Genetics of Schizophrenia: Recent Advances

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KEY WORDS

schizophrenia, genetics, population isolates

ABSTRACT

Genetic studies of schizophrenia have been fraught with challenges, yet molecular genetic and genomic methods remain essential to the discovery of the underlying biological mechanisms. Candidate genes and genome scan studies have played a significant role in the search for susceptibility loci. Studies in genetic isolates appear to be providing some of the most consistent results. These populations are characterized by a greater degree of homogeneity, which is hoped to be advantageous in the identification of genes contributing to the disease phenotype. The following review highlights some recent advances in schizophrenia research, with a focus on disease etiology, candidate genes, genome scan studies, and molecular genetic approaches. Mental Fitness. *2004;3(3):32-37.*

EPIDEMIOLOGY AND FAMILIAL RISK

Schizophrenia, one of the more debilitating neuropsychiatric syndromes, affects as much as 1% of the population worldwide. Despite the fact that schizophrenia is characterized by a strong genetic element, the mode of inheritance remains unclear.[1,2] It is apparent, however, that relatives of schizophrenic patients sustain the most consistent and significant risk for developing schizophrenia. The high degree of heritability (approximately 80%) of schizophrenia has instigated innumerable studies over the last 50 years, resulting in comprehensive twin and adoption studies, as well as family studies. These studies indicate that an individual's risk for schizophrenia is commensurate with their degree of relatedness to a schizophrenic.[3] The monozygotic twin of a schizophrenic is at the greatest risk for developing schizophrenia, approximated at 50%. The risk is only slightly less for an individual born to two schizophrenic parents. The risk for schizophrenia decreases to 10-15% for siblings, dizygotic twins, and individuals parented by only one schizophrenic. This pattern of heredity provides strong support for a significant genetic component, although non-genetic components are likely to contribute to the risk for and expression of schizophrenia.[4]

Our own studies have focused on the geographically and potentially genetically isolated islands of the Azores and Madeira.[5] Our research indicates that the most densely populated Azorean island has a lifetime prevalence for schizophrenia of less than 0.3%, while the familiality of schizophrenia is approximately 70% . The worldwide prevalence, however, is thought to be 1% with an estimated 10-15% familiality rate.

MOLECULAR GENETIC APPROACHES

Molecular genetic approaches range from variations on classic association studies that examine markers for a particular gene in patients versus those in controls, to linkage studies that focus on the inheritance patterns of a locus or region in the genome and illness in families. Linkage studies, in turn, are either parametric, meaning they test a specific model of inheritance, or non-parametric, defined as being inheritance model independent. In past studies, large multiplex families with schizophrenia were subjected to parametric linkage analysis, focusing on the identification of a single major locus. Given the difficulty encountered in replicating the findings, this analytical model may have been too simple to contend with the genetic complexities of schizophrenia.[4] Consequently, the emergence of non-parametric linkage analyses, which are based on shared alleles, shared by descent, has provided a potentially more replicable methodology. Indirectly, this has

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