ABSTRACT

Schizophrenia has plastic aspects including the involvement of genetic and environmental etiological factors. Transsynaptic regulation of gene expression is one of the molecular mechanisms that may underlie long-term and plastic effects of environmental factors on both the developing and adult brain. This study therefore explored the hypothesis that mutations of genes involved in transsynaptic regulation of gene expression could contribute to susceptibility to schizophrenia. Although many genes are apparently involved in this process, the present study focused on a single receptor, the 5-hydroxytryptamine 1A receptor (5-HT_{1A} receptor) and on two transcription factors; activator protein 2 (AP-2) and cyclic AMP-responsive element-binding protein (CREB). Each of these proteins has been implicated in schizophrenia. There is an abundance of evidence implicating serotonergic dysfunction in schizophrenia. Moreover, postmortem studies suggest that the 5-HT_{1A} receptor is increased in the prefrontal cortex of schizophrenics. This suggests that schizophrenia may involve an alteration in the expression of the 5-HT_{1A} receptor in the central nervous system. The gene for the transcription factor AP-2 is another possible candidate in the genetic etiology of schizophrenia. It has been mapped to a region near D6S470, a marker on chromosome 6p24, that provided evidence of linkage to schizophrenia. Finally, we considered the transcription factor CREB because of its involvement as a messenger molecule in intracellular signal transduction pathways used by most of the dopamine and serotonin receptor subtypes. In addition, CREB stimulates expression of a number of genes whose expression is altered in schizophrenic patients. Therefore, the promoter region and the coding region of the genes coding the 5-HT_{1A} receptor, AP-2, and CREB were analyzed to identify genetic variants, and a case-control study was conducted to explore the association between polymorphisms in these genes and schizophrenia.

Genomic DNA was isolated from whole blood samples obtained from schizophrenics (n=87) and controls (n=100). Polymerase chain reaction (PCR) was performed, and amplified products were screened by single-strand conformational polymorphism (SSCP) analysis. Aberrant SSCP patterns were analyzed by direct sequencing. The frequencies of the identified mutations were compared between schizophrenics and controls in order to investigate a possible correlation to the development of the disease.

Five novel mutations (-51T→C, -152C→G, -321G→C, -480delA and -581C→A) were found in the promoter region of the 5-HT_{1A} receptor gene. A novel missense mutation (Gly272Asp) was also found, in addition to several mutations that have been reported previously (Pro16Leu, 294G→A and 549C→T). No significant differences in either genotypic or allelic frequencies were found between patients and controls. Three novel polymorphisms were found in the promoter region of the AP-2 gene; two of which were relatively common (-90G→C, -803G→T) while the third was rare (-1769G→A). Polymorphic status at both loci suggested strong linkage disequilibrium between the -90 and -803 loci. Although no significant differences in genotypic or allelic frequencies at the -90 and -803 loci were found between patients and controls, significant differences in the distribution of genotypes at the -90 ($P = 0.008$) and -803 ($P = 0.037$) loci were observed in patients with episodic course, when compared with controls. However, the differences observed for these loci were not significant after Bonferroni correction. Two novel variants (-933T→C and -413G→A) in the promoter region of the CREB gene were identified, and were found only in schizophrenic patients. A patient with the -933T→C variant had unusual clinical characteristics in addition to typical schizophrenic symptoms.

The present study provided no direct evidence of an association between schizophrenia and the variants identified in the genes encoding the 5-HT_{1A} receptor, AP-2, or CREB. However, this study provides preliminary evidence

that schizophrenia characterized by an episodic course may correlate to the -90G→C and -803G→T polymorphisms in the promoter region of the AP-2 gene. Additionally schizophrenia with unusual clinical characteristics may be related to the -933T→C variant in the promoter region of the CREB gene. A larger sample size will be necessary to determine whether the AP-2 and CREB gene confer susceptibility towards these schizophrenic phenotypes at a statistically significant level. Detailed analysis is necessary to determine whether the transversions from -90G to C and from -803G to T in the AP-2 gene, and the transition from -933T to C in the CREB gene effect transcriptional activity.

Key Words

Genetic association study

Genetic polymorphism

5-HT_{1A} receptor

AP-2

CREB