

operative risks for an estimated third of patients undergoing surgery, such as anastomotic leak, infection, and bleeding.

[0005] The pathogenesis of inflammatory disease, fibrostenotic disease, and fibrotic disease, like IBD, is thought to involve an uncontrolled immune response that may be triggered by certain environmental factors in a genetically susceptible individual. The heterogeneity of disease pathogenesis and clinical course, combined with the variable response to treatment and its associated side effects, suggests a personalized medicine approach to treating these diseases is the best treatment strategy. Yet there are very few personalized therapies available to patients. Accordingly, there is a need to identify targeted therapeutic approaches for the treatment of inflammatory disease, fibrostenotic disease, and fibrotic disease and subclinical phenotypes thereof, and an even greater need to develop reliable methodology to identifying patients who, based on their genotype, may respond to any given therapeutic approach. The needed methodologies would also identify subjects not yet diagnosed who are at risk of developing the disease, for which preventative interventions could be prescribed to reduce the growing health burden.

SUMMARY

[0006] The genotypes described herein are associated with an increase in a level of *TNFSF15* (TL1A) protein expression in a sample obtained from a subject or patient, as compared to a reference level of *TNFSF15* (TL1A) protein expression (*e.g.*, derived from a normal individual). The genotypes disclosed herein are located at gene or genetic loci that are involved either directly or indirectly with TL1A-mediated or T-cell dependent inflammatory pathways. In addition, some of the genotypes provided herein are also significantly associated with inflammatory bowel disease (IBD), such as Crohn's disease (CD). The genotypes are useful for selecting a patient or a subject for treatment with an inhibitor of TL1A activity or expression. The patient may be diagnosed with IBD, CD, or both. The subject may be suspected of having IBD, CD, or both.

[0006a] Disclosed herein, in an aspect, is the use of an inhibitor of tumor necrosis factor-like cytokine 1A (TL1A) activity or expression ("TL1A inhibitor") in the manufacture of a medicament for treating an inflammatory, a fibrotic, or a fibrostenotic disease or condition in a subject, wherein at least three polymorphisms that are predictive of a positive therapeutic response in a subject to treatment with the TL1A inhibitor with a positive predictive value or a specificity of at least about 51%, are detected in a sample obtained from the subject of the treatment, and wherein the TL1A inhibitor is an antibody or antigen binding fragment thereof

that binds to TL1A, comprising a heavy chain variable domain comprising an amino acid sequence at least about 97% identical to SEQ ID NO: 104, and a light chain variable domain comprising an amino acid sequence at least about 97% identical to SEQ ID NO: 201 wherein optionally the heavy chain variable domain comprises an amino acid sequence at least about 98%, 99%, or 100% identical to SEQ ID NO: 104 and wherein optionally the light chain variable domain comprises an amino acid sequence at least about 98%, 99%, or 100% identical to SEQ ID NO: 201.

[0006b] In another aspect, disclosed herein is the use of of an inhibitor of tumor necrosis factor-like cytokine 1A (TL1A) activity or expression (“TL1A inhibitor”) in the manufacture of a medicament for treating an inflammatory, a fibrotic, or a fibrostenotic disease or condition in a subject, wherein at least three polymorphisms that are predictive of a positive therapeutic response in a subject to treatment with the TL1A inhibitor with a positive predictive value or a specificity of at least about 51%, are detected in a sample obtained from the subject of the treatment, and wherein the TL1A inhibitor is an antibody or antigen binding fragment thereof that binds to TL1A that comprises: (a) a heavy chain variable framework region comprising a human IGHV1-46*02 framework or a modified human IGHV1-46*02 framework; and (b) a light chain variable framework region comprising a human IGKV3-20 framework or a modified human IGKV3-20 framework; wherein the heavy chain variable framework region and the light chain variable framework region collectively comprise less than 14 amino acid modifications from the human IGHV1-46*02 framework and the human IGKV3-20 framework.

[0006c] In another aspect, disclosed herein is the use of of an inhibitor of tumor necrosis factor-like cytokine 1A (TL1A) activity or expression (TL1A inhibitor) in the manufacture of a medicament for treating an inflammatory, a fibrotic, or a fibrostenotic disease or condition in a subject, wherein at least three polymorphisms that are predictive of a positive therapeutic response in a subject to treatment with the TL1A inhibitor with a positive predictive value or a specificity of at least about 51%, are detected in a sample obtained from the subject of the treatment, and wherein the TL1A inhibitor is an antibody or antigen binding fragment thereof that binds to TL1A and comprises:

a heavy chain variable region comprising SEQ ID NO: 301

X1VQLVQSGAEVKKPGASVKVSCKAS[HCDR1]WVX2QX3PGQGLEWX4G[HCDR2]RX5TX6TX7DTSTSTX8YX9ELSSLRSEDTAVYYCAR[HCDR3]WGQGT
TVTVSS, and

a light chain variable region comprising SEQ ID NO: 303

EIVLTQSPGTLSPGERATLSC[LCDR1]WYQQKPGQAPRX10X11IY[LCDR2]GIPDR
FSGSGSGTDFTLTISRLEPEDFAVYYC[LCDR3]FGGGTKLEIK, wherein each of X1-X11
is independently selected from A, R, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y, or V.

[0007] Disclosed herein, in some aspects is a method of treating an inflammatory, a fibrotic, or a fibrostenotic disease or condition in a subject, the method comprising administering to the subject a therapeutically effective amount of an inhibitor of Tumor necrosis factor-like cytokine 1A (TL1A) activity or expression, wherein at least three polymorphisms that are predictive of a positive therapeutic response in the subject to a treatment with the inhibitor of TL1A activity or expression with a positive predictive value or a specificity of at least about 51%, are detected in a sample obtained from the subject, and