

Association Between Upstream Purine Complexes of Human Caveolin-1 Gene and Schizophrenia in Qazvin Province of Iran

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Background: Caveolin is a multifunctional and scaffolding membrane protein, which involves cholesterol trafficking to plasma lipid microdomain. It organizes and targets synaptic parts of the neurotransmitter and neurotrophic receptor signaling pathways. Caveolins are encoded by CAV-1, 2 and 3 genes. Disruption of the CAV1 would likely ruin the neuronal signaling, which leads to symptoms of schizophrenia in predisposed individuals.

Objectives: The upper area of CAV-1 gene is highly conserved and can have a regulatory role in neurodegenerative diseases. This study was designed to find out the possible association of polymorphisms of this area and schizophrenia.

Patients and Methods: In a case-control study, 254 blood samples were obtained from 127 patients with schizophrenia and 127 well matched controls referred to 22 Bahman Hospital of Qazvin University of Medical Sciences (QUMS) in Qazvin province, Iran, using simple random sampling method. After extracting DNA, the upper region of the human CAV1-gene was amplified by PCR in all collected samples. The products were visualized by silver staining in 10% polyacrylamide gel and then sequenced.

Results: We detected nine homozygotes in patients and 15 in control subjects. Homozygosity was 7.08% and 11.8% in cases and control, respectively. Nine types homozygote haplotype were detected in upper region of the CAV1 gene in cases and controls. Three haplotypes were common in cases and controls; four haplotypes were seen in controls only and two in cases.

Conclusions: Our findings implied a significant correlation between some haplotypes of upper region of CAV1 gene and schizophrenia. Existence of some haplotypes and lack of another in CAV1 upstream can suggest a significant correlation between schizophrenia and some haplotypes.

Keywords: Caveolin-1; Schizophrenia; Iran

1. Background

Schizophrenia is a serious and neurodevelopmental disorder, which affects approximately 1% of the general population often-devastating effects such as psychological, social and financial skills. Disease symptoms include delusions, auditory hallucinations and thinking disorder. Schizophrenia can disturb memory, attention, thought and motivation of affected patients (1). Twin concordance rates, family and adoption studies, genetic linkage and allelic association analyses revealed a strong genetic element contributing to schizophrenia (2). The heritability of schizophrenia is estimated to be 80% (3). Therefore, due to the high percentage of heredity involvement, over 1000 genes have been tested to assess such an association. This makes schizophrenia one of the most studied disorders through a candidate gene approach (4, 5). Caveolins are encoded by CAV-1, 2 and 3 genes (6). Caveolins (encoded by CAV1 gene) are multifunctional scaffolding and

cholesterol binding proteins organizing other lipids and proteins in surface domains; also they regulate various cellular functions such as lipid homeostasis, vesicular trafficking and signal transduction. In fact, Caveolin is extensively expressed in the nervous systems (7-11). In CAV1 knock-out mice, neurodegeneration and aging is more advanced than normal mice (12, 13). Current analyses of genomic structural variations in patients with schizophrenia showed that caveolin-1 gene (CAV1) is disrupted by an insertion mutation, therefore the CAV1 is identified as a rare structural variant correlated with schizophrenia (14). Given the importance of this region in neurodegenerative diseases, any changes in this area of genome may result in illnesses such as schizophrenia. CAV1 is also known as an interacting partner of G-protein and its loss can cause destruction of neuronal signaling leading to signs of schizophrenia in susceptible persons (9-11).

GGAA, GAAA and GGAA motifs, transcription consensus sites for the Ets and IRF (interferon regulatory factor) family members. The interaction between Ets and IRF family members has been shown in different studies (7, 8). Furthermore, inflammation plays a role in neurodegenerative diseases and several inflammatory transcription factors like STAT4 and interferon regulatory factor (IRF). In which, these factors bind to the CAV1 upstream purine complex and regulate target genes (12, 19, 20). Some literatures categorized Schizophrenia as a neurodegenerative disease (1, 14). To examine the hypothesis that purine complex of upstream CAV1 may be related to pathogenesis of schizophrenia, we investigated this region in a group of patients with schizophrenia and compared the results with well-matched controls. In this research, homozygote haplotypes of GGAA, GAAA and GGAA motifs were compared between cases and controls. Some haplotypes were found in patients only. Chi square test showed that these haplotypes significantly related to object (e.g. haplotype 4, Table 3, $P = 0.016$, $P < 0.05$). Nevertheless, some haplotypes were found in controls only. Statistical analysis showed no significant association between these haplotypes and schizophrenia (for example; haplotype 6, Table 3, $P = 0.15$, 7 and 8 $P = 0.25$, $P > 0.05$). These findings implied a significant correlation between schizophrenia and some haplotypes of this region of CAV1 gene. Existence of some haplotypes and lack of another in CAV1 upstream can suggest a significant correlation between schizophrenia and some haplotypes. To the best of our knowledge, this was the first study to assess the association between purine complex upstream region of human CAV1 and schizophrenia disease. These results could be useful for further researches in this field.

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Authors' Contributions

All authors cooperated in design, conduction, data gathering, data analysis and writing the manuscript. All authors read and approved the manuscript.

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