To the Editor: Premature ejaculation (PE) is one of the commonplace male sexual dysfunctions affecting about 30% of men worldwide. PE can either be lifelong or acquired. Genetic polymorphisms situated on the SLC6A4 gene encoding the 5-hydroxytryptamine transporter (serotonin transporter) (5-HTT) also called the serotonin transporter (SERT), a significant controller of serotonergic neurotransmission, were related to the pathogenesis of PE.[1,2] Polymorphisms in SLC6A4 are associated with the incidence of lifelong premature ejaculation (LPE). The effects of 5-hydroxytryptamine (serotonin) transporter gene-linked polymorphic region (5-HTTLPR) and serotonin transporter gene intron 2 (STin2) polymorphism on lifelong PE (LPE) are controversial. We aimed to determine possible relationships between 5-HTTLPR and STin2 polymorphisms in the SERT gene and clinical response of a selective serotonin reuptake inhibitor (dapoxetine) in LPE.

We recruited 95 patients of PE and 102 normal controls from the Urology Department of The First Affiliated Hospital, Xi’an Jiaotong University from September 2015 to March 2016. All the participants aged between 21 and 50 years. The patients experienced LPR and have been either married or have been in a normal sexual relationship with a female companion for >6 months. All patients who experienced sexual abuse or had a history of relationship with a female companion for 6 months. All patients who experienced sexual abuse or had a history of sexual dysfunction, reduced libido, prostatitis, urological diseases, psychiatric and neurological issues, depression, diabetes, cancer, and coronary heart were excluded from the study. One of the criteria to choose the subjects was the age at first sex, frequency of sex per month, and PEDT were related to the onset of PE (P < 0.05).

We used stopwatches to measure intra-vaginal ejaculation latency time (IELT). The deoxyribonucleic acid was extracted from the venous blood. The patients took 30 mg dapoxetine for 2 weeks and were analyzed for the efficacy of the treatment. 5-HTTLPR and STin2 were genotyped using the polymerase chain reaction technique. We evaluated the associations between 5-HTTLPR and STin2 variable number tandem repeat (VNTR) genotypic effects of 5-hydroxytryptamine (serotonin) transporter (SERT) a significant controller of serotonergic neurotransmission, were related to the pathogenesis of PE. The STin2 variable number tandem repeat (VNTR) genotypic and allelic frequencies and LPR. P value of < 0.05 was taken statistically significant. The study was approved by the Ethics Committee of the First Affiliated Hospital of Xi’an Jiaotong University (No. XJTU1AF2018LSK-192). Written informed consent was obtained from the patients.

Age, weight, height, marital status, alcohol consumption, smoking, and body mass index had no direct relation to the rate of PE. Career strongly affected the onset of PE. The proportion of mental workers was higher than physical workers in the case group. Age at first sex, frequency of sex per month, and PEDT were related to the onset of PE (P < 0.05).

The frequencies of 5-HTTLPR LS genotype and LS + SS genotype in the case and control groups were not statistically significantly different (P = 0.531 > 0.05). SS and LL genotype distribution frequency was statistically significantly different between the two groups (P = 0.017 < 0.05). The frequency distribution of the S and L allele was statistically significantly different between the two groups (P = 0.003 < 0.05). The frequency of SS genotype and S allele in 5-HTTLPR was significantly higher in the case group than that in the control group, while there was no significant difference in the distribution of LS and LL genotype between case and control groups. The
difference of frequency distribution of STin2.12/12 genotype and STin2.12 allele in Stin2 was statistically significant in the case and control groups ($P < 0.05$). The frequency of the Stin2.12/12 genotype and STin2.12 allele in the case group was significantly higher than that in the control group, and the distribution of Stin2.10/10 and Stin2.12/10 genotype was not statistically significantly different between the two groups. It concluded that the Stin2.12/12 genotype and STin2.12 allele were related to the incidence of PE. STin2.9 genotype was detected only in two patients and in one control because of its low incidence, it is therefore not included in the statistic.

According to the Clinician Global Impression of Change score, 66.3% (63/95) of the patients treated with dapoxetine showed efficacy. There were also significant changes in premature ejaculation profile scores before and after the treatment in LPE patients. The chi-square test for the frequencies of the 5-HTTLPR LS genotype, LS + SS genotype, and the LL genotype showed the P value and the odds ratio (OR) value (95% confidence interval [CI]) were $P = 0.735$, OR (95% CI) = 0.869 (0.272, 2.655), $P = 0.258$, OR (95% CI) = 0.330 (0.260, 1.522), indicating that the difference was not statistically significant ($P > 0.05$). The chi-square test for SS genotype and LL genotype distribution was $P = 0.018$, OR (95% CI) = 0.354 (0.130, 0.769), the difference was statistically significant ($P < 0.05$). The chi-square test for the distribution frequency of the S and L alleles was $P = 0.028$, OR (95% CI) = 0.460 (0.226, 0.798), $P < 0.05$, and the difference was statistically significant. The results are shown in Table 1. These results indicated that the distribution of SS genotype and S allele in 5-HTTLPR was statistically significant in the responding and non-responding groups ($P < 0.05$), therefore, we conclude that the SS genotype is less effective in PE patients than in controls and that the S allele is a risk factor with poor response to treatment.

The chi-square test for Stin2.12/12 genotype and Stin2.10/10 genotype distribution was statistically significantly different ($P = 0.018 < 0.05$, OR [95%CI] = 0.409 [0.215,0.986]). The chi-square test for the distribution frequency of Stin2.10 and Stin2.12 alleles was statistically significantly different ($P = 0.026 < 0.05$, OR [95% CI] = 0.438 [0.247,0.963]). The frequency of allele Stin2.12 was significantly higher in the non-responding group than that in the responding group. No significant significance was found in the distribution of STin2.10 genotypes and STin2.12/10 genotypes, as shown in Table 1. Based on our results, we hypothesized that PE patients with the SS genotype and allele and Stin2.12/12 genotype and Stin2.12 allele were less responsive to dapoxetine.

LPE is one of the most prevalent sexual dysfunctions worldwide but little remains understood regarding its pathogenesis. In 1940, the genetic etiology of PE in humans was speculated for the first time and was progressively affirmed by two studies that showed that about 30% of PE is because of genetic factors. Many authors have tried to explore the possible association between PE and 5-HTTLPR gene polymorphisms, the consequences presented were showing different results by different researchers, it is difficult to conclude. For instance, Janssen et al[2] surveyed Caucasians and observed that the 5-HTTLPR polymorphism is related to the mean IELT. IELT in individuals with the LL genotype was 100.0% shorter than individuals with SS or SL genotype. Ozbek et al[3] performed a study in the Turkish population and found that the frequency of

| Table 1: Genotype and allele of 5-HTTLPR and STin2 VNTR in patients treated with dapoxetine, n (%). |
|-------------------------------------------------|-------------------------------|-----------------|-----------------|-----------------|
| Items                                           | Effective                     | Ineffective     | $P$ values      | OR (95% CI)     |
| 5-HTTLPR                                        |                               |                 |                 |                 |
| n                                               | 63                            | 32              |                 |                 |
| Genotype                                        |                               |                 |                 |                 |
| LL                                              | 10 (15.8)                     | 2 (6.3)         | 0.735           | 0.869 (0.272, 2.655) |
| LS                                              | 25 (39.7)                     | 6 (18.7)        | 0.018           | 0.354 (0.130, 0.769) |
| SS                                              | 28 (44.5)                     | 24 (75.0)       | 0.258           | 0.330 (0.260, 1.522) |
| LS + SS                                         | 53 (84.2)                     | 30 (93.7)       |                 |                 |
| Allele                                          |                               |                 |                 |                 |
| L                                               | 45 (35.8)                     | 10 (15.7)       | 0.028           | 0.46 (0.226, 0.798) |
| S                                               | 81 (64.2)                     | 54 (84.3)       |                 |                 |
| STin2 VNTR                                      |                               |                 |                 |                 |
| n                                               | 62                            | 31              |                 |                 |
| Genotype                                        |                               |                 |                 |                 |
| Stin2.10/10                                     | 8 (12.9)                      | 3 (9.6)         | 0.273           | 0.525 (0.217, 1.528) |
| Stin2.12/10                                     | 31 (50.0)                     | 7 (22.6)        |                 | 0.409 (0.215, 0.986) |
| Stin2.12/10 + Stin2.12/10                       | 54 (87.1)                     | 28 (90.4)       | 0.755           | 0.538 (0.351, 1.633) |
| Allele                                          |                               |                 |                 |                 |
| Stin2.12                                        | 47 (37.9)                     | 13 (20.1)       | 0.026           | 0.438 (0.247, 0.963) |
| Stin2.12                                        | 77 (62.1)                     | 49 (79.9)       |                 |                 |

5-HTTLPR: 5-HydroxyTryptamine (serotonin) transporter gene-linked polymorphic region; STin2: Serotonin transporter gene intron 2; VNTR: Variable number tandem repeat.
the S allele was significantly higher in those of the PE patients compared with the normal individuals without PE. Janssen et al[1] investigated that the 5-HTTLPR polymorphism is associated with the IELT in males suffering from LPE. Men with the LL genotype ejaculate 100.00% and 90.00% faster than males with SS and SL genotypes, respectively. Safarinejad also presumed that the recurrence of the SS gene and S allele was higher in PE patients than in the general population.[4] No difference exists in SLC6A4 polymorphisms recurrence among patients of PE and controls. He concluded that no significant difference exists for both patients and controls, for the genotype frequencies of 5-HTTLPR, rs25531, and STin2. In 2016, Huang et al[5] conducted research that stated that the STin2 VNTR polymorphism is associated with IELT in LPR. IELT was significantly shorter in patients with STin2.12/12 genotype.

In our present research, the comparison of SS and LL genotype distribution frequency of 5-HTTLPR was statistically significantly different between the two groups. The difference between frequency of the S allele and L allele of 5-HTTLPR was statically significant. SS genotype and S allele were both significantly higher than in the controls. The frequency of STIN2.12/12 genotype and Stin2.12 allele in Stin2 was higher in PE patients than that in the control group (P < 0.05). We concluded that genotype Stin2.12/12 and Stin2.12 alleles correlated with PE. 66.30% (63/95 patients) responded to the treatment with dapoxetine. The SS genotype and S allele in 5-HTTLPR are less responsive to dapoxetine. STin2.12/12 genotype and Stin2.12 allele are also higher in the patients not responding to dapoxetine.

PE is a multifactor complex disease with different etiological aspects. The etiology of the disease involves psychological, environmental, neurobiological, endocrine, and genetic factors. Our study indicates that polymorphisms in 5-HTTLPR and STin2 are associated with LPR and its treatment with dapoxetine. PE is believed to be caused by psychological and environmental factors, anxiety, fear tension during sexual intercourse, lack of sexual knowledge, and heredity. At present, many valuable genes, loci, and regions related to this disease have been discovered in different research studies, but there is still no clear conclusion as all the results obtained from these studies are not consistent. Our study subjects were only from the Han ethnicity of northwest China and were limited in number. Presently, just a few studies are performed to understand the effects of STin2 polymorphism and PE. We recommend more research work with large numbers of study subjects to further clarify the pathophysiology and treatment of PE in different populations and ethnic groups.

Acknowledgements
The authors thank the participant of the study and their families.

Conflicts of interest
None.

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How to cite this article: Abdullah, Yang Y, Ding SS, Sun P, Huoyong-Wei, Hong T, Xing J. Association between 5-HTTLPR and STin2 VNTR polymorphisms in the serotonin transporter gene and clinical response of a selective serotonin reuptake inhibitor (dapoxetine) in lifelong premature ejaculation. Chin Med J 2022;135:1619–1621. doi: 10.1097/CM9.00000000000011843