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Significant associations between 5-hydroxytryptaminetransporter-linked promoter region polymorphisms of the serotonin transporter (solute carrier family 6 member 4) gene and Thai patients with autism spectrum disorder

Wikrom Wongpaiboonwattana, PhD[a], Oradawan Plong-On, MSc[b], Areerat Hnoonual, PhD[b], Pornprot Limprasert, MD, PhD[a,b,*]

Abstract

Autism spectrum disorder (ASD) is a form of pervasive developmental disorder manifested by impairment in social interactions and repetitive behaviors. Although genetic contribution is strongly suspected in autism, the specific genetic factors remain unidentified. Hyperserotoninemia has been reported in some autistic patients, and several studies have demonstrated an association between 5-hydroxytryptamine-transporter-linked promoter region (5-HTTLPR) polymorphisms and rs25531 single nucleotide polymorphism in the serotonin transporter gene (solute carrier family 6 member 4; *SLC6A4*) and ASD, indicating a possible involvement of the serotonin system in the etiology of ASD.

To explore this situation further, a case-control association study of 5-HTTLPR and rs25531 polymorphisms on Thai ASD patients was conducted. A total of 188 ASD cases fulfilling the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria (156 males and 32 females) and a total of 250 normal controls were recruited from the same ethnic backgrounds. 5-HTTLPR polymorphisms (Long, L; Short, S) and rs25531 (A/G) single nucleotide polymorphism were genotyped and compared between the patients and normal controls using chi-square statistics.

The L/L genotype was more common in patients than in the controls (13.8% vs 5.2%, $P = .006$), and the LA haplotype was found in patients more than the controls (16.9% vs 12.2%, $P = .048$). When male patients were analyzed alone (156 individuals), the associations were also statistically significant with $P = .017$ for L/L genotype, and $P = .019$ for LA haplotype distribution.

Our findings support previous reports suggesting an association between the 5-HTTLPR and rs25531 polymorphisms of *SLC6A4* and patients with ASD.

Abbreviations: 5-HTT = 5-hydroxytryptamine (serotonin) transporter, 5-HTTLPR = 5-hydroxytryptamine-transporter-linked promoter region, ASD = autism spectrum disorder, L = long allele, S = short allele, SLC6A4 = solute carrier family 6 member 4, TDT = transmission disequilibrium test.

Keywords: 5-HTTLPR, autism spectrum disorder, rs25531, *SLC6A4*

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder which causes impairment in social interactions and repetitive sensory-motor behaviors. ASD is a heritable disorder which is believed to have genetic contributions.[1] However, the genetic effects leading to ASD are believed not to derive from single mutations but rather, additive effects from many common and rare variants.[2,3] Broad studies in different populations are

Editor: Wen-Jun Tu.

This work was supported by the National Center for Genetic Engineering and Biotechnology (BT-B-01-MG-18-4814).

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Faculty of Medicine, King Mongkut's Institute of Technology Ladkrabang, Bangkok, [b] Department of Pathology, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand.

[*] Correspondence: Pornprot Limprasert, Faculty of Medicine, King Mongkut's Institute of Technology Ladkrabang, Bangkok 10520, Thailand (e-mail: lpornpro@yahoo.com).

How to cite this article: Wongpaiboonwattana W, Plong-On O, Hnoonual A, Limprasert P. Significant associations between 5-hydroxytryptaminetransporter-linked promoter region polymorphisms of the serotonin transporter (solute carrier family 6 member 4) gene and Thai patients with autism spectrum disorder. Medicine 2020;99:36(e21946).

Received: 25 April 2020 / Received in final form: 22 July 2020 / Accepted: 27 July 2020

http://dx.doi.org/10.1097/MD.0000000000021946

slowly building up a more complete picture of ASD-associated genes.

The *SLC6A4* gene (solute carrier family 6 member 4) has variants that various studies have suggested to be linked to ASD. This gene is located on chromosome 17q11 and encodes 5-hydroxytryptamine transporter (5-HTT, SERT) which transports serotonin to nerve cells. This transporter relates to serotonin imbalance which is a condition found to be linked to ASD in epigenetic, genetic, and biochemical levels.[4–8] On *SLC6A4*, there is a minisatellite at the promoter region called the 5-hydroxytryptamine-transporter-linked promoter region (5-HTTLPR). This region has 2 commonly found alleles, long (L, 16 repeats) and short (S, 14 repeats) alleles. Studies about this region in ASD have shown various findings. There are reports on the correlation of ASD with the L allele,[9–12] the S allele,[13–15] and even studies finding no correlations at this region.[16–19] Various meta-analyses on this region also failed to identify any correlations to ASD.[20–22] Apart from the L and S alleles, there is an A/G single nucleotide polymorphism in 5-HTTLPR named rs25531 which is a functional polymorphism. Two earlier studies reported that 5-HTTLPR with the L allele and A single nucleotide polymorphism on rs25531 (LA haplotype) had higher expression compared to other haplotypes,[23,24] which could affect serotonin levels.

Since the link between *SLC6A4* and ASD is not yet clear and has not been investigated in the Thai population, this study was undertaken to examine any correlations between ASD in the Thai population with variations in *SLC6A4*. We carried out a 188/250 case/control study which found that the L allele and LA haplotype were correlated with ASD. This study provides previously unreported evidence of *SLC6A4* in the Thai population.

2. Patients and methods

2.1. Patients

A total of 188 ASD patients, 156 males and 32 females, diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria were recruited in our previous study.[25] They were evaluated for common genetic causes of ASD. All patients possessed normal karyotype and negative DNA tests for Fragile X syndrome and *MECP2* mutations. Parents of 160 of the 188 ASD patients and 250 normal controls were recruited into the study as in a previous report.[26] Written informed consent was received from all participants or their guardians. The study was approved by the Institutional Review Board of the Faculty of Medicine, Prince of Songkla University (EC48/364-006), the Faculty of Medicine Ramathibodi Hospital, Mahidol University (MURA2006/188), and the Faculty of Medicine, Thammasat University (061/2548).

2.2. Determination of SLC6A4 variants

Variants of *SLC6A4* were analyzed using a polymerase chain reaction (PCR)-based method as described in a previous report.[27] This method analyzed 5-HTTLPR and rs25531 in a single PCR reaction (see Details, Supplemental Digital Content 1, http://links.lww.com/MD/E757, which gives details of this PCR-based variant analysis for 5-HTTLPR and rs25531).

2.3. Association analysis

The Hardy–Weinberg equilibrium test was performed for data quality control. Association analyses, transmission disequilibrium tests (TDT), and inheritance pattern analyses were done with PLINK 1.9 software (http://www.cog-genomics.org/plink2/).[28] The genotype and allele frequencies among ASD patients and controls were compared with the Chi-square test. Haplotype association analysis was done with Haploview software (https://www.broadinstitute.org/haploview/haploview).[29]

3. Results

In the association analysis between *SLC6A4* alleles and ASD (Table 1), L allele of 5-HTTLPR was associated with the patient group ($P = .012$, odds ratio 1.439, 95% confidence interval 1.075–1.926). However, no association was found in S allele and either alleles of rs25531. When only 156 male patients and 178 controls were analyzed, the L allele of 5-HTTLPR was also associated with the patient group ($P = .017$, odds ratio 1.496, 95% confidence interval 1.075–2.082). The S allele of 5-HTTLPR, A allele, and G allele of rs25531 showed no association with ASD ($P > .05$).

Genotype association analysis showed an association between ASD and the L/L genotype ($P = .006$) (Table 2). No association was found in S/S or L/S genotypes. Also, none of the rs25531 genotypes were associated with ASD ($P > .05$). The same associations were found when only male patients and controls

Table 1

Allele distributions of 5-HTTLPR and rs25531 variants.

Group of participants (patients/controls)	Position	Allele	Patients		Controls		χ^2	*P*-value
			Number	Frequency	Number	Frequency		
All participants (188/250)	5-HTTLPR	L	**128**	**0.340**	131	0.262	6.339	**.012***
		S	248	0.660	369	0.738		
	rs25531	A	308	0.819	422	0.844	0.953	.329 NS
		G	68	0.181	78	0.156		
Male participants (156/178)	5-HTTLPR	L	**110**	**0.353**	95	0.267	5.743	**.017***
		S	202	0.647	261	0.733		
	rs25531	A	255	0.817	300	0.843	0.763	.383 NS
		G	57	0.183	56	0.157		

5-HTTLPR = 5-hydroxytryptamine-transporter-linked promoter region, NS = not statistically significant.

* *P*-values $\leq .05$ which were considered to be statistically significant.

Table 2

Genotype distributions of 5-HTTLPR and rs25531 variants.

Group of participants (patients/controls)	Position	Allele	Patients		Controls		χ^2	*P*-value
			Number	Frequency	Number	Frequency		
All participants (188/250)	5-HTTLPR	L/L	**26**	**0.138**	13	0.052	10.113	**.006**[†]
		L/S	76	0.404	105	0.420		
		S/S	86	0.458	132	0.528		
	rs25531	A/A	131	0.697	181	0.724	3.427	.180 NS
		A/G	46	0.245	63	0.252		
		G/G	11	0.058	6	0.024		
Male participants (156/178)	5-HTTLPR	L/L	**23**	**0.148**	10	0.056	8.133	**.017**[*]
		L/S	64	0.410	75	0.421		
		S/S	69	0.442	93	0.523		
	rs25531	A/A	109	0.699	126	0.708	2.649	.266 NS
		A/G	37	0.237	47	0.264		
		G/G	10	0.064	5	0.028		

5-HTTLPR = 5-hydroxytryptamine-transporter-linked promoter region, NS = not statistically significant.
[*] *P*-values ≤ .05.
[†] *P*-values ≤ .01. Both were considered to be statistically significant.

were analyzed. Only L/L genotype was found associated with ASD ($P = .017$). Other genotypes of 5-HTTLPR and rs25531 showed no significant association with ASD. The genotype distribution of our control group was confirmed with the Hardy-Weinberg equilibrium ($P = .193$ and .632 for 5-HTTLPR and rs25531, respectively) (see Table, Supplemental Digital Content 2, http://links.lww.com/MD/E758, which shows the Hardy–Weinberg equilibrium test results for control group).

Genetic model prediction using model analysis suggested recessive and additive model of 5-HTTLPR ($P = .002$ and .015, respectively) (Table 3). However, no genetic model was found for rs25531. The same genetic model was found when only male patients and controls were analyzed (recessive and additive model of 5-HTTLPR, $P = .007$ and .018, respectively).

To test whether 5-HTTLPR and rs25531 together had any effect on ASD, haplotype analysis was done (Table 4). The frequency of LA haplotype was significantly higher in the ASD group than in the control group (16.9% and 12.2%, respectively, $P = .048$). Conversely, the frequency of SA haplotype was found significantly higher in the control group than in the ASD group (72.2% and 65.0%, respectively, $P = .022$). This pattern was also found when only the male participants were analyzed. When family-based associations were analyzed with a TDT, no significant linkage of any allele or haplotype were found in both 5-HTTLPR and rs25531 (see Tables, Supplemental Digital Content 3, http://links.lww.com/MD/E759 and 4, http://links.lww.com/MD/E760, which show the TDT results).

4. Discussion

The population-based case control analysis of this study suggests that L allele and L/L genotype were associated with ASD. This is the first population-based case control study showing an association between 5-HTTLPR and ASD in the Thai population. A similar finding was observed in South African and Egyptian autistic groups in case-control association studies.[30,31] However, no statistically significant association was found between 5-HTTLPR and ASD in several other case-control studies in several populations.[15,19,32–34] A number of studies have shown conflicting evidence of L and S alleles of 5-HTTLPR in patients with ASD (see Table, Supplemental Digital Content 5, http://links.lww.com/MD/E761, which reviews previous 5-HTTLPR population-based case-control studies on ASD). The L and S alleles have also been found to be significantly associated with

Table 3

Genetic inheritance model of 5-HTTLPR alleles.

Group of participants (patients/controls)	Position	Allele	Inheritance model (*P*-value)		
			Additive	Dominant	Recessive
All participants (188/250)	5-HTTLPR	L	.015[*]	.168	.002[†]
		S		NS	
	rs25531	A	.351	.662	.119 NS
		G	NS	NS	
Male participants (156/178)	5-HTTLPR	L	.018[*]	.144	.007[†]
		S		NS	
	rs25531	A	.463	.855	.123 NS
		G	NS	NS	

5-HTTLPR = 5-hydroxytryptamine-transporter-linked promoter region, NS = not statistically significant.
[*] *P*-values ≤ .05.
[†] *P*-values ≤ .01. Both were considered to be statistically significant.

Table 4

Distribution of 5-HTTLPR/rs25531 haplotype.

Group of participants	Haplotype	Frequency			χ^2	*P*-value
		Total	Patients	Control		
All participants (188/250)	LA	0.142	**0.169**	0.122	2.920	.048*
	LG	0.155	0.171	0.142	2.339	.236 NS
	SA	0.691	0.650	**0.722**	5.212	.022*
	SG	0.012	0.009	0.014	0.673	.553 NS
Male participants (156/178)	LA	0.143	**0.177**	0.113	5.488	.019*
	LG	0.164	0.176	0.153	0.592	.441 NS
	SA	0.686	0.640	**0.726**	5.738	.017*
	SG	0.007	0.007	0.007	0.110	.740 NS

5-HTTLPR = 5-hydroxytryptamine-transporter-linked promoter region, NS = not statistically significant.
* *P*-values ≤ 0.05 which were considered to be statistically significant.

neuropsychiatric disorders including bipolar disorder and depressive disorder.[35–38] Our genetic model analysis suggests both recessive and additive inheritance of 5-HTTLPR. It is known that ASD is multifactorial rather than resulting from a single mutation,[2,39] although some exceptions to this general rule have been suggested (eg, Fragile X syndrome).[40] The result from genetic model analysis in this study supports the theory that genetic variants of 5-HTTLPR could be one of the inherited factors causing ASD.

One study reported that the L allele causes higher expression of *SLC6A4* than the S allele, and the LA haplotype has higher expression than the LG, SA, and SG haplotypes.[24] Other studies have also reported that the LA/LA genotype was associated with high amounts of grey matter in the brain.[41–43] This genotype has also been correlated with social dysfunction and low connectivity between the amygdala and subgenual anterior cingulate cortex in ASD children.[44] In addition, a significant association was found between LA/LA genotype and mood instability in ASD patients.[19] In this study, we found an association between LA haplotype and ASD while SA haplotype associates with the control group, suggesting that the LA haplotype could be a risk factor and the SA haplotype could be a protective factor against ASD, probably due to the expression level of 5-HTT.

Our family-based case control analysis did not find any linkages between ASD and any specific allele or haplotype. Previous family-based studies have had varying results of linkage with L allele, S allele, or no linkage. The cause of these varying findings could be due to different recruiting criteria, ethnic backgrounds, or sample sizes of each study. A further study with larger sample size is needed to confirm the linkage between ASD and variants of 5-HTTLPR and rs25531.

This report supports the association of 5-HTTLPR and rs25531 in ASD which also suggests a possible relationship between serotonin system and ASD in the Thai population that has never been reported before.

Acknowledgments

The authors thank Dr. Thanya Sripo for laboratory supervision. The authors also thank the following pediatricians for sample recruitment: Dr. Juthamas Worachotekamjorn, Dr. Tippawan Hansakunachai, Dr. Rawiwan Roongpraiwan, Dr. Tasnawat Sombuntham, and Dr. Nichara Ruangdaraganon.

Author contributions

Conceptualization: Pornprot Limprasert.
Data curation: Oradawan Plong-On, Areerat Hnoonual.
Formal analysis: Wikrom Wongpaiboonwattana.
Funding acquisition: Pornprot Limprasert.
Investigation: Oradawan Plong-On, Areerat Hnoonual, Pornprot Limprasert.
Methodology: Pornprot Limprasert.
Validation: Wikrom Wongpaiboonwattana, Pornprot Limprasert.
Writing – original draft: Wikrom Wongpaiboonwattana.
Writing – review & editing: Wikrom Wongpaiboonwattana, Oradawan Plong-On, Areerat Hnoonual, Pornprot Limprasert.

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