

Precision Medicine for Anxiety Disorders: Objective Assessment, Risk Prediction, Pharmacogenomics, and Repurposed Drugs

STATEMENT OF GOVERNMENT SUPPORT

[0001] This invention was made with government support under MH117431 awarded by the National Institutes of Health and CX000139 merit award by the Veterans Administration. The government has certain rights in the invention.

BACKGROUND

[0002] Anxiety disorders are highly prevalent and insidious in their effects on one's ability to do things and quality of life. Psychiatric patients may have increased anxiety, as well as increased reasons for anxiety, due to their often, adverse life trajectory. Improvements are needed to adequately diagnose and treat all individuals suffering with anxiety disorders.

SUMMARY

[0003] Provided here are newly identified blood gene expression biomarkers for anxiety. The biomarkers provide a means of assessing state severity, short-term risk, and long-term risk. The biomarkers can also be used for drug repurposing.

[0003a] In an aspect, there is provided the use of a therapeutic compound, selected from one or more compounds from Tables 4 and Table 6, in the manufacture of a medicament for mitigating and anxiety disorder in a subject in need thereof for example wherein the therapy is a drug, a natural compound, and combinations thereof.

[0003b] In another aspect, there is provided a method for assessing and mitigating anxiety disorder, comprising determining an expression level of a panel of biomarkers listed in Table 2, Table 5 and Figure 2, in a sample for example wherein the sample comprises a peripheral tissue, blood, saliva, cerebrospinal fluid (CSF), serum, urine, or stool; wherein the expression level of the biomarkers in the sample is different relative to a reference expression level; and includes the steps of:

identifying the subject currently having or at risk of having an anxiety disorder based on a biomarker panel score relative to a biomarker panel score of a reference panel;

selecting a therapy based on the score from the biomarkers; and

administering one or more compounds selected from the group consisting of compounds selected from the groups consisting of compounds selected from Tables 4 and Table 6.

[0003c] In another aspect, there is provided the use of a composition comprising one or more compounds from Tables 4 and Table 6, in the manufacture of a medicament for treating anxiety disorder.

[0004] Some examples of the disclosure include methods for treating an individual experiencing or at a heightened risk for developing symptoms is anxiety disorders. Treating involves administered at least one course of treatment, treatment may include psychiatric counseling, administering certain physical intervention, and/or prescribing and/or administering at least one therapeutic compound. Treating may include at least one of the following outcomes, curing, mitigating, managing or otherwise recuing the severity and/or the number of frequency anxious behaviors, especially behaviors that negatively impact a individual's quality of life.

[0005] A first example is a therapeutic compound selected from one or more compounds in Tables 4 and Table 6, for use in a method of mitigating and anxiety disorder in a subject in need thereof for example wherein the therapy is a drug, a natural compound, and combinations thereof.

[0006] A second example is the therapeutic compound for use according to the first example, wherein the drug is selected from the group consisting of: estradiol, loperamide, omage-3 fatty acids, lithium, fluoxetine, norfluoxetine, imipramine, citalopram, carbamazepine,

aripiprazole, haloperidol, mianserin, SAM, vortioxetine, agomelatine, sertraline, benzodiazepine, clozapine, ketamine, valproate, clozapine, rofecoxib, berberine, methylphenidate, or berberine.

[0007] A third example is the therapeutic compound for use according to the first example, wherein the subject has an anxiety disorder.

[0008] A fourth example is a therapeutic compound for use according to the first example, wherein the subject is a male subject or a female subject.

[0009] A fifth example is a computer-implemented method for assessing the level of anxiety in a subject, and for assessing risk of developing anxiety disorder in the future in a subject, the method comprising: computing a score based on RNA level, protein level, DNA methylation, a single nucleotide polymorphism, for a panel of biomarkers chosen from Table 2, Table 5, and Figure 2, in a sample obtained from a subject; computing a score based on a reference expression level of the panel of biomarkers; and identifying a difference between the score in the sample obtained from the subject and the score in the reference sample, wherein the difference in the score in the sample obtained from the subject and the score in the reference sample indicates an anxiety disorder, and a risk of future anxiety disorders.

[0010] A sixth example is the method according to the fifth example, wherein the subject is: a male or a female and the biomarker is at least one biomarker selected from the group consisting of: ERCC6L2, SLC6A2, FZD10, and RPL14; or a female and the biomarker is at least one biomarker selected from the group consisting of: PHF21A, SLC6A2, 240253_at, and TRIM9; or a male and the biomarker is at least one biomarker selected from the group consisting of: ERCC6L2, ANKRD28, ACP1, and RP

[0011] A seventh example is the method according to the fifth or the sixth examples, further including the steps of: identifying a difference between the score in the sample obtained from the subject and the score in the reference sample, administering treatment to the subject, wherein the treatment reduces the difference between the score in the sample from the subject and the score in the reference sample, and mitigates anxiety in the subject, or the risk for developing anxiety disorder in the subject.

[0012] An eighth example is the method according to the seventh example, further including, the step of: measuring a change in the score after treatment.

[0013] A ninth example is the method according to the eighth example, wherein the treatment is at least one treatment selected from the group consisting of: lifestyle modification,

electro-magnetic intervention, and administering a therapeutic compound.

[0014] A tenth example is the method according to the ninth example, wherein the therapy is selected by a computer- implemented method selected from the group consisting of one or more psychiatric compounds from Table 6, and wherein each therapy selection is based on a panel of one or more individual biomarkers.

[0015] An eleventh example is the method according to the tenth example, wherein the therapy is selected based on a panel of individual biomarkers changed in a subject, by a computer-implemented method for therapy selection, and comprises, of one or more compounds in Table 4.

[0016] An twelfth example is a method for assessing and mitigating anxiety disorder, comprising determining an expression level of a panel of biomarkers listed in Table 2, Table 5 and Figure 2, in a sample for example wherein the sample comprises a peripheral tissue, blood, saliva, cerebrospinal fluid (CSF), serum, urine, or stool; wherein the expression level of the biomarkers in the sample is different relative to a reference expression level; and includes the steps of: identifying the subject currently having or at risk of having an anxiety disorder based on a biomarker panel score relative to a biomarker panel score of a reference; selecting a therapy based on the score from the biomarkers, wherein the therapy includes; and administering one or more compounds selected from the group consisting of compounds selected from the groups consisting of compounds selected from Tables 4 and Table 6.

[0017] A thirteenth example is a composition comprising one or more compounds selected from Tables 4 and Table 6, for use in a method for treating anxiety disorder.

BRIEF DESCRIPTION OF THE FIGURES

[0018] FIG. 1 A. Discovery cohort, within subject changes in anxiety state (N of 58).

[0019] FIG. 1 B. Discovery cohort 141 male and 17 female psychiatric participants have at least one switch between a low anxiety state visit and a high anxiety state visit.

[0020] FIG. 1 C. Convergent functional genomics. Multiple independent lines of evidence for identification and prioritization of anxiety biomarkers.

[0021] FIG. 1 D. Graphic presentation of data. Left panel, EFNAS, $P=2.02 \times 10^{-4}$.; right panel TG51, $P=2.3 \times 10^{-3}$.

[0022] FIG. 1 E. Graphic representation of Discovery, Prioritization and Validation of biomarkers.

Claims

1. Use of a therapeutic compound, selected from one or more compounds from Tables 4 and Table 6, in the manufacture of a medicament for mitigating and anxiety disorder in a subject in need thereof for example wherein the therapy is a drug, a natural compound, and combinations thereof.
2. The use according to claim 1, wherein the drug is estradiol, loperamide, omage-3 fatty acids, lithium, fluoxetine, norfluoxetine, imipramine, citalopram, carbamazepine, aripiprazole, haloperidol, mianserin, SAM, vortioxetine, agomelatine, sertraline, benzodiazepine, clozapine, ketamine, valproate, clozapine, rofecoxib, berberine, methylphenidate, or berberine.
3. The use according to claim 1, wherein the subject has anxiety disorder.
4. The use according to claim 1, wherein the subject is a male subject or a female subject.
5. A computer-implemented method for assessing the level of anxiety in a subject, and for assessing risk of developing anxiety disorder in the future in a subject, the method comprising: computing a score based on RNA level, protein level, DNA methylation, a single nucleotide polymorphism, for a panel of biomarkers chosen from Table 2, Table 5, and Figure 2, in a sample obtained from a subject; computing a score based on a reference expression level of the panel of biomarkers; and identifying a difference between the score in the sample obtained from the subject and the score in the reference sample, wherein the difference in the score in the sample obtained from the subject and the score in the reference sample indicates an anxiety disorder, and a risk of future anxiety disorders.
6. The computer implemented method according to claim 5, wherein the subject is:

a male or a female and the biomarker is at least one biomarker selected from the group consisting of: ERCC6L2, SLC6A2, FZD10, and RPL14; or

a female and the biomarker is at least one biomarker selected from the group consisting of: PHF21A, SLC6A2, 240253_at, and TRIM9; or

a male and the biomarker is at least one biomarker selected from the group consisting of: ERCC6L2, ANKRD28, ACP1, and RP

7. A method for assessing and mitigating anxiety disorder, comprising determining an expression level of a panel of biomarkers listed in Table 2, Table 5 and Figure 2, in a sample for example wherein the sample comprises a peripheral tissue, blood, saliva, cerebrospinal fluid (CSF), serum, urine, or stool; wherein the expression level of the biomarkers in the sample is different relative to a reference expression level; and includes the steps of:

identifying the subject currently having or at risk of having an anxiety disorder based on a biomarker panel score relative to a biomarker panel score of a reference panel;

selecting a therapy based on the score from the biomarkers; and

administering one or more compounds selected from the group consisting of compounds selected from the groups consisting of compounds selected from Tables 4 and Table 6.

8. Use of a composition comprising one or more compounds from Tables 4 and Table 6, in the manufacture of a medicament for treating anxiety disorder.