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(54) Title: METHOD FOR PREDICTING THE THERAPEUTIC RESPONSE TO ANTIPSYCHOTIC DRUGS

(57) Abstract: The present invention discloses a method for predicting, before treatment, the individual clinical response to antipsychotic medication in subjects suffering from psychosis. This method is based on a gene expression profile that is useful to predict the therapeutic response to antipsychotics in drug-naïve patients. Particularly, the gene signature proposed in the invention comprises six-genes (SLC9A3, HMOX1, SLC22A16, LOC284581, PF4V1 and GSTT1) which expression profile, preferably measured in blood samples collected from the patient, provides useful information to predict the clinical response to antipsychotics in psychotic patients, more preferably in schizophrenia patients, before treatment.

METHOD FOR PREDICTING THE THERAPEUTIC RESPONSE TO ANTIPSYCHOTIC DRUGS

This invention falls within the field of prognosis or predicting methods for identifying which patients suffering from a psychotic disorder will benefit from an antipsychotic treatment. Particularly, the invention provides genetic biomarkers or genes which expression levels allow predicting, before the treatment, which patients will show sensitivity and an adequate clinical response to an antipsychotic treatment. The invention relates thus to a method for predicting the clinical response to antipsychotic drugs before treatment in individuals diagnosed with a psychotic disorder, such as schizophrenia.

STATE OF THE ART

Antipsychotic drugs, also termed as tranquilizers or neuroleptics, are the cornerstone to treat psychotic disorders such as schizophrenia. They are also majorly used to treat several other psychotic disorders including bipolar disorder, delirium, dementia and psychotic depression and they can be also used to treat severe depression, personality disorders, autism and anxiety. Therefore, antipsychotic medications are among the most common and costly prescribed drugs with significant increases in overall prescription in recent years.

An adequate treatment at initial stages of the psychotic disorder is crucial to improve the prognosis of this clinical condition. However, only 55–60% of first episode patients will significantly reduce the severity of their psychopathology with adequate doses of antipsychotic drugs (responders) and 30% of patients will fail to respond to at least two antipsychotics after adequate trials.

Despite being one of the largest types of prescribed drugs and having large inter-individual differences in efficacy, no methodology to predict the treatment response in these patients is currently available.

The research to find predictors for the clinical outcome for antipsychotic treatment in schizophrenia is an old field of psychiatry. However, despite a wealth of large studies into prognostic factors, there are no molecular tests available that allow predicting the

clinical response to antipsychotic treatments. An early occurrence of the psychotic disorder and a delay in administering an effective treatment are among the main factors associated to a poor response to the medication in the subject (Marshall M *et al.* Arch. Gen. Psychiatry. 2005 Sep;62(9): 975-83; Crespo-Facorro B *et al.* J. Psychiatr. Res. 2007 Oct;41(8): 659-66). However, characterization of the molecular factors that may be useful for predicting a positive response to the pharmacological treatment is of crucial importance. Being able to determine if the patient will have a favourable response to the antipsychotic treatment before administering the same, would be very helpful in the clinical practice to early select the appropriate treatment for each individual case. This would allow improving the prognosis of the subject. Nevertheless, biomarkers for predicting this clinical response of each single patient to the treatment have not been identified yet.

It is postulated that the variability of several genetic factors could contribute to determine the clinical response to the antipsychotic treatment. Some studies have pointed out to functional mutations present in CYP metabolic enzymes (Ingelman-Sundberg M *et al.* Pharmacogenetics 2000 Feb;10(1): 91-3; Nebert DW *et al.* Pharmacology 2000 Sep;61(3): 124-35) and in genes related to dopaminergic and serotonergic neurotransmission (Zhang JP *et al.* Expert Opin. Drug Metab. Toxicol. 2011 Jan;7(1): 9-37).

On the other hand, in a previous study (Crespo-Facorro, *et al.*, 2015, Int J Neuropsychopharmacol, 18) the blood transcriptome of 22 schizophrenia patients was analyzed before and after medication with atypical antipsychotics and it was found that 17 genes had significantly altered expression after medication.

In another study (Aminollah Bahaoddini, *et al.*, 2009, Journal of Molecular Neuroscience, 38:173) the role of the polymorphism in GSTT1 gene over the QTc interval in patients diagnosed with schizophrenia was determined. It was concluded that, whereas several antipsychotics drugs lengthen the QT interval in a dose-dependent fashion, QTc was reduced in those patients with a positive GSTT1 genotype.

Paolo Gravina, *et al.*, 2011, Psychiatry research, Volume 187, Issue 3, Pages 454–456, described the role of the GSTP1, GSTM1, GSTT1 and GSTA1 genes in the

predisposition to suffer from schizophrenia. Likewise, Milica M. Pejovic-Milovancevic, *et al.,* 2016, Lab Med, 47 (3): 195-204, described the relationship between deletion polymorphisms in GSTM1 y GSTT1 genes and schizophrenia.

Christian Griñan-Ferré, *et al.*, 2016, Experimental Gerontology, Volume 80, Pages 57–69, identified the HMOX1 gene as a depression marker. US2008299125A1 mentions the LOC234581 gene within a list of sequences related to depression and WO2010036969A2 cites, among others, the SLC22A16 gene as a schizophrenia marker.

However, none of the above mentioned documents provides useful molecular markers (biomarkers) that allow predicting the clinical response to antipsychotics drugs in subjects diagnosed with psychosis in a reliable and simple manner, before treatment.

In this context, currently there are no predictive methods that allow the identification of the non-responding patients, making it hard to predict the effectiveness of the therapy prior to the treatment.

The existence of non-responder patients to the antipsychotic treatments makes it necessary to develop predicting methods that can be applied in the clinical practice to identify these patients at an early stage. This approach would help to design effective treatment strategies tailored to each patient.

DESCRIPTION OF THE INVENTION

The present invention discloses a method for predicting, before treatment, the individual clinical response to antipsychotic medication in subjects suffering from (diagnosed with) psychosis. This method of the invention is based on a gene expression profile that is useful to predict the therapeutic response to antipsychotics in drug-naïve patients, *i. e.* in patients diagnosed with a psychotic disorder who have not received antipsychotic medication yet. This method allows therefore the selection of patients for further or alternative antipsychotic therapies. This predicting method of the present invention is useful for the identification, in early stages before the treatment, of those patients that will or will not respond to the antipsychotic drugs, which allow designing specific individual therapeutic strategies for each patient.

Particularly, the inventors have identified six-genes (SLC9A3, HMOX1, SLC22A16, LOC284581, PF4V1 and GSTT1) which expression profile, preferably measured in blood samples collected from the patient, provides useful information to predict the clinical response to antipsychotics in psychotic patients, more preferably in schizophrenia patients, before treatment. The predicting method of the invention is therefore based on the analysis of the expression level of the gene SLC9A3, or its combination with at least one of the genes HMOX1, SLC22A16, LOC284581, PF4V1 and/or GSTT1.

To arrive to the invention, the inventors sequenced total mRNA from biological samples obtained from antipsychotic naive patients (Table 1) that, after 3 months of treatment, were in the top 40% with the best clinical response (15 patients) and in the bottom 40% with the poorer clinical response (15 patients) according to the Brief Psychiatric Rating Scale (Lukoff, *et al.*, 1986, Schizophrenia bulletin, 12, 578-602). The transcriptome before treatment of these 30 patients was characterized using next generation sequencing and 130 genes were found with significant differential expression (Padj value <0.01) between the responders and the poorer responders. Then, Random Forests, an ensemble learning method for classification and regression, was used to obtain a list of predictor genes (Koo, *et al.*, 2013, BioMed research international, 432375).

These predictor genes or new genetic markers identified in the invention showed, before treatment, significantly different expression between those patients that, after the treatment, had a positive response and those patients that had a poorer response to the treatment.

The six-gene expression profile identified with this methodology can predict the clinical response with a cross-validation estimate of accuracy of 0.83 and an area under the curve of 0.96 using a logistic regression. Thus, the method provided in the present invention allows determining the clinical response to antipsychotic drugs before the treatment in a reliable manner. This method is also simple since it can be performed by means of, for instance but without limitation, sequencing and/or immunohistochemical techniques commonly used in medicine and molecular biology. Finally, the method of the invention is non-invasive, as it can be performed on isolated biological samples obtained from the patients through non-invasive techniques, such as blood extraction.

Another advantage of this method is that in the proposed six-gene signature each individual gene has high predictive power (based on the Gini value). Thus, the expression level of each single gene provides useful information to predict the clinical response. The preferred gene for the prediction with a single biomarker is the SLC9A3 gene, since it shows the highest Gini value (see Table 6) and therefore the highest predictive capacity. The combination of this SLC9A3 gene with the other five genes also identified in this invention as biomarkers, HMOX1, SLC22A16, LOC284581, PF4V1 and GSTT1, improves the prediction value of the gene expression signature proposed herein.

Additionally, as mentioned before, these six predictor genes identified in this invention have, before treatment, significantly altered expression in those patients that after the treatment have a positive response compared to the expression before treatment in those patients that after the treatment have a poorer response. For this reason, this six-gene signature is useful to predict the therapeutic response to antipsychotic drugs. However, this significantly differential expression before treatment between responders and non-responders further evidences that these six genes must be direct or indirect targets for the antipsychotic drugs action. Thus, this invention also provides a method for the screening of compounds, molecules or compositions useful for the treatment of a psychotic disorder based on the measurement of the expression levels of the SLC9A3 gene or its combination with any of HMOX1, SLC22A16, LOC284581, PF4V1 and/or GSTT1 genes, before and after the treatment. This screening method will help, not only to discover and identify those drugs useful for the treatment of psychotic disorders but also, given that these genes are associated to the symptoms improved by the antipsychotics, could be used as targets to improve the existing drugs or to generate new drugs for the psychotic symptoms and, in turns, to select the specific antipsychotics that will produce the best clinical response for each specific patient.

Therefore, a first aspect of the invention refers to the use of the expression level value of the SLC9A3 gene in an isolated biological sample as a biomarker in an *in vitro* method for predicting the therapeutic response to antipsychotic drugs in a subject suffering from (who has been diagnosed with) a psychotic disorder or as a biomarker in an *in vitro* method for the screening or identification of compounds, molecules or compositions useful for the treatment of a psychotic disorder.

"Predicting the therapeutic response", as used in this invention, refers to determining, before administering the treatment, whether the antipsychotic treatment will have a favourable, positive or adequate response in the subject once treated (after administering the treatment). A "positive response" to an antipsychotic treatment or an antipsychotic drug occurs when an improvement or a reduction in the symptoms of the psychotic disorder is observed in the patient. The expression "positive response to the treatment with antipsychotic drugs" means a favourable response to the treatment that can be recognized when a significant reduction, for instance 40% reduction, in the symptoms of the psychotic disorder is observed in the patient according to the *Brief Phsychiatric Rating Scale* (BPRS) (Overall, JE y Gorham, DR (1962) *The Brief Psychiatric Rating Scale. Psychol Rep* 10: 799-812).

The term "*in vitro*" means that the methods of the invention are fully performed outside of the human or animal body.

The term "subject", "individual" or "patient", as used in the present invention, refers to a human or a non-human mammal, such as rodents, ruminants, cats or dogs. In a preferred embodiment, the subject is a human.

The expression levels of the genes indicated in the present invention may be previously normalized.

The "SLC9A3 gene" is the gene known by its identification number 6550 (*Gene ID NCBI*) (Solute carrier family 9 member A3).

In a preferred embodiment of the first aspect of the invention, the use further comprises the expression level of the HMOX1 gene.

The "HMOX1 gene" is the gene known by its identification number 3162 (*Gene ID NCBI*) (Heme oxygenase 1).

In a more preferred embodiment of the first aspect of the invention, the use further comprises the expression level of the SLC22A16 gene.

The "SLC22A16 gene" is the gene known by its identification number 85413 (*Gene ID NCBI*) (Solute carrier family 22 member 16).
In an even more preferred embodiment of the first aspect of the invention, the use further comprises the expression level of the LOC284581 gene.

The "LOC284581 gene" is the gene known by its identification number 284581 (*Gene ID NCBI*).

In an even more preferred embodiment of the first aspect of the invention, the use further comprises the expression level of the PF4V1 gene.

The "PF4V1 gene" is the gene known by its identification number 5197 (*Gene ID NCBI*) (Platelet factor 4 variant 1).

In an even more preferred embodiment of the first aspect of the invention, the use further comprises the expression level of the GSTT1 gene.

The "GSTT1 gene" is the gene known by its identification number 2952 (*Gene ID NCBI*) (Glutathione S-transferase theta 1).

In a particular embodiment of this aspect of the invention, the genes which expression levels are used as a biomarker in an *in vitro* method for predicting the therapeutic response to antipsychotic drugs in a subject suffering from a psychotic disorder or for the screening of compounds, molecules or compositions useful for the treatment of a psychotic disorder are SLC9A3, HMOX1, SLC22A16, LOC284581, PF4V1 and GSTT1.

A "psychotic disorder" is a group of severe mental disorders that cause abnormal thinking and perceptions. Psychotic disorders are a psychopathological condition in which symptoms such as delusions, hallucinations, delirium and altered behaviour are present. Subjects suffering from psychotic disorders have a disturbed reality perception.

In another preferred embodiment of the first aspect of the invention, the psychotic disorder is selected from the list consisting of: schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder, delusional disorder, delirium,

dementia and/or behavioral disorders. More preferably, the psychotic disorder is schizophrenia or bipolar disorder. Even more preferably, the psychotic disorder is schizophrenia.

"Schizophrenia" is the brain illness that course with the criteria indicated in Psychiatry American Society DSM-IV for schizophrenia, schizophreniform disorder, schizoaffective disorder or brief psychotic disorder. It is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves. Symptoms of schizophrenia usually start between ages 16 and 30. The symptoms of schizophrenia fall into three categories: positive, negative, and cognitive. "Positive" symptoms are psychotic behaviors not generally seen in healthy people. People with positive symptoms may "lose touch" with some aspects of reality. Positive symptoms include: hallucinations, delusions, thought disorders (unusual or dysfunctional ways of thinking) or movement disorders (agitated body movements). "Negative" symptoms are associated with disruptions to normal emotions and behaviors. Negative symptoms include: "Flat affect" (reduced expression of emotions via facial expression or voice tone), reduced feelings of pleasure in everyday life, difficulty beginning and sustaining activities or reduced speaking. Regarding the "cognitive" symptoms, for some patients, the cognitive symptoms of schizophrenia are subtle, but for others, they are more severe and patients may notice changes in their memory or other aspects of thinking. Cognitive symptoms include: poor "executive functioning" (the ability to understand information and use it to make decisions), trouble focusing or paying attention or problems with "working memory" (the ability to use information immediately after learning it). It is considered that a subject suffers from schizophrenia when these symptoms last at least six months.

In another preferred embodiment of the first aspect of the invention, the subject suffering from a psychotic disorder is a first-episode psychosis patient.

A "first-episode psychosis patient" is a subject who has only experienced his first episode of psychosis and who does not present affective psychosis. A first episode of psychosis is the first time a person experiences a psychotic episode.

"Antipsychotic drugs", "antipsychotic treatment" or "antipsychotic medication" is understood as the medication or actions known by the skilled in the art taken in order to

palliate, reduce, cure, mitigate, eliminate or the like, a psychotic disorder or episode. Preferably, the antipsychotic drug as used in the present invention is selected from the list consisting of: aripiprazole (Abilify®), risperidone (Risperdal®), olanzapine (Zyprexa®), paliperidone (Invega®), chlorpromazine (Largactil®, Thorapine®), clozapine (Clorazil®), quetiapine (Seroquel®), ziprasidone (Geodon®), asenapine, iloperidone (Zomaril®), zotepine, amisulpride (Solian@), fluphenazine (Prolixin®), haloperidol (Aldol®, Serenace®), loxapine (Loxapac®, Loxitane®), perphenazine, pimozide (Orap®), zuclopenthixol (Clopixol®), or any combination thereof. More preferably, the antipsychotic drug referred to in the present invention is selected from aripiprazole, risperidone, olanzapine, paliperidone and/or clozapine.

The term "expression level", as used in the present invention, refers to the expression level of any genetic expression product of the genes SLC9A3, HMOX1, SLC22A16, LOC284581, PF4V1 and GSTT1.

In another preferred embodiment of the first aspect of the invention, the expression levels are RNA and/or protein. The RNA may be mRNA or microRNA, preferably mRNA.

Another aspect of the invention refers to a method for obtaining information or data useful for predicting the therapeutic response to antipsychotic drugs in a subject suffering from a psychotic disorder, comprising measuring the expression level of the SLC9A3 gene in an isolated biological sample collected from the subject suffering from a psychotic disorder before the treatment with antipsychotic drugs, and comparing this expression level value obtained with an standard value. Preferably, this method further comprises measuring the expression level of at least one of the genes of the list consisting of HMOX1, SLC22A16, LOC284581, PF4V1 or GSTT1, in the isolated biological sample. More preferably, this method comprises measuring the expression level of the SLC9A3, HMOX1, SLC22A16, LOC284581, PF4V1 and GSTT1 genes, in the isolated biological sample.

Another aspect of the invention refers to an *in vitro* method for predicting the therapeutic response to antipsychotic drugs in a subject suffering from (who has been diagnosed with) a psychotic disorder, comprising the following steps:

a) measuring the expression level of the SLC9A3 gene in an isolated biological sample collected from the subject suffering from a psychotic disorder before the treatment with antipsychotic drugs,
b) comparing the expression level value obtained after step (a) with an standard value, and
c) assigning the subject of step (a) to the group of patients that will positively respond to the treatment with antipsychotic drugs when the expression level value obtained after step (a) is lower than the standard value,

wherein the standard value is the mean value obtained after measuring the expression level of the SLC9A3 gene in isolated biological samples collected from a group of subjects suffering from a psychotic disorder who have not been treated with antipsychotic drugs. This method will be also referred to as "the first method of the invention".

As used herein, the expression "before the treatment with antipsychotic drugs" or "subjects who have not been treated with antipsychotic drugs" means that the subject has not received prior treatment with antipsychotic medication. These subjects will be also called "antipsychotic drug-naïve patients".

The expression level of the genes indicated in this invention may, for example, be measured directly by assessing the protein levels soluble in the samples. For instance, these protein levels can be measured by immunohistochemistry, Western blot, ELISA, lateral flow devices or Luminex®. In another preferred embodiment, the mRNA expression levels can be measured instead. For example, mRNA expression levels can be measured by RT-PCR, Northern blot or array hybridization.

Thus, in a preferred embodiment of the first method of the invention, the expression levels are RNA and/or protein. The RNA may be mRNA or microRNA, preferably mRNA.

The measurement of the expression levels in the present invention refers to the measurement of the quantity or concentration. This measurement may be performed as a direct or an indirect measurement. The direct measurement refers to the measurement of the quantity or concentration of the expression levels based on a

signal directly obtained from the expression of the genes to be assessed. This signal is directly correlated with the number of product molecules present in the sample. This signal, also referred to as "intensity signal", may be obtained for instance by measuring an intensity value derived from a physical or chemical property of the product. The indirect measurement refers to the measurement obtained from a secondary component (for example, a component which is different from the gene products) or a measurement derived from, for example, cellular responses, ligands, tags or enzymatic reaction products associated to these molecules or their activities.

In a preferred embodiment of the first method of the invention, mRNA levels are measured. mRNA extractions protocols are well known for those skilled in the art. This measurement may be performed, but without limitation, by sequencing, amplification with the polymerase chain reaction (PCR), retrotranscription combined with ligase chain reaction (RTLCR), retrotranscription combined with PCR (RT-PCR), retrotranscription combined with quantitative PCR (qRT-PCR), SAGE or any other method for the amplification of nucleic acids; microarrays made with oligonucleotides deposited by any technique, microarrays made with *in situ* synthesized oligonucleotides, *in situ* hybridization using specific labeled probes, electrophoresis gels, membrane transfer and hybridization with a specific probe, RMN or any other image diagnosis technique using paramagnetic nanoparticles or other type of functionalized nanoparticles.

The term "microarray" (or "chip") refers to a solid support to which RNA or protein is bound being thus useful for the gene expression analysis through label and/or antibody hybridization.

The term "SAGE" refers to the detection and quantification of the gene expression by means of the RNA measurement. In the present invention SAGE variants may be used, such as *SuperSAGE*, *MicroSAGE* or *LongSAGE.*

Protein levels may also be measured in the present invention. This measurement may be performed, but without limitation, by incubation with a specific antibody against the protein or a fragment thereof in assays such as Western blot, electrophoresis gels, immunoprecipitation assays, protein arrays preferably antibodies based microarrays, immunofluorescence, immunohistochemistry, ELISA or any other enzymatic method,

by incubation with a specific ligand, RMN or any other image diagnosis technique or by chromatographic techniques preferably combined with mass spectrometry. Protein levels measurement may be performed by the specific recognition of any protein fragment by means of probes and/or antibodies. Proteins or fragments thereof may be quantified by electrophoresis and/or immunoassays. For the immunoassay the antibodies used may be labeled with, for instance, an enzyme, radioisotopes, magnetic tags or fluorescence.

The term "isolated biological sample" refers, but without limitations, to any biological tissue and/or fluid collected from a subject. Biological samples may be obtained by means of any method known by those skilled in the art. Preferably, the biological sample referred to in the present invention is a biological fluid, for instance, blood, plasma, serum, lymph, saliva, urine, tears, synovial fluid or the like. In another preferred embodiment, the biological sample in the present invention is blood, more preferably peripheral blood. The biological sample comprises RNA and/or protein, preferably mRNA. The biological sample may be fresh, frozen, fixed or fixed and paraffin-embedded.

In another preferred embodiment, the first method of the invention further comprises: measuring in step (a) the expression level of the HMOX1 gene, comparing in step (b) this expression level value with an standard value, and assigning in step (c) the subject to the group of patients that will positively respond to the treatment with antipsychotic drugs when this expression level value obtained after step (a) is higher than the standard value, wherein this standard value is the mean value obtained after measuring the expression level of the HMOX1 gene in isolated biological samples collected from a group of subjects suffering from a psychotic disorder who have not been treated with antipsychotic drugs.

In another preferred embodiment, the first method of the invention further comprises: measuring in step (a) the expression level of the SLC22A16 gene, comparing in step (b) this expression level value with an standard value, and assigning in step (c) the subject to the group of patients that will positively respond to the treatment with antipsychotic drugs when this expression level value obtained after step (a) is higher than the standard value, wherein this standard value is the mean value obtained after measuring the expression level of the SLC22A16 gene in isolated biological samples

collected from a group of subjects suffering from a psychotic disorder who have not been treated with antipsychotic drugs.

In another preferred embodiment, the first method of the invention further comprises: measuring in step (a) the expression level of the LOC284581 gene, comparing in step (b) this expression level value with an standard value, and assigning in step (c) the subject to the group of patients that will positively respond to the treatment with antipsychotic drugs when this expression level value obtained after step (a) is lower than the standard value, wherein this standard value is the mean value obtained after measuring the expression level of the LOC284581 gene in isolated biological samples collected from a group of subjects suffering from a psychotic disorder who have not been treated with antipsychotic drugs.

In another preferred embodiment, the first method of the invention further comprises: measuring in step (a) the expression level of the PF4V1 gene, comparing in step (b) this expression level value with an standard value, and assigning in step (c) the subject to the group of patients that will positively respond to the treatment with antipsychotic drugs when this expression level value obtained after step (a) is higher than the standard value, wherein this standard value is the mean value obtained after measuring the expression level of the PF4V1 gene in isolated biological samples collected from a group of subjects suffering from a psychotic disorder who have not been treated with antipsychotic drugs.

In another preferred embodiment, the first method of the invention further comprises: measuring in step (a) the expression level of the GSTT1 gene, comparing in step (b) this expression level value with an standard value, and assigning in step (c) the subject to the group of patients that will positively respond to the treatment with antipsychotic drugs when this expression level value obtained after step (a) is lower than the standard value, wherein this standard value is the mean value obtained after measuring the expression level of the GSTT1 gene in isolated biological samples collected from a group of subjects suffering from a psychotic disorder who have not been treated with antipsychotic drugs.

In the most preferred embodiment of the first method of the invention, said method comprises measuring in step (a) the expression levels of the SLC9A3, HMOX1, SLC22A16, LOC284581, PF4V1 and GSTT1 genes.

As used herein, the term "mean value" refers to the arithmetic mean of the gene expression level value considering every member of the sample population or group. The mean gene expression level of the sample population or group is equal to the sum of the gene expression levels of every individual divided by the total number of individuals in the sample group. Preferably, the "group of subjects suffering from a psychotic disorder who have not been treated with antipsychotic drugs" from which the mean value is obtained comprises at least 15, more preferably at least 30 individuals, and includes individuals of both conditions responders and non-responders to antipsychotic drugs once this medication is administered.

In a more preferred embodiment, the mean value for the SLC9A3 gene is 564, the mean value for the HMOX1 gene is 2923, the mean value for the SLC22A16 gene is 101, the mean value for the LOC284581 gene is 149, the mean value for the PF4V1 gene is 153 and the mean value for the GSTT1 gene is 158.

The terms "lower" and "higher" than the standard value, as used in the present invention, means that the value obtained after step (a) of the method of the invention is significantly lower or significantly higher than the standard value. The signification level may be calculated by statistical methods well known by those skilled in the art, such as confidence intervals, p-value, Student test or Fisher discriminant analysis.

Steps (a) and (b) of the first method of the invention may be total or partially computerized. Furthermore, the first method of the invention may comprise other additional steps, for example, related to the pre-treatment of the biological samples prior to the analysis.

In another preferred embodiment of the first method of the invention, the psychotic disorder is selected from the list consisting of: schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder, delusional disorder, delirium, dementia and/or behavioral disorders. More preferably, the psychotic disorder is

schizophrenia or bipolar disorder. Even more preferably, the psychotic disorder is schizophrenia.

In another preferred embodiment of the first method of the invention, the subject suffering from a psychotic disorder is a first-episode psychosis patient.

In another preferred embodiment of the first method of the invention, the antipsychotic drug is selected from the list consisting of: aripiprazole (Abilify®), risperidone (Risperdal®), olanzapine (Zyprexa®), paliperidone (Invega®), chlorpromazine (Largactil®, Thorapine®), clozapine (Clorazil®), quetiapine (Seroquel®), ziprasidone (Geodon®), asenapine, iloperidone (Zomaril®), zotepine, amisulpride (Solian@), fluphenazine (Prolixin®), haloperidol (Aldol®, Serenace®), loxapine (Loxapac®, Loxitane®), perphenazine, pimozide (Orap®), zuclopenthixol (Clopixol®), or any combination thereof. More preferably, the antipsychotic drug referred to in the first method of the invention is selected from aripiprazole, risperidone, olanzapine, paliperidone and/or clozapine.

Another aspect of the present invention refers to an *in vitro* method for the screening or identification of compounds, molecules or compositions useful for the treatment of a psychotic disorder that comprises: i) measuring the expression level of at least one gene of those included in Table 4 of the present invention or of the SLC9A3 gene in an isolated biological sample obtained from a subject suffering from a psychotic disorder before the administration of the compound, molecule or composition to be tested, ii) measuring the expression level of the same gene/s as that measured in step (i) in an isolated biological sample obtained from the same subject after the administration of the compound, molecule or composition to be tested, (iii) comparing the expression level values obtained in (i) and (ii), and (iv) classifying the compound, molecule or composition as useful for the treatment of a psychotic disorder when a significant difference in the expression level values has been detected in step (iii). This method will be also referred to as "the second method of the invention" and allows the discovery and identification of new drugs useful for the treatment of psychotic disorders as well as the improvement of the existing drugs in terms of, for instance, administering route, dosage regime, etc. This method also allows the selection of the specific antipsychotic drug that will produce the best clinical response for each specific patient.

This method represents thus a tool to select the antipsychotic that is expected to provide the best response.

In a preferred embodiment of the second method of the invention, said method further comprises measuring in step (i) the expression level of at least one gene selected from the list consisting of: HMOX1, SLC22A16, LOC284581, PF4V1 and/or GSTT1. More preferably, this second method comprises measuring in step (i) the expression level of the following genes: SLC9A3, HMOX1, SLC22A16, LOC284581, PF4V1 and GSTT1.

In another preferred embodiment of the second method of the invention, the psychotic disorder is selected from the list consisting of: schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder, delusional disorder, delirium, dementia and/or behavioral disorders. More preferably, the psychotic disorder is schizophrenia.

In another preferred embodiment of the second method of the invention, the expression levels are RNA and/or protein, preferably mRNA.

In another preferred embodiment of the second method of the invention, the isolated biological sample is peripheral blood.

Another aspect of the present invention refers to a kit comprising compounds capable of specifically binding SLC9A3 gene or its expression products. This kit comprises all those necessary elements for predicting the therapeutic response to antipsychotic drugs in a subject suffering from a psychotic disorder according to the first method of the invention or for the screening of compounds, molecules or compositions useful for the treatment of a psychotic disorder according to the second method of the invention. That is, this kit comprises all the elements needed for measuring the gene expression levels as explained before. Hereinafter this kit will be referred to as the “kit of the invention”.

In a preferred embodiment of this aspect of the invention, the kit further comprises compounds capable of specifically binding HMOX1, SLC22A16, LOC284581, PF4V1 and/or GSTT1 genes or their expression products.

In a more preferred embodiment of this aspect of the invention, the compounds comprised in the kit are labels, antibodies and/or primers, preferably primers capable of detecting and amplyfing the genes indicated in this invention or fragments thereof.

In the most preferred embodiment, the kit of the invention consists of labels, antibodies and/or primers capable of specifically binding SLC9A3, HMOX1, SLC22A16, LOC284581, PF4V1 and GSTT1 genes or their expression products.

The term "primer" refers to a nucleic acid sequence capable of acting as the starting point for the DNA synthesis when it hybridizes with the template nucleic acid. Preferably, the primer is a deoxyribose primer. Primers may be designed for instance by direct chemical synthesis. Primers may be designed to hybridize with specific sequences within the genes indicated in this invention (specific primers) or they may be randomly synthetized (arbitrary primers).

Furthermore, primers comprised in the kit of the invention may be labeled with detectable tags, such as radioactive isotopes, fluorescence tags, chemiluminescent or bioluminescent tags or enzymatic tags.

In another preferred embodiment, at least one of the antibodies comprised in the kit of the invention is labeled or immobilized. The antibody may be labeled with, for example, a tag selected from the list consisting of a radioisotope (such as 32P, 35S or 3H), a fluorescent or luminescent marker (such as fluorescein (FITC), rhodamine, *texas red*, ficoeritrine (PE), aloficocianine, 6-carboxyfluorescein (6-FAM), 2',7'-dimetoxi-4',5'-dichlore-6-carboxyfluorescein (JOE), 6-carboxy-X-rhodamine (ROX), 6-carboxy-2',4',7',4,7-hexachlorefluorescein (HEX), 5-carboxyfluorescein (5-FAM) o N,N,N',N'-tetramethyl-6-carboxyrhodamine (TAMRA)), a secondary antibody, an antibody fragment (such as F(ab)2), an affinity tag (such as biotin, avidin, agarose, BMP, haptens), an enzyme or a substrate of an enzyme (such as alkaline phosphatase (AP) and HRP) and the like. The antibody may be immobilized without losing its activity in, for example, a matrix (preferably a nylon or latex matrix), a microtiter plate or a similar plastic support, beads, glass support, gel, cellulosic support, adsorption resin, or the like.

The kit of the invention comprises all those reactives needed to perform the methods of the invention. Thus, the kit may further comprise elements such as buffers, enzymes, such as polymerases, cofactors needed to obtain an optimal activity of said enzymes, etc. The kit may comprise all those supports and recipients needed for the implementation of the methods of the invention. Finally, the kit may comprise other molecules, genes, proteins or probes suitable as positive or negative controls. Preferably, the kit of the invention further comprises instructions explaining how to perform the methods of the invention.

Another aspect of the invention refers to the use of the kit of the invention for predicting the therapeutic response to antipsychotic drugs in a subject suffering from a psychotic disorder or for the screening of compounds, molecules or compositions useful for the treatment of a psychotic disorder, preferably for performing the first or the second method of the invention.

Another aspect of the present invention refers to a method of treating a subject suffering from a psychotic disorder comprising: selecting a subject as responding or non-responding to the antipsychotic treatment in accordance with the first method of the invention; and administering an antipsychotic therapy to the patient. In a preferred embodiment of this aspect of the invention, the antipsychotic therapy is an antipsychotic drug as those defined herein, psychosocial treatment, coordinated specialty care (CSC), or any other antipsychotic treatment of those known in the art.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skilled in the art to which this invention belongs. Methods and materials similar or equivalent to those described herein can be used in the practice of the present invention. Throughout the description and claims the word "comprise" and its variations are not intended to exclude other technical features, additives, components, or steps. Additional objects, advantages and features of the invention will become apparent to those skilled in the art upon examination of the description or may be learned by practice of the invention. The following examples and drawings are provided by way of illustration and are not intended to be limiting of the present invention.

DESCRIPTION OF THE DRAWINGS

FIG. 1. Variable Importance (Gini) for the top 30 predictor genes. Gini variable importance measures reflect the mean decrease in impurity by splits of a given variable in the classification tree, weighted by the proportion of samples reaching that node. A greater "mean decrease Gini" indicates that the gene plays a greater role in partitioning the data into the defined classes.

FIG. 2. Receiver operating characteristic (ROC) curves. a) Using the best two genes (SCL9A3, HMOX1) for training the predictor it was obtain a ROC with an area under the curve (AUC) of 0.92. b) Using the best three genes (SCL9A3, HMOX1, SLC22A16) for training the predictor it was obtain a ROC with an AUC of 0.96. c) Using the best four genes (SCL9A3, HMOX1, SLC22A16, LOC284581) for training the predictor it was obtain a ROC with an AUC of 0.97.

FIG. 3. Predicted probability of response to antipsychotics. Scatter plot which represent the predicted probability of response (y-axis) for each input sample (x-axis) in the logistic regression predictor. Grey points represent no responder patients and black points represent responder patients.

EXAMPLES

With the goal of generating an expression profile that could predict the clinical outcome of treatment, the transcriptome of a drug-naïve cohort (before antipsychotic medication was initiated) of first episode schizophrenia patients was characterized. Patients were then divided into two groups according to their clinical response to antipsychotics after 3 months of treatment according to the Brief Psychiatric Rating Scale (BPRS) (Lukoff, D., *et al.*, 1986, Schizophrenia bulletin, 12, 578-602) that measure the positive, negative, and affective symptoms of individuals who have schizophrenia: one group including the top 40% patients that had the best response to treatment (highest absolute decrease of BPRS score) that were named "responders", and other group including the bottom 40% patients with the worst response (lower absolute decrease of BPRS score) that were named "no responders". The transcriptome of both groups were compared using the program Deseq (Anders, S. & Huber, W., 2010, Genome biology, 11, R106) to define the genes with significant differential expression. 130 genes with significant differential expression between both groups (Padj value <0.01) were found (Table 2). These genes were significantly enriched for schizophrenia related genes

according to the scientific literature in the Gene Reference into Function (GeneRIF) database that provides functional and morbid annotation of genes. 14 schizophrenia differential expression genes between responders and no responders were found (13.4% observed versus 6.8% expected; Fisher P value = 0.016). This data may suggest that the response to treatment could be due, at least partially, to the fact that the two groups of patients analyzed have different genetic background causing schizophrenia.

Furthermore, it was also analyzed the GeneRIF annotations for genes involved in drug processing (using the string "drug" combined with one of the strings "response", "toxicity", "resistance", "metabol" or "sensitivity") and it was found a significant enrichment of these type of genes among the 130 genes (11 out of the 104 annotated genes or 10,6% when we expect 4,5%; Fisher Pvalue = 0.0007). These data suggest that the response to antipsychotics could also depend of the expression profile of genes that process the drugs.

Thus, we hypothesize that the lack of response could be due to two different reasons, a different set of genes causative of schizophrenia for the responders compared to the no responders, and a different expression profile of genes related to drug metabolism and drug response. The enrichment of schizophrenia genes and in drug processing genes among the differential expression genes supports both hypotheses: the poorer clinical response might be due to different causative genes of schizophrenia and to different expression profiles in genes related to drug processing.

To obtain more information, we also sequenced the transcriptome of the patients after 3 months of treatment with antipsychotics. We defined 219 differential expression genes between responders and no responders after 3 months of medication (Table 3); these genes are also enriched significantly for schizophrenia (21 genes or 11.3% versus 6.8%; Fisher P value = 0.027). After 3 months of medication with antipsychotics, six out of the 14 schizophrenia-annotated genes with differential expression before medication between responders and no responders have no longer differential expression. These six genes are excellent candidates to be the targets used by the drugs to improve the symptoms of the responders: VWF, a glycoprotein with levels increased in plasma of not medicated patients and in bipolar disorder and schizophrenia compared to control individuals; UGT1A1, a gene with promoter

variations in patients with schizophrenia that result in lower serum bilirubin levels; HMOX1, an enzyme that has anti-inflammatory properties and mediates the first step of heme catabolism, is over-expressed in transgenic mice with schizophrenia-like features; IL8 (known also as CXCL8), a chemokine with altered expression in the dorsolateral prefrontal cortex of individuals with schizophrenia; NTNG2, a gene with haplotypes associated with schizophrenia and isoform expression significantly different between schizophrenic and control brains; and PTGDS, a prostaglandin that acts as neuromodulator as well as a trophic factor in the central nervous system and was studied as schizophrenia candidate and with reduced mRNA expression in peripheral blood of bipolar disorder patients compared with healthy control subjects. The differential expression genes between responders and non-responders after 3 months of medication indicates that 5 out the 11 genes involved in “drug processing” with differential expression before medication still have differential expression and similar expression profile after medication. These 5 genes are: GSTM1, a glutathione S-transferase involved in detoxification of electrophilic compounds, such as therapeutic drugs, by conjugation with glutathione, with genetic variations that affect the toxicity and efficacy of certain drugs; THBS1, an adhesive glycoprotein that mediates cell-to-cell and cell-to-matrix interactions and related to drug resistance; PRAME, an antigen related to cytotoxic drug sensitivity; GSTT1, a glutathione S-transferase that functions as a drug metabolizing enzyme; and SLC22A16, a solute carrier reported to be involved in response to drugs. These genes could be good candidates to be involved in the different clinical response of both groups of patients.

We also compared the transcriptome of the responders before and after medication and characterized 176 genes with differential expression (Table 4). These genes were also enriched for schizophrenia annotations (9.4% observed versus 6.7% expected). When we defined the differential expression genes of the worst responders, before and after medication, we found only 23 genes (Table 5) and they were not enriched for schizophrenia annotations (5.2% versus 6.7%). This data indicates that the individuals that respond worst to treatment have much fewer genes (a 7.6 fold decrease) altered in their expression by antipsychotics than the good responders. This also indicates that the genes altered in the no responders are less associated to schizophrenia that the ones altered in the responders. The previous data suggest that the efficacy of antipsychotics is dependent of the expression profile of the patient before medication

and that a predictor could be generated using a gene expression profile of untreated patients.

To generate a predictor test of response to antipsychotics before medication, we analyzed all 130 genes with significantly different expression between the responders and no responders using Random Forests, an ensemble learning method for classification, regression, among other tasks, that operate by constructing a multitude of decision trees (Koo, *et al.*, 2013, BioMed research international, 432375). Functional analyses of the 30 genes with the highest predictive power (Fig. 1; Table 6) indicated a significant enrichment of genes related to schizophrenia (29.2% observed versus 6.9% expected; Fisher P value = 0.0009) and bipolar disorder (16.7% versus 2.6%; Fisher P value = 0.003). In the complete list of 130 genes, the enrichment for schizophrenia genes was smaller (13.4%) indicating that genes related to schizophrenia tend to have a higher predictive value. This would suggest that schizophrenia genes are involved in the response and that the schizophrenia causative genes tend to be different between responders and no responders.

Using logistic regression we defined the area under the curve (AUC), representing the combined predictive power of the genes, and a cross-validation estimate of accuracy for the prediction using the first 2, 3 and 4 genes. We obtained that the prediction using two genes (SLC9A3 and HMOX1) had an area under the curve of 0.92 and a cross-validation estimate of accuracy of 0.73; with three genes (adding SLC22A16) the values were 0.96 and 0.833 respectively (Fig. 2); and with 4 genes (adding LOC284581) were 0.97 and 0.833 respectively. This data indicates that test with the three most predictive genes seems to be an appropriated choice. We tested the predictive power of the 3-gene predictor in our patients, and we found that the test would predict accurately 100% of the non-responders and 87% of the responders (Fig. 3). The gene with the highest predictive value, SLC9A3, is a Na/H exchanger and belongs to several pathways involved in transmembrane transportation of small molecules. The second best predictor is HMOX1, an essential enzyme in heme catabolism that is involved in the production of carbon monoxide, a putative neurotransmitter, belongs to a pathway for transmembrane transport of small molecules, and has been related to schizophrenia and to drug resistance in acute myeloid leukemia. The third predictor, SLC22A16, encodes a protein that been shown to be involved in the transport and response to anticancer drugs like bleomycin or

others and is located within a schizophrenia susceptibility locus in chromosome 6q. The fourth gene, LOC284581, is not annotated but locates within a Parkinson disease locus of 15.8 Mb.

This data have allowed generating a simple test (expression level of at least 1 gene) to predict the response to antipsychotics, one of the most prescribed type of drugs worldwide, and provide a tool to select the antipsychotic that is expected to provide the best response.

Methods

Study setting and subjects

The cohort analyzed in this study (Table 1) was obtained from an ongoing epidemiological and three-year longitudinal intervention program of first-episode psychosis (PAFIP) conducted at the outpatient clinic and the inpatient unit at the University Hospital Marques de Valdecilla, Cantabria, Spain. Conforming to international standards for research ethics, the research in this study was approved by the Cantabria Ethics Institutional Review Board (IRB). Patients meeting inclusion criteria and their families provided written informed consent to be included in the PAFIP. The biological samples of patients included in the study were provided by the Valdecilla biobank.

All referrals to PAFIP were screened for patients who met the following criteria: 1) 15-60 years; 2) living in the catchment area (Cantabria); 3) experiencing their first episode of psychosis; 4) no prior treatment with antipsychotic medication; 5) DSM-IV criteria for schizophrenia, schizophreniform disorder, schizoaffective disorder, or brief psychotic disorder. Patients were excluded for any of the following reasons: 1) meeting DSM-IV criteria for drug dependence, 2) meeting DSM-IV criteria for mental retardation, 3) having a history of neurological disease or head injury. The diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (SCID –I) carried out by an experienced psychiatrist 6 months on from the baseline visit. Our operational definition for a “first episode of psychosis” included individuals with a non-affective psychosis (meeting the inclusion criteria defined above) who have not received previously antipsychotic treatment regardless the duration of psychosis. 37 individuals who gave

written consent to their participation in the program, fulfilled inclusion criteria at 6 months and had mRNA samples at baseline and at 3 months were included in the analyses.

Premorbid and sociodemographic variables

Premorbid and sociodemographic information was recorded from patients (Table 1), relatives and medical records. Age of onset of psychosis was defined as the age when the emergence of the first continuous (present most of the time) psychotic symptom occurred. Duration of untreated illness (DUI) was defined as the time from the first unspecific symptoms related to psychosis (for such a symptom to be considered, there should be no return to previous stable level of functioning) to initiation of adequate antipsychotic drug treatment.

Sample and study design

Premorbid and sociodemographic information was recorded from patients (Table 1), relatives and medical records. After informed consent was signed, patients were included in a prospective, randomized, flexible-dose, open-label study. We used a simple randomization procedure. At study intake, all patients were antipsychotic naïve and were randomized to aripiprazole (N=17), risperidone (N=20). Initial dose ranges were 5–10 mg/day of aripiprazole and 1-2 mg/day of risperidone. Rapid titration schedule (5-day), until optimal dose was reached, was as a rule used unless severe side effects occur. At the treating physician´s discretion, the dose and type of antipsychotic medication could be changed based on clinical efficacy and the profile of side effects during the follow-up period. Antimuscarinic medication, lormetazepam and clonazepam were permitted for clinical reasons. No antimuscarinic agents were administered prophylactically. At 3-month follow-up patients were on: Aripiprazole (N=12), Risperidone (N=16), Olanzapine (N=8), Paliperidona (N=1). Mean daily dose of antipsychotics at baseline was 189.19 (51.55) mg/day chlorpormazine (CPZ) equivalent doses. Mean daily dose of antipsychotics at 3 months was 361.43 (179.50) mg/day CPZ equivalent doses.

Clinical assessment.

The severity scale of the Clinical Global Impression (CGI) scale, the Brief Psychiatric Rating Scale (BPRS) (expanded version of 24 items), the Scale for the Assessment of Positive symptoms (SAPS), the Scale for the Assessment of Negative symptoms (SANS), the Calgary Depression Scale for Schizophrenia (CDSS) and the Young Mania Rating Scale (YMRS) were used to evaluate clinical symptomatology. The same trained psychiatrist (BC-F) completed all clinical assessments. The analysis of clinical efficacy reveals that there was a significant improvement of general psychopathology (assessed by BPRS total score changes at 3 months) and positive symptoms (hallucinations, delusions, positive formal thought disorders, bizarre behavior) (assessed by SAPS total score changes at 3 months).

Laboratory assessments

Blood samples were assessed for biochemical and hematological parameters. To minimize the effects of diet and technique, blood samples were obtained from fasting subjects from 8:00 to 10:00 a.m. by the same personnel, in the same setting. No patient had a chronic inflammation or infection, or was taking medication that may apparently influence the results of blood tests.

RNA extraction

Total RNA was extracted from blood using the Tempus™ Blood RNA Tube and Tempus™ Spin RNA Isolation Kit (Applied Biosystems, Foster City, CA, USA) using the manufacturer protocols. To define expression profiles, a key factor is that the RNA is intact. To select only RNA with good quality, the RNA Integrity Number (RIN) was characterized with a Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA) and samples with a RIN of at least 7.2 were selected. The selected samples have RINs that range from 8 to 10 with an average of 9.11. RNA Next Generation Sequencing.

Total RNA was extracted from peripheral blood of each individual. The mRNA obtained from blood was sequenced at the Centro Nacional de Análisis Genómico (CNAG) using Illumina HiSeq instruments (San Diego, CA, USA). The mRNA was isolated from the total RNA and was fragmented once transformed in cDNA. Fragments of 300 bp on average were selected to construct the libraries for sequencing. Pair-end sequences of 70 nucleotides for each end were produced.

Alignment of reads to the human genome reference

Alignment of the reads was performed in an SLURM HPC server running Tophat 2.0.6 with default options. Tophat aligns RNA-Seq reads to genomes using the Bowtie 2.0.2 alignment program, and then analyzes the mapping results to identify splice junctions between exons.

Differential Expression Statistical Analyses

Bedtools 2.17.0 (multicov option) was used to count the amount of reads mapped to each gene. The Reference Sequence (RefSeq) gene coordinates were defined using the RefFlat file from the UCSC Genome Bioinformatics Site (as February 28th, 2014). DESeq 1.4 package, setting up fit-only as fitting method, was used to test for differential expression using gene-count data.

Prediction method

Gene selection was performed with the implementation of Random Forest method in the the RandomForest 4.6-12 package (Breiman, L., 2001, Mach Learn, 45, 5-32) of R. Expression values of the 130 genes with significantly different expression between the responders and no responders was used as input with default parameters. Genes with the best Gini were selected for the predictor. It was trained using Logistic regression (Cox, D. R., 1958, J Roy Stat Soc B, 20, 215-242) with the glm function of R 3.2.3 and the calculation of the estimated cross-validation was performed with the cv.glm function of boot package which implements bootstrapping methods (Hinkley, D. V., 1988, J Roy Stat Soc B Met, 50, 321-337).

Table 1. Characteristics of the patients assessed.

Characteristics	**Total**		**Male**		**Female**		**Responders**		**Non-Responders**	
	(n = 30)		**(n = 18)**		**(n = 12)**		**(n = 15)**		**(n = 15)**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age at admission	29,6	10,5	28,2	10,0	31,6	11,4	29,3	11,7	29,9	9,6

(years)										
Age at psychosis onset (years)	28,6	10,4	27,1	10,4	30,8	10,5	28,7	11,7	28,5	9,4
Duration of untreated psychosis (months)	16,4	23,8	15,9	17,2	17,1	30,6	14,9	25,5	18,0	22,9
Duration of untreated illness (months)	12,0	17,8	13,3	15,5	10,1	21,3	7,9	10,9	16,1	22,3
BPRS at admission	74,1	15,4	76,3	14,5	70,8	16,7	83,5	8,9	64,8	15,0
BPRS at 3 months of treatment	34,6	11,8	35,9	11,9	32,6	11,7	29,7	5,2	39,5	14,4

Table 2. Differential expression between responders and non-responders before antipsychotic medication. "GeneID" Gene Identification. "Gene Symbol" Official Symbol. "Base Mean" Mean normalized counts, averaged over all samples from both conditions. "Base Mean Responders" Mean normalized counts from condition A. "Base Mean No Responders" Mean normalized counts from condition B. "P value" P value for the statistical significance of this change. "Padj" P value adjusted for multiple testing with the Benjamini-Hochberg procedure, which controls false discovery rate.

geneID	Gene Symbol	Base Mean	Base Mean Responders	Base Mean Non-Responders	Pval	Padj
8120	AP3B2	179,54883	28,61862909	330,4790312	2,70026E-87	5,2291E-83
283692	RP11-752G15.3	149,363348	24,40337601	274,3233203	1,14595E-80	1,1096E-76
3045	HBD	1812,38923	404,3120784	3220,466372	9,02319E-71	5,8245E-67
9381	OTOF	152,342235	67,92108049	236,7633893	3,68188E-64	1,7825E-60
3429	IFI27	92,3540441	58,58726887	126,1208193	3,52597E-40	1,138E-36
84873	GPR128	20,0554459	39,01809655	1,092795208	3,06788E-40	1,138E-36
10917	BTNL3	352,036897	192,8013483	511,2724464	2,37163E-37	6,561E-34
23532	PRAME	15,3545481	30,01125722	0,697838948	7,22767E-30	1,7495E-26
759	CA1	826,658542	335,2370787	1318,080006	9,33357E-30	2,0083E-26

6614	SIGLEC1	1582,02793	1289,403479	1874,652381	2,80499E-29	5,4319E-26
56163	RNF17	20,8250848	38,40343274	3,246736923	1,42432E-28	2,5074E-25
10964	IFI44L	2952,08606	2469,297194	3434,874926	2,19718E-28	3,5457E-25
722	C4BPA	160,744383	108,7546491	212,734116	4,45811E-26	6,6409E-23
9911	TMCC2	1273,05598	574,6389256	1971,473032	1,368E-24	1,8922E-21
100506159	LOC100506159	138,072263	79,95407937	196,1904473	7,40859E-22	9,5645E-19
144453	BEST3	37,6224777	6,981928696	68,26302668	8,90692E-22	1,078E-18
55553	SOX6	99,8846393	32,68313208	167,0861465	5,36898E-21	6,1159E-18
10529	NEBL	176,057832	232,469139	119,6465257	2,11802E-18	2,2786E-15
124912	SPACA3	13,4844511	3,545824737	23,42307756	4,07119E-18	4,1494E-15
26807	SNORD43	492,179264	670,4751781	313,8833506	5,81509E-18	5,6305E-15
85495	RPPH1	20,3312947	2,636592365	38,02599701	7,10397E-18	6,5509E-15
284581	LOC284581	149,252075	91,9944404	206,5097103	3,84513E-16	3,3846E-13
2993	GYPA	63,8993718	23,65583147	104,1429122	7,9894E-16	6,7267E-13
10561	IFI44	4047,13862	3499,447596	4594,829648	1,53753E-15	1,2406E-12
219539	YPEL4	142,731883	60,15875858	225,305008	2,31251E-15	1,7913E-12
11227	GALNT5	27,7091835	5,462776355	49,95559067	3,36928E-15	2,5095E-12
85462	FHDC1	378,734781	167,9382211	589,5313403	5,21411E-14	3,7397E-11
2944	GSTM1	266,740043	350,4511766	183,0289092	6,98884E-14	4,8335E-11
6521	SLC4A1	3834,17519	2379,396165	5288,954212	1,51698E-13	1,013E-10
389396	GLYATL3	5,85949693	11,56882265	0,150171214	2,48687E-13	1,6053E-10
50509	COL5A3	340,846363	253,3287412	428,3639843	1,11927E-12	6,9918E-10
55225	RAVER2	381,975183	489,6067934	274,3435727	3,81373E-12	2,3079E-09
10107	TRIM10	136,702015	71,27014705	202,1338822	7,58663E-12	4,452E-09
64478	CSMD1	54,1116443	37,55338365	70,669904 94	1,05032E-11	5,9822E-09
55363	HEMGN	773,446934	467,3740966	1079,519772	1,16262E-11	6,4326E-09

10900	RUNDC3A	650,844179	406,6369534	895,0514041	2,05961E-11	1,1079E-08
253012	HEPACAM2	31,7969181	10,4842785	53,10956333	3,45345E-11	1,8075E-08
8444	DYRK3	58,7610061	24,2120506	93,30996009	5,99608E-11	2,9773E-08
51327	AHSP	347,644359	213,8315678	481,4571502	5,94869E-11	2,9773E-08
57156	TMEM63C	283,118218	337,5494348	228,6870006	9,7019E-11	4,6969E-08
5730	PTGDS	929,124144	729,6977326	1128,550556	2,03528E-10	9,613E-08
139189	DGKK	158,052393	114,9980312	201,1067553	2,91336E-10	1,3433E-07
3488	IGFBP5	9,94650744	3,4949856 67	16,39802922	3,40415E-10	1,5015E-07
138255	C9orf135	3,52760771	6,8776073 92	0,177608022	3,41151E-10	1,5015E-07
6231	RPS26	7889,96377	9809,03152	5970,896012	3,89352E-10	1,6755E-07
6708	SPTA1	153,69767	84,38209965	223,0132394	4,50717E-10	1,8571E-07
342184	FMN1	690,542306	490,5499026	890,5347085	4,48717E-10	1,8571E-07
138307	LCN8	41,5504766	59,7306358 8	23,370317 37	5,18263E-10	2,0909E-07
55655	NLRP2	372,921067	285,5793168	460,262817	6,72245E-10	2,6567E-07
146439	CCDC64B	194,879293	239,4091215	150,3494643	7,74025E-10	2,9978E-07
6513	SLC2A1	3167,25458	1862,827578	4471,681582	8,3719E-10	3,1558E-07
54855	FAM46C	4335,69809	2771,654398	5899,741773	8,63716E-10	3,1558E-07
85413	SLC22A16	101,247066	134,3722628	68,12186895	8,58566E-10	3,1558E-07
400566	C17orf97	82,7990741	109,9479168	55,65023137	2,2188E-09	7,9569E-07
84913	ATOH8	129,445439	170,8626256	88,02825309	2,79948E-09	9,8567E-07
790952	ESRG	20,9641211	7,952447756	33,97579436	3,4341E-09	1,1875E-06
54892	NCAPG2	537,374831	439,1977341	635,5519274	5,70578E-09	1,9385E-06
9509	ADAMTS2	94,7337793	129,281862	60,18569658	6,63856E-09	2,2165E-06
8938	BAIAP3	1602,60122	1868,731564	1336,470878	6,84446E-09	2,2465E-06
56603	CYP26B1	33,2376991	22,2123698 5	44,26302842	9,04846E-09	2,9204E-06
389337	ARHGEF37	45,1201263	19,9077018 3	70,33255087	1,80509E-08	5,7304E-06

383	ARG1	475,613371	349,6331584	601,5935845	5,06478E-08	1,5819E-05
2038	EPB42	490,843351	351,2373749	630,4493265	7,3477E-08	2,2585E-05
266727	MDGA1	520,389753	435,7446249	605,034882	8,73219E-08	2,6422E-05
7450	VWF	272,875984	311,4407917	234,3111765	1,12882E-07	3,363E-05
6423	SFRP2	71,6930724	36,55366032	106,8324845	1,46567E-07	4,3004E-05
160364	CLEC12A	9568,992	8072,72347	11065,26054	1,72186E-07	4,9767E-05
3434	IFIT1	3180,19449	3193,880063	3166,508927	1,94424E-07	5,5368E-05
165530	CLEC4F	176,497313	225,043568	127,9510583	2,08067E-07	5,8394E-05
10395	DLC1	41,5399408	60,09504158	22,98484008	2,27046E-07	6,2811E-05
140807	KRT72	514,596492	404,4470736	624,7459103	2,88967E-07	7,8815E-05
7057	THBS1	2155,78097	1848,889541	2462,672408	3,23149E-07	8,6914E-05
64284	RAB17	8,90295112	2,847414589	14,95848766	3,73704E-07	9,9134E-05
51162	EGFL7	97,3678146	122,9227518	71,8128775	5,24045E-07	0,00013714
6550	SLC9A3	564,976807	398,1514415	731,8021715	5,68418E-07	0,00014677
4070	TACSTD2	69,679868	50,13509082	89,22464509	5,82013E-07	0,000148 3
148534	TMEM56	107,494278	67,18018377	147,8083728	6,44659E-07	0,00016213
6563	SLC14A1	718,857326	489,9011656	947,8134859	8,17945E-07	0,00020307
6368	CCL23	19,794082	30,38107077	9,207093168	8,98878E-07	0,00022034
117854	TRIM6	77,4397174	60,76880086	94,11063388	9,36669E-07	0,00022673
3816	KLK1	46,4359601	57,64451886	35,22740131	9,8741E-07	0,00023319
7138	TNNT1	136,372116	95,71109159	177,03314	9,84562E-07	0,00023319
1305	COL13A1	75,9964815	56,20067961	95,79228343	1,03753E-06	0,00024207
1281	COL3A1	4,83710685	8,835809794	0,838403916	1,14603E-06	0,000264 2
219970	GLYATL2	11,4565289	19,76565357	3,147404226	1,28858E-06	0,00029357
253559	CADM2	21,224971	12,08294484	30,36699725	1,47543E-06	0,00033223
287	ANK2	196,316954	239,4981349	153,1357734	1,72268E-06	0,00038345

91543	RSAD2	2004,31544	2151,72514	1856,905742	1,87197E-06	0,00041194
3118	HLA-DQA2	428,80828	500,7488256	356,8677343	2,04675E-06	0,00044534
10398	MYL9	769,327749	889,7786757	648,876823	2,22955E-06	0,00047973
645843	TMEM14E	10,8712904	17,52230237	4,220278351	2,49216E-06	0,00053034
54659	UGT1A3	1,64909264	0	3,298185286	3,25906E-06	0,000686
2952	GSTT1	158,013556	115,524813	200,5022984	3,53764E-06	0,00073663
3042	HBM	1017,39197	791,3254738	1243,45847	4,21249E-06	0,00086609
7849	PAX8	1475,32242	1642,326707	1308,318128	4,24883E-06	0,00086609
728577	CNTNAP3B	21,5234399	32,14407787	10,90280193	4,72879E-06	0,00095389
57596	BEGAIN	190,690128	164,8616743	216,5185825	4,89019E-06	0,00097627
54658	UGT1A1	1,5793711	0	3,158742198	5,27759E-06	0,00104187
5197	PF4V1	153,19759	193,793687	112,6014922	5,32637E-06	0,00104187
954	ENTPD2	89,3929457	105,5354715	73,250419867	6,2304E-06	0,00120652
140733	MACROD2	269,636439	312,7980137	226,4748641	7,61071E-06	0,00145922
2537	IFI6	2117,50948	2050,923569	2184,095384	8,22731E-06	0,00154681
654433	PAX8-AS1	1197,05347	1329,061647	1065,045291	8,19658E-06	0,00154681
284751	RP11-290F20.1	1533,19174	1351,161781	1715,221697	9,12169E-06	0,00169848
643418	LIPN	617,261505	546,5314907	687,9915188	1,1326E-05	0,00208883
928	CD9	880,018349	967,6436798	792,3930179	1,20407E-05	0,00219971
55228	PNMAL1	11,2038673	6,072260169	16,33547439	1,46566E-05	0,00262801
202134	FAM153B	113,483797	91,42568758	135,5419066	1,46186E-05	0,00262801
346171	ZFP57	49,2808082	60,11521115	38,44640517	1,76629E-05	0,00313801
64105	CENPK	717,36388	623,8409479	810,8868125	2,04821E-05	0,00360578
642846	LOC642846	254,05304	209,6176028	298,4884775	2,37359E-05	0,00414096
439996	IFIT1B	274,615835	207,2169111	342,0147583	2,50117E-05	0,00432457
2213	FCGR2B	1713,15042	1898,041018	1528,259815	2,56269E-05	0,00435442

387837	CLEC12B	709,065816	628,5314042	789,6002274	2,56341E-05	0,00435442
1397	CRIP2	478,521426	375,8400945	581,2027565	2,82138E-05	0,00473115
101927586	RP11-290F20.2	714,293049	636,1588263	792,4272722	2,83405E-05	0,00473115
89872	AQP10	80,1898493	98,54998416	61,82971453	2,93224E-05	0,00485323
3162	HMOX1	2923,46962	3437,523124	2409,416115	3,42533E-05	0,00562131
440068	CARD17	159,678738	135,8124669	183,5450095	3,49447E-05	0,0056866
100272216	LOC100272216	457,536036	396,9557801	518,1162927	4,22406E-05	0,00681658
54600	UGT1A9	3,74418263	1,068001418	6,420363841	4,3976E-05	0,00703798
420	ART4	7,00550365	1,425497134	12,58551018	4,49777E-05	0,0070708
5473	PPBP	3554,04338	4097,653412	3010,433344	4,52765E-05	0,0070708
84628	NTNG2	4548,38936	3892,135414	5204,643298	4,4883E-05	0,0070708
440836	ODF3B	1892,18305	1723,22217	2061,143928	4,58289E-05	0,00709981
2740	GLP1R	14,0876098	8,700993545	19,474226066	5,32618E-05	0,00818582
3576	IL8	489,238041	387,593637	590,8824448	5,37871E-05	0,00820148
6517	SLC2A4	7,03895102	1,929687299	12,14821474	5,57307E-05	0,00843144
339975	RP11-138B4.1	24,9488824	33,00262023	16,89514453	5,72036E-05	0,0085872
284194	LGALS9B	79,5655685	64,44520993	94,68592708	5,97407E-05	0,00889907

Table 3. Differential expression between responders and non-responders after 3 months of antipsychotic medication. "GeneID" gene identification. "Gene symbol" official symbol. "Base mean" mean normalized counts, averaged over all samples from both conditions. "Base mean responders" mean normalized counts from condition A. "Base mean no responders" mean normalized counts from condition B. "P value" p value for the statistical significance of this change. "Padj" P value adjusted for multiple testing with the Benjamini-Hochberg procedure, which controls false discovery rate.

geneID	Gene Symbol	Base Mean	Base Mean Responders	Base Mean Non-Responders	Pval	Padj
100462981	MTRNR2L2	552,174891	123,891061	980,45872	6,636E-138	1,281E-133
8120	AP3B2	129,219145	28,2367073	230,201582	1,0615E-87	1,0243E-83
283692	RP11-752G15.3	109,644872	24,5525911	194,737154	2,7763E-79	1,786E-75
10562	OLFM4	474,080238	750,343818	197,816658	3,3552E-59	1,6188E-55
84873	GPR128	19,651856	38,6805391	0,6231745	8,0864E-51	3,1212E-47
3045	HBD	1029,6142	539,007043	1520,22138	3,6889E-43	1,1865E-39
56163	RNF17	19,415530	37,261607	1,5694540	2,0635E-41	5,689E-38
10917	BTNL3	320,459836	168,864292	472,055379	7,7401E-40	1,8672E-36
4317	MMP8	470,837163	703,030455	238,64387	6,9975E-36	1,5005E-32
23532	PRAME	18,619172	35,3175874	1,9207572	9,298E-35	1,7944E-31
4057	LTF	3926,5159	5762,89019	2090,14164	2,5228E-34	4,4261E-31
91543	RSAD2	1543,3001	885,847971	2200,7524	1,7445E-33	2,8056E-30
722	C4BPA	214,4128	97,7527532	331,072846	8,4691E-33	1,2573E-29
212	ALAS2	5103,16455	6871,25622	3335,07287	4,0073E-28	5,5241E-25
85462	FHDC1	274,440851	163,893515	384,988188	4,4797E-28	5,7636E-25
3934	LCN2	1072,8138	1532,40645	613,221157	1,4512E-27	1,7505E-24
10964	IFI44L	2221,93092	1379,96046	3063,90137	5,3086E-25	6,0266E-22
1088	CEACAM8	625,618432	883,948321	367,288543	3,2111E-24	3,4428E-21
221687	RNF182	75,4255258	113,175621	37,6754306	1,5421E-23	1,5663E-20
284581	LOC284581	162,602962	93,7263842	231,479539	1,3283E-22	1,2817E-19
55553	SOX6	63,764215	32,4988086	95,0296214	5,7727E-22	5,3051E-19
3434	IFIT1	2548,7926	1676,53448	3421,05072	1,2962E-21	1,1371E-18
10321	CRISP3	299,257818	421,073725	177,441911	1,8144E-21	1,5224E-18
10561	IFI44	3516,24953	2318,88171	4713,61735	1,9203E-21	1,5442E-18

1719	DHFR	1191,43371	775,339703	1607,52772	2,0249E-21	1,5632E-18
6614	SIGLEC1	1087,2586	706,543725	1467,97348	8,3501E-21	6,198E-18
154664	ABCA13	308,119539	429,625195	186,613884	4,5032E-20	3,2188E-17
100463486	MTRNR2L8	161,906401	95,5518467	228,260955	9,924E-20	6,8401E-17
9911	TMCC2	901,95545	633,160309	1170,75059	1,637E-19	1,0894E-16
3437	IFIT3	5156,77611	3553,56222	6759,98999	1,7509E-19	1,1264E-16
7057	THBS1	2540,71483	1725,05097	3356,3787	7,257E-19	4,5179E-16
138307	LCN8	37,4299529	58,144092	16,715813 9	3,1066E-18	1,8736E-15
9172	MYOM2	768,60801	943,023337	594,192682	4,7952E-18	2,8043E-15
219539	YPEL4	94,3929596	57,9004556	130,885464	1,5246E-17	8,6541E-15
820	CAMP	627,73713	838,841244	416,633016	1,2763E-16	7,0377E-14
1667	DEFA1	2085,14854	2693,95263	1476,34444	2,8164E-16	1,4304E-13
728358	DEFA1B	2085,14854	2693,95263	1476,34444	2,8164E-16	1,4304E-13
1668	DEFA3	2085,14854	2693,95263	1476,34444	2,8164E-16	1,4304E-13
100423062	IGLL5	2409,85102	1690,79016	3128,91188	3,4603E-16	1,7123E-13
2537	IFI6	1806,33892	1283,99804	2328,67981	4,3974E-16	2,1216E-13
3512	IGJ	4098,29208	2877,32542	5319,25873	5,1088E-16	2,4048E-13
2944	GSTM1	218,867092	290,198848	147,535335	4,5831E-15	2,1059E-12
50509	COL5A3	335,145794	232,241098	438,050489	7,7276E-15	3,4682E-12
759	CA1	520,050096	372,57793	667,522262	8,9205E-15	3,9126E-12
4680	CEACAM6	451,746967	596,196143	307,29779	6,467E-14	2,7735E-11
4973	OLR1	97,0742315	136,851344	57,2971189	6,9511E-14	2,9163E-11
100506159	LOC100506159	124,079361	79,9389594	168,219762	9,2285E-14	3,7894E-11
6708	SPTA1	126,503907	86,0213026	166,986511	3,4E-13	1,367E-10
85495	RPPH1	11,7920847	3,52171736	20,062452 1	4,2215E-13	1,6627E-10
9636	ISG15	1259,98783	940,834385	1579,14127	4,5685E-13	1,7633E-10

710	SERPING1	631,339195	466,823301	795,855088	6,7497E-13	2,5542E-10
389396	GLYATL3	5,19461175	10,1611077	0,22811584	9,3048E-13	3,4533E-10
7280	TUBB2A	100,48793	136,335025	64,640835 9	9,8535E-13	3,588E-10
129607	CMPK2	899,335528	661,597474	1137,07358	1,1283E-12	4,0324E-10
4599	MX1	5724,83572	4210,1318	7239,53964	1,4732E-12	5,1695E-10
54855	FAM46C	2993,80331	2295,02082	3692,58579	2,5335E-12	8,7311E-10
6513	SLC2A1	2274,59063	1762,40221	2786,77905	2,6787E-12	8,9131E-10
56603	CYP26B1	23,628429 1	12,7735778	34,483280 4	2,6479E-12	8,9131E-10
165530	CLEC4F	166,84194 9	210,719765	122,96413 4	2,8318E-12	9,2627E-10
284751	RP11-290F20.1	1461,10935	1140,12102	1782,09768	3,2868E-12	1,0572E-09
101927586	RP11-290F20.2	659,109519	510,316734	807,902304	3,3448E-12	1,0582E-09
5657	PRTN3	73,352548 8	103,586207	43,118890 8	3,6493E-12	1,1359E-09
55225	RAVER2	349,040614	453,320194	244,761034	4,5018E-12	1,3791E-09
144453	BEST3	18,096246 4	8,32807889	27,864413 9	4,9875E-12	1,504E-09
6285	S100B	261,519702	336,308329	186,731076	5,2581E-12	1,5612E-09
343171	OR2W3	229,326786	291,402211	167,251361	6,2267E-12	1,8207E-09
51191	HERC5	1417,41446	1053,57811	1781,25081	6,3749E-12	1,8362E-09
4940	OAS3	4833,09558	3637,69639	6028,49477	6,6098E-12	1,8759E-09
400566	C17orf97	84,5069727	111,471643	57,542301 9	2,8784E-11	8,0506E-09
11227	GALNT5	13,227464 5	5,14965259	21,305276 4	4,402E-11	1,2136E-08
6231	RPS26	6784,84525	8247,68888	5322,00161	5,2199E-11	1,4189E-08
389337	ARHGEF37	36,592492 5	21,916218 1	51,268766 9	5,6118E-11	1,5042E-08
81788	NUAK2	5971,73914	4517,00021	7426,47807	6,0802E-11	1,6074E-08
1669	DEFA4	443,127577	565,565393	320,689762	8,3947E-11	2,1893E-08
731424	RP11-701P16.5	260,17764	188,941554	331,413725	1,0041E-10	2,5838E-08
2731	GLDC	48,303915 9	29,564651	67,043180 7	2,8707E-10	7,2896E-08

3848	KRT1	384,340748	453,971248	314,710249	3,1103E-10	7,7957E-08
2993	GYPA	44,3877289	28,2851695	60,4902883	4,8447E-10	1,1987E-07
8991	SELENBP1	680,875496	818,830378	542,920613	8,0173E-10	1,9586E-07
3433	IFIT2	10039,9429	7870,08844	12209,7974	1,2118E-09	2,9233E-07
8444	DYRK3	34,204017 8	21,3413757	47,06666	1,8598E-09	4,4312E-07
57094	CPA6	113,840557	145,610012	82,0711033	2,3947E-09	5,636E-07
6550	SLC9A3	551,542899	417,381715	685,704083	2,6796E-09	6,2305E-07
55384	MEG3	101,252414	125,928598	76,5762299	3,5735E-09	8,1136E-07
608	TNFRSF17	129,482519	92,0069024	166,958136	3,5653E-09	8,1136E-07
1740	DLG2	5191,38635	6346,06507	4036,70763	4,1213E-09	9,2485E-07
3240	HP	215,956123	272,316589	159,595658	5,6657E-09	1,2568E-06
3772	KCNJ15	10831,4614	8493,89543	13169,0275	9,0434E-09	1,9678E-06
339975	RP11-138B4.1	23,798751 5	33,783338 9	13,814164 1	9,0747E-09	1,9678E-06
10410	IFITM3	5051,18597	3974,99989	6127,37206	9,3935E-09	2,0143E-06
5197	PF4V1	129,665703	165,968751	93,362654	1,1491E-08	2,437E-06
81796	SLCO5A1	19248,3133	23465,5532	15031,0734	1,2057E-08	2,5292E-06
116369	SLC26A8	711,299596	541,905899	880,693293	1,235E-08	2,5629E-06
91947	ARRDC4	1358,72272	1065,04992	1652,39552	1,7685E-08	3,6309E-06
164045	HFM1	33832,5142	41213,3609	26451,6675	1,7892E-08	3,6346E-06
100130889	PSORS1C3	28,313067 2	17,2550159	39,371118 5	1,9705E-08	3,9614E-06
55363	HEMGN	612,186407	490,068323	734,304491	2,0936E-08	4,1654E-06
5266	PI3	847,571486	691,844839	1003,29813	3,0378E-08	5,9823E-06
6097	RORC	383,736444	308,600021	458,872868	3,3054E-08	6,4435E-06
138255	C9orf135	3,1270045 8	5,9273024	0,3267067 6	5,9604E-08	1,1503E-05
4353	MPO	836,060484	1025,05318	647,06779	7,6186E-08	1,4558E-05
671	BPI	939,244071	1149,99832	728,489823	8,3453E-08	1,579E-05

2952	GSTT1	154,6793	117,065085	192,293515	8,4695E-08	1,5869E-05
10529	NEBL	184,803009	231,697256	137,908761	1,1543E-07	2,1421E-05
5013	OTX1	107,616532	79,7668664	135,466198	1,3618E-07	2,5031E-05
81567	TXNDC5	4622,38143	3693,52845	5551,23441	1,5613E-07	2,8427E-05
25893	TRIM58	3575,83517	4203,38629	2948,28405	1,9443E-07	3,5068E-05
6947	TCN1	304,085276	370,231259	237,939294	2,0438E-07	3,6186E-05
253012	HEPACAM2	19,218465 6	11,212232	27,224699 3	2,033E-07	3,6186E-05
7850	IL1R2	3233,76169	2626,24414	3841,27925	2,1184E-07	3,7166E-05
9623	TCL1B	38,257428 1	51,0870233	25,427832 9	2,1445E-07	3,7285E-05
51237	MZB1	549,740511	440,952786	658,528235	3,0357E-07	5,231E-05
1511	CTSG	131,569034	166,479728	96,6583394	3,0852E-07	5,2691E-05
6286	S100P	2083,7966	1703,83339	2463,7598	3,1563E-07	5,3433E-05
342184	FMN1	606,974503	472,627826	741,32118	3,3974E-07	5,7015E-05
7173	TPO	10,900134 7	5,21742955	16,582839 9	3,4489E-07	5,7379E-05
100133941	CD24	1465,51693	1746,77596	1184,25791	4,258E-07	7,0236E-05
64284	RAB17	7,237876 08	2,42344225	12,052309 9	4,6787E-07	7,652E-05
56729	RETN	179,353566	217,241513	141,465619	5,119E-07	8,3018E-05
6037	RNASE3	193,439799	239,756079	147,12352	5,4828E-07	8,8178E-05
64478	CSMD1	56,811513 1	43,3549019	70,268124 3	6,0376E-07	9,6298E-05
160364	CLEC12A	9225,01849	7419,86741	11030,169 6	6,2345E-07	9,8363E-05
83869	TTTY14	1493,65505	1775,87336	1211,43675	6,2691E-07	9,8363E-05
3627	CXCL10	85,6202314	66,0160187	105,224444	7,6135E-07	0,00011849
83999	KREMEN1	1566,49261	1266,54414	1866,44109	7,7246E-07	0,00011926
383	ARG1	511,827716	407,42176	616,233672	7,9043E-07	0,00012107
3624	INHBA	8,808254 98	13,9767183	3,63979168	8,2599E-07	0,00012552
85413	SLC22A16	90,229904 3	114,477537	65,982272	8,7146E-07	0,00013139

5909	RAP1GAP	60,3028196	74,0684386	46,5372006	9,394E-07	0,00014054
26577	PCOLCE2	17,398262	25,3108187	9,48570525	9,8762E-07	0,00014662
283120	H19	32,9622159	44,0106943	21,913737 6	1,0624E-06	0,00015652
10911	UTS2	58,1971485	46,7642045	69,630092 6	1,0809E-06	0,00015803
9828	ARHGEF17	120,981833	91,3255588	150,63810 8	1,1144E-06	0,000161 7
419	ART3	94,7000763	74,0761541	115,32399 8	1,134E-06	0,00016332
3823	KLRC3	695,43173	835,555862	555,30759 8	1,244E-06	0,00017784
6622	SNCA	2073,6717	2403,36293	1743,9804 7	1,4079E-06	0,00019979
1308	COL17A1	53,5030992	69,9112403	37,094958 1	1,5065E-06	0,00021222
2078	ERG	76,9928322	97,880857	56,104807 4	1,5312E-06	0,00021414
2999	GZMH	2177,1582	2580,0171	1774,2993	1,8283E-06	0,00025384
387755	INSC	80,8730345	58,6845575	103,06151 1	2,3218E-06	0,00032006
57282	SLC4A10	516,936148	434,437663	599,43463 3	3,0175E-06	0,00041301
287	ANK2	177,594592	210,125636	145,06354 9	3,3433E-06	0,00045438
114132	SIGLEC11	70,7886139	88,8754969	52,701730 9	3,4501E-06	0,00046562
10395	DLC1	34,3526082	46,4889899	22,216226 5	3,7217E-06	0,00049878
6783	SULT1E1	17,595484 8	11,0068392	24,184130 4	3,8097E-06	0,00050706
140733	MACROD2	237,944668	279,10785	196,78148 7	4,036E-06	0,0005335
4318	MMP9	4649,1595	3756,30028	5542,0187 1	4,6812E-06	0,00061457
54892	NCAPG2	484,670313	402,831931	566,50869 6	5,0573E-06	0,00065947
5159	PDGFRB	312,184522	373,381235	250,98780 8	5,3559E-06	0,00069371
9586	CREB5	11137,4031	9193,60831	13081,197 8	5,7017E-06	0,00073358
253559	CADM2	20,8152917	11,533866	30,096717 4	6,0106E-06	0,00076315
3092	HIP1	3686,97142	3053,3527	4320,5901 4	6,0003E-06	0,00076315
55228	PNMAL1	10,098568 8	4,83292738	15,364210 2	6,3086E-06	0,00079575
26807	SNORD43	396,629819	473,950318	319,30932	6,743E-06	0,00084503

6368	CCL23	21,8348119	29,5349909	14,1346329	7,311E-06	0,00090975
51326	ARL17A	312,680793	260,158064	365,203522	7,401E-06	0,00090975
100506084	ARL17B	312,469039	259,984935	364,953143	7,3843E-06	0,00090975
1832	DSP	181,824808	219,054895	144,594721	7,5623E-06	0,0009237
5359	PLSCR1	2771,05364	2306,07728	3236,03	8,0923E-06	0,00098222
1291	COL6A1	136,925943	110,168253	163,683634	8,7457E-06	0,00105489
10124	ARL4A	348,818974	291,868533	405,769416	8,8643E-06	0,00106257
92304	SCGB3A1	40,5067764	29,4079429	51,60561	8,9307E-06	0,00106392
26873	OPLAH	278,39758	226,738958	330,056201	9,043E-06	0,00107068
644248	RP11-67M1.1	329,813566	384,83712	274,790012	9,5359E-06	0,00112215
116071	BATF2	226,21337	187,964325	264,462415	9,6836E-06	0,00113263
7138	TNNT1	116,954797	89,8444675	144,065127	1,0513E-05	0,00122219
9884	LRRC37A	201,81408	165,722885	237,905275	1,136E-05	0,00131276
9289	GPR56	5593,89464	6456,74515	4731,04412	1,1656E-05	0,001339
57801	HES4	66,9401974	82,0673339	51,813061	1,4086E-05	0,00160855
60675	PROK2	6143,39426	5068,80554	7217,98298	1,5156E-05	0,00172051
391322	LOC391322	101,391375	80,216942	122,565807	1,57E-05	0,00177184
604	BCL6	28755,3717	24065,7903	33444,9531	1,6342E-05	0,00183363
84913	ATOH8	110,76711	136,675363	84,8588568	1,6695E-05	0,00186238
140807	KRT72	573,13038	487,689965	658,570796	1,7875E-05	0,00198258
7849	PAX8	1429,05753	1598,4959	1259,61916	1,8037E-05	0,00198916
100526836	BLOC1S5-TXNDC5	5509,0755	4603,16557	6414,98543	2,0662E-05	0,00226561
642846	LOC642846	254,359585	207,042547	301,676623	2,2129E-05	0,00240233
1991	ELANE	216,545469	263,801553	169,289385	2,2157E-05	0,00240233
94031	HTRA3	28,5207169	38,6500505	18,391382	2,3603E-05	0,00254479
3821	KLRC1	296,325637	354,413767	238,237506	2,4878E-05	0,0026673

1397	CRIP2	363,19694	305,598385	420,795496	2,5625E-05	0,00273222
125058	TBC1D16	240,831714	196,084683	285,578745	2,5875E-05	0,00274371
654433	PAX8-AS1	1162,48674	1296,90426	1028,06921	3,2201E-05	0,00339586
80310	PDGFD	351,568999	410,725287	292,412712	3,4904E-05	0,00366089
29065	ASAP1-IT1	7,522505 54	10,78813 1	4,256880 05	3,5513E-05	0,00370472
399697	CTXN2	60,547297 9	76,28159 64	44,812999 3	3,6582E-05	0,00379566
200315	APOBEC3A	6632,1100 7	5649,438 08	7614,7820 6	3,714E-05	0,00383296
6320	CLEC11A	150,08441 4	178,9598 1	121,20901 8	4,0065E-05	0,00411283
440068	CARD17	142,30692 7	113,5735 16	171,04033 7	4,0528E-05	0,00413831
566	AZU1	278,65322 9	335,1553	222,15115 7	4,3906E-05	0,00445972
619207	SCART1	566,80921 9	498,6298 86	634,98855 3	4,8453E-05	0,00489576
8843	HCAR3	2614,6208 4	2206,751 04	3022,4906 3	4,9708E-05	0,00499644
6563	SLC14A1	646,08618 7	547,2759 56	744,89641 7	5,3836E-05	0,00535889
875	CBS	179,63778 7	147,6379 5	211,63762 5	5,3869E-05	0,00535889
84418	CYSTM1	746,87023 5	625,7794 25	867,96104 5	5,4452E-05	0,0053891
83416	FCRL5	1496,0030 1	1231,458 61	1760,5474 1	5,5257E-05	0,00544079
100913187	APOBEC3A_B	7114,9352 1	6076,242 83	8153,6275 8	5,5721E-05	0,00545869
1870	E2F2	606,41110 8	519,3373 27	693,48488 9	5,9728E-05	0,00579243
3084	NRG1	226,57166	190,3771 7	262,76614 9	5,9443E-05	0,00579243
6535	SLC6A8	575,16442 3	657,2394 96	493,08935 1	6,0213E-05	0,00581026
117156	SCGB3A2	22,135681 1	14,49321 44	29,778147 8	6,3553E-05	0,00610203
79776	ZFHX4	5,5703250 8	9,020504 5	2,1201456 6	6,8558E-05	0,00655002
2180	ACSL1	33718,681 3	28281,45 17	39155,910 8	6,9079E-05	0,00656724
7367	UGT2B17	22,939816 9	15,01158 83	30,868045 5	7,3044E-05	0,00691014
420	ART4	4,0117517 9	1,551216 33	6,4722872 4	7,7728E-05	0,00731738
8638	OASL	1000,6430 7	853,0528 42	1148,2333 1	7,9805E-05	0,00747645

51733	UPB1	187,981745	156,024049	219,939441	8,3333E-05	0,00776038
9509	ADAMTS2	22,7026715	31,7805315	13,6248116	8,364E-05	0,00776038
366	AQP9	25361,4862	21542,9527	29180,0197	8,8121E-05	0,00813711
22846	VASH1	1764,26948	1992,99912	1535,53984	9,0142E-05	0,00828402
7380	UPK3A	97,8703286	115,177806	80,562851	9,1252E-05	0,00834632
2215	FCGR3B	81915,5707	70230,054	93601,0875	9,293E-05	0,00845903
356	FASLG	435,466514	502,505763	368,427265	9,3361E-05	0,00845903
266727	MDGA1	510,279246	447,434571	573,123922	0,00010065	0,00907672
1193	CLIC2	279,111134	234,243917	323,97835	0,00010199	0,00915533
8972	MGAM	12859,8286	10910,6113	14809,0458	0,00010361	0,00925741
8876	VNN1	1700,59051	1435,762 31	1965,4187	0,00010 47	0,00931167
7053	TGM3	181,282184	144,914287	217,650082	0,00010924	0,00967051
84073	MYCBPAP	67,9889898	54,6155482	81,362431 4	0,00011064	0,00974998

Table 4. Differential expression between responders before and after medication. "GeneID" gene identification. "Gene symbol" official symbol. "Base mean" mean normalized counts, averaged over all samples from both conditions. "Base mean before medication" mean normalized counts from condition A. "Base mean after medication" mean normalized counts from condition B. "P value" p value for the statistical significance of this change. "Padj" P value adjusted for multiple testing with the Benjamini-Hochberg procedure, which controls false discovery rate.

geneID	Gene Symbol	Base Mean	Base Mean Before Medication	Base Mean After Medication	Pval	Padj
10562	OLFM4	527,252901	238,816197	815,689605	5,9818E-57	1,158E-52
1088	CEACAM8	644,610726	328,226682	960,99477	3,8657E-51	3,7416E-47
4057	LTF	4321,7569	2376,66863	6266,84516	2,14E-47	1,3809E-43
10321	CRISP3	310,047653	162,331179	457,764128	9,847E-40	4,7654E-36

154664	ABCA13	314,929604	162,858245	467,000963	3,5116E-38	1,3595E-34
3934	LCN2	1192,71737	719,068096	1666,36664	1,7475E-37	5,638E-34
4317	MMP8	536,87566	309,435163	764,316158	4,7511E-37	1,3139E-33
9509	ADAMTS2	82,0014103	129,418637	34,5841839	1,0569E-34	2,5575E-31
100190986	LOC100190986	37,372509	7,9754786 7	66,769539 4	1,8272E-33	3,93E-30
1667	DEFA1	2240,08785	1549,99649	2930,17921	6,925E-33	1,1171E-29
728358	DEFA1B	2240,08785	1549,99649	2930,17921	6,925E-33	1,1171E-29
1668	DEFA3	2240,08785	1549,99649	2930,17921	6,925E-33	1,1171E-29
4680	CEACAM6	465,647191	283,109146	648,185235	1,7492E-30	2,6048E-27
100462981	MTRNR2L2	80,7516597	26,812259 5	134,69106	5,7677E-28	7,975E-25
1669	DEFA4	460,27306	305,467349	615,078772	5,9021E-27	7,6169E-24
100423062	IGLL5	2936,15302	4033,38348	1838,92255	4,3234E-26	5,2307E-23
671	BPI	943,029656	635,539838	1250,51947	9,4636E-25	1,0776E-21
820	CAMP	681,781508	451,333738	912,229277	5,4121E-23	5,8205E-20
4973	OLR1	102,464338	56,1250692	148,803607	1,6712E-22	1,7027E-19
3512	IGJ	4839,59161	6549,04461	3130,13861	4,251E-22	4,1146E-19
221687	RNF182	90,6758994	58,063648 1	123,288151	1,0538E-20	9,714E-18
4353	MPO	869,305633	624,263226	1114,34804	4,2754E-18	3,7619E-15
608	TNFRSF17	166,125601	232,164308	100,086893	3,0278E-17	2,5484E-14
566	AZU1	280,900442	197,356552	364,444331	4,6227E-17	3,7286E-14
81567	TXNDC5	5718,9484	7419,85707	4018,03973	3,4318E-16	2,6573E-13
1511	CTSG	136,395858	91,8198206	180,971896	1,4061E-15	1,0469E-12
3045	HBD	496,165664	404,97753	587,353798	5,7961E-15	4,1556E-12
91543	RSAD2	1559,22123	2154,7855	963,656958	1,9112E-14	1,3213E-11
2038	EPB42	438,401567	351,82781	524,975325	6,9296E-14	4,6256E-11
51237	MZB1	667,12726	854,590642	479,663879	8,2765E-14	5,3406E-11

9172	MYOM2	926,374981	825,365467	1027,38449	1,5513E-13	9,6873E-11
27181	SIGLEC8	555,243722	437,313471	673,173974	1,854E-13	1,1215E-10
212	ALAS2	6731,39437	5977,21051	7485,57823	2,4208E-13	1,4201E-10
1991	ELANE	227,677683	168,487438	286,867927	2,6937E-13	1,5336E-10
6521	SLC4A1	2780,57327	2383,72428	3177,42227	3,4142E-13	1,8884E-10
10720	UGT2B11	728,604704	547,980581	909,228826	1,2056E-12	6,4828E-10
25893	TRIM58	3988,87971	3400,59258	4577,16684	2,4243E-12	1,2684E-09
5166	PDK4	1850,31825	2292,57766	1408,05884	3,8297E-12	1,9509E-09
932	MS4A3	602,609213	475,53326	729,685166	5,0796E-12	2,5213E-09
100526836	BLOC1S5-TXNDC5	6727,05938	8446,51681	5007,60195	5,2383E-12	2,5351E-09
8991	SELENBP1	782,340761	673,06564	891,615882	1,0179E-11	4,806E-09
6948	TCN2	398,720185	501,978416	295,461954	1,1795E-11	5,4364E-09
3816	KLK1	42,4953484	57,713837	27,276858	2,5059E-11	1,1281E-08
10900	RUNDC3A	491,480371	407,319219	575,641523	2,7773E-11	1,2219E-08
2078	ERG	79,9829259	53,531363	106,434488	5,4569E-11	2,2964E-08
2731	GLDC	55,475458	78,792734	32,158181	5,4387E-11	2,2964E-08
6947	TCN1	325,818044	249,028974	402,607114	5,8124E-11	2,394E-08
712	C1QA	139,088941	181,84481	96,3330726	6,3419E-11	2,5576E-08
1308	COL17A1	57,091519 3	38,153971 2	76,029067 5	7,8452E-11	3,0993E-08
6037	RNASE3	217,834873	174,863143	260,806603	8,2043E-11	3,1764E-08
10410	IFITM3	6051,52124	7778,33131	4324,71117	1,0115E-10	3,8393E-08
246	ALOX15	1512,48143	1228,37382	1796,58903	1,4618E-10	5,4417E-08
3848	KRT1	428,761196	363,113881	494,408512	1,6598E-10	6,0624E-08
7145	TNS1	1044,56517	874,511422	1214,61892	2,1807E-10	7,8175E-08
5657	PRTN3	85,1089901	57,656510 7	112,56146 9	6,1899E-10	2,1786E-07
7180	CRISP2	7,97020677	2,00960403	13,930809 5	1,0291E-09	3,5573E-07

26577	PCOLCE2	17,9715337	8,43551116	27,5075562	1,6018E-09	5,4398E-07
4481	MSR1	238,441996	303,562392	173,3216	1,6995E-09	5,6722E-07
6622	SNCA	2356,50015	2095,75509	2617,24521	2,4261E-09	7,96E-07
6768	ST14	1223,30317	1482,70381	963,902538	5,0691E-09	1,6354E-06
1118	CHIT1	135,252427	96,3160069	174,188847	5,8869E-09	1,8682E-06
644248	RP11-67M1.1	369,36916	319,635005	419,103316	6,3053E-09	1,9687E-06
146439	CCDC64B	208,358082	239,743614	176,972551	9,1132E-09	2,8002E-06
3437	IFIT3	5089,18735	6312,59987	3865,77482	1,3406E-08	4,055E-06
10215	OLIG2	170,579812	138,986688	202,172935	2,4124E-08	7,1844E-06
710	SERPING1	673,67492	839,507293	507,842546	2,4835E-08	7,2842E-06
9672	SDC3	231,667358	283,869472	179,465244	2,7402E-08	7,9172E-06
713	C1QB	80,705202	106,259184	55,1512205	3,8784E-08	1,1041E-05
116071	BATF2	269,943915	335,404614	204,483216	4,4551E-08	1,2499E-05
55512	SMPD3	2046,17081	1734,8055	2357,53611	5,2622E-08	1,4552E-05
765	CA6	707,777656	572,489986	843,065326	7,0593E-08	1,9247E-05
1958	EGR1	163,737394	204,298497	123,17629	7,4754E-08	2,0099E-05
3620	IDO1	393,561766	343,930841	443,192691	7,782E-08	2,0636E-05
2039	DMTN	4657,10853	4072,01538	5242,20169	1,0335E-07	2,7035E-05
1278	COL1A2	6,95329294	12,3731451	1,53344081	1,0526E-07	2,7169E-05
3568	IL5RA	944,930454	820,371038	1069,48987	1,0906E-07	2,7779E-05
3434	IFIT1	2511,12645	3198,41488	1823,83802	1,3244E-07	3,3296E-05
94031	HTRA3	30,31593	18,604795	42,027064	1,5974E-07	3,9645E-05
343171	OR2W3	282,8729	248,507105	317,238694	1,7029E-07	4,1726E-05
8685	MARCO	520,178855	634,248141	406,109569	2,2124E-07	5,3534E-05
54674	LRRN3	1318,62322	1147,8332	1489,41323	2,4771E-07	5,9199E-05
23495	TNFRSF13B	181,055431	215,470615	146,640248	2,7143E-07	6,4078E-05

200132	TCTEX1D1	34,3574041	24,1802794	44,5345288	5,2304E-07	0,00011912
116285	ACSM1	231,116967	189,409961	272,823973	5,1899E-07	0,00011912
64105	CENPK	726,661789	624,711905	828,611673	5,218E-07	0,00011912
6382	SDC1	19,9222851	29,7335972	10,110973	5,5165E-07	0,00012417
51208	CLDN18	25,3410337	15,7738851	34,908182	5,8904E-07	0,00013106
1374	CPT1A	4130,94062	4783,06394	3478,81729	6,3985E-07	0,00014075
6279	S100A8	46177,5779	54173,1178	38182,038	8,1121E-07	0,00017644
714	C1QC	29,758045	41,096638 3	18,419451 6	8,5678E-07	0,00018428
139189	DGKK	147,052363	115,172577	178,932149	8,9316E-07	0,00019
3624	INHBA	9,64379057	4,09299464	15,194586 5	9,1112E-07	0,00019171
439996	IFIT1B	231,41184	207,565474	255,258206	1,0668E-06	0,0002212
57156	TMEM63C	315,333075	337,981377	292,684772	1,0741E-06	0,0002212
54094	C21orf15	273,936193	222,830107	325,04228	1,1512E-06	0,00023457
26790	SNORD58B	456,032789	548,917032	363,148546	1,1878E-06	0,00023952
9636	ISG15	1315,98043	1608,45427	1023,5066	1,2575E-06	0,00025096
1053	CEBPE	330,215478	284,098934	376,332022	1,336E-06	0,0002639
717	C2	305,744273	367,3737	244,114847	1,4178E-06	0,00027723
26509	MYOF	1564,55449	1854,16637	1274,94261	1,4655E-06	0,00028369
401399	PRRT4	65,5390511	47,1648793	83,9132228	1,6751E-06	0,00031822
11326	VSIG4	183,577837	217,946574	149,209099	1,6768E-06	0,00031822
51348	KLRF1	2790,49104	2292,59019	3288,3919	1,8283E-06	0,0003403
759	CA1	370,800143	335,824088	405,776198	1,819E-06	0,0003403
1232	CCR3	2605,5539	2323,03427	2888,07353	1,936E-06	0,00035692
100874264	AOAH-IT1	33,763351 2	46,101387 2	21,425315 2	2,119E-06	0,00038698
283120	H19	35,741644 7	23,614804 7	47,868484 7	2,5693E-06	0,00046483
10437	IFI30	20962,762 3	24541,673	17383,851 7	2,6782E-06	0,00048004

5273	SERPINB10	66,5947142	50,4581191	82,7313092	3,0531E-06	0,00054222
645843	TMEM14E	11,0618317	17,5312779	4,59238555	3,0911E-06	0,00054397
10581	IFITM2	39106,549	43532,9757	34680,1223	3,7802E-06	0,00065926
598	BCL2L1	7030,77686	6357,02001	7704,5337	3,9293E-06	0,00067913
5909	RAP1GAP	67,2192562	53,767598	80,670915	4,0162E-06	0,00068801
28	ABO	135,400904	109,624706	161,177102	4,0866E-06	0,00069394
83943	IMMP2L	1668,8289 8	1473,07201	1864,58596	4,2799E-06	0,00072044
3047	HBG1	214,987768	255,834139	174,141396	4,3411E-06	0,00072444
260429	PRSS33	776,401768	681,831387	870,972149	4,3832E-06	0,00072522
2209	FCGR1A	791,680475	928,644392	654,716558	4,4581E-06	0,00073136
441864	TARM1	19,655291 8	11,259905 7	28,050677 9	5,9465E-06	0,00096733
23251	KIAA1024	139,020234	115,218255	162,822214	6,0743E-06	0,00097988
991	CDC20	65,2402088	83,259775 7	47,220641 9	6,2286E-06	0,00099647
4883	NPR3	41,673399	31,917821 6	51,428976 4	6,3478E-06	0,00100722
125875	CLDND2	288,458188	229,98059	346,935787	6,8231E-06	0,00107383
79365	BHLHE41	148,365322	174,651583	122,079061	7,0404E-06	0,00109909
54490	UGT2B28	56,1017371	42,455613 1	69,747861 1	7,7457E-06	0,00119953
149345	SHISA4	139,735733	111,545761	167,925706	8,1438E-06	0,00125117
8347	HIST1H2BC	237,361905	268,004862	206,718949	8,6306E-06	0,00131552
59340	HRH4	380,836548	331,200312	430,472784	8,8577E-06	0,00133958
6280	S100A9	115029,062	132140,142	97917,9813	8,9709E-06	0,00134619
26807	SNORD43	593,6207	671,747892	515,493507	1,0551E-05	0,00157117
6038	RNASE4	439,209026	509,414897	369,003156	1,0852E-05	0,00160362
51339	DACT1	160,506274	135,29894	185,713608	1,1885E-05	0,00172986
3162	HMOX1	3001,44793	3442,31797	2560,57788	1,1821E-05	0,00172986
5097	PCDH1	135,323054	110,728949	159,917159	1,2551E-05	0,0018131

201305	SPNS3	1487,70569	1320,46535	1654,94603	1,3353E-05	0,00191467
9935	MAFB	2327,44669	2718,66239	1936,23099	1,3534E-05	0,00192633
59352	LGR6	512,954514	423,458983	602,450045	1,3785E-05	0,00194643
199675	C19orf59	767,807054	885,477222	650,136887	1,3876E-05	0,00194643
83999	KREMEN1	1572,52686	1767,54936	1377,50435	1,4985E-05	0,00208694
6614	SIGLEC1	1029,93932	1291,11428	768,76437	1,6083E-05	0,0022238
1281	COL3A1	4,941904244	8,844662133	1,039146355	1,9949E-05	0,00273618
2030	SLC29A1	1174,61905	1050,47696	1298,76113	2,0071E-05	0,00273618
440603	BCL2L15	103,771044	82,236179	125,305909	2,2044E-05	0,00298407
83742	MARVELD1	794,823167	917,567163	672,07917	2,4464E-05	0,00328864
2322	FLT3	639,278566	752,721975	525,835156	2,6253E-05	0,00350481
2900	GRIK4	68,216770 3	53,132006 3	83,301534 3	2,6885E-05	0,00356467
1277	COL1A1	10,784746 7	16,653638	4,9158554 6	2,8343E-05	0,00373234
360226	PRSS41	115,03644 8	95,286215 8	134,78667 9	2,9681E-05	0,00388225
59283	CACNG8	256,93192 2	226,09643 2	287,76741 1	3,3702E-05	0,00437851
432	ASGR1	451,70557 3	518,16678 2	385,24436 3	3,6605E-05	0,00472394
51629	SLC25A39	13521,955 3	12353,973 1	14689,937 4	3,9206E-05	0,0050261
151473	SLC16A14	69,000239 6	56,795139 1	81,20534	4,1858E-05	0,00533079
440689	HIST2H2BF	1639,7171	1839,22614	1440,20806	4,3092E-05	0,00545218
401258	RAB44	1152,66341	1009,01988	1296,30694	4,3536E-05	0,00547256
4938	OAS1	3580,04105	4236,23712	2923,84499	5,6053E-05	0,00699569
83869	TTTY14	1712,40892	1493,32604	1931,4918	5,6376E-05	0,00699569
7225	TRPC6	74,996466	60,464260 5	89,528671 5	5,8272E-05	0,00718491
29065	ASAP1-IT1	18,800023 8	25,863530 8	11,736516 8	5,8831E-05	0,00720796
10107	TRIM10	84,732794 5	71,368685 1	98,096903 9	6,0218E-05	0,00733147
57801	HES4	78,756566 9	68,169744 8	89,343389 1	6,123E-05	0,00740808

719	C3AR1	1858,34427	2144,70111	1571,98743	6,2004E-05	0,00745506
114990	VASN	113,090351	89,0969476	137,083755	6,2674E-05	0,00748919
83483	PLVAP	181,810999	159,707174	203,914824	6,4115E-05	0,00761436
6322	SCML1	804,04622	705,003323	903,089117	6,5111E-05	0,00768545
59286	UBL5	1723,98966	1958,37565	1489,60367	6,6584E-05	0,00781167
10501	SEMA6B	60,7466881	45,3618074	76,1315687	6,843E-05	0,00797998
2359	FPR3	218,518412	266,635153	170,401671	7,0092E-05	0,00807643
100133941	CD24	1685,68917	1471,54163	1899,8367	6,9765E-05	0,00807643
146857	SLFN13	1866,75843	1610,53219	2122,98466	7,4594E-05	0,00854437
10417	SPON2	4919,37355	4142,81526	5695,93185	7,8465E-05	0,00893482
91319	DERL3	456,480294	533,160533	379,800055	7,9726E-05	0,00902537
10409	BASP1	8417,77981	9266,47197	7569,08765	8,1337E-05	0,00915415
22807	IKZF2	1715,22604	1524,66897	1905,78311	8,2413E-05	0,00922172
6241	RRM2	252,660319	293,844247	211,476391	8,4701E-05	0,0094232
51314	NME8	727,952306	613,304941	842,599671	8,9808E-05	0,00993434
8510	MMP23B	74,830087	54,6923068	94,9678672	9,0329E-05	0,00993513

Table 5. Differential expression between non-responders before and after medication. "GeneID" gene identification. "Gene symbol" official symbol. "Base mean" mean normalized counts, averaged over all samples from both conditions. "Base mean before medication" mean normalized counts from condition A. "Base mean after medication" mean normalized counts from condition B. "P value" p value for the statistical significance of this change. "Padj" P value adjusted for multiple testing with the Benjamini-Hochberg procedure, which controls false discovery rate.

geneID	Gene Symbol	Base Mean	Base Mean Before Medication	Base Mean After Medication	Pval	Padj
100462981	MTRNR2L2	502,526259	24,1282146	980,924303	5,5928E-240	1,08E-235

9381	OTOF	140,042976	218,398634	61,6873175	1,67837E-52	1,6205E-48
3429	IFI27	77,6132971	116,330085	38,8965087	1,10363E-37	7,1037E-34
100190986	LOC100190986	35,8846871	9,85915988	61,9102142	5,76401E-30	2,7826E-26
1719	DHFR	1128,99041	651,122435	1606,85839	5,58372E-23	2,1564E-19
9509	ADAMTS2	34,3995765	55,2185707	13,5805824	6,7234E-20	2,1638E-16
29065	ASAP1-IT1	15,841337 9	27,4265372	4,25613857	6,37861E-19	1,7596E-15
100463486	MTRNR2L8	158,49617 6	88,8018169	228,190535	8,79429E-18	2,1227E-14
5139	PDE3A	856,12931	1108,7521	603,50652	7,22409E-15	1,55E-11
554226	ANKRD30BL	320,68094 4	421,951446	219,410442	3,68941E-14	7,1243E-11
3488	IGFBP5	8,6019496 6	15,1012774	2,1026219	1,47432E-12	2,5881E-09
81796	SLCO5A1	19740,039 6	24475,0927	15004,9865	2,52259E-10	4,0593E-07
212	ALAS2	4829,2444 9	6329,92618	3328,56281	3,69686E-10	5,4913E-07
164045	HFM1	34344,306 5	42282,9209	26405,6922	8,20303E-10	1,1314E-06
23500	DAAM2	346,92370 6	407,583301	286,26411	7,23624E-09	9,3155E-06
124912	SPACA3	14,796190 4	21,5754544	8,01692647	7,95253E-09	9,5977E-06
6614	SIGLEC1	1596,2983 1	1727,70644	1464,89018	6,84918E-08	7,7799E-05
246	ALOX15	1071,3974 6	898,952345	1243,84257	2,85356E-07	0,0003061 2
1740	DLG2	5040,8701 8	6052,12644	4029,61392	3,83212E-07	0,0003894 6
221687	RNF182	59,990631	82,3998153	37,5814466	9,83454E-07	0,0009495 2
3620	IDO1	260,26675 2	209,830713	310,70279	1,24997E-06	0,0011493 8
3047	HBG1	284,18984 2	366,594583	201,785101	1,90713E-06	0,0016739 4
714	C1QC	31,752459 8	40,2568902	23,2480295	2,38158E-06	0,0019994 9

Table 6. The 30 genes with the highest predictive power. "Gene Symbol" official symbol. "Chr" chromosome. "Start" Gene start coordinate. "End" Gene end coordinate. "Gini" Gini variable importance measures reflect the mean decrease in impurity by

splits of a given variable in the classification tree, weighted by the proportion of samples reaching that node.

Gene symbol	Chr	Start	End	Gini
SLC9A3	chr5	473333	524549	0,90692249
HMOX1	chr22	35777059	35790207	0,895315136
SLC22A16	chr6	110745891	110797844	0,505405963
LOC284581	chr1	205831206	205865215	0,501917214
PF4V1	chr4	74719012	74720198	0,392855982
GSTT1	chr22	24376138	24384284	0,380503482
DLC1	chr8	12940871	13372429	0,327980015
AQP10	chr1	154293591	154297801	0,303985142
NLRP2	chr19	55476651	55512510	0,287145296
C17orf97	chr17	260117	264457	0,260801575
CRIP2	chr14	105939274	105946507	0,258219847
EGFL7	chr9	139553307	139567130	0,23700338
LOC642846	chr12	9436252	9466684	0,235587821
ATOH8	chr2	85980908	86018506	0,231554415
FMN1	chr15	33057744	33486934	0,229543432
BTNL3	chr5	180415844	180433727	0,228373919
DGKK	chrX	50108405	50213737	0,210864272
FAM153B	chr5	175490711	175541801	0,199406607
C4BPA	chr1	207277606	207318317	0,195035924
TRIM6	chr11	5617330	5634188	0,193156146
KRT72	chr12	52979372	52995322	0,189711245
IL8	chr4	74606222	74609433	0,18594549
PTGDS	chr9	139871955	139876194	0,184917648
NTNG2	chr9	135037333	135118220	0,182725824
TMEM63C	chr14	77648101	77725838	0,176103025
LIPN	chr10	90521162	90537999	0,170802146
VWF	chr12	6058039	6233836	0,168301614
ANK2	chr4	113739238	114304896	0,157175476
CENPK	chr5	64813592	64858995	0,154019124
SIGLEC1	chr20	3667616	3687775	0,15289179

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CLAIMS

1. Use of the expression level of the SLC9A3 gene as a biomarker in an *in vitro* method for predicting the therapeutic response to antipsychotic drugs in a subject suffering from a psychotic disorder or for the screening of compounds, molecules or compositions useful for the treatment of a psychotic disorder.

2. Use according to claim 1, further comprising the use of the expression level of the HMOX1 gene.

3. Use according to any of claims 1 or 2, further comprising the use of the expression level of the SLC22A16 gene.

4. Use according to any one of claims 1 to 3, further comprising the use of the expression level of the LOC284581 gene.

5. Use according to any one of claims 1 to 4, further comprising the use of the expression level of the PF4V1 gene.

6. Use according to any one of claims 1 to 5, further comprising the use of the expression level of the GSTT1 gene.

7. Use according to any one of claims 1 to 6, wherein the genes are SLC9A3, HMOX1, SLC22A16, LOC284581, PF4V1 and GSTT1.

8. Use according to any one of claims 1 to 7, wherein the psychotic disorder is selected from the list consisting of: schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder, delusional disorder, delirium, dementia and/or behavioral disorders.

9. Use according to claim 8, wherein the psychotic disorder is schizophrenia.

10. Use according to any one of claims 1 to 9, wherein the antipsychotic drug is selected from the list consisting of: aripiprazole, risperidone, olanzapine, paliperidone, chlorpromazine, clozapine, quetiapine, ziprasidone, asenapine,

iloperidone, zotepine, amisulpride, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, zuclopenthixol, or any combination thereof.

11. Use according to any one of claims 1 to 10, wherein the expression levels are RNA and/or protein, preferably mRNA.

12. An *in vitro* method for predicting the therapeutic response to antipsychotic drugs in a subject suffering from a psychotic disorder, comprising the following steps:

a) measuring the expression level of the SLC9A3 gene in an isolated biological sample collected from the subject suffering from a psychotic disorder before the treatment with antipsychotic drugs,
b) comparing the expression level value obtained after step (a) with an standard value, and
c) assigning the subject of step (a) to the group of patients that will positively respond to the treatment with antipsychotic drugs when the expression level value obtained after step (a) is lower than the standard value,

wherein the standard value is the mean value obtained after measuring the expression level of the SLC9A3 gene in isolated biological samples collected from a group of subjects suffering from a psychotic disorder who have not been treated with antipsychotic drugs.

13. The method according to claim 12, further comprising: measuring in step (a) the expression level of the HMOX1 gene, comparing in step (b) this expression level value with an standard value, and assigning in step (c) the subject to the group of patients that will positively respond to the treatment with antipsychotic drugs when this expression level value obtained after step (a) is higher than the standard value, wherein this standard value is the mean value obtained after measuring the expression level of the HMOX1 gene in isolated biological samples collected from a group of subjects suffering from a psychotic disorder who have not been treated with antipsychotic drugs.

14. The method according to any of claims 12 or 13, further comprising: measuring in step (a) the expression level of the SLC22A16 gene, comparing in step (b) this

expression level value with an standard value, and assigning in step (c) the subject to the group of patients that will positively respond to the treatment with antipsychotic drugs when this expression level value obtained after step (a) is higher than the standard value, wherein this standard value is the mean value obtained after measuring the expression level of the SLC22A16 gene in isolated biological samples collected from a group of subjects suffering from a psychotic disorder who have not been treated with antipsychotic drugs.

15. The method according to any one of claims 12 to 14, further comprising: measuring in step (a) the expression level of the LOC284581 gene, comparing in step (b) this expression level value with an standard value, and assigning in step (c) the subject to the group of patients that will positively respond to the treatment with antipsychotic drugs when this expression level value obtained after step (a) is lower than the standard value, wherein this standard value is the mean value obtained after measuring the expression level of the LOC284581 gene in isolated biological samples collected from a group of subjects suffering from a psychotic disorder who have not been treated with antipsychotic drugs.

16. The method according to any one of claims 12 to 15, further comprising: measuring in step (a) the expression level of the PF4V1 gene, comparing in step (b) this expression level value with an standard value, and assigning in step (c) the subject to the group of patients that will positively respond to the treatment with antipsychotic drugs when this expression level value obtained after step (a) is higher than the standard value, wherein this standard value is the mean value obtained after measuring the expression level of the PF4V1 gene in isolated biological samples collected from a group of subjects suffering from a psychotic disorder who have not been treated with antipsychotic drugs.

17. The method according to any one of claims 12 to 16, further comprising: measuring in step (a) the expression level of the GSTT1 gene, comparing in step (b) this expression level value with an standard value, and assigning in step (c) the subject to the group of patients that will positively respond to the treatment with antipsychotic drugs when this expression level value obtained after step (a) is lower than the standard value, wherein this standard value is the mean value obtained after measuring the expression level of the GSTT1 gene in isolated biological

samples collected from a group of subjects suffering from a psychotic disorder who have not been treated with antipsychotic drugs.

18. The method according to any one of claims 12 to 17, wherein the psychotic disorder is selected from the list consisting of: schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder, delusional disorder, delirium, dementia and/or behavioral disorders.

19. The method according to claim 18, wherein the psychotic disorder is schizophrenia.

20. The method according to any one of claims 12 to 19, wherein the antipsychotic drug is selected from the list consisting of: aripiprazole, risperidone, olanzapine, paliperidone, chlorpromazine, clozapine, quetiapine, ziprasidone, asenapine, iloperidone, zotepine, amisulpride, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, zuclopenthixol, or any combination thereof.

21. The method according to any one of claims 12 to 20, wherein the expression levels are RNA and/or protein, preferably mRNA.

22. The method according to any one of claims 12 to 21, wherein the isolated biological sample is peripheral blood.

23. An *in vitro* method for the screening of compounds, molecules or compositions useful for the treatment of a psychotic disorder that comprises:

i) measuring the expression level of the SLC9A3 gene in an isolated biological sample obtained from a subject suffering from a psychotic disorder before the administration of the compound, molecule or composition to be tested,

ii) measuring the expression level of the same gene as that measured in step (i) in an isolated biological sample obtained from the same subject after the administration of the compound, molecule or composition to be tested,

iii) comparing the expression level values obtained in (i) and (ii), and

iv) classifying the compound, molecule or composition as useful for the treatment of a psychotic disorder when a significant difference in the expression level values has been detected in step (iii).

24. The method according to claim 23, wherein said method further comprises measuring in step (i) the expression level of at least one gene selected from the list consisting of: HMOX1, SLC22A16, LOC284581, PF4V1 and/or GSTT1.

25. The method according to claim 24, wherein said method comprises measuring in step (i) the expression level of the following genes: SLC9A3, HMOX1, SLC22A16, LOC284581, PF4V1 and GSTT1.

26. The method according to any one of claims 23 to 25, wherein the psychotic disorder is selected from the list consisting of: schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder, delusional disorder, delirium, dementia and/or behavioral disorders.

27. The method according to claim 26, wherein the psychotic disorder is schizophrenia.

28. The method according to any one of claims 23 to 27, wherein the expression levels are RNA and/or protein, preferably mRNA.

29. The method according to any one of claims 23 to 28, wherein the isolated biological sample is peripheral blood.

30. A kit for predicting the therapeutic response to antipsychotic drugs in a subject suffering from a psychotic disorder or for the screening of compounds, molecules or compositions useful for the treatment of a psychotic disorder, comprising compounds capable of specifically binding SLC9A3 gene or its expression products.

31. The kit according to claim 30, further comprising compounds capable of specifically binding HMOX1, SLC22A16, LOC284581, PF4V1 and/or GSTT1 genes or their expression products.

32. The kit according to any of claims 30 or 31, wherein the compounds are labels, antibodies and/or primers, preferably primers.

33. Use of the kit according to any one of claims 30 to 32 for performing the method according to any one of claims 12 to 22 or the method according to any one of claims 23 to 29.

FIG. 1

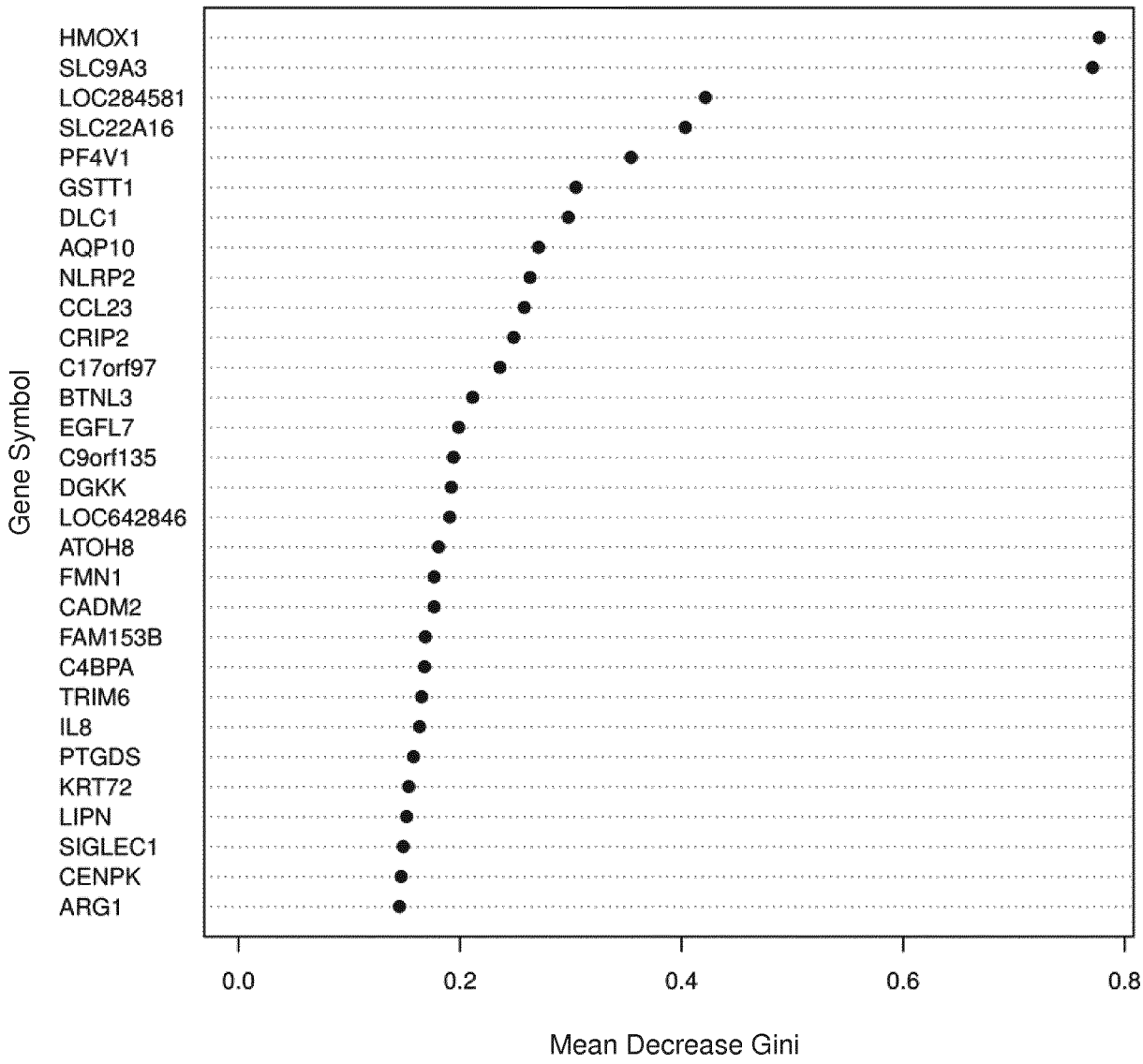

HMOX1
SLC9A3
LOC284581
SLC22A16
PF4V1
GSTT1
DLC1
AQP10
NLRP2
CCL23
CRIP2
C17orf97
BTNL3
EGFL7
C9orf135
DGKK
LOC642846
ATOH8
FMN1
CADM2
FAM153B
C4BPA
TRIM6
IL8
PTGDS
KRT72
LIPN
SIGLEC1
CENPK
ARG1
Gene Symbol
0.0
0.2
0.4
0.6
0.8
Mean Decrease Gini

FIG. 2

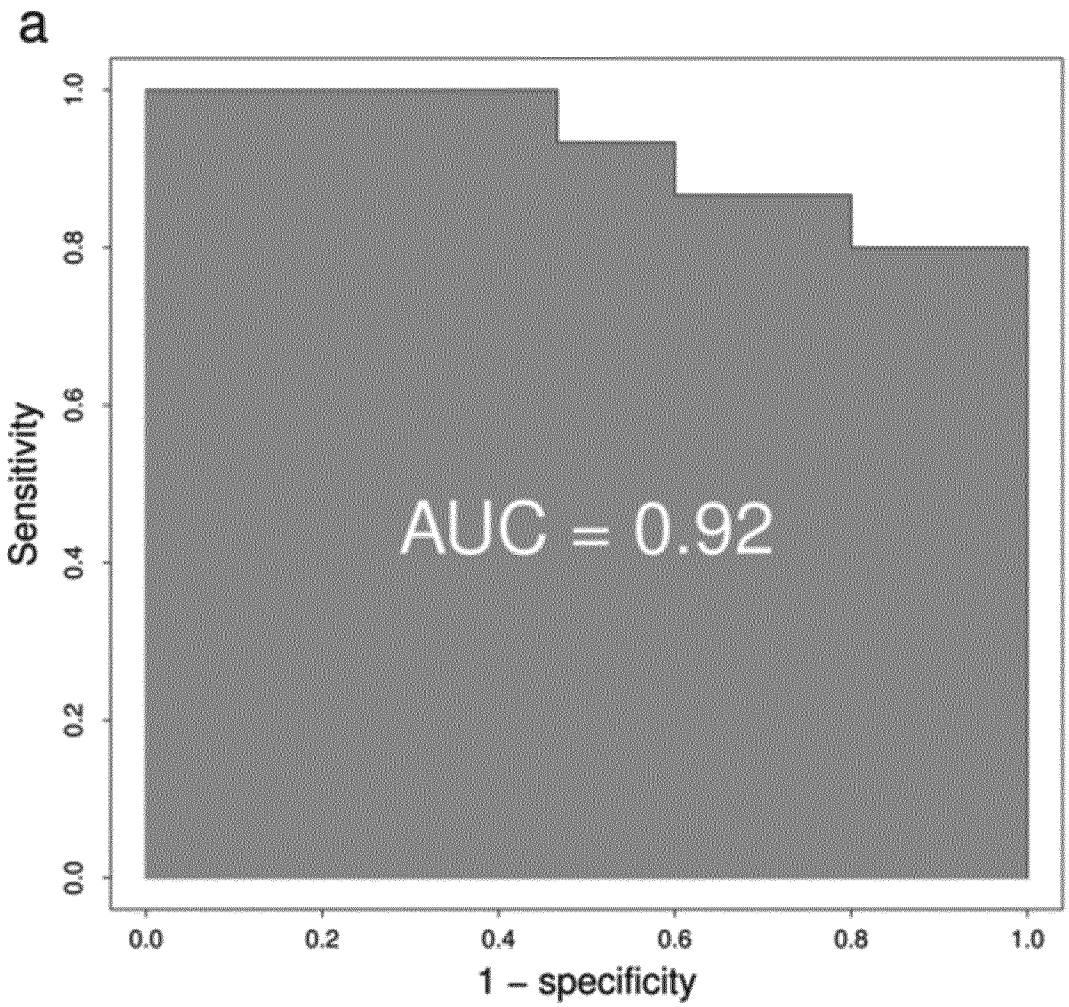

a
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
AUC = 0.92
0.0
0.2
0.4
0.6
0.8
1.0
1 – specificity

FIG. 2 (cont.)

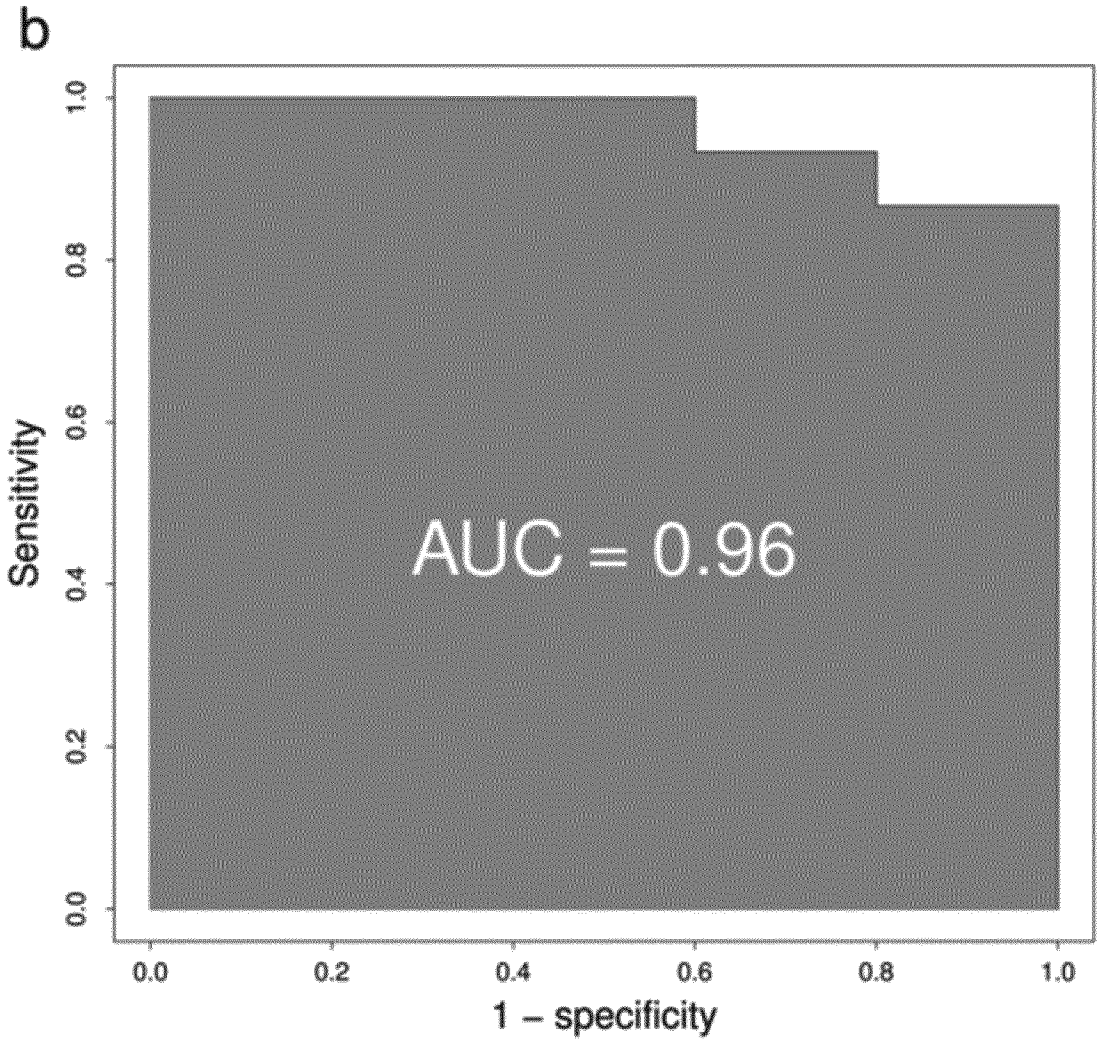

b
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
AUC = 0.96
0.0
0.2
0.4
0.6
0.8
1.0
1 – specificity

FIG. 2 (cont.)

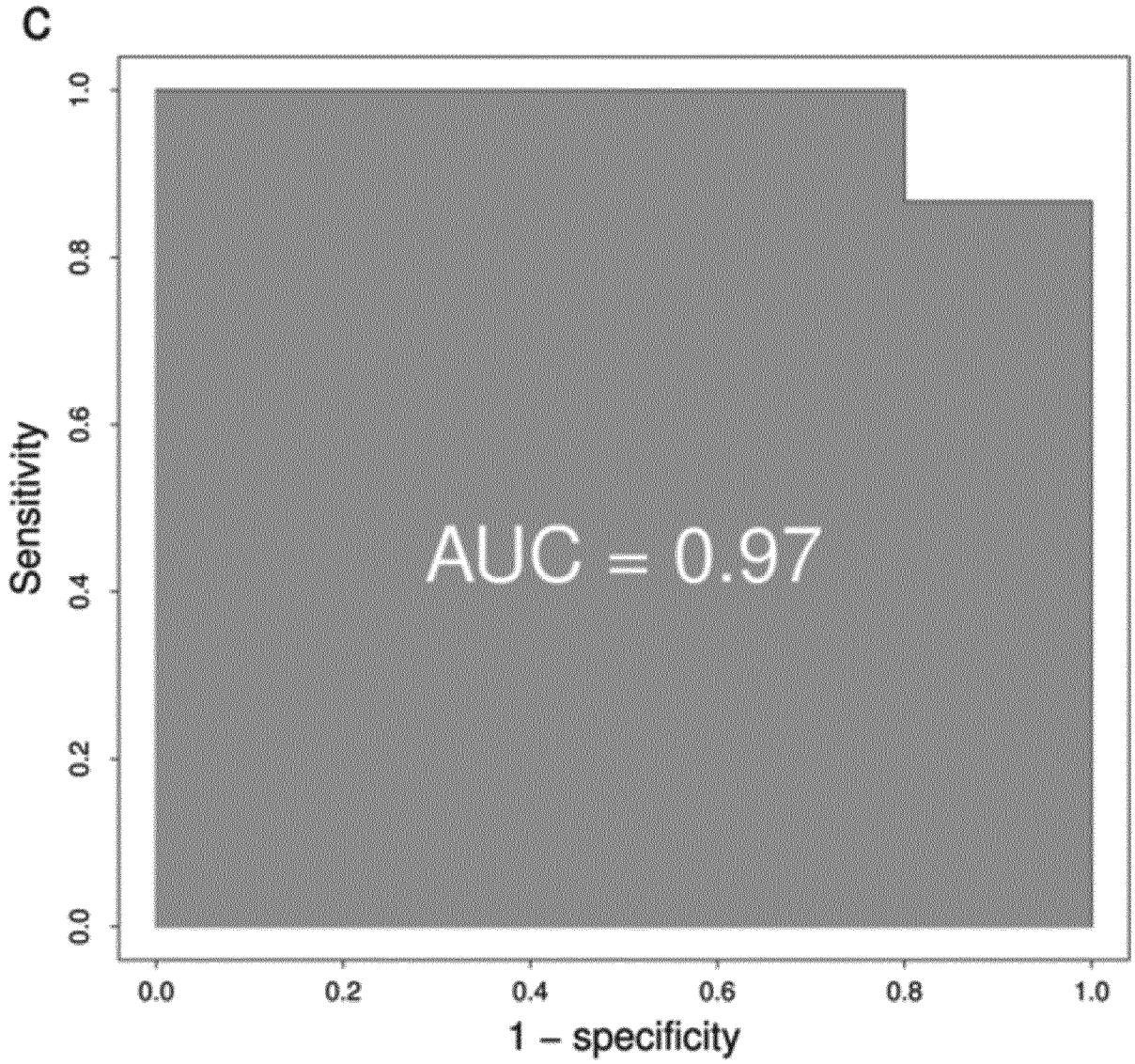
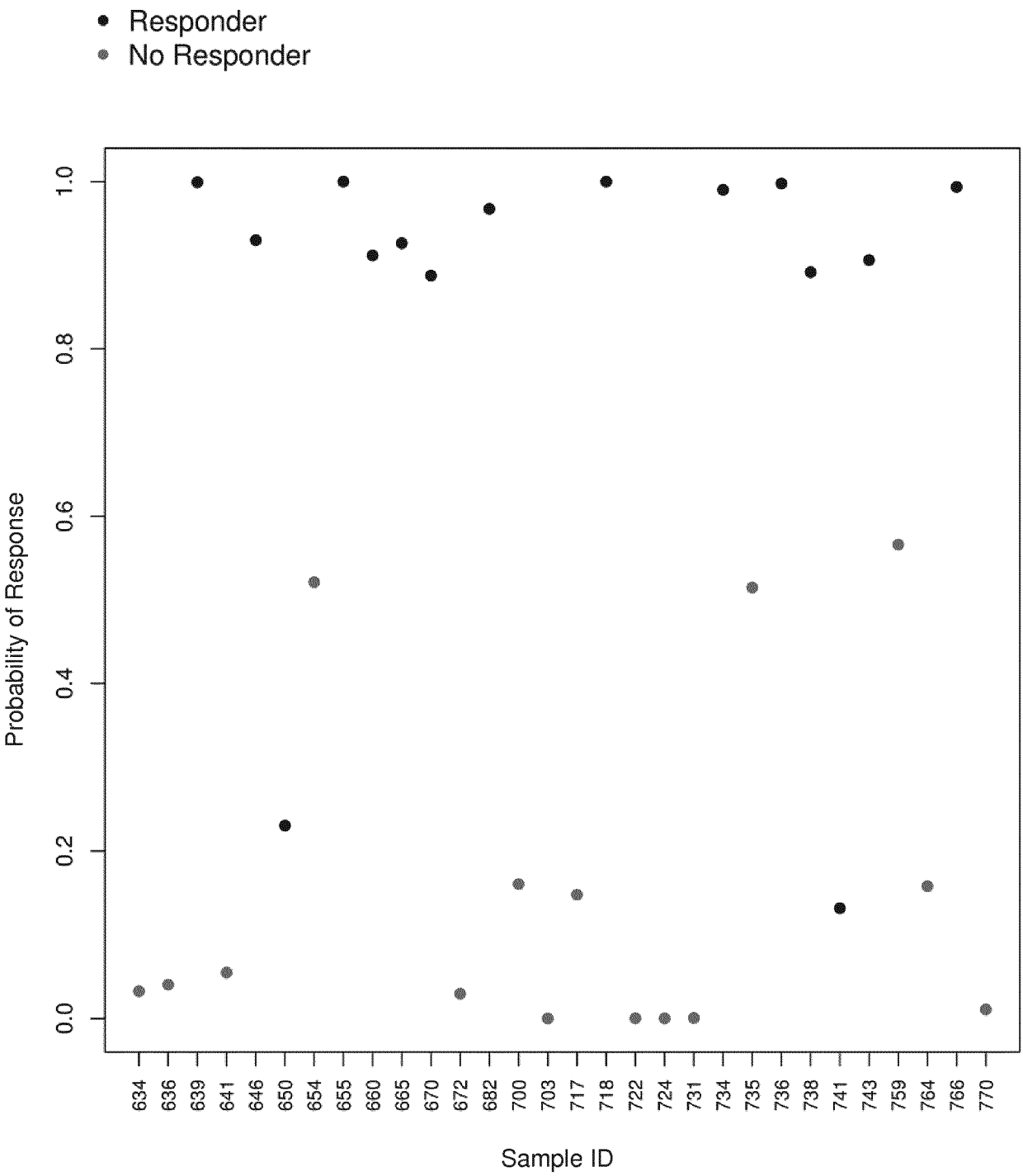

C
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
AUC = 0.97
0.0
0.2
0.4
0.6
0.8
1.0
1 – specificity

FIG. 3


Responder
No Responder
Probability of Response
0.0
0.2
0.4
0.6
0.8
1.0
634
636
639
641
646
650
654
655
660
665
670
672
682
700
703
717
718
722
724
731
734
735
736
738
741
743
759
764
766
770
Sample ID

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/057761

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/6876 G01N33/68
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HARDIMAN G: "MICROARRAY PLATFORMS - COMPARISONS AND CONTRASTS", PHARMACOGENOMICS, FUTURE MEDICINE, UK, vol. 5, no. 5, 1 January 2004 (2004-01-01) , pages 487-502, XP009079995, ISSN: 1462-2416, DOI: 10.1517/14622416.5.5.487 whole document, in particular Table 2	30-32

X	WO 2016/127070 A1 (UNIV FLORDIA RES FOUNDATION INC [US]) 11 August 2016 (2016-08-11) whole document, in particular page 13, lines 1-4	30,32

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 April 2018	04/05/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Vanmontfort, D

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BENEDICTO CRESPO-FACORRO ET AL: "Schizophrenia Gene Expression Profile Reverted to Normal Levels by Antipsychotics", INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY, vol. 18, no. 4, 29 January 2015 (2015-01-29), XP055469806, Cambridge ISSN: 1461-1457, DOI: 10.1093/ijnp/pyu066 cited in the application whole document, in particular abstract and Figure 1	1-33
A	WO 2016/020573 A1 (FUNDACIÓN INST DE INVESTIGACIONES MARQUES DE VALDECILLA [ES]; CONSEJO) 11 February 2016 (2016-02-11) whole document, in particular abstract and claims	1-33
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2018/057761

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		WO 2008055341 A1	15-05-2008