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The Role of MAOA Gene in the Etiology of Autism Spectrum Disorder in Males

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***Abstract*—**Monoamine oxidase A gene (MAOA) is suggested to be a candidate gene implicated in many neuropsychiatric disorders, including autism spectrum disorder (ASD). This meta-analytic review evaluates the relationship between ASD and MAOA markers such as 30 bp variable number tandem repeats in the promoter region (uVNTR) and single nucleotide polymorphisms (SNPs) by using findings from recently published studies. It seems that in Caucasian males, the risk of developing ASD increase with the presence of 4-repeat allele in the promoter region of MAOA gene whereas no differences were found between autistic patients and controls in Egyptian, West Bengal and Korean population. Some studies point to the importance of specific haplotype groups of SNPs and interaction of MAOA with others genes (e. g. FOXP2 or SRY). The results of existing studies are insufficient and further research is needed.

***Keywords*—**Autism spectrum disorder, MAOA, uVNTR, single nucleotide polymorphism.

I. Introduction

AUTISM spectrum disorder (ASD) is a neurodevelopmental disorder characterized by disturbances in social interactions, communication, as well as restricted, repetitive, or stereotyped behavior. ASD is a term used for group of disorders as Autistic disorder, Asperger syndrome and Pervasive developmental disorder not otherwise specified [1]. The population prevalence of ASD ranges 15–20 in 10000 whereas the male to female ratio is approximately 4:1 [2]. Clinical signs of ASD are frequently present at 3 years of age; however abnormalities in social, communication and play behavior can be detected as early as 14 months of age [3].

A normal brain development is disrupted in patients with ASD, which is manifested by abnormal neuroanatomical and neurochemical changes, mainly in neurotransmitter systems [4]. Recently, there have been a number of molecular genetic studies demonstrating that genetic factors play a major role in the etiology of this disease [5].

Monoamine oxidase A (MAOA) is an enzyme that metabolizes neurotransmitters such as serotonin, dopamine and norepinephrine, and its dysfunction can lead to various neuropsychiatric disorders, including autism [6]. MAOA is encoded by the gene localized on the X chromosome (Xq11.23–Xq11.4); it may be cause of higher prevalence of neurodevelopmental disorders in males compared to females.

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The MAOA gene contains a 30 bp variable number tandem repeat in the promoter (1.2 kb upstream) region (uVNTR), which may be present in 2, 3, 3.5, 4, 4.5, or 5 copies [7]. The two most common alleles are 3- and 4-repeats (3R and 4R) (97%) that affect the activity of the enzyme. The 3R allele (low activity allele) is transcribed 2-10 times less efficiently than 4R (high activity allele) [7]. In individuals without ASD, the 4R allele was found to be associated with anxiety, impulsivity, and possibly ADHD [8]-[10].

Studies investigating the role of the MAOA gene in etiology of ASD are limited and the results are inconsistent. This paper summarizes findings from recently published studies using a meta-analysis of obtained data.

II. Association of 30 bp uVNTR of MAOA with ASD

We analyzed the data obtained from various populations to assess the role of MAOA-uVNTR in the etiology of ASD (Table I) [11]–[18]. We calculated the average frequencies of 3R (0.35) and 4R allele (0.65) in Caucasian boys with ASD. Similar frequencies were also found in Egyptian autistic males (0.33 for 3R, resp. 0.67 for 4R) [17]. Conversely, significantly higher frequency of the 3R allele was detected in patients from West Bengal in India (0.63) and South Korea (0.62) [16], [18]. Comparing distribution of 3R and 4R alleles between boys with ASD and healthy group, significant difference was reported only in mixed population (55,5% of white Caucasians, 28,5% of Hispanic, 16% Black, Asian or Pacific Islander) [12]. These authors also suggested that mother's genotype (homozygous for 4R allele) may influence a prenatal brain development of her child. However, more information from a pure population is missing. There were no significant differences in allele frequencies between cases and controls in other populations [16], [17].

Although the association of uVNTR in the promoter region of MAOA with ASD has not been clearly confirmed, there are studies demonstrating that occurrence of 3R or 4R allele can affect a phenotypic expression of autism. Cohen et al. [11] detected that autistic boys with the 3R allele had severe sensory behaviors, arousal regulation problems, aggression, and worse social communication skills than males with the 4R allele. Roohi et al. [13] found that male children with the 4R allele suffered more severe symptoms of generalized anxiety.

These findings suggest that the distribution of 3R and 4R is different in various populations, whereas they did not clearly confirm the association of the MAOA-uVNTR promoter polymorphism with autism itself.

TABLE I
ALLELE FREQUENCIES OF A 30BP UVNTR POLYMORPHISM OF MAOA GENE IN DIFFERENT POPULATIONS

Study	Ethnicity	3R allele		P1 -value	4R allele		P1 - value
		ASD	Controls		ASD	Controls	
Cohen et al. [11]	mixed (83% Caucasian)	0.35			0.65		
Tassone et al. [12]	mixed (84 % Caucasian)	0.36	0.53	0.05	0.63	0.45	0.08
Roohi et al. [13]	Caucasian (USA)	0.28			0.72		
Hranilović et al. [14]	Caucasian (Europe)	0.44			0.56		
Davis et al. [15]	Caucasian (USA)	0.34			0.66		
Verma et al. [16]	West Bengal	0.63	0.69	0.61	0.37	0.31	0.43
Salem et al. [17]	Egyptian	0.33	0.33	1.0	0.67	0.67	1.0
Yoo et al. [18]	Korean	0.62	0.53	0.37			
P2 - value		0.003	0.26		0.06	0.11	

ASD = autism spectrum disorders, P1 = value from chi-square test – comparison of allele frequencies between ASD and controls, P2 = value from chi-square test – comparison of allele frequencies between different populations.

III. ASSOCIATION OF SNPS OF MAOA WITH ASD

There are limited studies investigating the role of SNPs of MAOA in the etiology of ASD. Verma et al. [16] studied association of rs5906883, rs1465107, rs5905809, rs6323 and rs1137070 with ASD in West Bengal population and there are two studies that demonstrated importance of rs5906883, rs1137070 and rs3027407, resp. rs6323, rs1137070 and rs3027407 in Korean population (Table III) [18], [19].

TABLE II
ALLELE FREQUENCIES OF SNPS IN MAOA GENE IN WEST BENGAL AND KOREAN POPULATION

SNP	Allele	Study	ASD	Controls	P1
rs5906883	A	Verma et al. [16]	0.59	0.69	0.44
		Yoo et al. [18]	0.63	0.52	0.34
		P2	0.74	0.17	
	C	Verma et al. [16]	0.41	0.31	0.27
		Yoo et al. [18]	0.37	0.48	0.24
		P2	0.66	0.07	
rs1465107	G	Verma et al. [16]	0.59	0.68	0.48
		Yoo et al. [18]			
	A	Verma et al. [16]	0.41	0.32	0.31
		Yoo et al. [18]			
rs5905809	G	Verma et al. [16]	0.59	0.63	0.75
		Yoo et al. [18]			
	C	Verma et al. [16]	0.41	0.37	0.67
		Yoo et al. [18]			
rs6323	G	Verma et al. [16]	0.45	0.61	0.14
		Yoo et al. [18]			
	T	Verma et al. [16]	0.55	0.39	0.12
		Yoo et al. [18]			
rs1137070	T	Verma et al. [16]	0.59	0.65	0.61
		Yoo et al. [18]	0.39	0.48	0.37
		P2	0.05	0.11	
	C	Verma et al. [16]	0.41	0.35	0.48
		Yoo et al. [18]	0.61	0.52	0.45
		P2	0.05	0.06	
rs3027407	A	Verma et al. [16]			
		Yoo et al. [18]	0.38	0.48	0.32
	G	Verma et al. [16]			
		Yoo et al. [18]	0.62	0.52	0.41

ASD = autism spectrum disorders, P1 = value from chi-square test – comparison of allele frequencies between ASD and controls, P2 = value from chi-square test – comparison of allele frequencies between West Bengal and Korean population.

No differences were detected in allele frequencies between ASD and healthy boys neither in West Bengal nor in Korea [16], [18]. However, if equal distribution of alleles between cases and controls in West Bengal population were assessed, for the marker rs6323 T allele was overrepresented in the ASD group in comparison to controls. Based on available data; we could only compare rs5906883 and rs1137070 between West Bengal and Korean population. We detected significantly higher frequency of C allele (rs1137070) in autistic boys in Korean (0.61) compared to West Bengal (0.41) population. For the marker rs5906883 A allele occurred with higher frequency in Korean autistic patients compared to control group. In West Bengal, A allele frequency was higher in control group.

These two case-control association studies didn´t show any significant association of ASD with any of the examined SNPs.

IV. ASSOCIATION OF MAOA HAPLOTYPES WITH ASD

Although in above mentioned studies [11]–[18], the promoter uVNTR polymorphism and SNPs revealed no statistically significant result, some authors demonstrated significant differences in haplotype frequencies between the MAOA gene and ASD (Table III) [16], [18]. Results in West Bengal population indicated a positive genetic association of T allele and various haplotypes of rs6323 formed with other markers with ASD in males [16]. In Korean population, association of the haplotype ACG of three SNPs (rs5906883-rs1137070-rs3027407) with ASD was found [18].

V. INTERACTION OF MAOA GENE WITH OTHER GENES

According to some studies, interaction of MAOA with other genes plays an important role in the etiology of ASD. Park et al. [19] showed that combination of the FOXP2 diplotype TCGC (rs12531289-rs1350135-rs10230087-rs2061183) and the MAOA haplotype TCG (rs6323-rs1801291-rs3027407) significantly increased the risk of ASD and affected the verbal communication skills in males. The FOXP2 gene encodes a transcription factor, which is included in speech developmental process and mutation in it can disrupt the development of speech [20], [21].

Wu et al. [22] demonstrated that the sex-determining region Y (SRY) protein (encoded by the SRY gene localized on Y chromosome) is capable of binding to the promoter region of the MAOA gene and so affect the MAOA expression. Moreover, they showed that SRY forms with Sp1 transcription

factor a transcriptional complex that synergistically activates MAOA. These mechanisms could contribute to sexual dimorphism in neural development and manifestation of neural disorders associated with MAOA dysfunction, including ASD.

TABLE III
HAPLOTYPIC GROUPS OF SNPS ASSOCIATED WITH ASD IN WEST BENGAL AND KOREAN POPULATION

Study	Haplotype		ASD	Controls	P
Verma et al. [16]	uVNTR-rs6323	4R-T	0.33	0.22	0.02
	rs5906883-rs6323	C-T	0.37	0.22	0.01
	rs1465107-rs6323	A-T	0.38	0.23	0.01
	rs5905809-rs6323	C-T	0.38	0.21	0.002
	rs1137070-rs6323	C-T	0.38	0.22	0.001
	rs5906883-rs1137070	C–T	0.06	0.01	0.02
Yoo et al. [18]	rs5906883-rs1137070-rs3027407	ACG/AGG	0.60	0.40	0.001

ASD = autism spectrum disorders, P1 = value from chi-square test – comparison of allele frequencies between ASD and controls, P2 = value from chi-square test – comparison of allele frequencies between Caucasian, West Bengal, Egyptian and Korean population.

Interesting finding was observation of changes in the binding site of GATA binding protein 2 (GATA-2) in the case of C allele of rs1137070 in the MAOA gene. GATA-2 is a transcription factor that interacts with SRY and its binding site was deleted in the presence of C allele of rs1137070 [16]. But the association of this allele with ASD was not confirmed by any of the two studies [16], [18].

VI. CONCLUSION

Recent studies have not clarified the role of the MAOA gene in the etiology of autism spectrum disorder. It seems that MAOA-uVNTR is not directly responsible for manifestation of ASD in males, but the presence of 3R, resp. 4R allele modifies phenotypic expressions in autistic patients. In other side, the specific haplotypes of SNPs are associated with the pathogenesis of ASD depending on the character of the population. Some investigations suggest that the importance of the MAOA gene in pathogenesis of ASD is in its interaction with other genes. Studies in this paper had limitations such as relatively small sample size, lack of information on phenotypes and environmental risk factors and they must be replicated in further research.

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