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(54) **Title:** ASSOCIATION OF SNPS IN THE DGCR2 LOCUS AND NEIGHBORING LOCI WITH SCHIZOPHRENIA

(57) **Abstract:** Methods and kits used for determining predisposition and/or diagnosis of schizophrenia, using genotypes in the DGCR2 locus are disclosed. Also disclosed are methods and drugs for treating schizophrenia. Further disclosed are methods and kits useful for prediction of drug responsiveness towards mental disorders drugs, and more specifically towards schizophrenia drugs.

# ASSOCIATION OF SNPS IN THE DGCR2 LOCUS AND NEIGHBORING LOCI WITH SCHIZOPHRENIA

## FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to (i) the use of genetic markers, such as single nucleotide polymorphisms (SNPs), in the DCGR2 locus and neighboring loci for the identification of genes related to and for determining a risk of developing schizophrenia, a complex (e.g., multigenic) disease; (ii) methods of identifying novel drugs for the treatment and/or prevention of schizophrenia; (iii) methods of treating and/or preventing schizophrenia; and (iv) pharmacogenomic methods of determining drug responsiveness in mental disorders, schizophrenia in particular.

***Common and complex disorders have genetic components***

Recent advances in the fields of genetics and molecular biology have allowed identification of forms, or alleles, of human genes, that are involved in genetic diseases. Most of the genetic variations responsible for human diseases identified so far belong to the class of single gene disorders, which are also referred to in the art as Mendelian disorders [Tom Strachan and Andrew P. Read (1996). Human Molecular Genetics. BIOS Scientific Publishers, pp. 61-66]. As the name implies, the development of single gene disorders is determined, or largely influenced, by the alleles of a single gene. The alleles that cause single gene disorders are, in general, highly deleterious to individuals who carry them. Therefore, these alleles and their associated diseases, with some exceptions, tend to be very rare.

Common diseases (e.g. certain mental disorders, various cancers, heart diseases and diabetes), as well as other traits of medical relevance (e.g. individual drug responsiveness), often aggregate in families, suggesting a genetic component. The genetic component of common diseases is further demonstrated by adoption and twin studies, which, for example, implicate genetic factors as major predisposing factors for most psychiatric diseases [Burmeister, M., (1999). Basic concepts in the study of diseases with complex genetics. Biol. Psychiatry 45: 522-532]. However, unlike single gene disorders, these diseases do not follow simple Mendelian inheritance, and their transmission pattern is best explained by models involving several genes, as well as non-genetic (environmental) factors. In order for a specific clinical end-result to be manifested, several different alleles and environmental factors must come together

additively, or in specific combinations. Thus, the contribution of each gene is often small and difficult to detect. In other words, predisposing alleles do not produce the disease in every person who carries them, but rather contribute to susceptibility to the disease. [Lander, E.S. and Schork, N.J. (1994) Genetic dissection of complex traits. Science 265: 2037-2048; Zak, N.B., Pisante-Shalom, A. and Darvasi, A. (2003) Population-based gene discovery in psychiatric diseases. Expert Rev. Neurotherapeutics 3: 51-57].

***Schizophrenia***

Schizophrenia (MIM 181500) is a common psychiatric disease that affects about 1% of the world population. It accounts for about 25% of all mental health costs and schizophrenic patients make up 1/3 of all psychiatric hospital beds [Kaplan, H. R. and Sadock, B. J. (1991). Synopsis of psychiatry: behavioral sciences, clinical psychiatry, Library of Congress Cataloging-in Publication Data]. Schizophrenia is used to describe a cluster of symptoms that typically include "positive" symptoms such as delusions, hallucinations and disordered thinking and "negative" symptoms such as social withdrawal, apathy, and emotional unresponsiveness. This psychiatric disease is considered one of the most devastating of mental illnesses; disease onset is early in a patient's life and its symptoms can be destructive to both patients and their immediate environment. Since genetic and molecular factors have not been identified, schizophrenia is diagnosed by phenotypic symptoms only.

Schizophrenia, like most other psychiatric disorders, is a complex disease that cannot be explained by a single genetic or environmental factor [McGuffin, P., Owen, M. J. and Farmer, A. E. (1995). Genetic basis of schizophrenia. Lancet 346: 678-82]. Although the genes increasing risk for schzophrenia have not been identified, there is strong evidence that schizophrenia has a significant genetic component. While the prevalence of schizophrenia in the general population is around 1%, it increases to 8-12% in the descendants and siblings of affected individuals, and up to 40% when both parents suffer from schizophrenia [Kaplan, H. R. and Sadock, B. J. (1991). Synopsis of psychiatry: behavioral sciences, clinical psychiatry, Library of Congress Cataloging-in Publication Data]. Linkage studies (see below) have provided suggestive evidence for many susceptibility loci, including on chromosome 22, but there has been little success in replication of these findings [Pulver, A. E. (2000). Search for schizophrenia susceptibility genes. *Biol Psychiatry* 47: 221-30].

Association studies, mainly with candidate genes, have also not provided any consistent results.

***Pharmacological treatment of schizophrenia***

Antipsychotic (neuroleptic) medication is the most important part of the treatment regimen for schizophrenic patients. Treatment with antipsychotics has been demonstrated to reduce rates of relapse and re-hospitalizations in a substantial number of patients over many years. [Moller HJ. (2000) State of the art of drug treatment of schizophrenia and the future position of the novel/atypical antipsychotics. World J Biol Psychiatry 1: 204-14; Bridler R, Umbricht D. (2003) Atypical antipsychotics in the treatment of schizophrenia. Swiss Med Wkly 133: 63-76]. Effective medications for schizophrenia have been available since the 1950s, and have revolutionized the treatment of schizophrenic patients by reducing and preventing recurrence of symptoms [Campbell M. et al., 1999 The use of atypical antipsychotics in the management of schizophrenia. Br J Clin Pharmacol 47: 13-22]. Conventional neuroleptics (including haloperidol, chlorpromazine, zuclopenthixol) exert their effect by blocking D2 dopamine receptors in the central nervous system, which results in reduced positive, but not negative, symptoms. However, this strong D2 receptor affinity produces extrapyramidal side-effects (EPS; parkinsonism, restlessness and dystonia) [Alao AO, Malhotra K, Dewan MJ. (2002) Comparing the side effect profile of the atypical antipsychotics. West Afr J Med ;21: 313-5]. In addition, prolonged treatment with these so-called typical antipsychotics is also associated with tardive dyskinesia (repetitive involuntary movements and dystonic movements in various muscle groups) and with increased prolactin secretion (leading to menstrual cycle dysfunction, loss of libido, and mamillary gland swelling). The high incidence of side effects results in relatively low patient compliance, a crucial factor in the treatment of schizophrenia.

In 1973, clozapine, the first "atypical" drug, was introduced. This drug showed excellent antispychotic efficacy in the absence of EPS. However the propensity of clozapine to cause agranulocytosis (a potentially lethal inability to produce white blood cells) led to its withdrawal in many countries and to restrictions on its use in others [Bridler R, Umbricht D. (2003) Atypical antipsychotics in the treatment of schizophrenia. Swiss Med Wkly 133: 63-76]. The high efficacy of clozapine led to the development of clozapine-like compounds without its negative side effects. These are

risperidone, olanzapine, quetiapine and amisulpride. Despite pharmacological and physiological heterogeneity, these atypical antipsychotics share several characteristics. Atypical antipsychotics are at least as effective as conventional antipsychotics in the treatment of positive symptoms, and differ in their ability to ameliorate negative symptoms. Most of these new-generation drugs demonstrate a high affinity for serotonin 5HT2 receptors and weak affinity for dopamine D2 receptors, resulting in less EPS than typical neuroleptics. In addition, atypical medications cause less tardive dyskinesia than do typical antipsychotics, and most do not cause increased prolactin secretion. However, other side effects, such as weight gain, and abnormal glucose regulation, are associated with many of the newer medications. [Bridler R, Umbricht D. (2003) Atypical antipsychotics in the treatment of schizophrenia. Swiss Med Wkly 133: 63-76].

***Need for identification of susceptibility genes***

Despite the clear beneficial effects of antipsychotic medications, all the known treatments for schizophrenia act against the symptoms of the disease and all are associated with side effects of varying severity. There is thus a strong need for new molecules directed against targets which are involved in the causal mechanisms of the disease. Therefore, tools facilitating the discovery and characterization of these targets are necessary and useful. Particularly, identification of genes involved in schizophrenia will allow understanding of the etiology of schizophrenia and could lead to the development of drugs and medications directed against the cause of the disease, rather than its symptoms.

In addition, up to 30% of chronic schizophrenia patients are defined as treatment-refractory. They show insufficient or complete lack of response to antipsychotic treatment. This is true for both typical and atypical agents (with the exception of clozapine). Identification of genes affecting schizophrenia may offer treatment for patients who are at present unable to be helped.

Moreover, identification of disease associated genes will allow the development of new methods for detecting susceptibility to schizophrenia, as well as for preventing the development of the disease. Early identification of subjects at risk of developing schizophrenia would enable administration of early prophylactic, (pharmacological and environmental) treatment. Knowledge of genetic variations in

causative genes will enable the development of pharmacogenomics, in which individualized treatment is genotype-specific.

***Description of the region of the associated gene: del22q11***

Velocardiofacial syndrome (VCFS [MIM 192430]) is associated with a micro-deletion in chromosome 22q11. The *del22q11* syndrome is the most common microdeletion syndrome, occurring in 1 out of every 4,000 live births. The symptoms of *del22q11* are many and diverse and they include cardiovascular, thymic, parathyroid and craniofacial abnormalities. In addition there is an increased prevalence of behavioral defects, such as deficits of learning and memory, speech and language development, attention-deficit disorder, and psychiatric diseases, especially schizophrenia. Some studies with VCFS patients have found that 20-30% of them developed schizophrenia [Murphy, K. C., et al., (1999). High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Arch Gen Psychiatry* 56: 940-5]. In addition, schizophrenia patients have an increased rate of the 22q11 micro-deletion compared to the general population [Karayiorgou, M., et al. (1995). Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. *Proc Natl Acad Sci U S A* 92: 7612-6; Usiskin, S. I., et al., (1999). Velocardiofacial syndrome in childhood-onset schizophrenia. *J Am Acad Child Adolesc Psychiatry* 38: 1536-43]. These findings suggest that the1.5-3 Mb 22q11 deletion region contains one or more genes that contribute to the risk of schizophrenia.

Mouse models provide additional data that supports linkage of the *del22q11* syndrome critical region with schizophrenia and may further define the chromosomal area involved [Lindsay, E. A. (2001). Chromosomal microdeletions: dissecting del22q11 syndrome. *Nat Rev Genet* 2: 858-68; Paylor, R., et al.. (2001). Mice deleted for the DiGeorge/velocardiofacial syndrome region show abnormal sensorimotor gating and learning and memory impairments. *Hum Mol Genet* 10: 2645-50]. The gene content of the human 22q11 deletion region is highly conserved and syntenous to a region of mouse chromosome 16. A mouse deletion model, *Df1*, has been generated with a 1 Mb deletion that encompasses about half of the approximately 30 genes which are removed in the majority of *del22q11* syndrome patients (with the ~3 Mb deletion). Mice heterozygously deleted for the ~1 Mb interval have sensorimotor gating, learning and memory impairments. The deficit in senorimotor gating is manifested as a decrease in pre-pulse inhibition of the acoustic startle response. This

is of particular significance, since patients with schizophrenia show similar deficits [Paylor, R., et al.. (2001). Mice deleted for the DiGeorge/velocardiofacial syndrome region show abnormal sensorimotor gating and learning and memory impairments. *Hum Mol Genet* 10: 2645-50]. This suggests that genes contained within the approximately 1 Mb deleted in the *Df1* mice (which are also absent in 8% of *del22q11* patients suffering from a 1.5 Mb deletion) are good candidates for schizophrenia predisposing genes.

One of these genes is DGCR2 (DiGeorge syndrome critical region gene 2). This gene encodes a putative adhesion receptor protein which could play a role in neural crest cells migration, a process which has been proposed to be altered in DiGeorge syndrome. Importantly, the mouse ortholog of DGCR2 (Dgcr2; previously sez12) is a seizure-related gene, expression of which is transiently down-regulated in the mouse brain by injection of pentylenetetrazol (a seizure-inducer) [Kajiwara K. et al., (1996) Cloning of SEZ-12 encoding seizure-related and membrane-bound adhesion protein. Biochem Biophys Res Commun 222: 144-8].

***Genetic strategies for the identification of disease-causing genes***

The traditional genetic strategy for the identification of disease-causing genes is based on linkage analysis. This approach employs family samples to compare the segregation patterns of mapped genetic markers with that of the disease state. If any marker variant tends to be inherited together with the disease in question, this implies that the marker and the gene responsible for the disease reside in physical proximity to each other [Tom Strachan and Andrew P. Read (1996). Human Molecular Genetics. BIOS Scientific Publishers, pp. 320-324]. Linkage analysis has been very successful in mapping hundreds of Mendelian disease genes. In addition, several large-effect genes involved in polygenic diseases have been detected by this approach. These include Apolipoprotein E (ApoE) in Alzheimer's disease [Hutton M, Perez-Tur J, Hardy J. (1998) Genetics of Alzheimer's disease. Essays Biochem 33:117-131] and human leukocyte antigen (HLA) in type I diabetes [Concannon P. et al., (1998) A second-generation screen of the human genome for susceptibility to insulin-dependent diabetes mellitus. Nat Genet 19:292-6]. In the above cases, despite the polygenic nature of the disease, the detected genes account for a large proportion of the disease risk. However, most genes affecting complex diseases are genes with smaller effects on phenotype that are not likely to be "captured" by linkage analysis [reviewed in Zak,

N.B., Pisante-Shalom, A. and Darvasi, A. (2003) Population-based gene discovery in psychiatric diseases. Expert Rev. Neurotherapeutics 3: 51-57]. Furthermore, linkage analysis is limited by its reliance on the choice of a genetic model suitable for each studied trait, whereas for complex diseases no probable disease model can be assumed, and model-independent analysis methods are required [Lander, E.S. and Schork, N.J. (1994) Genetic dissection of complex traits. Science 265: 2037-2048].

An alternative, model-independent, approach is that of allelic association which tests the increased or decreased occurrence of a marker allele in correlation with a disease trait. Association studies may be family-based, such as in the transmission disequililbrium test (TDT), in which trios of affected individual and their two parents are studied [Spielman RS, McGinnis RE, and Ewens WJ. (1993) Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes mellitus (IDDM). Am J Hum Genet 52: 506-16]. Alternatively, association studies may be population based, as in case-control studies, which compare unrelated, affected individuals and unrelated, unaffected controls. In the case-control design, care must be taken to avoid false positives arising as an artifact of population stratification [Lander, E.S. and Schork, N.J. (1994) Genetic dissection of complex traits. Science 265: 2037-2048]. Since such false positives typically arise as a result of inadequate ethnic matching of cases and controls, the use of a homogeneous population virtually eliminates artefactual associations caused by this factor [Zak NB, Shifman S, Shalom A, Darvasi A. (2001) Population-based gene discovery in the post-genomic era. Drug Discov Today 6 :1111-1115]. In association analyses, polymorphic markers are tested for differences in allele frequencies between cases and controls. Enrichment of one allele form in diseased individuals is taken as evidence of association.

There are several advantages to employing the association strategy, particularly in the case-control design, for uncovering genes of small effect. First, association studies offer greater statistical power than linkage analysis for uncovering such genes [Risch N, Merikangas K. (1996) The future of genetic studies of complex human diseases. Science 273: 1516-7]. In addition, the greater ease of matching cases to unrelated controls without the necessity of enrolling additional family members makes the case-control design simpler and more economically feasable than family-based approaches. Finally, population-based association studies have a greater potential than

family-based studies for accurate mapping and identification of the actual disease-linked gene confined within a narrow chromosomal region.

## SUMMARY OF THE INVENTION

According to one aspect of the present invention there is provided a method of determining predisposition of a subject to develop schizophrenia. The method according to this aspect of the present invention comprises determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, wherein the at least one genotype is associated with schizophrenia, thereby determining the predisposition of the subject to developing schizophrenia.

According to another aspect of the present invention there is provided a kit for determining a predisposition of a subject to develop schizophrenia. The kit according to this aspect of the present invention comprises a packaging material packaging at least one reagent, the at least one reagent being for determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, wherein the genotype is associated with schizophrenia. The kit further comprises a notification in or on the packaging material identifying the kit for use in determining a predisposition of developing schizophrenia. Preferably, the notification also provides for instructions of using the kit in determining a predisposition of developing schizophrenia.

According to yet another aspect of the present invention there is provided a method of assisting in diagnosing schizophrenia in a subject in need thereof. The method according to this aspect of the present invention comprises determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, wherein the at least one genotype is associated with schizophrenia, thereby assisting in diagnosing schizophrenia in the subject.

According to still another aspect of the present invention there is provided a kit for assisting in diagnosing schizophrenia in a subject in need thereof. The kit

according to this aspect of the present invention comprises a packaging material packaging at least one reagent, the at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, twherein the genotype is associated with schizophrenia. The kit further comprises a notification in or on the packaging material identifying the kit for use in assisting in diagnosing schizophrenia in a subject. Preferably, the notification also provides for instructions of using the kit in assisting in diagnosing schizophrenia of a subject.

According to yet a further aspect of the present invention there is provided a method of determining a predisposition to develop schizophrenia in a male subject. The method according to this aspect of the present invention comprises determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, the wherein the at least one genotype is associated with schizophrenia in males in higher association than in females, thereby determining the predisposition of the male subject of developing schizophrenia.

According to still a further aspect of the present invention there is provided a kit for determining a predisposition to develop schizophrenia in a male subject. The kit, according to this aspect of the present invention comprises a packaging material packaging at least one reagent, the at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, twherein the genotype is associated with schizophrenia in males in higher association than in females. The kit further comprises a notification in or on the packaging material, the notification identifying the kit for use in determining a predisposition of a male subject of developing schizophrenia. Preferably, the notification also provides for instructions of using the kit in determining the predisposition of a male subject of developing schizophrenia.

According to still a further aspect of the present invention there is provided method of assisting in diagnosing schizophrenia in a male subject in need thereof. The method according to this aspect of the present invention comprises determining a presence in a homozygous or heterozygous form, or an absence, of at least one

genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, the wherein the at least one genotype is associated with schizophrenia in males in higher association than in females, thereby assisting in diagnosing schizophrenia in the male subject.

According to still a further aspect of the present invention there is provided kit for assisting in diagnosing schizophrenia in a male subject in need thereof. The kit, according to this aspect of the present invention comprises a packaging material packaging at least one reagent, the at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, twherein the genotype is associated with schizophrenia in males in higher association than in females. The kit further comprises a notification in or on the packaging material, the notification identifying the kit for use in assisting in diagnosing schizophrenia in a male subject. Preferably, the notification also provides for instructions of using the kit in assisting in diagnosing schizophrenia of a male subject.

According to still a further aspect of the present invention there is provided a method of predicting drug responsiveness of a subject having schizophrenia to a schizophrenia drug. The method according to this aspect of the present invention comprises determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, the wherein the at least one genotype is associated with drug responsiveness to the drug, thereby predicting drug responsiveness of the subject to the drug.

According to still a further aspect of the present invention there is provided a kit for predicting drug responsiveness of a subject having schizophrenia to a schizophrenia drug. The kit, according to this aspect of the present invention comprises a packaging material packaging at least one reagent, the at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, twherein the genotype is associated with schizophrenia. The kit further comprises a notification in or on the packaging material, the notification identifying the kit for use in predicting drug responsiveness

of a subject having schizophrenia to the drug. Preferably, the notification also provides for instructions of using the kit in assisting in predicting drug responsiveness of a subject having schizophrenia to the drug.

According to still a further aspect of the present invention there is provided a method of predicting drug responsiveness of a subject having a given mental disorder to a mental disorder drug. The method according to this aspect of the present invention comprises determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, the wherein the at least one genotype is associated with drug responsiveness to the drug in at least one mental disorder, thereby predicting drug responsiveness of the subject having the given mental disorder to the drug.

According to still a further aspect of the present invention there is provided a kit for predicting drug responsiveness of a subject having a given mental disorder to a mental disorder drug. The kit, according to this aspect of the present invention comprises a packaging material packaging at least one reagent, the at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, twherein the genotype is associated with drug responsiveness to the drug in at least one mental disorder. The kit further comprises a notification in or on the packaging material, the notification identifying the kit for use in predicting drug responsiveness of a subject having the given mental disorder to the drug. Preferably, the notification also provides for instructions of using the kit in assisting in predicting drug responsiveness of a subject having the given mental disorder to the drug.

According to still a further aspect of the present invention there is provided a method of identifying a genetic association with, or a genetic cause to, varying drug responsiveness to a schizophrenia drug. The method according to this aspect of the present invention comprises determining via a population association study an association between a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, and responsiveness or non-responsiveness to the schizophrenia drug, thereby identifying a genetic

association with, or a genetic cause to, the varying drug responsiveness to the schizophrenia drug.

According to still a further aspect of the present invention there is provided a kit for identifying a genetic association with, or a genetic cause to, varying drug responsiveness to a schizophrenia drug. The kit, according to this aspect of the present invention comprises a packaging material packaging at least one reagent, the at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, twherein the genotype is associated with schizophrenia. The kit further comprises a notification in or on the packaging material, the notification identifying the kit for use in identifying a genetic association with, or a genetic cause to, varying drug responsiveness to the drug. Preferably, the notification also provides for instructions of using the kit in identifying a genetic association with, or a genetic cause to, varying drug responsiveness to the drug.

According to still a further aspect of the present invention there is provided a method of identifying a genetic association with, or a genetic cause to, varying drug responsiveness to a mental disorder drug. The method according to this aspect of the present invention comprises determining via a population association study an association between a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, the neighboring loci in linkage disequilibrium with the DGCR2 locus, and responsiveness or non-responsiveness to the mental disorder drug, thereby identifying a genetic association with, or a genetic cause to, the varying drug responsiveness to the mental disorder drug.

According to still a further aspect of the present invention there is provided a kit for identifying a genetic association with, or a genetic cause to, varying drug responsiveness of a subject having a given mental disorder to a mental disorder drug. The kit, according to this aspect of the present invention comprises a packaging material packaging at least one reagent, the at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, twherein the genotype is associated with drug

responsiveness to the drug in at least one mental disorder. The kit further comprises a notification in or on the packaging material, the notification identifying the kit for use in identifying a genetic association with, or a genetic cause to, varying drug responsiveness of a subject having the given mental disorder to the drug. Preferably, the notification also provides for instructions of using the kit in identifying a genetic association with, or a genetic cause to, varying drug responsiveness of a subject having the given mental disorder to the drug.

According to further features in preferred embodiments of the invention described below, the schizophrenia drug is selected from the group consisting of zuclopenthixol and olanzapine.

According to still further features in the described preferred embodiments the mental disorder drug is selected from the group consisting thioridazine, clozapine, haloperidol, fluphenazine, cholrpromazine, risperidone, levomepromazine, perhenazine, chlorprothixene, pimozide, sulpiride, olanzapine, zuclopenthixol, amitriptyline, imipramine, clomipramine, desipramine, doxepin, mianserin, maprotiline, phenelzine, fluoxetine, trazodone, fluvoxamine, sertraline, paroxetine, reboxetine, citalopram, nefazodone, venlafoxine, lithium salts, carbamazapine, valproic acid, and clonazepam.

According to still further features in the described preferred embodiments the mental disorder is selected from the group consisting of schizophrenia, schizoaffective disorder, bipolar disorder, depression, obsessive compulsive disorder, panic disorder, agoraphobia, specific phobia, social phobia, post-traumatic stress disorder, pain disorder, anxiety, somatization disorder, anorexia nervosa, bulimia, and nervosa.

According to still further features in the described preferred embodiments at least one genotype in the DGCR2 locus is a guanine nucleotide – and/or an adenosine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13.

According to still further features in the described preferred embodiments at least one genotype in the DGCR2 locus is a cytosine nucleotide – and/or a thymine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1.

According to still further features in the described preferred embodiments at least one genotype in the DGCR2 locus is an adenosine nucleotide – and/or a guanine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

According to still further features in the described preferred embodiments at least one genotype in the DGCR2 locus is an allelic haplotype comprising at least two of: a guanine nucleotide – and/or an adenosine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13; a cytosine nucleotide – and/or a thymine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and an adenosine nucleotide – and/or a guanine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

According to still further features in the described preferred embodiments at least one genotype in the DGCR2 locus is an allelic haplotype including at least one SNP selected from the group consisting of: a guanine nucleotide – and/or an adenosine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13; a cytosine nucleotide – and/or a thymine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; an adenosine nucleotide – and/or a guanine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5; and/or one of the following SNPs in the COMT locus: a cytosine nucleotide - and/or a thymine nucleotide - containing allele of SNP rs737865 set forth in SEQ ID NO:21; a guanine nucleotide - and/or an adenosine nucleotide containing allele of SNP rs4680 set forth in SEQ ID NO:22; and a guanine nucleotide - and/or an adenosine nucleotide containing allele of SNP rs165599 set forth in SEQ ID NO:23.

According to still further features in the described preferred embodiments at least one reagent is selected from the group consisting of at least one oligonucleotide, at least one antibody and a DNA chip.

According to still further features in the described preferred embodiments the at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, wherein the at least one oligonucleotide can differentiate between polymorphs of the SNP via differential hybridization.

According to still further features in the described preferred embodiments at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, wherein the at least one oligonucleotide can differentiate between polymorphs of the SNP via differential hybridization.

According to still further features in the described preferred embodiments at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, wherein the at least one oligonucleotide can differentiate between polymorphs of the SNP via a differential template dependent primer extension reaction or a differential template dependent ligation reaction.

According to still further features in the described preferred embodiments at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, wherein the at least one oligonucleotide can differentiate between polymorphs of the SNP via a differential template dependent primer extension reaction or a differential template dependent ligation reaction.

According to still further features in the described preferred embodiments at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, wherein the the at least one oligonucleotide can be used to amplify polymorphs of the SNP via an amplification reaction.

According to still further features in the described preferred embodiments at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, wherein the at least one oligonucleotide can be used to amplify polymorphs of the SNP via an amplification reaction.

According to still further features in the described preferred embodiments at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having an SNP rs2072123, wherein the the at least one antibody can differentiate between polymorphs of the DGCR2 protein via differential antibody interaction.

According to still further features in the described preferred embodiments at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having a non-synonymous SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, wherein the the at least one antibody can differentiate between polymorphs of the DGCR2 protein via differential antibody interaction.

According to still further features in the described preferred embodiments the DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, wherein the at least one oligonucleotide can differentiate between polymorphs of the SNP via differential hybridization.

According to still further features in the described preferred embodiments the DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, wherein the at least one oligonucleotide can differentiate between polymorphs of the SNP via differential hybridization.

According to still further features in the described preferred embodiments at least one reagent is designed for use in a detection method selected from the group consisting of a signal amplification method, a direct detection method and detection of at least one sequence change.

According to still further features in the described preferred embodiments the signal amplification method amplifies a molecule selected from the group consisting of a DNA molecule and an RNA molecule.

According to still further features in the described preferred embodiments the signal amplification method is selected from the group consisting of PCR, LCR (LAR), Self-Sustained Synthetic Reaction (3SR/NASBA) and Q-Beta (Qβ) Replicase reaction.

According to still further features in the described preferred embodiments the direct detection method is selected from the group consisting of a cycling probe reaction (CPR) and a branched DNA analysis.

According to still further features in the described preferred embodiments detection of at least one sequence change is effected by a method selected from the group consisting of the Allele Refractory Mutation System (ARMS), restriction fragment length polymorphism (RFLP analysis), primer extension, mini-sequencing, Pyrosequencing™, Competitive Oligonucleotide Single Base Extension (COSBE), Dynamic Allele Specific Hybridization (DASH), heteroduplex/homoduplex resolution

by Denaturing High Performance Liquid Chromatography (DHPLC), heteroduplex/homoduplex resolution by enzymatic cleavage, capillary electrophoresis - Single Strand Conformation Polymorphism (CE- SSCP), Conformation Sensitive Gel Electrophoresis (CSGE), Allele specific ligation (OLA), Matrix-Assisted Laser Desorption-Ionization (MALDI) time-of-flight (TOF) Mass Spectrometry (MS), Fluorescence Resonance Energy Transfer (FRET), Fluorescence polarization, TaqMan (5' exonuclease assay), Molecular beacons, Template-directed Dye Incorporation (TDI), Peptide Nucleic Acid (PNA) hybridization probes, Invader™ assay, Padlock probes, Light-up probes, Real Time PCR, and Kinetic PCR.

According to still further features in the described preferred embodiments the at least one reagent is designed for use in an immunological detection method for a DGCR2 protein encoded by the DGCR2 locus.

According to still further features in the described preferred embodiments the immunological detection method is selected from the group consisting of a radio-immunoassay (RIA), an enzyme linked immunosorbent assay (ELISA), a western blot, an immunohistochemical analysis, and fluorescence activated cell sorting (FACS).

According to still a further aspect of the present invention there is provided a method of identifying novel drugs for treatment of schizophrenia. The method according to this aspect of the present invention comprises incubating an integral membrane protein DGCR2 or any active portion thereof or cells expressing integral membrane protein DGCR2 or any active portion thereof with potential drugs and selecting for at least one drug of the potential drugs that modulates integral membrane protein DGCR2 activity or expression, thereby identifying novel drugs for treatment of schizophrenia.

According to still a further aspect of the present invention there is provided a method of treating schizophrenia. The method according to this aspect of the present invention comprises administering to a subject in need thereof a therapeutically effective amount of a drug for schizophrenia, the drug for schizophrenia having been identified capable of modulating integral membrane protein DGCR2 activity or expression using the method described hereinabove.

According to still further features in the described preferred embodiments the at least one drug of the potential drugs is selected from the group consisting of a peptide, a polynucleotide and a small molecule.

According to still further features in the described preferred embodiments the polynucleotide is selected from the group consisting of an antisense oligonucleotide, an siRNA, a ribozymes and a DNAzyme.

According to still further features in the described preferred embodiments the peptide is selected from the group consisting of a small peptide, a polypeptide and an antibody.

According to still a further aspect of the present invention there is provided a method of treating and/or preventing schizophrenia. The method according to this aspect of the present invention comprises administering to a subject in need thereof a therapeutically effective amount of at least one agent capable of modulating DGCR2 protein expression or activity.

According to still further features in the described preferred embodiments the at least one agent is selected from the group consisting of an anti-DGCR2 antibody, a polynucleotide encoding an intracellular anti-DGCR2 antibody, an anti-DGCR2 antisense molecule, an anti-DGCR2 siRNA, an anti-DGCR2 ribozyme, an anti-DGCR2 DNAzyme, and a DGCR2 inhibitor.

According to still a further aspect of the present invention there is provided a method of treating and/or preventing schizophrenia. The method according to this aspect of the present invention comprises administering to a subject in need thereof a therapeutically effective amount of recombinant integral membrane protein DGCR2 or any active portion thereof.

The present invention successfully addresses the shortcomings of the presently known configurations by providing methods and kits useful for predisposition, diagnosis and treatment of schizophrenia.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The following terms and phrases shall have the following meaning:

As used herein, the term "predisposition" refers to a situation of susceptibility to develop a disorder or disease. An individual with a predisposition to a disorder or disease is more likely than an individual without the predisposition to the disorder or disease to develop the disorder or disease.

Methods of "determining a predisposition" of an individual to a disorder or disease are used in genetic counseling, especially prior to making a decision to conceive a child. Also, application of methods for detecting genotypes of SNPs in the DCGR2 locus as described herein can be applied to the parents of an individual with schizophrenia. The transmission of the polymorphism refers to the distribution of a DCGR2 polymorphic allele from a parent to an offspring. When a parent is heterozygous for a polymorphism, for example, the guanine/adenosine (G/A) polymorphism of SNP rs807759 set forth in SEQ ID NO:13, the likelihood that the guanine allele will be transmitted is usually the same as the likelihood that the adenosine allele will be transmitted to the offspring. A genetic locus that is linked to another locus shows similar allelic transmission.

The term "polymorphism" refers to the occurrence of two or more genetically determined variant forms (alleles) of a particular nucleic acid, at a frequency where the rarer (or rarest) form could not be maintained by recurrent mutation alone. A single nucleotide polymorphism (SNP) results from a single base difference between related alleles at the same genetic locus. Exemplary nucleotide polymorphisms include the G/A polymorphism of SNP rs807759 set forth in SEQ ID NO:13.

The term "homozygous" refers to an individual having two identical alleles of a certain polymorphism. A non-limiting example is an individual having the GG genotype of SNP rs807759. This individual is referred to as a homozygote for this SNP.

The term "heterozygous" refers to an individual having two different alleles of a certain polymorphism. For example, an individual having the A/G genotype of SNP rs807759 is referred as a heterozygote individual for this SNP.

The phrase "absence of genotype" is used herein to describe the negative result of a specific genotype determination test. For example, if the genotype determination test is suitable for the identification of guanine nucleotide – containing allele of SNP rs807759 set forth in SEQ ID NO:13, and the individual on which the test is performed

is homozygote for the adenosine nucleotide - containing allele of SNP rs807759, then the result of the test will be "absence of genotype".

SNPs may be detectable at the protein level if the nucleotide change is in the coding sequence and encodes a different amino acid residue, creating two "polymorphs" of the protein. A non-limiting example of an amino acid change is the Val/Ala polymorphism at position 473 of the DGCR2 protein set forth in SEQ ID NO:24, which results from the C/T polymorphism of SNP rs2072123 set forth in SEQ ID NO:1 in the DGCR2 gene.

As used herein the phrase "DGCR2 locus" refers to the location of a DNA stretch in the human genome corresponding to a gene coding for the DGCR2 protein.

The phrase "neighboring loci" is used herein to describe DNA sequences (either genes or intergene sequences) that are in close vicinity of the DGCR2 locus and that include other SNPs that are in linkage disequilibrium with SNPs in the DGCR2 locus.

The phrase "linkage disequilibrium" (LD) is used to describe the statistical correlation between two neighboring polymorphic genotypes. Typically, LD refers to the correlation between the alleles of a random gamete at the two loci, assuming Hardy-Weinberg equilibrium (statistical independence) between gametes. LD is quantified with either Lewontin's parameter of association (D') or with Pearson correlation coefficient (r) [Devlin B, Risch N. (1995). A comparison of linkage disequilibrium measures for fine-scale mapping. Genomics. 29: 311-322.]. Two loci with a LD value of 1 are said to be in complete LD. At the other extreme, two loci with a LD value of 0 are termed to be in linkage equilibrium. Linkage disequilibrium is calculated following the application of the expectation maximization algorithm (EM) for the estimation of haplotype frequencies [Slatkin M, Excoffier L. (1996). Testing for linkage disequilibrium in genotypic data using the Expectation-Maximization algorithm. Heredity. 76: 377-83].

The phrase "genetic association" refers to a linkage between certain genetic markers such as SNPs, di-nucleotide or tri-nucleotide repeats and the like, with a certain phenotype such as disease, trait, drug responsiveness and the like.

The phrase "genetic cause" refers to the genetic basis of a phenomenon such as a disease or disorder or varying responsiveness to a drug. The genetic make-up of an

individual determines the individual various traits, including individual's risk of developing a disease and the response exerted in an individual by a specific drug.

The phrase "drug responsiveness" is used herein in reference to genotypes in the DGCR2 locus that determine the specific response an individual has to a specific drug. The response to the drug can be high- or low-efficiency, no-effect or adverse-effects. The knowledge of the specific genotype which predicts drug responsiveness, can be applied to dosing and/or drug selection, avoiding adverse reactions or therapeutic failure and thus can enhance therapeutic or prophylactic efficiency when treating a subject.

The phrase "mental disorder" refers to any disorder affecting an individual behavior, which has a central nervous system etiology.

The term "treating" refers to inhibiting or arresting the development of a disease, disorder or condition and/or causing the reduction, remission, or regression of a disease, disorder or condition. Those of skill in the art will understand that various methodologies and assays can be used to assess the development of a disease, disorder or condition, and similarly, various methodologies and assays may be used to assess the reduction, remission or regression of a disease, disorder or condition.

As used herein, the term "preventing" refers to keeping a disease, disorder or condition from occurring in a subject who may be at risk for the disease, but has not yet been diagnosed as having the disease.

As used herein, a "subject in need" refers to an individual who has been diagnosed with or is suspected of having a disease, disorder or condition, or who is predisposed to a disease, disorder or condition. Those of skill in the art will understand that a variety of methods may be used to determine a subject at risk for a disease, and that whether a subject is at risk for a disease, will depend on a variety of factors known to those of skill in the art, including genetic make-up of the subject, age, body weight, sex, diet, general health, occupation, exposure to environmental conditions, marital status, familial history and the like.

As used herein, "administering to a subject" refers to means for providing a compound that modulates DGCR2 activity and/or expression to a patient, using any suitable route, e.g., oral, sublingual intravenous, subcutaneous, transcutaneous, intramuscular, intracutaneous, intrathecal, epidural, intraoccular, intracranial, inhalation, rectal, vaginal, and the like administration. Administration of compounds

in the form of creams, lotions, tablets, capsules, pellets, dispersible powders, granules, suppositories, syrups, elixirs, lozenges, injectable solutions, sterile aqueous or non-aqueous solutions, suspensions or emulsions, patches, and the like, is also contemplated. The active ingredients may be compounded with non-toxic, pharmaceutically acceptable carriers including, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, dextrans, and the like.

As used herein, the phrase "therapeutically effective amount", when used in reference to the invention methods employing compounds that modulate DGCR2 activity and/or expression, refers to a dose of compound sufficient to provide circulating concentrations high enough to impart a beneficial effect on the recipient thereof. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated, the severity of the disorder, the activity of the specific compound used, the route of administration, the rate of clearance of the specific compound, the duration of treatment, the drugs used in combination or coincident with the specific compound, the age, body weight, sex, diet and general health of the patient, and like factors well known in the medical arts and sciences. Dosage levels typically fall in the range of about 0.001 up to 100 mg/kg/day; with levels in the range of about 0.05 up to 10 mg/kg/day being preferred.

The term "kit" refers to the combination of packaging material, reagents and a notification of use. The kit may be approved by a regulatory agency, such as the FDA, for the use identified in the notification. The notification may also include instructions to use.

The term "packaging material" refers to paper, plastic, foil, foamed substances and other materials commonly used in the packaging of chemical reagents into kits, in the form of tubes, containers, holders, wrappers, etc.

The term "notification" refers to the print, in any language, identifying the use of a kit and/or instructions of how to use the kit for that use.

As used herein the phrase "active portion" refers to any portion of the protein that participates in protein catalytic activity, ligand binding, correct protein folding or protein membrane anchoring.

As used herein the phrase "agent capable of modulating DGCR2 protein expression or activity" refers to any agent that can modulate transcription of the gene,

translation of the transcript and/or post-translational modification of the protein or any agent that is capable of modulating protein catalytic activity, ligand binding to the protein, protein folding or protein membrane anchoring.

## DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is of (i) the use of SNPs in the DGCR2 locus and neighboring loci for the identification of genes related to, and for determining a risk of developing schizophrenia; (ii) methods of identifying novel drugs for the treatment and/or prevention of schizophrenia; (iii) methods of treating and/or preventing schizophrenia; and (iv) pharmacogenomic methods of determining drug responsiveness in mental disorders, schizophrenia in particular.

The principles and operation of the methods, kits and drugs according to the present invention may be better understood with reference to the accompanying descriptions and examples.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Common diseases such as mental disorders, various cancers and heart diseases often aggregate in families, suggesting that there is a genetic component to the disease. However, such diseases, as well as individual drug responsiveness, are often due to the combined action of multiple genes, as well as environmental factors. The genetics of complex diseases is therefore more complicated than that of Mendelian diseases, since predisposing alleles do not produce the disease in every person who carries them, but rather cause increased susceptibility to the disease.

While reducing the present invention to practice it was uncovered that certain genotypes (specific alleles of single nucleotide polymorphysms, SNPs) in the DGCR2 locus and SNPs in neighboring loci, which are in linkage disequilibrium with SNPs rs807759, rs2072123 and rs2073776 of the DGCR2 locus, are highly and significantly associated with schizophrenia, as is further detailed and exemplified below.

Table 1 below summarizes the results of this study:

*Table 1*
*Association of DGCR2 genotypes with schizophrenia*

| Allele/ Genotype/ Haplotype | Studied group | Increased predisposition |
|---|---|---|
| Rs807759 G allele | All; Male | |
| Rs807759 GG genotype | All; Male; Female | x2.02 (All); x2.33 (Male); x1.67 (Female) |
| Rs2072123 C allele | All; Male | |
| Rs2072123 CC genotype | All; Male | x1.66 (All); x1.97 (Male) |
| Rs2073776 A allele | All; Male; Female | |
| Rs2073776 AA genotype | All; Male | x2.04 (All); x2.3 (Male); x1.73 (Female) |
| Rs807759/rs2072123/rs2073776 GCA haplotype | All; Male | |
| Rs807759/rs2072123/rs2073776 GG-CC-AA genotype | All; Male | x2.12 (All); x2.49 (Male) |
| Rs807759/rs2072123/rs2073776 ATG haplotype (protective) | All; Male * | |
| Rs807759/rs2072123/rs2073776/ rs737865/rs4680/rs165599 GCACGG haplotype | All; Male | |
| Rs807759/rs2072123/rs2073776/ rs737865/rs4680/rs165599 GG-CC-AA-CC-GG-GG genotype | All; Male | x5.54 (All); x6.96 (Male) |
| Rs807759/rs2072123/rs2073776/ rs737865/rs4680/rs165599 ATGTAA haplotype (protective) | All; Male * | |

Studied group of schizophrenia, associated with genotypes of the DGCR2 locus. The increased predisposition probability is the genotype relative risk (GRR) of the homozygous risk genotype over the homozygous protective genotype. All = males and females. * Inverse association.

Further while reducing the present invention to practice, it was uncovered that that genotypes of SNPs in the DGCR2 locus are associated with drug responsiveness towards schizophrenia drugs.

Based on these findings, the present invention discloses methods of predicting, preventing and treating schizophrenia.

## *PREDISPOSITION TO SCHIZOPHRENIA*

Velocardiofacial syndrome (VCFS [MIM 192430]) is associated with increased incidence of schizophrenia [Murphy, K. C., et al., (1999). High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Arch Gen Psychiatry* 56: 940-5] is caused by a micro-deletion in chromosome 22q11. DGCR2 (DiGeorge syndrome critical region gene 2), is a gene contained within the *del22q11* region. This gene encodes a putative adhesion receptor protein which could play a role in neural

crest cell migration and is a seizure-related gene in mouse, [Kajiwara K. et al., (1996) Cloning of SEZ-12 encoding seizure-related and membrane-bound adhesion protein. Biochem Biophys Res Commun 222: 144-8]. The present invention is the first to link DGCR2 with schizophrenia. It has established a strong and statistically significant association between genotypes in the DGCR2 locus and increased risk to develop schizophrenia.

More specifically, the inventors of the present invention have uncovered that the G allele of SNP rs807759 set forth in SEQ ID NO:13, the C allele of SNP rs2072123 set forth in SEQ ID NO:1 and the A allele of SNP rs2073776 set forth in SEQ ID NO:5 are highly and significantly associated with schizophrenia. As is further described in Example 1 of the Examples section that follows and in Table 1 hereinabove, individuals homozygote to the risk DGCR2 genotypes of SNPs rs807759, rs2072123 and rs2073776 in DGCR2 have increased predisposition of x2.02, x1.66 and x2.04, respectively, compared to individuals having the protective genotypes of these DGCR2 SNPs. Moreover, the increased predisposition to schizophrenia in individuals having the GG-CC-AA genotype of SNPs rs807759, rs2072123 and rs2073776 is 2.12-fold higher than in individuals having the protective genotype (AA-TT-GG). Furthermore, individuals carrying the GG-CC-AA-CC-GG-GG risk genotype in SNPs rs807759, rs2072123, rs2073776, rs737865, rs4680 and rs165599 of the DGCR2 and COMT genes are in 5.5-fold increased risk to develop schizophrenia over individuals carrying the protective genotype. Therefore, these results suggest the use of SNPs in the DGCR2 locus and any SNP in linkage disequilibrium with SNPs rs807759, rs2072123 and rs2073776 for the determination of a predisposition to schizophrenia in a subject.

Thus, according to one aspect of the present invention there is provided a method of determining a predisposition of a subject to develop schizophrenia. The method according to this aspect of the present invention comprises determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, the wherein the at least one genotype is associated with schizophrenia, thereby determining the predisposition of the subject of developing schizophrenia.

According to another aspect of the present invention there is provided a kit for determining a predisposition of a subject to develop schizophrenia. The kit according to this aspect of the present invention comprises a packaging material packaging at least one reagent, the at least one reagent is for determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, twherein the genotype is associated with schizophrenia. The kit further comprises a notification in or on the packaging material identifying the kit for use in determining a predisposition of developing schizophrenia. Preferably, the notification also provides for instructions of using the kit in determining a predisposition of developing schizophrenia.

Genotypes in the DGCR2 locus can also assist in the diagnosis of schizophrenia. Thus, according to yet another aspect of the present invention there is provided a method of assisting in diagnosing schizophrenia in a subject in need thereof (e.g., a subject suspected of having or having a specified disease). The method according to this aspect of the present invention comprises determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, the wherein the at least one genotype is associated with schizophrenia, thereby assisting in diagnosing schizophrenia in the subject.

According to still another aspect of the present invention there is provided a kit for assisting in diagnosing schizophrenia in a subject in need thereof. The kit according to this aspect of the present invention comprises a packaging material packaging at least one reagent, the at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, twherein the genotype is associated with schizophrenia. The kit further comprises a notification in or on the packaging material identifying the kit for use in assisting in diagnosing schizophrenia in a subject. Preferably, the notification also provides for instructions of using the kit in assisting in diagnosing schizophrenia of a subject.

As is further shown in Example 1 of the Examples section which follows and in Table 1 hereinabove, the G allele and the GG genotype of SNP rs807759, the C allele and the CC genotype of SNP rs2072123, and the A allele and AA genotype of SNP rs2073776 are highly and significantly associated with schizophrenia in males. Moreover, the predisposition probability for schizophrenia is 2.33-fold higher in males having the GG genotype of SNP rs807759 over males having the AA genotype, the predisposition probability for schizophrenia is 1.97-fold higher in males having the CC genotype of SNP rs2072123 over males having the TT genotype and the predisposition probability for schizophrenia is 2.3-fold higher in males having the AA genotype of SNP rs2073776 over males having the GG genotype. Moreover, the predisposition probability in males having the GG-CC-AA triple genotype of SNPs rs807759-rs2072123- rs2073776 is 2.49-fold higher than in males having the protective triple genotype. Furthermore, the probability for schizophrenia in males having the GG-CC-AA-CC-GG-GG genotype of SNPs rs807759- rs2072123- rs2073776- rs737865-rs4680- rs165599 is 7-fold higher than in males having the protective genotype.

Thus, according to yet a further aspect of the present invention there is provided a method of determining a predisposition to develop schizophrenia in a male subject. The method according to this aspect of the present invention comprises determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, the wherein the at least one genotype is associated with schizophrenia in males in higher association than in females, thereby determining the predisposition of the male subject of developing schizophrenia.

According to still a further aspect of the present invention there is provided a kit for determining a predisposition to develop schizophrenia in a male subject. The kit, according to this aspect of the present invention comprises a packaging material packaging at least one reagent, the at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, twherein the genotype is associated with schizophrenia in males in higher association than in females. The kit further comprises a notification in or on the packaging material, the notification identifying the kit for use in determining a

predisposition of a male subject of developing schizophrenia. Preferably, the notification also provides for instructions of using the kit in determining the predisposition of a male subject of developing schizophrenia.

Genotypes in the DGCR2 locus can also assist in the diagnosis of schizophrenia in a male subject. Thus, according to still a further aspect of the present invention there is provided method of assisting in diagnosing schizophrenia in a male subject in need thereof. The method according to this aspect of the present invention comprises determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, the wherein the at least one genotype is associated with schizophrenia in males in higher association than in females, thereby assisting in diagnosing schizophrenia in the male subject.

Thus, according to still a further aspect of the present invention there is provided kit for assisting in diagnosing schizophrenia in a male subject in need thereof. The kit, according to this aspect of the present invention comprises a packaging material packaging at least one reagent, the at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, twherein the genotype is associated with schizophrenia in males in higher association than in females. The kit further comprises a notification in or on the packaging material, the notification identifying the kit for use in assisting in diagnosing schizophrenia in a male subject. Preferably, the notification also provides for instructions of using the kit in assisting in diagnosing schizophrenia of a male subject.

## *DRUG RESPONSIVENESS*

The inventors of the present invention have uncovered that genotypes of SNPs in the DGCR2 locus are highly and significantly associated with drug responsiveness to schizophrenia drugs which are commonly used in treating schizophrenia and other mental disorders. More specifically, as is further shown in Example 2 of the Examples section which follows, the TC genotype of SNP rs2072123 was found to be highly and significantly associated with high efficiency of zuclopenthixol treatment in

schizophrenic males. In addition, the AA genotype of SNP rs2073776 was significantly associated with high efficiency of olanzapine in schizophrenic males.

These results clearly demonstrate the use of SNPs in the DGCR2 locus or SNPs in neighboring loci which are in linkage disequilibrium with SNPs rs2072123 and rs2073776 for the prediction of drug responsiveness to schizophrenia drugs. Moreover, since common schizophrenia treatment regimens include antipsychotics and neuroleptics drugs which are also widely used for treating patients having other mental disorders, in effect, the inventors of the present invention have uncovered methods for predicting the pharmacogenomic responsiveness of subjects having a variety of mental disorders to drugs used for treating these disorders using SNPs in the DGCR2 locus and neighboring loci.

Thus, according to still a further aspect of the present invention there is provided a method of predicting drug responsiveness of a subject having schizophrenia to a schizophrenia drug. The method according to this aspect of the present invention comprises determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, the wherein the at least one genotype is associated with drug responsiveness to the drug, thereby predicting drug responsiveness of the subject to the drug.

According to still a further aspect of the present invention there is provided a kit for predicting drug responsiveness of a subject having schizophrenia to a schizophrenia drug. The kit, according to this aspect of the present invention comprises a packaging material packaging at least one reagent, the at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, twherein the genotype is associated with schizophrenia. The kit further comprises a notification in or on the packaging material, the notification identifying the kit for use in predicting drug responsiveness of a subject having schizophrenia to the drug. Preferably, the notification also provides for instructions of using the kit in assisting in predicting drug responsiveness of a subject having schizophrenia to the drug.

According to still a further aspect of the present invention there is provided a method of predicting drug responsiveness of a subject having a given mental disorder

to a mental disorder drug. The method according to this aspect of the present invention comprises determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, the wherein the at least one genotype is associated with drug responsiveness to the drug in at least one mental disorder, thereby predicting drug responsiveness of the subject having the given mental disorder to the drug.

According to still a further aspect of the present invention there is provided a kit for predicting drug responsiveness of a subject having a given mental disorder to a mental disorder drug. The kit, according to this aspect of the present invention comprises a packaging material packaging at least one reagent, the at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, twherein the genotype is associated with drug responsiveness to the drug in at least one mental disorder. The kit further comprises a notification in or on the packaging material, the notification identifying the kit for use in predicting drug responsiveness of a subject having the given mental disorder to the drug. Preferably, the notification also provides for instructions of using the kit in assisting in predicting drug responsiveness of a subject having the given mental disorder to the drug.

According to still a further aspect of the present invention there is provided a method of identifying a genetic association with, or a genetic cause to, varying drug responsiveness to a schizophrenia drug. The method according to this aspect of the present invention comprises determining via a population association study an association between a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, and responsiveness or non-responsiveness to the schizophrenia drug, thereby identifying a genetic association with, or a genetic cause to, the varying drug responsiveness to the schizophrenia drug.

According to still a further aspect of the present invention there is provided a kit for identifying a genetic association with, or a genetic cause to, varying drug responsiveness to a schizophrenia drug. The kit, according to this aspect of the present

invention comprises a packaging material packaging at least one reagent, the at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus; twherein the genotype is associated with schizophrenia. The kit further comprises a notification in or on the packaging material, the notification identifying the kit for use in identifying a genetic association with, or a genetic cause to, varying drug responsiveness to the drug. Preferably, the notification also provides for instructions of using the kit in identifying a genetic association with, or a genetic cause to, varying drug responsiveness to the drug.

According to still a further aspect of the present invention there is provided a method of identifying a genetic association with, or a genetic cause to, varying drug responsiveness to a mental disorder drug. The method according to this aspect of the present invention comprises determining via a population association study an association between a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, the neighboring loci in linkage disequilibrium with the DGCR2 locus, and responsiveness or non-responsiveness to the mental disorder drug, thereby identifying a genetic association with, or a genetic cause to, the varying drug responsiveness to the mental disorder drug.

According to still a further aspect of the present invention there is provided a kit for identifying a genetic association with, or a genetic cause to, varying drug responsiveness of a subject having a given mental disorder to a mental disorder drug. The kit, according to this aspect of the present invention comprises a packaging material packaging at least one reagent, the at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, the neighboring loci being in linkage disequilibrium with the DGCR2 locus, twherein the genotype is associated with drug responsiveness to the drug in at least one mental disorder. The kit further comprises a notification in or on the packaging material, the notification identifying the kit for use in identifying a genetic association with, or a genetic cause to, varying drug responsiveness of a subject having the given mental disorder to the drug. Preferably, the notification also provides for instructions of using the kit in identifying a genetic

association with, or a genetic cause to, varying drug responsiveness of a subject having the given mental disorder to the drug.

According to further features in preferred embodiments the schizophrenia drug used by the present invention can be zuclopenthixol, and/or olanzapine. Other drugs used in treating a variety of mental disorders, inclusive future drugs, can also be tested pharmacogenomically in accordance with the teachings and the broad spirit of the present invention. Hence, the mental disorder drug can be any known antipsychotic and/or neuroleptic drug for the treatment of patients with mental disorder. Examples include, but are not limited to, thioridazine, clozapine, haloperidol, fluphenazine, cholrpromazine, risperidone, levomepromazine, perhenazine, chlorprothixene, pimozide, sulpiride, olanzapine, zuclopenthixol, amitriptyline, imipramine, clomipramine, desipramine, doxepin, mianserin, maprotiline, phenelzine, fluoxetine, trazodone, fluvoxamine, sertraline, paroxetine, reboxetine, citalopram, nefazodone, venlafoxine, lithium salts, carbamazapine, valproic acid, and clonazepam.

The mental disorder for which drug responsiveness can be determined using the methods of the present invention include, for example, schizophrenia, schizoaffective disorder, bipolar disorder, depression, obsessive compulsive disorder, panic disorder, agoraphobia, specific phobia, social phobia, post-traumatic stress disorder, pain disorder, anxiety, somatization disorder, anorexia nervosa, bulimia, and/or nervosa.

## *NOVEL DRUG IDENTIFICATION*

The strong association disclosed in the present invention between genotypes in the DGCR2 locus and schizophrenia, offers the use of the DGCR2 protein as a target for the identification of novel drugs for treating and/or preventing this disorder.

Therefore, according to still a further aspect of the present invention there is provided a method of identifying novel drugs for treatment of schizophrenia. The method according to this aspect of the present invention comprises incubating the integral membrane protein DGCR2, or any active portion thereof, or cells expressing integral membrane protein DGCR2, or any active portion thereof, with potential drugs and selecting for at least one drug of the potential drugs that modulates integral membrane protein DGCR2 activity or expression, thereby identifying novel drugs for treatment of schizophrenia.

According to still a further aspect of the present invention there is provided a method of treating schizophrenia. The method according to this aspect of the present invention comprises administering to a subject in need thereof a therapeutically effective amount of a drug for schizophrenia, the drug for schizophrenia having been identified capable of modulating integral membrane protein DGCR2 activity or expression.

The potential drug can be a peptide, a polynucleotide and/or a small molecule.

The polynucleotide used by the present invention can be an antisense oligonucleotide, an siRNA, a ribozymes and/or a DNAzyme.

The peptide used by the present invention can be a small peptide, a polypeptide and/or an antibody.

Assays of integral membrane protein DGCR2 expression may include monitoring integral membrane protein DGCR2 levels using an anti- integral membrane protein DGCR2 antibody, in assays such as, for example, in situ immunochemistry staining, Western blot, ELISA, fluorescence activated cell sorting, RIA, etc., and/or monitoring integral membrane protein DGCR2 mRNA levels using any one of a plurality of molecular methods based on hybridization of nucleic acids, such as, for example, in situ hybridization, Northern blot, dot blot, RNA protection assays, etc.

## *METHODS OF DETERMINING GENOTYPES*

According to various preferred embodiments of the present invention, determining the various alleles of SNPs in the DGCR2 locus is effected by any one of a variety of methods including, but not limited to, a signal amplification method, a direct detection method and detection of at least one sequence change. These methods can be employed to determine the genotype of the DGCR2 locus in a subject. As will be explained hereinbelow, determination of the DGCR2 genotype may also be accomplished directly by analysis of the DGCR2 gene products, and more particularly, analysis of the Val/Ala polymorphism at position 473 of the DGCR2 protein set forth in SEQ ID NO:24

### *Signal amplification methods*

According to various preferred embodiments of the present invention amplification of, for example, a DNA molecule or an RNA molecule is used. Signal

amplification methods which might be used as part of the methods and kits of the present invention include, but are not limited to PCR, LCR (LAR), Self-Sustained Synthetic Reaction (3SR/NASBA) or a Q-Beta (Qβ) Replicase reaction.

***Polymerase Chain Reaction (PCR):*** The polymerase chain reaction (PCR), as described in U.S. Pat. Nos. 4,683,195 and 4,683,202 to Mullis and Mullis *et al.*, is a method of increasing the concentration of a segment of target sequence in a mixture of genomic DNA without cloning or purification. This process for amplifying the target sequence involves the introduction of a molar excess of two oligonucleotide primers, which are complementary to their respective strands of the double-stranded target sequence to the DNA mixture containing the desired target sequence. The mixture is denatured and then allowed to hybridize. Following hybridization, the primers are extended with polymerase so as to form complementary strands. The steps of denaturation, hybridization (annealing), and polymerase extension (elongation) can be repeated as often as needed, in order to obtain relatively high concentrations of a segment of the desired target sequence. Because the desired segments of the target sequence become the dominant sequences (in terms of concentration) in the mixture, they are said to be "PCR-amplified".

***Ligase Chain Reaction (LCR or LAR):*** In the ligase chain reaction [LCR; sometimes referred to as "Ligase Amplification Reaction" (LAR)] described by Barany [Proc. Natl. Acad. Sci., 88:189 (1991); Barany, PCR Methods and Applic., 1:5 (1991)] and Wu and Wallace [Genomics 4:560 (1989)] four oligonucleotides, two adjacent oligonucleotides which uniquely hybridize to one strand of target DNA, and a complementary set of adjacent oligonucleotides, which hybridize to the opposite strand, are mixed and DNA ligase is added to the mixture. Provided that there is complete complementarity at the junction, ligase will covalently link each set of hybridized molecules. Importantly, in LCR, two probes are ligated together only when they base-pair with sequences in the target sample, without gaps or mismatches. Repeated cycles of denaturation, and ligation amplify a short segment of DNA. LCR has also been used in combination with PCR to achieve enhanced detection of single-base changes [Segev, PCT Publication No. W09001069 A1 (1990)].

***Self-Sustained Synthetic Reaction (3SR/NASBA):*** The self-sustained sequence replication reaction (3SR) (Guatelli *et al.*, Proc. Natl. Acad. Sci., 87:1874-

1878, 1990), with an erratum at Proc. Natl. Acad. Sci., 87:7797, (1990) is a transcription-based *in vitro* amplification system (Kwok *et al.*, Proc. Natl. Acad. Sci., 86:1173-1177, 1989) that can exponentially amplify RNA sequences at a uniform temperature. The amplified RNA can then be utilized for mutation detection (Fahy *et al.*, PCR Meth. Appl., 1:25-33, 1991). In this method, an oligonucleotide primer is used to add a phage RNA polymerase promoter to the 5' end of the sequence of interest. In a cocktail of enzymes and substrates that includes a second primer, reverse transcriptase, RNase H, RNA polymerase and ribo-and deoxyribonucleoside triphosphates, the target sequence undergoes repeated rounds of transcription, cDNA synthesis and second-strand synthesis to amplify the area of interest.

***Q-Beta* (Qβ) *Replicase:*** In this method, a probe that recognizes the sequence of interest is attached to the replicatable RNA template for Qβ replicase. A previously identified major problem with false positives resulting from the replication of unhybridized probes has been addressed through use of a sequence-specific ligation step. However, available thermostable DNA ligases are not effective on this RNA substrate, so the ligation must be performed by T4 DNA ligase at low temperatures (37 degrees C.). This prevents the use of high temperature as a means of achieving specificity as in the LCR, the ligation event can be used to detect a mutation at the junction site, but not elsewhere.

***Direct detection methods***

The direct detection method according to various preferred embodiments of the present invention may be, for example, a cycling probe reaction (CPR) or a branched DNA analysis. When a sufficient amount of a nucleic acid to be detected is available, there are advantages to detecting that sequence directly, instead of making more copies of that target, (e.g., as in PCR and LCR). Most notably, a method that does not amplify the signal exponentially is more amenable to quantitative analysis. Even if the signal is enhanced by attaching multiple dyes to a single oligonucleotide, the correlation between the final signal intensity and amount of target is direct. Such a system has an additional advantage that the products of the reaction will not themselves promote further reaction, so contamination of lab surfaces by the products is not as much of a concern. Traditional methods of direct detection including Northern and Southern band RNase protection assays usually require the use of radioactivity and are not

amenable to automation. Recently devised techniques have sought to eliminate the use of radioactivity and/or improve the sensitivity in automateable formats. Two examples are the "Cycling Probe Reaction" (CPR), and "Branched DNA" (bDNA).

***Cycling probe reaction (CPR):*** The cycling probe reaction (CPR) (Duck *et al.*, BioTech., 9:142, 1990), uses a long chimeric oligonucleotide in which a central portion is made of RNA while the two termini are made of DNA. Hybridization of the probe to a target DNA and exposure to a thermostable RNase H causes the RNA portion to be digested. This destabilizes the remaining DNA portions of the duplex, releasing the remainder of the probe from the target DNA and allowing another probe molecule to repeat the process. The signal, in the form of cleaved probe molecules, accumulates at a linear rate.

***Branched DNA:*** Branched DNA (bDNA), described by Urdea *et al.*, Gene 61:253-264 (1987), involves oligonucleotides with branched structures that allow each individual oligonucleotide to carry 35 to 40 labels (e.g., alkaline phosphatase enzymes). While this enhances the signal from a hybridization event, signal from non-specific binding is similarly increased.

***SNP genotyping technologies***

A number of technologies have been developed for SNP genotyping. Detailed technical reviews of these methods can be found elsewhere [Gray IC et al. (2000). Single nucleotide polymorphisms as tools in human genetics. *Human Molecular Genetics* 9, 2403-8, 2000]; [Landegren U, et al. (1988). A ligase-mediated gene detection technique. *Science* 241, 1077-80, 1998]; [Ravine D (1999). Automated mutation analysis. *Journal Of Inherited Metabolic Disease* 22, 503-18, 1999]; [Whitcombe D, et al. (1998). Advances in approaches to DNA-based diagnostics. *Current Opinion in Biotechnology* 9, 602-8, 1998]. The following sections describe the basic principle of the methods employed for SNP allele discrimination and detection as presented in [Shalom A, Darvasi A (2002) High-throughput SNP genotyping in: Pharmacogenetics of Psychotropic Drugs (Lerer, B., ed.) pp. 420-438, Cambridge University Press, 2002].

***Basic methods***

Identification of single base substitutions in DNA can be achieved in different ways. Most methods currently require a preliminary amplification, by the Polymerase

Chain Reaction (PCR), of a small DNA fragment (usually a few hundred bases long) around the SNP to be analyzed. The next step consists in resolving the allelic state of the fragment at the polymorphism point (usually a two-base alternative) by establishing an assessable discrimination between the alleles. The allelic state is later identified using a suitable detection method.

***Allele discrimination***

***Allele-specific amplification:*** For differential amplification of SNP alleles, a PCR primer is designed, where the 3' base corresponds to the polymorphic site. Consequently, only one of the two alleles will allow perfect matching and be amplified. In this case, SNP detection is concomitant to the amplification step. This strategy has been termed ARMS or Allele Refractory Mutation System [Newton CR, et al., (1989). Analysis of any point mutation in DNA. The amplification refractory mutation system (ARMS). *Nucleic Acids Research* 17, 2503-16, 1989]. In RealTime PCR, the allele specific primers are designed to differ significantly in their melting temperature (Tm), by addition of a GC-tail to one of the primers. Allele detection can be achieved by Tm shift measurement [Germer S, et al. (1999). Single-tube genotyping without oligonucleotide probes. *Genome Research* 9, 72-8, 1999].

***Restriction Fragment Langth Polymorphism (RFLP):*** When a nucleotide substitution creates or eliminates a restriction site, the alleles can be identified by appropriate restriction, followed by electrophoresis for resolution of the digestion products [Middle F, et al. (2000). Bipolar disorder and variation at a common polymorphism (A1832G) within exon 8 of the Wolfram gene. *American Journal of Medical Genetics* 96, 154-7, 2000].

***Primer-extension and minisequencing:*** After amplification of a fragment of the SNP-containing DNA, an oligonucleotide primer is annealed immediately upstream to the polymorphism. In the presence of the appropriate nucleotides, the primer is extended by one or more bases. The alleles can then be distinguished on the basis of size or mass of the extended product either by mass spectrometry or DHPLC (Denaturing High Performance Liquid Chromatography), according to specific fluorescence of the incorporated nucleotide (see TDI below), by regular electrophoresis-based sequencing techniques, or through hybridization on a high density oligonucleotide array [Yershov G, et al. (1996). DNA analysis and diagnostics on oligonucleotide microchips. *Proc. Natl. Acad. Sci. USA* 93, 4913-8, 1996]. The

Pyrosequencing™ strategy [Ahmadian et al. (2000). Single-nucleotide polymorphism analysis by pyrosequencing. *Analytical Biochemistry* 280, 103-10, 2000] detects pyrophosphate molecules as they are released during incorporation of the nucleotides in the minisequencing reaction. In the Competitive Oligonucleotide Single Base Extension (COSBE) assay [Higgins GS, et al. (1997). Competitive oligonucleotide single-base extension combined with mass spectrometric detection for mutation screening. *Biotechniques* 23, 710-4, 1997], two primers are simultaneously added to the reaction, corresponding to the alternative alleles; only the perfectly matched primer is extended.

***Allele-specific hybridization***: The amplified fragments are hybridized over an array of sequence-specific oligonucleotides, using high-stringency hybridization conditions to allow single-base mismatch detection [Saiki RK, et al. (1989). Genetic analysis of amplified DNA with immobilized sequence-specific oligonucleotide probes. *Proc. Nat. Acad. Sci. USA* 86, 6230-4, 1989]; [Sapolsky RJ, Hsie L, Berno A, Ghandour G, Mittmann M, Fan JB (1999). High-throughput polymorphism screening and genotyping with high-density oligonucleotide arrays. *Genetic Analysis* 14, 187-92, 1999]. By using multiplex PCR techniques, many SNPs can be tested simultaneously for each DNA sample [Wang DG, et al. (1998). Large-scale identification, mapping, and genotyping of single- nucleotide polymorphisms in the human genome. *Science* 280, 1077-82, 1998]. The Dynamic Allele Specific Hybridization (DASH) follows the fluorescence accumulating by a double strand dye (e.g. SYBR-green), as the PCR products are hybridized with an allele specific probe.

***Heteroduplex/homoduplex resolution***: If the two allelic forms are present during PCR amplification, heteroduplexes will be formed as a result of annealing between the alternative alleles. Homoduplexes can be distinguished from heteroduplexes, either through DHPLC [Giordano M, et al. (1999). Identification by denaturing high-performance liquid chromatography of numerous polymorphisms in a candidate region for multiple sclerosis susceptibility. *Genomics* 56, 247-53, 1999], or by enzymatic cleavage of the mismatched molecule [Youil R, et al. (1995). Screening for mutations by enzyme mismatch cleavage with T4 endonuclease VII. *Proc. Natl. Acad. Sci. USA*92, 87-91, 1995], followed by electrophoretical separation of the digested products. In both methods, artificial heteroduplexes are obtained by addition of wild-type DNA to the tested sample.

***Allele specific ligation: OLA*** or oligonucleotide ligation assay [Landegren U, et al. (1988). A ligase-mediated gene detection technique. *Science* 241, 1077-80, 1988] relies on the high sensitivity of the ligation reaction to mismatches. The amplified fragments are hybridized to allele specific fluorescent probes. Ligation to a second oligonucleotide will take place only when the probe is perfectly annealed at the polymorphic site. The reaction products are analyzed by ELISA [Tobe VO, et al. (1996). Single-well genotyping of diallelic sequence variations by a two-color ELISA-based oligonucleotide ligation assay. *Nucleic Acids Research* 24, 3728-32, 1996] or through FRET detection.

***Allele detection***

Various detection approaches are applicable to the different strategies based on separation of alternative alleles, or differential detection according to allele specific labels.

***Labeling:*** the amplified product is usually necessary, and can be achieved either homogeneously, or in an allele-specific way: Fluorimetric, colorimetric detection, and phosphorimaging are based on homogeneous internal labeling (fluorescent or radioactive, respectively) of the amplified product, or incorporation of a fluorescent dye (e.g. Ethidium Bromide, or SYBR green) to the final product. In the minisequencing format, the use of distinct fluorescent labels for the alternative dideoxynucleotides at the SNP site allows direct discrimination between the alleles.

***Electrophoresis:*** has for long been a choice separation technique for DNA molecular studies. Agarose, or acrylamide gel electrophoresis are used for low-throughput analysis of restriction digestion products, or sequencing reactions, respectively. These basic methods have been adapted to higher throughput demands, by means of MADGE (Microtiter Array Diagonal Electrophoresis), [Bolla MK, et al. (1995). High-throughput method for determination of apolipoprotein E genotypes with use of restriction digestion analysis by microplate array diagonal gel electrophoresis. *Clinical Chemistry* 41, 1599-604, 1995], or microchip electrophoresis [Schmalzing D, et al. (2000). Microchip electrophoresis: a method for high-speed SNP detection. *Nucleic Acids Research* 28, E43, 2000]. Acrylamide gels tend to be replaced by capillary electrophoresis.

***Molecular conformation,*** under partially denaturing conditions, is sensitive to single base substitutions, which allows allele identification by capillary electrophoresis

- Single Strand Conformation Polymorphism (CE- SSCP) - [Inazuka M, et al. (1997). A streamlined mutation detection system: multicolor post-PCR fluorescence labeling and single-strand conformational polymorphism analysis by capillary electrophoresis. *Genome Research* 7, 1094-103, 1997]. Heteroduplexes are identified according to the molecular conformation by CSGE (Conformation Sensitive Gel Electrophoresis), recently adapted to higher throughput by capillary CSGE [Rozycka M, et al. (2000). Rapid Detection of DNA Sequence Variants by Conformation-Sensitive Capillary Electrophoresis. *Genomics* 70, 34-40, 2000].

***Denaturing High Performance Liquid Chromatography (DHPLC):*** has proven an efficient method for heteroduplex identification. Each sample is tested in two separate wells, in one alone, and in the other after the wild-type allele is added. Heterozygotes give two peaks and homozygotes give one peak when tested alone. Homozygotes give two peaks after addition of the reference allele only if they possess the alternative allele. DHPLC is also efficient for minisequencing resolution [Hoogendoorn B, et al. (1999). Genotyping single nucleotide polymorphisms by primer extension and high performance liquid chromatography. *Human Genetics* 104, 89-93, 1999].

***MALDI-TOF Mass Spectrometry (MS)***: Mass spectrometry is used to measure the mass-to-charge ratio of ions – from which their molecular weight is inferred. A few MS techniques are applicable to DNA analysis. MALDI (Matrix-Assisted Laser Desorption-Ionization) allows the production of gas-phase ions from solution and solid phases. In MALDI -TOF, MALDI is coupled to a time-of-flight (TOF) analyzer, in which a detector accurately measures the time required for an ion to traverse the distance between the ion source and detector. SNPs are accurately analyzed by MALDI -TOF, in various allele discrimination formats [Griffin TJ, Smith LM (2000). Single-nucleotide polymorphism analysis by MALDI-TOF mass spectrometry. *Trends in Biotechnology* 18, 77-84, 2000].

***FRET*** or Fluorescence Resonance Energy Transfer occurs between a fluorescence donor (D) and a fluorescence acceptor (A) in close proximity, if the emission spectrum of the donor overlaps with the excitation spectrum of the acceptor. If the acceptor is non-fluorescent, it acts as a quencher, resulting in a net decrease in photon emission from the donor. If A is also fluorescent, the decrease in emission from D is concomitant with an increase in fluorescence at the emission wavelength of A.

The efficiency of energy transfer decreases very rapidly with increasing distance between the donor and acceptor, allowing its use for allele detection in a variety of applications [De Angelis DA (1999). Why FRET over genomics? [In Process Citation]. *Physiological Genomics* 1, 93-9, 1999]: TaqMan, Real time PCR, Molecular beacons, DOL, TDI, Invader (see below).

***Fluorescence polarization*** takes advantage of the mobility of molecules in solution: fluorescent free nucleotides are more mobile and will therefore show no polarization, while nucleotides that have been incorporated, in a primer extension reaction, to a larger oligonucleotide primer, will be detected as polarized molecules, resulting in an amplification of the fluorescence signal.

***Methods employing highly specialized probes***

Based on the above techniques, specialized probes have been developed, that enable a more accurate and/or sensitive assay for genotyping of SNPs.

***TaqMan (5' exonuclease assay):*** [Livak KJ, et al. (1995). Towards fully automated genome-wide polymorphism screening [letter]. *Nature Genetics* 9, 341-2, 1995]. The probes are short oligonucleotides probes that undergo FRET in their intact state because they are labeled at each end with a fluorescence donor and acceptor pair. The probe is designed to hybridize to a sequence being amplified in a PCR reaction. If there is a perfect match between the probe and the target, the 5'-exonuclease activity of Taq polymerase will digest the hybridized TaqMan probe during the elongation cycle, separating D from A and resulting in a decrease in FRET.

***Molecular beacons:*** *[Tyagi S, et al. (1998). Multicolor molecular beacons for allele discrimination. Nature Biotechnology 16, 49-53, 1998]* These oligonucleotide probes are chemically modified with a fluorescence donor D at their 5' end and a non-fluorescent quenching acceptor Q at their 3' end. In the absence of a perfectly matched target, they assume a stem-and-loop structure in solution. This hairpin conformation positions D and Q in extremely close proximity, much closer than a pair of fluorophores at opposite ends of a randomly coiled oligonucleotide, resulting in an effective fluorescence quenching. In the presence of a perfectly matched sequence, the hairpin loop hybridizes to the target, thus preventing the folding of the probe and separating D from Q and resulting in a fluorescence increase. The ability of molecular beacons to form hairpin structures significantly enhances their specificity compared with standard oligonucleotide probes of the same size. Scorpion primers [Thelwell N,

et al. (2000). Mode of action and application of scorpion primers to mutation detection *Nucleic Acids Research* 28, 3752-61, 2000] combine the properties of a PCR primer and of a FRET probe similar to the molecular beacons. Sunrise probes [Nazarenko IA, et al. (1997). A closed tube format for amplification and detection of DNA based on energy transfer. *Nucleic Acids Research* 25, 2516-21, 1997] are hairpin-FRET PCR probes, the FRET is allowed when the hairpin structure serves as a template in the PCR reaction, after a primary round resulting in incorporation of the primers in the template DNA.

***DOL:*** Dye-labeled Oligonucleotide Ligation [Chen X, (1998). A homogeneous, ligase-mediated DNA diagnostic test. *Genome Research* 8, 549-56, 1998] relies on a ligation assay. The method utilizes two oligonucleotides, one labeled with a fluorescence donor, the other with an acceptor. The probes are designed to hybridize adjacently across the polymorphic site; if both oligonucleotides match perfectly, DNA ligase can join the fragments together, resulting in FRET. A mismatch at the ligation site will result in failure of the ligase to link the labeled oligonucleotides, thus preventing FRET.

***TDI:*** Template-directed Dye Incorporation – [Chen X, (1997). Fluorescence energy transfer detection as a homogeneous DNA diagnostic method. Proc. Natl. Acad. Sci. USA 94, 10756-61, 1997] is a primer-extension strategy, based on the FRET detection assay. The primer to be extended is labeled with a fluorescent donor. Incorporation of an acceptor-labelled nucleotide, by the primer extension reaction, brings the fluorophores in close proximity, thus resulting in FRET.

***PNA hybridization probes:*** Peptide Nucleic Acid (PNA – [Corey DR (1997). Peptide nucleic acids: expanding the scope of nucleic acid recognition. Trends in Biotechnology 15, 224-9, 1997] is a DNA analog containing the four normal nucleotides of DNA attached to a neutrally charged amide backbone. The neutral backbone confers unique characteristics on the hybridization of PNA with DNA, resulting in improved hybridization specificity for complementary DNA sequences. Two similar SNP genotyping approaches using PNA have been independently developed recently [Griffin TJ, et al. (1997). Genetic analysis by peptide nucleic acid affinity MALDI-TOF mass spectrometry [see comments]. *Nature Biotechnology* 15, 1368-72, 1997]; [Ross PL, et al. (1997). Discrimination of single-nucleotide polymorphisms in human DNA using peptide nucleic acid probes detected by

MALDI-TOF mass spectrometry. *Analytical Chemistry* 69, 4197-20, 1997]. In both methods, allele specific PNA probes are hybridized to amplified SNP fragment. The captured PNA are later purified and analyzed by MALDI–TOF MS. Each uniquely mass-labeled PNA probe detected corresponds to a specific SNP allele present in the PCR amplicon.

***Non-PCR based strategies and further improvements of general techniques:***

***Invader™ assay:*** involves the sequence-specific hybridization of two oligonucleotides to form a one-base overlapping structure at the polymorphic position. This is followed by enzymatic cleavage of an allele specific downstream probe, using a "flap" endonuclease. A large excess of the overlapping probe in the reaction results in an amplification of the cleaved product, relative to the original DNA sample. The cleaved product serves as an invader upstream oligonucleotide in a secondary reaction, in which cleavage of the probe results in FRET. A modified version (Griffin et al., 1999) of this assay allows detection by MALDI-TOF MS.

***Padlock probes:*** [Nilsson M, et al. (1994). Padlock probes: circularizing oligonucleotides for localized DNA detection. *Science* 265, 2085-8, 1994]: The 5' and 3' end regions of these linear oligonucleotides are designed to base-pair next to each other on a target strand. If properly hybridized, then the ends can be joined by enzymatic ligation, converting the probes to circularly closed molecules that are catenated to the target sequences. Because the reaction products remain localized at their target, these probes are suitable for simultaneous analysis of many genes. Many tandem copies of the complement to the circularized molecule can be generated by rolling circle replication (RCR - Baner J, et al. (1998). Signal amplification of padlock probes by rolling circle replication. *Nucleic Acids Research* 26, 5073-8, 1998], resulting in amplification of the detection signals.

***Light-up probes:*** [Isacsson J, et al. (2000). Rapid and specific detection of PCR products using light-up probes [In Process Citation]. *Molecular and Cellular Probes* 14, 321-8, 2000] are PNA probes labeled with a fluorescent dye which has low fluorescence in its unbound state, but generates a readily detectable signal when hybridized to its target sequence. This eliminates the need to separate unbound probes from the hybridization complex prior to detection.

***Real Time PCR:*** This approach allows simultaneous allele discrimination and detection [Higuchi R, et al. (1993). Kinetic PCR analysis: real-time monitoring of

DNA amplification reactions. *Biotechnology (N Y)* 11, 1026-30, 1993]; [Nitsche A, et al. (1999). Different real-time PCR formats compared for the quantitative detection of human cytomegalovirus DNA. *Clinical Chemistry* 45, 1932-7, 1999]. A few techniques can be applied, and include: Taqman, Molecular beacons, Allele Specific Hybridization, and Allele Specific Amplification. Detection is achieved by FRET, or by fluorescence detection of SYBR-green (a fluorescent dye that binds to double-stranded DNA).

***Kinetic PCR*** is based on the differential amplification of the alternative alleles, due to mismatch pairing of an allele-specific primer. The mismatched product will be amplified at a lower rate, and thus its real-time detection will occur at a later cycle, than the full-match allele. RealTime PCR is conveniently performed on the LightCycler (Roche Molecular Biochemicals) or the ABI PRISM 7700 (Applied Biosystems), which combine a thermocycler with a fluorimeter.

## *TREATMENT/PREVENTION OF DISEASE*

The Val/Ala polymorphism of the DGCR2 enzyme encoded by SNP rs2072123 may affect the activity of the DGCR2 protein. The present invention discloses a strong association of one polymorph of the DGCR2 protein exhibiting the Ala amino acid at position 473 of SEQ ID NO:24 to schizophrenia. Therefore, it is possible that effective amounts of DGCR2 modulatory agents that affect DGCR2 expression or activity can be used to treat and/or prevent schizophrenia.

Thus, according to still a further aspect of the present invention there is provided a method of treating and/or preventing schizophrenia. The method according to this aspect of the present invention comprises administering to a subject in need thereof a therapeutically effective amount of at least one agent capable of modulating DGCR2 protein expression or activity.

The agent used in context of the present invention to inhibit DGCR2 activity or expression can be an anti-DGCR2 antibody, a polynucleotide encoding an intracellular anti-DGCR2 antibody, an anti-DGCR2 antisense molecule, an anti-DGCR2 siRNA, an anti-DGCR2 ribozyme, an anti-DGCR2 DNAzyme, and/or a DGCR2 inhibitor.

The agent used in context of the present invention to increase DGCR2 activity or expression can be recombinant DGCR2 protein or any active portion thereof.

***Anti-DGCR2 antibody and/or recombinant protein:*** An anti-DGCR2 antibody can be prepared by conventional antibody preparation methods.

Antibodies of the present invention can be used for recognition of the various DGCR2 polymorphs as well as for the inhibition of the DGCR2 activity and/or expression. Methods of making these antibodies are known in the art. See for example, Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York, 1988, incorporated herein by reference.

Humanized forms of non-human (e.g., murine) antibodies are chimeric molecules of immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Methods for humanizing non-human antibodies are well known in the art. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature 332:323-327 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such humanized antibodies are chimeric antibodies (U.S. Pat. No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage display libraries [Hoogenboom and Winter, J. Mol. Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222:581 (1991)]. The techniques of Cole et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies (Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985) and Boerner et al., J. Immunol., 147(1):86-95 (1991)]. Similarly, human antibodies can be made by introducing of human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Pat. Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425;

5,661,016, and in the following scientific publications: Marks et al., Bio/Technology 10, 779-783 (1992); Lonberg et al., Nature 368 856-859 (1994); Morrison, Nature 368 812-13 (1994); Fishwild et al., Nature Biotechnology 14, 845-51 (1996); Neuberger, Nature Biotechnology 14, 826 (1996); Lonberg and Huszar, Intern. Rev. Immunol. 13 65-93 (1995).

Methods for creating recombinant protein or fragments thereof are also known in the art [e.g. U.S. Patents: 5,656,722, 5,370,629, and 5,509,905; Giroir BP, Scannon PJ & Levin M (2001) Bacericidal/permeability-increasing protein--lessons learned from the phase III, randomized, clinical trial of rBPI21 for adjunctive treatment of children with severe meningococcemia. Crit Care Med 29:s130-135].

***Intracellular anti-DGCR2 antibody or recombinant protein:*** The polynucleotide encoding an anti-DGCR2 antibody or recombinant protein, obtained as described above, is inserted into a suitable mammalian expression vector dedicated for intracellular expression of a protein encoded thereby.

To generate such an expression vector, a polynucleotide segment encoding a anti-DGCR2 antibody or recombinant protein, devoid of extracellular secretion signal peptide sequence, is ligated into, for example, a commercially available expression vector system suitable for transforming mammalian cells and for directing the expression of the anti-DGCR2 antibody within the transformed cells. It will be appreciated that such commercially available vector systems can easily be modified via commonly used recombinant techniques in order to replace, duplicate or mutate existing promoter or enhancer sequences and/or introduce any additional polynucleotide sequences such as for example, sequences encoding additional selection markers or sequences encoding reporter polypeptides, etc.

Suitable mammalian expression vectors for use with the present invention include, but are not limited to, pcDNA3, pcDNA3.1(+/-), pZeoSV2(+/-), pSecTag2, pDisplay, pEF/myc/cyto, pCMV/myc/cyto, pCR3.1, which are available from Invitrogen, pCI which is available from Promega, pBK-RSV and pBK-CMV which are available from Strategene, pTRES which is available from Clontech, and their derivatives.

Viral expression vectors can be particularly useful for introducing an anti-DGCR2 antibody polynucleotide or recombinant protein into a cell. The host cell can be a cell in a subject, a cell in vivo, or a cell ex vivo (see, for example U.S. Pat. No.

5,399, 346). The expression vector can be delivered into cells using a variety of delivery approaches, including, but not limited to, microinjection, electroporation, liposomes, epidermal patches, iontophoresis or receptor-mediated endocytosis. The selection of a particular method will depend, for example, on the cell into which the polynucleotide is to be introduced, as well as whether the cell is isolated in culture, or is in a tissue or organ in culture or in situ.

***Anti-DGCR2 antisense oligonucleotides/vectors:*** In human gene therapy, antisense nucleic acid technology has been one of the major tools of choice to inactivate genes where expression causes disease and is thus undesirable [Walton et al., 1999, Biotechnol Bioeng 65(1):1-9; Matveeva et al., 1998, Nature Biotechnology 16, 1374 – 1375].

The antisense oligonucleotides used by the present invention can be expressed from a nucleic acid construct administered into the tissue, in which case constitutive or preferably inducible promoters are preferly used such that antisense expression can be switched on and off, or alternatively such oligonucleotides can be chemically synthesized and administered directly into the tissue, as part of, for example, a pharmaceutical composition.

Several prior art studies have shown that antisense oligonucleotides can be effective *in vivo*. For example, antisense molecules have been used to arrest hematopoietic cell proliferation (Szczylik et al., Science 253: 562 1991), growth (Calabretta et al. Proc. Natl. Acad. Sci. USA 88:2351, 1991), or entry into the S phase of the cell cycle (Heikhila et al., Nature, 328:445, 1987) and to prevent receptor mediated responses (Burch and Mahan, J. Clin. Invest. 88:1190, 1991).

Recent scientific publications have validated the efficacy of antisense compounds in animal models of hepatitis, cancers, coronary artery restenosis and other diseases. The first antisense drug was recently approved by the FDA. The drug, Fomivirsen, was developed by Isis, and is indicated for local treatment of cytomegalovirus in patients with AIDS who are intolerant of or have a contraindication to other treatments for CMV retinitis or who were insufficiently responsive to previous treatments for CMV retinitis (Pharmacotherapy News Network).

Several antisense compounds are now in clinical trials in the United States. These include locally administered antivirals, systemic cancer therapeutics. Antisense

therapeutics has the potential to treat many life-threatening diseases with a number of advantages over traditional drugs. Traditional drugs intervene after a disease-causing protein is formed. Antisense therapeutics, however, block mRNA transcription/translation and intervene before a protein is formed, and since antisense molecules target only one specific mRNA, such therapeutic agents should be more effective with fewer side effects than current protein-inhibiting therapy.

A second option for disrupting gene expression at the level of transcription uses synthetic oligonucleotides capable of hybridizing with double stranded DNA. A triple helix is formed. Such oligonucleotides may prevent binding of transcription factors to the gene's promoter and therefore inhibit transcription. Alternatively, they may prevent duplex unwinding and, therefore, transcription of genes within the triple helical structure.

***Anti-DGCR2 siRNA:*** Another mechanism of down regulating enzymes at the transcript level is RNA interference (RNAi), an approach which utilizes small interfering dsRNA (siRNA) molecules that are homologous to the target mRNA and lead to its degradation [Carthew, 2001, Curr Opin Cell Biol 13(2):244-8]. RNAi is an evolutionarily conserved surveillance mechanism that responds to double-stranded RNA by sequence-specific silencing of homologous genes (Fire et al., 1998, Nature 391, 806-811; Zamore et al., 2000, Cell 101, 25-33). RNAi is initiated by the dsRNA-specific endonuclease dicer, which promotes cleavage of long dsRNA into double-stranded fragments between 21 and 25 nucleotides long, termed small interfering RNA (siRNAs) (Zamore et al., 2000, Cell 101, 25-33; Elbashir et al., 2001, Genes Dev. 15, 188-200; Hammond et al., 2000, Nature 404, 293-296; Bernstein et al., 2001, Nature 409, 363-366). siRNA are incorporated into a protein complex that recognizes and cleaves target mRNAs (Nykanen et al., 2001, Cell 107, 309-321).

RNAi has been increasingly used for the sequence-specific inhibition of gene expression. The possibility of interfering with any specific target RNA has rendered RNAi a valuable tool in both basic research and therapeutic applications. RNAi was first used for gene silencing in nematodes (Fire et al., 1998, Nature 391, 806-811).

Recent scientific publications have validated the efficacy of such short double stranded RNA molecules in inhibiting target mRNA expression and thus have clearly demonstrated the therapeutic potential of such molecules. For example, RNAi has been utilized to inhibit expression of hepatitis C (McCaffrey et al., 2002, Nature 418,

38-39), HIV-1 (Jacque et al., 2002, Nature 418, 435–438), HPV in cervical cancer cells (Jiang and Milner 2002, Oncogene 21, 6041-8) and BCR/ABL fusion gene in leukemic cells (Wilda et al., 2002, Oncogene 21, 5716-24).

The siRNA used by the present invention can be transcribed *in vitro* from plasmids and administered into the tissue. Transcripts that include two self-complementary siRNAs annealed to form a loop region can be further processed by single-stranded ribonucleases and/or other proteins into a functional duplex siRNA molecule (Leirdal and Sioud, 2002, Biochem Biophys Res Commun 295, 744-8). siRNA can also be prepared from dsRNA by Escherichia coli RNase III cleavage into endoribonuclease-prepared siRNA (esiRNA).

Since approaches for introducing synthetic siRNA into cells by lipofection can result in low transfection efficiencies in some cell types and/or short-term persistence of silencing effects, vector mediated methods have been developed.

Thus, siRNA molecules utilized by the present invention are preferably delivered into cell using retroviruses. Delivery of siRNA using retroviruses provides several advantages over methods, such as lipofection, since retroviral delivery is more efficient, uniform and immediately selects for stable "knock-down" cells.

Thus, siRNA molecules of the present invention are preferably transcribed from expression vectors which can facilitate stable expression of the siRNA transcripts once introduced into a host cell. These vectors are engineered to express small hairpin RNAs (shRNAs), which are processed *in vivo* into siRNA molecules capable of carrying out gene-specific silencing [Brummelkamp, T.R., et al., (2002) Science 296: 550-53; Paddison, P.J., et al., (2002) Genes Dev. 16:948-58; Paul et al. (2002) Nature Biotech. 20: 505-08, Yu, J.Y et al., (2002) Proc. Natl. Acad. Sci. USA 99: 6047-52].

An example of a suitable expression vector is the pSUPER$^{TM}$, which includes the polymerase-III H1-RNA gene promoter with a well defined start of transcription and a termination signal consisting of five thymidines in a row (T5) (Brummelkamp, 2002, Science 296: 550-53).

Another suitable siRNA expression vector encodes the sense and antisense siRNA under the regulation of separate polIII promoters (Miyagishi and Taira (2002) Nature Biotech. 20:497-500). The siRNA, generated by this vector also includes a 5 thymidine termination signal.

As an alternative to anti-sense molecules, catalytic nucleic acid molecules have shown promise as therapeutic agents for suppressing gene expression, and are widely discussed in the literature (Haseloff, J. & Gerlach, W.A. Nature 1988;334: 585; Breaker, R.R. and Joyce, G. Chemistry and Biology 1994; 1:223; Koizumi, M., et al. Nucleic Acids Research 1989;17:7059; Otsuka, E. and Koizumi, M., Japanese Patent No.4,235,919; Kashani-Sabet, M., et al. Antisense Research and Development 1992;2:3-15; Raillard, S.A. and Joyce, G.F. Biochemistry 1996;35:11693; and Carmi, N. et al. Chemistry and Biology 1996;3:1039). Unlike conventional anti-sense inhibition, a catalytic nucleic acid molecule functions by binding to and actually cleaving its target mRNA. Cleavage of the target sequence depends on complementation of the target with the hybridizing regions of the catalytic nucleic acid, and the presence of a specific cleavage sequence.

The term enzymatic nucleic acid is used interchangeably with phrases such as ribozymes, catalytic RNA, enzymatic RNA, catalytic DNA, nucleozyme, DNAzyme, RNA enzyme, endoribonuclease, minizyme, leadzyme, oligozyme or DNA enzyme, as used in the art. All of these terminologies describe nucleic acid molecules with enzymatic activity.

***Anti-DGCR2 ribozymes:*** Ribozymes are being increasingly used for the sequence-specific inhibition of gene expression by the cleavage of mRNAs encoding proteins of interest. The possibility of designing ribozymes to cleave any specific target RNA has rendered them valuable tools in both basic research and therapeutic applications. In the therapeutics area, ribozymes have been exploited to target viral RNAs in infectious diseases, dominant oncogenes in cancers and specific somatic mutations in genetic disorders. Most notably, several ribozyme gene therapy protocols for HIV patients are already in Phase 1 trials (Welch et al., 1998, Curr. Opin. Biotechnol., 9:486-496). More recently, ribozymes have been used for transgenic animal research, gene target validation and pathway elucidation. Several ribozymes are in various stages of clinical trials. ANGIOZYME was the first chemically synthesized ribozyme to be studied in human clinical trials. ANGIOZYME specifically inhibits formation of the VEGF-r (Vascular Endothelial Growth Factor receptor), a key component in the angiogenesis pathway. Ribozyme Pharmaceuticals, Inc., as well as other firms have demonstrated the importance of anti-angiogenesis therapeutics in animal models. HEPTAZYME, a ribozyme designed to selectively

destroy Hepatitis C Virus (HCV) RNA, was found effective in decreasing Hepatitis C viral RNA in cell culture assays (Ribozyme Pharmaceuticals, Incorporated). As described above, novel ribozymes can be designed to cleave known substrate, using either random variants of a known ribozyme or random-sequence RNA as a starting point (Pan, T. and Uhlenbeck, O.C. Biochemistry 1996;31:3887; Tsang, J. and Joyce, G.F. Biochemistry 1994;33:5966; Breaker, R.R. and Joyce, G. Chemistry and Biology 1994; 1:223).

***Anti-DGCR2 DNAzymes:*** Recently, a new class of catalytic molecules called "DNAzymes" was created (Breaker, R.R. and Joyce, G. Chemistry and Biology 1995;2:655; Santoro, S.W. & Joyce, G.F. Proc. Natl, Acad. Sci. USA 1997;943:4262). DNAzymes are single-stranded, and cleave RNA. A general model (the "10-23" model) for the DNAzyme has been proposed. "10-23" DNAzymes have a catalytic domain of 15 deoxyribonucleotides, flanked by two substrate-recognition domains of seven to nine deoxyribonucleotides each. This type of DNAzyme can effectively cleave its substrate RNA at purine:pyrimidine junctions (Santoro, S.W. & Joyce, G.F. Proc. Natl, Acad. Sci. USA 199; for rev of DNAzymes see Khachigian, LM Curr Opin Mol Ther 2002;4:119-21).

Examples of construction and amplification of synthetic, engineered DNAzymes recognizing single and double-stranded target cleavage sites have been disclosed in U.S. Pat. No. 6,326,174 to Joyce et al. DNAzymes of similar design directed against the human Urokinase receptor were recently observed to inhibit Urokinase receptor expression, and successfully inhibit colon cancer cell metastasis in vivo (Itoh et al., 20002, Abstract 409, Ann Meeting Am Soc Gen Ther www.asgt.org.). In another application, DNAzymes complementary to bcr-ab1 oncogenes were successful in inhibiting the oncogenes expression in leukemia cells, and lessening relapse rates in autologous bone marrow transplant in cases of CML and ALL.

Additional objects, advantages, and novel features of the present invention will become apparent to one ordinarily skilled in the art upon examination of the following examples, which are not intended to be limiting. Additionally, each of the various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below finds experimental support in the following examples.

## *EXAMPLES*

Reference is now made to the following examples, which together with the above descriptions, illustrate the invention in a non-limiting fashion.

Generally, the nomenclature used herein and the laboratory procedures utilized in the present invention include molecular, biochemical, microbiological and recombinant DNA techniques. Such techniques are thoroughly explained in the literature. See, for example, "Molecular Cloning: A laboratory Manual" Sambrook et al., (1989); "Current Protocols in Molecular Biology" Volumes I-III Ausubel, R. M., ed. (1994); Ausubel et al., "Current Protocols in Molecular Biology", John Wiley and Sons, Baltimore, Maryland (1989); Perbal, "A Practical Guide to Molecular Cloning", John Wiley & Sons, New York (1988); Watson et al., "Recombinant DNA", Scientific American Books, New York; Birren et al. (eds) "Genome Analysis: A Laboratory Manual Series", Vols. 1-4, Cold Spring Harbor Laboratory Press, New York (1998); methodologies as set forth in U.S. Pat. Nos. 4,666,828; 4,683,202; 4,801,531; 5,192,659 and 5,272,057; "Cell Biology: A Laboratory Handbook", Volumes I-III Cellis, J. E., ed. (1994); "Culture of Animal Cells - A Manual of Basic Technique" by Freshney, Wiley-Liss, N. Y. (1994), Third Edition; "Current Protocols in Immunology" Volumes I-III Coligan J. E., ed. (1994); Stites et al. (eds), "Basic and Clinical Immunology" (8th Edition), Appleton & Lange, Norwalk, CT (1994); Mishell and Shiigi (eds), "Selected Methods in Cellular Immunology", W. H. Freeman and Co., New York (1980); available immunoassays are extensively described in the patent and scientific literature, see, for example, U.S. Pat. Nos. 3,791,932; 3,839,153; 3,850,752; 3,850,578; 3,853,987; 3,867,517; 3,879,262; 3,901,654; 3,935,074; 3,984,533; 3,996,345; 4,034,074; 4,098,876; 4,879,219; 5,011,771 and 5,281,521; "Oligonucleotide Synthesis" Gait, M. J., ed. (1984); "Nucleic Acid Hybridization" Hames, B. D., and Higgins S. J., eds. (1985); "Transcription and Translation" Hames, B. D., and Higgins S. J., eds. (1984); "Animal Cell Culture" Freshney, R. I., ed. (1986); "Immobilized Cells and Enzymes" IRL Press, (1986); "A Practical Guide to Molecular Cloning" Perbal, B., (1984) and "Methods in Enzymology" Vol. 1-317, Academic Press; "PCR Protocols: A Guide To Methods And Applications", Academic Press, San Diego, CA (1990); Marshak et al., "Strategies for Protein Purification and Characterization - A Laboratory Course Manual" CSHL Press (1996); "Approaches to Gene Mapping in Complex Human Diseases" Jonathan L. Haines and Margaret A.

Pericak-Vance eds., Wiley-Liss (1998); "Genetic Dissection of Complex Traits" D.C. Rao and Michael A. Province eds., Academic Press (1999); "Introduction to Quantitative Genetics" D.S. Falconer and Trudy F.C. Mackay, Addison Wesley Longman Limited (1996); all of which are incorporated by reference as if fully set forth herein. Other general references are provided throughout this document. The procedures therein are believed to be well known in the art and are provided for the convenience of the reader. All the information contained therein is incorporated herein by reference.

***Materials and Experimental Methods***

***Study subjects*** – Study subjects were Ashkenazi Jewish with known ethnic origin of at least two generations. Subjects were recruited to study upon signing an informed consent form with approved Institutional Review Board (IRB) protocols.

***Schizophrenic cases*** - Diagnosis included a direct interview using structured clinical interview for personality disorder (SCID), a questionnaire with inclusion and exclusion criteria and cross-references to medical records. The inclusion criteria specified diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Questionnaires also included information regarding drugs taken and their effects on the patient.

***Control individuals*** – Healthy Jewish Ashkenazi individuals.

***Sample preparation*** - Genomic DNA was prepared from peripheral blood samples using the Nucleon$^{TM}$ kit (Pharmacia, North Peapack, New Jersey, USA) according to manufacturer's instructions. DNA was diluted to 100 ng/µl and equal aliquots of DNA samples were pooled together according to disease classification or were used for individual genotyping. Prior to genotyping reactions, pool and individual DNA samples were diluted to 10 and 2 ng/µl, respectively.

***SNP selection*** – SNPs were selected from the National Center for Biotechnology Information (NCBI) SNP data base (www.ncbi.nlm.nih.gov/entrez/query.fcgi? db=snp). Preferred SNPs were potentially functional (e.g., non-synonymous, SNPs in regulatory regions) and had records of being validated on genomic DNA samples. SNPs were relatively equally spaced to

reach maximal coverage of the gene. SNPs were analyzed by the Pyrosequencing software (Pyrosequencing™, Uppsala, Sweden) for primer design.

*Table 2*
*SNPs and primers from the DGCR2 locus*

| SNP SEQ ID | SNP ID# | Primer SEQ ID and sequence 5'→3': |
|---|---|---|
| NO:1 | rs2072123 | NO:2 (F): CACCCCTCTGTCTCTTCCTG<br>NO:3 (R-B) CCGGAGTAATGCACCTTCAC<br>NO:4 (P) TGATGCTTTTGAGCC |
| NO:5 | rs2073776 | NO:6 (F-B) TTGGAGAAGGGCTGCTACTT<br>NO:7 (R) ATGCTTCCTGCTTCGTCCT<br>NO:8 (P) AGCCAGTAGGGGACTC |
| NO:9 | rs10160 | NO:10 (F-B) AGGCAGGGAATGAAGAAGGT<br>NO:11 (R) CTGGGTCAGCAGGTCTCTCT<br>NO:12 (P) GCACACTGCACCAAGTA |
| NO:13 | rs807759 | NO:14 (F-B) CCAGAGCTGAAAGGTGAGTGA<br>NO:15 (R) ATAAAGCCTGCGCTCCTCTAC<br>NO:16 (P) GGGGTACCTCGGCA |
| NO:17 | 1557845 | NO:18 (F-B) ACTCCCCTCTCTCCCTTTTCT<br>NO:19 (R) GCTCTCCCAGCTGTTATCCTT<br>NO:20 (P) GTTGGCCAGCCCC |

SNP and primers from the DGCR2 locus. F = forward primer, R = reverse primer, B = biotynilated at 5', P = pyro primer.

In the DGCR2 locus the analyzed SNPs were: rs2072123 (SEQ 1; non synonymous), rs2073776 (SEQ 5) and rs10160 (SEQ 9) from the 5' UTR, rs807759 (SEQ 13) and rs1557845 (SEQ 17) in the introns (Table 2).

***Pyrosequencing analysis*** – PCR primers flanking the SNP were selected using the Primer3 software (http://www.genome.wi.mit.edu) to yield an average PCR product of 150 base pairs (bp). For an avidin-based magnetic bead separation of the PCR product, one of the flanking primers was 5'-conjugated to a biotin molecule. PCR reactions included 45 cycles of denaturation (20 seconds at 94 °C), annealing (30 seconds at 55 °C) and elongation (30 seconds at 72 °C) using the HotStar Taq Polymerase kit (Qiagen, Valencia, CA, USA) according to manufacturer's instructions. Pool DNA PCR products were subsequently subjected to Pyrosequencing analysis using the Pyrosequencing specific internal primers on the PSQ™ 96 System (Pyrosequencing™, Uppsala, Sweden) according to manufacturer's protocol.

***Restriction Fragment Length Polymorphism (RFLP) analysis*** – PCR products of SNPs rs2072123 and rs807759 were digested using restriction enzymes

AciI and NlaIII (both from NEBiolabs, MA, USA) respectively, and were further analyzed on 3 % agarose (BMA, ME, USA) gels.

***Statistical analysis***

***Linkage disequilibrium estimates*** - To measure the linkage disequilibrium (LD) between SNPs, haplotype frequencies were estimated using the expectation maximization (EM) [Slatkin M, Excoffier L. (1996). Testing for linkage disequilibrium in genotypic data using the Expectation-Maximization algorithm. Heredity. 76: 377-83] algorithm on 24 individual genotypes and calculating the Lewontin's (D') and Pearson correlation (r).

***Test for association*** - Association of a specific SNP to a disease was evaluated in a case-control study by comparing the frequency of a specific allele and/or genotype in the case population (*i.e.,* patients) with those of the control population, using standard $\chi^2$ and proportion tests under normal approximation.

***Odds ratios*** – is an estimate of the relative risk, *i.e.,* the increased probability of disease in populations exposed to the risk allele. OR and approximate confidence intervals, were computed in a standard way [Alan Agresti (1990). Categorical data analysis. New York: Wiley, pp. 54-55] in order to examine the structure and strength of association between genotype and disease.

***Genotype relative risk (GRR)*** – is the increased chance of an individual with a particular genotype to develop the disease. Thus, the GRR of the risk genotype G, with respect to the protective genotype $G_0$, is the ratio between the risk of an individual carrying genotype G to develop the disease, and the risk of an individual carrying genotype $G_0$ to develop the disease. The GRR used herein is represented in terms of an appropriate odds ratio (OR) of G versus $G_0$ in cases and controls. Computation of the GRR of the haplotypes was based on a multiplicative model in which the GRR of an homozygote individual was the square of the GRR of an heterozygote individual. For further details see Risch and Merikangas, 1996 [The future of genetic studies of complex human diseases. Science 273: 1516-1517].

***Population attributable risk (PAR)*** – is the percentage of cases that would not have been affected if the population was monomorphic for the protective allele and genotype. The PAR value of a certain allele is calculated by the following equation:

(K-1)/K, wherein K is $\Sigma f_i \cdot g_i$, $f_i$ is the frequency of the i genotype or double genotype and $g_i$ is the estimated GRR of the i genotype or double genotype, respectively.

***Haplotype-Trait Association***- was analyzed by a haplotype-specific chi-square test for association. The p-value computation is based on an asymptotic approximation (ChiSq).

***The overall effect of the haplotypes:*** P-value computation is based on a simulation applying 10,000 iterations.

***Computation of the Genetic Relative Risk (GRR) associated with the haplotype.*** In the computation of the GRR, the multiplicative model was assumed. This leads to the conclusion the GRR of a heterozygote for the risk haplotype is equal to the odds ratio associated with the haplotype. Also, the GRR of a homozygote for the risk haplotype is the square of the GRR for an heterozygote. More generally, the GRR of a heterozygote with neither of the protective haplotypes is the product of the associated heterozygote with protective GRR's. Only the GRR for homozygotes with risk hapltypes were computed. Note: in DGCR2 the associated haplotype A-T-G is actually a protective haplotype. For the computation, risk haplotypes are considered all haplotypes other than that haplotype.

***Computation of the Population Attributed Risk (PAR) associated with the protective haplotype.*** In DGCR2 the protective haplotype is A-T-G. All other haplotypes were collapsed into a single class and computed the GRR of that class. This GRR corresponds to the risk associated with a heterozygote which has a single protective haplotype. Based on this GRR, and based on the multiplicative assumption, the PAR was computed using the following formula:

$$PAR = \frac{(GRR \times (1-p) + p)^2 - 1}{(GRR \times (1-p) + p)^2}$$

## *EXAMPLE 1*

## *SNPS IN THE DGCR2 LOCUS ARE ASSOCIATED WITH SCHIZOPHRENIA*

***Experimental Results***

***Association of the SNPs in the DGCR2 locus by population–based pool genotyping.*** PCR products were prepared from pooled DNA samples of 660

schizophrenia cases (SZP) and 2771 control individuals (CTL), and allele frequency was determined using the Pyrosequencer™. The calculated difference in allele frequency between cases and controls was tested for significance using a standard $\chi^2$ analysis. SNPs from the DGCR2 locus exhibited a significant difference in the allele frequency: SNPs rs807759 (p=2.04E-04), rs10160 (p=2.91E-04), rs2072123 (p=2.59E-02), rs2073776 (p=9.08E-0.3); rs1557845 (p=1.26E-2) see Table 3. Thus, these results suggest that SNPs in the DGCR2 locus are associated with increased risk for schizophrenia and suggest their further analysis by large-scale individual genotyping.

*Table 3*

***Allele frequency differences of SNPs in the DGCR2 locus in a schizophrenia case-control study***

| Seq ID | NCBI SNP ID | Allele frequency difference | P-value |
|---|---|---|---|
| 13 | rs807759 | 5.8 | 2.04E-04 |
| 9 | rs10160 | 6.1 | 2.91E-04 |
| 1 | rs 2072123 | 3.5 | 2.59E-02 |
| 5 | rs 2073776 | 5.0 | 9.08E-03 |
| 17 | rs1557845 | 3.8 | 1.26E-02 |

Differences in allele frequencies of SNPs in the DGCR2 locus determined by pooled DNA genotyping of 660 schizophrenia cases and 2771 control individuals.

***Linkage disequilibrium between SNPs in the DGCR2 locus.***

To determine the linkage disequilibrium (LD) status of SNPs in the DGCR2 locus in the Ashkenazi Jewish population, SNP genotyping was performed on DNA samples from 24 control individuals. SNP rs10160 exhibited high Linkage Disequilibrium with SNPs rs2073776 (D'=0.8967, $r^2$=0.4570); rs2072123 (D'=1, $r^2$=0.4928); rs807759 (D'=1, $r^2$= 0.9411) and rs1557845 (D'=1, $r^2$=1). SNP rs1557845 is also in high linkage disequilibrum with SNPs rs807759 (D'=1, $r^2$=0.9429), rs2072123 (D'=1, $r^2$=0.5111), and rs2073776 (D'=0.8968, $r^2$ =0.4387). SNP rs807759 is in partial Linkage Disequilibrium with SNPs rs2072123 (D'=0.8970, $r^2$ =0.4362) and rs2073776 (D'=0.8004, $r^2$ =0.3706). Low Linkage Disequilibrium has been found between the SNPs rs2072123 and rs2073776 (D'=0.4567, $r^2$=0.1954). Therefore, to substantiate the association between SNPs in the DGCR2 locus and increased risk for

schizophrenia, large-scale individual genotyping was conducted using SNPs rs807759, rs2072123, rs2073776.

***Individual genotyping results***

SNPs rs807759, rs2072123, rs2073776 were subjected to individual genotyping to validate the association of the DGCR2 gene locus with schizophrenia.

***The G allele and the GG genotype of SNP rs807759 are risk factors for schizophrenia***

Genotyping of SNP rs807759 was performed on 511 case and 550 control subjects using Pyrosequencing and RFLP technologies. As shown in Table 4, the G allele was more frequent in schizophrenia patients (males and females) than in controls (p=1.35E-04, Table 4). This difference was even more prominent when schizophrenic males alone were compared with the controls (p=6.22E-05, Table 4). In addition, the GG phenotype was more frequent in schizophrenic patients than in controls (p=5.89E-05, Table 4), and was again slightly more significant when affected males were compared with the controls (p=1.19E-05, Table 4). A modest increase in the GG homozygote could be observed in female schizophrenics in comparison to the control group (p=6.54E-2, Table 4). In addition, the risk probability for schizophrenia is twice as high for the homozygous genotype and x1.18 higher for the heterozygous genotype, over the protective genotype (AA), (GRR, Table 5). Similarly, the predisposition probabilities to schizophrenia in males are 2.3-fold and 1.19-fold higher for the homozygous and the heterozygous genotypes, respectively (GRR, Table 5). To further evaluate the association of SNP rs807759 with schizophrenia, the population attributable risk (PAR) was calculated for the protective genotype (AA). This demonstrated that 23 % of schizophrenic patients (27 % of males and 19% of females) would not have been affected if the population were monomorphic for the AA genotype (Table 5). The allele and the GG genotype Odds Ratios were calculated to further substantiate the assumption that the GG genotype in this SNP is associated with schizophrenia. The results were as following: the allele Odds Ratio=1.39 (with 95% confidence interval (CI): 1.18-1.65), the GG Genotype Odds Ratio=1.79 (95% CI:1.35-2.37) for all patients compared to controls (Table 5). Even stronger results were obtained when only male patients were compared to controls: 1.49 (95% CI:1.23-1.82), and 2.05 (95% CI:1.5-2.6) respectively, for allele and GG genotype Odds Ratios (Table 5). The same tendency could be seen in female schizophrenics, compared to

controls (Table 5). Altogether, these results demonstrate that the G allele and the GG genotype of SNP rs807759 are associated with schizophrenia.

*Table 4*

*Allele and genotype frequencies of SNP rs807759 in schizophrenia case-control study.*

| Studied group | G Freq. (affected) | G Freq. (control) | Allele P value | AA genotype P value | GG genotype P value |
|---|---|---|---|---|---|
| SZP A/CTL | 0.554 | 0.471 | 1.35E-04 | 2.42E-02 | 5.89E-05 |
| SZP M/CTL | 0.571 | 0.471 | 6.22E-05 | 2.80E-02 | 1.19E-05 |
| SZP F/CTL | 0.526 | 0.471 | 6.27E-02 | 1.99E-01 | 6.54E-02 |

Allele and genotype frequencies revealed by individual genotyping. Affected = schizophrenia (SZP) cases; Control (CTL) = healthy individuals; P values reflect the significance of differences between cases and controls; M = males, F = females, A = all (males and females).

*Table 5*

*SNP rs807759: Odds ratios, Genotype Related Risk (GRR), and Population Attributable Risk (PAR) in schizophrenia*

| Studied Group | Allele Odds Ratio | GG Homozygote Odds Ratio | GG Homozygote GRR | Heterozygote GRR | Genotypic PAR (%) |
|---|---|---|---|---|---|
| SZP A/CTL | 1.39 (1.18-1.65) | 1.79 (1.35-2.37) | 2.02 | 1.18 | 23.08 |
| SZP M/CTL | 1.49 (1.23-1.82) | 2.05 (1.5-2.6) | 2.33 | 1.19 | 26.92 |
| SZP F/CTL | ns | 1.49 (1.02-2.17) | 1.67 | 1.19 | 19.23 |

Odds ratios, Genotype Related Risk (GRR), and Population Attributable Risk (PAR) Affected = schizophrenia (SZP) cases; Control (CTL) = healthy individuals; M = males, F = females, A = all (males and females).

***The C-allele and the CC genotype of SNP rs2072123 are associated with schizophrenia***

Genotyping of 756 schizophrenic subjects and 644 control males by a combination of technologies (Pyrosequencing technology and restriction fragment length polymorphism analysis) revealed that the C allele of SNP rs2072123 was more prominent among schizophrenia subjects than among controls (p=2.79E-03, Table 6). Furthermore, more significant results were obtained when schizophrenic males were compared to the control group (p=6.92E-04, Table 6). Additionally, the results demonstrated that there are significantly more CC homozygotes among the schizophrenic subjects than among the controls (p=3.49E-03, Table 6). This tendency was even stronger in schizophrenic males compared to controls (p=6.72E-04, Table 6).

The risk of schizophrenia is 66% higher in CC homozygotes and 1.14-fold higher in heterozygotes than in individuals with the protective genotype (TT), (GRR, Table 7). This tendency is more prominent in affected males: there is a 1.97-fold and 1.21-fold higher probability for homozygous and heterozygous genotypes respectively. Furthermore, 12% of all schizophrenia patients and 17% of male patients would not have been affected if the population were monomorphic for the protective allele and genotype (PAR, Table 7). The allele and genotype Odds Ratios are 1.26 (95% CI: 1.08-1.48) and 1.54 (95% CI: 1.12-2.11) in patients vs. controls and 1.34 (95% CI: 1.13-1.59) and 1.76 (95% CI: 1.26-2.47) in male patients vs. controls. Altogether these results suggest that the C allele in SNP rs 2072123 represents a risk allele for schizophrenia.

*Table 6*
***Allele and genotype frequencies of SNP rs2072123 in schizophrenia case-control study.***

| Studied group | C Freq. (affected) | C Freq. (control) | Allele P value | TT genotype P value | CC genotype P value |
|---|---|---|---|---|---|
| SZP A/CTL | 0.403 | 0.348 | 2.79E-03 | 3.20E-02 | 3.49E-03 |
| SZP M/CTL | 0.418 | 0.348 | 6.92E-04 | 1.81E-02 | 6.72E-04 |

Allele and genotype frequencies revealed by individual genotyping. Affected = schizophrenia (SZP) cases; Control (CTL) = healthy individuals; P values reflect the significance of differences between cases and controls. M = males, A = all males and females.

*Table 7*
***SNP rs2072123: Odds ratios, Genotype Related Risk (GRR), and Population Attributable Risk (PAR) in schizophrenia***

| Studied Group | Allele Odds Ratio | CC Homozygote Odds Ratio | CC Homozygote GRR | Heterozygote GRR | Genotypic PAR (%) |
|---|---|---|---|---|---|
| SZP A/CTL | 1.26 (1.08-1.48) | 1.54 (1.12-2.11) | 1.66 | 1.14 | 12.19 |
| SZP M/CTL | 1.34 (1.13-1.59) | 1.76 (1.26-2.47) | 1.97 | 1.21 | 17.07 |

Odds ratios, Genotype Related Risk (GRR), and Population Attributable Risk (PAR) Affected = schizophrenia (SZP) cases; Control (CTL) = healthy individuals; M = males, A = all (males and females).

***The A-allele and AA homozygote of the SNP rs2073776 are associated with schizophrenia***

Genotyping of SNP rs2073776 in 563 cases and 549 controls revealed that the A allele was much more frequent among schizophrenia subjects than among the

controls (p = 4.31E-05, Table 8). Testing the allele frequency difference in male patients showed even greater association of the A allele of this SNP with schizophrenia (p=2.6E-05, Table 8). There was also a modest increase in the A allele frequency among the schizophrenic females compared to controls (p=2.93E-02, Table 8). Additionally, the AA homozygote frequency was significantly higher, and the GG homozygote frequency significantly lower, in cases than in controls (p=9.86E-4, and p=7.14E-4, respectively; Table 8). The same tendency could be observed in male subjects versus controls (p=4.0E-3, and p=7.52E-5, Table 8). Schizophrenic females also showed a statistically significant increase in the AA genotype (p=8.43E-3). According to the PAR calculation, 25% of all patients, 33% of male patients and 10% of affected females would not have been affected if the population were monomorphic for the protective allele and genotype (G and GG) (Table 9). The Genotype Relative Risk shows that there is a two-fold and a 39% higher probability for the disease in those possessing an AA genotype and a heterozygous genotype, respectively, than in individuals having a protective (GG) genotype (Table 9). In males, there is a 2.3-fold and a 1.66-fold higher risk in the AA homozygotes and the heterozygotes, over the protective genotype (Table 9). GRR calculation for the schizophrenic females showed a slightly milder tendency of the same character. The A Allele and the AA genotype Odds Ratios are 1.42 (1.2-1.68) and 1.69 (1.25-2.3), respectively (Table 9). There is additional data, regarding Odds Ratio calculations in Table 9. Altogether these results demonstrate that the A allele in SNP rs 2073776 is associated with schizophrenia.

***Table 8***
***Allele and genotype frequencies of SNP rs2073776 in schizophrenia case-control study.***

| Studied group | A Freq. (affected) | A Freq. (control) | Allele P value | GG genotype P value | AA genotype P value |
|---|---|---|---|---|---|
| SZP A/CTL | 0.481 | 0.395 | 4.31E-05 | 7.14E-04 | 9.86E-04 |
| SZP M/CTL | 0.496 | 0.395 | 2.60E-05 | 7.52E-05 | 4.00E-03 |
| SZP F/CTL | 0.457 | 0.395 | 2.93E-02 | 2.80E-01 | 8.43E-03 |

Allele and genotype frequencies revealed by individual genotyping. Affected = schizophrenia (SZP) cases; Control (CTL) = healthy individuals; P values reflect the significance of differences between cases and controls. M = males, F = females, A = all (males and females).

*Table 9*
*SNP rs2073776: Odds ratios, Genotype Related Risk (GRR), and Population Attributable Risk (PAR) in schizophrenia*

| Studied Group | Allele Odds Ratio | AA Homozygote Odds Ratio | AA Homozygote GRR | Heterozygote GRR | Genotypic PAR (%) |
|---|---|---|---|---|---|
| SZP A/CTL | 1.42 (1.2-1.68) | 1.69 (1.25-2.30) | 2.04 | 1.39 | 25 |
| SZP M/CTL | 1.50 (1.24-1.82) | 1.69 (1.20-2.38) | 2.3 | 1.66 | 33.33 |
| SZP F/CTL | 1.29 (1.02-1.62) | 1.7 (1.14-2.53) | 1.73 | 1.03 | 10.21 |

Odds ratios, Genotype Related Risk (GRR), and Population Attributable Risk (PAR) Affected = schizophrenia (SZP) cases; Control (CTL) = healthy individuals; M = males, F = females, A = all (males and females).

***Association of the haplotypes of SNPs from the DGCR2 region with schizophrenia***

To further substantiate the association between schizophrenia and SNPs in the DGCR2 locus, the frequencies of all possible haplotypes comprised of SNPs: rs807759, rs2072123, and rs2073776 were compared between schizophrenia cases and controls. The overall haplotype effect on schizophrenia was found to be significant in all schizophrenia patients (males and females) and in male patients alone (p=9.47E-03, and p=1.4E-03, respectively, Table 10). A strong association with schizophrenia was observed for the G-C-A haplotype of the three SNPs in all patients vs. controls, and male patients vs. controls (p = 7.3E-04, and p=3.47E-04, respectively, Table 10). An even stronger association was observed when the frequency of the protective A-T-G haplotype was compared in cases and controls in the same groups (p=3.17E-05, p=4.36E-06, respectively, Table 10). Significantly, alleles in each one of the two haplotypes represent, respectively, the risk and the protective alleles, as observed when the association with the disease was studied separately for each SNP.

According to the GRR calculation, G-C-A homozygotes are 2.12-fold more likely, and heterozygotes (G-C-A/A-T-G) are 1.46-fold more likely to be affected with schizophrenia, than homozygotes for the protective haplotype (A-T-G). Even more prominent results were obtained when a GRR for male patients vs. controls was calculated. It was found that there is a 2.49-fold, and 1.58-fold higher predisposition to schizophrenia in male homozygous and heterozygous for the risk haplotype, respectively. Furthermore, there is a 1.37-fold higher risk for schizophrenia in individuals having any other haplotype than in those that are homozygous for the

protective haplotype. Thirty percent of patients would not have been affected if the population were monomorphic for the protective haplotype (ATG/ATG). The Odds Ratio calculation results confirm the haplotype associations as described above (risk haplotype G-C-A: 1.78 (1.26-1.51); protective haplotype A-T-G: 0.51 (0.37-0.71) for all patients vs. controls, Table 10).

***Table 10***
***G-C-A, and A-T-G Haplotype frequencies and Odds Ratios in schizophrenia case-control study***

| Haplotype | P-value (all affected vs. controls) | Odds Ratio (all affected vs. controls) | P-value (affected males vs. controls) | Odds Ratio (affected males vs. controls) |
|---|---|---|---|---|
| G-C-A | 7.30E-04 | 1.78 (1.26-1.51) | 3.47E-04 | 1.99 (1.36-2.93) |
| A-T-G | 3.17E-05 | 0.51(0.37-0.71) | 4.36E-06 | 0.44 (0.30-0.63) |

P-values and Odds ratios for all patients vs. controls, and male patients vs. controls for the G-C-A and A-T-G haplotypes of SNPs rs807759, rs2072123, and rs2073776.

***Association of the DGCR2 and COMT SNP haplotypes with schizophrenia***

Cathecol-O-Methyl Transferase (COMT) has previously been shown to be associated with schizophrenia [Shifman et al., (2002). A highly significant association between a COMT haplotype and Schizophrenia. Am. J. Hum. Genet. 71:1296-1302, 2002]; [Darvasi, Zak, PCT Patent Application No. PCT/IL03/00140, 2003]. To check the additive effect of SNPs in the DGCR2 and COMT loci and schizophrenia, the frequencies of all possible haplotypes comprised of the DGCR2 SNPs- rs807759, rs2072123, rs2073776, and the COMT SNPs- rs737865, rs4680, rs165599 (SEQ. 21-23, respectively) were compared between schizophrenia cases and controls. The overall haplotype effect on schizophrenia was found to be significant in all schizophrenia patients (p=1.06E-02). The strongest association was observed for the A-T-G-T-A-A haplotype in all schizophrenia patients vs. controls (p = 1.07E-7). The association is negative, meaning that this haplotype is a "protective haplotype" for schizophrenia. It is noteworthy that this haplotype consists of two "protective" haplotypes: in the DGCR2 (A-T-G, see above), and in the COMT (T-A-A), [Shifman et al., (2002). A highly significant association between a COMT haplotype and Schizophrenia. Am. J. Hum. Genet. 71:1296-1302, 2002; Darvasi, Zak, PCT Patent Application No. PCT/IL03/00140, 2003]. Haplotype G-C-A-C-G-G also showed a positive association with schizophrenia (p=4.05E-03). This "risk" haplotype consists

of two "risk" haplotypes: G-C-A in DGCR2, see above; and C-G-G in COMT [Shifman et al., (2002). A highly significant association between a COMT haplotype and Schizophrenia. Am. J. Hum. Genet. 71:1296-1302, 2002; Darvasi, Zak, PCT Patent Application No. PCT/IL03/00140, 2003]. The Odds Ratio value for the A-T-G-T-A-A haplotype was found to be 0.33 (95% CI: 0.2-0.54), meaning that this haplotype is a protective haplotype.

The GRR calculations point out an increased disease probability in individuals that are homozygous or heterozygous for the "risk" haplotype (GRR=5.54, GRR=2.35, respectively) than in homozygotes for the protective haplotype. Homozygosity and heterozygosity to the "risk" haplotype displayed a more profound effect on predisposition to schizophrenia when GRR was calculated for affected men vs. controls (GRR=6.96, GRR=2.64, respectively).

The relation between DGCR2 and COMT is also supported by expression studies that showed a significant (p=0.0002) correlation of 0.6304 between brain expression levels of COMT and DGCR2 in different mouse strains (*i.e.* when examining 30 mouse strains for expression of different genes in the brain, it is found that the expression levels of these two genes tend to vary similarly among the strains). Such a correlation with COMT expression was not found for any other gene in the 200Kb vicinity of DGCR2 (http://webqtl.roswellpark.org/). The similarity in regulation of expression of these two genes suggests that they may function in related biochemical pathways.

## *EXAMPLE 2*

### *GENOTYPE-DEPENDENT DRUG EFFICACY USING THE DGCR2 SNPS*

The common treatment regimes of schizophrenia aim to reduce the severity of the symptoms and include the use of antipsychotics and neuroleptics drugs. However, these drugs are of only limited effectiveness in many patients while causing severe side effects in others. To understand the reasons for variability in drug responsiveness a comprehensive genotype-phenotype analysis was performed using information from patients' questionnaires and their genotypic status for SNPs in the DGCR2 locus as established by individual genotyping.

*Experimental Results*

***Genotype subclasses in the DGCR2 locus display different responsiveness towards schizophrenia treatment*** – The genotypic status of SNPs rs2072123 and rs2073776 in the DGCR2 locus were tested for association with patient's drug response. This analysis revealed that the TC genotype of SNP rs2072123 was correlated with high efficiency of zuclopenthixol treatment in males (p = 5.73E-03). In addition, the AA genotype of SNP rs2073776 was correlated with high efficiency of olanzapine treatment in males (p = 2.66E-03). These results demonstrate that variability in drug responsiveness could result from specific genotypic status of SNPs in the DGCR2 locus. Furthermore, these results suggest the use of the SNPs in the DGCR2 locus for the prediction of drug responsiveness and effectiveness of schizophrenia drugs.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims. All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.

WHAT IS CLAIMED IS:

1. A method of determining a predisposition of a subject to develop schizophrenia, the method comprising determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, said neighboring loci being in linkage disequilibrium with said DGCR2 locus, said wherein the at least one genotype is associated with schizophrenia, thereby determining the predisposition of the subject of developing schizophrenia.

2. The method of claim 1, wherein said at least one genotype in said DGCR2 locus is a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13.

3. The method of claim 1, wherein said at least one genotype in said DGCR2 locus is a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1.

4. The method of claim 1, wherein said at least one genotype in said DGCR2 locus is an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

5. The method of claim 1, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least two SNPs selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

6. The method of claim 1, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype comprising at least one SNP selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5;

and at least one SNP selected from the group consisting of:

a cytosine nucleotide - containing allele of SNP rs737865 set forth in SEQ ID NO:21;

a guanine nucleotide - containing allele of SNP rs4680 set forth in SEQ ID NO:22; and

a guanine nucleotide - containing allele of SNP rs165599 set forth in SEQ ID NO:23.

7. A method of determining a predisposition to develop schizophrenia in a male subject, the method comprising determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, said neighboring loci being in linkage disequilibrium with said DGCR2 locus, said wherein the at least one genotype is associated with schizophrenia in males in higher association than in females, thereby determining the predisposition of the male subject of developing schizophrenia.

8. The method of claim 7, wherein said at least one genotype in said DGCR2 locus is a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13.

9. The method of claim 7, wherein said at least one genotype in said DGCR2 locus is a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1.

10. The method of claim 7, wherein said at least one genotype in said DGCR2 locus is an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

11. The method of claim 7, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least two SNPs selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

12. The method of claim 7, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least one SNP selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5;

and at least one SNP selected from the group consisting of:

a cytosine nucleotide - containing allele of SNP rs737865 set forth in SEQ ID NO:21;

a guanine nucleotide - containing allele of SNP rs4680 set forth in SEQ ID NO:22; and

a guanine nucleotide - containing allele of SNP rs165599 set forth in SEQ ID NO:23.

13. A method of assisting in diagnosing schizophrenia in a subject in need thereof, the method comprising determining a presence in a homozygous or

heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, said neighboring loci being in linkage disequilibrium with said DGCR2 locus, said wherein the at least one genotype is associated with schizophrenia, thereby assisting in diagnosing schizophrenia in the subject.

14. The method of claim 13, wherein said at least one genotype in said DGCR2 locus is a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13.

15. The method of claim 13, wherein said at least one genotype in said DGCR2 locus is a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1.

16. The method of claim 13, wherein said at least one genotype in said DGCR2 locus is an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

17. The method of claim 13, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least two SNPs selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

18. The method of claim 13, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least one SNP selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5;

and at least one SNP selected from the group consisting of:

a cytosine nucleotide - containing allele of SNP rs737865 set forth in SEQ ID NO:21;

a guanine nucleotide - containing allele of SNP rs4680 set forth in SEQ ID NO:22; and

a guanine nucleotide - containing allele of SNP rs165599 set forth in SEQ ID NO:23.

19. A method of assisting in diagnosing schizophrenia in a male subject in need thereof, the method comprising determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, said neighboring loci being in linkage disequilibrium with said DGCR2 locus, said wherein the at least one genotype is associated with schizophrenia in males in higher association than in females, thereby assisting in diagnosing schizophrenia in the male subject.

20. The method of claim 19, wherein said at least one genotype in said DGCR2 locus is a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13.

21. The method of claim 19, wherein said at least one genotype in said DGCR2 locus is a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1.

22. The method of claim 19, wherein said at least one genotype in said DGCR2 locus is an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

23. The method of claim 19, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least two SNPs selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

24. The method of claim 19, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least one SNP selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5;

and at least one SNP selected from the group consisting of:

a cytosine nucleotide - containing allele of SNP rs737865 set forth in SEQ ID NO:21;

a guanine nucleotide - containing allele of SNP rs4680 set forth in SEQ ID NO:22; and

a guanine nucleotide - containing allele of SNP rs165599 set forth in SEQ ID NO:23.

25. A method of predicting drug responsiveness of a subject having schizophrenia to a schizophrenia drug, the method comprising determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, said neighboring loci being in linkage disequilibrium with said DGCR2 locus, said wherein the at least one genotype is

associated with drug responsiveness to the drug, thereby predicting drug responsiveness of the subject to the drug.

26. The method of claim 25, wherein said at least one genotype in said DGCR2 locus is a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1.

27. The method of claim 25, wherein said at least one genotype in said DGCR2 locus is an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

28. The method of claim 25, wherein said drug is selected from the group consisting of zuclopenthixol and olanzapine.

29. A method of predicting drug responsiveness of a subject having a given mental disorder to a mental disorder drug, the method comprising determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, said neighboring loci being in linkage disequilibrium with said DGCR2 locus, said wherein the at least one genotype is associated with drug responsiveness to the drug in at least one mental disorder, thereby predicting drug responsiveness of the subject having the given mental disorder to the drug.

30. The method of claim 29, wherein said mental disorder is selected from the group consisting of schizophrenia, schizoaffective disorder, bipolar disorder, depression, obsessive compulsive disorder, panic disorder, agoraphobia, specific phobia, social phobia, post-traumatic stress disorder, pain disorder, anxiety, somatization disorder, anorexia nervosa, bulimia, and nervosa.

31. The method of claim 29, wherein said drug is selected from the group consisting of thioridazine, clozapine, haloperidol, fluphenazine, cholrpromazine, risperidone, levomepromazine, perhenazine, chlorprothixene, pimozide, sulpiride, olanzapine, zuclopenthixol, amitriptyline, imipramine, clomipramine, desipramine,

doxepin, mianserin, maprotiline, phenelzine, fluoxetine, trazodone, fluvoxamine, sertraline, paroxetine, reboxetine, citalopram, nefazodone, venlafoxine, lithium salts, carbamazapine, valproic acid, and clonazepam.

32. The method of claim 29, wherein said at least one genotype in said DGCR2 locus is a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13.

33. The method of claim 29, wherein said at least one genotype in said DGCR2 locus is a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1.

34. The method of claim 29, wherein said at least one genotype in said DGCR2 locus is an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

35. The method of claim 29, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least two SNPs selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

36. The method of claim 29, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least one SNP selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5;

and at least one SNP selected from the group consisting of:

a cytosine nucleotide - containing allele of SNP rs737865 set forth in SEQ ID NO:21;

a guanine nucleotide - containing allele of SNP rs4680 set forth in SEQ ID NO:22; and

a guanine nucleotide - containing allele of SNP rs165599 set forth in SEQ ID NO:23.

37. A method of identifying a genetic association with, or a genetic cause to, varying drug responsiveness to a schizophrenia drug, the method comprising determining via a population association study an association between a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, said neighboring loci being in linkage disequilibrium with said DGCR2 locus, and responsiveness or non-responsiveness to the schizophrenia drug, thereby identifying a genetic association with, or a genetic cause to, the varying drug responsiveness to the schizophrenia drug.

38. The method of claim 37, wherein said at least one genotype in said DGCR2 locus is a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1.

39. The method of claim 37, wherein said at least one genotype in said DGCR2 locus is an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

40. The method of claim 37, wherein said drug is selected from the group consisting of zuclopenthixol and olanzapine.

41. A method of identifying a genetic association with, or a genetic cause to, varying drug responsiveness to a mental disorder drug, the method comprising determining via a population association study an association between a presence in a

homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, said neighboring loci in linkage disequilibrium with said DGCR2 locus, and responsiveness or non-responsiveness to the mental disorder drug, thereby identifying a genetic association with, or a genetic cause to, the varying drug responsiveness to the mental disorder drug.

42. The method of claim 41, wherein said mental disorder is selected from the group consisting of schizophrenia, schizoaffective disorder, bipolar disorder, depression, obsessive compulsive disorder, panic disorder, agoraphobia, specific phobia, social phobia, post-traumatic stress disorder, pain disorder, anxiety, somatization disorder, anorexia nervosa, bulimia, and nervosa.

43. The method of claim 41, wherein said drug is selected from the group consisting of thioridazine, clozapine, haloperidol, fluphenazine, cholrpromazine, risperidone, levomepromazine, perhenazine, chlorprothixene, pimozide, sulpiride, olanzapine, zuclopenthixol, amitriptyline, imipramine, clomipramine, desipramine, doxepin, mianserin, maprotiline, phenelzine, fluoxetine, trazodone, fluvoxamine, sertraline, paroxetine, reboxetine, citalopram, nefazodone, venlafoxine, lithium salts, carbamazapine, valproic acid, and clonazepam.

44. The method of claim 41, wherein said at least one genotype in said DGCR2 locus is a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13.

45. The method of claim 41, wherein said at least one genotype in said DGCR2 locus is a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1.

46. The method of claim 41, wherein said at least one genotype in said DGCR2 locus is an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

47. The method of claim 41, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least two SNPs selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

48. The method of claim 41, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least one SNP selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5;

and at least one SNP selected from the group consisting of:

a cytosine nucleotide - containing allele of SNP rs737865 set forth in SEQ ID NO:21;

a guanine nucleotide - containing allele of SNP rs4680 set forth in SEQ ID NO:22; and

a guanine nucleotide - containing allele of SNP rs165599 set forth in SEQ ID NO:23.

49. A kit for determining a predisposition of a subject to develop schizophrenia, the kit comprising a packaging material packaging at least one reagent, said at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of at least one genotype in the DGCR2 locus or in neighboring loci, said neighboring loci being in linkage disequilibrium with said DGCR2 locus, wherein said genotype is associated with schizophrenia, the kit further comprising a

notification in or on said packaging material, said notification identifying the kit for use in determining a predisposition of developing schizophrenia.

50. The kit of claim 49, wherein said notification also provides for instructions of using the kit in determining a predisposition of developing schizophrenia.

51. The kit of claim 50, wherein said at least one genotype in said DCGR2 locus is a guanine nucleotide – and/or an adenosine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13.

52. The kit of claim 50, wherein said at least one genotype in said DGCR2 locus is a cytosine nucleotide – and/or a thymine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1.

53. The kit of claim 50, wherein said at least one genotype in said DGCR2 locus is an adenosine nucleotide – and/or a guanine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

54. The kit of claim 50, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least two SNPs selected from the group consisting of:

a guanine nucleotide – and/or an adenosine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide – and/or a thymine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide – and/or a guanine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

55. The method of claim 50, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least one SNP selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5;

and at least one SNP selected from the group consisting of:

a cytosine nucleotide - containing allele of SNP rs737865 set forth in SEQ ID NO:21;

a guanine nucleotide - containing allele of SNP rs4680 set forth in SEQ ID NO:22; and

a guanine nucleotide - containing allele of SNP rs165599 set forth in SEQ ID NO:23.

56. The kit of claim 50, wherein said at least one reagent is selected from the group consisting of at least one oligonucleotide, at least one antibody and a DNA chip.

57. The kit of claim 56, wherein said at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

58. The kit of claim 56, wherein said at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

59. The kit of claim 56, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at

least one oligonucleotide can differentiate between polymorphs of said SNP via a differential template dependent primer extension reaction or a differential template dependent ligation reaction.

60. The kit of claim 56, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via a differential template dependent primer extension reaction or a differential template dependent ligation reaction.

61. The kit of claim 56, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can be used to amplify polymorphs of said SNP via an amplification reaction.

62. The kit of claim 56, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can be used to amplify polymorphs of said SNP via an amplification reaction.

63. The kit of claim 56, wherein said at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having an SNP rs2072123, said at least one antibody can differentiate between polymorphs of said DGCR2 protein via differential antibody interaction.

64. The kit of claim 56, wherein said at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having a non-synonymous SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one antibody can differentiate between polymorphs of said DGCR2 protein via differential antibody interaction.

65. The kit of claim 56, wherein said DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

66. The kit of claim 56, wherein said DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

67. The kit of claim 50, wherein said at least one reagent is designed for use in a detection method selected from the group consisting of a signal amplification method, a direct detection method and detection of at least one sequence change.

68. The kit of claim 67, wherein said signal amplification method amplifies a molecule selected from the group consisting of a DNA molecule and an RNA molecule.

69. The kit of claim 67, wherein said signal amplification method is selected from the group consisting of PCR, LCR (LAR), Self-Sustained Synthetic Reaction (3SR/NASBA) and Q-Beta (Qβ) Replicase reaction.

70. The kit of claim 67, wherein said direct detection method is selected from the group consisting of a cycling probe reaction (CPR) and a branched DNA analysis.

71. The kit of claim 67, wherein said detection of at least one sequence change is effected by a method selected from the group consisting of the Allele Refractory Mutation System (ARMS), restriction fragment length polymorphism (RFLP analysis), primer extension, mini-sequencing, Pyrosequencing™, Competitive

Oligonucleotide Single Base Extension (COSBE), Dynamic Allele Specific Hybridization (DASH), heteroduplex/homoduplex resolution by Denaturing High Performance Liquid Chromatography (DHPLC), heteroduplex/homoduplex resolution by enzymatic cleavage, capillary electrophoresis - Single Strand Conformation Polymorphism (CE- SSCP), Conformation Sensitive Gel Electrophoresis (CSGE), Allele specific ligation (OLA), Matrix-Assisted Laser Desorption-Ionization (MALDI) time-of-flight (TOF) Mass Spectrometry (MS), Fluorescence Resonance Energy Transfer (FRET), Fluorescence polarization, TaqMan (5' exonuclease assay), Molecular beacons, Template-directed Dye Incorporation (TDI), Peptide Nucleic Acid (PNA) hybridization probes, Invader™ assay, Padlock probes, Light-up probes, Real Time PCR, And Kinetic PCR.

72. The kit of claim 50, wherein said at least one reagent is designed for use in an immunological detection method for a DGCR2 protein encoded by said DGCR2 locus.

73. The kit of claim 72, wherein said immunological detection method is selected from the group consisting of a radio-immunoassay (RIA), an enzyme linked immunosorbent assay (ELISA), a western blot, an immunohistochemical analysis, and fluorescence activated cell sorting (FACS).

74. A kit for determining a predisposition to develop schizophrenia in a male subject, the kit comprising a packaging material packaging at least one reagent, said at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, said neighboring loci being in linkage disequilibrium with said DGCR2 locus, wherein said genotype is associated with schizophrenia in males in higher association than in females, the kit further comprising a notification in or on said packaging material, said notification identifying the kit for use in determining a predisposition of a male subject of developing schizophrenia.

75. The kit of claim 74, wherein said notification also provides for instructions of using the kit in determining the predisposition of a male subject of developing schizophrenia.

76. The kit of claim 75, wherein said at least one genotype in said DCGR2 locus is a guanine nucleotide – and/or an adenosine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13.

77. The kit of 75, wherein said at least one genotype in said DGCR2 locus is a cytosine nucleotide – and/or a thymine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1.

78. The kit of claim 75, wherein said at least one genotype in said DGCR2 locus is an adenosine nucleotide – and/or a guanine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

79. The kit of claim 75, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least two SNPs selected from the group consisting of:

a guanine nucleotide – and/or an adenosine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide – and/or a thymine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide – and/or a guanine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

80. The method of claim 75, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least one SNP selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5;

and at least one SNP selected from the group consisting of:

a cytosine nucleotide - containing allele of SNP rs737865 set forth in SEQ ID NO:21;

a guanine nucleotide - containing allele of SNP rs4680 set forth in SEQ ID NO:22; and

a guanine nucleotide - containing allele of SNP rs165599 set forth in SEQ ID NO:23.

81. The kit of claim 75, wherein said at least one reagent is selected from the group consisting of at least one oligonucleotide, at least one antibody and a DNA chip.

82. The kit of claim 81, wherein said at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

83. The kit of claim 81, wherein said at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

84. The kit of claim 81, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via a differential template dependent primer extension reaction or a differential template dependent ligation reaction.

85. The kit of claim 81, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via a differential template dependent primer extension reaction or a differential template dependent ligation reaction.

86. The kit of claim 81, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can be used to amplify polymorphs said SNP via an amplification reaction.

87. The kit of claim 81, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can be used to amplify polymorphs said SNP via an amplification reaction.

88. The kit of claim 81, wherein said at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having an SNP rs2072123, said at least one antibody can differentiate between polymorphs of said DGCR2 protein via differential antibody interaction.

89. The kit of claim 81, wherein said at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having a non-synonymous SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one antibody can differentiate between polymorphs of said DGCR2 protein via differential antibody interaction.

90. The kit of claim 81, wherein said DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP selected from the group consisting of

rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

91. The kit of claim 81, wherein said DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

92. The kit of claim 75, wherein said at least one reagent is designed for use in a detection method selected from the group consisting of a signal amplification method, a direct detection method and detection of at least one sequence change.

93. The kit of claim 92, wherein said signal amplification method amplifies a molecule selected from the group consisting of a DNA molecule and an RNA molecule.

94. The kit of claim 92, wherein said signal amplification method is selected from the group consisting of PCR, LCR (LAR), Self-Sustained Synthetic Reaction (3SR/NASBA) and Q-Beta (Qβ) Replicase reaction.

95. The kit of claim 92, wherein said direct detection method is selected from the group consisting of a cycling probe reaction (CPR) and a branched DNA analysis.

96. The kit of claim 92, wherein said detection of at least one sequence change is effected by a method selected from the group consisting of the Allele Refractory Mutation System (ARMS), restriction fragment length polymorphism (RFLP analysis), primer extension, mini-sequencing, Pyrosequencing™, Competitive Oligonucleotide Single Base Extension (COSBE), Dynamic Allele Specific Hybridization (DASH), heteroduplex/homoduplex resolution by Denaturing High Performance Liquid Chromatography (DHPLC), heteroduplex/homoduplex resolution

by enzymatic cleavage, capillary electrophoresis - Single Strand Conformation Polymorphism (CE- SSCP), Conformation Sensitive Gel Electrophoresis (CSGE), Allele specific ligation (OLA), Matrix-Assisted Laser Desorption-Ionization (MALDI) time-of-flight (TOF) Mass Spectrometry (MS), Fluorescence Resonance Energy Transfer (FRET), Fluorescence polarization, TaqMan (5' exonuclease assay), Molecular beacons, Template-directed Dye Incorporation (TDI), Peptide Nucleic Acid (PNA) hybridization probes, Invader™ assay, Padlock probes, Light-up probes, Real Time PCR, And Kinetic PCR.

97. The kit of claim 75, wherein said at least one reagent is designed for use in an immunological detection method for a DGCR2 protein encoded by said DGCR2 locus.

98. The kit of claim 97, wherein said immunological detection method is selected from the group consisting of a radio-immunoassay (RIA), an enzyme linked immunosorbent assay (ELISA), a western blot, an immunohistochemical analysis, and fluorescence activated cell sorting (FACS).

99. A kit for assisting in diagnosing schizophrenia in a subject in need thereof, the kit comprising a packaging material packaging at least one reagent, said at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, said neighboring loci being in linkage disequilibrium with said DGCR2 locus, wherein said genotype is associated with schizophrenia, the kit further comprising a notification in or on said packaging material, said notification identifying the kit for use in assisting in diagnosing schizophrenia in a subject.

100. The kit of claim 99, wherein said notification also provides for instructions of using the kit in assisting in diagnosing schizophrenia of a subject.

101. The kit of claim 100, wherein said at least one genotype in said DCGR2 locus is a guanine nucleotide – and/or an adenosine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13.

102. The kit of claim 100, wherein said at least one genotype in said DGCR2 locus is a cytosine nucleotide – and/or a thymine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1.

103. The kit of claim 100, wherein said at least one genotype in said DGCR2 locus is an adenosine nucleotide – and/or a guanine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

104. The kit of claim 100, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype comprising at least two of:

a guanine nucleotide – and/or an adenosine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide – and/or a thymine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide – and/or a guanine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

105. The method of claim 100, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least one SNP selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5;

and at least one SNP selected from the group consisting of:

a cytosine nucleotide - containing allele of SNP rs737865 set forth in SEQ ID NO:21;

a guanine nucleotide - containing allele of SNP rs4680 set forth in SEQ ID NO:22; and

a guanine nucleotide - containing allele of SNP rs165599 set forth in SEQ ID NO:23.

106. The kit of 100, wherein said at least one reagent is selected from the group consisting of at least one oligonucleotide, at least one antibody and a DNA chip.

107. The kit of claim 106, wherein said at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

108. The kit of claim 106, wherein said at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

109. The kit of claim 106, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via a differential template dependent primer extension reaction or a differential template dependent ligation reaction.

110. The kit of claim 106, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via a differential template dependent primer extension reaction or a differential template dependent ligation reaction.

111. The kit of claim 106, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at

least one oligonucleotide can be used to amplify polymorphs said SNP via an amplification reaction.

112. The kit of claim 106, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can be used to amplify polymorphs said SNP via an amplification reaction.

113. The kit of claim 106, wherein said at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having an SNP rs2072123, said at least one antibody can differentiate between polymorphs of said DGCR2 protein via differential antibody interaction.

114. The kit of claim 106, wherein said at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having a non-synonymous SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one antibody can differentiate between polymorphs of said DGCR2 protein via differential antibody interaction.

115. The kit of claim 106, wherein said DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

116. The kit of claim 106, wherein said DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

117. The kit of claim 100, wherein said at least one reagent is designed for use in a detection method selected from the group consisting of a signal amplification method, a direct detection method and detection of at least one sequence change.

118. The kit of claim 117, wherein said signal amplification method amplifies a molecule selected from the group consisting of a DNA molecule and an RNA molecule.

119. The kit of claim 117, wherein said signal amplification method is selected from the group consisting of PCR, LCR (LAR), Self-Sustained Synthetic Reaction (3SR/NASBA) and Q-Beta (Qβ) Replicase reaction.

120. The kit of claim 117, wherein said direct detection method is selected from the group consisting of a cycling probe reaction (CPR) and a branched DNA analysis.

121. The kit of claim 117, wherein said detection of at least one sequence change is effected by a method selected from the group consisting of the Allele Refractory Mutation System (ARMS), restriction fragment length polymorphism (RFLP analysis), primer extension, mini-sequencing, Pyrosequencing™, Competitive Oligonucleotide Single Base Extension (COSBE), Dynamic Allele Specific Hybridization (DASH), heteroduplex/homoduplex resolution by Denaturing High Performance Liquid Chromatography (DHPLC), heteroduplex/homoduplex resolution by enzymatic cleavage, capillary electrophoresis - Single Strand Conformation Polymorphism (CE- SSCP), Conformation Sensitive Gel Electrophoresis (CSGE), Allele specific ligation (OLA), Matrix-Assisted Laser Desorption-Ionization (MALDI) time-of-flight (TOF) Mass Spectrometry (MS), Fluorescence Resonance Energy Transfer (FRET), Fluorescence polarization, TaqMan (5' exonuclease assay), Molecular beacons, Template-directed Dye Incorporation (TDI), Peptide Nucleic Acid (PNA) hybridization probes, Invader™ assay, Padlock probes, Light-up probes, Real Time PCR, And Kinetic PCR.

122. The kit of claim 100, wherein said at least one reagent is designed for use in an immunological detection method for a DGCR2 protein encoded by said DGCR2 locus.

123. The kit of claim 122, wherein said immunological detection method is selected from the group consisting of a radio-immunoassay (RIA), an enzyme linked immunosorbent assay (ELISA), a western blot, an immunohistochemical analysis, and fluorescence activated cell sorting (FACS).

124. A kit for assisting in diagnosing schizophrenia in a male subject in need thereof, the kit comprising a packaging material packaging at least one reagent, said at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, said neighboring loci being in linkage disequilibrium with said DGCR2 locus, wherein said genotype is associated with schizophrenia in males in higher association than in females, the kit further comprising a notification in or on said packaging material, said notification identifying the kit for use in assisting in diagnosing schizophrenia in a male subject.

125. The kit of claim 124, wherein said notification also provides for instructions of using the kit in assisting in diagnosing schizophrenia of a male subject.

126. The kit of claim 125, wherein said at least one genotype in said DCGR2 locus is a guanine nucleotide – and/or an adenosine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13.

127. The kit of claim 125, wherein said at least one genotype in said DGCR2 locus is a cytosine nucleotide – and/or a thymine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1.

128. The kit of claim 125, wherein said at least one genotype in said DGCR2 locus is an adenosine nucleotide – and/or a guanine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

129. The kit of claim 125, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least two SNPs selected from the group consisting of:

a guanine nucleotide – and/or an adenosine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide – and/or a thymine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide – and/or a guanine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

130. The method of claim 125, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least one SNP selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5;

and at least one SNP selected from the group consisting of:

a cytosine nucleotide - containing allele of SNP rs737865 set forth in SEQ ID NO:21;

a guanine nucleotide - containing allele of SNP rs4680 set forth in SEQ ID NO:22; and

a guanine nucleotide - containing allele of SNP rs165599 set forth in SEQ ID NO:23.

131. The kit of claim 125, wherein said at least one reagent is selected from the group consisting of at least one oligonucleotide, at least one antibody and a DNA chip.

132. The kit of claim 131, wherein said at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an

SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

133. The kit of claim 131, wherein said at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

134. The kit of claim 131, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via a differential template dependent primer extension reaction or a differential template dependent ligation reaction.

135. The kit of claim 131, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via a differential template dependent primer extension reaction or a differential template dependent ligation reaction.

136. The kit of claim 131, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can be used to amplify polymorphs said SNP via an amplification reaction.

137. The kit of claim 131, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one

oligonucleotide can be used to amplify polymorphs said SNP via an amplification reaction.

138. The kit of claim 131, wherein said at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having an SNP rs2072123, said at least one antibody can differentiate between polymorphs of said DGCR2 protein via differential antibody interaction.

139. The kit of claim 131, wherein said at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having a non-synonymous SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one antibody can differentiate between polymorphs of said DGCR2 protein via differential antibody interaction.

140. The kit of claim 131, wherein said DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

141. The kit of claim 131, wherein said DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

142. The kit of claim 125, wherein said at least one reagent is designed for use in a detection method selected from the group consisting of a signal amplification method, a direct detection method and detection of at least one sequence change.

143. The kit of claim 142, wherein said signal amplification method amplifies a molecule selected from the group consisting of a DNA molecule and an RNA molecule.

144. The kit of claim 142, wherein said signal amplification method is selected from the group consisting of PCR, LCR (LAR), Self-Sustained Synthetic Reaction (3SR/NASBA) and Q-Beta (Qβ) Replicase reaction.

145. The kit of claim 142, wherein said direct detection method is selected from the group consisting of a cycling probe reaction (CPR) and a branched DNA analysis.

146. The kit of claim 142, wherein said detection of at least one sequence change is effected by a method selected from the group consisting of the Allele Refractory Mutation System (ARMS), restriction fragment length polymorphism (RFLP analysis), primer extension, mini-sequencing, Pyrosequencing™, Competitive Oligonucleotide Single Base Extension (COSBE), Dynamic Allele Specific Hybridization (DASH), heteroduplex/homoduplex resolution by Denaturing High Performance Liquid Chromatography (DHPLC), heteroduplex/homoduplex resolution by enzymatic cleavage, capillary electrophoresis - Single Strand Conformation Polymorphism (CE- SSCP), Conformation Sensitive Gel Electrophoresis (CSGE), Allele specific ligation (OLA), Matrix-Assisted Laser Desorption-Ionization (MALDI) time-of-flight (TOF) Mass Spectrometry (MS), Fluorescence Resonance Energy Transfer (FRET), Fluorescence polarization, TaqMan (5' exonuclease assay), Molecular beacons, Template-directed Dye Incorporation (TDI), Peptide Nucleic Acid (PNA) hybridization probes, Invader™ assay, Padlock probes, Light-up probes, Real Time PCR, And Kinetic PCR.

147. The kit of claim 125, wherein said at least one reagent is designed for use in an immunological detection method for a DGCR2 protein encoded by said DGCR2 locus.

148. The kit of claim 147, wherein said immunological detection method is selected from the group consisting of a radio-immunoassay (RIA), an enzyme linked immunosorbent assay (ELISA), a western blot, an immunohistochemical analysis, and fluorescence activated cell sorting (FACS).

149. A kit for predicting drug responsiveness of a subject having schizophrenia to a schizophrenia drug, the kit comprising a packaging material packaging at least one reagent, said at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, said neighboring loci being in linkage disequilibrium with said DGCR2 locus, wherein said genotype is associated with schizophrenia, the kit further comprising a notification in or on said packaging material, said notification identifying the kit for use in predicting drug responsiveness of a subject having schizophrenia to the drug.

150. The kit of claim 149, wherein said notification also provides for instructions of using the kit in assisting in predicting drug responsiveness of a subject having schizophrenia to the drug.

151. The kit of claim 150, wherein said at least one genotype in said DGCR2 locus is a cytosine nucleotide – and/or a thymine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1.

152. The kit of claim 150, wherein said at least one genotype in said DGCR2 locus is an adenosine nucleotide – and/or a guanine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

153. The kit of claim 150, wherein said drug is selected from the group consisting of zuclopenthixol and olanzapine.

154. The kit of claim 150, wherein said at least one reagent is selected from the group consisting of at least one oligonucleotide, at least one antibody and a DNA chip.

155. The kit of claim 154, wherein said at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

156. The kit of claim 154, wherein said at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

157. The kit of claim 154, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via a differential template dependent primer extension reaction or a differential template dependent ligation reaction.

158. The kit of claim 154, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via a differential template dependent primer extension reaction or a differential template dependent ligation reaction.

159. The kit of claim 154, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can be used to amplify polymorphs said SNP via an amplification reaction.

160. The kit of claim 154, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can be used to amplify polymorphs said SNP via an amplification reaction.

161. The kit of claim 154, wherein said at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having an SNP rs2072123, said at least one antibody can differentiate between polymorphs of said DGCR2 protein via differential antibody interaction.

162. The kit of claim 154, wherein said at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having a non-synonymous SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one antibody can differentiate between polymorphs of said DGCR2 protein via differential antibody interaction.

163. The kit of claim 154, wherein said DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

164. The kit of claim 154, wherein said DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

165. The kit of claim 150, wherein said at least one reagent is designed for use in a detection method selected from the group consisting of a signal amplification method, a direct detection method and detection of at least one sequence change.

166. The kit of claim 165, wherein said signal amplification method amplifies a molecule selected from the group consisting of a DNA molecule and an RNA molecule.

167. The kit of claim 165, wherein said signal amplification method is selected from the group consisting of PCR, LCR (LAR), Self-Sustained Synthetic Reaction (3SR/NASBA) and Q-Beta (Qβ) Replicase reaction.

168. The kit of claim 165, wherein said direct detection method is selected from the group consisting of a cycling probe reaction (CPR) and a branched DNA analysis.

169. The kit of claim 165, wherein said detection of at least one sequence change is effected by a method selected from the group consisting of the Allele Refractory Mutation System (ARMS), restriction fragment length polymorphism (RFLP analysis), primer extension, mini-sequencing, Pyrosequencing™, Competitive Oligonucleotide Single Base Extension (COSBE), Dynamic Allele Specific Hybridization (DASH), heteroduplex/homoduplex resolution by Denaturing High Performance Liquid Chromatography (DHPLC), heteroduplex/homoduplex resolution by enzymatic cleavage, capillary electrophoresis - Single Strand Conformation Polymorphism (CE- SSCP), Conformation Sensitive Gel Electrophoresis (CSGE), Allele specific ligation (OLA), Matrix-Assisted Laser Desorption-Ionization (MALDI) time-of-flight (TOF) Mass Spectrometry (MS), Fluorescence Resonance Energy Transfer (FRET), Fluorescence polarization, TaqMan (5' exonuclease assay), Molecular beacons, Template-directed Dye Incorporation (TDI), Peptide Nucleic Acid (PNA) hybridization probes, Invader™ assay, Padlock probes, Light-up probes, Real Time PCR, And Kinetic PCR.

170. The kit of claim 150, wherein said at least one reagent is designed for use in an immunological detection method for a DGCR2 protein encoded by said DGCR2 locus.

171. The kit of claim 170, wherein said immunological detection method is selected from the group consisting of a radio-immunoassay (RIA), an enzyme linked immunosorbent assay (ELISA), a western blot, an immunohistochemical analysis, and fluorescence activated cell sorting (FACS).

172. A kit for predicting drug responsiveness of a subject having a given mental disorder to a mental disorder drug, the kit comprising a packaging material packaging at least one reagent, said at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, said neighboring loci being in linkage disequilibrium with said DGCR2 locus, wherein said genotype is associated with drug responsiveness to the drug in at least one mental disorder, the kit further comprising a notification in or on said packaging material, said notification identifying the kit for use in predicting drug responsiveness of a subject having the given mental disorder to the drug.

173. The kit of claim 172, wherein said notification also provides for instructions of using the kit in assisting in predicting drug responsiveness of a subject having the given mental disorder to the drug.

174. The kit of claim 173, wherein said mental disorder is selected from the group consisting of schizophrenia, schizoaffective disorder, bipolar disorder, depression, obsessive compulsive disorder, panic disorder, agoraphobia, specific phobia, social phobia, post-traumatic stress disorder, pain disorder, anxiety, somatization disorder, anorexia nervosa, bulimia, and nervosa.

175. The kit of claim 173, wherein said drug is selected from the group consisting of thioridazine, clozapine, haloperidol, fluphenazine, cholrpromazine, risperidone, levomepromazine, perhenazine, chlorprothixene, pimozide, sulpiride, olanzapine, zuclopenthixol, amitriptyline, imipramine, clomipramine, desipramine, doxepin, mianserin, maprotiline, phenelzine, fluoxetine, trazodone, fluvoxamine, sertraline, paroxetine, reboxetine, citalopram, nefazodone, venlafoxine, lithium salts, carbamazapine, valproic acid, and clonazepam.

176. The kit of claim 173, wherein said at least one genotype in said DCGR2 locus is a guanine nucleotide – and/or an adenosine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13.

177. The kit of claim 173, wherein said at least one genotype in said DGCR2 locus is a cytosine nucleotide – and/or a thymine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1.

178. The kit of claim 173, wherein said at least one genotype in said DGCR2 locus is an adenosine nucleotide – and/or a guanine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

179. The kit of claim 173, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least two SNPs selected from the group consisting of:

a guanine nucleotide – and/or an adenosine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide – and/or a thymine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide – and/or a guanine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

180. The method of claim 173, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least one SNP selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5;

and at least one SNP selected from the group consisting of:

a cytosine nucleotide - containing allele of SNP rs737865 set forth in SEQ ID NO:21;

a guanine nucleotide - containing allele of SNP rs4680 set forth in SEQ ID NO:22; and

a guanine nucleotide - containing allele of SNP rs165599 set forth in SEQ ID NO:23.

181. The kit of claim 173, wherein said at least one reagent is selected from the group consisting of at least one oligonucleotide, at least one antibody and a DNA chip.

182. The kit of claim 181, wherein said at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

183. The kit of claim 181, wherein said at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequlibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

184. The kit of claim 181, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via a differential template dependent primer extension reaction or a differential template dependent ligation reaction.

185. The kit of claim 181, wherein said at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequlibrium with rs807759, rs2072123 or rs2073776, said at least

one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

186. The kit of claim 181, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can be used to amplify polymorphs said SNP via an amplification reaction.

187. The kit of claim 181, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP in linkage disequlibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can be used to amplify polymorphs said SNP via an amplification reaction.

188. The kit of claim 181, wherein said at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having an SNP rs2072123, said at least one antibody can differentiate between polymorphs of said DGCR2 protein via differential antibody interaction.

189. The kit of claim 181, wherein said at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having a non-synonymous SNP in linkage disequlibrium with rs807759, rs2072123 or rs2073776, said at least one antibody can differentiate between polymorphs of said DGCR2 protein via differential antibody interaction.

190. The kit of claim 181, wherein said DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

191. The kit of claim 181, wherein said DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequlibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

192. The kit of claim 173, wherein said at least one reagent is designed for use in a detection method selected from the group consisting of a signal amplification method, a direct detection method and detection of at least one sequence change.

193. The kit of claim 192, wherein said signal amplification method amplifies a molecule selected from the group consisting of a DNA molecule and an RNA molecule.

194. The kit of claim 192, wherein said signal amplification method is selected from the group consisting of PCR, LCR (LAR), Self-Sustained Synthetic Reaction (3SR/NASBA) and Q-Beta (Qβ) Replicase reaction.

195. The kit of claim 192, wherein said direct detection method is selected from the group consisting of a cycling probe reaction (CPR) and a branched DNA analysis.

196. The kit of claim 192, wherein said detection of at least one sequence change is effected by a method selected from the group consisting of the Allele Refractory Mutation System (ARMS), restriction fragment length polymorphism (RFLP analysis), primer extension, mini-sequencing, Pyrosequencing™, Competitive Oligonucleotide Single Base Extension (COSBE), Dynamic Allele Specific Hybridization (DASH), heteroduplex/homoduplex resolution by Denaturing High Performance Liquid Chromatography (DHPLC), heteroduplex/homoduplex resolution by enzymatic cleavage, capillary electrophoresis - Single Strand Conformation Polymorphism (CE- SSCP), Conformation Sensitive Gel Electrophoresis (CSGE), Allele specific ligation (OLA), Matrix-Assisted Laser Desorption-Ionization (MALDI)

time-of-flight (TOF) Mass Spectrometry (MS), Fluorescence Resonance Energy Transfer (FRET), Fluorescence polarization, TaqMan (5' exonuclease assay), Molecular beacons, Template-directed Dye Incorporation (TDI), Peptide Nucleic Acid (PNA) hybridization probes, Invader™ assay, Padlock probes, Light-up probes, Real Time PCR, And Kinetic PCR.

197. The kit of claim 173, wherein said at least one reagent is designed for use in an immunological detection method for a DGCR2 protein encoded by said DGCR2 locus.

198. The kit of claim 197, wherein said immunological detection method is selected from the group consisting of a radio-immunoassay (RIA), an enzyme linked immunosorbent assay (ELISA), a western blot, an immunohistochemical analysis, and fluorescence activated cell sorting (FACS).

199. A kit for identifying a genetic association with, or a genetic cause to, varying drug responsiveness to a schizophrenia drug, the kit comprising a packaging material packaging at least one reagent, said at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, said neighboring loci being in linkage disequilibrium with said DGCR2 locus, wherein said genotype is associated with schizophrenia, the kit further comprising a notification in or on said packaging material, said notification identifying the kit for use in identifying a genetic association with, or a genetic cause to, varying drug responsiveness to the drug.

200. The kit of claim 199, wherein said notification also provides for instructions of using the kit in identifying a genetic association with, or a genetic cause to, varying drug responsiveness to the drug.

201. The kit of claim 200, wherein said at least one genotype in said DGCR2 locus is a cytosine nucleotide – and/or a thymine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1.

202. The kit of claim 200, wherein said at least one genotype in said DGCR2 locus is an adenosine nucleotide – and/or a guanine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

203. The kit of claim 200, wherein said drug is selected from the group consisting of zuclopenthixol and olanzapine.

204. The kit of claim 200, wherein said at least one reagent is selected from the group consisting of at least one oligonucleotide, at least one antibody and a DNA chip.

205. The kit of claim 204, wherein said at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

206. The kit of claim 204, wherein said at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

207. The kit of claim 204, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via a differential template dependent primer extension reaction or a differential template dependent ligation reaction.

208. The kit of claim 204, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one

oligonucleotide can differentiate between polymorphs of said SNP via a differential template dependent primer extension reaction or a differential template dependent ligation reaction.

209. The kit of claim 204, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can be used to amplify polymorphs said SNP via an amplification reaction.

210. The kit of claim 204, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can be used to amplify polymorphs said SNP via an amplification reaction.

211. The kit of claim 204, wherein said at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having an SNP rs2072123, said at least one antibody can differentiate between polymorphs of said DGCR2 protein via differential antibody interaction.

212. The kit of claim 204, wherein said at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having a non-synonymous SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one antibody can differentiate between polymorphs of said DGCR2 protein via differential antibody interaction.

213. The kit of claim 204, wherein said DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

214. The kit of claim 204, wherein said DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

215. The kit of claim 200, wherein said at least one reagent is designed for use in a detection method selected from the group consisting of a signal amplification method, a direct detection method and detection of at least one sequence change.

216. The kit of claim 215, wherein said signal amplification method amplifies a molecule selected from the group consisting of a DNA molecule and an RNA molecule.

217. The kit of claim 215, wherein said signal amplification method is selected from the group consisting of PCR, LCR (LAR), Self-Sustained Synthetic Reaction (3SR/NASBA) and Q-Beta (Qβ) Replicase reaction.

218. The kit of claim 215, wherein said direct detection method is selected from the group consisting of a cycling probe reaction (CPR) and a branched DNA analysis.

219. The kit of claim 215, wherein said detection of at least one sequence change is effected by a method selected from the group consisting of the Allele Refractory Mutation System (ARMS), restriction fragment length polymorphism (RFLP analysis), primer extension, mini-sequencing, Pyrosequencing™, Competitive Oligonucleotide Single Base Extension (COSBE), Dynamic Allele Specific Hybridization (DASH), heteroduplex/homoduplex resolution by Denaturing High Performance Liquid Chromatography (DHPLC), heteroduplex/homoduplex resolution by enzymatic cleavage, capillary electrophoresis - Single Strand Conformation Polymorphism (CE- SSCP), Conformation Sensitive Gel Electrophoresis (CSGE), Allele specific ligation (OLA), Matrix-Assisted Laser Desorption-Ionization (MALDI)

time-of-flight (TOF) Mass Spectrometry (MS), Fluorescence Resonance Energy Transfer (FRET), Fluorescence polarization, TaqMan (5' exonuclease assay), Molecular beacons, Template-directed Dye Incorporation (TDI), Peptide Nucleic Acid (PNA) hybridization probes, Invader™ assay, Padlock probes, Light-up probes, Real Time PCR, And Kinetic PCR.

220. The kit of claim 200, wherein said at least one reagent is designed for use in an immunological detection method for a DGCR2 protein encoded by said DGCR2 locus.

221. The kit of claim 220, wherein said immunological detection method is selected from the group consisting of a radio-immunoassay (RIA), an enzyme linked immunosorbent assay (ELISA), a western blot, an immunohistochemical analysis, and fluorescence activated cell sorting (FACS).

222. A kit for identifying a genetic association with, or a genetic cause to, varying drug responsiveness of a subject having a given mental disorder to a mental disorder drug, the kit comprising a packaging material packaging at least one reagent, said at least one reagent for determining a presence in a homozygous or heterozygous form, or an absence, of a genotype in the DGCR2 locus or in neighboring loci, said neighboring loci being in linkage disequilibrium with said DGCR2 locus, wherein said genotype is associated with drug responsiveness to the drug in at least one mental disorder, the kit further comprising a notification in or on said packaging material, said notification identifying the kit for use in identifying a genetic association with, or a genetic cause to, varying drug responsiveness of a subject having the given mental disorder to the drug.

223. The kit of claim 222, wherein said notification also provides for instructions of using the kit in identifying a genetic association with, or a genetic cause to, varying drug responsiveness of a subject having the given mental disorder to the drug.

224. The kit of claim 223, wherein said mental disorder is selected from the group consisting of schizophrenia, schizoaffective disorder, bipolar disorder, depression, obsessive compulsive disorder, panic disorder, agoraphobia, specific phobia, social phobia, post-traumatic stress disorder, pain disorder, anxiety, somatization disorder, anorexia nervosa, bulimia, and nervosa.

225. The kit of claim 223, wherein said drug is selected from the group consisting of thioridazine, clozapine, haloperidol, fluphenazine, cholrpromazine, risperidone, levomepromazine, perhenazine, chlorprothixene, pimozide, sulpiride, olanzapine, zuclopenthixol, amitriptyline, imipramine, clomipramine, desipramine, doxepin, mianserin, maprotiline, phenelzine, fluoxetine, trazodone, fluvoxamine, sertraline, paroxetine, reboxetine, citalopram, nefazodone, venlafoxine, lithium salts, carbamazapine, valproic acid, and clonazepam.

226. The kit of claim 223, wherein said at least one genotype in said DCGR2 locus is a guanine nucleotide – and/or an adenosine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13.

227. The kit of claim 223, wherein said at least one genotype in said DGCR2 locus is a cytosine nucleotide – and/or a thymine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1.

228. The kit of claim 223, wherein said at least one genotype in said DGCR2 locus is an adenosine nucleotide – and/or a guanine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

229. The kit of claim 223, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least two SNPs selected from the group consisting of:

a guanine nucleotide – and/or an adenosine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide – and/or a thymine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide – and/or a guanine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5.

230. The method of claim 223, wherein said at least one genotype in said DGCR2 locus is an allelic haplotype including at least one SNP selected from the group consisting of:

a guanine nucleotide - containing allele of SNP rs807759 set forth in SEQ ID NO:13;

a cytosine nucleotide - containing allele of SNP rs2072123 set forth in SEQ ID NO:1; and

an adenosine nucleotide - containing allele of SNP rs2073776 set forth in SEQ ID NO:5;

and at least one SNP selected from the group consisting of:

a cytosine nucleotide - containing allele of SNP rs737865 set forth in SEQ ID NO:21;

a guanine nucleotide - containing allele of SNP rs4680 set forth in SEQ ID NO:22; and

a guanine nucleotide - containing allele of SNP rs165599 set forth in SEQ ID NO:23.

231. The kit of claim 223, wherein said at least one reagent is selected from the group consisting of at least one oligonucleotide, at least one antibody and a DNA chip.

232. The kit of claim 231, wherein said at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

233. The kit of claim 231, wherein said at least one oligonucleotide has a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least

one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

234. The kit of claim 231, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via a differential template dependent primer extension reaction or a differential template dependent ligation reaction.

235. The kit of claim 231, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via a differential template dependent primer extension reaction or a differential template dependent ligation reaction.

236. The kit of claim 231, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can be used to amplify polymorphs said SNP via an amplification reaction.

237. The kit of claim 231, wherein said at least one oligonucleotide has a sequence selected capable of hybridizing to a sequence region adjacent to an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can be used to amplify polymorphs said SNP via an amplification reaction.

238. The kit of claim 231, wherein said at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having an SNP rs2072123, said at least one antibody can differentiate between polymorphs of said DGCR2 protein via differential antibody interaction.

239. The kit of claim 231, wherein said at least one antibody is differentially interactable with at least one form of a DGCR2 protein encoded by a DGCR2 allele having a non-synonymous SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one antibody can differentiate between polymorphs of said DGCR2 protein via differential antibody interaction.

240. The kit of claim 231, wherein said DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP selected from the group consisting of rs807759, rs2072123 and rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

241. The kit of claim 231, wherein said DNA chip comprises attached thereto at least one oligonucleotide having a sequence selected capable of differentially hybridizing with at least one allele of an SNP in linkage disequilibrium with rs807759, rs2072123 or rs2073776, said at least one oligonucleotide can differentiate between polymorphs of said SNP via differential hybridization.

242. The kit of claim 223, wherein said at least one reagent is designed for use in a detection method selected from the group consisting of a signal amplification method, a direct detection method and detection of at least one sequence change.

243. The kit of claim 242, wherein said signal amplification method amplifies a molecule selected from the group consisting of a DNA molecule and an RNA molecule.

244. The kit of claim 242, wherein said signal amplification method is selected from the group consisting of PCR, LCR (LAR), Self-Sustained Synthetic Reaction (3SR/NASBA) and Q-Beta (Qβ) Replicase reaction.

245. The kit of claim 242, wherein said direct detection method is selected from the group consisting of a cycling probe reaction (CPR) and a branched DNA analysis.

246. The kit of 242, wherein said detection of at least one sequence change is effected by a method selected from the group consisting of the Allele Refractory Mutation System (ARMS), restriction fragment length polymorphism (RFLP analysis), primer extension, mini-sequencing, Pyrosequencing™, Competitive Oligonucleotide Single Base Extension (COSBE), Dynamic Allele Specific Hybridization (DASH), heteroduplex/homoduplex resolution by Denaturing High Performance Liquid Chromatography (DHPLC), heteroduplex/homoduplex resolution by enzymatic cleavage, capillary electrophoresis - Single Strand Conformation Polymorphism (CE- SSCP), Conformation Sensitive Gel Electrophoresis (CSGE), Allele specific ligation (OLA), Matrix-Assisted Laser Desorption-Ionization (MALDI) time-of-flight (TOF) Mass Spectrometry (MS), Fluorescence Resonance Energy Transfer (FRET), Fluorescence polarization, TaqMan (5' exonuclease assay), Molecular beacons, Template-directed Dye Incorporation (TDI), Peptide Nucleic Acid (PNA) hybridization probes, Invader™ assay, Padlock probes, Light-up probes, Real Time PCR, And Kinetic PCR.

247. The kit of claim 223, wherein said at least one reagent is designed for use in an immunological detection method for a DGCR2 protein encoded by said DGCR2 locus.

248. The kit of claim 247, wherein said immunological detection method is selected from the group consisting of a radio-immunoassay (RIA), an enzyme linked immunosorbent assay (ELISA), a western blot, an immunohistochemical analysis, and fluorescence activated cell sorting (FACS).

249. A method of identifying novel drugs for treatment and/or prevention of schizophrenia, the method comprising incubating integral membrane protein DGCR2 or any active portion thereof or cells expressing integral membrane protein DGCR2 or

any active portion thereof with potential drugs and selecting for at least one drug of said potential drugs that modulates integral membrane protein DGCR2 activity or expression, thereby identifying novel drugs for treatment of schizophrenia.

250. The method of claim 249, wherein at least one drug of said potential drugs is selected from the group consisting of a peptide, a polynucleotide and a small molecule.

251. The method of claim 250, wherein said polynucleotide is selected from the group consisting of an antisense oligonucleotide, an siRNA, a ribozymes and a DNAzyme.

252. The method of claim 250, wherein said peptide is selected from the group consisting of a small peptide, a polypeptide and an antibody.

253. A method of treating and/or preventing schizophrenia, the method comprising administering to a subject in need thereof a therapeutically effective amount of a drug for schizophrenia, said drug for schizophrenia having been identified using the method of claim 249.

254. A method of treating and/or preventing schizophrenia, the method comprising administering to a subject in need thereof a therapeutically effective amount of at least one agent capable of modifying DGCR2 protein expression or activity.

255. The method of claim 254, wherein said at least one agent is selected from the group consisting of an anti-DGCR2 antibody, a polynucleotide encoding an intracellular anti-DGCR2 antibody, an anti-DGCR2 antisense molecule, an anti-DGCR2 siRNA, an anti-DGCR2 ribozyme, an anti-DGCR2 DNAzyme, and a DGCR2 inhibitor.

256. A method of treating and/or preventing schizophrenia, the method comprising administering to a subject in need thereof a therapeutically effective

amount of recombinant integral membrane protein DGCR2 or any active portion thereof.

SEQUENCE LISTING

<110> Darvasi, Ariel
Zak, Neomi

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Phe His Ala Val Asn Val Ala Gln Pro Val Arg Phe Ser Ser Phe Leu
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35 40 45

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