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The Relationship between Gene SLC6A3 Variable Number of Tandem Repeat (VNTR) and Attention-Deficit/Hyperactivity Disorder

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Abstract

Objective: This research investigates the alleles of Variable Number of Tandem Repeats (VNTR) intron 8 of the gene SLC6A3 with attention-deficit / hyperactivity disorder (ADHD) in children and adolescents.
Method: The study's target population consisted of children and adolescents referred to the specialized clinic, as well as students attending school in Rasht city during 2021-2022. A sample of 95 children between the ages of 6 and 10 with ADHD was selected as the ADHD group, and 95 healthy children were selected as the control group using purposive sampling. The subjects completed the Child Symptom Inventory-4 (CSI-4) checklist after a clinical interview, and demographic information was collected. Genetic sampling was carried out through hair follicles. The sequence of interest was proliferated using the Polymerase Chain Reaction technique (PCR); afterward, the samples were used for genotype identification on polyacrylamide gel electrophoresis.
Results: The chi-square test results indicated that the 5R / 5R genotype (P = 0.026, $\chi 2$ = 7.26) and the 5R allele (P = 0.002, $\chi 2$ = 9.35) had a higher frequency compared to the control group. Additionally, the odds ratio test indicated that, compared to other genotypes and alleles, the 5R / 5R genotype (OR = 2.75, 95% CI = 1.29-5.82, P = 0.01) and the 5R allele (OR = 2.02, 95% CI = 1.28-3.19, P = 0.002) increase the odds of developing ADHD by 2.7 and 2 times higher, respectively.
Conclusion: The present study successfully showed the association between intron 8 gene polymorphism, which is responsible for encoding the dopamine transporter as well as ADHD in children and adolescents in Iran.

Key words: *Attention Deficit Disorder with Hyperactivity; DAT1 Protein; Gene Polymorphisms; Human; Variable Number of Tandem Repeat*

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Attention deficit / hyperactivity disorder (ADHD) is a complicated early-onset neurodevelopmental disorder, which is characterized by three main symptoms: attention deficit, hyperactivity, and impulsive disturbances (1). Most prevalent comorbid conditions in children with this disorder include oppositional defiant disorder, specific learning disorders, and anxiety disorders (2). Reportedly, the prevalence rate of ADHD is 7.2% worldwide (3); the independently conducted studies overall estimated a 74% contribution of genetic factors on average (4). In addition, environmental factors, such as family issues, economic status of the family, drinking, and smoking during pregnancy, exposure to toxic environmental agents, hypoxias, and low weight at birth have been reported among the significant etiologies of this disorder (5–7). Likewise, structural and functional brain imaging studies of patients with ADHD have reported decreased activity in the prefrontal cortex (8), increased white matter asymmetry (9), as well as the shrinkage of the amygdala (10), hippocampus, and putamen (11), and lastly, decreased volume of caudate nuclei (12), nucleus accumbens (13), and broad areas of their brains.

Methylphenidate ameliorates many symptoms of ADHD (14). It works by inhibiting the dopamine transporter protein which is one of the most prominent factors regulating the function of dopamine on the presynaptic membrane (15, 16). So far, the critical role of dopamine in ADHD etiology has been demonstrated in the malfunctions of many brain areas in the dopaminergic system; this role is further elucidated by reward center defects (17, 18) and the methylphenidate mechanism of action.

DAT1 is among the most prominent factors regulating dopamine activity. The gene encoding the dopamine transporter (SLC6A3) has been introduced as the most promising candidate to study ADHD (19,20); it has several polymorphisms, the best-known of which contains 40-base pair Variable number of tandem repeats (VNTR) and exists in the 3'-UTR of this gene. This polymorphism has been scrutinized in relation to ADHD, and there exist reports surrounding the response disparity between the variable allele carriers to methylphenidate therapy (21–23). Another VNTR fragment, located in intron 8 of the same gene (rs3836790), has been reportedly associated with different psychological disorders such as attention-deficit / hyperactivity disorder (24, 25), autism spectrum disorder (26), bipolar disorder (27), crack and cocaine addiction (28), heroin dependence (29), and nicotine dependence (30). This polymorphism has several variable repetitions, among which 5 and 6 repetitions (known as 5R and 6R alleles, respectively) pervade variegated populations more than the others. Investigations on the two alleles of 5R and 6R have indicated the increased expression of SLC6A3 when containing the allele 5R, compared to 6R (31, 32). Moreau *et al*. found that the genotype 6R / 6R possesses an advantage over other genotypes in this gene fragment (VNTR). This genotype enhances methylphenidate's inhibitory effect on dopamine transporter protein, resulting in increased extracellular dopamine concentration. Conversely, the repercussion of such an event is that individuals with genotype carriers for 5R / 5R would respond weakly to methylphenidate (33). While the regulatory competence of the rs3836790 polymorphism has been patently demonstrated, the study results regarding ADHD are replete with contradictory findings. Other meaningful studies on this polymorphism have presented the 6R allele as the risk allele, either independently (34) or as a haplotype with the 9R allele of rs28363170 (25, 35). In contrast, Maitra's study reported the 5R allele as the risk allele (24).

Since no study has been carried out in Iran to cast light on this variant, this study aimed to delve into the probable cause of this polymorphism by investigating children and adolescents with and without ADHD as the ADHD group and the control group, respectively. It is worth noting that in a society like Iran with many children prone to the disorder, investigating this issue is of paramount importance.

Materials and Methods

Subjects

The study population included two sets of subjects: an ADHD group and a control group. The subjects of the ADHD group were selected based on the commentary of a psychiatrist specialized in children and adolescents, while those in the control group were selected according to the DSM-5 criteria. A total of 95 children and adolescent cases for the ADHD group and 95 school-attending in the corresponding ages for the control group were chosen and recruited from the psychiatric center of Guil of Rasht and the Rasht schools, respectively. Any subject diagnosed with any psychological and neurological disorders was excluded from the control group. In the ADHD group, subjects with learning disorders, anxiety disorders, and oppositional defiant disorder were included in the study, given their high prevalence in this group. Any other neurological and psychological disorder were included in the exclusion criteria. The aims of the study were presented to the parents and a written informed consent was obtained from all participants and their parents. In accordance with the Declaration of Helsinki, the Ethics Committee of the Department of Psychology, Guilan University (Guilan.ac.ir-161548-1400-12-17) approved the study before its start.

Genotyping

A number of hair follicles samples were collected into sterile microtubes. The DNA samples were extracted using the appropriate kit and submitted to 1% agarose gel electrophoresis to assess the sample quality. PCR

materials were composed of 30 ng of DNA 2 pmol of each primer, 0.1 mM dNTP, 1.5 mM MgCl2, 10×PCR buffer (10 mM Tris-HCl, 50 mM KCl and 0.1% Triton X-100), and 0.5 unit of Taq DNA polymerase. The primer design was conducted using OLIGO primer analysis software (version 7.54, molecular Biology Insight Inc., Cascade, CO, USA) and synthesized by German Metabion company (including Forward 5'-TTAGTTTTCTGCACATACCAT-3' primer sequence and 5'-GTTCTTGCATGTATGAGTTTGAAT-3' reverse primer sequence). The amplification protocol was: an initial 5 min denaturation at 94 ◦C and 35 cycles of repeated denaturation at 94◦C for 45 s, annealing at 56◦C for 45 s, and extension at 72◦C for 45 s and final extension at 72◦C for 1 minute. The amplified fragments were submitted to 12% polyacrylamide gel electrophoresis to assess the sample quality.

Statistical Analysis

Statistical analyses were conducted using SPSS 25 software. The chi-square test and OR tests were used to compare the two groups regarding the alleles and genotypes frequency and odds ratio, respectively. Furthermore, the association of the genotypes and ADHD were estimated by odds ratios (ORs) in different models of inheritance including codominant, dominant, recessive, and over-dominant, with 95% confidence intervals.

Results

According to the results, the ratio of girl to boy subjects in the ADHD group was 1:3.1; the mean and standard deviation of age was calculated as 10.07 ± 2.05 and 10.13 ± 2.193 for the ADHD and control group, respectively. The percentages of subjects diagnosed with ADHD were 16.8% for the predominantly inattentive type, 3.2% for the predominantly hyperactive-impulsive type, and 80% for the combination type. Moreover, the ratio of subjects with comorbid conditions was 8.4% for learning disorders, 12.6% for anxiety disorders, and 35.8% for the oppositional defiant disorder. Further information about the participants is presented in Table 1.

Table 1. Comparison of Frequency of Sociodemographic Characteristics and Descriptive Information of the Sample Groups

	ADHD Group % (n)	Control Group % (n)
Gender		
Boy	75.8 % (72)	63.3 % (57)
Girl	24.2 % (23)	36.7 % (38)
Age (Mean ± SD)	10.07 ± 2.05	10.13 ± 2.19
ADHD Subtypes		
Inattentive	16.8 % (16)	
Impulsive / Hyperactive	3.2 % (3)	
Combined	8 % (76)	
Comorbid Disorders	56.8 % (54)	
LD [a]	8.4 % (8)	
AD [b]	12.6 % (12)	
ODD [c]	35.8 % (34)	

[a] Learning Disorders, [b] Anxiety Disorders, [c] Oppositional Defiant Disorder

Different genotypes of the PCR products were determined using 12% polyacrylamide gel electrophoresis as previously described. A 100 bp marker was used for more accurate measurements. As seen in Figure 1, genotypes 5R / 5R and 6R / 6R formed 250bp and 280bp segments, respectively. The heterozygous 6R / 5R genotype also produced two fragments of 280 and 250 bp in length.

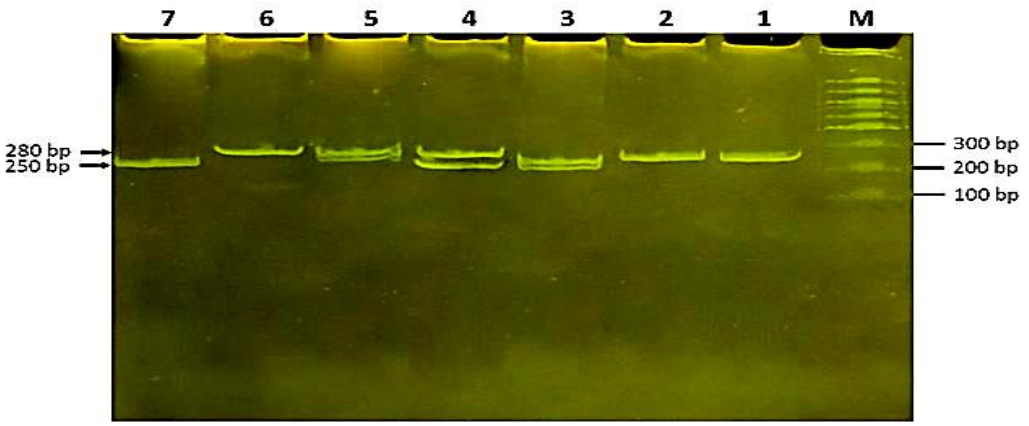

Figure 1. 12% Polyacrylamide Gel Image Obtained from Electrophoresis of the Polymerase Chain Reaction Technique Products

The frequency of various alleles and genotypes was compared between the two groups, the results of which are displayed in Table 2. The 6R allele is predominant in both populations with the 6R homozygote genotype being the most frequent in both groups. The 5R allele frequency was 35.80% in the ADHD group and 21.58% in the control group. This disparity is statistically meaningful ($\chi2$ = 9.350, P = 0.002) as well as the disparity in the genotype frequency ($\chi2$ = 7.260, P = 0.026). The frequency of 5R / 5R in the ADHD group and the control group were calculated as 28.42% and 12.63%, respectively.

Table 2. Comparison of Frequency and Ratio of Alleles and Genotypes of the Polymorphism rs3836790 of Intron 8 in the SLC6A3 Gene

rs3836790	ADHD (n = 95) % (n)	Controls (n = 95) % (n)	P-value	OR (95 % CI)	P-value
6R	64.20 % (122)	78.42 % (149)	0.002	1	-
5R	35.80 % (68)	21.58 % (41)		2.02 (1.28 – 3.19)	0.002 **
6R / 6R	56.84 % (54)	69.47 % (66)	0.026	1	-
5R / 5R	28.42 % (27)	12.63 % (12)		2.75 (1.29 – 5.82)	0.01 **
6R / 5R	14.74 % (14)	17.90 % (17)		1.006 (0.45 – 2.22)	0.98

** P < 0.05

Additionally, the odds ratio was calculated with a 95% confidence interval for the different types of alleles and genotypes and the results are represented in Table 2. Based on the results, the 5R allele and the genotype 5R / 5R increase the probability of developing ADHD by 2 and 2.75 times, respectively.

Table 3. Comparison of Intron 8 Variable Number of Tandem Repeats Genotypes under Models of Inheritance

Models of Inheritances	Genotypes	ADHD	Controls	OR (95 % CI)	P-value
Codominant	6R / 6R	56.84 % (54)	69.47 % (66)	0.58 (0.32 - 1.05)	0.07
	6R / 5R	14.74 % (14)	17.9 % (17)	0.79 (0.37 - 1.71)	0.59
	5R / 5R	28.42 % (27)	12.63 % (12)	2.75 (1.29 – 5.82)	0.01 **
Dominant	6R / 6R	56.84 % (54)	69.47 % (66)	0.58 (0.32 - 1.05)	0.07
	6R / 5R + 5R / 5R	43.16 % (41)	30.53 % (29)	1.72 (0.95 – 3.13)	0.07
Recessive	6R / 6R + 6R / 5R	71.58 % (68)	87.37 % (83)	1	-
	5R / 5R	28.42 % (27)	12.63 % (12)	2.75 (1.29 – 5.82)	0.01 **
Over Dominant	6R / 6R + 5R / 5R	85.26 % (81)	82.1 % (78)	1.00	-
	6R / 5R	14.74 % (14)	17.9 % (17)	0.79 (0.36 – 1.71)	0.55

** P < 0.05

Based on the higher frequency of the 6R allele compared to the 5R allele, the models of inheritances were investigated and the results are listed in Table 3. Based on the results of the Odds Ratio test, a significant correlation can be seen (OR = 2.75, 95% CI = 1.29-5.82, P = 0.01), revealing that people with the 5R / 5R heterozygous genotype, compared to the 6R / 6R genotype, have more than 2.5 times higher risk of ADHD compared to other genotypes (i.e., 6R / 6R and 6R / 5R). Therefore, the importance of the 5R / 5R genotype as a risk genotype in ADHD can also be observed in the recessive model.

Table 4. Comparison of the Frequency of Genotypes in Polymorphism rs3836790 of Intron 8 in the SLC6A3 Gene in the Subgroups and the Comorbid Conditions of ADHD

Genotypes	5R / 5R % (n)	6R / 6R % (n)	6R / 5R % (n)	Total Number	P-value
ADHD Subtypes					
Inattentive	37.5% (6)	43.8% (7)	18.8% (3)	16	
Impulsive / Hyperactive	0% (0)	66.7% (2)	33.3% (1)	3	0.566
Combined	27.6% (21)	59.2% (45)	13.2% (10)	76	
Comorbid Disorders with ADHD					
LD [a]	50 % (4)	50 % (4)	0 % (0)	8	0.777
ODD [b]	26.5 % (9)	67.6 % (23)	5.9 % (2)	34	0.137
AD [c]	33.3 % (4)	58.3 % (7)	8.3 % (1)	12	0.248
LD + ODD + AD	30 % (15)	64 % (32)	6 % (3)	50	0.039 **

[a] Learning Disorders, [b] Anxiety Disorders, [c] Oppositional Defiant Disorder

Table 4 presents the comparison between different types of genotypes in the three subgroups of ADHD and the comorbid conditions of the disease. According to the results of the chi-squared test, the frequency of various genotypes 5R / 5, 6R / 6R, and 6R / 5R in the subgroups was approximately the same and no significant distribution differences were observed ($\chi 2 = 3.991$, P = 0.407). The chi-square test was carried out for the comparing genotype frequency of the comorbidities, none of which showed any significant disparity between the frequency distribution of the genotypes of rs3836790 polymorphism. Nevertheless, when a comparison was made between the subjects with or without the comorbidities, a higher frequency of the genotype 6R / 5R over other genotypes was observed in the comorbidity group ($\chi 2 = 6.511$, P = 0.039).

Discussion

The present study, conducted for the first time in Iran, successfully reported the association between the polymorphism rs3836790 and ADHD. According to the results in Table 2, the 5R allele and homozygote genotype 5R have a potentially higher frequency. This study aligns with the studies carried out by Maitra *et al*. in India, which reported that the presence of the 5R allele in ADHD patients is associated with a high ADHD index (24). Conversely, the study by Silva *et al*. reported an association between ADHD and the 6R allele in adults (34). The DAT1 protein is one of the major mechanisms by which dopamine regulation is accomplished in dopaminergic synapses; by the reuptake of excess dopamine, this protein helps recycle the neurotransmitter (15).

Studies related to gene expression have also reported that the 5R allele in the gene locus enhances the SLC6A3 expression (31, 32). It is presumably considered that the increased expression of this gene and DAT1 density is in concordance with the existing etiology hypothesis of the ADHD disorder. Pharmacological results also have reports referring to methylphenidate sensitivity to alleles of rs3836790; it has been reported in a study that 5R genotype carriers have weaker therapeutic results compared to 6R allele carriers. According to these results, the expression level of the SLC6A3 gene and response to methylphenidate therapy has been considerably diminished in the carriers of genotype 6R / 6R, leading to increased extracellular dopamine level in the striatum region, compared to other genotypes (33). Thus, polymorphism of intron 8 in SLC6A3 could be regulated and utilized as a potential agent for the assessment of variable disorders associated with the dopamine transporter.

Some studies on this polymorphism failed to find an independent association between the 6R repetition and ADHD. In a report by Hoogman *et al*. and Frank *et al*., it was posited that the 6R allele is associated with ADHD, only when this allele and the 9R allele of 40-bp 3′-UTR polymorphism (rs28363170) simultaneously exist in this gene (25, 35). Other studies have also been carried out examining the association between this

polymorphism and ADHD, and no association was reported (36–39). Albeit the 5R allele succeeded to be linked to ADHD, as Table 3 demonstrates, no difference was found between the frequency of the various genotypes of rs3836790 and the subgroups of the disorder at hand. This result may be the repercussions of a small number of subjects in both groups. However, Maitra *et al*. reported that this polymorphism might be associated with the hyperactivity manifestations in ADHD.

As mentioned in the results section and as seen in Table 3, a recessive inheritance pattern appears to be important for this polymorphism in ADHD. The Odds Ratio test results showed that a person with the 5R allele at both loci had a greater than 2.5 times likelihood of exhibiting the disorder phenotype compared to those without this genotype. Unfortunately, similar studies have not examined inheritance patterns for this polymorphism, and results cannot be compared.

The present study also investigated the association between variable genotypes of this polymorphism and the comorbid disorders. According to the results displayed in Table 4, the frequency of heterozygous 6R / 5R genotype is significantly higher in patients who have at least one comorbidity, compared to those who have no comorbidities. Maitra posits that the 5R / 5R genotype has a meaningfully higher frequency in patients who have ADHD or comorbidities compared to those who lack these conditions (24). This result is discordant with our findings. It is worthwhile mentioning that the comorbidities assessed in the Maitra study are not completely consistent with those of the present study. For example, Maitra's study also assessed mood disorders, whereas our study did not. Furthermore, some studies have reported some disparity in genetic markers among different races; this disparity between the sequences has exhibited more differentiations in the non-coding regions such as introns (40). This description could justify the reported contradictions about the VNTR within intron 8 in ADHD patients in our study.

Taking the ages of ADHD patients into consideration is also of paramount importance for the assessment of SLC6A3 gene variants. Studies have reported the efficacy of the rs3836790 polymorphism 10R allele in children and adolescents with ADHD as well as the 9R allele in adults with ADHD (21). This suggests that the genetic factors involved in the two disorders are different. The etiology of this disorder is depicted by the reduced SCL6A3 gene expression and alterations in environmental factors (such as smoking) in adults and, as a corollary, those with different variants of this polymorphism may exhibit varying responses (41). There is a lack of consensus regarding the age-related evidence for the rs3836790 polymorphism in our study. However, the regulatory potential of this polymorphism and the large differences in the mean ages of the subjects in other consistent studies could serve as tenable assumptions to elucidate the prevailing discrepancies. The ADHD comorbidities could also comprise the association of the other different variants and their corresponding alleles (24). Therefore, controlling the associative factors of any ADHD comorbidity is almost impossible, which, in turn, to some extent thwarts the elucidation of the results.

Limitation

Even though this study examined and confirmed the associative role of the polymorphism within intron 8 of the gene SLC6A3 for the first time in Iran, it is important to exercise caution when generalizing the findings of this study. The small sample size used in this research necessitates subsequent studies to further investigate and verify the findings of this study.

Conclusion

In this study, a relationship between intron 8 VNTR polymorphism and ADHD was found in children and adolescents. Our results showed that the 5R allele and 5R / 5R genotype is significantly more common in the ADHD group compared to the control group. Moreover, the heterozygote 6R / 5R genotype is more prevalent in ADHD subjects with at least one comorbid disorder than the control subjects. These results suggest that regulatory polymorphisms can affect the expression of SLC6A3 gene in cells, and as a result, contribute to the etiology of dopamine-related disorders. Methylphenidate is one of the stimulants which specifically targets this protein, and different alleles in the related locus of this gene can elicit various responses to drug treatment. Although this polymorphism has a proven regulatory role in the expression of the SLC6A3 gene, most studies focused on its 3-UTR polymorphism and its relationship with ADHD.

This research adds to previous knowledge as this is the first study that aimed at exploring the relationship between intron 8 VNTR and ADHD and comorbid disorders in school-aged children in Iran.

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Conflict of Interest

None.

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