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

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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 ($p<5\times10^{-6}$).

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

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-

tions.

3. Genotyping and quality control

In this study, we selcted Thermo Scientific Genotyping Chip (Thermo Fisher Scientific Inc., Waltham, MA, USA), and using Gene Titan 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, maker 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. We also constructed the relevant Manhattan graph and quantile-quantile graph. At the same time, we used online tools to conduct locus zoom plots of genetic loci significantly associated to LPE (https://statgen.github.io/localzoom/). Finally, in order to verify the reliability of the results, we also used GAS Power Calculator (https://csg.sph.umich.edu/abecasis/gas_power_calculator/) to perform 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, rs6825224), *LINC01098/NONE* (rs6837438, rs11736013, rs66508088, rs7698777, rs1510618, rs6814432, rs1110342, rs11735490, rs2063393, rs1022119), and *SULF2* (rs872111) may significantly reduce the PLE risk. 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	3.62±3.19	18.30±2.26	<0.0001
IELT (s)	687.49±350.27	69.59±32.47	<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.

Table 2. The association between genetic loci and LPE risk reached suggestive genome-wide significance

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
LINC02486; TMEM154	rs28689703	4	Intergenic	A	0.362	0.455	0.322–0.644	3.01E-06
LINC02486; TMEM154	rs6825224	4	Intergenic	G	0.367	0.446	0.315–0.632	1.65E-06
LINC01098; NONE	rs6837438	4	Intergenic	C	0.472	0.503	0.372–0.682	4.50E-06
LINC01098; NONE	rs11736013	4	Intergenic	C	0.471	0.488	0.359–0.663	2.07E-06
LINC01098; NONE	rs66508088	4	Intergenic	T	0.470	0.476	0.349–0.649	1.06E-06
LINC01098; NONE	rs7698777	4	Intergenic	G	0.465	0.485	0.356–0.661	2.10E-06
LINC01098; NONE	rs1510618	4	Intergenic	A	0.469	0.486	0.355–0.665	3.07E-06
LINC01098; NONE	rs6814432	4	Intergenic	G	0.469	0.486	0.355–0.665	3.07E-06
LINC01098; NONE	rs1110342	4	Intergenic	A	0.468	0.488	0.357–0.668	3.34E-06
LINC01098; NONE	rs11735490	4	Intergenic	C	0.468	0.489	0.357–0.669	3.44E-06
LINC01098; NONE	rs2063393	4	Intergenic	C	0.468	0.489	0.357–0.669	3.44E-06
LINC01098; NONE	rs1022119	4	Intergenic	G	0.468	0.489	0.357–0.669	3.44E-06
HCG27; 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.

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 (λ) 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 ($p < 5 \times 10^{-6}$). 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
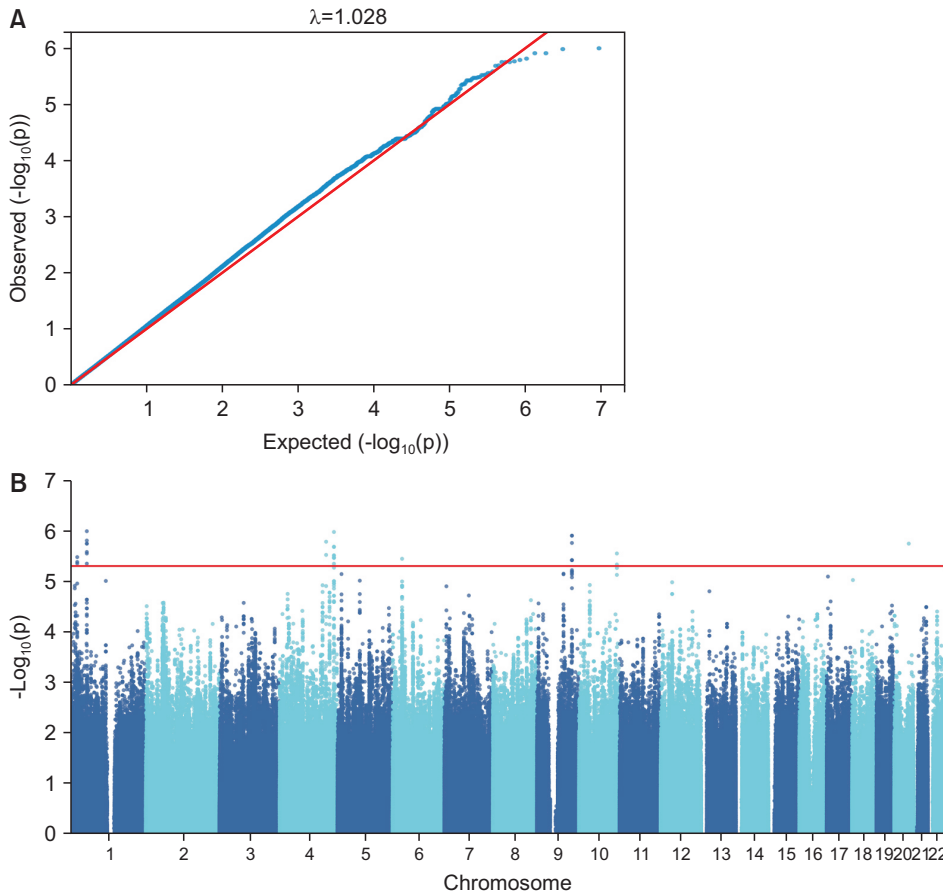
Fig. 1. Quantile-quantile plots (A) and Manhattan graph (B) of the results of the genome-wide association study. The red line in (B) represents the cut-off value of the suggestively genome-wide significance (5.0×10^{-6}), the chromosomes are displayed on the x-axis, while the y-axis represents the $-\log_{10}$ of the p-value.

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, *LACTBL1* 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
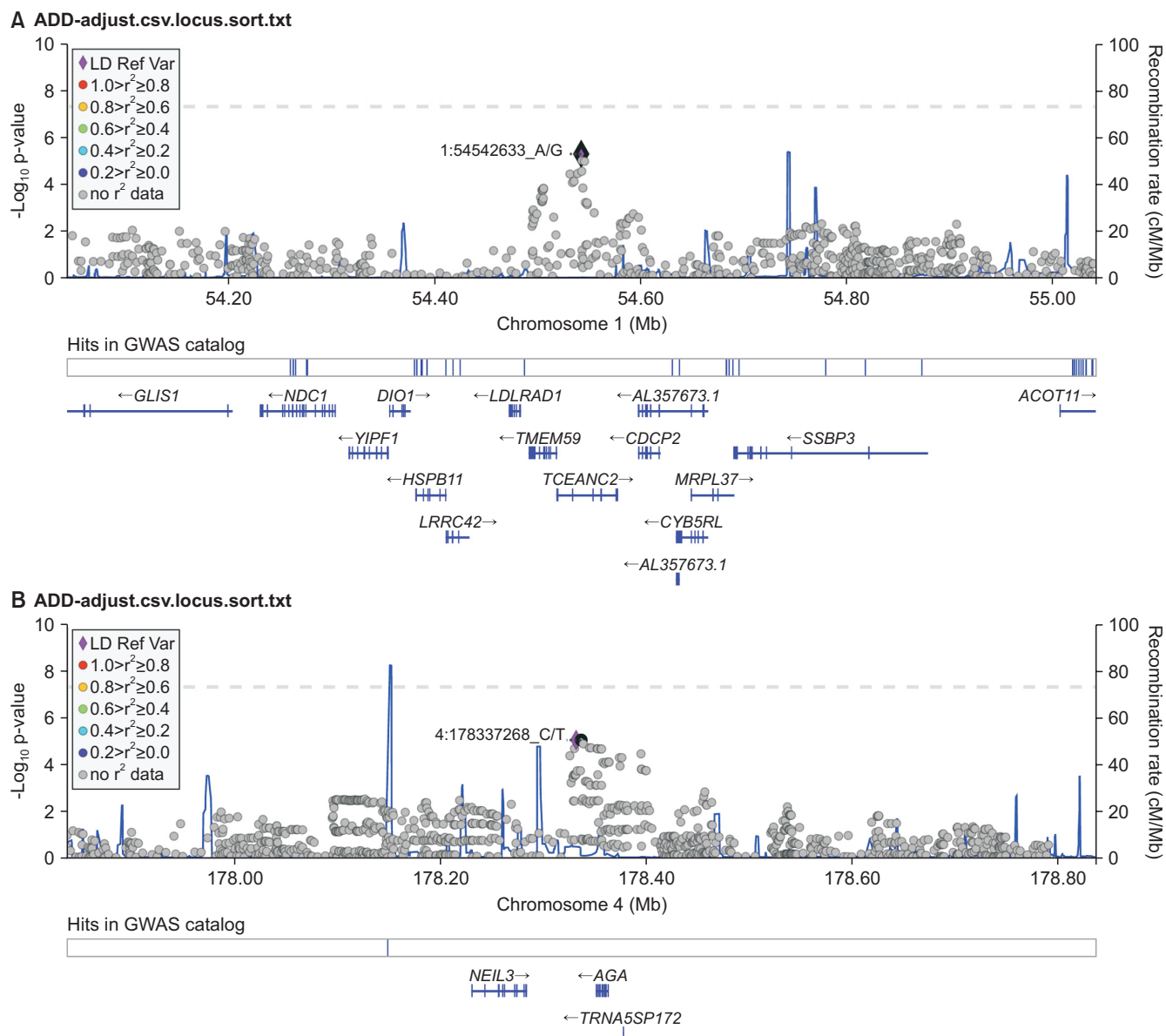
Fig. 2. A map of the associated regions on different chromosomes. (A) Associated region on chromosome 1. (B) Associated region on chromosome 4. (C) Associated region on chromosome 6. (D) Associated region on chromosome 9. (E) Associated region on chromosome 10. (F) Associated region on chromosome 20.

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 1p32.3, *LINC02486/TMEM154* located at 4q31.3, *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
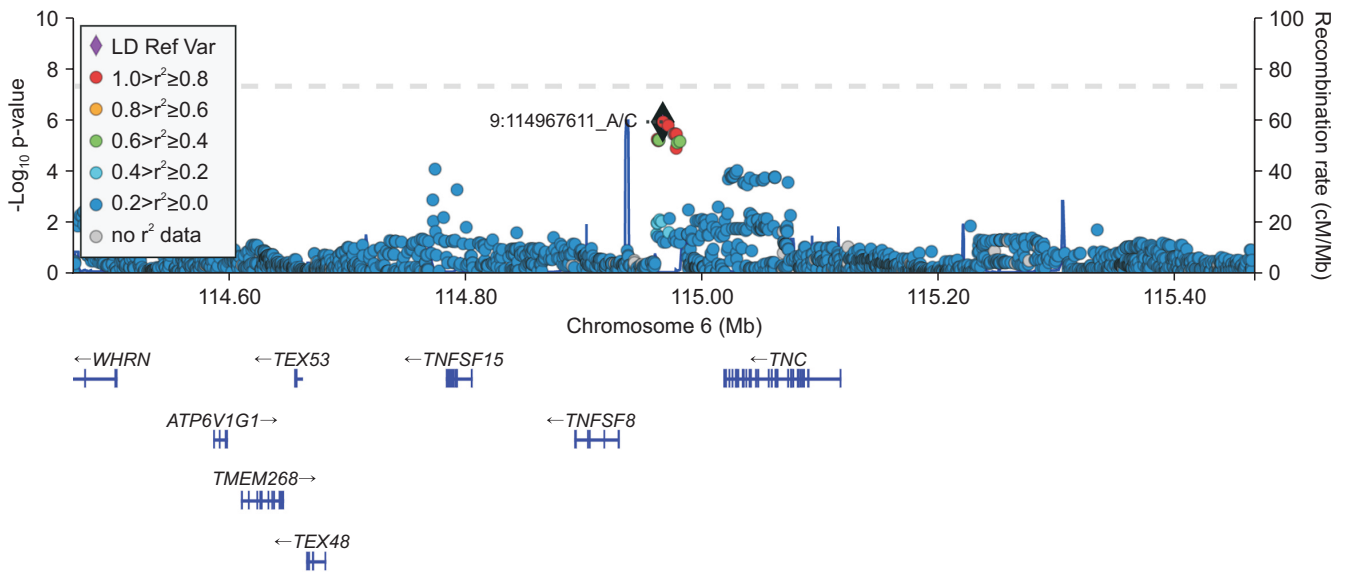
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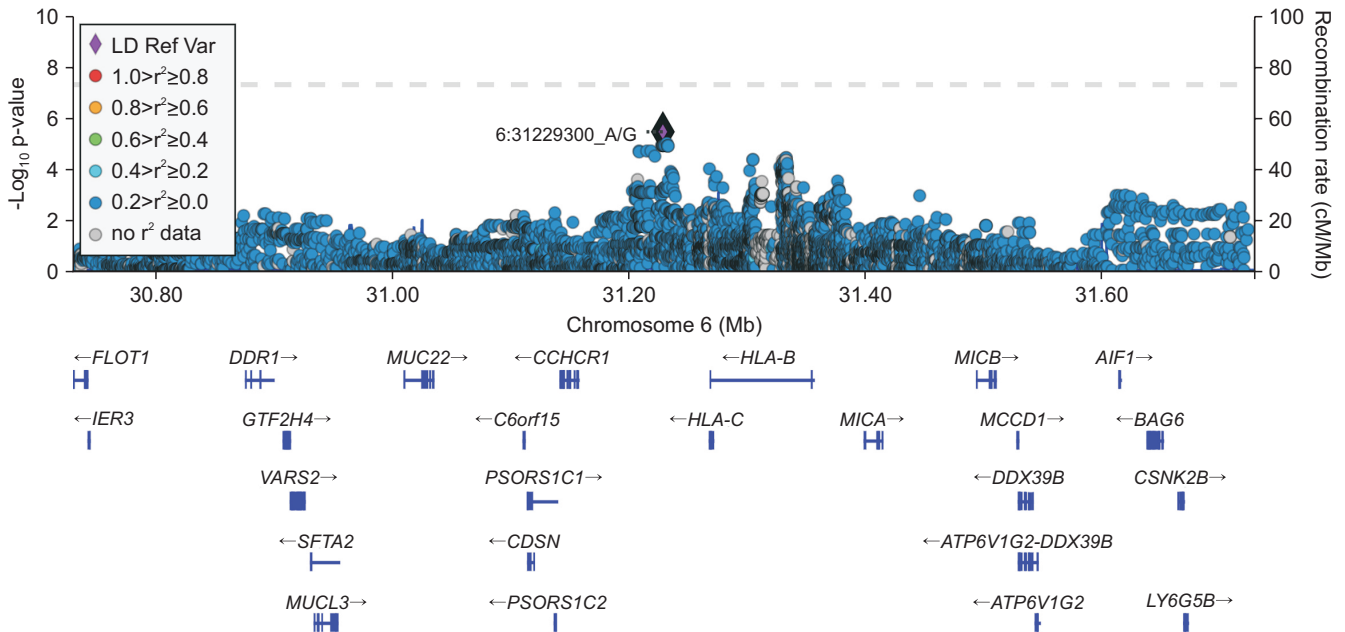
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Fig. 2. Continued 1.

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-
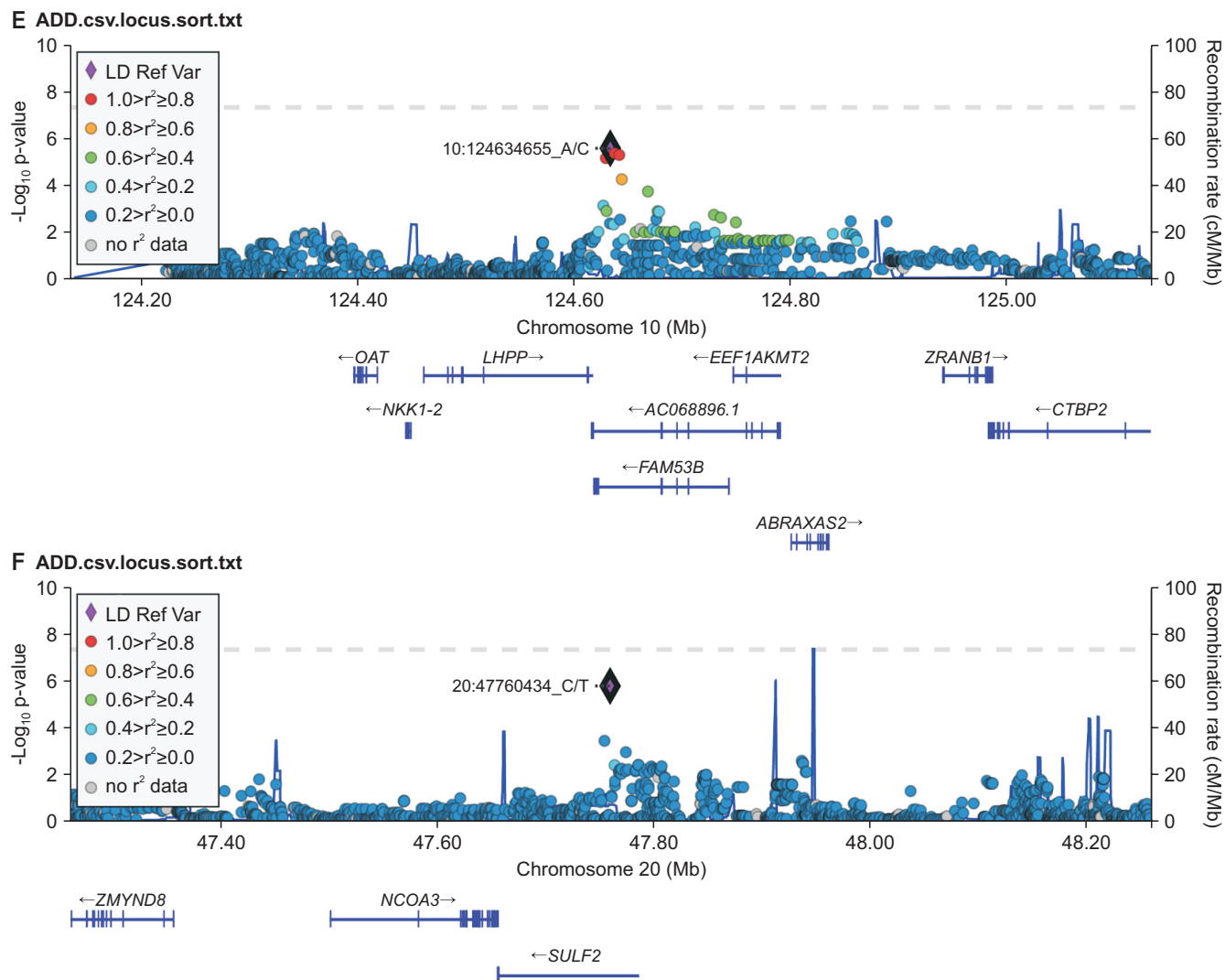
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Fig. 2. Continued 2.

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

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 Cuiqing 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.

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