Transgenic mouse for impaired expression of endogenous ZDHHC8 as Marker for Schizophrenia

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Schizophrenia prediction and diagnosis using genetic-based method : Microdeletions in chromosome region 22q11 are associated, with relatively high frequency, with severe mental illness. Whereas a person in the general population has a risk of about 1% of developing schizophrenia, that risk may be 25-30 times higher in persons having a deletion in the 22q11 region. It therefore seems likely that the 22q11 region harbors genes that, alone or in combination, are causally implicated in schizophrenia.

An emerging “genetic” picture is that the 22q11 microdeletion-associated schizophrenia may have the characteristics of a contiguous gene syndrome where more than one gene may contribute to the dramatic increase in disease risk. Linkage disequilibrium (LD) analysis identified that PRODH2 may play an important role, although comparison of the increase in the morbidity risk of schizophrenia associated with the identified PRODH2 variation to the risk associated with the 22q11 microdeletion could not exclude contribution from other genes in the region. Further LD studies revealed a limited number of candidate genes, including a membrane associated protein, ZDHHC8, which is highly expressed in brain regions implicated in schizophrenia.

Biomarker for developing schizophrenia using transgenic mouse: This invention relates to the role of mutations that perturb expression of ZDHHC8 in increased susceptibility to schizophrenia and related disorders. It is based on discoveries that (1) a point mutation associated with increased risk of schizophrenia prevented proper splicing of ZDHHC8 mRNA; (2) ZDHHC8 interacts with two homologous proteins (PSD95 and PSD93) which are key signaling molecules in glutamatergic synapses; (3) ZDHHC8 palmitoylates and facilitates membrane translocation of PSD95; and (4) palmitoylation of PSD95 by ZDHHC8 is necessary for maintaining a homeostatic balance between excitatory glutamatergic and inhibitory GABAergic synapses.

Applications: • Provides genetic-based methods for identifying an individual at risk of developing schizophrenia or a related disorder, including schizoaffective disorder, schizophreniform disorder, schizotypal disorder, and schizoid disorder, by identifying a mutation that decreases or prevents expression of wild-type ZDHHC8 • Provides genetic-based methods that may be used to aid in establishing a diagnosis of schizophrenia or a related disorder • Provides transgenic animal with impaired expression of endogenous ZDHHC8, which may be used as experimental models of schizophrenia and related disorders • Provides methods and assay system for identifying agents useful in treating schizophrenia and/or related disorders in a subject carrying a mutation that decreases or prevents ZDHHC expression • Provides a method of treating a subject suffering from schizophrenia or a related disorder comprising administering to the subject, an effective amount of an isolated nucleic acid encoding human ZDHHC8

Advantages: • Provides a novel target gene for the diagnosis and treatment of schizophrenia and related disorders • Provides a novel target gene for identifying the risk of developing schizophrenia and related disorders • Transgenic animals can serve as a novel model of schizophrenia • Methods and assays described here can identify therapeutic compounds that have a novel mechanism of action compared to current treatments
• Provides a novel method of treatment by directly administering an isolated nucleic acid encoding human ZDHHC8 to a subset of patients

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