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Genetic Analysis of Dopamine Receptors (DRD4 and DRD5) in Patients with Autism with Attention Deficit Hyperactivity Disorder (ADHD) in Thi-Qar Governorate –Iraq

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Abstract

Autism is a neurodevelopmental disorder that has recently been recognized as a public health problem. Attention Deficit Hyperactivity Disorder (ADHD) is a condition that impacts the brain, leading to abnormal levels of hyperactivity and impulsive behavior. This study aims to perform DNA sequencing to identify the genotypes of the DRD4 and DRD5 polymorphisms and to detect any mutations present in the target gene sequences. The study examined the genetic polymorphisms of DRD4 and DRD5 in autism and ADHD patients compared to the control group. For the DRD4 gene, no significant differences were found between the CT and TT genotypes and the wild CC genotype in both the autism and control groups (OR 0.92 and OR 0.30, respectively). Five mutations were identified in the DRD4 promoter region. Regarding the DRD5 gene, significant differences were found, particularly for the GA genotype in autism patients (OR 4) and the AA genotype (OR 12), with increased risk associated with the A allele (OR 6.50). In ADHD patients, the GG genotype increased the risk by four times (OR 4), while the GA genotype increased it by 4.5 times (OR 4.50). The allele frequencies differed significantly between patients and controls (G: 26.67%, A: 73.33%). Additionally, 11 mutations were documented in the DRD5 gene region. These findings highlight the potential genetic contributions to autism and ADHD our results found that the DRD4-376 CT genotype is associated with the development of ADHD. Regarding DRD5 (rs77434921), GA and AA genotypes are related to ADHD and autism in Iraqi children.

Key Words: Autism, ADHD, Dopamine receptor (D4), Dopamine receptor (D5).

Introduction

The autism spectrum encompasses various conditions categorized as neurodevelopmental disorders according to (1). These disorders, which typically manifest through difficulties in social interactions, communication challenges (both verbal and non-verbal), and repetitive behaviors or fixated interests, as further documented (2,3).

ADHD affects brain function, resulting in unusually high levels of hyperactivity and impulsive behavior. Global statistics reveal that approximately 8.4% of children worldwide

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experience ADHD. Children with this disorder often exhibit excessive movement, act impulsively, and struggle with attention, which negatively impacts their social interactions and typically leads to diminished academic performance (4). The origins of ADHD fall into two main categories: organic and environmental factors. Organic causes primarily involve pre-perinatal elements that individuals cannot predict or prevent, which ultimately trigger the disorder (5). Brain damage and certain dysfunctions, potentially occurring even during fetal development, represent significant organic causes. Growing evidence now supports a genetic component in ADHD development (6).

Dopamine plays vital roles throughout the central nervous system, where it helps control movement, drive, focus, and reward processing. When dopamine systems malfunction, various psychiatric conditions can develop, including bipolar disorder, ADHD, and autism spectrum disorder (7). The neurobiological understanding of dopamine receptor mechanisms has substantially advanced in recent years, elucidating that dopamine mediates its physiological effects through interactions with D1 and D2 receptor subtypes. These distinct receptor classes initiate separate biological signaling pathways via their associations with specific G protein complexes. revealed that D1 receptors form functional complexes with Gs proteins, thereby stimulating adenylyl cyclase activity, whereas D2 receptors associate with GI proteins, resulting in suppression of cAMP synthesis (8).

Advanced molecular screening techniques have facilitated the identification of three additional dopamine receptor subtypes: D3, D4, and D5. Structural analyses indicate that D1 and D5 receptors share significant homology, with approximately 79% identical transmembrane domains. However, these receptors exhibit only 40-45% sequence similarity with D2, D3, and D4 receptors. Conversely, D2, D3, and D4 receptors demonstrate considerable structural relatedness among themselves (51-75% sequence identity), supporting their classification into two discrete receptor families: D1-like and D2-like. Recent investigations (9) have identified polymorphic variations in the human D4 receptor characterized by variable numbers of 48 base-pair sequence repeats within the third cytoplasmic loop. These genetic variations manifest across different individuals, constituting a distinctive polymorphism that generates functionally diverse D4 receptor variants. Notably, these repetitive sequences are absent in rodent genomes, suggesting this polymorphism represents a human-specific evolutionary development. The receptor variants exhibit differential pharmacological profiles regarding ligand recognition properties (10).

Dopamine receptors regulate numerous physiological functions, particularly neurological processes, including cognitive function, memory consolidation, learning mechanisms, and motor coordination. Additionally, these receptors modulate neuroendocrine signaling pathways, implicating them in the pathophysiology of various psychiatric and neurological conditions, including attention deficit hyperactivity disorder and autism spectrum disorders (11). Empirical evidence suggests that the 148-bp allelic variant correlates with increased susceptibility to ADHD, while the 136-bp allele appears to confer protective effects against ADHD development, as corroborated by four independent investigations (12). Earlier research examining the relationship between DRD5 variable number tandem repeats and persistent ADHD has yielded inconsistent findings (13).

This research aims to investigate the genetics of dopamine receptors, specifically the D4 and D5 receptors, in Iraqi children with autism and ADHD, and to clarify their effects. This focus addresses a significant gap, as limited research exists on these two receptors, both in Iraq and globally.

Materials and Methods

Blood collection and genetic analyses were performed by drawing venous blood samples in EDTA tubes as an anticoagulant. We extracted genomic DNA from 200 µl of blood using the Geneaid™ DNA Isolation Kit, following the manufacturer's protocol. For the evaluation of DRD4 and DRD5 genes, we employed specific primer pairs as detailed below:

Genes	Primer sequences	Product size (bp)	References
DRD4	F-5- GAGGTCGAGGCGAGTCC -3 R-5-AAAGAGACGGGAATGAAGCG-3	300	This study
DRD5	F-5- TAGGCACCTGGACAGATGGT-3 R-5- AGTGTTTCGGCCTCTACTGG -3	325	This study

The polymerase chain reaction (PCR) methodology was implemented utilizing a total reaction volume of 20 µl, comprising 5 µl of genomic DNA template, 1 µl each of forward and reverse oligonucleotide primers, and 13 µl of nuclease-free distilled water.

The thermal cycling protocol commenced with an initial denaturation phase at 95°C, maintained for 10 minutes to ensure complete separation of DNA strands. This was followed by a series of 30 sequential amplification cycles, each consisting of three distinct thermal phases: a denaturation step at 95°C for 30 seconds to separate the DNA strands, an annealing phase conducted at receptor-specific temperatures (60°C for DRD4 amplification or 62°C for DRD5 amplification) for 30 seconds to facilitate primer hybridization, and an extension phase at 72°C for 30 seconds to enable DNA polymerase-mediated synthesis. The amplification protocol concluded with a terminal extension period at 72°C maintained for 10 minutes to ensure completion of all nascent DNA strands.

The resultant PCR amplification products were subsequently analyzed via electrophoretic separation on 2% agarose gel matrices supplemented with ethidium bromide as a nucleic acid intercalating agent, enabling visualization of the amplicons under ultraviolet illumination.

The PCR products (45 samples per gene) were sent to Macrogen Company (South Korea) for DNA sequencing, which was carried out using a Genetic Analyzer device. The DNA sequencing was carried out to determine the genotypes of DRD4 and DRD5 polymorphisms and to detect any mutation that occurred in the target sequences of genes.

Statistical analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20. The chi-square test was used to test the distribution of genotypes and allele frequencies for deviations from the Hardy-Weinberg equilibrium. OR was used to compare the allele and genotype frequencies between the patient group and controls.

Results

The polymerase chain reaction (PCR) technique was used to amplify a 300 bp fragment in the promoter region of the DRD4 gene. The electrode transfer results were based on 2% agarose gel, as shown in Figure 1.

Genotypes and allele frequencies of the DRD4 gene polymorphism in autism:

The current study showed no significant differences between CT and TT genotypes compared to CC (wild genotype) as a reference allele in the autism patients and controls group (OR 0.92, 95% CI 0.11 – 7.62, OR 0.30, 95% CI 0.01 – 8.30) for CT and TT genotypes, respectively. Also, no significant differences were found when comparing the T allele with the C allele in all genotypes of patients and the control group (OR 0.46, 95% CI 0.08 – 2.75) as shown in Table 1.

Genotypes and allele frequencies of the DRD4 gene polymorphism in ADHD:

This showed that the CC genotype was common in controls and ADHD patients 80% and 73%, respectively. The presence of the CT genotype relative significantly associated with ADHD (OR 1.63, 95% CI 0.22 – 11.70), while there were no significant differences in patients with the TT genotype compared to the CC genotype (OR = 1.09, 95% CI 0.06 – 19.63). Also, the C allele was calculated in all genotypes of the ADHD and control group. There was no significant difference between the C and T allele (OR 1.25, 95% CI 0.30 – 5.20), Table 2.

Mutation in the DRD4 gene

The current study recorded 5 mutations within the promoter region of the DRD4 gene. These mutations included transition and deletion types as shown in fig. 1 and 2. The sequences were recorded in the gene bank with accession numbers, which are shown in Table 3.

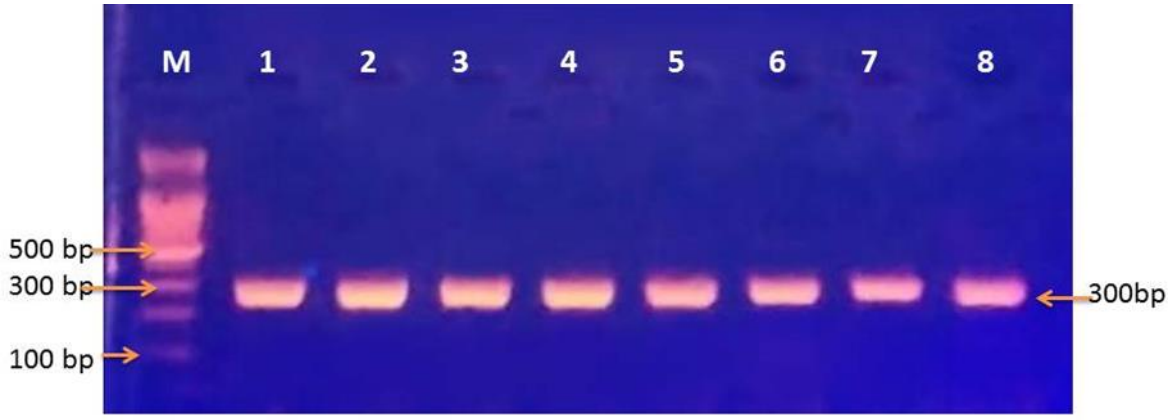

Figure 1: **PCR product of the DRD4 gene on a 2%agarose gel (DNA marker 100 bp).**

Table 1: Genotypes and allele frequencies of DRD4 gene polymorphism in the Autism and control groups

Genotype	Control n (%)	Autism n (%)	OR	95 % CI
CC	12 (80.00%)	13 (86.67%)	1.00	———
CT	2(13.33%)	2 (13.33%)	0.92	0.11 – 7.62
TT	1 (6.77%)	0 (0.00%)	0.30	0.01 – 8.30
Total	15 (100.00%)	15(100.00%)	———	———
C allel	26 (86.67%)	28 (93.33%)	1.00	———
T allel	4 (13.33%)	2 (6.67%)	0.46	0.08– 2.75
Total	30 (100.00%)	30 (100.00%)	———	———

CI, Confidence Interval. OR, Odds ratio. 95%

Table 2: Genotypes and allele frequencies of DRD4 gene polymorphism in the ADHD and control group.

Genotype	Control n (%)	ADHD n (%)	OR	95 % CI
CC	12 (80.00%)	11 (73.33%)	1.00	———
CT	2(13.33%)	3 (20.00%)	1.63*	0.22 – 11.70
TT	1 (6.77%)	1 (6.77%)	1.09	0.06 – 19.63
Total	15 (100.00%)	15 (100.00%)	———	———
C allel	26 (86.67%)	25 (83.33%)	1.00	———
Tallel	4 (13.33%)	5 (16.67%)	1.25	0.30 – 5.20
Total	30 (100.00%)	30(100.00%)	———	———

CI, Confidence Interval. OR, Odds ratio. 95%

Table 3: Mutation in the DRD4 gene in study subjects

Mutation	Type	Frequency	Accession numbers
g. 4524 *del* A	Deletion	2 (40.00%)	LC812896
g. 4707 C>T	Transition	1 (20.00%)	LC812897
g. 4531 *del* C	Deletion	1 (20.00%)	LC812898
g. 4706 C>T	Transition	1 (20.00%)	LC812899
g. 4558 A>G	Transition	1 (20.00%)	LC812900

DRD5 gene polymorphism

The polymerase chain reaction (PCR) technique was used to amplify a 325 bp fragment of the DRD5 gene. The electrode transfer results were based on 2% agarose gel, as shown in Figure 2.

Genotype and allele frequencies of the DRD5 gene polymorphism in the Autism and control groups

The current study showed highly significant differences between genotypes in the autism patients and controls group (OR 4, 95% CI 0.25 – 63.6) for the GA genotype. Odd ratio increased by 12 times in the patients with the AA genotype (OR 12, 95% CI 1.16 – 123). The risk of autism was increased significantly in cases with the A allele compared to the G allele (OR 6.50, 95% CI 1.82 – 23.2), Table 4.

Genotype and allele frequencies of the DRD5 gene polymorphism in the ADHD and control groups

The genotype frequencies in the ADHD and control groups are shown in Table 5. The risk of ADHD increased by 4 times in cases with the GG genotype (OR 4, 95% CI 0.44 – 35.72). Also, the presence of the GA genotype contributes to the development of ADHD by four and a half times (OR 4.50, 95% CI 0.66 – 30.23). Both G and A alleles in the control group were frequent in 50% while in patients, they were 26.67% and 73.33% with a significant difference of 1.65 (OR 1.65, 95% CI 0.61 – 4.48).

Mutation in the DRD5 gene

The current study recorded 11 mutations within the studied region of the DRD5 gene. These mutations included transition, trans version, and deletion types, and the sequences were recorded in the gene bank (appendix-) with accession numbers, which are shown in Table 6.

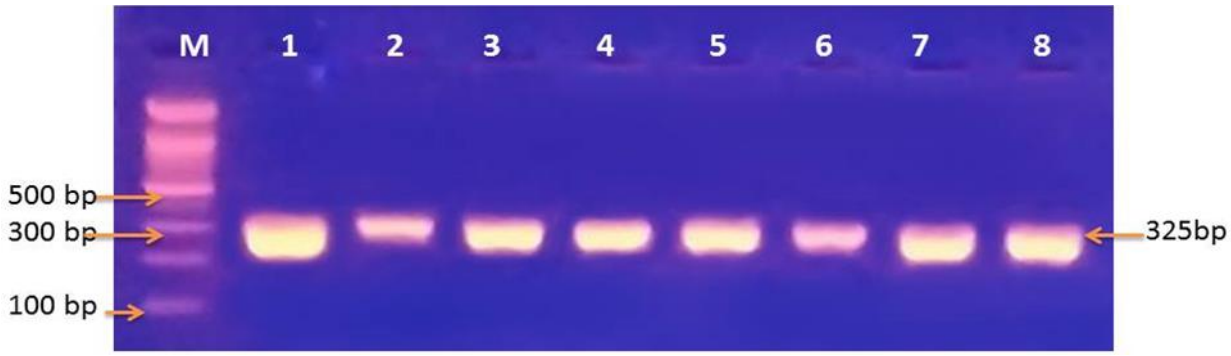

Figure 2: PCR product of the DRD4 gene on a 2% agarose gel (DNA marker 100 bp)

Table 4: Genotype frequencies of DRD5 gene polymorphism in the Autism and control groups

Genotype	Control n (%)	Autism n (%)	OR	95 % CI
GG	6 (40.00%)	1 (6.67%)	1.00	———
GA	3 (20.00%)	2 (13.33%)	4*	0.25 – 63.6
AA	6 (40.00%)	12 (80.00%)	12*	1.16 – 123
Total	15 (100.00%)	15 (100.00%)	———	———
G allel	15 (50%)	4 (13.33%)	1.00	———
A allel	15 (50%)	26 (86.67%)	6.50	1.82 – 23.2
Total	30(100.00%)	30 (100.00%)	———	———

95% CI, Confidence Interval. OR, Odds ratio.

Table 5: Genotype frequencies of DRD5 gene polymorphism in the ADHD and control groups

Genotype	Control n (%)	ADHD n (%)	OR	95 % CI
GG	6 (40.00%)	2 (13.33%)	1.00	———
GA	3 (20.00%)	4 (26.67%)	4*	0.44 – 35.72
AA	6 (40.00%)	9 (60.00%)	4.50*	0.66 – 30.23
Total	15 (100.00%)	15(100.00%)	———	———
G allel	15 (50%)	8 (26.67%)	1.00	———
A allel	15 (50%)	22 (73.33%)	2.75*	0.93 – 8.10
Total	30(100.00%)	30(100.00%)	———	———

95% CI, Confidence Interval. OR, Odds ratio.

Table 6: Mutation in the DRD5 gene in study subjects

Mutation	Type	Frequency	Accession numbers
g. 3846 T>C	Transition	2(18.18%)	LC811430
g. 3875 A>G	Transition	2(18.18%)	LC811430
g. 3803 *del* G	Transition	2(18.18)%	LC811431
g. 3894 G>A	Transition	1(9.09%)	LC811432
g. 4068 C>G	Transversion	1(9.09%)	LC811433
g. 3999 G>A	Transition	1(9.09%)	LC811434
g. 3860 G>C	Transversion	1(9.09%)	LC811435
g. 3989 A>G	Transition	1(9.09%)	LC811436
g. 4026 T>C	Transition	1(9.09%)	LC811437
g. 3947 T>A	Transversion	1(9.09%)	LC811438
g. 3906 G>A	Transition	1(19.09%)	LC811439

Discussion

DRD4 gene polymorphism

Autism has increasingly been recognized as a major public health issue with its characteristic neurodevelopmental features. pointed out, detecting at-risk individuals early allows for timely interventions that might lessen ADHD symptom severity or possibly prevent symptoms from developing altogether. An in-depth exploration of the relevant genetic components could markedly enhance our comprehension of the fundamental mechanisms underlying this disorder (14-16). It is

particularly noteworthy that the correlation between DRD4 gene polymorphism and autism manifestation specifically within the Iraqi pediatric population remains an uncharted territory in contemporary scientific literature.

A limitation in most autism studies is the small sample size used for genetic analysis, resulting from strict patient recruitment criteria (15). This limitation certainly hinders definitive conclusions regarding the connection between DRD4 polymorphism and autism. Clearly, more research is needed to investigate various gene polymorphisms that may contribute to autism development. Positioned within the transcription mediator domain of the dopamine D4 receptor gene, the -376SNP (rs916455) polymorphism potentially modulates D4 receptor gene transcription efficiency. Various research teams have examined potential associations between the −376C/T SNP variant and attention deficit hyperactivity disorder manifestation in pediatric populations (17- 20), proposing that the DRD4 rs916455 C allele confers elevated susceptibility to ADHD development. This hypothesis gained further support, which demonstrated a statistically significant correlation between the C allele and ADHD pathogenesis (P=0.04) (21). Additional findings from Li's investigations suggested that the C allele exhibited potential over-transmission patterns specifically within Chinese children diagnosed with ADHD. Nevertheless, the scientific literature presents contradictory perspectives regarding this association. Several independent research teams (17-19) failed to identify statistically meaningful correlations between the rs916455 polymorphism and childhood ADHD. These inconsistent findings underscore the critical necessity for further rigorous investigations, particularly studies focusing on Iraqi ADHD cohorts, to better evaluate and comprehend the putative relationship between ADHD etiology and DRD4 gene variations.

DRD5 gene polymorphism

Autism has been attributed to multiple factors, encompassing both environmental and genetic influences (22,23). Epigenetics plays a crucial role in autism's development by integrating genetic and environmental factors to affect neurodevelopmental processes (24). proposed that SNP allelic association methodologies serve as valuable tools for identifying genetic factors predisposing individuals to common diseases. Consequently, analyzing single-nucleotide polymorphisms in autism may reveal risk factors through their presence as genomic evidence. Autism rates have increased dramatically—approximately 50-fold—over recent decades, emphasizing the urgent need to develop new diagnostic and preventative approaches (25).

Our research revealed a significant association between the genotype distribution and allele frequencies of rs77434921 and ADHD in Iraqi patients. ADHD patients exhibited an increased frequency of the A allele, suggesting this allele may elevate ADHD risk. In a study focusing on paranoid schizophrenia. Identified a significant relationship between allele frequencies of rs77434921 and paranoid schizophrenia in the Han Chinese population. The researchers proposed this connection might exist because rs77434921 is located in the promoter region of the DRD5 gene, potentially influencing DRD5 expression by altering binding sites for transcription factors (25,26, 27).

Conclusion

Our results found that the DRD4-376 CT genotype is associated with the development of ADHD. Regarding DRD5 (rs77434921), GA and AA genotypes are related to ADHD and autism in Iraqi children.

Conflict of interest: NIL

Funding: NIL

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