

Schizophrenia: A genetic perspective (Review)

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Abstract. Schizophrenia is a complex neurodevelopmental disorder characterized by mental dysfunction across multiple domains of the brain. It affects 1% of world's general population and the nature of neurobiological lesions in the schizophrenic brain are not known. Although the exact etiology of the disorder is not understood, twin, family and adoption studies have provided consistent evidence that genetic factors play a major role in the pathogenesis. A genomewide genetic linkage screen identified loci on chromosomes 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 13, 15, 18, 22 and the X with positive lod scores, thus excluding a single major locus for schizophrenia. Association studies have generated disappointing results in identifying the susceptible DNA sequence variants and the anticipation hypothesis on trinucleotide repeat expansion provided equivocal results or lack of enthusiasm. Although there are no biological markers at present, the recent finding that human endogenous retrovirus is activated in cerebrospinal fluid as well as in the postmortem schizophrenic brain may change our understanding of the etiopathogenesis of this disease. Meanwhile, treatment with newly developed anti-psychotic drugs combined with educational and cognitive rehabilitation procedure may help the patients to cope with the illness.

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1. Introduction

Neurological disorders affect the quality of daily lives. In several degenerative neurological diseases, clinical manifestations are found to be associated with certain parts of

the brain and their circuits as well as cellular and biochemical abnormalities. For instance, in Alzheimer disease (AD), progressive degeneration of neurons in hippocampal and neocortex as well as other regions cause memory and cognitive impairments. In Parkinson disease (PD), dysfunctioning and degeneration of dopaminergic neurons cause tremor and muscular rigidity. Thus, certain brain areas are involved in the clinical signs of degenerative disorders. When biochemical abnormalities of diseases are known, their management can be undertaken more effectively. This past decade has witnessed a tremendous insight into the pathogenesis of several of neurological disorders and generated hopes for their prevention (1). Unfortunately, however, such extensive efforts resulted mostly in frustration for a complex neurological disease, schizophrenia (2).

Schizophrenia is a severe, complex and common psychiatric condition affecting approximately 1% of the world's general population (3). It is a multifactorial, neurodevelopmental disorder, characterized by mental dysfunction across multiple domains of the brain. The clinical symptoms include third-person auditory delusions, attention deficits, memory impairment and social isolation. It is not a degenerative disease like many other neurological disorders and the nature of neurobiological lesions in the schizophrenic brain are not understood (4). It is considered a major world-wide problem. The pathophysiological signs are believed to be due to disturbances in brain development (5,6), because of brain structural changes as well as the lack of visible neuropathological markers such as plaques, tangles and Lewy bodies. Many affected individuals require long-term care and the age of onset varies but it often occurs in the late teens or early twenties.

2. Morphological studies

Morphological studies performed on the postmortem brains of affected individuals revealed disturbed brain development in numerous brain regions. This includes enlarged lateral ventricles (7) and abnormalities in frontal (8) and temporal lobes (9-12) as well as in other regions such as parietal, occipital, thalamus and cerebellum (13-17). Thus, unlike other mental disorders such as AD and PD, where the pathophysiology is localized to a certain region of the brain, schizophrenia involves multiple domains of the brain. Recent studies on first episode patients support the notion that schizophrenia could be due to a progressive brain structural change (8,18-22). However, attempts to establish relationships between the morphological changes and schizophrenia are

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disappointing. This failure is mainly attributed to the variability of the disorder as well as overlap of the structural changes with control subjects (12,23-28). Additionally, in the past, there was a disagreement among clinicians regarding its diagnosis but now there are several standardized diagnostic criteria and recent advancements such as sustained attention deficits, eye movement dysfunction and neurobehavioral deficits, which are also useful to identify predictors of illness (29-31).

3. Linkage studies

Schizophrenia is a debilitating multifactorial mental disease. The mode of inheritance is complex and non-Mendelian (32,33). The phenotype could be the result of gene-environmental factors - developmental interactions. While the exact etiology of schizophrenia is not understood and there are no biological markers (e.g. plaques, tangles and Lewy body), epidemiological studies have identified a number of environmental factors associated with schizophrenia. This includes place, season of birth and perinatal infection (34-36). Twin, family and adoption studies have also provided consistent evidence for genetic factors in the pathogenesis of the disorder (33,37-42) and has been estimated to contribute 65-85% of the total risk. However, because of the variability of the schizophrenia phenotype as well as its complex mode of inheritance, identification of genes involved using traditional genetic strategies such as segregation and linkage analysis has become a challenging problem (43,44). Recently, an extensive genomewide linkage as well as family based analysis suggests multiple susceptibility loci on chromosomes 1q32.2, 4q31, 5q33.2, 7q22, 8p21-22, 9q21, 11q23.3-24, 20q12.1-11.23 (45-47). Additionally, several other studies have reported linkage to 1q21-22, 3p, 5q, 6p21.3, 6p23, 6q, 8p, 9q, 10p, 13q32, 15q, 20p, 22q and Xp22 (48-71). Presently, the above loci have been identified based on positive lod scores and some of them are found numerous times but none of the genes have been unequivocally mapped or cloned. Although some of the studies have not been replicated or they have been refuted (72-77) [Riley BP, *et al*, *Psychiatr Genet* 5 (Suppl.): abs. 34, 1995; Sasaki T, *et al*, *Am J Hum Genet* 57 (Suppl.): abs. 1165, 1995], it appears that there is no common gene or a single locus of major effect for schizophrenia (78). In addition to the above linkage studies, several chromosomal abnormalities such as deletion, translocation and inversion have been reported (reviewed in refs. 51,79,80).

4. Association and trinucleotide repeat expansion studies

In the case of non-Mendelian disorders with a complex mode of inheritance, identification of susceptibility loci by segregation and linkage analysis is difficult. For this purpose, association studies may help to identify genes contributing to the disorder (81). The association study is based on the assumption that a genetic marker occurs more frequently in conditions than in controls. Such polymorphic markers are likely to be associated with the susceptibility locus or in linkage disequilibrium with the susceptibility region (82). However, such studies are not free of artifacts. For instance, when a genetically distinct population is included in the study, it can cause an artifactual association. In such cases, a transmission

disequilibrium test as well as use of multiple and independent populations are needed (83).

When these association studies have been employed to examine a number of schizophrenia candidate genes (these genes are selected with their presumed functional significance for the disease) such as dopamine D2, D3 and D5 receptors, serotonin 2A receptor, cholecystokinin B receptor, brain derived neurotrophic factor, α -spectrin and phospholipase A2 genes, results were either disappointing or refuted by other studies (27,84-96). Thus, the molecular pathway involved in the pathogenesis of schizophrenia is severely hampered. It also remains to be seen in the future whether the recently reported mouse model expressing a reduced level of NMDA receptor (N-methyl-D-aspartate) is of any use to understand schizophrenia (97).

In some cases of schizophrenic patients, trinucleotide repeat expansion was reported to be involved in the etiology of schizophrenia (98-105). Although these results are very promising, these studies should be interpreted with caution because, population based case-control studies have their own limitations. In support of this notion, some of the above studies once again refuted by others (106-110) and not confirmed in monozygotic twins. Moreover, this dynamic mutation is not specific for schizophrenia and has been observed in bipolar disorder as well as in other diseases.

5. Retroviral theory

It was previously proposed that retroviruses may be etiological factors for the development of schizophrenia (36). During pregnancy, retroviral infection is believed to cause impairment in fetal brain development. However, for quite some time, it was lacking support and remained unproved (111). Recently, it was found that the cerebrospinal fluid of 28.6% of patients with recent onset schizophrenia contained human endogenous retroviral sequence [(HERV)-W], and the gene is found to be transcriptionally activated in the postmortem frontal cortex of individuals with schizophrenia (112,113). This is the first evidence supporting the previous proposal on viral etiology of schizophrenia. If it is replicated by others in the future, then it may mean that in some patients the onset of schizophrenia could be due to the activation of a certain viral element in the brain which could change our understanding of the etiopathogenesis of the disorder.

6. Concluding remarks

Schizophrenia is a complex psychiatric condition for which neurobiological lesions in the brain are not known. The phenotypic and genetic heterogeneity of the disorder impose burdens in determining the etiology of the disease. Modern diagnostic classification as well as the recent report on the activation of human endogenous virus may change our understanding of its etiopathogenesis and provide a better handle for its management in the future, although it is not clear at present whether schizophrenia is a single or several different disorders.

At present, anti-psychotic drugs such as clozapine and risperidone have been used to treat the psychosis but 30% of patients displayed significant difference in its response (114). In addition, these drugs showed a wide-range of unacceptable

side effects in the cardiovascular, gastrointestinal and hematological systems, which severely curtailed their use. Several other new drugs such as ziprasidone are under consideration and it is expected that these drugs have less side effect as well as better clinical outcome. In addition to drug therapy, providing educational and cognitive rehabilitation in the community may help patients coping with the disease and is considered to be another important form of treatment. In the future, it is also possible to improve drug response at the level of the individual patient by detecting single nucleotide polymorphism (SNP) in patients' DNA. Although it requires a large scale analysis, such approaches are needed and possible to carry out particularly now because of the completion of the Human Genome Project (115). Thus, for schizophrenia patients, opportunities to cope with the disease are better than ever before.

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