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Ming T. Tsuang

Harvard Medical School Department of Psychiatry, Massachusetts Mental Health Center and Harvard Institute of Psychiatric Epidemiology and Genetics, Boston, Mass., USA

Recent Advances in Genetic Research on Schizophrenia

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Abstract
Evidence for genetic factors in schizophrenia is reviewed with regard to family, twin and adoption studies, and recent advances in molecular genetic technology are applied to explore possible gene loci susceptible to schizophrenia. Application of neuropsychological and neuroimaging methodologies are also reviewed with an aim to develop criteria for defining phenotypes for genetic studies.

Studies of nuclear and extended families have consistently found higher rates of schizophrenia among relatives of schizophrenic patients compared with relatives of normal controls and relatives of patients with mood disorders [28]. Moreover, the more closely a person is related to a schizophrenic, the greater is that person's risk of having schizophrenia. For example, the rate of schizophrenic disorders among the parents, siblings and children of schizophrenic patients is about 10%, but the risk to uncles, aunts, grandparents and grandchildren is only about 3%.

The fact that schizophrenia runs in families suggests that it has a genetic etiology. But disorders can run in families for nongenetic reasons such as cultural transmission, or the effects of common environmental circumstances (e.g. social class, poor nutrition, exposure to viruses or other toxins). To determine if a familial disorder is genetic, researchers use twin and adoption studies.

The twin study is based on the fact that monozygotic (MZ) twins are genetically identical but dizygotic (DZ) twins share, on the average, only one half of their genes. Therefore a higher concordance rate for schizophrenia among MZ compared with DZ twins would provide strong evidence for the importance of genetic mechanisms in the etiology of a disorder. The logic of twin research requires the assumption that both MZ and DZ twins share a common environment, but differ in the degree to which they share genes. Current evidence supports this assumption [12].

The twin study data for schizophrenia is unequivocal in implicating genetic factors. For example, Gottesman and Shields [8] studied a pooled sample of 550 MZ and 776 DZ twin pairs in a review of the literature. They reported concordance rates of 57.7 and 12.8% for MZ and DZ twins, respectively. Kendler [12] reviewed the evidence for environmental influences peculiar to MZ twins that might make their likelihood of developing schizophrenia greater than that of DZ twins. He concluded that there is little evidence of such a difference. He also summarized nine twin studies from eight countries involving 401 MZ twin pairs and 478 DZ twin pairs. Overall, 53% of the MZ twin pairs were concordant for schizophrenia, whereas only 15% of the DZ twin pairs were concordant. This significant difference between concordance rates for the two types of twin pairs strongly implicates genetic fac-

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Ming T. Tsuang, MD, PhD, DSc
Harvard Medical School Department of Psychiatry
Massachusetts Mental Health Center
74 Fenwood Road, Boston, MA 02115 (USA)
Tel. +1 617 734 65 46, Fax +1 617 734 79 15

tors in the causation of schizophrenia. Although twin studies implicate genetic factors, they also underscore the effects of the environment. Because the MZ twin concordance rate is less than 100%, environmental factors must play a critical role.

Adoption studies assess the genetic contribution to schizophrenia by studying children of schizophrenics who were not raised by their schizophrenic parent. Heston [10] found higher rates of schizophrenia in the adopted-away children of schizophrenic mothers compared with the adopted-away children of nonschizophrenic mothers. The Danish-American adoption study of schizophrenia found that the biological relatives of adoptees with schizophrenia had significantly higher rates of schizophrenia than the biological relatives of control adoptees without schizophrenia and the nonbiological adoptive relatives of schizophrenics [13]. Both of these studies confirm the twin data by implicating genes in the genesis of schizophrenia.

The methodology for finding genes, known as linkage analysis, is now fairly routine. It has been successful for many medical diseases but has only produced suggestive findings for schizophrenia. Attempts to examine all chromosomes have failed to produce unequivoval linkage findings [2, 3]. Pulver et al. [18] suggested the possibility of linkage to the long arm of chromosome 22 and consistent findings were reported by other investigators [4, 17, 29]. However, a collaborative study reported by Pulver et al. [19] excluded linkage to chromosome 22 loci and another study could not find evidence of linkage [11]. Gill et al. [21] reported a combined analysis of eleven schizophrenia linkage data sets. As a group, these data provided statistically significant evidence for linkage. However, their analyses suggested that the putative schizophrenia gene accounted for about 2% of the variability in the liability to develop the disorder.

Evidence implicated a schizophrenia gene on chromosome 6p in a series of 186 Irish schizophrenia families [25, 30]. Findings consistent with this work have subsequently been reported [15, 23], although not consistently [1, 9, 16]. A multicenter study examined the 6p linkage and also a locus in chromosome 8 [22]. Their results were described as inconclusive, but suggestive of a linkage.

The difficulty in finding genes linked to schizophrenia suggests that, although developments in molecular and statistical genetics have made it straightforward to find a replicate linkage for simple single gene disorders, it will be more challenging to map etiologically complex disorders such as schizophrenia [20]. We have suggested that diagnostic categories, and the psychiatric signs and symptoms that constitute them, probably reflect relatively remote and variable effects of genes that predispose to schizophrenia [5, 27]. In contrast, neurobiological features may be more closely tied to brain function than clinical psychiatric diagnoses.

To address this issue, we have studied the nonpsychotic relatives of schizophrenic patients with neuropsychological tests and magnetic resonance imaging of the brain. These relatives show impaired abilities to abstract information, attend to auditory stimuli, and remember verbal material [5–7]. These impairments are associated with one another in schizophrenia families [26] and are more marked in females [14]. Using high resolution magnetic resonance imaging, we showed structural abnormalities among adult siblings of schizophrenic patients [24]. Gray matter volumes of subcortical structures were consistently smaller and ventricular volumes were larger among relatives than controls. These results suggest that some relatives of schizophrenic patients, even though they are not schizophrenic, suffer from a neurodevelopmental disorder that has a pathophysiology which is similar to but milder than that observed among schizophrenic patients.

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