Biallelic and Triallelic 5-Hydroxytyramine Transporter Gene-Linked Polymorphic Region (5-HTTLPR) Polymorphisms and Their Relationship with Lifelong Premature Ejaculation: A Case-Control Study in a Chinese Population

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCE Yuanyuan Huang
ABFG Xiansheng Zhang
CF Jingjing Gao
BC Dongdong Tang
BC Pan Gao
BC Chao Li
BD Weiqun Liu
A Chaozhao Liang

Department of Urology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, P.R. China

Corresponding Author: Xiangsheng Zhang, e-mail: xiansheng-zhang@163.com
Source of support: This study was funded by the National Natural Science Foundation of China (No. 81571429)

Background: This study aimed to explore the relationship between premature ejaculation (PE) and the serotonin transporter gene-linked polymorphic region (5-HTTLPR) with respect to the biallelic and triallelic classifications.

Material/Methods: A total of 115 outpatients who complained of ejaculating prematurely and who were diagnosed as having lifelong premature ejaculation (LPE) and 101 controls without PE complaint were recruited. All subjects completed a detailed questionnaire and were genotyped for 5-HTTLPR polymorphism using PCR-based technology. We evaluated the associations between 5-HTTLPR allelic and genotypic frequencies and their association with LPE, as well as the intravaginal ejaculation latency time (IELT) of different 5-HTTLPR genotypes among LPE patients.

Results: The patients and controls did not differ significantly in terms of any characteristic except age. The results showed no significant difference regarding biallelic 5-HTTLPR. According to the triallelic classification, no significant difference was found when comparing the genotypic distribution (P=0.091). However, the distribution of the S, L_G, and L_A alleles in the cases was significantly different from the controls (P=0.018). We found a significantly lower frequency of L_A allele and higher frequency of L_G allele in patients. Based on another classification by expression, we found a significantly lower frequency of the L'L' genotype (OR=0.37; 95%CI=0.15–0.91, P=0.025) in patients with LPE. No significant association was detected between IELT of LPE and different genotypes.

Conclusions: Contrary to the general classification based on S/L alleles, triallelic 5-HTTLPR was associated with LPE. Triallelic 5-HTTLPR may be a promising field for genetic research in PE to avoid false-negative results in future studies.

MeSH Keywords: Polymorphism, Genetic • Premature Ejaculation • Serotonin Plasma Membrane Transport Proteins

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/896768

📄 2394   🗂 5   📊 2   📖 35

Background

Premature ejaculation (PE) has been widely acknowledged as the most common sexual dysfunction, and the global prevalence rate is estimated to range from 3% to 30% according to different definitions [1,2]. In general, PE is divided into lifelong PE (LPE) and acquired PE (APE) [3]. The International Society for Sexual Medicine (ISSM) recommended the first evidence-based definition for LPE as an ejaculation that occurs prior to or within the first minute after penetration in the majority of sexual encounters, the inability to delay ejaculation, and associated with negative personal consequences such as embarrassment and avoidance of sexual activity [4].

While the pathogenesis of PE remains unknown, several factors, such as psychological [5], neurobiological [6], endocrine [7], genetic, and environmental effects [8–10], have been implicated. A twins study in Finnish men indicated that about 28% of the etiology was a result of hereditary effect [11]. Selective serotonin reuptake inhibitors (SSRIs) induced ejaculation delay in men [12] and laboratory rats [13–15], indicating the involvement of central serotonin (5-HT) neurotransmission in the regulation of ejaculation. The 5-HT transporter (5-HTT), which transports 5-HT from synapses into presynaptic neurons, is a membrane-bound protein and the target of SSRIs [16], so 5-HTT has become the best choice for related studies in PE.

SLC6A4, which encodes 5-HTT, locates on chromosome 17q11.1–17q12 of the human genome. Over the past decade there has been an increasing emphasis on the role of the promoter polymorphisms of SLC6A4, called the 5-HTT gene-linked polymorphic region (5-HTTLPR) [17]. A 44bp del/ins results in an S or L allele, while the former could reduce the expression of 5-HTT proteins [18,19]. The rs25531 is a single-nucleotide polymorphism (SNP) in L allele, which further leads to an A-G polymorphism. Thus, it provided a functional triallelic polymorphism as S, L_G, and L_A. Because the S and L_G alleles had almost the same transcriptional and expressive levels, both of which were lower than that of L_A, we reclassified the alleles according to the expression level [20]. In previous studies of PE, a biallelic classification of 5-HTTLPR was used, with inconsistent results in different countries and populations (Table 1). From a functional point of view, and beyond the purely biallelic classification considering the L/S alleles, using a triallelic classification considering the role of S, L_G, and L_A alleles of the 5-HTTLPR polymorphism in the pathogenesis of PE may be more appropriate.

Material and Methods

Subjects and assessments

The current study was carried out between October 2012 and March 2015. A flow chart of participant enrollment and data collection is shown in Figure 1. Each participant was informed of the purpose of the study and signed the informed consent. In the initial evaluation, each subject completed a detailed face-to-face interview with an andrologist, including a questionnaire and physical examination. The questionnaire included the following items: (I) demographic and clinical characteristics, (II) duration of relationship and marital status; and (III) self-estimated IELTs. The IELT was the time from the insertion of the penis into the vagina to the start of intravaginal ejaculation. Every participant was asked to give an estimation of the IELTs, which were called self-estimated IELTs. LPE in our study was defined according to the definition of ISSM. Finally, 115 patients with LPE were recruited by referral from the Andrology Outpatient Clinic. At the same time, 101 controls without PE complaint were enrolled from the medical examination center. Patients diagnosed as having LPE were required to measure the IELTs by stopwatch at least 4 times during 1 month.

Subjects also had to meet the following conditions: (I) heterosexual male patient aged 20–60 years; (II) Han descent and speaking Chinese; and (III) in a regular sexual relationship with 1 female partner for ≥6 months. None of the subjects had mental or other major medical diseases. None of the participants had received antidepressants or phosphodiesterase type 5 inhibitors before enrolling in the trial. Patients with a urinary infection or nervous system disorder were also excluded. We obtained 2-ml EDTA-anticoagulated peripheral blood samples from every participant. The study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (No. 20150047).

Genotyping

Genomic DNA was extracted from peripheral blood using the Puregene DNA extraction kit (Qiagen, Hilden, Germany) following the manufacturer's protocol.

Direct polymerase chain reaction (PCR) was used to determine the insertion/deletion polymorphism (L/S allele). We designed a pair of PCR primers by using the Primer3 Software Online Program (*http://frodo.wi.mit.edu/cgi-bin/ primer3/primer3_www.cgi*). Oligonucleotide primers: forward 5'-CGGGATGCGGGGGGAATACTGGT-3' and reverse 5'-TTGCCGCTCTGAATGCCAGCAC-3' were used to amplify the 5-HTTLPR region. PCR amplification was carried out in a final volume of 10 µl consisting of 3 µl of DNA solution (Qiagen Inc.), PCR buffer (Qiagen Inc.), 0.2 mM deoxynucleotide triphosphates,

Table 1. Review of the existing literature on the biallelic 5-HTTLPR.

Reference	Country	Inclusion criteria	Stop-watch	Count		Genotype frequency(%)						HWE	Conclusions
				pt	ctrl	SS		SL		LL			
						pt	ctrl	pt	ctrl	pt	ctrl		
Janssen et al. 2009	Holland	ISSM criteria	Yes	89	92	21.3	26.1	48.3	44.6	30.3	29.3	Yes	No difference in genotypes between the cass and controls. SS and SL genotypes had longer IELT than LL
Ozbek et al. 2009	Turkey	IELT<60 s and lifelong	No	69	69	53.6	29.0	30.4	53.6	15.9	17.4	No	S allele was more frequent in cases than in controls
Luo et al. 2011	China	IELT<60 s and lifelong	Yes	119	90	51.3	37.8	28.6	34.4	20.2	27.8	No	S allele was more frequent in cases than in controls
Jern et al. 2013	Finland	ISSM criteria	No	33	33	15.2	15.2	45.5	48.5	39.4	36.4	Yes	No significant difference in genotypes between the cases and controls
Janssen et al. 2014	Holland	ISSM criteria	Yes	54	92	20.4	26.1	53.7	44.6	25.9	29.3	Yes	5-HTTLPR was not associated with SSRI treatment-induced ejaculation delay in LPE
Ozbek et al. 2014	Turkey	ISSM criteria	Yes	69	–	23.2	–	40.6	–	36.2	–	Yes	SS genotype respond well to SSRI therapy

pt – patients; ctrl – controls; HWE – Hardy-Weinberg equilibrium; ISSM – International Society for Sexual Medicine; SSRI – selective serotonin reuptake inhibitor.

1 μl primers (2 μM), 1 U HotStar Taq polymerase (Qiagen Inc.), and 1 μl of 10 ng/μl genomic DNA. The PCR system consisted of 2 min of initial denaturation at 95°C, followed by 35 cycles of 20 s of denaturation at 94°C and 2 min of extension at 68°C, and a final extension of 60 min at 68°C, then kept at 4ºC awaiting further use.

We tested the SNP rs25531 (A/G) using restriction fragment length polymorphism (RFLP) technology. The L allele created an additional *MspI* site besides a constant restriction site, so we could make a distinction between L_G and L_A (Figure 2). Briefly, 1 μl PCR products were digested with 4 U of *MspI* restriction enzyme at 37°C for 4 h, recognizing a 5'-CC/GG-3' sequence. After digestion, the products were analyzed on a 3730 DNA analyzer (ABI, Carlsbad, California). The fragments in S 63, 293; L_A 63, 337; and L_G 63, 174, 163 allowed both polymorphisms to be analyzed simultaneously. Two technicians classified genotypes independently by visual observation of peak sizes using GeneMapper 4.0 with reference to explicit standards.

Statistical analyses

The participants were classified according to alleles and genotypes. For the quantitative data, results are expressed as mean ± standard deviation (SD) and a 2-tailed *t*-test was used. Chi square and Fisher exact tests were used to compare the genotype proportions. After normality and homoscedasticity

testing, analyses of variance (ANOVA) or Kruskal-Wallis test using IELT as a variate were performed to test differences between different genotypes, and genotypes grouped by expression [L'L' (higher expression, i.e. $L_A L_A$) *vs.* S'S' and S'L' (lower expression, i.e., SS SL_G, $L_G L_G$)]. All statistical analyses were performed with SPSS 17.0 (SPSS Inc., Chicago, United States) for Windows. *P*<0.05 was considered statistically significant.

Results

Demographic characteristics

Among 216 subjects who met the inclusion criteria, genotypes were available for 215 subjects, including 114 patients and 101 controls. One sample failed because of coagulation. The data on baseline characteristics are shown in Table 2. The patients and controls showed no significant difference in terms of any characteristics except age (35.3±7.8 *vs.* 31.7±8.1, *P*<0.001). However, because LPE is assumed to be lifelong, the difference did not affect the comparability of the 2 groups.

Association between PE and biallelic 5-HTTLPR alleles and genotypes

According to the biallelic classification (Table 3), the distribution of genotypes in patients with LPE *vs.* controls was as
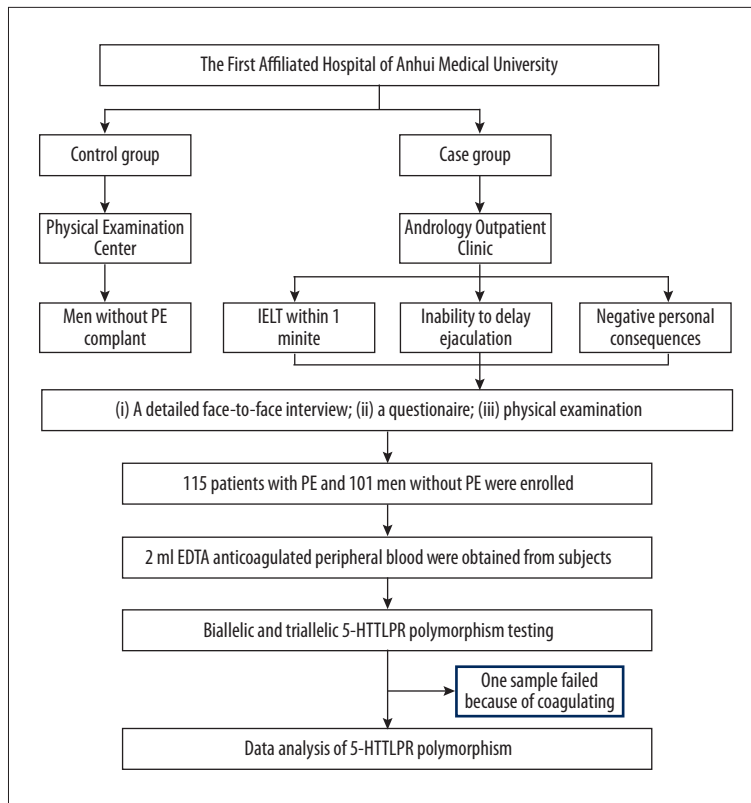
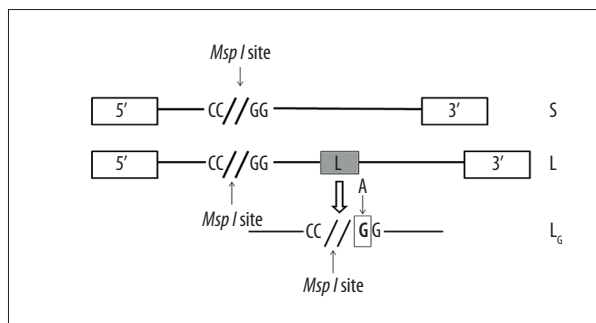**Figure 1.** Flow chart of participant enrolment.

Figure 2. Schematic of 5-HTTLPR: the 5-HTTLPR insertion polymorphism (gray area), containing the SNP rs25531, an A→G substitution (boxed letter).

follow: SS 35 *vs.* 31; SL 61 *vs.* 48; LL 18 *vs.* 22, respectively, and no significant difference was found ($P=0.494$). The allele frequency of S and L was 131 (57.5%) *vs.* 110 (54.5%) and 97 (42.5%) *vs.* 92 (45.5%), respectively, and no significant difference was found ($P=0.532$). The distribution of genotypes was consistent with Hardy-Weinberg equilibrium (HWE) (LPE: $\chi^2=1.018$, $P=0.313$; control: $\chi^2=0.177$, $P=0.674$).

Association between PE and triallelic 5-HTTLPR alleles and genotypes

Table 4 shows the frequency distribution of 5-HTTLPR according to the triallelic classification. Comparing the genotypes

distribution of SS, SL_G, SL_A, L_GL_G, L_GL_A, and L_AL_A between LPE and controls, the results showed no significant difference ($P=0.091$). However, the distribution of the S, L_G, and L_A alleles was 57.5%, 13.2%, and 29.4% in patients with LPE, which was significantly different from the distribution of controls with 54.5%, 6.4%, and 39.1%, respectively ($P=0.018$). We found a significantly lower frequency of the L_A allele and higher frequency of the L_G allele in patients with LPE than in the controls. Another classification by expression was used in our study ($S'=S+L_G$, $L'=L_A$). We found a significantly lower frequency of the L'L' genotype (OR=0.37; 95%CI=0.15–0.91, $P=0.025$) in patients with LPE.

Comparison of IELT of different biallelic and triallelic 5-HTTLPR genotypes in LPE group

As seen in Table 5, the geometric mean, median, and mean IELTs of the LPE group were 22.5, 25.0, and 26.0±11.9 s, respectively. However, there was significant heterogeneity of variance between groups when using mean IELT as a variate (biallelic genotype: $P=0.001$; triallelic genotype: $P=0.020$). Therefore, statistical analysis of IELT was performed after logarithmic transformation. After normality and homoscedasticity testing in different groups, the results of biallelic classification and genotype grouped by expression showed normal distribution and homogeneity of variance. ANOVA of the natural logarithm (ln) of IELT showed no statistically significant difference (biallelic: $F=0.164$, $P=0.849$; genotype grouped by

Table 2. Comparision of the demographic characteristics in PE and control group.

Characteristics	PE group N=114 (%)		Control group N=101 (%)		t/χ^2	P value*
Age, years	35.3±7.8		31.7±8.1		16.135	<0.001
BMI, kg/m^2	22.1±2.1		21.6±1.9		1.576	0.116
Duration of relation, years	10.7±5.1		9.4±5.3		1.832	0.068
Smoking					2.939	0.860
Yes	76	(66.7)	78	(77.2)		
No	38	(33.3)	23	(22.8)		
Drinking					0.181	0.671
Yes	62	(54.4)	52	(51.5)		
No	52	(45.6)	49	(48.5)		
Marital status					0.974	0.324
Merried	99	(86.8)	92	(91.1)		
Not merried	15	(13.2)	9	(8.9)		
Educational level					7.718	0.052
Primary school	9	(7.9)	11	(10.9)		
Middle school	25	(21.9)	20	(19.8)		
High school	19	(16.7)	31	(30.7)		
University	61	(53.5)	39	(38.6)		
Occupational status					-	0.064**
Workers	22	(19.3)	27	(26.7)		
Drivers	10	(8.8)	5	(5.0)		
Farmers	6	(5.3)	1	(1.0)		
Officials	17	(14.9)	27	(26.7)		
Businessmen	15	(13.2)	11	(10.9)		
Other occupations	44	(38.6)	30	(29.7)		
Monthly income (RMB)					4.132	0.127
<1,000	5	(4.4)	12	(11.9)		
1,000–3,000	49	(43.0)	40	(39.6)		
>3,000	60	(52.6)	49	(48.5)		

Data were expressed as mean ± standard deviation (SD) or number (percentage), as appropriate. * Difference between two subgroups was assessed by two-tailed t-test or Chi-square test, as appropriate. Except** results of Fisher exact test. BMI – body mass index; RMB – renminbi; PE – premature ejaculation.

expression: F=0.006, P=0.940). Because the result of triallelic genotype classification was still not consistent with homogeneity of variance, the Kruskal-Wallis test was used when no statistically significant difference was found (P=0.916).

Discussion

We aimed to delineate whether the 5-HTTLPR polymorphism is associated with LPE in a Chinese Han population, and to determine the relationship between 5-HTTLPR genotypes and IELT

behavior. The major finding of this study was that LPE was associated with triallelic 5-HTTLPR but not biallelic 5-HTTLPR. We found that men carrying higher expression genotype (L_AL_A) with LPE had a significantly decreased risk than the controls. Another finding of the current study was that IELT in patients with LPE was not associated with 5-HTTLPR polymorphism in biallelic or triallelic classification.

In the present study, results were in agreement with the results of Janssen et al. [21] and Jern et al. [22], who found no statistically significant difference in the frequencies of biallelic

Table 3. Results of 5-HTTLPR polymorphism according to the biallelic classification.

	PE group		Control group		χ^2	P value*
	Number (N=114)	Percent (%)	Number (N=101)	Percent (%)		
Allele					0.391	0.532
S	131	57.5	110	54.5		
L	97	42.5	92	45.5		
Genotype					1.412	0.494
SS	35	30.7	31	30.7		
SL	61	53.5	48	47.5		
LL	18	15.8	22	21.8		

Data were expressed as number and percentage. * Difference between two subgroups was assessed by Chi-square test.

Table 4. Results of 5-HTTLPR polymorphism according to the triallelic classification.

	Number (%)* of cases N=114	Number (%) of controls N=101	χ^2	P value	OR	95% CI
Tiallelic allele			7.994	0.018**		
S	131 (57.5)	110 (54.5)	0.391	0.532	1.13	0.77 to 1.65
L_G	30 (13.2)	13 (6.4)	5.378	0.020**	2.20	1.12 to 4.35
L_A	67 (29.4)	79 (39.1)	4.515	0.034**	0.65	0.43 to 0.97
Tiallelic genotype			9.495	0.091		
SS	35 (30.7)	31 (30.7)	<0.001	0.999	1.00	0.56 to 1.79
SL_G	17 (14.9)	8 (7.9)	2.547	0.110	2.04	0.84 to 4.95
SL_A	44 (38.6)	40 (39.6)	0.023	0.880	0.96	0.55 to 1.66
$L_G L_G$	3 (2.6)	0 (0)	–	–	–	–
$L_G L_A$	7 (6.1)	5 (5.0)	0.144	0.704	1.26	0.39 to 4.09
$L_A L_A$	8 (7.0)	17 (16.8)	5.020	0.025**	0.37	0.15 to 0.91
Genotype'(grouped by expression)						
S'S' or S'L' (lower expression)	106 (93.0)	84 (84.2)	5.020	0.025**	2.68	1.10 to 6.52
L'L'(higher expression)	8 (7.0)	17 (16.8)	5.020	0.025**	0.37	0.15 to 0.91

* Data were expressed as number and percentage; ** Significant difference compared with control. S'=S+L_G; L'=L_A; S'S'=SS+SL_G+$L_G L_G$; S'L'=SL_A+$L_G L_A$; L'L'=$L_A L_A$. OR – odds ratio; 95% CI – 95% confidence interval.

5-HTTLPR allelic or genotypic polymorphisms in LPE patients and controls. However, Janssen et al. [21] showed that different 5-HTTLPR genotypes were associated with the IELT in LPE patients. Patients with LL genotype had statistically shorter IELT than those other genotypes. Ozbek et al. [23] and Luo et al. [24] both reported a significantly higher occurrence of the S allele in the PE group. Regarding the treatment of SSRIs in LPE,

Janssen et al. [25] investigated the association between the 5-HTTLPR polymorphism and the response to paroxetine in men with LPE, reporting no difference in 5-HTTLPR allelic and genotypic variations. Ozbek et al. [26] evaluated the association between the 5-HTTLPR polymorphism and 20-mg paroxetine-induced ejaculation delay in LPE patients. The study showed the S allele was significantly more frequent in responders. They

Table 5. Results of IELTs in LPE group by biallelic and triallelic 5-HTTLPR genotypes.

	Geometric mean IELT	Median IELT	Mean IELT	Mean ln IELT*	95% CI of mean
Biallelic genotype					
SS	21.5	22.0	24.7±11.5	3.07±0.59	20.79 to 28.70
SL	23.1	27.0	27.2±13.2	3.14±0.63	23.78 to 30.55
LL	22.8	23.5	24.2±8.3	3.12±0.37	20.03 to 28.31
Triallelic genotype					
SS	21.5	22.0	24.7±11.5	3.07±0.59	20.79 to 28.70
SL_G	24.1	27.0	26.1±9.3	3.18±0.44	21.26 to 30.86
SL_A	22.7	29.0	27.6±14.5	3.12±0.70	23.17 to 32.01
L_GL_G	22.9	17.0	25.7±15.9	3.13±0.57	−13.79 to 65.13
L_GL_A	23.4	22.0	23.7±4.5	3.15±0.19	19.59 to 27.84
L_AL_A	22.2	26.0	24.0±8.8	3.10±0.45	16.62 to 31.38
Genotype'(grouped by expression)					
S'S' or S'L' (lower expression)	22.6	25.0	26.1±12.3	3.12±0.60	23.73 to 28.46
L'L'(higher expression)	22.2	26.0	24.0±8.8	3.10±0.45	16.62 to 31.38
Sum	22.5	25.0	26.0±11.9	3.12±0.59	23.71 to 28.18

Data were expressed as mean ± standard deviation (SD). S'=S+L_G; L'=L_A; S'S'=SS+SL_G+L_GL_G; S'L'=SL_A+L_GL_A; L'L'=L_AL_A. * ln IELT – natural logarithm of intravaginal ejaculation latency time. 95% CI – 95% confidence interval.

concluded that premature ejaculation patients with the SS genotype responded well to SSRI therapy. As most findings were contradictory, a meta-analysis by Zhu et al. [27] showed evidence that at least 1 L allele could protect individuals against PE. However, a critical analysis by Janssen et al. [28] showed that measurement errors in PCR are a confounding factor in studies that were not consistent with HWE. Based on the 3 studies in HWE, there was no indication that men with LPE deviate from the general male population.

In the studies cited above, only a biallelic classification was performed. A study in Iran performed by Safarinejad [29] evaluated the triallelic 5-HTTLPR in PE. The results indicated that men with SS, L_GL_G, or SL_G genotype had increased risk of PE. However, a letter from Waldinger et al. [30] pointed out that genotype prevalence was not consistent with HWE. Safarinejad [31] investigated whether the triallelic 5-HTTLPR was related with the therapeutic effects of sertraline in PE patients. The results showed that ejaculation delay was significantly longer in patients with L_AL_A genotype than in the S or L_G allele carriers. In Italy, Zuccarello et al. [32] analyzed the 5-HTTLPR and STin2 polymorphisms, which showed there was no difference between PE patients and controls, and no association was found between the IELT of LPE patients and different genotypes. These results suggest the need for a study of the polymorphisms in a larger sample in order to test for

the genetic pathogenesis of PE. Other linked genes involved in PE are still unexplored.

In the literature, genotype and allele frequencies of 5-HTTLPR polymorphism varied from population to population. Our sample size of participants, as well as the relative homogeneity of demographic and clinical characteristics, makes our sample rather distinct. In addition, it has been emphasized that the biallelic classification may lead to false-negative results [33]. Using a triallelic classification is necessary to further study and reevaluate the relationship between 5-HTTLPR and other diseases. Our study just adds to this knowledge.

The present study has some limitations that should be considered. First, although the present study had an adequate number of subjects compared to previous studies, the number of some genotypes was too small; larger samples are usually important to have sufficient statistical power for genetic association studies [34]. Second, the relationship between gene and LPE is probably very complex, and 5-HTTLPR may act in a synergistic way with other polymorphisms to contribute to the development of LPE. Research on gene-gene and gene-environment effects in LPE is needed. Moreover, the IELTs of the controls were not measured by using a stopwatch in this study. A previous study by Lee et al. [35] showed that the self-estimated IELT was overestimated by approximately 1 min and

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

2072

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System]
[ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica]
[Chemical Abstracts/CAS] [Index Copernicus]

had lower clinical utility than the stopwatch-measured IELT. They suggested that the self-estimated IELT and stopwatch-measured IELT cannot be directly interchanged.

Conclusions

To the best of our knowledge, this is the first study to explore the association between LPE and 5-HTTLPR with respect to both the biallelic and triallelic classifications in a Chinese Han population. The present results indicate that triallelic 5-HTTLPR polymorphism is related to LPE in a Chinese Han population and highlight the necessity of using a triallelic approach in studying 5-HTTLPR. These results support the finding that higher expression of the genotype $L_A L_A$ is a protective factor for LPE.

Triallelic 5-HTTLPR may be a promising field for genetic research in PE. Further research in this interesting field is needed to replicate our results.

Competing interests

There are no conflicts of interests to disclose.

References:

1. Montorsi F: Prevalence of premature ejaculation: A global and regional perspective. J Sex Med, 2005; 296–102

2. Hatzimouratidis K, Amar E, Eardley I et al: Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. Eur Urol, 2010; 57(5): 804–14

3. Godpodinoff ML: Premature ejaculation: clinical subgroups and etiology. J Sex Marital Ther, 1989; 15(2): 130–34

4. McMahon CG, Althof SE, Waldinger MD et al: An evidence-based definition of lifelong premature ejaculation: report of the International Society for Sexual Medicine (ISSM) ad hoc committee for the definition of premature ejaculation. J Sex Med, 2008; 5(7): 1590–606

5. Gao J, Zhang X, Su P et al: Prevalence and factors associated with the complaint of premature ejaculation and the four premature ejaculation syndromes: a large observational study in China. J Sex Med, 2013; 10(7): 1874–81

6. Waldinger MD: The neurobiological approach to premature ejaculation. J Urol, 2002; 168(6): 2359–67

7. Corona G, Jannini EA, Lotti F et al: Premature and delayed ejaculation: two ends of a single continuum influenced by hormonal milieu. Int J Androl, 2011; 34(1): 41–48

8. Schapiro B: Premature ejaculation, a review of 1130 cases. J Urol, 1943; 50: 374–79

9. Waldinger M, Rietschel M, Nothen M et al: Familial occurrence of primary premature ejaculation. Psychiatric Genetics, 1998; 8: 37–40

10. Jern P, Santtila P, Witting K et al: Premature and delayed ejaculation: genetic and environmental effects in a population-based sample of Finnish twins. J Sex Med, 2007; 4(6): 1739–49

11. Jern P, Santtila P, Johansson A et al: Evidence for a genetic etiology to ejaculatory dysfunction. Int J Impot Res, 2009; 21(1): 62–67

12. Waldinger MD, Zwinderman AH, Schweitzer DH et al: Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis. Int J Impot Res, 2004; 16(4): 369–81

13. Ahlenius S, Larsson K: Evidence for an involvement of 5-HT1B receptors in the inhibition of male rat ejaculatory behavior produced by 5-HTP. Psychopharmacology, 1998; 137: 374–82

14. de Jong TR, Pattij T, Veening JG et al: Effects of chronic paroxetine pretreatment on (+/–)-8-hydroxy-2-(di-n-propyl-amino)tetralin induced c-fos expression following sexual behavior. Neuroscience, 2005; 134(4): 1351–61

15. de Jong TR, Pattij T, Veening JG et al: Citalopram combined with WAY 100635 inhibits ejaculation and ejaculation-related Fos immunoreactivity. Eur J Pharmacol, 2005; 509(1): 49–59

16. Qian Y, Melikian H, Rye D et al: Identification and characterization of antidepressant-sensitive serotonin transporter proteins using site-specific antibodies. J Neurosci, 1995; 15: 1261–74

17. Smith GS, Lotrich FE, Malhotra AK et al: Effects of serotonin transporter promoter polymorphisms on serotonin function. Neuropsychopharmacology, 2004; 29(12): 2226–34

18. Collier DA, Stober G, Li T et al: A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. Mol Psychiatry, 1996; 1(6): 453–60

19. Heils A, Teufel A, Petri S et al: Allelic variation of human serotonin transporter gene expression. J Neurochem, 1996; 66(6): 2621–24

20. Lesch KP: Variation of serotonergic gene expression: neurodevelopment and the complexity of response to psychopharmacologic drugs. Eur Neuropsychopharmacol, 2001; 11(6): 457–74

21. Janssen PK, Bakker SC, Rethelyi J et al: Serotonin transporter promoter region (5-HTTLPR) polymorphism is associated with the intravaginal ejaculation latency time in Dutch men with lifelong premature ejaculation. J Sex Med. 2009; 6(1): 276–84

22. Jern P, Eriksson E, Westberg L: A reassessment of the possible effects of the serotonin transporter gene linked polymorphism 5-HTTLPR on premature ejaculation. Arch Sex Behav, 2013; 42(1): 45–49

23. Ozbek E, Tasci AI, Tugcu V et al: Possible association of the 5-HTTLPR serotonin transporter promoter gene polymorphism with premature ejaculation in a Turkish population. Asian J Androl, 2009; 11(3): 351–55

24. Luo S, Wang F, Xie Z et al: Study on the correlation of the 5-HTTLPR polymorphism with premature ejaculation in Han Chinese population. Beijing Da Xue Xue Bao, 2011; 43: 514–18

25. Janssen PK, Zwinderman AH, Olivier B et al: Serotonin transporter promoter region (5-HTTLPR) polymorphism is not associated with paroxetine-induced ejaculation delay in Dutch men with lifelong premature ejaculation. Korean J Urol, 2014; 55(2): 129–33

26. Ozbek E, Otunctemur A, Simsek A et al: Genetic polymorphism in the serotonin transporter gene-linked polymorphic region and response to serotonin reuptake inhibitors in patients with premature ejaculation. Clinics, 2014; 69(11): 710–13

27. Zhu L, Mi Y, You X et al: A meta-analysis of the effects of the 5-hydroxytryptamine transporter gene-linked promoter region polymorphism on susceptibility to lifelong premature ejaculation. PLoS One, 2013; 8(1): e54994

28. Janssen P, Olivier B, Zwinderman A et al: Measurement errors in polymerase chain reaction are a confounding factor for a correct interpretation of 5-HTTLPR polymorphism effects on lifelong premature ejaculation: A critical analysis of a previously published meta-analysis of six studies. PLoS One, 2014; 9(3): e88031

29. Safarinejad MR: Polymorphisms of the serotonin transporter gene and their relation to premature ejaculation in individuals from Iran. J Urol, 2009; 181(6): 2656–61

30. Waldinger M, Janssen P, Schweitzer D: Re: Polymorphisms of the serotonin transporter gene and their relation to premature ejaculation in individuals from Iran: M.R. Safarinejad. J Urol, 2009; 1822983–84

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

2073

Indexed in: [Current Contents/Clinical Medicine]   [SCI Expanded]   [ISI Alerting System]
[ISI Journals Master List]   [Index Medicus/MEDLINE]   [EMBASE/Excerpta Medica]
[Chemical Abstracts/CAS]   [Index Copernicus]

31. Safarinejad MR: Analysis of association between the 5-HTTLPR and STin2 polymorphisms in the serotonin-transporter gene and clinical response to a selective serotonin reuptake inhibitor (sertraline) in patients with premature ejaculation. BJU Int, 2009; 105(1): 73–78

32. Zuccarello D, Ghezzi M, Pengo M et al: No difference in 5-HTTLPR and Stin2 polymorphisms frequency between premature ejaculation patients and controls. J Sex Med, 2012; 9(6): 1659–68

33. Hu XZ, Lipsky RH, Zhu G et al: Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. Am J Hum Genet, 2006; 78(5): 815–26

34. Abou-Sleiman PM, Hanna MG, Wood NW: Genetic association studies of complex neurological diseases. J Neurol Neurosurg Psychiatry, 2006; 77(12): 1302–4

35. Lee WK, Cho ST, Lee YS et al: Can estimated intravaginal ejaculatory latency time be used interchangeably with stopwatch-measured intravaginal ejaculatory latency time for the diagnosis of lifelong premature ejaculation? Urology, 2015; 85(2): 375–80