Subject Area:

Association study between polymorphisms of dopamine transporter gene (SLC6A3), dopamine D1 receptor gene (DRD1), and autism

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Association study between polymorphisms of dopamine transporter gene (SLC6A3), dopamine D1 receptor gene (DRD1), and autism

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Abstract

Introduction

Autism is an etiologically and clinically heterogeneous group of disorders, collectively referred to as 'autism spectrum disorders'. Dopamine (DA) modulates a wide variety of processes, functions, and behaviors that are abnormal in individuals with autism spectrum disorders. The DA transporter gene SLC6A3 (solute carrier family 6, member 3) is a crucial regulator of DA homeostasis and neurotransmission. SLC6A3 gene has many polymorphisms which are associated with hangs in gene expression that may affect extracellular DA levels. The rs2550936 single-nucleotide polymorphism (SNP) at SLC6A3 gene decreased SLC6A3 expression or DA transporter availability. Also, the rs4532 SNP at dopamine D1 receptors (DRD1) is apparently a good candidate for affecting autism risk or modifying the classical symptoms of autism.

Aim

This study aimed to analyze the association between rs2550936 SNP at SLC6A3 gene and rs4532 SNP at the DRD1 gene and autism and their association with various demographic and clinical data of autistic children.

Patients and methods

This study included 50 autistic patients (36 males and 14 females) and 50 age-matched and sex-matched nonautistic controls for comparison. All patients were subjected to history taking, physical examination, language assessment, intelligence quotient, and childhood autism rating scale as well as analysis of SLC6A3 gene rs2550936 SNP and DRD1 gene rs4532 SNP using PCR–restriction fragment length polymorphism (RFLP), which was done for both patients and nonautistic controls.

Results

There has been a statistically significant relationship between the age of mother and different genotypes of SLC6A3 gene in autistic patients ($P = 0.030$). DRD1 rs4532 A/G and A/A genotype frequencies were significantly higher in autistic patients (52%) compared with nonautistic controls (40%) ($P = 0.043$).

Conclusion

DRD1 rs4532 polymorphism might be a risk factor increasing autism susceptibility as well as the association of the patient age with its different genotypes. There was a significant difference in the mother's age at conception and different genotypes of the SLC6A3 gene in autistic patients.

Keywords: Autism, gene polymorphism, PCR-RFLP, SLC6A3 gene

INTRODUCTION

Autism is defined as a severe neurodevelopmental disorder of childhood marked by difficulties in communication and forming relationships with other people. It is a chronic disorder with an onset before the age of 3 years, characterized by the

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following three main sets of disturbances: social abnormalities, language abnormalities, and stereotyped repetitive patterns of behavior [1].

About one in 68 children has been identified with autism spectrum disorder (ASD) according to estimates from the Centers for Disease Control. Autism is more common in boys by about 4.5 times (one in 42) than in girls (one in 189) [2]. The causes of autism are still unclear. It was also found that autism has an essential genetic component although the number of genes involved remains unclear [3]. The possible causes of autism include many factors such as neonatal anemia, high incidence of respiratory distress syndrome, and high incidence of medication use during pregnancy in mothers of autistic children and also maternal bleeding in the first trimester and meconium in the amniotic fluid. It was also found that autism has a substantial genetic component. The most frequently described ones are the structural and numerical abnormalities of sex chromosomes, anomalies of chromosome 15 and chromosome 17q21. Environmental components such as mercury, radiation, measles, mumps and rubella and diphtheria, pertussis, and tetanus vaccination are other significant risk factors. The parental characteristics, such as age and the level of education, may be associated with a risk of autism [4].

Individuals with autism are impaired in their cognitive processes including executive functions, memory, and learning. There is a decreased performance in measures of set-shifting abilities and planning in children with autism. Individuals with autism have been found to perform poorly in several tasks of working memory [5]. Children with autism were impaired in reversal learning as measured using a spatial–reversal task [6]. They have difficulty in understanding and expressing emotional prosody [7].

As core features of ASDs, individuals with autism are impaired in aspects of social interaction [8] and have repetitive behaviors and stereotypes, of which there is evidence for a role of dopamine (DA) in the pathophysiology. Furthermore, children with autism had altered sleep–wake cycles (i.e., increased night-time waking), elevated blood pressure, and gastrointestinal tract problems (i.e., constipation or diarrhea), respectively [9].

DA is a hormone and neurotransmitter of the catecholamine and may also be classified as a substituted phenethylamine that plays some essential roles in the human brain and body [10].

The DA system plays a central role in autism. DA modulates a broad variety of processes, functions, and behaviors that are abnormal in individuals with ASDs including motor functions, cognitive processes, emotional regulation, social interaction, and homeostatic processes such as blood pressure and sleep patterns as well as gastrointestinal tract function. The SLC6A3 dopamine transporter (DAT) is a crucial regulator of DA homeostasis and neurotransmission, which plays a role in the regulation of dopaminergic neurotransmission by removing

DA from the synaptic cleft through reuptake through the transporter [11].

The dopamine transporter gene (SLC6A3)

The solute carrier family 6, member 3: the DAT, which is encoded by the SLC6A3 gene is located at chromosome 5p15.3. The DAT gen is a key regulator of DA homeostasis and neurotransmission. Functional polymorphisms in DAT have been associated with neuropsychiatric disorders [12]. The brains of autistic individuals have abnormalities in DAT binding. Individuals with different genotypes of functional variants at the SLC6A3 locus have shown differences in their dopaminergic activity affecting neuronal networks involved in working memory and episodic memory. Some of the studied polymorphisms showed association as a risk factor [13]. The polymorphisms which spanned the SLC6A3 gene are associated with hangs in gene expression that may affect extracellular DA levels [14]. Moreover, there is evidence that decreased DAT activity results in impairments in episodic memory and stereotypic behaviors in mice that resemble those in individuals with autism, and that alleles associated with decreased SLC6A3 expression or DAT availability resulting from the rs2975226 A, I8 VNTR 5-repeat, Rs2550936 A, rs28363149 Ins, or EX15 VNTR 9-repeat alleles will be increased in families with ASD [12].

The D1 dopamine receptor gene

Dopamine D1 receptor (DRD1) is encoded by the DRD1 gene which is located on the 5q35.1 chromosome. DRD1 is the most abundant DA receptor in the central nervous system. Thirty-one single-nucleotide polymorphisms (SNPs) have been identified (Gorwoodet, 2012). Adequate DA neurotransmission affects the working memory which is the key function of human cognition. The training for improving working memory capacity is associated with changes in the density of cortical DRD1 [15]. DRD1 modulate a feed-forward inhibitory circuit involved in amygdala activation [16]. Which is an essential structure involved in emotional regulation and social behavior, for which there is evidence of dysfunction in individuals with autism [17] The DRD1 gene is apparently a good candidate for affecting autism risk or modifying the classical symptoms of autism [11].

Aim

This study aimed to analyze the association between rs2550936 single-SNP at SLC6A3 gene and rs4532 SNP at DRD1 gene and autism and their association with various demographical and clinical data of the patients.

Patients and methods

The present randomized case–control study included 50 autistic patients (36 males and 14 females) with ages less than 10 years as well as 50 age-matched and sex-matched nonautistic controls (38 males and 12 females), with ages of less than 10 years, for comparison. The patients were recruited from the Phoniatrics Department, Hearing and Speech Institute. The approval of the local ethics committee in Hearing and

Speech Institute, as well as fully informed consent from each of the parent of participating patients, was obtained. Inclusion criteria: patients with autism of both sexes and their age less than 10 years. Exclusion criteria: autistic patients with any other medical conditions.

Phoniatrics assessment

The diagnosis of autism was made according to language evaluation and childhood autism rating scale (CARS) at the Phoniatrics Department at the Hearing and Speech Institute. All patients were subjected to the following:

(1) Proper history taking including age, sex, the residence of autistic patient, and the age of the mothers at conception
(2) Language assessment using (modified preschool language scale-4) to express the total language age [18]
(3) The intelligence quotient (IQ) using Stanford–Binet intelligence scale (1986) [19]
(4) CARS [20]
(5) Genomic DNA extraction and analysis of SLC6A3 gene rs2550936 SNP and DRD1 gene rs4532 SNP using PCR–restriction fragment length polymorphism (RFLP) for patients and controls.

Laboratory study

Sample collection and storage

A measure of 2 ml venous blood samples was withdrawn by sterile venipuncture into EDTA vacutainer for DNA extraction and analysis of SLC6A3 gene rs2550936 SNP and DRD1 gene rs4532 NP using PCR-RFLP. Samples were immediately stored at −20°C till the time of DNA extraction and analysis.

Analysis of SLC6A3 gene rs2550936 SNP and DRD1 gene rs4532 NPS polymorphism by PCR followed by RFLP [13].

This test was conducted in five main steps [13]:

(1) Extraction of genomic DNA from EDTA anticoagulated whole blood
(2) Amplification of genomic DNA by PCR
(3) Detection of PCR amplification products using 2% agarose gel electrophoresis containing ethidium bromide and ultraviolet (UV) light transillumination
(4) Digestion of amplificon with the restriction endonuclease enzyme, RsaI for SLC6A3 gene and DdeI for DRD1 gene
(5) Identification of SLC6A3 gene rs2550936 SNP and DRD1 gene rs4532 SNP by agarose gel electrophoresis and visualization by UV transillumination [13].

The identified bands after UV transillumination denoting the different genotypes of SLC6A3 gene: One band [homozygous wild genotype (C/C)] and two bands [homozygous minor genotype (A/A)], and three bands [heterozygous genotype (A/C)].

The identified bands after UV transillumination denoting the different genotypes of DRD1 gene: One band [homozygous wild genotype (G/G)] and two bands [homozygous minor genotype (A/A)], and three bands [heterozygous genotype (A/G)].

Statistical analysis

Analysis of data was performed using SPSS 21 for Windows (statistical package for social sciences; SPSS Inc., Chicago, Illinois, USA) [21]. Description of variables was presented as follows: description of numerical variables was in the form of mean, SD, median, 25th and 75th percentiles. Description of categorical variables was in the form of numbers and percentage. Numerical data were not normally distributed. Accordingly, nonparametric tests were used for comparison. This was carried out by Mann–Whitney U-test when comparing between two groups of independent variables. Kruskal–Wallis test was used when comparing between more than two groups of independent variables. Results were expressed in the form of P values. Comparison between categorical variables was carried out by χ^2. Fisher's exact test was used when one expected cell or more were less than or equal to 5. Odds ratio with 95% CI was calculated for 2×2 cross tables of categorical variables. The significance of the results was assessed in the form of P value that was differentiated into: nonsignificant when P value greater than 0.05 and significant when P value of less than or equal to 0.05.

RESULTS

The current study included: 50 autistic patients [36 (72%) males and 14 (28%) females]. Their age ranged from 2 to 9 years with a mean of 4.144 ± 1.503. The studied control group included 50 nonautistic controls age-matched and sex-matched participants (38 males and 12 females). Their age ranged from 2 to 9 years with a mean of 4.316 ± 2.454. All patients were subjected to IQ assessment, Thirty-seven (74%) autistic patients were classified by CARS as mild-moderate autism whereas the remaining 13 (26%) patients were classified under severe autism. All patients and controls were subjected to language assessment. They were also subjected to laboratory investigation including detection SLC6A3 gene rs2550936 SNP and DRD1 gene rs4532 SNP using PCR-RFLP.

SLC6A3 rs2550936 genotypes of autistic patients

Twenty-three (46%) autistic patients had the homozygous wild genotype (C/C), whereas 17 (34%) autistic patients had the heterozygous genotype (A/C) and only 10 (20%) autistic patients had the homozygous minor genotype (A/A) (Fig. 1).

SLC6A3 rs2550936 genotypes of the nonautistic control group

Out of the 50 healthy controls included in this study, 24 (48%) of them had the homozygous wild genotype (C/C), whereas eight of them (16%, controls) had the heterozygous genotype (A/C) and 18 of them (36%, controls) had the homozygous minor genotype (A/A) (Fig. 1).

DRD1 rs4532 genotypes of autistic patients

Twenty-four (48%) autistic patients had the homozygous wild genotype (G/G), whereas 20 (40%) autistic patients had the heterozygous genotype (A/G) and six (12%) autistic patients had the homozygous minor genotype (A/A) (Fig. 2).
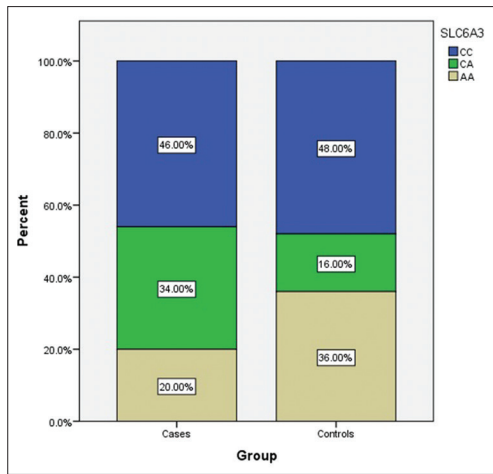
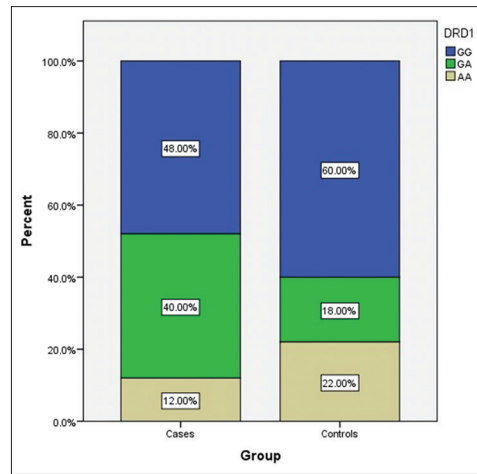**Figure 1:** SLC6A3 genotype of autistic patients and nonautistic controls.

Figure 2: DRD1 genotype of autistic patients and nonautistic controls.

DRD1 rs4532 genotypes of the control group

Out of the 50 healthy controls included in this study, 30 (60%) had the homozygous wild genotype (G/G), whereas nine (18%) controls had the heterozygous genotype (A/G) and 11 (22%) had the homozygous minor genotype (A/A) (Fig. 2).

Comparative statistics

The comparison was made between the autistic patients and the nonautistic controls as regards clinical data (Tables 1 and 2).

This study included 50 autistic patients and 50 healthy controls subjected to a comparison between them as regards sex, age, mother's age at the time of birth of the autistic patient, IQ, CARS, and language age.

Comparison between autistic patients and nonautistic controls as regards SLC6A3 rs2550936 genotypes

This study included 50 autistic patients to SLC6A3 rs2550936 genotypes, 23 (46%) had the homozygous wild genotype (C/C), 17 (34%) had the heterozygous genotype (A/C), and only 10 (20%) had the homozygous minor genotype (A/A). On the other hand, 24 (48%) of the nonautistic controls had the homozygous wild genotype (C/C), eight (16%) had the heterozygous genotype (A/C), and only 18 (36%) had the homozygous minor genotype (A/A). Comparison between the two groups showed no statistically significant difference ($P = 0.062$) (Table 3).

Comparison between SLC6A3 rs2550936 genotypes as regard the clinical data of autistic patients

The autistic patients were classified according to the different SLC6A3 genotypes into three distinct groups: the C/C genotype group which included 23 patients, the A/C genotype group which included 17 patients, and the A/A genotype group which included only 10 patients. These three groups were compared clinically as regards sex, age, mother's age at the time of birth of the autistic patient, IQ, CARS, and language age (Tables 4 and 5).

Comparison between autistic patients and nonautistic controls as regards DRD1 rs4532 genotypes

This study included 50 autistic patients to DRD1 rs4532 genotypes, 24 (48%) had the homozygous wild genotype (G/G),

Table 1: Comparison between autistic patients and the healthy controls as regards clinical data reveals no significant difference as regards sex

Clinical data	Autistic patients ($n=50$) [n (%)]	Nonautistic controls ($n=50$) [n (%)]	P
Sex			
Male	36 (72)	38 (76)	0.648
Female	14 (28)	12 (24)	

$P \le 0.05$, significant. $P > 0.05$, nonsignificant.

Table 2: Comparison between autistic patients and nonautistic controls as regards age and their mother's age at delivery reveals no significant differences

Clinical data	Autistic patients ($n=50$)	Nonautistic controls ($n=50$)	P
Age (years)			
Mean±SD	4.144±1.503	4.316±2.454	0.326
Their mother's age at delivery			
Mean±SD	28.360±3.957	27.300±4.674	0.187
IQ			
Mean±SD	67.600±7.521	76.040±8.439	0.001***
CARS			
Mean±SD	34.810±2.484	19.540±5.163	0.001***
Language age			
Mean±SD	1.918±1.231	3.162±2.319	0.001***

However, there is highly significant difference between the two groups as regards language age, IQ, and CARS ($P=0.001$). CARS, childhood autism rating scale; IQ, intelligence quotient. $P \le 0.05$, significant. $P > 0.05$, nonsignificant.

20 (40%) had the heterozygous genotype (A/G), and six (12%) had the homozygous minor genotype (A/A). On the other hand, 30 (60%) of the nonautistic controls had the homozygous wild genotype (G/G), nine (18%) had the heterozygous genotype (A/G), and 11 (22%) had the homozygous minor genotype (A/A). Comparison between the two groups showed a statistically significant difference ($P = 0.043$) (Table 6).

Comparison between DRD1 rs4532 genotypes as regards the clinical data of autistic patients

The autistic patients were classified according to the different DRD1 genotypes into three distinct groups: the G/G genotype group which included 24 patients, the A/G genotype group which included 20 patients, and the A/A genotype group which included six patients. These three groups were compared clinically as regards sex, age, mother's age at the time of their pregnancy of autistic patient, IQ, and CARS (Tables 7 and 8).

DISCUSSION

Our study included 50 autistic patients who were diagnosed with autism by the CARS in clinical environments to assess the severity of autism based on observation of children [4].

In the current study, no statistical significance could be elicited between both autistic patients and nonautistic controls regarding age and sex.

Table 3: Comparison between autistic patients and nonautistic controls as regards SLC6A3 rs2550936 genotypes reveals no significant difference ($P=0.062$)

SLC6A3 genotype	Autism patients ($n=50$) [n (%)]	Nonautistic controls ($n=50$) [n (%)]	P
C/C	23 (46%)	24 (48%)	0.062*
A/C	17 (34%)	8 (16%)	
A/A	10 (20%)	18 (36%)	

*Significant, $P\leq0.05$, significant. $P>0.05$, nonsignificant.

Table 4: Comparison between SLC6A3 rs2550936 genotypes as regards sex shows no significant difference

Clinical data	Genotype groups [n (%)]			P
	C/C group ($n=23$)	A/C group ($n=17$)	A/A group ($n=10$)	
Sex				
Male	17 (73.9)	12 (70.6)	7 (70)	0.962
Female	6 (26.1)	5 (29.4)	3 (30)	

$P\leq0.05$, significant. $P>0.05$, nonsignificant.

The age of the autistic patients ranged from 2 to 9 years; the mean age of identification was 4.1 years [22]. It has been found that there is often wide variation in the age of children present for diagnosis or to obtain necessary therapy and found that the median age of identification was 5.7 years according to the severity of autism and the affection of language.

Our results pointed to the higher risk of autism in boys than girls. This finding was consistent with that reported by Itzchak *et al.* [23] who found that 461 (81%) children out of 564 participants were male autistic patients. Shu *et al.* [24] observed that autism is more than twice as common in boys than girls, and this ratio increases to 5: 1 at the high-ability end of the autism spectrum.

There is no statistical significance that could be elicited between autistic patients and nonautistic controls regarding mother's age at conception. This is a study conducted by Sandin *et al.* [25], which showed that an advanced maternal age at the time of birth is independently associated with risk for ASD in the offspring. This is in contrast to a study conducted by Idring *et al.* [26], which showed that advancing mother's age increases the risk of ASDs, particularly for ASD with intellectual disability.

Assessment of mental age using the Stanford–Binet intelligence scale (1986), to calculate the intelligence quotient

This test is used to measure the child's cognitive abilities. The current study included autistic patients with IQ ranging from 50 to 85 with a mean of 67.6. There is the highly significant difference between autistics and nonautistic patients as regards IQ ($P = 0.001$). This is explained by the effect of the behavior abnormality of the autistic patient on the outcome of IQ results. McTiernan *et al.* [27] showed that IQ was found to be a significant predictor of the frequency and severity of the behaviors measured. Lower IQ predicted greater frequencies of stereotyped behavior, aggression and self-injurious behavior along with the increased severity of stereotyped behavior and self-injurious behavior. Constantino [28] found that autism can occur in the context of low IQ, high IQ, or anything in between, and it is often difficult to know whether combined

Table 5: Comparison between SLC6A3 rs2550936 genotypes as regards the clinical data of autistic patients show no significant difference except for the factor of maternal age at delivery ($P=0.030$)

Clinical data	Genotype groups			P
	C/C group ($n=23$)	A/C group ($n=17$)	A/A group ($n=10$)	
Age (years)				
Mean±SD	4.345±2.229	4.092±1.828	4.161±1.890	0.231
Their mother's age at delivery				
Mean±SD	26.766±4.033	29.240±3.961	28.357±4.8321	0.030**
IQ				
Mean±SD	72.638±9.090	70.920±8.626	71.250±9.418	0.173
CARS				
Mean±SD	34.06±2.471	36.47±2.37	34.80±2.85	0.828
Language age				
Mean±SD	2.034±1.547	1.782±0.825	1.880±1.060	0.955

**0.001 is highly significant. CARS, childhood autism rating scale; IQ, intelligence quotient. $P\leq0.05$, significant. $P>0.05$, nonsignificant.

social and cognitive impairment represents a cognitive disorder with secondary social impairment or some combination of two independent conditions.

The Childhood Autism Rating Scale

CARS is a behavior-rating scale intended to help in the diagnoses of autism. A total score of 15–29.5 is considered nonautistic; a score of 30–36.5 is considered mild to moderate autism; and a score of 37–60 is considered moderate to severe autism [13]. By comparing the CARS results between autistic and nonautistic patients, it was found that there is the highly significant difference between autistic and nonautistic patients as regards CARS (P = 0.001). According to CARS scores, 13% of our cases had a severe degree of autism and 37% had mild to moderate degree.

Language assessment

It was found that there is a highly significant difference between autistic and nonautistic patients as regards this factor (P = 0.001). This is because autism is a severe psychiatric

disorder of childhood marked by severe difficulties in communication and forming relationships with other people.

As regards SLC6A3 rs2550936 genotypes and DRD1 genotype

Hettinger [11] showed that the rs2550936 polymorphism of the SLC6A3 gene is associated with changes in gene expression that may affect extracellular DA levels. There is evidence that decreased DAT activity results in impairments in episodic memory and stereotypic behaviors in mice that resemble those in individuals with autism.

Analysis of SLC6A3 genotype distribution among autistic patients and controls in this study showed no statistical significance of C/C and A/C genotypes of SC6A3 gene. This is in contrast to a study conducted by El-Tarras *et al*. [13], which showed that patients carrying the A/C genotype of SLC6A3 might be about autism. These contradictory findings from our study and other results may be due to the different ethnic backgrounds of the patients.

Analysis of DRD1 genotype distribution among autistic patients and controls showed a higher frequency of A/G and A/A genotypes in autistic patients (40 and 12%, respectively) compared with the controls (18 and 22%, respectively), and this difference was statistically significant (P = 0.043). Thus, in our study, the presence of at least one minor A allele is shown to increase autism susceptibility compared with the G/G wild-type carriers. This is a study conducted by El-Tarras *et al*. [13], which showed that patients carrying the GA genotype of DRD1 might be about autism.

The autistic patients in our study were classified according to the different SLC6A3 and DRD1 genotypes into three distinct groups: C/C, A/C, and A/A, for SLC6A3 gene and G/G, A/G, and A/A for DRD1 gene. These groups were compared clinically as regards sex, age, CARS, and IQ test and language evaluation. Comparison between SLC6A3 rs2550936 genotypes as regards the previous clinical data of autistic patients showed no significant difference.

The different genotypes of SLC6A3 gene were statistically significant at the maternal age at the time of birth of autistic

Table 6: Comparison between autistic patients and healthy controls as regards DRD1 rs4532 genotypes

DRD1 genotype	Autism patients (n=50) [n (%)]	Nonautistic controls (n=50) [n (%)]	P
G/G	24 (48)	30 (60)	0.043*
A/G	20 (40)	9 (18)	
A/A	6 (12)	11 (22)	

*Significant, $P \leq 0.05$, significant, $P > 0.05$, nonsignificant.

Table 7: Comparison between DRD1 rs4532 genotypes as regards the clinical data of autistic patients

Clinical data	Genotype groups [n (%)]			P
	G/G group (n=24)	A/G group (n=20)	A/A group (n=6)	
Sex				
Male	18 (75)	15 (75)	3 (50)	0.441
Female	6 (25)	5 (25)	3 (50)	

$P \leq 0.05$, significant. $P > 0.05$, nonsignificant.

Table 8: Comparison between DRD1 rs4532 genotypes as regards the clinical data of autistic patients

Clinical data	Genotype groups			P
	G/G group (n=24)	A/G group (n=20)	A/A group (n=6)	
Age (years)				
Mean±SD	4.343±1.962	4.017±2.121	4.235±2.157	0.220
Their mother's age at delivery				
Mean±SD	28.000±4.408	27.207±3.629	28.353±5.302	0.116
Language age				
Mean±SD	2.291±1.437	1.395±0.848	2.166±0.882	0.033*
IQ				
Mean±SD	72.259±8.919	71.276±9.372	71.353±9.164	0.870
CARS				
Mean±SD	32.537±2.971	37.793±2.845	31.882±2.326	0.140

*Significant, The only significant difference is the factor of the language age. CARS, childhood autism rating scale; IQ, intelligence quotient. $P \leq 0.05$, significant. $P > 0.05$, nonsignificant.

patient ($P = 0.030$). Our study is the first to associate the SLC6A3 gene rs2550936 polymorphism with the age of the mother in the autistic patient.

Also, we found no statistical significance as regards sex, the age of the mother at the time of birth, IQ, CARS, and the different DRD1 genotype groups. The only significant difference is the factor of the language age ($P = 0.033$) which showed the effect of A/G genotype on the factor of language age.

CONCLUSION

DRD1 rs4532 polymorphism might be a risk factor increasing autism susceptibility as well as the association of the maternal age at conception with its different genotypes.

Recommendations

It is recommended to perform additional studies with larger sample sizes to validate the genetic effects of SLC6A3 and DRD1 polymorphisms on autism. Also, more studies are needed to investigate the different SLC6A3 and DRD1 gene polymorphisms and their biological function in Egyptian autistic patients. Finally, a better understanding of the underlying molecular mechanism of the disease may allow therapeutic or preventive agents for autism to be explored.

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Conflicts of interest

There are no conflicts of interest.

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