An overview of the genetic risk of developing schizophrenia in relatives of schizophrenic patients

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ABSTRACT

In this article, we review the recent research evidence of genetic risks in the relatives of patients with schizophrenia, with particular focus on family, twin, adoptive, and gene studies. All current evidence supports a greater role for genetic transmission of vulnerability in the etiology of schizophrenia. Environmental factors appear to play an important role in the timing of expression, the severity and the clinical evolution of the illness.

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Schizophrenia-spectrum disorders are considered to be complex genetic disorders.[1] While there have been significant advances in the scientific understanding of the genetics of schizophrenia and related psychosis, the exact mechanism and pattern of inheritance are not yet clear. Clinical practice and recent studies of the epidemiology of the illness have revealed that the vulnerability to psychosis can often be aggregated in some families. Numerous linkage studies involving pedigrees with a family history of schizophrenia have increased our understanding of the complex hereditary factors that contribute to an individual's increased risk of becoming ill. In this review, we present the results of research conducted on the genetic factors for those individuals at risk for the development of illness, focusing primarily on both the offspring and the relatives of individuals with a diagnosis of schizophrenia and related psychosis. The identification of biological markers may be of clinical utility in prediction of the risk for developing schizophrenia spectrum disorders, and this will ultimately prove of benefit in the early detection and treatment of individuals who are at high genetic risk for developing the illness.

Familial studies. Most familial studies indicate that schizophrenia runs in families. Rüdin[2] conducted the first genetic family study of schizophrenia in 1916 when he examined the familial distribution of schizophrenia and found that the inheritance of schizophrenia is of variable penetrance and did not follow a simple Mendelian dominant or recessive mode of transmission. He also projected that approximately 4.5% of the siblings of his schizophrenic subjects were at risk to develop schizophrenia. Several subsequent studies have shown that the risk that a child with a parent with the disorder of developing either a schizophrenia-spectrum disorder or schizophrenia during adolescence or young adulthood is high. Studies have shown that if one parent has schizophrenia, the risk in children is estimated to be in the order of 10% and increases to approximately 35-45% if both parents are affected. This risk is consistent irrespective of the gender of the affected parent.[3,4] Similarly, higher risks were found in the relatives of individuals with schizophrenia. Gottesman[5] found a 9% risk in siblings, a 6% risk in parents of schizophrenic individual, a 6% risk in half siblings, and a 2-4% risk in second-degree relatives (uncles, cousins, and nephews) compared with a 1% risk in the general population. Although researchers have used rigorous research methods and narrower criterion-based diagnosis in various studies, all have reported comparable figures, which are much higher than rates in the general population.[6-8]

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Twin studies. Twin studies have also substantiated important genetic contribution to the etiology and risk for schizophrenia. It is known that monozygotic twins (MZ) share 100% of the genes while dizygotic (DZ) twins share 50% of the genes. Twins are considered to be concordant for schizophrenia when both members of a twin pair develop the illness, while they are referred to as discordant for schizophrenia when only one member develops schizophrenia.[9,10] Pairwise concordance rates are usually expressed as the percentage of concordant pairs out of the total number of pairs of twins in which at least one twin is reported to have schizophrenia. Proband-wise concordance rate assesses the probability that a twin has schizophrenia if his twin has schizophrenia.[11,12] If the risk of developing schizophrenia is influenced by genetic factors, then the concordance rate for monozygotic twins will be higher than the concordance rate for dizygotic twins; similar concordance rates between monozygotic and dizygotic twins would suggest a greater causal role for environmental influences.[13] Kendler,[14] in 1983 found proband-wise concordance for schizophrenia was significantly greater in MZ twins (30.9%) than in DZ twins (6.5%), while Moldin and Gottesman,[15] in 1997 estimated concordance rate for schizophrenia to be 46% for MZ twins and 14% for DZ twins. Cardno et al[16] reviewed recent studies conducted in both Europe and Japan and found the proband-wise concordance range between 41-65% in MZ pairs and 0-28% in DZ pairs.[16]

Fischer[17] studied the risk of schizophrenia in the offspring of MZ twins discordant for schizophrenia in Denmark. She found that the risk of schizophrenia was equal in the offspring of MZ twins diagnosed with schizophrenia compared to the offspring of their normal co-twins. Eighteen years later, Gottesman and Bertelsen[18] re-examined the same sample in a follow-up study and found that the morbid risk (age-corrected) for developing schizophrenia and related disorders in the offspring of schizophrenic members of discordant MZ twins was 16.8% compared to 17.4% in their normal co-twins' offspring. The risk, however in the offspring of schizophrenic DZ twins and their normal co-twins was 17.4% and 2.1%.

Heritability is the variance in liability to develop a disease, which is attributed to genetic factors and is defined as difference in concordance rates between MZ and DZ twins divided by 100 minus the concordance rate in DZ twins.[19] Although the concordance rate for schizophrenia is approximately 50% in MZ twins, heritability for schizophrenia has been estimated to be as high as 80-85%.[16,19] While this indicates that genetic factors are very important in predicting the emergence of the illness, it is clear that non-genetic or environmental factors are also important in determining the emergence and expression of the disease. The theory of increased maternal transmission of schizophrenia has not been substantiated, as no deferential transmission by sex has been observed.[4]

Adoption studies. Adoption studies have also contributed to characterizing the genetic risk for developing schizophrenia. Heston[20] found 10.6% (5/47) of adopted-away offspring who were born to schizophrenic mothers developed schizophrenia while none of the 50 adopted-away offspring of mothers without a psychiatric history did. Kety[21] examined a sample of 5483 adults who had been adopted in early life by persons who were not biologically related to them. He identified 33 subjects in his sample who were later diagnosed with schizophrenia and blindly compared them to a sample of healthy adopted matched individuals. He found that schizophrenia and probable schizophrenia diagnoses were more concentrated in the biological offspring of parents with schizophrenia. However, their adoptive relatives did not differ from the control populations in the prevalence of schizophrenic illness. Kendler[22] applied DSM III criteria in the same sample and found that the prevalence of schizophrenia-spectrum disorder in the sample was significantly greater in biological relatives of schizophrenia spectrum when compared to control adoptees. His results have also provided strong evidence for genetic transmission of schizophrenia and for genetic associations between DSM-III schizophrenia, schizoaffective disorder, and schizotypal personality disorder. Tienari,[23] in The Finnish Adoptive Family Study of Schizophrenia, blindly compared 124 offspring given up for adoption by schizophrenic women with matched controls of 147 adopted-away offspring of a non-schizophrenic biologic parent. He found 7.3% of the offspring of schizophrenic mothers became psychotic compared with 1.4% of normal control offspring. He also replicated the same findings in 2000 when he applied DSM-III-R diagnoses in the Finnish Adoption Study and reported a 6.7% lifetime prevalence of typical schizophrenia in 164 adoptees compared with a 2% risk in a matched control sample of 197 adoptees. He also reported that the liability also extended to other psychotic and non-psychotic disorders.[24]

Linkage studies. There are a number of studies that link specific genetic mutations to an increased risk of developing schizophrenia. Regions on more than half of the 23 chromosomes have been implicated to be associated with schizophrenia. However, the strongest evidence for susceptibility loci has been identified on chromosomes 1q21-q22,[25] 6p, 8p, 10p,

and 22. Other loci on chromosomes 5q, 13q, and 18p have also been reported but have not been consistently replicated.[26] Difficulties in achieving consistent results in linkage analyses have been affected by several factors including diagnostic reliability, heterogeneity (2 or more independent loci resulting in the same phenotype), population differences, and a large number of interacting interloci involvement.[27]

It is theorized that the liability to develop schizophrenia can potentially arise from polygenic effects. This model was initially described by Gottesman and Shields,[28] and the liability was found to take the shape of a normal distribution curve.[5] Schizophrenia likely requires a model that involves relatively common variation in a number of susceptibility genes, and a combination of these alleles in an individual may predispose to the disorder.[29] Some researchers indicated that each predisposing allele alone might contribute only to a small increase in risk.[29] While it appears that the individuals may inherit the predisposition to develop schizophrenia, it is likely that the genotype will ultimately affect the probability of expression of the clinical symptoms. This probability may be modified by several factors such as stress, physical, and environmental changes. When the individual exceeds a certain threshold, the illness may begin to express itself.[28,30]

A major challenge in studying the genetics of schizophrenia is to understand how genetic expression can translate into behavior. This may be very complex as genes have the property of pleiotropy, which refers to multiple effects on phenotype of a mutant gene that cause simultaneous variations in characteristics it affects. For example, a gene responsible for developing a particular illness may be responsible for developing another unrelated illness.[31] The simplest model indicates that the gene codes for the protein, which in turn determine brain function. Gene expression is highly regulated at all levels, and gene-gene interaction and gene-environment interaction are an integral part of this process.[32]

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