http://pmjournal.ir Original Article

Spring 2021, Volume 6, Issue 21 (1-3)

Association between rs362746 Polymorphism of RELN and Schizophrenia in Iranian Patients

Fateme Frootan[1], Shima Alimohammadi[2*]

[1]Maya Milk, Inc, Delaware, USA

[2]Department of microbiology, karaj branch, Islamic Azad University, karaj, Iran

Corresponding author: Shima Alimohammadi, Department of microbiology, karaj branch, Islamic Azad University, karaj, Iran. Email: sh1390am@gmail.com

DOI: 10.22034/pmj.2021.244727

Submitted: 2021-04-21
Accepted: 2021-05-12

Keywords:
Schizophrenia
Reelin gene
Single Nucleotide
Polymorphism
Sequencing

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.

REFERENCE

1. Alkelai A, Lupoli S, Greenbaum L, Kohn Y, Kanyas-Sarner K, Ben-Asher E, et al. (2012). DOCK4 and CEACAM21 as novel schizophrenia candidate genes in the Jewish population. Int J Neuropsychopharmacol 15:459–469.

2. Chen N, Bao, Y, Xue Y, Sun, Y, Hu D, Meng S, et al. (2017). Meta-analyses of RELN variants in neuropsychiatric disorders. Behav Brain Res 332:110–119.

3. Fatemi SH, Earle JA, McMenomy T (2000). Reduction in reelin immunoreactivity in hippocampus of subjects with schizophrenia, bipolar disorder and major depression. Mol Psychiatry 5:654–663, 571.

4. Gaiano N (2008). Strange bedfellows: reelin and notch signaling interact to regulate cell migration in the developing neocortex. Neuron 60:189–191.

5. Impagnatiello F, Guidotti AR, Pesold C, Dwivedi Y, Caruncho H, Pisu MG, et al. (1998). A decrease of reelin expression as a putative vulnerability factor in schizophrenia. Proc Natl Acad Sci U S A 95:15718–15723.

6. Kuang WJ, Sun RF, Zhu YS, Li SB (2011). A new single-nucleotide mutation (rs362719) of the reelin (RELN) gene associated with schizophrenia in female Chinese Han. Genet Mol Res 10:1650–1658.

7. Kwon HJ, Jang WC, Lim MH (2016). Association between RELN gene polymorphisms and attention deficit hyperactivity disorder in Korean children. Psychiatry Investig 13:210–216.

8. Li M, Luo XJ, Xiao X, Shi L, Liu XY, Yin LD, et al. (2013). Analysis of common genetic variants identifies RELN as a risk gene for schizophrenia in Chinese population. World J Biol Psychiatry 14:91–99.

9. Miyata T, Nakajima K, Mikoshiba K, Ogawa M (1997). Regulation of purkinje cell alignment by reelin as revealed with CR-50 antibody. J Neurosci 17:3599–3609.

10. O'Donovan MC, Craddock N, Norton N, Williams H, Peirce T, Moskvina V, et al.; Molecular Genetics of Schizophrenia

Collaboration (2008). Identification of loci associated with schizophrenia by genome-wide association and follow-up. Nat Genet 40:1053–1055.
11. Shifman S, Johannesson M, Bronstein M, Chen SX, Collier DA, Craddock NJ, et al.(2008). Genome-wide association identifies a common variant in the reelin gene that increases the risk of schizophrenia only in women. PLoS Genet 4:e28.
12. Smalheiser NR, Costa E, Guidotti A, Impagnatiello F, Auta J, Lacor P, et al. (2000). Expression of reelin in adult mammalian blood, liver, pituitary pars intermedia, and adrenal chromaffin cells. Proc Natl Acad Sci U S A 97:1281–1286.
13. Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM, et al. (2008). Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science 320:539–543.
14. Zhou Z, Hu Z, Zhang L, Hu Z, Liu H, Liu Z, et al. (2016). Identification of RELN variation p.thr3192ser in a Chinese family with schizophrenia. Sci Rep 6: 24327.