

Full Length Research Paper

Association between polymorphisms of SLC6A3 and DRD1 genes and autism among Saudi Arabia Taif population using PCR-restriction fragment length polymorphism (PCR- RFLP)

Adel E. El-Tarras^{1*}, Nabil S. Awad¹, Nahla Mitwaly², Adnan A. Alsulaimani³ and Manal M. Said⁴

¹College of Medicine, Biotechnology and Genetic Engineering Unit, Taif University, Kingdom of Saudi Arabia.

²Department of Psychology, Faculty of Education, Taif University, Kingdom of Saudi Arabia.

³College of Medicine, Taif University, Kingdom of Saudi Arabia.

⁴Department of Biotechnology, College of Science, Taif University, Kingdom of Saudi Arabia.

Accepted 8 May, 2012

The prevalence of autism in Saudi Arabia is 18 per 10,000, higher than the 13 per 10,000 reported in developed countries. The etiology of autism is still not completely understood. Different studies support the involvement of dopaminergic neurotransmitter system in the etiology of autism. Several lines of evidences suggest the role of some dopamine related genes, such as DRD1 and SLC6A3 in the etiology of autism. The aim of the present work was to study the possible role of rs2550936 A/C polymorphism at SLC6A3 locus as well as rs4532 A/G polymorphism at DRD1 locus in the etiology of autism among Saudi population. The polymorphisms of DRD1 and LC6A3 were genotyped in the case-control study using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique. Significant association as risk factor was found between autism and GA genotype of DRD1 [OR = 3.5 CI (1.04, 12.41*)] as well as CA genotype of SLC6A3 [OR = 2.53 CI (1.03, 6.26*)], while CC genotype of SLC6A3 revealed protective effect. In conclusion, possible risk genotypes for autism in the DRD1 and SLC6A3 genes were observed. This is the first report in Saudi Arabia population and Arab world. Therefore further investigations of these markers and other SNPs of SLC6A3 and DRD1 genes are considered in large replication samples with other causal factors to enable positive identification of risk genotypes and generalize obtained results.

Key words: Etiology, polymorphism, autism, genotype.

INTRODUCTION

Autism is the most common of the Pervasive Developmental Disorders (PDD) (Lord et al., 2002). Autism is a neuropsychiatric condition with a distinct pattern of social deficits, communication impairment, and rigid ritualistic interests (American Psychiatric Association, 1994; Al-Salehi et al., 2009). It is a neuropsychiatric disorder with profound family and social consequences (Johnson and Myers, 2007). Although autism is a global disorder,

relatively little is known about its presentation and occurrence in many developing countries, such as Saudi Arabia. The prevalence of autism in Saudi Arabia is 18 per 10,000, higher than the 13 per 10,000 reported in developed countries (Al-Salehi et al., 2009). The etiology of autism is still unknown. Thus, these finding supports the strong needs of more concentrated studies on the autism in Saudi Arabia. For more than three decades, there has been crucial evidence that most psychiatric disorders, including schizophrenia, bipolar disorder and autism, have a strong genetic component. An extraordinary number of genetical, clinical, cytogenetics

*Corresponding author. E-mail: nabilfaris151@yahoo.com.

and molecular studies were done (Carvalho et al., 2004). Different studies support the involvement of dopaminergic, serotonergic and noradrenergic neurotransmitter systems in the etiology of autism (Cook et al., 1997; Zhong et al., 1999; Maestrini et al., 1999; Nakamura et al., 2010).

The dopamine transporter (DAT) plays a critical role in dopaminergic neurotransmission, through taking up extracellular dopamine (DA) into pre-synaptic terminals (Jones et al., 1999; Kelada et al., 2006). The dopamine transporter is encoded by the SLC6A3 gene, which is located at chromosome 5p15.3 and consists of 15 exons. SLC6A3 gene has a role as a biological candidate gene for various behavioral and neurological disorders, such as pediatric bipolar disorder (Mick et al., 2008) and schizophrenia (Cordeiro et al., 2010), and affect personality traits (Shibuya et al., 2009). Nakamura et al. (2010) reported that the brains of autistic individuals have abnormalities in dopamine transporter binding.

Among human SLC6A3 functional variants, there are different genotypes which shows differences in dopaminergic activities, which affects neuronal networks involved in both working and episodic memories (Bertolino et al., 2006; Schott et al., 2006; Hettinger, 2009). Dong et al. (2009) identified association between two SLC6A3 SNPs rs8179029 and rs2550936, with major depressive disorder (MDD) (Opmeer et al., 2010). In animals, SLC6A3-1- mice faced difficulties in spatial learning and memory (Gainetdinov et al., 1999) and social interaction (Rodriguez et al., 2004). Hyperdopaminergic activities were reported with mice either lacking of SLC6A3 or expressing 10% of normal gene function (Gainetdinov et al., 1999; Berridge et al., 2005).

Dopamine D1 receptor encoded by the DRD1 gene which is located at chromosome 5q35.1 (Grandy et al., 1990) consists of two exons, separated by a single intron (Minowa et al., 1992). The D1 receptors modulate and many of the DA-related behaviors are abnormal in individuals with autism (Hettinger, 2009). DRD1 gene is a risk gene for core symptoms of autism spectrum disorders (ASDs) in families having only affected males (Hettinger et al., 2008). Several evidences supported the association between DRD1 gene with neuropsychiatric disorders, including bipolar disorder (Dmitrzak-Weglarz et al., 2006), Parkinson's disease (Juyal et al., 2006), schizophrenia (Rybakowski et al., 2009), alcohol dependence (Batel et al., 2008), intentional ability without overlap for reading ability (Luca et al., 2007) and smoking behavior (Novak et al., 2010). Hettinger (2009) showed strong evidence of association between rs4532 A/G polymorphism at DRD1 locus and social interaction, nonverbal communication and stereotypes in affected autistic males, against comparison group.

The objective of the present work was to investigate the possible association between autism and rs4532 A/G polymorphism at DRD1 locus, as well as rs2550936 A/C polymorphism at SLC6A3 locus among Saudi Taif

population.

MATERIALS AND METHODS

Subjects

The study sample composed of 50 Saudi autistic children with age range from 6 to 10 years (males = 30, 60% and; females = 20, 40%) and recruited from Pediatric and Prince Mansour hospitals at Taif city. The diagnosis of autism was made according to autism diagnostic interview-revised (Lord, 1997) and the autism diagnostic observation schedule, modules 1, 2 or 3 (DiLavore et al., 1995; Joseph et al., 2002; Lord et al., 2002). All subjects were clinical referrals from hospital neurologists. In addition, 50 healthy age-matched controls were recruited (male = 25, 50% and; female = 25, 50%). Controls and autistic subjects were matched according to age, gender, geographical and socioeconomic conditions at Taif city. Non Saudi subjects, as well as other neurological or behavioral disorders cases were excluded from the study. All parents of the patients and control subjects provided informed consent. The study was approved by Taif University and all institutional requirements were met.

Genotyping of SLC6A3 DRD1 polymorphisms

Genotyping of rs2550936 A/C and rs4532 A/G polymorphisms was carried out through polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique using Phusion blood direct PCR kit (Finnzymes) according to the manufacturer's instructions. PCR 20 μ l reaction volume consisted of 1 μ l blood, 10 Pmol of each primer specific for each studied polymorphism which are: rs2550936 F 5'-ACGCTCCCTCTGTCCTCAG-3' and R 5'-GTCAAGGACAGGAGGTCTGG-3'; rs4532 F 5'-GCAGCAAGGG-AGTCAGAAGA-3' and R 5'-TCTGACACCCCTCAAGTTCC-3' (Jena Bioscience, Jena, Germany); 10 μ l of 2x phusion blood PCR buffer (Finnzymes) and 0.4 μ l phusion blood DNA polymerase. PCR amplification of rs2550936 A/C and rs4532 A/G polymorphisms was conducted at 60°C. The PCR products were visualized on 1.5% agarose gel (Bioshop, Canada) under UV Transilluminator, with DNA ladder standard (100 bp, Bioshop, Canada). The product of PCR amplification (230 bp) was subsequently digested with 0.5U of the RsaI and 0.4U of DdeI restriction enzymes for rs2550936 A/C and rs4532 A/G, respectively. The digested products were run in 2.5% agarose gel stained by 0.5 μ g/ml ethidium bromide (Bioshop, Canada), with ladder standard 50 bp (Bioshop Canada) and the digestion patterns were used to determine the genotypes of each polymorphism.

Statistical analysis

Statistical analysis was carried out using epitools package of R statistical software (Aragon, 2010). The program (HardyWeinberg: Graphical tests for Hardy-Weinberg equilibrium, R package version 1.4.1) (Graffelman, 2012) was used to test for deviations from Hardy-Weinberg equilibrium by means of Chi-square (χ^2) test. Allelic and genotype distribution of the studied polymorphisms were calculated by direct counting method and the difference in allele and genotype frequencies between the autism subjects and controls was tested using χ^2 test. Odds ratio (ORs) was used to estimate the association between the studied SNPs and autism. ORs were constructed separately for each genotype. The magnitude of this association was estimated by 95% confidence interval (95% CI). CIs were constructed using exact methods (mid-p

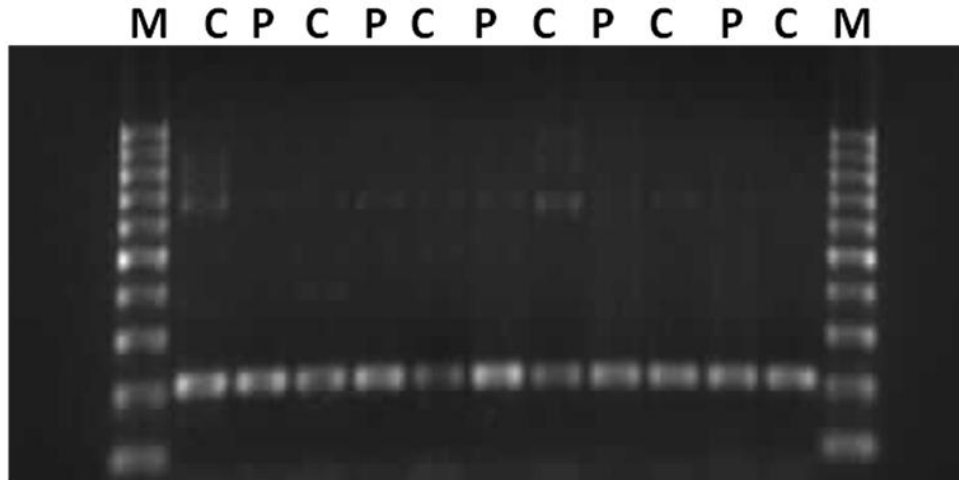


Figure 1. PCR amplification of rs4532 A/G polymorphism at DRD1 locus among autistic patients (P) and healthy control subjects (C).

and Fisher). The significance of CIs was tested using Chi-square test.

RESULTS

The present study was motivated by a relatively moderate sample size of 50 autistic patients and 50 healthy controls. Statistical analysis indicate that there were no deviations from Hardy Weinberg equilibrium in the patient samples for SLC6A3 rs2550936 A/C polymorphism ($X^2 = 4.793678$) and for DRD1 rs4532 A/G polymorphism ($X^2 = 2.661608$). Genomic DNA from 50 autistic patients and 50 control subjects were used to carry out PCR amplifications for SLC6A3 rs2550936 A/C and DRD1 rs4532 A/G polymorphisms. The PCR 230 bp amplified bands of rs2550936 and rs4532 polymorphisms, among autistic patients (P) and healthy control subjects (C) were determined (Figure 1). The SLC6A3 rs2550936 A/C PCR amplicons (230 bp) was digested with RsaI into cut (A allele), or uncut (C allele). Two genotypes CC 24 (48%) and CA 26 (52%) were obtained (Figure 3); whereas, AA genotype was not observed. The digestion of rs4532 amplicon (230 bp) with DdeI, based on A/G substitution revealed cut (A allele) and uncut (G allele). Then three genotypes were observed: GG 6 (12%), GA 14 (28%) and AA 30 (60%). Electrophoretic banding pattern of cleaved amplified bands is shown in Figures 2 and 3. The genotypes and allele frequencies for each studied polymorphism are illustrated in Table 1. Association between autism and rs2550936 polymorphism at SLC6A3 locus was observed, with CA genotype as a risk factor [OR = 2.53 and CI = (1.03, 6.26*)] (Table 2), while genotype CC revealed significant protective effect. Significant association between GA genotype and autism among the obtained three genotypes for rs4532 at DRD1 locus was

recorded [OR = 3.5 and CI = (1.04, 12.41*)] (Table 2).

DISCUSSION

Several indirect evidences were introduced from human and nonhuman studies, suggesting that, the dysregulation of dopaminergic function may be part of the complex neurochemical basis for autistic behaviors (Goldman-Rakic, 1996; Adolphs et al., 1998, 2002; Stone et al., 2003) and demonstrates a dose-dependent modulatory effect of DA on working memory (Brozoski et al., 1979; Sawaguchi et al., 1988; Williams and Goldman-Rakic, 1995; Williams and Castner, 2006). Sun et al. (2008) reported that dopaminergic nervous system is dysfunctioning in the brain of children with autism.

The main objective of the present study was to investigate the association between DRD1 and SLC6A3 polymorphisms in the etiology of autism among Saudi autistic subjects. The obtained results indicate that there is statistical association between some genotypes and autism. Some of the studied polymorphism showed association as a risk factor and other statistically associated as a protective factor. Two genotypes were observed for the rs2550936 A/C polymorphism at SLC6A3 locus CC (48%) and CA (52%), while AA genotype was absent. The absence of AA genotype might be due to moderate sample size. It is also possible that, the AA genotype is a rare genotype in the sample included in the present study. However, the association of CA genotype as a risk factor with autism, flags the possibility that the rs2550936 A/C polymorphism at SLC6A3 locus is in part a risk factor for autism. Jones et al. (1999) and Giros et al. (1992) reported that dopamine transporter plays important role in DAergic neurotransmission, through intake of extracellular DA into

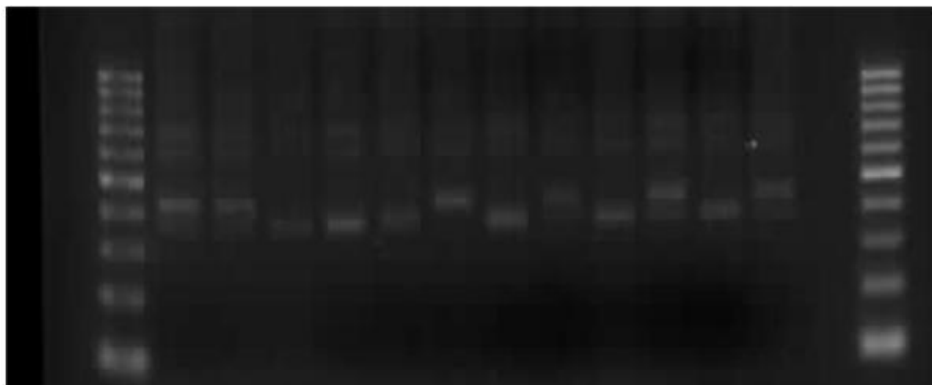


Figure 2. PCR amplification of rs4532 A/G polymorphism at DRD1 locus with Ddel among autistic patients (P) and healthy control subjects (C).

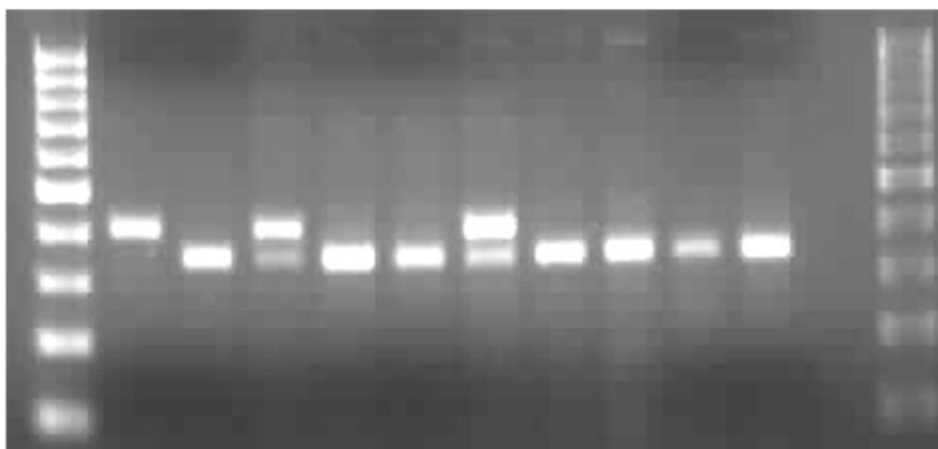


Figure 3. PCR amplification of rs2550936 A/C polymorphism at SLC6A3 locus with RsaI among autistic patients (P) and healthy control subjects (C).

Table 1. Genotypes and allele frequencies of SNPs and association analysis of each SNP in population-based samples.

Polymorphism	n	Genotype						Allele frequency	
		CC (230 bp)		CA (230, 180, 50 bp)		AA (180, 50 bp)		A	C
		n	%	n	%	n	%		
SLC6A3 rs2550936 A/C	100								
Autistic	50	24	48	26	52	0	0	0.74	0.26
Control	50	35	70	15	30	0	0	0.85	0.15
DRD1rs4532 A/G	100								
		GG (230bp)		AG (230, 180, 50 bp)		AA (180, 50 bp)		A	G
		n	%	n	%	n	%		
Autistic		6	12	14	28	30	60	0.74	0.26
Control		9	18	5	10	36	72	0.77	0.23

terminals. The previous studies carried out by Bertolino et al. (2006) and Schott et al. (2006) reported that the functional variants of human SLC6A3 have some genotypes that reveal differences in dopaminergic activities, which affects neuronal networks involved in both working

and episodic memories. In animals, SLC6A3-1- mice show impairment in spatial learning and memory (Gainetdinov et al., 1999) and social interaction (Rodriguez et al., 2004) as well as disrupted sleep-wake patterns (Wisor et al., 2001). In addition mice either

Table 2. Odds ratio and confidence interval for association of genotypes within gene SLC6A3 and DRD1 polymorphisms and risk of autism.

Polymorphism	Genotype	Case (n = 50)	Control (n = 50)	OR (95% CI)	Significant
SLC6A3 rs2550936 A/C	CC	24	35	0.40(0.16, 0.97*)	Significant protective
	CA	26	15	2.53(1.03, 6.26*)	Significant risk
	AA	0	0		
DRD1 rs4532 A/G	GG	6	9	0.62(0.18, 2.13)	NS
	GA	14	5	3.50(1.04, 12.41*)	Significant risk
	AA	30	36	0.58(0.23, 1.46)	NS

NS, Not significant.

lacking, the SLC6A3 gene (Gainetdinov et al., 1999) or expressing 10% of normal gene function (Berridge et al., 2005) were hyperdopaminergic, and had increased stereotypies. So, depending on the suggestions of the previously mentioned studies, it is possible to assume that the CA genotype of SLC6A3 might be in relation with autism, through affecting some dopaminergic activities.

Three genotypes were observed for the rs4532 A/G polymorphism at DRD1 locus: GG 6 (12%), GA 14 (28%) and CA 30 (60%). Association between autism and GA genotype as a risk factor was noticed. The DRD1 gene encodes the dopamine D1 receptor, which modulates many of the DA-related behaviors that are abnormal in individuals with autism. For example, administration of high doses of D1 receptor antagonists to the PFC was found to disrupt performance on working memory tasks in non-human primates (Sawaguchi and Goldman-Rakic, 1994; Williams and Goldman-Rakic, 1995) and attentional set-shifting in rats (Ragozzino, 2002), while D1 receptor blockade in the OFC or striatum of rats impaired reversal learning (Calaminus and Hauber, 2008) and procedural learning (Willuhn and Steiner, 2008), respectively. Dopamine D1 receptors modulate a feed-forward inhibitory circuit involved in amygdala activation (Marowsky et al., 2005), which is a key structure involved in emotional regulation and social behaviour, for which there is evidence of dysfunction in individuals with autism (Baron-Cohen et al., 2000) while the administration of D1 receptor agonists or antagonists induced or attenuated stereotypies in a DA-deficient mouse model (Chartoff et al., 2001).

Thus, the DRD1 gene is clearly a good candidate for affecting autism risk or modifying the classical symptoms of autism, despite the absence of D1 receptor binding measurements in individuals with autism (Hettinger et al., 2008). In the shadow of the obtained results of the above mentioned studies and present study, it could be possible that, the GA genotype of the rs4532 A/G polymorphism at DRD1 locus might have a role in the etiology of autism, through affecting some dopaminergic activities. In general, in the present study, moderate sample size was recruited. In addition, gender was not included as

covariate. No additional factors were studied rather than genotypes effects. These limitations might affect the obtained results.

Conclusion

In the present study, some polymorphisms at DRD1 and SLC6A3 loci were genotyped. This is the first report in the Saudi Arabia population. Both risk and protective effects in the etiology of autism were observed with some studied genotypes. The resulted risk effect might play a role with other casual factors. The moderate used sample size might be a contributor to the resulted effects. Further investigations of these markers are required in large replication samples with other causal factors to enable positive identification of risk genotypes and generalize obtained results.

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