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SNP Research of Korean Schizophrenia Patients: Preliminary Candidate Gene Mapping

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The exact pathogenesis of schizophrenia is unknown. The dopamine hypothesis for schizophrenia is the most fully developed of several hypothesis and is the basis for much of the rationale for drug therapy. Several lines of circumstantial evidence suggest that excessive dopaminergic activity plays a role in the disorder. However, largely as a result of study stimulated by the discovery of antipsychotic drugs, the genetic predisposition has been proposed as a necessary but not always sufficient condition underlying psychotic disorder. This hypothesis has been demonstrated by the observed familiar incidence of schizophrenia. After the human genome project, several researchers have an opportunity of identifying multiple genes that contribute to the various clinical phenotypes subsumed the broad diagnostic classification of schizophrenia. For example, neuregulin 1 is associated with schizophrenia in European population (1). To date, a lot of molecular genetic studies have been focused on the understanding of pathogenesis of schizophrenia. Two main approaches, linkage analysis and association studies, are known to have the power to find the susceptibility genes in schizophrenia using genetic polymorphisms (1). Albeit most of positive results were not replicated, several strong and well-established linkages to some genes have been demonstrated. Because of the limitation in linkage analysis, a lot of genetic results were achieved through association studies using candidate genes. Recently several genes, including dysbindin (DTNBP1), catechol-O-methyl transferase (COMT), regulator of G protein signaling-4 (RGS4) and p53, were shown to be susceptibility genes for schizophrenia (1,2,3). However, in what way it really contributes to schizophrenia and whether it applies to other populations have to be determined yet. One of candidate gene approaches, we considered epidemiological studies on the relationship between schizophrenia and cancer. The relationship between schizophrenia and cancer has posed an epidemiological puzzle for decades (4). Lower incidences of malignancies, especially lung cancer, in patients of schizophrenia compared to the general population has been demonstrated in several researches. Particular attention has been paid to the question whether genetic predisposition towards schizophrenia confers genetically reduced susceptibility to cancer. It has been suggested that the reduced incidence of cancer observed in schizophrenia patients may be related to differences in genetic background. Catts and Catts (5) suggested that the reduced incidence of cancer observed in schizophrenia patients might be linked to differences in apoptosis, and proposed p53, a tumor suppressor gene, which is considered as a candidate gene for the susceptibility. The p53 gene is one of the most frequently mutated genes in all types of cancers including lung cancer. Therefore, we tested the genetic association between schizophrenia and lung cancer by analyzing polymorphic sites in the p53 gene. Genotype and allele frequencies at two SNP sites in the p53 gene (BstUI and MspI restriction sites in exon 4 and intron 6, respectively) were studied in Korean schizophrenia and lung cancer patients. Comparisons of the genotype and allele frequencies of the MspI polymorphism revealed significant differences between schizophrenia and lung cancer patients. The results suggested that the p53 polymorphism specially found in schizophrenia patients may be associated with reduced vulnerability to lung cancer. In our laboratory, we also selected the more than one hundred candidate genes from previously published works with positive results on various viewpoints, such as immunological, neurodevelopmental, endocrinological and cell death. More than one hundred Korean schizophrenia patients and healthy controls were studied in each association study. Genotype and allele frequencies of several genes showed significantly difference between Korean schizophrenia and normal controls. Also, significant differences were showed in several genes by haplotype or association study. We have mapping those possible candidate genes preliminarily in Korean schizophrenia patients. In the future, this map might be used as a powerful tool for molecular genetic study in pathogenesis of schizophrenia.

◆ Candidate gene mapping : IL1 receptor antagonist, synapsin 2, GSK3 beta, glial cell-derived neurotrophic factor, complexin 2 gene, estrogen receptor 1, catalase gene etc.

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