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Joint effect of *CENTD2* and *KCNQ1* polymorphisms on the risk of type 2 diabetes mellitus among Chinese Han population

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ABSTRACT

Genome-wide association studies (GWAS) in populations of European ancestry have identified nine single nuclear polymorphisms (SNP) on chromosome 11 related to type 2 diabetes (T2D) susceptibility. Herein, we further evaluate the association of these SNPs and T2D in a Chinese Han population. We performed a case-control study of 2925 T2D cases and 3281 controls to evaluate the association of five SNPs of *KCNJ11*, *MTNR1B*, *CENTD2* and *LOC387761* and T2D in addition to the previously reported four SNPs of *KCNQ1*. Multiple logistic regression was used to evaluate SNP's effect by adjustment for confounding factor age, sex and BMI. In the first stage, SNPs rs1552224 at *CENTD2* were significantly associated with T2D and the association was statistically significant in the whole study population ($P = 0.001$) although it was not replicated in the second stage. rs1552224 and rs2237897 of *KCNQ1* showed significant joint effect on T2D and there was a significant decreased risk of T2D with the number increase of risk alleles (P for trend $= 3.81 \times 10^{-17}$). Compared to those without carrying any risk allele, individuals carrying one, two, and three or four risk alleles had a 30.7%, 44.8% and 62.0% decreased risk for developing T2D, respectively. Our finding suggests that genetic variant rs1552224 of *CENTD2* on chromosome 11 contributes to an independent effect as well as joint cumulative effect with rs2237897 of *KCNQ1* on the risk of T2D in Chinese Han population, and further functional research would be warranted.

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Introduction

Diabetes mellitus (DM) is due to an absolute or relative lack of insulin induced chronic endocrine and metabolic disease, characterized by hyperglycemia, and more than 90% of that are type 2 diabetes mellitus (T2D) (Clark and Kinney, 1992). T2D is a chronic and complex disease and both genetic and environmental factors contribute to the etiology.

More than 30 genome-wide association studies (GWAS) screening search the susceptibility genes for T2D and more than 250 single nucleotide polymorphisms (SNPs) were identified to be associated with T2D or related traits including impaired fasting glucose (IFG), impaired glucose tolerance (IGT), homeostatic model assessment of insulin resistance (HOMA-IR), HOMA of β-cell function (HOMA-B), area under the curve of insulin (AUCi), the area under the curve of glucose (AUCg), the change of glucagon-likepeptide1(GLP-1) level as well as obesity in European-ancestry population particularly in Caucasian populations (Diabetes Genetics Initiative of Broad Institute of Harvard and MIT et al., 2007; Li et al., 2013; Palmer et al., 2010; Ruchat et al., 2010). The findings confirmed the important role of genetic determinants in the pathogenesis of T2D (Grant et al., 2006; Hayes et al., 2007; Palmer et al., 2010; Rampersaud et al., 2007; Reiman, 2007; Rich et al., 2009; Ruchat et al., 2009a; Saxena et al., 2007; Tan et al., 2010; Tsai et al., 2010). Some susceptible loci for T2D identified from GWAS were further replicated in other ethics populations (Duesing et al., 2008; Grant et al., 2006; Ruchat et al., 2009a, 2009b; Tsai et al., 2010; Zeggini et al., 2007), whereas there is some differential risk loci for T2D among different racial populations (Kong et al., 2009; Palmer et al., 2010; Reiling et al., 2010; Richards et al., 2009; Ruchat et al., 2009a; Tsai et al., 2010). Given the considerable differences in genetic heterogeneity across ethnic groups, it is necessary to further investigate and evaluate the genetic effect of GWAS-identified SNPs on T2D in non-European populations. Identical research results across ethic populations will help to elucidate and well understand the pathogenesis mechanism of T2D and related traits, as well as provide a scientific research basis improving individualized drug therapy for patients with T2D.

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GWAS have identified 9 SNPs associated with T2D at five genes, *KCNJ11*, *KCNQ1*, *MTNR1B*, *CENTD2* and *LOC387761* on chromosome 11 in the European populations (Diabetes Genetics Initiative of Broad Institute of Harvard and MIT et al., 2007; Tsai et al., 2010; Yasuda et al., 2008; Scott et al., 2007). Previously, we have reported that four SNPs of *KCNQ1* were significantly associated with T2D in Chinese Han (Lin et al., 2013). Herein, we sought to test the association of the remain five GWAS-identified SNPs at *KCNJ11*, *MTNR1B*, *CENTD2* and *LOC387761* on chromosome 11 and T2D by a case-control study of 2925 T2D cases and 3281 controls and further evaluate whether there is interaction between different loci.

Methods

Participants

In this study, a two-stage case-control study was conducted by a community-based epidemiological survey and the subjects aged over 30 years old were enrolled. The first-stage (discovery-phase) which was used to generate the hypothesis consisted of 1200 cases and 1200 age- and sex-matched healthy controls in an urban community of Wuxi, Jiangsu province, China. The second stage which was used to replicate the hypothesis from stage 1 recruited 3806 subjects including 1725 T2D cases and 2081 age- and sex-matched healthy controls from Changzhou and Nantong areas next to Wuxi. T2D case was defined as having a self-reported history of T2D or impaired fasting glucose ≥7.0 mmol/L, and the controls with fasting blood glucose (FBG) <5.6 mmol/L were included, whereas those who had a history of diabetes, coronary heart disease, stroke or cancer disease were excluded. All participants in this study were unrelated Han Chinese.

A questionnaire by interview was managed to collect the information including demographic characteristics, disease history, family history of diabetes and individual's habits. All the participants received physical examination and height, weight, waist and hip circumferences and blood pressure were measured. Body mass index (BMI) was calculated as weight (in kilograms) divided by the square of height (in meters).

Blood samples were drawn after 10 hours of overnight fasting to measure total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and glucose (GLU).

This study was approved by the Ethical Committee of Nanjing Medical University. Written informed consent was obtained from all participants prior to interview.

SNP genotyping

Genomic DNA was extracted from a leukocyte pellet by proteinase K digestion, phenol-chloroform extraction and ethanol precipitation. DNA integrity was checked by electrophoresis method on 1% agarose gels. UV spectrophotometer was used to detect DNA concentration and the ratio value 1.8–1.9 of wavelengths 260 and 280 was accepted for further genotyping. All nine GWAS-identified SNPs on chromosome 11 in association with T2D (Supplementary Fig. S1) have a minor allele frequency (MAF) over 0.05 in Chinese Beijing (CHB) population. The tool online of LD TAG SNP (TagSNP) selection (http://snpinfo.niehs.nih.gov/snpinfo/snptag.htm) was used to calculate linkage disequilibrium (LD) and 7 SNPs available showed low LD value in CHB (Supplementary Fig. S2A and S2B).

We further predict the SNP's biological function by using FastSNP (http://fastsnp.ibms.sinica.edu.tw/) and 7 SNPs were predicted to be linked to some certain biological function (Supplementary Table S1).

Besides of the four SNPs in *KCNQ1* reported in the previous study, in this study we further genotyped the remained five GWAS-identified SNPs on chromosome 11 including rs5215 and rs5129 at *KCNJ11*, rs9300039 at *LOC387761*, rs1552224 at *CENTD2* and rs1387153 at *MTNR1B*. At the first stage (discovery stage), genotyping was performed using the TaqMan OpenArray Genotyping System (Life Technologies, Carlsbad, USA) as previously reported in detail (Lu et al., 2012a). DNA samples with standardized concentration were loaded and amplified on 48-sample arrays following the manufacturer's protocol. For quality control, the equal amounts of cases and controls and two no template controls (NTCs) were simultaneously detected in each chip. The successful call rates were over 99.9% for all 5 SNPs.

In the second stage (replication stage) with 1725 T2D cases and 2081 controls, iPLEX Sequenom MassARRAY platform (Sequenom, Inc) was used to genotype the significant SNP from the discovery stage. Genotyping was conducted blindly for all samples and two NTCs in each 384-sample plate were used for quality control. The overall call rates were >99% for the four SNPs.

Statistical analyses

The allele frequencies and genotype distributions of the cases and controls were compared by two-sided chi-squared (χ^2) tests. Among the controls, the genotype frequencies for each SNP were tested using Fisher's exact χ^2 test for Hardy–Weinberg equilibrium (HWE) (Guo and Thompson, 1992). A logistic regression model was used to calculate the odds ratio (OR) and 95% confidence interval (95% CI) as well as adjust for covariates including age, sex and BMI. Additionally, a general linear model (GLM) was applied to analyze the difference of the FBG levels between the genotypes and age, sex and BMI were adjusted. Bonferroni correction was used for multiple comparison tests. The joint effect of multiple SNPs on the risk of T2D was assessed by logistic regression model categorizing the participants into groups according to the number of risk alleles carried and individuals with no risk alleles served as the reference group. Two-tailed P value of ≤0.05 was defined to be statistically significant. All the statistical analysis was performed with Statistical Product and Service Solutions 15.0 (SPSS; SPSS Inc, Chicago, IL, USA).

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of the two stage populations were summarized in Table 1. No significant differences of sex were observed in both stages and the combined population ($P > 0.05$). T2D case group was about 1 year higher than control group ($P < 0.05$) although age group (5 years) matching method was used. As expected, T2D cases generally had significantly higher levels of BMI and FBG compared with controls in both two stages and combined study population respectively ($P < 0.05$).

Association analysis for T2D

The genotype distributions of the five SNPs were all in Hardy–Weinberg equilibrium ($P > 0.1$). Association analysis showed that SNP rs1552224 was significantly associated with T2D with a P value less than 0.01 in the discovery stage of 2400 individuals (Table 2). After adjustment for age, sex and BMI, the OR (95%CI) of additive model was 0.715 (0.575–0.889) and P values was 0.003. Thus, the significant SNP rs1552224 from the discovery stage entered the second stage for replication but the association was not repeated after adjustment for confounding factors (Table 2). The joint analysis

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