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(54) **KCNQ2-15 POTASSIUM CHANNEL**

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C12N 5/00	(2006.01)
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C07H 21/02	(2006.01)

(52) **U.S. Cl.** **435/69.1**; 435/320.1; 435/325; 530/350; 536/23.1

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

The invention encompasses polypeptides and polynucleotides of three novel bipolar disorder-associated potassium channel polypeptides, KCNQ2-15bx, KCNQ2-15by and KCNQ2-15bz. The invention further relates to the use of potassium channels comprising KCNQ2 subunits for screening for modulators thereof, the use of these modulators for treating mental disorders such as bipolar disorder, schizophrenia and depression, and drugs comprising these modulators. The invention also discloses biallelic markers located in the KCNQ2 gene and their use for diagnosing mental disorders.

8 Claims, 4 Drawing Sheets

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RefseqN Accession No. NT_006051, Aug. 29, 2006.

Fig. 1A

```
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SEQ ID NO:2    1 MVQRSRNGGVYPGPSGEKKLKVGFVGLDPGAPDSTRDGALLIAGSEAPKRGSILSKPRAG
SEQ ID NO:4    1 MVQRSRNGGVYPGPSGEKKLKVGFVGLDPGAPDSTRDGALLIAGSEAPKRGSILSKPRAG
SEQ ID NO:6    1 MVQRSRNGGVYPGPSGEKKLKVGFVGLDPGAPDSTRDGALLIAGSEAPKRGSILSKPRAG
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SEQ ID NO:7   61 GAGAGKPPKRNAFYRKLQNFLYNVLERPRGWAFIYHAYVFLLVFSCLVLSVFSTIKEYEK
SEQ ID NO:2   61 GAGAGKPPKRNAFYRKLQNFLYNVLERPRGWAFIYHAYVFLLVFSCLVLSVFSTTKEYEK
SEQ ID NO:4   61 GAGAGKPPKRNAFYRKLQNFLYNVLERPRGWAFIYHAYVFLLVFSCLVLSVFSTTKEYEK
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SEQ ID NO:2  121 SSBGALYILEIVTVVFGVEYFVRIWAAGCCCRYRGWRGRLKFARKPFCVIDIMVLIASI
SEQ ID NO:4  121 SSBGALYILEIVTVVFGVEYFVRIWAAGCCCRYRGWRGRLKFARKPFCVIDIMVLIASI
SEQ ID NO:6  121 SSBGALYILEIVTVVFGVEYFVRIWAAGCCCRYRGWRGRLKFARKPFCVIDIMVLIASI
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SEQ ID NO:7  181 AVLAAGSQGNVFATSALRSLRFLQILRMFNVDRRGGTWKLLGSVVFAHSKELVTAWYIGF
SEQ ID NO:2  181 AVLAAGSQGNVFATSALRSLRFLQILRMFMDRRGGTWKLLGSVVFAHSKELVTAWYIGF
SEQ ID NO:4  181 AVLAAGSQGNVFATSALRSLRFLQILRMFMDRRGGTWKLLGSVVFAHSKELVTAWYIGF
SEQ ID NO:6  181 AVLAAGSQGNVFATSALRSLRFLQILRMFMDRRGGTWKLLGSVVFAHSKELVTAWYIGF
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SEQ ID NO:7  241 LCLIIASFLVYLAAEKGEMDHFDTYADALAWGLITITIVGYGDKVPQTWNGRLLAATFLLI
SEQ ID NO:2  241 LCLIIASFLVYLAAEKGEMDHFDTYADALAWGLITITIVGYGDKVPQTWNGRLLAATFLLI
SEQ ID NO:4  241 LCLIIASFLVYLAAEKGEMDHFDTYADALAWGLITITIVGYGDKVPQTWNGRLLAATFLLI
SEQ ID NO:6  241 LCLIIASFLVYLAAEKGEMDHFDTYADALAWGLITITIVGYGDKVPQTWNGRLLAATFLLI
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SEQ ID NO:7  301 GVSFFALPAGILGSGFALKVQEQHRQKHFEKRRNPAAGLIQSAWRFYATNLSRTDLHSTW
SEQ ID NO:2  301 GVSFFALPAGILGSGFALKVQEQHRQKHFEKRRNPAAGLIQSAWRFYATNLSRTDLHSTW
SEQ ID NO:4  301 GVSFFALPAGILGSGFALKVQEQHRQKHFEKRRNPAAGLIQSAWRFYATNLSRTDLHSTW
SEQ ID NO:6  301 GVSFFALPAGILGSGFALKVQEQHRQKHFEKRRNPAAGLIQSAWRFYATNLSRTDLHSTW
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SEQ ID NO:4  361 QIYEHTVTVPMYSSQTQTYGASRLIPPIANQLELLRNIAKSKSGLAFRKDPPEPSPS----
SEQ ID NO:6  361 QIYEHTVTVPMY----------KLIPPLNQLELLRNLKSKSGLAFRKDPPEPSPS----
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SEQ ID NO:7  421 CRGPLCGCCPGRSSQRVSLKDRVFSSPRGVAAKGKGSPQAQTVRRSFSADQSLEDSPSKV
SEQ ID NO:2  421 CRGPLCGCCPGRSSQRVSLKDRVFSSPRGVAAKGKGSPQAQTVRRSFSADQSLEDSPSKV
SEQ ID NO:4  417 ----------QKVSLKDRVFSSPRGVAAKGKGSPQAQTVRRSFSADQSLEDSPSKV
SEQ ID NO:6  407 ----------QKVSLKDRVFSSPRGVAAKGKGSPQAQTVRRSFSADQSLEDSPSKV
                           ************************************************

SEQ ID NO:7  481 PKSWSFGDRSRARQAFRIKGAASRQNSEEASLPGEDIVDDRSCPCEFVTEDLTPGLKVSI
SEQ ID NO:2  481 PKSWSFGDRSRARQAFRIKGAASRQNSEEASLPGEDIVDDRSCPCEFVTEDLTPGLKVSI
SEQ ID NO:4  463 PKSWSFGDRSRARQAFRIKGAASRQNSEEASLPGEDIVDDKSCPCEFVTEDLTPGLKVSI
SEQ ID NO:6  453 PKSWSFGDRSRARQAFRIKGAASRQNSEEASLPGEDIVDDRSCPCEFVTEDLTPGLKVSI
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SEQ ID NO:2  541 RAVCVMRFLVSKRKFKESLRPYDVMDVIEQVSAGHLDMLSRIKSLQSRQEPRLPVQQGTR
SEQ ID NO:4  523 RAVCVMRFLVSKRKFKESLRPYDVMDVIEQVSAGHLDMLSRIKSLQSRQEPRLPVQQGIR
SEQ ID NO:6  513 RAVCVMRFLVSKRKFKESLRPYDVMDVIEQVSAGHLDMLSRIKSLQSRQEPRLPVQQGTR
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SEQ ID NO:7  601 PKDRTKGPARAELPEDPSWMGRLGKVEKQVLSMSKKLDELVNIYMQRMGIPPTEIEAYFG
SEQ ID NO:2  601 TGWASGPKPPVRHGGSAGGVWAGPPEPHRRPLDSRSVVSSQSLG----------------
SEQ ID NO:4  583 LGWASGTKPTVAHGGSAGGVWAGPPEPHRRPLSASVVSSQSLE----------------
SEQ ID NO:6  573 TGWASGTKPTVAHGGSAGGVWAGPPEPHRRPLSASVVSSQSLE----------------
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SEQ ID NO:7  661 AKKPEPAPPVHSPEDSRERHVDHGCIVKIVRSSSSTCQKNFSAPPAAPEVQCPPSTSMQP
SEQ ID NO:2  ----------------------------------------------------------------
SEQ ID NO:4  ----------------------------------------------------------------
SEQ ID NO:6  ----------------------------------------------------------------
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SEQ ID NO:7  721 QSHPRQGHGTSPVGDHGSLVRIPPPPAHERSLSAYGGGNRASMEFLRQEDTPGCRPPEGN
SEQ ID NO:2  ----------------------------------------------------------------
SEQ ID NO:4  ----------------------------------------------------------------
SEQ ID NO:6  ----------------------------------------------------------------
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SEQ ID NO:7  781 LRDSDTSISIPSVDHEELERSPSGFSISQSKENLQALNSCYAAVAPCAKVRPYIAEGESD
SEQ ID NO:2  ----------------------------------------------------------------
SEQ ID NO:4  ----------------------------------------------------------------
SEQ ID NO:6  ----------------------------------------------------------------
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SEQ ID NO:7  841 TDSDLCTPCGPPRSATGEGPFGDVGWAGPRK
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SEQ ID NO:6  ---------------------------------
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Fig. 1B

Figure 2

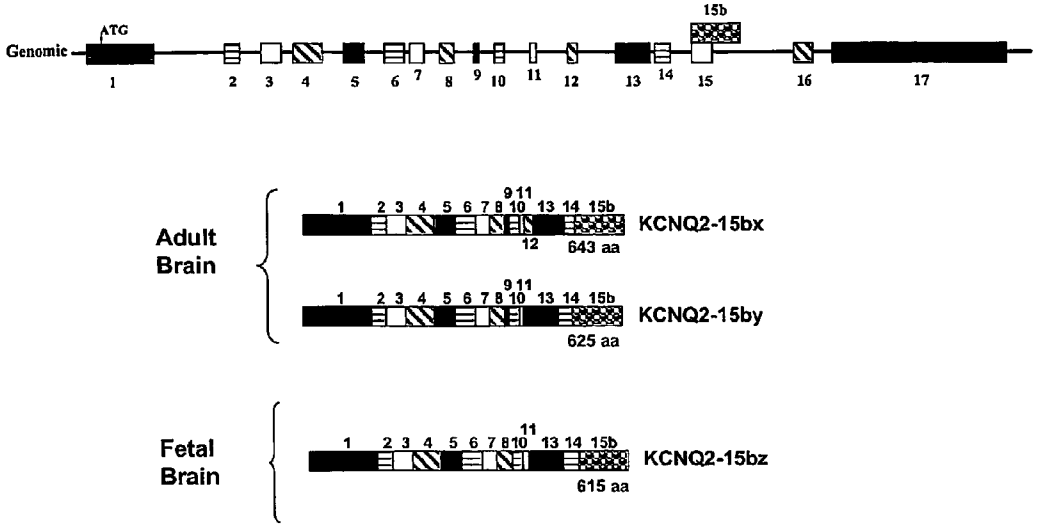


Figure 3

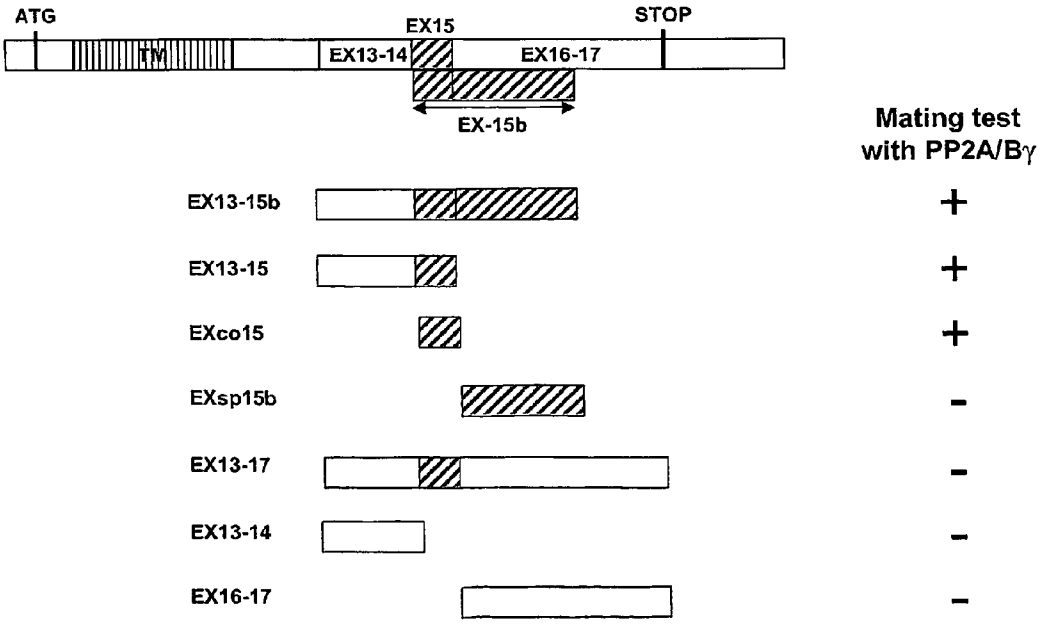


Figure 4

	Ex 13-17	Ex-13-15b	Ex 13-15
Ex 13-17	++	- / +	- / +
Ex 13-15b	-	+ +	+ +
Ex 13-15	-	+ +	+

Figure 5

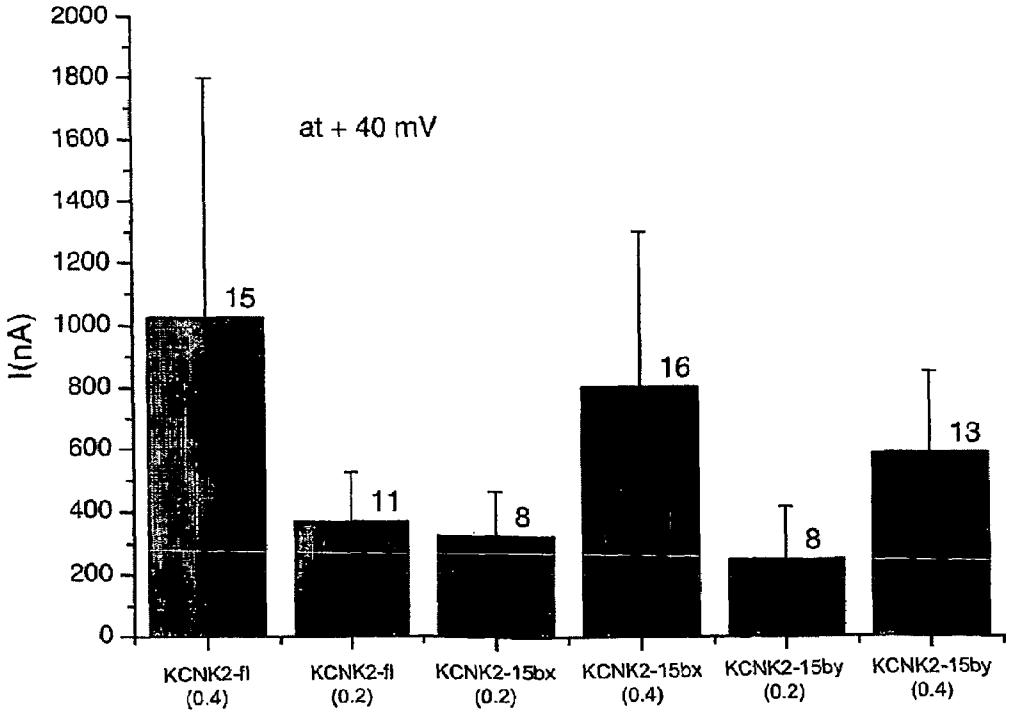


Figure 6A

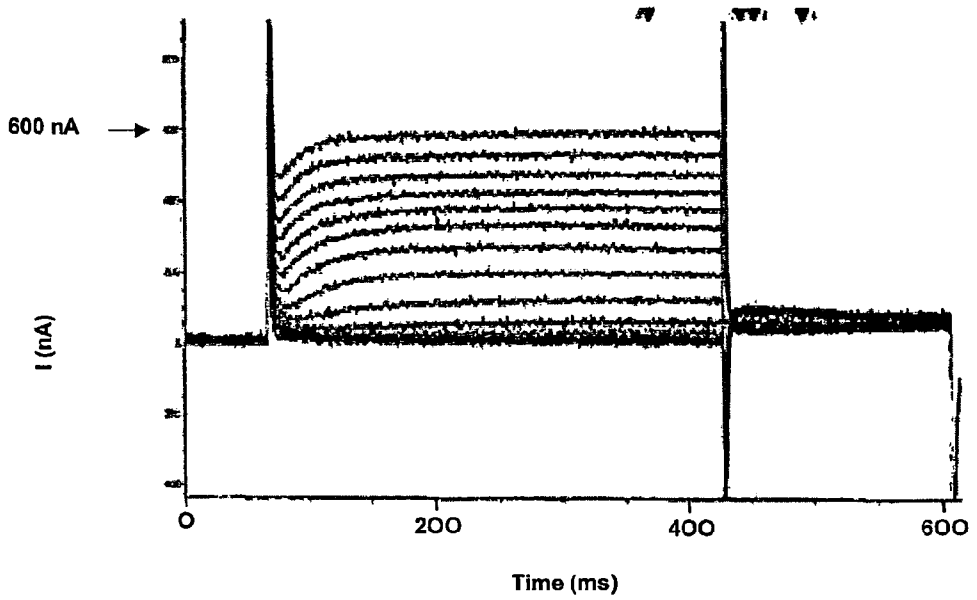
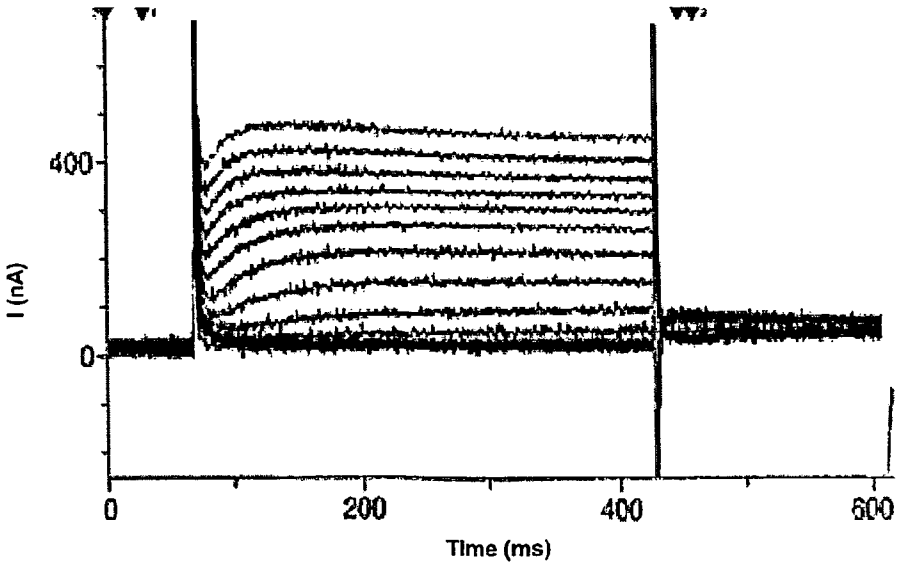


Figure 6B



KCNQ2-15 POTASSIUM CHANNEL

CROSS-REFERENCE TO RELATED APPLICATION

This application is the U.S. national stage application of International Patent Application No. PCT/EP2003/050246, filed Jun. 20, 2003, which claims the benefit of U.S. Provisional Patent Application No. 60/391,359, filed Jun. 25, 2002.

The Sequence Listing for this application is on duplicate compact discs labeled "Copy 1" and "Copy 2." Copy 1 and Copy 2 each contain only one file named "G-194US03PCT-Subst-Seq-List.txt" which was created on Jun. 22, 2005, and is 264 KB. The entire contents of each of the computer discs are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

This invention is in the field of mental disorders such as bipolar disorder, schizophrenia, depression and other mood disorders. More specifically, this invention relates to three novel potassium channels subunits, KCNQ2-15bx, KCNQ2-15by and KCNQ2-15bz. The invention also relates the use of potassium channels comprising KCNQ2 subunits for screening for modulators, and to the use of said modulators for treating said mental disorders. The invention further relates to the use of biallelic markers located in the KCNQ2 gene for diagnosing said mental disorders.

BACKGROUND

1. KCNQ Potassium Channels

Malfunction in ion channels, due to mutations in genes encoding channel proteins or the presence of autoantibodies, are increasingly being implicated in causing disease conditions, termed channelopathies. For instance, dysfunction of potassium channels has been associated with the pathophysiology of a number of neurological disorders both affecting the central and peripheral nervous system (e.g., episodic ataxia, epilepsy, neuromyotonia, Parkinson's disease, congenital deafness, long QT syndrome). Potassium channels, which demonstrate a high degree of diversity and ubiquity, are fundamental in the control of membrane depolarisation and cell excitability. A common feature of potassium channelopathies is a reduction or loss of membrane potential repolarisation. Marketed potassium channels openers include for example flupirtine, an analgesic drug used for treating pain.

KCNQ polypeptides belong to the potassium channel family. KCNQ polypeptides associate to form homomeric or heteromeric potassium channels, each polypeptide corresponding to a subunit of the channel. Currently, five different members of the KCNQ family are known: KCNQ1, KCNQ2, KCNQ3, KCNQ4 and KCNQ5. Heteromeric KCNQ potassium channels can be comprised either of different members of the KCNQ family, or of KCNQ polypeptides associated with other members of the potassium channel family. KCNQ potassium channels underlie the M-current, an important regulator of neuronal excitability. Both their amino-terminal and their carboxyl-terminal extremities are located on the intracellular side of the membrane. These extremities play an important role both in interactions with other proteins and in modulation of the channel's activity.

KCNQ1 is expressed in heart, cochlea, intestine and kidney. It assembles with either the product of the KCNE1 gene or with the product of the KCNE3 gene. Mutations in the KCNQ1 gene have been shown to cause one form of inherited long QT syndrome and a form of deafness.

KCNQ2 was first cloned in 1996. In 1998, geneticists discovered that an inherited form of juvenile epilepsy, the benign familial neonatal convulsions, is caused by mutations in the potassium channel KCNQ2 (Singh et al. Nat Genet, 1998, 18:25-9; Biervert et al., Science, 1998, 279:403-6). More specifically, Bievert et al. showed that a five-base pair insertion deleting more than 300 amino acids from the carboxyl-terminus of KCNQ2 leads to impairment of potassium-selective currents in vitro. It was thus demonstrated that loss of function mutations in KCNQ2 causes the epileptic syndrome. Wang et al. showed KCNQ2 to be expressed in brain, and to be associated with KCNQ3. In addition, they showed that the KCNQ2/3 heteromultimers underlie the M-current (Wang et al., Science, 1998, 282:1890-3). In 2000, Main et al. showed that KCNQ2 is the molecular target of retigabine, a potent anticonvulsant compound, and that retigabine acts as a KCNQ2/3 potassium channel opener (Mol Pharmacol, 2000, 58:253-62). Biervert et al. determined that the KCNQ2 gene has at least 18 exons, occupying more than 50 kb of genomic DNA (Genet., 1999, 104:234-240). Until now six different isoforms of KCNQ2 produced by alternative splicing have been described (see, e.g., SwissProt Accession No. O43526).

KCNQ4 is expressed in inner ear, and it has been shown that mutation in the KCNQ4 gene lead to a form of inherited deafness.

KCNQ5 is expressed in brain and skeletal muscle, and can co-assemble with KCNQ3, suggesting that it may also play a role in the M-current heterogeneity. It has been suggested that KCNQ5 deficiency leads to retinal degeneration.

The activity of KCNQ channels has been shown to be modulated by Protein kinase A (PKA) and by the c-Src tyrosine kinase (Src). Schroeder et al. showed that currents generated by heteromeric KCNQ2/KCNQ3 channels can be increased by intracellular cyclic AMP, and that this effect is mediated by PKA. PKA stimulated current intensity by 66% (Schroeder et al., Epilepsia (2000) 41:1068-1069). Gamper et al. showed that coexpression of Src with KCNQ2/KCNQ3 heteromeric channels resulted in a 4.5-fold reduction of current density and a 2-fold slowing of activation kinetics at 0 mV. However, Src had no effect on currents generated by KCNQ2 homomultimeric channels (J. Neurosci. (2003) 23:84-95). In view of these results, modulation of KCNQ channels by kinases and phosphatases is believed to be important for control of neuronal excitability.

Studying KCNQ channels in humans and animal models is of great importance for the understanding of how M-channels control excitability at the cellular, network, and behavioral levels. A better understanding of the physiological role of KCNQ channels is a promising way of finding of new targets for novel diseases, thus leading to the possibility of novel screenings of drug candidates.

2. The PP2A Phosphatase

The PP2A phosphatase is an intracellular serine/threonine protein phosphatase constituted by two or three subunits. PP2A phosphatases comprise of a catalytic subunit (PP2A/C), a scaffolding subunit (PP2A/A) and eventually a regulatory subunit (PP2A/B).

Regulatory subunits are thought to confer tissue specificity, subcellular localization and developmental regulation to PP2A. More than eleven ndifferent regulatory subunits are currently known, and PP2A/Bγ is one of them. PP2A/Bγ is encoded by the PPP2R2C gene that was mapped to human chromosome 4p16 between markers D4S2925 and D4S3007 (Hu et al., Genomics., 2000, 67:83-6). The PP2A/Bγ protein can only be detected in brain and is enriched in the cytosolic fraction of the cell. Furthermore, PPP2R2C is developmentally regulated.

3. Mental Disorders

Mental disorders encompass a wide range of CNS disorders. Mental disorders include, e.g., mood disorders, psychotic disorders, anxiety disorders, childhood disorders, eating disorders and personality disorders, all these terms being defined according to the DSM-IV classification (Diagnosis and Statistical Manual of Mental Disorders, Fourth Edition, American Psychiatric Association, Washington D.C., 1994). Mood Disorders encompass bipolar I disorder (mania with or without major depression), bipolar II disorder (hypomania with major depression), cyclothymic disorder (numerous brief episodes of hypomania and minor depression), dysthymic disorder (prolonged minor depression without mania/hypomania) and major depressive disorder (major depression without mania). Psychotic disorders encompass schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, delusional disorder and shared psychotic disorder. Bipolar disorder, schizophrenia and depression are three particularly serious and widespread mental disorders.

3.1. Bipolar Disorder

Bipolar disorders are relatively common disorders, occurring in about 1.3% of the population, and have been reported to constitute about half of the mood disorders seen in psychiatric clinics with severe and potentially disabling effects. Bipolar disorders have been found to vary with gender depending of the type of disorder; for example, bipolar disorder I is found equally among men and women, while bipolar disorder II is reportedly more common in women. The age of onset of bipolar disorders is typically in the teenage years and diagnosis is typically made in the patient's early twenties. Bipolar disorders also occur among the elderly, generally as a result of a neurological disorder or other medical conditions. In addition to the severe effects on patients' social development, suicide completion rates among bipolar patients are reported to be about 15%.

Bipolar disorders are characterized by phases of excitement and often depression; the excitement phases, referred to as mania or hypomania, and depressive phases can alternate or occur in various admixtures, and can occur to different degrees of severity and over varying duration. Since bipolar disorders can exist in different forms and display different symptoms, the classification of bipolar disorder has been the subject of extensive studies resulting in the definition of bipolar disorder subtypes and widening of the overall concept to include patients previously thought to be suffering from different disorders. Bipolar disorders often share certain clinical signs, symptoms, treatments and neurobiological features with psychotic illnesses in general and therefore present a challenge to the psychiatrist to make an accurate diagnosis. Furthermore, because the course of bipolar disorders and various mood and psychotic disorders can differ greatly, it is critical to characterize the illness as early as possible in order to offer means to manage the illness over a long term.

The mania associated with the disease impairs performance and causes psychosis, and often results in hospitalization. This disease places a heavy burden on the patient's family and relatives, both in terms of the direct and indirect costs involved and the social stigma associated with the illness, sometimes over generations. Such stigma often leads to isolation and neglect. Furthermore, the earlier the onset, the more severe are the effects of interrupted education and social development.

The DSM-IV classification of bipolar disorder distinguishes among four types of disorders based on the degree and duration of mania or hypomania as well as two types of disorders which are evident typically with medical conditions or their treatments, or to substance abuse. Mania is recognized by elevated, expansive or irritable mood as well as by distractability, impulsive behavior, increased activity, grandiosity, elation, racing thoughts, and pressured speech. Of the four types of bipolar disorder characterized by the particular degree and duration of mania, DSM-IV includes:

- bipolar disorder I, including patients displaying mania for at least one week;
- bipolar disorder II, including patients displaying hypomania for at least 4 days, characterized by milder symptoms of excitement than mania, who have not previously displayed mania, and have previously suffered from episodes of major depression;
- bipolar disorder not otherwise specified (NOS), including patients otherwise displaying features of bipolar disorder II but not meeting the 4 day duration for the excitement phase, or who display hypomania without an episode of major depression; and
- cyclothymia, including patients who show numerous manic and depressive symptoms that do not meet the criteria for hypomania or major depression, but which are displayed for over two years without a symptom-free interval of more than two months.

The remaining two types of bipolar disorder as classified in DSM-VI are disorders evident or caused by various medical disorder and their treatments, and disorders involving or related to substance abuse. Medical disorders which can cause bipolar disorders typically include endocrine disorders and cerebrovascular injuries, and medical treatments causing bipolar disorder are known to include glucocorticoids and the abuse of stimulants. The disorder associated with the use or abuse of a substance is referred to as "substance induced mood disorder with manic or mixed features".

Evidence from twin and adoption studies, and the lack of variation in incidence worldwide, indicate that bipolar disorder is primarily a genetic condition, although environmental risk factors are also involved at some level as necessary, sufficient, or interactive causes. Aggregation of bipolar disorder and schizophrenia in families suggests that these two distinct disorders share some common genetic susceptibility. Several linkage studies of bipolar disorder have been reported, and several susceptibility regions have been identified. The regions that are associated with bipolar disorder include 1q31-q32, 4p16, 7q31, 12q23-q24, 13q32, 18p11.2, 21q22 and 22q11-q13 (Detera-Wadleigh et al. (1999) Proc Natl Acad Sci USA A96(10):5604-9). Some of these regions, like 4p16, 12q24, 18p11, 21q21 and 22q11 have been repeatedly implicated by independent investigators. Furthermore, some regions that are linked to bipolar disorder such as, e.g., 13q32 and 18p11.2, are also implicated in genome scans of schizophrenia, confirming that these two distinct disorders share some common genetic susceptibility. However, the genes underlying bipolar disorder and/or schizophrenia have not yet been identified.

3.2. Schizophrenia

There are an estimated 45 million people with schizophrenia in the world, with more than 33 million of them in the developing countries. In developed countries schizophrenia occurs in approximately 1% of the adult population at some point during their lives. If there is one grandparent with schizophrenia, the risk of getting the illness increases to about 3%; one parent with Schizophrenia, to about 10%. When both parents have schizophrenia, the risk rises to approximately 40%. Most schizophrenia patients are never able to work. Standardized mortality ratios (SMRs) for schizophrenic patients are estimated to be two to four times higher than the general population and their life expectancy overall is 20%

shorter than for the general population. The most common cause of death among schizophrenic patients is suicide (in 10% of patients) which represents a 20 times higher risk than for the general population. Deaths from heart disease and from diseases of the respiratory and digestive system are also increased among schizophrenic patients.

Schizophrenia comprises a group of psychoses with either 'positive' or 'negative' symptoms. Positive symptoms consist of hallucinations, delusions and disorders of thought; negative symptoms include emotional flattening, lack of volition and a decrease in motor activity.

A number of biochemical abnormalities have been identified and, in consequence, several neurotransmitter based hypotheses have been advanced over recent years; the most popular one has been "the dopamine hypothesis," one variant of which states that there is over-activity of the mesolimbic dopamine pathways at the level of the D_2 receptor. However, researchers have been unable to consistently find an association between various receptors of the dopaminergic system and schizophrenia.

3.3. Depression

Depression is a serious medical illness that affects 340 million people worldwide. In contrast to the normal emotional experiences of sadness, loss, or passing mood states, clinical depression is persistent and can interfere significantly with an individual's ability to function. As a result, depression is the leading cause of disability throughout the world.

Symptoms of depression include depressed mood, diminished interest or pleasure in activities, change in appetite or weight, insomnia or hypersomnia, psycho-motor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, anxiety, inability to concentrate or act decisively, and recurrent thoughts of death or suicide. A diagnosis of unipolar major depression (or major depressive disorder) is made if a person has five or more of these symptoms and impairment in usual functioning nearly every day during the same two-week period. The onset of depression generally begins in late adolescence or early adult life; however, recent evidence suggests depression may be occurring earlier in life in people born in the past thirty years.

The World Health Organization predicts that by the year 2020 depression will be the greatest burden of ill-health to people in the developing world, and that by then depression will be the second largest cause of death and disability. Beyond the almost unbearable misery it causes, the big risk in major depression is suicide. Within five years of suffering a major depression, an estimated 25% of sufferers try to kill themselves. In addition, depression is a frequent and serious complication of heart attack, stroke, diabetes, and cancer. According to one recent study that covered a 13-year period, individuals with a history of major depression were four times as likely to suffer a heart attack compared to people without such a history. Depression may also be a feature in up to 50% of patients with mental disorders such as Parkinson's disease and Alzheimer's disease.

3.4. Treatment

There are currently no cures for mental disorders such as bipolar disorder, schizophrenia, depression and other mood disorders, so the objective of treatment is to reduce the severity of the symptoms, if possible to the point of remission. Due to the similarities in symptoms, schizophrenia, depression and bipolar disorder are often treated with some of the same medicaments.

3.4.1. Treatment of Bipolar Disorder

Depressive episodes may be treated like depression. However, most antidepressants can cause swings from depression to hypomania or mania and sometimes cause rapid cycling between them. Therefore, these drugs are used for only short periods, and their effect on mood is closely monitored. At the first sign of a swing to hypomania or mania, the antidepressant is stopped. Most people with manic-depressive disorder are given drugs with a mood-stabilizing effect such as lithium, carbamazepine and divalproex.

Lithium has no effect on normal mood but reduces the tendency toward mood swings in about 70% of the people with manic-depressive illness. A doctor monitors the level of lithium in the blood with blood tests. Possible adverse effects of lithium include tremor, muscle twitching, nausea, vomiting, diarrhea, thirst, excessive urination, and weight gain. Lithium can make acne or psoriasis worse, can cause the blood levels of thyroid hormone to fall, and rarely can cause excessive urination. A very high level of lithium in the blood can cause a persistent headache, mental confusion, drowsiness, seizures, and abnormal heart rhythms. Adverse effects are more likely to occur in the elderly. Women who are trying to become pregnant must stop taking lithium, because lithium may cause heart defects in a developing fetus.

Newer drug treatments have evolved over the past several years. These include the carbamazepine and divalproex. However, carbamazepine can seriously reduce the number of red and white blood cells, and divalproex can cause liver damage (primarily in children). With careful monitoring by a doctor, these problems are rare, and carbamazepine and divalproex are useful alternatives to lithium, especially for people with the mixed or rapid cycling form of manic-depressive illness who haven't responded to other treatments.

3.4.2. Treatment of Schizophrenia

For schizophrenia, antipsychotic medications are the most common and most valuable treatments. There are four main classes of antipsychotic drugs which are commonly prescribed for schizophrenia. The first, neuroleptics, exemplified by chlorpromazine (Thorazine), has revolutionized the treatment of schizophrenic patients by reducing positive (psychotic) symptoms and preventing their recurrence. Patients receiving chlorpromazine have been able to leave mental hospitals and live in community programs or their own homes. But these drugs are far from ideal. Some 20% to 30% of patients do not respond to them at all, and others eventually relapse. These drugs were named neuroleptics because they produce serious neurological side effects, including rigidity and tremors in the arms and legs, muscle spasms, abnormal body movements, and akathisia (restless pacing and fidgeting). These side effects are so troublesome that many patients simply refuse to take the drugs. Besides, neuroleptics do not improve the so-called negative symptoms of schizophrenia and the side effects may even exacerbate these symptoms. Thus, despite the clear beneficial effects of neuroleptics, even some patients who have a good short-term response will ultimately deteriorate in overall functioning.

The well known deficiencies in the standard neuroleptics have stimulated a search for new treatments and have led to a new class of drugs termed atypical neuroleptics. The first atypical neuroleptic, Clozapine, is effective for about one third of patients who do not respond to standard neuroleptics. It seems to reduce negative as well as positive symptoms, or at least exacerbates negative symptoms less than standard neuroleptics do. Moreover, it has beneficial effects on overall functioning and may reduce the chance of suicide in schizophrenic patients. It does not produce the troubling neurological symptoms of the standard neuroleptics, or raise blood levels of the hormone prolactin, excess of which may cause menstrual irregularities and infertility in women, impotence or breast enlargement in men. Many patients who cannot tolerate standard neuroleptics have been able to take clozap-

ine. However, clozapine has serious limitations. It was originally withdrawn from the market because it can cause agranulocytosis, a potentially lethal inability to produce white blood cells. Agranulocytosis remains a threat that requires careful monitoring and periodic blood tests. Clozapine can also cause seizures and other disturbing side effects (e.g., drowsiness, lowered blood pressure, drooling, bed-wetting, and weight gain). Thus only patients who do not respond to other drugs usually take Clozapine.

Researchers have developed a third class of antipsychotic drugs that have the virtues of clozapine without its defects. One of these drugs is risperidone (Risperdal). Early studies suggest that it is as effective as standard neuroleptic drugs for positive symptoms and may be somewhat more effective for negative symptoms. It produces more neurological side effects than clozapine but fewer than standard neuroleptics. However, it raises prolactin levels. Risperidone is now prescribed for a broad range of psychotic patients, and many clinicians seem to use it before clozapine for patients who do not respond to standard drugs, because they regard it as safer. Another new drug is Olanzapine (Zyprexa) which is at least as effective as standard drugs for positive symptoms and more effective for negative symptoms. It has few neurological side effects at ordinary clinical doses, and it does not significantly raise prolactin levels. Although it does not produce most of clozapine's most troubling side effects, including agranulocytosis, some patients taking olanzapine may become sedated or dizzy, develop dry mouth, or gain weight. In rare cases, liver function tests become transiently abnormal.

3.4.3. Treatment of Depression

Several types of antidepressants are available. These antidepressants belong to four main categories: tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and psychostimulants. Tricyclic antidepressants include, e.g., Amitriptyline, Amoxapine, Bupropion, Clomipramine, Desipramine, Doxepin, Imipramine, Maprotiline, Nefazodone, Nortriptyline, Protriptyline, Trazodone, Trimipramine and Venlafaxine. Selective serotonin reuptake inhibitors include, e.g., Fluoxetine, Fluvoxamine, Paroxetine and Sertraline. Monoamine oxidase inhibitors include, e.g., Isocarboxazid, Pargyline, Phenelzine and Tranylcypromine. Psychostimulants include, e.g., Dextroamphetamine and Methylphenidate.

All these antidepressants must be taken regularly for at least several weeks before they begin to work. The chances that any given antidepressant will work for a particular person are about 65%. However, most of these drugs have side effects varying with each type of drug. For example, the tricyclic antidepressants often cause sedation and lead to weight gain. They can also be associated with side effects such as an increased heart rate, a decrease in blood pressure when the person stands or blurred vision.

Thus, for mental disorders such as bipolar disorder, schizophrenia, depression and other mood disorders, known molecules used for the treatment have side effects and act only against the symptoms of the disease. Consequently, there is a strong need for new molecules without associated side effects that are specifically directed against targets which are involved in the causal mechanisms of such mental disorders. Therefore, there is a need to identify proteins involved in bipolar disorder and schizophrenia. Providing new targets involved in bipolar disorder and schizophrenia will allow new screenings for drugs, resulting in new drugs that are efficient in treatment of these serious mental disorders.

Furthermore, there is also a need for diagnostic tools. There is increasing evidence that leaving schizophrenia untreated for long periods early in course of the illness may negatively affect the outcome. However, the use of drugs is often delayed for patients experiencing a first episode of the illness. The patients may not realize that they are ill, or they may be afraid to seek help; family members sometimes hope the problem will simply disappear or cannot persuade the patient to seek treatment; clinicians may hesitate to prescribe antipsychotic medications when the diagnosis is uncertain because of potential side effects. Indeed, at the first manifestation of the disease, schizophrenia or bipolar disorder is difficult to distinguish from, e.g., drug-related disorders and stress-related disorders. Accordingly, there is a need for new methods for detecting a susceptibility to mental disorders such as bipolar disorder, schizophrenia, and depression.

SUMMARY OF THE INVENTION

The present invention is based on the identification of novel splice variants of the KCNQ2 potassium channel.

Therefore, in a first aspect, the present invention is directed to an isolated KCNQ2-15b polypeptide selected from the group consisting of:

a) a polypeptide comprising a span of at least ten amino acids of amino acids 589 to 643 of SEQ ID NO: 2;

b) a polypeptide comprising amino acids 589 to 643 of SEQ ID NO: 2;

c) a polypeptide comprising amino acids 545 to 643 of SEQ ID NO: 2;

d) a polypeptide comprising SEQ ID NO: 2;

e) a polypeptide comprising SEQ ID NO: 4;

f) a polypeptide comprising SEQ ID NO: 6;

g) a mutein of any of (a) to (f), wherein the amino acid sequence has at least 50% or 60% or 70% or 80% or 90% or 95% or 99% identity to at least one of the sequences in (a) to (f);

h) a mutein of any of (a) to (f) which is encoded by a DNA sequence which hybridizes to the complement of the DNA sequence encoding any of (a) to (f) under moderately stringent conditions or under highly stringent conditions; and

i) a mutein of any of (a) to (f) wherein any changes in the amino acid sequence are conservative amino acid substitutions to the amino acid sequences in (a) to (f).

The present invention further relates to a potassium channel comprising at least one KCNQ2-15b polypeptide.

The invention further relates to a purified KCNQ2-15b polynucleotide encoding a KCNQ2-15b polypeptide or a polynucleotide complementary thereto.

An expression vector comprising a KCNQ2-15b polynucleotides, a host cell comprising an expression vector comprising a KCNQ2-15b polynucleotides and an antibody that specifically binds to a KCNQ2-15b polypeptide are also within the present invention.

Further, the present invention pertains to a method of making a polypeptide, said method comprising the steps of culturing a host cell comprising an expression vector comprising a KCNQ2-15b polynucleotides under conditions suitable for the production of a KCNQ2-15b polypeptide within said host cell.

The present invention is further based on the finding that KCNQ2 is associated with the onset and the development of mental disorders.

Therefore, in a second aspect, the present invention is directed to the use of a KCNQ2 polypeptide as a target for screening candidate modulators.

The present invention further relates to the use of a modulator of a KCNQ2 polypeptide for preparing a medicament for the treatment of a mental disorder.

The invention also concerns a method of assessing the efficiency of a modulator of a KCNQ2 polypeptide for the treatment of a mental disorder, said method comprising administering said modulator to an animal model for said mental disorder; wherein a determination that said modulator ameliorates a representative characteristic of said mental disorder in said animal model indicates that said modulator is a drug for the treatment of said mental disorder.

In the frame of the present invention, biallelic markers located in the KCNQ2 gene have been identified and validated.

Therefore, a third object of the invention consists of the use of at least one KCNQ2-related biallelic marker for diagnosing whether an individual suffers from or is at risk of suffering from a mental disorder.

The invention further encompasses the use of at least one KCNQ2-related biallelic marker for determining whether there is a significant association between said marker and a mental disorder.

The invention also relates to a method of genotyping comprising the step of determining the identity of a nucleotide at a KCNQ2-related biallelic marker or the complement thereof in a biological sample.

The invention further pertains to a method of diagnosing a mental disorder in an individual comprising the step of genotyping at least one KCNQ2-related biallelic marker using a method of genotyping comprising the step of determining the identity of a nucleotide at said KCNQ2-related biallelic marker or the complement thereof in a biological sample.

BRIEF DESCRIPTION OF THE FIGURES

FIGS. **1**A and **1**B show an alignment between the full-length KCNQ2 polypeptide (KCNQ2-fl, SEQ ID NO: 7), KCNQ2-15bx (SEQ ID NO: 2), KCNQ2-15by (SEQ ID NO: 4) and KCNQ2-15bz (SEQ ID NO: 6). The box shows highlights the amino acids that are unique to KCNQ2-15bx, KCNQ2-15by and KCNQ2-15bz compared to KCNQ2-fl.

FIG. **2** shows a sheme of the structure of the KCNQ2-15bx, KCNQ2-15by and KCNQ2-15bz cDNAs.

FIG. **3** shows the results of a mating test between PP2A/Bγ and different KCNQ2 polypeptides, as described in detail in Example 3.

FIG. **4** shows the results of a mating test between different KCNQ2 polypeptides, as described in detail in Example 3.

FIG. **5** compares the intensity of the currents generated by homotetrameric potassium channels comprised of KCNQ2-15bx, KCNQ2-15by, KCNQ2-15bz or KCNQ2-fl subunits respectively.

FIG. **6**A shows the voltage clamp traces of the current generated by a homotetrameric potassium channels comprised of KCNQ2-15bx subunits.

FIG. **6**B shows the voltage clamp traces of the current generated by a homotetrameric potassium channels comprised of KCNQ2-15by subunits.

BRIEF DESCRIPTION OF THE SEQUENCES OF THE SEQUENCE LISTING

SEQ ID NO: 1 corresponds to a polynucleotide consisting of the CDS of KCNQ2-15bx

SEQ ID NO: 2 corresponds to the KCNQ2-15bx polypeptide.

SEQ ID NO: 3 corresponds to a polynucleotide consisting of the CDS of KCNQ2-15by

SEQ ID NO: 4 corresponds to the KCNQ2-15by polypeptide.

SEQ ID NO: 5 corresponds to a polynucleotide consisting of the CDS of KCNQ2-15bz

SEQ ID NO: 6 corresponds to the KCNQ2-15bz polypeptide.

SEQ ID NO: 7 corresponds to the KCNQ2-fl polypeptide.

SEQ ID Nos. 8 to 36 correspond to primers and probes used in Examples 1 to 4.

SEQ ID NO: 37 corresponds to the PPP2R2C gene which encodes the PP2A/Bγ subunit, on which PP2A/Bγ-related biallelic markers are indicated.

SEQ ID NO: 38 corresponds to the PP2A/Bγ subunit.

SEQ ID Nos. 39 to 41 correspond to primers used for microsequencing some of the PP2A/Bγ-related biallelic markers.

SEQ ID Nos. 42 to 47 correspond to regions of the KCNQ2 gene, on which KCNQ2-related biallelic markers are indicated.

BRIEF DESCRIPTION OF THE TABLES

Table 1 presents the structure of KCNQ2-fl, KCNQ2-15bx KCNQ2-15by and KCNQ2-15bz.

Tables 2A and 2B present the location of the primers used for amplification of genomic DNA by PCR in PPP2R2C and in the KCNQ2 gene respectively

Table 3A and 3B present biallelic markers located in the PP2R2C and in the KCNQ2 gene respectively.

Tables 4A and 4B present the the primers used for microsequencing biallelic markers located in PP2R2C and in the KCNQ2 gene respectively.

Tables 5A and 5B present the p-values for biallelic markers located in PPP2R2C and in the KCNQ2 gene respectively.

Tables 6A and 6B present the genotypic odds ratios for a biallelic marker located in PPP2R2C and in the KCNQ2 gene respectively.

Tables 7A and 7B present the risk haplotypes for two sets of biallelic markers located in PPP2R2C

DETAILED DESCRIPTION OF THE INVENTION

The present invention stems from the cloning and the sequencing of three novel splice variants of the KCNQ2 gene, KCNQ2-15bx, KCNQ2-15by and KCNQ2-15bz. These splice variants all display a novel exon (exon 15b), corresponding to amino acids 545 to 643 of SEQ ID NO: 2. Data showing that KCNQ2-15bx and KCNQ2-15by can assemble as functional homotetrameric potassium channels are provided. In the frame of the present invention, it has been demonstrated that these novel splice variants interact with the Bγ subunit of the serine/threonine protein phosphatase 2A (PP2A/Bγ) both in vitro and in vivo. Furthermore, association studies are described in example 15, and it was shown that both the KCNQ2 gene and the gene coding for PP2A/Bγ are strongly associated with bipolar disorder. Novel validated biallelic markers located in the KCNQ2 gene and associated with bipolar disorder are provided. In the frame of the present invention it was further shown that KCNQ2-15bx, KCNQ2-15by and KCNQ2-15bz are (i) dephosphorylated by PP2A; and (ii) phosphorylated by the PKA and GSK3β kinases. Moreover, the phosphorylation of KCNQ2-15bx, KCNQ2-15by and KCNQ2-15bz is inhibited in the presence of lithium, a known mood-stabilizing agent.

Accordingly, the present invention provides novel KCNQ2 polypeptides and means to identify compounds useful in the treatment of mental disorders such as bipolar disorder, schizophrenia, depression and other mood disorders. The invention further relates to the use of KCNQ2 polypeptides as targets for screening for modulators thereof. The use of said modulators for treating mental disorders, and the use of biallelic markers located in the KCNQ2 gene for diagnosing mental disorders are further aspects of the present invention.

1. Definitions

The term "treat" or "treating" as used herein is meant to ameliorate, alleviate symptoms, eliminate the causation of the symptoms either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms of the named disorder or condition. The term "treatment" as used herein also encompasses the term "prevention of the disorder", which is, e.g., manifested by delaying the onset of the symptoms of the disorder to a medically significant extent. Treatment of the disorder is, e.g., manifested by a decrease in the symptoms associated with the disorder or an amelioration of the reoccurrence of the symptoms of the disorder.

The term "mental disorder" refers to diseases characterized as mood disorders, psychotic disorders, anxiety disorders, childhood disorders, eating disorders, personality disorders, adjustment disorder, autistic disorder, delirium, dementia, multi-infarct dementia and Tourette's disorder in the DSM-IV classification (Diagnosis and Statistical Manual of Mental Disorders, Fourth Edition, American Psychiatric Association, Washington D.C., 1994).

The term "schizophrenia" refers to a condition characterized as schizophrenia in the DSM-IV classification (Diagnosis and Statistical Manual of Mental Disorders, Fourth Edition, American Psychiatric Association, Washington D.C., 1994).

The term "bipolar disorder" as used herein refers to a condition characterized as a Bipolar Disorder in the DSM-IV. Bipolar disorder may be bipolar I and bipolar disorder II as described in the DSM-IV. The term further includes cyclothymic disorder. Cyclothymic disorder refers to an alternation of depressive symptoms and hypomanic symptoms. The skilled artisan will recognize that there are alternative nomenclatures, posologies, and classification systems for pathologic psychological conditions and that these systems evolve with medical scientific progress.

The terms "comprising", "consisting of", or "consisting essentially of" have distinct meanings. However, each term may be substituted for another herein to change the scope of the invention.

As used interchangeably herein, the term "oligonucleotides", and "polynucleotides" include RNA, DNA, or RNA/DNA hybrid sequences of more than one nucleotide in either single chain or duplex form. The term "nucleotide" as used herein as an adjective to describe compounds comprising RNA, DNA, or RNA/DNA hybrid sequences of any length in single-stranded or duplex form. The term "nucleotide" is also used herein as a noun to refer to individual nucleotides or varieties of nucleotides, meaning a compound, or individual unit in a larger nucleic acid compound, comprising a purine or pyrimidine, a ribose or deoxyribose sugar moiety, and a phosphate group, or phosphodiester linkage in the case of nucleotides within an oligonucleotide or polynucleotide. Although the term "nucleotide" is also used herein to encompass "modified nucleotides" which comprise at least one modifications (a) an alternative linking group, (b) an analogous form of purine, (c) an analogous form of pyrimidine, or (d) an analogous sugar, for examples of analogous linking groups, purine, pyrimidines, and sugars see for example PCT publication No. WO 95/04064, the disclosure of which is incorporated herein by reference. However, the polynucleotides of the invention are preferably comprised of greater than 50% conventional deoxyribose nucleotides, and most preferably greater than 90% conventional deoxyribose nucleotides. The polynucleotide sequences of the invention may be prepared by any known method, including synthetic, recombinant, ex vivo generation, or a combination thereof, as well as utilizing any purification methods known in the art.

The term "isolated" requires that the material be removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide or polypeptide present in a living animal is not isolated, but the same polynucleotide or DNA or polypeptide, separated from some or all of the coexisting materials in the natural system, is isolated. Such polynucleotide could be part of a vector and/or such polynucleotide or polypeptide could be part of a composition, and still be isolated in that the vector or composition is not part of its natural environment.

The term "primer" denotes a specific oligonucleotide sequence which is complementary to a target nucleotide sequence and used to hybridize to the target nucleotide sequence. A primer serves as an initiation point for nucleotide polymerization catalyzed by either DNA polymerase, RNA polymerase or reverse transcriptase.

The term "probe" denotes a defined nucleic acid segment (or nucleotide analog segment, e.g., polynucleotide as defined herein) which can be used to identify a specific polynucleotide sequence present in samples, said nucleic acid segment comprising a nucleotide sequence complementary of the specific polynucleotide sequence to be identified.

The terms "complementary" or "complement thereof" are used herein to refer to the sequences of polynucleotides which are capable of forming Watson & Crick base pairing with another specified polynucleotide throughout the entirety of the complementary region. This term is applied to pairs of polynucleotides based solely upon their sequences and not any particular set of conditions under which the two polynucleotides would actually bind.

The term "polypeptide" refers to a polymer of amino acids without regard to the length of the polymer; thus, peptides, oligopeptides, and proteins are included within the definition of polypeptide. This term also does not specify or exclude prost-expression modifications of polypeptides, for example, polypeptides which include the covalent attachment of glycosyl groups, acetyl groups, phosphate groups, lipid groups and the like are expressly encompassed by the term polypeptide. Also included within the definition are polypeptides which contain one or more analogs of an amino acid (including, for example, non-naturally occurring amino acids, amino acids which only occur naturally in an unrelated biological system, modified amino acids from mammalian systems etc.), polypeptides with substituted linkages, as well as other modifications known in the art, both naturally occurring and non-naturally occurring.

As used herein, the term "exon" refers as well to the portion of a DNA that codes for portion of spliced mRNA as to the amino acids encoded by said part of a DNA.

As used herein, "splice variants" refer to different mRNAs produced by alternative splicing events and translated from the same gene. The term splice variant refers as well to the mRNA as to the corresponding polypeptide.

As used herein, the term "non-human animal" refers to any non-human vertebrate, birds and more usually mammals, preferably primates, farm animals such as swine, goats, sheep, donkeys, and horses, rabbits or rodents, more preferably rats or mice. As used herein, the term "animal" is used to refer to any vertebrate, preferable a mammal. Both the terms "animal" and "mammal" expressly embrace human subjects unless preceded with the term "non-human".

The terms "trait" and "Phenotype" are used interchangeably herein and refer to any clinically distinguishable, detectable or otherwise measurable property of an organism such as symptoms of, or susceptibility to a disease for example. Typically the terms "trait" or "phenotype" are used herein to refer to symptoms of, or susceptibility to bipolar disorder; or to

refer to an individual's response to an agent acting on bipolar disorder; or to refer to symptoms of, or susceptibility to side effects to an agent acting on bipolar disorder.

As used herein, the term "allele" refers to one of the variant forms of a biallelic marker, differing from other forms in its nucleotide sequence. Typically the first identified allele is designated as the original allele whereas other alleles are designated as alternative alleles. Diploid organisms may be homozygous or heterozygous for an allelic form.

The term "polymorphism" as used herein refers to the occurrence of two or more alternative genomic sequences or alleles between or among different genomes or individuals. "Polymorphic" refers to the condition in which two or more variants of a specific genomic sequence can be found in a population. A "polymorphic site" is the locus at which the variation occurs. A polymorphism may comprise a substitution, deletion or insertion of one or more nucleotides. A single nucleotide polymorphism is a single base pair change. Typically a single nucleotide polymorphism is the replacement of one nucleotide by another nucleotide at the polymorphic site. A "single nucleotide polymorphism" (SNP) refers to a sequence polymorphism differing in a single base pair.

2. KCNQ2-15b Polypeptides of the Present Invention

The term "KCNQ2-15b polypeptides" is used herein to embrace all of the polypeptides of the present invention.

Preferably, the KCNQ2-15b is selected from a peptide, a polypeptide or a protein selected from the group consisting of:

a) a polypeptide comprising a span of at least ten amino acids of amino acids 589 to 643 of SEQ ID NO: 2;

b) a polypeptide comprising amino acids 589 to 643 of SEQ ID NO: 2;

c) a polypeptide comprising amino acids 545 to 643 of SEQ ID NO: 2;

d) a polypeptide comprising SEQ ID NO: 2;

e) a polypeptide comprising SEQ ID NO: 4;

f) a polypeptide comprising SEQ ID NO: 6;

g) a mutein of any of (a) to (f), wherein the amino acid sequence has at least 50% or 60% or 70% or 80% or 90% or 95% or 99% identity to at least one of the sequences in (a) to (f);

h) a mutein of any of (a) to (f) which is encoded by a DNA sequence which hybridizes to the complement of the DNA sequence encoding any of (a) to (f) under moderately stringent conditions or under highly stringent conditions; and

i) a mutein of any of (a) to (f) wherein any changes in the amino acid sequence are conservative amino acid substitutions to the amino acid sequences in (a) to (f).

KCNQ2-15b polypeptides of the present invention all comprise an amino acid sequence of a span of at least 10 amino acids of SEQ ID NO: 2, wherein said span falls within amino acids 589 to 643 of SEQ ID NO: 2. Preferably, KCNQ2-15b polypeptides comprise amino acids 589 to 643 of SEQ ID NO: 2.

In an embodiment of the invention, KCNQ2-15b polypeptides comprise any of SEQ ID NO: 2, SEQ ID NO: 4 or SEQ ID NO: 6. Preferred KC NQ2-15b polypeptides consist of SEQ ID NO: 2, SEQ ID NO: 4 or SEQ ID NO: 6. As further used herein, "KCNQ2-15bx" refers to a polypeptide of SEQ ID NO: 2, "KCNQ2-15by" refers to a polypeptide of SEQ ID NO: 4 and "KCNQ2-15bz" refers to a polypeptide of SEQ ID NO: 6.

In a preferred embodiment, KCNQ2-15b polypeptides are capable of binding to the Bγ subunit of the PP2A phosphatase (PP2A/Bγ). In other words, said KCNQ2-15b polypeptides bind to PP2A/Bγ when the binding is tested by any suitable assay. Such assay s encompass, e.g., the yeast mating test described in example 9 and the solid phase overlay assay described in example 6. As further used herein, the term "KCNQ2-15b binding activity" or "binding activity" refers to the capacity of the KCNQ2-15b polypeptide to bind to PP2A/Bγ.

In another preferred embodiment, KCNQ2-15b polypeptides correspond to a subunit of a potassium channel. In a more preferred embodiment, KCNQ2-15b polypeptides correspond to isoforms of the KCNQ2 polypeptide that are produced by alter native splicing events. Such KCNQ2-15b polypeptides may associate either with other KCNQ2-15b polypeptides or with other potassium channels subunits to form a potassium channel. As further used herein, the term "KCNQ2-15b biological activity" or "biological activity" refers to the activity of a potassium channel comprising the KCNQ2-15b polypeptide.

A preferred embodiment is directed to a potassium channel comprising at least one KCNQ2-15b polypeptide. The potassium channel may be a homomeric potassium channel comprised of several KCNQ2-15b polypeptides. Alternatively, the potassium channel may be a heteromeric potassium channel comprised of a KCNQ2-15b polypeptide associated with other KCNQ polypeptides and/or other potassium channel subunits. The KCNQ2-15b biological activity can be measured by methods well known by those skilled in the art such as, e.g., measurement of the M current.

As further used herein, the terms "KCNQ2-15b biological properties", "biological properties" and "activity" encompass both the biological activity and the binding activity of the KCNQ2-15b polypeptide. KCNQ2-15b biological properties further include, but are not limited to, e.g., KCNQ2-15b-specific antibody binding, binding to KCNQ subunits and modulation of potassium channel activity.

In further preferred embodiments, KCNQ2-15b polypeptides comprise the novel exon 15b. The term "exon 15b" refers to the amino acids at position 545 to 643 of SEQ ID NO: 2. Preferably, exon 15b is the most carboxyl-terminal exon of said KCNQ2-15b polypeptide. KCNQ2-15b polypeptides may further comprise any combination of exons 1 to 14 of the KCNQ2 gene.

The present invention is also directed to fragments of at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600 or 610 amino acids of KCNQ2-15bx, KCNQ2-15by or KCNQ2-15bz.

Further embodiments are directed to muteins. As used herein the term "muteins" refers to analogs of KCNQ2-15bx, KCNQ2-15by or KCNQ2-15bz, in which one or more of the amino acid residues of a natural KCNQ2-15bx, KCNQ2-15by or KCNQ2-15bz are replaced by different amino acid residues, or are deleted, or one or more amino acid residues are added to the natural sequence of KCNQ2-15bx, KCNQ2-15by or KCNQ2-15bz, without lowering considerably the activity of the resulting products as compared with the wild-type KCNQ2-15bx, KCNQ2-15by or KCNQ2-15bz. These muteins are prepared by known synthesis and/or by site-directed mutagenesis techniques, or any other known technique suitable therefore.

Muteins of KCNQ2-15bx, KCNQ2-15by or KCNQ2-15bz, which can be used in accordance with the present invention, or nucleic acid coding thereof, include a finite set of substantially corresponding sequences as substitution peptides or polynucleotides which can be routinely obtained by

one of ordinary skill in the art, without undue experimentation, based on the teachings and guidance presented herein.

KCNQ2-15bx, KCNQ2-15by or KCNQ2-15bz in accordance with the present invention include proteins encoded by a nucleic acid, such as DNA or RNA, which hybridizes to DNA or RNA, which encodes KCNQ2-15b, in accordance with the present invention, under moderately or highly stringent conditions. The term "stringent conditions" refers to hybridization and subsequent washing conditions, which those of ordinary skill in the art conventionally refer to as "stringent". See Ausubel et al., Current Protocols in Molecular Biology, supra, Interscience, N.Y., §§6.3 and 6.4 (1987, 1992), and Sambrook et al. (Sambrook, J. C., Fritsch, E. F., and Maniatis, T. (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.).

Without limitation, examples of stringent conditions include washing conditions 12-20° C. below the calculated Tm of the hybrid under study in, e.g., 2×SSC and 0.5% SDS for 5 minutes, 2×SSC and 0.1% SDS for 15 minutes; 0.1×SSC and 0.5% SDS at 37° C. for 30-60 minutes and then, a 0.1× SSC and 0.5% SDS at 68° C. for 30-60 minutes. Those of ordinary skill in this art understand that stringency conditions also depend on the length of the DNA sequences, oligonucleotide probes (such as 10-40 bases) or mixed oligonucleotide probes. If mixed probes are used, it is preferable to use tetramethyl ammonium chloride (TMAC) instead of SSC.

The polypeptides of the present invention include muteins having an amino acid sequence at least 50% identical, more preferably at least 60% identical, and still more preferably 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to a KCNQ2-15b polypeptide of the present invention. By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% (5 of 100) of the amino acid residues in the subject sequence may be inserted, deleted, or substituted with another amino acid.

For sequences where there is not an exact correspondence, a "% identity" may be determined. In general, the two sequences to be compared are aligned to give a maximum correlation between the sequences. This may include inserting "gaps" in either one or both sequences, to enhance the degree of alignment. A % identity may be determined over the whole length of each of the sequences being compared (so-called global alignment), that is particularly suitable for sequences of the same or very similar length, or over shorter, defined lengths (so-called local alignment), that is more suitable for sequences of unequal length.

Methods for comparing the identity and homology of two or more sequences are well known in the art. Thus for instance, programs available in the Wisconsin Sequence Analysis Package, version 9.1 (Devereux J et al., 1984), for example the programs BESTFIT and GAP, may be used to determine the % identity between two polynucleotides and the % identity and the % homology between two polypeptide sequences. BESTFIT uses the "local homology" algorithm of Smith and Waterman (1981) and finds the best single region of similarity between two sequences. Other programs for determining identity and/or similarity between sequences are also known in the art, for instance the BLAST family of programs (Altschul S F et al, 1990, Altschul S F et al, 1997, accessible through the home page of the NCBI at world wide web site ncbi.nim.nih.gov) and FASTA (Pearson W R, 1990; Pearson 1988).

Preferred changes for muteins in accordance with the present invention are what are known as "conservative" substitutions. Conservative amino acid substitutions of KCNQ2-15bx, KCNQ2-15by or KCNQ2-15bz polypeptides, may include synonymous amino acids within a group which have sufficiently similar physicochemical properties that substitution between members of the group will preserve the biological function of the molecule (Grantham, 1974). It is clear that insertions and deletions of amino acids may also be made in the above-defined sequences without altering their function, particularly if the insertions or deletions only involve a few amino acids, e.g. under thirty, and preferably under ten, and do not remove or displace amino acids which are critical to a functional conformation, e.g. cysteine residues. Proteins and muteins produced by such deletions and/or insertions come within the purview of the present invention.

Preferably, the synonymous amino acid groups are those defined in Table I. More preferably, the synonymous amino acid groups are those defined in Table II; and most preferably the synonymous amino acid groups are those defined in Table III.

TABLE I

Preferred Groups of Synonymous Amino Acids

Amino Acid	Synonymous Group
Ser	Ser, Thr, Gly, Asn
Arg	Arg, Gln, Lys, Glu, His
Leu	Ile, Phe, Tyr, Met, Val, Leu
Pro	Gly, Ala, Thr, Pro
Thr	Pro, Ser, Ala, Gly, His, Gln, Thr
Ala	Gly, Thr, Pro, Ala
Val	Met, Tyr, Phe, Ile, Leu, Val
Gly	Ala, Thr, Pro, Ser, Gly
Ile	Met, Tyr, Phe, Val, Leu, Ile
Phe	Trp, Met, Tyr, Ile, Val, Leu, Phe
Tyr	Trp, Met, Phe, Ile, Val, Leu, Tyr
Cys	Ser, Thr, Cys
His	Glu, Lys, Gln, Thr, Arg, His
Gln	Glu, Lys, Asn, His, Thr, Arg, Gln
Asn	Gln, Asp, Ser, Asn
Lys	Glu, Gln, His, Arg, Lys
Asp	Glu, Asn, Asp
Glu	Asp, Lys, Asn, Gln, His, Arg, Glu
Met	Phe, Ile, Val, Leu, Met
Trp	Trp

TABLE II

More Preferred Groups of Synonymous Amino Acids

Amino Acid	Synonymous Group
Ser	Ser
Arg	His, Lys, Arg
Leu	Leu, Ile, Phe, Met
Pro	Ala, Pro
Thr	Thr
Ala	Pro, Ala
Val	Val, Met, Ile
Gly	Gly
Ile	Ile, Met, Phe, Val, Leu
Phe	Met, Tyr, Ile, Leu, Phe
Tyr	Phe, Tyr
Cys	Cys, Ser
His	His, Gln, Arg
Gln	Glu, Gln, His
Asn	Asp, Asn

TABLE II-continued

More Preferred Groups of Synonymous Amino Acids

Amino Acid	Synonymous Group
Lys	Lys, Arg
Asp	Asp, Asn
Glu	Glu, Gln
Met	Met, Phe, Ile, Val, Leu
Trp	Trp

TABLE III

Most Preferred Groups of Synonymous Amino Acids

Amino Acid	Synonymous Group
Ser	Ser
Arg	Arg
Leu	Leu, Ile, Met
Pro	Pro
Thr	Thr
Ala	Ala
Val	Val
Gly	Gly
Ile	Ile, Met, Leu
Phe	Phe
Tyr	Tyr
Cys	Cys, Ser
His	His
Gln	Gln
Asn	Asn
Lys	Lys
Asp	Asp
Glu	Glu
Met	Met, Ile, Leu
Trp	Met

Examples of production of amino acid substitutions in proteins which can be used for obtaining muteins of KCNQ2-15bx, KCNQ2-15by or KCNQ2-15bz, polypeptides for use in the present invention include any known method steps, such as presented in U.S. Pat. Nos. 4,959,314, 4,588,585 and 4,737,462, to Mark et al; U.S. Pat. No. 5,116,943 to Koths et al., U.S. Pat. No. 4,965,195 to Namen et al; U.S. Pat. No. 4,879,111 to Chong et al; and U.S. Pat. No. 5,017,691 to Lee et al; and lysine substituted proteins presented in U.S. Pat. No. 4,904,584 (Shaw et al).

Preferably, the muteins of the present invention exhibit substancially the same biological properties as the KCNQ2-15b polypeptide to which it corresponds.

In some embodiments, KCNQ2-15b polypeptides and muteins or fragments thereof have biological activity or binding activity as defined above. In other embodiments, KCNQ2-15b polypeptides and muteins or fragments thereof do not have activity as defined above. Other uses of the polypeptides of the present invention include, inter alia, as epitope tags, in epitope mapping, and as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods known to those of skill in the art. Such polypeptides can be used to raise polyclonal and monoclonal antibodies, which are useful in assays for detecting KCNQ2-15bx, KCNQ2-15by and KCNQ2-15bz expression, or for purifying KCNQ2-15bx, KCNQ2-15by and KCNQ2-15bz. As a matter of example, a further specific use for KCNQ2-15b polypeptides is the use of such polypeptides the yeast two-hybrid system to capture KCNQ2-15bx, KCNQ2-15by or KCNQ2-15bz binding proteins, which are candidate modulators according to the present invention, as further detailed below.

3. KCNQ2-15b Polynucleotides of the Present Invention

The present invention is further directed to KCNQ2-15b polynucleotides encoding any of the KCNQ2-15b polypeptides described above, and to sequence complementary thereto.

In a preferred embodiment, said polynucleotide is selected from the group consisting of:

a) a polynucleotide comprising nucleotides 1776 to 1929 of SEQ ID NO: 2.

b) a polynucleotide comprising nucleotides 1632 to 1929 of SEQ ID NO: 2.

c) a polynucleotide comprising SEQ ID NO: 1,

d) a polynucleotide comprising SEQ ID NO: 3,

e) a polynucleotide comprising SEQ ID NO: 5,

f) a polynucleotide complementary to the polynucleotides of (a) to (e).

The invention encompasses a purified, isolated and/or recombinant nucleic acid comprising a nucleotide sequence selected from the group consisting of polynucleotides encoding a KCNQ2-15b polypeptides, including splice variants as well as allelic variants, and fragments of KCNQ2-15bx, KCNQ2-15by and KCNQ2-15bz polypeptides. Preferably, said fragments comprise nucleotides at position 1776 to 1929 of SEQ ID NO: 2. More preferably, said fragments comprise nucleotides at position 1632 to 1929 of SEQ ID NO: 2.

Preferred KCNQ2-15b polynucleotides of the invention include isolated and/or recombinant polynucleotides comprising a contiguous span of at least 8, 12, 15, 18, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700 or 1800 nucleotides of SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 5.

In a further preferred embodiment, the purified KCNQ2-15b polynucleotide has at least 70, 80, 85, 90, 95, 96, 97, 98 or 99% nucleotide identity with a polynucleotide selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 5, sequences complementery thereto and fragments thereof.

Another object of the invention relates to purified polynucleotides that hybridize under moderately stringent conditions or under highly stringent conditions with a polynucleotide selected from the group consisting of sequences complementery thereto and fragments thereof.

Most preferred KCNQ2-15b polynucleotides of the invention include polynucleotides encoding a KCNQ2-15bx polypeptide, a KCNQ2-15by polypeptide or a KCNQ2-15bz polypeptide. A KCNQ2-15bx polynucleotide corresponds to a polynucleotide encoding a KCNQ2-15bx polypeptide. A KCNQ2-15by polynucleotide corresponds to a polynucleotides encoding a KCNQ2-15by polypeptide. A KCNQ2-15bz polynucleotide corresponds to a polynucleotide encoding a KCNQ2-15bz polypeptide.

In some embodiments, said KCNQ2-15b polynucleotide comprises or consists of the coding sequence (CDS) encoding the KCNQ2-15b polypeptide. In other embodiments, said KCNQ2-15b polynucleotide comprises or consists of the messenger RNA (mRNA) encoding the KCNQ2-15b polypeptide. In further embodiments, said KCNQ2-15b polynucleotide comprises or consists of the complementary DNA (cDNA) encoding the KCNQ2-15b polypeptide. Preferred KCNQ2-15b polynucleotides are polynucleotides comprising a CDS having the sequence of SEQ ID NO: 1, SEQ ID NO; 3 or SEQ ID NO: 5, mRNAs comprising these CDSs and cDNAs comprising these CDSs.

The present invention also encompasses fragments of KCNQ2-15bx, KCNQ2-15by or KCNQ2-15bz polynucleotides for use as primers and probes. Such primers are useful

in order to detect the presence of at least a copy of a KCNQ2-15bx, KCNQ2-15by or KCNQ2-15bz polynucleotide, complement, or variant thereof in a test sample. The probes of the present invention are useful for a number of purposes. They can notably be used in Southern hybridization to genomic DNA. The probes can also be used to detect PCR amplification products. They may also be used to detect mismatches in the KCNQ2-15bx, KCNQ2-15by or KCNQ2-15bz mRNAs using other techniques. They may further be used for in situ hybridization.

Any of the polynucleotides, primers and probes of the present invention can be conveniently immobilized on a solid substrate, such as, e.g., a microarray. A substrate comprising a plurality of oligonucleotide primers or probes of the invention may be used either for detecting or amplifying targeted sequences in the KCNQ2-15bx, KCNQ2-15by or KCNQ2-15bz gene, may be used for detecting mutations in the coding or in the non-coding sequences of the KCNQ2-15bx, KCNQ2-15by or KCNQ2-15bz mRNAs, and may also be used to determine expression of KCNQ2-15bx, KCNQ2-15by or KCNQ2-15bz mRNAs in different contexts such as in different tissues, at different stages of a process (embryo development, disease treatment), and in patients versus healthy individuals.

Methods of cloning or constructing KCNQ2-15b polynucleotides are well known by those of skill in the art. For example, the methods described in the examples may be used to clone or construct the KCNQ2-15b polynucleotides of the present invention.

4. Vectors, Host Cells and Host Organisms of the Present Invention

The present invention also relates to vectors including the KCNQ2-15b polynucleotides of the present invention. More particularly, the present invention relates to expression vectors which include a KCNQ2-15b polynucleotide. Preferably, such expression vectors comprise a polynucleotide encoding a KCNQ2-15bx, a KCNQ2-15by, a KCNQ2-15bz polypeptide, a mutein thereof or a fragment thereof.

The term "vector" is used herein to designate either a circular or a linear DNA or RNA compound, which is either double-stranded or single-stranded, and which comprise at least one polynucleotide of the present invention to be transferred in a cell host or in a unicellular or multicellular host organism. An "expression vector" comprises appropriate signals in the vectors, said signals including various regulatory elements, such as enhancers/promoters from both viral and mammalian sources that drive expression of the inserted polynucleotide in host cells. Selectable markers for establishing permanent, stable cell clones expressing the products such as, e.g., a dominant drug selection, are generally included in the expression vectors of the invention, as they are elements that link expression of the drug selection markers to expression of the polypeptide.

Additionally, the expression vector may be a fusion vector driving the expression of a fusion polypeptide between a KCNQ2-15b polypeptide and a heterologous polypeptide. For example, the heterologous polypeptide may be a selectable marker such as, e.g., a luminescent protein, or a polypeptide allowing the purification of the fusion polypeptide.

The polynucleotides of the present invention may be used to, e.g., express the encoded polypeptide in a host cell for producing the encoded polypeptide. The polynucleotides of the present invention may further be used to express the encoded polypeptide in a host cell for screening assays. Screenings assays are of particular interest for identifying modulators and/or binding partners of KCNQ2-15b polypeptides as further detailed below. The polynucleotides of the present invention may also be used to express the encoded polypeptide in a host organism for producing a beneficial effect. In such procedures, the encoded protein may be transiently expressed in the host organism or stably expressed in the host organism. The encoded polypeptide may have any of the properties described herein. The encoded polypeptide may be a protein which the host organism lacks or, alternatively, the encoded protein may augment the existing levels of the protein in the host organism.

In one embodiment, the expression vector is a gene therapy vector. Viral vector systems that have application in gene therapy have been derived from, e.g., herpes virus, vaccinia virus, and several RNA viruses. In particular, herpes virus vectors may provide a unique strategy for persistence of inserted gene expression in cells of the central nervous system and ocular tissue.

Another object of the invention comprises a host cell that has been transformed, transfected or transduced with a polynucleotide encoding a KCNQ2-15b polypeptide. Also included are host cells that are transformed, transfected or transduced with a recombinant vector such as one of those described above. The cell hosts of the present invention can comprise any of the polynucleotides of the present invention.

Any host cell known by one of skill in the art may be used. Preferred host cells used as recipients for the polynucleotides and expression vectors of the invention include:

a) Prokaryotic host cells: *Escherichia coli* strains (I.E.DH5-α strain), *Bacillus subtilis, Salmonella typhimurium*, and strains from species like *Pseudomonas, Streptomyces* and *Staphylococcus.*

b) Eukaryotic host cells: CHO (ATCC No. CCL-61), HeLa cells (ATCC No. CCL2; No. CCL2.1; No. CCL2.2), Cv 1 cells (ATCC No. CCL70), COS cells (ATCC No. CRL1650; No. CRL1651), Sf-9 cells (ATCC No. CRL1711), C127 cells (ATCC No. CRL-1804), 3T3 (ATCC No. CRL-6361), human kidney 293. (ATCC No. 45504; No. CRL-1573), BHK (ECACC No. 84100501; No. 84111301), *Saccharomyces cerevisiae* strains such as AH109 and Y184, and *Aspergillus niger* strains.

Another object of the invention comprises methods of making the above vectors and host cells by recombinant techniques. Any well-known technique for constructing an expression vector and for delivering it to a cell may be used for construction and delivering the vectors of the present invention. Such techniques include but are not limited to the techniques detailed in the examples.

Another object of the present invention is a transgenic animal which includes within a plurality of its cells a cloned recombinant KCNQ2-15b polynucleotide. The terms "transgenic animals" or "host animals" are used herein to designate animals that have their genome genetically and artificially manipulated so as to include one of the nucleic acids according to the invention. The cells affected may be somatic, germ cells, or both. Preferred animals are non-human mammals and include those belonging to a genus selected from *Mus* (e.g. mice), *Rattus* (e.g. rats) and *Oryctogalus* (e.g. rabbits) which have their genome artificially and genetically altered by the insertion of a nucleic acid according to the invention. In one embodiment, the invention encompasses non-human host mammals and animals comprising a recombinant vector of the invention or a KCNQ2-15b polynucleotide disrupted by homologous recombination with a knock out vector.

In a preferred embodiment, these transgenic animals may be good experimental models in order to study diverse pathologies related to KCNQ2-15b function. In particular, a transgenic animal wherein (i) an antisense mRNA binding to

naturally occurring KC NQ2-15b mRNAs is transcribed; or (ii) an mRNA expressing a KCNQ2-15b polypeptide; may be a good animal model for bipolar disorders and/or other mood-disorders.

5. Methods of Making the Polypeptides of the Present Invention

The present invention also relates to methods of making a KCNQ2-15b polypeptide.

In one embodiment, the KCNQ2-15b polypeptides of the present invention are isolated from natural sources, including tissues and cells, whether directly isolated or cultured cells, of humans or non-human animals. Soluble forms of KCNQ2-15b may be isolated from body fluids. Methods for extracting and purifying natural membrane spanning proteins are known in the art, and include the use of detergents or chaotropic agents to disrupt particles followed by, e.g., differential extraction and separation of the polypeptides by ion exchange chromatography, affinity chromatography, sedimentation according to density, and gel electrophoresis. The method described in Example 4 may for example be used. Polypeptides of the invention also can be purified from natural sources using antibodies directed against the polypeptides of the invention, such as those described herein, in methods which are well known in the art of protein purification.

In a preferred embodiment, the KCNQ2-15b polypeptides of the invention are recombinantly produced using routine expression methods known in the art. The polynucleotide encoding the desired polypeptide is operably linked to a promoter into an expression vector suitable for any convenient host. Both eukaryotic and prokaryotic host systems may be used in forming recombinant polypeptides. The polypeptide is then isolated from lysed cells or, if a soluble form is produced, from the culture medium and purified to the extent needed for its intended use.

Consequently, a further embodiment of the present invention is a method of making a polypeptide of the present invention, said method comprising the steps of:

a) obtaining a polynucleotide encoding a KCNQ2-15b polypeptide;
b) inserting said polynucleotide in an expression vector such that the polynucleotide is operably linked to a promoter; and
c) introducing said expression vector into a host cell whereby said host cell produces said polypeptide.

In a preferred embodiment, the method further comprises the step of isolating the polypeptide. The skilled person will appreciate that any step of this method may be carried out separately. The product of each step may be transferred to another step in order to carry out the subsequent step.

In further embodiments, said polynucleotide consists of a CDS. In another aspect of this embodiment, said polynucleotide is a polynucleotide consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or a fragment thereof.

A further aspect of the invention relates to a method of making a polypeptide, said method comprising the steps of culturing a host cell comprising an expression vector comprising a KCNQ2-15b polynucleotide under conditions suitable for the production of a KCNQ2-15b polypeptide within said host cell. In a preferred embodiment, the method further comprises the step of purifying said polypeptide from the culture.

In another embodiment, it is often advantageous to add to the recombinant polynucleotide encoding a KCNQ2-15b polypeptide additional nucleotide sequence which codes for secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues or GST tags, or an additional sequence for stability during recombinant production. Soluble portions of the KCNQ 2-15b polypeptide may be, e.g., linked to an Ig-Fc part in order to generate stable soluble variants.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including but not limited to differential extraction, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, high performance liquid chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography, immunochromatography and lectin chromatography.

The expressed KCNQ2-15b polypeptide may be purified using any standard immunochromatography techniques. In such procedures, a solution containing the polypeptide of interest, such as the culture medium or a cell extract, is applied to a column having antibodies against the polypeptide attached to the chromatography matrix. The recombinant protein is allowed to bind the immunochromatography column. Thereafter, the column is washed to remove non-specifically bound proteins. The specifically bound secreted protein is then released from the column and recovered using standard techniques.

6. Antibodies of the Present Invention

The present invention further relates to antibodies that specifically bind to the polypeptides of the present invention. More specifically, said antibodies bind to the epitopes of the polypeptides of the present invention. The antibodies of the present invention include IgG (including IgG1, IgG2, IgG3, and IgG4), IgA (including IgA1 and IgA2), IgD, IgE, or IgM, and IgY. The term "antibody" (Ab) refers to a polypeptide or group of polypeptides which are comprised of at least one binding domain, where a binding domain is formed from the folding of variable domains of an antibody compound to form three-dimensional binding spaces with an internal surface shape and charge distribution complementary to the features of an antigenic determinant of an antigen, which allows an immunological reaction with the antigen. As used herein, the term "antibody" is meant to include whole antibodies, including single-chain whole antibodies, and antigen binding fragments thereof. In a preferred embodiment the antibodies are human antigen binding antibody fragments of the present invention include, but are not limited to, Fab, Fab' F(ab)2 and F(ab')2, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a V_L or V_H domain. The antibodies may be from any animal origin including birds and mammals. Preferably, the antibodies are from human, mouse, rabbit, goat, guinea pig, camel, horse or chicken. The present invention further includes chimeric, humanized, and human monoclonal and polyclonal antibodies, which specifically bind the polypeptides of the present invention.

Preferred antibodies of the present invention recognize an epitope within amino acids 589 to 643 of SEQ ID NO: 2, wherein said one or more amino-acids are required for binding of the antibody to a KCNQ2-15b polypeptide. Other preferred antibodies of the present invention recognize one or more of the amino acids at positions 545 to 643 of SEQ ID NO: 2, wherein said one or more amino-acids are required for binding of the antibody to a KCNQ2-15b polypeptide. Most preferably, the antibodies of the present invention bind to a KCNQ2 polypeptide comprising exon 15b but not to a KCNQ2 polypeptide lacking exon 15b.

A preferred embodiment of the invention is a method of specifically binding an antibody of the present invention to a

KCNQ2-15b polypeptide. This method comprises the step of contacting the antibody of the present invention with a KCNQ2-15b polypeptide under conditions in which said antibody can specifically bind to said polypeptide. Such conditions are well known to those skilled in the art. This method may be used to, e.g., detect, purify, or activate or inhibit the activity of KCNQ2-15b polypeptides.

The invention further relates to antibodies that act as modulators of the polypeptides of the present invention. Preferred antibodies are modulators that enhance the binding activity or the biological activity of the KCNQ2-15b polypeptide to which they bind. These antibodies may act as modulators for either all or less than all of the biological properties of the KCNQ2-15b polypeptide.

7. Uses of the Polypeptides of the Present Invention

The present invention is also directed to the use of a KCNQ2 polypeptide as a target for screening candidate modulators. As used herein, the term "KCNQ2 polypeptide" refers to any polypeptide encoded by the KCNQ2 gene. Thus the term "KCNQ2 polypeptide" encompasses all alternative splice variants encoded by the KCNQ2 gene, such as, e.g., KCNQ2-15b polypeptides and all previously described isoforms (see, e.g., SwissProt Accession No. 043526). As further used herein, the term "KCNQ2-fl" refers to a polypeptide of SEQ ID NO: 7.

As used herein, the term "modulator" refers to a compound that increases or decreases any of the properties of a KCNQ2 polypeptide. As used herein, a "KCNQ2 modulator" refers to a compound that increases or decreases the activity of a KCNQ2 polypeptide and/or to a compound that increases or decreases the transcription level of the KCNQ2 mRNA encoding said polypeptide. The term "modulator" encompasses both agonists and antagonists.

As used herein, a "KCNQ2 antagonist" refers to a compound that decreases the activity of a KCNQ2 polypeptide and/or to a compound that decreases the expression level of the KCNQ2 mRNA encoding said polypeptide. The terms "antagonist" and "inhibitor" are considered to be synonymous and can be used interchangeably throughout the disclosure.

As used herein, a "KCNQ2 agonist" refers to a compound that increases the activity of a KCNQ2 polypeptide and/or to a compound that increases the expression level of the KCNQ2 mRNA encoding said polypeptide. The terms "agonist" and "activator" are considered to be synonymous and can be used interchangeably throughout the disclosure.

Methods that can be used for testing modulators for their ability to increase or decrease the activity of a KCNQ2 polypeptide or to increase or decrease the expression of a KCNQ2 mRNA are well known in the art and further detailed below. Preferred modulators of the present invention are modulators of KCNQ2-15bx, KCNQ2-15by, KCNQ2-15bz or KCNQ2-fl. The assays described herein and known in the art for measuring KCNQ2 activity can be performed either in vitro or in vivo.

Candidate compounds according to the present invention include naturally occurring and synthetic compounds. Such compounds include, e.g., natural ligands, small molecules, antisense mRNAs, antibodies, aptamers and short interfering RNAs. As used herein, the term "natural ligand" refers to any signaling molecule that binds to a phosphatase comprising PP2A/Bγ in vivo and includes molecules such as, e.g., lipids, nucleotides, polynucleotides, amino acids, peptides, polypeptides, proteins, carbohydrates and inorganic molecules. As used herein, the term "small molecule" refers to an organic compound. As used herein, the term "antibody" refers to a protein produced by cells of the immune system or to a fragment thereof that binds to an antigen. As used herein, the term "antisense mRNA" refers an RNA molecule complementary to the strand normally processed into mRNA and translated, or complemantary to a region thereof. As used herein, the term "aptamer" refers to an artificial nucleic acid ligand (see, e.g., Ellington and Szostak (1990) Nature 346: 818-822). As used herein, the term "short interfering RNA" refers to a double-stranded RNA inducing sequence-specific posttranscriptional gene silencing (see, e.g., Elbashir et al. (2001) Genes Dev. 15:188-200).

Such candidate compounds can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including, e.g., biological libraries, spatially addressable parallel solid phase or solution phase libraries, and synthetic library methods using affinity chromatography selection. The biological library approach is generally used with peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomers, aptamers or small molecule libraries of compounds.

One example of a method that may be used for screening candidate compounds for a modulator is a method comprising the steps of:

a) contacting a KCNQ2 polypeptide with the candidate compound; and

b) testing the activity of said KCNQ2 polypeptide in the presence of said candidate compound,

wherein a difference in the activity of said KCNQ2 polypeptide in the presence of said compound in comparison to the activity in the absence of said compound indicates that the compound is a modulator of said KCNQ2 polypeptide.

Alternatively, the assay may be a cell-based assay comprising the steps of:

a) contacting a cell expressing a KCNQ2 polypeptide with the candidate compound; and

b) testing the activity of said KCNQ2 polypeptide in the presence of said candidate compound,

wherein a difference in the activity of said KCNQ2 polypeptide in the presence of said compound in comparison to the activity in the absence of said compound indicates that the compound is a modulator of said KCNQ2 polypeptide.

The modulator may modulate any activity of said KCNQ2 polypeptide. The modulator may for example modulate KCNQ2 mRNA expression within a cell, or modulate the M-current generated by a potassium channel comprising the KCNQ2 polypeptide. Further activities that may be measured include KCNQ2 binding to PP2A/Bγ, and to KCNQ2 binding to other potassium channel subunits. The phosphorylation state of a KCNQ2 polypeptide is a further activity of KCNQ2 that may be assessed in order to screen compounds. Most preferably, the activity of the KCNQ2 polypeptide is assessed by measuring the M-current. Methods for testing the above mentioned activities are well known to those of skill in the art, and may for example be performed as further detailed below.

Preferred modulators of the invention are modulators that increase or decrease:

KCNQ2 mRNA expression within a cell;

the M-current generated by a potassium channel comprising a KCNQ2 polypeptide;

binding of the KCNQ2 polypeptide to PP2A/Bγ; and/or

binding of the KCNQ2 polypeptide to other potassium channel subunits.

In a preferred embodiment, the activity of a KCNQ2 polypeptide is assessed by measuring the M-current generated by a potassium channel comprising the KCNQ2 polypeptide. Assays for measuring the M-current generated

by a potassium channel are known by those of skill the art. An electrophysiologic assay for measuring the activity of the M-current generated by a potassium channel is for example described by Pan et al. and by Schwake et al. (Pan et al. (2001), J. Physiol., 531:347-358; Schwake et al. (2000), J. Biol. Chem., 275:13343-13348). High-throughput fluorescence assays using membrane potential sensitive dyes has also been described to screen compounds on potassium channels. For example, EVOTEC has developed assays for testing the activity of ion channels (see, e.g., the world wide website evotecoai.com). In such assays, the activity both of ho momeric KCNQ2 channels and of heteromeric channels may be tested. Homomeric channels that may be tested include, e.g., homomeric KCNQ2-fl and homomeric KCNQ2-15b channels. Heteromeric channels that may be tested include, e.g., heteromeric KCNQ2-15b/KCNQ2-fl, heteromeric KCNQ2-fl/KCNQ3 and heteromeric KCNQ2-15b/KCNQ3 channels.

In another preferred embodiment, the activity of a KCNQ2 polypeptide is assessed by measuring the binding of the KCNQ2 polypeptide to PP2A/Bγ. The binding of a KCNQ2 polypeptide to PP2A/Bγ can for example be measured by the yeast mating test as described in example 3 or by the solid phase overlay assay as described in example 6.

In another preferred embodiment, the activity of a KCNQ2 polypeptide is assessed by measuring the binding of the KCNQ2 polypeptide to other potassium channels subunits. This assay may also be performed using the yeast mating test or the solid phase overlay assay described in examples 3 and 6.

In a further preferred embodiment, the activity of a KCNQ2 polypeptide is assessed by measuring the KCNQ2 mRNA levels within a cell. In this embodiment, the activity can for example be measured using Northern blots, RT-PCR, quantitative RT-PCR with primers and probes specific for KCNQ2 mRNAs. The term "KCNQ2 mRNA" as used herein encompasses all alternative splice variants translated from the KCNQ2 gene such as, e.g., SEQ ID Nos 1, 3, 5 and EMBL Accession Nos. NM_172107, NM_172106, NM_004518, NM_172108 and NM_172109. The primers and probes may detect one specific KCNQ2 splice variant or detect all alternative splice variants translated from the KCNQ2 gene. Alternatively, the expression of the KCNQ2 mRNA is measured at the polypeptide level, by using labeled antibodies that specifically bind to the KCNQ2 polypeptide in immunoassays such as ELISA assays, or RIA assays, Western blots or immunohistochemical assays. The KCNQ2 antibody may detect one specific KCNQ2 splice variant or detect all alternative splice variants translated from the KCNQ2 gene.

In another embodiment, the activity of a KCNQ2 polypeptide is measured by determining the phosphorylation state of the KCNQ2 polypeptide as described in example 7. In the frame of the present invention, it has been found that (I) KCNQ2-15b polypeptides are dephosphorylated by a PP2A phosphatase comprising a PP2A/Bγ subunit, the gene encoding the PP2A/Bγ subunit being associated with bipolar disorder; and (ii) phosphorylated by GSK3β, a kinase that is inhibited by mood stabilizing agents. Thus the phosphorylation state of a KCNQ2 polypeptide is believed to be correlated with the biological activity of the KCNQ2 polypeptide. The phosphorylation state of a KCNQ2 polypeptide may for example be measured in an assay as described in example 7.

One preferred embodiment is directed to the use of a KCNQ2-15b polypeptide as a target for screening candidate modulators. Another preferred embodiment is directed to the use of a KCNQ2-fl polypeptide as a target for screening candidate modulators.

Modulators of KCNQ2 polypeptides, which may be found, e.g., by any of the above screenings, are candidate drugs for the treatment of a mental disorder. Thus a preferred embodiment of the present invention is the use of a KCNQ2 polypeptide as a target for screening candidate compounds for candidate drugs for the treatment of a mental disorder.

As used herein, the term "Mental disorder" includes bipolar disorder, schizophrenia, depression as well as other mood disorders and psychotic disorders. Preferably, said mental disorder is bipolar disorder, schizophrenia or depression. Most preferably, said mental disorder is bipolar disorder.

A further aspect of the present invention is the use of a modulator of a KCNQ2 polypeptide for screening for drugs for the treatment of a mental disorder. One example of a method that can be used for screening for drugs for the treatment of a mental disorder and/or for assessing the efficiency of an modulator of a KCNQ2 polypeptide for the treatment of a mental disorder is a method comprising the step of administering said modulator to an animal model for said mental disorder, wherein a determination that said modulator ameliorates a representative characteristic of said mental disorder in said animal model indicates that said modulator is a drug for the treatment of said mental disorder.

Animal models for mental disorders and assays for determining whether a compound ameliorates a representative characteristic of said mental disorder in said animal model are described and used. For example, animal models that may be used in the above method include but are not limited to the conditioned avoidance behaviour model in rats, which is a standard behavioural test predictive of antipsychotic activity, the behavioral activity assessment of mice and rats in the Omnitech Digiscan animal activity monitors, the purpose of which is to evaluate compounds for antipsychotic-like CNS effects and a variety of other behavioral effects generally associated with CNS activity, the blockade of amphetamine-stimulated locomotion in rat, the protocol for the prepulse inhibition of acoustic startle model in rats, the inhibition of apomorphine-induced climbing behaviour and the inhibition of DOI-induced head twitches and scratches. A preferred animal model is the STOP –/– mice with synaptic defects and severe behavioral disorders described by Andrieux et al. (2002, Genes Dev., 16:2350-2364).

A further aspect of the present invention is directed to the use of a modulator of a KCNQ2 polypeptide for preparing a medicament for the treatment of a mental disorder. Such a medicament comprises said modulator of a KCNQ2 polypeptide in combination with any physiologically acceptable carrier. Physiologically acceptable carriers can be prepared by any method known by those skilled in the art. Physiologically acceptable carriers include but are not limited to those described in Remington's Pharmaceutical Sciences (Mack Publishing Company, Easton, USA 1985). Pharmaceutical compositions comprising a modulator of a KCNQ2 polypeptide and a physiologically acceptable carrier can be for, e.g., intravenous, topical, rectal, local, inhalant, subcutaneous, intradermal, intramuscular, oral, intracerebral and intrathecal use. The compositions can be in liquid (e.g., solutions, suspensions), solid (e.g., pills, tablets, suppositories) or semi-solid (e.g., creams, gels) form. Dosages to be administered depend on individual needs, on the desired effect and the chosen route of administration.

Such a medicament comprising a KCNQ2 modulator or a gene therapy vector of the invention may be used in combination with any known drug for the treatment of a mental disorder. The modulator may for example be administered in combination with a mood-stabilizing drug used for treating bipolar disorder such as, e.g., lithium, carbamazepine or

divalproex. The modulator may also be administered in combination with an antidepressant such as, e.g., a tricyclic antidepressant, a selective serotonin reuptake inhibitor, a monoamine oxidase inhibitor or a psychostimulant. When treating schizophrenia and other psychotic disorders, the modulator may for example be administered in combination with an antipsychotic drugs such as, e.g., chlorpromazine, clozapine, risperidone or olanzapine.

In all the above embodiments, preferred modulators are modulators of KCNQ2-15b polypeptides or of KCNQ2-fl. Preferred modulators of KCNQ2-15b polypeptides are modulators that specifically modulate a polypeptide comprising exon 15b shown at position 545 to 643 of SEQ ID NO: 2. Preferred KCNQ2-fl modulators are modulators that specifically modulate a polypeptide comprising exons 16 and 17 shown at position 588 to 872 of SEQ ID NO: 7.

The present invention further relates to methods for screening for natural binding partners of a KCNQ2 polypeptide. Such methods include the yeast two-hybrid screening that is described in example 1. Identifying natural biding partners of a KCNQ2 polypeptide may be preformed by replacing the CDS encoding PP2A/Bγ with a polynucleotides encoding a KCNQ2 polypeptide. Using a KCNQ2 polypeptide as a target has a great utility for the identification of proteins involved in bipolar disorder and for providing new intervention points in the treatment of bipolar disorder and other mood disorders.

8. Biallelic Markers of the Present Invention

The present invention is directed to the use of at least one KCNQ2-related biallelic marker for diagnosing whether an individual suffers from or is at risk of suffering from a mental disorder. As used herein, the term "KCNQ2-related biallelic marker" refers to a biallelic marker located in an exon of the KCNQ2 gene, in an intron of the KCNQ2 gene, or in the regulatory regions of the KCNQ2 gene. KCNQ2-related biallelic markers encompass the biallelic markers shown in table 3B in Example 12. In one embodiment, a single biallelic marker is used for diagnosing whether an individual suffers from or is at risk of suffering from a mental disorder by determining the genotype of an individual. In another embodiment, a combination of several biallelic markers may be used for diagnosing whether an individual suffers from or is at risk of suffering from a mental disorder by determining the haplotype of an individual. For example, a two-markers haplotype, a three-markers haplotype or a four-markers haplotype may be determined.

As used herein, the term "biallelic marker" refers to a polymorphism having two alleles at a fairly high frequency in the population, preferably a single nucleotide polymorphism. Typically the frequency of the less common allele of the biallelic markers of the present invention has been validated to be greater than 1%, preferably the frequency is greater than 10%, more preferably the frequency is at least 20% (i.e. heterozygosity rate of at least 0.32), even more preferably the frequency is at least 30% (i.e. heterozygosity rate of at least 0.42). In the present specification, the term "biallelic marker" is used to refer both to the polymorphism and to the locus carrying the polymorphism.

As used herein, the term "genotype" refers to the identity of the alleles present in an individual or a sample. The term "genotype" preferably refers to the description of both copies of a single biallelic marker that are present in the genome of an individual. The individual is homozygous if the two alleles of the biallelic marker present in the genome are identical. The individual is heterozygous if the two alleles of the biallelic marker present in the genome are different.

The term "genotyping" a sample or an individual for a biallelic marker involves determining the specific alleles or the specific nucleotides carried by an individual at a biallelic marker.

As used herein, the term "haplotype" refers to a set of alleles of closely linked biallelic markers present on one chromosome and which tend to be inherited together.

Methods for determining the alleles, genotypes or haplotypes carried by an individual are well known by those of skill in the art and further detailed below.

In all embodiments, preferred "mental disorders" include bipolar disorder, schizophrenia and depression. Most preferred mental disorder is bipolar disorder.

In the context of the present invention, the individual is generally understood to be human.

As shown in Example 15, biallelic markers 30-2/62 and 30-7/30 are bipolar disorder-associated markers. Preferred embodiments of the present invention are thus directed to the use of biallelic markers 30-2/62 and 30-7/30. The alternative alleles of biallelic markers 30-2/62 and 30-7/30 are indicated in table 3B in example 12. Positions of biallelic markers 30-2/62 and 30-7/30 on SEQ ID NO: 43 and SEQ ID NO: 45 respectively are also indicated in table 3B. Other preferred embodiments are directed to the use of biallelic markers complementary to 30-2/62 and 30-7/30, i.e., the corresponding alternative alleles that are located on the complementary strand of DNA.

Accordingly, a preferred embodiment of the present invention is directed to the use of biallelic markers 30-2/62 and 30-7/30 and the complements thereof for diagnosing whether an individual suffers from or is at risk of suffering from a mental disorder. Preferably, the individual is a Caucasian individual. Most preferably, the individual is a Caucasian individual of British Isles origin.

The risk genotypes for biallelic markers 30-2/62 and 30-7/30 are indicated in table 6B. "Risk genotype" means that the probability of having bipolar disorder is higher for an individual carrying the risk genotype than for an individual carrying another genotype. The risk genotype for biallelic marker 30-2/62 is "AG". Thus a preferred embodiment of the present invention is the use of biallelic markers 30-2/62 or the complement thereof for diagnosing whether an individual suffers from or is at risk of suffering from a mental disorder, wherein the presence of a genotype "AG" at biallelic marker 30-2/62 is indicative of said individual suffering from or being at risk of suffering from said mental disorder. The risk genotype for biallelic marker 30-7/30 is "CC". Thus a preferred embodiment of the present invention is the use of biallelic markers 30-2/62 or the complement thereof for diagnosing whether an individual suffers from or is at risk of suffering from a mental disorder, wherein the presence of a genotype "CC" at biallelic marker 30-7/30 is indicative of said individual suffering from or being at risk of suffering from said mental disorder.

The present invention is further directed to the use of at least one KCNQ2-related biallelic marker for determining whether there is a significant association between said marker and a mental disorder. Such determination can for example be performed using methods described in examples 10 to 15 below but using populations that are different from the UCL and the Labimo populations, such as populations having different ethnic origins. The KCNQ2-related biallelic marker may be selected from the group consisting of 30-2162 and 30-7/30 and the complements thereof. Alternatively, The KCNQ2-related biallelic marker may be selected from the group consisting of 30-4/58, 30-17/37, 30-84/37 and 30-15/54 and the complements thereof. The KCNQ2-related biallelic marker may also be a marker that is not specifically disclosed by the present specification. Preferably, the mental disorder is selected from the group consisting of bipolar disorder, schizophrenia and depression. Most preferably, the mental disorder is bipolar disorder.

The present invention is further directed to a method of genotyping comprising the step of determining the identity of

a nucleotide at a KCNQ2-related biallelic marker or the complement thereof in a biological sample. Preferably, said biological sample is derived from a single subject. It is preferred that the identity of the nucleotides at said biallelic marker is determined for both copies of said biallelic marker present in said individual's genome. In a preferred embodiment, the identity of the nucleotide at said biallelic marker is determined by a microsequencing assay. Preferably, a portion of a sequence comprising the biallelic marker is amplified prior to the determination of the identity of the nucleotide. The amplification may preferably be performed by PCR. Such a method of genotyping may for example be performed using any of the protocols described in examples 10 to 14 of the present specification. Further methods of genotyping are well known by those of skill in the art and any other known protocol may be used.

Methods well-known to those skilled in the art that may be used for genotyping in order to detect biallelic polymorphisms include methods such as, conventional dot blot analyzes, single strand conformational polymorphism analysis (SSCP) (Orita et al. (1989) Proc Natl Acad Sci USA 86:2766-2770), denaturing gradient gel electrophoresis (DGGE) (Borresen et al. (1988) Mutat Res. 202:77-83.), heteroduplex analysis (Lessa et al. (1993) Mol Ecol. 2:119-129), mismatch cleavage detection (Grompe et al. (1989) Proc Natl Acad Sci USA. 86:5888-5892). Another method for determining the identity of the nucleotide present at a particular polymorphic site employs a specialized exonuclease-resistant nucleotide derivative as described in U.S. Pat. No. 4,656,127. Oligonucleotide microarrays or solid-phase capturable dideoxynucleotides and mass spectrometry may also be used (Wen et al. (2003) World J Gastroenterol. 9:1342-1346; Kim et al. (2003) Anal Biochem. 316:251-258). Preferred methods involve directly determining the identity of the nucleotide present at a biallelic marker site by sequencing assay, microsequencing assay, enzyme-based mismatch detection assay, or hybridization assay.

As used herein, the term "biological sample" refers to a sample comprising nucleic acids. Any source of nucleic acids, in purified or non-purified form, can be utilized as the starting nucleic acid, provided it contains or is suspected of containing the specific nucleic acid sequence desired. DNA or RNA may be extracted from cells, tissues, body fluids and the like.

Methods of genotyping find use in, e.g., in genotyping case-control populations in association studies as well as in genotyping individuals in the context of detection of alleles of biallelic markers which are known to be associated with a given trait. In the context of the present invention, a preferred trait is a mental disorder selected from the group of bipolar disorder, schizophrenia and depression, and most preferably bipolar disorder.

Accordingly, a preferred embodiment is directed to a method of diagnosing a mental disorder in an individual comprising the step of genotyping at least one KCNQ2-related biallelic marker using a method of genotyping comprising the step of determining the identity of a nucleotide at a KCNQ2-related biallelic marker or the complement thereof in a biological sample derived from said individual. Such a diagnosing method may further comprise the step of correlating the result of the genotyping step with a risk of suffering from said mental disorder. Typically, the presence of the risk allele, risk genotype or risk haplotype of the genotyped KCNQ2-related biallelic marker(s) is correlated with a risk of suffering from the mental disorder. Preferably, said KCNQ2-related biallelic marker is selected from the group consisting of 30-2/62 and 30-7/30 and the complements thereof. In one embodiment, the presence of a genotype "AG" at biallelic marker 30-2/62218 is indicative of a risk of suffering from said mental disorder. In another embodiment, the presence of a genotype "CC" at biallelic marker 30-7130 is indicative of a risk of suffering from said mental disorder. Preferably, the mental disorder is selected from the group consisting of bipolar disorder, schizophrenia and depression. Most preferably, the mental disorder is bipolar disorder.

The present invention is further directed to the use of at least one KCNQ2-2-related biallelic marker for determining the haplotype of an individual. When determining the haplotype of an individual, each single chromosome should be studied independently. Methods of determining the haplotype of an individual are well known in the art and include, e.g., asymmetric PCR amplification (Newton et al. (1989) Nucleic Acids Res. 17:2503-2516; Wu et al. (1989) Proc. Natl. Acad. Sci. USA. 86:2757-2760), isolation of single chromosome by limit dilution followed by PCR amplification (Ruano et al. (1990) Proc. Natl. Acad. Sci. USA. 87:6296-6300) and, for sufficiently close biallelic markers, double PCR amplification of specific alleles (Sarkar and Sommer, (1991) Biotechniques. 10:436-440).

Thus the present invention is further directed to the use of at least one KCNQ2-related biallelic marker for determining the haplotype of an individual. For example, a method for determining a haplotype for a set of biallelic markers in an individual may comprise the steps of: a) genotyping said individual for at least one KCNQ2 related biallelic marker, b) genotyping said individual for a second biallelic marker by determining the identity of the nucleotides at said second biallelic marker. Preferably, both markers are KCNQ2-related biallelic markers. Methods of determining a haplotype for a combination of more than two biallelic markers comprising at least one KCNQ2-related biallelic marker in an individual are also encompassed by the present invention. In such methods, step (b) is repeated for each of the additional markers of the combination. Such a combination may comprise, e.g., 3, 4 or 5 biallelic markers. These biallelic markers may all be KCNQ2-related biallelic markers.

When estimating haplotype frequencies in a population, one may use methods without assigning haplotypes to each individual. Such methods use a statistical method of haplotype determination. Thus another aspect of the present invention encompasses methods of estimating the frequency of a haplotype for a set of biallelic markers in a population, comprising the steps of: a) genotyping each individual in said population for at least one KCNQ2-related biallelic marker, b) genotyping each individual in said population for a second biallelic marker by determining the identity of the nucleotides at said second biallelic marker; and c) applying a haplotype determination method to the identities of the nucleotides determined in steps a) and b) to obtain an estimate of said frequency. Such a method may also be performed for a combination of more than 2 biallelic markers. Step (c) may be performed using any method known in the art to determine or to estimate the frequency of a haplotype in a population. Preferably, a method based on an expectation-maximization (EM) algorithm (Dempster et al. (1977) JRSSB, 39:1-38; Excoffier and Slatkin, (1995) Mol Biol Evol. 12:921-7) leading to maximum-likelihood estimates of haplotype frequencies under the assumption of Hardy-Weinberg proportions (random mating) is used for performing step (c).

EXAMPLES

Example 1

Yeast Two-Hybrid Screening

1. Construction of pGBKT7-PPP2R2C

The full-length coding region of the PPP2R2C gene, which encodes the PP2A/Bγ subunit, was first amplified from a Human fcetal brain cDNA library (Marathon-Ready cDNA,

Clontech) with the two gene-specific primers of SEQ ID NO: 8 and of SEQ ID NO: 9. This first PCR product was then amplified with a new combination of primers of SEQ ID NO: 10 and of SEQ ID NO: 11. The amplified fragment encompassed nucleotides 52-1540 of the full-length cDNA, genbank accession number AF086924 extended, respectively, with EcoRI and BamHI cloning sites. The resulting 1503-bp fragment was digested with EcoRI and BamHI, purified and inserted into EcoRI and BamHI cloning sites of the pGBKT7 vector (Clontech).

2. The Yeast Two-Hybrid Screening

A yeast two-hybrid screening was performed to find polypeptides interacting with the PP2A/Bγ subunit. The *Saccharomyces cerevisiae* strain AH109 (MATa, trp1-901, leu2-3, 112, ura3-52, his3-200, gal4Δ, gal80Δ, LYS2::$GAL1_{UAS}$-$GAL1_{TATA}$-HIS3, $GAL2_{UAS}$-$GAL2_{TATA}$-ADE2, URA3::$MEL1_{UAS}$-$MEL1_{TATA}$-lacZ) was transformed with the pGBKT7-PPP2R2C construction. A lithium acetate transformation procedure was done according to the manufacturer's instructions (Matchmaker Two-Hybrid system, Clontech). The MATa transformed cells expressing the bait were then mixed with a pretransformed Matchmaker Human brain cDNA library in the Y187 strain (MAT α, ura3-52, his3-200, ade2-101, trp1-901, leu2-3, 112, gal4Δ, met^-; gal80Δ, URA3::$GAL1_{UAS}$-$GAL1_{TATA}$-lacZ). Three independent mating were performed with respectively 5.10^6, 5.10^6 and 2.10^5 clones of the Human brain cDNA library. The resulting diploid cells able to grow on SD/-Leu/-Trp medium containing plates were further selected onto the medium-stringency SD/-Leu/-Trp/-His selective medium for the identification of bait-prey interactions. Positive colonies were then picked up and plated onto the high-stringency SD/-Leu/-Trp/-His/-Ade selective medium. Only cDNA of colonies able to grow at the same time on SDI-Leu/-Trp and SDI-Leu/-Trp/-His/-Ade media was retained for sequencing and further studies.

3. Results of the He Yeast Two-Hybrid Screening

494 clones were obtained, sequenced and analyzed. Among these clones, the 2E11 and 1D3 clones comprised partial cDNAs encoding a novel splice variant of the KCNQ2 potassium channel. 2E11 comprised a cDNA encoding amino acids 433 to 643 of SEQ ID NO: 2, and 1D3 comprised a cDNA encoding amino acids 454 to 643 of SEQ ID NO: 2. The full-length splice variants were cloned and sequenced as described in Example 2.

Example 2

Cloning of the Full-Length KCNQ2 Splice Variants

1. Cloning and Sequencing

Poly(A)+ mRNA from Human brain, thalamus (Clontech) were reversed transcribed (RT) using the murine Moloney leukemia virus reverse transcriptase (RT-PCR Advantage kit, Clontech) with a primer of SEQ ID NO: 12 hybridizing specifically with the novel splice variant cloned in 2E11. After a phenol-chloroform extraction and precipitation steps, the products obtained by the previous RT-PCR were directly PCR-amplified using the following gene-specific primers of SEQ ID NO: 13 and of SEQ ID NO: 14. The amplified fragment encompassed nucleotides 127-148 of the KCNQ2 full-length cDNA, genbank accession number AF033348. These primers were respectively extended with EcoRI and BglII cloning sites. The PCR products were digested with EcoRI and BglII restriction enzymes (New England Biolabs), purified and then ligated into the EcoRI and BglII cloning sites of the pCMV-Myc vector (Clontech). The two pCMV-Myc-3H9 and pCMV-Myc-3H2 clones were fully sequenced. The sequence of the insert in pCMV-Myc-3H2 comprises SEQ ID NO: 1, and the sequence of the insert in pCMV-Myc-3H9 comprises SEQ ID NO: 3.

Similarly, a cDNA was cloned from a poly(A)+ mRNA library from human foetal brain. One clone was obtained and fully sequenced. Its insert comprised SEQ ID NO: 5.

2. Description of the Novel Splice Variants

SEQ ID NO: 1 encodes the polypeptide of SEQ ID NO: 2 (KCNQ2-15bx). SEQ ID NO: 3 encodes the polypeptide of SEQ ID NO: 4 (KCNQ2-15by). SEQ ID NO: 5 encodes the polypeptide of SEQ ID NO: 6 (KCNQ2-15bz). SEQ ID NO: 7 corresponds to the full-length KCNQ2 polypeptide (KCNQ2-fl).

As shown on the alignment between SEQ ID NO: 7, SEQ ID NO: 2, SEQ ID NO: 4 and SEQ ID NO: 6 (FIG. **1**), the three splice variants display a novel carboxyl-terminal extremity compared to KCNQ2. The 55 carboxyl-terminal amino acids of SEQ ID NO: 2, SEQ ID NO: 4 and SEQ ID NO: 6 are unique to these three splice variants. These 55 amino acids correspond to the amino acids at position 589 to 643 of SEQ ID NO: 2.

The genomic structure of the KCNQ2 gene is shown on FIG. **3** and in table 1. The KCNQ2 gene is comprised of 17 exons. None of the novel splice variants displays the exons corresponding to exons 15, 16 and 17 of the KCNQ2 gene. They all display a novel exon, exon 15b, which encodes the amino acids at position 545 to 643 of SEQ ID NO: 2. The 44 first amino acids encoded by exons 15 and 15b are identical (amino acids at position 545 to 588 of SEQ ID NO: 2). The 55 last amino acids encoded by exon 15b are unique to exon 15b (amino acids at position 589 to 643 of SEQ ID NO: 2). Furthermore, the novel splice variants do not display exons 16 and 17 of KCNQ2-fl. The most carboxyl-terminal exon of these splice variants is exon 15b. SEQ ID NO: 2 further comprises exon 1 to exon 14 of KCNQ2. Exon 12 of KCNQ2 is lacking in SEQ ID NO: 4. Exons 9 and 12 of KCNQ2 are lacking in SEQ ID NO: 6.

The insert of the 2E11 clone, which corresponds to a partial cDNA, comprises exons 13, 14 and 15b.

TABLE 1

Exon No.	SEQ ID NO: 1	Encodes AA of SEQ ID NO: 2	SEQ ID NO: 3	Encodes AA of SEQ ID NO: 4	SEQ ID NO: 5	Encodes AA of SEQ ID NO: 6	Encodes AA of SEQ ID NO: 7
1	1-296	1-98	1-296	1-98	1-296	1-98	1-98
2	297-387	100-129	297-387	100-129	297-387	100-129	100-129
3	388-514	130-171	388-514	130-171	388-514	130-171	130-171
4	515-690	173-230	515-690	173-230	515-690	173-230	173-230
5	691-816	231-272	691-816	231-272	691-816	231-272	231-272
6	817-927	273-309	817-927	273-309	817-927	273-309	273-309
7	928-1023	310-341	928-1023	310-341	928-1023	310-341	310-341
8	1024-1118	342-372	1024-1118	342-372	1024-1118	342-372	342-372
9	1119-1148	374-382	1119-1148	374-382	/	/	374-382

TABLE 1-continued

Exon No.	SEQ ID NO: 1	Encodes AA of SEQ ID NO: 2	SEQ ID NO: 3	Encodes AA of SEQ ID NO: 4	SEQ ID NO: 5	Encodes AA of SEQ ID NO: 6	Encodes AA of SEQ ID NO: 7
10	1149-1217	384-405	1149-1217	384-405	1119-1187	374-395	384-405
11	1218-1247	407-415	1218-1247	407-415	1188-1217	397-405	407-415
12	1248-1301	417-433	/	/	/	/	417-433
13	1302-1525	435-508	1248-1471	417-490	1218-1441	407-480	435-508
14	1526-1631	510-543	1472-1577	492-525	1442-1547	482-515	510-543
15	/	/	/	/	/	/	545-587
15b	1632-1929	545-643	1578-1875	527-625	1548-1845	517-615	/
16	/	/	/	/	/	/	588-629
17	/	/	/	/	/	/	630-872

Example 3

Yeast Mating Test

1. Construction of Vectors

1.1. EX13-17, which Comprises Exons 13, 14, 15, 16 and 17.

The pGADT7-EX13-17 plasmid was constructed as follows: a 1414-bp fragment was first PCR-amplified from a Human total brain cDNA library (Marathon-Ready cDNA, Clontech) with two gene-specific primers of SEQ ID NO: 15 and of SEQ ID NO: 16. This first PCR product was then amplified with a second set of gene-specific primers of SEQ ID NO: 17 and 5' of SEQ ID NO: 18. These primers are extended, respectively, with EcoRI and BamHI cloning sites. After digestion With EcoRI and BamHI restriction enzymes, the 1338-bp purified fragment was ligated to the same cloning sites of pGADT7 (Clontech).

1.2. EX13-15, which Comprises Exons 13, 14 and 15.

The pGADT7-EX13-15 plasmid was obtained as follows: a 484-bp fragment was PCR-amplified with primers of SEQ ID NO: 19 and of SEQ ID NO: 20, which are respectively extended with EcoRI and BamHI cloning sites, from the first PCR product of the pGADT7-EX13-17 construction. The resulting fragment was then digested with EcoRI and BamHI, purified, and ligated to the same cloning sites of pGADT7 (Clontech).

1.3. EX16-17, which Comprises Exons 16 and 17.

The pGADT7-EX16,17 plasmid was obtained as follows: a 883-bp fragment was PCR-amplified with primers of SEQ ID NO: 21 and of SEQ ID NO: 22, which are respectively extended with EcoRI and BamHI cloning sites, from the first PCR product of the pGADT7-EX13-17 construction. The resulting fragment was then digested with EcoRI and BamHI, purified, and ligated to the same cloning sites of pGADT7 (Clontech).

1.4. EXsp15b, which Comprises the Region Unique to Exon 15b.

The pGADT7-EXsp15b plasmid was constructed as follows: a 400-bp fragment was PCR-amplified with a primer of SEQ ID NO: 23 extended with EcoRI cloning site, and with a primer of SEQ ID NO: 24 from the pACT2-2E11 plasmid (see example 1). The resulting fragment was then digested with EcoRI and XhoI, purified, and ligated to the same cloning sites of pGAD7 (Clontech).

1.5. EXco15, which Comprises the Region Common to Exon 15 and Exon 15b.

The pGADT7-EXco15 domain plasmid was constructed as follows: a 146-bp fragment was PCR-amplified with primers of SEQ ID NO: 25 and of SEQ ID NO: 26, which are respectively extended with EcoRI and BamHI cloning sites, from the pACT2-2E11 plasmid. The resulting fragment was then digested with EcoRI and BamHI, purified, and ligated to the same cloning sites of pGADT7 (Clontech).

1.6. EX13-14, which Comprises Exons 13 and 14.

The pGADT7-EX13-14 plasmid was constructed as follows: a 300-bp fragment was PCR-amplified with primers of SEQ ID NO: 27 and of SEQ ID NO: 28, which are respectively extended with EcoRI and BamHI cloning sites, from the pACT2-2E11 plasmid. The resulting fragment was then digested with EcoRI and BamHI, purified, and ligated to the same cloning sites of pGADT7 (Clontech).

2. Protocol of the Yeast Mating Test

Yeast mating tests were performed to map the interaction domains between the different partners. The chosen *Saccharomyces cerevisiae* mating partner strains (AH109 and Y184) were transformed separately with the plasmids to be tested in combination with the plasmid of interest. The lithium acetate transformation procedure was done according to the manufacturer's instructions (Matchmaker Two-Hybrid system, Clontech). Transformants were selected on the appropriate SD dropout medium (Clontech). One fresh colony of each type to use was picked from the working stock plates and both placed in one 1.5 ml microcentrifuge tube containing 0.5 ml of YPD medium (Clontech). Cells were then incubated for 24 hr at 30° C. with shaking at 200 rpm. 10 μl of a 1:100 dilution of the mating culture were then spread on the appropriate SD medium: SD/-Leu/-Trp, and SDI-Leu/-Trp/-His/-Ade. After 7 to 15 days of growth on selective medium positive colonies were counted.

3. Results of the Direct Mating Tests Between KCNQ2 Polypeptides and PP2A/Bγ

Mating tests between each of the above constructions and the pGBKT7-PPP2R2C construction described in example 1 were performed. The results are shown on FIG. **2**. The sign "+" indicates that colonies grew, thus indicating that the tested polypeptide is capable of interacting with PP2A/Bγ. The sign "−" indicates that no colony grew, thus indicating that the tested polypeptide does not interact with PP2A/Bγ.

EX13-17, EX16-17, EX13-14 and EXsp15b do not interact with PP2A/Bγ. EX13-15b, EX13-15 and EXco15 interact with PP2A/Bγ. EX13-15b interacts with PP2A/Bγ, showing that KCNQ2-15b polypeptides are capable of interacting with PP2A/Bγ. Since EX13-15b, EX13-15 and EXco15 but not EXsp15b interact with PP2A/Bγ, the common region between exon 15 and exon 15b plays a role in this interaction. Furthermore, since EX13-17 does not interact with PP2A/Bγ, the fact that exon 15 or that exon 15b is located at the most carboxyl extremity of the KCNQ2 polypeptide is of importance for efficient interaction with PP2A/Bγ.

4. Results of the Direct Mating Tests Between Different KCNQ2 Polypeptides

Mating tests between the different above constructions were performed, and the results are shown on FIG. **4**. 4 mating tests were performed for each pair of constructs and the results are shown on FIG. **3**. The sign "++" indicates that all 4 colonies grew. The sign "+" indicates that 3 colonies out of 4 grew. The sign "−/+" indicates that 1 colony out of 4 grew. The sign "−" indicates that no colony grew.

This experiment shows that KCNQ2-15b polypeptides can associate and form homodimers. KCNQ2-15b polypeptides can also associate and form heterodimers with KCNQ2 polypeptides comprising exon 15 at their carboxyl-terminal extremity. KCNQ2-15b polypeptides associate with KCNQ2-fl polypeptides at a lesser extent.

Example 4

Expression and Purification of Glutathione S-Transferase Fusion Proteins

1. Construction of Plasmids

1.1. pGBKT7-2E11

The pACT2-2E11 plasmid rescued from yeast two-hybrid screening was digested with EcoRI and BglII and the resulting 687-bp fragment inserted after purification into EcoRI and BamHI cloning sites of the pGBKT7 vector (Clontech).

2.2. pGEX-2TK-2E11

A partial cDNA of the KCNQ2 splice variants was PCR-amplified from the pACT2-2E11 plasmid rescued from yeast two-hybrid screening using a gene-specific primer of SEQ ID NO: 29 and a primer in the pACT2 vector of SEQ ID NO: 30. These primers were respectively extended with BamHI and EcoRI cloning sites. The 892-bp PCR product was digested with BamHI and EcoRI, purified and inserted into BamHI and EcoRI sites of pGEX-2TK vector (Amersham Pharmacia Biotech). The pACT2 plasmid used for this construction was recovered from diploid cells as follows: a fresh colony of diploid cells was inoculated into 5 ml of SD/-Leu/-Trp (Clontech) and let to grow overnight at 30° C. with shacking at 200-250 rpm. Cells corresponding to 2 ml of the overnight culture were spun down by centrifuging at 4300 rpm for 10 min. The pellet was resuspended in 100 μl of zymolyase (1 U/μl) (Seikagaku Corporation) and incubated 1 hr at 30° C. Then 100 μl of a proteinase K mix (100 mM NaCl, 10 mM Tris-HCl pH [pH 8.0], 25 mM EDTA, 0.5% SDS, 0.1 mg/ml proteinase K) were added for 2.5 hr at 40° C. DNA was extracted by two successive phenol:chloroform steps and precipitated with 0.3 M sodium acetate and 2.5 volumes of ethanol. DH10B ElectroMAX competent cells (Invitrogen) were transformed with DNA and selected on agar plates supplemented with 120 μg/ml Ampicillin. The protein encoded by pGEX-2TK-2E11 was named GST-2E11.

1.3. pGEX-2TK-PPP2R2C

A 1485-bp fragment of PPP2R2C encompassing nucleotides 55-1540 of the full-length cDNA of PP2A/Bγ (genbank accession number AF086924) was PCR-amplified from the pGBKT7-PPP2R2C plasmid using gene-specific primers of SEQ ID NO: 31 and of SEQ ID NO: 32, which are respectively extended with BamHI and EcoRI cloning sites. The fragment was digested by BamHI and EcoRI, purified and ligated to the same cloning sites of pGEX-2TK vector (Amersham Pharmacia Biotech). The protein encoded by pGEX-2TK-2E11 is named GST-PPP2R2C.

1.4. pGEX-2TK-KCNQ2-Cter

A 1393-bp fragment of a KCNQ2-fl encompassing nucleotides 1544-2924 of the full-length cDNA (genbank accession number AF033348) was PCR-amplified from the pCMV-HA-KCNQ2-isol construction using gene-specific primers: of SEQ ID NO: 33 and of SEQ ID NO: 34, which are respectively extended with XhoI and EcoRI cloning sites. This PCR product was digested with XhoI and EcoRI, purified and substituted at the same sites for a 767-bp XhoI-EcoRI fragment of the pGEX-2TK-2E11 plasmid. The pCMV-HA-KCNQ2-isol plasmid used for the construction of pGEX-2TK-KCNQ2-Cter was obtained as follows: the full-length coding region for KCNQ2-fl (encompassing nucleotides 126-2924 of the full-length cDNA, genbank accession number AF033348) was first amplified from a Human brain cDNA library (Marathon-Ready cDNA, Clontech) using gene specific primers of SEQ ID NO: 35 and of SEQ ID NO: 36, which are respectively extended with EcoRI and BglII cloning sites. The PCR product was digested with EcoRI and BglII, purified and ligated to the same cloning sites of the pCMV-HA vector (Clontech). The protein encoded by pGEX-2TK-2E11 is named GST-KCNQ2-Cter.

2. Expression and Purification

Glutathione S-transferase fusion protein expression and purification by adapting the method described by Kaelin et al. (1991, Cell, 64:521-532). Overnight cultures of MAX Efficiency DH5αF'IQ competents cells (Invitrogen) transformed with either the pGEX2TK plasmid or the pGEX2TK-2E11, pGEX2TK-KCNQ2-Cter, and pGEX2TK-PPP2R2C recombinants were diluted 1:10 in LB medium containing ampicillin (100 μg/ml) and incubated for 1 hr at 37° C. Isopropyl-β-D-thiogalactopyranoside (IPTG, Promega) was then added to a final concentration of 0.1 mM and bacteria let to grow for 3 additional hours at 37° C. For fusion proteins recovery using the glutathione-Sepharose 4B beads (Amersham Biosciences), bacterial cultures were pelleted by centrifugation at 5000×g for 15 min at 4° C. and resuspended in 1/10 vol NETN (20 mM Tris-HCl [pH 8.0], 120 mM NaCl, 1 mM EDTA, 0.5% Nonidet P-40) supplemented with 1 mM phenylmethylsulfonyl fluoride (PMSF, Sigma) and one tablet of protease inhibitors cocktail (Complete™ mini, Roche) for 7 ml of buffer. The bacteria were then lysed on ice by mild sonication and centrifuged at 10,000×g for 10 min at 4° C. Aliquots (1 ml) of bacterial clear lysates were then rocked for 1 hr at 4° C. with 50 μl of glutathione-Sepharose 4B beads, which had been previously washed four times in NETN containing 1% Albumin Bovine (BSA fraction V, Sigma) and resuspended (final concentration 1:1 [v/v]) in NETN. The glutathione-Sepharose 4B beads were then washed three times with NETN. For recovery of the bound recombinants proteins, beads were washed two more times with 100 mM Tris-HCl [pH 8.0], 120 mM NaCl and elution was performed in the same buffer containing 20 mM glutathione (Sigma). Quantification of the eluted fusion proteins w performed by the standard Bradford's method (Biorad Protein Assay).

Example 5

In Vitro Labeling of the GST Fusion Proteins

Beads with bound GST fusion proteins corresponding to 1 ml of bacterial clear lysate were washed three times in NETN and one time with HMK buffer without DTT (20 mM Tris-HCl [pH 7.5], 120 mM NaCl, 12 mM $MgCl_2$). Beads were then resuspended in 30 μl of reaction mix (3 μl of 10×HMK Buffer with 20 mM DTT, 10 units of Protein Kinase A Catalytic Subunit [PKA from bovine heart, 250 units/vial, Sigma] in 40 mM DTT, 2 μl of [^{32}P]-γATP 6000 Ci/mMole and 24 μl of distilled water) and incubated at 4° C. for 30 min. During incubation beads were resuspended time to time by flicking. Reaction was stopped by adding 1 ml of HMK stop buffer (10

mM Sodium Phosphate [pH 8.0], 10 mM Sodium Pyrophosphate, 10 mM EDTA, 1 mg/ml BSA) and beads washed five times with NETN buffer. Elution of radiolabeled fusion proteins was carried out with 1 ml of freshly prepared 20 mM glutathione in 100 mM Tris-HCl [pH 8.0], 120 mM NaCl as previously described.

Example 6

Solid Phase Overlay assay

1. Protocol of the Solid Phase Overlay Assay

Solid phase overlay assays were performed by adapting the method described by Kaelin and collaborators (Kaelin et al., 1992, Cell, 70:351-364). 100 ng, 10 ng and 0.1 ng of GST and GST-2E11 recombinant proteins were resolved by 9% SDS-PAGE and were transferred by electroblotting onto nitrocellulose membrane (nitrocellulose transfer membrane Protran BA 83, Schleicher and Schuell). The membrane were then blocked in HBB buffer (25 mM Hepes-KOH [pH 7.7], 25 mM NaCl, 5 mM $MgCl_2$) with 5% (w/v) non-fat dry milk, 1 mM DTT, 0.05% Nonidet P-40 for 1 hr at room temperature. The binding reaction was carried out at room temperature in Hyb75 buffer (20 mM Hepes [pH 7.7], 75 mM KCl, 2.5 mM $MgCl_2$, 0.1 mM EDTA, 0.05% Nonidet P-40) with 1% (w/v) non-fat dry milk, 1 mM DTT, 1 mM PMSF and 3.5 10^5dpm of a [^{32}P]-γATP GST-PPP2R2C radiolabeled recombinant protein used as a probe. After 4.5 hr of incubation, the membrane was washed with Hyb75 buffer, 1 mM DTT, 1% (w/v) non-fat dry milk three times for 15 min at room temperature. The blots were analyzed by autoradiography.

2. Results

This experiment was performed to validate the interaction between KCNQ2-15b polypeptides and PP2A/Bγ. In this experiment, the PP2A/Bγ subunit was radiolabeled but not the proteins present on the nitrocellulose membrane. Thus, a signal appears when visualized by autoradiography only if the loaded protein interacts with PP2A/Bγ. GST-2E11 corresponds to a fusion protein between a KCNQ2-15b polypeptide comprising exons 13, 14 and 15b and GST. GST corresponds to the negative control. In the three lines loaded with the GST-2E11 recombinant protein, bands located at a position corresponding to a protein of a size of about 45 kD appeared. This corresponds to the protein size expected for the GST-2E11 protein. Furthermore, the intensity of the bands was proportional to the quantity of loaded GST-2E11. Thus GST-2E11 interacts with PP2A/Bγ. In the three lines loaded with the GST protein, no band appeared, showing that PP2A/Bγ does not interact with the GST protein. Thus the interaction between PP2A/Bγ and the GST-2E11 fusion protein is due to the part of the protein encoding 2E11 and not to the part of the protein encoding GST. This experiment indicates that KCNQ2-15b polypeptides can interact with PP2A/Bγ in vitro. Furthermore, this shows that KCNQ2-15b polypeptides can interact with PP2A/Bγ without a third binding partner, a hypothesis that can not be excluded by a yeast-two hybrid assay.

Example 7

In Vitro Phosphorylation Assay With Recombinant GSK-3β Kinase and In Vitro Dephosphorylation with HTB-14 Whole Cell Extracts

1. Phosphorylation Assays

Phosphorylation assays were performed to determine whether the phsophorylation state of KCNQ2-15b is modulated by GSK3β, a kinase that plays an important role in the central nervous system by regulating various cytoskeletal processes through its effects on MAP1B, tau and synapsin 1. GSK3β is known to be inhibited by two mood stabilizing agents used in treatment of bipolar disorder, lithium and valporate.

1.1. Protocol

Expression and purification of the GST-2E11 fusion protein were performed as described above. Beads with bound fusion protein corresponding to 1 ml of bacterial clear lysate were washed three times in NETN and one time with HMK buffer without DTT (20 mM Tris-HCl [pH 7.5], 120 mM NaCl, 12 mM $MgCl_2$). Beads were resuspended in 240 μl of reaction mix (24 μl of 10×HMK Buffer with 20 mM DTT, 40 units of Protein Kinase A Catalytic Subunit [PKA from bovine heart, 250 units/vial, Sigma] in 40 mM DTT, 5 μl of 24 mM ATP and 207 μl of distilled water) and incubated for 30 min at room temperature. Beads were then washed three times in NETN buffer and one time in GSK-3β reaction buffer (20 mM Tris-HCl [pH 7.5], 10 mM $MgCl_2$, 5 mM DTT) (New England Biolabs). Beads were then resuspended in 50 μl of reaction mix (5 μl of 10×GSK-3β reaction buffer, 1 μl of [^{32}P]γATP 10 mCi/ml, 50 U of recombinant GSK-3β[New England Biolabs], and distilled water for a final volume of 50 μl) and incubated at room temperature for 30 min. After three washes in NETN buffer, phosphorylated proteins were boiled in 2×Sample Buffer (125 mM Tris-HCl [pH 6.8], 4% SDS, 20% glycerol, 1.4 M β-Mercapto ethanol), resolved by 10% SDS-PAGE, and visualized by autoradiography.

1.2. Results

In this phosphorylation assay, non-radiolabeled polypeptides to be tested are incubated in the presence of GSK-3β, PKA and radioactive ATP. The proteins are then resolved by a 10% SDS-PAGE migration and visualized by autoradiography. A signal is visualized by autography only if the protein to be tested is phosphorylated by GSK-3β and PKA during incubation. In the line loaded with the GST-2E11 protein, which corresponds to the fusion protein between a KCNQ2-15b polypeptide comprising exons 13, 14 and 15b and the GST polypeptide, a band located at a position corresponding to a protein of a size of about 45 kD did appear. This is the size expected for the GST-2E11 protein. Thus the GST-2E11 protein is phosphorylated by GSK-3β and PKA in vitro. Three experiments corresponding to negative controls were performed in parallel. One experiment was performed without adding the GSK-3β kinase during incubation, one was performed without adding the PKA kinase during incubation, and one was performed with a GST protein instead of a GST-2E11 protein. No bands appeared in the three lines corresponding to the negative controls.

Accordingly, this experiment shows that KCNQ2-15b polypeptides are synergistically phosphorylated by the GSK-3β and PKA kinases in vitro.

This result was confirmed by a competition experiment in which CREB phosphopeptides, which are known to be phosphorylated by GSK-3β and PKA, were added during incubation. In this competition experiment, 5 μg of CREB phosphopeptides (New England Biolabs) was added to the kination mix. A band did still appear at a position corresponding to the size of GST-2E11, but the intensity of the band was very significantly lower.

The influence of LiCl on the phosphorylation state of GST-2E11 was further studied by adding LiCl to the kination mix at a final concentration of 0, 8.3, 25, 75 and 225 mM respectively. The intensity of the band appearing at a position of about 45 kD decreased in the presence of LiCl, and the intensity of the signal was negatively correlated with the concen-

tration of LiCl added to the kination mix. In the presence of about 50 mM LiCl, the phosphorylation state of GST-2E11 was reduced by 50%.

This shows that LiCl, a well-known mood-stabilizing agent used in the treatment of bipolar disorder, inhibits phosphorylation of KCNQ2-15b polypeptides in vitro.

2. Dephosphorylation Assays

Dephosphorylation assays were performed to determine whether the phophorylation state of KCNQ2-15b polypeptides is modulated by PP2A.

2.1. Protocol

In vitro phosphorylated GST-2E11 fusion protein was incubated at room temperature for 30 min with 500 μg of whole cell extracts of Human glioblastoma, astrocytoma cell line (ATCC number: HTB-14) with or without 400 μM of the PP2A phosphatase inhibitor okadaic acid (Sigma). HTB-14 whole cell extracts were prepared as follow: cells were washed three times with ice-cold TBS buffer (10 mM Tris-HCl [pH 8.0], 120 mM NaCl) and lysed at 4° C. for 30 min in EBC buffer (50 mM Tris-HCl [pH 8.0], 120 mM NaCl, 0.5% Nonidet P-40). Then the lysate was centrifugated for 10 min at 13.000×g at 4° C. to pellet cell debris. Proteins present in the supernatant were quantified by the standard Bradford's method (Bio-Rad Protein Assay). The proteins were then resolved by 10% SDS-PAGE, and visualized by autoradiography.

2.2. Results

The phosphorylated radiolabeled GST-2E11 proteins obtained from the previous assay were incubated in the presence of HTB-14 cell extracts containing the PP2A phosphatase to determine whether PP2A is capable of dephosphorylating G ST-2E11 proteins. In this experiment, a protein that is dephosphorylated by PP2A is not radioactive after incubation in the presence of HTB-14 cell extracts any more. Thus dephosphorylation of the GST-2E11 protein is monitored by disappearance of the signal visualized by autoradiography. One line of the 10% SDS-PAGE gel was loaded with phosphorylated GST-2E11 fusion proteins incubated in the absence of HTB-14 cell extracts, as reference for the intensity of the band appearing for phosphorylated GST-2E11 proteins. In the line loaded with GST-2E11 fusion proteins incubated in the presence of HTB-14 cell extracts, the band had an extremely weaker intensity. Thus GST-2E11 fusion proteins are dephosphorylated when incubated in the presence of HTB-14 cell extracts. When the GST-2E11 fusion protein was incubated in the presence of HTB-14 cell extracts and okadaic acid, a known PP2A phosphatase inhibitor, the intensity of the band was only slightly weaker than the intensity of the band corresponding to phosphorylated GST-2E11.

Thus the PP2A phosphatase is responsible of the dephosphorylation observed for GST-2E11 fusion proteins incubated in the presence of HTB-14 cell extracts. Accordingly, this experiment shows that KCNQ2-15b polypeptides are dephosphorylated by the PP2A phosphatase in vitro.

Example 8

Cell Culture, Transfection, Immunoprecipitation and Western Blot Analysis

1. Cell Cultures

HEK293-H cells (Gibco Invitrogen Corporation) were grown in DMEM medium (Gibco Invitrogen Corporation) supplemented with 0.1 mM Non-Essential Amino Acids and 10% Fetal Bovine Serum (Gibco Invitrogen Corporation), and transiently transfected with 20 μg of the pCMV-Myc-3H9 or pCMV-Myc-3H2 plasmids per 60 mm dish using the Invitrogen calcium phosphate transfection kit and protocols. 48 hr after transfection cells were washed three times with ice-cold phosphate buffer (PBS, Gibco Invitrogen Corporation), scraped and solubilized for 2 hr at 4° C. in solubilization buffer containing 150 mM NaCl, 5 mM EDTA, 1% Triton X-100, 0.1% sodium deoxycholate, 10 mM Tris-HCl [pH 8.0] and supplemented with protease inhibitors (1 mM phenylmethylsulfonyl fluoride, one tablet of Complete™ mini protease inhibitors cocktail [Roche]) and phosphatase inhibitors (1 mM Na_3VO_4 and 1 mM NaF). The lysate was then centrifugated for 10 min at 13.000×g at 4° C. to pellet cell debris. Proteins present in the supernatant were quantified by the standard Bradford's method (Bio-Rad Protein Assay).

2. Immunoprecipitation

500 μg (final volume: 500 μl) of the clear cell lysate were incubated for 2 hr at 4° C. with 1 μd of rabbit preimmune serum and 50 μl of protein A Sepharose CL4B beads (Amersham Pharmacia Biotech) saturated with 1% Albumin Bovine (BSA fraction V, Sigma). Depleted supernatants were then incubated overnight at 4° C. with 1 μg of anti-Myc monoclonal antibody (Myc-Tag 9B11 monoclonal antibody, Cell Signaling). Protein A Sepharose CL4B beads saturated with 1% Albumin Bovine were then added and the mixture incubated at 4° C. for 2 addtional hours. After five washes with ice-cold solubilization buffer immuno-complexes were boiled in 2×Sample Buffer (125 mM Tris-HCl [pH 6.8], 4% SDS, 20% glycerol, 1.4 M β-Mercapto ethanol), resolved by 8% SDS-PAGE and subjected to

3. Western Blot

Proteins were transferred onto nitrocellulose membrane (nitrocellulose transfer membrane Protran BA 83, Schleicher and Schuell) using Towbin buffer (Towbin et al., 1979, PNAS, 76:4350-4354) and an electrotransfer device. After transfer, membranes were blocked, in 5% non-fat dried milk in TBST (10 mM Tris-HCl [pH 8.0], 150 mM NaCl, 0.05% Tween 20) supplemented with sodium azide (0.1%) for 2 hr, and then incubated for 16 hr at room temperature with the anti-Myc monoclonal antibody (Myc-Tag 9B11 monoclonal antibody, Cell Signaling) diluted 1:1000 in the same buffer. After several washes with TBST, the blot was incubated with a horseradish peroxidase-conjugated secondary antibody (Anti-mouse IgG, Fab specific, peroxidase conjugate, Sigma) diluted 1:5000 and developed using ECL Western blotting detection reagents (Amersham Biosciences).

Example 9

Electrophysiological Analysis

1. Protocols

1.1. cDNA injection in *Xenopus laevis oocytes*

The animal was anesthetized and pieces of the ovary were surgically removed and individual oocytes were dissected away in a saline solution (ND96) containing 96 mM NaCl, 2 mM KCl, 2 mM CaCl2, 2 mM MgCl2 and 5 mM HEPES at pH 7.4. Stage V and VI oocytes were treated at room temperanre for 2 h with collagenase type 1A (1 mg/ml) in the presence of 0.2 mg/ml trypsin inhibitor in saline solution to discard follicular cells. The concentrations were determined by measuring the absorbance at 260 nm. DNA corresponding to KCNQ2, 3H2 and 3H9 K+ channels were subcloned in PEKO vector in order to generate the respective cRNAS. cRNA concentrations were measured by absorbance at 260 nM. cRNA solutions were injected (about 50 nL/oocyte) using a

pressure microinjector (Inject+matic, Geneve). Oocytes were then kept for 2-6 days in ND96 solution supplemented wirn 50 U/mL penicillin and 50 U/mL streptomycin.

1.2. Electrophysiological Measurements

In a 0.3 mL perfusion chamber, a single oocyte was impaled with two standard glass microelectrode (0.5-2 Mohm resistance) filled with 3M KCl and maintained under voltage clamp using a Dagan TEV200 amplifier system, USA. Electrical stimulations, data acquisition and analyses were performed using pClamp software (Axon Instruments, USA). Current to voltage relationships were obtained applying incremental depolarizing voltage steps (10 mV increment) from a holding potential of −80 mV (equilibrium potential for K+ ions) Repolarizations to −60 mV allowed K^+ channel deactivation measurements from the "tail currents".

2. Results

The activity of KCNQ2-15bx and of KCNQ2-15by homotetrameric potassium channels was tested and compared to the activity of KCNQ2-fl homotetrameric potassium channels. 0.2 ng or 0.4 ng of DNA were injected to the oocytes. The results are shown on FIG. **5**, on which the intensity of the M-current generated by the potassium channels is indicated. An intensity of about 1 μA is found for the current generated by a of KCNQ2-fl homotetrameric potassium channel when 0.4 ng of DNA is injected. This value is similar to the value reported by scientific literature. A KCNQ2-15bx homotetrameric potassium channel yields a current of about 800 nA when 0.4 ng of DNA is injected, and a KCNQ2-15by homotetrameric potassium channel yields a courant of about 700 nA when 0.4 ng of DNA is injected. Thus the KCNQ2-15bx and KCNQ2-15by splice variants can associate as functional homomeric potassium channels in vivo.

FIG. **6**A and FIG. **6**B show the voltage clamp traces corresponding to the currents generated at different voltages by KCNQ2-15bx (FIG. **6**A) and by KCNQ2-15by (FIG. **6**B) homotetrameric potassium channels. The slow activation that is observed on the traces is a characteristic feature of members of the KCNQ potassium channel family.

Example 10

Collection Of DNA Samples From Affected And Non-Affected Individuals

Donors were unrelated and healthy. The DNA from 100 individuals was extracted and tested for the detection of the biallelic markers.

30 ml of peripheral venous blood were taken from each donor in the presence of EDTA. Cells (pellet) were collected after centrifugation for 10 minutes at 2000 rpm. Red cells were lysed by a lysis solution (50 ml final volume: 10 mM Tris pH7.6; 5 mM MgCl 2; 10 mM NaCl). The solution was centrifuged (10 minutes, 2000 rpm) as many times as necessary to eliminate the residual red cells present in the supernatant, after resuspension of the pellet in the lysis solution.

The pellet of white cells was lysed overnight at 42° C. with 3.7 ml of lysis solution composed of:

- 3 ml TE 10-2 (Tris-HCl 10 mM, EDTA 2 mM)/NaCl 0.4 M
- 200 μl SDS 10%
- 500 μl K-proteinase (2 mg K-proteinase in TE 10-2/NaCl 0.4 M).

For the extraction of proteins, 1 ml saturated NaCl (6M) (1/3.5 v/v) was added. After vigorous agitation, the solution was centrifuged for 20 minutes at 10000 rpm.

For the precipitation of DNA, 2 to 3 volumes of 100% ethanol were added to the previous supernatant, and the solution was centrifuged for 30 minutes at 2000 rpm. The DNA solution was rinsed three times with 70% ethanol to eliminate salts, and centrifuged for 20 minutes at 2000 rpm. The pellet was dried at 37° C., and resuspended in 1 ml TE 10-1 or 1 ml water. The DNA concentration was evaluated by measuring the OD at 260 nm (1 unit OD=50 μg/ml DNA). To determine the presence of proteins in the DNA solution, the OD 260/OD 280 ratio was determined. Only DNA preparations having a OD 260/OD 280 ratio between 1.8 and 2 were used in the subsequent examples described below.

The pool was constituted by mixing equivalent quantities of DNA from each individual.

Example 11

Amplification of Genomic DNA by PCR

The amplification of specific genomic sequences of the DNA samples of Example 10 was carried out on the pool of DNA obtained previously. In addition, 50 individual samples were similarly amplified.

PCR assays were performed using the following protocol:

Final volume	25 μl
DNA	2 ng/μl
$MgCl_2$	2 mM
dNTP (each)	200 μM
primer (each)	2.9 ng/μl
Ampli Taq Gold DNA polymerase	0.05 unit/μl
PCR buffer (10x = 0.1 M TrisHCl pH 8.3 0.5M KCl)	1x

Each pair of first primers was designed using the sequence information of genomic DNA sequences and the OSP software (Hillier & Green, 1991).

Primers Biallelic Markers Located in PPP2R2C

The genomic sequence of PPP2R2C that is shown as SEQ ID NO: 37 was constructed upon bioinformatic analysis based on (i) BAC clones constructed at Genset S. A.; (ii) BAC clones corresponding to EMBL Accesion Nos. AC114815.5, AC004599.6, AC122939.3 and AC004689.5; and (iii) RefseqN Accession No. NT_006051. The polymorphisms were identified as described in examples 12 and 13, and validated as described in example 14.

Biallelic Markers Located in the KCNQ2 Gene

The biallelic markers located in the KCNQ2 gene were found using data provided by Celera. Each of these markers were further validated as described in example 14.

Table 2A indicates the position on SEQ ID NO: 37 of pairs of primers that were used to amplify specific regions of PPP2R2C. Table 2B indicates the position of the primers on SEQ ID Nos 42 to 47, which were used to amplify specific regions of KCNQ2. The orientation of the primer is indicated in the third column. The sign (+1) indicates that the sequence of the primer is identical to the corresponding region of SEQ ID Nos. 37 and 42 to 47. The sign (−1) indicates that the sequence of the primer is complementary to the corresponding region of SEQ ID Nos. 37 and 42 to 47.

TABLE 2A

	Primer location in PPP2R2C	
Name of the amplified region	Position on SEQ ID NO: 37	Orientation
24-257	109495 to 109512	(+1)
	109963 to 109982	(−1)
99-24169	83709 to 83729	(+1)
	84146 to 84164	(−1)

TABLE 2A-continued

Primer location in PPP2R2C		
Name of the amplified region	Position on SEQ ID NO: 37	Orientation
99-24175	117228 to 117248	(+1)
	117659 to 117677	(−1)
24-247	99290 to 99309	(+1)
	99719 to 99738	(−1)

TABLE 2B

Primer location in the KCNQ2 gene			
Name of the amplified region	SEQ ID No.	Position	Orientation
30-4	SEQ ID NO: 42	244 to 263	(+1)
		324 to 343	(−1)
30-2	SEQ ID NO: 43	240 to 258	(+1)
		319 to 338	(−1)
30-17	SEQ ID NO: 44	265 to 284	(+1)
		345 to 364	(−1)
30-7	SEQ ID NO: 45	272 to 291	(+1)
		315 to 333	(−1)
30-84	SEQ ID NO: 46	265 to 284	(+1)
		334 to 353	(−1)
30-15	SEQ ID NO: 47	248 to 267	(+1)
		312 to 331	(−1)

Preferably, the primers contained a common oligonucleotide tail upstream of the specific bases targeted for amplification which was useful for sequencing.

The synthesis of these primers was performed following the phosphoramidite method, on a GENSET UFPS 24.1 synthesizer.

DNA amplification was performed on a Genius II thermocycler. After heating at 95° C. for 10 min, 40 cycles were performed. Each cycle comprised: 30 sec at 95° C., 54° C. for 1 min, and 30 sec at 72° C. For final elongation, 10 min at 72° C. ended the amplification. The quantities of the amplification products obtained were determined on 96-well microtiter plates, using a fluorometer and Picogreen as intercalant agent (Molecular Probes).

Example 12

Identification of Biallelic Markers from Amplified Genomic DNA

The sequencing of the amplified DNA obtained in Example 11 was carried out on ABI 377 sequencers. The sequences of the amplification products were determined using automated dideoxy terminator sequencing reactions with a dye terminator cycle sequencing protocol. The products of the sequencing reactions were run on sequencing gels and the sequences were determined using gel image analysis (ABI Prism DNA Sequencing Analysis software (2.1.2 version)).

The sequence data were further evaluated to detect the presence of biallelic markers within the amplified fragments. The polymorphism search was based on the presence of superimposed peaks in the electrophoresis pattern resulting from different bases occurring at the same position as described previously.

The locations of the biallelic markers detected in the fragments of amplification are as shown below in Tables 3A and 3B.

TABLE 3A

Biallelic Markers in the PPP2R2C gene					
amplified region	BM name	Strand	polymorphism All 1	polymorphism All 2	BM position on SEQ ID NO: 37
24-257	24-257/320	(−)	A	G	109663
99-24169	99-24169/139	(−)	A	G	84026
99-24175	99-24175/218	(−)	A	G	117460
24-247	24-247/216	(+)	A	G	99505

TABLE 3B

Biallelic Markers in the KCNQ2 gene						
amplified region	BM name	Strand	polymorphism All 1	polymorphism All 2	SEQ ID No.	BM position on indicated SEQ ID No.
30-4	30-4/58	(+)	A	G	SEQ ID NO: 42	301
30-2	30-2/62	(+)	A	G	SEQ ID NO: 43	301
30-17	30-17/37	(+)	A	G	SEQ ID NO: 44	301
30-7	30-7/30	(+)	C	T	SEQ ID NO: 45	301
30-84	30-84/37	(+)	A	G	SEQ ID NO: 46	301
30-15	30-15/54	(+)	A	C	SEQ ID NO: 47	301

BM refers to "biallelic marker". All 1 and All 2 refer respectively to allele 1 and allele 2 of the biallelic marker. The (+) or (−) sign in the column "strand of BM" indicates the strand on which the indicated alternative alleles are found. SEQ ID Nos. 37 and 42 to 47 correspond to strands (+). As a matter of example, the biallelic marker 24-257/320 corresponds to a polymorphism "a or g" at position 109663 on strand (−). Thus the nucleotide at position 109663 of SEQ ID NO: 37 will be "y", which corresponds to "t or c" according to the standard PCT nomenclature. The biallelic marker 24-247/216 corresponds to a polymorphism "a or g" at position 99505 on strand (+). Thus the nucleotide at position 99505 of SEQ ID NO: 37 will be "r", which corresponds to "a or g" according to the standard PCT nomenclature.

Example 13

Identification of Polymorphisms by Comparison of Genomic DNA from Overlapping BACs

Genomic DNA from multiple BAC clones derived from the same DNA donor sample and overlapping in regions of genomic DNA of SEQ ID NO: 37 was sequenced. Sequencing was carried out on ABI 377 sequencers. The sequences of the amplification products were determined using automated dideoxy terminator sequencing reactions with a dye terminator cycle sequencing protocol. The products of the sequencing reactions were run on sequencing gels and the sequences were determined using gel image analysis (ABI Prism DNA Sequencing Analysis software (2.1.2 version)).

Example 14

Validation of the Polymorphisms Through Microsequencing

The biallelic markers identified in Examples 12 and 13 were further confirmed and their respective frequencies were

determined through microsequencing. Microsequencing was carried out for each individual DNA sample described in Example 11.

Amplification from genomic DNA of individuals was performed by PCR as described above for the detection of the biallelic markers with the same set of PCR primers described in tables 1A and 1 B.

The preferred primers used in microsequencing were about 19 nucleotides in length and hybridized just upstream of the considered polymorphic base. According to the invention, the primers used for microsequencing are detailed in tables 4A and 4B.

TABLE 4A

Primers in the PPP2R2C gene

amplified region	Marker name	Orientation of the primer	Position of the primer on SEQ ID NO: 37	SEQ ID No. of the primer
24-257	24-257/320	(+1)	109644 to 109662	SEQ ID NO: 40
99-24169	99-24169/139	(+1)	84007 to 84025	SEQ ID NO: 39
99-24175	99-24175/218	(+1)	117441 to 117459	SEQ ID NO: 41
24-247	24-247/216	(+1)	99486 to 99504	

TABLE 4B

Primers in the KCNQ2 gene

amplified region	Marker name	Orientation of the primer	SEQ ID No.	Position of the primer on indicated SEQ ID No.
30-4	30-4/58	(−1)	SEQ ID NO: 42	302 to 319 (primer B18)
30-4	30-4/58	(+1)	SEQ ID NO: 42	282 to 300 (primer A19)
30-2	30-2/62	(−1)	SEQ ID NO: 43	302 to 320
30-17	30-17/37	(−1)	SEQ ID NO: 44	302 to 324
30-7	30-7/30	(+1)	SEQ ID NO: 45	280 to 300
30-84	30-84/37	(−1)	SEQ ID NO: 46	302 to 318
30-15	30-15/54	(−1)	SEQ ID NO: 47	302 to 323

As for the primers in tables 2A and 2B, the sign (+1) in the column "orientation" indicates that the sequence of the primer is identical to the corresponding region of SEQ ID Nos. 37 and 42 to 47, and the sign (−1) indicates that the sequence of the primer is complementary to the corresponding region of SEQ ID Nos. 37 and 42 to 47.

The microsequencing reaction performed as follows. After purification of the amplification products, the microsequencing reaction mixture was prepared by adding, in a 20 μl final volume: 10 μmol microsequencing oligonucleotide, 1 U Thermosequenase (Amersham E79000G), 1.25 μl Thermosequenase buffer (260 mM Tris HCl pH 9.5, 65 mM $MgCl_2$), and the two appropriate fluorescent ddNTPs (Perkin Elmer, Dye Terminator Set 401095) complementary to the nucleotides at the polymorphic site of each biallelic marker tested, following the manufacturer's recommendations. After 4 minutes at 94° C., 20 PCR cycles of 15 sec at 55° C., 5 sec at 72° C., and 10 sec at 94° C. were carried out in a Tetrad PTC-225 thermocycler (MJ Research). The unincorporated dye terminators were then removed by ethanol precipitation. Samples were finally resuspended in formamide-EDTA loading buffer and heated for 2 min at 95° C. before being loaded on a polyacrylamide sequencing gel. The data were collected by an ABI PRISM 377 DNA sequencer and processed using the GENESCAN software (Perkin Elmer).

Following gel analysis, data were automatically processed with software that allows the determination of the alleles of biallelic markers present in each amplified fragment.

The software evaluates such factors as whether the intensities of the signals resulting from the above microsequencing procedures are weak, normal, or saturated, or whether the signals are ambiguous. In addition, the software identifies significant peaks (according to shape and height criteria). Among the significant peaks, peaks corresponding to the targeted site are identified based on their position. When two significant peaks are detected for the same position, each sample is categorized dassification as homozygous or heterozygous type based on the height ratio.

Example 15

Association Study Between Bipolar Disorder and the Biallelic Markers of the Invention

5.1. Collection of DNA Samples from Affected and Non-Affected Individuals

The association studies were performed on two different populations. One collection of samples was provided by Hospital Pinero, Buenos-Aires, Argentina (the "Labimo" collection). The other collection of samples was provided by the University College of London (the "UCL" collection). Both collections are constituted by individuals that are affected or not by bipolar disorder.

A) The Labimo Collection

a) Affected Population

206 DNA samples from patients suffering from bipolar disorder (cases) were collected for genotyping analysis.

All patients fulfilled DSM-IV and ICD-10 criteria for bipolar type I (ICD-10: F30.x, F31.x) or bipolar type II (ICD-10: F31.8). All patients were of Caucasian ethnic origin up to the 2^{nd} generation.

All potential patients suffering from a medical disorder or from a drug abuse were excluded.

According to DSM-IV criteria, 115 cases were classified as bipolar type I, 69 were bipolar type II, 22 were unclassified, and information concerning the type of bipolar disorder was lacking in 20 cases (8.5%)

The main phenotypic data of the cases were as follows:

- Mean age at first symptoms: 25.6 years (SD, 11; range, 8-58)
- Mean age at inclusion: 43.3 years (SD, 13.8; range, 17-76)
- Gender: 142 females and 84 males (ratio, 1.7)
- Ethnic origin: 213 were European Caucasian, 7 were non-European Caucasians, and information was lacking in 6 cases (2.5%)
- Family history of bipolar disorder was found in 18.5%, whereas schizophrenia was found in 0.9%.

b) Unaffected Population

201 DNA samples from individuals not suffering from bipolar disorder (controls) were collected for genotyping analysis.

All controls were individuals lacking personal or familial history of psychiatric disease.

The main phenotypic data of the controls were as follows:

Mean age: 43.8 years (SD, 12; range, 21-72)

Gender: 118 females and 83 males (ratio, 1.4)

180 controls were European Caucasian, and 21 had mixed ethnic origin

c) Cases and Control Populations Selected for the Association Study

The case control populations were matched for ethnicity and sex which resulted in 159 cases and 159 control individuals. Among the cases, 96 cases suffered from type I bipolar disorder, 56 cases suffered from type II bipolar disorder, and 7 cases suffered from an undetermined type of bipolar disorder. 33.8% of the cases were males. The mean age of the cases was of 43 and the median age was of 44. 41.4% of the controls were males. The mean age of the controls was of 44 and the median age was of 46.

The presence of population structure can result in spurious association, which is an association between phenotypes and markers that is not linked to any causative loci but due to a different ethnic origin. The Fst test is a general statistical tool for analyzing variances and that can be used to verify that a collection is homogeneous, i.e., that found associations are not linked to the structure of the population. The Fst value is calculated using random markers that are (i) unlinked and (ii) not associated with the trait to be studied. An Fst value close to 0 indicates that the collection is homogeneous and that any significant associations that are found are due to the trait under investigation (see, e.g., Bruce S. Weir, Genetic Data Analysis II, Edition Sinauer, San Francisco and Hartl and Clark, Populations genetics, Edition Sinauer, San Francisco). 66 random markers that were (i) unlinked and (ii) not associated with bipolar disorder were used to calculate the Fst value. An Fst value of 1.68e-01 was found for the found in the Labimo collection, indicating that this collection is homogeneous.

B) The UCL Collection

a) Affected Population

All patients fulfilled DSM-IV criteria for bipolar type I (ICD-10: F30.x, F31.x) or bipolar type II (ICD-10: F31.8). All patients were unrelated individuals of Caucasian origins from the British Isles (including English, Welsh, Scottish and Irish) up to the 2^{nd} generation.

b) Unaffected Population

300 samples from unaffected control individuals (not suffering from bipolar disorder) were collected for genotyping analysis.

All control individuals showed (i) absence of personal history of psychiatric disease; and (ii) absence of familial history of psychiatric disease in first-degree relatives. All controls individuals of Caucasian origins from the British Isles (including English, Welsh, Scottish and Irish) up to the 2^{nd} generation.

c) Cases and Control Populations Selected for the Association Study

The population retained for the study was composed of 315 cases and 295 controls. Among the cases, 256 cases suffered from type I bipolar disorder, 26 cases suffered from type II bipolar disorder, and 33 cases suffered from an undetermined type of bipolar disorder. About 36% of the cases were males. The mean age of the cases was of 46 and the median age was of 46. 48% of the controls were males. The mean age of the controls was of 37 and the median age was of 32.

59 random markers that were (i) unlinked; and (ii) not associated with bipolar disorder were used to calculate the Fst value. A Fst value of 3.41e-01 was found for the UCL collection, indicating that this collection is homogeneous.

5.2. Association Studies

A) Genotyping of Affected and Control Individuals

The general strategy to perform the association studies was to individually scan the DNA samples from all individuals in each of the populations described above in order to establish the allele frequencies of biallelic markers, and among them the biallelic markers of the invention, in the diploid genome of the tested individuals belonging to each of these populations.

Frequencies of every biallelic marker in each population (cases and controls) were determined by performing microsequencing reactions on amplified fragments obtained by genomic PCR performed on the DNA samples from each individual. Genomic PCR and microsequencing were performed as detailed above in Examples 11 to 13 using the described PCR primers and microsequencing primers.

B) Single Biallelic Marker Frequency Analysis

The difference between the allelic frequencies in the unaffected population and in the population affected by bipolar disorder was calculated for all five markers located in the KCNQ2 gene, and for all four markers located in the PPP2R2C gene. The allelic frequency of markers between cases and controls were investigated using the Pearson Chi squared test for allelic frequency and genotypic frequency distributions. A significant difference between observed and expected alleles/genotypes of a specific marker between case and control populations implies an association between the gene harboring this particular biallelic marker and bipolar disease. Both allelic and genotypic p-values were calculated for all markers. The p-values in tables 5A and 5B indicate the probability of no association between a biallelic marker and bipolar disorder considering the frequency. A p-value under 5e-02 indicates a significant association between the biallelic marker and bipolar disorder.

Odds ratio determination is a way of comparing the probability of having the disease when carrying a given allele versus when not carrying the said allele. An odds ratio higher than 1 indicates that the probability of having bipolar disorder is higher when carrying one of the alternative alleles, haplotypes or genotypes than when carrying the other ones. The genotypic odds ratio allows the identification of the "risk" allele, haplotype or genotype for an associated biallelic marker. The genotypic odds ratio was calculated for one biallelic marker located in PPP2R2C and for two markers located in the KCNQ2 gene (tables 6A and 6B).

TABLE 5A

p-values for biallelic markers located in PPP2R2C

Marker Name	Location in PPP2R2C	Collection	Chosen allele	All. Freq Diff.	All. Odds Ratio	Allelic p-value	Genotypic p-value
99-24169/139	Intron 1d	UCL	A	0.095	1.733	2.19e−04	3.61e−04
		Labimo	A	0.002	1.012	9.46e−01	5.98e−01
24-247/216	intron 4	UCL	G	0.047	1.275	7.75e−02	2.29e−02
		Labimo	G	0.024	1.125	4.86e−01	7.65e−01
24-257/320	Intron 5	UCL	A	0.018	1.079	5.52e−01	8.22e−01
		Labimo	A	0.102	1.557	4.04e−03	1.19e−02
99-24175/218	Intron 5	UCL	G	0.035	1.162	2.62e−01	3.99e−03
		Labimo	A	0.096	1.546	6.69e−03	2.34e−02

TABLE 5B

p-values for biallelic markers in the KCNQ2 gene

Marker Name	Location in the KCNQ2 gene	Collection	Chosen allele	All. Freq Diff.	All. Odds Ratio	Allelic p-value	Genotypic p-value
30-4/58	5' of the gene	UCL	—	—	—	—	—
		Labimo	G	0.03	1.24	3.03e−01	5.85e−01
30-2/62	intron 1	UCL	A	0.05	1.23	7.76e−02	5.20e−03
		Labimo	A	0.03	1.13	4.42e−01	1.15e−01
30-17/37	intron 4	UCL	A	0.01	1.03	7.77e−01	9.12e−01
		Labimo	G	0.03	1.13	4.70e−01	7.10e−01
30-7/30	intron 12	UCL	C	0.05	1.21	1.05e−01	3.02e−02
		Labimo	C	0.02	1.06	7.03e−01	5.32e−01
30-84/37	3' of gene	UCL	A	0.02	1.20	3.06e−01	3.69e−01
		Labimo	—	—	—	—	—
30-15/54	3' of gene	UCL	A	0.01	1.06	6.92e−01	7.68e−01
		Labimo	—	—	—	—	—

TABLE 6A

genotypic odds ratios for a biallelic marker located in PPP2R2C

Biallelic marker	collection	genotype	odds ratio	p-value
99-24169/139	UCL	AA vs GG	1.9	8.50e−02
		AA vs AG	2.06	7.20e−05
		AA vs (AG + GG)	2.04	4.60e−05

TABLE 6B

genotypic odds ratios for biallelic markers located in the KCNQ2 gene

Biallelic marker	collection	genotype	odds ratio	p-value
30-2/62	UCL	(AG + GG) vs AA	1.05	4.60E−01
		AG vs AA	1.28	1.70E−01
		AA vs GG	1.51	8.00E−02
		AG vs (GG + AA)	1.62	3.00e−03
		(AG + AA) vs GG	1.82	1.50e−03
30-7/30	UCL	(CC + CT) vs TT	1.04	4.40E−01
		TT vs CT	1.14	2.90E−01
		(CC + TT) vs CT	1.37	3.80e−02
		CC vs TT	1.58	3.80e−02
		CC vs (TT + CT)	1.71	7.00e−03

Biallelic Markers in PPP2R2C

Thus the four biallelic markers located in the PPP2R2C gene are found to be associated with bipolar disorder. More specifically, 99-24169/139 is found to be highly associated with bipolar disorder in the UCL collection (significant allelic and genotypic p-values). 24-257/320 and 99-24175/218 are highly associated with bipolar disorder in the Labimo collection (significant allelic p-values). In addition, 99-24175/218 is also associated with bipolar disorder in the UCL collection (significant genotypic p-value). 24-247/216 is associated with bipolar disorder in the UCL collection (significant genotypic p-value).

The risk allele for the 99-24169/139 biallelic marker is "A". The risk alleles for the 24-257/320 biallelic marker and for the 99-24175/218 biallelic marker are also "A". The risk genotype for the 99-24169/139 biallelic marker is "AA". Thus an individual carrying the genotype "AA" at biallelic marker 99-24169/13 is at risk of developing bipolar disorder.

Biallelic Markers in the KCNQ2 Gene

Two biallelic markers located in the KCNQ2 gene, 30-2/62 and 30-7/30, are associated with bipolar disorder. More specifically, 30-2/62 is found to be highly associated with bipolar disorder in the UCL collection (significant allelic and genotypic p-values). 30-7/30 is associated with bipolar disorder in the UCL collection (significant genotypic p-value).

The risk genotype for 30-2/62 is "AG". The risk genotype for 30-7130 is "CC". Thus individuals carrying the genotype "AG" at biallelic marker 30-2/62 and individuals carrying the genotype "CC" at biallelic marker 30-7/30 are at risk of developing bipolar disorder.

The association results of the single biallelic marker frequency analysis show that both the PPP2R2C gene and the KCNQ2 gene are associated with bipolar disorder. Accordingly, deregulation and/or dysfunction of KCNQ2 polypeptides and PP2A phosphatases comprising the PP2A/Bγ regulatory subunit contribute to the onset and to the development of bipolar disorder.

C) Haplotype Frequency Analysis

The analysis of haplotype frequencies cannot readily be derived from observed genotypic data. The EM (Expectation-Maximization) algorithm (Excoffier L & Slatkin M, 1995) allows the estimation of haplotypes for the population under investigation. Haplotype frequency estimations were performed by applying the OMNIBUS likelihood ratio test (PCT publication WO 01/091026)

The haplotype analysis was performed for two sets of markers located in PPP2R2C. The haplotype analysis for 24-257/320 and 99-24175/218 was performed in the Labimo collection. The haplotype analysis for 99-24169/139 and 24-247/216 was performed in the UCL collection. The results are shown in tables 7 (p-values) and 7B (odds ratios).

TABLE 7A

markers	Samples	Haplotype	Chi-S	Ave Chi-S	SD Chi-S	Max Chi-S	p-value
24-257/320	Labimo	AA	7.78	0.96	1.34	14.02	3.9e−03
and		AG	0.02	1.02	1.40	11.19	8.79e−01
99-24175/218		GA	0.14	0.96	1.35	11.62	6.77e−01
		GG	7.35	0.98	1.35	14.31	5.5e−03
99-24169/139	UCL	AA	1.49641	1.03501	1.46687	14.67815	2.28e−01
and		AG	5.19606	1.0854	1.52336	14.42852	2.73e−02
24-247/216		GA	13.91081	1.29859	1.81182	16.01507	5e−04
		GG	0.42929	1.57482	2.19562	23.4845	6.03e−01

TABLE 7B

markers	haplotype	overall	cases	controls	odds ratio
24-257/320	AA	60.9%	65.9%	55.5%	1.55
and	AG	2.8%	2.7%	2.9%	0.93
99-24175/218	GA	5.9%	5.5%	6.2%	0.88
	GG	30.4%	25.8%	35.4%	0.64
99-24169/139 and	AA	60.0%	62.0%	58.2%	1.17
24-247/216	AG	17.4%	20.0%	14.5%	1.47
	GA	13.6%	9.5%	17.6%	0.49
	GG	8.9%	8.5%	9.7%	0.86

The risk haplotype for 24-257/320 and 99-24175/218 is "AA". The risk haplotype for 99-24169/139 and 24-247/216 is "AG". Thus an individual carrying the haplotype "AA" at biallelic markers 24-257/320 and 99-24175/218 is at risk of developing bipolar disorder, and an individual carrying the haplotype "AG" at biallelic markers 99-24169/139 and 24-247/216 is also at risk of developing bipolar disorder.

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SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 47

<210> SEQ ID NO 1
<211> LENGTH: 1932
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1932)

<400> SEQUENCE: 1

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1               5                   10                  15

gag aag aag ctg aag gtg ggc ttc gtg ggg ctg gac ccc ggc gcg ccc       96
Glu Lys Lys Leu Lys Val Gly Phe Val Gly Leu Asp Pro Gly Ala Pro
            20                  25                  30

gac tcc acc cgg gac ggg gcg ctg ctg atc gcc ggc tcc gag gcc ccc      144
Asp Ser Thr Arg Asp Gly Ala Leu Leu Ile Ala Gly Ser Glu Ala Pro
        35                  40                  45

aag cgc ggc agc atc ctc agc aaa cct cgc gcg ggc ggc gcg ggc gcc      192
Lys Arg Gly Ser Ile Leu Ser Lys Pro Arg Ala Gly Gly Ala Gly Ala
    50                  55                  60

ggg aag ccc ccc aag cgc aac gcc ttc tac cgc aag ctg cag aat ttc      240
Gly Lys Pro Pro Lys Arg Asn Ala Phe Tyr Arg Lys Leu Gln Asn Phe
65                  70                  75                  80

ctc tac aac gtg ctg gag cgg ccg cgc ggc tgg gcg ttc atc tac cac      288
Leu Tyr Asn Val Leu Glu Arg Pro Arg Gly Trp Ala Phe Ile Tyr His
                85                  90                  95

gcc tac gtg ttc ctc ctg gtt ttc tcc tgc ctc gtg ctg tct gtg ttt      336
Ala Tyr Val Phe Leu Leu Val Phe Ser Cys Leu Val Leu Ser Val Phe
            100                 105                 110

tcc acc atc aag gag tat gag aag agc tcg gag ggg gcc ctc tac atc      384
Ser Thr Ile Lys Glu Tyr Glu Lys Ser Ser Glu Gly Ala Leu Tyr Ile
        115                 120                 125

ctg gaa atc gtg act atc gtg gtg ttt ggc gtg gag tac ttc gtg cgg      432
Leu Glu Ile Val Thr Ile Val Val Phe Gly Val Glu Tyr Phe Val Arg
    130                 135                 140

atc tgg gcc gca ggc tgc tgc tgc cgg tac cgt ggc tgg agg ggg cgg      480
Ile Trp Ala Ala Gly Cys Cys Cys Arg Tyr Arg Gly Trp Arg Gly Arg
145                 150                 155                 160

ctc aag ttt gcc cgg aaa ccg ttc tgt gtg att gac atc atg gtg ctc      528
Leu Lys Phe Ala Arg Lys Pro Phe Cys Val Ile Asp Ile Met Val Leu
                165                 170                 175

atc gcc tcc att gcg gtg ctg gcc gcc ggc tcc cag ggc aac gtc ttt      576
Ile Ala Ser Ile Ala Val Leu Ala Ala Gly Ser Gln Gly Asn Val Phe
            180                 185                 190

gcc aca tct gcg ctc cgg agc ctg cgc ttc ctg cag att ctg cgg atg      624
Ala Thr Ser Ala Leu Arg Ser Leu Arg Phe Leu Gln Ile Leu Arg Met
        195                 200                 205

atc cgc atg gac cgg cgg gga ggc acc tgg aag ctg ctg ggc tct gtg      672
Ile Arg Met Asp Arg Arg Gly Gly Thr Trp Lys Leu Leu Gly Ser Val
    210                 215                 220

gtc tat gcc cac agc aag gag ctg gtc act gcc tgg tac atc ggc ttc      720
Val Tyr Ala His Ser Lys Glu Leu Val Thr Ala Trp Tyr Ile Gly Phe
225                 230                 235                 240

ctt tgt ctc atc ctg gcc tcg ttc ctg gtg tac ttg gca gag aag ggg      768
Leu Cys Leu Ile Leu Ala Ser Phe Leu Val Tyr Leu Ala Glu Lys Gly
                245                 250                 255
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gag aac gac cac ttt gac acc tac gcg gat gca ctc tgg tgg ggc ctg      816
Glu Asn Asp His Phe Asp Thr Tyr Ala Asp Ala Leu Trp Trp Gly Leu
            260                 265                 270

atc acg ctg acc acc att ggc tac ggg gac aag tac ccc cag acc tgg      864
Ile Thr Leu Thr Thr Ile Gly Tyr Gly Asp Lys Tyr Pro Gln Thr Trp
        275                 280                 285

aac ggc agg ctc ctt gcg gca acc ttc acc ctc atc ggt gtc tcc ttc      912
Asn Gly Arg Leu Leu Ala Ala Thr Phe Thr Leu Ile Gly Val Ser Phe
    290                 295                 300

ttc gcg ctg cct gca ggc atc ttg ggg tct ggg ttt gcc ctg aag gtt      960
Phe Ala Leu Pro Ala Gly Ile Leu Gly Ser Gly Phe Ala Leu Lys Val
305                 310                 315                 320

cag gag cag cac agg cag aag cac ttt gag aag agg cgg aac ccg gca     1008
Gln Glu Gln His Arg Gln Lys His Phe Glu Lys Arg Arg Asn Pro Ala
                325                 330                 335

gca ggc ctg atc cag tcg gcc tgg aga ttc tac gcc acc aac ctc tcg     1056
Ala Gly Leu Ile Gln Ser Ala Trp Arg Phe Tyr Ala Thr Asn Leu Ser
            340                 345                 350

cgc aca gac ctg cac tcc acg tgg cag tac tac gag cga acg gtc acc     1104
Arg Thr Asp Leu His Ser Thr Trp Gln Tyr Tyr Glu Arg Thr Val Thr
        355                 360                 365

gtg ccc atg tac agt tcg caa act caa acc tac ggg gcc tcc aga ctt     1152
Val Pro Met Tyr Ser Ser Gln Thr Gln Thr Tyr Gly Ala Ser Arg Leu
    370                 375                 380

atc ccc ccg ctg aac cag ctg gag ctg ctg agg aac ctc aag agt aaa     1200
Ile Pro Pro Leu Asn Gln Leu Glu Leu Leu Arg Asn Leu Lys Ser Lys
385                 390                 395                 400

tct gga ctc gct ttc agg aag gac ccc ccg ccg gag ccg tct cca agt     1248
Ser Gly Leu Ala Phe Arg Lys Asp Pro Pro Pro Glu Pro Ser Pro Ser
                405                 410                 415

aaa ggc agc ccg tgc aga ggg ccc ctg tgt gga tgc tgc ccc gga cgc     1296
Lys Gly Ser Pro Cys Arg Gly Pro Leu Cys Gly Cys Cys Pro Gly Arg
            420                 425                 430

tct agc cag aag gtc agt ttg aaa gat cgt gtc ttc tcc agc ccc cga     1344
Ser Ser Gln Lys Val Ser Leu Lys Asp Arg Val Phe Ser Ser Pro Arg
        435                 440                 445

ggc gtg gct gcc aag ggg aag ggg tcc ccg cag gcc cag act gtg agg     1392
Gly Val Ala Ala Lys Gly Lys Gly Ser Pro Gln Ala Gln Thr Val Arg
    450                 455                 460

cgg tca ccc agc gcc gac cag agc ctc gag gac agc ccc agc aag gtg     1440
Arg Ser Pro Ser Ala Asp Gln Ser Leu Glu Asp Ser Pro Ser Lys Val
465                 470                 475                 480

ccc aag agc tgg agc ttc ggg gac cgc agc cgg gca cgc cag gct ttc     1488
Pro Lys Ser Trp Ser Phe Gly Asp Arg Ser Arg Ala Arg Gln Ala Phe
                485                 490                 495

cgc atc aag ggt gcc gcg tca cgg cag aac tca gaa gaa gca agc ctc     1536
Arg Ile Lys Gly Ala Ala Ser Arg Gln Asn Ser Glu Glu Ala Ser Leu
            500                 505                 510

ccc gga gag gac att gtg gat gac aag agc tgc ccc tgc gag ttt gtg     1584
Pro Gly Glu Asp Ile Val Asp Asp Lys Ser Cys Pro Cys Glu Phe Val
        515                 520                 525

acc gag gac ctg acc ccg ggc ctc aaa gtc agc atc aga gcc gtg tgt     1632
Thr Glu Asp Leu Thr Pro Gly Leu Lys Val Ser Ile Arg Ala Val Cys
    530                 535                 540

gtc atg cgg ttc ctg gtg tcc aag cgg aag ttc aag gag agc ctg cgg     1680
Val Met Arg Phe Leu Val Ser Lys Arg Lys Phe Lys Glu Ser Leu Arg
545                 550                 555                 560

ccc tac gac gtg atg gac gtc atc gag cag tac tca gcc ggc cac ctg     1728
Pro Tyr Asp Val Met Asp Val Ile Glu Gln Tyr Ser Ala Gly His Leu
                565                 570                 575
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gac atg ctg tcc cga att aag agc ctg cag tcc agg caa gag ccc cgc     1776
Asp Met Leu Ser Arg Ile Lys Ser Leu Gln Ser Arg Gln Glu Pro Arg
            580                 585                 590

ctg cct gtc cag cag ggg aca aga acg ggg tgg gct tct ggg aca aag     1824
Leu Pro Val Gln Gln Gly Thr Arg Thr Gly Trp Ala Ser Gly Thr Lys
        595                 600                 605

ccc act gtg gcc cat ggt ggg agt gca ggg ggt gtg tgg gcg ggg cct     1872
Pro Thr Val Ala His Gly Gly Ser Ala Gly Gly Val Trp Ala Gly Pro
    610                 615                 620

cct ccc cac cca cgt cgg cct ctg tca gct tct gtt gtg tct tca caa     1920
Pro Pro His Pro Arg Arg Pro Leu Ser Ala Ser Val Val Ser Ser Gln
625                 630                 635                 640

agt ctg ttt taa                                                    1932
Ser Leu Phe


<210> SEQ ID NO 2
<211> LENGTH: 643
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

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1               5                   10                  15

Glu Lys Lys Leu Lys Val Gly Phe Val Gly Leu Asp Pro Gly Ala Pro
            20                  25                  30

Asp Ser Thr Arg Asp Gly Ala Leu Leu Ile Ala Gly Ser Glu Ala Pro
        35                  40                  45

Lys Arg Gly Ser Ile Leu Ser Lys Pro Arg Ala Gly Gly Ala Gly Ala
    50                  55                  60

Gly Lys Pro Pro Lys Arg Asn Ala Phe Tyr Arg Lys Leu Gln Asn Phe
65                  70                  75                  80

Leu Tyr Asn Val Leu Glu Arg Pro Arg Gly Trp Ala Phe Ile Tyr His
                85                  90                  95

Ala Tyr Val Phe Leu Leu Val Phe Ser Cys Leu Val Leu Ser Val Phe
            100                 105                 110

Ser Thr Ile Lys Glu Tyr Glu Lys Ser Ser Glu Gly Ala Leu Tyr Ile
        115                 120                 125

Leu Glu Ile Val Thr Ile Val Val Phe Gly Val Glu Tyr Phe Val Arg
    130                 135                 140

Ile Trp Ala Ala Gly Cys Cys Cys Arg Tyr Arg Gly Trp Arg Gly Arg
145                 150                 155                 160

Leu Lys Phe Ala Arg Lys Pro Phe Cys Val Ile Asp Ile Met Val Leu
                165                 170                 175

Ile Ala Ser Ile Ala Val Leu Ala Ala Gly Ser Gln Gly Asn Val Phe
            180                 185                 190

Ala Thr Ser Ala Leu Arg Ser Leu Arg Phe Leu Gln Ile Leu Arg Met
        195                 200                 205

Ile Arg Met Asp Arg Arg Gly Gly Thr Trp Lys Leu Leu Gly Ser Val
    210                 215                 220

Val Tyr Ala His Ser Lys Glu Leu Val Thr Ala Trp Tyr Ile Gly Phe
225                 230                 235                 240

Leu Cys Leu Ile Leu Ala Ser Phe Leu Val Tyr Leu Ala Glu Lys Gly
                245                 250                 255

Glu Asn Asp His Phe Asp Thr Tyr Ala Asp Ala Leu Trp Trp Gly Leu
            260                 265                 270
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Ile Thr Leu Thr Thr Ile Gly Tyr Gly Asp Lys Tyr Pro Gln Thr Trp
        275                 280                 285

Asn Gly Arg Leu Leu Ala Ala Thr Phe Thr Leu Ile Gly Val Ser Phe
    290                 295                 300

Phe Ala Leu Pro Ala Gly Ile Leu Gly Ser Gly Phe Ala Leu Lys Val
305                 310                 315                 320

Gln Glu Gln His Arg Gln Lys His Phe Glu Lys Arg Arg Asn Pro Ala
                325                 330                 335

Ala Gly Leu Ile Gln Ser Ala Trp Arg Phe Tyr Ala Thr Asn Leu Ser
            340                 345                 350

Arg Thr Asp Leu His Ser Thr Trp Gln Tyr Tyr Glu Arg Thr Val Thr
        355                 360                 365

Val Pro Met Tyr Ser Ser Gln Thr Gln Thr Tyr Gly Ala Ser Arg Leu
    370                 375                 380

Ile Pro Pro Leu Asn Gln Leu Glu Leu Leu Arg Asn Leu Lys Ser Lys
385                 390                 395                 400

Ser Gly Leu Ala Phe Arg Lys Asp Pro Pro Pro Glu Pro Ser Pro Ser
                405                 410                 415

Lys Gly Ser Pro Cys Arg Gly Pro Leu Cys Gly Cys Cys Pro Gly Arg
            420                 425                 430

Ser Ser Gln Lys Val Ser Leu Lys Asp Arg Val Phe Ser Ser Pro Arg
        435                 440                 445

Gly Val Ala Ala Lys Gly Lys Gly Ser Pro Gln Ala Gln Thr Val Arg
    450                 455                 460

Arg Ser Pro Ser Ala Asp Gln Ser Leu Glu Asp Ser Pro Ser Lys Val
465                 470                 475                 480

Pro Lys Ser Trp Ser Phe Gly Asp Arg Ser Arg Ala Arg Gln Ala Phe
                485                 490                 495

Arg Ile Lys Gly Ala Ala Ser Arg Gln Asn Ser Glu Glu Ala Ser Leu
            500                 505                 510

Pro Gly Glu Asp Ile Val Asp Asp Lys Ser Cys Pro Cys Glu Phe Val
        515                 520                 525

Thr Glu Asp Leu Thr Pro Gly Leu Lys Val Ser Ile Arg Ala Val Cys
    530                 535                 540

Val Met Arg Phe Leu Val Ser Lys Arg Lys Phe Lys Glu Ser Leu Arg
545                 550                 555                 560

Pro Tyr Asp Val Met Asp Val Ile Glu Gln Tyr Ser Ala Gly His Leu
                565                 570                 575

Asp Met Leu Ser Arg Ile Lys Ser Leu Gln Ser Arg Gln Glu Pro Arg
            580                 585                 590

Leu Pro Val Gln Gln Gly Thr Arg Thr Gly Trp Ala Ser Gly Thr Lys
        595                 600                 605

Pro Thr Val Ala His Gly Gly Ser Ala Gly Gly Val Trp Ala Gly Pro
    610                 615                 620

Pro Pro His Pro Arg Arg Pro Leu Ser Ala Ser Val Val Ser Ser Gln
625                 630                 635                 640

Ser Leu Phe
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<210> SEQ ID NO 3
<211> LENGTH: 1878
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<213> ORGANISM: Homo sapiens
<220> FEATURE:
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1               5                  10                  15

gag aag aag ctg aag gtg ggc ttc gtg ggg ctg gac ccc ggc gcg ccc       96
Glu Lys Lys Leu Lys Val Gly Phe Val Gly Leu Asp Pro Gly Ala Pro
            20                  25                  30

gac tcc acc cgg gac ggg gcg ctg ctg atc gcc ggc tcc gag gcc ccc      144
Asp Ser Thr Arg Asp Gly Ala Leu Leu Ile Ala Gly Ser Glu Ala Pro
        35                  40                  45

aag cgc ggc agc atc ctc agc aaa cct cgc gcg ggc ggc gcg ggc gcc      192
Lys Arg Gly Ser Ile Leu Ser Lys Pro Arg Ala Gly Gly Ala Gly Ala
    50                  55                  60

ggg aag ccc ccc aag cgc aac gcc ttc tac cgc aag ctg cag aat ttc      240
Gly Lys Pro Pro Lys Arg Asn Ala Phe Tyr Arg Lys Leu Gln Asn Phe
65                  70                  75                  80

ctc tac aac gtg ctg gag cgg ccg cgc ggc tgg gcg ttc atc tac cac      288
Leu Tyr Asn Val Leu Glu Arg Pro Arg Gly Trp Ala Phe Ile Tyr His
                85                  90                  95

gcc tac gtg ttc ctc ctg gtt ttc tcc tgc ctc gtg ctg tct gtg ttt      336
Ala Tyr Val Phe Leu Leu Val Phe Ser Cys Leu Val Leu Ser Val Phe
            100                 105                 110

tcc acc atc aag gag tat gag aag agc tcg gag ggg gcc ctc tac atc      384
Ser Thr Ile Lys Glu Tyr Glu Lys Ser Ser Glu Gly Ala Leu Tyr Ile
        115                 120                 125

ctg gaa atc gtg act atc gtg gtg ttt ggc gtg gag tac ttc gtg cgg      432
Leu Glu Ile Val Thr Ile Val Val Phe Gly Val Glu Tyr Phe Val Arg
    130                 135                 140

atc tgg gcc gca ggc tgc tgc tgc cgg tac cgt ggc tgg agg ggg cgg      480
Ile Trp Ala Ala Gly Cys Cys Cys Arg Tyr Arg Gly Trp Arg Gly Arg
145                 150                 155                 160

ctc aag ttt gcc cgg aaa ccg ttc tgt gtg att gac atc atg gtg ctc      528
Leu Lys Phe Ala Arg Lys Pro Phe Cys Val Ile Asp Ile Met Val Leu
                165                 170                 175

atc gcc tcc att gcg gtg ctg gcc gcc ggc tcc cag ggc aac gtc ttt      576
Ile Ala Ser Ile Ala Val Leu Ala Ala Gly Ser Gln Gly Asn Val Phe
            180                 185                 190

gcc aca tct gcg ctc cgg agc ctg cgc ttc ctg cag att ctg cgg atg      624
Ala Thr Ser Ala Leu Arg Ser Leu Arg Phe Leu Gln Ile Leu Arg Met
        195                 200                 205

atc cgc atg gac cgg cgg gga ggc acc tgg aag ctg ctg ggc tct gtg      672
Ile Arg Met Asp Arg Arg Gly Gly Thr Trp Lys Leu Leu Gly Ser Val
    210                 215                 220

gtc tat gcc cac agc aag gag ctg gtc act gcc tgg tac atc ggc ttc      720
Val Tyr Ala His Ser Lys Glu Leu Val Thr Ala Trp Tyr Ile Gly Phe
225                 230                 235                 240

ctt tgt ctc atc ctg gcc tcg ttc ctg gtg tac ttg gca gag aag ggg      768
Leu Cys Leu Ile Leu Ala Ser Phe Leu Val Tyr Leu Ala Glu Lys Gly
                245                 250                 255

gag aac gac cac ttt gac acc tac gcg gat gca ctc tgg tgg ggc ctg      816
Glu Asn Asp His Phe Asp Thr Tyr Ala Asp Ala Leu Trp Trp Gly Leu
            260                 265                 270

atc acg ctg acc acc att ggc tac ggg gac aag tac ccc cag acc tgg      864
Ile Thr Leu Thr Thr Ile Gly Tyr Gly Asp Lys Tyr Pro Gln Thr Trp
        275                 280                 285

aac ggc agg ctc ctt gcg gca acc ttc acc ctc atc ggt gtc tcc ttc      912
Asn Gly Arg Leu Leu Ala Ala Thr Phe Thr Leu Ile Gly Val Ser Phe
    290                 295                 300
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ttc gcg ctg cct gca ggc atc ttg ggg tct ggg ttt gcc ctg aag gtt      960
Phe Ala Leu Pro Ala Gly Ile Leu Gly Ser Gly Phe Ala Leu Lys Val
305                 310                 315                 320

cag gag cag cac agg cag aag cac ttt gag aag agg cgg aac ccg gca     1008
Gln Glu Gln His Arg Gln Lys His Phe Glu Lys Arg Arg Asn Pro Ala
                325                 330                 335

gca ggc ctg atc cag tcg gcc tgg aga ttc tac gcc acc aac ctc tcg     1056
Ala Gly Leu Ile Gln Ser Ala Trp Arg Phe Tyr Ala Thr Asn Leu Ser
            340                 345                 350

cgc aca gac ctg cac tcc acg tgg cag tac tac gag cga acg gtc acc     1104
Arg Thr Asp Leu His Ser Thr Trp Gln Tyr Tyr Glu Arg Thr Val Thr
        355                 360                 365

gtg ccc atg tac agt tcg caa act caa acc tac ggg gcc tcc aga ctt     1152
Val Pro Met Tyr Ser Ser Gln Thr Gln Thr Tyr Gly Ala Ser Arg Leu
    370                 375                 380

atc ccc ccg ctg aac cag ctg gag ctg ctg agg aac ctc aag agt aaa     1200
Ile Pro Pro Leu Asn Gln Leu Glu Leu Leu Arg Asn Leu Lys Ser Lys
385                 390                 395                 400

tct gga ctc gct ttc agg aag gac ccc ccg ccg gag ccg tct cca agc     1248
Ser Gly Leu Ala Phe Arg Lys Asp Pro Pro Pro Glu Pro Ser Pro Ser
                405                 410                 415

cag aag gtc agt ttg aaa gat cgt gtc ttc tcc agc ccc cga ggc gtg     1296
Gln Lys Val Ser Leu Lys Asp Arg Val Phe Ser Ser Pro Arg Gly Val
            420                 425                 430

gct gcc aag ggg aag ggg tcc ccg cag gcc cag act gtg agg cgg tca     1344
Ala Ala Lys Gly Lys Gly Ser Pro Gln Ala Gln Thr Val Arg Arg Ser
        435                 440                 445

ccc agc gcc gac cag agc ctc gag gac agc ccc agc aag gtg ccc aag     1392
Pro Ser Ala Asp Gln Ser Leu Glu Asp Ser Pro Ser Lys Val Pro Lys
    450                 455                 460

agc tgg agc ttc ggg gac cgc agc cgg gca cgc cag gct ttc cgc atc     1440
Ser Trp Ser Phe Gly Asp Arg Ser Arg Ala Arg Gln Ala Phe Arg Ile
465                 470                 475                 480

aag ggt gcc gcg tca cgg cag aac tca gaa gaa gca agc ctc ccc gga     1488
Lys Gly Ala Ala Ser Arg Gln Asn Ser Glu Glu Ala Ser Leu Pro Gly
                485                 490                 495

gag gac att gtg gat gac aag agc tgc ccc tgc gag ttt gtg acc gag     1536
Glu Asp Ile Val Asp Asp Lys Ser Cys Pro Cys Glu Phe Val Thr Glu
            500                 505                 510

gac ctg acc ccg ggc ctc aaa gtc agc atc aga gcc gtg tgt gtc atg     1584
Asp Leu Thr Pro Gly Leu Lys Val Ser Ile Arg Ala Val Cys Val Met
        515                 520                 525

cgg ttc ctg gtg tcc aag cgg aag ttc aag gag agc ctg cgg ccc tac     1632
Arg Phe Leu Val Ser Lys Arg Lys Phe Lys Glu Ser Leu Arg Pro Tyr
    530                 535                 540

gac gtg atg gac gtc atc gag cag tac tca gcc ggc cac ctg gac atg     1680
Asp Val Met Asp Val Ile Glu Gln Tyr Ser Ala Gly His Leu Asp Met
545                 550                 555                 560

ctg tcc cga att aag agc ctg cag tcc agg caa gag ccc cgc ctg cct     1728
Leu Ser Arg Ile Lys Ser Leu Gln Ser Arg Gln Glu Pro Arg Leu Pro
                565                 570                 575

gtc cag cag ggg aca aga acg ggg tgg gct tct ggg aca aag ccc act     1776
Val Gln Gln Gly Thr Arg Thr Gly Trp Ala Ser Gly Thr Lys Pro Thr
            580                 585                 590

gtg gcc cat ggt ggg agt gca ggg ggt gtg tgg gcg ggg cct cct ccc     1824
Val Ala His Gly Gly Ser Ala Gly Gly Val Trp Ala Gly Pro Pro Pro
        595                 600                 605
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cac cca cgt cgg cct ctg tca gct tct gtt gtg tct tca caa agt ctg     1872
His Pro Arg Arg Pro Leu Ser Ala Ser Val Val Ser Ser Gln Ser Leu
    610                 615                 620

ttt taa                                                           1878
Phe
625
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<210> SEQ ID NO 4
<211> LENGTH: 625
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

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1               5                   10                  15

Glu Lys Lys Leu Lys Val Gly Phe Val Gly Leu Asp Pro Gly Ala Pro
            20                  25                  30

Asp Ser Thr Arg Asp Gly Ala Leu Leu Ile Ala Gly Ser Glu Ala Pro
        35                  40                  45

Lys Arg Gly Ser Ile Leu Ser Lys Pro Arg Ala Gly Gly Ala Gly Ala
    50                  55                  60

Gly Lys Pro Pro Lys Arg Asn Ala Phe Tyr Arg Lys Leu Gln Asn Phe
65                  70                  75                  80

Leu Tyr Asn Val Leu Glu Arg Pro Arg Gly Trp Ala Phe Ile Tyr His
                85                  90                  95

Ala Tyr Val Phe Leu Leu Val Phe Ser Cys Leu Val Leu Ser Val Phe
            100                 105                 110

Ser Thr Ile Lys Glu Tyr Glu Lys Ser Ser Glu Gly Ala Leu Tyr Ile
        115                 120                 125

Leu Glu Ile Val Thr Ile Val Val Phe Gly Val Glu Tyr Phe Val Arg
    130                 135                 140

Ile Trp Ala Ala Gly Cys Cys Cys Arg Tyr Arg Gly Trp Arg Gly Arg
145                 150                 155                 160

Leu Lys Phe Ala Arg Lys Pro Phe Cys Val Ile Asp Ile Met Val Leu
                165                 170                 175

Ile Ala Ser Ile Ala Val Leu Ala Ala Gly Ser Gln Gly Asn Val Phe
            180                 185                 190

Ala Thr Ser Ala Leu Arg Ser Leu Arg Phe Leu Gln Ile Leu Arg Met
        195                 200                 205

Ile Arg Met Asp Arg Arg Gly Gly Thr Trp Lys Leu Leu Gly Ser Val
    210                 215                 220

Val Tyr Ala His Ser Lys Glu Leu Val Thr Ala Trp Tyr Ile Gly Phe
225                 230                 235                 240

Leu Cys Leu Ile Leu Ala Ser Phe Leu Val Tyr Leu Ala Glu Lys Gly
                245                 250                 255

Glu Asn Asp His Phe Asp Thr Tyr Ala Asp Ala Leu Trp Trp Gly Leu
            260                 265                 270

Ile Thr Leu Thr Thr Ile Gly Tyr Gly Asp Lys Tyr Pro Gln Thr Trp
        275                 280                 285

Asn Gly Arg Leu Leu Ala Ala Thr Phe Thr Leu Ile Gly Val Ser Phe
    290                 295                 300

Phe Ala Leu Pro Ala Gly Ile Leu Gly Ser Gly Phe Ala Leu Lys Val
305                 310                 315                 320

Gln Glu Gln His Arg Gln Lys His Phe Glu Lys Arg Arg Asn Pro Ala
                325                 330                 335
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Ala Gly Leu Ile Gln Ser Ala Trp Arg Phe Tyr Ala Thr Asn Leu Ser
            340                 345                 350

Arg Thr Asp Leu His Ser Thr Trp Gln Tyr Tyr Glu Arg Thr Val Thr
        355                 360                 365

Val Pro Met Tyr Ser Ser Gln Thr Gln Thr Tyr Gly Ala Ser Arg Leu
    370                 375                 380

Ile Pro Pro Leu Asn Gln Leu Glu Leu Leu Arg Asn Leu Lys Ser Lys
385                 390                 395                 400

Ser Gly Leu Ala Phe Arg Lys Asp Pro Pro Pro Glu Pro Ser Pro Ser
                405                 410                 415

Gln Lys Val Ser Leu Lys Asp Arg Val Phe Ser Ser Pro Arg Gly Val
            420                 425                 430

Ala Ala Lys Gly Lys Gly Ser Pro Gln Ala Gln Thr Val Arg Arg Ser
        435                 440                 445

Pro Ser Ala Asp Gln Ser Leu Glu Asp Ser Pro Ser Lys Val Pro Lys
    450                 455                 460

Ser Trp Ser Phe Gly Asp Arg Ser Arg Ala Arg Gln Ala Phe Arg Ile
465                 470                 475                 480

Lys Gly Ala Ala Ser Arg Gln Asn Ser Glu Glu Ala Ser Leu Pro Gly
                485                 490                 495

Glu Asp Ile Val Asp Asp Lys Ser Cys Pro Cys Glu Phe Val Thr Glu
            500                 505                 510

Asp Leu Thr Pro Gly Leu Lys Val Ser Ile Arg Ala Val Cys Val Met
        515                 520                 525

Arg Phe Leu Val Ser Lys Arg Lys Phe Lys Glu Ser Leu Arg Pro Tyr
    530                 535                 540

Asp Val Met Asp Val Ile Glu Gln Tyr Ser Ala Gly His Leu Asp Met
545                 550                 555                 560

Leu Ser Arg Ile Lys Ser Leu Gln Ser Arg Gln Glu Pro Arg Leu Pro
                565                 570                 575

Val Gln Gln Gly Thr Arg Thr Gly Trp Ala Ser Gly Thr Lys Pro Thr
            580                 585                 590

Val Ala His Gly Gly Ser Ala Gly Gly Val Trp Ala Gly Pro Pro Pro
        595                 600                 605

His Pro Arg Arg Pro Leu Ser Ala Ser Val Val Ser Ser Gln Ser Leu
    610                 615                 620

Phe
625
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<210> SEQ ID NO 5
<211> LENGTH: 1848
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1848)

<400> SEQUENCE: 5

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atg gtg cag aag tcg cgc aac ggc ggc gta tac ccc ggc ccg agc ggg       48
Met Val Gln Lys Ser Arg Asn Gly Gly Val Tyr Pro Gly Pro Ser Gly
1               5                   10                  15

gag aag aag ctg aag gtg ggc ttc gtg ggg ctg gac ccc ggc gcg ccc       96
Glu Lys Lys Leu Lys Val Gly Phe Val Gly Leu Asp Pro Gly Ala Pro
            20                  25                  30

gac tcc acc cgg gac ggg gcg ctg ctg atc gcc ggc tcc gag gcc ccc      144
Asp Ser Thr Arg Asp Gly Ala Leu Leu Ile Ala Gly Ser Glu Ala Pro
        35                  40                  45
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aag cgc ggc agc atc ctc agc aaa cct cgc gcg ggc ggc gcg ggc gcc      192
Lys Arg Gly Ser Ile Leu Ser Lys Pro Arg Ala Gly Gly Ala Gly Ala
    50                  55                  60

ggg aag ccc ccc aag cgc aac gcc ttc tac cgc aag ctg cag aat ttc      240
Gly Lys Pro Pro Lys Arg Asn Ala Phe Tyr Arg Lys Leu Gln Asn Phe
65                  70                  75                  80

ctc tac aac gtg ctg gag cgg ccg cgc ggc tgg gcg ttc atc tac cac      288
Leu Tyr Asn Val Leu Glu Arg Pro Arg Gly Trp Ala Phe Ile Tyr His
                85                  90                  95

gcc tac gtg ttc ctc ctg gtt ttc tcc tgc ctc gtg ctg tct gtg ttt      336
Ala Tyr Val Phe Leu Leu Val Phe Ser Cys Leu Val Leu Ser Val Phe
            100                 105                 110

tcc acc atc aag gag tat gag aag agc tcg gag ggg gcc ctc tac atc      384
Ser Thr Ile Lys Glu Tyr Glu Lys Ser Ser Glu Gly Ala Leu Tyr Ile
        115                 120                 125

ctg gaa atc gtg act atc gtg gtg ttt ggc gtg gag tac ttc gtg cgg      432
Leu Glu Ile Val Thr Ile Val Val Phe Gly Val Glu Tyr Phe Val Arg
    130                 135                 140

atc tgg gcc gca ggc tgc tgc tgc cgg tac cgt ggc tgg agg ggg cgg      480
Ile Trp Ala Ala Gly Cys Cys Cys Arg Tyr Arg Gly Trp Arg Gly Arg
145                 150                 155                 160

ctc aag ttt gcc cgg aaa ccg ttc tgt gtg att gac atc atg gtg ctc      528
Leu Lys Phe Ala Arg Lys Pro Phe Cys Val Ile Asp Ile Met Val Leu
                165                 170                 175

atc gcc tcc att gcg gtg ctg gcc gcc ggc tcc cag ggc aac gtc ttt      576
Ile Ala Ser Ile Ala Val Leu Ala Ala Gly Ser Gln Gly Asn Val Phe
            180                 185                 190

gcc aca tct gcg ctc cgg agc ctg cgc ttc ctg cag att ctg cgg atg      624
Ala Thr Ser Ala Leu Arg Ser Leu Arg Phe Leu Gln Ile Leu Arg Met
        195                 200                 205

atc cgc atg gac cgg cgg gga ggc acc tgg aag ctg ctg ggc tct gtg      672
Ile Arg Met Asp Arg Arg Gly Gly Thr Trp Lys Leu Leu Gly Ser Val
    210                 215                 220

gtc tat gcc cac agc aag gag ctg gtc act gcc tgg tac atc ggc ttc      720
Val Tyr Ala His Ser Lys Glu Leu Val Thr Ala Trp Tyr Ile Gly Phe
225                 230                 235                 240

ctt tgt ctc atc ctg gcc tcg ttc ctg gtg tac ttg gca gag aag ggg      768
Leu Cys Leu Ile Leu Ala Ser Phe Leu Val Tyr Leu Ala Glu Lys Gly
                245                 250                 255

gag aac gac cac ttt gac acc tac gcg gat gca ctc tgg tgg ggc ctg      816
Glu Asn Asp His Phe Asp Thr Tyr Ala Asp Ala Leu Trp Trp Gly Leu
            260                 265                 270

atc acg ctg acc acc att ggc tac ggg gac aag tac ccc cag acc tgg      864
Ile Thr Leu Thr Thr Ile Gly Tyr Gly Asp Lys Tyr Pro Gln Thr Trp
        275                 280                 285

aac ggc agg ctc ctt gcg gca acc ttc acc ctc atc ggt gtc tcc ttc      912
Asn Gly Arg Leu Leu Ala Ala Thr Phe Thr Leu Ile Gly Val Ser Phe
    290                 295                 300

ttc gcg ctg cct gca ggc atc ttg ggg tct ggg ttt gcc ctg aag gtt      960
Phe Ala Leu Pro Ala Gly Ile Leu Gly Ser Gly Phe Ala Leu Lys Val
305                 310                 315                 320

cag gag cag cac agg cag aag cac ttt gag aag agg cgg aac ccg gca     1008
Gln Glu Gln His Arg Gln Lys His Phe Glu Lys Arg Arg Asn Pro Ala
                325                 330                 335

gca ggc ctg atc cag tcg gcc tgg aga ttc tac gcc acc aac ctc tcg     1056
Ala Gly Leu Ile Gln Ser Ala Trp Arg Phe Tyr Ala Thr Asn Leu Ser
            340                 345                 350

cgc aca gac ctg cac tcc acg tgg cag tac tac gag cga acg gtc acc     1104
Arg Thr Asp Leu His Ser Thr Trp Gln Tyr Tyr Glu Arg Thr Val Thr
        355                 360                 365
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gtg ccc atg tac aga ctt atc ccc ccg ctg aac cag ctg gag ctg ctg     1152
Val Pro Met Tyr Arg Leu Ile Pro Pro Leu Asn Gln Leu Glu Leu Leu
    370                 375                 380

agg aac ctc aag agt aaa tct gga ctc gct ttc agg aag gac ccc ccg     1200
Arg Asn Leu Lys Ser Lys Ser Gly Leu Ala Phe Arg Lys Asp Pro Pro
385                 390                 395                 400

ccg gag ccg tct cca agc cag aag gtc agt ttg aaa gat cgt gtc ttc     1248
Pro Glu Pro Ser Pro Ser Gln Lys Val Ser Leu Lys Asp Arg Val Phe
                405                 410                 415

tcc agc ccc cga ggc gtg gct gcc aag ggg aag ggg tcc ccg cag gcc     1296
Ser Ser Pro Arg Gly Val Ala Ala Lys Gly Lys Gly Ser Pro Gln Ala
            420                 425                 430

cag act gtg agg cgg tca ccc agc gcc gac cag agc ctc gag gac agc     1344
Gln Thr Val Arg Arg Ser Pro Ser Ala Asp Gln Ser Leu Glu Asp Ser
        435                 440                 445

ccc agc aag gtg ccc aag agc tgg agc ttc ggg gac cgc agc cgg gca     1392
Pro Ser Lys Val Pro Lys Ser Trp Ser Phe Gly Asp Arg Ser Arg Ala
    450                 455                 460

cgc cag gct ttc cgc atc aag ggt gcc gcg tca cgg cag aac tca gaa     1440
Arg Gln Ala Phe Arg Ile Lys Gly Ala Ala Ser Arg Gln Asn Ser Glu
465                 470                 475                 480

gaa gca agc ctc ccc gga gag gac att gtg gat gac aag agc tgc ccc     1488
Glu Ala Ser Leu Pro Gly Glu Asp Ile Val Asp Asp Lys Ser Cys Pro
                485                 490                 495

tgc gag ttt gtg acc gag gac ctg acc ccg ggc ctc aaa gtc agc atc     1536
Cys Glu Phe Val Thr Glu Asp Leu Thr Pro Gly Leu Lys Val Ser Ile
            500                 505                 510

aga gcc gtg tgt gtc atg cgg ttc ctg gtg tcc aag cgg aag ttc aag     1584
Arg Ala Val Cys Val Met Arg Phe Leu Val Ser Lys Arg Lys Phe Lys
        515                 520                 525

gag agc ctg cgg ccc tac gac gtg atg gac gtc atc gag cag tac tca     1632
Glu Ser Leu Arg Pro Tyr Asp Val Met Asp Val Ile Glu Gln Tyr Ser
    530                 535                 540

gcc ggc cac ctg gac atg ctg tcc cga att aag agc ctg cag tcc agg     1680
Ala Gly His Leu Asp Met Leu Ser Arg Ile Lys Ser Leu Gln Ser Arg
545                 550                 555                 560

caa gag ccc cgc ctg cct gtc cag cag ggg aca aga acg ggg tgg gct     1728
Gln Glu Pro Arg Leu Pro Val Gln Gln Gly Thr Arg Thr Gly Trp Ala
                565                 570                 575

tct ggg aca aag ccc act gtg gcc cat ggt ggg agt gca ggg ggt gtg     1776
Ser Gly Thr Lys Pro Thr Val Ala His Gly Gly Ser Ala Gly Gly Val
            580                 585                 590

tgg gcg ggg cct cct ccc cac cca cgt cgg cct ctg tca gct tct gtt     1824
Trp Ala Gly Pro Pro Pro His Pro Arg Arg Pro Leu Ser Ala Ser Val
        595                 600                 605

gtg tct tca caa agt ctg ttt taa                                    1848
Val Ser Ser Gln Ser Leu Phe
    610                 615


<210> SEQ ID NO 6
<211> LENGTH: 615
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

Met Val Gln Lys Ser Arg Asn Gly Gly Val Tyr Pro Gly Pro Ser Gly
1               5                   10                  15

Glu Lys Lys Leu Lys Val Gly Phe Val Gly Leu Asp Pro Gly Ala Pro
            20                  25                  30
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Asp Ser Thr Arg Asp Gly Ala Leu Leu Ile Ala Gly Ser Glu Ala Pro
        35                  40                  45

Lys Arg Gly Ser Ile Leu Ser Lys Pro Arg Ala Gly Gly Ala Gly Ala
    50                  55                  60

Gly Lys Pro Pro Lys Arg Asn Ala Phe Tyr Arg Lys Leu Gln Asn Phe
65                  70                  75                  80

Leu Tyr Asn Val Leu Glu Arg Pro Arg Gly Trp Ala Phe Ile Tyr His
                85                  90                  95

Ala Tyr Val Phe Leu Leu Val Phe Ser Cys Leu Val Leu Ser Val Phe
            100                 105                 110

Ser Thr Ile Lys Glu Tyr Glu Lys Ser Ser Glu Gly Ala Leu Tyr Ile
        115                 120                 125

Leu Glu Ile Val Thr Ile Val Val Phe Gly Val Glu Tyr Phe Val Arg
    130                 135                 140

Ile Trp Ala Ala Gly Cys Cys Cys Arg Tyr Arg Gly Trp Arg Gly Arg
145                 150                 155                 160

Leu Lys Phe Ala Arg Lys Pro Phe Cys Val Ile Asp Ile Met Val Leu
                165                 170                 175

Ile Ala Ser Ile Ala Val Leu Ala Ala Gly Ser Gln Gly Asn Val Phe
            180                 185                 190

Ala Thr Ser Ala Leu Arg Ser Leu Arg Phe Leu Gln Ile Leu Arg Met
        195                 200                 205

Ile Arg Met Asp Arg Arg Gly Gly Thr Trp Lys Leu Leu Gly Ser Val
    210                 215                 220

Val Tyr Ala His Ser Lys Glu Leu Val Thr Ala Trp Tyr Ile Gly Phe
225                 230                 235                 240

Leu Cys Leu Ile Leu Ala Ser Phe Leu Val Tyr Leu Ala Glu Lys Gly
                245                 250                 255

Glu Asn Asp His Phe Asp Thr Tyr Ala Asp Ala Leu Trp Trp Gly Leu
            260                 265                 270

Ile Thr Leu Thr Thr Ile Gly Tyr Gly Asp Lys Tyr Pro Gln Thr Trp
        275                 280                 285

Asn Gly Arg Leu Leu Ala Ala Thr Phe Thr Leu Ile Gly Val Ser Phe
    290                 295                 300

Phe Ala Leu Pro Ala Gly Ile Leu Gly Ser Gly Phe Ala Leu Lys Val
305                 310                 315                 320

Gln Glu Gln His Arg Gln Lys His Phe Glu Lys Arg Arg Asn Pro Ala
                325                 330                 335

Ala Gly Leu Ile Gln Ser Ala Trp Arg Phe Tyr Ala Thr Asn Leu Ser
            340                 345                 350

Arg Thr Asp Leu His Ser Thr Trp Gln Tyr Tyr Glu Arg Thr Val Thr
        355                 360                 365

Val Pro Met Tyr Arg Leu Ile Pro Pro Leu Asn Gln Leu Glu Leu Leu
    370                 375                 380

Arg Asn Leu Lys Ser Lys Ser Gly Leu Ala Phe Arg Lys Asp Pro Pro
385                 390                 395                 400

Pro Glu Pro Ser Pro Ser Gln Lys Val Ser Leu Lys Asp Arg Val Phe
                405                 410                 415

Ser Ser Pro Arg Gly Val Ala Ala Lys Gly Lys Gly Ser Pro Gln Ala
            420                 425                 430

Gln Thr Val Arg Arg Ser Pro Ser Ala Asp Gln Ser Leu Glu Asp Ser
        435                 440                 445
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Pro Ser Lys Val Pro Lys Ser Trp Ser Phe Gly Asp Arg Ser Arg Ala
    450                 455                 460

Arg Gln Ala Phe Arg Ile Lys Gly Ala Ala Ser Arg Gln Asn Ser Glu
465                 470                 475                 480

Glu Ala Ser Leu Pro Gly Glu Asp Ile Val Asp Asp Lys Ser Cys Pro
                485                 490                 495

Cys Glu Phe Val Thr Glu Asp Leu Thr Pro Gly Leu Lys Val Ser Ile
            500                 505                 510

Arg Ala Val Cys Val Met Arg Phe Leu Val Ser Lys Arg Lys Phe Lys
        515                 520                 525

Glu Ser Leu Arg Pro Tyr Asp Val Met Asp Val Ile Glu Gln Tyr Ser
    530                 535                 540

Ala Gly His Leu Asp Met Leu Ser Arg Ile Lys Ser Leu Gln Ser Arg
545                 550                 555                 560

Gln Glu Pro Arg Leu Pro Val Gln Gln Gly Thr Arg Thr Gly Trp Ala
                565                 570                 575

Ser Gly Thr Lys Pro Thr Val Ala His Gly Gly Ser Ala Gly Gly Val
            580                 585                 590

Trp Ala Gly Pro Pro Pro His Pro Arg Arg Pro Leu Ser Ala Ser Val
        595                 600                 605

Val Ser Ser Gln Ser Leu Phe
    610                 615


<210> SEQ ID NO 7
<211> LENGTH: 872
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

Met Val Gln Lys Ser Arg Asn Gly Gly Val Tyr Pro Gly Pro Ser Gly
1               5                   10                  15

Glu Lys Lys Leu Lys Val Gly Phe Val Gly Leu Asp Pro Gly Ala Pro
            20                  25                  30

Asp Ser Thr Arg Asp Gly Ala Leu Leu Ile Ala Gly Ser Glu Ala Pro
        35                  40                  45

Lys Arg Gly Ser Ile Leu Ser Lys Pro Arg Ala Gly Gly Ala Gly Ala
    50                  55                  60

Gly Lys Pro Pro Lys Arg Asn Ala Phe Tyr Arg Lys Leu Gln Asn Phe
65                  70                  75                  80

Leu Tyr Asn Val Leu Glu Arg Pro Arg Gly Trp Ala Phe Ile Tyr His
                85                  90                  95

Ala Tyr Val Phe Leu Leu Val Phe Ser Cys Leu Val Leu Ser Val Phe
            100                 105                 110

Ser Thr Ile Lys Glu Tyr Glu Lys Ser Ser Glu Gly Ala Leu Tyr Ile
        115                 120                 125

Leu Glu Ile Val Thr Ile Val Val Phe Gly Val Glu Tyr Phe Val Arg
    130                 135                 140

Ile Trp Ala Ala Gly Cys Cys Cys Arg Tyr Arg Gly Trp Arg Gly Arg
145                 150                 155                 160

Leu Lys Phe Ala Arg Lys Pro Phe Cys Val Ile Asp Ile Met Val Leu
                165                 170                 175

Ile Ala Ser Ile Ala Val Leu Ala Ala Gly Ser Gln Gly Asn Val Phe
            180                 185                 190

Ala Thr Ser Ala Leu Arg Ser Leu Arg Phe Leu Gln Ile Leu Arg Met
        195                 200                 205
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Ile Arg Met Asp Arg Arg Gly Gly Thr Trp Lys Leu Leu Gly Ser Val
    210                 215                 220

Val Tyr Ala His Ser Lys Glu Leu Val Thr Ala Trp Tyr Ile Gly Phe
225                 230                 235                 240

Leu Cys Leu Ile Leu Ala Ser Phe Leu Val Tyr Leu Ala Glu Lys Gly
                245                 250                 255

Glu Asn Asp His Phe Asp Thr Tyr Ala Asp Ala Leu Trp Trp Gly Leu
            260                 265                 270

Ile Thr Leu Thr Thr Ile Gly Tyr Gly Asp Lys Tyr Pro Gln Thr Trp
        275                 280                 285

Asn Gly Arg Leu Leu Ala Ala Thr Phe Thr Leu Ile Gly Val Ser Phe
    290                 295                 300

Phe Ala Leu Pro Ala Gly Ile Leu Gly Ser Gly Phe Ala Leu Lys Val
305                 310                 315                 320

Gln Glu Gln His Arg Gln Lys His Phe Glu Lys Arg Arg Asn Pro Ala
                325                 330                 335

Ala Gly Leu Ile Gln Ser Ala Trp Arg Phe Tyr Ala Thr Asn Leu Ser
            340                 345                 350

Arg Thr Asp Leu His Ser Thr Trp Gln Tyr Tyr Glu Arg Thr Val Thr
        355                 360                 365

Val Pro Met Tyr Ser Ser Gln Thr Gln Thr Tyr Gly Ala Ser Arg Leu
    370                 375                 380

Ile Pro Pro Leu Asn Gln Leu Glu Leu Leu Arg Asn Leu Lys Ser Lys
385                 390                 395                 400

Ser Gly Leu Ala Phe Arg Lys Asp Pro Pro Pro Glu Pro Ser Pro Ser
                405                 410                 415

Lys Gly Ser Pro Cys Arg Gly Pro Leu Cys Gly Cys Cys Pro Gly Arg
            420                 425                 430

Ser Ser Gln Lys Val Ser Leu Lys Asp Arg Val Phe Ser Ser Pro Arg
        435                 440                 445

Gly Val Ala Ala Lys Gly Lys Gly Ser Pro Gln Ala Gln Thr Val Arg
    450                 455                 460

Arg Ser Pro Ser Ala Asp Gln Ser Leu Glu Asp Ser Pro Ser Lys Val
465                 470                 475                 480

Pro Lys Ser Trp Ser Phe Gly Asp Arg Ser Arg Ala Arg Gln Ala Phe
                485                 490                 495

Arg Ile Lys Gly Ala Ala Ser Arg Gln Asn Ser Glu Glu Ala Ser Leu
            500                 505                 510

Pro Gly Glu Asp Ile Val Asp Asp Lys Ser Cys Pro Cys Glu Phe Val
        515                 520                 525

Thr Glu Asp Leu Thr Pro Gly Leu Lys Val Ser Ile Arg Ala Val Cys
    530                 535                 540

Val Met Arg Phe Leu Val Ser Lys Arg Lys Phe Lys Glu Ser Leu Arg
545                 550                 555                 560

Pro Tyr Asp Val Met Asp Val Ile Glu Gln Tyr Ser Ala Gly His Leu
                565                 570                 575

Asp Met Leu Ser Arg Ile Lys Ser Leu Gln Ser Arg Val Asp Gln Ile
            580                 585                 590

Val Gly Arg Gly Pro Ala Ile Thr Asp Lys Asp Arg Thr Lys Gly Pro
        595                 600                 605

Ala Glu Ala Glu Leu Pro Glu Asp Pro Ser Met Met Gly Arg Leu Gly
    610                 615                 620
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Lys Val Glu Lys Gln Val Leu Ser Met Glu Lys Lys Leu Asp Phe Leu
625                 630                 635                 640

Val Asn Ile Tyr Met Gln Arg Met Gly Ile Pro Pro Thr Glu Thr Glu
                645                 650                 655

Ala Tyr Phe Gly Ala Lys Glu Pro Glu Pro Ala Pro Pro Tyr His Ser
            660                 665                 670

Pro Glu Asp Ser Arg Glu His Val Asp Arg His Gly Cys Ile Val Lys
        675                 680                 685

Ile Val Arg Ser Ser Ser Ser Thr Gly Gln Lys Asn Phe Ser Ala Pro
    690                 695                 700

Pro Ala Ala Pro Pro Val Gln Cys Pro Pro Ser Thr Ser Trp Gln Pro
705                 710                 715                 720

Gln Ser His Pro Arg Gln Gly His Gly Thr Ser Pro Val Gly Asp His
                725                 730                 735

Gly Ser Leu Val Arg Ile Pro Pro Pro Pro Ala His Glu Arg Ser Leu
            740                 745                 750

Ser Ala Tyr Gly Gly Gly Asn Arg Ala Ser Met Glu Phe Leu Arg Gln
        755                 760                 765

Glu Asp Thr Pro Gly Cys Arg Pro Pro Glu Gly Asn Leu Arg Asp Ser
    770                 775                 780

Asp Thr Ser Ile Ser Ile Pro Ser Val Asp His Glu Glu Leu Glu Arg
785                 790                 795                 800

Ser Phe Ser Gly Phe Ser Ile Ser Gln Ser Lys Glu Asn Leu Asp Ala
                805                 810                 815

Leu Asn Ser Cys Tyr Ala Ala Val Ala Pro Cys Ala Lys Val Arg Pro
            820                 825                 830

Tyr Ile Ala Glu Gly Glu Ser Asp Thr Asp Ser Asp Leu Cys Thr Pro
        835                 840                 845

Cys Gly Pro Pro Pro Arg Ser Ala Thr Gly Glu Gly Pro Phe Gly Asp
    850                 855                 860

Val Gly Trp Ala Gly Pro Arg Lys
865                 870


<210> SEQ ID NO 8
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 8

acctctgcgg attgcatcgg tgtgtgg                                          27


<210> SEQ ID NO 9
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 9

ggatgacttg catgaggctg ggtgg                                            25


<210> SEQ ID NO 10
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide
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<400> SEQUENCE: 10

agcgaattct caatgggcga ggacacggac acgcg 35

<210> SEQ ID NO 11
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 11

tccggatcct cctgtgtcca cacactgcca cctc 34

<210> SEQ ID NO 12
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 12

aatattaaaa cagactttgt gaagacacaa cagaa 35

<210> SEQ ID NO 13
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 13

atcagaattc acatggtgca gaagtcgcgc aac 33

<210> SEQ ID NO 14
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 14

tgacagatct taaaacagac tttgtgaaga cacaacagaa gc 42

<210> SEQ ID NO 15
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 15

gtgtggatgc tgccccg 17

<210> SEQ ID NO 16
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 16

tcccgcctca aaacctcg 18

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<210> SEQ ID NO 17
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 17

actagaattc agccagaagg tcagtttgaa agatc 35

<210> SEQ ID NO 18
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 18

atcaggatcc gcgccgcctc acttcct 27

<210> SEQ ID NO 19
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 19

actagaattc agccagaagg tcagtttgaa agatc 35

<210> SEQ ID NO 20
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 20

actaggatcc ctactggact gcaggctctt aattcg 36

<210> SEQ ID NO 21
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 21

aactagaatt cgtggaccag atcgtggggc g 31

<210> SEQ ID NO 22
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 22

atcaggatcc gcgccgcctc acttcct 27

<210> SEQ ID NO 23
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

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<400> SEQUENCE: 23

aatcagaatt ccaagagccc cgcctgcc 28

<210> SEQ ID NO 24
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 24

gcacgatgca cagttgaagt ga 22

<210> SEQ ID NO 25
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 25

tactgaattc ttcctggtgt ccaagcgga 29

<210> SEQ ID NO 26
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 26

acatggatcc tcacctggac tgcaggctct taattcg 37

<210> SEQ ID NO 27
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 27

acatgaattc cagaaggtca gtttgaaaga tcgtgtc 37

<210> SEQ ID NO 28
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 28

tgatggatcc tcaccgcatg acacacacgg c 31

<210> SEQ ID NO 29
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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Ser Glu Phe His Pro His His Cys Asn Leu Phe Val Tyr Ser Ser Ser
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Lys Gly Ser Leu Arg Leu Cys Asp Met Arg Ala Ala Ala Leu Cys Asp
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Lys His Ser Lys
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agc agc aag ccc cgg gct gtg ctc aag cca cgg cgc gtg tgc gtg ggg   151451
Ser Ser Lys Pro Arg Ala Val Leu Lys Pro Arg Arg Val Cys Val Gly
                385                 390                 395

ggc aag cgc cgg cgt gat gac atc agt gtg gac agc ttg gac ttc acc   151499
Gly Lys Arg Arg Arg Asp Asp Ile Ser Val Asp Ser Leu Asp Phe Thr
            400                 405                 410

aag aag atc ctg cac acg gcc tgg cac ccg gct gag aac atc att gcc   151547
Lys Lys Ile Leu His Thr Ala Trp His Pro Ala Glu Asn Ile Ile Ala
        415                 420                 425

atc gcc gcc acc aac aac ctg tac atc ttc cag gac aag gta aac tct   151595
Ile Ala Ala Thr Asn Asn Leu Tyr Ile Phe Gln Asp Lys Val Asn Ser
    430                 435                 440

gac atg cac tag g tatgtgcagt tcccggcccc tgccacccag cctcatgcaa     151648
Asp Met His
445

gtcatccccg acatgacctt cacgaccgca atgcaaggag gggaagaaag tcacagcact 151708

gatgaggaca gctgcagagg tggcagtgtg tggacacagg aagtttgggc cccctccctg 151768

ccccagcttt cctaggccag aattgtgttt ggcagtaatt gtctgtttaa aaaaataaaa 151828

ag                                                                151830


<210> SEQ ID NO 38
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

Met Gly Glu Asp Thr Asp Thr Arg Lys Ile Asn His Ser Phe Leu Arg
1               5                   10                  15

Asp His Ser Tyr Val Thr Glu Ala Asp Ile Ile Ser Thr Val Glu Phe
            20                  25                  30

Asn His Thr Gly Glu Leu Leu Ala Thr Gly Asp Lys Gly Gly Arg Val
        35                  40                  45

Val Ile Phe Gln Arg Glu Pro Glu Ser Lys Asn Ala Pro His Ser Gln
    50                  55                  60

Gly Asp Tyr Asp Val Tyr Ser Thr Phe Gln Ser His Glu Pro Glu Phe
65                  70                  75                  80

Asp Tyr Leu Lys Ser Leu Glu Ile Glu Glu Lys Ile Asn Lys Ile Lys
                85                  90                  95

Trp Leu Pro Gln Gln Asn Ala Ala His Ser Leu Leu Ser Thr Asn Asp
            100                 105                 110

Lys Thr Ile Lys Leu Trp Lys Ile Thr Glu Arg Asp Lys Arg Pro Glu
        115                 120                 125

Gly Tyr Asn Leu Lys Asp Glu Glu Gly Lys Leu Lys Asp Leu Ser Thr
    130                 135                 140

Val Thr Ser Leu Gln Val Pro Val Leu Lys Pro Met Asp Leu Met Val
145                 150                 155                 160

Glu Val Ser Pro Arg Arg Ile Phe Ala Asn Gly His Thr Tyr His Ile
                165                 170                 175

Asn Ser Ile Ser Val Asn Ser Asp Cys Glu Thr Tyr Met Ser Ala Asp
            180                 185                 190

Asp Leu Arg Ile Asn Leu Trp His Leu Ala Ile Thr Asp Arg Ser Phe
        195                 200                 205
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Asn Ile Val Asp Ile Lys Pro Ala Asn Met Glu Asp Leu Thr Glu Val
    210                 215                 220

Ile Thr Ala Ser Glu Phe His Pro His His Cys Asn Leu Phe Val Tyr
225                 230                 235                 240

Ser Ser Ser Lys Gly Ser Leu Arg Leu Cys Asp Met Pro Ala Ala Ala
                245                 250                 255

Leu Cys Asp Lys His Ser Lys Leu Phe Glu Glu Pro Glu Asp Pro Ser
            260                 265                 270

Asn Arg Ser Phe Phe Ser Glu Ile Ile Ser Ser Val Ser Asp Val Lys
        275                 280                 285

Phe Ser His Ser Asp Arg Tyr Met Leu Thr Arg Asp Tyr Leu Thr Val
    290                 295                 300

Lys Val Trp Asp Leu Asn Met Glu Ala Arg Pro Ile Glu Thr Tyr Gln
305                 310                 315                 320

Val His Asp Tyr Leu Arg Ser Lys Leu Cys Ser Leu Tyr Glu Asn Asp
                325                 330                 335

Cys Ile Phe Asp Lys Phe Glu Cys Ala Trp Asn Gly Ser Asp Ser Val
            340                 345                 350

Ile Met Thr Gly Ala Tyr Asn Asn Phe Phe Arg Met Phe Asp Arg Asn
        355                 360                 365

Thr Lys Arg Asp Val Thr Leu Glu Ala Ser Arg Glu Ser Ser Lys Pro
    370                 375                 380

Arg Ala Val Leu Lys Pro Arg Arg Val Cys Val Gly Gly Lys Arg Arg
385                 390                 395                 400

Arg Asp Asp Ile Ser Val Asp Ser Leu Asp Phe Thr Lys Lys Ile Leu
                405                 410                 415

His Thr Ala Trp His Pro Ala Glu Asn Ile Ile Ala Ile Ala Ala Thr
            420                 425                 430

Asn Asn Leu Tyr Ile Phe Gln Asp Lys Val Asn Ser Asp Met His
        435                 440                 445


<210> SEQ ID NO 39
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer 99-24169/139

<400> SEQUENCE: 39

ctggctgagg cctccttgt                                                19


<210> SEQ ID NO 40
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer 24-257/320

<400> SEQUENCE: 40

gtccttctga tggcctgcc                                                19


<210> SEQ ID NO 41
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer 99-24175/218
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<400> SEQUENCE: 41

caagctggat tcgcaatca 19

<210> SEQ ID NO 42
<211> LENGTH: 601
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: amplicon 30-4
<220> FEATURE:
<221> NAME/KEY: allele
<222> LOCATION: (301)..(301)
<223> OTHER INFORMATION: polymorphism 30-4/58
<220> FEATURE:
<221> NAME/KEY: allele
<222> LOCATION: (301)..(301)
<223> OTHER INFORMATION: biallelic marker 30-4/58

<400> SEQUENCE: 42

tgaagccgac gttgtcgccg ggcagagctt cgctcagagc ctcgtggtgc atctccactg 60

acttcacctc agtggtgatg ttcactggcg caaaggtcac caccatgccc ggccgcagga 120

tgccggtctc cacccggccc acgggcaccg tgccaatgcc tgcagagggg agggggtgtg 180

aggggaaggt ggggcccgag gggatgctgg ggcaggatat tcggggacag agcctggaaa 240

ccaacaaagc ctgggactgg atccccccga caggcctggg ggttggggcc acatgggcgg 300

rgtgcagggg aagggaggcc agggacaagg gcagacacag agattccaag ggaagtgggg 360

gctctcccac ccagctgggg aaataagagg ctgagcagca gagctcccag gaacccacgg 420

aaaagccaca gggacagaga agcgggagga tgggcagaga ggggctgtct gaacctgggg 480

tcccatcctt gcccccggag agcactttcc ctcaaaggag gcactatggg acccctcctt 540

tgtctgagga ctcctccctg tgagtgtggg cggggcgact gactgcttct gcctggggcc 600

t 601

<210> SEQ ID NO 43
<211> LENGTH: 601
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: amplicon 30-2
<220> FEATURE:
<221> NAME/KEY: allele
<222> LOCATION: (301)..(301)
<223> OTHER INFORMATION: biallelic marker 30-2/62

<400> SEQUENCE: 43

gctaacagga gaaagcacct gcacactagc tccccgacgc tggaacaggg ccatggccct 60

gcgccccaca ctccagctcc actctccaca ggaaaaggct cccagaatcc agccactcag 120

tgtgtggggg caggggccct gctgacttag aaacaagtgg cacattgatc cgcattcaaa 180

cttgccagcc aatcaaccac agccccgcgc acagactctc ccaggtggga ctgagggggt 240

ctcccctgtc cttggcaggg gcgtctcccc cacgcacccc cagtcccgtc ctctccacag 300

rctccagatg cccacatccc cagaacactc aatgggacaa ctcagagcag gttacagaga 360

aagaaaagcc acacaagctc accaagggca cgctatttca gaagtgcctt ctcctcctgg 420

aaatgtcgac cccaaagctc tcactgggaa acctctggcc tggccccggg aagcgacagg 480

cgcaggtttg gggctgaggc cgtcccagca gctctgtggc ctgccagacc tcagagcact 540

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cccatcaggg gccacaagag cagagagctc ttcagcccca tgttctcctg gacgaattaa 600

a 601

<210> SEQ ID NO 44
<211> LENGTH: 601
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: amplicon 30-17
<220> FEATURE:
<221> NAME/KEY: allele
<222> LOCATION: (301)..(301)
<223> OTHER INFORMATION: biallelic marker 30-17/37

<400> SEQUENCE: 44

caccacccgc cacctgcctc caggagcact gcagcctcgc cagtcagccc actttgggct 60

ctgtctccag ggatataggg gctggatgga cccgtctcct gaggccagca gaggctccac 120

gccagggtcg gtggcagggc tggcacaggg gaaccaggag gcgccgctgg cttcaccatc 180

ttagctacgg cagcccattc ccctgagcct cctggcctgg gcaacagtgg ctcgcatggc 240

cagcccaccg tgccctccag ggtcagtagc gtctattctg gcggccagca gggctggaga 300

rtcttgggac tgttgagacc ctcccccaac ctccctgagc ctccgggcac agatgtgaaa 360

agggtgccca ctgcagtcag cactcaaccc ccacagcgtc cagggaggga gaggggccac 420

cgggggctga cccctgccca ttctgcagac aaagccacca ccctgccagg gctcaagagg 480

gaagaaaatg gggagggggc catttgagca aatgagccca cccgtgagca aggtggaggg 540

acagcacagt ctggcaggat ggggtctcgg tcactggggg gcctggggcc cctggaactc 600

a 601

<210> SEQ ID NO 45
<211> LENGTH: 601
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: amplicon 30-7
<220> FEATURE:
<221> NAME/KEY: allele
<222> LOCATION: (301)..(301)
<223> OTHER INFORMATION: biallelic marker 30-7/30

<400> SEQUENCE: 45

gccgagatcc cccgagtccc gaggcgtcgc gtgcttgggg acgtcaggag ccgatggtac 60

aggctcgctc aggaccccag tcctgagtcc acacccctgc actgcctgag gccaacacac 120

cgtgcccatg ggggccaggg gtgctcagag tcctggtgct gtgggtgcct ctgtcccaac 180

ggcctctggt ccccatccca acaacaaaag cacaggtggt cggggagaac cggacggggg 240

ccaggggagc acatgggcac aggctcagcg ggactcctgg aatgttctct ctttctccac 300

ygcacgagcc atttcaaagg caagaatagg cccctcctga ccccgctcag gcaggcctca 360

gggcaagtgg gagtcactgg aagactcaat tcctctctct gcgtttccac ccgaggcagg 420

tccagtcacc agagagagaa gcagccacct cctttctcac ggcagctggc aaagcaccgg 480

gtggaggaca gagccggtcg gcccaactgt agcttcgggg ctgcccttgg ctggtctctg 540

ggcagagccc ggtgctgagg gcttgcagtg ggaaaggcac agcttgagga atgggcatca 600

g 601

-continued

<210> SEQ ID NO 46
<211> LENGTH: 601
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: amplicon 30-84
<220> FEATURE:
<221> NAME/KEY: allele
<222> LOCATION: (301)..(301)
<223> OTHER INFORMATION: biallelic marker 30-84/37

<400> SEQUENCE: 46

tgtgctaaaa catagtggct taaaaataat gataaccatt tatcgtctca gtttctgcag 60

ctcaggagtc ggacggcacg cagccgatct ccactcccaa cgtgcagggc ctctgccata 120

agccttgaag gcactcattc actcacgcat cgggggctag tacaggctgt gacagaggcc 180

tgagctggaa ctgttgacca ggacacacac atggccatgt ggcctctggg cttcctcaca 240

gcatggtgtc tggattccag gagttggcat cctgagaaac aaccatgcag aagcagccct 300

rtggatcctg gcctggcctt ggagtcaggc agtgtcactc ctgtgccttc taacctgggc 360

ccccgggccc aaggggagga aatggagacc ccacctccca gtggagggaa ggcaaggtcc 420

cactgtgggg gtagcacatg ggatacaccc atgtggctgc cgctggagac gttagtttgc 480

cacacccgtt tcttctacgt gaacatttgc ctgcatctca ccttctaact cctgggtgct 540

gtttgtccat tttcactaca ccaggggccc ccacagtata tgcagaccag gtttcctggc 600

c 601

<210> SEQ ID NO 47
<211> LENGTH: 601
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: amplicon 30-15
<220> FEATURE:
<221> NAME/KEY: allele
<222> LOCATION: (301)..(301)
<223> OTHER INFORMATION: biallelic marker 30-15/54

<400> SEQUENCE: 47

gatgctgaat aagccaggaa gaagatccgg ctaaatgttg gcacattcta aagtctacgt 60

gaggccagtc tgaccctggg aacctccatg aagacatggg cgtggagggt ctgccttttg 120

cagggcccac caggggctca caggaaaggt cgtggaaaat tacaagaaat cttccctctg 180

gcactagcgg gtgaggggaa tggaagccac cgccagacag caccatctcc tcaccctcct 240

gtgaagcaca agactcactt gcagagggaa gagcgcagaa accgtcaccc caggacgctg 300

mggttgaacg agaggaagcg agaatggaga agccctggcc ctggggaaca ggatggaaaa 360

cgcttggctc agctccgtgg ctgcgaagga accggcgcgc tcgcggaggc cacaccccga 420

gacccgagga cacagtgcct gcctgagatg gagccagaaa cattctccac cctttcacgc 480

aagactaaca agggctccat gaaaataaaa ctggaagagc tgaaagagaa gcattctccc 540

tgggtgtgaa accaagaaaa gacacaaagc caaggaaaag ccattgagaa aacacctggc 600

a 601

The invention claimed is:

1. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 2.

2. A purified polynucleotide encoding the polypeptide of SEQ ID NO: 2, or a polynucleotide fully complementary thereto.

3. The polynucleotide according to claim **2**, wherein said polynucleotide comprises the polynucleotide sequence of SEQ ID NO: 1 or a polynucleotide fully complementary thereto.

4. A vector comprising a polynucleotide encoding the polypeptide of SEQ ID NO: 2.

5. A host cell comprising a vector that comprises a polynucleotide encoding the polypeptide of SEQ ID NO: 2.

6. A method of making a polypeptide, said method comprising the steps of culturing a host cell comprising a vector that comprises a polynucleotide encoding the polypeptide of SEQ ID NO: 2 under conditions suitable for the production of a polypeptide comprising SEQ ID NO: 2.

7. The method according to claim **6**, further comprising the step of purifying said polypeptide comprising SEQ ID NO: 2 from the culture.

8. A composition comprising at least one polypeptide comprising the amino acid sequence of SEQ ID NO: 2 and a physiologically acceptable carrier.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,442,519 B2
APPLICATION NO. : 10/519335
DATED : October 28, 2008
INVENTOR(S) : Laurent Cavarec et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 12,
Line 62, ""Phenotype"" should read --"phenotype"--.

Column 14,
Line 2, "such assay s" should read --such assays--.
Line 12, "alter native" should read --alternative--.

Column 16,
Line 2, "ncbi.nim.nih.gov)" should read --ncbi.nlm.nih.gov)--.

Column 17,
Line 47, "substancially the same" should read --substantially the same--.

Column 18,
Line 37, "complementery thereto" should read --complementary thereto--.
Line 43, "complementery thereto" should read --complementary thereto--.
Lines 49-50, "to a polynucleotides" should read --to a polynucleotide--.
Line 63, "NO; 3" should read --NO: 3--.

Column 23,
Line 23, "Accession No. 043526" should read --Accession No. O43526--.

Column 25,
Lines 11-12, "ho momeric" should read --homomeric--.
Line 53, "that (I)" should read --that (i)--.

Column 28,
Line 56, "consisting of 30-2162" should read --consisting of 30-2/62--.

Column 30,
Line 1, "marker 30-7130" should read --marker 30-7/30--.
Line 67, "Human fcetal" should read --Human foetal--.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,442,519 B2
APPLICATION NO. : 10/519335
DATED : October 28, 2008
INVENTOR(S) : Laurent Cavarec et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 31,
Line 33, "SDI-Leu/-Trp and SDI-Leu/-Trp/-His/-Ade" should read
--SD/-Leu/-Trp and SD/-Leu/-Trp/-His/-Ade--.
Line 35, "the He Yeast" should read --the Yeast--.

Column 33,
Line 32, "digestion With EcoRi" should read --digestion with EcoRi--.
Line 61, "pGAD7" should read --pGADT7--.

Column 34,
Line 42, "10 μl" should read --100 μl--.
Line 44, "SDI-Leu/-Trp/-His/-Ade" should read --SD/-Leu/-Trp/-His/-Ade--.

Column 36,
Line 50, "w performed" should read --was performed--.

Column 37,
Lines 19-20, "membrane were then blocked" should read
--membrane was then blocked--.
Line 66, "phsophorylation" should read --phosphorylation--.

Column 39,
Line 9, "phophorylation" should read --phosphorylation--.

Column 40,
Line 17, "1 μd" should read --1 μl--.

Column 45,
Line 57, "10 μmol" should read --10 pmol--.

Column 46,
Line 20, "dassification" should read --classification--.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

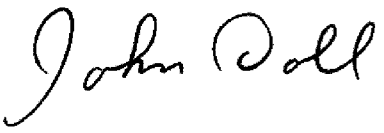
PATENT NO. : 7,442,519 B2
APPLICATION NO. : 10/519335
DATED : October 28, 2008
INVENTOR(S) : Laurent Cavarec et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 50,
Line 64, "for 30-7130" should read --for 30-7/30--.

Signed and Sealed this

Twenty-eighth Day of April, 2009



JOHN DOLL
Acting Director of the United States Patent and Trademark Office