The relationship between attention deficit hyperactivity disorder and reelin gene polymorphisms in Turkish population

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most frequent chronic neurodevelopmental disorders in childhood, which is characterized by lack of attention, hyperactivity, and impulsivity symptoms [1]. Studies about ADHD etiology have become more important in recent years, as this is a heterogeneous disorder causing deterioration and destruction in many areas including social and academic functionality and may continue into adulthood [2,3]. Although there is ongoing genetic, neurochemical, and brain monitoring research to determine the psychological and environmental factors in ADHD etiology, there has still not been a full explanation of the etiology, although genetic and environmental factors are commonly thought to play a major role [4].

The view that the molecular mechanism of neurodevelopment can affect many cognitive functions such as learning, memory, and management functions has been supported by many studies [5–7]. In accord with this, it has been shown that changes in some proteins responsible for neurodevelopment can create an increased risk for neuropsychiatric diseases which accompany the disruption of cognitive functions. Reelin (RELN), a protein with an important role in the development of the central nervous system, is an extracellular matrix protein that is synthesized by the RELN gene located in the 7th chromosome (7q22) of humans. A number of studies have reported that RELN signalling plays a role in the dopaminergic system, in particular in the expression of dopamine receptors in nucleus accumbens [8,9]. It has been indicated that any kind of mutation or change in the expression of the RELN gene leads to some neuropsychiatric diseases such as schizophrenia, bipolar disorder, major depression, Alzheimer’s disease, autism, and lissencephaly [10–12]. Although reelin anomalies have been studied in many neuropsychiatric diseases, there have been few studies performed with reelin gene about ADHD etiology. In an animal study, it was found that hyperactivity developed in transgenic rats with VLDRL overexpression [13]. In the same study, it was reported that VLDRL overexpression altered reelin signalling in transgenic rats, causing hyperactivity. In a recent study, Kwon et al. (2016) determined a relationship between RELN single-nucleotide polymorphisms (SNPs) and ADHD, and a significant correlation was found between rs736707 and ADHD [14].

The aim of this study was to determine the etiopathological role of this gene by investigating the relationship between ADHD and RELN gene, and thereby provide further insight on this subject for future studies.

ABSTRACT

PURPOSE: Although attention deficit hyperactivity disorder (ADHD) is one of the most frequently seen psychiatric disorders in childhood, its etiology and pathophysiology are not fully elucidated. The aim of the present study was to investigate the association between ADHD and RELN gene in Turkish children.

METHOD: DNA samples were harvested from 102 patients with ADHD and 94 healthy controls. Three single-nucleotide polymorphisms of reelin gene (rs1270519, rs362691, and rs734147) were genotyped using real-time polymerase chain reaction.

RESULTS: A significant difference was detected between ADHD and control groups regarding rs1270519 polymorphism while no significant difference was detected between the groups regarding reelin rs362691 and rs734147 polymorphisms.

CONCLUSION: It was found that reelin rs12705169 gene polymorphism could play a role in ADHD etiology, indicating the need for further studies to investigate the relationship between ADHD and reelin gene polymorphism.
Material and method

Evaluation was made of a total of 102 cases who presented at the Psychiatry and Pediatric Psychiatry Clinics and were diagnosed with ADHD according to the DSM-IV-TR criteria [15]. Patients with another chronic disease, additional psychiatric disease or intellectual disability were excluded. The control group consisted of 94 healthy age and gender-matched children with no history of chronic illnesses who referred to the Department of Pediatrics of the hospital for routine check-up. The schedule for affective disorders and schizophrenia for school-age children-present and life-time version was applied to support the diagnosis of ADHD and to rule out comorbid psychiatric disorders [16]. This is a semi-structured interview, the Turkish adaptation of which was conducted by Gökler et al. [17]. The control group subjects were selected as children with no known neurodevelopmental/neurological disorder, or infection. Medical disorders were excluded through medical history screening, clinical examination findings of the pediatrician, and routine laboratory test results, including biochemical, hematological, and thyroid function tests. For both groups, those with an IQ of over 80 were included in the study.

The parents of the children were given the Conners’ Parent Rating Scale-Revised Long Form [18,19]. The teachers of the patient and control group subjects completed the Conners’ Teacher Rating Scale [20–22].

The cases determined with ADHD were classified into three subtype groups of inattentive, hyperactive/impulsive, and combined.

Approval for the study was granted by the Local Ethics Committee of Mugla Sitki Kocman University, Faculty of Medicine, Mugla, Turkey (approval date: 28.03.2013). All study procedures were conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardian of each participant.

Genotyping

Blood samples were taken from the control and patient groups into 2 ccEDTA (ethylenediaminetetraacetic acid) tubes. The samples were stored at −20°C until DNA isolation using DNA isolation protocols (PureLink® Genomic DNA Mini Kit, Invitrogen, Carlsbad, CA 92008, USA) and target SNPs (rs7341475, rs362691, rs12705169) were studied using the ABI Prism StepOnePlus Real Time System with TaqMan probes.

For each polymerase chain reaction (PCR) mix: TaqMan Genotyping Master Mix: 5 µl, TaqMan genotyping assay (40X): 0.25 µl, DNase-free, RNase free water, 2.75 µl, total: 8 µl, mix was prepared. The PCR programme was applied with 40 cycles in the StepOne-Plus Real Time System for 30 s at 60°C, 10 min at 95°C, 15 s at 95°C, 1 min at 60°C, and 30 s at 60°C. Homozygote normal, homozygote, and heterozygote mutant genotypes were determined according to the discrimination of allele 1 and allele 2 using system software.

Statistical analysis

Statistical Package for Social Science (SPSS) 20.0 software was used for the statistical analyses. The Hardy–Weinberg balance adaptation of genetic distribution was analysed with the Chi-square goodness-of-fit test. Genotypic and alleric distribution differences between the patient and control groups were evaluated with the χ²-test. The differences between the normally distributed numerical values and the genotypic and allele gene distribution were evaluated with the one-way ANOVA test. A value of p < .05 was accepted as statistically significant in all statistical tests.

Results

In this study, we included 102 patients with ADHD 4–18 years old, and 94 age- and gender-matched healthy controls. No significant difference was found between the groups regarding the age (ADHD group: 12.41 ± 3.77; controls: 12.77 years ± 3.72; p > .05) and gender (ADHD male/female ratio: 72/30, controls male/female: 65/29; p > .05). The demographic characteristics of the ADHD and the control groups are summarized in Table 1. The Conners’ Teacher Rating Scale and the Conners’ Parent Rating Scale–Revised Long Form Scale scores were higher in the patient group than the control group (Table 2).

Of the patients with ADHD, 7.8% (n = 8) were classified as hyperactive/impulsive subtype, 42.2% (n = 43) as inattentive subtype and 50% (n = 51) as combined subtype.

When the ADHD cases were evaluated according to ADHD family history, 62 (59.6%) were found to have

| Table 1. Demographic characteristics of the ADHD and control groups. |
|------------------|------------------|
|                  | ADHD group | Control group | p       |
| Gender male n (%) | 72 (70.5)  | 65 (69.1)    | .819    |
| Female n (%)      | 30 (29.5)   | 29 (30.9)    |         |
| Age (Mean ± SD)   | 12.41 ± 3.77 | 12.77 ± 3.72 | .499    |
| Educational status | 6(5.8)     | 4 (4.2)      | .940    |
| Primary school    | 28(27.5)    | 25 (26.6)    |         |
| Secondary school  | 30(29.5)    | 29 (30.9)    |         |
| High school       | 37(36.3)    | 35 (37.2)    |         |
| University        | 1(0.9)      | 1(1.1)       | .292    |
| Number of siblings| 1.74 ± 0.74 | 1.84 ± 0.72  | .292    |
| Maternal age at birth (years) | 25.4 ± 4.77 | 26.04 ± 4.62 | .370 |
| Paternal age at birth (years) | 30.5 ± 5.78 | 31.07 ± 5.73 | .510 |
| Duration of breastfeeding (months) | 9.12 ± 8.20 | 8.96 ± 7.15 | .890 |
| Age of walking (months) | 13.63 ± 7.57 | 13.53 ± 7.26 | .864 |
| Age of speaking (months) | 17.52 ± 7.57 | 17.48 ± 7.69 | .985 |
The most frequently observed five haplotypes that were observed in the haplotype analysis for three single-nucleotide polymorphism using SNP analysis software are shown in Table 5. Haplotype ATG was observed most frequently in both the patient and control groups and a significant difference was detected between the groups (p < .001). The difference between the AGG haplotype groups was found to be statistically significant in the haplotype analyses of these three SNPs (p < .000).

When the cases were evaluated by gender, ADHD history in the family and mental disorder history in the family, no statistically significant difference was determined between the groups in respect of the reelin rs326691 (G/C), rs734147 (A/G), and rs12705169 (T/G) gene polymorphisms (Table 6).

Discussion

In this study, a significant difference was detected between the ADHD and control groups in respect of rs12705169 polymorphism. When subjects with ADHD were assessed according to gender, family history of ADHD, or psychiatric disorder, no significant difference was detected in reelin rs326691(G/C), rs734147(A/G), and rs12705169(T/G) gene polymorphisms.

Reelin has been reported to have an important role in neurodevelopment by regulating neuronal migration, laminar organization, dendritic arbour, and neurotransmission [23]. Animal studies have shown that non-foliated cerebellum of double knock-out RELN genes caused deficiencies in the lamination of the hippocampus and disorganization in the amigdala [24,25]. Mice with reelin deficiency have shown to have largely inverted cortex layers, which strongly support the idea that reelin is a key regulator in cortical development. In previous animal studies, a more complex model has been shown rather than the cortex laminar formation by reelin in the brain, which was previously thought [24,26].

It has been shown that reelin modulates neurogenesis not only during the development process but also at an adult age. In adulthood, reelin is released from GABAAergic interneurons of the hippocampus which play an important role in neuroplasticity. In addition, reelin proteins bind to alpha3 subunits of integrin receptors expressed on the neuronal cell surface such as apolipoprotein E receptor 2 (ApoER2) and very low-density lipoprotein receptor. Activation of reelin signalling has significant effects on long-term potentiation, regulation, cell proliferation, cell migration, brain development such as dendritic spine morphogenesis and adult neurogenesis [27]. It is known that any mutation or altered expression in the reelin gene, which has an essential role in the neuronal development process, predisposes to neuropsychiatric diseases [8]. The reelin gene has been shown to play a role in

![Table 2. The Conners’ parent and teacher rating scale scores of ADHD and control group.](#)

| Scale score       | ADHD group Mean ± SD | Control group Mean ± SD | p     |
|-------------------|-----------------------|--------------------------|-------|
| Oppositional      | 18.51 ± 6.76          | 8.19 ± 5.36              | .000  |
| Hyperactivity     | 17.38 ± 6.16          | 5.02 ± 3.81              | .000  |
| Anxiety-ephoria   | 8.61 ± 4.68           | 5.60 ± 4.88              | .000  |
| Social problems   | 5.74 ± 3.70           | 1.74 ± 1.60              | .000  |
| Psychosomatic     | 6.30 ± 4.61           | 2.73 ± 2.21              | .000  |
| ADHD index        | 28.07 ± 5.09          | 8.34 ± 5.55              | .000  |
| DSM-N inattentiveness | 20.09 ± 4.27   | 5.90 ± 3.98              | .000  |
| DSM-N hyperactivity | 18.21 ± 6.77    | 5.89 ± 4.27              | .000  |
| DSM-N total       | 38.31 ± 9.50          | 11.79 ± 7.51             | .000  |
| CGI-irritability  | 16.01 ± 4.56          | 6.74 ± 3.16              | .000  |
| CGI-emotional lability | 5.58 ± 2.32 | 2.60 ± 2.03              | .000  |
| Conners’ Teacher Rating Scale |
| Inattentiveness   | 12.67 ± 4.36          | 3.22 ± 2.93              | .000  |
| Hyperactivity     | 12.74 ± 4.29          | 4.55 ± 3.16              | .000  |
| Conduct problems  | 10.60 ± 4.10          | 2.40 ± 2.21              | .000  |

Note: ADHD: attention deficit hyperactivity disorder; DSM-N: the fourth edition of diagnostic and statistical manual of disorders; CGI: clinical global impression.

![Table 3. Genotype and allele distributions of reelin rs362691, rs734147, and rs12705169 gene polymorphisms in the patient and control groups.](#)

| Genotype allele | Patient (n=m) | Control (n=m) | X² | p     |
|-----------------|--------------|--------------|----|-------|
| rs362691        |              |              |    |       |
| GG              | 85 (0.850)   | 79 (0.849)   | 2.005 | .366  |
| GC              | 13 (0.130)   | 14 (0.151)   |    |       |
| CC              | 2 (0.020)    | 1 (0.011)    |    |       |
| G               | 0.915        | 0.925        | 0.123 | .725  |
| C               | 0.085        | 0.075        |    |       |
| rs734147        |              |              |    |       |
| AA              | 66 (0.642)   | 61 (0.656)   | 2.802 | .246  |
| AG              | 33 (0.324)   | 32 (0.344)   |    |       |
| GG              | 3 (0.029)    | 1 (0.011)    |    |       |
| A               | 0.809        | 0.828        | 0.239 | .624  |
| G               | 0.191        | 0.172        |    |       |
| rs12705169      |              |              |    |       |
| TT              | 59 (0.578)   | 61 (0.649)   | 7.778 | .020  |
| TG              | 35 (0.343)   | 33 (0.351)   |    |       |
| GG              | 8 (0.078)    | 9 (0.098)    |    |       |
| T               | 0.750        | 0.824        | 3.222 | .072  |
| G               | 0.250        | 0.176        |    |       |
Table 4. Analyses of reelin rs12705169 gene polymorphisms according to ADHD subtypes.

| Genotype | Hyperactive/impulsive subtype (n %) | Inattentive subtype (n %) | Combined subtype (n %) | X² | p  
|----------|----------------------------------|-------------------------|----------------------|-----|-----|
| rs12705169 TT | 4 (0.50) | 23 (0.534) | 32 (0.627) | 2.905 | .574 |
| TG | 3 (0.375) | 18 (0.418) | 14 (0.264) | |
| GG | 1 (0.125) | 2 (0.046) | 5 (0.094) | |

RELN has been studied as potential biomarker for autism as it has important roles in brain development and a previous study concluded that rs36269 can have a high risk for autism rather than rs736707 or GGC repeat variant [37]. Previous studies have shown that there are ADHD symptoms of 30–50% in cases diagnosed as autism spectrum disorder and cases with ADHD also display features of autism spectrum disorder [38]. Although there is marked difference between the clinical presentations of Autism Spectrum Disorders and ADHD, both disorders display similar derangements in developmental and cognitive domains. Both are more common among males and have marked intellectual limitations. They also have shared learning and developmental difficulties, particularly in language, reading and motor domains, and impaired executive functions are also common findings in both diseases. It has been suggested that genetic factors contributing to both diseases overlap by 50–72% [39]. These common genetic and neurobiological factors explain why these disorders are frequently observed in the same patient and family. In the current study, RELN gene polymorphism, which has been shown to have a role in autism etiology, was detected in cases with ADHD.

Although reelin anomalies have been studied in many neuropsychiatric diseases, there have been few studies performed with reelin gene about ADHD etiology. In an animal study, Iwata et al. [13] have shown that hyperactivity developed in transgenic rats with VLDRL overexpression. In the same study, it was reported that VLDRL overexpression alters reelin signalling, which causes hyperactivity in transgenic rats. In the first and only study of the relationship between

Table 5. Haplotype analysis in the patient and control groups.

| Haplotype | Patient | Control | X² | p  
|-----------|---------|---------|----|-----|
| AGC⁺ | 2.91 (0.015) | 6.36 (0.035) | 1.621 | 0.202 |
| AGG⁺ | 40.05 (0.200) | 12.36 (0.067) | 14.481 | 0.000 |
| ATC⁺ | 12.45 (0.062) | 6.56 (0.036) | 1.453 | 0.228 |
| ATG⁺ | 105.6 (0.528) | 126.72 (0.689) | 10.286 | 0.001 |
| GGC⁺ | 8.04 (0.040) | 13.28 (0.072) | 1.852 | 0.173 |

Table 6. Analysis of reelin rs362691, rs734147, and rs12705169 gene polymorphisms according to gender, family history of ADHD and family history of psychiatric disease in the patients with ADHD.

| Gender | Family history of ADHD | Family history of psychiatric disease | M(n) | F(n) | p  
|--------|------------------------|--------------------------------------|------|-----|-----|
| rs362691 | | | | | |
| GG | 49 (0.81) | 21 (0.91) | .48 | 49 (0.81) | 21 (0.91) | .48 | 51 (0.83) | 19 (0.91) | .57 |
| GC | 9 (0.15) | 2 (0.08) | | 9 (0.15) | 2 (0.08) | | 9 (0.14) | 2 (0.09) | |
| CC | 2 (0.03) | – | | 2 (0.03) | – | | 2 (0.03) | – | |
| rs734147 | | | | | |
| AA | 45 (0.36) | 13 (0.28) | .17 | 45 (0.72) | 13 (0.56) | .17 | 46 (0.71) | 12 (0.57) | .23 |
| AG | 15 (0.24) | 10 (0.43) | | 15 (0.24) | 10 (0.43) | | 16 (0.25) | 9 (0.42) | |
| GG | 2 (0.03) | | | 2 (0.03) | | | 2 (0.03) | | |
| rs1270519 | | | | | |
| TT | 38 (0.61) | 11 (0.47) | .5 | 38 (0.61) | 11 (0.47) | .51 | 40 (0.62) | 9 (0.42) | .27 |
| TG | 19 (0.31) | 10 (0.43) | | 19 (0.30) | 10 (0.43) | | 19 (0.29) | 10 (0.47) | |
| GG | 5 (0.08) | 2 (0.09) | | 5 (0.08) | 2 (0.09) | | 5 (0.07) | 2 (0.09) | |
RELN SNPs and ADHD conducted by Kwon et al. [14] in 2016, which investigated the association between rs736707, rs2229864, rs362746, rs362726, rs362691, rs1062831, rs607755, and rs2072403 in Korean children with ADHD, a significant relationship was found between rs736707 and ADHD.

The limitations of this study include the small sample size and its cross-sectional design. However, only three of the SNPs related to the RELN gene have been evaluated. The fact that other polymorphisms associated with ADHD in previous study have not been studied is also considered as one of the important limitations of the study.

In conclusion, ADHD is a disorder for which there have been increasing genetic etiology studies as it is a disorder that shows middle-high level genetic hereditary transfer. In the current study, ADHD cases and a control group were evaluated through reelin gene polymorphism, and RELN was proven to have a genetic predisposition for ADHD. Future gene and expression studies of large samples from different populations will open new horizons in the clarification of ADHD etiology, thereby contributing to improvements in the treatment and prevention of the disorder.

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Ethical approval

Approval for the study was granted by the Local Ethics Committee of Mugla Sitki Kocman University, Faculty of Medicine, Mugla, Turkey.

Disclosure statement

No potential conflict of interest was reported by the authors.

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