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ORIGINAL ARTICLE

Female gender specific association of the Reelin (*RELN*) gene rs7341475 variant with schizophrenia

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Abstract

RELN gene encodes a large extracellular matrix protein which is critical for neuronal migration, cell positioning and cell–cell interactions. It also controls the synaptic plasticity of neurons for initiation and maintenance of long term potentiation. The aim of this study is to investigate the association of *RELN* rs7341475 variant with schizophrenia. Genomic DNA isolation was performed from 105 schizophrenic patients and 137 healthy controls to determine *RELN* rs7341475 genotypes. Genotype and allele frequencies were determined by a polymerase chain reaction-restriction fragment length polymorphism method developed in our laboratory. Statistical analysis was performed using χ^2 test. The frequencies for G allele were 79.5% in cases and 81.0% in controls, for A allele 20.5% in cases and 19.0% in controls in the overall population. The genotype frequencies of the *RELN* gene rs7341475 variant were GG; 63.8%, GA; 31.4% and AA; 4.8% in cases, GG; 63.5%, GA; 35.0% and AA; 1.5% in controls in the overall population. There was no statistically significant association between the rs7341475 variant of *RELN* gene and schizophrenia in the overall population ($\chi^2 = 2.473$, $p = 0.290$). In the gender specific analysis, female gender specific association was only found. The *RELN* rs7341475 variant GG genotype was significantly associated with schizophrenia ($p = 0.034$, OR 2.760, 95% CI 1.058–7.197) and A allele was protective against schizophrenia ($p = 0.034$, OR 0.362, 95% CI 0.139–0.945). All cases and controls were in Hardy–Weinberg equilibrium ($p > 0.05$). Population size can be increased to improve the statistical power. Moreover, other *RELN* gene variants which are especially involved in neuronal migration and epigenetic regulation may be analyzed for revealing the complex genetic architecture of schizophrenia. In conclusion, there was only association between the RELN rs7341475 variant and schizophrenia in the female gender in a Turkish population.

Keywords *RELN* gene · Schizophrenia · Polymorphism · rs7341475 · Female gender · Specific association · Turkish population

Introduction

Schizophrenia is a complex and chronic psychiatric disorder with a lifetime prevalence of 1% worldwide. The investigation of schizophrenia genetics is challenging due to its multifactorial nature. Beside the genetic variations such as mutations, translocations, polymorphisms and copy number variations, environmental and epigenetic factors may also play a role in the etiology of the disease [1–3].

Genome wide association studies (GWAs) are systematic and objective studies based on "common disease, common variant" hypothesis that allow to identify population specific and disease associated variants especially involved in polygenic and multifactorial diseases such as schizophrenia [4].

Shifman et al. showed association between the *RELN* gene and schizophrenia in the Ashkenazi Jewish population

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as a GWAs in which the rs7341475 variant of *RELN* gene was associated with schizophrenia only in women (GG genotype was $p = 2.92 \times 10^{-5}$, OR 2.0). This specific variant was consequently analyzed in four other populations (English, Irish, Chinese and USA) for understanding whether that was a population specific variant. This result for schizophrenia was only replicated in women for the English population (GG genotype, $p = 1.8 \times 10^{-3}$, OR 1.85) [5].

The *RELN* gene encodes a serine protease enzyme that plays a role in receptor-related pathways of neurons and in corticogenesis. Although there are studies of gender differences for schizophrenia, the underlying mechanism is not yet clear. The *RELN* gene expression is higher in females than males and the level of *RELN* gene expression is decreased in schizophrenic males according to the layer I neuron studies [6].

The *RELN* gene is located on chromosome 7q22.1, which consists of 65 exons and 3460 amino acids. The gene encodes an extracellular matrix protein which plays a critical role in neuronal migration and cell positioning during brain development, and also controls cell–cell interactions. The *RELN* gene is expressed in the adult brain; GABA-ergic interneurons, temporal cortex, hippocampus, glutamatergic granule cells which are located in cerebellum, and also expressed in fetal and adult liver tissues [7, 8]. Although reelin expression starts at early development, the expression continues in the adult brain. Long-term potentiation starts and continues by regulating synaptic plasticity. It also stimulates dendritic spine development and regulates the migration of neuroblasts generated in adult neurogenesis. Enzymatic activity is important for the modulation of cell adhesion because it binds to the extracellular regions of lipoprotein receptors apolipoprotein E receptor-2 (ApoER2) or very-low density lipoprotein receptor (VLDR) and induces the phosphorylation of Tau and Disabled-1 (Dab1) [9].

The reelin protein starts with a signaling peptide of 27 amino acids and followed by a F-spondin-like region, reelin specific "H regions" and reelin repeats consisting of 300–380 amino acids. Epidermal growth factor (EGF) motif is located in the center of the reelin repeats and divides every repetitive region into A (BNR/ASP -box repeat) and B (EGF-like region). These A and B regions directly contact to each other to form a compact structure. The end of the reelin region contains a basic and short C terminal region (CTR) which consists of 32 amino acids. This region is higly conserved, 100% identical in all mammals studied. Previously, this region was considered as an essential, but further studies have shown that CTR is not essential for secretion alone, only mutations which cause CTR region loss could effect the signaling pathway [10].

Reelin name comes from the reeler mice, which are homozygous for a mutation in the *RELN* gene. These mice lack of Reelin protein which causes abnormalities for neuronal positioning in the central nervous system especially in the cerebral cortex. Although heterozygous mice have less neuroanatomical defects, they have some cognitive abnormalities which are common in psychotic disorders. Postmortem studies of hippocampus, cerebellum, basal ganglia and cortex; showed that reelin expression is decreased in schizophrenia and bipolar disorder. In some regions, the reelin reduction could reach up to 50% and simultaneously the expression of glutamic acid decarboxylase 67 kDa (GAD-67) enzyme which catalyzes the conversion of glutamate into GABA decreases about 70%. It has been also shown that reelin levels in the blood decrease in the schizophrenia and mood disorder patients [11–13].

In the present study, we wanted to determine whether the RELN gene rs7341475 variant was associated with schizophrenia in a case control study of 105 schizophrenic patients and 137 healthy controls in a gender specific manner in a Turkish population.

Materials and methods

Patients

In this study; 105 schizophrenic patients (40 female, 65 male) (the age range was between 18 to 75 in patients (mean age; 37 ± 3.830) and 18 to 73 in controls (mean age: 38 ± 4.180), and 137 voluntary healthy controls (65 female, 72 male) were included. All subjects were recruited from the psychiatry clinic in Kocaeli University Hospital, and diagnosis of the schizophrenia was based on DSM-V criteria [14]. Inclusion criteria for patients, those who were diagnosed with schizophrenia above 18 years of age were included. Exclusion criteria for schizophrenia patients, those who had comorbidity were excluded, for controls those who had any disease were excluded. Schizophrenia patients and healthy controls provided written informed consent and the Kocaeli University institutional review board approved the study (KAEK 35, 2011/35).

Genotyping

Genomic DNA isolated from all subjects using the conventional salting-out method [15]. Genotype and allele frequencies for the *RELN* rs7341475 variant were analyzed by using a polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP) method developed in our laboratory. The 211 bp fragment was amplified with 10 pmol each of the forward primer 5′-AGGCTCTTGGGAATGGTATGC AGT-3′ and the reverse primer 5′-TAGCTCTCCACTTCC TTGGTGCTT-3′ (Integrated DNA Technologies, Coralville, IA, USA). PCR thermal conditions were; 95 °C for 5 min for first denaturation step followed by 30 cycles of 95 °C for

1 min, 61 °C for 30 s, 72 °C for 1 min and a final extension step at 72 °C for 10 min. The PCR reaction was performed in T100 Thermal cycler (Bio-Rad Laboratories, Inc., Hercules, CA, USA). The digestion of the amplified 211 bp fragment with the *Apo*I restriction endonuclease (New England Bio-Labs, Ipswich, MA, USA) was carried out at 37 °C overnight. Digested fragments were electrophoresed at 20 W for 40 min on a 8% polyacrylamide gel and followed by silver staining and scanning. *Apo*I digestion of PCR–RFLP product produced 115 bp and 96 bp fragments for the GG genotype, 96 bp, 85 bp and 30 bp fragments for the AA genotype and 115 bp, 96 bp, 85 bp and 30 bp fragments for the GA genotype (Fig. 1).

Statistical analysis

The Hardy–Weinberg equilibrium (HWE) was verified for both groups (http://ihg.gsf.de/cgi-bin/hw/hwal.pl) Statistical analysis was performed using the SPSS software package, version 21.0. Allelic distributions and genotype frequencies were compared by the χ^2 test and Student's *t* test. The relative risk as odds ratio (OR) analysis was carried out with 2×2 cross tabulation and binary logistic regression model for gender. The p value <0.05 was considered statistically significant. Statistical power was also calculated. (https://www.stat.ubc.ca/rollin/stats/ssize/b2.html).

Results

The *RELN* gene rs7341475 allele and genotype frequencies were analyzed for 105 schizophrenia patients and 137 healthy controls. The G allele frequencies were 79.5% in cases and 81.0% in controls. The genotype frequencies of the *RELN* gene rs7341475 variant were GG; 63.8%, GA; 31.4% and AA; 4.8% in cases, GG; 63.5%, GA; 35.0% and AA; 1.5% in controls. Statistically significant association was not found between the rs7341475 variant of *RELN* gene and schizophrenia in the overall population ($\chi^2=2.473$, $p=0.290$). (Table 1) Gender specific statistical analysis was also performed and a female gender specific association was found. The *RELN* gene rs7341475 GG genotype was associated with schizophrenia in female patients with schizophrenia ($p=0.034$, OR 2.760, 95% CI 1.058–7.197) and A allele

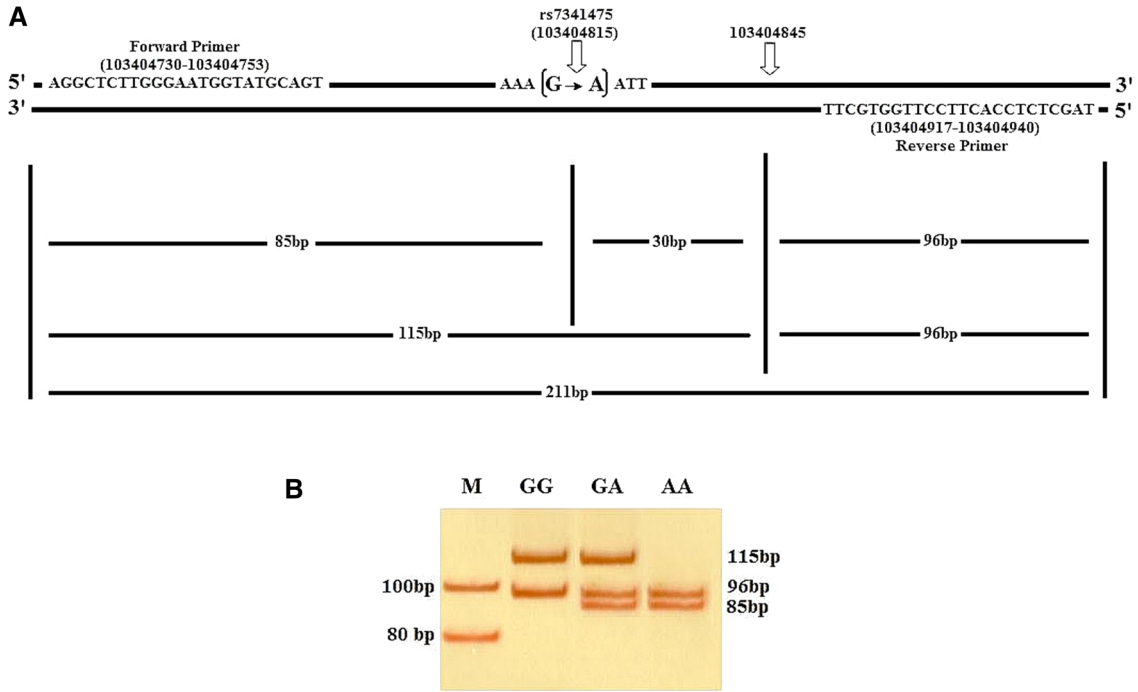

Fig. 1 **a** A schematic illustration of *RELN* gene showing the location of *Apo*I recognition sequences (5′…R/AATTY…3′) relative to the primers annealing sites (Genomic Reference Consortium:GRCh37.p13). Forward and reverse primers shown on the gene can produce a fragment of 211 bp of which there is always an *Apo*I restriction site at position of 103404845 which produces two fragments of 115 bp and 96 bp. Another *Apo*I restriction site created upon the transition of G base to A base at position of 103404815 which produces three fragments of 96 bp, 85 bp and 30 bp. **b** Polyacrylamide gel electrophoresis (PAGE) of the *RELN* gene rs7341475 was digested with *Apo*I restriction endonuclease and was run on a 8% PAGE at 20 W for 40 min followed by silver staining. Lane M shows the marker, lane GG showing the GG genotype with two fragments of 115 bp and 96 bp, lane AA showing the AA genotype with three fragments of 96 bp and 85 bp but 30 bp run out of the gel, lane GA showing the GA genotype with four fragments of 115 bp, 96 bp, 85 bp and 30 bp fragment run out of the gel

Table 1 Allele and Genotype frequencies of *RELN* gene rs7341475 variant in overall patients with schizophrenia and controls

Gene	Cases (%)	Controls (%)	χ^2	p value	OR; 95% CI
RELN (rs7341475)	105 (100.0)	137 (100.0)	2.473	0.290	
GG	67 (63.8)	87 (63.5)	0.002	0.961	1.013 (0.597–1.719)
AA	5 (4.8)	2 (1.5)	2.307	0.129	3.375 (0.642–17.752)
GA	33 (31.4)	48 (35.0)	0.347	0.556	0.850 (0.495–1.460)
Allele frequency					
G allele	(79.5)	(81.0)	2.307	0.129	0.296 (0.0056–1.558)
A allele	(20.5)	(19.0)	0.002	0.961	0.987 (0.582–1.674)
HWE exact (p)	0.763	0.161			

HWE Hardy–Weinberg equilibrium, *OR* odds ratio, *CI* confidence interval

was protective against schizophrenia only (p = 0.034, OR 0.362, 95% CI 0.139–0.945). All cases and controls were in Hardy–Weinberg Equilibrium (p > 0.05) (Table 2). The statistical power was 0.05 in overall schizophrenia patients and 0.89 for A allele and GG genotype and 0.92 for GA genotype in female schizophrenic patients.

Discussion

Schizophrenia is a common and complex mental disorder. It is known to be highly heritable (81%) and environmental factors (hypoxia, stress, malnutrition, socioeconomic conditions etc.) are also contributing to development of the disease [16].

It is known that two alternative isoforms of *RELN* gene have been conserved well between species. One of these isoforms is the result of an alternative splicing, that involves a microexon region of 6 nucleotides. This microexon is only specific to the brain. The other isoform is produced by alternative polyadenylation which creates a loss at the 3′ end of the C-terminal of the Reelin protein. Because of these two isoforms affect the 3′ end of the *RELN* gene, they are expected to have a regulatory role in the signaling pathway. These isoforms were investigated in schizophrenia and bipolar disorder. The *RELN* isoform which lacks of the C-terminal region is expressed less in bipolar disorder compared to the controls but this result was not observed between schizophrenia and controls [17].

Abnormalities in *RELN* gene cause autosomal recessive lissencephaly with cerebellar hypoplasia. Mutations decrease *RELN* expression level by affecting especially transcriptional splicing. These patients have severe intellectual disability, delayed development, hypotonia and ataxia. It is more common in consanguineous marriages [18]. *RELN* gene is also known to play a role in Alzheimer's disease, temporal lobe epilepsy and autism [19–22]

Reelin receptors (ApoER2 and VLDLR) are members of the low-density lipoprotein (LDL) receptor gene family. All members of this family are a receptor for Apolipoprotein E (ApoE). Three allelic isoforms of ApoE (E2, E3, E4) are found in human. ApoE4 allele is the primary genetic risk factor for the late-onset Alzheimer's disease. It is known that ApoE receptors play a central role in Alzheimer's disease. Alzheimer's patients and controls are compared for reelin expression and glycosylation, the level of reelin in the cortex was found to be 40% higher in Alzheimer's patients but the level of cerebellar reelin was in normal levels [22].

VLDLR expression levels decreased in peripheral lymphocytes in schizophrenia. After 6 months of psychotherapeutic treatment, VLDLR expression level was increased. It is suggested that the level of the peripheral VLDLR could be a biomarker for schizophrenia [9, 23].

Table 2 Allele and genotype frequencies of *RELN* gene rs7341475 variant in female patients with schizophrenia and controls

Gene	Female cases (%)	Female controls (%)	χ^2	p value	OR; 95% CI
RELN (rs7341475)	40 (100.0)	65 (100.0)	5.171	0.075	
GG	33 (82.5)	41 (63.1)	4.490	0.034	2.760 (1.058–7.197)
AA	1 (2.5)	1 (1.5)	0.123	0.726	1.641 (0.100–26.993)
GA	6 (15)	23 (35.4)	5.174	0.023	0.322 (0.118–0.881)
Allele frequency					
G allele	(90.0)	(80.8)	0.123	0.726	0.609 (0.037–10.024)
A allele	(10.0)	(19.2)	4.490	0.034	0.362 (0.139–0.945)
HWE exact (p)	0.320	0.433			

HWE Hardy–Weinberg equilibrium, *OR* odds ratio, CI confidence interval

In Finland, chromosome 7q21-32 region was especially analyzed in 352 schizophrenia in a family based study. The *RELN* gene allelic variations in that region were associated with functions such a memory, especially, visual and verbal working memory [24].

Transcriptional start region and the first exon of the *RELN* gene are GC rich so there are extended CpG islands. The decrease of *RELN* expression in psychiatric diseases is thought to be related with CpG islands hypermethylation. Several epigenetic markers have been tested in schizophrenia and bipolar disorder, but most of the abnormalities were identified in reelin and decarboxylase GAD-67. These two proteins are expressed in the mammalian cortex GABAergic neurons simultaneously. Schizophrenia postmortem studies have shown that reelin and GAD-67 were downregulated and the level of DNA methylation enzyme (Dnmt1) was increased in the patients. A study with the aim to test the relationship between these two events, the level of methylation of CpG islands in the *RELN* gene protomor was compared in schizophrenia and control groups, especially high level of promoter methylation were determined in the previously identified cis-acting region ($p < 0.001$) and *RELN* expression was reduced in the patients. It was also determined that the inhibitors of *DNMT1* increased the level of expression of *GAD67* and reelin in mouse. For example; histone deacetylases and methylation inhibitors such as valproic acid increase the mRNA level of Reelin [25, 26]

The *RELN* rs7341475 variant is an intronic, synonymous variant which is located in the intron four of *RELN* gene. Its genomic location is on chromosome 7:103404815 [27].

Some studies failed to show an association between the *RELN* rs7341475 variant and schizophrenia. In a case–control study with 400 Han-Chinese schizophrenics and 400 controls, it was shown that the *RELN* rs7341475 variant was not a risk factor for schizophrenia ($p = 0.927$, OR 1.02, 95% CI 0.71–1.45). These findings were analyzed according to gender, but no association was found [28]. The *RELN* rs7341475 variant was also not found to be associated in another case–control study using a PCR–RFLP method for 84 schizophrenia patients and 300 controls in a Chinese population [28].

The rs7341475 variant of the RELN gene has also been revealed to be associated with schizophrenia, but the results remain controversial. A meta-analysis of RELN gene SNPs and related neuropsychiatric disorders has been reported in which RELN rs736707 variant was significantly related with psychiatric disorders in Asian populations (OR 1.26, 95% CI 1.13–1.41, $p = 0.01$) and rs7341475 variant was only significantly associated with reduced risk for schizophrenia in A allele in Caucasian (OR 0.88, 95% CI 0.82–0.95, $p = 0.01$). The findings of the meta-analysis is in good agreements with our findings we report here. The results of this meta-analysis also may imply that RELN gene variants are involved in a spectrum of psychiatric disorders [29].

Another meta-analysis was also performed to reveal whether there was association between RELN rs7341475 and rs 262355 variants with schizophrenia. The A allele of the rs7341475 variant was shown to be associated with decreased risk for schizophrenia in a dominant genetic model (OR 0.90, 95% CI 0.83–0.98) and additive model (OR 0.90, 95% CI 0.84–0.97). In subgroup analysis, the association was only shown in Caucasian between rs7341475 and rs262355 and schizophrenia, but not in Asian [30].

Schizophrenia is known to have some differences according to the gender. For example, disease onset is 5 years earlier and prevalence is 40% greater for the males. Epigenetic changes (DNA methylation etc.) also follow a gender specific manner which some examples were shown above. *RELN, MTHFR* and *NNMT* genes are all involved in epigenetic pathways so research about these genes and variations should continue with more samples and in different populations. Environmental factors should be considered very well because of the multifactorial nature of the disease. Females and males are also exposed to some of the environmental factors (Giving birth, socio-economic conditions etc.) differently in some populations which can explain the gender specific expression of the *RELN* gene. Another possible explanation is the difference of the male and female sex hormones. It has been shown that increase of testosterone hormone level can reduce the brain reelin expression in males European starling. This result can lead to a sex hormone associated pathway and it should be evaluated in human.

Conclusion

Our study supports the female gender specific association of the *RELN* rs7341475 variant with schizophrenia in a Turkish population. It is known that synonymous mutations do not change the amino acid sequences but they can effect the secondary structures of mRNAs and regulate the mRNA stability therefore this study needs further replication and functional analysis for understanding the underlying mechanism. It is still not clear how *RELN* involves in psychiatric disorders but genetic overlaps with other neurodevelopmental diseases point out a shared neuronal pathway. Proper neuronal migration and cortical structure are very important for brain development which are the critical functions of *RELN*. Population size should be increased for statistical power and population specific replication studies are required for determining the effect of the variation in the world.

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Compliance with ethical standards

Conflict of interest No conflict of interest exists.

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