Association between polymorphisms in the human serotonin transporter gene and lifelong premature ejaculation in the Han population

Dang-Wei Peng*, Jing-Jing Gao*, Yuan-Yuan Huang, Dong-Dong Tang, Pan Gao, Chao Li, Wei-Qun Liu, Xian-Ming Dou, Jun Mao, Yao Zhang, Hao Geng, Xian-Sheng Zhang

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Dear Editor,

Lifelong premature ejaculation (LPE) is a type of sexual dysfunction in males and has three characteristics: (1) an intravaginal ejaculatory latency time (IELT) of ≤1 min; (2) insufficient control over delaying ejaculation; and (3) negative personal consequences, such as distress, frustration, and/or the avoidance of sexual intimacy.1 Its etiologies involve the 5-hydroxytryptamine (5-HT) system. The use of 5-HT transporter (5-HTT) blockers (e.g., selective serotonin reuptake inhibitors, SSRIs) was found to prevent the reuptake of 5-HT from the synaptic cleft into the presynaptic serotonergic neurons, which leads to increased extracellular 5-HT levels, thereby delaying ejaculation.2 The 5-HTT gene (SLC6A4) on human chromosome 17 thus became a candidate target gene for treating LPE and had been isolated and characterized. All of the gene’s exons and the adjacent intronic sequences, as well as a tandem repeat DNA polymorphism within the SLC6A4 gene, have been sequenced.3 Polymorphisms in the serotonin transporter gene-linked polymorphic region (5-HTTLPR) and in the second intron (5HTn2) have been studied in LPE, but the findings were inconsistent.4 Other polymorphisms (e.g., single-nucleotide polymorphisms) in this gene have been widely studied in patients with psychosis5,6 but not in patients with LPE.

In the present study, our team explored the association with LPE of single-nucleotide polymorphisms (SNPs) in the 3’ untranslated region (UTR) and 5’ UTR, and of single-nucleotide variants (SNVs) in all exons of SLC6A4. We enrolled 101 men diagnosed with LPE from our outpatient clinics and 99 age-matched healthy controls from the health examination center. All subjects were genotyped for polymorphisms in the 3’ UTR, 5’ UTR and all exons of SLC6A4. For both the LPE group and the control group showed no significant deviation (P > 0.05) from the Hardy-Weinberg equilibrium (HWE). The SNPs including rs25533, rs6354, rs7224199, rs8066731, and rs1042173 in the 3’ UTR were located in the observed LD block. Haplotype association analyses for the block, with respect to LPE, were performed with HAPLOVIEW (version 4.1, Broad Institute of Harvard and MIT, Cambridge, MA, USA). The results showed no significant haplotype association with LPE (P > 0.05).

LPE is a complex sexual dysfunction involving the 5-HT system. Multiple, well-controlled evidence-based studies have demonstrated the efficacy and safety of SSRIs for delaying ejaculation, thus confirming their role as first-line agents for the treatment of LPE and acquired premature ejaculation (APE).6 Medications for SSRI-associated sexual side effects inhibit 5-HTT and increase the synaptic latency period of 5-HT molecules, thereby facilitating the modulation of postsynaptic serotonin receptors.7 To explore the moderate effect of genes on LPE, studies have attempted to uncover whether there is an association between LPE and the SLC6A4 gene. Zuccarello et al.8 reported that no significant differences were found in the frequency of 5-HTTLPR gene polymorphisms in LPE patients and controls. In contrast, a significant association between LPE and the 5-HTTLPR short (S) allele and the SS genotype has been reported.9 However, this study was criticized because the sample population deviated from HWE.9 In the current study, we explored whether polymorphisms in the 3’ UTR, 5’ UTR and the exons of SLC6A4 were associated with LPE. The results of our study showed that polymorphisms in the UTRs and the exons were not significantly associated with LPE in the Han population (P > 0.05). However, PE is a complex sexual dysfunction, and its moderate genetic effect cannot be explained by a single gene. For example, in the Han population, Luo et al.10 explored whether 5-HT6 receptor gene polymorphism in LPE influenced IELT in men with LPE.

To the best of our knowledge, this is the first study to test the association between LPE and SNPs or SNVs in the SLC6A4 gene. In the sample population, no significant association was found between LPE and polymorphisms in the SLC6A4 gene. Further investigation in this field is needed.

*These authors contributed equally to this work.

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

1 Correspondence: Dr. XS Zhang (xiansheng-zhang@163.com)

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AUTHOR CONTRIBUTIONS
DWP, YYH, and XSZ designed the study. DWP, YYH, DDT, PG, CL, WQL, XMD, JM, YZ, and HG acquired the data. DWP, JJG, and XSZ performed the statistical analysis and wrote the paper. All authors read and approved the final manuscript.

COMPETING INTERESTS
The authors declare no competing interests.

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REFERENCES
1 Althof SE, McMahon CG, Waldinger MD, Serefoglu EC, Shindel AW, et al. An update of the International Society of Sexual Medicine’s Guidelines for the diagnosis and treatment of premature ejaculation (PE). Sex Med 2014; 2: 60–90.
2 Giuliano F, Clement P. Serotonin and premature ejaculation: from physiology to patient management. Eur Urol 2006; 50: 454–66.
3 Lesch KP, Balling U, Gross J, Strauss K, Wolozin BL, et al. Organization of the human serotonin transporter gene. J Neural Transm Gen Sect 1994; 95: 157–62.
4 Zuccarello D, Ghezzi M, Pengo M, Forzan M, Frigo AC, et al. No difference in 5-HTTLPR and Stin2 polymorphisms frequency between premature ejaculation patients and controls. J Sex Med 2012; 9: 1659–68.
5 Ozbek E, Tasci AI, Tugcu V, Ilbey YO, Simsek A, 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: 351–5.
6 Ozaki N, Goldman D, Kaye WH, Plotnicov K, Greenberg BD, et al. Serotonin transporter missense mutation associated with a complex neuropsychiatric phenotype. Mol Psychiatry 2003; B: 933–6.
7 Hu XZ, Lipsky RH, Zhu G, Akhtar LA, Taubman J, et al. Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. Am J Hum Genet 2006; 78: 815–26.
8 Waldinger MD, Zwinderman AH, Schweitzer DH, Olivier B. 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: 369–81.
9 Waldinger MD, Janssen PK, Schweitzer DH. Hardy Weinberg equilibrium in genetic PE research remains critical to avoid misinterpretation. Asian J Androl 2009; 11: 524.
10 Luo S, Lu Y, Wang F, Xie Z, Huang X, et al. Association between polymorphisms in the serotonin 2C receptor gene and premature ejaculation in Han Chinese subjects. Urol Int 2010; 85: 204–8.

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