

findings in a recent genome-wide meta-analysis of obesity²³, making it an appealing candidate gene for further investigation in obesity and related phenotypes.

[0005] There is also accumulating evidence for alterations in GABA neurotransmission by various antipsychotic drugs²⁴⁻²⁶. Clozapine and olanzapine, in particular, may exert their anxiolytic activity by increasing GABA-ergic neurotransmission²⁷ through the allosteric action of neuroactive steroids including allopregnanolone at the GABA_A receptor²⁸. Olanzapine-induced weight gain and adiposity has been correlated to increased levels of the GABA synthesis enzyme GAD65²⁹.

[0006] The *GABRA2* gene (HGNC:4076), which is mapped to chromosomal region 4p12, codes for the GABA_A receptor, alpha 2 subunit. While the *GABRA2* gene was implicated in obesity²³, it has not been investigated in relation to antipsychotic induced weight gain.

[0007] There is a need in the art for novel genetic markers. Further, there is a need in the art for novel genetic markers associated with antipsychotic-induced weight gain. Further, there is a need in the art for genetic diagnostic markers for antipsychotic-induced weight gain that provide physicians and other health care professionals with the opportunity to generate educated decisions for prescribing medications for treatment of psychosis. Moreover, there is a need in the art for personalized medicine approaches that lower the risk of developing antipsychotic induced weight gain and related ailments such diabetes and cardiovascular disease.

SUMMARY OF THE INVENTION

[0008] The present ~~invention~~-disclosure relates to genetic markers. More specifically, the present ~~invention~~-disclosure relates to genetic markers in *GABRA2* that are associated with antipsychotic induced weight gain and use thereof.

[0009] As a convention, all references to nucleotide sequences herein are recited with respect to the positive strand. As will be understood by a person of skill in the art, *GABRA2* gene is transcribed off the negative strand. Thus it is fully contemplated that the subject matter herein

[0011] According to the present ~~invention~~ disclosure there is provided a method of predicting a subject's weight change in response to antipsychotic drug treatment comprising,

- a) obtaining a biological sample comprising genomic DNA from the subject;
- b) determining the presence or absence of one or more polymorphisms in the *GABRA2* gene of the subject, wherein the presence of said one or more polymorphisms is predictive of the subject's weight change in response to antipsychotic drug treatment.

[0011a] In one aspect of the present disclosure, there is provided a method for identifying a subject who is at increased risk of weight gain in response to treatment with an antipsychotic drug, the method comprising

- a) obtaining or receiving the subject's genotype or haplotype, or both, at one or more genetic markers selected from the group consisting of rs279858 (T/T), rs1442062 (G/G), rs16859227 (C/C), rs11503014 (G/C, G/G), rs6856130 (G/A, G/G), rs1372472 (A/A); and
- b) identifying the subject as at increased risk of weight gain in response to treatment with an antipsychotic drug if the subject's genotype matches one or more genotypes selected from the group consisting of:
 - rs279858 (T/T),
 - rs1442062 (G/G),
 - rs16859227 (C/C),
 - rs11503014 (G/C, G/G),
 - rs6856130 (G/A, G/G), or
 - rs1372472 (A/A).

[0012] In a further embodiment, there is provided a method as described above, further comprising at least one step selected from the group consisting of a) treating the subject with one or more therapeutics based on the results obtained from said determining the presence or absence of one or more polymorphisms in the *GABRA2* gene b) advising and/or counseling the subject with respect to the results of determining the presence or absence of one or more polymorphisms in the *GABRA2* gene; c) transmitting, advising and/or conveying the results to a physician, medical service provider or other third party; d) treating the subject with one or more particular antipsychotic treatment(s) based on the results; e) treating the subject prior to, concurrently with

or after antipsychotic treatment with one or more therapies or therapeutics to control weight gain; f) monitoring the subject's weight over a period of time; g) prescribing, recommending or subjecting the patient or subject to exercise or diet changes; h) monitoring the subject for metabolic syndrome, i) monitoring the subject for cardiovascular disease or symptoms thereof, or
5 any combination of a-i) .

[0013] Also provided by the present ~~invention~~-disclosure is a method as described above, wherein the subject has been diagnosed with schizophrenia or schizoaffective disorder, is likely to develop schizophrenia or schizoaffective disorder, or exhibits one or more symptoms of schizophrenia or schizoaffective disorder. In a further embodiment, which is not meant to be
10 limiting in any manner, it is also contemplated that the subject has not yet been diagnosed with schizophrenia or schizoaffective disorder before the method as described herein is performed.

[0014] According to a further embodiment, there is provided a method as described above wherein the one or more polymorphisms in the *GABRA2* gene are relative to:

b) one or more probes that hybridize to any one of SEQ ID NOs:1-9, over a region of nucleotides comprising the polymorphic site, wherein said probe hybridizes to a particular variant of the polymorphisms shown at the polymorphic site. Without wishing to be limiting in any manner, the probes may be labeled with an appropriate group, for example, a fluorescent tag, fluorophore, radioactive label or the like. Further, the one or more probes may be attached covalently or physically associated with a support for example, but not limited to a biochip, array, slide, multiwell plate, bead or the like. In an embodiment, which is not meant to be limiting in any manner, the probes may comprise an array of nucleic acids.

c) one or more reagents and/or products including, but not limited to, one or more buffers for performing PCR or probe hybridization, or any step in such as process as would be known to a person of skill in the art, one or more DNA amplifying enzymes, or any combination thereof;

d) one or more reagents, components and products for genotyping the polymorphisms as described herein, including, but not limited to those used in exonuclease assays, nucleotide sequencing, or any combination thereof;

e) one or more reagents, components or products for performing a DNA sequencing reaction that determines the sequence of a nucleotide sequence comprising any one of SEQ ID NOs: 1-9 or a combination thereof, and;

f) one or more sets of instructions for using the components as described herein, practicing the methods of the present ~~invention~~ disclosure as described herein, interpreting the data obtained from practicing the methods of the present ~~invention~~ disclosure or any combination thereof.

[0020] This summary ~~of the invention~~ does not necessarily describe all features of the ~~invention~~ present disclosure.

WHAT IS CLAIMED IS:

1. A method of predicting a subject's weight change in response to antipsychotic drug treatment comprising,

a) obtaining a biological sample comprising genomic DNA from the subject; and

5 b) determining the presence or absence of one or more polymorphisms in the *GABRA2* gene of the subject or the complement thereof, wherein the presence of said one or more polymorphisms is predictive of the subject's weight response to antipsychotic drug treatment.

2. The method of claim 1, wherein the method further comprises at least one step of a) treating
10 the subject with one or more therapeutics based on the results obtained from said determining the presence or absence of one or more polymorphisms in the *GABRA2* gene; b) advising and/or counseling the subject with respect to the results of determining the presence or absence of one or more polymorphisms in the *GABRA2* gene; c) transmitting, advising and/or conveying the results to a physician, medical service provider or other third party; d) treating the subject with
15 one or more particular antipsychotic treatment(s) based on the results; e) treating the subject prior to, concurrently with or after antipsychotic treatment with one or more therapies or therapeutics to control weigh gain; f) monitoring the subject's weight over a period of time; g) prescribing recommending or subjecting the patient or subject to exercise or diet changes; h) monitoring the subject for metabolic syndrome or one or more symptoms thereof; i) monitoring
20 the subject for cardiovascular disease or one or more symptoms thereof or j) any combination of a-i).

3. The method of claim 1, wherein the subject has been diagnosed with schizophrenia or schizoaffective disorder, is likely to develop schizophrenia or schizoaffective disorder, or exhibits one or more symptoms of schizophrenia or schizoaffective disorder.

25 4. The method of claim 1, wherein said subject displays one or more psychotic symptoms or is at risk of displaying one or more psychotic symptoms.

5. The method of claim 1, wherein the one or more polymorphisms in the *GABRA2* gene are relative to:

a) rs16859227

CCTTGGTTTTATACAAGCATGCAAAG[C/T]ATATAATAGAATCACATGGAAACAA

5 (SEQ ID NO:1);

b) rs279858

ATTGTCATATTATGAGCTACTGATTTT[T/C]TTCCCATTTGTGAAAAAAGGTATCTG

(SEQ ID NO:2);

c) rs1442060

10 GTAAAGTGTACATCAATGCCATATC[A/G]TATTCTGTAGATGGCATGTTATCAT
(SEQ ID NO:3),

d) rs3849591

CTCATTTCCTTGCTTCTAAGGTAGGG[G/T]TCATCAATTTATCTATCTCATGGGA
(SEQ ID NO:4),

15 e) rs1442062

GAGAAGGTGAAATAGATTTAACATCA[A/G]TATCAAATTAAGATTGCACCTTAAA
(SEQ ID NO:5),

f) rs16859354

20 TACAATATCTTGACTCAATGAGCTTC[G/T]AATCTTAATAAGGTAACAAGAGAAA
(SEQ ID NO:6),

g) rs11503014

AAGCTATGGAGATTACTTCCTGGACT[C/G]TGTGTAGGACTTGATGATTGAGAGA
(SEQ ID NO:7),

h) rs6856130

25 TCTGTTCTGTTTTATCTGAGGCGATA[A/G]AATCCAAACGTGCAACTTGAACAAC
(SEQ ID NO:8), or

i) rs1372472

ATAAACTCTGGTAATTCAAACCAAA[A/T]ATTCCTCACTGAAAACCTATGCTTG
(SEQ ID NO:9)

30 or the complement thereof, and wherein the polymorphic site is in brackets, underlined and in bold.

6. The method of claim 5, wherein the one or more polymorphisms in *GABRA2* comprise SEQ ID NO:1, SEQ ID NO:2 or both SEQ ID NO:1 and 2, or the complement thereof.
7. The method of claim 6, wherein the one or more polymorphisms further comprise the polymorphism in SEQ ID NO:3, or the complement thereof.
- 5 8. The method of claim 6, wherein the one or more polymorphisms further comprise one or more polymorphisms in SEQ ID NOs 3-9, or the complement thereof.
9. The method of claim 1, wherein at least one of the polymorphisms is defined by SEQ ID NO:1 or 2, or a variant or fragment thereof comprising the polymorphic site.
- 10 10. The method of claim 1, wherein the presence of the T/T genotype of the rs279858 polymorphism (SEQ ID NO: 2) is associated with a higher percentage weight gain in subjects.
11. The method of claim 1, wherein the sample is a blood sample.
12. A kit comprising one or more of the following:
- a) one or more primers to amplify a nucleotide sequence that comprises the polymorphism as defined in SEQ ID NOs:1-9 or a combination thereof;
- 15 b) one or more probes that hybridize to any one of SEQ ID NOs:1-9, over a region of nucleotides comprising the polymorphic site, wherein said probe hybridizes to a particular variant of the polymorphisms shown at the polymorphic site;
- c) one or more reagents and/or products comprising one or more buffers for performing PCR or probe hybridization, one or more DNA amplifying enzymes, or any combination thereof;
- 20 d) one or more reagents, components and products for genotyping the polymorphisms comprising those used in exonuclease assays, nucleotide sequencing, or any combination thereof;
- e) one or more reagents, components or products for performing a DNA sequencing reaction that determines the sequence of a nucleotide sequence comprising any one of SEQ ID NOs: 1-2 or a combination thereof,

f) a gene chip, or microarray comprising one or more of SEQ ID NOs: 1-9 or the complement thereof;

g) one or more sets of instructions;

or any combination thereof.

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WHAT IS CLAIMED IS:

1. A method for identifying a subject who is at increased risk of weight gain in response to treatment with an antipsychotic drug, the method comprising

5 a) obtaining or receiving the subject's genotype or haplotype, or both, at one or more genetic markers selected from the group consisting of rs279858 (T/T), rs1442062 (G/G), rs16859227 (C/C), rs11503014 (G/C, G/G), rs6856130 (G/A, G/G), rs1372472 (A/A); and

b) identifying the subject as at increased risk of weight gain in response to treatment with an antipsychotic drug if the subject's genotype matches one or more genotypes selected from the group consisting of:

10 rs279858 (T/T),

rs1442062 (G/G),

rs16859227 (C/C),

rs11503014 (G/C, G/G),

rs6856130 (G/A, G/G), or

15 rs1372472 (A/A).

2. The method of claim 1, wherein step a) comprises obtaining or receiving the subject's genotype for at least two of the genetic markers.

20 3. The method of claim 2, wherein step a) comprises obtaining or receiving the subject's genotype for rs16859227 and rs279858 and step b) comprises identifying the subject as at increased risk of weight gain in response to treatment with an antipsychotic drug if the subject's haplotype is C-T at rs16859227 and rs279858.

25 4. The method of claim 2, wherein step a) comprises obtaining or receiving the subject's genotype for rs279858 and rs1442060 and step b) comprises identifying the subject as at increased risk of weight gain in response to treatment with an antipsychotic drug if the subject's haplotype is T-A at rs279858 and rs1442060.

30 5. The method of claim 1, wherein step a) comprises obtaining or receiving the subject's genotype for rs279858 and step b) comprises identifying the subject as at increased risk of

weight gain in response to treatment with an antipsychotic drug if the subject's genotype is T/T at rs279858.

5 6. The method of any one of claims 1-5, wherein the antipsychotic drug is selected from clozapine or olanzapine.

10 7. The method of any one of claims 1-5, wherein the method further comprises a recommendation that the physician avoid prescribing clozapine and olanzapine for the subject at increased risk of weight gain.

15 8. The method of any one of claims 1-5, wherein the method further comprises a recommendation that the physician prescribe an antipsychotic selected from paliperidone, perphenazine, thioridazine, chlorpromazine, risperidone and quetiapine for the subject at increased risk of weight gain.

20 9. The method of any one of claims 1-5, wherein the method further comprises a recommendation that the physician prescribe an antipsychotic selected from loxapine, iloperidone, asenapine, lurasidone, ziprasidone, aripiprazole, fluphenazine, and haloperidol for the subject at increased risk of weight gain.

10. The method of any one of claims 1-9, wherein the subject is human.