The C/At is out of the bag: a gene for mental illness

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Has the first 'schizophrenia' gene been identified? The knowledge that genes play a considerable role in the etiology of schizophrenia is well recognized. However, failures of consistent replication of any of the several chromosomal regions implicated in schizophrenia have left investigators frustrated, especially in this last decade. It seems that now, signs for an era of new definitions of nosological entities in psychiatry are appearing on the horizon. With the recent work by Meyer *et al* from Lesch's group that appeared in *Molecular Psychiatry*,[1] the first C/At is out of the bag. What we call schizophrenia appears to actually be a syndromal definition encompassing various heterogenous diseases. One of those diseases is a type of periodic catatonia, which is a subform of catatonic schizophrenia (MIM 181500, OMIM™, Online Mendelian inheritance in Man, http://www.ncbi.nlm.nih.gov/Omin). Periodical catatonia is a heterologous, Mendelian dominant disease with a major-gene effect and it has loci mapped at 22q13.33 and 15q15.[2] In the recent report in *Molecular Psychiatry*, the results of a restricted genome-wide linkage scan study followed by positional gene approach on periodic catatonia have resulted in the finding of an association of a gene encoding a novel putative cation channel in the 22q13 locus and periodic catatonia.[1]

Schizophrenia is possibly the most severe, incapacitating and devastating psychiatric disorder, with a lifetime risk of 1% in the general population and a peak onset in early adulthood. The diagnosis of schizophrenia is currently made by criterion-based systems, including positive (eg, hallucinations and delusions) and negative (eg, avolition and alogia) symptoms. Psychotic symptoms, such as hallucinations and paranoid delusions, are notable for their aberrant representations of, and relation to the external world. A core clinical manifestation of schizophrenia is disruption of thought, which is a mental process that is poorly localized in the brain and influenced by multiple neural systems. Recent studies suggest that schizophrenia may involve cortical, limbic, and subcortical structures as well as multiple neurotransmitter systems. Lesch's group has used Leonard's classification of schizophrenia, which unlike the DSM (Diagnostic and Statistical Manual of the American Psychiatric Association) classification of schizophrenia, catatonia type, makes a distinction between periodic and systematic catatonia based on different types of symptoms, longitudinal course and outcome.

Several twin and adoption studies have provided clear evidence for a considerable genetic contribution to schizophrenia. Though the evidence for shared environments has not been convincing in the familial clustering of the disorder, environmental risk factors could still play a role in the disease. Among these environmental risk factors obstetric complications and viral infections have been the most implicated ones. Decades of genetic studies seem to indicate that schizophrenia is a complex, non-Mendelian, polygenic disease that involves epistatic interactions between loci and environmental influences. There has been a worldwide search for the genetic markers of schizophrenia. This search has resulted in a long list of implicated chromosomes (1,2,4,5,6,7, 8,9,10,13,15,18,22, and the X) thus far (see Riley and McGuffin for a recent review[3]). These results have been controversial due to the difficulties encountered in replication. To complicate matters, schizophrenia has variable clinical presentations, natural history, and response to medication that implies a pathologically heterogeneous group of diseases. Therefore, the assumption that schizophrenia could be a syndrome, thus a collection of several nosological entities, had been lingering in the field, though most investigators had not examined this concept carefully enough to systematically study the genetics of disease subtypes. Ironically, soon after experts have ascertained that the recurrence risks of schizophrenia have conclusively allowed the rejection of the possibility that schizophrenia could be caused by a single gene disorder or collection of single gene disorders, even when taking into account incomplete penetrance, we are confronted with the surprising findings of Meyer *et al*.

In this recent report, Meyer *et al*[1] were looking for a trinucleotide repeat when they discovered a mutation in a novel gene encoding a protein, provisionally named WKL1, which is expressed highly in the amygdala, caudate nucleus, thalamus and hippocampus, and detected exclusively in brain. In one large pedigree, Meyer *et al*[1] have demonstrated that a 1121C → A transversion occurred in all seven affected individuals and all unaffected obligate carriers. This transversion results in a Leu309Met substitution. But this mutation was not present in three other pedigrees of periodic catatonia, which further supports the notion that periodic catatonia is genetically heterogeneous. Their strategy started with the examination of a well-characterized cohort of periodic catatonia, a clinical subtype of schizophrenia in which a major gene effect has been already predicted. A total of 12 large pedigrees with 135 individuals were examined with a genome-wide linkage scan that identified two susceptibility loci, the main one in chromosome 15q15 and another locus on chromosome 22q13.[2] The 22q13 locus has been mainly supported by the family that was further characterized

in their report in *Molecular Psychiatry*. Patients with periodic catatonia have acute psychotic episodes with hallucinations and delusions but they also have noteworthy psychomotor disturbances that vary from inhibition (akinetic negativism) to excitement (hyperkinesia, postural stereotypes, parakinesis, grimacing etc). A distinct residual state in the form of lack of motivation, poverty of movements, and blunted affect remains during remission. It is possible that the understanding of the actions of the WKL1 protein can help identify novel pathways that may be beyond the scope of the established neurotransmitter hypothesis for schizophrenia.

The report by Meyer *et al* seems to have defeated all odds, but in reality a number of clues have been accumulating for over two decades, suggesting that chromosome 22q11–13 is strongly implicated in certain neuropsychiatric symptoms. Among the most known genetic syndromes and anomalies associated with chromosome 22q11–13, are the deletions at the 22q11 locus, which have a wide phenotypic range, extending from DiGiorge, Shprintzen's or velocardiofacial (VCFS), and conotruncal anomaly face (Takao) syndromes. The most common manifestations of the 22q11 deletion are also known by the acronym CATCH22 (Cardiac Anomality, T-cell deficit, Clefting, and Hypocalcaemia).[4] A relationship between VCFS and psychiatric disorders has been suggested. Intellectual impairment and pervasive developmental disorders have been a common neuropsychiatric presentation during childhood and bipolar disorder, schizophrenia and schizoaffective disorders among adults with this syndrome. Chromosomal terminal deletions at the 22q13 locus have also recently been associated with pervasive developmental disorders and mental retardation. Overlapping clinical features to 22q11 deletions, such as minor craniofacial dysmorphism, normal to advanced growth, autistic spectrum syndrome, and expressive speech delay have been described.[5]

The current efficacy of antipsychotic drug therapy is moderate; it would therefore be reasonable to presume that pharmacological treatments based on molecular genetic data would be more efficacious. Under this still unproven concept, the discovery of 'schizophrenia' genes should lead to more effective treatments by implementation of novel strategies in pharmacogenomics, pharmacogenetics and prevention through the identification of high-risk children. We have been now been presented with a new gene that could potentially be the first pharmacogenomic target for the development of new types of medications to treat schizophrenia. This gene is also likely to help us gain insights into other psychiatric disorders known to be part of the schizophrenia spectrum, such as schizotypal personality disorder, affective disorder with mood-incongruent delusions, schizotypal personality disorder, and atypical psychosis. Additionally, it is important to keep in mind the high probability that many more mutations in several other genes will be identified as causes of schizophrenia and related disorders. I predict that many more cats will come out of this bag.

DUALITY OF INTEREST

None declared.

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