ORIGINAL PAPER

Submitted: 13.03.2022
Accepted: 28.04.2022
Early publication date: 28.07.2022

Endokrynologia Polska
DOI: 10.5603/EP.a2022.0054
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 73; Number/Numer 5/2022

Genome-wide association study of fasting proinsulin, fasting insulin, 2-hour postprandial proinsulin, and 2-hour postprandial insulin in Chinese Han people

Leweihua Lin[1], Huibiao Quan[1], Tuanyu Fang[1], Lu Lin[1], Qianying Ou[1], Huachuan Zhang[2], Kaining Chen[1], Zhiguang Zhou[3]

[1]Department of Endocrinology, Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, Haikou, China
[2]Laboratory of Endocrine, Hainan General Hospital, Haikou, Hainan Province, China
[3]Department of Endosecretory Metabolic Diseases, The Second Xiangya Hospital of Central South University, Changsha, Hunan Province, China

Abstract

Introduction: Fasting proinsulin (FPI) and fasting insulin (FI) have been demonstrated to be associated with impaired β-cell function, T2DM, and insulin resistance. This genome-wide association study (GWAS) was performed to contribute to our understanding of the genetic basis of FPI, FI, 2-hour postprandial proinsulin (2hPI), and 2-hour postprandial insulin (2hI) of the pathophysiology of prediabetes in the Chinese population.

Material and methods: The levels of fasting plasma glucose (FPG), FPI, FI, 2hPI, and 2hI were examined by an automatic biochemical analyser. The Applied Biosystems™ Axiom™ Precision Medicine Diversity Array, the Gene Titan Multi-Channel instrument, and Axiom Analysis Suite 6.0 Software were used for genotyping. Imputation was performed with IMPUTE 2.0 software from HapMap, 1000 Genomes Phase 3 as a reference panel.

Results: Six single nucleotide polymorphisms (SNPs) in *DLG1-AS1, SORCS1,* and *CTAGE11P* for FPI, and 27 SNPs in *ZNF718, MARCHF2,* and *HNRNPM* for 2hPI reached genome-wide significance. Genome-wide significance was reached for associations of 6 SNPs in *KRT71* to FI. Also, 14 SNPs in *UBE2U, ABO,* and *GRID1-AS1* were genome-wide significant in their relationship with 2hI. Among these, the genetic loci of *CTAGE11P*, *MARCHF2, KRT71,* and *ABO* have the strongest association with FPI, 2hPI, FI, and 2hI.

Conclusions: The genetic variants of *CTAGE11P*, *MARCHF2, KRT71,* and *ABO* are significantly correlated with FPI, 2hPI, FI, and 2hI, respectively, in Chinese Han people. These genetic variants may serve as new biomarkers for the prevention of prediabetes. **(Endokrynol Pol 2022; 73 (5): 856–862)**

Key words: *GWAS; fasting proinsulin (FPI); fasting insulin (FI); 2hPI; 2hI*

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease caused by abnormal glucose metabolism, which is mainly characterized by hyperglycaemia. There are approximately 382 million people affected with DM worldwide, and type 2 diabetes mellitus (T2DM) accounts for 90% of DM patients [1, 2]. Prediabetes refers to blood glucose levels above normal but below diabetes thresholds. The prevalence of prediabetes is increasing worldwide, and it is estimated that 470 million people will suffer from prediabetes in 2030 [3]. In China, it is reported that the overall prevalence of diabetes is 10.9% and that for prediabetes it is 35.7% [4]. It has been demonstrated that prediabetes is a high-risk state of diabetes, and it also increases the risk of myocardial infarction, stroke, and cardiovascular death [5]. There is accumulating evidence to demonstrate that prediabetes could cause damage to the kidneys and the nervous system [6, 7]. Additionally, prediabetes imposes a huge economic burden on individuals and society [8]. Therefore, effective prevention strategies for prediabetes are increasingly important.

Proinsulin (PI), the precursor form of insulin (I), is synthesized and secreted in pancreatic β-cells. PI only accounts for 10–20% of fasting insulin (FI) under physiological conditions. However, some research indicates that the level of PI was highly expressed in glucose-intolerant and insulin-resistant individuals [9, 10]. Also, fasting proinsulin (FPI) has been demonstrated to be associated with impaired β-cell function, T2DM and insulin resistance, and it could be used as a specific predictor of T2DM [10, 11]. Insulin is a well-known hormone to reduce the level of blood glucose via the stimulation of glucose uptake into muscle cells and adipocytes, etc. by binding to its receptor in the target cells. It has been shown that elevated fasting insulin (FI) is a hallmark of T2DM [12]. Our previous study demonstrated that FPI, 2-hour postprandial proinsulin (2hPI), FI, and 2-hour postprandial insulin (2hI)

Huibiao Quan, #19 Xiuhua Road, Xiuying District, Haikou, Hainan Province, 570311, China, tel: +86 13876078153; e-mail: qhb13876078153@hainmc.edu.cn

were associated with an increased risk of prediabetes [13]. Despite these findings, it is still unclear how these common phenotypes affect T2DM.

In this study, we performed a genome-wide association study (GWAS) of FPI, 2hPI, FI, and 2hI in 451 prediabetes subjects from the Chinese Han population. The Biosystems™ Axiom™ Precision Medicine Diversity Array (PMDA) was used to identify single nucleotide polymorphisms (SNPs) associated with FPI, 2hPI, FI, and 2hI. Our study will provide an effective diagnostic method for early screening of people who are susceptible to T2DM, and for controlling and preventing the development of prediabetes to T2DM.

Material and methods

Participants

In this study, we recruited 451 prediabetes subjects aged ≥ 18 years from the Hainan Affiliated Hospital of Hainan Medical University. Participants with 100 mg/dL (5.6 mmol/L) ≤ fasting plasma glucose < 125 mg/dL (6.9 mmol/L) or 5.7% ≤ glycated haemoglobin (HbA_{1c}) < 6.4% were defined as prediabetes [14]. Individuals without a history of diabetes and malignant tumours, or severe liver and kidney diseases were included in this research. This study was conducted with ethical approval from the Hainan Affiliated Hospital of Hainan Medical University Ethics Committees, and was performed in line with the Declaration of Helsinki. We also obtained consent forms signed by each participant.

Metabolic variables

Fasting blood samples were collected from all subjects after an overnight fast. The levels of fasting plasma glucose (FPG), FPI, FI, 2hPI, and 2hI were examined by an automatic biochemical analyser.

Genotyping and imputation

Genomic DNA was isolated from a whole blood sample using a DNA Extraction Kit (GoldMag Co. Ltd., Xi'an, China), as described previously [15]. The Applied Biosystems™ Axiom ™ Precision Medicine Diversity Array (PMDA, Thermo Scientific, USA), the Gene Titan Multi-Channel instrument, and Axiom Analysis Suite 6.0 Software were used for genotyping.

Genotype data in subjects was cleaned using standard thresholds (HWE $p > 5 \times 10^{-6}$, call rate > 95%). Imputation for chromosomes 1 to 22 was performed with IMPUTE 2.0 software from HapMap 1000 Genomes Phase 3 as a reference panel.

Statistical analyses

The association analysis was conducted using Gold Helix SNP and Variation Suite 8.7 software. The association between SNPs and FPI, 2hPI, FI, and 2hI was evaluated using linear regression assuming an additive genetic model. The 4 traits were analysed with adjustments for age and sex. A $p < 5.0 \times 10^{-6}$ was used as the threshold of genome-wide significance.

Results

A total of 451 prediabetes individuals aged ≥ 18 years (216 men and 235 women) were included and genotyped in the present study. The average age of the subjects was 51.78 ± 14.49 years. The clinical parameters of participants are summarized in Table 1.

Table 1. *Participants characteristics*

Variable	Subjects
Number of individuals	451
Age (years, mean ± SD)	51.78 ± 14.49
Gender	
Male	216 (47.9%)
Female	235 (52.1%)
FPG [mmol/L]	5.88 ± 1.42
FPI [mU/L]	15.74 ± 12.18
2hPI [mU/L]	63.42 ± 44.10
FI [mU/L]	72.10 ± 43.08
2hI [mU/L]	578.22 ± 435.40

FPG — fasting plasma glucose; FPI — fasting proinsulin; 2hPI — 2-hour postprandial proinsulin; FI — fasting insulin; 2hI — 2-hour postprandial insulin; SD — standard deviation

As presented in Table 2, we found that 6 loci in 3 genes (*DLG1-AS1, SORCS1, CTAGE11P*) reached genome-wide significance associated with FPI, and 27 SNPs in 3 genes (*ZNF718, MARCHF2,* and *HNRNPM*) were associated with 2hPI. In addition, the correlation of 6 SNPs in the *KRT71* gene with FI reached genome-wide significance. Also, 14 SNPs in 3 genes (*UBE2U, ABO,* and *GRID1-AS1*) were genome-wide significant in their relationship with 2hI. The distributions of association p-values for FPI, 2hPI, FI, and 2hI are presented in Figure 1 (the quantile-quantile plots and Locus zoom are shown in Fig. S1 and Fig. S2). Among these, the genetic loci of *CTAGE11P*, *MARCHF2*, *KRT71*, and *ABO* have the strongest association with FPI, 2hPI, FI, and 2hI, respectively.

Discussion

The current study illustrated that the genetic variants of *CTAGE11P*, *MARCHF2*, *KRT71*, and *ABO* were significantly correlated with FPI, 2hPI, FI, and 2hI in Chinese Han people, respectively. Our research will provide scientific methods and ideas for the prevention and diagnosis of prediabetes, and it will contribute to controlling and reducing the progression of prediabetes to T2DM.

Recently, GWAS was performed by Strawbridge et al., which found that 9 SNPs in 8 genes were associated with FPI levels in the European population [16]. Subsequently, Huyghe et al. also identified low-frequency coding variants associated with FPI at SGM2 and MADD gene in Finnish males [17]. Moreover, it is suggested that IGF-1 genetic variants were associated with FI in European ancestry [18]. Manning et al. also observed that 6 SNPs in *COBLL1-GRB14*, *IRS1*, *PPP1R3B*, *PDGFC*, *UHRF1BP1*, and *LYPLAL1* are correlated with the FI level [19]. However, those SNPs explained only

Table 2. *Significant loci associated with fasting proinsulin (FPI), 2h proinsulin (2hPI), fasting insulin (FI), and 2h insulin (2hI) in study populations*

Gene	Traits	Description	SNP	Chr	Position	Allele	Minor allele	MAF	p
DLG1-AS1;LINC02012	FPI	DLG1 antisense RNA1	rs78022276	3	197482798	T/C	T	0.029	2.88E-06
DLG1-AS1;LINC02012	FPI	DLG1 antisense RNA1	rs78750477	3	197483030	C/G	C	0.029	2.88E-06
*SORCS*1	FPI	Sortilin related VPS10 domain containing receptor	rs58879794	10	106889263	C/A	C	0.150	3.94E-06
CTAGE11P	FPI	CTAGE family member 11, preudogene	rs9600432	13	75107716	A/C	A	0.453	1.42E-06
CTAGE11P	FPI		rs9565135	13	75122830	A/G	A	0.454	3.75E-06
CTAGE11P	FPI		rs9543852	13	75124005	T/G	T	0.454	2.51E-06
ZNF718	2hPI	Zinc finger protein 718	rs56128594	4	188333	T/C	T	0.446	5.88E-08
ZNF718	2hPI		rs4690234	4	192200	T/C	T	0.446	2.41E-08
*MARCHF*2	2hPI	Membrane associated ring-CH-type finger 2	rs12979798	19	8419748	G/A	G	0.395	4.05E-07
MARCHF2	2hPI		rs12978137	19	8420144	C/T	C	0.405	2.02E-08
MARCHF2	2hPI		rs62117527	19	8421448	C/T	C	0.405	2.02E-08
MARCHF2	2hPI		rs11259979	19	8435167	C/T	C	0.444	8.99E-07
MARCHF2	2hPI		rs12975669	19	8435935	T/G	T	0.445	1.20E-06
MARCHF2	2hPI		rs35562870	19	8436208	C/T	C	0.445	8.84E-07
*HNRNP*M	2hPI	Heterogeneous nuclear ribonuclaoprotein M	rs17160491	19	8448056	T/G	T	0.469	9.47E-07
HNRNPM	2hPI		rs2081197	19	8448452	A/C	A	0.439	7.83E-07
HNRNPM	2hPI		rs11666117	19	8449010	A/C	A	0.441	6.15E-07
HNRNPM	2hPI		rs11259983	19	8450491	A/C	A	0.447	4.20E-07
HNRNPM	2hPI		rs868781681	19	8450732	T/A	T	0.460	2.17E-06
HNRNPM	2hPI		rs200358539	19	8450735	T/A	T	0.459	1.97E-06
HNRNPM	2hPI		rs17160495	19	8451394	A/T	A	0.447	4.20E-07
HNRNPM	2hPI		rs11259985	19	8451793	A/T	A	0.447	4.20E-07
HNRNPM	2hPI		rs34337793	19	8454339	A/G	A	0.447	3.61E-07
HNRNPM	2hPI		rs34244685	19	8458122	T/C	T	0.441	6.40E-07
HNRNPM	2hPI		rs3764570	19	8463393	A/G	A	0.446	3.38E-07
HNRNPM	2hPI		rs3794997	19	8465003	A/T	A	0.446	3.38E-07
HNRNPM	2hPI		rs34445564	19	8468214	A/T	A	0.439	6.01E-07

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Table 2. *Significant loci associated with fasting proinsulin (FPI), 2h proinsulin (2hPI), fasting insulin (FI), and 2h insulin (2hI) in study populations*

Gene	Traits	Description	SNP	Chr	Position	Allele	Minor allele	MAF	p
HNRNPM	2hPI	Heterogeneous nuclear ribonuclaoprotein M	rs17159302	19	8469632	A/C	A	0.439	6.01E-07
HNRNPM	2hPI		rs17159303	19	8469677	G/A	G	0.446	3.38E-07
HNRNPM	2hPI		rs74180130	19	8479935	C/T	C	0.452	1.19E-06
HNRNPM	2hPI		rs17160520	19	8483705	G/A	G	0.453	1.01E-06
HNRNPM	2hPI		rs2277987	19	8487389	A/G	A	0.440	5.76E-08
HNRNPM	2hPI		rs1599870	19	8488516	G/A	G	0.440	6.62E-08
KRT71	FI	Keratin 71	rs12308719	12	52548451	G/T	G	0.482	2.31E-06
KRT71	FI		rs10876309	12	52548517	C/T	C	0.482	2.31E-06
KRT71	FI		rs3803084	12	52548843	A/G	A	0.495	1.02E-06
KRT71	FI		rs3803085	12	52548910	C/T	C	0.483	1.08E-06
KRT71	FI		rs4761930	12	52549360	G/A	G	0.487	1.52E-06
KRT71	FI		rs4761933	12	52555091	C/T	C	0.491	2.12E-06
UBE2U	2hI	Ubiquitin conjugating enzyme E2 U	rs11585260	1	64315831	G/C	G	0.024	4.94E-06
UBE2U	2hI		rs11577590	1	64315842	C/G	C	0.024	4.94E-06
ABO	2hI	Alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosaminyltransferase	rs9411372	9	133258677	A/G	A	0.138	9.59E-07
ABO	2hI		rs977371848	9	133266456	T/C	T	0.163	1.56E-07
ABO	2hI		rs879055593	9	133271182	T/C	T	0.163	1.56E-07
ABO	2hI		rs992108547	9	133273983	A/G	A	0.163	1.56E-07
ABO	2hI		rs947073006	9	133274414	A/G	A	0.163	1.56E-07
ABO	2hI		rs600038	9	133276354	C/T	C	0.159	7.95E-07
ABO	2hI		rs651007	9	133278431	T/C	T	0.159	3.84E-07
ABO	2hI		rs579459	9	133278724	C/T	C	0.159	3.84E-07
ABO	2hI		rs495828	9	133279294	T/G	T	0.159	3.84E-07
ABO	2hI		rs635634	9	133279427	T/C	T	0.159	3.84E-07
LINC01520;GRID1-AS1	2hI	GRID1 antisense RNA1	rs375709957	10	85558056	T/A	T	0.176	1.87E-06
LINC01520;GRID1-AS1	2hI		rs77136415	10	85558059	T/C	T	0.176	1.87E-06

SNP — single nucleotide polyphormisms; Chr — chromosome; MAF — minor allele frequency

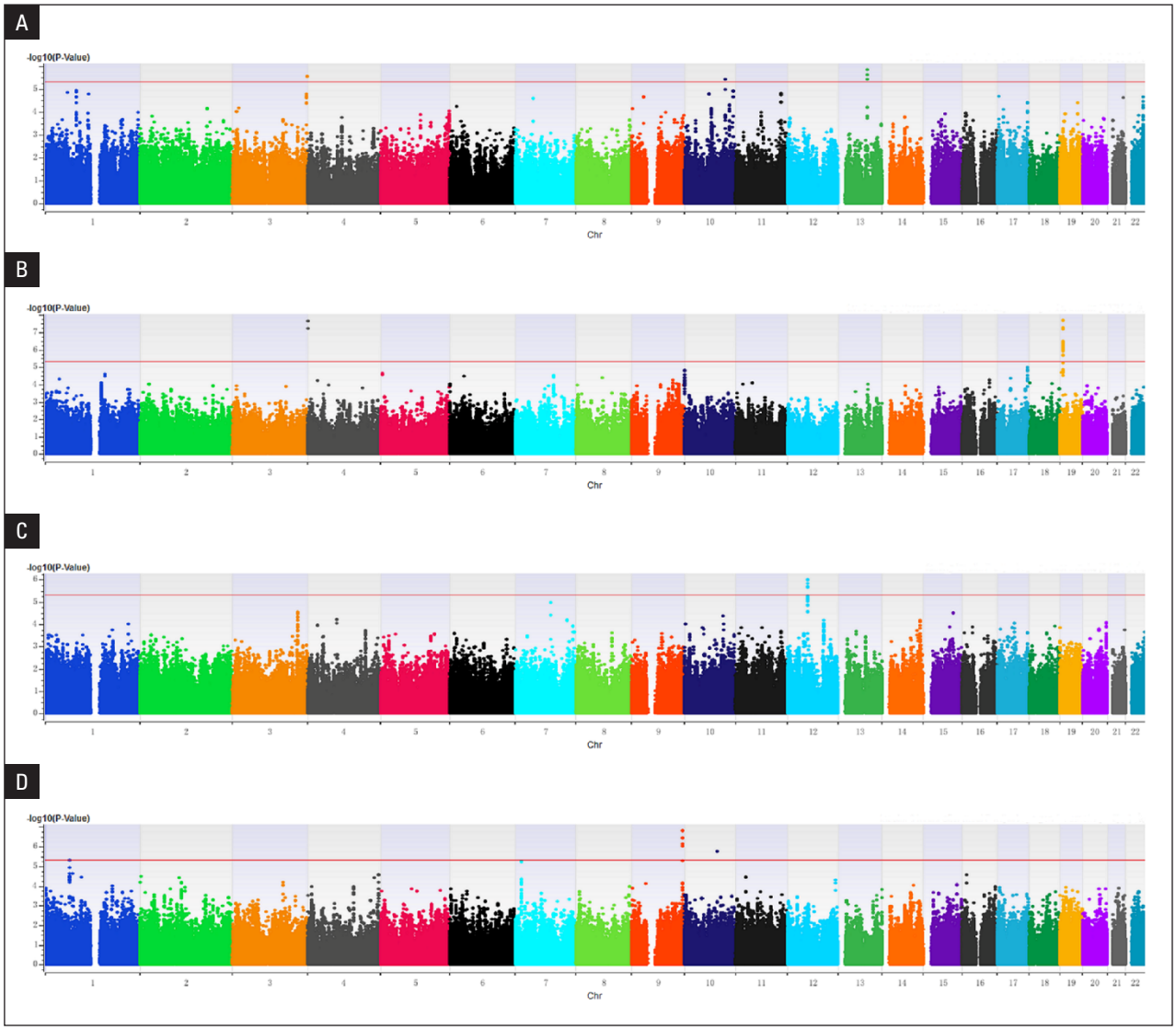

Figure. 1 *Manhattan plot for loci associated with fasting proinsulin (FPI)* (**A**)*, 2-hour postprandial proinsulin (2hPI)* (**B**)*, fasting insulin (FI)* (**C**)*, and 2-hour postprandial insulin (2hI)* (**D**)

a small percentage of the total variation in FPI and FI. In the present study, we found 6 SNPs in *DLG1-AS1*, *SORCS1*, and *CTAGE11P* for FPI, 27 SNPs in *ZNF718*, *MARCHF2*, and *HNRNPM* for 2hPI, 6 SNPs in *KRT71* for FI, and 14 SNPs in *UBE2U*, *ABO*, and *GRID1-AS1* for 2hI. Among these, the genetic variants of *CTAGE11P*, *MARCHF2*, *KRT71*, and *ABO* have the strongest association with FPI, 2hPI, FI, and 2hI.

The E3 ubiquitin ligase membrane-associated ring-CH-type finger 2 (*MARCHF2*) is a member of the membrane-associated RING-CH E3 ubiquitin ligase family (*MARCH*) and localizes to the endoplasmic reticulum and Golgi [20]. The known substrate of *MARCHF2* includes cystic fibrosis transmembrane conductance regulator (*CFTR*) [21]. Some studies have indicated that patients with *CFTR* gene variants show an insufficiency of insulin secretion, leading to the development of DM [22, 23]. Moreover, Khan et al. found that inhibition of *CFTR* decreased the concentrations of plasma insulin and pancreatic insulin in *CFTR*-inhibited animals [24]. Another study demonstrated that the mutation of *CFTR* is associated with insulin resistance and decreased β-cell mass in mice [25]. This evidence led us to believe that *MARCHF2* is involved in the development of pancreas and DM by interacting with *CFTR*.

Keratin 71 (*KRT71*) is a member of the keratin family and is located on chromosome 12q13.13. Keratin constitutes the intermediate filament proteins of epithelial cells. It is documented that the loss of keratin 8 decreased fasting blood glucose levels, and increased glucose uptake and glycogen synthesis [26, 27]. The abnormal expression of keratin 1 and 10 reduced insulin secretion, thus leading to the development of DM [28].

The ABO gene encodes glycosyltransferases that catalyse the transfer of nucleotide donor sugars to the H antigen to form the A and B antigens. Variation in the ABO gene is the basis of the ABO blood group. Meo et al. found that blood group "B" is associated with a higher risk of T2DM, while blood group "O" has a weak correlation with T2DM [29]. Also, a GWAS reported that ABO variants are associated with increased levels of plasma lipid and soluble intercellular adhesion molecule 1 and tumour necrosis factor 2 (TNF-2). These molecules could affect insulin and its receptors and contribute to the development of DM [30].

CTAGE family member 11 pseudogene (*CTAGE11P*) belongs to the cutaneous T-cell lymphoma-associated antigen (CTAGE) family and is located on 13q22.2. It is reported that the mutation of family members reduces cholesterol and triglyceride levels in mice [31]. Another family member can regulate the plasma low-density lipoprotein-cholesterol concentration and is associated with coronary artery disease [32]. Our study found for the first time that *CTAGE11P* genetic variants are associated with FPI in the Chinese people.

Conclusions

We found that the genetic variants of *CTAGE11P*, *MARCHF2*, *KRT71*, and *ABO* are significantly correlated with FPI, 2hPI, FI, and 2hI in Chinese Han people, respectively. These genetic variants may serve as new biomarkers for the prevention of prediabetes.

Conflict of interest
All authors declare that they have no competing interests.

Funding
This study received the support of the major research and development program of Hainan Province (no. ZDYF2021SHFZ078), and received the support of project supported by Hainan Province Clinical Medical Center.

Acknowledgments
The authors thank all participants and volunteers in this study. We also thank the Hainan Affiliated Hospital of Hainan Medical University for their help with sample collections.

Data availability statement
The data that support the findings of this study are available from the supporting information files of this manuscript.

Ethical approval
This study was conducted with ethical approval from the Hainan Affiliated Hospital of Hainan Medical University Ethics Committees, and it was performed in line with the Declaration of Helsinki. We also obtained consent forms signed by each participant.

Consent to participate
Not applicable.

Code availability
Not applicable.

Authors' contributions
Le.L. and H.Q. designed this study protocol and drafted the manuscript; T.F. and Lu.L. performed the DNA extraction and genotyping; Q.O. performed the data analysis; H.Z. performed the sample collection and information recording; K.C. and Z.Z. revised the manuscript; H.Q. conceived and supervised the study. All authors read and approved the final manuscript.

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