Genome-Wide Association Analysis to Search for New Loci Associated with Lifelong Premature Ejaculation Risk in Chinese Male Han Population

Fei Wang¹,*†, Defan Luo²,*†, Jianxiang Chen³, Cuiqing Pan¹, Zhongyao Wang¹, Houzheng Fu¹, Jianbing Xu¹, Meng Yang¹, Shaowei Mo⁴, Liying Zhuang⁵, Liefu Ye⁶, Weifu Wang¹

¹Department of Urology, Hainan General Hospital, Affiliated Hainan Hospital of Hainan Medical University, Haikou, Hainan, ²Department of Urology, Hainan General Hospital, Affiliated Hainan Hospital of Hainan Medical University, Haikou, Hainan, ³Department of Urology, Affiliated Hospital of Xiangnan University, Chenzhou, Hunan, ⁴Ministry of Science and education, Hainan Women and Children’s Medical Center, Haikou, Hainan, ⁵Library, Hainan Medical University, Haikou, Hainan, ⁶Department of Urology, Fujian Provincial Hospital, Shengli Clinical Medical College of Fujian Medical University, Fuzhou, China

Purpose: Genetic factors play an indispensable role in the pathogenesis of lifelong premature ejaculation (LPE). The susceptibility genes/SNPs that have been discovered are very limited and can only explain part of the genetic effects of LPE. Therefore, discovering more genetic polymorphisms associated with the occurrence and development of LPE will help reveal the pathogenesis of LPE.

Materials and Methods: We conducted a genome-wide association study of LPE in 486 Chinese male Han people (cases and controls). We used Gene Titan multi-channel instrument and Axiom Analysis Suite 6.0 software for genotyping. Imputation was performed by IMPUTE2 software and the 1000 Genomes Project (Phase3) was used as reference for haplotype. Finally, logistic regression analysis was performed on all loci that passed the quality control. The odds ratio and 95% confidence interval were calculated to determine the association between each SNPs and Chinese male Han population LPE risk.

Results: The results showed that a total of 33 genetic variants in 13 genes (LACTBL1, SSBP3, ACOT11, LINC02486, TMEM154, LINC01098, NONE, HCG27, HLA-C, TNFSF8, TNC, FAM53B, SULF2) have a suggestively significant genome-wide association with LPE risk (p<5×10⁻⁶).

Conclusions: This study is the first to conduct a GWAS on LPE in Chinese male Han population 33 genetic polymorphisms have a suggestive genome-wide association with LPE risk. This study have provided data supplement for the genetic loci of LPE risk, and laid a scientific foundation for the pathogenesis and the targeted therapy of LPE.

Keywords: Chinese male Han population; Genetic Loci; Genome-wide association analysis; Lifelong premature ejaculation

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
INTRODUCTION

Premature ejaculation (PE) is one of the most common male sexual dysfunction diseases in urology clinic. PE is generally divided into fragmented lifelong premature ejaculation (LPE) and acquired premature ejaculation (APE) [1]. The incidence of PE is between 20% to 30% [2,3] and has been rising in recent years [4,5]. Gao et al [6] conducted a survey among Chinese population and found that the incidence of PE was 25.8%, and it was mainly LPE. Studies have found that factors such as psychology [7], endocrine [8], genetic variation, and neurobiology [9] are related to the occurrence and development of LPE. However, the research on the etiology and pathogenesis of LPE is still in its infancy, and the pathogenesis of LPE is still unclear. In summary, further in-depth research is very necessary.

Studies have shown that genetic variation plays an indispensable role in the occurrence and development of LPE. In a large sample study based on the Finnish population, Jern et al [10] found that LPE has obvious familial characteristics. In recent years, with the development of molecular biology and molecular epidemiology, as well as the improvement and application of genetic testing technology, some genetic loci associated with LPE have been identified one after another. These genetic loci are mainly concentrated in 5-hydroxytryptamine (5-HT) -related genes and dopamine-related genes, such as 5-HTT [11-13], DAT1 [14], OVT and AVP receptor genes [15], etc. Since the expression of neurotransmitters (such as 5-HT) involved in the ejaculation process is usually regulated by multiple genes, a single gene and genetic polymorphism may not directly determine its expression [16]. Therefore, it is very necessary to explore the genetic polymorphisms associated with the pathogenesis of LPE, which will provide new ideas for further elucidating the pathogenesis of LPE. It will also lay a scientific foundation for the clinically targeted therapy of LPE.

In recent years, Genome-wide association study (GWAS) has become the main method to identify the genetic loci of complex diseases [17]. GWAS can cover single nucleotide polymorphisms in the whole genome, so it can more effectively find genetic variants that are associated with the occurrence and development of diseases. At present, GWAS of a series of complex diseases has been reported one after another. However, GWAS for LPE in any population has not been reported.

Therefore, within the Chinese male Han population, we used LPE patients as the case group and healthy individuals as the control group, and used GWAS to discover genetic variants associated with the occurrence and development of LPE. This study will lay a valuable scientific foundation for early clinical LPE screening, disease monitoring or individualized prevention and treatment.

MATERIALS AND METHODS

1. Ethics statement

This study was conducted under the standard approved by the Ethics Committee of Hainan General Hospital, and conformed to the ethical principles for medical research involving humans of the World Medical Association Declaration of Helsinki. All participants signed informed consent forms before participating in this study.

2. Study subject and DNA extraction

This study conducted a GWAS of Chinese male Han population with primary PE. From April 2018 to May 2020, the peripheral blood of a total of 486 participants were recruited at Hainan General Hospital. Among them, 120 LPE patients were selected as the case group. LPE patients were subjected to standard questionnaire surveys and physical examinations by professional medical staff. And LPE patients were determined in strict accordance with the standard definition of ISSM [18]. The inclusion criteria of the case group are as follows: (1) At the beginning of the first sexual life, more than 80% of intravaginal ejaculatory latency time (IELT) lasted for 30 to 60 seconds or 1 to 2 minutes, premature ejaculation diagnostic tool (PEDT) score ≥11. The duration of the above symptoms is greater than 6 months; (2) LPE patients are between 20 and 50 years old; (3) They have had a normal sexual relationship with their female partner in the past 6 months or more; (4) Have not received medication before participating in the research; (5) No mental illness or other major diseases. And 366 healthy male individuals recruited from the health examination center of the same hospital during the same period were selected as the control group. All participants are not genetically related. Subsequently, whole genome DNA (GoldMag, Xi’an, China) was extracted, and the specific operation procedure was carried out according to the kit instruc-
3. Genotyping and quality control

In this study, we selected Thermo Scientific Genotyping Chip (Thermo Fisher Scientific Inc., Waltham, MA, USA), and using GeneTitan multi-channel instrument (Affymetrix, Inc., Santa Clara, CA, USA) and Axiom Analysis Suite 6.0 software (Thermo Fisher Scientific Inc.) for genotyping. Within the scope of our study subjects, we conducted a genome-wide scan through Axiom and the results showed that it contained a total of 819,009 million loci. After excluding insertion-deletion, copy number variation, and duplication, 756,558 loci remain. These loci meet the following conditions: sample call rate >0.95, marker call rate >0.90 and Hardy–Weinberg equilibrium (HWE) >5×10^−6.

4. Imputation and quality control

We then removed the sex chromosome loci from the 756,558 loci left. With the haplotype reference of the 1000 Genomes Project (Phase 3), IMPUTE2 software was used for imputation. After imputation, keep the loci that meet the following conditions: sample call rate >92%, marker call rate >85%, HWE-control >1×10^−6. Finally, a total of 4,572,568 SNPs were used for GWAS of our study.

5. Statistical Analysis

We use Gold Helix SNP & Variation Suite 8.7 version (Golden Helix®, Golden Helix, Inc., Bozeman, MT, USA; www.goldenhelix.com) for correlation analysis. Basing on the additive model, we performed logistic regression analysis, then calculated the odds ratio and 95% confidence interval to determine the association between each SNPs and the risk of LPE. All data in this study were adjusted by age. The p-value is less than 5×10^−8, which means the genetic polymorphism is genome-wide significantly associated with the LPE risk. Genetic polymorphism with p-value less than 5×10^−6 suggests that it may have a significant genome-wide association with the LPE risk. Moreover, these genetic loci can generally increase the risk of PLE by more than two times. SSBP3/ACOT11 (rs72668248, rs77599229, rs7516649, rs7554205, rs72668249, rs72668250, rs72668252), LINC02486/TMEM154 (rs28689703, rs68252224), LINCO1098/NONE (rs6837438, rs11376013, rs66508088, rs7698777, rs1510618, rs6814432, rs110342, rs11735490, rs2063393, rs1022119), and SULF2 (rs872111) may significantly reduce the risk of PLE. And these genetic loci can reduce the risk of LPE by more than a half. Finally, we have performed power analysis for sample size. The specific parameters were set as follows: disease prevalence of 0.258, significance level of 5×10^−6, and genotype relative risk (GRR) of 1.8/2.0 (the GRR value depends on allele frequencies of polymorphisms) [19].

RESULTS

In this study, the LPE genome-wide association study was conducted in 120 LPE patients and 366 healthy individuals. The sample characteristics of the study subjects were shown in Table 1. The results showed that there were significant differences in IELT and PEDT scores between the control and the case group (p<0.05).

The results showed that based on the additive model, we did not find any genetic loci significantly genome-wide associated with LPE risk (p<5×10^−8). However, we found that a total of 33 genetic variants in 13 genes have a suggestively significant genome-wide association with LPE risk (p<5×10^−6). The relevant information of these genetic loci and the corresponding genes were shown in Table 2. The results suggested that LACTBL1 (rs2013948, rs2869051, rs2903994), HCG27/HLA-C (rs9279036), TNFSF8/TNC (rs10114657, rs10120850, rs12335994, rs56742741, rs12342713, rs7864266, rs10120312), FAM53B (rs11818135, rs73379047) may significantly increase the risk of LPE. Moreover, these genetic loci can generally increase the risk of PLE by more than two times. SSBP3/ACOT11 (rs72668248, rs77599229, rs7516649, rs7554205, rs72668249, rs72668250, rs72668252), LINC02486/TMEM154 (rs28689703, rs68252224), LINCO1098/NONE (rs6837438, rs11376013, rs66508088, rs7698777, rs1510618, rs6814432, rs110342, rs11735490, rs2063393, rs1022119), and SULF2 (rs872111) may significantly reduce the risk of PLE. And these genetic loci can reduce the risk of LPE by more than a half. Finally, we have performed power analysis for sample size. For genotype

Table 1. Basic characteristics of study subjects

| Characteristic | Control | Case | p-value |
|---------------|---------|------|---------|
| Number        | 366     | 120  | -       |
| PEDT (s)      | 687.49±350.27 | 69.59±32.47 | <0.0001 |
| IELT (s)      | 3.62±3.19  | 18.30±2.26 | <0.0001 |

Values are presented as number only or mean±standard deviation. *: not available, PEDT: premature ejaculation diagnostic tool, IELT: intravaginal ejaculatory latency time.

p<0.05 indicates statistical significance.
relative risk was 1.8 and the minor allele frequency ranged from 0.276 to 0.472, the power ranged from 70.5% to 78.5%. For genotype relative risk was 2 and the minor allele frequency ranged from 0.081 to 0.197, the power ranged from 23.8% to 68.9% (Supplement Table).

Quantile-quantile plots were shown in Fig. 1A. We also calculated the genomic inflation factor (\(\lambda\)) from a GWAS analysis to compare the genome-wide distribution of the test statistics with the expected null distribution (Fig. 1A). Manhattan plots was shown in Fig. 1B. The red line in Fig. 1B represents the suggestive cut-off value with genome-wide significance (p<5×10^{-6}). In addition, locus zoom plots of genetic loci on different chromosomes that are significantly associated with the LPE risk were shown in Fig. 2.

**DISCUSSION**

LPE is the most common male sexual dysfunction disease. In recent years, research on the pathogenesis of LPE has been increasing, especially in genetics. However, the susceptibility genes/SNPs found so far are very limited, which can only explain part of the

| Gene           | SNPs ID       | Chr | Function | Alleles | MAF  | Odds ratio | 95% confidence interval | p-value |
|----------------|---------------|-----|----------|---------|------|------------|-------------------------|---------|
| LACTBL1        | rs2013948     | 1   | Intronic | G       | 0.318| 2.109      | 1.533–2.901              | 3.32E-06|
| LACTBL1        | rs2869051     | 1   | Intronic | G       | 0.320| 2.090      | 1.519–2.875              | 4.44E-06|
| LACTBL1        | rs2903994     | 1   | Intronic | G       | 0.324| 2.053      | 1.506–2.799              | 4.14E-06|
| SSBP3; ACOT11  | rs72668248    | 1   | Intergenic | G   | 0.081| 0.149      | 0.053–0.415              | 1.80E-06|
| SSBP3; ACOT11  | rs77599229    | 1   | Intergenic | T   | 0.081| 0.149      | 0.053–0.415              | 1.80E-06|
| SSBP3; ACOT11  | rs7516649     | 1   | Intergenic | T   | 0.081| 0.148      | 0.053–0.411              | 1.56E-06|
| SSBP3; ACOT11  | rs7554205     | 1   | Intergenic | G   | 0.083| 0.144      | 0.052–0.401              | 1.02E-06|
| SSBP3; ACOT11  | rs72668249    | 1   | Intergenic | A   | 0.084| 0.179      | 0.071–0.452              | 4.47E-06|
| SSBP3; ACOT11  | rs72668250    | 1   | Intergenic | C   | 0.086| 0.177      | 0.07–0.444               | 2.82E-06|
| SSBP3; ACOT11  | rs72668252    | 1   | Intergenic | T   | 0.087| 0.176      | 0.07–0.442               | 2.63E-06|
| LINCO2486; TMEM154 | rs28689703    | 4   | Intergenic | A   | 0.362| 0.455      | 0.322–0.644              | 3.01E-06|
| LINCO2486; TMEM154 | rs6825224    | 4   | Intergenic | G   | 0.367| 0.446      | 0.315–0.632              | 1.65E-06|
| LINCO1098; NONE | rs6837438     | 4   | Intergenic | C   | 0.472| 0.503      | 0.372–0.682              | 4.50E-06|
| LINCO1098; NONE | rs11736013    | 4   | Intergenic | C   | 0.471| 0.488      | 0.359–0.663              | 2.07E-06|
| LINCO1098; NONE | rs66508088    | 4   | Intergenic | T   | 0.470| 0.476      | 0.349–0.649              | 1.06E-06|
| LINCO1098; NONE | rs7698777    | 4   | Intergenic | G   | 0.465| 0.485      | 0.356–0.661              | 2.10E-06|
| LINCO1098; NONE | rs1510618     | 4   | Intergenic | A   | 0.469| 0.486      | 0.355–0.665              | 3.07E-06|
| LINCO1098; NONE | rs6814432     | 4   | Intergenic | G   | 0.469| 0.486      | 0.355–0.665              | 3.07E-06|
| LINCO1098; NONE | rs1110342     | 4   | Intergenic | A   | 0.468| 0.488      | 0.357–0.668              | 3.34E-06|
| LINCO1098; NONE | rs11735490    | 4   | Intergenic | C   | 0.468| 0.489      | 0.357–0.669              | 3.44E-06|
| LINCO1098; NONE | rs2063393     | 4   | Intergenic | C   | 0.468| 0.489      | 0.357–0.669              | 3.44E-06|
| LINCO1098; NONE | rs1022119     | 4   | Intergenic | C   | 0.468| 0.489      | 0.357–0.669              | 3.44E-06|
| HC27; HLA-C    | rs9279036     | 6   | Intergenic | G   | 0.363| 2.100      | 1.526–2.892              | 3.59E-06|
| TNFSF8; TNC    | rs10114657    | 9   | Intergenic | C   | 0.197| 2.423      | 1.691–3.472              | 1.25E-06|
| TNFSF8; TNC    | rs10120850    | 9   | Intergenic | A   | 0.197| 2.423      | 1.691–3.472              | 1.25E-06|
| TNFSF8; TNC    | rs12335994    | 9   | Intergenic | G   | 0.197| 2.389      | 1.669–3.419              | 1.75E-06|
| TNFSF8; TNC    | rs56742741    | 9   | Intergenic | G   | 0.197| 2.310      | 1.618–3.298              | 3.82E-06|
| TNFSF8; TNC    | rs12342713    | 9   | Intergenic | G   | 0.197| 2.310      | 1.618–3.298              | 3.82E-06|
| TNFSF8; TNC    | rs7864266     | 9   | Intergenic | T   | 0.197| 2.310      | 1.618–3.298              | 3.82E-06|
| TNFSF8; TNC    | rs10120312    | 9   | Intergenic | T   | 0.197| 2.310      | 1.618–3.298              | 3.82E-06|
| FAM53B         | rs11818135    | 10  | Intronic | C   | 0.289| 2.290      | 1.609–3.259              | 2.82E-06|
| FAM53B         | rs73379047    | 10  | Intronic | G   | 0.289| 2.242      | 1.578–3.185              | 4.65E-06|
| SULF2          | rs872111      | 20  | Intronic | T   | 0.276| 0.417      | 0.284–0.614              | 1.80E-06|

LPE: lifelong premature ejaculation, Chr: chromosome, MAF: minor allele frequency.
genetic characteristics of LPE. Jannssen et al [13] have put forward the hypothesis that the combined effect of multiple genetic polymorphisms and/or multiple genetic factors that can accelerate ejaculation activity leads to persistent short IELT in LPE patients. Therefore, discovering more genetic loci associated with the occurrence and development of LPE will help reveal the pathogenesis of LPE.

Up to now, some genetic loci of LPE have been identified in traditional association studies conducted in a small sample size. Such as 5-HTTLPR polymorphism in 89 Dutch men [13], polymorphism of the 5-HT1A receptor gene in 54 men [20], Cys23Ser polymorphism of the 5-HT2c receptor in 64 Dutch Caucasian men [21] and SLC6A4 polymorphisms in Chinese Han men [22]. These studies preliminarily showed that LPE gene polymorphisms can play a certain guiding role for future clinical medication. It is worth noting that the above-mentioned genetic loci were not identified in this study to be associated with the LPE risk. It may be affected by differences in the sample size or the genetic background of the research object.

This study is the first to perform a LPE GWAS in Chinese male Han population. Thirty-three genetic polymorphisms were found to have a suggestive genome-wide significant association with the risk of PLE. And these 33 genetic loci have never been reported to be associated with LPE susceptibility, they are potential new genetic loci for LPE.

We found that 13 genetic loci of 6 genes are associated with an increased risk of LPE in Chinese male Han population. Specifically, LACTBLI located at 1p36.12, HCG27/HLA-C located at 6p21.33, TNFSF8/TNC located at 9q33.1, and FAM53B located at 10q26.13 can significantly increase the risk of LPE. We found that LACTBL1 polymorphism was associated with anthropometric characteristics (weight) among British population when we searched for previous studies [23]. The HCG27/HLA-C polymorphism has been identified as a novel susceptibility locus in the genome-wide association study of coronary artery disease [24]. The TNFSF8/TNC polymorphism is considered to be a susceptibility locus in genetic studies on the interaction between humans and mosquito bites [25]. In the

Fig. 1. Quantile-quantile plots (A) and Manhattan graph (B) of the results of the genome-wide association study. The red line in (B) represents the cut-off value of the suggestively genome-wide significance (5.0×10^{-6}), the chromosomes are displayed on the x-axis, while the y-axis represents the -log_{10} of the p-value.
Fei Wang, et al: GWAS for Lifelong Premature Ejaculation

In the genome-wide association study of the human metabolome, it was found that the FAM53B polymorphism was associated with the level of human metabolism [26]. However, studies between these genetic polymorphisms and LPE have never been reported. Our findings suggested that these polymorphisms may be associated with the risk of LPE. Our study have provided data supplement for LPE susceptibility loci, and laid a scientific foundation for the research on the pathogenesis of LPE.

In addition, we also found evidence that 20 genetic loci were associated with a reduction in the risk of LPE. Specifically, SSBP3/ACOT11 located at 1p323, LINC02486/TMEM154 located at 4q313, LINC01098/NONE located at 4q34.3, and SULF2 located at 20q13.12 can significantly reduce the LPE risk. After consulting the literature, it was found that the association between these gene polymorphisms and other complex diseases has been reported [27-31]. Although the study on association analysis between these genetic loci and LPE risk have never been reported, we were pleasantly surprised to find evidence that SULF2 may be potentially associated with the occurrence and development of LPE. SULF2 is an endosulfatase that...
can cleave 6-O-sulfate groups from HSPG. More importantly, multiple studies have reported that HSPG and leptin are related [32,33]. Leptin is an important factor in the 5-HT regulatory system, and it has been clinically proven that measuring plasma 5-HT and leptin levels can be used as objective diagnostic indicators for LPE [34]. The above studies suggest that the new genetic signal SULF2 identified by GWAS may associated with the occurrence and development of LPE. It will be very meaningful to further explore the mechanism of SULF2 in the occurrence and development of LPE. Our study have provided new ideas for elucidating the pathogenesis of LPE and the targeted therapy of PE.

However, it is worth noting that this study has certain limitations. The results of the power analysis for the sample size showed that the power ranged 17.1% to 57.4%. The smaller power may be caused by the small sample size. A large and extensive sample size is very necessary for genome-wide association studies of complex diseases. It will make the data highly reproducible and the results be more convincing. Therefore, subsequent studies are needed to verify the new genetic sig...
nals identified in this study.

CONCLUSIONS

All in all, this study was the first to conduct GWAS for LPE in Chinese male Han population. Thirty-three genetic polymorphisms have a suggestive genome-wide association with the risk of LPE. This study have provided data supplement for the genetic loci of PE susceptibility, and laid a scientific foundation for elucidating the pathogenesis of LPE and the targeted therapy of LPE.

ACKNOWLEDGEMENTS

We thank the Hainan General Hospital for providing blood samples and all the people involved in this study. This study was funded by National Natural Science Foundation of China: Project of Regional Science Foundation (No. 81560250).

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Weifu Wang and Liefu Ye conceived and designed the experiments; Defan Luo, Jianxiang Chen and Cuiping Pan performed the experiments; Zhongyao Wang and Housheng Fu collected samples; Jianbing Xu and Meng Yang analyzed the data; Shaowei Mo and Liying...
Zhuang contributed reagents/materials/analysis tools; Fei Wang and Defan Luo drafted and revised the paper.

Supplementary Material

Supplementary material can be found via https://doi.org/10.5534/wjmh.210084.

Data Sharing Statement

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Ye N, Huang Y, Zhao H, Li G. Association between the serotonin transporter linked polymorphic region and lifelong premature ejaculation: an updated meta-analysis of case-control studies. Medicine (Baltimore) 2020;99:e22169.
2. Raveendran AV, Agarwal A. Premature ejaculation - current concepts in the management: a narrative review. Int J Reprod Biomed 2021;19:5-22.
3. Gao P, Gao J, Wang Y, Peng D, Zhang Y, Li H, et al. Temperament-character traits and attitudes toward premature ejaculation in 4 types of premature ejaculation. J Sex Med 2021;18:72-82.
4. Hui J, Wang L, Liu R, Yang C, Zhang H, He S, et al. A bibliometric analysis of international publication trends in premature ejaculation research (2008-2018). Int J Impot Res 2021;33:86-95.
5. Li G, Chang D, Chen D, Zhang P, You Y, Huang X, et al. Selective dorsal neurotomy in the treatment of premature ejaculation: a protocol for systematic review and meta-analysis. Medicine (Baltimore) 2020;99:e21866.
6. Gao J, Zhang X, Su P, Liu J, Xia L, Yang J, 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;10:1874-81.
7. Althof S. The psychology of premature ejaculation: therapies and consequences. J Sex Med 2006;3 Suppl 4:324-31.
8. Donatucci CF. Etiology of ejaculation and pathophysiology of premature ejaculation. J Sex Med 2006;3 Suppl 4:303-8.
9. Waldinger MD. The neurobiological approach to premature ejaculation. J Urol 2002;168:2359-67.
10. Jern P, Santtila P, Johansson A, Varjonen M, Witting K, von der Pahlen B, et al. Evidence for a genetic etiology to ejaculatory dysfunction. Int J Impot Res 2009;21:62-7.
11. Ozbek E, Tasci AI, Tugcu V, Ilbey YO, Simsek A, Ozcan L, 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.
12. Roaiah MF, Elkhayat YI, Rashed LA, GamaEl Din SF, El Guindi AM, Soliman IF, et al. 5HT-1A receptor polymorphism effects ejaculatory function in Egyptian patients with lifelong premature ejaculation. Rev Int Androl 2019;17:138-42.
13. Janssen PK, Bakker SC, Rethelyi J, Zwinderman AH, Touw DJ, Olivier B, 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;6:276-84.
14. Santtila P, Jern P, Westberg L, Walum H, Pedersen CT, Eriksson E, et al. The dopamine transporter gene (DAT1) polymorphism is associated with premature ejaculation. J Sex Med 2010;7(4 Pt 1):1538-46.
15. Jern P, Westberg L, Johansson A, Jonsson L, Corander J, Sandnabba NK, et al. Are single nucleotide polymorphisms in the oxytocin and vasopressin 1A/1B receptor genes likely candidates for variation in ejaculatory function? BJU Int 2012;110(11 Pt C):E1173-80.
16. Albert PR, Le François B, Millar AM. Transcriptional dysregulation of 5-HT1A autoreceptors in mental illness. Mol Brain 2011;4:21.
17. Hirschhorn JN, Daly MJ. Genome-wide association studies for common diseases and complex traits. Nat Rev Genet 2005;6:95-108.
18. Althof SE, McMahon CG, Waldinger MD, Serefolgu EC, Shindel AW, Adaikan PG, 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.
19. Hoenicka J, Garrido E, Ponce G, Rodríguez-Jiménez R, Martínez I, Rubio G, et al. Sexually dimorphic interaction between the DRD1 and COMT genes in schizophrenia. Am J Med Genet B Neuropsychiatr Genet 2010;153B:948-54.
20. Janssen PK, van Schaik R, Waldinger MD, Serefolgu EC, Shindel AW, Adaikan PG, 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.
21. Althof SE, McMahon CG, Waldinger MD, Serefolgu EC, Shindel AW, Adaikan PG, 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.
Rs9303628 and rs2054847 of SLC6A4 are protective factors for the onset of lifelong premature ejaculation among the Chinese population. Andrologia 2021;53:e13650.

23. Tachmazidou I, Süveges D, Min JL, Ritchie GR, Steinberg J, Walter K, et al. Whole-genome sequencing coupled to imputation discovers genetic signals for anthropometric traits. Am J Hum Genet 2017;100:865-84.

24. Davies RW, Wells GA, Stewart AF, Erdmann J, Shah SH, Ferguson JF, et al. A genome-wide association study for coronary artery disease identifies a novel susceptibility locus in the major histocompatibility complex. Circ Cardiovasc Genet 2012;5:217-25.

25. Jones AV, Tilley M, Gutteridge A, Hyde C, Nagle M, Ziemek D, et al. GWAS of self-reported mosquito bite size, itch intensity and attractiveness to mosquitoes implicates immune-related predisposition loci. Hum Mol Genet 2017;26:1391-406.

26. Rhee EP, Ho JE, Chen MH, Shen D, Cheng S, Larson MG, et al. A genome-wide association study of the human metabolome in a community-based cohort. Cell Metab 2013;18:130-43.

27. Hong X, Hao K, Ladd-Acosta C, Hansen KD, Tsai HJ, Liu X, et al. Genome-wide association study identifies peanut allergy-specific loci and evidence of epigenetic mediation in US children. Nat Commun 2015;6:6304.

28. Xue A, Wu Y, Zhu Z, Zhang F, Kemper KE, Zheng Z, et al. Genome-wide association analyses identify 143 risk variants and putative regulatory mechanisms for type 2 diabetes. Nat Commun 2018;9:2941.

29. Bonás-Guarch S, Guindo-Martínez M, Miguel-Escalada I, Grarup N, Sebastian D, Rodriguez-Fos E, et al. Re-analysis of public genetic data reveals a rare X-chromosomal variant associated with type 2 diabetes. Nat Commun 2018;9:321.

30. Spracklen CN, Horikoshi M, Kim YJ, Lin K, Bragg F, Moon S, et al. Identification of type 2 diabetes loci in 433,540 East Asian individuals. Nature 2020;582:240-5.

31. Zhou H, Cheng Z, Bass N, Krystal JH, Farrer LA, Kranzler HR, et al. Genome-wide association study identifies glutamate ionotropic receptor GRIA4 as a risk gene for comorbid nicotine dependence and major depression. Transl Psychiatry 2018;8:208.

32. Joy MT, Vrbova G, Dhoot GK, Anderson PN. Sul1 and Sul2 expression in the nervous system and its role in limiting neurite outgrowth in vitro. Exp Neurol 2015;263:150-60.

33. Gougoula C, Bielfeld AP, Pour SJ, Sager M, Krüssel JS, Benten WPM, et al. Metabolic and behavioral parameters of mice with reduced expression of Syndecan-1. PLoS One 2019;14:e0219604.

34. Xia J, Zhang Q, Wang Y, Luan J, Yang J, Cong R, et al. Association of NE, leptin, and 5-HT with electrophysiological parameters in patients with primary premature ejaculation. Andrology 2020;8:1070-5.