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Association between rs362746 Polymorphism of RELN and Schizophrenia in Iranian Patients

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Abstract

Genetic studies, there is a potential association of *RELN* with some psychological disorders such as Autism Spectrum Disorders (ASD) schizophrenia (SCZ). The *RELN* gene is located on chromosome 7q22.1 and encodes a large secretory protein of the extracellular matrix (Reelin). In the present case-control study, we intended to investigate the relationship between the rs362746 polymorphism of *RELN* and schizophrenia in a group of schizophrenic and healthy subjects from northeastern Iran.

30 unrelated schizophrenic patients and 30 matched control subjects were recruited. The samples from the participants underwent PCR and sequencing for *RELN* genotype identification.

The genotype distribution for both study and control groups were not in Hardy–Weinberg equilibrium ($P > 0.05$). However, it was found that the prevalence of rs362746 polymorphism was significantly different between the groups.

The present study supported the evidence that rs362746 polymorphism of *RELN* was a genetic factor for schizophrenia susceptibility. However, there is a need for replication studies on different populations and further investigations on the sex-specific association of this gene with schizophrenia.

INTRODUCTION

Schizophrenia is a common psychiatric disorder that affects approximately 1% of the global population. This problem is characterized by psychosocial disturbances and psychotic symptoms, including hallucinations, delusions, inappropriate emotional responses, and altered cognition and volition (1). Different studies, including family, twin, and adoption studies, have proved the role of an inheritable component in its development (2); however, the involved genes are still unknown. Genome-wide association studies have investigated the role of different Single Nucleotide Polymorphisms (SNPs) and Copy Number Variations (CNV) in the pathogenesis of this disease (3). The *RELN* gene located on chromosome 7q22.1 encodes a large secretory protein of extracellular matrix named Reelin (4). It is mainly secreted by Cajal-Retzius cells. The protein is involved in the neuronal migration and laminar structure development of the cerebral cortex during embryonic development (5), while in adults, it is produced by cerebral GABAergic interneurons and plays a role in synaptic plasticity, dendritic

morphology, and cognitive functions (6). In cerebral tissue, the secreted Reelin binds to its specific receptors, Apolipoprotein E Receptor 2 (APOER2), and Very-Low-Density-Lipoprotein Receptors (VLDLR), thereby inducing the phosphorylation of intracellular adaptor protein Disabled-1 (DAB1) (7). According to genetic studies, there is a potential association of *RELN* with disorders such as Autism Spectrum Disorders (ASD) and schizophrenia (SCZ). There have been several studies supporting this potential role of *RELN* in schizophrenia (8). Some rare variants of *RELN*, including de novo or rare missense variants and also an exonic deletion of *RELN*, have been shown to be potential risk factors for SCZ (9). In recent years, several SNPs in *RELN* gene loci have been reported to be associated with schizophrenia onset or severity. However, the results available are still controversial. In the present case-control study, we intended to investigate the relationship between the rs362746 polymorphism of *RELN* and schizophrenia in a group of schizophrenic and healthy subjects from northeastern Iran.

METHODS AND MATERIALS

The study included 30 unrelated schizophrenic patients and 30 matched control subjects with a mean age of 39.4 and an age range of 27-63 years old. The exclusion criteria were the presence of organic brain diseases, mental retardation, severe physical disorders, drug or alcohol abuse, and people with low comprehension skills. For *RELN* genotype identification, the samples from the participants underwent PCR using specific primers (Table 1) designed for the target area where the polymorphism was located. Then, the resulting product underwent sequencing using a Genetic Analyzer 3130XL. The

results were analyzed using the FinchTV software and were compared with the reference sequence available in the NCBI database.

RESULTS

There was not significantly different from that of Hardy-Weinberg in both study and control groups ($P > 0.05$). However, it was found that the prevalence of rs362746 polymorphism and the distribution pattern were significantly different between the groups. The allelic and genotypic distribution of the mentioned polymorphism in the groups is presented in Table 2.

Table 1. Sequencing primers

Primer No	Sequence
Rs362746	F: 5'- CTATGACAGAGGCAGCCACA -3' R: 5'- GTGATGCCCTGGTCTTCATT- 3'

Table 2. Frequency of rs362746 allele and related genotypes by group

Allele & Genotype Frequency	Study Group	Control Group	P-Value
A allele	38 (63.33%)	41 (68.33%)	0.172
G allele	22 (36.67%)	19 (31.66%)	
AA genotype	13 (43.33%)	15 (50.00%)	0.002
AG genotype	12 (40.00%)	11 (36.66%)	
GG genotype	5 (16.67%)	4 (13.34%)	

DISCUSSION

According to our results, there was a significant relationship between the rs362746 polymorphism of *RELN* and schizophrenia. This finding was compatible with other studies on this potential association (10, 11). A genome-wide association study investigated the relationship between *RELN* polymorphism and schizophrenia in an Ashkenazi Jewish population and found a female-specific association of *RELN* and schizophrenia (12). Moreover, a replication study on four different populations (UK, Ireland, USA, and China) also found a female-specific association after the combination of all replication samples (13). Also, a recent meta-analysis integrated the results from some published case-control studies and found the roles of certain SNPs of *RELN* in neuropsychiatric diseases (14).

In conclusion, the present study supported the evidence that the rs362746 polymorphism of *RELN* was a genetic factor for schizophrenia susceptibility. However, there is a need for replication studies on different populations and further investigations on the sex-specific association of this gene with schizophrenia.

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