate (Trexall, Otrexup), leflunomide (Arava), hydroxychloroquine (Plaquenil) and sulfasalazine (Azulfidine).

[007] Embodiment 2.21. The method of embodiment 2.20, wherein the biologic DMARD is selected from abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), baricitinib (Olumiant), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), rituximab (Rituxan), sarilumab (Kevzara), tocilizumab (Actemra) and tofacitinib (Xeljanz).

[008] Embodiment 2.22. The method of embodiment 2.20, wherein the biologic DMARD is a tumor necrosis factor (TNF) inhibitor.

[009] Embodiment 2.23. The method of embodiment 2.20, wherein the biologic DMARD is combined with an NSAID and/or with methotrexate.

[0010] Embodiment 2.24. The method of embodiment 2.20, wherein the JAK inhibitor is selected from tofacitinib (Xeljanz and Xeljanz XR), baricitinib (Olumiant), and upadacitinib (Rinvoq).

[0011] Embodiment 2.25. The method of embodiment 2.14, wherein the disease-modifying agent for treating RA is an IL-17 antibody or an IL-17RD blocking antibody.

[0012] Embodiment 2.26. A method of treating a patient having an impending RA flare or increased RA disease activity, the method comprising

[0013] (a) selecting a patient who has been diagnosed as having increased amounts of a panel of markers as compared to a control blood sample,

[0014] wherein the panel of markers comprise one or more AC3 markers as listed in Table 10 and/or one or more AC2 markers listed in Table 7, and

[0015] (b) administering to the patient a therapeutically effective amount of one or more disease-modifying agent prior to the onset of RA.

[0016] Embodiment 2.27. The method of any of the preceding embodiments, wherein the panel of markers comprise one or more AC3 markers as listed in Table 11.

[0017] Embodiment 2.28. The method of any of the preceding embodiments, wherein the panel of markers comprises one or more AC3 markers as listed in Table 12.

[0018] Embodiment 2.29. A panel of AC3 markers for evaluating and predicting an impending RA flare or increased RA disease activity in a patient comprising the markers selected from one or more antecedent RNA markers or protein markers listed in Table 10, or Table 11, or Table 12.

[0019] Embodiment 2.30. A collection of primer pairs for amplifying the AC3 markers in embodiment 2.29.

[0020] Embodiment 2.31. The collection of primer pairs for amplifying the AC3 markers in Table 12, wherein the collection of primers comprise one or more of the following:

- i) a primer pair for amplifying COL14A1, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO: 17 and 18;
- ii) a primer pair for amplifying DCLK1, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO:19 and 20;
- iii) a primer pair for amplifying FNDC1, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO:21 and 22;
- iv) a primer pair for amplifying COL16A1, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO:23 and 24; and
- v) a primer pair for amplifying COL1A2, wherein the primer pair comprise oligonucleotides having sequences of SEQ ID NO:25 and 26.

[0021] Embodiment 2.32. A system or kit for predicting an impending RA flare or increased RA disease activity comprising a set of markers of embodiment 29, or a set of primers and/or antibodies for evaluating a set of markers of embodiment 29.

[0022] Embodiment 2.33. The system or kit of embodiment 2.32, which further comprises a means for collecting the patient's blood by fingerstick.

[0023] Embodiment 3.1 A method for monitoring a patient for increased probability of a rheumatoid arthritis (RA) flare or increased RA disease activity comprising: (a) detecting in a blood

sample expression or amounts of a panel of markers, wherein the panel comprises one or more AC3 markers listed in Table 10 or Table 11, wherein the changes in expression or amounts of the AC3 markers predict an impending RA flare or increased RA disease activity.

[0024] Embodiment 3.2 The method of Embodiment 3.1, wherein the monitoring leads to a prediction of impending rheumatoid arthritis (RA) flare or increased RA disease activity.

[0025] Embodiment 3.3 The method of Embodiment 3.2, wherein the expression or amounts of the panel of markers are increased.

[0026] The present disclosure may be better understood by reference to the following non-limiting Examples, which are provided as exemplary of the present disclosure. The following examples are presented in order to more fully illustrate the preferred embodiments of the present disclosure and should in no way be construed, however, as limiting the broad scope of the present disclosure.

EXAMPLE 1

[0027] Longitudinal Genomics Identifies PRIME cells as Antecedents of Rheumatoid Arthritis Flares

[0028] Rheumatoid arthritis (RA), like many inflammatory diseases, is characterized by episodes of quiescence and exacerbation (flares). The molecular events leading to flares are unknown. We established a clinical and technical protocol for repeated home blood collection in RA patients to allow for longitudinal RNA sequencing (RNAseq). Samples were obtained from 364 time points from eight flares over four years in our index patient, and 235 time points from flares in three additional patients. We identified transcripts that were differentially expressed antecedent to flares and compared these to synovial single-cell RNAseq (scRNAseq). Flow cytometry and sorted blood cell RNAseq in additional RA patients were used to validate the findings.

[0029] Consistent changes were observed in blood transcriptional profiles one to two weeks antecedent to RA flare. B cell activation was followed by expansion of a previously unexplored circulating CD45-/CD31-/PDPN+, PRe-Inflammatory MEsenchymal ("PRIME") cell in RA patient blood, which shared features of inflammatory synovial fibroblasts. Circulating PRIME cells decreased during flares from all four patients, and flow cytometry and sorted cell RNAseq confirmed the presence of PRIME cells in 19 additional RA patients.

[0030] Longitudinal genomic analysis of RA flares reveals PRIME cells in RA blood, and suggests a model in which they become activated by B cells in the weeks prior to RA flare, and then migrate out of the blood to the synovium. Longitudinal RNAseq analysis can be used to reveal dynamic changes leading to flares of chronic inflammatory disease.

[0031] Rheumatoid arthritis (RA) symptoms are highly dynamic, with stable periods interrupted by unpredictable flares of disease activity. Such waxing/waning clinical courses are characteristic of many autoimmune diseases, including multiple sclerosis (1), systemic lupus erythematosus (2), and inflammatory bowel disease (3,4), underscoring a need to develop approaches to understand what triggers transitions from quiescence to flare in autoimmune disease.

[0032] This study explores disease pathophysiology with a longitudinal, prospective analysis of blood transcriptional profiles in individual RA patients over time. Previous microarray studies of RA blood samples from relatively sparse time series data have identified few significant gene changes associated with disease activity (5-8). Here we provide the first RA study to look for molecular changes in blood that anticipate clinical flares. To do so we optimized methods by which RA patients themselves could collect high quality fingerstick blood samples for RNA sequencing (RNAseq), facilitating weekly blood sampling for months to years.

[0033] We analyzed patient reports of clinical disease activity and RNAseq data from four patients across multiple clinical flares. In our most deeply studied index case, we assessed 364 time points by RAPID3 from eight flares over four years, and analyzed 84 time points assessed by RNAseq. Collecting samples longitudinally enabled a search for transcriptional signatures that preceded clinical symptoms. Comparing these blood RNA profiles to synovial single-cell RNAseq (scRNAseq) data (9) provided evidence that a biologically coherent set of transcripts are significantly increased in the blood prior to symptom onset, and a panel of these decrease as the patients begin to experience symptoms. These latter transcripts overlap with and likely demarcate cellular precursors to a novel panel of synovial sublining fibroblast cell types detected in inflamed RA synovium using scRNAseq. Analysis in 19 additional RA patients corroborated our findings. Our data suggests a model in which a previously unexplored circulating mesenchymal cell type, detectable in the weeks prior to RA flare, becomes activated by B cells and subsequently leaves the blood, traffics to synovium, and contributes to disease activity.

METHODS

[0034] Patient data

[0035] All patients met American College of Rheumatology/European League Against Rheumatism 2010 (10,11) criteria for RA and were seropositive for cyclized citrullinated protein antibody (CCP). Disease activity was assessed from home each week, or up to 4 times daily during escalation of flares, using the routine assessment of patient index data 3 (RAPID3) questionnaire (12). Disease activity was also assessed at clinic visits, each month, and during flares, using both the RAPID3 and the disease activity score 28 (DAS28), which incorporates tenderness and swelling from 28 joints, erythrocyte sedimentation rate (ESR) and patient global assessment of disease activity. Complete

blood counts (CBC) including white blood cells (WBC), neutrophils, monocytes, lymphocytes, and platelets were performed by the clinical lab at Memorial Sloan Kettering Cancer Center. We collected 43 clinic visits from the index patient, and 25, 14 and 12 clinic visits for the other three patients studied longitudinally. Nineteen additional seropositive RA patients and 18 age and sex matched non-RA patients, for whom peripheral blood mononuclear cells (PBMC) were available, were also studied for the presence of PRIME cells by FACS and RNAseq analysis.

[0036] RNA preparation from Fingerstick blood

[0037] Patients self-performed fingersticks at home to collect three drops of blood into a microtainer tube prefilled with fixative, and samples were mailed overnight each week. RNA was extracted using the PAXgene® RNA kit and purified per manufacturer's protocols, except the volume of all washes and elutions was decreased to 25% of the recommended volume by the manufacturer. RNA was assessed using the Agilent BioAnalyzer for quantity and quality. For library preparation, we used the GlobinZero kit (EpiCentre #GZG1224) and Illumina's Truseq mRNA Stranded Library kit, with 11-12 PCR cycles for 5-8nM input and sequenced on HiSeq2500 with 150 base paired-end reads. Reads were aligned to Gencodev18 using STAR and quantified using featureCounts (v1.5.0-p2). Samples with at least four million paired-end reads were retained for analysis.

[0038] Data analysis:

[0039] Comparison of disease activity measures

[0040] To describe the bivariate relationship of disease activity with RAPID3, we used the locally weighted scatterplot smoothing (LOWESS) technique. R^2 were calculated to assess correlations of CBC counts inferred from CIBERSORTx and counts measured by clinical labs. Inferred CIBERSORTx lymphocyte counts were the sum of B cells naive + B cells memory + T cells CD8 + T cells CD4 naive + T cells CD4 memory resting + T cells CD4 memory activated. Monocytes, Macrophages M0, Macrophages M1, and Macrophages M2 were summed to infer CIBERSORTx monocyte counts. One-way ANOVA was used to test for significant differences among various clinical features according to disease activity state.

[0041] Differential expression analyses across patients

[0042] Samples were labeled "baseline" (stable RAPID3), "flare" (RAPID3 scores rose over two standard deviations above the baseline mean), or "steroid". EdgeR (v3.24.3) (13) was used to analyze flare vs baseline differential gene expression. Permutation test ($n=1 \times 10^6$) was used to test for the significance of overlap between genes decreased in flares in the index patient and patients 2, 3, and 4. GO enrichment (goana, from limma v3.38.3) (14) was used to identify enriched pathways in significantly differentially expressed genes in the index patient ($FDR < 0.1$) and consistent in the

direction of expression in both the index and replication patients (*i.e.*, log fold change either both positive or both negative).

[0043] Time series analysis of index patient

[0044] We performed longitudinal data analysis on the index patient using ImpulseDE2 (v1.8.0) (15). Flare onset was defined clinically (as above) and samples from 8 weeks prior to flare up to 4 weeks after flare were analyzed (excluding any samples during which the patient was taking steroids, n=65 samples). The date of library preparation was included in the model for batch correction, and the genefilter (v1.64.0) package (16) was used to filter out lowly expressed genes.

[0045] Identification and characterization of coexpressed gene modules

[0046] We hierarchically clustered mean expression of significantly differentially expressed genes identified in the ImpulseDE2 analysis by week to flare initiation (batch corrected logrpkm expression values were calculated using edgeR) and identified five coexpressed gene modules (Clusters 1-5). We analyzed these five modules for GO term enrichment (goana).

[0047] To compare differentially expressed gene modules and to further characterize expression patterns in gene modules over time, for each module, the mean expression level for each gene was calculated across flares per week, then normalized across weeks. ABIS (17) and CIBERSORTx (18) were used to deconvolute gene expression data. To aggregate a given cluster of genes or cell type with gene markers, the mean of standardized gene expression scores or deconvolved cell type scores, respectively, within each week were plotted. To identify synovial scRNAseq cluster specific marker gene signatures, we used a previously published dataset (18) to compare the cells from one scRNAseq cluster with cells from all the other scRNAseq clusters using the single-cell RNA-seq log2(CPM + 1) matrix. We generated lists of the top 200 marker genes for each cluster using the criteria of 1) log2FC greater than 1, 2) auc greater than 0.6, and 3) percent of expressing cells greater than 0.4. We used Fisher's exact test to evaluate enrichment of synovial cell subtype marker genes in the 5 coexpressed gene modules. P-values were corrected for multiple hypothesis test correction using the Benjamini-Hochberg procedure.

[0048] Flow cytometry and sorting

[0049] To assess percentages of PRIME cells in peripheral blood mononuclear cells, samples from PBMC were stained with antibodies to: CD31-APC, (WM59), Mouse IgG1-APC (MOPC-21), PDPN-PerCP (NZ1.3), Rat IgG2a (eBR2a)-PerCP, CD45-PE (HI30), Mouse IgG1-PE (MOPC-21) and TO-PRO®-3 and analyzed on BD-FACSCalibur using FlowJo 10.6.1. To flow sort and sequence PRIME cells, 20-100 Million cells from CD14-depleted leukapheresates were stained with CD31-APC(WM59), Mouse IgG1-APC(MOPC-21), PDPN-PerCP(NZ1.3), Rat IgG2a-PerCP(eBR2a),

CD45-FITC(HI30), Mouse IgG1-FITC(MOPC-21), and DAPI (4',6-Diamidino-2-Phenylindole, Dihydrochloride) and sorted on a BD FACS Aria II. Illumina Stranded TruSeq library kit was used to generate cDNA libraries that were sequenced on MiSeq. DESeq2 (v1.24.0) (19) was used for differential expression analysis.

[0050] Statistics

[0051] R2 and Pearson correlation coefficients were calculated to assess the bivariate linear fit of disease activity measured by RAPID3 and DAS28 as well as CBC counts inferred from CIBERSORT cell counts and counts measured by clinical labs. Inferred CIBERSORTx lymphocyte counts were the sum of B cells naive + B cells memory + T cells CD8 + T cells CD4 naive + T cells CD4 memory resting + T cells CD4 memory activated. One way ANOVA was used to test for significant differences among various clinical features according to disease activity state. Monocytes, Macrophages M0, Macrophages M1, and Macrophages M2 were summed to infer CIBERSORTx monocytes.

RESULTS

[0052] Clinical Protocol Development

[0053] We developed strategies for home blood collection that would allow high quality and quantity RNA for sequencing (Figures 6-12; 15-50 ng RNA; RNA integrity (RIN) scores (mean 6.9 +/- standard deviation 1.7). Study patients also documented disease activity (RAPID3 questionnaires). Four RA patients were followed for one to four years with weekly home collection of fingerstick blood samples coupled with completion of RAPID3 and monthly clinic visits, where DAS28 were collected (Figure 1A). RNA was sequenced from a total of 189 fingerstick blood samples from 4 patients, of which 162 (87%) passed quality control filtering.

[0054] To assess the validity of patient reported disease activity, we compared their RAPID3 scores with clinician collected DAS28. Significant correlations were evident between RAPID3 and DAS28 for each of the four patients (Figure 1B and Figure 13). To assess the validity of fingerstick blood data, we compared RNAseq inferred white blood cell counts with clinical laboratory measurements of complete blood counts and again observed significant correlations (Figure 1C), suggesting RNAseq of fingerstick blood was of sufficient quality to provide information that correlated with gold standard clinical measurements of blood counts. Taken together, these data indicate that patient reports of disease activity paired with fingerstick blood samples provide a high quality and robust means by which individuals can participate in longitudinal clinical research studies.

[0055] Clinical and Molecular Features of RA Flare Compared to Baseline

[0056] Flares were associated with increases in objective clinical and laboratory measures of RA related disease activity in the index patient (Figure 2A and Figure 14). Fingerstick RNAseq identified 2613 genes differentially expressed at flare versus baseline (FDR<0.1), with 1437 increased during flare (logFC>0; Figure 2B and Table 1).

TABLE 1

Genes differentially expressed at flare vs baseline	FDR<0.1	2613 genes
Genes increased during flare	logFC>0	1437 genes

[0057] Pathway analysis identified enrichment in myeloid, neutrophil, Fc receptor signaling and platelet activation (Figure 2C and Table 2), consistent with clinical blood count measurements during flares (Figure 14). Interestingly, 1176 genes were significantly decreased during flare, and pathway analysis of these genes were enriched for extracellular matrix, collagen and connective tissue development (Figure 2D and Table 2).

[0058] Time Series Analysis of Molecular Events Leading to RA Flares

[0059] To analyze the trajectories of gene expression over time and identify potential antecedents to flare, we performed time series analysis of the RNAseq data (Figure 3A). Notably, disease activity scores in the weeks just prior to flare were the same as baseline scores two months prior to flare, underscoring the challenges of identifying both a time frame and gene expression signature that is antecedent to flare. We focused the analysis on 65 samples acquired 8 weeks prior to flare and 4 weeks after flare initiation, binning samples according to the week they were drawn. This identified 2791 genes with significant differential expression over a period of time relative to flare (FDR<0.05), and hierarchical clustering of gene expression identified five clusters (Figure 3B and Table 3).

TABLE 3

Pathway Analysis of Differentially Expressed Genes

27,775 genes analyzed	2,791 genes with significant differential expression over time to flare (FDR<0.5)
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[0060] Cluster 1 represented a group of genes which increased after symptom onset (Figure 3C and D) and was highly overlapping (Figure 3E) with genes increased in the flare versus baseline analysis (Figure 2B). These gene expression clusters were reproducibly altered in 5 separate clinical flare events (Figure 15).

[0061] We further focused on two clusters that were differentially expressed antecedent to flare (Figure 3C-D). Antecedent cluster 2 (AC2) transcripts increased two weeks prior to flare and were enriched with developmental pathways for naive B cells and leukocytes. Two additional means of deconvoluting the RNAseq data, CIBERSORTx and ABIS, independently confirmed evidence of B

cell and T cell populations antecedent to flare, and all analyses showed evidence of innate inflammatory signatures (neutrophils and monocytes) during flare (Figures 16-17).

[0062] Antecedent cluster 3 (AC3) transcripts increased the week prior to flare and then decreased for the duration of flare (Figure 3C and D). AC3 was enriched for pathways not typical of blood samples, including cartilage morphogenesis, endochondral bone growth, and extracellular matrix organization (Figure 3E and Table 4), suggesting the presence of an uncharacterized cell type, a mesenchymal cell.

TABLE 4

go.id	Term	N	fdr.DE1	fdr.DE2	fdr.DE3	fdr.DE4	fdr.DE5
GO:0032501	multicellular organismal process	7510	0.33779658	0.996446813	1.90E-13	0.18155513	0.996446813
GO:0009887	animal organ morphogenesis	982	1	1	2.60E-09	0.426866243	1
GO:0009653	anatomical structure morphogenesis	2604	0.017009962	0.739725387	3.66E-08	0.089707123	0.890858017
GO:0048468	cell development	2093	0.325922506	0.824909599	4.99E-08	0.826157616	1
GO:0007275	multicellular organism development	5330	0.646941518	0.106039186	4.42E-07	0.016979265	0.129190893
GO:0048856	anatomical structure development	5810	0.111685048	0.184216961	5.65E-07	0.026184522	0.332210519
GO:0030154	cell differentiation	4100	0.314553949	0.088217999	6.95E-07	0.437802459	0.771708045
GO:0032502	developmental process	6212	0.143287026	0.135556704	7.02E-07	0.017411509	0.228640051
GO:0007399	nervous system development	2296	0.818972317	0.660623511	1.57E-06	0.179563884	1
GO:0043269	regulation of ion transport	660	1	1	1.82E-06	1	1
GO:0048869	cellular developmental process	4282	0.131591479	0.07488625	3.00E-06	0.474081007	0.996446813
GO:0060536	cartilage morphogenesis	29	1	1	3.34E-06	1	1
GO:0048731	system development	4783	0.739725387	0.088328136	3.53E-06	0.025908171	0.266607283
GO:0034220	ion transmembrane transport	1122	1	1	3.55E-06	1	1
GO:0048729	tissue morphogenesis	612	0.996446813	1	6.32E-06	1	1
GO:0006811	ion transport	1638	1	1	6.53E-06	1	1
GO:0006812	cation transport	1128	1	1	9.04E-06	1	1
GO:0098660	inorganic ion transmembrane transport	824	1	1	9.45E-06	1	1
GO:0003008	system process	2148	1	1	9.57E-06	1	1
GO:0034765	regulation of ion transmembrane transport	454	1	1	1.87E-05	1	1
GO:0003414	chondrocyte morphogenesis involved in endochondral bone morphogenesis	18	1	1	1.93E-05	1	1
GO:0003429	growth plate cartilage chondrocyte morphogenesis	18	1	1	1.93E-05	1	1

GO:0090171	chondrocyte morphogenesis	18	1	1	1.93E-05	1	1
GO:0030001	metal ion transport	858	0.616825534	1	2.52E-05	1	1
GO:0003422	growth plate cartilage morphogenesis	19	1	1	2.83E-05	1	1
GO:0022008	neurogenesis	1555	0.665596251	1	3.83E-05	0.139859641	1
GO:0007155	cell adhesion	1390	0.001076518	1	4.21E-05	0.598967854	1
GO:0048699	generation of neurons	1459	0.650883021	1	4.35E-05	0.280105182	1
GO:0022610	biological adhesion	1398	0.001270754	1	5.07E-05	0.445725934	1
GO:0034762	regulation of transmembrane transport	535	1	1	5.53E-05	1	1
GO:0055085	transmembrane transport	1514	1	1	6.85E-05	1	1
GO:0030182	neuron differentiation	1317	0.768500111	1	7.84E-05	0.415235372	1
GO:0003416	endochondral bone growth	43	1	1	8.11E-05	1	1
GO:0003433	chondrocyte development involved in endochondral bone morphogenesis	23	1	1	0.000111249	1	1
GO:0098868	bone growth	45	1	1	0.000118729	1	1
GO:0032989	cellular component morphogenesis	1079	0.019925787	0.99915203	0.000144687	0.890858017	0.757703978
GO:0003418	growth plate cartilage chondrocyte differentiation	24	1	1	0.000151713	1	1
GO:0003417	growth plate cartilage development	36	1	1	0.000217688	1	1
GO:0007268	chemical synaptic transmission	690	0.480223653	1	0.000225474	0.324979313	1
GO:0098916	anterograde trans-synaptic signaling	690	0.480223653	1	0.000225474	0.324979313	1
GO:0006814	sodium ion transport	215	1	1	0.00025748	1	1
GO:0099537	trans-synaptic signaling	698	0.517697406	1	0.000288644	0.347784599	1
GO:0099536	synaptic signaling	703	0.275739603	1	0.000337001	0.357514166	1
GO:0009888	tissue development	1961	1	1	0.000413598	1	1
GO:0050954	sensory perception of mechanical stimulus	161	1	1	0.000527109	1	1
GO:0003413	chondrocyte differentiation involved in endochondral bone morphogenesis	29	1	1	0.000545066	1	1
GO:0007605	sensory perception of sound	142	1	1	0.000581084	1	1
GO:0032879	regulation of localization	2746	4.21E-05	1	0.000674069	1	1
GO:0060350	endochondral bone morphogenesis	71	1	0.901231612	0.000675474	1	1
GO:0098655	cation transmembrane transport	827	1	1	0.00080515	1	1
GO:2001223	negative regulation of neuron migration	12	1	1	0.00080515	1	1
GO:0000904	cell morphogenesis involved in differentiation	712	0.890858017	0.965146807	0.001032945	0.616825534	0.410213141
GO:0002063	chondrocyte development	45	1	1	0.001076518	1	1

GO:0048513	animal organ development	3455	1	0.063098951	0.00108333	0.745168516	0.665596251
GO:0060349	bone morphogenesis	111	1	0.469843251	0.00108657	1	1
GO:0060351	cartilage development involved in endochondral bone morphogenesis	46	1	1	0.001251135	1	1
GO:0000902	cell morphogenesis	980	0.022949891	1	0.001401799	0.797071186	0.796314167
GO:0007267	cell-cell signaling	1584	0.543286651	1	0.001964875	0.171334526	1
GO:0015672	monovalent inorganic cation transport	526	1	1	0.002079582	1	1
GO:0098662	inorganic cation transmembrane transport	739	1	1	0.002079582	1	1
GO:0044703	multi-organism reproductive process	1004	1	1	0.002354643	1	1
GO:0048666	neuron development	1071	0.745168516	1	0.002354643	0.489378401	1
GO:0042391	regulation of membrane potential	424	1	1	0.003216776	0.716801532	1
GO:0006936	muscle contraction	351	0.357514166	1	0.004649326	1	1
GO:0048589	developmental growth	646	1	1	0.004771785	1	1
GO:0051049	regulation of transport	1806	0.0059057	1	0.006500421	1	1
GO:1904062	regulation of cation transmembrane transport	314	1	1	0.008881305	1	1
GO:0048705	skeletal system morphogenesis	236	1	1	0.009182742	0.996446813	1
GO:0032412	regulation of ion transmembrane transporter activity	238	1	1	0.009921143	1	1
GO:0031175	neuron projection development	941	0.594734994	1	0.010301477	0.317513419	1
GO:0007389	pattern specification process	434	1	1	0.011108198	1	1
GO:0030198	extracellular matrix organization	348	1	1	0.011108198	1	1
GO:0098656	anion transmembrane transport	268	1	1	0.011788736	1	1
GO:0048812	neuron projection morphogenesis	621	1	1	0.012239952	0.507490051	0.717048855
GO:0032990	cell part morphogenesis	655	1	1	0.01290706	0.646941518	0.802166171
GO:0022898	regulation of transmembrane transporter activity	245	1	1	0.013282485	1	1
GO:0007160	cell-matrix adhesion	222	0.005606843	1	0.014820961	1	1
GO:0022414	reproductive process	1423	1	1	0.015397049	1	1
GO:0072025	distal convoluted tubule development	5	1	1	0.015849029	1	1
GO:0072221	metanephric distal convoluted tubule development	5	1	1	0.015849029	1	1
GO:0000003	reproduction	1426	1	1	0.015996351	1	1
GO:0002009	morphogenesis of an epithelium	479	1	1	0.016789679	1	1
GO:0120039	plasma membrane bounded cell projection morphogenesis	635	1	1	0.016801155	0.56362124	0.745168516

GO:0048858	cell projection morphogenesis	636	1	1	0.017059196	0.568448591	0.745168516
GO:0017156	calcium ion regulated exocytosis	153	1	0.996446813	0.017665674	1	1
GO:0098661	inorganic anion transmembrane transport	110	1	1	0.019146167	1	1
GO:0007215	glutamate receptor signaling pathway	90	1	1	0.019925787	0.665596251	1
GO:0035249	synaptic transmission, glutamatergic	90	1	1	0.019925787	1	1
GO:0050877	nervous system process	1406	1	1	0.019979972	1	1
GO:0003012	muscle system process	456	0.371617002	1	0.020005602	1	1
GO:1901018	positive regulation of potassium ion transmembrane transporter activity	24	1	1	0.020370955	1	1
GO:0060429	epithelium development	1227	1	1	0.020590857	1	1
GO:0007417	central nervous system development	948	1	0.996446813	0.021561593	0.922242032	1
GO:0051216	cartilage development	206	1	1	0.021561593	0.78080559	1
GO:0019226	transmission of nerve impulse	72	1	1	0.022053268	1	1
GO:0051179	localization	6555	4.55E-10	1	0.022789146	0.56362124	1
GO:0032409	regulation of transporter activity	260	1	1	0.022963874	1	1
GO:0060348	bone development	208	1	0.489378401	0.023314211	1	1
GO:0030048	actin filament-based movement	136	1	1	0.023984508	1	1
GO:0030049	muscle filament sliding	39	1	1	0.024126389	1	1
GO:0033275	actin-myosin filament sliding	39	1	1	0.024126389	1	1
GO:0070252	actin-mediated cell contraction	114	1	1	0.024126389	1	1
GO:2001222	regulation of neuron migration	39	1	1	0.024126389	1	1
GO:0061448	connective tissue development	263	1	1	0.02536056	0.219616377	1
GO:2001257	regulation of cation channel activity	162	1	1	0.026700112	1	1
GO:0007423	sensory organ development	532	1	1	0.027749721	1	1
GO:0002062	chondrocyte differentiation	117	1	1	0.0280421	1	1
GO:0044057	regulation of system process	569	0.278182469	1	0.031028127	1	1
GO:0001501	skeletal system development	506	1	0.823129385	0.031162918	1	0.996446813
GO:1903818	positive regulation of voltage-gated potassium channel activity	15	1	1	0.031196003	1	1
GO:0098742	cell-cell adhesion via plasma-membrane adhesion molecules	270	1	1	0.03127218	1	1
GO:0007269	neurotransmitter secretion	167	1	1	0.032811717	1	1
GO:0099643	signal release from synapse	167	1	1	0.032811717	1	1
GO:0050804	modulation of chemical synaptic	418	0.844000933	1	0.034515558	0.102842968	1

	transmission						
GO:0099177	regulation of trans-synaptic signaling	419	0.857332482	1	0.035278512	0.10434846	1
GO:0035265	organ growth	195	1	1	0.037148224	1	1
GO:0044706	multi-multicellular organism process	221	1	1	0.037148224	1	1
GO:0021537	telencephalon development	248	1	1	0.037418398	1	1
GO:0016079	synaptic vesicle exocytosis	123	1	1	0.038417362	1	1
GO:0051960	regulation of nervous system development	883	0.107843848	1	0.039675644	0.335240873	1
GO:0072235	metanephric distal tubule development	7	1	1	0.039896554	1	1
GO:0120036	plasma membrane bounded cell projection organization	1462	0.430289651	1	0.040423722	0.184216961	1
GO:0060537	muscle tissue development	395	1	1	0.041122974	1	1
GO:0043062	extracellular structure organization	402	1	1	0.04968339	1	1
GO:0006928	movement of cell or subcellular component	2138	8.70E-05	1	0.052850381	0.108871927	1
GO:0030029	actin filament-based process	732	0.028430549	1	0.055807618	1	1
GO:0065008	regulation of biological quality	3891	1.72E-06	1	0.092517809	0.598967854	1
GO:0031589	cell-substrate adhesion	338	0.004206765	1	0.093681736	0.890858017	1
GO:0051239	regulation of multicellular organismal process	3093	2.64E-05	0.748743161	0.123095655	0.575098872	1
GO:2000026	regulation of multicellular organismal development	2064	0.030521352	0.966211545	0.211865167	0.24144412	1
GO:0007154	cell communication	6522	1.26E-09	1	0.2315925	0.035576453	1
GO:0048167	regulation of synaptic plasticity	173	0.756136312	1	0.247322371	0.025766984	1
GO:0009612	response to mechanical stimulus	204	0.016589491	1	0.264413515	1	1
GO:0048646	anatomical structure formation involved in morphogenesis	1151	0.017059196	0.665596251	0.278694883	0.131591479	1
GO:0007166	cell surface receptor signaling pathway	2974	2.22E-07	0.664638292	0.280083899	0.024	1
GO:0050793	regulation of developmental process	2607	0.00358275	0.489378401	0.299390486	0.136920059	1
GO:0045944	positive regulation of transcription by RNA polymerase II	1181	1	0.028430549	0.358787418	1	1
GO:0006937	regulation of muscle contraction	164	0.004919038	1	0.405813243	1	1
GO:0006810	transport	5065	6.95E-11	1	0.455598256	1	1
GO:0022603	regulation of anatomical structure morphogenesis	1098	0.027537974	0.80941255	0.48419276	0.376392302	1
GO:0023052	signaling	6475	5.74E-10	1	0.489378401	0.028424743	1
GO:0060284	regulation of cell development	910	0.043655125	1	0.490789374	0.61494051	1

GO:0051234	establishment of localization	5179	1.10E-10	1	0.491060511	1	1
GO:0051270	regulation of cellular component movement	1052	0.001076518	1	0.604011244	1	1
GO:0031644	regulation of neurological system process	127	1	1	0.649678872	0.017681195	1
GO:0051240	positive regulation of multicellular organismal process	1753	0.000807618	1	0.664849722	1	1
GO:0001568	blood vessel development	756	0.027692049	1	0.665596251	0.190308867	1
GO:0072358	cardiovascular system development	799	0.039048021	1	0.670434263	0.08846971	1
GO:0048518	positive regulation of biological process	6054	2.12E-09	0.078665529	0.745168516	0.670434263	1
GO:0010574	regulation of vascular endothelial growth factor production	32	0.006085233	1	0.762819911	1	1
GO:0050896	response to stimulus	9106	1.30E-09	0.767683656	0.762982012	0.125702334	1
GO:0001944	vasculature development	790	0.032663645	1	0.778782489	0.263544992	1
GO:0043410	positive regulation of MAPK cascade	562	0.000386618	1	0.794945764	1	1
GO:0010573	vascular endothelial growth factor production	34	0.008756837	1	0.823129385	1	1
GO:0045595	regulation of cell differentiation	1788	0.004325196	1	0.877494832	0.996446813	1
GO:1903523	negative regulation of blood circulation	36	0.012075239	1	0.890858017	1	1
GO:0045893	positive regulation of transcription, DNA-templated	1511	1	0.00087738	0.918797783	1	1
GO:1902680	positive regulation of RNA biosynthetic process	1597	1	0.00087738	0.922242032	1	1
GO:1903508	positive regulation of nucleic acid-templated transcription	1596	1	0.00086646	0.922242032	1	1
GO:0002223	stimulatory C-type lectin receptor signaling pathway	65	0.017009962	1	0.972458544	1	1
GO:0010628	positive regulation of gene expression	1957	1	0.004755649	0.995169577	1	1
GO:0040011	locomotion	1909	2.16E-05	1	0.995169577	0.474177846	1
GO:0002220	innate immune response activating cell surface receptor signaling pathway	68	0.022623601	1	0.996446813	1	1
GO:0010646	regulation of cell communication	3532	3.18E-07	0.996446813	0.996446813	0.007264557	1
GO:0048514	blood vessel morphogenesis	677	0.026184522	1	0.996446813	0.161086801	1
GO:0071495	cellular response to endogenous stimulus	1373	0.011622623	0.308597466	0.996446813	1	0.161929325
GO:0000122	negative regulation of transcription by RNA polymerase II	835	1	4.26E-10	1	1	1
GO:0000165	MAPK cascade	926	0.000542536	1	1	1	1
GO:0000186	activation of MAPKK activity	52	0.000574544	1	1	1	1
GO:0000271	polysaccharide	74	0.009838404	1	1	1	1

	biosynthetic process						
GO:0000272	polysaccharide catabolic process	23	0.007542869	1	1	1	1
GO:0001525	angiogenesis	587	0.009359443	1	1	0.211865167	1
GO:0001702	gastrulation with mouth forming second	28	1	1	1	1	0.007070407
GO:0001774	microglial cell activation	33	0.007271618	1	1	1	1
GO:0001775	cell activation	1407	9.24E-23	0.890858017	1	1	1
GO:0001776	leukocyte homeostasis	88	0.03127218	1	1	1	1
GO:0001780	neutrophil homeostasis	16	0.012199993	1	1	1	1
GO:0001816	cytokine production	716	8.54E-07	0.243930235	1	1	1
GO:0001817	regulation of cytokine production	647	9.86E-06	0.457630758	1	1	1
GO:0001819	positive regulation of cytokine production	422	0.000246192	1	1	1	1
GO:0001932	regulation of protein phosphorylation	1427	3.03E-07	1	1	1	1
GO:0001934	positive regulation of protein phosphorylation	1008	1.75E-07	1	1	1	1
GO:0002218	activation of innate immune response	252	3.46E-05	1	1	1	1
GO:0002221	pattern recognition receptor signaling pathway	179	0.004057705	1	1	1	1
GO:0002224	toll-like receptor signaling pathway	131	0.01844494	1	1	1	1
GO:0002237	response to molecule of bacterial origin	337	0.000205114	1	1	1	1
GO:0002244	hematopoietic progenitor cell differentiation	111	1	0.002200796	1	1	1
GO:0002252	immune effector process	1246	7.83E-19	1	1	1	1
GO:0002253	activation of immune response	645	4.02E-06	1	1	1	1
GO:0002262	myeloid cell homeostasis	146	0.041941486	0.025357726	1	1	1
GO:0002263	cell activation involved in immune response	701	2.15E-17	1	1	1	1
GO:0002269	leukocyte activation involved in inflammatory response	33	0.007271618	1	1	1	1
GO:0002274	myeloid leukocyte activation	638	9.90E-23	1	1	1	1
GO:0002275	myeloid cell activation involved in immune response	540	3.02E-20	1	1	1	1
GO:0002283	neutrophil activation involved in immune response	488	6.49E-20	1	1	1	1
GO:0002366	leukocyte activation involved in immune response	697	1.62E-17	1	1	1	1
GO:0002367	cytokine production involved in immune response	95	0.016140011	1	1	1	1
GO:0002376	immune system	3074	1.22E-20	0.892839413	1	1	1

	process						
GO:0002429	immune response-activating cell surface receptor signaling pathway	414	0.006508093	1	1	1	1
GO:0002443	leukocyte mediated immunity	868	9.50E-17	1	1	1	1
GO:0002444	myeloid leukocyte mediated immunity	548	5.49E-20	1	1	1	1
GO:0002446	neutrophil mediated immunity	499	5.03E-20	1	1	1	1
GO:0002520	immune system development	912	0.009644361	0.000500171	1	1	0.405813243
GO:0002521	leukocyte differentiation	501	0.212378102	0.017749668	1	1	1
GO:0002576	platelet degranulation	128	1.37E-05	1	1	1	1
GO:0002682	regulation of immune system process	1545	1.30E-09	1	1	1	1
GO:0002684	positive regulation of immune system process	1098	1.33E-08	1	1	1	1
GO:0002685	regulation of leukocyte migration	180	0.013038389	1	1	1	1
GO:0002687	positive regulation of leukocyte migration	121	0.009448392	0.931021722	1	1	1
GO:0002688	regulation of leukocyte chemotaxis	109	0.013452901	1	1	1	1
GO:0002697	regulation of immune effector process	439	0.029881063	1	1	1	1
GO:0002704	negative regulation of leukocyte mediated immunity	45	0.037418398	1	1	1	1
GO:0002718	regulation of cytokine production involved in immune response	77	0.046629493	0.997059037	1	1	1
GO:0002755	MyD88-dependent toll-like receptor signaling pathway	36	0.001691861	1	1	1	1
GO:0002757	immune response-activating signal transduction	568	1.34E-05	1	1	1	1
GO:0002758	innate immune response-activating signal transduction	233	0.000110092	1	1	1	1
GO:0002764	immune response-regulating signaling pathway	599	8.40E-06	1	1	1	1
GO:0002768	immune response-regulating cell surface receptor signaling pathway	445	0.003916178	1	1	1	1
GO:0002790	peptide secretion	582	0.028669624	1	1	1	1
GO:0005976	polysaccharide metabolic process	109	0.003588731	1	1	1	1
GO:0006022	aminoglycan metabolic process	167	0.01778747	0.870337648	1	1	1
GO:0006139	nucleobase-containing compound metabolic process	6264	1	0.002380221	1	1	1
GO:0006351	transcription, DNA-templated	3600	1	5.47E-06	1	1	1
GO:0006355	regulation of transcription, DNA-templated	3445	1	3.35E-06	1	1	1
GO:0006357	regulation of	2632	1	6.40E-06	1	1	1

	transcription by RNA polymerase II						
GO:0006366	transcription by RNA polymerase II	2768	1	8.50E-06	1	1	1
GO:0006464	cellular protein modification process	4066	1.66E-05	0.93115264	1	1	1
GO:0006468	protein phosphorylation	1910	1.14E-06	1	1	0.635655637	1
GO:0006629	lipid metabolic process	1415	0.034515558	1	1	1	1
GO:0006725	cellular aromatic compound metabolic process	6467	1	0.008831261	1	1	1
GO:0006793	phosphorus metabolic process	3236	1.32E-06	1	1	1	1
GO:0006796	phosphate-containing compound metabolic process	3209	7.74E-07	1	1	1	1
GO:0006826	iron ion transport	61	0.044765835	1	1	1	1
GO:0006886	intracellular protein transport	1126	0.006155434	1	1	1	1
GO:0006887	exocytosis	897	1.08E-23	1	1	1	1
GO:0006897	endocytosis	783	2.44E-05	1	1	1	1
GO:0006909	phagocytosis	342	0.011958563	1	1	1	1
GO:0006914	autophagy	466	0.003701303	1	1	1	1
GO:0006915	apoptotic process	1966	0.001910279	1	1	1	1
GO:0006935	chemotaxis	619	0.01174754	1	1	1	1
GO:0006940	regulation of smooth muscle contraction	62	0.049426883	1	1	1	1
GO:0006950	response to stress	3908	5.50E-12	1	1	1	1
GO:0006952	defense response	1658	5.06E-10	1	1	1	1
GO:0006954	inflammatory response	780	4.60E-06	1	1	1	1
GO:0006955	immune response	2183	1.32E-19	1	1	1	1
GO:0007159	leukocyte cell-cell adhesion	327	0.002534667	1	1	1	1
GO:0007165	signal transduction	6031	1.51E-09	1	1	0.0521109	1
GO:0007169	transmembrane receptor protein tyrosine kinase signaling pathway	694	0.006256544	1	1	0.996446813	1
GO:0007249	I-kappaB kinase/NF-kappaB signaling	258	0.00466681	1	1	1	1
GO:0007264	small GTPase mediated signal transduction	547	0.00566515	1	1	1	1
GO:0007369	gastrulation	181	1	1	1	1	0.031028127
GO:0007568	Aging	311	1	0.019378819	1	1	1
GO:0007596	blood coagulation	334	1.70E-08	1	1	1	1
GO:0007599	hemostasis	339	6.82E-09	0.901976979	1	1	1
GO:0008104	protein localization	2693	2.67E-05	1	1	1	1
GO:0008152	metabolic process	1242	1	0.031337146	1	1	1
GO:0008154	actin polymerization or depolymerization	206	0.043279439	1	1	1	1
GO:0008219	cell death	2232	0.003677466	1	1	1	1

GO:0009056	catabolic process	2490	1.66E-09	1	1	1	1
GO:0009057	macromolecule catabolic process	1346	9.85E-07	1	1	1	1
GO:0009058	biosynthetic process	6176	1	4.50E-06	1	1	1
GO:0009059	macromolecule biosynthetic process	4998	1	1.65E-06	1	1	1
GO:0009251	glucan catabolic process	19	0.024975729	1	1	1	1
GO:0009267	cellular response to starvation	146	0.015656927	1	1	1	1
GO:0009306	protein secretion	550	0.024183556	1	1	1	1
GO:0009605	response to external stimulus	2410	1.65E-09	1	1	1	1
GO:0009607	response to biotic stimulus	1014	3.97E-08	1	1	1	1
GO:0009611	response to wounding	655	9.77E-07	1	1	0.876970475	1
GO:0009615	response to virus	315	0.000527109	1	1	1	1
GO:0009617	response to bacterium	683	0.000497498	1	1	1	1
GO:0009636	response to toxic substance	513	0.03174739	1	1	1	1
GO:0009889	regulation of biosynthetic process	4259	1	7.74E-06	1	1	1
GO:0009890	negative regulation of biosynthetic process	1625	1	1.64E-06	1	1	1
GO:0009891	positive regulation of biosynthetic process	1978	1	0.001496726	1	1	1
GO:0009892	negative regulation of metabolic process	3395	1	0.026947894	1	1	1
GO:0009893	positive regulation of metabolic process	3558	2.54E-05	0.065080058	1	0.796254883	1
GO:0009894	regulation of catabolic process	875	5.35E-06	0.995169577	1	1	1
GO:0009896	positive regulation of catabolic process	407	0.002076463	1	1	1	1
GO:0009966	regulation of signal transduction	3183	8.98E-08	0.668982235	1	0.022834087	1
GO:0009967	positive regulation of signal transduction	1606	4.08E-09	1	1	1	1
GO:0009987	cellular process	1677 9	0.004881927	0.604011244	1	1	1
GO:0009991	response to extracellular stimulus	513	0.03174739	0.520071834	1	1	1
GO:0010033	response to organic substance	3172	1.22E-08	0.197199227	1	0.967833783	1
GO:0010243	response to organonitrogen compound	950	5.79E-05	1	1	1	1
GO:0010468	regulation of gene expression	4989	1	0.017606755	1	1	1
GO:0010543	regulation of platelet activation	30	0.027236556	1	1	1	1
GO:0010556	regulation of macromolecule	4041	1	3.35E-06	1	1	1
GO:0010557	biosynthetic process positive regulation of macromolecule	1844	1	0.000674069	1	1	1
GO:0010558	biosynthetic process negative regulation of macromolecule	1536	1	3.22E-07	1	1	1
GO:0010562	biosynthetic process positive regulation of phosphorus metabolic process	1124	3.91E-07	1	1	1	1

GO:0010604	positive regulation of macromolecule metabolic process	3299	1.05E-05	0.09101847	1	0.665596251	1
GO:0010605	negative regulation of macromolecule metabolic process	3164	1	0.009382245	1	1	1
GO:0010629	negative regulation of gene expression	2326	1	0.011891493	1	1	1
GO:0010638	positive regulation of organelle organization	602	0.014166664	1	1	1	1
GO:0010647	positive regulation of cell communication	1768	1.33E-08	1	1	0.957657142	1
GO:0010720	positive regulation of cell development	529	0.026184522	1	1	1	1
GO:0010821	regulation of mitochondrion organization	176	0.00334288	1	1	1	1
GO:0010822	positive regulation of mitochondrion organization	112	0.049884217	1	1	1	1
GO:0010941	regulation of cell death	1707	0.038843865	1	1	1	1
GO:0010942	positive regulation of cell death	689	0.001270746	1	1	1	1
GO:0010950	positive regulation of endopeptidase activity	171	0.022053268	1	1	0.933555354	1
GO:0010952	positive regulation of peptidase activity	189	0.007469011	1	1	1	1
GO:0012501	programmed cell death	2099	0.002691077	1	1	1	1
GO:0015031	protein transport	1974	1.57E-05	1	1	1	1
GO:0015669	gas transport	19	1	1	1	1	0.035229966
GO:0015833	peptide transport	2009	3.25E-05	1	1	1	1
GO:0016043	cellular component organization	6334	0.034533479	0.905458796	1	0.489378401	0.102751857
GO:0016045	detection of bacterium	12	0.037418398	1	1	1	1
GO:0016050	vesicle organization	314	0.003665448	1	1	1	1
GO:0016070	RNA metabolic process	5106	1	0.001250472	1	1	1
GO:0016192	vesicle-mediated transport	2058	7.47E-19	1	1	1	1
GO:0016310	phosphorylation	2303	9.46E-06	1	1	1	1
GO:0016477	cell migration	1537	1.08E-05	1	1	0.442735373	1
GO:0018130	heterocycle biosynthetic process	4233	1	8.40E-06	1	1	1
GO:0019219	regulation of nucleobase-containing compound metabolic process	4013	1	5.63E-06	1	1	1
GO:0019220	regulation of phosphate metabolic process	1736	7.18E-07	1	1	1	1
GO:0019221	cytokine-mediated signaling pathway	728	2.37E-07	1	1	1	1
GO:0019222	regulation of metabolic process	7129	0.108871927	0.001496726	1	1	1
GO:0019438	aromatic compound biosynthetic process	4242	1	9.45E-06	1	1	1
GO:0019538	protein metabolic process	5855	0.000885922	1	1	0.93226801	1
GO:0022604	regulation of cell	474	0.040355298	1	1	1	1

	morphogenesis						
GO:0023014	signal transduction by protein phosphorylation	944	0.000451981	1	1	1	1
GO:0023051	regulation of signaling	3567	1.20E-07	0.918797783	1	0.00944828	1
GO:0023056	positive regulation of signaling	1775	3.71E-09	1	1	0.984890815	1
GO:0030097	hemopoiesis	819	0.034690044	0.000140896	1	1	0.686175641
GO:0030098	lymphocyte differentiation	344	1	0.026584093	1	1	1
GO:0030099	myeloid cell differentiation	405	0.04295607	0.134152259	1	1	1
GO:0030100	regulation of endocytosis	260	0.013452901	1	1	1	1
GO:0030155	regulation of cell adhesion	668	0.002919532	1	1	1	1
GO:0030163	protein catabolic process	900	0.002021862	1	1	1	1
GO:0030168	platelet activation	152	4.20E-07	0.996446813	1	1	1
GO:0030193	regulation of blood coagulation	77	0.002919532	1	1	1	1
GO:0030213	hyaluronan biosynthetic process	13	0.049467321	0.93226801	1	1	1
GO:0030218	erythrocyte differentiation	111	0.897478797	0.002200796	1	1	0.879865755
GO:0030220	platelet formation	20	1	0.023984508	1	1	1
GO:0030334	regulation of cell migration	910	0.001353029	1	1	1	1
GO:0030335	positive regulation of cell migration	519	4.00E-06	1	1	1	1
GO:0030593	neutrophil chemotaxis	101	0.007127455	1	1	1	1
GO:0030595	leukocyte chemotaxis	217	0.001379065	1	1	1	1
GO:0030851	granulocyte differentiation	32	1	0.027161313	1	1	1
GO:0031098	stress-activated protein kinase signaling cascade	313	0.008881305	1	1	1	1
GO:0031323	regulation of cellular metabolic process	6127	0.000154745	5.63E-06	1	1	1
GO:0031324	negative regulation of cellular metabolic process	2571	0.231941565	3.05E-05	1	1	1
GO:0031325	positive regulation of cellular metabolic process	3260	1.46E-05	0.026184522	1	1	1
GO:0031326	regulation of cellular biosynthetic process	4184	1	6.54E-06	1	1	1
GO:0031327	negative regulation of cellular biosynthetic process	1601	1	1.75E-06	1	1	1
GO:0031328	positive regulation of cellular biosynthetic process	1943	1	0.000816714	1	1	1
GO:0031329	regulation of cellular catabolic process	765	6.52E-05	0.896075185	1	1	1
GO:0031331	positive regulation of cellular catabolic process	347	0.006173714	0.989561623	1	1	1
GO:0031334	positive regulation of protein complex assembly	259	0.029415629	0.973367399	1	1	1
GO:0031347	regulation of defense response	765	5.92E-06	1	1	1	1

GO:0031349	positive regulation of defense response	427	5.88E-06	1	1	1	1
GO:0031399	regulation of protein modification process	1821	2.37E-07	1	1	1	1
GO:0031401	positive regulation of protein modification process	1220	8.58E-07	1	1	1	1
GO:0031646	positive regulation of neurological system process	58	1	1	1	0.009678209	1
GO:0031663	lipopolysaccharide-mediated signaling pathway	56	0.006197688	1	1	1	1
GO:0031667	response to nutrient levels	481	0.026184522	0.675996209	1	1	1
GO:0031668	cellular response to extracellular stimulus	258	0.062580021	0.032811717	1	1	1
GO:0031669	cellular response to nutrient levels	228	0.045842089	0.056922458	1	1	1
GO:0032092	positive regulation of protein binding	94	0.048234344	1	1	1	1
GO:0032101	regulation of response to external stimulus	840	0.001513988	1	1	1	1
GO:0032103	positive regulation of response to external stimulus	297	0.024975729	1	1	1	1
GO:0032147	activation of protein kinase activity	323	3.00E-05	1	1	1	1
GO:0032268	regulation of cellular protein metabolic process	2616	1.27E-07	1	1	1	1
GO:0032269	negative regulation of cellular protein metabolic process	1083	0.033725236	1	1	1	1
GO:0032270	positive regulation of cellular protein metabolic process	1584	8.98E-08	1	1	1	1
GO:0032496	response to lipopolysaccharide	324	0.002200796	1	1	1	1
GO:0032611	interleukin-1 beta production	73	0.033780469	1	1	1	1
GO:0032612	interleukin-1 production	87	0.029127228	1	1	1	1
GO:0032637	interleukin-8 production	73	0.001845049	1	1	1	1
GO:0032640	tumor necrosis factor production	129	0.046405569	1	1	1	1
GO:0032677	regulation of interleukin-8 production	66	0.000765005	1	1	1	1
GO:0032680	regulation of tumor necrosis factor production	127	0.041122974	1	1	1	1
GO:0032757	positive regulation of interleukin-8 production	46	0.000194198	1	1	1	1
GO:0032760	positive regulation of tumor necrosis factor production	73	0.033780469	1	1	1	1
GO:0032774	RNA biosynthetic process	3659	1	5.18E-06	1	1	1
GO:0032880	regulation of protein localization	963	9.45E-06	1	1	1	1
GO:0032940	secretion by cell	1478	1.08E-23	1	1	1	1
GO:0033036	macromolecule localization	3037	2.71E-05	1	1	1	1

GO:0033043	regulation of organelle organization	1237	0.018565448	0.869543798	1	1	1
GO:0033554	cellular response to stress	1928	0.000334829	1	1	1	1
GO:0033674	positive regulation of kinase activity	552	1.79E-09	1	1	1	1
GO:0034097	response to cytokine	1114	1.30E-07	1	1	1	1
GO:0034101	erythrocyte homeostasis	120	1	0.004673466	1	1	0.940589364
GO:0034109	homotypic cell-cell adhesion	76	0.04283723	0.996446813	1	1	1
GO:0034123	positive regulation of toll-like receptor signaling pathway	22	0.043674424	1	1	1	1
GO:0034134	toll-like receptor 2 signaling pathway	16	0.000949328	1	1	1	1
GO:0034135	regulation of toll-like receptor 2 signaling pathway	11	0.027946094	1	1	1	1
GO:0034198	cellular response to amino acid starvation	45	0.037418398	1	1	1	1
GO:0034504	protein localization to nucleus	269	0.042659462	1	1	1	1
GO:0034613	cellular protein localization	1830	0.000731018	1	1	1	1
GO:0034641	cellular nitrogen compound metabolic process	6998	1	0.006520896	1	1	1
GO:0034645	cellular macromolecule biosynthetic process	4853	1	8.55E-06	1	1	1
GO:0034654	nucleobase-containing compound biosynthetic process	4171	1	5.52E-06	1	1	1
GO:0034976	response to endoplasmic reticulum stress	264	0.015996351	1	1	1	1
GO:0035556	intracellular signal transduction	2817	1.30E-12	1	1	0.13056033	1
GO:0036211	protein modification process	4066	1.66E-05	0.93115264	1	1	1
GO:0036230	granulocyte activation	505	4.83E-21	1	1	1	1
GO:0036344	platelet morphogenesis	21	1	0.028400502	1	1	1
GO:0038093	Fc receptor signaling pathway	187	0.000173731	1	1	1	1
GO:0038094	Fc-gamma receptor signaling pathway	138	0.02750321	1	1	1	1
GO:0040012	regulation of locomotion	1042	0.000435941	1	1	1	1
GO:0040017	positive regulation of locomotion	570	6.01E-06	1	1	1	1
GO:0042035	regulation of cytokine biosynthetic process	94	0.048234344	0.24587016	1	1	1
GO:0042060	wound healing	543	2.91E-08	1	1	1	1
GO:0042108	positive regulation of cytokine biosynthetic process	57	0.031006288	1	1	1	1
GO:0042110	T cell activation	451	0.000878164	1	1	1	1
GO:0042119	neutrophil activation	498	1.09E-20	1	1	1	1
GO:0042221	response to chemical	4641	6.82E-06	0.969666228	1	1	1
GO:0042325	regulation of phosphorylation	1536	7.74E-07	1	1	1	1

GO:0042327	positive regulation of phosphorylation	1053	7.48E-08	1	1	1	1
GO:0042330	Taxis	621	0.012287565	1	1	1	1
GO:0042494	detection of bacterial lipoprotein	4	0.016140011	1	1	1	1
GO:0042592	homeostatic process	1867	0.022963874	1	1	0.996446813	0.345762208
GO:0042886	amide transport	2037	3.30E-05	1	1	1	1
GO:0042981	regulation of apoptotic process	1572	0.029061136	1	1	1	1
GO:0043065	positive regulation of apoptotic process	632	0.001982857	1	1	1	1
GO:0043067	regulation of programmed cell death	1586	0.024126389	1	1	1	1
GO:0043068	positive regulation of programmed cell death	636	0.001058108	1	1	1	1
GO:0043085	positive regulation of catalytic activity	1392	1.94E-09	1	1	1	1
GO:0043086	negative regulation of catalytic activity	795	0.036082289	1	1	1	1
GO:0043087	regulation of GTPase activity	481	0.049277258	1	1	1	1
GO:0043112	receptor metabolic process	184	0.040035288	1	1	1	1
GO:0043122	regulation of I-kappaB kinase/NF-kappaB signaling	226	0.018065402	1	1	1	1
GO:0043123	positive regulation of I-kappaB kinase/NF-kappaB signaling	181	0.00461387	1	1	1	1
GO:0043207	response to external biotic stimulus	984	3.89E-07	1	1	1	1
GO:0043249	erythrocyte maturation	15	1	0.006823622	1	1	1
GO:0043280	positive regulation of cysteine-type endopeptidase activity involved in apoptotic process	126	0.038843865	1	1	1	1
GO:0043281	regulation of cysteine-type endopeptidase activity involved in apoptotic process	209	0.007862201	1	1	1	1
GO:0043299	leukocyte degranulation	531	3.32E-21	1	1	1	1
GO:0043312	neutrophil degranulation	485	5.35E-20	1	1	1	1
GO:0043405	regulation of MAP kinase activity	335	2.37E-06	1	1	1	1
GO:0043406	positive regulation of MAP kinase activity	258	5.07E-06	1	1	1	1
GO:0043408	regulation of MAPK cascade	776	1.92E-05	1	1	1	1
GO:0043412	macromolecule modification	4269	8.87E-05	0.680217842	1	1	1
GO:0043434	response to peptide hormone	417	0.015891141	1	1	1	1
GO:0043549	regulation of kinase activity	837	5.71E-07	1	1	1	1
GO:0044093	positive regulation of molecular function	1736	5.74E-10	1	1	1	1
GO:0044237	cellular metabolic process	11116	0.145299351	0.000447254	1	1	1

GO:0044238	primary metabolic process	11112	1	0.007170056	1	1	1
GO:0044247	cellular polysaccharide catabolic process	21	0.004611115	1	1	1	1
GO:0044248	cellular catabolic process	2204	5.16E-08	0.87520387	1	1	1
GO:0044249	cellular biosynthetic process	6015	1	5.07E-06	1	1	1
GO:0044260	cellular macromolecule metabolic process	8207	0.110332446	0.000171375	1	1	1
GO:0044265	cellular macromolecule catabolic process	1118	0.015397049	0.748743161	1	1	1
GO:0044267	cellular protein metabolic process	5151	0.000173216	0.901236414	1	1	1
GO:0044271	cellular nitrogen compound biosynthetic process	4905	1	1.09E-05	1	1	1
GO:0044275	cellular carbohydrate catabolic process	40	0.021226881	1	1	1	1
GO:0045055	regulated exocytosis	788	1.08E-23	1	1	1	1
GO:0045087	innate immune response	908	1.30E-09	1	1	1	1
GO:0045088	regulation of innate immune response	365	1.57E-07	1	1	1	1
GO:0045089	positive regulation of innate immune response	309	4.50E-06	1	1	1	1
GO:0045123	cellular extravasation	54	0.000802516	1	1	1	1
GO:0045184	establishment of protein localization	2079	2.55E-05	1	1	1	1
GO:0045321	leukocyte activation	1257	4.94E-18	1	1	1	1
GO:0045597	positive regulation of cell differentiation	974	0.020370955	0.831969884	1	1	1
GO:0045785	positive regulation of cell adhesion	397	0.034129341	1	1	1	1
GO:0045859	regulation of protein kinase activity	762	1.59E-07	1	1	1	1
GO:0045860	positive regulation of protein kinase activity	512	4.71E-09	1	1	1	1
GO:0045862	positive regulation of proteolysis	352	0.001187493	1	1	1	1
GO:0045892	negative regulation of transcription, DNA-templated	1199	1	4.69E-09	1	0.469442217	1
GO:0045932	negative regulation of muscle contraction	27	0.017009962	1	1	1	1
GO:0045934	negative regulation of nucleobase-containing compound metabolic process	1457	1	6.60E-07	1	0.923274969	1
GO:0045935	positive regulation of nucleobase-containing compound metabolic process	1862	1	0.001568173	1	1	1
GO:0045937	positive regulation of phosphate metabolic process	1124	3.91E-07	1	1	1	1
GO:0045987	positive regulation of smooth muscle contraction	32	0.036082289	1	1	1	1
GO:0046483	heterocycle metabolic process	6422	1	0.005792173	1	1	1

GO:0046649	lymphocyte activation	713	0.019063382	0.345762208	1	1	1
GO:0046898	response to cycloheximide	4	1	0.013583116	1	1	1
GO:0046903	secretion	1614	1.08E-23	1	1	1	1
GO:0048010	vascular endothelial growth factor receptor signaling pathway	91	0.038843865	1	1	1	1
GO:0048013	ephrin receptor signaling pathway	80	0.000841417	1	1	1	1
GO:0048519	negative regulation of biological process	5698	0.222729944	0.002085165	1	0.955645847	1
GO:0048522	positive regulation of cellular process	5330	2.61E-08	0.01290706	1	0.892839413	1
GO:0048523	negative regulation of cellular process	4759	0.050048478	5.46E-05	1	0.681771571	1
GO:0048534	hematopoietic or lymphoid organ development	861	0.009678209	0.000236607	1	1	0.533565531
GO:0048583	regulation of response to stimulus	4234	2.15E-08	1	1	0.400677758	1
GO:0048584	positive regulation of response to stimulus	2373	3.55E-10	1	1	1	1
GO:0048821	erythrocyte development	31	1	0.00036786	1	1	1
GO:0048870	cell motility	1688	6.00E-05	1	1	0.629638536	1
GO:0048872	homeostasis of number of cells	248	0.019367226	0.052531007	1	1	1
GO:0050663	cytokine secretion	210	0.008352331	1	1	1	1
GO:0050701	interleukin-1 secretion	56	0.0280421	1	1	1	1
GO:0050702	interleukin-1 beta secretion	48	0.011788736	1	1	1	1
GO:0050776	regulation of immune response	1022	2.37E-08	1	1	1	1
GO:0050778	positive regulation of immune response	823	1.39E-07	1	1	1	1
GO:0050789	regulation of biological process	1189	0.000110092	0.002209175	1	1	1
GO:0050790	regulation of catalytic activity	2281	2.61E-08	1	1	0.899460453	1
GO:0050794	regulation of cellular process	1082	4.85E-07	0.000104586	1	0.922242032	1
GO:0050817	coagulation	340	7.31E-09	1	1	1	1
GO:0050818	regulation of coagulation	82	0.001058702	1	1	1	1
GO:0050820	positive regulation of coagulation	26	0.014166664	1	1	1	1
GO:0050863	regulation of T cell activation	305	0.015271277	1	1	1	1
GO:0050865	regulation of cell activation	587	0.017981836	1	1	1	1
GO:0050866	negative regulation of cell activation	184	0.040035288	1	1	1	1
GO:0050878	regulation of body fluid levels	493	1.93E-05	1	1	1	0.966588903
GO:0050900	leukocyte migration	478	0.000176302	1	1	1	1
GO:0051050	positive regulation of transport	936	0.016217447	1	1	1	1
GO:0051090	regulation of DNA-binding transcription factor activity	412	0.026984947	0.792082077	1	1	1
GO:0051091	positive regulation of	255	0.004012175	0.922242032	1	1	1

	DNA-binding transcription factor activity						
GO:0051092	positive regulation of NF-kappaB transcription factor activity	146	1.92E-05	0.922242032	1	1	1
GO:0051094	positive regulation of developmental process	1395	0.038843865	0.830036129	1	1	1
GO:0051128	regulation of cellular component organization	2457	3.72E-05	0.996446813	1	1	1
GO:0051130	positive regulation of cellular component organization	1210	4.29E-05	1	1	1	1
GO:0051171	regulation of nitrogen compound metabolic process	5907	0.008673409	5.89E-05	1	1	1
GO:0051172	negative regulation of nitrogen compound metabolic process	2410	0.348615674	8.40E-06	1	1	1
GO:0051173	positive regulation of nitrogen compound metabolic process	3140	2.20E-05	0.072497165	1	1	1
GO:0051174	regulation of phosphorus metabolic process	1738	7.55E-07	1	1	1	1
GO:0051222	positive regulation of protein transport	402	0.001684062	1	1	1	1
GO:0051223	regulation of protein transport	672	0.023649461	1	1	1	1
GO:0051246	regulation of protein metabolic process	2860	6.36E-08	1	1	1	1
GO:0051247	positive regulation of protein metabolic process	1681	1.05E-09	1	1	1	1
GO:0051248	negative regulation of protein metabolic process	1144	0.008981555	0.996446813	1	1	1
GO:0051252	regulation of RNA metabolic process	3738	1	2.45E-06	1	1	1
GO:0051253	negative regulation of RNA metabolic process	1330	1	3.23E-08	1	0.633161182	1
GO:0051254	positive regulation of RNA metabolic process	1680	1	0.001413106	1	1	1
GO:0051272	positive regulation of cellular component movement	553	7.10E-06	1	1	1	1
GO:0051336	regulation of hydrolase activity	1281	0.001796452	1	1	1	1
GO:0051338	regulation of transferase activity	941	2.18E-06	1	1	1	1
GO:0051345	positive regulation of hydrolase activity	763	0.002761855	1	1	1	1
GO:0051347	positive regulation of transferase activity	626	3.58E-08	1	1	1	1
GO:0051607	defense response to virus	228	0.007642349	1	1	1	1
GO:0051641	cellular localization	2847	0.024959734	1	1	1	1
GO:0051674	localization of cell	1688	6.00E-05	1	1	0.629638536	1
GO:0051704	multi-organism process	2485	3.72E-05	1	1	1	1

GO:0051707	response to other organism	982	3.62E-07	1	1	1	1
GO:0051716	cellular response to stimulus	7432	3.67E-09	0.87520387	1	0.07488625	1
GO:0060079	excitatory postsynaptic potential	103	1	1	1	0.026564194	1
GO:0060218	hematopoietic stem cell differentiation	34	1	0.035278512	1	1	1
GO:0060255	regulation of macromolecule metabolic process	6630	0.443316572	0.00566515	1	1	1
GO:0060319	primitive erythrocyte differentiation	4	1	0.013583116	1	1	1
GO:0060326	cell chemotaxis	295	0.010056469	1	1	1	1
GO:0060341	regulation of cellular localization	879	0.024731895	1	1	1	1
GO:0060627	regulation of vesicle-mediated transport	498	0.021966072	1	1	1	1
GO:0060969	negative regulation of gene silencing	35	1	0.040035288	1	1	1
GO:0061003	positive regulation of dendritic spine morphogenesis	19	1	1	1	1	0.035229966
GO:0061024	membrane organization	846	0.012347546	1	1	1	1
GO:0061041	regulation of wound healing	134	0.022218406	1	1	1	1
GO:0061298	retina vasculature development in camera-type eye	18	1	1	1	1	0.031028127
GO:0061515	myeloid cell development	67	0.52528845	7.08E-05	1	1	1
GO:0061900	glial cell activation	40	0.003561051	1	1	1	1
GO:0061919	process utilizing autophagic mechanism	466	0.003701303	1	1	1	1
GO:0065007	biological regulation	12576	1.85E-06	0.018565448	1	0.356365961	1
GO:0065009	regulation of molecular function	3187	1.56E-06	1	1	0.478489879	1
GO:0070201	regulation of establishment of protein localization	715	0.011042006	1	1	1	1
GO:0070340	detection of bacterial lipopeptide	3	0.005055861	1	1	1	1
GO:0070498	interleukin-1-mediated signaling pathway	55	0.025766984	1	1	1	1
GO:0070527	platelet aggregation	57	0.031006288	1	1	1	1
GO:0070727	cellular macromolecule localization	1840	0.00087738	1	1	1	1
GO:0070887	cellular response to chemical stimulus	3144	7.43E-11	0.481144832	1	1	0.916075135
GO:0071216	cellular response to biotic stimulus	229	2.35E-05	1	1	1	1
GO:0071219	cellular response to molecule of bacterial origin	206	0.000693746	1	1	1	1
GO:0071222	cellular response to lipopolysaccharide	199	0.012917217	1	1	1	1
GO:0071260	cellular response to mechanical stimulus	78	1.92E-05	1	1	1	1
GO:0071310	cellular response to organic substance	2595	9.32E-10	0.179921038	1	1	0.883468397

GO:0071345	cellular response to cytokine stimulus	1028	1.59E-07	1	1	1	1
GO:0071346	cellular response to interferon-gamma	178	0.030521352	1	1	1	1
GO:0071375	cellular response to peptide hormone stimulus	307	0.016372759	1	1	1	1
GO:0071417	cellular response to organonitrogen compound	555	7.77E-06	1	1	1	0.519887215
GO:0071496	cellular response to external stimulus	328	1.37E-05	0.133254818	1	1	1
GO:0071621	granulocyte chemotaxis	120	0.002310269	1	1	1	1
GO:0071622	regulation of granulocyte chemotaxis	42	0.026791027	1	1	1	1
GO:0071675	regulation of mononuclear cell migration	42	0.026791027	1	1	1	1
GO:0071702	organic substance transport	2745	0.000324796	1	1	1	0.739725387
GO:0071705	nitrogen compound transport	2335	0.001910279	1	1	1	1
GO:0071706	tumor necrosis factor superfamily cytokine production	135	0.007547433	1	1	1	1
GO:0071840	cellular component organization or biogenesis	6506	0.075463572	0.686175641	1	0.698373195	0.046322431
GO:0071900	regulation of protein serine/threonine kinase activity	496	1.59E-07	1	1	1	1
GO:0071902	positive regulation of protein serine/threonine kinase activity	323	2.62E-08	1	1	1	1
GO:0072672	neutrophil extravasation	10	0.001140246	1	1	1	1
GO:0080090	regulation of primary metabolic process	6069	0.004520227	9.52E-06	1	1	1
GO:0080134	regulation of response to stress	1452	6.85E-08	1	1	1	1
GO:0080135	regulation of cellular response to stress	684	0.009359443	1	1	1	1
GO:0090087	regulation of peptide transport	701	0.0256708	1	1	1	1
GO:0090304	nucleic acid metabolic process	5634	1	0.001513988	1	1	1
GO:0090316	positive regulation of intracellular protein transport	158	0.010740006	1	1	1	1
GO:0097529	myeloid leukocyte migration	199	0.000433484	1	1	1	1
GO:0097530	granulocyte migration	134	0.000500171	1	1	1	1
GO:0097659	nucleic acid-templated transcription	3642	1	3.98E-06	1	1	1
GO:0098542	defense response to other organism	548	0.041421832	1	1	1	1
GO:0098543	detection of other organism	13	0.049467321	1	1	1	1
GO:0098657	import into cell	900	1.17E-05	1	1	0.996446813	1
GO:0098771	inorganic ion homeostasis	722	0.039539873	1	1	0.875764979	1

GO:0098976	excitatory chemical synaptic transmission	8	1	1	1	0.013930431	1
GO:0099565	chemical synaptic transmission, postsynaptic neuroinflammatory response	111	1	1	1	0.037418398	1
GO:0150076	regulation of hemostasis	47	0.0002357	1	1	1	1
GO:1900046	positive regulation of NIK/NF-kappaB signaling	77	0.002919532	1	1	1	1
GO:1901224	organic cyclic compound metabolic process	70	0.026584093	1	1	1	1
GO:1901360	organic cyclic compound biosynthetic process	6676	1	0.011793821	1	1	1
GO:1901362	organonitrogen compound metabolic process	4387	1	1.89E-05	1	1	1
GO:1901564	organonitrogen compound catabolic process	6899	9.53E-05	1	1	1	1
GO:1901565	organic substance catabolic process	1253	0.000953023	1	1	1	1
GO:1901575	organic substance biosynthetic process	2071	3.56E-07	1	1	1	1
GO:1901576	response to peptide	6099	1	2.53E-06	1	1	1
GO:1901652	cellular response to peptide	481	0.000512427	1	1	1	1
GO:1901653	response to nitrogen compound	356	0.000545066	1	1	1	1
GO:1901698	cellular response to nitrogen compound	1037	2.06E-05	1	1	1	1
GO:1901699	response to oxygen-containing compound	612	1.40E-05	1	1	1	0.402781503
GO:1901700	cellular response to oxygen-containing compound	1577	1.54E-05	1	1	1	1
GO:1901701	regulation of chromatin organization	1092	5.13E-05	1	1	1	0.795980333
GO:1902275	regulation of intracellular signal transduction	175	1	0.038417362	1	1	1
GO:1902531	positive regulation of intracellular signal transduction	1881	1.13E-09	1	1	1	1
GO:1902533	regulation of neutrophil migration	1077	3.91E-07	1	1	1	1
GO:1902622	negative regulation of RNA biosynthetic process	31	0.03127218	1	1	1	1
GO:1902679	regulation of leukocyte cell-cell adhesion	1251	1	1.26E-08	1	0.604011244	1
GO:1903037	regulation of nucleic acid-templated transcription	293	0.021687327	1	1	1	1
GO:1903506	negative regulation of nucleic acid-templated transcription	3499	1	2.97E-06	1	1	1
GO:1903507	mucopolysaccharide metabolic process	1249	1	1.21E-08	1	0.598967854	1
GO:1903510		110	0.014483105	1	1	1	1

GO:1903555	regulation of tumor necrosis factor superfamily cytokine production	131	0.01844494	1	1	1	1
GO:1903557	positive regulation of tumor necrosis factor superfamily cytokine production	76	0.04283723	1	1	1	1
GO:1903747	regulation of establishment of protein localization to mitochondrion	70	0.026584093	1	1	1	1
GO:1903749	positive regulation of establishment of protein localization to mitochondrion	56	0.0280421	1	1	1	1
GO:1903827	regulation of cellular protein localization	508	0.000254902	1	1	1	1
GO:1903829	positive regulation of cellular protein localization	318	0.004402893	1	1	1	1
GO:1904951	positive regulation of establishment of protein localization	437	0.000496601	1	1	1	1
GO:1905268	negative regulation of chromatin organization	60	1	0.028370428	1	1	1
GO:1990266	neutrophil migration	112	0.001132309	1	1	1	1
GO:1990928	response to amino acid starvation	47	0.046835063	1	1	1	1
GO:2000112	regulation of cellular macromolecule biosynthetic process	3918	1	1.43E-05	1	1	1
GO:2000113	negative regulation of cellular macromolecule biosynthetic process	1459	1	3.40E-07	1	1	1
GO:2000116	regulation of cysteine-type endopeptidase activity	232	0.00334288	1	1	1	1
GO:2000145	regulation of cell motility	968	0.00318429	1	1	0.995169577	1
GO:2000147	positive regulation of cell motility	539	9.45E-06	1	1	1	1
GO:2000377	regulation of reactive oxygen species metabolic process	185	0.041941486	1	1	1	1
GO:2000463	positive regulation of excitatory postsynaptic potential	27	1	1	1	0.032162807	1
GO:2001056	positive regulation of cysteine-type endopeptidase activity	143	0.035857337	1	1	0.716801532	1
GO:2001141	regulation of RNA biosynthetic process	3507	1	3.35E-06	1	1	1
GO:2001233	regulation of apoptotic signaling pathway	391	0.014166664	1	1	1	1

[0063] Time Series Analysis of Synovial Cell Marker Genes in RA Flares

[0064] To better characterize the relevance of the clusters identified by the time series analysis to synovitis (Figure 3C), we examined them for enrichment in synovial cell subtypes characterized by

scRNAseq. This analysis of 5265 single RA and osteoarthritis patient synovial cells identified four fibroblast, four B cell, six T cell, and four monocyte subpopulations (Figure 4A). We identified approximately 200 marker genes that best distinguished each of 18 synovial cell types. AC2 was enriched with naive B cell genes (Figure 4A and Figure 17), and AC3 was enriched with three sublining fibroblast genes (CD34+, HLA-DR+, and DKK3+) (Figure 4A). Two of these fibroblast panels, CD34+ and HLA-DR+, are more abundant in inflamed synovium (20). We plotted expression of those transcripts that were common to both synovial sublining fibroblasts and AC3 over time and again noted their increased expression in blood one week prior to flare and decreased expression during flare (Figure 4B, Figure 18, and Table 5).

[0065] Overall, 622 of 625 AC3 genes decreased during flare in patient 1, and a panel (194 genes) also decreased in flares from at least 3 out of 4 RA patients (and 22 genes in 4 out of 4 patients; Figure 4C and Table 6), and permutation test indicated this overlap was greater than expected by chance ($p=0.0001$). Pathway analysis of the panel of 194 overlapping genes was again enriched for extracellular matrix and secreted glycoprotein.

[0066] We further tested whether cells that expressed surface markers of synovial fibroblasts were detectable in RA blood by flow cytometry (Figures 19 and 20). CD45-/CD31-/PDPN+ cells were increased in 19 additional RA patient blood relative to healthy controls (Figure 4D). RNAseq of these cells confirmed they were enriched with AC3 cluster genes (Figure 4E), synovial fibroblast genes (Figure 21). Given their expression of classical mesenchymal surface markers and genes, we refer to these as PRe-Inflammatory Mesenchymal Cells (PRIME cells). Taken together, our observations suggest a model in which sequential activation of B cells activate PRIME cells just prior to flares, which are then evident at flare in inflamed synovium as inflammatory sublining fibroblasts (Figure 5).

DISCUSSION

[0067] We present longitudinal genomics as a strategy to study the antecedents to RA flare that may be generalizable to autoimmune diseases associated with waxing/waning clinical courses. We developed easy-to-use tools for patients to acquire both quantifiable clinical symptoms and molecular data at home over many years. This allowed us to capture data prior to the onset of clinical flares and retrospectively analyze it, identifying different RNA signatures (AC2 and AC3) evident in peripheral blood 1-2 weeks prior to flare.

[0068] The RNA signature of AC3 and sorted CD45-/CD31-/PDPN+ circulating cells revealed enrichment for pathways including cartilage morphogenesis, endochondral bone growth, and extracellular matrix organization (Figure 3E) and strongly overlapped with synovial sublining fibroblasts. We therefore propose antecedent PRIME cells are the precursors to inflammatory sublining fibroblasts previously found adjacent to blood vessels in inflamed RA synovium (21).

[0069] Significantly, inflamed sublining fibroblasts are pathogenic in an animal model of arthritis (22). Our discovery that human AC3 genes share molecular characteristics of sublining fibroblasts, together with the observation that these cells spike prior to flare but are less detectable in blood during flare (Figure 2 and 4) support a model in which PRIME cells immigrate acutely from blood to the synovium where they contribute to the inflammatory process (Figure 5). This model is consistent with the observation that RA synovial fibroblasts can traffic to cartilage implants and are sufficient to passively transfer synovial inflammation in mice (23). Together our data suggest the mesenchymal signal detected in AC3 prior to flares represent a previously uncharacterized type of trafficking fibroblast that circulates in blood.

[0070] In addition, we observed a second RNA signature, AC2, activated in blood prior to the spike in AC3. AC2 bear RNA hallmarks of naive B cells. This finding is reminiscent of recent studies demonstrating autoreactive naive B cells are specifically activated in RA patients (24). While the triggers of these are unknown, infectious (for example bacterial or viral antigens), environmental or endogenous toxins (25-27) could provide a source of either specific antigens or activate pattern recognition receptors.

[0071] In conclusion, we demonstrate methods for densely collecting longitudinal clinical and gene expression data that can be used to discover changes in transcriptional profiles in the blood weeks prior to symptom onset. This approach led to discovery of PRIME cells, bearing hallmarks of synovial fibroblasts, which are more common in RA patients and increase in blood just prior to flares. In modeling all our data (Figure 5), we suggest that prior to clinical flare, systemic B cell immune activation (detected as AC2) acts on PRIME cells, which traffic to the blood (detected as AC3) and subsequently to the synovial sublining during flares of disease activity. More generally, this work in RA provides an exemplar of an approach to waxing/waning inflammatory disease, suggesting a general strategy relevant to additional disorders such as lupus, multiple sclerosis, and vasculitis.

[0072] Tables 2, 5 and 6 referenced in the above are provided as follows.

TABLE 2
Pathway Analysis of Differentially Expressed Genes in Flare Versus Baseline

<u>ID</u>	<u>TERM</u>	<u>nGenes</u>	<u>sig up.</u> <u>ngenes</u>	<u>sig down.</u> <u>ngenes</u>	<u>fdr.up</u>	<u>fdr.down</u>
GO:0002274	myeloid leukocyte activation	607	112	3	1.78E-29	1
GO:0006955	immune response	1725	205	16	8.83E-29	1
GO:0032940	secretion by cell	1354	176	12	8.83E-29	1
GO:0043299	leukocyte degranulation	510	100	3	1.04E-28	1
GO:0036230	granulocyte activation	486	97	3	1.74E-28	1

GO:0001775	cell activation	1250	166	14	2.26E-28	1	
GO:0002275	myeloid cell activation involved in immune response	520	100	3	2.26E-28	1	
GO:0002376	immune system process	2531	260	31	2.26E-28	1	
GO:0002446	neutrophil mediated immunity	482	96	3	2.26E-28	1	
GO:0042119	neutrophil activation	480	96	3	2.26E-28	1	
GO:0046903	secretion	1468	183	13	2.41E-28	1	
GO:0043312	neutrophil degranulation	469	94	3	5.05E-28	1	
GO:0002444	myeloid leukocyte mediated immunity	527	100	3	5.52E-28	1	
GO:0002283	neutrophil activation involved in immune response	472	94	3	7.33E-28	1	
GO:0002366	leukocyte activation involved in immune response	652	111	5	4.28E-27	1	
GO:0002263	cell activation involved in immune response	655	111	5	6.10E-27	1	
GO:0045321	leukocyte activation	1111	150	10	2.96E-26	1	
GO:0006887	exocytosis	857	128	5	4.51E-26	1	
GO:0002443	leukocyte mediated immunity	726	116	5	5.52E-26	1	
GO:0002252	immune effector process	1063	145	7	8.77E-26	1	
GO:0045055	regulated exocytosis	755	118	4	1.23E-25	1	
GO:0016192	vesicle-mediated transport	1859	186	26	1.74E-17	1	
GO:0006950	response to stress	3333	273	39	5.46E-15	1	
GO:0050896	response to stimulus	7448	500	104	5.71E-15	1	
GO:0023052	signaling	5257	380	73	5.88E-14	1	
GO:0007165	signal transduction	4852	356	65	1.41E-13	1	
GO:0007154	cell communication	5297	379	74	3.76E-13	1	
GO:0009611	response to wounding	571	78	17	1.05E-12	0.129037518	
GO:0002684	positive regulation of immune system process	896	104	9	1.19E-12	1	
GO:0048584	positive regulation of response to stimulus	1994	181	22	1.19E-12	1	
GO:0051716	cellular response to stimulus	6105	420	85	1.63E-12	1	
GO:0002682	regulation of immune system process	1283	130	12	9.76E-12	1	
GO:0002253	activation of immune response	494	69	1	1.47E-11	1	
GO:0050776	regulation of immune response	831	96	8	1.89E-11	1	
GO:0050778	positive regulation of immune response	653	82	5	1.89E-11	1	
GO:0070887	cellular response to chemical stimulus	2747	224	40	2.59E-11	1	
GO:0045087	innate immune response	695	85	2	2.61E-11	1	
GO:0006952	defense response	1291	129	6	3.05E-11	1	
GO:0042060	wound healing	470	66	16	3.70E-11	0.059726283	
GO:0044093	positive regulation of molecular function	1569	147	20	6.93E-11	1	
GO:0080134	regulation of response to stress	1248	124	5	1.45E-10	1	
GO:0048583	regulation of response to stimulus	3614	272	43	2.27E-10	1	
GO:0050794	regulation of cellular process	9002	557	112	3.98E-10	1	
GO:0002757	immune response-activating signal transduction	426	60	1	4.31E-10	1	
GO:0048518	positive regulation of biological process	5233	362	71	4.36E-10	1	
GO:0006810	transport	4550	324	60	4.63E-10	1	
GO:0043085	positive regulation of catalytic activity	1257	123	17	4.63E-10	1	

GO:0065007	biological regulation	10244	616	138	4.63E-10	1
GO:0051234	establishment of localization	4659	330	64	4.65E-10	1
GO:0071310	cellular response to organic substance	2268	189	35	5.77E-10	1
GO:0002764	immune response-regulating signaling pathway	455	62	2	6.66E-10	1
GO:0035556	intracellular signal transduction	2501	202	29	1.41E-09	1
GO:0009605	response to external stimulus	1977	169	23	1.55E-09	1
GO:0048522	positive regulation of cellular process	4633	326	60	1.63E-09	1
GO:0050790	regulation of catalytic activity	2027	171	24	3.27E-09	1
GO:0010033	response to organic substance	2769	216	37	5.32E-09	1
GO:0051179	localization	5807	386	89	1.23E-08	1
GO:0050817	coagulation	299	45	7	2.98E-08	1
GO:0042221	response to chemical	3714	268	52	3.46E-08	1
GO:0007599	hemostasis	301	45	7	3.61E-08	1
GO:0006954	inflammatory response	616	71	5	3.81E-08	1
GO:0071900	regulation of protein serine/threonine kinase activity	453	58	3	3.85E-08	1
GO:0043549	regulation of kinase activity	765	82	4	4.63E-08	1
GO:0050789	regulation of biological process	9629	577	124	5.25E-08	1
GO:1902531	regulation of intracellular signal transduction	1644	142	15	5.25E-08	1
GO:0007596	blood coagulation	296	44	7	6.48E-08	1
GO:1990266	neutrophil migration	80	21	3	1.44E-07	1
GO:0002429	immune response-activating cell surface receptor signaling pathway	282	42	1	1.54E-07	1
GO:0033674	positive regulation of kinase activity	508	61	2	1.54E-07	1
GO:0031347	regulation of defense response	625	70	2	1.63E-07	1
GO:0007166	cell surface receptor signaling pathway	2548	196	44	1.91E-07	0.908411304
GO:0045859	regulation of protein kinase activity	696	75	4	2.14E-07	1
GO:0097530	granulocyte migration	99	23	3	2.69E-07	1
GO:0034097	response to cytokine	979	95	13	2.71E-07	1
GO:0002768	immune response-regulating cell surface receptor signaling pathway	382	44	2	2.87E-07	1
GO:0045088	regulation of innate immune response	335	46	0	3.13E-07	1
GO:0071345	cellular response to cytokine stimulus	900	89	11	3.74E-07	1
GO:0097529	myeloid leukocyte migration	156	29	4	4.42E-07	1
GO:0065009	regulation of molecular function	2746	206	37	4.67E-07	1
GO:0051338	regulation of transferase activity	863	86	5	4.88E-07	1
GO:0043405	regulation of MAP kinase activity	306	43	2	5.15E-07	1
GO:0071902	positive regulation of protein serine/threonine kinase activity	396	42	1	5.88E-07	1
GO:0009607	response to biotic stimulus	775	79	4	8.36E-07	1
GO:0032879	regulation of localization	2382	183	32	8.36E-07	1
GO:0045860	positive regulation of protein kinase activity	469	56	2	8.36E-07	1
GO:0009967	positive regulation of signal transduction	1414	122	17	1.12E-06	1
GO:0051347	positive regulation of transferase activity	578	64	3	1.22E-06	1
GO:0019221	cytokine-mediated signaling pathway	619	67	9	1.30E-06	1
GO:0031349	positive regulation of defense response	379	48	1	1.72E-06	1

GO:1902533	positive regulation of intracellular signal transduction	934	89	8	1.99E-06	1
GO:0009966	regulation of signal transduction	2771	204	36	2.46E-06	1
GO:0071621	granulocyte chemotaxis	86	20	2	2.75E-06	1
GO:0030593	neutrophil chemotaxis	70	18	2	2.76E-06	1
GO:0023056	positive regulation of signaling	1565	130	20	3.03E-06	1
GO:1901700	response to oxygen-containing compound	1398	119	24	3.59E-06	1
GO:0038093	Fc receptor signaling pathway	124	24	0	4.29E-06	1
GO:0010942	positive regulation of cell death	615	65	5	5.18E-06	1
GO:0023051	regulation of signaling	3129	223	39	5.75E-06	1
GO:0010647	positive regulation of cell communication	1558	128	20	7.38E-06	1
GO:0051707	response to other organism	747	74	4	7.77E-06	1
GO:0043207	response to external biotic stimulus	748	74	4	8.13E-06	1
GO:0008219	cell death	1947	152	18	8.16E-06	1
GO:0043068	positive regulation of programmed cell death	569	61	5	8.16E-06	1
GO:0002218	activation of innate immune response	233	34	0	8.37E-06	1
GO:0051247	positive regulation of protein metabolic process	1469	122	16	8.56E-06	1
GO:0010646	regulation of cell communication	3097	220	39	9.07E-06	1
GO:0042110	T cell activation	414	49	4	9.07E-06	1
GO:0040017	positive regulation of locomotion	481	54	8	1.08E-05	1
GO:0043406	positive regulation of MAP kinase activity	237	34	1	1.23E-05	1
GO:0009987	cellular process	13404	738	179	1.26E-05	1
GO:0045089	positive regulation of innate immune response	284	38	0	1.31E-05	1
GO:0043065	positive regulation of apoptotic process	565	60	5	1.38E-05	1
GO:0040012	regulation of locomotion	848	80	13	1.54E-05	1
GO:0012501	programmed cell death	1824	143	17	1.62E-05	1
GO:0030335	positive regulation of cell migration	437	50	8	1.81E-05	1
GO:0001816	cytokine production	653	66	4	1.87E-05	1
GO:0006915	apoptotic process	1721	136	15	2.24E-05	1
GO:0000186	activation of MAPKK activity	49	14	0	2.35E-05	1
GO:1901698	response to nitrogen compound	931	85	12	2.35E-05	1
GO:0033554	cellular response to stress	1775	139	14	2.63E-05	1
GO:0032147	activation of protein kinase activity	294	38	1	3.02E-05	1
GO:0050878	regulation of body fluid levels	433	49	8	3.25E-05	1
GO:0051246	regulation of protein metabolic process	2429	178	24	3.25E-05	1
GO:0002758	innate immune response-activating signal transduction	214	31	0	3.39E-05	1
GO:0044248	cellular catabolic process	2063	156	13	3.41E-05	1
GO:0051272	positive regulation of cellular component movement	462	51	8	3.82E-05	1
GO:0051270	regulation of cellular component movement	855	79	14	3.97E-05	1
GO:0030595	leukocyte chemotaxis	172	27	4	4.04E-05	1
GO:2000147	positive regulation of cell motility	450	50	8	4.04E-05	1
GO:0051092	positive regulation of NF-kappaB transcription factor activity	24	24	0	4.12E-05	1
GO:0016477	cell migration	1236	104	27	4.44E-05	0.374640189

GO:0042327	positive regulation of phosphorylation	892	81	7	5.46E-05	1	
GO:0050900	leukocyte migration	365	43	11	5.85E-05	0.391246	998
GO:0046649	lymphocyte activation	592	60	7	5.94E-05	1	
GO:0038094	Fc-gamma receptor signaling pathway	78	17	0	6.74E-05	1	
GO:0040011	locomotion	1566	124	33	7.17E-05	0.318994	972
GO:0032268	regulation of cellular protein metabolic process	2258	166	19	7.19E-05	1	
GO:0030168	platelet activation	146	24	3	7.58E-05	1	
GO:0009056	catabolic process	2322	169	21	0.000102197	1	
GO:0010562	positive regulation of phosphorus metabolic process	852	84	7	0.000102197	1	
GO:0045937	positive regulation of phosphate metabolic process	952	84	7	0.000102197	1	
GO:1901701	cellular response to oxygen-containing compound	984	86	22	0.000109264	0.469765	814
GO:0030334	regulation of cell migration	733	69	12	0.00011376	1	
GO:1901699	cellular response to nitrogen compound	563	57	12	0.000115015	1	
GO:0043408	regulation of MAPK cascade	648	63	6	0.000117993	1	
GO:0010243	response to organonitrogen compound	868	78	12	0.000126448	1	
GO:2000145	regulation of cell motility	780	72	13	0.000129242	1	
GO:0048870	cell motility	1366	110	28	0.000148918	0.546976	826
GO:0051674	localization of cell	1366	110	28	0.000148918	0.546976	826
GO:0071417	cellular response to organonitrogen compound	513	53	12	0.000148943	0.802988	607
GO:0051345	positive regulation of hydrolase activity	684	65	12	0.000166794	1	
GO:0098657	import into cell	757	70	16	0.000169245	0.853144	703
GO:0032880	regulation of protein localization	891	79	5	0.000173297	1	
GO:0032101	regulation of response to external stimulus	686	65	4	0.00018111	1	
GO:0001934	positive regulation of protein phosphorylation	849	76	7	0.00019432	1	
GO:0042325	regulation of phosphorylation	1329	107	11	0.000207752	1	
GO:0032270	positive regulation of cellular protein metabolic process	2278	110	11	0.000215866	1	
GO:1901652	response to peptide	426	46	7	0.000230098	1	
GO:0051049	regulation of transport	1607	124	21	0.000238452	1	
GO:0061024	membrane organization	736	68	8	0.000239587	1	
GO:0001932	regulation of protein phosphorylation	1225	100	11	0.000255758	1	
GO:0007159	leukocyte cell-cell adhesion	299	36	5	0.000269107	1	
GO:0009306	protein secretion	483	50	4	0.000269107	1	
GO:0002687	positive regulation of leukocyte migration	106	19	2	0.000274565	1	
GO:0006468	protein phosphorylation	1678	128	21	0.000274565	1	
GO:0031098	stress-activated protein kinase signaling cascade	287	35	0	0.000274565	1	
GO:0071216	cellular response to biotic stimulus	203	28	0	0.000274689	1	
GO:0065008	regulation of biological quality	3483	233	50	0.000278675	1	
GO:0033036	macromolecule localization	2816	195	28	0.000293603	1	
GO:0043410	positive regulation of MAPK cascade	473	49	4	0.000320863	1	
GO:0007155	cell adhesion	1250	101	32	0.000336573	0.040286	053
GO:0019220	regulation of phosphate metabolic process	1507	117	13	0.000343159	1	
GO:0031667	response to nutrient levels	421	45	3	0.000362009	1	

GO:0051174	regulation of phosphorus metabolic process	1509	117	13	0.000362009	1
GO:0006909	phagocytosis	230	30	2	0.000365939	1
GO:0002431	Fc receptor mediated stimulatory signaling pathway	80	16	0	0.000387008	1
GO:0022610	biological adhesion	1257	101	32	0.000417147	0.043138
GO:0050663	cytokine secretion	185	26	1	0.000425866	1
GO:0023014	signal transduction by protein phosphorylation	797	71	10	0.000463812	1
GO:0015031	protein transport	1831	136	17	0.000473998	1
GO:0071496	cellular response to external stimulus	308	36	4	0.000486676	1
GO:0060326	cell chemotaxis	234	30	5	0.0005037	1
GO:0045184	establishment of protein localization	1934	142	19	0.000506381	1
GO:0030155	regulation of cell adhesion	609	58	8	0.000509038	1
GO:0045932	negative regulation of muscle contraction	20	8	0	0.000531728	1
GO:0071702	organic substance transport	2515	176	27	0.000535431	1
GO:0006914	autophagy	443	46	0	0.000565442	1
GO:0061919	process utilizing autophagic mechanism	443	46	0	0.000565442	1
GO:0051336	regulation of hydrolase activity	1127	92	16	0.000599955	1
GO:0006897	endocytosis	645	60	15	0.000695764	0.678522254
GO:0071260	cellular response to mechanical stimulus	75	15	2	0.000730688	1
GO:0042886	amide transport	1885	138	19	0.000791641	1
GO:0032612	interleukin-1 production	76	15	0	0.000859296	1
GO:0006796	phosphate-containing compound metabolic process	2886	196	26	0.000875096	1
GO:0032103	positive regulation of response to external stimulus	254	31	3	0.000898772	1
GO:0002790	peptide secretion	508	50	6	0.000925557	1
GO:0031401	positive regulation of protein modification process	1046	86	7	0.000925557	1
GO:0010952	positive regulation of peptidase activity	171	24	1	0.000939318	1
GO:0015833	peptide transport	1859	136	19	0.000941858	1
GO:0009991	response to extracellular stimulus	453	46	3	0.000954405	1
GO:1901653	cellular response to peptide	319	36	5	0.000970827	1
GO:0034134	toll-like receptor 2 signaling pathway	16	7	0	0.001002353	1
GO:1901564	organonitrogen compound metabolic process	6040	367	60	0.00113986	1
GO:0009894	regulation of catabolic process	823	71	4	0.001233752	1
GO:0000165	MAPK cascade	779	68	10	0.001302406	1
GO:0002237	response to molecule of bacterial origin	299	34	2	0.001448175	1
GO:0010950	positive regulation of endopeptidase activity	153	22	1	0.001467807	1
GO:0016310	phosphorylation	2046	146	21	0.001473433	1
GO:0006793	phosphorus metabolic process	2913	196	26	0.001490737	1
GO:0009617	response to bacterium	490	48	3	0.001514023	1
GO:0051046	regulation of secretion	679	61	5	0.001556577	1
GO:0043067	regulation of programmed cell death	1367	105	13	0.001586821	1
GO:2000116	regulation of cysteine-type endopeptidase activity	213	27	1	0.001630423	1
GO:0030162	regulation of proteolysis	651	59	3	0.001650328	1
GO:0051091	positive regulation of DNA-binding transcription factor activity	228	29	0	0.001674787	1

GO:0042981	regulation of apoptotic process	1354	104	13	0.001724948	1
GO:0002286	T cell activation involved in immune response	81	15	1	0.001731296	1
GO:0070498	interleukin-1-mediated signaling pathway	54	12	0	0.001861726	1
GO:0002685	regulation of leukocyte migration	156	22	2	0.001893805	1
GO:0080135	regulation of cellular response to stress	625	57	3	0.001893805	1
GO:0008150	biological_process	14638	780	198	0.001926983	1
GO:0051704	multi-organism process	2076	147	14	0.001926983	1
GO:0031399	regulation of protein modification process	1590	118	12	0.002015929	1
GO:0010941	regulation of cell death	1477	111	13	0.00215311	1
GO:1903037	regulation of leukocyte cell-cell adhesion	267	31	3	0.00215311	1
GO:2001056	positive regulation of cysteine-type endopeptidase activity	125	20	1	0.002158532	1
GO:0050867	positive regulation of cell activation	294	33	4	0.002322146	1
GO:0008104	protein localization	2517	172	25	0.002381633	1
GO:0050701	interleukin-1 secretion	47	11	0	0.002404685	1
GO:0002688	regulation of leukocyte chemotaxis	94	16	2	0.002570483	1
GO:0002223	stimulatory C-type lectin receptor signaling pathway	56	12	0	0.00259536	1
GO:0032611	interleukin-1 beta production	65	13	0	0.00259536	1
GO:0001817	regulation of cytokine production	589	54	4	0.002597853	1
GO:0002694	regulation of leukocyte activation	446	44	4	0.002664683	1
GO:0002696	positive regulation of leukocyte activation	284	32	4	0.002776889	1
GO:0002433	immune response-regulating cell surface receptor signaling pathway involved in phagocytosis	51	14	0	0.002791965	1
GO:0038096	Fc-gamma receptor signaling pathway involved in phagocytosis	7	0	0	0.002791965	1
GO:0051770	positive regulation of nitric-oxide synthase biosynthetic process	6	0	0	0.002791965	1
GO:0050863	regulation of T cell activation	285	32	3	0.002907125	1
GO:0098542	defense response to other organism	365	38	0	0.002907125	1
GO:0048519	negative regulation of biological process	4605	287	58	0.003060718	1
GO:0010604	positive regulation of macromolecule metabolic process	2003	193	37	0.003155111	1
GO:0045862	positive regulation of proteolysis	326	35	2	0.003155111	1
GO:0051050	positive regulation of transport	851	71	13	0.003155111	1
GO:0050851	antigen receptor-mediated signaling pathway	174	23	1	0.003171354	1
GO:0031329	regulation of cellular catabolic process	715	62	0	0.003331165	1
GO:0050865	regulation of cell activation	480	46	4	0.00340888	1
GO:0052548	regulation of endopeptidase activity	341	36	2	0.003414219	1
GO:0051223	regulation of protein transport	612	55	3	0.00355489	1
GO:0001819	positive regulation of cytokine production	383	39	4	0.003612705	1
GO:0051222	positive regulation of protein transport	370	38	2	0.003761834	1
GO:0002220	innate immune response activating cell surface receptor signaling pathway	59	12	0	0.004134873	1
GO:0038095	Fc-epsilon receptor signaling pathway	59	12	0	0.004134873	1
GO:1903530	regulation of secretion by cell	631	56	4	0.004194911	1
GO:0072672	neutrophil extravasation	9	5	1	0.004323416	1
GO:0051240	positive regulation of multicellular organismal process	666	111	22	0.004358097	1
GO:0050702	interleukin-1 beta secretion	42	10	0	0.004383898	1

GO:0002697	regulation of immune effector process	348	36	3	0.00505513	1
GO:0002221	pattern recognition receptor signaling pathway	168	22	0	0.005171898	1
GO:0009893	positive regulation of metabolic process	3126	204	38	0.005271532	1
GO:0051239	regulation of multicellular organismal process	2648	177	41	0.005403955	1
GO:0002755	MyD88-dependent toll-like receptor signaling pathway	35	9	0	0.005460604	1
GO:1904951	positive regulation of establishment of protein localization	405	40	3	0.005460604	1
GO:0002250	adaptive immune response	350	36	4	0.005571526	1
GO:0016050	vesicle organization	296	32	1	0.005571526	1
GO:0045785	positive regulation of cell adhesion	364	37	4	0.005594484	1
GO:0052547	regulation of peptidase activity	364	37	2	0.005594484	1
GO:0070201	regulation of establishment of protein localization	654	57	4	0.005626218	1
GO:0006928	movement of cell or subcellular component	1787	127	41	0.005781787	0.054108794
GO:0002367	cytokine production involved in immune response	91	15	1	0.005828657	1
GO:0071219	cellular response to molecule of bacterial origin	182	23	0	0.005892329	1
GO:0061041	regulation of wound healing	113	17	0	0.006255149	1
GO:0032757	positive regulation of interleukin-8 production	44	10	0	0.006351224	1
GO:0071675	regulation of mononuclear cell migration	36	9	1	0.006679936	1
GO:0051403	stress-activated MAPK cascade	260	29	0	0.006850318	1
GO:0031323	regulation of cellular metabolic process	5315	322	54	0.006855097	1
GO:0050707	regulation of cytokine secretion	160	21	1	0.006933616	1
GO:0032496	response to lipopolysaccharide	287	31	2	0.007057627	1
GO:0071705	nitrogen compound transport	2158	148	22	0.007275744	1
GO:0010256	endomembrane system organization	384	38	3	0.007555502	1
GO:0001776	leukocyte homeostasis	83	14	3	0.007636898	1
GO:0002690	positive regulation of leukocyte chemotaxis	73	13	2	0.007690198	1
GO:0071674	mononuclear cell migration	54	11	1	0.007715492	1
GO:0098609	cell-cell adhesion	724	61	10	0.007721864	1
GO:0000187	activation of MAPK activity	138	19	0	0.007734155	1
GO:1903523	negative regulation of blood circulation	29	8	0	0.007734155	1
GO:0050793	regulation of developmental process	2215	151	40	0.007916914	0.781661155
GO:0071622	regulation of granulocyte chemotaxis	37	9	0	0.008028146	1
GO:0090087	regulation of peptide transport	635	55	4	0.008354822	1
GO:0051130	positive regulation of cellular component organization	1623	86	17	0.00860929	1
GO:0031325	positive regulation of cellular metabolic process	2873	188	31	0.00899248	1
GO:0001525	angiogenesis	445	42	6	0.0090508	1
GO:0043087	regulation of GTPase activity	431	41	10	0.009152495	0.989075954
GO:0071347	cellular response to interleukin-1	106	16	0	0.009152495	1
GO:1903827	regulation of cellular protein localization	489	45	3	0.009195558	1
GO:0016236	macroautophagy	266	29	0	0.00959439	1
GO:1902622	regulation of neutrophil migration	30	8	0	0.009698552	1
GO:0051249	regulation of lymphocyte activation	376	37	4	0.009906385	1
GO:0050715	positive regulation of cytokine secretion	108	16	1	0.01128157	1

GO:0009743	response to carbohydrate	204	24	3	0.011633007	1
GO:0070302	regulation of stress-activated protein kinase signaling cascade	247	25	0	0.011808339	1
GO:0048013	ephrin receptor signaling pathway	77	13	1	0.012690739	1
GO:0007169	transmembrane receptor protein tyrosine kinase signaling pathway	614	59	11	0.012718363	1
GO:0006464	cellular protein modification process	3634	229	39	0.012821559	1
GO:0036211	protein modification process	3634	229	39	0.012821559	1
GO:0043281	regulation of cysteine-type endopeptidase activity involved in apoptotic process	193	27	0	0.012949805	1
GO:0051767	nitric-oxide synthase biosynthetic process	17	6	0	0.013035488	1
GO:0051769	regulation of nitric-oxide synthase biosynthetic process	6	0	0	0.013035488	1
GO:0070340	detection of bacterial lipopeptide	3	3	0	0.01315179	1
GO:0002460	adaptive immune response based on somatic recombination of immune receptors built from 427636 immunoglobulin superfamily domains	253	26	4	0.014276364	1
GO:0002576	platelet degranulation	122	17	1	0.014503148	1
GO:0050727	regulation of inflammatory response	314	32	2	0.014538693	1
GO:0002224	toll-like receptor signaling pathway	123	17	0	0.01594757	1
GO:0043123	positive regulation of I-kappaB kinase/NF-kappaB signaling	21	1	1	0.016024765	1
GO:0045597	positive regulation of cell differentiation	858	68	15	0.017105336	1
GO:0043547	positive regulation of GTPase activity	359	35	9	0.017159123	0.870477156
GO:1903034	regulation of response to wounding	136	18	0	0.017874522	1
GO:0051128	regulation of cellular component organization	2275	152	32	0.017920515	1
GO:0030099	myeloid cell differentiation	360	35	5	0.017939107	1
GO:0051173	positive regulation of nitrogen compound metabolic process	177	180	34	0.01800847	1
GO:0051094	positive regulation of developmental process	1201	89	21	0.018331106	1
GO:0032677	regulation of interleukin-8 production	60	11	0	0.018411813	1
GO:0070997	neuron death	305	31	1	0.018600627	1
GO:0098543	detection of other organism	12	5	0	0.018875179	1
GO:0051048	negative regulation of secretion	186	22	2	0.01891199	1
GO:0009057	macromolecule catabolic process	1269	93	10	0.018999165	1
GO:0045916	negative regulation of complement activation	7	4	0	0.01930961	1
GO:0051056	regulation of small GTPase mediated signal transduction	306	31	6	0.01930961	1
GO:0071476	cellular hypotonic response	7	4	0	0.01930961	1
GO:2000258	negative regulation of protein activation cascade	7	4	0	0.01930961	1
GO:0031663	lipopolysaccharide-mediated signaling pathway	51	10	0	0.019532324	1
GO:0045123	cellular extravasation	51	10	3	0.019532324	0.669150896
GO:0044267	cellular protein metabolic process	4551	277	47	0.019796909	1
GO:1901575	organic substance catabolic process	1934	132	16	0.020007773	1
GO:0006937	regulation of muscle contraction	138	18	1	0.020374992	1
GO:0043434	response to peptide hormone	364	35	6	0.021070827	1
GO:0050921	positive regulation of chemotaxis	115	16	2	0.02118087	1
GO:0048523	negative regulation of cellular process	4113	253	52	0.021899591	1
GO:0051051	negative regulation of transport	408	38	6	0.021899591	1
GO:0010661	positive regulation of muscle cell apoptotic process	36	7	1	0.02192505	1
GO:0019538	protein metabolic process	5067	304	56	0.022521548	1

GO:0032872	regulation of stress-activated MAPK cascade	215	24	0	0.022830475	1
GO:0035743	CD4-positive, alpha-beta T cell cytokine production	19	6	0	0.023474679	1
GO:0033673	negative regulation of kinase activity	216	24	2	0.024339447	1
GO:0009896	positive regulation of catabolic process	382	36	4	0.024678993	1
GO:0080090	regulation of primary metabolic process	5208	311	55	0.025290195	1
GO:0002718	regulation of cytokine production involved in immune response	12	1	1	0.025671832	1
GO:0070482	response to oxygen levels	312	31	3	0.025671832	1
GO:0042594	response to starvation	166	20	0	0.026248102	1
GO:0043086	negative regulation of catalytic activity	669	55	6	0.026248102	1
GO:0051348	negative regulation of transferase activity	244	26	2	0.026248102	1
GO:0060759	regulation of response to cytokine stimulus	154	19	0	0.027030672	1
GO:0050714	positive regulation of protein secretion	218	24	1	0.027033414	1
GO:0090022	regulation of neutrophil chemotaxis	27	7	0	0.027033414	1
GO:1904646	cellular response to amyloid-beta	27	7	1	0.027033414	1
GO:0008283	cell proliferation	1761	121	28	0.027213333	1
GO:0022407	regulation of cell-cell adhesion	356	34	4	0.027337401	1
GO:0006508	proteolysis	1576	110	15	0.029222209	1
GO:0072593	reactive oxygen species metabolic process	246	26	3	0.029222209	1
GO:0043280	positive regulation of cysteine-type endopeptidase activity involved in apoptotic process	16	1	0	0.029336158	1
GO:0002526	acute inflammatory response	131	17	0	0.029626108	1
GO:0032868	response to insulin	233	25	4	0.029731739	1
GO:0050708	regulation of protein secretion	387	36	2	0.030095053	1
GO:0044247	cellular polysaccharide catabolic process	20	6	0	0.0301116	1
GO:0090025	regulation of monocyte chemotaxis	20	6	1	0.0301116	1
GO:0007160	cell-matrix adhesion	207	23	5	0.03037299	1
GO:0006935	chemotaxis	537	46	11	0.031747962	1
GO:0051251	positive regulation of lymphocyte activation	248	26	4	0.032193807	1
GO:0035744	T-helper 1 cell cytokine production	8	4	0	0.032836459	1
GO:0007264	small GTPase mediated signal transduction	523	45	10	0.032933819	1
GO:0019222	regulation of metabolic process	5763	339	59	0.032947746	1
GO:0042330	taxis	539	46	11	0.033892587	1
GO:0050852	T cell receptor signaling pathway	133	17	1	0.034161479	1
GO:0051090	regulation of DNA-binding transcription factor activity	37	35	2	0.036224025	1
GO:0050920	regulation of chemotaxis	184	21	2	0.036574118	1
GO:0009267	cellular response to starvation	134	17	0	0.0368303	1
GO:0032637	interleukin-8 production	66	11	0	0.0368303	1
GO:0061025	membrane fusion	134	17	0	0.0368303	1
GO:1903901	negative regulation of viral life cycle	66	11	0	0.0368303	1
GO:0090026	positive regulation of monocyte chemotaxis	14	5	1	0.037038122	1
GO:0006469	negative regulation of protein kinase activity	198	22	2	0.03826875	1
GO:0006979	response to oxidative stress	408	37	3	0.03826875	1
GO:0036473	cell death in response to oxidative stress	77	12	0	0.03826875	1

GO:0048534	hematopoietic or lymphoid organ development	777	61	11	0.03826875	1
GO:0050818	regulation of coagulation	77	12	0	0.03826875	1
GO:1903039	positive regulation of leukocyte cell-cell adhesion	198	22	3	0.03826875	1
GO:0001782	B cell homeostasis	29	7	1	0.039601018	1
GO:0001999	renal response to blood flow involved in circulatory renin-angiotensin regulation of systemic blood pressure	4	3	0	0.039601018	1
GO:0002001	renin secretion into blood stream	4	3	0	0.039601018	1
GO:0042494	detection of bacterial lipoprotein	4	3	0	0.039601018	1
GO:1903223	positive regulation of oxidative stress-induced neuron death	3	0	0	0.039601018	1
GO:0002720	positive regulation of cytokine production involved in immune response	47	9	0	0.040286053	1
GO:0070265	necrotic cell death	47	9	0	0.040286053	1
GO:0030888	regulation of B cell proliferation	57	10	1	0.041271788	1
GO:0032729	positive regulation of interferon-gamma production	57	10	1	0.041271788	1
GO:0070527	platelet aggregation	57	10	0	0.041271788	1
GO:0002822	regulation of adaptive immune response based on clonal selection of immune receptors from immunoglobulin superfamily	46	15	0	0.041344115	1
GO:0097300	programmed necrotic cell death	38	8	0	0.041379424	1
GO:2000377	regulation of reactive oxygen species metabolic process	16	19	0	0.041379424	1
GO:0006629	lipid metabolic process	1274	91	10	0.041845478	1
GO:0043112	receptor metabolic process	174	20	5	0.041928718	1
GO:0005976	polysaccharide metabolic process	101	14	1	0.043569205	1
GO:0043122	regulation of I-kappaB kinase/NF-kappaB signaling	214	23	1	0.043569205	1
GO:0022603	regulation of anatomical structure morphogenesis	912	69	18	0.043665082	1
GO:0043412	macromolecule modification	3819	234	41	0.043813518	1
GO:0071453	cellular response to oxygen levels	162	19	1	0.043846908	1
GO:0000271	polysaccharide biosynthetic process	68	11	0	0.044145176	1
GO:0050870	positive regulation of T cell activation	188	21	3	0.044145176	1
GO:0071222	cellular response to lipopolysaccharide	175	20	0	0.044145176	1
GO:1901214	regulation of neuron death	269	27	1	0.044145176	1
GO:0070555	response to interleukin-1	125	16	1	0.044185913	1
GO:0032269	negative regulation of cellular protein metabolic process	828	68	8	0.045826564	1
GO:1904645	response to amyloid-beta	30	7	1	0.045966802	1
GO:0000272	polysaccharide catabolic process	22	6	0	0.046155493	1
GO:0090257	regulation of muscle system process	202	22	2	0.046184075	1
GO:0006971	hypotonic response	9	4	0	0.049853168	1
GO:0002673	regulation of acute inflammatory response	80	12	0	0.049885523	1
GO:0051047	positive regulation of secretion	357	33	3	0.049885523	1
GO:0016043	cellular component organization	5721	325	104	0.246813039	0.031675655
GO:0006607	NLS-bearing protein import into nucleus	27	3	4	1	0.038603188
GO:0030198	extracellular matrix organization	321	15	18	1	0.000116024
GO:0030199	collagen fibril organization	47	2	7	1	0.000569572
GO:0043062	extracellular structure organization	368	18	18	1	0.000615349
GO:0060351	cartilage development involved in endochondral bone morphogenesis	4	5	1	1	0.02192505
GO:0061138	morphogenesis of a branching epithelium	166	9	9	1	0.039793054

GO:0061448	connective tissue development	233	6	13	1	0.002884	637
GO:0070208	protein heterotrimerization	12	0	3	1	0.040528	723
GO:0071229	cellular response to acid chemical	195	10	10	1	0.032559	128
GO:0071230	cellular response to amino acid stimulus	65	5	6	1	0.024461	895

Note: The IDs are according to GeneOntology, available on the website: geneontology.org. “nGene” refers to the number of genes in the pathway. “sig_up_ngenes” and “sig_down_ngenes” represent the number of genes that were upregulated and the number of genes that were downregulated, respectively. Throughout the disclosure, “FDR” refers to false discovery rate, and an FDR of less than 0.05 indicates the change or difference in expression is significant. For example, a FDR.up of less than 0.05 indicates the upregulation of the gene expression is significant.

TABLE 5
Genes Common to Synovial Sublining Fibroblasts and AC3

cluster	Geneset	ensembl	symbol	auc	pct_nonzero	pct_nonzero_other
SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG00000187955	COL14A1	0.8869058	0.98347107	0.30535427
SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG00000164692	COL1A2	0.84468179	1	0.53280998
SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG00000168542	COL3A1	0.82353841	1	0.53301127
SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG00000130635	COL5A1	0.76918996	0.80991736	0.26348631
SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG00000105664	COMP	0.72267741	0.5268595	0.09178744
SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG00000133083	DCLK1	0.78673115	0.70041322	0.16807568
SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG00000146648	EGFR	0.76375622	0.72933884	0.23007246
SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG00000120738	EGR1	0.75381699	0.95041322	0.6507649
SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG00000164694	FND1C1	0.7526103	0.63842975	0.15116747
SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG00000131386	GALNT15	0.7329481	0.59297521	0.14351852
SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG00000168079	SCARA5	0.74916074	0.78512397	0.28965378
SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG00000137573	SULF1	0.73367922	0.67561983	0.23389694
SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG00000091656	ZFXH4	0.77838039	0.71487603	0.2071256
SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG00000187955	COL14A1	0.91760718	0.99165508	0.27044158
SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG00000084636	COL16A1	0.87323477	0.83588317	0.10585252
SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG00000164692	COL1A2	0.92139483	1	0.50961335
SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG00000168542	COL3A1	0.93074592	1	0.50982464
SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG00000134871	COL4A2	0.84125266	0.86648122	0.18761885
SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG00000130635	COL5A1	0.88489277	0.95132128	0.21487429
SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG00000133083	DCLK1	0.83131283	0.79972184	0.12655821
SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG00000146648	EGFR	0.80327353	0.82058414	0.19142193
SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG00000120738	EGR1	0.80507545	0.9930459	0.62941052
SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG00000130508	PXDN	0.84330642	0.83171071	0.16670188
SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG00000166444	ST5	0.83349089	0.81641168	0.15867315

SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG00000187955	COL14A1	0.85231287	0.96929825	0.33920368
SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG00000164692	COL1A2	0.90670253	1	0.55570444
SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG00000168542	COL3A1	0.90184724	1	0.55589587
SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG00000130635	COL5A1	0.91728082	0.98245614	0.28273354
SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG00000105664	COMP	0.81905082	0.71929825	0.10470904
SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG00000164694	FNDCC1	0.8072182	0.76315789	0.16960184
SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG00000131386	GALNT15	0.81963055	0.76754386	0.15792496
SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG00000164294	GPX8	0.80951068	0.8245614	0.22396631
SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG00000167779	IGFBP6	0.83772643	0.78947368	0.16807044
SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG00000130508	PXDN	0.83692715	0.88157895	0.2270291
SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG00000168079	SCARA5	0.81990132	0.89035088	0.3093415
SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG00000137573	SULF1	0.83014503	0.86403509	0.24732006
SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG00000091656	ZFHX4	0.78976712	0.80263158	0.22817764

TABLE 6
Differential Gene Expression (Baseline versus Flare) of AC3 Genes Across Four RA Patients

ensembl	name	name_source	description	pl.logFC	pl.FDR	pl6.logFC	pl6.FDR	pl7.logFC	pl7.FDR	pl8.logFC	pl8.FDR
ENSG00000002746	HECW1	HGNC Symbol	"HECT, C2 and WW domain containing E3 ubiquitin protein ligase 1 [Source:HGNC Symbol;Acc:HGNC:22195]"	-0.324338854	0.572555903	-0.328868097	1	0.438047831	0.908516526	0.257695957	1
ENSG00000004948	CALCR	HGNC Symbol	calcitonin receptor [Source:HGNC Symbol;Acc:HGNC:1440]	-0.383180659	0.45624237	0.278685382	1	2.655446254	0.69984612	0.32802543	1
ENSG00000006071	ABCC8	HGNC Symbol	ATP binding cassette subfamily C member 8 [Source:HGNC Symbol;Acc:HGNC:59]	-0.439216452	0.462869018	-0.18343093	1	-0.15122162	0.972940456	0.06066206	1
ENSG00000006128	TAC1	HGNC Symbol	tachykinin precursor 1 [Source:HGNC Symbol;Acc:HGNC:11517]	-0.578738859	0.3633924977	-0.42309978	1	-0.824588596	0.86142478	0.616538787	1
ENSG00000006301	CX3CL1	HGNC Symbol	C-X3-C motif chemokine ligand 1 [Source:HGNC Symbol;Acc:HGNC:11517]	-0.471842178	0.456192882	0.394954483	1	0.142838807	0.984792321	-0.05867018	1

[illegible]

ENSG00000009431	ABCC9	HGNC Symbol	ATP binding cassette subfamily C member 9 [Source:HGNC Symbol;Acc:HGNC:60]	-0.755227404	0.20828346	-0.698467209	I	1.50464862	0.754933936	0.42710844	I
ENSG00000007086	EPHA8	HGNC Symbol	EPH receptor A8 [Source:HGNC Symbol;Acc:HGNC:3381]	-0.506558126	0.338005351	0.03742847	I	0.618749206	0.876857452	-0.18880882	I
ENSG00000007204	SLC6A15	HGNC Symbol	solute carrier family 6 member 15 [Source:HGNC Symbol;Acc:HGNC:18521]	-0.23655442	0.738227168	-0.0729174802	I	0.598327652	0.910193163	0.218044555	I
ENSG00000007589	PAX2	HGNC Symbol	paired box 2 [Source:HGNC Symbol;Acc:HGNC:8816]	-0.76916818	0.140101294	-0.139680455	I	0.666537779	0.859477376	0.023400033	I
ENSG00000007708	ACTL6B	HGNC Symbol	actin like 6B [Source:HGNC Symbol;Acc:HGNC:160]	-0.59184773	0.349654025	-0.291947443	I	2.05248954	0.734558921	-0.579843889	I
ENSG00000007752	ACTN2	HGNC Symbol	actinin alpha 2 [Source:HGNC Symbol;Acc:HGNC:164]	-0.423228174	0.461775497	-0.359543665	I	1.055057551	0.816563802	0.056205006	I
ENSG00000007825	ADCY2	HGNC Symbol	adenylate cyclase 2 [Source:HGNC Symbol;Acc:HGNC:233]	-0.350850534	0.538385503	-0.153182167	I	0.050300816	0.91823026	-0.160263243	I
ENSG00000007854	ADCYAP1R1	HGNC Symbol	ADCYAP receptor type 1 [Source:HGNC Symbol;Acc:HGNC:242]	-0.265394484	0.716597682	-0.548781669	I	0.436616106	0.918571237	0.282001957	I
ENSG00000007888	BPIFB2	HGNC Symbol	BPI fold containing family B member 2 [Source:HGNC Symbol;Acc:HGNC:16177]	-0.585629177	0.3553536504	-0.1863303102	I	0.6079104762	0.87446638	0.447655584	I
ENSG00000007912	CDH17	HGNC Symbol	cadherin 17 [Source:HGNC Symbol;Acc:HGNC:1756]	-0.61532191	0.2802103448	-0.174510118	I	1.290358643	0.794377353	-0.241687928	I
ENSG00000007984	RIMS1	HGNC Symbol	regulating synaptic membrane exocytosis 1 [Source:HGNC Symbol;Acc:HGNC:17282]	-0.387854778	0.537171359	-0.220371451	I	0.260822706	0.957654277	0.360367388	I
ENSG00000008248	CACNA1S	HGNC Symbol	calcium voltage-gated channel subunit alpha 1 S [Source:HGNC Symbol;Acc:HGNC:1397]	-0.562402388	0.274520413	-0.185575362	I	-0.292828267	0.939971429	0.087334946	I
ENSG00000008180	SLC3A1	HGNC Symbol	solute carrier family 13 member 1 [Source:HGNC Symbol;Acc:HGNC:10916]	-0.711148359	0.288055754	-0.365791689	I	0.415484856	0.928156195	-0.12942855	I
ENSG00000008275	PGR	HGNC Symbol	progesterone receptor [Source:HGNC Symbol;Acc:HGNC:8910]	-0.458377988	0.411610075	-0.172803447	I	1.97789178	0.699433544	-0.170595574	I
ENSG00000008436	COL6A1	HGNC Symbol	collagen type XVI alpha 1 chain [Source:HGNC Symbol;Acc:HGNC:2193]	-0.790050487	0.055725925	-0.166089061	I	0.586078349	0.853985444	-0.026623098	I

ENSG00000088340	FER1L4	HGNC Symbol	"fer-1 like family member 4, pseudogene [Source:HGNC Symbol;Acc:HGNC:45801]"	-0.667873	0.6530461	-0.078004571	1	0.34966341	0.90714926	-0.239607349	1
ENSG00000089116	LHX5	HGNC Symbol	LHX5 homeobox 5 [Source:HGNC Symbol;Acc:HGNC:14216]	-0.803770937	0.08286409	0.0653190166	1	0.185916509	0.972840456	0.479688913	1
ENSG00000089199	CH68	HGNC Symbol	chromogranin 8 [Source:HGNC Symbol;Acc:HGNC:19301]	-0.637146342	0.265673795	-0.320702315	1	0.377523248	0.9251665462	-0.124040006	1
ENSG00000089225	TBX5	HGNC Symbol	T-box 5 [Source:HGNC Symbol;Acc:HGNC:1604]	-0.5632296	0.348100747	-0.186556677	1	0.596701642	0.888550448	0.18780501	1
ENSG00000089128	LAMB4	HGNC Symbol	laminin subunit beta 4 [Source:HGNC Symbol;Acc:HGNC:8491]	-0.48817715	0.358139517	0.074990997	1	1.134840911	0.76609006	0.591653405	1
ENSG00000089137	SLC26A4	HGNC Symbol	solute carrier family 26 member 4 [Source:HGNC Symbol;Acc:HGNC:8818]	-0.554256156	0.194213389	-0.379548372	1	0.990597508	0.77684279	0.184013228	1
ENSG00000089166	ZFX4	HGNC Symbol	zinc finger homeobox 4 [Source:HGNC Symbol;Acc:HGNC:30935]	-0.447229174	0.37818144	0.068997085	1	0.573719306	0.878468837	-0.078950263	1
ENSG00000089587	TLL2	HGNC Symbol	tallitid like 2 [Source:HGNC Symbol;Acc:HGNC:11844]	-0.408359463	0.40882038	-0.26361606	1	1.33832395	0.748037903	0.081668368	1
ENSG000000895637	SORBS1	HGNC Symbol	sortin and SH3 domain containing 1 [Source:HGNC Symbol;Acc:HGNC:14655]	-0.32424573	0.084190364	-0.086812706	1	0.07210715	0.980464761	0.233872426	1
ENSG00000089625	CBAIP	HGNC Symbol	CACN beta subunit associated regulatory protein [Source:HGNC Symbol;Acc:HGNC:28617]	-0.61658751	0.305918323	0.924708632	1	4.5106100591	0.630714789	-0.556807911	1
ENSG00000089033	PRODH	HGNC Symbol	proline dehydrogenase 1 [Source:HGNC Symbol;Acc:HGNC:9453]	-0.72993766	0.14187223	0.392602047	1	0.416466508	0.92725613	0.024209613	1
ENSG00000089065	CARD10	HGNC Symbol	caspase recruitment domain family member 10 [Source:HGNC Symbol;Acc:HGNC:16422]	-0.704322375	0.16976862	-0.094316814	1	1.184451362	0.73778088	0.01459367	1
ENSG00000089078	PLA2G3	HGNC Symbol	phospholipase A2 group III [Source:HGNC Symbol;Acc:HGNC:17934]	-0.639102704	0.855160771	0.365462718	1	-0.809130599	0.880905808	0.273159772	1
ENSG00000089032	ACR	HGNC Symbol	acrossin [Source:HGNC Symbol;Acc:HGNC:126]	-0.595590525	0.367166088	-0.436425953	1	-0.816265078	0.843731885	0.905100759	1
ENSG00000089004	NNIL	HGNC Symbol	ninilin like [Source:HGNC Symbol;Acc:HGNC:29163]	-0.461697247	0.140557083	-0.139393033	1	0.111085893	0.958051922	0.007374673	1

ENSG0000010157	MYBL2	HGNC Symbol	MYB proto-oncogene like 2 [Source:HGNC Symbol;Acc:HGNC:7548]	-0.348282275	0.163757922	0.065559297	1	-0.316760009	0.853985444	-0.363998202	1
ENSG0000010157	COL20A1	HGNC Symbol	collagen type XX alpha 1 chain [Source:HGNC Symbol;Acc:HGNC:44670]	-0.61027042	0.16213506	0.172380322	1	1.371012438	0.716500857	0.256210081	1
ENSG0000010157	SLC52A3	HGNC Symbol	solute carrier family 52 member 3 [Source:HGNC Symbol;Acc:HGNC:46187]	-0.619177881	0.31981017	0.082884294	1	1.803271866	0.760816797	-0.182694116	1
ENSG0000010157	LAMA1	HGNC Symbol	laminin subunit alpha 1 [Source:HGNC Symbol;Acc:HGNC:5481]	-0.36627167	0.534719981	-0.203871279	1	0.400062263	0.922861341	0.572594666	1
ENSG0000010157	MID1	HGNC Symbol	midline 1 [Source:HGNC Symbol;Acc:HGNC:7095]	-0.530388862	0.160705439	0.208637567	1	-0.26871891	0.95125433	-0.036170874	1
ENSG0000010157	GABRE	HGNC Symbol	gamma-aminobutyric acid type A receptor epsilon subunit [Source:HGNC Symbol;Acc:HGNC:4085]	-0.67192592	0.162788559	-0.178338056	1	0.538971034	0.907527268	0.37680591	1
ENSG0000010157	PCDH1X	HGNC Symbol	protocadherin 11 X-linked [Source:HGNC Symbol;Acc:HGNC:9556]	-0.646927871	0.279252696	-0.633443604	1	0.867626644	0.84830486	0.353167708	1
ENSG0000010157	NALCN	HGNC Symbol	"sodium leak channel, non-selective" [Source:HGNC Symbol;Acc:HGNC:49082]	-0.587200069	0.349930069	-0.228025142	1	0.395274547	0.92775245	0.236838494	1
ENSG0000010157	CORO2B	HGNC Symbol	coronin 2B [Source:HGNC Symbol;Acc:HGNC:2256]	-0.36456888	0.361299257	0.479287145	1	0.161416617	0.954367943	0.394858842	1
ENSG0000010157	COD2F	HGNC Symbol	COD2F molecule [Source:HGNC Symbol;Acc:HGNC:19327]	-0.789492702	0.123893703	-0.043746659	1	2.881620875	0.655801493	0.339884759	1
ENSG0000010157	TBM5	HGNC Symbol	transglutaminase 5 [Source:HGNC Symbol;Acc:HGNC:4781]	-0.744478896	0.156127955	0.346808998	1	2.8575116	0.68458936	0.48659696	1
ENSG0000010157	EYAI	HGNC Symbol	EYA transcriptional coactivator and phosphatase 1 [Source:HGNC Symbol;Acc:HGNC:3519]	-0.54795524	0.332328891	-0.088328083	1	0.904381457	0.824540952	-0.145400561	1
ENSG0000010157	STMN2	HGNC Symbol	stathmin 2 [Source:HGNC Symbol;Acc:HGNC:10577]	-0.538149899	0.377735541	-0.070221779	1	2.139741005	0.743863355	0.679714458	1
ENSG0000010157	ANXA3	HGNC Symbol	annexin A3 [Source:HGNC Symbol;Acc:HGNC:536]	-0.296597524	0.666104371	-0.197734314	1	0.962189734	0.845260843	0.15906724	1
ENSG0000010157	NOVA2	HGNC Symbol	NOVA alternative splicing regulator 2	-0.906429895	0.09601667	-0.408162724	1	-0.24866658	0.967431863	-0.288237016	1

04967			[Source:HGNc Symbol+Acc:HGNc:7887]								
ENS6000001	APlP1	HGNC Symbol	amyloid beta precursor like protein I [Source:HGNc Symbol+Acc:HGNc:597]	-0.626897604	0.28026695	0.23991450	I	0.61629374	0.884845783	-0.023517235	I
05290											
ENS6000001	MTH4	HGNC Symbol	mynsin heavy chain 14 [Source:HGNc Symbol+Acc:HGNc:23212]	-0.39612836	0.489919147	-0.105194384	I	-0.286257636	0.93772207	0.02225136	I
05357											
ENS6000001	CPRX	HGNC Symbol	cane-rod homeobox [Source:HGNc Symbol+Acc:HGNc:2383]	-0.652077271	0.295697	-0.14080995	I	1.350403461	0.78293897	0.0282333	I
05392											
ENS6000001	THER	HGNC Symbol	tleg spermatal protein [Source:HGNc Symbol+Acc:HGNc:13706]	-0.56730048	0.345650275	-0.675865699	I	0.43424405	0.93376275	-0.01546944	I
05549											
ENS6000001	CACNG7	HGNC Symbol	calcium voltage-gated channel auxiliary subunit gamma 7 [Source:HGNc Symbol+Acc:HGNc:13626]	-0.825394915	0.173466676	-0.044046243	I	-0.078930301	0.997236528	-0.364251039	I
05605											
ENS6000001	COMP	HGNC Symbol	cartilage oligomeric matrix protein [Source:HGNc Symbol+Acc:HGNc:22277]	-0.799032187	0.027432398	0.234783584	I	0.07692469	0.97327079	-0.69703559	I
05664											
ENS6000001	COBL	HGNC Symbol	cardon-blue WH2 repeat protein [Source:HGNc Symbol+Acc:HGNc:22189]	-0.492882526	0.263675081	-0.596349691	I	1.300744474	0.79130915	0.097709392	I
06078											
ENS6000001	SFAMI	HGNC Symbol	sperm adhesion molecule I [Source:HGNc Symbol+Acc:HGNc:10277]	-0.294698557	0.697859656	-0.454358675	I	1.27878032	0.80083555	0.772079094	I
06304											
ENS6000001	GALNTL5	HGNC Symbol	polypeptide N-acetylglactosaminyltransferase like 5 [Source:HGNc Symbol+Acc:HGNc:21725]	-0.610689222	0.36620383	-0.06446058	I	1.570956079	0.742949496	0.243774247	I
06548											
ENS6000001	LHX2	HGNC Symbol	LIM homeobox 2 [Source:HGNc Symbol+Acc:HGNc:6594]	-0.630789543	0.278430947	0.429000081	I	-0.07510984	0.995803452	0.046916551	I
06689											
ENS6000001	SHSCL2	HGNC Symbol	"SV3 domain containing GRB2-like 2; endophilin A1 [Source:HGNc Symbol+Acc:HGNc:10830]"	-0.633805457	0.350665788	-0.72458486	I	2.464703425	0.69994444	-0.086266666	I
07295											
ENS6000001	TLXI	HGNC Symbol	T-cell leukemia homeobox 1 [Source:HGNc Symbol+Acc:HGNc:5056]	-0.773774408	0.156228514	0.137827715	I	0.544587691	0.9109798	0.23021497	I
07807											
ENS6000001	SORCS1	HGNC Symbol	sorlin related VPS10 domain-containing receptor 1 [Source:HGNc Symbol+Acc:HGNc:16697]	-0.57187073	0.324225606	-0.547468752	I	0.85269341	0.84343981	0.729297049	I
08018											
ENS6000001	FDMN	HGNC Symbol	farkhead box M [Source:HGNc Symbol+Acc:HGNc:12765]	-0.551457548	0.309062169	0.53940893	I	-0.082464276	0.93533942	-0.472244905	I

ENSG0000010786	PTPN5	HGNC Symbol	"protein tyrosine phosphatase, non-receptor type 5 [Source:HGNC Symbol;Acc:HGNC:9657]"	-0.733454811	0.20453963	0.191602596	1	0.06896957	0.99765152	-0.238995372	1
ENSG0000010887	DAO	HGNC Symbol	D-amino acid oxidase [Source:HGNC Symbol;Acc:HGNC:2671]	-0.596549208	0.394229719	0.13111108	1	-0.14449679	0.979953114	0.597447393	1
ENSG0000010975	SYT10	HGNC Symbol	synaptotagmin 10 [Source:HGNC Symbol;Acc:HGNC:19265]	-0.84217722	0.205970599	-0.291499943	1	-0.31391037	0.946363384	-0.965079899	1
ENSG0000011262	KCNJ1	HGNC Symbol	potassium voltage-gated channel subfamily A member 1 [Source:HGNC Symbol;Acc:HGNC:5218]	-0.775204639	0.165026428	-0.466826427	1	1.142878791	0.806478894	0.642772917	1
ENSG0000011799	COL2A1	HGNC Symbol	collagen type XI alpha 1 chain [Source:HGNC Symbol;Acc:HGNC:2188]	-0.950476274	0.050288873	-0.14919957	1	0.78218884	0.83203161	0.238185895	1
ENSG0000012166	CAP2	HGNC Symbol	cyclase associated actin cytoskeleton regulatory protein 2 [Source:HGNC Symbol;Acc:HGNC:21039]	-0.981736845	0.075743598	-0.024260504	1	0.733866999	0.86758445	0.324860966	1
ENSG0000012238	PROM1B	HGNC Symbol	PR/SET domain 13 [Source:HGNC Symbol;Acc:HGNC:19598]	-0.71815787	0.166103748	0.393170104	1	0.320967557	0.953891446	1.15377245	1
ENSG0000012337	SLC7A2	HGNC Symbol	solute carrier family 7 member 2 [Source:HGNC Symbol;Acc:HGNC:10930]	-0.701065633	0.275381582	-0.3332394833	1	0.738233667	0.881823991	0.694826788	1
ENSG0000012499	SLC22A2	HGNC Symbol	solute carrier family 22 member 2 [Source:HGNC Symbol;Acc:HGNC:10965]	-0.585273819	0.283511169	-0.305955711	1	0.0010100383	1	0.402578655	1
ENSG0000014019	AMOTL2	HGNC Symbol	angiomotin like 2 [Source:HGNC Symbol;Acc:HGNC:17812]	-0.638655464	0.208042203	0.19358618	1	0.925741653	0.7871604	-0.086135088	1
ENSG0000015041	KCNIP3	HGNC Symbol	potassium voltage-gated channel interacting protein 3 [Source:HGNC Symbol;Acc:HGNC:16523]	-0.390671023	0.447854968	-9.28E-06	1	-0.126754251	0.980723343	0.26502642	1
ENSG0000015155	OTOF	HGNC Symbol	otofelin [Source:HGNC Symbol;Acc:HGNC:8515]	-0.549744866	0.12106339	0.197616374	1	-0.204893956	0.934184441	-0.285355542	1
ENSG0000015648	MILPH	HGNC Symbol	melanophilin [Source:HGNC Symbol;Acc:HGNC:29543]	-0.344672976	0.1017643704	-0.639405576	1	-0.162231941	0.978305518	0.334016525	1
ENSG0000016176	TPSG1	HGNC Symbol	tryptase gamma 1 [Source:HGNC Symbol;Acc:HGNC:14134]	-0.696548839	0.245497404	0.767919399	1	-1.73416835	0.616129741	0.133366977	1
ENSG000001	PRAMEF1	HGNC Symbol	PRAME family member 1 [Source:HGNC]	-0.908385699	0.148992939	-0.28160328	1	2.477257959	0.726218814	0.947323758	1

6721	AMPO1	HGNC Symbol	SymbolAcc:HGNC:288401	-0.630797468	0.33507314	-0.29856016	1	-0.62451573	0.885080104	0.63256343	1
ENSG000000016748			adenosine monophosphate deaminase 1 [Source:HGNC SymbolAcc:HGNC:468]								
ENSG000000016833	NR5A2	HGNC Symbol	nuclear receptor subfamily 5 group A member 2 [Source:HGNC SymbolAcc:HGNC:7984]	-0.795732603	0.069795635	-0.31214377	1	-0.114723584	0.99823026	-0.21082797	1
ENSG000000017114	ADGR12	HGNC Symbol	adhesion G protein-coupled receptor 12 [Source:HGNC SymbolAcc:HGNC:18582]	-0.80940103	0.08058928	0.580532431	1	1.383018381	0.725470307	0.382752752	1
ENSG000000017501	MRDH9	HGNC Symbol	meastro heat like repeat family member 9 [Source:HGNC SymbolAcc:HGNC:26287]	-0.770918244	0.08973062	-0.242525931	1	-0.356771873	0.923537499	-0.094478934	1
ENSG000000018194	TNNI2	HGNC Symbol	"troponin T2, cardiac type [Source:HGNC SymbolAcc:HGNC:11949]"	-0.546314355	0.341682105	-0.184780553	1	-0.045145649	1	-0.028707775	1
ENSG000000018733	OLFM3	HGNC Symbol	olfactomedin 3 [Source:HGNC SymbolAcc:HGNC:17990]	-0.801018321	0.20328346	-0.168306891	1	0.457037361	0.92621162	0.31777164	1
ENSG000000019125	GDA	HGNC Symbol	guanine deaminase [Source:HGNC SymbolAcc:HGNC:4212]	-0.747333668	0.216288278	-0.247436947	1	0.000296093	1	0.467310042	1
ENSG000000019283	TRIM67	HGNC Symbol	tripartite motif containing 67 [Source:HGNC SymbolAcc:HGNC:31859]	-0.692548587	0.18978734	-0.304232198	1	0.887258927	0.818796586	0.26292956	1
ENSG000000019547	ONECUT2	HGNC Symbol	one cut homeobox 2 [Source:HGNC SymbolAcc:HGNC:8139]	-0.384105499	0.566818453	-0.244656357	1	1.784782986	0.723498808	0.103628364	1
ENSG000000020251	GRIA2	HGNC Symbol	glutamate ionotropic receptor AMPA type subunit 2 [Source:HGNC SymbolAcc:HGNC:4572]	-0.536759703	0.3936639567	-0.09039807	1	1.488077153	0.724767358	0.0464217	1
ENSG000000020332	TNN	HGNC Symbol	tetraspin N [Source:HGNC SymbolAcc:HGNC:22942]	-0.797308943	0.054902439	-0.518957551	1	0.742858998	0.858968348	0.159739349	1
ENSG000000020738	EBR1	HGNC Symbol	early growth response 1 [Source:HGNC SymbolAcc:HGNC:3238]	0.387004274	0.467739752	-0.092535102	1	-1.388358877	0.627166863	0.333462255	1
ENSG000000021207	LRAT	HGNC Symbol	lecithin retinol acyltransferase [Source:HGNC SymbolAcc:HGNC:6685]	-0.478671249	0.448666849	-0.195310435	1	0.231716596	0.969503557	0.0166207	1
ENSG000000022121	XPMP2	HGNC Symbol	X-prolyl aminopeptidase 2 [Source:HGNC SymbolAcc:HGNC:12823]	-0.787898058	0.044947173	-0.108623373	1	0.864638822	0.777250738	-0.249193554	1
ENSG000000022511	KIAA1549	HGNC Symbol	KIAA1549 [Source:HGNC SymbolAcc:HGNC:22249]	-0.516890518	0.088627673	-0.127759628	1	0.2186278029	0.951773266	0.218627809	1

22778	ITIH5	HGNC Symbol	inter-alpha-trypsin inhibitor heavy chain family member 5 [Source:HGNC Symbol;Acc:HGNC:21449]	-0.57168831	0.310806911	-0.505623699	1	1.24741502	0.73235655	0.195676108	1
ENSG00000123243											
ENSG00000123572	NRK	HGNC Symbol	Nrk related kinase [Source:HGNC Symbol;Acc:HGNC:25391]	-0.485349518	0.4201910239	-0.203352014	1	0.663557554	0.886167233	0.615018071	1
ENSG00000123977	DAWI	HGNC Symbol	dynein assembly factor with WD repeats 1 [Source:HGNC Symbol;Acc:HGNC:26383]	-0.654416876	0.276598737	0.488719569	1	1.503532086	0.767987908	-0.29219265	1
ENSG00000124092	CTCF	HGNC Symbol	CCCTC-binding factor like [Source:HGNC Symbol;Acc:HGNC:16234]	-0.443308442	0.467030393	0.002752214	1	0.80865262	0.840530754	-0.019073803	1
ENSG00000124253	PKCI	HGNC Symbol	phosphoenolpyruvate carboxykinase 1 [Source:HGNC Symbol;Acc:HGNC:8724]	-0.720216315	0.251094538	0.271913906	1	0.276714195	0.916711576	0.284767529	1
ENSG00000124440	HIF3A	HGNC Symbol	hypoxia inducible factor-3 alpha subunit [Source:HGNC Symbol;Acc:HGNC:15825]	-0.743934584	0.17017086	-0.2732765415	1	1.359557585	0.762363148	0.14892327	1
ENSG00000124466	LYPD3	HGNC Symbol	LY6/PLAUR domain containing 3 [Source:HGNC Symbol;Acc:HGNC:24880]	-0.753602142	0.045770183	0.289895975	1	0.763945067	0.843837914	-0.097673747	1
ENSG00000124749	COL2A1	HGNC Symbol	collagen type XXI alpha 1 chain [Source:HGNC Symbol;Acc:HGNC:17025]	-0.382109802	0.564354144	-0.514235619	1	1.41316074	0.762593024	0.092662892	1
ENSG00000125255	SLC10A2	HGNC Symbol	solute carrier family 10 member 2 [Source:HGNC Symbol;Acc:HGNC:10906]	-0.716865675	0.2573922534	-0.027182702	1	0.044489879	1	0.555402909	1
ENSG00000125492	BARHL1	HGNC Symbol	BarH like homeobox 1 [Source:HGNC Symbol;Acc:HGNC:9553]	-0.65397437	0.822410461	0.87984443	1	0.899120028	0.855882707	-0.754557485	1
ENSG00000125740	FOSB	HGNC Symbol	"FosB proto-oncogene, AP-1 transcription factor subunit [Source:HGNC Symbol;Acc:HGNC:3787]"	0.168491491	0.82332641	-0.208014548	1	-0.722999194	0.725297356	-0.122863284	1
ENSG00000127129	EDN2	HGNC Symbol	endothelin 2 [Source:HGNC Symbol;Acc:HGNC:3177]	-0.396163266	0.501431956	0.552586146	1	0.492127351	0.930180704	-0.351665411	1
ENSG00000128573	FDP2	HGNC Symbol	forkhead box P2 [Source:HGNC Symbol;Acc:HGNC:18875]	-0.425678065	0.495653487	-0.163662169	1	1.204504792	0.787794769	-0.19108142	1
ENSG00000128917	DLL4	HGNC Symbol	delta like canonical Notch ligand 4 [Source:HGNC Symbol;Acc:HGNC:2910]	-0.702458943	0.166145207	-0.165547246	1	-0.27626558	0.951033674	0.21955616	1

ENSG00000129946	SHC2	HGNC Symbol	SHC adaptor protein 2 [Source:HGNC Symbol;Acc:HGNC:29869]	-0.843357696	0.08141031	0.430826667	1	0.9960606391	0.754933936	0.443770016	1
ENSG00000129990	SYT5	HGNC Symbol	synaptotagmin 5 [Source:HGNC Symbol;Acc:HGNC:11513]	-0.81970687	0.1657771371	-0.01628682	1	1.631732813	0.745077552	-0.016149728	1
ENSG00000130045	NNX12	HGNC Symbol	nucleoredoxin like 2 [Source:HGNC Symbol;Acc:HGNC:30482]	-0.594016522	0.278225713	0.144594627	1	-0.278497988	0.946565677	0.334270957	1
ENSG00000130226	DPP6	HGNC Symbol	dipeptidyl peptidase like 6 [Source:HGNC Symbol;Acc:HGNC:3010]	-0.086732477	0.915560052	-0.491623663	1	0.401022019	0.91715467	0.04935684	1
ENSG00000130287	NCAN	HGNC Symbol	neurecan [Source:HGNC Symbol;Acc:HGNC:2465]	-0.665537698	0.28766504	0.316905174	1	0.421088275	0.92077063	-0.642008684	1
ENSG00000130477	UNC13A	HGNC Symbol	unc-13 homolog A [Source:HGNC Symbol;Acc:HGNC:23150]	-0.493441844	0.310975629	-0.048109609	1	0.394154019	0.9105148192	-0.28674943	1
ENSG00000130508	PXD1	HGNC Symbol	peroxidasin [Source:HGNC Symbol;Acc:HGNC:14966]	-0.703310686	0.123498419	-0.472385684	1	0.226774257	0.954203705	-0.18172062	1
ENSG00000130528	HRC	HGNC Symbol	histidine rich calcium binding protein [Source:HGNC Symbol;Acc:HGNC:5178]	-0.692484637	0.295903841	0.225433939	1	1.996649839	0.722740931	-0.3636368666	1
ENSG00000130540	SULT4A1	HGNC Symbol	sulfatransferase family 4A member 1 [Source:HGNC Symbol;Acc:HGNC:14913]	-0.6722718131	0.247255807	0.11638129	1	2.178253808	0.722217784	0.071276285	1
ENSG00000130635	COL5A1	HGNC Symbol	collagen type V alpha 1 chain [Source:HGNC Symbol;Acc:HGNC:2219]	-1.059536259	0.005145777	-0.01160205	1	-0.056854342	0.990946263	0.076795389	1
ENSG00000130644	TTL19	HGNC Symbol	tubulin tyrosine ligase like 9 [Source:HGNC Symbol;Acc:HGNC:1618]	-0.646555965	0.080577407	-0.193372839	1	0.74810611	0.828000591	0.08600403	1
ENSG00000131183	SLC34A1	HGNC Symbol	solute carrier family 34 member 1 [Source:HGNC Symbol;Acc:HGNC:11019]	-0.553608839	0.222662052	0.132968094	1	-0.76403911	0.832983886	0.13172828	1
ENSG00000131386	GALNT15	HGNC Symbol	polypeptide N-acetylglucosaminyltransferase 15 [Source:HGNC Symbol;Acc:HGNC:21531]	-0.249169422	0.57936334	-0.012465071	1	-0.275997847	0.960786648	0.115571653	1
ENSG00000132297	HHLA1	HGNC Symbol	HERV-H LTR-associated 1 [Source:HGNC Symbol;Acc:HGNC:4914]	-0.5693103197	0.347618221	-0.45057748	1	0.335685966	0.946406426	0.544916255	1
ENSG00000132321	IDCA1	HGNC Symbol	IQ motif containing with AAA domain 1 [Source:HGNC Symbol;Acc:HGNC:26195]	-0.491444855	0.302209736	-0.329452064	1	0.488440298	0.910756217	0.375551655	1

ENSG000000132639	SNAP25	HGNC Symbol	synaptosome associated protein 25 [Source:HGNC Symbol;Acc:HGNC:11832]	-0.484337596	0.393579181	-0.408665796	1	1.905967427	0.726386579	0.425545535	1
ENSG000000132972	RNF7	HGNC Symbol	ring finger protein 7 [Source:HGNC Symbol;Acc:HGNC:10060]	-0.539876442	0.323158258	-0.231290586	1	0.046100411	1	0.169976455	1
ENSG000000132975	GPR12	HGNC Symbol	G protein-coupled receptor 12 [Source:HGNC Symbol;Acc:HGNC:4466]	-0.559571507	0.380221581	-0.229055555	1	0.860729873	0.878558735	0.035899532	1
ENSG000000133083	DCLK1	HGNC Symbol	doublecortin like kinase 1 [Source:HGNC Symbol;Acc:HGNC:2700]	-0.693023499	0.188550204	-0.20329481	1	0.45308712	0.908558976	0.023848382	1
ENSG000000133110	POSTN	HGNC Symbol	periostin [Source:HGNC Symbol;Acc:HGNC:18553]	-1.95711401	0.0014871	-0.34938544	1	-0.086735544	0.992429838	-0.345362803	1
ENSG000000133124	IRS4	HGNC Symbol	insulin receptor substrate 4 [Source:HGNC Symbol;Acc:HGNC:6128]	-0.486576537	0.45362956	-0.72052378	1	5.343238343	0.627668963	0.002765328	1
ENSG000000133454	MYO18B	HGNC Symbol	myosin XVIIIB [Source:HGNC Symbol;Acc:HGNC:18500]	-0.556047442	0.18461856	-0.273385213	1	0.357760747	0.892320091	0.190816003	1
ENSG000000134240	HMGCS2	HGNC Symbol	3-hydroxy-3-methylglutaryl-CoA synthase 2 [Source:HGNC Symbol;Acc:HGNC:5008]	-0.568886518	0.322294501	0.097873964	1	-0.238140625	0.963278892	0.024389102	1
ENSG000000134871	COL4A2	HGNC Symbol	collagen type IV alpha 2 chain [Source:HGNC Symbol;Acc:HGNC:2203]	-0.723958851	0.078843824	0.140639769	1	-0.425505673	0.850838998	-0.091086456	1
ENSG000000135097	MSI1	HGNC Symbol	musashi 1 RNA binding protein 1 [Source:HGNC Symbol;Acc:HGNC:7330]	-0.681488708	0.233945897	-0.20338644	1	0.497310389	0.937722107	-0.05653922	1
ENSG000000135409	AMHR2	HGNC Symbol	anti-Müllerian hormone receptor type 2 [Source:HGNC Symbol;Acc:HGNC:465]	-0.365902207	0.57936334	0.204280771	1	-0.27558101	0.956707132	-0.438149966	1
ENSG000000135454	B4GALNT1	HGNC Symbol	"beta-1,4-N-acetyl-galactosaminyltransferase 1 [Source:HGNC Symbol;Acc:HGNC:4107]"	-0.838916247	0.09476195	0.29957806	1	0.6454358	0.867558968	-0.208851705	1
ENSG000000135472	FAIM2	HGNC Symbol	Fas apoptotic inhibitory molecule 2 [Source:HGNC Symbol;Acc:HGNC:170167]	-0.68324772	0.166816589	0.202004682	1	0.818056333	0.844324446	-0.2451895	1
ENSG000000135817	SLC18A3	HGNC Symbol	solute carrier family 18 member 3 [Source:HGNC Symbol;Acc:HGNC:16265]	-0.940946251	0.097071433	-0.339203408	1	1.852245487	0.724400969	-0.4030865239	1
ENSG000000135931	ARMCS	HGNC Symbol	armadillo repeat containing 9 [Source:HGNC Symbol;Acc:HGNC:20730]	-0.671665301	0.040773449	-0.131277463	1	0.80438724	0.819067405	0.374946273	1

ENSG00000136352	NKX2-1	HGNC Symbol	NKX2 homeobox 1 [Source:HGNC Symbol;Acc:HGNC:10825]	-0.828072024	0.143000566	1.366180821	1	1.260865582	0.79962726	0.31676709	1
ENSG00000136535	TBR1	HGNC Symbol	"T-box brain 1 [Source:HGNC Symbol;Acc:HGNC:16590]"	-0.569543976	0.29480105	-0.306732856	1	1.986072677	0.725297356	0.298842535	1
ENSG00000136574	GATA4	HGNC Symbol	GATA binding protein 4 [Source:HGNC Symbol;Acc:HGNC:4473]	-0.43785431	0.458853715	-0.085495591	1	-0.352802935	0.937737302	0.6187766	1
ENSG00000136695	IL36RN	HGNC Symbol	interleukin 36 receptor antagonist [Source:HGNC Symbol;Acc:HGNC:15561]	-0.1116253	0.88785479	-0.281913506	1	0.46108841	0.936621903	-0.051268805	1
ENSG00000137203	TFAP2A	HGNC Symbol	transcription factor AP-2, alpha [Source:HGNC Symbol;Acc:HGNC:1742]	-0.71960678	0.197926578	-0.53802252	1	-0.20209526	0.966677784	-0.033229666	1
ENSG00000137573	SULF1	HGNC Symbol	sulfatase 1 [Source:HGNC Symbol;Acc:HGNC:20391]	-0.721090487	0.165302568	-0.087328771	1	0.825205342	0.843454046	0.191859508	1
ENSG00000137648	TMPRSS4	HGNC Symbol	transmembrane serine protease 4 [Source:HGNC Symbol;Acc:HGNC:10878]	-0.697399848	0.100318089	-0.536595553	1	1.978852185	0.690920831	-0.033954499	1
ENSG00000137766	UNC18C	HGNC Symbol	unc-18 homolog C [Source:HGNC Symbol;Acc:HGNC:23443]	-0.345900067	0.592753582	-0.800918915	1	0.083965679	0.99633075	0.528354487	1
ENSG00000137819	PAQR5	HGNC Symbol	pregenin and adipon receptor family member 5 [Source:HGNC Symbol;Acc:HGNC:29645]	-0.465088604	0.254871322	-0.28179588	1	-0.022161664	1	-0.150321964	1
ENSG00000138162	TACC2	HGNC Symbol	transforming acidic coiled-coil containing protein 2 [Source:HGNC Symbol;Acc:HGNC:1623]	-0.59822058	0.215791657	-0.39401457	1	0.090343402	0.988800576	-0.138236443	1
ENSG00000138650	PCDH10	HGNC Symbol	protocadherin 10 [Source:HGNC Symbol;Acc:HGNC:16404]	-0.333300016	0.504591273	0.04230206	1	0.227487401	0.96989385	0.091490003	1
ENSG00000138675	FBF5	HGNC Symbol	fibroblast growth factor 5 [Source:HGNC Symbol;Acc:HGNC:3663]	-0.605345738	0.362679738	0.09437515	1	1.662399062	0.754933336	0.390565845	1
ENSG00000138759	FRA1	HGNC Symbol	Fraser extracellular matrix complex subunit 1 [Source:HGNC Symbol;Acc:HGNC:19185]	-0.22294616	0.747027813	-0.230470196	1	0.716330438	0.828463409	0.168376531	1
ENSG00000138892	TTL18	HGNC Symbol	tubulin tyrosine ligase like 18 [Source:HGNC Symbol;Acc:HGNC:34000]	-0.89716888	0.092191936	0.346403716	1	-0.418379015	0.92963834	0.177510233	1
ENSG00000139144	PIK3C2G	HGNC Symbol	phosphatidylinositol 4-phosphate 3-kinase catalytic subunit type 2 gamma [Source:HGNC]	-0.65595171	0.833030115	0.29979592	1	1.47251311	0.75410584	0.429551463	1

ENSG00000139220	PPF1A2	HGNC Symbol	Symbol/Acc:HGNC:89733	-0.378470282	0.538516358	-0.08653108	I	0.23575627	0.956883515	-0.18497909	I
ENSG00000139767	SRRM4	HGNC Symbol	serine/arginine repetitive matrix 4 [Source:HGNC Symbol/Acc:HGNC:29389]	-0.3343885	0.61076368	-0.184960482	I	0.895758938	0.818749045	0.114253744	I
ENSG00000139865	TTC6	HGNC Symbol	tetratricopeptide repeat domain 6 [Source:HGNC Symbol/Acc:HGNC:18739]	-0.5461875	0.377281018	0.138883348	I	0.239155025	0.964093129	0.4431004	I
ENSG00000140278	DJX2	HGNC Symbol	dual oxidase 2 [Source:HGNC Symbol/Acc:HGNC:18273]	-0.6018929	0.67597775	0.347497074	I	0.459255659	0.910883337	-0.062628479	I
ENSG00000140527	WDR63	HGNC Symbol	WD repeat domain 63 [Source:HGNC Symbol/Acc:HGNC:26924]	-0.51023896	0.363810238	0.121581454	I	0.32761064	0.945240895	0.342334255	I
ENSG00000140600	SH3GL3	HGNC Symbol	"SH3 domain containing BRB2 like 3, endophilin A3 [Source:HGNC Symbol/Acc:HGNC:10832]"	-0.348680711	0.57659031	-0.050610896	I	0.773782722	0.88197857	0.265947406	I
ENSG0000014434	MCPH1	HGNC Symbol	meprin A subunit beta [Source:HGNC Symbol/Acc:HGNC:7020]	-0.835489508	0.100858384	-0.274970362	I	1.075438474	0.81861697	0.454970747	I
ENSG00000144668	CBLN2	HGNC Symbol	ceredellin 2 precursor [Source:HGNC Symbol/Acc:HGNC:1544]	-0.408816782	0.515836432	0.075687803	I	1.6387007	0.781543823	0.04990264	I
ENSG00000144946	ZIM3	HGNC Symbol	zinc finger imprinted 3 [Source:HGNC Symbol/Acc:HGNC:16366]	-0.553189901	0.481027916	-0.091028345	I	0.08223031	0.996460723	0.118192705	I
ENSG00000142408	CACNG8	HGNC Symbol	calcium voltage-gated channel auxiliary subunit gamma 8 [Source:HGNC Symbol/Acc:HGNC:16628]	-0.654089337	0.014843697	-0.032988868	I	0.659966588	0.75144627	0.04748452	I
ENSG00000142449	FBX3	HGNC Symbol	fibroblast 3 [Source:HGNC Symbol/Acc:HGNC:18794]	-0.447182665	0.423778362	-0.470497888	I	-0.031000224	I	0.0276109401	I
ENSG00000142549	IGLON5	HGNC Symbol	IgLN family member 5 [Source:HGNC Symbol/Acc:HGNC:34550]	-0.544479933	0.395566456	-0.005610726	I	0.73291036	0.889236595	-0.165464006	I
ENSG00000142611	PROM16	HGNC Symbol	PR/SET domain 16 [Source:HGNC Symbol/Acc:HGNC:14010]	-0.743776119	0.10743572	-0.210729578	I	0.541607842	0.876517598	-0.17193595	I
ENSG00000142623	PAD11	HGNC Symbol	peptidyl arginine deiminase 1 [Source:HGNC Symbol/Acc:HGNC:18367]	-0.616861527	0.338644986	-0.168164899	I	0.648164813	0.880022596	-0.307236278	I

ENSG00000142975	CNKSR1	HGNC Symbol	connector enhancer of kinase suppressor of Ras 1 [Source:HGNC Symbol;Acc:HGNC:19700]	-0.498623814	0.188703102	0.288721284	1	-0.167267919	0.812662354	0.64084458	1
ENSG00000142910	TINAGL1	HGNC Symbol	tubulointerstitial nephritis antigen like 1 [Source:HGNC Symbol;Acc:HGNC:19168]	-0.695339191	0.168108446	0.16587273	1	-0.10198103802	0.814581081	0.0163107454	1
ENSG00000143107	FNDC7	HGNC Symbol	fibronectin type III domain containing 7 [Source:HGNC Symbol;Acc:HGNC:26668]	-0.533451774	0.237237415	-0.167664787	1	1.06558764	0.789188535	0.167596527	1
ENSG00000143355	LUX8	HGNC Symbol	LIM homeobox 8 [Source:HGNC Symbol;Acc:HGNC:14222]	-0.48768367	0.355710069	0.142003448	1	2.142940772	0.665271436	0.633424086	1
ENSG00000143450	DAZ3	HGNC Symbol	ornithine decarboxylase antizyme 3 [Source:HGNC Symbol;Acc:HGNC:8197]	-0.731031098	0.04178294	-0.014524812	1	0.151630747	0.977891056	-0.210681052	1
ENSG00000143469	SYT14	HGNC Symbol	synaptotagmin 14 [Source:HGNC Symbol;Acc:HGNC:23443]	-0.529977175	0.425161633	-0.447510386	1	-0.956862615	0.814402007	0.45714936	1
ENSG00000143857	DSR1	HGNC Symbol	odd-skipped related transcription factor 1 [Source:HGNC Symbol;Acc:HGNC:8111]	-0.350861532	0.593032035	-0.581637838	1	1.27734954	0.767398021	-0.24655505	1
ENSG00000144115	THNSL2	HGNC Symbol	threonine synthase like 2 [Source:HGNC Symbol;Acc:HGNC:25602]	-0.327316109	0.332009313	0.096951022	1	1.406766298	0.627668963	-0.093030536	1
ENSG00000144488	ESPWL	HGNC Symbol	espin like [Source:HGNC Symbol;Acc:HGNC:27937]	-0.5776310971	0.255952723	0.12783529	1	0.1193673104	0.984168271	-0.472455254	1
ENSG00000144648	ACKR2	HGNC Symbol	atypical chemokine receptor 2 [Source:HGNC Symbol;Acc:HGNC:15655]	-0.4773139108	0.145840057	0.0313716573	1	-0.0183310853	1	0.2894910869	1
ENSG00000144681	STAC	HGNC Symbol	SH3 and cysteine rich domain [Source:HGNC Symbol;Acc:HGNC:11553]	-0.560050605	0.182121883	-0.063452505	1	2.442386148	0.655810493	-0.180358616	1
ENSG00000144730	IL-17RD	HGNC Symbol	interleukin 17 receptor D [Source:HGNC Symbol;Acc:HGNC:17616]	-0.5610610788	0.294689324	-0.325294976	1	-0.187758677	0.965332255	0.08073396	1
ENSG00000144820	ADGR67	HGNC Symbol	adhesion G protein-coupled receptor 67 [Source:HGNC Symbol;Acc:HGNC:19241]	-0.492318851	0.438131721	-0.373299237	1	1.0547197157	0.807195259	-0.1065161935	1
ENSG00000144908	ALDH1L1	HGNC Symbol	aldehyde dehydrogenase 1 family member 11 [Source:HGNC Symbol;Acc:HGNC:3978]	-0.412949192	0.450102188	0.073431653	1	0.613763867	0.869925678	0.034576065	1
ENSG00000145242	EPHA5	HGNC Symbol	EPH receptor A5 [Source:HGNC Symbol;Acc:HGNC:3388]	-0.56128279	0.397810397	-0.091518559	1	0.91278714	0.85681037	0.14627144	1

ENSG00000145526	CDH8	HGNC Symbol	cadherin 8 [Source:HGNC Symbol;Acc:HGNC:1757]	-0.147075064	0.255000028	-0.802285847	1	1.00099442	0.843439811	0.179252073	1
ENSG00000145542	SHISA2B	HGNC Symbol	shisa like 2B [Source:HGNC Symbol;Acc:HGNC:34236]	-1.490085497	0.001461516	0.2716550832	1	0.854782399	0.897785147	1.025590395	1
ENSG00000145832	SLC25A48	HGNC Symbol	solute carrier family 25 member 48 [Source:HGNC Symbol;Acc:HGNC:30451]	-0.3826507037	0.565480846	-0.280573959	1	1.538859271	0.770970716	0.102672102	1
ENSG00000146005	PSD2	HGNC Symbol	pleckstrin and Sec7 domain containing 2 [Source:HGNC Symbol;Acc:HGNC:19092]	-0.474391279	0.322955191	0.021403556	1	0.480468991	0.905793309	-0.1064717	1
ENSG00000146521	LINC01558	HGNC Symbol	long intergenic non-protein coding RNA 1558 [Source:HGNC Symbol;Acc:HGNC:21235]	-0.93073164	0.014996052	-0.374380824	1	1.066067068	0.84097873	0.248763858	1
ENSG00000146548	EGFR	HGNC Symbol	epidermal growth factor receptor [Source:HGNC Symbol;Acc:HGNC:32236]	-0.464347302	0.323083336	-0.33233532	1	0.951029589	0.797043771	0.222515644	1
ENSG00000146839	ZAN	HGNC Symbol	zonadhesin (gene/pseudogene) [Source:HGNC Symbol;Acc:HGNC:12857]	-0.501910108	0.397563388	-0.125191006	1	0.079846162	0.992989533	-0.139877955	1
ENSG00000146950	SHROOM2	HGNC Symbol	shroom family member 2 [Source:HGNC Symbol;Acc:HGNC:6301]	-0.547481224	0.163040816	0.20278038	1	0.778222778	0.849002793	-0.06543559	1
ENSG00000147573	TRIM55	HGNC Symbol	tripartite motif containing 55 [Source:HGNC Symbol;Acc:HGNC:14216]	-0.416271036	0.529220394	-0.594055397	1	1.095002077	0.799860378	-0.162457891	1
ENSG00000147655	RSPD2	HGNC Symbol	R-spondin 2 [Source:HGNC Symbol;Acc:HGNC:28583]	-0.425816624	0.4901916964	-0.332531076	1	1.27191102	0.794524832	0.504706196	1
ENSG00000147689	FAM83A	HGNC Symbol	family with sequence similarity 83 member A [Source:HGNC Symbol;Acc:HGNC:28210]	-0.471846383	0.295555482	0.16948171	1	-0.903328622	0.77316391	0.066442976	1
ENSG00000148357	HMCN2	HGNC Symbol	hemieritin 2 [Source:HGNC Symbol;Acc:HGNC:21293]	-0.535586286	0.290997361	0.264805329	1	1.320603031	0.732397555	-0.167042982	1
ENSG00000148408	CACNA1B	HGNC Symbol	calcium voltage-gated channel subunit alpha 1B [Source:HGNC Symbol;Acc:HGNC:13891]	-0.501468836	0.284867302	0.046380959	1	0.530519495	0.874668309	-0.0310898439	1
ENSG00000148513	ANKRD31A	HGNC Symbol	ankyrin repeat domain 31A [Source:HGNC Symbol;Acc:HGNC:17234]	-0.871448013	0.164735964	-0.305026977	1	0.953450117	0.839264767	0.371091001	1
ENSG00000148702	HABP2	HGNC Symbol	hyaluronan binding protein 2 [Source:HGNC Symbol;Acc:HGNC:4798]	-0.565571725	0.372562084	-0.70168564	1	0.691616599	0.891304498	-0.267216198	1

ENSG00000148942	SLC5A12	HGNC Symbol	solute carrier family 5 member 12 [Source:HGNC Symbol;Acc:HGNC:28750]	-0.603891229	0.317483763	0.58909502	I	2.0217846	0.724555033	0.288059588	I
ENSG00000149533	KIAA1755	HGNC Symbol	KIAA1755 [Source:HGNC Symbol;Acc:HGNC:29372]	-0.626269466	0.2955535482	-0.002950944	I	0.845177683	0.84263185	0.020108457	I
ENSG00000149554	CDH22	HGNC Symbol	cadherin 22 [Source:HGNC Symbol;Acc:HGNC:18250]	-0.3618549	0.564754244	0.406594264	I	1.642451251	0.704650879	0.373083932	I
ENSG00000149926	FAM57B	HGNC Symbol	family with sequence similarity 57 member B [Source:HGNC Symbol;Acc:HGNC:25295]	-0.826512075	0.147540268	0.338790638	I	0.63666601	0.8772676	0.22332443	I
ENSG00000150086	NA	NA	NA	-0.38789029	0.543943649	0.101383742	I	0.08254318	0.99302382	0.0182046	I
ENSG00000150893	FRM2	HGNC Symbol	FRS1 related extracellular matrix protein 2 [Source:HGNC Symbol;Acc:HGNC:25396]	-0.27918432	0.68553075	-0.016022791	I	0.68359736	0.858353069	0.230697523	I
ENSG00000151224	MAT1A	HGNC Symbol	methionine adenosyltransferase 1A [Source:HGNC Symbol;Acc:HGNC:6903]	-0.656829857	0.25715468	0.197653503	I	2.604150819	0.659467056	0.028446108	I
ENSG00000151474	FRM4A	HGNC Symbol	FERM domain containing 4A [Source:HGNC Symbol;Acc:HGNC:25491]	-0.26679579	0.183727706	0.076464676	I	-1.08547325	0.525549357	0.101780987	I
ENSG00000151572	AND4	HGNC Symbol	anoctamin 4 [Source:HGNC Symbol;Acc:HGNC:23837]	-0.42748862	0.474520364	-0.114230143	I	1.695485335	0.73188014	0.34018558	I
ENSG00000152822	GRM1	HGNC Symbol	glutamate metabotropic receptor 1 [Source:HGNC Symbol;Acc:HGNC:4593]	-0.560201862	0.321666526	0.199572202	I	0.951055318	0.849012793	0.351771006	I
ENSG00000152910	CNTNAP4	HGNC Symbol	contactin associated protein like 4 [Source:HGNC Symbol;Acc:HGNC:18747]	-0.144213925	0.859543676	-0.42488187	I	0.369465713	0.937722107	-0.22837856	I
ENSG00000153165	RBP3	HGNC Symbol	RANBP2-like and GRP domain containing 3 [Source:HGNC Symbol;Acc:HGNC:32416]	-0.866486535	0.003638752	-0.234684905	I	2.095559153	0.627668963	-0.26547248	I
ENSG00000154099	DNAI1	HGNC Symbol	dynein axonemal assembly factor 1 [Source:HGNC Symbol;Acc:HGNC:30539]	-0.616204423	0.217695484	0.345094508	I	1.56795966	0.738962739	-0.424945152	I
ENSG00000154478	GRP25	HGNC Symbol	G protein-coupled receptor 25 [Source:HGNC Symbol;Acc:HGNC:4481]	-0.494816205	0.406550218	-0.603462454	I	3.14725066	0.63230269	0.299935738	I
ENSG00000155816	FMN2	HGNC Symbol	formin 2 [Source:HGNC Symbol;Acc:HGNC:14074]	-0.41873015	0.528626826	-0.266666973	I	-0.182230828	0.97215979	0.364878442	I

ENSG00000156076	WIFI	HGNC Symbol	WNT inhibitory factor 1 [Source:HGNC Symbol;Acc:HGNC:16080]	-0.701895845	0.249971053	-0.29165474	I	-0.18957606	0.99267537	0.39962807	I
ENSG0000015603	MMP16	HGNC Symbol	matrix metalloproteinase 16 [Source:HGNC Symbol;Acc:HGNC:7162]	-0.62940918	0.35495337	0.178584644	I	1.561003497	0.737781088	0.049120893	I
ENSG00000156222	SLC28A1	HGNC Symbol	solute carrier family 28 member 1 [Source:HGNC Symbol;Acc:HGNC:10001]	-0.484780444	0.3943014144	0.02974247	I	-0.178812352	0.97374933	0.08314459	I
ENSG0000015643	FUT6	HGNC Symbol	fucosyltransferase 6 [Source:HGNC Symbol;Acc:HGNC:4017]	-0.59042874	0.29165914	0.04072306	I	1.98694434	0.76035827	-0.12602335	I
ENSG0000015687	UNC5D	HGNC Symbol	unc-5 netrin receptor D [Source:HGNC Symbol;Acc:HGNC:18634]	-0.678558916	0.219237459	-0.175857955	I	-0.04484555	I	0.37233405	I
ENSG00000157214	STEAP2	HGNC Symbol	STEAP2 metalloendopeptidase [Source:HGNC Symbol;Acc:HGNC:17885]	-0.75247183	0.154094301	-0.183833013	I	3.283888598	0.6271668963	0.194759	I
ENSG00000157423	HYDIN	HGNC Symbol	"HYDIN, axonemal central pair apparatus protein [Source:HGNC Symbol;Acc:HGNC:19368]"	-0.339331962	0.50165362	-0.307482345	I	0.77155018	0.824915096	0.345889545	I
ENSG00000157927	RADIL	HGNC Symbol	Rar associating with DIL domain [Source:HGNC Symbol;Acc:HGNC:22226]	-0.542930842	0.218274573	0.149636954	I	0.477550274	0.905148092	-0.15547528	I
ENSG00000158077	NLRP4	HGNC Symbol	NLR family pyrin domain containing 14 [Source:HGNC Symbol;Acc:HGNC:22939]	-0.395550124	0.501806622	0.068101817	I	0.259016203	0.96631839	0.259994409	I
ENSG00000158125	XDH	HGNC Symbol	xanthine dehydrogenase [Source:HGNC Symbol;Acc:HGNC:12805]	-0.856880381	0.164947162	-0.505018354	I	1.290307308	0.756996807	0.187029284	I
ENSG00000158258	CLSTN2	HGNC Symbol	calsytinin 2 [Source:HGNC Symbol;Acc:HGNC:17448]	-0.47246595	0.46827728	-0.4395559401	I	1.26103511	0.752976057	0.22548257	I
ENSG00000159251	ACT1	HGNC Symbol	"actin, alpha, cardiac muscle 1 [Source:HGNC Symbol;Acc:HGNC:143]"	-0.407779393	0.500035053	-0.381085345	I	1.51616689	0.749009777	0.188962838	I
ENSG00000159337	PLA2G4D	HGNC Symbol	phospholipase A2 group IV [Source:HGNC Symbol;Acc:HGNC:30038]	-0.62384411	0.222267492	0.452174015	I	0.95816216	0.824540952	-0.148948276	I
ENSG00000159650	URDC1	HGNC Symbol	uracinate hydratase [Source:HGNC Symbol;Acc:HGNC:26444]	-0.597610834	0.295239234	-0.050043865	I	1.288104367	0.750144627	-0.172852982	I
ENSG00000160460	SPTBN4	HGNC Symbol	"spectrin beta, non-erythrocytic 4 [Source:HGNC Symbol;Acc:HGNC:14896]"	-0.68223524	0.189882704	0.00048346	I	0.227969832	0.95544991	-0.204422386	I

ENSG00000016094	CCDC105	HGNC Symbol	coiled-coil domain containing 105 [Source:HGNC Symbol;Acc:HGNC:26866]	-0.455466884	0.442646097	0.124559299	1	4.22482034	0.676195287	0.347165754	1
ENSG00000016103	AC008132.1	Clone-based (Ensembl) gene		-0.52829433	0.317152409	-0.608562688	1	1.675951687	0.777991096	0.130918148	1
ENSG00000016143	FBXO27	HGNC Symbol	F-box protein 27 [Source:HGNC Symbol;Acc:HGNC:18753]	-0.817434469	0.1659310422	-0.627240471	1	2.046992131	0.708025594	0.793324098	1
ENSG00000016170	NPHS1	HGNC Symbol	"NPHS1, nephrin [Source:HGNC Symbol;Acc:HGNC:7908]"	-0.59448236	0.3042161	-0.677560856	1	-0.316527889	0.936527297	-0.164586694	1
ENSG00000016109	CCDC155	HGNC Symbol	coiled-coil domain containing 155 [Source:HGNC Symbol;Acc:HGNC:26520]	-0.559684333	0.31465888	0.321856534	1	1.2778202	0.776886286	-0.254407597	1
ENSG00000016182	FAM71A2	HGNC Symbol	family with sequence similarity 71 member A2 [Source:HGNC Symbol;Acc:HGNC:30480]	-0.837058843	0.1064801456	0.2623244	1	0.789426772	0.87657598	0.081403063	1
ENSG00000016140	BCL6B	HGNC Symbol	B cell CLL/lymphoma 6B [Source:HGNC Symbol;Acc:HGNC:1002]	-0.733676229	0.161835527	0.3016629089	1	1.015557853	0.82066818	0.229086895	1
ENSG00000016206	MSLN	HGNC Symbol	mesothelin-like [Source:HGNC Symbol;Acc:HGNC:1470]	-0.82468069	0.109149457	1.067686879	1	0.162688447	0.974864202	-0.300187609	1
ENSG000000162052	TEO22	HGNC Symbol	tubulin epsilon and delta complex 2 [Source:HGNC Symbol;Acc:HGNC:25849]	-0.659328887	0.160877424	0.450095579	1	-0.0462343	1	0.295162575	1
ENSG000000162510	MATN1	HGNC Symbol	"matrilin 1, cartilage matrix protein [Source:HGNC Symbol;Acc:HGNC:6907]"	-0.622999455	0.185310926	-0.101994244	1	-0.576818273	0.854897053	0.272474864	1
ENSG000000162631	NTNG1	HGNC Symbol	netrin G1 [Source:HGNC Symbol;Acc:HGNC:23318]	-0.620320047	0.18727821	-0.401679035	1	0.274332455	0.948978235	0.539361847	1
ENSG000000162706	CAOM3	HGNC Symbol	cell adhesion molecule 3 [Source:HGNC Symbol;Acc:HGNC:1760]	-0.682331042	0.208106324	0.3713010869	1	-0.555096986	0.875275045	0.057571637	1
ENSG000000162738	VANGL2	HGNC Symbol	VANG1, planar cell polarity protein 2 [Source:HGNC Symbol;Acc:HGNC:16510]	-0.566370145	0.256559503	-0.114710186	1	0.109931608	0.985016079	-0.152716741	1
ENSG000000163395	IGFNI	HGNC Symbol	immunoglobulin-like and fibronectin type III domain containing 1 [Source:HGNC Symbol;Acc:HGNC:24607]	-0.426568352	0.487780556	-0.487480191	1	0.683264747	0.84907793	0.200522973	1
ENSG000000163467	C3orf67	HGNC Symbol	chromosome 3 open reading frame 67	-0.465955576	0.282307208	-0.21641226	1	1.02148208	0.773447218	0.232500831	1

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65379			domain containing 5 [Source:HNC SymbolAcc:HNC:20360]									
ENS6000001	PKNIX2	HGNC Symbol	PBX/knotted 1/homeobox 2 [Source:HNC SymbolAcc:HNC:H6714]	-0.17205851	0.813551285	-0.354534906	I	2.475038628	0.627666953	0.013822717	I	
65495												
ENS6000001	AMEP2	HGNC Symbol	APC membrane recruitment protein 2 [Source:HNC SymbolAcc:HNC:26360]	-0.383500908	0.550047859	-0.32625258	I	2.213746235	0.6989448	-0.05804664	I	
65566												
ENS6000001	JCAD	HGNC Symbol	junctional cadherin 5 associated [Source:HNC SymbolAcc:HNC:29283]	-0.687536793	0.0530314	-0.072388796	I	-0.743888409	0.79276686	0.488556874	I	
65757												
ENS6000001	VWA2	HGNC Symbol	von Willebrand factor A domain containing 2 [Source:HNC SymbolAcc:HNC:24709]	-0.616558529	0.228016995	-0.077014904	I	-0.17170948	0.977382049	0.345080658	I	
65816												
ENS6000001	PDZRN4	HGNC Symbol	PDZ domain containing ring finger 4 [Source:HNC SymbolAcc:HNC:30552]	-0.710183651	0.283637569	-0.285064897	I	0.808503061	0.853575695	0.178661023	I	
65966												
ENS6000001	SIC6A5	HGNC Symbol	solute carrier family 6 member 5 [Source:HNC SymbolAcc:HNC:H050]	-0.44556406	0.467030333	-0.374532483	I	0.402947708	0.939065966	0.607693459	I	
65970												
ENS6000001	NELL1	HGNC Symbol	neural EGF like 1 [Source:HNC SymbolAcc:HNC:7750]	-0.775652603	0.22065101	-0.007894805	I	0.550648336	0.937665503	0.368089989	I	
65973												
ENS6000001	SPATA19	HGNC Symbol	spermatogenesis associated 19 [Source:HNC SymbolAcc:HNC:30614]	-0.77800429	0.2735445	0.006439727	I	0.773848003	0.865676998	0.035744334	I	
66118												
ENS6000001	LPTM2	HGNC Symbol	leucine rich repeats and transmembrane domains 2 [Source:HNC SymbolAcc:HNC:32443]	-0.85369222	0.085585739	0.373039904	I	0.725763036	0.871961627	-0.08445978	I	
66169												
ENS6000001	TWEM10	HGNC Symbol	transmembrane protein 10 [Source:HNC SymbolAcc:HNC:25607]	-0.25098468	0.758060139	-0.406445456	I	5.30152728	0.627666953	0.57966656	I	
66292												
ENS6000001	MGBAT2	HGNC Symbol	monoacylglycerol O-acyltransferase 2 [Source:HNC SymbolAcc:HNC:23248]	-0.64873495	0.349052284	-0.609893038	I	0.02785563	0.9944458	0.44502466	I	
66391												
ENS6000001	ST5	HGNC Symbol	suppression of tumorigenicity 5 [Source:HNC SymbolAcc:HNC:H1350]	-0.623988928	0.08234925	-0.216522069	I	-0.270216766	0.916970637	-0.025992347	I	
66444												
ENS6000001	PQOIL2	HGNC Symbol	polyoystin 1 like 2 (gene/pseudogene) [Source:HNC SymbolAcc:HNC:27115]	-0.290071825	0.668316557	0.069479982	I	0.803294803	0.825562858	0.0355795592	I	
66473												
ENS6000001	SIC3B4.8	HGNC Symbol	solute carrier family 38 member 8	-0.595390451	0.349528978	0.28492019	I	0.46103781	0.922504678	0.143250087	I	

[illegible]

ENSG000000168481	LG13	HGNC Symbol	leucine rich repeat (L1) family member 3 [Source:HGNC Symbol;Acc:HGNC:18710]	-0.57256523	0.30228963	-0.17768002	1	-0.176051427	0.975621881	-0.361893393	1
ENSG000000168484	SFTPC	HGNC Symbol	surfactant protein C [Source:HGNC Symbol;Acc:HGNC:10802]	-1.037382046	0.1063132935	-0.55159713	1	-0.306770833	0.950916889	0.177687701	1
ENSG000000168542	COL3A1	HGNC Symbol	collagen type III alpha 1 chain [Source:HGNC Symbol;Acc:HGNC:2201]	-1.474761632	0.10291146	0.063619584	1	-0.36621653	0.905049562	-0.25532392	1
ENSG000000168907	PLA2G4F	HGNC Symbol	phospholipase A2 group IVF [Source:HGNC Symbol;Acc:HGNC:27395]	-0.587140167	0.29944708	-0.34434884	1	0.02776124	1	0.095854026	1
ENSG000000168959	GRM5	HGNC Symbol	glutamate metabotropic receptor 5 [Source:HGNC Symbol;Acc:HGNC:4597]	-0.453630369	0.440916003	-0.377363911	1	0.590871081	0.882007771	0.084617918	1
ENSG000000169126	ARMC4	HGNC Symbol	armadillo repeat containing 4 [Source:HGNC Symbol;Acc:HGNC:25583]	-0.575622675	0.29944708	-0.488364348	1	1.8169210531	0.732816758	0.9043102929	1
ENSG000000169169	CPT1C	HGNC Symbol	carnitine palmitoyltransferase 1C [Source:HGNC Symbol;Acc:HGNC:16540]	-0.34161456	0.476106503	0.63079572	1	-0.065612355	0.98993439	-0.345407025	1
ENSG000000169344	UMOD	HGNC Symbol	uromodulin [Source:HGNC Symbol;Acc:HGNC:12559]	-0.76971558	0.18167665	-0.135743663	1	0.408164074	0.931976942	-0.17551803	1
ENSG000000169436	COL22A1	HGNC Symbol	collagen type XXII alpha 1 chain [Source:HGNC Symbol;Acc:HGNC:22988]	-0.374487855	0.528676826	-0.280059254	1	0.747486195	0.821188312	0.140488858	1
ENSG000000169862	CTNND2	HGNC Symbol	catenin delta 2 [Source:HGNC Symbol;Acc:HGNC:2516]	-0.3501914798	0.521012355	-0.072724035	1	0.660129393	0.84175646	0.294817064	1
ENSG000000169876	MUC17	HGNC Symbol	"mucin 17, cell surface associated [Source:HGNC Symbol;Acc:HGNC:16800]"	-0.566443746	0.387167501	0.684807971	1	1.393210612	0.747487389	0.615964856	1
ENSG000000170381	SEMA3E	HGNC Symbol	semaphorin 3E [Source:HGNC Symbol;Acc:HGNC:10727]	-0.598738051	0.385408727	0.0756861	1	0.396729287	0.943408874	0.074345074	1
ENSG000000170426	SORBS7	HGNC Symbol	short chain dehydrogenase/reductase family 9C member 7 [Source:HGNC Symbol;Acc:HGNC:29558]	-0.869644519	0.163679446	-0.50740439	1	0.508730318	0.9165188245	0.170350896	1
ENSG000000170442	KRT16	HGNC Symbol	keratin 16 [Source:HGNC Symbol;Acc:HGNC:5463]	-0.370773529	0.370851028	0.67524677	1	0.47253733	0.916510397	-0.700899984	1
ENSG000000170500	TTLG6	HGNC Symbol	tubulin tyrosine ligase like 6 [Source:HGNC]	-0.589944567	0.344781215	-0.096172488	1	0.735266188	0.869343866	0.301659858	1

70703				Symbol/Accession:HGNC:26664	-0.56526371	0.38290683	-0.087908478	I	-0.189830775	0.97308836	0.6448673	I
ENSG00000170777	TP53L3	HGNC Symbol		tumor protein D52 like 3 [Source:HGNC Symbol/Accession:HGNC:23382]	-0.56526371	0.38290683	-0.087908478	I	-0.189830775	0.97308836	0.6448673	I
ENSG00000170927	PKHD1	HGNC Symbol		"PKHD1, fibrocystin/polyductin [Source:HGNC Symbol/Accession:HGNC:90163]"	-0.246997015	0.708016783	-0.285697631	I	0.248532627	0.95482234	0.04604883	I
ENSG00000174435	KSR2	HGNC Symbol		kinase suppressor of ras 2 [Source:HGNC Symbol/Accession:HGNC:16610]	-0.42805876	0.450661319	-0.365728855	I	0.31957308	0.943590641	0.315694928	I
ENSG00000174487	NLRP5	HGNC Symbol		NLR family pyrin domain containing 5 [Source:HGNC Symbol/Accession:HGNC:21269]	-0.238462882	0.710453033	-0.770914894	I	0.15434667	0.98736879	0.065527602	I
ENSG00000171533	MAP6	HGNC Symbol		microtubule associated protein 6 [Source:HGNC Symbol/Accession:HGNC:5868]	-0.731727753	0.165311461	0.090811472	I	1.502755649	0.722328586	0.137116361	I
ENSG00000171564	F88	HGNC Symbol		fibrinogen beta chain [Source:HGNC Symbol/Accession:HGNC:3652]	-0.538885417	0.353987755	-0.649314018	I	0.346586491	0.948978235	0.333405568	I
ENSG00000171587	DSCAM	HGNC Symbol		DS cell adhesion molecule [Source:HGNC Symbol/Accession:HGNC:3039]	-0.37928207	0.536270648	-0.580745445	I	-0.030878088	I	0.195786971	I
ENSG00000171804	WDR87	HGNC Symbol		WD repeat domain 87 [Source:HGNC Symbol/Accession:HGNC:29534]	-0.524912283	0.382145688	-0.682786048	I	0.444774723	0.909669442	0.373156363	I
ENSG00000172137	CALB2	HGNC Symbol		calbindin 2 [Source:HGNC Symbol/Accession:HGNC:1435]	-0.440233971	0.434741137	0.21779933	I	2.09457605	0.708026594	-0.205290856	I
ENSG00000172350	ABCG4	HGNC Symbol		ATP binding cassette subfamily 5 member 4 [Source:HGNC Symbol/Accession:HGNC:13884]	-0.405715033	0.501052173	0.314257023	I	1.422637709	0.764917559	-0.1292136	I
ENSG00000172752	COL6A5	HGNC Symbol		collagen type VI alpha 5 chain [Source:HGNC Symbol/Accession:HGNC:26674]	-0.361607057	0.544895906	-0.407459921	I	0.034008655	I	0.39718527	I
ENSG00000172910	AP002387.1	Clone-based (Ensembl) gene			-0.66726617	0.284084703	-0.075973221	I	0.242189975	0.969429601	-0.18878485	I
ENSG00000172995	ARPP21	HGNC Symbol		cAMP regulated phosphoprotein 21 [Source:HGNC Symbol/Accession:HGNC:16968]	-0.416436637	0.360187156	-0.454427275	I	1.644518848	0.729803191	-0.254249133	I
ENSG00000173013	CCDC56	HGNC Symbol		coiled-coil domain containing 96 [Source:HGNC Symbol/Accession:HGNC:26900]	-0.507224369	0.11847151	0.507436345	I	0.129993356	0.97157073	-0.352824188	I
ENSG000001	SYT12	HGNC Symbol		synaptotagmin 12 [Source:HGNC Symbol/Accession:HGNC:26664]	-0.752963578	0.17604345	0.610713148	I	0.81026281	0.844324446	-0.328292543	I

73227			Symbol:HGNC:16381	-0.33748808	0.604591273	0.1382629	I			-0.470050345	0.905838541	0.42555982	I
ENSG00000173572	NLRP3	HGNC Symbol	NLR family pyrin domain containing 3 [Source:HGNC Symbol;Acc:HGNC:22937]	-0.33748808	0.604591273	0.1382629	I			-0.470050345	0.905838541	0.42555982	I
ENSG00000173702	MUC13	HGNC Symbol	"mucin 13, cell surface associated [Source:HGNC Symbol;Acc:HGNC:7511]"	-0.770938778	0.184683607	-0.5282705461	I			1.168800706	0.794618344	0.833393032	I
ENSG00000173769	TOPAZ1	HGNC Symbol	testis and ovary specific PAZ domain containing 1 [Source:HGNC Symbol;Acc:HGNC:24746]	-0.580049747	0.337975386	-0.47844312	I			-0.338583882	0.9365972232	1.035469015	I
ENSG00000173826	KCNH6	HGNC Symbol	potassium voltage-gated channel subfamily H member 6 [Source:HGNC Symbol;Acc:HGNC:18862]	-0.668262344	0.228310769	0.394938306	I			1.100529597	0.828704895	-0.56022732	I
ENSG00000174279	EVX2	HGNC Symbol	even-skipped homeobox 2 [Source:HGNC Symbol;Acc:HGNC:3507]	-0.532607087	0.366352883	-0.57054964	I			0.799078553	0.889485378	0.127210495	I
ENSG00000174358	SLC6A19	HGNC Symbol	solute carrier family 6 member 19 [Source:HGNC Symbol;Acc:HGNC:27960]	-0.552428142	0.225701299	0.13921652	I			-0.774625877	0.768821837	0.337627528	I
ENSG00000174498	IGDCC3	HGNC Symbol	immunoglobulin superfamily DCC subclass member 3 [Source:HGNC Symbol;Acc:HGNC:9700]	-0.50046529	0.388556	-0.506918157	I			1.666251621	0.73188104	-0.167547923	I
ENSG00000174502	SLC26A9	HGNC Symbol	solute carrier family 26 member 9 [Source:HGNC Symbol;Acc:HGNC:14469]	-0.707161365	0.159137172	-0.29131487	I			0.667466569	0.881825991	-0.1082688663	I
ENSG00000174963	ZIC4	HGNC Symbol	Zic family member 4 [Source:HGNC Symbol;Acc:HGNC:20393]	-0.741912748	0.189304778	0.015294782	I			0.73795342	0.888736761	-0.4251763	I
ENSG00000175084	DES	HGNC Symbol	desmin [Source:HGNC Symbol;Acc:HGNC:2770]	-0.749695034	0.140474867	0.245561209	I			1.76995268	0.686547614	-0.118495503	I
ENSG00000175267	VWA3A	HGNC Symbol	von Willebrand factor A domain containing 3A [Source:HGNC Symbol;Acc:HGNC:27088]	-0.718694352	0.137008563	-0.162720501	I			0.187461706	0.958051922	0.05746752	I
ENSG00000175267	VWA3A	HGNC Symbol	von Willebrand factor A domain containing 3A [Source:HGNC Symbol;Acc:HGNC:27088]	-0.718694352	0.137008563	-0.162720501	I			0.187461706	0.958051922	0.05746752	I
ENSG00000175329	ISX	HGNC Symbol	intestinal specific homeobox [Source:HGNC Symbol;Acc:HGNC:28084]	-0.48812621	0.42503449	-0.551353563	I			1.20778078	0.81501072	-0.735778555	I
ENSG00000175329	PNLIP	HGNC Symbol	pancreatic lipase [Source:HGNC]	-0.830503663	0.166474844	-0.389366106	I			0.958606296	0.850895463	0.152818215	I

75535			Symbol:Acc:HGN:91655	-0.30777252	0.660657448	-0.264696304	1	1.96668803	0.744348791	-0.027916483	1
ENSG00000176584	DMBTP1	HGNC Symbol	deleted in malignant brain tumors pseudogene 1 [Source:HGNC Symbol;Acc:HGN:49497]	-0.433973597	0.471807255	-0.23701654	1	0.48299916	0.923307954	0.07382279	1
ENSG00000176769	TGERGIL	HGNC Symbol	transcription elongation regulator 1 like [Source:HGNC Symbol;Acc:HGN:23533]	-0.49222255	0.30754939	0.34671465	1	-0.883712439	0.810351631	0.13841864	1
ENSG00000177045	SIX5	HGNC Symbol	SIX homeobox 5 [Source:HGNC Symbol;Acc:HGN:10891]	-0.501025251	0.288065754	0.366761609	1	0.160265906	0.96794435	-0.148492038	1
ENSG00000177103	DSCAM1	HGNC Symbol	DS cell adhesion molecule like 1 [Source:HGNC Symbol;Acc:HGN:14656]	-0.437224218	0.467988721	0.35497182	1	-0.247144947	0.955305328	0.2797618	1
ENSG00000177354	C10orf71	HGNC Symbol	chromosome 10 open reading frame 71 [Source:HGNC Symbol;Acc:HGN:26973]	-0.634752306	0.297333593	0.055097244	1	2.826182561	0.687959091	0.32761642	1
ENSG00000177511	ST8SIA3	HGNC Symbol	"ST8 alpha-N-acetyl-neuraminidase alpha-2,8-sialyltransferase 3 [Source:HGNC Symbol;Acc:HGN:14269]"	-0.492445704	0.438965661	0.06184014	1	6.104847404	0.627668963	0.000430184	1
ENSG00000177551	NHLH2	HGNC Symbol	nascent helix-loop-helix 2 [Source:HGNC Symbol;Acc:HGN:7818]	-0.351255676	0.529103555	-0.209982696	1	1.83083159	0.786977233	0.220809557	1
ENSG00000178031	ADAMTS1	HGNC Symbol	ADAMTS like 1 [Source:HGNC Symbol;Acc:HGN:14632]	-0.45777165	0.43225924	0.229558372	1	1.021029291	0.800489011	0.163647887	1
ENSG00000178171	AMER3	HGNC Symbol	APC membrane recruitment protein 3 [Source:HGNC Symbol;Acc:HGN:26711]	-0.165645558	0.837547319	-0.189812542	1	0.875337112	0.82843164	0.142857609	1
ENSG00000178568	ERBB4	HGNC Symbol	erb-b2 receptor tyrosine kinase 4 [Source:HGNC Symbol;Acc:HGN:3432]	-0.503971682	0.476649736	-0.131401788	1	-0.029554337	1	0.592068389	1
ENSG00000178645	C10orf53	HGNC Symbol	chromosome 10 open reading frame 53 [Source:HGNC Symbol;Acc:HGN:27421]	-0.468692104	0.391850792	-0.463966108	1	1.267106841	0.755765503	0.225343111	1
ENSG00000178965	ERIC3	HGNC Symbol	glutamate rich 3 [Source:HGNC Symbol;Acc:HGN:25346]	-0.402370572	0.557284045	-0.360707151	1	1.892588105	0.755052776	-0.210521021	1
ENSG00000179008	C14orf39	HGNC Symbol	chromosome 14 open reading frame 39 [Source:HGNC Symbol;Acc:HGN:19849]	-0.507994532	0.427813498	0.036818661	1	0.399238913	0.939106996	0.45023468	1
ENSG00000179178	TMEM25	HGNC Symbol	transmembrane protein 25 [Source:HGNC Symbol;Acc:HGN:28275]								

ENSG00000179270	C2orf71	HGNC Symbol	chromosome 2 open reading frame 71 [Source:HGNC Symbol;Acc:HGNC:34383]	-0.0942048	0.758600069	-0.01658454	1	1.21207623	0.773820479	-0.018033757	1
ENSG00000179709	NLRP8	HGNC Symbol	NLR family pyrin domain containing 8 [Source:HGNC Symbol;Acc:HGNC:27940]	-0.380100885	0.5558810858	-0.183052797	1	-0.638700795	0.876079103	0.499537451	1
ENSG00000179766	ATP8B5P	HGNC Symbol	"ATPase phospholipid transporting 8B5, pseudogene [Source:HGNC Symbol;Acc:HGNC:27245]"	-1.080550104	0.00897767	-0.483317498	1	2.875052037	0.655599592	0.080758193	1
ENSG00000179813	FAM216B	HGNC Symbol	family with sequence similarity 216 member 8 [Source:HGNC Symbol;Acc:HGNC:26883]	-0.305849787	0.706073351	-0.066443991	1	1.117423548	0.855882707	0.510481003	1
ENSG00000180251	SLC9A4	HGNC Symbol	solute carrier family 9 member A4 [Source:HGNC Symbol;Acc:HGNC:10777]	-0.349423486	0.580627041	0.354323333	1	1.853862248	0.729803191	0.137552884	1
ENSG00000181043	MUC16	HGNC Symbol	"mucin 16, cell surface associated [Source:HGNC Symbol;Acc:HGNC:15582]"	-0.329348592	0.430361654	0.265140388	1	-0.610345242	0.829802444	0.370527471	1
ENSG00000181655	DFCC1	HGNC Symbol	orofacial cleft 1 candidate 1 [Source:HGNC Symbol;Acc:HGNC:21077]	-0.532352428	0.437614901	-0.6518974	1	0.495357178	0.913357086	-0.37543806	1
ENSG00000181878	CFAP65	HGNC Symbol	cilia and flagella associated protein 65 [Source:HGNC Symbol;Acc:HGNC:25325]	-0.434847926	0.442646097	-0.142589287	1	-0.442095435	0.88530895	-0.140868213	1
ENSG00000182256	GABRG3	HGNC Symbol	gamma-aminobutyric acid type A receptor gamma3 subunit [Source:HGNC Symbol;Acc:HGNC:4088]	-0.256253297	0.695478261	0.00161851	1	1.678376167	0.747180575	0.537162329	1
ENSG00000183016	NA	NA	NA	-0.30865823	0.66044616	-0.409663712	1	0.214055917	0.953151217	0.164903336	1
ENSG00000183067	IGSF5	HGNC Symbol	immunoglobulin superfamily member 5 [Source:HGNC Symbol;Acc:HGNC:5952]	-0.51802971	0.45724594	0.01001437	1	5.552457083	0.627668963	0.610657108	1
ENSG00000183206	POTEC	HGNC Symbol	POTE ankyrin domain family member C [Source:HGNC Symbol;Acc:HGNC:33894]	-0.327817046	0.614566385	0.288269994	1	1.44511872	0.771574746	0.091740315	1
ENSG00000183242	WT1-AS	HGNC Symbol	WT1 antisense RNA [Source:HGNC Symbol;Acc:HGNC:18135]	-0.327487007	0.635330315	-0.249101635	1	2.831419192	0.689955785	0.271993402	1
ENSG00000183287	CCBE1	HGNC Symbol	collagen and calcium binding EGF domains 1 [Source:HGNC Symbol;Acc:HGNC:29426]	-0.590879294	0.238072541	-0.108476557	1	0.677199826	0.88616233	0.102473963	1

ENSG000000183304	FAM6A	HGNC Symbol	family with sequence similarity 9 member A [Source:HGNC Symbol;Acc:HGNC:18403]	-0.938058237	0.096563875	0.782998855	1	1.285285772	0.817952528	-0.064655486	1
ENSG000000183317	EPHA10	HGNC Symbol	EPH receptor A10 [Source:HGNC Symbol;Acc:HGNC:18987]	-0.4656692797	0.372910955	-0.327048168	1	0.884261146	0.827048984	0.189214369	1
ENSG000000183580	FBXL7	HGNC Symbol	F-box and leucine rich repeat protein 7 [Source:HGNC Symbol;Acc:HGNC:18604]	-0.591833997	0.365077842	-0.524694327	1	0.925469737	0.860534878	0.671873557	1
ENSG000000183668	PSC9	HGNC Symbol	pregnancy specific beta-1-glycoprotein 9 [Source:HGNC Symbol;Acc:HGNC:9526]	-0.7812682	0.219746846	-0.250813779	1	-0.395330668	0.939971429	0.5854285	1
ENSG000000183778	B3GALT5	HGNC Symbol	"beta-1,3-galactosyltransferase 5 [Source:HGNC Symbol;Acc:HGNC:920]"	-0.49369755	0.401627772	-0.981381657	1	2.317782659	0.722505857	0.66367188	1
ENSG000000183780	SLC35F3	HGNC Symbol	solute carrier family 35 member F3 [Source:HGNC Symbol;Acc:HGNC:23616]	-0.289176693	0.42216105	0.083035636	1	0.842283744	0.692730659	-0.242552512	1
ENSG000000183856	IQGAP3	HGNC Symbol	IQ motif containing GTPase activating protein 3 [Source:HGNC Symbol;Acc:HGNC:20669]	-0.465335464	0.302087891	-0.18178081	1	-0.438153854	0.859665429	0.160570003	1
ENSG000000183876	AKR1	HGNC Symbol	arylsulfatase family member 1 [Source:HGNC Symbol;Acc:HGNC:32521]	-0.487563606	0.409216661	0.27277552	1	1.28686611	0.787338888	-0.216444352	1
ENSG000000183908	LRRCS5	HGNC Symbol	leucine rich repeat containing 55 [Source:HGNC Symbol;Acc:HGNC:32324]	-0.306233165	0.504776413	0.04564564	1	2.382698282	0.7135474	0.020004922	1
ENSG000000184012	TMPPSS2	HGNC Symbol	transmembrane serine protease 2 [Source:HGNC Symbol;Acc:HGNC:18716]	-0.918134548	0.037008563	-0.246437402	1	0.101566228	0.991823026	-0.08984279	1
ENSG000000184227	ACOT1	HGNC Symbol	acyl-CoA thioesterase 1 [Source:HGNC Symbol;Acc:HGNC:33128]	-0.665239244	0.162555375	0.52223814	1	-0.626385273	0.79452482	-0.42718998	1
ENSG000000184302	SIX6	HGNC Symbol	SIX homeobox 6 [Source:HGNC Symbol;Acc:HGNC:10892]	-0.504088891	0.444451067	0.558233399	1	-0.45856923	1	0.23867606	1
ENSG000000184304	PRK01	HGNC Symbol	protein kinase D1 [Source:HGNC Symbol;Acc:HGNC:9407]	-0.428597371	0.45595988	-0.063709292	1	1.432135626	0.74753826	0.035035921	1
ENSG000000184809	B3GALT5-AS1	HGNC Symbol	B3GALT5 antisense RNA 1 [Source:HGNC Symbol;Acc:HGNC:16424]	-0.338454269	0.194566385	0.140091076	1	-0.05616504	0.99937713	0.744088602	1
ENSG000000184908	CLCNK8	HGNC Symbol	chloride voltage-gated channel K8 [Source:HGNC Symbol;Acc:HGNC:2027]	-0.357681839	0.540451079	0.402220282	1	-0.836321916	0.799148915	0.13433106	1

ENSG00000185038	MRDH2A	HGNC Symbol	maestro heat like repeat family member 2A [Source:HGNC Symbol;Acc:HGNC:27936]	-0.3843993	0.52383994	-0.192967031	1	0.867416789	0.82438292	-0.16523539	1
ENSG00000185059	KRT76	HGNC Symbol	keratin 76 [Source:HGNC Symbol;Acc:HGNC:24430]	-0.55801061	0.3653399635	-0.1624748239	1	-0.169532548	0.1855426705	-0.328689771	1
ENSG00000185303	SFTPA2	HGNC Symbol	surfactant protein A2 [Source:HGNC Symbol;Acc:HGNC:10799]	-0.8033555633	0.1896336469	-0.4046666554	1	2.140855914	0.727590986	0.3019447	1
ENSG00000185303	SCN10A	HGNC Symbol	sodium voltage-gated channel alpha subunit 10 [Source:HGNC Symbol;Acc:HGNC:10582]	-0.230551689	0.73525037	-0.456626467	1	0.167482357	0.97338649	0.143189125	1
ENSG00000185467	KPNA7	HGNC Symbol	karyopherin subunit alpha 7 [Source:HGNC Symbol;Acc:HGNC:21838]	-0.169440359	0.827997131	-0.275420291	1	-0.3087587	0.948256578	0.279772356	1
ENSG00000185686	PRAME	HGNC Symbol	preferentially expressed antigen in melanoma [Source:HGNC Symbol;Acc:HGNC:9336]	-0.683189263	0.238379249	-0.341640386	1	0.328835819	0.94835771	0.181682549	1
ENSG00000185737	NREG3	HGNC Symbol	neuregulin 3 [Source:HGNC Symbol;Acc:HGNC:7959]	-0.337077231	0.60833718	-0.587514657	1	-0.202080434	0.974607748	0.35711249	1
ENSG00000185739	SRL	HGNC Symbol	sarcalumenin [Source:HGNC Symbol;Acc:HGNC:14295]	-0.718970248	0.182933474	-0.41889582	1	1.10100047	0.794748396	0.04037772	1
ENSG00000185823	NPAPI	HGNC Symbol	nuclear pore associated protein 1 [Source:HGNC Symbol;Acc:HGNC:1190]	-0.709480544	0.238778807	-0.22845567	1	0.3798295	0.939781849	0.780350439	1
ENSG00000185974	GRK1	HGNC Symbol	G protein-coupled receptor kinase 1 [Source:HGNC Symbol;Acc:HGNC:10013]	-0.524927614	0.3655633153	0.327610652	1	0.846577371	0.185513218	0.105802313	1
ENSG00000186185	KIF18B	HGNC Symbol	kinesin family member 18B [Source:HGNC Symbol;Acc:HGNC:27102]	-0.5339102601	0.18735537	0.134590856	1	1.659755026	0.627668963	-0.143354427	1
ENSG00000186393	KRT26	HGNC Symbol	keratin 26 [Source:HGNC Symbol;Acc:HGNC:30840]	-0.509610904	0.3393531656	-0.574819347	1	-0.273830863	0.967516048	-0.245635919	1
ENSG00000186487	MYT1L	HGNC Symbol	myelin transcription factor 1 like [Source:HGNC Symbol;Acc:HGNC:7623]	-0.551259763	0.323477526	-0.24557518	1	1.189653359	0.773755142	0.273450958	1
ENSG00000186526	CYP4F8	HGNC Symbol	cytochrome P450 family 4 subfamily F member 8 [Source:HGNC Symbol;Acc:HGNC:2648]	-0.63355634	0.284297086	-0.29164062	1	0.19497069	0.976100317	0.046848148	1
ENSG00000186862	PDZ7	HGNC Symbol	PDZ domain containing 7 [Source:HGNC Symbol;Acc:HGNC:26257]	-0.554675047	0.16405126	0.24786803	1	0.223054668	0.933489898	0.072654071	1

ENSG00000187068	C3orf70	HGNC Symbol	chromosome 3 open reading frame 70 [Source:HGNC Symbol;Acc:HGNC:33731]	-0.68322704	0.73584403	-0.165105326	1	-0.093299772	0.99623026	0.304445716	1
ENSG00000187094	CCX	HGNC Symbol	cholecystokinin [Source:HGNC Symbol;Acc:HGNC:15659]	-0.809919388	0.14882769	1.13454622	1	0.058535969	1	-0.258457511	1
ENSG00000187123	LYPD6	HGNC Symbol	LY6/PLAUR domain containing 6 [Source:HGNC Symbol;Acc:HGNC:28751]	-0.509808838	0.40101695	-0.57357905	1	0.866181631	0.820682968	0.56627688	1
ENSG00000187527	ATP13A5	HGNC Symbol	ATPase 13A5 [Source:HGNC Symbol;Acc:HGNC:31789]	-0.467545509	0.42873196	-0.4127252	1	1.18986564	0.76677233	0.279380903	1
ENSG00000187772	LIN28B	HGNC Symbol	lin-28 homolog B [Source:HGNC Symbol;Acc:HGNC:32207]	-0.23447087	0.763770257	0.216214401	1	-0.08347151	1	0.066218621	1
ENSG00000187905	LRRIC748	HGNC Symbol	leucine rich repeat containing 748 [Source:HGNC Symbol;Acc:HGNC:34301]	-0.46104362	0.40745351	-0.031748982	1	1.2449596	0.78518502	0.049322593	1
ENSG00000187955	COL14A1	HGNC Symbol	collagen type XIV alpha 1 chain [Source:HGNC Symbol;Acc:HGNC:2191]	-0.807542914	0.060883822	-0.101927735	1	0.493543	0.886562045	0.093906397	1
ENSG00000187997	C17orf99	HGNC Symbol	chromosome 17 open reading frame 99 [Source:HGNC Symbol;Acc:HGNC:34490]	-0.54593757	0.228439083	0.090918915	1	-0.722809509	0.77316391	0.2829164	1
ENSG00000188086	PRSS45	HGNC Symbol	serine protease 45 [Source:HGNC Symbol;Acc:HGNC:30717]	-0.561061502	0.385562803	-0.219432799	1	2.05684047	0.71431936	0.081688504	1
ENSG00000188112	C6orf182	HGNC Symbol	chromosome 6 open reading frame 182 [Source:HGNC Symbol;Acc:HGNC:21288]	-0.912928908	0.01832144	-0.309851842	1	1.835030288	0.697833232	-0.5432910558	1
ENSG00000188162	DTG6	HGNC Symbol	atropalin [Source:HGNC Symbol;Acc:HGNC:8516]	-0.501929759	0.346681837	-0.004039957	1	0.595459788	0.858968348	0.031693298	1
ENSG00000188338	SLC38A3	HGNC Symbol	solute carrier family 38 member 3 [Source:HGNC Symbol;Acc:HGNC:18044]	-0.78738167	0.162708524	-0.516375224	1	0.918485421	0.81817296	0.112758663	1
ENSG00000188488	SERPINA5	HGNC Symbol	serpin family A member 5 [Source:HGNC Symbol;Acc:HGNC:81723]	-0.692734716	0.249884109	-0.3988627059	1	-0.0669861093	0.99928282	0.034654676	1
ENSG00000188706	ZDHHC9	HGNC Symbol	zinc finger DHHC-type containing 9 [Source:HGNC Symbol;Acc:HGNC:18475]	-0.385110334	0.031930967	0.055051422	1	0.707442896	0.705378609	0.08497174	1
ENSG00000188782	CATSPER4	HGNC Symbol	cation channel sperm associated 4 [Source:HGNC Symbol;Acc:HGNC:23220]	-0.823398746	0.157965233	0.371662979	1	-0.078094345	0.955880337	0.022695997	1

ENSG00000188803	SHISA6	HGNC Symbol	shisa family member 6 [Source:HGNC Symbol;Acc:HGNC:34491]	-0.56218657	0.4827683	0.142754216	1	0.753257085	0.861916553	0.190594903	1
ENSG00000188886	ASTL	HGNC Symbol	astacin like metalloendopeptidase [Source:HGNC Symbol;Acc:HGNC:37014]	-1.137621915	0.1005079261	-0.606540007	1	0.9491025586	0.791067562	-0.021026839	1
ENSG00000195091	MYBP1	HGNC Symbol	"myosin binding protein C, slow type" [Source:HGNC Symbol;Acc:HGNC:7549]"	-0.4301673258	0.437393542	-0.625720148	1	0.3195888777	0.933370884	-0.01044474	1
ENSG00000195186	SERPINA3	HGNC Symbol	serpin family A member 3 [Source:HGNC Symbol;Acc:HGNC:16]	-0.909099758	0.106147674	-0.356107603	1	0.191407925	0.97700652	-0.282370334	1
ENSG00000196361	ELAVL3	HGNC Symbol	ELAV like RNA binding protein 3 [Source:HGNC Symbol;Acc:HGNC:3314]	-0.75893849	0.14285189	0.301485434	1	1.953137262	0.706495236	-0.235289109	1
ENSG00000196415	PRTN3	HGNC Symbol	proteinase 3 [Source:HGNC Symbol;Acc:HGNC:9495]	-1.443754633	0.102256568	-0.30167102	1	1.102437354	0.834510279	-0.376208763	1
ENSG00000196555	HBE2	HGNC Symbol	hemoglobin subunit gamma 2 [Source:HGNC Symbol;Acc:HGNC:48322]	-0.934242715	0.01495659	-0.512955497	1	-0.260328339	0.915138245	-0.54797429	1
ENSG00000196862	RBP04	HGNC Symbol	RANBP2-like and GRP domain containing 4 [Source:HGNC Symbol;Acc:HGNC:32417]	-0.694081274	0.03331637	-0.37604602	1	6.58910869	0.402387206	0.140028952	1
ENSG00000197179	KRT35	HGNC Symbol	keratin 35 [Source:HGNC Symbol;Acc:HGNC:6453]	-0.6586105324	0.248428762	-0.0910695231	1	2.153446723	0.697833232	-0.6327012814	1
ENSG00000197085	NPSR1-AS1	HGNC Symbol	NPSR1 antisense RNA 1 [Source:HGNC Symbol;Acc:HGNC:22128]	-0.47182751	0.3853333526	-0.3210916913	1	6.218739468	0.6271668953	0.689886278	1
ENSG00000197406	DIO3	HGNC Symbol	iodothyronine deiodinase 3 [Source:HGNC Symbol;Acc:HGNC:2885]	-0.582483597	0.278225713	0.404297609	1	0.463541897	0.935206684	-0.223986968	1
ENSG00000197408	CYP2B6	HGNC Symbol	cytochrome P450 family 2 subfamily B member 6 [Source:HGNC Symbol;Acc:HGNC:2615]	-0.59880912	0.385101274	-0.632533554	1	0.912342099	0.837574131	-0.552716613	1
ENSG00000197893	NRAP	HGNC Symbol	nebulin related anchoring protein [Source:HGNC Symbol;Acc:HGNC:7988]	-0.32565366	0.53782084	-0.271589128	1	0.792610765	0.853462632	0.153166107	1
ENSG00000197991	AL592490.1	Clone-based (Ensembl) gene		-0.605428219	0.3431010516	0.070232594	1	-0.413722368	0.916194501	-0.158852377	1
ENSG00000198010	DLGAP2	HGNC Symbol	DLG associated protein 2 [Source:HGNC Symbol;Acc:HGNC:2906]	-0.462914925	0.409741714	0.068714455	1	1.089410281	0.791327824	0.195394349	1

ENSG00000188597	ZNF536	HGNC Symbol	zinc finger protein 536 [Source:HGNC Symbol;Acc:HGNC:29025]	-0.38101683	0.61244809	-0.44524084	1	0.638644973	0.872919273	0.385147069	1
ENSG00000188765	SYCP1	HGNC Symbol	synaptonemal complex protein 1 [Source:HGNC Symbol;Acc:HGNC:14487]	-0.47425869	0.465583509	0.018210108	1	-0.44549302	0.913883645	0.55351793	1
ENSG00000188788	MUC2	HGNC Symbol	"mucin 2, oligomeric mucus/gel-forming" [Source:HGNC Symbol;Acc:HGNC:7512]"	-0.356594229	0.524792504	0.28921094	1	0.760765909	0.824640952	-0.243937903	1
ENSG00000188944	POU3F3	HGNC Symbol	POU class 3 homeobox 3 [Source:HGNC Symbol;Acc:HGNC:9216]	-0.566373551	0.325222565	-0.01913062	1	2.50137942	0.707562018	0.163345574	1
ENSG00000188929	NOS1AP	HGNC Symbol	nitric oxide synthase 1 adaptor protein [Source:HGNC Symbol;Acc:HGNC:16859]	-0.522447538	0.23360559	-0.482658569	1	2.16915026	0.640562142	0.142426268	1
ENSG00000183805	PLPP4	HGNC Symbol	phospholipid phosphatase 4 [Source:HGNC Symbol;Acc:HGNC:23531]	-0.645887167	0.226621278	-0.402456377	1	-0.697719625	0.843135524	-0.146576451	1
ENSG00000183900	ALU18271	Clone-based (Ensembl) gene		-0.907580244	0.059158339	0.236165065	1	-0.168928987	0.97893783	0.2578666836	1
ENSG00000184055	ALU181611	Clone-based (Ensembl) gene		-0.30965998	0.531561049	-0.010051371	1	0.074072995	0.992995239	-0.246765108	1
ENSG00000184241	AP0009111	Clone-based (Ensembl) gene		-0.52422921	0.047699169	-0.232933883	1	0.294013453	0.908187547	0.165068872	1
ENSG00000184283	LINC01873	HGNC Symbol	long intergenic non-protein coding RNA 1873 [Source:HGNC Symbol;Acc:HGNC:52800]	-0.688310921	0.054758167	-0.228184457	1	0.631351983	0.869751079	0.435875025	1
ENSG00000184335	SP5	HGNC Symbol	Sp5 transcription factor [Source:HGNC Symbol;Acc:HGNC:14529]	-0.7810125	0.179308229	-0.693704258	1	3.816503481	0.654405468	-0.629007298	1
ENSG00000184624	DISP3	HGNC Symbol	dispatched RND transporter family member 3 [Source:HGNC Symbol;Acc:HGNC:29251]	-0.55601574	0.12163059	0.072435023	1	0.368182364	0.908517399	-0.01202324	1
ENSG00000184661	C5orf60	HGNC Symbol	chromosome 5 open reading frame 60 [Source:HGNC Symbol;Acc:HGNC:27753]	-0.728340381	0.247590568	0.228008501	1	1.464324916	0.818753547	0.320839584	1
ENSG00000184929	AC007389.1	Clone-based (Ensembl) gene		-0.64685442	0.287661756	-0.866338929	1	0.579187938	0.895714972	0.775627303	1
ENSG00000184941	PSS5	HGNC Symbol	pregnancy specific beta-1-glycoprotein 5 [Source:HGNC Symbol;Acc:HGNC:9522]	-0.38745193	0.571961572	-0.013942807	1	0.234391505	0.959072561	0.627451691	1

ENSG00000205054	LINC0121	HGNC Symbol	long intergenic non-protein coding RNA 121 [Source:HGNC Symbol;Acc:HGNC:49266]	-0.287245288	0.59120517	-1.112595252	1	1.432991369	0.762363148	0.218446559	1
ENSG00000205176	REXOLIP	HGNC Symbol	"REXOLIP like 1, pseudogene [Source:HGNC Symbol;Acc:HGNC:24660]"	-0.633446922	0.361284725	-0.149338523	1	1.703370547	0.729530842	0.03289074	1
ENSG00000205312	KRT17P4	HGNC Symbol	keratin 17 pseudogene 4 [Source:HGNC Symbol;Acc:HGNC:50722]	-0.714632956	0.27101304	-0.895507246	1	4.115403356	0.6271668963	-0.335992563	1
ENSG00000205396	LINC00661	HGNC Symbol	long intergenic non-protein coding RNA 661 [Source:HGNC Symbol;Acc:HGNC:27002]	-0.690094998	0.181897869	-0.726364755	1	-0.15814647	0.979462675	0.06687752	1
ENSG00000205592	MUC19	HGNC Symbol	"mucin 19, oligomeric [Source:HGNC Symbol;Acc:HGNC:14362]"	-0.30661845	0.552328817	-0.434301209	1	0.984766625	0.78782192	0.298495845	1
ENSG00000205667	ARSH	HGNC Symbol	arylsulfatase family member 1 [Source:HGNC Symbol;Acc:HGNC:32488]	-0.537559532	0.388914138	-0.055380476	1	4.99427616	0.634030703	0.00757458	1
ENSG00000205922	ONECUT3	HGNC Symbol	one cut homeobox 3 [Source:HGNC Symbol;Acc:HGNC:13399]	-0.673545388	0.251061423	-0.5855676548	1	-0.72491049	0.849107793	-0.305046492	1
ENSG00000205976	AC099511	Clone-based (Ensembl) gene		-0.7212746	0.22466354	0.261966231	1	0.948881624	0.86678933	-0.382218884	1
ENSG00000210121	MT-1A	HGNC Symbol	mitochondrially encoded tRNA alanine [Source:HGNC Symbol;Acc:HGNC:7475]	-0.731149542	0.078668146	-0.731653603	1	0.561715026	0.861305803	-0.165210137	1
ENSG00000213467	HMGBP37	HGNC Symbol	high mobility group box 1 pseudogene 37 [Source:HGNC Symbol;Acc:HGNC:39184]	-1.143333337	0.007876108	0.64533241	1	5.32914463	0.6271668963	0.131234386	1
ENSG00000213864	EEF1B2P2	HGNC Symbol	eukaryotic translation elongation factor 1 beta 2 pseudogene 2 [Source:HGNC Symbol;Acc:HGNC:3209]	-1.164371093	0.00451201	0.09851276	1	0.671113155	0.884405435	0.368107814	1
ENSG00000213834	HBB1	HGNC Symbol	hemoglobin subunit gamma 1 [Source:HGNC Symbol;Acc:HGNC:4831]	-1.510612934	0.00753409	0.5718763	1	-1.38189497	0.687959091	-0.59732425	1
ENSG00000214128	TNEM213	HGNC Symbol	transmembrane protein 213 [Source:HGNC Symbol;Acc:HGNC:27220]	-0.72138795	0.18125378	0.013627618	1	0.8347191087	0.852992821	0.02681621	1
ENSG00000214181	NA	NA	NA	-0.570789127	0.013222867	-0.0244144	1	1.472777831	0.681271684	0.54410143	1
ENSG00000214211	LCN11	HGNC Symbol	lipocalin like 1 [Source:HGNC]	-0.706465394	0.073719528	0.314468107	1	1.403831014	0.74059294	-0.20441238	1

[illegible]

ENSG00000224209	LINC00466	HGNC Symbol	SymbolAcc:HGNC:44931	-1.176748621	0.039870431	-0.329957707	1	4.996688997	0.63590801	1.016744481	1
ENSG00000224271	ALI07329.1	Clone-based (Ensembl) gene	long intergenic non-protein coding RNA 466 [Source:HGNC SymbolAcc:HGNC:27794]	-0.653993539	0.277648202	0.307895578	1	0.668981891	0.905148092	0.475804877	1
ENSG00000224367	DACYLP	HGNC Symbol	"D-acyltransferase like, pseudogene [Source:HGNC SymbolAcc:HGNC:44362]"	-0.608155491	0.290095547	-0.302440554	1	-0.18114355	0.930683948	0.288576794	1
ENSG00000224435	NFP6	HGNC Symbol	neurofilament 1 pseudogene 6 [Source:HGNC SymbolAcc:HGNC:7771]	-0.892662327	0.117501042	-0.465472953	1	2.806924373	0.70712199	0.467188001	1
ENSG00000224668	IP08P1	HGNC Symbol	importin 8 pseudogene 1 [Source:HGNC SymbolAcc:HGNC:41955]	-0.694655462	0.0993833688	0.021954815	1	2.071297623	0.688182163	0.145327181	1
ENSG00000224743	TEX2B-AS1	HGNC Symbol	TEX2B antisense RNA 1 [Source:HGNC SymbolAcc:HGNC:42784]	-0.608219016	0.2801832709	-0.442966632	1	5.7891038398	0.627668963	0.154270252	1
ENSG00000225637	AP00046.1	Clone-based (Ensembl) gene		-0.681940896	0.281827155	-0.627749272	1	1.545301662	0.79452432	-0.165724697	1
ENSG00000225649	AC064875.1	Clone-based (Ensembl) gene		-0.698790548	0.326326486	-0.296958899	1	2.053521976	0.74015481	0.77587026	1
ENSG00000225813	AC009291.1	Clone-based (Ensembl) gene		-0.210665195	0.744296595	-0.127561246	1	3.10429709	0.638925887	-0.104909586	1
ENSG00000225953	SATB2-AS1	HGNC Symbol	SATB2 antisense RNA 1 [Source:HGNC SymbolAcc:HGNC:26490]	-0.527452178	0.302410719	-0.107115886	1	-0.105927318	0.930101886	0.108210165	1
ENSG00000226057	PHF2P2	HGNC Symbol	PHD finger protein 2 pseudogene 2 [Source:HGNC SymbolAcc:HGNC:38808]	-0.337399658	0.358165552	-0.10126026	1	-0.168330573	0.79452432	0.065890247	1
ENSG00000226068	HNRNP3B4	HGNC Symbol	heterogeneous nuclear ribonucleoprotein A3 pseudogene 4 [Source:HGNC SymbolAcc:HGNC:39773]	-1.210081983	0.113553682	-0.1686354837	1	0.7651075801	0.86439314	0.359560736	1
ENSG00000226440	AL365214.2	Clone-based (Ensembl) gene		-0.69946602	0.287180065	-0.357778931	1	1.048188407	0.839325295	-0.182057491	1
ENSG00000226741	LINC02554	HGNC Symbol	long intergenic non-protein coding RNA 2554 [Source:HGNC SymbolAcc:HGNC:53594]	-0.684878038	0.273232765	-0.102695967	1	5.955412377	0.627668963	0.158850168	1

ENSG00000226790	HNRNP43P1	HGNC Symbol	Heterogeneous nuclear ribonucleoprotein A3 pseudogene 1 [Source:HGNC Symbol;Acc:HGNC:43729]	-1.384734034	0.000189579	-0.396590339	1	0.3016281	0.90474007	0.46236358	1
ENSG00000227036	LINC00511	HGNC Symbol	long intergenic non-protein coding RNA 511 [Source:HGNC Symbol;Acc:HGNC:43564]	-0.508830538	0.163757922	-0.081842392	1	1.073510076	0.75693946	0.134099004	1
ENSG00000227471	AKR1B5	HGNC Symbol	aldo-keto reductase family 1 member B5 [Source:HGNC Symbol;Acc:HGNC:37281]	-0.827071435	0.17195362	-0.187879279	1	0.846340303	0.90427395	-0.165761865	1
ENSG00000227525	RPL7P6	HGNC Symbol	ribosomal protein L7 pseudogene 6 [Source:HGNC Symbol;Acc:HGNC:32430]	-12.09818266	0.003030406	0.16827018	1	0.14051591	0.980905392	0.636393422	1
ENSG00000227744	LINC01940	HGNC Symbol	long intergenic non-protein coding RNA 1940 [Source:HGNC Symbol;Acc:HGNC:52763]	-0.601989106	0.304426384	-0.78870485	1	2.498837138	0.73088271	-0.334768949	1
ENSG00000227827	AC108959.2	Clone-based (Ensembl) gene		-0.592806597	0.166783813	0.347455004	1	-0.893238125	0.689965785	0.037220004	1
ENSG00000228549	BX294659.2	Clone-based (Ensembl) gene		-0.68006559	0.067244282	-0.066990016	1	1.550659524	0.6635464	0.142348654	1
ENSG00000228983	SLC47A1P1	HGNC Symbol	solute carrier family 47 member 1 pseudogene 1 [Source:HGNC Symbol;Acc:HGNC:51849]	-0.809448556	0.2081298	-0.07857477	1	0.169220954	0.989052009	-0.316269274	1
ENSG00000229447	SMPD4P2	HGNC Symbol	sphingomyelin phosphodiesterase 4 pseudogene 2 [Source:HGNC Symbol;Acc:HGNC:39574]	-0.546120346	0.3669203078	0.163672911	1	4.59874887	0.647433395	0.03574788	1
ENSG00000229240	LINC00710	HGNC Symbol	long intergenic non-protein coding RNA 710 [Source:HGNC Symbol;Acc:HGNC:27386]	-0.349696304	0.639769038	-0.463371659	1	2.389547223	0.723566719	0.812962187	1
ENSG00000229817	AL133412.1	Clone-based (Ensembl) gene		-1.13495271	0.03108855	-1.461271915	1	5.016959101	0.627668963	0.574333178	1
ENSG00000229972	IDCF3	HGNC Symbol	IQ motif containing F3 [Source:HGNC Symbol;Acc:HGNC:31816]	-0.707465438	0.238864276	0.069756894	1	4.84144043	0.657456325	-0.00510713	1
ENSG00000230102	LINC02028	HGNC Symbol	long intergenic non-protein coding RNA 2028 [Source:HGNC Symbol;Acc:HGNC:27718]	-0.849953172	0.166994187	0.080231664	1	0.129736947	0.98819763	-0.097566507	1
ENSG00000230183	LINC01721	HGNC Symbol	long intergenic non-protein coding RNA 1721 [Source:HGNC Symbol;Acc:HGNC:52508]	-0.269403043	0.710155514	-0.336765938	1	4.610759813	0.671541129	0.054222063	1
ENSG00000230483.1	AC004835.1	Clone-based		-0.84709631	0.10286431	-0.67554528	1	1.884314398	0.75297145	-0.465467109	1

3039Z	(Ensembl) gene		-0.38967666	0.57101555	-0.477976855	I				
ENS6000002	Clone-based (Ensembl) gene	AC092162.2				I	2.786369729	0.657456325	0.10748725	I
3055Z	(Ensembl) gene									
ENS6000002	Clone-based (Ensembl) gene	AL135270.2	-0.52204036	0.382707592	-0.0775818	I	2.277546357	0.701343297	0.278688325	I
3061S	(Ensembl) gene									
ENS6000002	HGNC Symbol	STMN1	-0.36029628	0.61243615	-0.60677596	I	1.869543521	0.749476591	-0.089168797	I
30873										
ENS6000002	HGNC Symbol	LINC01468	-0.539334563	0.42759164	-0.717745459	I	4.703091051	0.634030703	-0.018903925	I
3131	[Source:HGNC Symbol;Acc:HGNC:50913]									
ENS6000002	HGNC Symbol	LINC01516	-0.556465466	0.39546555	-0.448523675	I	1.461416413	0.750080465	0.581697176	I
3142Z	[Source:HGNC Symbol;Acc:HGNC:51211]									
ENS6000002	Clone-based (Ensembl) gene	AC007366.1	-0.504607303	0.318754361	0.14052029	I	-0.415516591	0.937772107	0.3049833976	I
3239Z	(Ensembl) gene									
ENS6000002	Clone-based (Ensembl) gene	AC004862.1	-0.37142132	0.617985726	-1.160261087	I	1.003284752	0.858986348	-0.087700714	I
3266T	(Ensembl) gene									
ENS6000002	Clone-based (Ensembl) gene	AC004390.1	-0.532711499	0.428875064	-0.325138065	I	5.470222099	0.638925887	0.24855089	I
3275S	(Ensembl) gene									
ENS6000002	Clone-based (Ensembl) gene	AL138889.1	-0.644340746	0.293569058	-0.4610286974	I	1.142684211	0.795694369	-0.057403209	I
33183	(Ensembl) gene									
ENS6000002	HGNC Symbol	LINC01841	-0.755094485	0.24458107	-0.305990277	I	2.164161494	0.727990586	0.34561188	I
3339S										
ENS6000002	Clone-based (Ensembl) gene	AL03283.2	-0.639007269	0.29517571	0.130714248	I	-0.844030822	0.823283606	-0.389027234	I
3348S	(Ensembl) gene									
ENS6000002	Clone-based (Ensembl) gene	AC010294.1	-0.707276432	0.262329375	-0.342774764	I	0.7990016026	0.895729958	-0.14359571	I
33539	(Ensembl) gene									
ENS6000002	HGNC Symbol	LINC01360	-0.427335916	0.5466910871	-0.5187510937	I	0.1067106038	0.994504436	0.819352419	I
33973										
ENS6000002	Clone-based (Ensembl) gene	AC099691.3	-1.218272617	0.027526442	-0.38785005	I	4.91323959	0.627686963	-0.065503493	I
3397T	(Ensembl) gene									
ENS6000002	NA	NA	-0.525516832	0.310266093	-0.658589656	I	0.7078914	0.8791510351	-0.066786642	I

[illegible]

37222			[Source:HGNC Symbol;Acc:HGNC:52794]	-0.84497088	0.225602335	-0.12960044	1	0.190846578	0.98354954	0.160652494	1
ENSG00000237250	AL358924.1	Clone-based (Ensembl) gene									
ENSG00000237289	CKMT1B	HGNC Symbol	"creatine kinase, mitochondrial 1B [Source:HGNC Symbol;Acc:HGNC:16955]"	-0.216490618	0.195077893	-0.294425419	1	1.787760281	0.752827393	0.548281639	1
ENSG00000237390	AL139130.1	Clone-based (Ensembl) gene		-0.68458963	0.222325794	-0.081316173	1	5.346520356	0.627668963	0.08606809	1
ENSG00000237545	SHISA9	HGNC Symbol	shisa family member 9 [Source:HGNC Symbol;Acc:HGNC:37231]	-0.809010055	0.10640732	-0.06056577	1	-0.125175047	0.984792321	-0.034481521	1
ENSG00000237636	ANKRD2P3	HGNC Symbol	ankyrin repeat domain 26 pseudogene 3 [Source:HGNC Symbol;Acc:HGNC:39689]	-0.387705186	0.561900253	-0.65236109	1	1.235736516	0.785004308	-0.203879103	1
ENSG00000238106	Z95377.1	Clone-based (Ensembl) gene		-1.006307186	0.059635061	-0.374099681	1	2.5061065249	0.627668963	1.135768642	1
ENSG00000239921	LINC01471	HGNC Symbol	long intergenic non-protein coding RNA 1471 [Source:HGNC Symbol;Acc:HGNC:51006]	-0.433400557	0.515402598	0.03107749	1	5.195146623	0.627668963	0.324780279	1
ENSG00000240021	TEX35	HGNC Symbol	testis expressed 35 [Source:HGNC Symbol;Acc:HGNC:25366]	-0.374999293	0.569064774	0.083051695	1	-0.457221847	0.91399121	0.205779598	1
ENSG00000240694	PNMA2	HGNC Symbol	PNMA family member 2 [Source:HGNC Symbol;Acc:HGNC:9159]	-0.5378910532	0.101844882	-0.057174748	1	0.827514444	0.842124589	-0.225622808	1
ENSG00000240707	LINC0168	HGNC Symbol	long intergenic non-protein coding RNA 168 [Source:HGNC Symbol;Acc:HGNC:49537]	-0.848355897	0.086801762	0.45768823	1	1.563066998	0.764869401	-0.165990548	1
ENSG0000024168	ADAMTS9-AS1	HGNC Symbol	ADAMTS9 antisense RNA 1 [Source:HGNC Symbol;Acc:HGNC:40625]	-0.406694485	0.583233437	-0.020040533	1	0.908350636	0.844324446	0.688461622	1
ENSG00000242512	LINC01206	HGNC Symbol	long intergenic non-protein coding RNA 1206 [Source:HGNC Symbol;Acc:HGNC:49637]	-0.706615823	0.298614672	-0.520138982	1	2.09559188	0.718736978	0.480753033	1
ENSG00000242866	STRC	HGNC Symbol	stereocilin [Source:HGNC Symbol;Acc:HGNC:16035]	-0.378482507	0.423980174	-0.277882673	1	0.218329488	0.952666024	0.474792962	1
ENSG00000243030	PSG1	HGNC Symbol	pregnancy specific beta-1-glycoprotein II [Source:HGNC Symbol;Acc:HGNC:9516]	-0.640818905	0.353755564	0.21669666	1	0.420866737	0.936406883	0.45645169	1
ENSG00000243040	PTCHD4	HGNC Symbol	patched domain containing 4 [Source:HGNC Symbol;Acc:HGNC:16035]	-0.961630256	0.109326576	-0.585266938	1	0.280162262	0.95747604	-0.059184384	1

44694	USP2-AS1	HGNC Symbol	SymbolAcc:HGNC:21345	-0.52076811	0.390756877	-0.502445862	1	2.757269299	0.77228729	-0.309889654	1
ENSG00000245248			USP2 antisense RNA 1 (head to head) [Source:HGNC Symbol;Acc:HGNC:48673]	-0.54469632	0.389467898	-0.043949133	1	4.637420367	0.64365872	0.080391919	1
ENSG00000245551	AC083805.1	Clone-based (Ensembl) gene		-0.616821021	0.307209736	-0.396633621	1	5.163032019	0.631753875	-0.020381824	1
ENSG00000246695	RASSF8-AS1	HGNC Symbol	RASSF8 antisense RNA 1 [Source:HGNC Symbol;Acc:HGNC:48537]	-0.955409024	0.07829748	-0.016315976	1	0.94818357	0.836663776	-0.04897474	1
47213	LINC01498	HGNC Symbol	long intergenic non-protein coding RNA 1498 [Source:HGNC Symbol;Acc:HGNC:51664]	-1.050991069	0.073837393	-0.168355722	1	4.403825386	0.630714789	0.238205542	1
ENSG00000247699	AC008609.1	Clone-based (Ensembl) gene		-0.698157573	0.21408791	-0.270935153	1	1.525731524	0.778988681	-0.027239838	1
ENSG00000248587	GDNF-AS1	HGNC Symbol	GDNF antisense RNA 1 (head to head) [Source:HGNC Symbol;Acc:HGNC:43592]	-0.540718726	0.305645261	-0.16925333	1	-0.560389013	0.859477376	0.271840562	1
ENSG00000248713	AC083902.2	Clone-based (Ensembl) gene	"Homo sapiens uncharacterized LOC285556 (LOC285556). mRNA. [Source:RefSeq mRNA;Acc:NM_00354435]"	-0.8335558399	0.085185005	0.56472696	1	-0.464953446	0.884053868	0.124065725	1
ENSG00000248746	ACTN3	HGNC Symbol	actinin alpha 3 (gene/pseudogene) [Source:HGNC Symbol;Acc:HGNC:165]	-0.901854794	0.005426121	-0.3637616	1	0.606226987	0.80060544	-0.394401901	1
ENSG00000248966	BC1AF1P1	HGNC Symbol	BC12 associated transcription factor 1 pseudogene 1 [Source:HGNC Symbol;Acc:HGNC:51329]	-0.655164585	0.316527442	-0.696726955	1	0.734788549	0.906091083	0.54443164	1
ENSG00000248975	AL183372.2	Clone-based (Ensembl) gene		-1.255534276	0.00750713	-0.628092072	1	2.895430103	0.654655709	0.516230804	1
ENSG00000249119	MTND6P4	HGNC Symbol	mitochondrially encoded NADH:ubiquinone oxidoreductase core subunit 6 pseudogene 4 [Source:HGNC Symbol;Acc:HGNC:39467]	-1.29709171	0.000187132	0.154736731	1	-1.04023217	0.627668963	0.421347089	1
ENSG00000249215	NC0A4P4	HGNC Symbol	nuclear receptor coactivator 4 pseudogene 4 [Source:HGNC Symbol;Acc:HGNC:52405]	-0.755105061	0.228670526	-0.256125279	1	6.337647595	0.627668963	-0.491593301	1
ENSG00000249267	LINC00939	HGNC Symbol	long intergenic non-protein coding RNA 939 [Source:HGNC Symbol;Acc:HGNC:48631]								

ENSG00000249341	AC024077.1	Clone-based (Ensembl) gene		-0.638158018	0.180191425	-0.880234432	1	0.9881847	0.865395845	-0.229478865	1
ENSG00000249464	LINC010191	HGNC Symbol	long intergenic non-protein coding RNA 1091 [Source:HGNC Symbol;Acc:HGNC:27721]	-0.527878847	0.10897106109	-0.514600069	1	1.18197515	0.8001835595	0.297158453	1
ENSG00000249584	LINC02225	HGNC Symbol	long intergenic non-protein coding RNA 2225 [Source:HGNC Symbol;Acc:HGNC:53094]	-0.580958221	0.346216369	-0.582748024	1	0.905397905	0.853001039	0.662950173	1
ENSG00000249618	LINC02465	HGNC Symbol	long intergenic non-protein coding RNA 2465 [Source:HGNC Symbol;Acc:HGNC:53403]	-0.594691733	0.1825447	-0.722916516	1	5.291010405	0.627668963	0.977525841	1
ENSG00000250049	AC14316.2	Clone-based (Ensembl) gene		-0.734378499	0.217922591	0.5655567149	1	4.638749643	0.649773207	-0.025857469	1
ENSG00000250230	AP002754.1	Clone-based (Ensembl) gene		-1.010448463	0.1716383023	-0.704891533	1	4.5389610207	0.631753875	0.181526143	1
ENSG00000250420	AACSP1	HGNC Symbol	acetyl-CoA synthetase pseudogene 1 [Source:HGNC Symbol;Acc:HGNC:18226]	-0.85134716	0.188525408	0.006459177	1	1.165649749	0.805758305	0.299943939	1
ENSG00000250423	K14A1210	HGNC Symbol	K14A1210 [Source:HGNC Symbol;Acc:HGNC:28218]	-0.816623881	0.302589969	-0.582659414	1	0.396772621	0.936402935	0.459665173	1
ENSG00000250493	AP004471.1	Clone-based (Ensembl) gene		-0.423518837	0.487573965	-0.290397732	1	1.178346789	0.83585817	0.221318975	1
ENSG00000250519	AP002784.1	Clone-based (Ensembl) gene		-0.661885269	0.310238544	-0.521459048	1	0.714452444	0.886928104	0.294331525	1
ENSG00000250546	AC079160.1	Clone-based (Ensembl) gene		-0.594876334	0.407745799	-0.546662826	1	0.645898296	0.908465718	0.158618765	1
ENSG00000251557	HNRNP3	HGNC Symbol	heterogeneous nuclear ribonucleoprotein K pseudogene 3 [Source:HGNC Symbol;Acc:HGNC:42376]	-0.983225003	0.165739901	0.173767605	1	4.903173168	0.636992081	0.380350496	1
ENSG00000251596	HA0HAP1	HGNC Symbol	"hydroxyacyl-CoA dehydrogenase/3-oxoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), alpha subunit pseudogene 1 [Source:HGNC Symbol;Acc:HGNC:4802]"	-0.74831099	0.215412986	-0.876823316	1	5.588638432	0.627668963	-0.106327841	1
ENSG00000251596	RNA5-5SP6	HGNC Symbol	"RNA, 5.5S ribosomal pseudogene 6"	-0.425991465	0.294278305	-0.480692883	1	0.605481991	0.905148192	0.973651682	1

[illegible]

ENSG00000257576	HSPDIP4	HGNC Symbol	heat shock protein family D (Hsp60) member 1 pseudogene 4 [Source:HGNC Symbol;Acc:HGNC:35146]	-0.870496882	0.027959144	-0.488873257	1	2.343052713	0.64677342	-0.638576554	1
ENSG00000257907	EEF1AP17	HGNC Symbol	eukaryotic translation elongation factor 1 alpha 1 pseudogene 17 [Source:HGNC Symbol;Acc:HGNC:37890]	-1.061838051	0.012387251	-0.502436059	1	0.588842988	0.88207703	-0.175387446	1
ENSG00000258628	AC126603.1	Clone-based (Ensembl) gene		-0.49638087	0.388904638	-0.07230617	1	2.185749014	0.669487849	-0.047239297	1
ENSG00000258679	AC12758.1	Clone-based (Ensembl) gene		-0.657256137	0.26827188	-0.525392989	1	0.183725694	0.97949691	-0.287680838	1
ENSG00000259010	AL048859.1	Clone-based (Ensembl) gene		-1.06237153	0.004353922	-0.240255224	1	0.187186861	0.95687068	0.060147849	1
ENSG00000259166	CHEK2P2	HGNC Symbol	checkpoint kinase 2 pseudogene 2 [Source:HGNC Symbol;Acc:HGNC:46578]	-0.8161692698	0.100260967	-0.563040176	1	0.6762214	0.863255934	0.753375248	1
ENSG00000259716	NA	NA	NA	-0.689127052	0.24300017	-0.530144663	1	2.106754077	0.722808749	1.540061641	1
ENSG00000259880	AC087473.1	Clone-based (Ensembl) gene		-0.259518718	0.707119428	-0.58933832	1	5.11915559	0.671668963	0.287497927	1
ENSG00000259458	AC100839.1	Clone-based (Ensembl) gene		-0.710267016	0.226889647	0.447253019	1	0.442861703	0.946558275	0.559307634	1
ENSG00000259790	ANP32BP1	HGNC Symbol	acidic nuclear phosphoprotein 32 family member B pseudogene 1 [Source:HGNC Symbol;Acc:HGNC:24267]	-0.99159785	0.001291068	-0.210937874	1	-1.346501099	0.655801493	0.633164315	1
ENSG00000259841	LINC01666	HGNC Symbol	long intergenic non-protein coding RNA 1666 [Source:HGNC Symbol;Acc:HGNC:27555]	-0.459757166	0.519493356	-0.79107658	1	1.107914278	0.836986961	0.76989445	1
ENSG00000260027	H0X87	HGNC Symbol	homeobox B7 [Source:HGNC Symbol;Acc:HGNC:5118]	-0.542434326	0.225372271	0.660163746	1	0.4761835227	0.9106333972	-0.1996631653	1
ENSG00000260072	AC008938.1	Clone-based (Ensembl) gene		-0.616656682	0.313455888	-0.789539115	1	0.86310797	0.821508914	0.128280001	1
ENSG00000260921	AC092115.1	Clone-based		-0.846632007	0.007999598	0.104471638	1	-0.836870858	0.675458806	0.197375256	1

[illegible]

[illegible]

Note: results in Table 6, 7, and 8 are based on GENCODE Release 18 (GRCh37)

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EXAMPLE 2AC2 and AC3 Genes and PRIME Cell Markers**[0074]** RNAs and Markers

[0075] As detailed above, RNA analysis of fingerstick blood samples from RA patients has identified RNAs suitable as markers of RA flares. A first set of markers and RNAs, denoted AC2, was increased 2 weeks prior to flare. AC2 RNAs were enriched with developmental pathways for naïve B cells and leukocytes. A second set of markers, denoted AC3, was increased the week prior to flare and was then decreased for the duration of the flare. AC3 was enriched for pathways not typical of blood samples, particularly cartilage morphogenesis, endochondral bone growth, extracellular matrix organization. AC3 was enriched with sublining fibroblast genes (CD34+HLADR+DKK3+). The AC2 markers are listed below in Table 7. AC3 gene markers are listed below in Table 8.

TABLE 7AC2 GENES

<u>Ensembl</u>	<u>Symbol</u>	<u>Description</u>	<u>Score/AUC</u>
ENSG00000204632	HLA-G	“major histocompatibility complex, class I, G [Source:HGNC Symbol;Acc:HGNC:4964]”	5.77E-05
ENSG00000184792	OSBP2	oxysterol binding protein 2 [Source:HGNC Symbol;Acc:HGNC:8504]	6.39E-05
ENSG00000198892	SHISA4	shisa family member 4 [Source:HGNC Symbol;Acc:HGNC:27139]	0.00012762
ENSG00000187017	ESPN	espin [Source:HGNC Symbol;Acc:HGNC:13281]	0.000131036
ENSG00000233762			0.000323289
ENSG00000175130	MARCKSL1	MARCKS like 1 [Source:HGNC Symbol;Acc:HGNC:7142]	0.000358619
ENSG00000125534	PPDPF	pancreatic progenitor cell differentiation and proliferation factor [Source:HGNC Symbol; Acc:HGNC:16142]	0.00037025
ENSG00000158856	DMTN	dematin actin binding protein [Source:HGNC Symbol;Acc:HGNC:3382]	0.000376535
ENSG00000121413	ZSCAN18	zinc finger and SCAN domain containing 18 [Source:HGNC Symbol;Acc:HGNC:21037]	0.000443873
ENSG00000230715			0.000528797
ENSG00000215030	RPL13P12	ribosomal protein L13 pseudogene 12 [Source:HGNC Symbol;Acc:HGNC:35701]	0.000588454
ENSG00000146540	C7orf50	chromosome 7 open reading frame 50 [Source:HGNC Symbol;Acc:HGNC:22421]	0.000639272
ENSG00000029534	ANK1	ankyrin 1 [Source:HGNC Symbol;Acc:HGNC:492]	0.000697583
ENSG00000121104	FAM117A	family with sequence similarity 117 member A	0.000697583

ENSG00000260231	JHDM1D-AS1	[Source:HGNC Symbol;Acc:HGNC:24179] JHDM1D antisense RNA 1 (head to head)	0.00070319
ENSG00000211895	IGHA1	[Source:HGNC Symbol;Acc:HGNC:48959] immunoglobulin heavy constant alpha 1	0.000707226
ENSG00000173581	CCDC106	[Source:HGNC Symbol;Acc:HGNC:5478] coiled-coil domain containing 106	0.000730947
ENSG00000008441	NFIX	[Source:HGNC Symbol;Acc:HGNC:30181] nuclear factor I X	0.000837162
ENSG00000105701	FKBP8	[Source:HGNC Symbol;Acc:HGNC:7788] FK506 binding protein 8	0.000994972
ENSG00000079308	TNS1	[Source:HGNC Symbol;Acc:HGNC:3724] tensin 1	0.00113151
ENSG00000264063	MIR3687-2	[Source:HGNC Symbol;Acc:HGNC:11973] microRNA 3687-2	0.001218296
ENSG00000049089	COL9A2	[Source:HGNC Symbol;Acc:HGNC:50835] collagen type IX alpha 2 chain	0.001236713
ENSG00000126461	SCAF1	[Source:HGNC Symbol;Acc:HGNC:2218] SR-related CTD associated factor 1	0.00126185
ENSG00000243679		[Source:HGNC Symbol;Acc:HGNC:30403] 0.001292673	
ENSG00000169136	ATF5	activating transcription factor 5	0.001421682
ENSG00000181588	MEX3D	[Source:HGNC Symbol;Acc:HGNC:790] mex-3 RNA binding family member D	0.001421682
ENSG00000103257	SLC7A5	[Source:HGNC Symbol;Acc:HGNC:16734] solute carrier family 7 member 5	0.001574737
ENSG00000175931	UBE2O	[Source:HGNC Symbol;Acc:HGNC:11063] ubiquitin conjugating enzyme E2 O	0.001669619
ENSG00000065268	WDR18	[Source:HGNC Symbol;Acc:HGNC:29554] WD repeat domain 18	0.001764407
ENSG00000130300	PLVAP	[Source:HGNC Symbol;Acc:HGNC:17956] plasmalemma vesicle associated protein	0.001779673
ENSG00000232434	AJM1	[Source:HGNC Symbol;Acc:HGNC:13635] apical junction component 1 homolog	0.001937905
ENSG00000197256	KANK2	[Source:HGNC Symbol;Acc:HGNC:37284] KN motif and ankyrin repeat domains 2	0.001945859
ENSG00000229809	ZNF688	[Source:HGNC Symbol;Acc:HGNC:29300] zinc finger protein 688	0.002041059
ENSG00000130433	CACNG6	[Source:HGNC Symbol;Acc:HGNC:30489] calcium voltage-gated channel auxiliary subunit gamma 6	0.002327494
ENSG00000126254	RBM42	[Source:HGNC Symbol;Acc:HGNC:13625] RNA binding motif protein 42	0.002342133
ENSG00000013306	SLC25A39	[Source:HGNC Symbol;Acc:HGNC:28117] solute carrier family 25 member 39	0.002354141
ENSG00000179837	NA	[Source:HGNC Symbol;Acc:HGNC:24279] NA	0.002482976

ENSG00000265714	NA	NA	0.002482976
ENSG00000172460	PRSS30P	“serine protease 30, pseudogene [Source:HGNC Symbol;Acc:HGNC:28753]”	0.002490713
ENSG00000104983	CCDC61	coiled-coil domain containing 61 [Source:HGNC Symbol;Acc:HGNC:33629]	0.002565172
ENSG00000211898	IGHD	immunoglobulin heavy constant delta [Source:HGNC Symbol;Acc:HGNC:5480]	0.002565172
ENSG0000055118	KCNH2	potassium voltage-gated channel subfamily H member 2 [Source:HGNC Symbol;Acc:HGNC:6251]	0.002637584
ENSG00000260335			0.002639596
ENSG00000104903	LYL1	“LYL1, basic helix-loop-helix family member [Source:HGNC Symbol;Acc:HGNC:6734]”	0.002696079
ENSG00000099958	DERL3	derlin 3 [Source:HGNC Symbol;Acc:HGNC:14236]	0.002709927
ENSG00000179526	SHARPIN	SHANK associated RH domain interactor [Source:HGNC Symbol;Acc:HGNC:25321]	0.002709927
ENSG00000133069	TMCC2	transmembrane and coiled-coil domain family 2 [Source:HGNC Symbol;Acc:HGNC:24239]	0.002940811
ENSG00000240342	RPS2P5	ribosomal protein S2 pseudogene 5 [Source:HGNC Symbol;Acc:HGNC:31386]	0.002940811
ENSG00000264462	MIR3648-2	microRNA 3648-2 [Source:HGNC Symbol;Acc:HGNC:50843]	0.003313878
ENSG00000256576	LINC02361	long intergenic non-protein coding RNA 2361 [Source:HGNC Symbol;Acc:HGNC:53283]	0.003383286
ENSG00000007968	E2F2	E2F transcription factor 2 [Source:HGNC Symbol;Acc:HGNC:3114]	0.003400809
ENSG00000141858	SAMD1	sterile alpha motif domain containing 1 [Source:HGNC Symbol;Acc:HGNC:17958]	0.003623721
ENSG00000126705	AHDC1	AT-hook DNA binding motif containing 1 [Source:HGNC Symbol;Acc:HGNC:25230]	0.004035577
ENSG00000141456	PELP1	“proline, glutamate and leucine rich protein 1 [Source:HGNC Symbol;Acc:HGNC:30134]”	0.00422876
ENSG00000159713	TPPP3	tubulin polymerization promoting protein family member 3 [Source:HGNC Symbol;Acc:HGNC:24162]	0.004525344
ENSG00000104897	SF3A2	splicing factor 3a subunit 2 [Source:HGNC Symbol;Acc:HGNC:10766]	0.004539725
ENSG00000063245	EPN1	epsin 1 [Source:HGNC Symbol;Acc:HGNC:21604]	0.004540184
ENSG00000162783	IER5	immediate early response 5 [Source:HGNC Symbol;Acc:HGNC:5393]	0.004549021
ENSG00000141582	CBX4	chromobox 4 [Source:HGNC Symbol;Acc:HGNC:1554]	0.004686524
ENSG00000168159	RNF187	ring finger protein 187 [Source:HGNC Symbol;Acc:HGNC:27146]	0.004686524
ENSG00000136826	KLF4	Kruppel like factor 4	

		[Source:HGNC Symbol;Acc:HGNC:6348]	0.004891089
ENSG00000237214			0.004891089
ENSG0000066336	SPI1	Spi-1 proto-oncogene	
		[Source:HGNC Symbol;Acc:HGNC:11241]	0.005082358
ENSG00000172270	BSG	basigin (Ok blood group)	
		[Source:HGNC Symbol;Acc:HGNC:1116]	0.005082358
ENSG00000173868	PHOSPHO1	phosphoethanolamine/phosphocholine phosphatase	
		[Source:HGNC Symbol;Acc:HGNC:16815]	0.005082358
ENSG00000167182	SP2	Sp2 transcription factor	
		[Source:HGNC Symbol;Acc:HGNC:11207]	0.005118791
ENSG00000104805	NUCB1	nucleobindin 1	
		[Source:HGNC Symbol;Acc:HGNC:8043]	0.005119064
ENSG0000099381	SETD1A	SET domain containing 1A	
		[Source:HGNC Symbol;Acc:HGNC:29010]	0.00514547
ENSG00000185340	GAS2L1	growth arrest specific 2 like 1	
		[Source:HGNC Symbol;Acc:HGNC:16955]	0.00514547
ENSG0000007541	PIGQ	phosphatidylinositol glycan anchor biosynthesis class Q	
		[Source:HGNC Symbol;Acc:HGNC:14135]	0.005166641
ENSG00000105610	KLF1	Kruppel like factor 1	
		[Source:HGNC Symbol;Acc:HGNC:6345]	0.005217627
ENSG00000137193	PIM1	"Pim-1 proto-oncogene, serine/threonine kinase	
		[Source:HGNC Symbol;Acc:HGNC:8986]"	0.005247531
ENSG00000171552	BCL2L1	BCL2 like 1	
		[Source:HGNC Symbol;Acc:HGNC:992]	0.005530506
ENSG00000172889	EGFL7	EGF like domain multiple 7	
		[Source:HGNC Symbol;Acc:HGNC:20594]	0.005530506
ENSG00000213402	PTPRCAP	"protein tyrosine phosphatase, receptor type C associated protein	
		[Source:HGNC Symbol;Acc:HGNC:9667]"	0.00560032
ENSG0000099330	OCEL1	occludin/ELL domain containing 1	
		[Source:HGNC Symbol;Acc:HGNC:26221]	0.005671418
ENSG00000147443	DOK2	docking protein 2	
		[Source:HGNC Symbol;Acc:HGNC:2991]	0.005857886
ENSG00000182240	BACE2	beta-site APP-cleaving enzyme 2	
		[Source:HGNC Symbol;Acc:HGNC:934]	0.005857886
ENSG00000170128	GPR25	G protein-coupled receptor 25	
		[Source:HGNC Symbol;Acc:HGNC:4480]	0.006101348
ENSG00000140406	TLNRD1	talin rod domain containing 1	
		[Source:HGNC Symbol;Acc:HGNC:13519]	0.0061541
ENSG00000117394	SLC2A1	solute carrier family 2 member 1	
		[Source:HGNC Symbol;Acc:HGNC:11005]	0.006158727
ENSG00000141854	MISP3	MISP family member 3	
		[Source:HGNC Symbol;Acc:HGNC:26963]	0.006204755
ENSG00000129757	CDKN1C	cyclin dependent kinase inhibitor 1C	
		[Source:HGNC Symbol;Acc:HGNC:1786]	0.006380434
ENSG00000186891	TNFRSF18	TNF receptor superfamily member 18	

ENSG00000184897	H1FX	[Source:HGNC Symbol;Acc:HGNC:11914] H1 histone family member X	0.006421961
ENSG00000185236	RAB11B	[Source:HGNC Symbol;Acc:HGNC:4722] "RAB11B, member RAS oncogene family	0.006465512
ENSG00000030582	GRN	[Source:HGNC Symbol;Acc:HGNC:9761]" granulin precursor	0.006602734
ENSG00000071564	TCF3	[Source:HGNC Symbol;Acc:HGNC:4601] transcription factor 3	0.006751675
ENSG00000267749		[Source:HGNC Symbol;Acc:HGNC:11633] 0.006772165	0.006848491
ENSG00000105373	NOP53	NOP53 ribosome biogenesis factor	
ENSG00000240445	FOXO3B	[Source:HGNC Symbol;Acc:HGNC:4333] forkhead box O3B pseudogene	0.006952696
ENSG00000127528	KLF2	[Source:HGNC Symbol;Acc:HGNC:3822] Kruppel like factor 2	0.006952696
ENSG00000254858	MPV17L2	[Source:HGNC Symbol;Acc:HGNC:6347] MPV17 mitochondrial inner membrane protein like 2	0.00698206
ENSG00000130595	TNNT3	[Source:HGNC Symbol;Acc:HGNC:28177] "troponin T3, fast skeletal type	0.006997113
ENSG00000130749	ZC3H4	[Source:HGNC Symbol;Acc:HGNC:11950]" zinc finger CCCH-type containing 4	0.007133196
ENSG00000132819	RBM38	[Source:HGNC Symbol;Acc:HGNC:17808] RNA binding motif protein 38	0.007141116
ENSG00000135925	WNT10A	[Source:HGNC Symbol;Acc:HGNC:15818] Wnt family member 10A	0.007141116
ENSG00000205639	MFSD2B	[Source:HGNC Symbol;Acc:HGNC:13829] major facilitator superfamily domain containing 2B	0.007141116
ENSG00000213763	ACTBP2	[Source:HGNC Symbol;Acc:HGNC:37207] "actin, beta pseudogene 2	0.007141116
ENSG00000261221	ZNF865	[Source:HGNC Symbol;Acc:HGNC:135]" zinc finger protein 865	0.007141116
ENSG00000171611	PTCRA	[Source:HGNC Symbol;Acc:HGNC:38705] pre T cell antigen receptor alpha	0.007141116
ENSG00000161642	ZNF385A	[Source:HGNC Symbol;Acc:HGNC:21290] zinc finger protein 385A	0.007255358
ENSG00000226608	FTLP3	[Source:HGNC Symbol;Acc:HGNC:17521] ferritin light chain pseudogene 3	0.007304748
ENSG00000170684	ZNF296	[Source:HGNC Symbol;Acc:HGNC:4000] zinc finger protein 296	0.007304748
ENSG00000213638	ADAT3	[Source:HGNC Symbol;Acc:HGNC:15981] "adenosine deaminase, tRNA specific 3	0.007327997
ENSG00000179262	RAD23A	[Source:HGNC Symbol;Acc:HGNC:25151]" "RAD23 homolog A, nucleotide excision repair protein	0.007343983
		[Source:HGNC Symbol;Acc:HGNC:9812]"	0.0073448

ENSG00000196126	HLA-DRB1	“major histocompatibility complex, class II, DR beta 1 [Source:HGNC Symbol;Acc:HGNC:4948]”	0.00745996
ENSG00000197149			0.007535198
ENSG00000213820	RPL13P2	ribosomal protein L13 pseudogene 2 [Source:HGNC Symbol;Acc:HGNC:16342]	0.007619923
ENSG00000225331	LINC01678	long intergenic non-protein coding RNA 1678 [Source:HGNC Symbol;Acc:HGNC:52466]	0.007619923
ENSG00000235605			0.007619923
ENSG00000183092	BEGAIN	brain enriched guanylate kinase associated [Source:HGNC Symbol;Acc:HGNC:24163]	0.007755013
ENSG00000105369	CD79A	CD79a molecule [Source:HGNC Symbol;Acc:HGNC:1698]	0.007835589
ENSG00000160256	FAM207A	family with sequence similarity 207 member A [Source:HGNC Symbol;Acc:HGNC:15811]	0.007901726
ENSG00000105516	DBP	D-box binding PAR bZIP transcription factor [Source:HGNC Symbol;Acc:HGNC:2697]	0.007955596
ENSG00000179094	PER1	period circadian regulator 1 [Source:HGNC Symbol;Acc:HGNC:8845]	0.008010463
ENSG00000154146	NRGN	neurogranin [Source:HGNC Symbol;Acc:HGNC:8000]	0.008019602
ENSG00000160813	PPP1R35	protein phosphatase 1 regulatory subunit 35 [Source:HGNC Symbol;Acc:HGNC:28320]	0.008019602
ENSG00000152082	MZT2B	mitotic spindle organizing protein 2B [Source:HGNC Symbol;Acc:HGNC:25886]	0.008149414
ENSG00000115274	INO80B	INO80 complex subunit B [Source:HGNC Symbol;Acc:HGNC:13324]	0.008388785
ENSG00000185112	FAM43A	family with sequence similarity 43 member A [Source:HGNC Symbol;Acc:HGNC:26888]	0.008409751
ENSG00000130592	LSP1	lymphocyte-specific protein 1 [Source:HGNC Symbol;Acc:HGNC:6707]	0.00866593
ENSG00000077348	EXOSC5	exosome component 5 [Source:HGNC Symbol;Acc:HGNC:24662]	0.008679008
ENSG00000196498	NCOR2	nuclear receptor corepressor 2 [Source:HGNC Symbol;Acc:HGNC:7673]	0.008729326
ENSG00000132382	MYBBP1A	MYB binding protein 1a [Source:HGNC Symbol;Acc:HGNC:7546]	0.008886691
ENSG00000104885	DOT1L	DOT1 like histone lysine methyltransferase [Source:HGNC Symbol;Acc:HGNC:24948]	0.008912378
ENSG00000153443	UBALD1	UBA like domain containing 1 [Source:HGNC Symbol;Acc:HGNC:29576]	0.008912378
ENSG00000070182	SPTB	“spectrin beta, erythrocytic [Source:HGNC Symbol;Acc:HGNC:11274]”	0.008927471
ENSG00000168517	HEXIM2	hexamethylene bisacetamide inducible 2 [Source:HGNC Symbol;Acc:HGNC:28591]	0.008959412
ENSG00000090674	MCOLN1	mucolipin 1	

		[Source:HGNC Symbol;Acc:HGNC:13356]	0.009327518
ENSG00000198816	ZNF358	zinc finger protein 358	
		[Source:HGNC Symbol;Acc:HGNC:16838]	0.009506451
ENSG00000175334	BANF1	barrier to autointegration factor 1	
		[Source:HGNC Symbol;Acc:HGNC:17397]	0.009647997
ENSG00000125520	SLC2A4RG	SLC2A4 regulator	
		[Source:HGNC Symbol;Acc:HGNC:15930]	0.009686596
ENSG00000141084	RANBP10	RAN binding protein 10	
		[Source:HGNC Symbol;Acc:HGNC:29285]	0.009715508
ENSG00000149016	TUT1	“terminal uridylyl transferase 1, U6 snRNA-specific	
		[Source:HGNC Symbol;Acc:HGNC:26184]”	0.009768686
ENSG00000178951	ZBTB7A	zinc finger and BTB domain containing 7A	
		[Source:HGNC Symbol;Acc:HGNC:18078]	0.009810065
ENSG00000186111	PIP5K1C	phosphatidylinositol-4-phosphate 5-kinase type 1 gamma	
		[Source:HGNC Symbol;Acc:HGNC:8996]	0.009810065
ENSG00000184481	FOXO4	forkhead box O4	
		[Source:HGNC Symbol;Acc:HGNC:7139]	0.009820284
ENSG00000064961	HMG20B	high mobility group 20B	
		[Source:HGNC Symbol;Acc:HGNC:5002]	0.009858965
ENSG00000108309	RUNDC3A	RUN domain containing 3A	
		[Source:HGNC Symbol;Acc:HGNC:16984]	0.010055443
ENSG00000130165	ELOF1	elongation factor 1 homolog	
		[Source:HGNC Symbol;Acc:HGNC:28691]	0.010212535
ENSG00000130159	ECSIT	ECSIT signalling integrator	
		[Source:HGNC Symbol;Acc:HGNC:29548]	0.010245658
ENSG00000244560			0.010245658
ENSG00000125148	MT2A	metallothionein 2A	
		[Source:HGNC Symbol;Acc:HGNC:7406]	0.01061889
ENSG00000131116	ZNF428	zinc finger protein 428	
		[Source:HGNC Symbol;Acc:HGNC:20804]	0.010712491
ENSG00000105617	LENG1	leukocyte receptor cluster member 1	
		[Source:HGNC Symbol;Acc:HGNC:15502]	0.010999325
ENSG00000139718	SETD1B	SET domain containing 1B	
		[Source:HGNC Symbol;Acc:HGNC:29187]	0.011038344
ENSG00000106665	CLIP2	CAP-Gly domain containing linker protein 2	
		[Source:HGNC Symbol;Acc:HGNC:2586]	0.011064297
ENSG00000130821	SLC6A8	solute carrier family 6 member 8	
		[Source:HGNC Symbol;Acc:HGNC:11055]	0.011213055
ENSG00000184232	OAF	out at first homolog	
		[Source:HGNC Symbol;Acc:HGNC:28752]	0.011286635
ENSG00000179820	MYADM	myeloid associated differentiation marker	
		[Source:HGNC Symbol;Acc:HGNC:7544]	0.011330192
ENSG00000127580	WDR24	WD repeat domain 24	
		[Source:HGNC Symbol;Acc:HGNC:20852]	0.011570001

ENSG0000004939	SLC4A1	solute carrier family 4 member 1 (Diego blood group) [Source:HGNC Symbol;Acc:HGNC:11027]	0.011732314
ENSG00000130522	JUND	“JunD proto-oncogene, AP-1 transcription factor subunit [Source:HGNC Symbol;Acc:HGNC:6206]”	0.011813745
ENSG00000148362	PAXX	“PAXX, non-homologous end joining factor [Source:HGNC Symbol;Acc:HGNC:27849]”	0.011821074
ENSG00000262902	MTCO1P40	mitochondrially encoded cytochrome c oxidase I pseudogene 40 [Source:HGNC Symbol;Acc:HGNC:52105]	0.011821074
ENSG00000167671	UBXN6	UBX domain protein 6 [Source:HGNC Symbol;Acc:HGNC:14928]	0.011831088
ENSG00000125457	MIF4GD	MIF4G domain containing [Source:HGNC Symbol;Acc:HGNC:24030]	0.011851589
ENSG00000146066	HIGD2A	HIG1 hypoxia inducible domain family member 2A [Source:HGNC Symbol;Acc:HGNC:28311]	0.011914767
ENSG00000184221	OLIG1	oligodendrocyte transcription factor 1 [Source:HGNC Symbol;Acc:HGNC:16983]	0.011914767
ENSG00000260316			0.0119947
ENSG00000124762	CDKN1A	cyclin dependent kinase inhibitor 1A [Source:HGNC Symbol;Acc:HGNC:1784]	0.012077375
ENSG00000103148	NPRL3	“NPR3 like, GATOR1 complex subunit [Source:HGNC Symbol;Acc:HGNC:14124]”	0.012137266
ENSG00000179115	FARSA	phenylalanyl-tRNA synthetase alpha subunit [Source:HGNC Symbol;Acc:HGNC:3592]	0.012137266
ENSG00000120896	SORBS3	sorbin and SH3 domain containing 3 [Source:HGNC Symbol;Acc:HGNC:30907]	0.012150664
ENSG00000174886	NDUFA11	NADH:ubiquinone oxidoreductase subunit A11 [Source:HGNC Symbol;Acc:HGNC:20371]	0.012268883
ENSG00000102145	GATA1	GATA binding protein 1 [Source:HGNC Symbol;Acc:HGNC:4170]	0.012285964
ENSG00000166428	PLD4	phospholipase D family member 4 [Source:HGNC Symbol;Acc:HGNC:23792]	0.012401569
ENSG00000213015	ZNF580	zinc finger protein 580 [Source:HGNC Symbol;Acc:HGNC:29473]	0.012630003
ENSG00000142544	CTU1	cytosolic thioridylase subunit 1 [Source:HGNC Symbol;Acc:HGNC:29590]	0.012676606
ENSG00000085644	ZNF213	zinc finger protein 213 [Source:HGNC Symbol;Acc:HGNC:13005]	0.012935817
ENSG00000003249	DBNDD1	dysbindin domain containing 1 [Source:HGNC Symbol;Acc:HGNC:28455]	0.013109402
ENSG00000221288	MIR663B	microRNA 663b [Source:HGNC Symbol;Acc:HGNC:35270]	0.013333238
ENSG00000042062	RIPOR3	RIPOR family member 3 [Source:HGNC Symbol;Acc:HGNC:16168]	0.013356858
ENSG00000105329	TGFB1	transforming growth factor beta 1 [Source:HGNC Symbol;Acc:HGNC:11766]	0.013356858

ENSG00000116871	MAP7D1	MAP7 domain containing 1 [Source:HGNC Symbol;Acc:HGNC:25514]	0.013356858
ENSG00000168298	HIST1H1E	histone cluster 1 H1 family member e [Source:HGNC Symbol;Acc:HGNC:4718]	0.013400191
ENSG00000127666	TICAM1	toll like receptor adaptor molecule 1 [Source:HGNC Symbol;Acc:HGNC:18348]	0.013447765
ENSG00000166886	NAB2	NGFI-A binding protein 2 [Source:HGNC Symbol;Acc:HGNC:7627]	0.013572419
ENSG00000112787	FBRSL1	fibrosin like 1 [Source:HGNC Symbol;Acc:HGNC:29308]	0.013760569
ENSG00000100243	CYB5R3	cytochrome b5 reductase 3 [Source:HGNC Symbol;Acc:HGNC:2873]	0.013883197
ENSG00000197457	STMN3	stathmin 3 [Source:HGNC Symbol;Acc:HGNC:15926]	0.013964273
ENSG00000255441		0.013965194	
ENSG00000173801	JUP	junction plakoglobin [Source:HGNC Symbol;Acc:HGNC:6207]	0.014437619
ENSG00000224614	TNK2-AS1	TNK2 antisense RNA 1 [Source:HGNC Symbol;Acc:HGNC:49093]	0.014437619
ENSG00000058453	CROCC	"ciliary rootlet coiled-coil, rootletin [Source:HGNC Symbol;Acc:HGNC:21299]"	0.014522615
ENSG00000079313	REXO1	RNA exonuclease 1 homolog [Source:HGNC Symbol;Acc:HGNC:24616]	0.014579462
ENSG00000154102	C16orf74	chromosome 16 open reading frame 74 [Source:HGNC Symbol;Acc:HGNC:23362]	0.014732236
ENSG00000172650	AGAP5	"ArfGAP with GTPase domain, ankyrin repeat and PH domain 5 [Source:HGNC Symbol;Acc:HGNC:23467]"	0.014761715
ENSG00000159733	ZFYVE28	zinc finger FYVE-type containing 28 [Source:HGNC Symbol;Acc:HGNC:29334]	0.014792652
ENSG00000019582	CD74	CD74 molecule [Source:HGNC Symbol;Acc:HGNC:1697]	0.014946895
ENSG00000211771	TRBJ2-7	T cell receptor beta joining 2-7 [Source:HGNC Symbol;Acc:HGNC:12175]	0.014961068
ENSG00000214309	MBLAC1	metallo-beta-lactamase domain containing 1 [Source:HGNC Symbol;Acc:HGNC:22180]	0.014976932
ENSG00000187266	EPOR	erythropoietin receptor [Source:HGNC Symbol;Acc:HGNC:3416]	0.015342955
ENSG00000108106	UBE2S	ubiquitin conjugating enzyme E2 S [Source:HGNC Symbol;Acc:HGNC:17895]	0.015459542
ENSG00000185838	GNB1L	G protein subunit beta 1 like [Source:HGNC Symbol;Acc:HGNC:4397]	0.015552452
ENSG00000228594	FNDC10	fibronectin type III domain containing 10 [Source:HGNC Symbol;Acc:HGNC:42951]	0.015552452
ENSG00000126464	PRR12	proline rich 12 [Source:HGNC Symbol;Acc:HGNC:29217]	0.015622838

ENSG0000084092	NOA1	nitric oxide associated 1 [Source:HGNC Symbol;Acc:HGNC:28473]	0.015753463
ENSG00000105227	PRX	periaxin [Source:HGNC Symbol;Acc:HGNC:13797]	0.015787169
ENSG00000260401			0.015787169
ENSG00000159840	ZYX	zyxin [Source:HGNC Symbol;Acc:HGNC:13200]	0.015829354
ENSG00000197483	ZNF628	zinc finger protein 628 [Source:HGNC Symbol;Acc:HGNC:28054]	0.015834462
ENSG00000182572	NA	NA	0.015908819
ENSG00000154035	NA	NA	0.015942034
ENSG00000161618	ALDH16A1	aldehyde dehydrogenase 16 family member A1 [Source:HGNC Symbol;Acc:HGNC:28114]	0.015942034
ENSG00000124575	HIST1H1D	histone cluster 1 H1 family member d [Source:HGNC Symbol;Acc:HGNC:4717]	0.015948868
ENSG00000196092	PAX5	paired box 5 [Source:HGNC Symbol;Acc:HGNC:8619]	0.01597311
ENSG00000105429	MEGF8	multiple EGF like domains 8 [Source:HGNC Symbol;Acc:HGNC:3233]	0.015986308
ENSG00000213753	CENPBD1P1	CENPB DNA-binding domains containing 1 pseudogene 1 [Source:HGNC Symbol;Acc:HGNC:28421]	0.016008143
ENSG00000179627	ZBTB42	zinc finger and BTB domain containing 42 [Source:HGNC Symbol;Acc:HGNC:32550]	0.016166469
ENSG00000107816	LZTS2	leucine zipper tumor suppressor 2 [Source:HGNC Symbol;Acc:HGNC:29381]	0.016243979
ENSG00000183779	ZNF703	zinc finger protein 703 [Source:HGNC Symbol;Acc:HGNC:25883]	0.016243979
ENSG00000203950	RTL8A	retrotransposon Gag like 8A [Source:HGNC Symbol;Acc:HGNC:24514]	0.01630694
ENSG0000088826	SMOX	spermine oxidase [Source:HGNC Symbol;Acc:HGNC:15862]	0.016416472
ENSG00000105298	CACTIN	"cactin, spliceosome C complex subunit [Source:HGNC Symbol;Acc:HGNC:29938]"	0.016416472
ENSG00000137218	FRS3	fibroblast growth factor receptor substrate 3 [Source:HGNC Symbol;Acc:HGNC:16970]	0.016416472
ENSG00000175550	DRAP1	DR1 associated protein 1 [Source:HGNC Symbol;Acc:HGNC:3019]	0.016587059
ENSG00000166165	CKB	creatine kinase B [Source:HGNC Symbol;Acc:HGNC:1991]	0.01659925
ENSG00000162366	PDZK1IP1	PDZK1 interacting protein 1 [Source:HGNC Symbol;Acc:HGNC:16887]	0.016705327
ENSG00000184428	TOP1MTDNA	topoisomerase I mitochondrial [Source:HGNC Symbol;Acc:HGNC:29787]	0.016722415
ENSG00000130479	MAP1S	microtubule associated protein 1S	

ENSG00000171222	SCAND1	[Source:HGNC Symbol;Acc:HGNC:15715] SCAN domain containing 1	0.016796937
ENSG00000171223	JUNB	[Source:HGNC Symbol;Acc:HGNC:10566] "JunB proto-oncogene, AP-1 transcription factor subunit	0.016821415
ENSG00000107902	LHPP	[Source:HGNC Symbol;Acc:HGNC:6205]" phospholysine phosphohistidine inorganic pyrophosphate phosphatase	0.016966042
ENSG00000170271	FAXDC2	[Source:HGNC Symbol;Acc:HGNC:30042] fatty acid hydroxylase domain containing 2	0.017052413
ENSG00000100325	ASCC2	[Source:HGNC Symbol;Acc:HGNC:1334] activating signal cointegrator 1 complex subunit 2	0.017052413
ENSG00000142694	EVA1B	[Source:HGNC Symbol;Acc:HGNC:24103] eva-1 homolog B	0.017132234
ENSG00000064201	TSPAN32	[Source:HGNC Symbol;Acc:HGNC:25558] tetraspanin 32	0.017132234
ENSG00000157911	PEX10	[Source:HGNC Symbol;Acc:HGNC:13410] peroxisomal biogenesis factor 10	0.017210927
ENSG00000079432	CIC	[Source:HGNC Symbol;Acc:HGNC:8851] capicua transcriptional repressor	0.017211726
ENSG00000188825	LINC00910	[Source:HGNC Symbol;Acc:HGNC:14214] long intergenic non-protein coding RNA 910	0.017339051
ENSG00000196961	AP2A1	[Source:HGNC Symbol;Acc:HGNC:44361] adaptor related protein complex 2 alpha 1 subunit	0.017339051
ENSG00000214279	SCART1	[Source:HGNC Symbol;Acc:HGNC:561] scavenger receptor family member expressed on T cells 1	0.017339051
ENSG00000272449		[Source:HGNC Symbol;Acc:HGNC:32411] mediator complex subunit 25	0.017339051
ENSG00000104973	MED25	[Source:HGNC Symbol;Acc:HGNC:28845] carbohydrate sulfotransferase 13	0.017392388
ENSG00000180767	CHST13	[Source:HGNC Symbol;Acc:HGNC:21755] WAS protein family homolog 7 pseudogene	0.017392388
ENSG00000227232	WASH7P	[Source:HGNC Symbol;Acc:HGNC:38034] ribosomal protein S6 kinase A4	0.017392388
ENSG00000162302	RPS6KA4	[Source:HGNC Symbol;Acc:HGNC:10433] "ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 4	0.017767827
ENSG00000136840	ST6GALNAC4	[Source:HGNC Symbol;Acc:HGNC:17846]" torsin family 2 member A	0.017832974
ENSG00000160404	TOR2A	[Source:HGNC Symbol;Acc:HGNC:11996] coiled-coil domain containing 28B	0.018020454
ENSG00000233038		[Source:HGNC Symbol;Acc:HGNC:28163] semaphorin 7A (John Milton Hagen blood group)	0.018071818
ENSG00000243449	C4orf48	[Source:HGNC Symbol;Acc:HGNC:34437] chromosome 4 open reading frame 48	0.018116836
ENSG00000160050	CCDC28B	[Source:HGNC Symbol;Acc:HGNC:10741] semaphorin 7A (John Milton Hagen blood group)	0.01812987
ENSG00000138623	SEMA7A	[Source:HGNC Symbol;Acc:HGNC:10741] semaphorin 7A (John Milton Hagen blood group)	0.01834001

ENSG00000101439	CST3	cystatin C [Source:HGNC Symbol;Acc:HGNC:2475]	0.018421259
ENSG00000100368	CSF2RB	colony stimulating factor 2 receptor beta common subunit [Source:HGNC Symbol;Acc:HGNC:2436]	0.01865112
ENSG00000006015	REX1BD	required for excision 1-B domain containing [Source:HGNC Symbol;Acc:HGNC:26098]	0.01871477
ENSG00000011451	WIZ	widely interspaced zinc finger motifs [Source:HGNC Symbol;Acc:HGNC:30917]	0.018812736
ENSG00000160888	IER2	immediate early response 2 [Source:HGNC Symbol;Acc:HGNC:28871]	0.018812736
ENSG00000174807	CD248	CD248 molecule [Source:HGNC Symbol;Acc:HGNC:18219]	0.018812736
ENSG00000099821	POLRMT	RNA polymerase mitochondrial [Source:HGNC Symbol;Acc:HGNC:9200]	0.018832922
ENSG00000211899	IGHM	immunoglobulin heavy constant mu [Source:HGNC Symbol;Acc:HGNC:5541]	0.018832922
ENSG00000130313	PGLS	6-phosphogluconolactonase [Source:HGNC Symbol;Acc:HGNC:8903]	0.019015294
ENSG00000165702	GFI1B	growth factor independent 1B transcriptional repressor [Source:HGNC Symbol;Acc:HGNC:4238]	0.019015294
ENSG00000196557	CACNA1H	calcium voltage-gated channel subunit alpha1 H [Source:HGNC Symbol;Acc:HGNC:1395]	0.019108077
ENSG00000188486	H2AFX	H2A histone family member X [Source:HGNC Symbol;Acc:HGNC:4739]	0.019120708
ENSG00000103260	METRNL	"meteorin, glial cell differentiation regulator [Source:HGNC Symbol;Acc:HGNC:14151]"	0.01915234
ENSG00000166925	TSC22D4	TSC22 domain family member 4 [Source:HGNC Symbol;Acc:HGNC:21696]	0.01920241
ENSG00000106266	SNX8	sorting nexin 8 [Source:HGNC Symbol;Acc:HGNC:14972]	0.019236897
ENSG00000110400	NECTIN1	nectin cell adhesion molecule 1 [Source:HGNC Symbol;Acc:HGNC:9706]	0.01926502
ENSG00000088992	TESC	tescalcin [Source:HGNC Symbol;Acc:HGNC:26065]	0.019687862
ENSG00000126368	NR1D1	nuclear receptor subfamily 1 group D member 1 [Source:HGNC Symbol;Acc:HGNC:7962]	0.019740714
ENSG00000103202	NME4	NME/NM23 nucleoside diphosphate kinase 4 [Source:HGNC Symbol;Acc:HGNC:7852]	0.019829586
ENSG00000213626	LBH	limb bud and heart development [Source:HGNC Symbol;Acc:HGNC:29532]	0.019900152
ENSG00000138629	UBL7	ubiquitin like 7 [Source:HGNC Symbol;Acc:HGNC:28221]	0.019916102
ENSG00000254614			0.019916102
ENSG00000116521	SCAMP3	secretory carrier membrane protein 3 [Source:HGNC Symbol;Acc:HGNC:10565]	0.019953714

ENSG00000132481	TRIM47	tripartite motif containing 47 [Source:HGNC Symbol;Acc:HGNC:19020]	0.019989295
ENSG00000105699	LSR	lipolysis stimulated lipoprotein receptor [Source:HGNC Symbol;Acc:HGNC:29572]	0.019999965
ENSG00000125503	PPP1R12C	protein phosphatase 1 regulatory subunit 12C [Source:HGNC Symbol;Acc:HGNC:14947]	0.020063533
ENSG00000103056	SMPD3	sphingomyelin phosphodiesterase 3 [Source:HGNC Symbol;Acc:HGNC:14240]	0.020115844
ENSG00000156381	ANKRD9	ankyrin repeat domain 9 [Source:HGNC Symbol;Acc:HGNC:20096]	0.020225168
ENSG00000197471	SPN	sialophorin [Source:HGNC Symbol;Acc:HGNC:11249]	0.020225168
ENSG00000197471	SPN	sialophorin [Source:HGNC Symbol;Acc:HGNC:11249]	0.020225168
ENSG00000063854	HAGH	hydroxyacylglutathione hydrolase [Source:HGNC Symbol;Acc:HGNC:4805]	0.020247513
ENSG00000130590	SAMD10	sterile alpha motif domain containing 10 [Source:HGNC Symbol;Acc:HGNC:16129]	0.020258063
ENSG00000167664	TMIGD2	transmembrane and immunoglobulin domain containing 2 [Source:HGNC Symbol;Acc:HGNC:28324]	0.020258063
ENSG00000146083	RNF44	ring finger protein 44 [Source:HGNC Symbol;Acc:HGNC:19180]	0.020327471
ENSG00000231925	TAPBP	TAP binding protein [Source:HGNC Symbol;Acc:HGNC:11566]	0.020387859
ENSG00000198858	R3HDM4	R3H domain containing 4 [Source:HGNC Symbol;Acc:HGNC:28270]	0.020462672
ENSG00000135924	DNAJB2	DnaJ heat shock protein family (Hsp40) member B2 [Source:HGNC Symbol;Acc:HGNC:5228]	0.020505106
ENSG00000239732	TLR9	toll like receptor 9 [Source:HGNC Symbol;Acc:HGNC:15633]	0.02065324
ENSG00000115268	RPS15	ribosomal protein S15 [Source:HGNC Symbol;Acc:HGNC:10388]	0.020839375
ENSG00000108798	ABI3	ABI family member 3 [Source:HGNC Symbol;Acc:HGNC:29859]	0.02085252
ENSG00000119669	IRF2BPL	interferon regulatory factor 2 binding protein like [Source:HGNC Symbol;Acc:HGNC:14282]	0.02099734
ENSG00000160446	ZDHHC12	zinc finger DHHC-type containing 12 [Source:HGNC Symbol;Acc:HGNC:19159]	0.02150253
ENSG00000063169	BICRA	BRD4 interacting chromatin remodeling complex associated protein [Source:HGNC Symbol;Acc:HGNC:4332]	0.021525887
ENSG00000141933	TPGS1	tubulin polyglutamylase complex subunit 1 [Source:HGNC Symbol;Acc:HGNC:25058]	0.021539966
ENSG00000088256	GNA11	G protein subunit alpha 11 [Source:HGNC Symbol;Acc:HGNC:4379]	0.021557835
ENSG00000169583	CLIC3	chloride intracellular channel 3	

ENSG00000188511	C22orf34	[Source:HGNC Symbol;Acc:HGNC:2064] chromosome 22 open reading frame 34	0.021557835
ENSG00000165406	8-Mar	[Source:HGNC Symbol;Acc:HGNC:28010] membrane associated ring-CH-type finger 8	0.021557835
ENSG00000173762	CD7	[Source:HGNC Symbol;Acc:HGNC:23356] CD7 molecule	0.021577416
ENSG00000188322	SBK1	[Source:HGNC Symbol;Acc:HGNC:1695] SH3 domain binding kinase 1	0.021879276
ENSG00000204310	AGPAT1	[Source:HGNC Symbol;Acc:HGNC:17699] 1-acylglycerol-3-phosphate O-acyltransferase 1	0.021879276
ENSG00000167797	CDK2AP2	[Source:HGNC Symbol;Acc:HGNC:324] cyclin dependent kinase 2 associated protein 2	0.021895705
ENSG00000142669	SH3BGR13	[Source:HGNC Symbol;Acc:HGNC:30833] SH3 domain binding glutamate rich protein like 3	0.022007819
ENSG00000155034	FBXL18	[Source:HGNC Symbol;Acc:HGNC:15568] F-box and leucine rich repeat protein 18	0.022133956
ENSG00000187840	EIF4EBP1	[Source:HGNC Symbol;Acc:HGNC:21874] eukaryotic translation initiation factor 4E binding protein 1	0.02227554
ENSG00000185187	SIGIRR	[Source:HGNC Symbol;Acc:HGNC:3288] single Ig and TIR domain containing	0.022615882
ENSG00000158545	ZC3H18	[Source:HGNC Symbol;Acc:HGNC:30575] zinc finger CCCH-type containing 18	0.022649486
ENSG00000184730	APOBR	[Source:HGNC Symbol;Acc:HGNC:25091] polipoprotein B receptor	0.022689972
ENSG00000204463	BAG6	[Source:HGNC Symbol;Acc:HGNC:24087] BCL2 associated athanogene 6	0.022689972
ENSG00000071242	RPS6KA2	[Source:HGNC Symbol;Acc:HGNC:13919] ribosomal protein S6 kinase A2	0.022776502
ENSG00000146701	MDH2	[Source:HGNC Symbol;Acc:HGNC:10431] malate dehydrogenase 2	0.02289018
ENSG00000180155	LYNX1	[Source:HGNC Symbol;Acc:HGNC:6971] Ly6/neurotoxin 1	0.02289018
ENSG00000213563	C8orf82	[Source:HGNC Symbol;Acc:HGNC:29604] chromosome 8 open reading frame 82	0.023112388
ENSG00000105281	SLC1A5	[Source:HGNC Symbol;Acc:HGNC:33826] solute carrier family 1 member 5	0.023356543
ENSG00000162882	HAAO	[Source:HGNC Symbol;Acc:HGNC:10943] "3-hydroxyanthranilate 3,4-dioxygenase	0.02337834
ENSG00000181513	ACBD4	[Source:HGNC Symbol;Acc:HGNC:4796]" acyl-CoA binding domain containing 4	0.02337834
ENSG00000185730	ZNF696	[Source:HGNC Symbol;Acc:HGNC:23337] zinc finger protein 696	0.02337834
ENSG00000007520	TSR3	[Source:HGNC Symbol;Acc:HGNC:25872] "TSR3, acp transferase ribosome maturation factor	0.023637109
		[Source:HGNC Symbol;Acc:HGNC:14175]"	

ENSG0000090006	LTBP4	latent transforming growth factor beta binding protein 4 [Source:HGNC Symbol;Acc:HGNC:6717]	0.023637109
ENSG00000146535	GNA12	G protein subunit alpha 12 [Source:HGNC Symbol;Acc:HGNC:4380]	0.023652058
ENSG00000141965	FEM1A	fem-1 homolog A [Source:HGNC Symbol;Acc:HGNC:16934]	0.023707215
ENSG00000160957	RECQL4	RecQ like helicase 4 [Source:HGNC Symbol;Acc:HGNC:9949]	0.023710452
ENSG00000135916	ITM2C	integral membrane protein 2C [Source:HGNC Symbol;Acc:HGNC:6175]	0.023733416
ENSG00000177732	SOX12	SRY-box 12 [Source:HGNC Symbol;Acc:HGNC:11198]	0.023733416
ENSG00000184508	HDDC3	HD domain containing 3 [Source:HGNC Symbol;Acc:HGNC:30522]	0.023802652
ENSG00000175591	P2RY2	purinergic receptor P2Y2 [Source:HGNC Symbol;Acc:HGNC:8541]	0.023918507
ENSG00000127903	ZNF835	zinc finger protein 835 [Source:HGNC Symbol;Acc:HGNC:34332]	0.023926586
ENSG00000176022	B3GALT6	“beta-1,3-galactosyltransferase 6 [Source:HGNC Symbol;Acc:HGNC:17978]”	0.023926586
ENSG00000255319	ENPP7P8	ectonucleotide pyrophosphatase/phosphodiesterase 7 pseudogene 8 [Source:HGNC Symbol;Acc:HGNC:48691]	0.02392953
ENSG00000105479	CCDC114	coiled-coil domain containing 114 [Source:HGNC Symbol;Acc:HGNC:26560]	0.02398767
ENSG00000130529	TRPM4	transient receptor potential cation channel subfamily M member 4 [Source:HGNC Symbol;Acc:HGNC:17993]	0.024020687
ENSG00000133250	ZNF414	zinc finger protein 414 [Source:HGNC Symbol;Acc:HGNC:20630]	0.024020687
ENSG00000215908	CROCCP2	“ciliary rootlet coiled-coil, rootletin pseudogene 2 [Source:HGNC Symbol;Acc:HGNC:28170]”	0.024052859
ENSG00000118046	STK11	serine/threonine kinase 11 [Source:HGNC Symbol;Acc:HGNC:11389]	0.024056107
ENSG00000034152	MAP2K3	mitogen-activated protein kinase kinase 3 [Source:HGNC Symbol;Acc:HGNC:6843]	0.024155164
ENSG00000142453	CARM1	coactivator associated arginine methyltransferase 1 [Source:HGNC Symbol;Acc:HGNC:23393]	0.024155164
ENSG00000256323	NA	NA	0.024155164
ENSG00000160094	ZNF362	zinc finger protein 362 [Source:HGNC Symbol;Acc:HGNC:18079]	0.024171066
ENSG00000104884	ERCC2	“ERCC excision repair 2, TFIIH core complex helicase subunit [Source:HGNC Symbol;Acc:HGNC:3434]”	0.024345083
ENSG00000149257	SERPINH1	serpin family H member 1 [Source:HGNC Symbol;Acc:HGNC:1546]	0.024345083
ENSG00000169635	HIC2	HIC ZBTB transcriptional repressor 2	

ENSG00000143416	SELENBP1	[Source:HGNC Symbol;Acc:HGNC:18595] selenium binding protein 1	0.024354637
ENSG00000148411	NACC2	[Source:HGNC Symbol;Acc:HGNC:10719] NACC family member 2	0.024421599
ENSG00000085872	CHERP	[Source:HGNC Symbol;Acc:HGNC:23846] calcium homeostasis endoplasmic reticulum protein	0.02443315
ENSG00000176182	MYPOP	[Source:HGNC Symbol;Acc:HGNC:16930] "Myb related transcription factor, partner of profiling	0.024463522
ENSG00000160113	NR2F6	[Source:HGNC Symbol;Acc:HGNC:20178]" nuclear receptor subfamily 2 group F member 6	0.024477311
ENSG00000108262	GIT1	[Source:HGNC Symbol;Acc:HGNC:7977] GIT ArfGAP 1	0.024505177
ENSG00000161395	PGAP3	[Source:HGNC Symbol;Acc:HGNC:4272] post-GPI attachment to proteins 3	0.024614621
ENSG00000142089	IFITM3	[Source:HGNC Symbol;Acc:HGNC:23719] interferon induced transmembrane protein 3	0.024705126
ENSG00000070444	MNT	[Source:HGNC Symbol;Acc:HGNC:5414] MAX network transcriptional repressor	0.024765171
ENSG00000112514	CUTA	[Source:HGNC Symbol;Acc:HGNC:7188] cutA divalent cation tolerance homolog	0.025148395
ENSG00000167394	ZNF668	[Source:HGNC Symbol;Acc:HGNC:21101] zinc finger protein 668	0.025148395
ENSG00000167965	MLST8	[Source:HGNC Symbol;Acc:HGNC:25821] "MTOR associated protein, LST8 homolog	0.025148395
ENSG00000244187	TMEM141	[Source:HGNC Symbol;Acc:HGNC:24825]" transmembrane protein 141	0.025148395
ENSG00000218175		[Source:HGNC Symbol;Acc:HGNC:28211] 0.02527518	
ENSG00000110063	DCPS	"decapping enzyme, scavenger [Source:HGNC Symbol;Acc:HGNC:29812]"	0.025300524
ENSG00000128805	ARHGAP22	Rho GTPase activating protein 22 [Source:HGNC Symbol;Acc:HGNC:30320]	0.025318552
ENSG00000148400	NOTCH1	notch 1 [Source:HGNC Symbol;Acc:HGNC:7881]	0.025506427
ENSG00000186076		0.0257616	
ENSG00000167470	MIDN	midnolin [Source:HGNC Symbol;Acc:HGNC:16298]	0.02580767
ENSG00000188305	PEAK3	PEAK family member 3 [Source:HGNC Symbol;Acc:HGNC:24793]	0.02580767
ENSG00000181396	OGFOD3	2-oxoglutarate and iron dependent oxygenase domain containing 3 [Source:HGNC Symbol;Acc:HGNC:26174]	0.026198035
ENSG00000240877	RN7SL521P	"RNA, 7SL, cytoplasmic 521, pseudogene [Source:HGNC Symbol;Acc:HGNC:46537]"	0.026492508

ENSG00000130511	SSBP4	single stranded DNA binding protein 4 [Source:HGNC Symbol;Acc:HGNC:15676]	0.026588317
ENSG00000063177	RPL18	ribosomal protein L18 [Source:HGNC Symbol;Acc:HGNC:10310]	0.026698079
ENSG00000172663	TMEM134	transmembrane protein 134 [Source:HGNC Symbol;Acc:HGNC:26142]	0.026698079
ENSG00000130706	ADRM1	adhesion regulating molecule 1 [Source:HGNC Symbol;Acc:HGNC:15759]	0.026721536
ENSG00000214063	TSPAN4	tetraspanin 4 [Source:HGNC Symbol;Acc:HGNC:11859]	0.026759131
ENSG00000161677	JOSD2	Josephin domain containing 2 [Source:HGNC Symbol;Acc:HGNC:28853]	0.026798474
ENSG00000189060	H1FO	H1 histone family member 0 [Source:HGNC Symbol;Acc:HGNC:4714]	0.027109095
ENSG00000256811			0.027109095
ENSG00000133317	LGALS12	galectin 12 [Source:HGNC Symbol;Acc:HGNC:15788]	0.027164347
ENSG00000012061	ERCC1	"ERCC excision repair 1, endonuclease non-catalytic subunit [Source:HGNC Symbol;Acc:HGNC:3433]"	0.027196959
ENSG00000007376	RPUSD1	RNA pseudouridylate synthase domain containing 1 [Source:HGNC Symbol;Acc:HGNC:14173]	0.027275974
ENSG00000108175	ZMIZ1	zinc finger MIZ-type containing 1 [Source:HGNC Symbol;Acc:HGNC:16493]	0.027331142
ENSG00000132003	ZSWIM4	zinc finger SWIM-type containing 4 [Source:HGNC Symbol;Acc:HGNC:25704]	0.027331142
ENSG00000148296	SURF6	surfeit 6 [Source:HGNC Symbol;Acc:HGNC:11478]	0.027362837
ENSG00000186056	MATN1-AS1	MATN1 antisense RNA 1 [Source:HGNC Symbol;Acc:HGNC:40364]	0.02742002
ENSG00000115649	CNPPD1	cyclin Pas1/PHO80 domain containing 1 [Source:HGNC Symbol;Acc:HGNC:25220]	0.027574972
ENSG00000065057	NTHL1	nth like DNA glycosylase 1 [Source:HGNC Symbol;Acc:HGNC:8028]	0.027763734
ENSG00000272098	NA	NA	0.027825114
ENSG00000011009	LYPLA2	lysophospholipase II [Source:HGNC Symbol;Acc:HGNC:6738]	0.028071412
ENSG00000110025	SNX15	sorting nexin 15 [Source:HGNC Symbol;Acc:HGNC:14978]	0.028074538
ENSG00000095321	CRAT	carnitine O-acetyltransferase [Source:HGNC Symbol;Acc:HGNC:2342]	0.028133383
ENSG00000108515	ENO3	enolase 3 [Source:HGNC Symbol;Acc:HGNC:3354]	0.028133383
ENSG00000123064	DDX54	DEAD-box helicase 54 [Source:HGNC Symbol;Acc:HGNC:20084]	0.028358899
ENSG00000169564	PCBP1	poly(rC) binding protein 1	

ENSG00000171045	TSNARE1	[Source:HGNC Symbol;Acc:HGNC:8647] t-SNARE domain containing 1	0.028645846
ENSG00000225978	HAR1A	[Source:HGNC Symbol;Acc:HGNC:26437] highly accelerated region 1A (non-protein coding)	0.028645846
ENSG00000128283	CDC42EP1	[Source:HGNC Symbol;Acc:HGNC:33117] CDC42 effector protein 1	0.028645846
ENSG00000174282	ZBTB4	[Source:HGNC Symbol;Acc:HGNC:17014] zinc finger and BTB domain containing 4	0.028675863
ENSG00000167685	ZNF444	[Source:HGNC Symbol;Acc:HGNC:23847] zinc finger protein 444	0.028871519
ENSG00000110104	CCDC86	[Source:HGNC Symbol;Acc:HGNC:16052] coiled-coil domain containing 86	0.028919683
ENSG00000171703	TCEA2	[Source:HGNC Symbol;Acc:HGNC:28359] transcription elongation factor A2	0.028929404
ENSG00000177600	RPLP2	[Source:HGNC Symbol;Acc:HGNC:11614] ribosomal protein lateral stalk subunit P2	0.029117009
ENSG00000182095	TNRC18	[Source:HGNC Symbol;Acc:HGNC:10377] trinucleotide repeat containing 18	0.029298722
ENSG00000167106	FAM102A	[Source:HGNC Symbol;Acc:HGNC:11962] family with sequence similarity 102 member A	0.029299181
ENSG00000126458	RRAS	[Source:HGNC Symbol;Acc:HGNC:31419] RAS related	0.029415219
ENSG00000105063	PPP6R1	[Source:HGNC Symbol;Acc:HGNC:10447] protein phosphatase 6 regulatory subunit 1	0.02952737
ENSG00000125730	C3	[Source:HGNC Symbol;Acc:HGNC:29195] complement C3	0.02959944
ENSG00000237973	MTCO1P12	[Source:HGNC Symbol;Acc:HGNC:1318] mitochondrially encoded cytochrome c oxidase I pseudogene 12	0.029997906
ENSG00000267412		[Source:HGNC Symbol;Acc:HGNC:52014] 0.030144659	0.030144659
ENSG00000185813	PCYT2	“phosphate cytidyltransferase 2, ethanolamine [Source:HGNC Symbol;Acc:HGNC:8756]”	0.030317293
ENSG00000163462	TRIM46	tripartite motif containing 46 [Source:HGNC Symbol;Acc:HGNC:19019]	0.030614393
ENSG00000157933	SKI	SKI proto-oncogene [Source:HGNC Symbol;Acc:HGNC:10896]	0.030701411
ENSG00000161091	MFSD12	major facilitator superfamily domain containing 12 [Source:HGNC Symbol;Acc:HGNC:28299]	0.030704292
ENSG00000185163	DDX51	DEAD-box helicase 51 [Source:HGNC Symbol;Acc:HGNC:20082]	0.030735268
ENSG00000171813	PWWP2B	PWWP domain containing 2B [Source:HGNC Symbol;Acc:HGNC:25150]	0.030810478
ENSG00000137267	TUBB2A	tubulin beta 2A class IIa [Source:HGNC Symbol;Acc:HGNC:12412]	0.030847037
ENSG00000188747	NOXA1	NADPH oxidase activator 1	

ENSG00000108557	RAI1	[Source:HGNC Symbol;Acc:HGNC:10668] retinoic acid induced 1	0.030853611
ENSG00000137166	FOXP4	[Source:HGNC Symbol;Acc:HGNC:9834] forkhead box P4	0.030977697
ENSG00000204420	MPIG6B	[Source:HGNC Symbol;Acc:HGNC:20842] megakaryocyte and platelet inhibitory receptor G6b	0.030977697
ENSG00000133265	HSPBP1	[Source:HGNC Symbol;Acc:HGNC:13937] HSPA (Hsp70) binding protein 1	0.031369168
ENSG00000008710	PKD1	[Source:HGNC Symbol;Acc:HGNC:24989] "polycystin 1, transient receptor potential channel interacting	0.031442624
ENSG00000099624	ATP5F1D	[Source:HGNC Symbol;Acc:HGNC:9008]" ATP synthase F1 subunit delta	0.031566582
ENSG00000108819	PPP1R9B	[Source:HGNC Symbol;Acc:HGNC:837] protein phosphatase 1 regulatory subunit 9B	0.031657927
ENSG00000158292	GPR153	[Source:HGNC Symbol;Acc:HGNC:9298] G protein-coupled receptor 153	0.031695534
ENSG00000130382	MLLT1	[Source:HGNC Symbol;Acc:HGNC:23618] "MLLT1, super elongation complex subunit	0.031750316
ENSG00000269352	PTOV1-AS2	[Source:HGNC Symbol;Acc:HGNC:7134]" PTOV1 antisense RNA 2	0.031828022
ENSG00000162585	FAAP20	[Source:HGNC Symbol;Acc:HGNC:51284] Fanconi anemia core complex associated protein 20	0.031850457
ENSG00000157240	FZD1	[Source:HGNC Symbol;Acc:HGNC:26428] frizzled class receptor 1	0.0320507
ENSG00000135736	CCDC102A	[Source:HGNC Symbol;Acc:HGNC:4038] coiled-coil domain containing 102A	0.032151732
ENSG00000020181	ADGRA2	[Source:HGNC Symbol;Acc:HGNC:28097] adhesion G protein-coupled receptor A2	0.032302006
ENSG00000198546	ZNF511	[Source:HGNC Symbol;Acc:HGNC:17849] zinc finger protein 511	0.032424937
ENSG00000123144	TRIR	[Source:HGNC Symbol;Acc:HGNC:28445] telomerase RNA component interacting RNase	0.032576231
ENSG00000156860	FBRF	[Source:HGNC Symbol;Acc:HGNC:28424] fibrosin	0.032671184
ENSG00000162910	MRPL55	[Source:HGNC Symbol;Acc:HGNC:20442] mitochondrial ribosomal protein L55	0.032671184
ENSG00000130731	METTL26	[Source:HGNC Symbol;Acc:HGNC:16686] methyltransferase like 26	0.032697662
ENSG00000101986	ABCD1	[Source:HGNC Symbol;Acc:HGNC:14141] ATP binding cassette subfamily D member 1	0.032833764
ENSG00000020633	RUNX3	[Source:HGNC Symbol;Acc:HGNC:61] runt related transcription factor 3	0.032886018
ENSG00000184640	9-Sep	[Source:HGNC Symbol;Acc:HGNC:10473] septin 9	0.033016587
		[Source:HGNC Symbol;Acc:HGNC:7323] 0.033101928	

ENSG00000260521	NA	NA	0.033101928
ENSG00000125787	GNRH2	gonadotropin releasing hormone 2 [Source:HGNC Symbol;Acc:HGNC:4420]	0.033349502
ENSG00000229391	HLA-DRB6	“major histocompatibility complex, class II, DR beta 6 (pseudogene) [Source:HGNC Symbol;Acc:HGNC:4954]”	0.033349502
ENSG00000160223	ICOSLG	inducible T cell costimulator ligand [Source:HGNC Symbol;Acc:HGNC:17087]	0.033394348
ENSG00000105204	DYRK1B	dual specificity tyrosine phosphorylation regulated kinase 1B [Source:HGNC Symbol;Acc:HGNC:3092]	0.033465567
ENSG00000142173	COL6A2	collagen type VI alpha 2 chain [Source:HGNC Symbol;Acc:HGNC:2212]	0.033483825
ENSG00000169710	FASN	fatty acid synthase [Source:HGNC Symbol;Acc:HGNC:3594]	0.033483825
ENSG00000176533	GNG7	G protein subunit gamma 7 [Source:HGNC Symbol;Acc:HGNC:4410]	0.033483825
ENSG00000179253			0.033483825
ENSG00000169972	PUSL1	pseudouridylate synthase-like 1 [Source:HGNC Symbol;Acc:HGNC:26914]	0.033509544
ENSG00000160360	GPSM1	G protein signaling modulator 1 [Source:HGNC Symbol;Acc:HGNC:17858]	0.033771567
ENSG00000171159	C9orf16	chromosome 9 open reading frame 16 [Source:HGNC Symbol;Acc:HGNC:17823]	0.033853634
ENSG00000215375	MYL5	myosin light chain 5 [Source:HGNC Symbol;Acc:HGNC:7586]	0.033853634
ENSG00000105402	NAPA	NSF attachment protein alpha [Source:HGNC Symbol;Acc:HGNC:7641]	0.034044441
ENSG00000038532	CLEC16A	C-type lectin domain containing 16A [Source:HGNC Symbol;Acc:HGNC:29013]	0.034108157
ENSG00000165175	MID1IP1	MID1 interacting protein 1 [Source:HGNC Symbol;Acc:HGNC:20715]	0.03418982
ENSG00000166947	EPB42	erythrocyte membrane protein band 4.2 [Source:HGNC Symbol;Acc:HGNC:3381]	0.03418982
ENSG00000168286	THAP11	THAP domain containing 11 [Source:HGNC Symbol;Acc:HGNC:23194]	0.03418982
ENSG00000168476	REEP4	receptor accessory protein 4 [Source:HGNC Symbol;Acc:HGNC:26176]	0.034591261
ENSG00000107521	HPS1	“HPS1, biogenesis of lysosomal organelles complex 3 subunit 1 [Source:HGNC Symbol;Acc:HGNC:5163]”	0.034688533
ENSG00000267436			0.034821851
ENSG00000099991	CABIN1	calcineurin binding protein 1 [Source:HGNC Symbol;Acc:HGNC:24187]	0.034858474
ENSG00000169718	DUS1L	dihydrouridine synthase 1 like [Source:HGNC Symbol;Acc:HGNC:30086]	0.034980702
ENSG00000105325	FZR1	fizzy and cell division cycle 20 related 1 [Source:HGNC Symbol;Acc:HGNC:24824]	0.035034499

ENSG00000167291	TBC1D16	TBC1 domain family member 16 [Source:HGNC Symbol;Acc:HGNC:28356]	0.035082388
ENSG00000213399			0.035085538
ENSG00000175040	CHST2	carbohydrate sulfotransferase 2 [Source:HGNC Symbol;Acc:HGNC:1970]	0.035106231
ENSG00000228544	CCDC183-AS1	CCDC183 antisense RNA 1 [Source:HGNC Symbol;Acc:HGNC:44105]	0.035154264
ENSG00000167658	EEF2	eukaryotic translation elongation factor 2 [Source:HGNC Symbol;Acc:HGNC:3214]	0.03521308
ENSG00000090238	YPEL3	yippee like 3 [Source:HGNC Symbol;Acc:HGNC:18327]	0.035223199
ENSG00000172508	CARNS1	carnosine synthase 1 [Source:HGNC Symbol;Acc:HGNC:29268]	0.03555645
ENSG00000173272	MZT2A	mitotic spindle organizing protein 2A [Source:HGNC Symbol;Acc:HGNC:33187]	0.035664739
ENSG00000141522	ARHGDIA	Rho GDP dissociation inhibitor alpha [Source:HGNC Symbol;Acc:HGNC:678]	0.03575577
ENSG00000149541	B3GAT3	“beta-1,3-glucuronyltransferase 3 [Source:HGNC Symbol;Acc:HGNC:923]”	0.03575577
ENSG00000171206	TRIM8	tripartite motif containing 8 [Source:HGNC Symbol;Acc:HGNC:15579]	0.035790036
ENSG00000027869	SH2D2A	SH2 domain containing 2A [Source:HGNC Symbol;Acc:HGNC:10821]	0.035871776
ENSG00000149823	VPS51	“VPS51, GARP complex subunit [Source:HGNC Symbol;Acc:HGNC:1172]”	0.035906645
ENSG00000196355	NA	NA	0.035938935
ENSG00000165804	ZNF219	zinc finger protein 219 [Source:HGNC Symbol;Acc:HGNC:13011]	0.035996581
ENSG00000177542	SLC25A22	solute carrier family 25 member 22 [Source:HGNC Symbol;Acc:HGNC:19954]	0.035996581
ENSG00000130202	NECTIN2	nectin cell adhesion molecule 2 [Source:HGNC Symbol;Acc:HGNC:9707]	0.036025366
ENSG00000006638	TBXA2R	thromboxane A2 receptor [Source:HGNC Symbol;Acc:HGNC:11608]	0.036065767
ENSG00000025770	NCAPH2	non-SMC condensin II complex subunit H2 [Source:HGNC Symbol;Acc:HGNC:25071]	0.036065767
ENSG00000100316	RPL3	ribosomal protein L3 [Source:HGNC Symbol;Acc:HGNC:10332]	0.036065767
ENSG00000110665	C11orf21	chromosome 11 open reading frame 21 [Source:HGNC Symbol;Acc:HGNC:13231]	0.036065767
ENSG00000160445	ZER1	zyg-11 related cell cycle regulator [Source:HGNC Symbol;Acc:HGNC:30960]	0.036065767
ENSG00000173786	CNP	“2’,3’-cyclic nucleotide 3’ phosphodiesterase [Source:HGNC Symbol;Acc:HGNC:2158]”	0.036065767
ENSG00000229368			0.036065767

ENSG00000160789	LMNA	lamin A/C [Source:HGNC Symbol;Acc:HGNC:6636]	0.036188381
ENSG00000166189	HPS6	“HPS6, biogenesis of lysosomal organelles complex 2 subunit 3 [Source:HGNC Symbol;Acc:HGNC:18817]”	0.036188381
ENSG00000261226			0.036342968
ENSG00000185049	NELFA	negative elongation factor complex member A [Source:HGNC Symbol;Acc:HGNC:12768]	0.036383164
ENSG0000005882	PDK2	pyruvate dehydrogenase kinase 2 [Source:HGNC Symbol;Acc:HGNC:8810]	0.036423123
ENSG00000163050	COQ8A	coenzyme Q8A [Source:HGNC Symbol;Acc:HGNC:16812]	0.036459828
ENSG0000060138	YBX3	Y-box binding protein 3 [Source:HGNC Symbol;Acc:HGNC:2428]	0.03651176
ENSG00000122971	ACADS	acyl-CoA dehydrogenase short chain [Source:HGNC Symbol;Acc:HGNC:90]	0.036511776
ENSG00000205927	OLIG2	oligodendrocyte transcription factor 2 [Source:HGNC Symbol;Acc:HGNC:9398]	0.036582868
ENSG00000092096	SLC22A17	solute carrier family 22 member 17 [Source:HGNC Symbol;Acc:HGNC:23095]	0.036619295
ENSG00000090554	FLT3LG	fms related tyrosine kinase 3 ligand [Source:HGNC Symbol;Acc:HGNC:3766]	0.036780281
ENSG00000078902	TOLLIP	toll interacting protein [Source:HGNC Symbol;Acc:HGNC:16476]	0.036796695
ENSG00000136802	LRRC8A	leucine rich repeat containing 8 VRAC subunit A [Source:HGNC Symbol;Acc:HGNC:19027]	0.036860551
ENSG00000236976			0.036972133
ENSG00000100908	EMC9	ER membrane protein complex subunit 9 [Source:HGNC Symbol;Acc:HGNC:20273]	0.037054085
ENSG00000105364	MRPL4	mitochondrial ribosomal protein L4 [Source:HGNC Symbol;Acc:HGNC:14276]	0.03712252
ENSG00000157184	CPT2	carnitine palmitoyltransferase 2 [Source:HGNC Symbol;Acc:HGNC:2330]	0.03712252
ENSG00000168056	LTBP3	latent transforming growth factor beta binding protein 3 [Source:HGNC Symbol;Acc:HGNC:6716]	0.037135417
ENSG00000196313	POM121	POM121 transmembrane nucleoporin [Source:HGNC Symbol;Acc:HGNC:19702]	0.037140956
ENSG00000170604	IRF2BP1	nterferon regulatory factor 2 binding protein 1 [Source:HGNC Symbol;Acc:HGNC:21728]	0.037222007
ENSG00000110697	PITPNM1	phosphatidylinositol transfer protein membrane associated 1 [Source:HGNC Symbol;Acc:HGNC:9003]	0.037374978
ENSG00000100348	TXN2	thioredoxin 2 [Source:HGNC Symbol;Acc:HGNC:17772]	0.037546969
ENSG00000102007	PLP2	proteolipid protein 2 [	
ENSG00000132005	RFX1	Source:HGNC Symbol;Acc:HGNC:9087] regulatory factor X1 [	0.037630556

ENSG00000141499	WRAP53	Source:HGNC Symbol;Acc:HGNC:9982] WD repeat containing antisense to TP53 [Source:HGNC Symbol;Acc:HGNC:25522]	0.037671165 0.037678229
ENSG00000189114	BLOC1S3	biogenesis of lysosomal organelles complex 1 subunit 3 [Source:HGNC Symbol;Acc:HGNC:20914]	0.037963219
ENSG00000123154	WDR83	WD repeat domain 83 [Source:HGNC Symbol;Acc:HGNC:32672]	0.038059131
ENSG00000127663	KDM4B	lysine demethylase 4B [Source:HGNC Symbol;Acc:HGNC:29136]	0.038059131
ENSG00000175274	TP53I11	tumor protein p53 inducible protein 11 [Source:HGNC Symbol;Acc:HGNC:16842]	0.038059131
ENSG00000249115	HAUS5	HAUS augmin like complex subunit 5 [Source:HGNC Symbol;Acc:HGNC:29130]	0.038059131
ENSG00000130764	LRRC47	leucine rich repeat containing 47 [Source:HGNC Symbol;Acc:HGNC:29207]	0.038286929
ENSG00000176946	THAP4	THAP domain containing 4 [Source:HGNC Symbol;Acc:HGNC:23187]	0.038286929
ENSG00000137497	NUMA1	nuclear mitotic apparatus protein 1 [Source:HGNC Symbol;Acc:HGNC:8059]	0.038678067
ENSG00000143761	ARF1	ADP ribosylation factor 1 [Source:HGNC Symbol;Acc:HGNC:652]	0.038678067
ENSG00000198931	APRT	adenine phosphoribosyltransferase [Source:HGNC Symbol;Acc:HGNC:626]	0.038678067
ENSG00000186174	BCL9L	B cell CLL/lymphoma 9 like [Source:HGNC Symbol;Acc:HGNC:23688]	0.039375488
ENSG00000104894	CD37	CD37 molecule [Source:HGNC Symbol;Acc:HGNC:1666]	0.039523734
ENSG00000235314	LINC00957	long intergenic non-protein coding RNA 957 [Source:HGNC Symbol;Acc:HGNC:22332]	0.039534059
ENSG00000076864	RAP1GAP	RAP1 GTPase activating protein [Source:HGNC Symbol;Acc:HGNC:9858]	0.039534171
ENSG00000179348	GATA2	GATA binding protein 2 [Source:HGNC Symbol;Acc:HGNC:4171]	0.039644975
ENSG00000223496	EXOSC6	exosome component 6 [Source:HGNC Symbol;Acc:HGNC:19055]	0.039646513
ENSG00000174004	NRROS	negative regulator of reactive oxygen species [Source:HGNC Symbol;Acc:HGNC:24613]	0.039697731
ENSG00000185736	ADARB2	“adenosine deaminase, RNA specific B2 (inactive) [Source:HGNC Symbol;Acc:HGNC:227]”	0.039813584
ENSG00000177595	PIDD1	p53-induced death domain protein 1 [Source:HGNC Symbol;Acc:HGNC:16491]	0.039841437
ENSG00000114767	RRP9	“ribosomal RNA processing 9, U3 small nucleolar RNA binding protein [Source:HGNC Symbol;Acc:HGNC:16829]”	0.039852243
ENSG00000198336	MYL4	myosin light chain 4 [Source:HGNC Symbol;Acc:HGNC:7585]	0.040061329

ENSG00000267427	NA	NA	0.040061329
ENSG00000123159	GIPC1	GIPC PDZ domain containing family member 1 [Source:HGNC Symbol;Acc:HGNC:1226]	0.040207239
ENSG00000139405	RITA1	RBPJ interacting and tubulin associated 1 [Source:HGNC Symbol;Acc:HGNC:25925]	0.040571361
ENSG00000149929	HIRIP3	HIRA interacting protein 3 [Source:HGNC Symbol;Acc:HGNC:4917]	0.040590193
ENSG00000198517	MAFK	MAF bZIP transcription factor K [Source:HGNC Symbol;Acc:HGNC:6782]	0.040590193
ENSG00000164897	TMUB1	transmembrane and ubiquitin like domain containing 1 [Source:HGNC Symbol;Acc:HGNC:21709]	0.040938395
ENSG00000070047	PHRF1	PHD and ring finger domains 1 [Source:HGNC Symbol;Acc:HGNC:24351]	0.041015111
ENSG00000100403	ZC3H7B	zinc finger CCCH-type containing 7B [Source:HGNC Symbol;Acc:HGNC:30869]	0.041151359
ENSG00000205147	NA	NA	0.041207854
ENSG00000184470	TXNRD2	thioredoxin reductase 2 [Source:HGNC Symbol;Acc:HGNC:18155]	0.04134465
ENSG00000103145	HCFC1R1	host cell factor C1 regulator 1 [Source:HGNC Symbol;Acc:HGNC:21198]	0.041366672
ENSG00000087086	FTL	ferritin light chain [Source:HGNC Symbol;Acc:HGNC:3999]	0.041631474
ENSG00000102870	ZNF629	zinc finger protein 629 [Source:HGNC Symbol;Acc:HGNC:29008]	0.041631474
ENSG00000181444	ZNF467	zinc finger protein 467 [Source:HGNC Symbol;Acc:HGNC:23154]	0.041868067
ENSG00000142444	TIMM29	translocase of inner mitochondrial membrane 29 [Source:HGNC Symbol;Acc:HGNC:25152]	0.041933219
ENSG00000204252	HLA-DOA	“major histocompatibility complex, class II, DO alpha [Source:HGNC Symbol;Acc:HGNC:4936]”	0.041944166
ENSG00000224051	CPTP	ceramide-1-phosphate transfer protein [Source:HGNC Symbol;Acc:HGNC:28116]	0.041944166
ENSG00000103253	HAGHL	hydroxyacylglutathione hydrolase like [Source:HGNC Symbol;Acc:HGNC:14177]	0.042027801
ENSG00000011590	ZBTB32	zinc finger and BTB domain containing 32 [Source:HGNC Symbol;Acc:HGNC:16763]	0.042101327
ENSG00000182566	CLEC4G	C-type lectin domain family 4 member G [Source:HGNC Symbol;Acc:HGNC:24591]	0.042114834
ENSG00000244165	P2RY11	purinergic receptor P2Y11 [Source:HGNC Symbol;Acc:HGNC:8540]	0.042114834
ENSG00000267275			0.042114834
ENSG00000173327	MAP3K11	mitogen-activated protein kinase kinase kinase 11 [Source:HGNC Symbol;Acc:HGNC:6850]	0.042395519
ENSG00000149418	ST14	suppression of tumorigenicity 14 [Source:HGNC Symbol;Acc:HGNC:11344]	0.04243773

ENSG00000112658	SRF	serum response factor	
		[Source:HGNC Symbol;Acc:HGNC:11291]	0.042440717
ENSG00000106003	LFNG	LFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase	
		[Source:HGNC Symbol;Acc:HGNC:6560]	0.042450091
ENSG00000164896	FASTK	Fas activated serine/threonine kinase	
		[Source:HGNC Symbol;Acc:HGNC:24676]	0.042450091
ENSG00000196544	BORCS6	BLOC-1 related complex subunit 6	
		[Source:HGNC Symbol;Acc:HGNC:25939]	0.042514351
ENSG00000134107	BHLHE40	basic helix-loop-helix family member e40	
		[Source:HGNC Symbol;Acc:HGNC:1046]	0.042517218
ENSG00000151176	PLBD2	phospholipase B domain containing 2	
		[Source:HGNC Symbol;Acc:HGNC:27283]	0.042582368
ENSG00000183397	C19orf71	chromosome 19 open reading frame 71	
		[Source:HGNC Symbol;Acc:HGNC:34496]	0.042902315
ENSG00000105738	SIPA1L3	signal induced proliferation associated 1 like 3	
		[Source:HGNC Symbol;Acc:HGNC:23801]	0.043052047
ENSG00000157353	FUK	fucokinase	
		[Source:HGNC Symbol;Acc:HGNC:29500]	0.043381308
ENSG00000126062	TMEM115	transmembrane protein 115	
		[Source:HGNC Symbol;Acc:HGNC:30055]	0.043382452
ENSG00000179632	MAF1	"MAF1 homolog, negative regulator of RNA polymerase III	
		[Source:HGNC Symbol;Acc:HGNC:24966]"	0.043386409
ENSG00000254910			0.043544967
ENSG00000073111	MCM2	minichromosome maintenance complex component 2	
		[Source:HGNC Symbol;Acc:HGNC:6944]	0.043556269
ENSG00000105698	USF2	"upstream transcription factor 2, c-fos interacting	
		[Source:HGNC Symbol;Acc:HGNC:12594]"	0.043737282
ENSG00000261043			0.043870446
ENSG00000078808	SDF4	stromal cell derived factor 4	
		[Source:HGNC Symbol;Acc:HGNC:24188]	0.043914575
ENSG00000182154	MRPL41	mitochondrial ribosomal protein L41	
		[Source:HGNC Symbol;Acc:HGNC:14492]	0.044022575
ENSG00000237476	LINC01637	long intergenic non-protein coding RNA 1637	
		[Source:HGNC Symbol;Acc:HGNC:52424]	0.044022575
ENSG00000264577			0.044022575
ENSG00000160877	NACC1	nucleus accumbens associated 1	
		[Source:HGNC Symbol;Acc:HGNC:20967]	0.044046233
ENSG00000162032	SPSB3	splA/ryanodine receptor domain and SOCS box containing 3	
		[Source:HGNC Symbol;Acc:HGNC:30629]	0.044046233
ENSG00000123933	MXD4	MAX dimerization protein 4	
		[Source:HGNC Symbol;Acc:HGNC:13906]	0.044146857
ENSG00000149260	CAPN5	calpain 5 [Source:HGNC Symbol;Acc:HGNC:1482]	0.044146857
ENSG00000197324	LRP10	LDL receptor related protein 10	
		[Source:HGNC Symbol;Acc:HGNC:14553]	0.044146857
ENSG00000128011	LRFN1	leucine rich repeat and fibronectin type III domain containing 1	

		[Source:HGNC Symbol;Acc:HGNC:29290]	0.044424476
ENSG00000103126	AXIN1	axin 1 [Source:HGNC Symbol;Acc:HGNC:903]	0.044490553
ENSG00000183134	PTGDR2	prostaglandin D2 receptor 2	
		[Source:HGNC Symbol;Acc:HGNC:4502]	0.044490553
ENSG00000185905	C16orf54	chromosome 16 open reading frame 54	
		[Source:HGNC Symbol;Acc:HGNC:26649]	0.044574634
ENSG00000185905	C16orf54	chromosome 16 open reading frame 54	
		[Source:HGNC Symbol;Acc:HGNC:26649]	0.044574634
ENSG00000176974	SHMT1	serine hydroxymethyltransferase 1	
		[Source:HGNC Symbol;Acc:HGNC:10850]	0.044717969
ENSG00000105327	BBC3	BCL2 binding component 3	
		[Source:HGNC Symbol;Acc:HGNC:17868]	0.044899327
ENSG00000212123	PRR22	proline rich 22	
		[Source:HGNC Symbol;Acc:HGNC:28354]	0.044899327
ENSG00000171798	KNDC1	kinase non-catalytic C-lobe domain containing 1	
		[Source:HGNC Symbol;Acc:HGNC:29374]	0.045139854
ENSG00000073150	PANX2	pannexin 2	
		[Source:HGNC Symbol;Acc:HGNC:8600]	0.045237232
ENSG00000126453	BCL2L12	BCL2 like 12	
		[Source:HGNC Symbol;Acc:HGNC:13787]	0.04527356
ENSG00000159692	CTBP1	C-terminal binding protein 1	
		[Source:HGNC Symbol;Acc:HGNC:2494]	0.04527356
ENSG00000105248	CCDC94	coiled-coil domain containing 94	
		[Source:HGNC Symbol;Acc:HGNC:25518]	0.045450088
ENSG00000101220	C20orf27	chromosome 20 open reading frame 27	
		[Source:HGNC Symbol;Acc:HGNC:15873]	0.045474144
ENSG00000188735	TMEM120B	transmembrane protein 120B	
		[Source:HGNC Symbol;Acc:HGNC:32008]	0.045474144
ENSG00000149476	TKFC	triokinase and FMN cyclase	
		[Source:HGNC Symbol;Acc:HGNC:24552]	0.045497488
ENSG00000100105	PATZ1	POZ/BTB and AT hook containing zinc finger 1	
		[Source:HGNC Symbol;Acc:HGNC:13071]	0.045500961
ENSG00000136295	TTYH3	tweety family member 3	
		[Source:HGNC Symbol;Acc:HGNC:22222]	0.045528908
ENSG00000104823	ECH1	enoyl-CoA hydratase 1	
		[Source:HGNC Symbol;Acc:HGNC:3149]	0.045555559
ENSG00000167930	FAM234A	family with sequence similarity 234 member A	
		[Source:HGNC Symbol;Acc:HGNC:14163]	0.045584551
ENSG00000125505	MBOAT7	membrane bound O-acyltransferase domain containing 7	
		[Source:HGNC Symbol;Acc:HGNC:15505]	0.045601783
ENSG00000136720	HS6ST1	heparan sulfate 6-O-sulfotransferase 1	
		[Source:HGNC Symbol;Acc:HGNC:5201]	0.045601783
ENSG00000156853	ZNF689	zinc finger protein 689	
		[Source:HGNC Symbol;Acc:HGNC:25173]	0.045601783
ENSG00000176108	CHMP6	charged multivesicular body protein 6	

ENSG00000205336	ADGRG1	[Source:HGNC Symbol;Acc:HGNC:25675] adhesion G protein-coupled receptor G1	0.045601783
ENSG00000186350	RXRA	[Source:HGNC Symbol;Acc:HGNC:4512] retinoid X receptor alpha	0.045601783
ENSG00000164849	GPR146	[Source:HGNC Symbol;Acc:HGNC:10477] G protein-coupled receptor 146	0.045691236
ENSG00000124313	IQSEC2	[Source:HGNC Symbol;Acc:HGNC:21718] IQ motif and Sec7 domain 2	0.045781
ENSG00000148341	SH3GLB2	[Source:HGNC Symbol;Acc:HGNC:29059] "SH3 domain containing GRB2 like, endophilin B2	0.045921742
ENSG00000213654	GPSM3	[Source:HGNC Symbol;Acc:HGNC:10834]" G protein signaling modulator 3	0.045931004
ENSG00000171219	CDC42BPG	[Source:HGNC Symbol;Acc:HGNC:13945] CDC42 binding protein kinase gamma	0.045963746
ENSG00000125741	OPA3	[Source:HGNC Symbol;Acc:HGNC:29829] "OPA3, outer mitochondrial membrane lipid metabolism regulator	0.046017697
ENSG00000089693	MLF2	[Source:HGNC Symbol;Acc:HGNC:8142]" myeloid leukemia factor 2	0.046210538
ENSG00000267283		[Source:HGNC Symbol;Acc:HGNC:7126] 0.046269835	0.046536749
ENSG00000238164	TNFRSF14-AS1	TNFRSF14 antisense RNA 1	
ENSG00000167815	PRDX2	[Source:HGNC Symbol;Acc:HGNC:26966] peroxiredoxin 2	0.046584081
ENSG00000140564	FURIN	[Source:HGNC Symbol;Acc:HGNC:9353] "furin, paired basic amino acid cleaving enzyme	0.046640005
ENSG00000059122	FLYWCH1	[Source:HGNC Symbol;Acc:HGNC:8568]" FLYWCH-type zinc finger 1	0.046653045
ENSG00000070423	RNF126	[Source:HGNC Symbol;Acc:HGNC:25404] ring finger protein 126	0.046934685
ENSG00000027847	B4GALT7	[Source:HGNC Symbol;Acc:HGNC:21151] "beta-1,4-galactosyltransferase 7	0.047070015
ENSG00000108518	PFN1	[Source:HGNC Symbol;Acc:HGNC:930]" profilin 1	0.047130774
ENSG00000110711	AIP	[Source:HGNC Symbol;Acc:HGNC:8881] aryl hydrocarbon receptor interacting protein	0.047157356
ENSG00000164068	RNF123	[Source:HGNC Symbol;Acc:HGNC:358] ring finger protein 123	0.04721490
ENSG00000137216	TMEM63B	[Source:HGNC Symbol;Acc:HGNC:21148] transmembrane protein 63B	0.047214902
ENSG00000179588	ZFPM1	[Source:HGNC Symbol;Acc:HGNC:17735] "zinc finger protein, FOG family member 1	0.047244731
ENSG00000188070	C11orf95	[Source:HGNC Symbol;Acc:HGNC:19762]" chromosome 11 open reading frame 95	0.047461433
ENSG00000162722	TRIM58	[Source:HGNC Symbol;Acc:HGNC:28449] tripartite motif containing 58	0.047461433

ENSG00000068724	TTC7A	[Source:HGNC Symbol;Acc:HGNC:24150] tetratricopeptide repeat domain 7A	0.047475759
ENSG00000142227	EMP3	[Source:HGNC Symbol;Acc:HGNC:19750] epithelial membrane protein 3	0.0476766
ENSG00000159714	ZDHHC1	[Source:HGNC Symbol;Acc:HGNC:3335] zinc finger DHHC-type containing 1	0.0476766
ENSG00000196182	STK40	[Source:HGNC Symbol;Acc:HGNC:17916] serine/threonine kinase 40	0.04772167
ENSG00000099875	MKNK2	[Source:HGNC Symbol;Acc:HGNC:21373] MAP kinase interacting serine/threonine kinase 2	0.047779011
ENSG00000132514	CLEC10A	[Source:HGNC Symbol;Acc:HGNC:7111] C-type lectin domain containing 10A	0.047824795
ENSG00000197982	C1orf122	[Source:HGNC Symbol;Acc:HGNC:16916] chromosome 1 open reading frame 122	0.047824795
ENSG00000204348	DXO	[Source:HGNC Symbol;Acc:HGNC:24789] decapping exoribonuclease	0.047824795
ENSG00000259856	RAB43P1	[Source:HGNC Symbol;Acc:HGNC:2992] RAB43 pseudogene 1	0.047913021
ENSG00000103254	FAM173A	[Source:HGNC Symbol;Acc:HGNC:33153] family with sequence similarity 173 member A	0.048194625
ENSG00000196453	ZNF777	[Source:HGNC Symbol;Acc:HGNC:14152] zinc finger protein 777	0.048206847
ENSG00000167173	C15orf39	[Source:HGNC Symbol;Acc:HGNC:22213] chromosome 15 open reading frame 39	0.048246269
ENSG00000172534	HCFC1	[Source:HGNC Symbol;Acc:HGNC:24497] host cell factor C1	0.048259142
ENSG00000198804	MT-CO1	[Source:HGNC Symbol;Acc:HGNC:4839] mitochondrially encoded cytochrome c oxidase I	0.04840783
ENSG00000244486	SCARF2	[Source:HGNC Symbol;Acc:HGNC:7419] scavenger receptor class F member 2	0.048409706
ENSG00000125652	ALKBH7	[Source:HGNC Symbol;Acc:HGNC:19869] alkB homolog 7	0.048617065
ENSG00000176101	SSNA1	[Source:HGNC Symbol;Acc:HGNC:21306] SS nuclear autoantigen 1	0.048746819
ENSG00000129103	SUMF2	[Source:HGNC Symbol;Acc:HGNC:11321] sulfatase modifying factor 2	0.048934402
ENSG00000115756	HPCAL1	[Source:HGNC Symbol;Acc:HGNC:20415] hippocalcin like 1	0.048950286
ENSG00000243566	UPK3B	[Source:HGNC Symbol;Acc:HGNC:5145] uroplakin 3B	0.049011448
ENSG00000149150	SLC43A1	[Source:HGNC Symbol;Acc:HGNC:21444] solute carrier family 43 member 1	0.049012128
ENSG00000103227	LMF1	[Source:HGNC Symbol;Acc:HGNC:9225] lipase maturation factor 1	0.049128197
		[Source:HGNC Symbol;Acc:HGNC:14154]	0.049193782

ENSG00000271959			0.049311473
ENSG00000261222			0.049471704
ENSG00000126217	MCF2L	MCF.2 cell line derived transforming sequence like [Source:HGNC Symbol;Acc:HGNC:14576]	0.049648177
ENSG00000104964	AES	amino-terminal enhancer of split [Source:HGNC Symbol;Acc:HGNC:307]	0.049726662
ENSG00000127831	VIL1	villin 1 [Source:HGNC Symbol;Acc:HGNC:12690]	0.049726662
ENSG00000169738	DCXR	dicarbonyl and L-xylulose reductase [Source:HGNC Symbol;Acc:HGNC:18985]	0.049760492
ENSG00000086015	MAST2	microtubule associated serine/threonine kinase 2 [Source:HGNC Symbol;Acc:HGNC:19035]	0.04998097

TABLE 8**AC3 GENES**

<u>Ensembl</u>	<u>Symbol</u>	<u>Description</u>	<u>Score/AUC</u>
ENSG00000251705	RNA5-8SP6	“RNA, 5.8S ribosomal pseudogene 6 [Source:HGNC Symbol;Acc:HGNC:41960]”	5.29E-67
ENSG00000133110	POSTN	periostin [Source:HGNC Symbol;Acc:HGNC:16953]	1.78E-06
ENSG00000142449	FBN3	fibrillin 3 [Source:HGNC Symbol;Acc:HGNC:18794]	2.85E-05
ENSG00000183668	PSG9	pregnancy specific beta-1-glycoprotein 9 [Source:HGNC Symbol;Acc:HGNC:9526]	9.26E-05
ENSG00000258628			0.000107247
ENSG00000260290			0.000163871
ENSG00000224367	OACYLP	“O-acyltransferase like, pseudogene [Source:HGNC Symbol;Acc:HGNC:44362]”	0.000275943
ENSG00000108018	SORCS1	sortilin related VPS10 domain containing receptor 1 [Source:HGNC Symbol;Acc:HGNC:16697]	0.000366056
ENSG00000135454	B4GALNT1	“beta-1,4-N-acetyl-galactosaminyltransferase 1 [Source:HGNC Symbol;Acc:HGNC:4117]”	0.000429017
ENSG00000266172	NA	NA	0.000574378
ENSG00000173769	TOPAZ1	testis and ovary specific PAZ domain containing 1 [Source:HGNC Symbol; Acc:HGNC:24746]	0.00059023
ENSG00000181378	CFAP65	cilia and flagella associated protein 65 [Source:HGNC Symbol;Acc:HGNC:25325]	0.000602774
ENSG00000174498	IGDCC3	immunoglobulin superfamily DCC subclass member 3 [Source:HGNC Symbol;Acc:HGNC:9700]	0.00062895
ENSG00000089116	LHX5	LIM homeobox 5 [Source:HGNC Symbol;Acc:HGNC:14216]	0.000639272
ENSG00000161270	NPHS1	“NPHS1, nephrin [Source:HGNC Symbol;Acc:HGNC:7908]”	0.000697583
ENSG00000006210	CX3CL1	C-X3-C motif chemokine ligand 1	

ENSG00000249618	LINC02465	[Source:HGNC Symbol;Acc:HGNC:10647] long intergenic non-protein coding RNA 2465	0.000730947
ENSG00000253871		[Source:HGNC Symbol;Acc:HGNC:53403]	0.000730947
ENSG00000130540	SULT4A1	sulfotransferase family 4A member 1	0.000789684
ENSG00000148942	SLC5A12	[Source:HGNC Symbol;Acc:HGNC:14903] solute carrier family 5 member 12	0.000791019
ENSG00000226790	HNRNPA3P1	[Source:HGNC Symbol;Acc:HGNC:28750] heterogeneous nuclear ribonucleoprotein A3 pseudogene 1	0.000819378
ENSG00000160460	SPTBN4	[Source:HGNC Symbol;Acc:HGNC:13729] "spectrin beta, non-erythrocytic 4	0.000826721
ENSG00000243130	PSG11	[Source:HGNC Symbol;Acc:HGNC:14896]" pregnancy specific beta-1-glycoprotein 11	0.000837162
ENSG00000244694	PTCHD4	[Source:HGNC Symbol;Acc:HGNC:9516] patched domain containing 4	0.000837162
ENSG00000249464	LINC01091	[Source:HGNC Symbol;Acc:HGNC:21345] long intergenic non-protein coding RNA 1091	0.000837162
ENSG00000011677	GABRA3	[Source:HGNC Symbol;Acc:HGNC:27721] gamma-aminobutyric acid type A receptor alpha3 subunit	0.000837162
ENSG00000256343		[Source:HGNC Symbol;Acc:HGNC:4077] 0.000896018	0.00097441
ENSG00000039139	DNAH5	dynein axonemal heavy chain 5	0.001236713
ENSG00000130635	COL5A1	[Source:HGNC Symbol;Acc:HGNC:2950] collagen type V alpha 1 chain	0.001236713
ENSG00000242512	LINC01206	[Source:HGNC Symbol;Acc:HGNC:2209] long intergenic non-protein coding RNA 1206	0.001253551
ENSG00000164692	COL1A2	[Source:HGNC Symbol;Acc:HGNC:49637] collagen type I alpha 2 chain	0.00126185
ENSG00000259841	LINC01566	[Source:HGNC Symbol;Acc:HGNC:2198] long intergenic non-protein coding RNA 1566	0.001274332
ENSG00000170777	TPD52L3	[Source:HGNC Symbol;Acc:HGNC:27555] tumor protein D52 like 3	0.001484087
ENSG00000186487	MYT1L	[Source:HGNC Symbol;Acc:HGNC:23382] myelin transcription factor 1 like	0.001774703
ENSG00000082175	PGR	[Source:HGNC Symbol;Acc:HGNC:7623] progesterone receptor	0.001879127
ENSG00000205922	ONECUT3	[Source:HGNC Symbol;Acc:HGNC:8910] one cut homeobox 3	0.001993667
ENSG00000249341		[Source:HGNC Symbol;Acc:HGNC:13399] 0.002126073	
ENSG00000139865	TTC6	tetratricopeptide repeat domain 6	0.002268239
		[Source:HGNC Symbol;Acc:HGNC:19739]	

ENSG00000154478	GPR26	G protein-coupled receptor 26 [Source:HGNC Symbol;Acc:HGNC:4481]	0.002268239
ENSG00000174358	SLC6A19	solute carrier family 6 member 19 [Source:HGNC Symbol;Acc:HGNC:27960]	0.002268239
ENSG00000235711	ANKRD34C	ankyrin repeat domain 34C [Source:HGNC Symbol;Acc:HGNC:33888]	0.002268239
ENSG00000170381	SEMA3E	semaphorin 3E [Source:HGNC Symbol;Acc:HGNC:10727]	0.002327494
ENSG00000142611	PRDM16	PR/SET domain 16 [Source:HGNC Symbol;Acc:HGNC:14000]	0.002350766
ENSG00000205396	LINC00661	long intergenic non-protein coding RNA 661 [Source:HGNC Symbol;Acc:HGNC:27002]	0.002366966
ENSG00000253288			0.00239082
ENSG00000171435	KSR2	kinase suppressor of ras 2 [Source:HGNC Symbol;Acc:HGNC:18610]	0.002607962
ENSG00000256616			0.002639596
ENSG00000171804	WDR87	WD repeat domain 87 [Source:HGNC Symbol;Acc:HGNC:29934]	0.002806683
ENSG00000237125	HAND2-AS1	HAND2 antisense RNA 1 (head to head) [Source:HGNC Symbol;Acc:HGNC:48872]	0.00289999
ENSG000002406 94	PNMA2	PNMA family member 2 [Source:HGNC Symbol;Acc:HGNC:9159]	0.002940811
ENSG00000102452	NALCN	sodium leak channel, non-selective [Source:HGNC Symbol;Acc:HGNC:19082]”	0.003094645
ENSG00000214929	SPATA31D1	SPATA31 subfamily D member 1 [Source:HGNC Symbol;Acc:HGNC:37283]	0.003264148
ENSG00000115041	KCNIP3	potassium voltage-gated channel interacting protein 3 [Source:HGNC Symbol;Acc:HGNC:15523]	0.00328034
ENSG00000185038	MROH2A	maestro heat like repeat family member 2A [Source:HGNC Symbol;Acc:HGNC:27936]	0.003313878
ENSG00000138892	TTL8	tubulin tyrosine ligase like 8 [Source:HGNC Symbol;Acc:HGNC:34000]	0.003497603
ENSG00000147573	TRIM55	tripartite motif containing 55 [Source:HGNC Symbol;Acc:HGNC:14215]	0.003573936
ENSG00000165323	FAT3	FAT atypical cadherin 3 [Source:HGNC Symbol;Acc:HGNC:23112]	0.003629544
ENSG00000142623	PADI1	peptidyl arginine deiminase 1 [Source:HGNC Symbol;Acc:HGNC:18367]	0.003697796
ENSG00000146521	LINC01558	long intergenic non-protein coding RNA 1558 [Source:HGNC Symbol;Acc:HGNC:21235]	0.003779666
ENSG00000125255	SLC10A2	solute carrier family 10 member 2 [Source:HGNC Symbol;Acc:HGNC:10906]	0.003857127
ENSG00000103855	CD276	CD276 molecule [Source:HGNC Symbol;Acc:HGNC:19137]	0.004037668

ENSG00000168907	PLA2G4F	phospholipase A2 group IVF [Source:HGNC Symbol;Acc:HGNC:27396]	0.00413675
ENSG00000141668	CBLN2	cerebellin 2 precursor [Source:HGNC Symbol;Acc:HGNC:1544]	0.004198501
ENSG00000197991			0.004252179
ENSG00000149633	KIAA1755	KIAA1755 [Source:HGNC Symbol;Acc:HGNC:29372]	0.004331797
ENSG00000157927	RADIL	Rap associating with DIL domain [Source:HGNC Symbol;Acc:HGNC:22226]	0.004332718
ENSG00000138759	FRAS1	Fraser extracellular matrix complex subunit 1 [Source:HGNC Symbol;Acc:HGNC:19185]	0.004539725
ENSG00000174963	ZIC4	Zic family member 4 [Source:HGNC Symbol;Acc:HGNC:20393]	0.004539725
ENSG00000177551	NHLH2	nescient helix-loop-helix 2 [Source:HGNC Symbol;Acc:HGNC:7818]	0.004560802
ENSG00000250230			0.004576049
ENSG00000204929			0.00461274
ENSG00000163975	MELTF	melanotransferrin [Source:HGNC Symbol;Acc:HGNC:7037]	0.004655716
ENSG00000095587	TLL2	tolloid like 2 [Source:HGNC Symbol;Acc:HGNC:11844]	0.004686524
ENSG00000221826	PSG3	pregnancy specific beta-1-glycoprotein 3 [Source:HGNC Symbol;Acc:HGNC:9520]	0.004686524
ENSG00000105392	CRX	cone-rod homeobox [Source:HGNC Symbol;Acc:HGNC:2383]	0.004730282
ENSG00000188338	SLC38A3	solute carrier family 38 member 3 [Source:HGNC Symbol;Acc:HGNC:18044]	0.004737254
ENSG00000167654	ATCAY	“ATCAY, caytaxin [Source:HGNC Symbol;Acc:HGNC:779]”	0.004891089
ENSG00000177511	ST8SIA3	“ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 3 [Source:HGNC Symbol;Acc:HGNC:14269]”	0.00498476
ENSG00000215895			0.005091461
ENSG00000124466	LYPD3	LY6/PLAUR domain containing 3 [Source:HGNC Symbol;Acc:HGNC:24880]	0.005118791
ENSG00000084636	COL16A1	collagen type XVI alpha 1 chain [Source:HGNC Symbol;Acc:HGNC:2193]	0.00516436
ENSG00000104537	ANXA13	annexin A13 [Source:HGNC Symbol;Acc:HGNC:536]	0.005166641
ENSG00000145526	CDH18	cadherin 18 [Source:HGNC Symbol;Acc:HGNC:1757]	0.005245896
ENSG00000161103			0.005294938
ENSG00000168484	SFTPC	surfactant protein C [Source:HGNC Symbol;Acc:HGNC:10802]	0.005473496
ENSG00000188886	ASTL	astacin like metalloendopeptidase [Source:HGNC Symbol;Acc:HGNC:31704]	0.005530506

ENSG00000198765	SYCP1	synaptonemal complex protein 1 [Source:HGNC Symbol;Acc:HGNC:11487]	0.005554714
ENSG00000234177	LINC01114	long intergenic non-protein coding RNA 1114 [Source:HGNC Symbol;Acc:HGNC:49245]	0.005808942
ENSG00000091656	ZFX4	zinc finger homeobox 4 [Source:HGNC Symbol;Acc:HGNC:30939]	0.005809417
ENSG00000151572	ANO4	anoctamin 4 [Source:HGNC Symbol;Acc:HGNC:23837]	0.005857886
ENSG00000178965	ERICH3	glutamate rich 3 [Source:HGNC Symbol;Acc:HGNC:25346]	0.005890875
ENSG00000248587	GDNF-AS1	GDNF antisense RNA 1 (head to head) [Source:HGNC Symbol;Acc:HGNC:43592]	0.005890875
ENSG00000144908	ALDH1L1	aldehyde dehydrogenase 1 family member L1 [Source:HGNC Symbol;Acc:HGNC:3978]	0.006015103
ENSG00000152822	GRM1	glutamate metabotropic receptor 1 [Source:HGNC Symbol;Acc:HGNC:4593]	0.006033529
ENSG00000138675	FGF5	fibroblast growth factor 5 [Source:HGNC Symbol;Acc:HGNC:3683]	0.006101348
ENSG00000187772	LIN28B	lin-28 homolog B [Source:HGNC Symbol;Acc:HGNC:32207]	0.006111478
ENSG00000227471	AKR1B15	aldo-keto reductase family 1 member B15 [Source:HGNC Symbol;Acc:HGNC:37281]	0.006366933
ENSG00000174502	SLC26A9	solute carrier family 26 member 9 [Source:HGNC Symbol;Acc:HGNC:14469]	0.006716425
ENSG00000078549	ADCYAP1R1	ADCYAP receptor type I [Source:HGNC Symbol;Acc:HGNC:242]	0.006848491
ENSG00000159650	UROCI	urocanate hydratase 1 [Source:HGNC Symbol;Acc:HGNC:26444]	0.006848491
ENSG00000217094	PPIAP31	peptidylprolyl isomerase A pseudogene 31 [Source:HGNC Symbol;Acc:HGNC:44962]	0.006866623
ENSG00000006128	TAC1	tachykinin precursor 1 [Source:HGNC Symbol;Acc:HGNC:11517]	0.006929673
ENSG00000158077	NLRP14	NLR family pyrin domain containing 14 [Source:HGNC Symbol;Acc:HGNC:22939]	0.006952696
ENSG00000223414	LINC00473	long intergenic non-protein coding RNA 473 [Source:HGNC Symbol;Acc:HGNC:21160]	0.006952696
ENSG00000144488	ESPNL	espin like [Source:HGNC Symbol;Acc:HGNC:27937]	0.007039881
ENSG00000144730	IL-17RD	interleukin 17 receptor D [Source:HGNC Symbol;Acc:HGNC:17616]	0.007141116
ENSG00000137819	PAQR5	progesterone and adipoQ receptor family member 5 [Source:HGNC Symbol;Acc:HGNC:29645]	0.007179081
ENSG00000162631	NTNG1	netrin G1 [Source:HGNC Symbol;Acc:HGNC:23319]	0.007255358

ENSG00000185974	GRK1	G protein-coupled receptor kinase 1 [Source:HGNC Symbol;Acc:HGNC:10013]	0.007327997
ENSG00000261275			0.007327997
ENSG00000249267	LINC00939	long intergenic non-protein coding RNA 939 [Source:HGNC Symbol;Acc:HGNC:48631]	0.007349367
ENSG00000227827			0.007403828
ENSG00000100065	CARD10	caspase recruitment domain family member 10 [Source:HGNC Symbol;Acc:HGNC:16422]	0.007527421
ENSG00000119125	GDA	guanine deaminase [Source:HGNC Symbol;Acc:HGNC:4212]	0.007619923
ENSG00000106304	SPAM1	sperm adhesion molecule 1 [Source:HGNC Symbol;Acc:HGNC:11217]	0.00781679
ENSG00000250493			0.007835589
ENSG00000158258	CLSTN2	calsyntenin 2 [Source:HGNC Symbol;Acc:HGNC:17448]	0.008149414
ENSG00000175329	ISX	intestine specific homeobox [Source:HGNC Symbol;Acc:HGNC:28084]	0.008233566
ENSG00000188488	SERPINA5	serpin family A member 5 [Source:HGNC Symbol;Acc:HGNC:8723]	0.008534971
ENSG00000249584	LINC02225	long intergenic non-protein coding RNA 2225 [Source:HGNC Symbol;Acc:HGNC:53094]	0.00866593
ENSG00000147655	RSPO2	R-spondin 2 [Source:HGNC Symbol;Acc:HGNC:28583]	0.008823914
ENSG00000171587	DSCAM	DS cell adhesion molecule [Source:HGNC Symbol;Acc:HGNC:3039]	0.008841283
ENSG00000120738	EGR1	early growth response 1 [Source:HGNC Symbol;Acc:HGNC:3238]	0.008960131
ENSG00000127129	EDN2	endothelin 2 [Source:HGNC Symbol;Acc:HGNC:3177]	0.009244272
ENSG00000157423	HYDIN	“HYDIN, axonemal central pair apparatus protein [Source:HGNC Symbol;Acc:HGNC:19368]”	0.009244272
ENSG00000196565	HBG2	hemoglobin subunit gamma 2 [Source:HGNC Symbol;Acc:HGNC:4832]	0.009327518
ENSG00000235881			0.009327518
ENSG00000111262	KCNA1	potassium voltage-gated channel subfamily A member 1 [Source:HGNC Symbol;Acc:HGNC:6218]	0.009418575
ENSG00000187527	ATP13A5	ATPase 13A5 [Source:HGNC Symbol;Acc:HGNC:31789]	0.009514824
ENSG00000188803	SHISA6	shisa family member 6 [Source:HGNC Symbol;Acc:HGNC:34491]	0.009514824
ENSG00000175535	PNLIP	pancreatic lipase [Source:HGNC Symbol;Acc:HGNC:9155]	0.009619326
ENSG00000225953	SATB2-AS1	SATB2 antisense RNA 1 [Source:HGNC Symbol;Acc:HGNC:26490]	0.009647997

ENSG00000136695	IL36RN	interleukin 36 receptor antagonist [Source:HGNC Symbol;Acc:HGNC:15561]	0.009810065
ENSG00000259790	ANP32BP1	acidic nuclear phosphoprotein 32 family member B pseudogene 1 [Source:HGNC Symbol;Acc:HGNC:24267]	0.009820284
ENSG00000225813			0.009894409
ENSG00000179008	C14orf39	chromosome 14 open reading frame 39 [Source:HGNC Symbol;Acc:HGNC:19849]	0.009896903
ENSG00000150893	FREM2	FRAS1 related extracellular matrix protein 2 [Source:HGNC Symbol;Acc:HGNC:25396]	0.009945757
ENSG00000197079	KRT35	keratin 35 [Source:HGNC Symbol;Acc:HGNC:6453]	0.009945757
ENSG00000231131	LINC01468	long intergenic non-protein coding RNA 1468 [Source:HGNC Symbol;Acc:HGNC:50913]	0.010123625
ENSG00000268388	FENDRR	FOXF1 adjacent non-coding developmental regulatory RNA [Source:HGNC Symbol;Acc:HGNC:43894]	0.010151023
ENSG00000159251	ACTC1	“actin, alpha, cardiac muscle 1 [Source:HGNC Symbol;Acc:HGNC:143]”	0.010212535
ENSG00000158125	XDH	xanthine dehydrogenase [Source:HGNC Symbol;Acc:HGNC:12805]	0.010258334
ENSG00000156222	SLC28A1	solute carrier family 28 member 1 [Source:HGNC Symbol;Acc:HGNC:11001]	0.010392835
ENSG00000260759			0.010741484
ENSG00000110975	SYT10	synaptotagmin 10 [Source:HGNC Symbol;Acc:HGNC:19266]	0.010787993
ENSG00000186185	KIF18B	kinesin family member 18B [Source:HGNC Symbol;Acc:HGNC:27102]	0.010844893
ENSG00000110887	DAO	D-amino acid oxidase [Source:HGNC Symbol;Acc:HGNC:2671]	0.011064297
ENSG00000132297	HHLA1	HERV-H LTR-associating 1 [Source:HGNC Symbol;Acc:HGNC:4904]	0.011064297
ENSG00000146839	ZAN	zonadhesin (gene/pseudogene) [Source:HGNC Symbol;Acc:HGNC:12857]	0.011064297
ENSG00000215864	NBPF7	NBPF member 7 [Source:HGNC Symbol;Acc:HGNC:31989]	0.01113278
ENSG00000233395	LINC00841	long intergenic non-protein coding RNA 841 [Source:HGNC Symbol;Acc:HGNC:27430]	0.011213055
ENSG00000177354	C10orf71	chromosome 10 open reading frame 71 [Source:HGNC Symbol;Acc:HGNC:26973]	0.011268372
ENSG00000148357	HMCN2	hemicentin 2 [Source:HGNC Symbol;Acc:HGNC:21293]	0.01150342
ENSG00000215405	NA	NA	0.011599767
ENSG00000203900			0.011732314
ENSG00000218672			0.011732314
ENSG00000261104			0.011732314
ENSG00000123243	ITIH5	inter-alpha-trypsin inhibitor heavy chain family member 5	

ENSG00000213467	HMGB1P37	[Source:HGNC Symbol;Acc:HGNC:21449] high mobility group box 1 pseudogene 37	0.011851589
ENSG00000119283	TRIM67	[Source:HGNC Symbol;Acc:HGNC:39184] tripartite motif containing 67	0.011876979
ENSG00000166984	TCP10L2	[Source:HGNC Symbol;Acc:HGNC:31859] t-complex 10 like 2	0.011900585
ENSG00000204941	PSG5	[Source:HGNC Symbol;Acc:HGNC:21254] pregnancy specific beta-1-glycoprotein 5	0.012009181
ENSG00000230552		[Source:HGNC Symbol;Acc:HGNC:9522]	0.012022323
ENSG00000115155	OTOF	otoferlin	0.012137266
ENSG00000163395	IGFN1	[Source:HGNC Symbol;Acc:HGNC:8515] immunoglobulin-like and fibronectin type III domain containing 1	0.012228668
ENSG00000122778	KIAA1549	[Source:HGNC Symbol;Acc:HGNC:24607] KIAA1549	0.012230791
ENSG00000169169	CPT1C	[Source:HGNC Symbol;Acc:HGNC:22219] carnitine palmitoyltransferase 1C	0.012393242
ENSG00000160994	CCDC105	[Source:HGNC Symbol;Acc:HGNC:18540] coiled-coil domain containing 105	0.012437719
ENSG00000237515	SHISA9	[Source:HGNC Symbol;Acc:HGNC:26866] shisa family member 9	0.012486932
ENSG00000105605	CACNG7	[Source:HGNC Symbol;Acc:HGNC:37231] calcium voltage-gated channel auxiliary subunit gamma 7	0.012486932
ENSG00000185739	SRL	[Source:HGNC Symbol;Acc:HGNC:13626] sarcalumenin	0.012676606
ENSG00000101680	LAMA1	[Source:HGNC Symbol;Acc:HGNC:11295] laminin subunit alpha 1	0.012676606
ENSG00000240021	TEX35	[Source:HGNC Symbol;Acc:HGNC:6481] testis expressed 35	0.012767139
ENSG00000250423	KIAA1210	[Source:HGNC Symbol;Acc:HGNC:25366] KIAA1210	0.012795538
ENSG00000198788	MUC2	[Source:HGNC Symbol;Acc:HGNC:29218] "mucin 2, oligomeric mucus/gel-forming	0.012935817
ENSG00000205312	KRT17P4	[Source:HGNC Symbol;Acc:HGNC:7512]" keratin 17 pseudogene 4	0.012968601
ENSG00000214128	TMEM213	[Source:HGNC Symbol;Acc:HGNC:50722] transmembrane protein 213	0.013016002
ENSG00000178568	ERBB4	[Source:HGNC Symbol;Acc:HGNC:27220] erb-b2 receptor tyrosine kinase 4	0.013016002
ENSG00000175084	DES	[Source:HGNC Symbol;Acc:HGNC:3432] desmin	0.013045986
ENSG00000078295	ADCY2	[Source:HGNC Symbol;Acc:HGNC:2770] adenylate cyclase 2	0.013296119
		[Source:HGNC Symbol;Acc:HGNC:233]	0.013400191

ENSG00000132639	SNAP25	synaptosome associated protein 25 [Source:HGNC Symbol;Acc:HGNC:11132]	0.013440348
ENSG00000187094	CCK	cholecystokinin [Source:HGNC Symbol;Acc:HGNC:1569]	0.013447765
ENSG0000018625	ATP1A2	ATPase Na+/K+ transporting subunit alpha 2 [Source:HGNC Symbol;Acc:HGNC:800]	0.013509365
ENSG00000168542	COL3A1	collagen type III alpha 1 chain [Source:HGNC Symbol;Acc:HGNC:2201]	0.013843652
ENSG00000239921	LINC01471	long intergenic non-protein coding RNA 1471 [Source:HGNC Symbol;Acc:HGNC:51106]	0.013848913
ENSG00000233183			0.013964273
ENSG00000167798	C3P1	complement component 3 precursor pseudogene [Source:HGNC Symbol;Acc:HGNC:34414]	0.013987555
ENSG00000183778	B3GALT5	"beta-1,3-galactosyltransferase 5 [Source:HGNC Symbol;Acc:HGNC:920]"	0.01405326
ENSG00000168481	LGI3	leucine rich repeat LGI family member 3 [Source:HGNC Symbol;Acc:HGNC:18711]	0.014132769
ENSG00000227744	LINC01940	long intergenic non-protein coding RNA 1940 [Source:HGNC Symbol;Acc:HGNC:52763]	0.014149077
ENSG00000138162	TACC2	transforming acidic coiled-coil containing protein 2 [Source:HGNC Symbol;Acc:HGNC:11523]	0.014184675
ENSG00000250049			0.014522615
ENSG00000236445	LINC00608	long intergenic non-protein coding RNA 608 Source:HGNC Symbol;Acc:HGNC:27179]	0.014606813
ENSG00000165966	PDZRN4	PDZ domain containing ring finger 4 [Source:HGNC Symbol;Acc:HGNC:30552]	0.014718872
ENSG00000169876	MUC17	"mucin 17, cell surface associated [Source:HGNC Symbol;Acc:HGNC:16800]"	0.014749092
ENSG00000078898	BPIFB2	BPI fold containing family B member 2 [Source:HGNC Symbol;Acc:HGNC:16177]	0.014831419
ENSG00000130528	HRC	histidine rich calcium binding protein [Source:HGNC Symbol;Acc:HGNC:5178]	0.014902982
ENSG00000111799	COL12A1	collagen type XII alpha 1 chain [Source:HGNC Symbol;Acc:HGNC:2188]	0.015069239
ENSG00000185303	SFTPA2	surfactant protein A2 [Source:HGNC Symbol;Acc:HGNC:10799]	0.015347263
ENSG00000146648	EGFR	epidermal growth factor receptor [Source:HGNC Symbol;Acc:HGNC:3236]	0.015466899
ENSG00000205592	MUC19	"mucin 19, oligomeric [Source:HGNC Symbol;Acc:HGNC:14362]"	0.015539471
ENSG00000198597	ZNF536	zinc finger protein 536 [Source:HGNC Symbol;Acc:HGNC:29025]	0.015552452
ENSG00000120332	TNN	tenascin N [Source:HGNC Symbol;Acc:HGNC:22942]	0.015559411

ENSG00000197406	DIO3	iodothyronine deiodinase 3 [Source:HGNC Symbol;Acc:HGNC:2885]	0.015755832
ENSG00000204283	LINC01973	long intergenic non-protein coding RNA 1973 [Source:HGNC Symbol;Acc:HGNC:52800]	0.015755832
ENSG00000151224	MAT1A	methionine adenosyltransferase 1A [Source:HGNC Symbol;Acc:HGNC:6903]	0.015829354
ENSG00000257008	GPR142	G protein-coupled receptor 142 [Source:HGNC Symbol;Acc:HGNC:20088]	0.015942034
ENSG00000139220	PPFIA2	PTPRF interacting protein alpha 2 [Source:HGNC Symbol;Acc:HGNC:9246]	0.015986308
ENSG00000141946	ZIM3	zinc finger imprinted 3 [Source:HGNC Symbol;Acc:HGNC:16366]	0.015986308
ENSG00000178171	AMER3	APC membrane recruitment protein 3 [Source:HGNC Symbol;Acc:HGNC:26771]	0.015986308
ENSG00000232756			0.015986308
ENSG00000130477	UNC13A	unc-13 homolog A [Source:HGNC Symbol;Acc:HGNC:23150]	0.016007101
ENSG00000070886	EPHA8	EPH receptor A8 [Source:HGNC Symbol;Acc:HGNC:3391]	0.016008143
ENSG00000253301	LINC01606	long intergenic non-protein coding RNA 1606 [Source:HGNC Symbol;Acc:HGNC:51656]	0.016008143
ENSG00000006788	MYH13	myosin heavy chain 13 [Source:HGNC Symbol;Acc:HGNC:7571]	0.01606756
ENSG00000183287	CCBE1	collagen and calcium binding EGF domains 1 [Source:HGNC Symbol;Acc:HGNC:29426]	0.016243979
ENSG00000262691			0.016243979
ENSG00000125740	FOSB	"FosB proto-oncogene, AP-1 transcription factor subunit [Source:HGNC Symbol;Acc:HGNC:3797]"	0.016263717
ENSG00000133083	DCLK1	doublecortin like kinase 1 [Source:HGNC Symbol;Acc:HGNC:2700]	0.01630694
ENSG00000144820	ADGRG7	adhesion G protein-coupled receptor G7 [Source:HGNC Symbol;Acc:HGNC:19241]	0.01630694
ENSG00000178031	ADAMTSL1	ADAMTS like 1 [Source:HGNC Symbol;Acc:HGNC:14632]	0.016324743
ENSG00000187905	LRRC74B	leucine rich repeat containing 74B [Source:HGNC Symbol;Acc:HGNC:34301]	0.016416472
ENSG00000221878	PSG7	pregnancy specific beta-1-glycoprotein 7 (gene/pseudogene) [Source:HGNC Symbol;Acc:HGNC:9524]	0.016416472
ENSG00000254101	LINC02055	long intergenic non-protein coding RNA 2055 [Source:HGNC Symbol;Acc:HGNC:52895]	0.016416472
ENSG00000120251	GRIA2	glutamate ionotropic receptor AMPA type subunit 2 [Source:HGNC Symbol;Acc:HGNC:4572]	0.016488676
ENSG00000233991	NA	NA	0.016488676
ENSG00000214402	LCNL1	lipocalin like 1 [Source:HGNC Symbol;Acc:HGNC:34436]	0.016554945

ENSG00000224271			0.016611527
ENSG00000257576	HSPD1P4	heat shock protein family D (Hsp60) member 1 pseudogene 4 [Source:HGNC Symbol;Acc:HGNC:35146]	0.016611527
ENSG00000228549			0.016653065
ENSG00000178645	C10orf53	chromosome 10 open reading frame 53 [Source:HGNC Symbol;Acc:HGNC:27421]	0.016654478
ENSG00000100078	PLA2G3	phospholipase A2 group III [Source:HGNC Symbol;Acc:HGNC:17934]	0.016825197
ENSG00000154099	DNAAF1	dynein axonemal assembly factor 1 [Source:HGNC Symbol;Acc:HGNC:30539]	0.016918546
ENSG00000183242	WT1-AS	WT1 antisense RNA [Source:HGNC Symbol;Acc:HGNC:18135]	0.016918546
ENSG00000124253	PCK1	phosphoenolpyruvate carboxykinase 1 [Source:HGNC Symbol;Acc:HGNC:8724]	0.016968016
ENSG00000183304	FAM9A	family with sequence similarity 9 member A [Source:HGNC Symbol;Acc:HGNC:18403]	0.016968016
ENSG00000210127	MT-TA	mitochondrially encoded tRNA alanine [Source:HGNC Symbol;Acc:HGNC:7475]	0.016968016
ENSG00000258679			0.016968016
ENSG00000130287	NCAN	neurocan [Source:HGNC Symbol;Acc:HGNC:2465]	0.016985672
ENSG00000088340	FER1L4	"fer-1 like family member 4, pseudogene [Source:HGNC Symbol;Acc:HGNC:15801]"	0.017112355
ENSG00000196415	PRTN3	proteinase 3 [Source:HGNC Symbol;Acc:HGNC:9495]	0.017180036
ENSG00000135917	SLC19A3	solute carrier family 19 member 3 [Source:HGNC Symbol;Acc:HGNC:16266]	0.017339051
ENSG00000233539			0.017342649
ENSG00000176584	DMBT1P1	deleted in malignant brain tumors 1 pseudogene 1 [Source:HGNC Symbol;Acc:HGNC:49497]	0.017392388
ENSG00000135097	MSI1	musashi RNA binding protein 1 [Source:HGNC Symbol;Acc:HGNC:7330]	0.017394805
ENSG00000091128	LAMB4	laminin subunit beta 4 [Source:HGNC Symbol;Acc:HGNC:6491]	0.017415673
ENSG00000168367	LINC00917	long intergenic non-protein coding RNA 917 [Source:HGNC Symbol;Acc:HGNC:48607]	0.017415673
ENSG00000224668	IPO8P1	importin 8 pseudogene 1 [Source:HGNC Symbol;Acc:HGNC:41955]	0.017704945
ENSG00000165757	JCAD	junctional cadherin 5 associated [Source:HGNC Symbol;Acc:HGNC:29283]	0.017712329
ENSG00000166558	SLC38A8	solute carrier family 38 member 8 [Source:HGNC Symbol;Acc:HGNC:32434]	0.017722732
ENSG00000185467	KPNA7	karyopherin subunit alpha 7 [Source:HGNC Symbol;Acc:HGNC:21839]	0.017767827
ENSG00000247699			0.017813935

ENSG00000248975			0.017824111
ENSG00000179813	FAM216B	family with sequence similarity 216 member B [Source:HGNC Symbol;Acc:HGNC:26883]	0.01797203
ENSG00000188706	ZDHHC9	zinc finger DHHC-type containing 9 [Source:HGNC Symbol;Acc:HGNC:18475]	0.018020454
ENSG00000135472	FAIM2	Fas apoptotic inhibitory molecule 2 [Source:HGNC Symbol;Acc:HGNC:17067]	0.018071818
ENSG00000173572	NLRP13	NLR family pyrin domain containing 13 [Source:HGNC Symbol;Acc:HGNC:22937]	0.018071818
ENSG00000089199	CHGB	chromogranin B [Source:HGNC Symbol;Acc:HGNC:1930]	0.018179173
ENSG00000188112	C6orf132	chromosome 6 open reading frame 132 [Source:HGNC Symbol;Acc:HGNC:21288]	0.018577564
ENSG00000187068	C3orf70	chromosome 3 open reading frame 70 [Source:HGNC Symbol;Acc:HGNC:33731]	0.018587013
ENSG00000233973	LINC01360	long intergenic non-protein coding RNA 1360 [Source:HGNC Symbol;Acc:HGNC:50593]	0.018588752
ENSG00000164265	SCGB3A2	secretoglobin family 3A member 2 [Source:HGNC Symbol;Acc:HGNC:18391]	0.018614288
ENSG00000176769	TCERG1L	transcription elongation regulator 1 like [Source:HGNC Symbol;Acc:HGNC:23533]	0.018783363
ENSG00000179709	NLRP8	NLR family pyrin domain containing 8 [Source:HGNC Symbol;Acc:HGNC:22940]	0.018812736
ENSG00000251557	HNRNPKP3	heterogeneous nuclear ribonucleoprotein K pseudogene 3 [Source:HGNC Symbol;Acc:HGNC:42376]	0.018866754
ENSG00000149654	CDH22	cadherin 22 [Source:HGNC Symbol;Acc:HGNC:13251]	0.018978105
ENSG00000170426	SDR9C7	short chain dehydrogenase/reductase family 9C member 7 [Source:HGNC Symbol;Acc:HGNC:29958]	0.018978105
ENSG00000225637			0.019088297
ENSG00000142408	CACNG8	calcium voltage-gated channel auxiliary subunit gamma 8 [Source:HGNC Symbol;Acc:HGNC:13628]	0.019108077
ENSG00000230873	STMND1	stathmin domain containing 1 [Source:HGNC Symbol;Acc:HGNC:44668]	0.01920241
ENSG00000236404	VLDLR-AS1	VLDLR antisense RNA 1 [Source:HGNC Symbol;Acc:HGNC:49621]	0.01920241
ENSG00000170927	PKHD1	"PKHD1, fibrocystin/polyductin [Source:HGNC Symbol;Acc:HGNC:9016]"	0.019345013
ENSG00000237289	CKMT1B	"creatine kinase, mitochondrial 1B [Source:HGNC Symbol;Acc:HGNC:1995]"	0.019345013
ENSG00000229817			0.019542531
ENSG00000259176	NA	NA	0.019829586
ENSG00000124092	CTCFL	CCCTC-binding factor like [Source:HGNC Symbol;Acc:HGNC:16234]	0.019839425

ENSG00000259156	CHEK2P2	checkpoint kinase 2 pseudogene 2 [Source:HGNC Symbol;Acc:HGNC:43578]	0.019859771
ENSG00000203805	PLPP4	phospholipid phosphatase 4 [Source:HGNC Symbol;Acc:HGNC:23531]	0.019917239
ENSG00000163914	RHO	rhodopsin [Source:HGNC Symbol;Acc:HGNC:10012]	0.019927103
ENSG00000224435	NF1P6	neurofibromin 1 pseudogene 6 [Source:HGNC Symbol;Acc:HGNC:7771]	0.019927103
ENSG00000240707	LINC01168	long intergenic non-protein coding RNA 1168 [Source:HGNC Symbol;Acc:HGNC:49537]	0.019935944
ENSG00000130045	NXNL2	nucleoredoxin like 2 [Source:HGNC Symbol;Acc:HGNC:30482]	0.020063533
ENSG00000162062	TEDC2	tubulin epsilon and delta complex 2 [Source:HGNC Symbol;Acc:HGNC:25849]	0.020213465
ENSG00000172752	COL6A5	collagen type VI alpha 5 chain [Source:HGNC Symbol;Acc:HGNC:26674]	0.020225168
ENSG00000101871	MID1	midline 1 [Source:HGNC Symbol;Acc:HGNC:7095]	0.020247513
ENSG00000137648	TMPRSS4	transmembrane serine protease 4 [Source:HGNC Symbol;Acc:HGNC:11878]	0.020387859
ENSG00000166473	PKD1L2	polycystin 1 like 2 (gene/pseudogene) [Source:HGNC Symbol;Acc:HGNC:21715]	0.020387859
ENSG00000257907	EEF1A1P17	eukaryotic translation elongation factor 1 alpha 1 pseudogene 17 [Source:HGNC Symbol;Acc:HGNC:37890]	0.020486161
ENSG00000128917	DLL4	delta like canonical Notch ligand 4 [Source:HGNC Symbol;Acc:HGNC:2910]	0.020505106
ENSG00000259380			0.020626924
ENSG00000179766	ATP8B5P	"ATPase phospholipid transporting 8B5, pseudogene [Source:HGNC Symbol;Acc:HGNC:27245]"	0.02065324
ENSG00000204624	DISP3	dispatched RND transporter family member 3 [Source:HGNC Symbol;Acc:HGNC:29251]	0.02065324
ENSG00000163689	C3orf67	chromosome 3 open reading frame 67 [Source:HGNC Symbol;Acc:HGNC:24763]	0.020743462
ENSG00000132321	IQCA1	IQ motif containing with AAA domain 1 [Source:HGNC Symbol;Acc:HGNC:26195]	0.020807093
ENSG00000249119	MTND6P4	mitochondrially encoded NADH:ubiquinone oxidoreductase core subunit 6 pseudogene 4 [Source:HGNC Symbol;Acc:HGNC:39467]	0.020807093
ENSG00000019505	SYT13	synaptotagmin 13 [Source:HGNC Symbol;Acc:HGNC:14962]	0.020829887
ENSG00000143469	SYT14	synaptotagmin 14 [Source:HGNC Symbol;Acc:HGNC:23143]	0.020885035
ENSG00000196136	SERPINA3	serpin family A member 3 [Source:HGNC Symbol;Acc:HGNC:16]	0.02099734
ENSG00000165816	VWA2	von Willebrand factor A domain containing 2 [Source:HGNC Symbol;Acc:HGNC:24709]	0.021329095

ENSG00000183317	EPHA10	EPH receptor A10 [Source:HGNC Symbol;Acc:HGNC:19987]	0.021329095
ENSG00000072041	SLC6A15	solute carrier family 6 member 15 [Source:HGNC Symbol;Acc:HGNC:13621]	0.021369466
ENSG00000009709	PAX7	paired box 7 [Source:HGNC Symbol;Acc:HGNC:8621]	0.021525887
ENSG00000172350	ABCG4	ATP binding cassette subfamily G member 4 [Source:HGNC Symbol;Acc:HGNC:13884]	0.021525887
ENSG00000183876	ARSI	arylsulfatase family member I [Source:HGNC Symbol;Acc:HGNC:32521]	0.021711339
ENSG00000213934	HBG1	hemoglobin subunit gamma 1 [Source:HGNC Symbol;Acc:HGNC:4831]	0.02185053
ENSG00000186526	CYP4F8	cytochrome P450 family 4 subfamily F member 8 [Source:HGNC Symbol;Acc:HGNC:2648]	0.021913633
ENSG00000161940	BCL6B	B cell CLL/lymphoma 6B [Source:HGNC Symbol;Acc:HGNC:1002]	0.021959359
ENSG00000164093	PITX2	paired like homeodomain 2 [Source:HGNC Symbol;Acc:HGNC:9005]	0.02227554
ENSG00000110786	PTPN5	“protein tyrosine phosphatase, non-receptor type 5 [Source:HGNC Symbol;Acc:HGNC:9657]”	0.022304898
ENSG00000145642	SHISAL2B	shisa like 2B [Source:HGNC Symbol;Acc:HGNC:34236]	0.022689972
ENSG00000260411	NA	NA	0.022689972
ENSG00000135409	AMHR2	anti-Mullerian hormone receptor type 2 [Source:HGNC Symbol;Acc:HGNC:465]	0.022721606
ENSG00000259458			0.022776502
ENSG00000068078	FGFR3	fibroblast growth factor receptor 3 [Source:HGNC Symbol;Acc:HGNC:3690]	0.022896021
ENSG00000161243	FBXO27	F-box protein 27 [Source:HGNC Symbol;Acc:HGNC:18753]	0.023440646
ENSG00000101004	NINL	ninein like [Source:HGNC Symbol;Acc:HGNC:29163]	0.023637109
ENSG00000121207	LRAT	lecithin retinol acyltransferase [Source:HGNC Symbol;Acc:HGNC:6685]	0.023637109
ENSG00000140527	WDR93	WD repeat domain 93 [Source:HGNC Symbol;Acc:HGNC:26924]	0.023652058
ENSG00000236824	BCYRN1	brain cytoplasmic RNA 1 [Source:HGNC Symbol;Acc:HGNC:1022]	0.023652058
ENSG00000101203	COL20A1	collagen type XX alpha 1 chain [Source:HGNC Symbol;Acc:HGNC:14670]	0.023671204
ENSG00000233977			0.023671204
ENSG00000148408	CACNA1B	calcium voltage-gated channel subunit alpha1 B [Source:HGNC Symbol;Acc:HGNC:1389]	0.02389629
ENSG00000134240	HMGCS2	3-hydroxy-3-methylglutaryl-CoA synthase 2 [Source:HGNC Symbol;Acc:HGNC:5008]	0.023926586

ENSG00000112186	CAP2	cyclase associated actin cytoskeleton regulatory protein 2 [Source:HGNC Symbol;Acc:HGNC:20039]	0.024121501
ENSG00000182256	GABRG3	gamma-aminobutyric acid type A receptor gamma3 subunit [Source:HGNC Symbol;Acc:HGNC:4088]	0.024155164
ENSG00000166159	LRTM2	leucine rich repeats and transmembrane domains 2 [Source:HGNC Symbol;Acc:HGNC:32443]	0.024214399
ENSG00000132972	RNF17	ring finger protein 17 [Source:HGNC Symbol;Acc:HGNC:10060]	0.024283188
ENSG00000156076	WIF1	WNT inhibitory factor 1 [Source:HGNC Symbol;Acc:HGNC:18081]	0.024283188
ENSG00000261649	GOLGA6L7	golgin A6 family like 7 [Source:HGNC Symbol;Acc:HGNC:37442]	0.024421599
ENSG00000112238	PRDM13	PR/SET domain 13 [Source:HGNC Symbol;Acc:HGNC:13998]	0.02443315
ENSG00000166391	MOGAT2	monoacylglycerol O-acyltransferase 2 [Source:HGNC Symbol;Acc:HGNC:23248]	0.024463522
ENSG00000166869	CHP2	calcineurin like EF-hand protein 2 [Source:HGNC Symbol;Acc:HGNC:24927]	0.024463522
ENSG00000218823	PAPOLB	poly(A) polymerase beta [Source:HGNC Symbol;Acc:HGNC:15970]	0.024463522
ENSG00000265041			0.024463522
ENSG00000133124	IRS4	insulin receptor substrate 4 [Source:HGNC Symbol;Acc:HGNC:6128]	0.024526611
ENSG00000118733	OLFM3	olfactomedin 3 [Source:HGNC Symbol;Acc:HGNC:17990]	0.024577949
ENSG00000196091	MYBPC1	“myosin binding protein C, slow type [Source:HGNC Symbol;Acc:HGNC:7549]”	0.024577949
ENSG00000105357	MYH14	myosin heavy chain 14 [Source:HGNC Symbol;Acc:HGNC:23212]	0.025148395
ENSG00000167757	KLK11	kallikrein related peptidase 11 [Source:HGNC Symbol;Acc:HGNC:6359]	0.025148395
ENSG00000226068	HNRNPA3P4	heterogeneous nuclear ribonucleoprotein A3 pseudogene 4 [Source:HGNC Symbol;Acc:HGNC:39773]	0.025148395
ENSG00000260072			0.025148395
ENSG00000130226	DPP6	dipeptidyl peptidase like 6 [Source:HGNC Symbol;Acc:HGNC:3010]	0.02515224
ENSG00000144648	ACKR2	atypical chemokine receptor 2 [Source:HGNC Symbol;Acc:HGNC:1565]	0.02527518
ENSG00000169862	CTNND2	catenin delta 2 [Source:HGNC Symbol;Acc:HGNC:2516]	0.025318552
ENSG00000137766	UNC13C	unc-13 homolog C [Source:HGNC Symbol;Acc:HGNC:23149]	0.025345898
ENSG00000261177			0.025565995
ENSG00000060656	PTPRU	“protein tyrosine phosphatase, receptor type U [Source:HGNC Symbol;Acc:HGNC:9683]”	0.025652607

ENSG00000260305	NTRK3-AS1	NTRK3 antisense RNA 1 [Source:HGNC Symbol;Acc:HGNC:27532]	0.02580767
ENSG00000187955	COL14A1	collagen type XIV alpha 1 chain [Source:HGNC Symbol;Acc:HGNC:2191]	0.025820696
ENSG00000089225	TBX5	T-box 5 [Source:HGNC Symbol;Acc:HGNC:11604]	0.025834296
ENSG00000224209	LINC00466	long intergenic non-protein coding RNA 466 [Source:HGNC Symbol;Acc:HGNC:27294]	0.025987072
ENSG00000151474	FRMD4A	FERM domain containing 4A [Source:HGNC Symbol;Acc:HGNC:25491]	0.026041989
ENSG00000039987	BEST2	bestrophin 2 [Source:HGNC Symbol;Acc:HGNC:17107]	0.026152714
ENSG00000266795	NA	NA	0.026198035
ENSG00000181143	MUC16	"mucin 16, cell surface associated [Source:HGNC Symbol;Acc:HGNC:15582]"	0.026247081
ENSG00000069431	ABCC9	ATP binding cassette subfamily C member 9 [Source:HGNC Symbol;Acc:HGNC:60]	0.026486685
ENSG00000100312	ACR	acrosin [Source:HGNC Symbol;Acc:HGNC:126]	0.02666392
ENSG00000254042			0.026721536
ENSG00000180251	SLC9A4	solute carrier family 9 member A4 [Source:HGNC Symbol;Acc:HGNC:11077]	0.026759131
ENSG00000237390			0.026759131
ENSG00000246695	RASSF8-AS1	RASSF8 antisense RNA 1 [Source:HGNC Symbol;Acc:HGNC:48637]	0.026759131
ENSG00000256612	CYP2B7P	"cytochrome P450 family 2 subfamily B member 7, pseudogene [Source:HGNC Symbol;Acc:HGNC:2616]"	0.026759131
ENSG00000165973	NELL1	neural EGFL like 1 [Source:HGNC Symbol;Acc:HGNC:7750]	0.026774963
ENSG00000172900			0.02698221
ENSG00000149926	FAM57B	family with sequence similarity 57 member B [Source:HGNC Symbol;Acc:HGNC:25295]	0.02707614
ENSG00000107295	SH3GL2	"SH3 domain containing GRB2 like 2, endophilin A1 [Source:HGNC Symbol;Acc:HGNC:10831]"	0.027164347
ENSG00000173227	SYT12	synaptotagmin 12 [Source:HGNC Symbol;Acc:HGNC:18381]	0.027164347
ENSG00000173013	CCDC96	coiled-coil domain containing 96 [Source:HGNC Symbol;Acc:HGNC:26900]	0.027208218
ENSG00000268460			0.02723306
ENSG00000234512	TLR12P	"toll like receptor 12, pseudogene [Source:HGNC Symbol;Acc:HGNC:31754]"	0.027406947
ENSG00000135931	ARMC9	armadillo repeat containing 9 [Source:HGNC Symbol;Acc:HGNC:20730]	0.02759323
ENSG00000148702	HABP2	hyaluronan binding protein 2 [Source:HGNC Symbol;Acc:HGNC:4798]	0.027601758

ENSG00000136535	TBR1	“T-box, brain 1 [Source:HGNC Symbol;Acc:HGNC:11590]”	0.028071412
ENSG00000122121	XPNPEP2	X-prolyl aminopeptidase 2 [Source:HGNC Symbol;Acc:HGNC:12823]	0.028133383
ENSG00000170442	KRT86	keratin 86 [Source:HGNC Symbol;Acc:HGNC:6463]	0.028133383
ENSG00000197408	CYP2B6	cytochrome P450 family 2 subfamily B member 6 [Source:HGNC Symbol;Acc:HGNC:2615]	0.028133383
ENSG00000107807	TLX1	T cell leukemia homeobox 1 [Source:HGNC Symbol;Acc:HGNC:5056]	0.028207054
ENSG00000164694	FNDC1	fibronectin type III domain containing 1 [Source:HGNC Symbol;Acc:HGNC:21184]	0.028207054
ENSG00000185313	SCN10A	sodium voltage-gated channel alpha subunit 10 [Source:HGNC Symbol;Acc:HGNC:10582]	0.028207054
ENSG00000164107	HAND2	heart and neural crest derivatives expressed 2 [Source:HGNC Symbol;Acc:HGNC:4808]	0.028335907
ENSG00000133454	MYO18B	myosin XVIIIIB [Source:HGNC Symbol;Acc:HGNC:18150]	0.028417113
ENSG00000167723	TRPV3	transient receptor potential cation channel subfamily V member 3 [Source:HGNC Symbol;Acc:HGNC:18084]	0.028422765
ENSG00000184012	TMPRSS2	transmembrane serine protease 2 [Source:HGNC Symbol;Acc:HGNC:11876]	0.028422765
ENSG00000233485			0.028645846
ENSG00000261466			0.028645846
ENSG00000119547	ONECUT2	one cut homeobox 2 [Source:HGNC Symbol;Acc:HGNC:8139]	0.028669408
ENSG00000237222	LINC01968	long intergenic non-protein coding RNA 1968 [Source:HGNC Symbol;Acc:HGNC:52794]	0.028800664
ENSG00000137573	SULF1	sulfatase 1 [Source:HGNC Symbol;Acc:HGNC:20391]	0.028919683
ENSG00000161609	CCDC155	coiled-coil domain containing 155 [Source:HGNC Symbol;Acc:HGNC:26520]	0.028967146
ENSG00000250546			0.028987628
ENSG00000226057	PHF2P2	PHD finger protein 2 pseudogene 2 [Source:HGNC Symbol;Acc:HGNC:38808]	0.029139308
ENSG00000177045	SIX5	SIX homeobox 5 [Source:HGNC Symbol;Acc:HGNC:10891]	0.029298722
ENSG00000124440	HIF3A	hypoxia inducible factor 3 alpha subunit [Source:HGNC Symbol;Acc:HGNC:15825]	0.029322985
ENSG00000234828	IQCM	IQ motif containing M [Source:HGNC Symbol;Acc:HGNC:53443]	0.029461236
ENSG00000116721	PRAMEF1	PRAME family member 1 [Source:HGNC Symbol;Acc:HGNC:28840]	0.029473652
ENSG00000238116			0.029473652

ENSG00000106689	LHX2	LIM homeobox 2 [Source:HGNC Symbol;Acc:HGNC:6594]	0.029512187
ENSG00000169344	UMOD	uromodulin [Source:HGNC Symbol;Acc:HGNC:12559]	0.02959944
ENSG00000174279	EVX2	even-skipped homeobox 2 [Source:HGNC Symbol;Acc:HGNC:3507]	0.029661965
ENSG00000128573	FOXP2	forkhead box P2 [Source:HGNC Symbol;Acc:HGNC:13875]	0.029779428
ENSG00000251596	HADHAP1	“hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), alpha subunit pseudogene 1 [Source:HGNC Symbol;Acc:HGNC:4802]”	0.029954508
ENSG00000002746	HECW1	“HECT, C2 and WW domain containing E3 ubiquitin protein ligase 1 [Source:HGNC Symbol;Acc:HGNC:22195]”	0.029980732
ENSG00000081248	CACNA1S	calcium voltage-gated channel subunit alpha1 S [Source:HGNC Symbol;Acc:HGNC:1397]	0.029997906
ENSG00000166596	CFAP52	cilia and flagella associated protein 52 [Source:HGNC Symbol;Acc:HGNC:16053]	0.030027148
ENSG00000205176	REXO1L1P	“REXO1 like 1, pseudogene [Source:HGNC Symbol;Acc:HGNC:24660]”	0.030066221
ENSG00000152910	CNTNAP4	contactin associated protein like 4 [Source:HGNC Symbol;Acc:HGNC:18747]	0.030144659
ENSG00000106078	COBL	cordons-bleu WH2 repeat protein [Source:HGNC Symbol;Acc:HGNC:22199]	0.030263618
ENSG00000177103	DSCAML1	DS cell adhesion molecule like 1 [Source:HGNC Symbol;Acc:HGNC:14656]	0.030299369
ENSG00000131044	TTLL9	tubulin tyrosine ligase like 9 [Source:HGNC Symbol;Acc:HGNC:16118]	0.030317293
ENSG00000170703	TTLL6	tubulin tyrosine ligase like 6 [Source:HGNC Symbol;Acc:HGNC:26664]	0.030472844
ENSG00000165379	LRFN5	leucine rich repeat and fibronectin type III domain containing 5 [Source:HGNC Symbol;Acc:HGNC:20360]	0.030532839
ENSG00000198929	NOS1AP	nitric oxide synthase 1 adaptor protein [Source:HGNC Symbol;Acc:HGNC:16859]	0.030532839
ENSG00000236253	SLC25A3P1	solute carrier family 25 member 3 pseudogene 1 [Source:HGNC Symbol;Acc:HGNC:26869]	0.030574302
ENSG00000205667	ARSH	arylsulfatase family member H [Source:HGNC Symbol;Acc:HGNC:32488]	0.030639161
ENSG00000226440			0.030639161
ENSG00000131183	SLC34A1	solute carrier family 34 member 1 [Source:HGNC Symbol;Acc:HGNC:11019]	0.030803937
ENSG00000225649			0.030847037
ENSG00000006283	CACNA1G	calcium voltage-gated channel subunit alpha1 G [Source:HGNC Symbol;Acc:HGNC:1394]	0.030936635
ENSG00000230392			0.030977697
ENSG00000234130			0.031067495

ENSG00000095637	SORBS1	sorbin and SH3 domain containing 1 [Source:HGNC Symbol;Acc:HGNC:14565]	0.031086939
ENSG00000198010	DLGAP2	DLG associated protein 2 [Source:HGNC Symbol;Acc:HGNC:2906]	0.031235492
ENSG00000102290	PCDH11X	protocadherin 11 X-linked [Source:HGNC Symbol;Acc:HGNC:8656]	0.031415941
ENSG00000260027	HOXB7	homeobox B7 [Source:HGNC Symbol;Acc:HGNC:5118]	0.031452441
ENSG00000105664	COMP	cartilage oligomeric matrix protein [Source:HGNC Symbol;Acc:HGNC:2227]	0.031516506
ENSG00000006071	ABCC8	ATP binding cassette subfamily C member 8 [Source:HGNC Symbol;Acc:HGNC:59]	0.031578145
ENSG00000077522	ACTN2	actinin alpha 2 [Source:HGNC Symbol;Acc:HGNC:164]	0.031657927
ENSG00000248966	BCLAF1P1	BCL2 associated transcription factor 1 pseudogene 1 [Source:HGNC Symbol;Acc:HGNC:51329]	0.031733491
ENSG00000124749	COL21A1	collagen type XXI alpha 1 chain [Source:HGNC Symbol;Acc:HGNC:17025]	0.031814031
ENSG00000142675	CNKSRI	connector enhancer of kinase suppressor of Ras 1 [Source:HGNC Symbol;Acc:HGNC:19700]	0.031815396
ENSG00000116748	AMPD1	adenosine monophosphate deaminase 1 [Source:HGNC Symbol;Acc:HGNC:468]	0.031850457
ENSG00000181355	OFCC1	orofacial cleft 1 candidate 1 [Source:HGNC Symbol;Acc:HGNC:21017]	0.03221007
ENSG00000162510	MATN1	"matrilin 1, cartilage matrix protein [Source:HGNC Symbol;Acc:HGNC:6907]"	0.032424937
ENSG00000232392			0.032424937
ENSG00000123572	NRK	Nik related kinase [Source:HGNC Symbol;Acc:HGNC:25391]	0.032537919
ENSG00000267324			0.032537919
ENSG00000196361	ELAVL3	ELAV like RNA binding protein 3 [Source:HGNC Symbol;Acc:HGNC:3314]	0.032579843
ENSG00000204661	C5orf60	chromosome 5 open reading frame 60 [Source:HGNC Symbol;Acc:HGNC:27753]	0.032697662
ENSG00000224059	HSPA8P16	heat shock protein family A (Hsp70) member 8 pseudogene 16 [Source:HGNC Symbol;Acc:HGNC:44931]	0.03275969
ENSG00000114019	AMOTL2	angiomotin like 2 [Source:HGNC Symbol;Acc:HGNC:17812]	0.033101928
ENSG00000134871	COL4A2	collagen type IV alpha 2 chain [Source:HGNC Symbol;Acc:HGNC:2203]	0.033101928
ENSG00000162706	CADM3	cell adhesion molecule 3 [Source:HGNC Symbol;Acc:HGNC:17601]	0.033101928
ENSG00000188782	CATSPER4	cation channel sperm associated 4 [Source:HGNC Symbol;Acc:HGNC:23220]	0.033196706
ENSG00000147689	FAM83A	family with sequence similarity 83 member A	

ENSG00000079841	RIMS1	[Source:HGNC Symbol;Acc:HGNC:28210] regulating synaptic membrane exocytosis 1	0.033349502
ENSG00000103647	CORO2B	[Source:HGNC Symbol;Acc:HGNC:17282] coronin 2B	0.033394348
ENSG00000112499	SLC22A2	[Source:HGNC Symbol;Acc:HGNC:2256] solute carrier family 22 member 2	0.033419797
ENSG00000183856	IQGAP3	[Source:HGNC Symbol;Acc:HGNC:10966] IQ motif containing GTPase activating protein 3	0.033434322
ENSG00000165300	SLITRK5	[Source:HGNC Symbol;Acc:HGNC:20669] SLIT and NTRK like family member 5	0.033434322
ENSG00000229972	IQCF3	[Source:HGNC Symbol;Acc:HGNC:20295] IQ motif containing F3	0.033483825
ENSG00000261949	GFY	[Source:HGNC Symbol;Acc:HGNC:31816] golgi associated olfactory signaling regulator	0.033483825
ENSG00000171487	NLRP5	[Source:HGNC Symbol;Acc:HGNC:44663] NLR family pyrin domain containing 5	0.033483825
ENSG00000129946	SHC2	[Source:HGNC Symbol;Acc:HGNC:21269] SHC adaptor protein 2	0.033631095
ENSG00000117501	MROH9	[Source:HGNC Symbol;Acc:HGNC:29869] maestro heat like repeat family member 9	0.033699292
ENSG00000136574	GATA4	[Source:HGNC Symbol;Acc:HGNC:26287] GATA binding protein 4	0.03391477
ENSG00000106648	GALNTL5	[Source:HGNC Symbol;Acc:HGNC:4173] polypeptide N-acetylgalactosaminyltransferase like 5	0.034539616
ENSG00000188086	PRSS45	Source:HGNC Symbol;Acc:HGNC:21725] serine protease 45	0.034620414
ENSG00000234537		[Source:HGNC Symbol;Acc:HGNC:30717] 0.034840251	0.034858474
ENSG00000226741	LINC02554	long intergenic non-protein coding RNA 2554	
ENSG00000004948	CALCR	[Source:HGNC Symbol;Acc:HGNC:53594] calcitonin receptor	0.034969314
ENSG00000142549	IGLON5	[Source:HGNC Symbol;Acc:HGNC:1440] IgLON family member 5	0.034980702
ENSG00000250519		[Source:HGNC Symbol;Acc:HGNC:34550] 0.034980702	0.034980702
ENSG00000183908	LRRC55	leucine rich repeat containing 55	
ENSG00000253974	NRG1-IT1	[Source:HGNC Symbol;Acc:HGNC:32324] NRG1 intronic transcript 1	0.035005257
ENSG00000162738	VANGL2	[Source:HGNC Symbol;Acc:HGNC:43633] VANGL planar cell polarity protein 2	0.035154264
ENSG00000115648	MLPH	[Source:HGNC Symbol;Acc:HGNC:15511] melanophilin	0.035338561
ENSG00000187997	C17orf99	[Source:HGNC Symbol;Acc:HGNC:29643] chromosome 17 open reading frame 99	0.03575577
		[Source:HGNC Symbol;Acc:HGNC:34490] 0.03575577	0.03575577

ENSG00000140279	DUOX2	dual oxidase 2 [Source:HGNC Symbol;Acc:HGNC:13273]	0.035790036
ENSG00000168077	SCARA3	scavenger receptor class A member 3 [Source:HGNC Symbol;Acc:HGNC:19000]	0.035804565
ENSG00000159337	PLA2G4D	phospholipase A2 group IVD [Source:HGNC Symbol;Acc:HGNC:30038]	0.035823277
ENSG00000183580	FBXL7	F-box and leucine rich repeat protein 7 [Source:HGNC Symbol;Acc:HGNC:13604]	0.035823277
ENSG00000218586			0.035823277
ENSG00000184809	B3GALT5-AS1	B3GALT5 antisense RNA 1 [Source:HGNC Symbol;Acc:HGNC:16424]	0.035845893
ENSG00000132975	GPR12	G protein-coupled receptor 12 [Source:HGNC Symbol;Acc:HGNC:4466]	0.035938935
ENSG00000142910	TINAGL1	tubulointerstitial nephritis antigen like 1 [Source:HGNC Symbol;Acc:HGNC:19168]	0.035938935
ENSG00000075891	PAX2	paired box 2 [Source:HGNC Symbol;Acc:HGNC:8616]	0.035996581
ENSG00000186393	KRT26	keratin 26 [Source:HGNC Symbol;Acc:HGNC:30840]	0.036025366
ENSG00000167779	IGFBP6	insulin like growth factor binding protein 6 [Source:HGNC Symbol;Acc:HGNC:5475]	0.036065767
ENSG00000232667			0.036065767
ENSG00000263711			0.036105875
ENSG00000205054	LINC01121	long intergenic non-protein coding RNA 1121 [Source:HGNC Symbol;Acc:HGNC:49266]	0.036340531
ENSG00000146950	SHROOM2	shroom family member 2 [Source:HGNC Symbol;Acc:HGNC:630]	0.036393162
ENSG00000143867	OSR1	odd-skipped related transcription factor 1 [Source:HGNC Symbol;Acc:HGNC:8111]	0.036631586
ENSG00000205976			0.037140956
ENSG00000196862	RGPD4	RANBP2-like and GRIP domain containing 4 [Source:HGNC Symbol;Acc:HGNC:32417]	0.037154755
ENSG00000148513	ANKRD30A	ankyrin repeat domain 30A [Source:HGNC Symbol;Acc:HGNC:17234]	0.037278195
ENSG00000101057	MYBL2	MYB proto-oncogene like 2 [Source:HGNC Symbol;Acc:HGNC:7548]	0.037361359
ENSG00000139144	PIK3C2G	phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 Gamma[Source:HGNC Symbol;Acc:HGNC:8973]	0.037546969
ENSG00000247213	LINC01498	long intergenic non-protein coding RNA 1498 [Source:HGNC Symbol;Acc:HGNC:51164]	0.037546969
ENSG00000145242	EPHA5	EPH receptor A5 [Source:HGNC Symbol;Acc:HGNC:3389]	0.037630556
ENSG00000249215	NCOA4P4	nuclear receptor coactivator 4 pseudogene 4 [Source:HGNC Symbol;Acc:HGNC:52405]	0.037740576
ENSG00000079112	CDH17	cadherin 17	

ENSG00000166118	SPATA19	[Source:HGNC Symbol;Acc:HGNC:1756] spermatogenesis associated 19	0.037745905
ENSG00000162006	MSLN	[Source:HGNC Symbol;Acc:HGNC:30614] mesothelin-like	0.037802718
ENSG00000187123	LYPD6	[Source:HGNC Symbol;Acc:HGNC:14170] LY6/PLAUR domain containing 6	0.037970738
ENSG00000104313	EYA1	[Source:HGNC Symbol;Acc:HGNC:28751] EYA transcriptional coactivator and phosphatase 1	0.037980544
ENSG00000237250		[Source:HGNC Symbol;Acc:HGNC:3519] 0.038059131	0.038171217
ENSG00000105290	APLP1	amyloid beta precursor like protein 1	
ENSG00000138650	PCDH10	[Source:HGNC Symbol;Acc:HGNC:597] protocadherin 10	0.038576481
ENSG00000198914	POU3F3	[Source:HGNC Symbol;Acc:HGNC:13404] POU class 3 homeobox 3	0.038631087
ENSG00000117114	ADGRL2	[Source:HGNC Symbol;Acc:HGNC:9216] adhesion G protein-coupled receptor L2	0.03865691
ENSG00000185737	NRG3	[Source:HGNC Symbol;Acc:HGNC:18582] neuregulin 3	0.039101789
ENSG00000197085	NPSR1-AS1	[Source:HGNC Symbol;Acc:HGNC:7999] NPSR1 antisense RNA 1	0.039101789
ENSG00000230102	LINC02028	[Source:HGNC Symbol;Acc:HGNC:22128] long intergenic non-protein coding RNA 2028	0.039361047
ENSG00000241158	ADAMTS9-AS1	[Source:HGNC Symbol;Acc:HGNC:27718] ADAMTS9 antisense RNA 1	0.039602594
ENSG00000146005	PSD2	[Source:HGNC Symbol;Acc:HGNC:40625] pleckstrin and Sec7 domain containing 2	0.039646513
ENSG00000171533	MAP6	[Source:HGNC Symbol;Acc:HGNC:19092] microtubule associated protein 6	0.039852243
ENSG00000164294	GPX8	[Source:HGNC Symbol;Acc:HGNC:6868] glutathione peroxidase 8 (putative)	0.040171006
ENSG00000054356	PTPRN	[Source:HGNC Symbol;Acc:HGNC:33100] "protein tyrosine phosphatase, receptor type N	0.040207131
ENSG00000077080	ACTL6B	[Source:HGNC Symbol;Acc:HGNC:9676]" actin like 6B	0.040248543
ENSG00000141434	MEP1B	[Source:HGNC Symbol;Acc:HGNC:160] mepirin A subunit beta	0.040248543
ENSG00000183067	IGSF5	[Source:HGNC Symbol;Acc:HGNC:7020] immunoglobulin superfamily member 5	0.040590193
ENSG00000112337	SLC17A2	[Source:HGNC Symbol;Acc:HGNC:5952] solute carrier family 17 member 2	0.040590193
ENSG00000161682	FAM171A2	[Source:HGNC Symbol;Acc:HGNC:10930] family with sequence similarity 171 member A2	0.040803316
ENSG00000116833	NR5A2	[Source:HGNC Symbol;Acc:HGNC:30480] nuclear receptor subfamily 5 group A member 2	0.040923418

ENSG00000143355	LHX9	[Source:HGNC Symbol;Acc:HGNC:7984] LIM homeobox 9	0.040938395
ENSG00000139767	SRRM4	[Source:HGNC Symbol;Acc:HGNC:14222] serine/arginine repetitive matrix 4	0.041155655
ENSG00000227036	LINC00511	[Source:HGNC Symbol;Acc:HGNC:29389] long intergenic non-protein coding RNA 511	0.041207854
ENSG00000105549	THEG	[Source:HGNC Symbol;Acc:HGNC:43564] theg spermatid protein	0.041207854
ENSG00000104967	NOVA2	[Source:HGNC Symbol;Acc:HGNC:13706] NOVA alternative splicing regulator 2	0.041581527
ENSG00000183206	POTEC	[Source:HGNC Symbol;Acc:HGNC:7887] POTE ankyrin domain family member C	0.041600384
ENSG00000184302	SIX6	[Source:HGNC Symbol;Acc:HGNC:33894] SIX homeobox 6	0.041620804
ENSG00000245651		[Source:HGNC Symbol;Acc:HGNC:10892] transmembrane protein 125	0.041631474
ENSG00000179178	TMEM125	[Source:HGNC Symbol;Acc:HGNC:28275] long intergenic non-protein coding RNA 1516	0.041631474
ENSG00000231422	LINC01516	[Source:HGNC Symbol;Acc:HGNC:51211] stathmin 2	0.041791867
ENSG00000104435	STMN2	[Source:HGNC Symbol;Acc:HGNC:10577] keratin 76	0.041868067
ENSG00000185069	KRT76	[Source:HGNC Symbol;Acc:HGNC:24430] RIMS binding protein 2	0.041944166
ENSG00000060709	RIMBP2	[Source:HGNC Symbol;Acc:HGNC:30339] transmembrane protein 178B	0.042071807
ENSG00000261115	TMEM178B	[Source:HGNC Symbol;Acc:HGNC:44112] long intergenic non-protein coding RNA 2179	0.042101327
ENSG00000261623	LINC02179	[Source:HGNC Symbol;Acc:HGNC:53041] RANBP2-like and GRIP domain containing 3	0.042193233
ENSG00000153165	RGPD3	[Source:HGNC Symbol;Acc:HGNC:32416] long intergenic non-protein coding RNA 599	0.042224694
ENSG00000253230	LINC00599	[Source:HGNC Symbol;Acc:HGNC:27231] long intergenic non-protein coding RNA 1447	0.042347063
ENSG00000236078	LINC01447	[Source:HGNC Symbol;Acc:HGNC:50783] long intergenic non-protein coding RNA 1721	0.042450091
ENSG00000230133	LINC01721	[Source:HGNC Symbol;Acc:HGNC:52508] ankyrin repeat domain 26 pseudogene 3	0.042463159
ENSG00000237636	ANKRD26P3	[Source:HGNC Symbol;Acc:HGNC:39689] PRR29 antisense RNA 1	0.042512831
ENSG00000264954	PRR29-AS1	[Source:HGNC Symbol;Acc:HGNC:51822] pleckstrin homology domain containing A7	0.042582368
ENSG00000166689	PLEKHA7	[Source:HGNC Symbol;Acc:HGNC:27049] potassium voltage-gated channel subfamily H member 6	0.042699245
ENSG00000173826	KCNH6		0.04272194

		[Source:HGNC Symbol;Acc:HGNC:18862]	0.042801591
ENSG00000253864	NA	NA	0.042900836
ENSG00000166292	TMEM100	transmembrane protein 100	
		[Source:HGNC Symbol;Acc:HGNC:25607]	0.043052047
ENSG00000137203	TFAP2A	transcription factor AP-2 alpha	
		[Source:HGNC Symbol;Acc:HGNC:11742]	0.043105155
ENSG00000165970	SLC6A5	solute carrier family 6 member 5	
		[Source:HGNC Symbol;Acc:HGNC:11051]	0.043105155
ENSG00000184908	CLCNKB	chloride voltage-gated channel Kb	
		[Source:HGNC Symbol;Acc:HGNC:2027]	0.043516345
ENSG00000197893	NRAP	nebulin related anchoring protein	
		[Source:HGNC Symbol;Acc:HGNC:7988]	0.043567821
ENSG00000169126	ARMC4	armadillo repeat containing 4	
		[Source:HGNC Symbol;Acc:HGNC:25583]	0.043632647
ENSG00000245248	USP2-AS1	USP2 antisense RNA 1 (head to head)	
		[Source:HGNC Symbol;Acc:HGNC:48673]	0.043635087
ENSG00000242866	STRC	stereocilin	
		[Source:HGNC Symbol;Acc:HGNC:16035]	0.043658722
ENSG00000164393	ADGRF2	adhesion G protein-coupled receptor F2	
		[Source:HGNC Symbol;Acc:HGNC:18991]	0.044026611
ENSG00000100033	PRODH	proline dehydrogenase 1	
		[Source:HGNC Symbol;Acc:HGNC:9453]	0.044045719
ENSG00000136352	NKX2-1	NK2 homeobox 1	
		[Source:HGNC Symbol;Acc:HGNC:11825]	0.044046233
ENSG00000165566	AMER2	APC membrane recruitment protein 2	
		[Source:HGNC Symbol;Acc:HGNC:26360]	0.044155809
ENSG00000163995	ABLIM2	actin binding LIM protein family member 2	
		[Source:HGNC Symbol;Acc:HGNC:19195]	0.044231879
ENSG00000165495	PKNOX2	PBX/knotted 1 homeobox 2	
		[Source:HGNC Symbol;Acc:HGNC:16714]	0.044261202
ENSG00000144115	THNSL2	threonine synthase like 2	
		[Source:HGNC Symbol;Acc:HGNC:25602]	0.044590058
ENSG00000157214	STEAP2	STEAP2 metalloredutase	
		[Source:HGNC Symbol;Acc:HGNC:17885]	0.044717969
ENSG00000229240	LINC00710	long intergenic non-protein coding RNA 710	
		[Source:HGNC Symbol;Acc:HGNC:27386]	0.044849493
ENSG00000168356	SCN11A	sodium voltage-gated channel alpha subunit 11	
		[Source:HGNC Symbol;Acc:HGNC:10583]	0.044881812
ENSG00000130508	PXDN	peroxidasin	
		[Source:HGNC Symbol;Acc:HGNC:14966]	0.044899327
ENSG00000166444	ST5	suppression of tumorigenicity 5	
		[Source:HGNC Symbol;Acc:HGNC:11350]	0.044899327
ENSG00000140600	SH3GL3	"SH3 domain containing GRB2 like 3, endophilin A3	
		[Source:HGNC Symbol;Acc:HGNC:10832]"	0.045237232
ENSG00000214181	NA	NA	0.045237232

ENSG00000144681	STAC	SH3 and cysteine rich domain [Source:HGNC Symbol;Acc:HGNC:11353]	0.045389235
ENSG00000166863	TAC3	tachykinin 3 [Source:HGNC Symbol;Acc:HGNC:11521]	0.045474144
ENSG00000169436	COL22A1	collagen type XXII alpha 1 chain [Source:HGNC Symbol;Acc:HGNC:22989]	0.045474144
ENSG00000172137	CALB2	calbindin 2 [Source:HGNC Symbol;Acc:HGNC:1435]	0.045474144
ENSG00000223566	TNRC18P2	trinucleotide repeat containing 18 pseudogene 2 [Source:HGNC Symbol;Acc:HGNC:34014]	0.045474144
ENSG00000175267	VWA3A	von Willebrand factor A domain containing 3A [Source:HGNC Symbol;Acc:HGNC:27088]	0.045495146
ENSG00000175267	VWA3A	von Willebrand factor A domain containing 3A [Source:HGNC Symbol;Acc:HGNC:27088]	0.045495146
ENSG00000183780	SLC35F3	solute carrier family 35 member F3 [Source:HGNC Symbol;Acc:HGNC:23616]	0.045495146
ENSG00000228983	SLC47A1P1	solute carrier family 47 member 1 pseudogene 1 [Source:HGNC Symbol;Acc:HGNC:51849]	0.045495146
ENSG00000269332	GOLGA2P9	golgin A2 pseudogene 9 [Source:HGNC Symbol;Acc:HGNC:49921]	0.045495146
ENSG00000081800	SLC13A1	solute carrier family 13 member 1 [Source:HGNC Symbol;Acc:HGNC:10916]	0.045528908
ENSG00000155816	FMN2	formin 2 [Source:HGNC Symbol;Acc:HGNC:14074]	0.045528908
ENSG00000091137	SLC26A4	solute carrier family 26 member 4 [Source:HGNC Symbol;Acc:HGNC:8818]	0.045601783
ENSG00000129990	SYT5	synaptotagmin 5 [Source:HGNC Symbol;Acc:HGNC:11513]	0.045601783
ENSG00000173702	MUC13	"mucin 13, cell surface associated [Source:HGNC Symbol;Acc:HGNC:7511]"	0.045601783
ENSG00000116176	TPSG1	tryptase gamma 1 [Source:HGNC Symbol;Acc:HGNC:14134]	0.045645845
ENSG00000250420	AACSP1	acetoacetyl-CoA synthetase pseudogene 1 [Source:HGNC Symbol;Acc:HGNC:18226]	0.045645845
ENSG00000104055	TGM5	transglutaminase 5 [Source:HGNC Symbol;Acc:HGNC:11781]	0.045691236
ENSG00000109101	FOXP1	forkhead box N1 [Source:HGNC Symbol;Acc:HGNC:12765]	0.045781
ENSG00000131386	GALNT15	polypeptide N-acetylgalactosaminyltransferase 15 [Source:HGNC Symbol;Acc:HGNC:21531]	0.045798489
ENSG00000183016	NA	NA	0.045937358
ENSG00000248746	ACTN3	actinin alpha 3 (gene/pseudogene) [Source:HGNC Symbol;Acc:HGNC:165]	0.045937358
ENSG00000259010			0.04595318
ENSG00000156687	UNC5D	unc-5 netrin receptor D	

ENSG00000213864	EEF1B2P2	[Source:HGNC Symbol;Acc:HGNC:18634] eukaryotic translation elongation factor 1 beta 2 pseudogene 2	0.046099925
ENSG00000143107	FNDC7	[Source:HGNC Symbol;Acc:HGNC:3209] fibronectin type III domain containing 7	0.046129239
ENSG00000230615		[Source:HGNC Symbol;Acc:HGNC:26668]	0.046229298
ENSG00000184227	ACOT1	acyl-CoA thioesterase 1	0.046269835
ENSG00000118194	TNNT2	[Source:HGNC Symbol;Acc:HGNC:33128] "troponin T2, cardiac type"	0.046363122
ENSG00000172995	ARPP21	[Source:HGNC Symbol;Acc:HGNC:11949]" cAMP regulated phosphoprotein 21	0.046453265
ENSG00000156103	MMP16	[Source:HGNC Symbol;Acc:HGNC:16968] matrix metalloproteinase 16	0.046453265
ENSG00000164904	ALDH7A1	[Source:HGNC Symbol;Acc:HGNC:7162] aldehyde dehydrogenase 7 family member A1	0.04649564
ENSG00000224743	TEX26-AS1	[Source:HGNC Symbol;Acc:HGNC:877] TEX26 antisense RNA 1	0.04649564
ENSG00000185823	NPAP1	[Source:HGNC Symbol;Acc:HGNC:42784] nuclear pore associated protein 1	0.04652545
ENSG0000018607	ZNF806	[Source:HGNC Symbol;Acc:HGNC:1190] zinc finger protein 806	0.046600673
ENSG00000179270	C2orf71	[Source:HGNC Symbol;Acc:HGNC:33228] chromosome 2 open reading frame 71	0.046600673
ENSG00000186862	PDZD7	[Source:HGNC Symbol;Acc:HGNC:34383] PDZ domain containing 7	0.046710668
ENSG00000227525	RPL7P6	[Source:HGNC Symbol;Acc:HGNC:26257] ribosomal protein L7 pseudogene 6	0.046989116
ENSG00000236229	VEZF1P1	[Source:HGNC Symbol;Acc:HGNC:32430] vascular endothelial zinc finger 1 pseudogene 1	0.047105132
ENSG00000171564	FGB	[Source:HGNC Symbol;Acc:HGNC:32320] fibrinogen beta chain	0.047251427
ENSG00000257175		[Source:HGNC Symbol;Acc:HGNC:3662]	0.047316621
ENSG00000248713	LOC285556	"Homo sapiens uncharacterized mRNA. [Source:RefSeq mRNA;Acc:NM_001354435]"	0.047420932
ENSG00000102287	GABRE	[Source:HGNC Symbol;Acc:HGNC:4085] gamma-aminobutyric acid type A receptor epsilon subunit	0.047603565
ENSG00000150086	NA	NA	0.0476766
ENSG00000168959	GRM5	[Source:HGNC Symbol;Acc:HGNC:4597] glutamate metabotropic receptor 5	0.0476766
ENSG00000184304	PRKD1	[Source:HGNC Symbol;Acc:HGNC:9407] protein kinase D1	0.0476766
ENSG00000204055			0.047795615
ENSG00000164122	ASB5	[Source:HGNC Symbol;Acc:HGNC:17180] ankyrin repeat and SOCS box containing 5	0.047913021

ENSG00000123977	DAW1	dynein assembly factor with WD repeats 1 [Source:HGNC Symbol;Acc:HGNC:26383]	0.047973
ENSG00000156413	FUT6	fucosyltransferase 6 [Source:HGNC Symbol;Acc:HGNC:4017]	0.047988989
ENSG00000101276	SLC52A3	solute carrier family 52 member 3 [Source:HGNC Symbol;Acc:HGNC:16187]	0.048129781
ENSG00000168079	SCARA5	scavenger receptor class A member 5 [Source:HGNC Symbol;Acc:HGNC:28701]	0.048129781
ENSG00000254561			0.048129781
ENSG00000223949	ROR1-AS1	ROR1 antisense RNA 1 [Source:HGNC Symbol;Acc:HGNC:40508]	0.048194625
ENSG00000204335	SP5	Sp5 transcription factor [Source:HGNC Symbol;Acc:HGNC:14529]	0.048312303
ENSG00000204241			0.04840783
ENSG00000099625	CBARP	CACN beta subunit associated regulatory protein [Source:HGNC Symbol;Acc:HGNC:28617]	0.048411296
ENSG00000143450	OAZ3	ornithine decarboxylase antizyme 3 [Source:HGNC Symbol;Acc:HGNC:8097]	0.048617065
ENSG0000015520	NPC1L1	NPC1 like intracellular cholesterol transporter 1 [Source:HGNC Symbol;Acc:HGNC:7898]	0.048746819
ENSG00000188162	OTOG	otogelin [Source:HGNC Symbol;Acc:HGNC:8516]	0.048746819
ENSG00000125492	BARHL1	BarH like homeobox 1 [Source:HGNC Symbol;Acc:HGNC:953]	0.048820483
ENSG00000145832	SLC25A48	solute carrier family 25 member 48 [Source:HGNC Symbol;Acc:HGNC:30451]	0.048934402
ENSG00000185686	PRAME	preferentially expressed antigen in melanoma [Source:HGNC Symbol;Acc:HGNC:9336]	0.048934402
ENSG00000229147	SMPD4P2	sphingomyelin phosphodiesterase 4 pseudogene 2 [Source:HGNC Symbol;Acc:HGNC:39674]	0.049012128

[0076] A listing of selected and preferred AC3 RNA markers of impending flare, based on their scores and relevance to sublining fibroblast cells is provided below in Table 9. These markers are particularly selected for determining and predicting impending RA flares. The markers are selected from COL1A2, COL5A1, COL16A1, COL14A1, COL4A2, PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFH4.

[0077] The markers include several genes for collagen alpha chain subunits, including COL1A2, COL5A1, COL16A1, COL14A1 and COL4A2, as follows: COL1A2 Collagen alpha-2(I) chain. This gene encodes the alpha 2 (pro- $\alpha 2(1)$) chain component of type I collagen, the fibrillary collagen found in most connective tissues; COL5A1 Collagen Type V Alpha 1 Chain a component of type V collagen, which is a low abundance fibrillar collagen; COL16A1 Collagen alpha-1(XVI) chain. This gene encodes the alpha chain of type XVI collagen, a member of the FACIT collagen family (fibril-

associated collagens with interrupted helices). Collagen type XVI is a fibril-forming collagen that maintains the integrity of the extracellular matrix; COL14A1 Collagen alpha-1(XIV) chain is a protein that in humans is encoded by the *COL14A1* gene. It likely plays a role in collagen binding and cell-cell adhesion; COL4A2 The COL4A2 gene encodes the alpha-2 chain of type IV collagen. Type IV collagen is associated with laminin, entactin, and heparan sulfate proteoglycans to form the sheetlike basement membranes that separate epithelium from connective tissue.

[0078] Additional markers are PXDN, ST5, DCLK1, SCARA5, EGFR, EGR1 and ZFH4. PXDN (peroxidase) is a heme-containing peroxidase that is secreted into the extracellular matrix and is involved in extracellular matrix formation. ST5 (Suppression Of Tumorigenicity 5 protein), also called DENN Domain Containing 2B. This gene was identified by its ability to suppress the tumorigenicity of Hela cells in nude mice. The protein encoded by this gene contains a C-terminal region that shares similarity with the Rab 3 family of small GTP binding proteins. This protein preferentially binds to the SH3 domain of c-Abl kinase, and acts as a regulator of MAPK1/ERK2 kinase, which may contribute to its ability to reduce the tumorigenic phenotype in cells. May be involved in cytoskeletal organization and tumorigenicity. DCLK1 (Doublecortin Like Kinase 1) is a microtubule-associated protein kinase - a serine/threonine-protein kinase. Doublecortin Like Kinase 1 has been identified as a tuft cell marker in the small intestine and has been reported to mark tumor stem cells in the intestine and pancreas. SCARA5 (Scavenger receptor class A, member 5) is involved in lineage commitment and differentiation of mesenchymal stem cells to adipocytes. EGFR corresponds to epidermal growth factor receptor and is a cell membrane spanning protein induces cell differentiation and proliferation. Alteration and overexpression associated with various cancers. Numerous EGFR antibodies, including specific neutralizing antibodies, have been developed and are in clinical development or clinical practice for applications in cancer. EGR1 (Early growth response protein 1) - also known as ZNF268 (zinc finger protein 268) or NGFI-A (nerve growth factor-induced protein A). *EGR-1* is a mammalian transcription factor. *EGR-1* is a mechano-sensitive transcriptional factor that stimulates IGF-1R transcription, resulting in vascular remodeling of vein grafts. Early growth response protein 1 is a transcription factor that is rapidly induced by growth factors, cytokines, and stress signals such as radiation, injury, or mechanical stress. ZFH4 (Zinc Finger Homeobox 4) Predicted to have RNA polymerase II proximal promoter sequence-specific DNA binding activity. RNA polymerase II specific DNA-binding transcription factor activity.

[0079] Notably all of the markers provided in Table 9 are also listed in Table 5 above, which provided transcripts common to synovial sublining fibroblasts and AC3. Table 5 also included the α collagen chain gene COL3A1, COMP, FNDC1, GALNT15, SULF1, GPX8 and IGFBP6. COL3A2 corresponds to collagen Type III alpha 1 chain. COMP (cartilage oligomeric matrix protein) Can mediate the interaction of chondrocytes with the cartilage extracellular matrix and may play a role in the structural integrity of cartilage via its interaction with other extracellular matrix proteins such as

the collagens and fibronectin. FNDC1 (fibronectin Type III domain containing 1) has alternative names Activation-associated cDNA protein and expressed in synovial lining protein and is an activator of G-protein signaling. GALNT15 (Polypeptide N-Acetylgalactosaminyltransferase 15) is a membrane-bound polypeptide N-acetylgalactosaminyltransferases that catalyzes the first step in mucin-type O-glycosylation of peptides in the Golgi apparatus. SULF1 (Sulfatase 1) is an extracellular heparan sulfate endosulfatase. The enzyme is secreted through the Golgi and is subsequently localized to the cell surface and selectively removes 6-O-sulfate groups from heparan sulfate chains of heparan sulfate proteoglycans. GPX8 (Glutathione Peroxidase 8) is a protein disulfide isomerase and is involved in cellular response to oxidative stress, reducing H₂O₂ content and oxidative stress in the ER. IGFBP6 (Insulin-like growth factor-binding protein 6) binds insulin-like growth factor and fibronectin and has been shown to modulate the growth promoting effects of the IGFs on cell culture.

TABLE 9
RNA Markers of Impending Flare

<u>SYMBOL</u>	<u>Column 1</u>	<u>geneset</u>	<u>ENSG</u>	<u>Gene</u>	<u>AUC</u>	<u>PCT nonzero</u>	<u>pct nonzero other</u>	<u>baseMean_prime</u>
COL1A2	SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG00000164692	ENSG00000164692.13	0.84468179	1	0.532809984	51.509861398
COL1A2	SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG00000164692	ENSG00000164692.13	0.921394835	1	0.509613353	51.509861398
COL1A2	SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG00000164692	ENSG00000164692.13	0.906702534	1	0.555704441	51.509861398
PXDN	SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG00000130508	ENSG00000130508.6	0.843306415	0.831710709	0.16670188	24.409015138
PXDN	SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG00000130508	ENSG00000130508.6	0.836927155	0.881578947	0.227029096	24.409015138
COL5A1	SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG00000130635	ENSG00000130635.11	0.769189965	0.809917355	0.263486312	24.050387975
COL5A1	SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG00000130635	ENSG00000130635.11	0.884892773	0.95132128	0.214874287	24.050387975
COL5A1	SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG00000130635	ENSG00000130635.11	0.917280819	0.98245614	0.282733538	24.050387975
ZFHx4	SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG00000091656	ENSG00000091656.11	0.778380395	0.714876033	0.207125604	23.828346616
ZFHx4	SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG00000091656	ENSG00000091656.11	0.789767117	0.802631579	0.228177642	23.828346616
COL16A1	SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG00000084636	ENSG00000084636.12	0.87323477	0.835883171	0.105852525	23.789446496
ST5	SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG00000166444	ENSG00000166444.13	0.833490889	0.816411683	0.158673146	23.39530374
DCLK1	SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG00000133083	ENSG00000133083.10	0.786731154	0.700413223	0.168075684	23.123692573

DCLK1	SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG000000133083	ENSG000000133083.10	0.831312828	0.799721836	0.126558208	23.123692573
EGR1	SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG000000120738	ENSG000000120738.7	0.753816991	0.950413223	0.650764895	21.499587093
EGR1	SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG000000120738	ENSG000000120738.7	0.805075452	0.993045897	0.629410522	21.499587093
COL14A1	SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG000000187955	ENSG000000187955.7	0.886990583	0.983471074	0.305354267	21.350721991
COL14A1	SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG000000187955	ENSG000000187955.7	0.917607177	0.991655076	0.27044158	21.350721991
COL14A1	SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG000000187955	ENSG000000187955.7	0.852312874	0.969298246	0.339203675	21.350721991
SCARA5	SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG000000168079	ENSG000000168079.12	0.749160744	0.785123967	0.289653784	20.554709341
SCARA5	SC-F3	Fibroblast-DKK3+ sublining (SC-F3)	ENSG000000168079	ENSG000000168079.12	0.819901316	0.890350877	0.309341501	20.554709341
COL4A2	SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG000000134871	ENSG000000134871.13	0.841252655	0.866481224	0.187618846	12.249482672
EGFR	SC-F1	Fibroblast-CD34+ sublining (SC-F1)	ENSG000000146648	ENSG000000146648.11	0.763756222	0.729338843	0.230072464	10.692550335
EGFR	SC-F2	Fibroblast-HLA-DRAhi sublining (SC-F2)	ENSG000000146648	ENSG000000146648.11	0.803273527	0.820584145	0.191421931	10.692550335

[0080] PRIME CELLS

[0081] These unusual RNAs identified in blood as indicators of an RA flare, particularly those of AC3, identified a unique cell in blood samples denoted Pre-Inflammatory Mesenchymal Cells (PRIME cells). RNA sequencing of these cells confirmed that they were enriched with AC3 cluster genes, synovial fibroblast genes, and expressed classic synovial fibroblast genes such as FAP, DKK3, CDH11 as well as collagens and laminins. PRIME cells are activated just prior to flare and are then evident at flare in inflamed synovium as inflammatory sublining fibroblasts.

[0082] Cell surface markers characteristic of the PRIME cells identified and described herein are PDPN+, CD45- and CD31-. PRIME cells can be sorted or characterized as CD45-,CD31-PDPN+ cells. Also, the cell surface receptor and marker IL-17RD+ can additionally be utilized to differentiate, identify and characterize PRIME cells. IL-17RD is an AC3 gene marker (see Table 3 above). CD45 and CD31 are often present on cells in blood, therefore a blood cell which lacks both of these specific markers would be unusual. CD45 is a pan-leukocyte protein with tyrosine phosphatase activity involved in the regulation of signal transduction in hematopoiesis. CD45 is also known as protein tyrosine phosphatase, receptor type, C (PTPRC). CD45 was originally designated leukocyte common antigen, reflecting its general expression on leukocytes. CD31 represents platelet endothelial cell adhesion molecule (PECAM-1). This molecule plays a key role in removing aged neutrophils from the body, and is found on the surface of platelets, monocytes, neutrophils and some types of T cells.

[0083] In contrast, the presence of PDPN – and also of IL-17RD – on the surface of a population of cells, particularly CD45- and CD31- cells in blood, is unusual. PDPN (Podoplanin) is a well conserved mucin-type transmembrane protein and is heavily O-glycosylated with diverse distribution in human tissues. Podoplanin binds to C-type lectin receptor-2 (CLEC-2) and is associated with malignant progression and tumor metastasis in several types of cancer. Anti-podoplanin antibody has been evaluated and shown effective in LPS-induced lung injury (Lax S *et al* (2017) *BMJ Open Respiratory Res* 4:e000257.doi:10.1136/bmjresp-2017-000257). Podoplanin antibodies have been investigated in pulmonary metastasis and in malignant mesothelioma (Kato Y (2015) *Oncotarget* 6(34):36003-36018; Abe S *et al* (2013) *J Immunol* 190(12):6239-6249).

[0084] IL-17RD (IL-17 Receptor D), a membrane protein of the IL-17 receptor family, is a feedback loop inhibitor of fibroblast growth factor mediated Ras-MAPK signaling and ERK activation. IL-17RD binds IL-17A and mediates pro-inflammatory gene expression downstream of IL-17A.

[0085] Antibodies targeting IL-17 cytokines and their receptors are being used in treatment of some autoimmune diseases. In RA, IL-17A acts locally on synoviocytes and osteoblasts contributing to synovitis and joint disruption. Although some positive results have been seen in psoriasis and psoriatic arthritis, results with biologics targeting IL-17 in RA have been mixed, underscoring the

need to identify patients or clinical/biological scenarios where therapeutics such as IL-17 biologics will be effective (Robert M and Miossec P (2019) *Front Med* 5:364; doi:10.3389/fmed.2018.00364; Fragoulis GE *et al* (2016) *Ann Rev Med* 67:337-353). Targeting IL-17 or IL-17D based on RNA markers and/or PRIME cell analysis may be a more effective approach to treatment of RA, particularly if administration upon recognition of an imminent flare could be implemented.

EXAMPLE 3

Selecting genes for detection of PRIME cells

[0086] In this example, a series of filtering studies were performed to focus in on more and more unique genes. We started with 625 that were increased prior to (*e.g.*, one week or about 5-7 days prior to) flare in whole blood (Table 6), then we filtered to 283 by selecting genes that were increased in PRIME cells relative to circulating white blood cell, then we filtered again by selecting genes that were specific to synovial fibroblasts versus other synovial tissue infiltrating white blood cells.

[0087] We examined a cluster of genes (AC3) that were antecedents to symptomatic flare for relevance to RA from a previously published scRNAseq dataset that were defined into 18 synovial cell types. *See*, Zhang, F., *et al.*, Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry. *Nat Immunol*, 2019. 20(7): p. 928-942. We identified 625 transcripts were increased just prior to flare and 194 of these were also expressed by synovial sublining fibroblasts. See Table 6. We also examined the blood of 23 RA patients for the presence of an outstanding single synovial signature of these cells (CD45-/CD31-/PDPN+) and found these cells are enriched in the blood of RA patients (Figure 4D). Comparing sorted RNAseq signatures of these PDPN+ cells with AC3 gene clusters and found these PDPN+ cells have enriched expression of synovial fibroblast genes such as *FAP*, *DKK3*, *CDH11*, as well as collagens and laminins. FIG. 22). Discovering that AC3 genes are also enriched in synovial fibroblasts was useful because it increased the specificity of the signature since fibroblasts do not normally circulate in blood.

[0088] A process illustrated in FIG. 24 is used to refine the dataset to narrow down the number of markers we used. We began with the set of 625 AC3 genes that were previously found to have decreased expression during RA flares, and refined this to the smaller set of the most highly expressed genes (top quartile) that would be easiest to detect by PCR or FACS. We then filtered those genes that were enriched in PRIME cells relative to other hematopoietic cells, using the differential volcano plotting strategy (PDPN+ vs CD45+) as in FIG. 22 (focusing on the equivalent group of genes to the right of the plot, with significant fold changes (>0) relative to hematopoietic cells). This analysis yielded an (unpublished) dataset of 283 genes enriched with PRIME cell markers. See Table 10, which shows expression of a panel of 283 genes that were significantly increased in whole blood prior

to flare, and these 283 genes were also significantly increased in PRIME cells compared to peripheral blood mononuclear cells in the same individual, as indicated by that the significance of Log2FC PRIME cells / PBMC (“padj_prime”) less than 0.05.

[0089] We next further refined this dataset by selecting the subgroup of 283 genes identified that are also published synovial marker genes (CD14, CD20, CD3) in published datasets (accession # SDY998). This analysis yielded a dataset of 65 genes. See Table 11, which shows a panel of 65 genes i) significantly increased in expression levels in whole blood prior to flare, ii) significantly increased in expression levels in PRIME cells compared to peripheral blood mononuclear cells, and iii) significantly increased in expression levels in synovial tissue fibroblasts compared to synovial tissue monocytes, B cells and T cells, as indicated by that the ratio of gene expression in fibroblasts to the sum of gene expression in B cells, Monocytes and T cells (“fibroblast / (B+M+T)” is greater than 1).

[0090] Finally, we further refined this dataset by selecting the subgroup of 65 genes that overlapped published single-cell RNAseq data (accession # SDY998) that were enriched for synovial sublining genes relative to fibroblast genes. *See, Zhang, F., et al., Nat Immunol, 2019. 20(7): p. 928-942.* We suspect synovial sublining genes to be most relevant to PRIME cells and RA pathophysiology. This analysis yielded a dataset of 8 genes, which are shown in Table 12, which shows a panel of 8 genes that were i) significantly increased in expression levels in whole blood prior to flare, ii) significantly increased in expression levels in PRIME cells compared to peripheral blood mononuclear cells, iii) significantly increased in expression levels in synovial tissue fibroblasts compared to synovial tissue monocytes, B cells and T cells, iv) expressed in sublining fibroblasts in significantly higher level than in lining layer synovial fibroblasts.

[0091] The AC3 markers and the primers that can be used to detect these RNA expression in RNAseq are shown in Table 13.

Table 10. 283 genes in PRIME cells

Ensemble GENE ID	GENE SYMBOL	Log2FoldChage PRIME cells / PBMC	Significance of Log2FC PRIME cells / PBMC (“padj_prime”)
ENSG00000181143.11	MUC16	10.0855436	7.9386E-20
ENSG00000171435.9	KSR2	11.8018796	3.0049E-14
ENSG00000165323.11	FAT3	12.1409422	3.3332E-13
ENSG00000138759.13	FRAS1	11.4663395	4.2845E-12
ENSG00000169436.12	COL22A1	11.2957133	8.8587E-12
ENSG00000119547.5	ONECUT2	11.6439194	1.6669E-11
ENSG00000188162.6	OTOG	11.4779014	1.9696E-11
ENSG00000133454.11	MYO18B	8.64409108	1.3105E-10
ENSG00000205592.8	MUC19	10.6062292	2.0866E-10
ENSG00000142449.8	FBN3	11.2240728	2.2122E-10
ENSG00000078295.11	ADCY2	11.2421588	3.32E-10

ENSG00000130226.12	DPP6	11.2046162	3.32E-10
ENSG00000157214.9	STEAP2	11.068942	3.4359E-10
ENSG00000137766.12	UNC13C	10.7491846	5.9062E-10
ENSG00000261115.1	TMEM178B	7.88414812	6.2418E-10
ENSG00000170927.10	PKHD1	10.944145	7.3843E-10
ENSG00000178568.9	ERBB4	10.7872402	1.3478E-09
ENSG00000128573.18	FOXP2	10.8375719	1.3769E-09
ENSG00000002746.9	HECW1	10.7347811	1.4252E-09
ENSG00000124749.12	COL21A1	10.7884891	2.1212E-09
ENSG00000069431.6	ABCC9	11.307877	2.5167E-09
ENSG00000120251.14	GRIA2	10.6331048	3.2019E-09
ENSG00000158258.11	CLSTN2	11.1567218	3.6938E-09
ENSG00000144908.9	ALDH1L1	9.8829159	3.7495E-09
ENSG00000084636.12	COL16A1	10.5120707	3.7567E-09
ENSG00000088340.11	FER1L4	10.5353056	4.4615E-09
ENSG00000164692.13	COL1A2	11.6422745	9.7979E-09
ENSG00000174963.13	ZIC4	10.574388	2.5507E-08
ENSG00000091656.11	ZFHX4	9.57608804	3.272E-08
ENSG00000079841.14	RIMS1	10.2678036	3.3081E-08
ENSG00000039139.9	DNAH5	11.1877289	3.4819E-08
ENSG00000170777.9	TPD52L3	10.4382661	4.0608E-08
ENSG00000198788.7	MUC2	10.5539222	5.5502E-08
ENSG00000144648.9	ACKR2	10.1770267	6.2846E-08
ENSG00000148357.12	HMCN2	11.2528227	6.4777E-08
ENSG00000123243.10	ITIH5	10.356014	7.5441E-08
ENSG00000187527.6	ATP13A5	10.1275523	7.9099E-08
ENSG00000163395.12	IGFN1	10.6666204	1.0443E-07
ENSG00000130508.6	PXDN	7.7050129	1.0612E-07
ENSG00000187068.2	C3orf70	9.67322943	1.1207E-07
ENSG00000130477.10	UNC13A	11.348469	1.5587E-07
ENSG00000236445.2	LINC00608	10.0271293	1.8548E-07
ENSG00000165970.7	SLC6A5	10.208198	3.5377E-07
ENSG00000186862.12	PDZD7	6.74925767	4.2539E-07
ENSG00000130635.11	COL5A1	6.30822442	4.7142E-07
ENSG00000172752.10	COL6A5	10.5737724	5.2374E-07
ENSG00000009709.7	PAX7	10.1290357	7.2306E-07
ENSG00000152822.9	GRM1	10.3735166	7.6561E-07
ENSG00000119283.11	TRIM67	9.85988714	9.3759E-07
ENSG00000095637.16	SORBS1	7.4923642	9.6242E-07
ENSG00000132297.7	HHLA1	10.4722764	1.0254E-06
ENSG00000185038.9	MROH2A	10.2250561	1.0374E-06
ENSG00000157423.13	HYDIN	7.24026448	1.0532E-06
ENSG00000214929.3	SPATA31D1	9.78447505	1.24E-06
ENSG00000162631.14	NTNG1	8.04063292	1.2555E-06

[illegible]

ENSG00000175267.10	VWA3A	6.86579745	5.3792E-05
ENSG00000175267.10	VWA3A	6.86579745	5.3792E-05
ENSG0000015520.10	NPC1L1	9.88092763	6.0092E-05
ENSG00000164904.11	ALDH7A1	5.47673693	6.1387E-05
ENSG00000183876.8	ARSI	9.31161098	6.5162E-05
ENSG00000138162.13	TACC2	10.9079109	6.8589E-05
ENSG00000060656.15	PTPRU	7.27711274	6.8677E-05
ENSG00000161243.4	FBXO27	7.24482957	7.9276E-05
ENSG00000169169.10	CPT1C	8.09351669	7.9973E-05
ENSG00000257008.2	GPR142	8.56229961	8.5521E-05
ENSG00000101680.9	LAMA1	10.6992197	0.00010128
ENSG00000178171.6	AMER3	10.6794817	0.00010499
ENSG00000111799.16	COL12A1	10.7382323	0.00010546
ENSG00000081248.6	CACNA1S	9.80041569	0.00012856
ENSG00000164093.11	PITX2	10.422723	0.00012858
ENSG00000187094.7	CCK	9.16123651	0.0001322
ENSG00000116833.9	NR5A2	10.5500444	0.00016126
ENSG00000174502.14	SLC26A9	10.5281245	0.00016126
ENSG00000165300.6	SLITRK5	7.99902598	0.00018194
ENSG00000112499.7	SLC22A2	10.3025109	0.00019563
ENSG00000170381.8	SEMA3E	10.4226159	0.00021084
ENSG00000146005.3	PSD2	6.72463576	0.00022891
ENSG00000169126.11	ARMC4	10.4923335	0.00022891
ENSG00000229147.1	SMPD4P2	10.4382553	0.00026303
ENSG00000134871.13	COL4A2	7.74572011	0.00028096
ENSG00000122778.5	KIAA1549	9.14112261	0.00034123
ENSG00000146839.14	ZAN	9.1693989	0.0003457
ENSG00000095587.8	TLL2	9.98109668	0.00035474
ENSG00000158125.5	XDH	10.2397661	0.00037082
ENSG00000250420.4	AACSP1	8.93443911	0.00037467
ENSG00000139144.5	PIK3C2G	9.19770133	0.00037518
ENSG00000172350.5	ABCG4	10.2578105	0.00038747
ENSG00000150893.9	FREM2	10.1857757	0.00041483
ENSG00000179766.13	ATP8B5P	10.2928738	0.00041559
ENSG00000148408.8	CACNA1B	9.12553182	0.00042841
ENSG00000133083.10	DCLK1	10.4763853	0.0004357
ENSG00000148702.10	HABP2	9.93507316	0.00043749
ENSG00000146648.11	EGFR	9.32416759	0.00047166
ENSG00000145832.8	SLC25A48	10.3732943	0.00048682
ENSG00000171533.7	MAP6	10.1100079	0.00050118
ENSG00000245248.3	USP2-AS1	10.3915304	0.00050576
ENSG00000166444.13	ST5	7.03013101	0.00051906
ENSG00000183856.6	IQGAP3	7.66144499	0.00055556
ENSG00000167654.13	ATCAY	9.02455288	0.00056242

ENSG00000168356.7	SCN11A	7.9058759	0.00059864
ENSG00000186487.13	MYT1L	10.3013562	0.00060125
ENSG00000139767.4	SRRM4	9.1322541	0.00060437
ENSG00000147689.12	FAM83A	8.68477341	0.00064925
ENSG00000187955.7	COL14A1	10.3457395	0.00065046
ENSG00000204661.5	C5orf60	7.98854519	0.00065089
ENSG00000111262.4	KCNA1	10.0799494	0.00065233
ENSG00000123572.12	NRK	9.77398063	0.00068182
ENSG00000242866.5	STRC	7.89404297	0.00069439
ENSG00000108018.11	SORCS1	10.4860855	0.00074009
ENSG00000237125.4	HAND2-AS1	9.93585238	0.00080912
ENSG00000143355.11	LHX9	9.07176393	0.00080992
ENSG00000197893.9	NRAP	10.1582696	0.00087519
ENSG00000110786.13	PTPN5	10.1020442	0.00087704
ENSG00000177103.9	DSCAML1	6.69871332	0.00097226
ENSG00000101203.12	COL20A1	10.0926992	0.00103622
ENSG00000152910.14	CNTNAP4	9.58161879	0.00111905
ENSG00000169344.11	UMOD	9.57480249	0.00119192
ENSG00000187123.10	LYPD6	9.6224591	0.00121851
ENSG00000196091.8	MYBPC1	9.64996378	0.00123954
ENSG00000006788.7	MYH13	9.77503542	0.00132102
ENSG00000115648.9	MLPH	9.94753399	0.00135935
ENSG00000156222.7	SLC28A1	9.47454797	0.00149201
ENSG00000151224.8	MAT1A	9.67253653	0.00155075
ENSG00000188488.9	SERPINA5	9.74848797	0.00155075
ENSG00000162738.5	VANGL2	8.18945891	0.00156613
ENSG00000172995.12	ARPP21	9.46656103	0.00176545
ENSG00000169876.9	MUC17	9.63391559	0.00181592
ENSG00000198010.7	DLGAP2	9.73919587	0.00181592
ENSG00000165973.13	NELL1	9.73919587	0.00181592
ENSG00000198597.4	ZNF536	9.63391559	0.00181592
ENSG00000130287.8	NCAN	9.51783924	0.00188441
ENSG00000143107.4	FNDC7	6.94089227	0.00226789
ENSG00000089199.5	CHGB	8.37600881	0.00226861
ENSG00000138650.6	PCDH10	9.52030811	0.0022794
ENSG00000004948.9	CALCR	9.56275025	0.0022794
ENSG00000091128.8	LAMB4	9.56275025	0.0022794
ENSG00000169862.14	CTNND2	9.59457564	0.00239769
ENSG00000156687.6	UNC5D	9.83690372	0.00239769
ENSG00000179008.4	C14orf39	9.59457564	0.00239769
ENSG00000268388.1	FENDRR	9.59457564	0.00239769
ENSG00000205922.4	ONECUT3	9.59457564	0.00239769
ENSG00000142408.2	CACNG8	9.45372393	0.00243109
ENSG00000151474.15	FRMD4A	4.26915376	0.00252682

ENSG00000144730.12	IL-17RD	9.47740902	0.00256297
ENSG00000178031.11	ADAMTSL1	9.30109081	0.00256297
ENSG00000197085.7	NPSR1-AS1	9.82478961	0.00273892
ENSG00000165566.11	AMER2	9.82478961	0.00273892
ENSG00000174279.4	EVX2	9.23221912	0.00287805
ENSG00000160460.11	SPTBN4	7.90179181	0.00297008
ENSG00000139865.12	TTC6	9.43374983	0.00335063
ENSG00000054356.9	PTPRN	9.35015286	0.00361961
ENSG00000112186.7	CAP2	9.35015286	0.00361961
ENSG00000259156.3	CHEK2P2	9.35015286	0.00361961
ENSG00000185823.2	NPAP1	9.35015286	0.00361961
ENSG00000106304.11	SPAM1	9.2402676	0.00370324
ENSG00000159251.6	ACTC1	9.64814054	0.00376653
ENSG00000224743.2	TEX26-AS1	9.46689834	0.00384057
ENSG00000183317.12	EPHA10	7.75193464	0.00387013
ENSG00000166391.10	MOGAT2	9.30177815	0.00387013
ENSG00000188803.9	SHISA6	9.30177815	0.00387013
ENSG00000135931.13	ARMC9	7.57025316	0.00388201
ENSG00000119125.12	GDA	9.39828095	0.00388201
ENSG00000006210.6	CX3CL1	9.39828095	0.00388201
ENSG00000145242.9	EPHA5	9.55424849	0.00396734
ENSG00000178645.8	C10orf53	9.42301327	0.00406126
ENSG00000124092.7	CTCFL	9.09328581	0.00422446
ENSG00000114019.10	AMOTL2	8.07387917	0.00452094
ENSG00000101871.10	MID1	8.04439073	0.00461599
ENSG00000115041.8	KCNIP3	9.25262887	0.0047579
ENSG00000188886.3	ASTL	4.75628627	0.0047579
ENSG00000070886.6	EPHA8	9.10352401	0.00487397
ENSG00000142611.12	PRDM16	6.26811025	0.00497995
ENSG00000164694.12	FNDC1	9.10174997	0.00614899
ENSG00000185737.8	NRG3	9.10174997	0.00614899
ENSG00000196136.11	SERPINA3	9.15752037	0.00614899
ENSG00000171804.5	WDR87	9.15752037	0.00614899
ENSG00000124440.11	HIF3A	9.10174997	0.00614899
ENSG00000006283.13	CACNA1G	7.29179036	0.00676935
ENSG00000105290.7	APLP1	7.01702864	0.00703809
ENSG00000237636.2	ANKRD26P3	9.04536192	0.00728432
ENSG00000182256.8	GABRG3	9.04536192	0.00728432
ENSG00000140279.8	DUOX2	9.04536192	0.00728432
ENSG00000137573.9	SULF1	9.20219199	0.00738189
ENSG00000224059.1	HSPA8P16	10.5118456	0.00760264
ENSG00000156103.11	MMP16	9.21388586	0.00776909
ENSG00000091137.7	SLC26A4	7.81519145	0.00821577
ENSG00000143469.12	SYT14	9.03182628	0.00838462

ENSG00000183668.13	PSG9	10.4307525	0.00992099
ENSG00000120332.11	TNN	8.86959591	0.01092105
ENSG00000230873.4	STMND1	8.98752678	0.01092105
ENSG00000106648.9	GALNTL5	8.98752678	0.01092105
ENSG00000141668.5	CBLN2	8.98752678	0.01092105
ENSG00000104967.6	NOVA2	8.98752678	0.01092105
ENSG00000174358.11	SLC6A19	8.87308109	0.01142733
ENSG00000185313.6	SCN10A	8.80310292	0.01200226
ENSG00000125492.5	BARHL1	8.80310292	0.01200226
ENSG00000140527.10	WDR93	8.80310292	0.01200226
ENSG00000179270.6	C2orf71	8.93637024	0.01274995
ENSG00000165379.9	LRFN5	8.93637024	0.01274995
ENSG00000161270.15	NPHS1	8.71784874	0.01285489
ENSG00000226057.2	PHF2P2	5.94495217	0.01427779
ENSG00000161940.6	BCL6B	8.58900305	0.0148154
ENSG00000100065.10	CARD10	7.61171168	0.0148154
ENSG00000116721.9	PRAMEF1	8.73511268	0.01716161
ENSG00000183242.7	WT1-AS	8.73511268	0.01716161
ENSG00000104055.10	TGM5	8.73511268	0.01716161
ENSG00000149633.7	KIAA1755	8.73511268	0.01716161
ENSG00000250423.2	KIAA1210	8.73511268	0.01716161
ENSG00000077522.8	ACTN2	8.51176056	0.02199638
ENSG00000226068.1	HNRNPA3P4	8.59391365	0.02260172
ENSG00000167723.10	TRPV3	4.55901439	0.02266943
ENSG00000223414.2	LINC00473	9.76187181	0.02336738
ENSG00000197406.6	DIO3	9.80247266	0.02410841
ENSG00000132321.12	IQCA1	5.74183061	0.02461755
ENSG00000138892.7	TTLL8	9.669433	0.02680035
ENSG00000185974.6	GRK1	8.42879991	0.02836865
ENSG00000197079.4	KRT35	8.42879991	0.02836865
ENSG00000106689.6	LHX2	9.5706152	0.03023653
ENSG00000183908.5	LRRC55	9.5706152	0.03023653
ENSG00000168907.9	PLA2G4F	9.5706152	0.03023653
ENSG00000144115.12	THNSL2	4.66118466	0.03458112
ENSG00000138675.12	FGF5	9.51283135	0.03534253
ENSG00000132975.6	GPR12	9.50675823	0.03706847
ENSG00000257907.2	EEF1A1P17	5.43581118	0.03999134
ENSG00000134240.7	HMGCS2	9.34987098	0.04100703
ENSG00000185303.11	SFTPA2	9.34987098	0.04100703
ENSG00000115155.12	OTOF	4.23436155	0.04404224
ENSG00000184908.13	CLCNKB	9.34282178	0.04416808
ENSG00000260305.1	NTRK3-AS1	9.34282178	0.04416808
ENSG00000141434.7	MEP1B	9.34282178	0.04416808
ENSG00000116748.15	AMPD1	8.14697124	0.04465983

ENSG00000166159.6	LRTM2	8.14697124	0.04465983
ENSG00000139220.12	PPFIA2	8.14697124	0.04465983
ENSG00000089116.3	LHX5	8.14697124	0.04465983
ENSG00000109101.3	FOXN1	8.14697124	0.04465983
ENSG00000183287.9	CCBE1	8.14697124	0.04465983
ENSG00000196361.5	ELAVL3	8.07040565	0.04534929
ENSG00000154099.13	DNAAF1	6.27100113	0.04646486
ENSG00000132972.13	RNF17	6.23370242	0.04856254

Table 11. Comparison of gene expression level of 65 genes in sorted synovial cells

Analysis Columns	Mean expression in B cell	Mean expression in Fibroblast	Mean expression in Monocyte	Mean expression in T cell	fibroblast / (B+M+T)
DIO3	0.005898	0.568446	0.012513	0.012674	18.28676
ZIC4	0.040445	2.794642	0.082367	0.048743	16.29007
KCNA1	0.007163	0.845192	0.028432	0.020589	15.04338
FBXL7	0.01174	1.390057	0.041241	0.041037	14.7851
FNDC1	0.04824	3.390032	0.113013	0.072297	14.5152
ARSI	0.010528	0.896302	0.041211	0.0208	12.35612
NRAP	0.002079	0.084748	0.004413	0.00293	8.994018
PTPRU	0.017946	1.587554	0.110434	0.07467	7.818552
C14orf39	0.020927	1.169926	0.078181	0.050739	7.807468
PGR	0.021031	0.908659	0.031519	0.070138	7.406261
COL12A1	0.101297	4.658146	0.295869	0.23946	7.316921
SEMA3E	0.116105	4.591674	0.317588	0.223195	6.990037
EGFR	0.046741	3.586856	0.302146	0.202491	6.505261
STEAP2	0.159893	4.446441	0.282877	0.327752	5.770686
NRK	0.016676	0.440618	0.023194	0.037504	5.694656
SERPINA5	0.073307	2.938701	0.189757	0.27953	5.416022
KCNIP3	0.06369	1.527446	0.190652	0.053125	4.967833
NPC1L1	0.012326	0.231116	0.013956	0.025922	4.427196
LINC00473	0.084001	1.670193	0.123524	0.177062	4.342824
COL14A1	0.377592	6.658365	0.659155	0.61882	4.021805
COL5A1	0.195882	5.152502	0.406335	0.76069	3.780524
AMOTL2	0.212456	4.011784	0.342912	0.514269	3.750603
CAP2	0.018429	1.046753	0.070727	0.197247	3.654824
COL6A5	0.031141	0.433145	0.039923	0.049849	3.58229
KIAA1755	0.210203	3.295953	0.386915	0.340558	3.515026
SCARA5	0.397929	7.948255	1.207422	0.828519	3.265686
IQCA1	0.121789	1.492112	0.153691	0.202833	3.119531
PSD2	0.023408	0.281469	0.040438	0.028933	3.033749
LHX9	0.051171	1.053767	0.148808	0.152183	2.992278
SERPINA3	0.20254	3.073661	0.409223	0.451665	2.890334
IL-17RD	0.051696	0.85624	0.096036	0.14902	2.885379
ADAMTSL1	0.420496	4.552426	0.558634	0.604709	2.874299
MID1	0.306231	2.183956	0.267049	0.208137	2.794864
DNAH5	0.039732	0.46464	0.05278	0.079678	2.698414
CCBE1	0.178558	1.739894	0.189602	0.283328	2.670645
RADIL	0.050587	1.022948	0.185301	0.172746	2.503331
CX3CL1	0.140927	1.802906	0.24785	0.335124	2.49054
ITIH5	0.353934	3.49945	0.471817	0.617776	2.424235
MROH2A	0.004796	0.041373	0.009127	0.004261	2.275224

Analysis Columns	Mean expression in B cell	Mean expression in Fibroblast	Mean expression in Monocyte	Mean expression in T cell	fibroblast / (B+M+T)
LRFN5	0.175952	1.073433	0.194453	0.103999	2.262694
COL16A1	0.54871	5.199992	0.794715	1.037929	2.183629
HECW1	0.269484	1.282021	0.15447	0.174378	2.14266
ACTC1	0.038088	0.537753	0.104089	0.111694	2.118223
COL21A1	0.275376	1.631425	0.323602	0.191552	2.063711
FAT3	0.035617	0.291937	0.058087	0.049205	2.042804
RIMBP2	0.078437	0.580567	0.118093	0.088082	2.039855
SULF1	0.828528	8.126898	1.719874	1.537547	1.988987
COL22A1	0.227464	3.068647	0.76669	0.562446	1.971379
COBL	0.067772	0.779173	0.122777	0.2072	1.958957
DCLK1	0.386336	2.825789	0.532844	0.570433	1.896995
SORBS1	0.23154	1.78414	0.302128	0.414584	1.881503
NALCN	0.166223	1.330218	0.201117	0.36335	1.820496
B4GALNT1	0.178822	1.051208	0.207279	0.206557	1.773718
PXDN	0.651408	3.949243	0.757244	0.998328	1.640745
COL1A2	1.634163	11.30866	3.133569	2.358078	1.587
TACC2	0.574502	3.967579	0.874585	1.054203	1.584946
TNN	0.023226	0.236661	0.033165	0.093681	1.57698
ACKR2	0.441855	2.320834	0.563379	0.480746	1.56182
NTNG1	1.350033	2.578216	0.154202	0.193997	1.518177
FGF5	0.226262	0.688995	0.129544	0.103465	1.500193
PPFIA2	0.463127	1.777311	0.447252	0.275962	1.498146
C2orf71	0.006667	0.062577	0.013228	0.023256	1.450165
DUOX2	0.095781	0.662764	0.133862	0.233645	1.430565
HMCN2	0.259065	1.440545	0.304932	0.459232	1.407843
CLCNKB	0.031294	0.107496	0.013261	0.031801	1.407827

Note: “fibroblast / (B+M+T)” refers to the ratio of gene expression in fibroblasts to the sum of gene expression in B cells, Monocytes and T cells.

Table 12. 8 marker genes and their expression in 4 subsets of synovial fibroblasts

Gene Name	SC-F1	SC-F2	SC-F3	SC-F4
COL14A1	1	0	0	0
DCLK1	1	0	0	0
FNDC1	1	0	0	0
COL16A1	0	1	0	0
COL1A2	0	1	0	0
KIAA1755	0	1	0	0
PXDN	0	1	0	0
COL5A1	0	0	1	0

Note: SC-F1 refers to fibroblast-CD34+ sublining cells; SC-F2 refers to fibroblast-HLA-DRAhi sublining cells; SC-F3 refers to fibroblast-DKK3+ sublining cells; and SC-F4 refers to CD55+ lining fibroblasts.

“1” indicates the gene is enriched in the cells; “0” indicates the gene is not enriched in the cells.

Table 13. Primers for amplifying the markers in Table 12

GENE	PRIMER PAIRS:	SEQ ID	
COL14A1 (NM_021110.4)	Forward Sequence 1	1	CACAAACCTCCTCAGCGGAATG
	Reverse Sequence 1	2	GGCTTGGAGATTGGTAACACCC
COL14A1 (NM_021110.4)	Forward Sequence 2	3	ATACTCCGAGGGAAGAGAGCA
	Reverse Sequence 2	4	CAACCAGTACCGCATCTTGC
DCLK1 (NM_001330071.2)	Forward Sequence 1	5	ACCGATGCCATCAAGCTGGACT
	Reverse Sequence 1	6	TCCTGGTAACGGAATTCTCCG
DCLK1 (NM_001330071.2)	Forward Sequence 2	7	GCATTTCAATGAGGACGGGC
	Reverse Sequence 2	8	TACAGGCGTTTCACCACTCC
FNDC1 (NM_032532)	Forward Sequence 1	9	TGCATCTTGGGATGCGCTACCA
	Reverse Sequence 1	10	GGCAGAAGTAGTGTCTCCAGGA
FNDC1 (NM_032532)	Forward Sequence 2	11	GATGCTACCAGTAGACCTGTG
	Reverse Sequence 2	12	GGCACTTCCTTTTCTGTGACG
COL16A1 (NM_001856.4)	Forward Sequence 1	13	AGGCTATGGCAAGATGGGTG
	Reverse Sequence 1	14	TGTTCTGGGACTAAACGGG
COL16A1 (NM_001856.4)	Forward Sequence 2	15	AACAGTGAGGGAGATCCTGGCT
	Reverse Sequence 2	16	CAACAGCACCAAGGAAAACCTGG
COL1A2 (NM_000089.4)	Forward Sequence 1	17	CCTCTGGAGAGGCTGGTACT
	Reverse Sequence 1	18	TAACCACCACCGCTTACACC
COL1A2 (NM_000089.4)	Forward Sequence 2	19	CCTGGTGCTAAAGGAGAAAGAGG
	Reverse Sequence 2	20	ATCACCACGACTTCCAGCAGGA
KIAA1755 (NM_001348708.2)	Forward Sequence	21	GGTGTCAAGGTTTTCCGCTCCA
	Reverse Sequence	22	CTTGGTGACCTCTGAAACTGTGC
PXDN (NM_012293.3)	Forward Sequence	23	CGGACATTGCAGCTCATTCAGG
	Reverse Sequence	24	CCGACAGGTTTGCGATGAGGTT

COL5A1	Forward Sequence 1	25	CAAAGAAAACCCGGGCTCCTG
(NM_000093.5)	Reverse Sequence 1	26	TGTGACGCTTCACCGAAGTC
COL5A1	Forward Sequence 2	27	GAATTCAAGCGTGGGAACTG
(NM_000093.5)	Reverse Sequence 2	28	ACTTTGGGGGTGTCGATCTC

[0092] This invention may be embodied in other forms or carried out in other ways without departing from the spirit or essential characteristics thereof. The present disclosure is therefore to be considered as in all aspects illustrated and not restrictive, the scope of the present disclosure being indicated by the appended Claims, and all changes which come within the meaning and range of equivalency are intended to be embraced therein.

[0093] Various references are cited throughout this Specification, each of which is incorporated herein by reference in its entirety.

WHAT IS CLAIMED IS:

1. A method for monitoring and/or predicting a rheumatoid arthritis (RA) flare or increased RA disease activity in a patient comprising:
 - (a) detecting in a blood sample increased amounts of a panel of antecedent RA markers, wherein the panel comprise one or more AC3 markers listed in Table 10;
 - (b) wherein the expression or quantitatively increased amounts of the AC3 markers predicts an impending RA flare or increased RA disease activity.
2. The method of claim 1, wherein the panel comprise one or more AC3 markers listed in Table 11.
3. The method of claim 1, wherein the one or more or all AC3 markers are selected from those listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1).
4. The method of claim 1, wherein a panel of antecedent RA markers comprising at least 2 or more of the markers listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1) are evaluated to detect increased amounts of one or more of the AC3 markers evaluated.
5. The method of claim 1, wherein a panel of antecedent RA markers comprising those listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1) are evaluated to detect increased amounts of one or more of the AC3 markers listed in Table 12.
6. The method of any of the preceding claims, wherein the increased amounts of the AC3 RNA markers or the AC3 protein markers predicts an RA flare in about 1 week or about 5-7 days or up to 2 weeks.
7. The method of any one of the preceding claims, wherein the panel consists of 2 to 283 antecedent markers.
8. The method of any one of the preceding claims, wherein a panel of at least 3, at least 4, at least 5 or at least 6 of the AC3 markers are evaluated.
9. The method of any one of the preceding claims, wherein the method further comprises detecting increased amounts of one or more AC2 markers listed in Table 7.

10. The method of any one of the preceding claims, wherein the increased amounts of one or more AC3 markers predicts an RA flare in about 1 week or about 5-7 days or up to 2 weeks.
11. The method of claim 1, wherein the increased amounts of one or more AC3 RNA markers are detected using RNAseq or RT-PCR.
12. The method of claim 11, wherein the detecting the increased amounts of the one or more AC3 RNA markers comprises amplifying the one or more AC3 RNA markers in Table 12 using primer pairs listed in Table 13.
13. The method of any one of the preceding claims, the increased amount of the one or more AC3 protein markers is detected using antibodies specific for the AC3 protein markers.
14. The method of claim 1 wherein the amount of antecedent AC3 markers are decreased in peripheral blood during an RA flare or once a patient exhibits symptoms of an RA flare.
15. A computer implemented method for predicting an impending RA flare or increased RA disease activity in a patient comprising:
 - a) detecting amounts of a panel of AC3 markers, wherein the panel comprise one or more AC3 markers listed in Table 10, and
 - b) determining, using one or more computer processors, that the patient has an impending RA flare or increased RA disease activity if the amounts of the panel of AC3 markers are higher than the amounts of the AC3 markers in a control blood sample.
16. A method for predicting or treating an impending RA flare in a patient, the method comprising:
 - a) contacting a blood sample from the patient with reagents specific for detecting a panel of AC3 markers, wherein the panel comprise one or more AC3 markers listed in Table 10,
 - b) detecting amounts of the markers of the panel in the blood sample, wherein detection of increased amounts serves to predict an impending RA flare in a patient,
 - c) comparing the amounts of the markers in the panel to the amounts of the markers in a control blood sample, and
 - d) administering a therapeutically effective amount of one or more disease-modifying agent for treating RA if the amounts of the markers of the panel in the blood sample is increased relative to the amounts of the markers in the control blood sample, thereby treating the impending flare in the patient.
17. The method of claim 16, wherein the one or more AC3 markers are selected from those listed

in Table 11.

18. The method of claim 16, wherein the one or more or all AC3 markers are selected from those listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1).

19. The method of claim 16, wherein a panel of antecedent RA markers comprising at least 2 or more of the AC3 markers listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1) are evaluated to detect increased amounts of one or more of the AC3 markers.

20. The method of claim 16, wherein a panel of antecedent RA markers comprising those AC3 markers listed in Table 12 (COL14A1, DCLK1, FNDC1, COL16A1, COL1A2, KIAA1755, PXDN, and COL5A1) are evaluated to detect increased amounts of one or more of the AC3 markers.

21. The method of claim 16, wherein the increased amounts of the AC3 markers predicts an RA flare in about 1 week or about 5-7 days.

22. The method of claim 16, wherein step (d) is performed within one (1) week or within 5-7 days from the step (a).

23. The method of claim 16, wherein the disease-modifying agent for treating RA is one or more agent selected from a nonsteroidal anti-inflammatory drug (NSAID), steroid, methotrexate, disease-modifying antirheumatic drug (DMARDs), biologic DMARD, and oral janus kinase (JAK) inhibitor.

24. The method of claim 23, wherein the DMARD is selected from methotrexate (Trexall, Otrexup), leflunomide (Arava), hydroxychloroquine (Plaquenil) and sulfasalazine (Azulfidine).

25. The method of claim 24, wherein the biologic DMARD is selected from abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), baricitinib (Olmiant), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), rituximab (Rituxan), sarilumab (Kevzara), tocilizumab (Actemra) and tofacitinib (Xeljanz).

26. The method of claim 24, wherein the biologic DMARD is a tumor necrosis factor (TNF) inhibitor.

27. The method of claim 24, wherein the biologic DMARD is combined with an NSAID and/or with methotrexate.

28. The method of claim 24, wherein the JAK inhibitor is selected from tofacitinib (Xeljanz and Xeljanz XR), baricitinib (Olumiant), and upadacitinib (Rinvoq).
29. The method of claim 16, wherein the disease-modifying agent for treating RA is an IL-17 antibody or an IL-17RD blocking antibody.
30. A method of treating a patient having an impending RA flare or increased RA disease activity, the method comprising
- (a) selecting a patient who has been diagnosed as having increased amounts of a panel of markers as compared to a control blood sample, wherein the panel of markers comprise one or more AC3 markers as listed in Table 10 and/or one or more AC2 markers listed in Table 7, and
 - (b) administering to the patient a therapeutically effective amount of one or more disease-modifying agent prior to the onset of RA.
31. The method of claim 30, wherein the panel of markers comprise one or more AC3 markers as listed in Table 11.
32. The method of claim 30, wherein the panel of markers comprises one or more AC3 markers as listed in Table 12.
33. A panel of AC3 markers for evaluating and predicting an impending RA flare or increased RA disease activity in a patient comprising the markers selected from one or more antecedent RNA markers or protein markers listed in Table 10, or Table 11, or Table 12.
34. A collection of primer pairs for amplifying the AC3 markers in claim 33.
35. The collection of primer pairs for amplifying the AC3 markers in Table 12, wherein the collection of primers comprise one or more of the primers listed in Table 13.
36. A system or kit for predicting an impending RA flare or increased RA disease activity comprising a set of markers of claim 33, or a set of primers and/or antibodies for evaluating a set of markers of claim 33.
37. The system or kit of claim 36, which further comprises a means for collecting the patient's blood by fingerstick.