ARTICLE

Variants in *KCNQ1* are associated with susceptibility to type 2 diabetes in the population of mainland China

Y. Liu · D. Z. Zhou · D. Zhang · Z. Chen · T. Zhao ·
Z. Zhang · M Ning · X. Hu · Y. F. Yang · Z. F. Zhang ·
L. Yu · L. He · H. Xu

Abstract

Aims/hypothesis Two recent genome-wide association studies have identified several novel type 2 diabetes susceptibility variants in intron 15 of the *KCNQ1* gene. We aimed to evaluate the effects of the variants in *KCNQ1* on type 2 diabetes and metabolic traits in the population of mainland China.

Methods Three candidate single nucleotide polymorphisms were genotyped in 1,912 individuals with type 2 diabetes and 2,041 normal controls using the ligase detection reaction method.

Results We confirmed the association of *KCNQ1* with type 2 diabetes in the population of mainland China. Allele frequency ORs of the three single nucleotide polymorphisms (SNPs) were: rs2237892 (OR 1.19, 95% CI 1.08–1.31, $p=3.0\times10^{-4}$); rs2237895 (OR 1.20, 95% CI 1.09–1.32, $p=1.9\times10^{-4}$); and rs2237897 (OR 1.24, 95% CI 1.13–1.36, $p=3.9\times10^{-5}$). We also found a significant difference in the distribution of the global haplotypes between the type 2 diabetes group and the normal control group ($p=2.6\times10^{-5}$). In addition, in the control group SNP rs2237892 was marginally associated with increasing fasting plasma glucose and SNPs rs2237892 and rs2237897 were associated with HbA$_{1c}$. Furthermore, for all three variants, homozygous carriers of the diabetes-associated allele had significantly decreased BMI and waist circumferences.

Conclusions/interpretation Our investigation confirmed the effects of *KCNQ1* variants on type 2 diabetes risk in the Chinese population.

Keywords Association · *KCNQ1* · Mainland Chinese population · Type 2 diabetes

Y. Liu and D. Z. Zhou contributed equally to this study.

Y. Liu · D. Z. Zhou · D. Zhang · Z. Chen · T. Zhao · Z. Zhang ·
M. Ning · Y. F. Yang · L. He (✉) · H. Xu (✉)
Key Laboratory of Nutrition and Metabolism, Institute for
Nutritional Sciences, Shanghai Institutes for Biological Sciences,
Graduate School of the Chinese Academy of Sciences,
Chinese Academy of Sciences,
294 Taiyuan Road,
Shanghai 200031, People's Republic of China
e-mail: helin@bio-x.cn
e-mail: hexuc@yahoo.com.cn

Y. Liu · D. Z. Zhou · D. Zhang · Z. Chen · T. Zhao · Z. Zhang ·
M. Ning · Y. F. Yang · L. Yu · L. He · H. Xu
Bio-X Center, Shanghai Jiao Tong University,
Shanghai, People's Republic of China

X. Hu
Ruijin Hospital, Luwan Branch,
Shanghai, People's Republic of China

Z. F. Zhang
Department of Epidemiology, UCLA School of Public Health,
Los Angeles, CA, USA

L. He
Institutes of Biomedical Sciences, Fudan University,
Shanghai, People's Republic of China

Abbreviations
LD   Linkage disequilibrium
PAR   Population attributable risk
SNP   Single nucleotide polymorphism

Introduction

Type 2 diabetes is a major health problem affecting more than 200 million individuals worldwide. Its prevalence is

increasing in many countries, especially in the developing countries [1]. For example, the total number of people with diabetes in China is estimated to increase from 20.8 million in 2000 to 42.3 million by 2030. Type 2 diabetes is characterised by the presence of insulin resistance and pancreatic beta cell dysfunction, resulting from the interaction of genetic and environmental factors.

So far a few genes, identified through linkage scans or the candidate gene approach, have been confirmed as being associated with type 2 diabetes e.g. *PPARG*, *KCNJ11* and *TCF7L2* [2–4]. Recently, the use of genome-wide association scans as an investigative tool has led to a qualitative leap in identifying diabetes-related genes. Genome-wide association studies conducted in large-scale case–control samples by several independent European and American research groups have identified several novel genes and loci with modest effects on the risk of type 2 diabetes (OR 1.14–1.20), such as *SLC30A8*, *HHEX*, *CDKAL1*, *CDKN2A*, *CDKN2B*, *IGF2BP2* and *FTO* [5–10]. These studies have been replicated and results confirmed in several other ethnic groups [11–17].

The two most recent genome-wide association studies, in the Japanese population, have identified the association of a novel gene (*KCNQ1*) with the risk of type 2 diabetes; a similar association was also detected in some Asian and European populations in these studies [18, 19]. Recently, Tan et al. also found variants in *KCNQ1* to be associated with type 2 diabetes, fasting glucose and beta cell function in 3,734 individuals belonging to three ethnic groups living in Singapore [20]. It is well known that there are significant differences in the frequencies of some genetic variations among different ethnic groups and geographic regions. Therefore, we decided to investigate further the contribution of *KCNQ1* to the aetiology of type 2 diabetes and to determine whether variants of the *KCNQ1* gene were associated with the susceptibility to type 2 diabetes and diabetes-related metabolic traits in the population of mainland China. We also used haplotype analysis and the best-fitting model test in our investigation.

Methods

Participants In this study, 3,953 Chinese Han participants were recruited from Shanghai, China; these comprised 1,912 unrelated type 2 diabetic individuals (785 men, 1,127 women; age 63.9±9.5 years) and 2,041 control individuals (635 men, 1,406 women; age 58.1±9.4 years). The study population overlapped completely with that used in our previous study [16]. Diabetic participants were defined in accordance with WHO criteria. Controls with a fasting plasma glucose concentration <6.1 mmol/l were enrolled from the same geographical region. A standard informed consent procedure was included in the protocol, and was reviewed and approved by the Ethics Committee of the Shanghai Institute for Biological Sciences. Participants gave their consent after the nature of study had been fully explained.

Blood samples were drawn for biochemical measurements (fasting plasma glucose, HbA$_{1c}$, total cholesterol, triacylglycerol, HDL-cholesterol and LDL-cholesterol). Height, weight, waist and hip circumferences, and blood pressure were measured in all individuals. Data are showed as medians (25–75% range) or means±SD (Table 1).

Single nucleotide polymorphism selection For the *KCNQ1* gene, five single nucleotide polymorphisms (SNPs) (rs2237892, rs2237895, rs2237897, rs2074196 and rs2283228) were identified as having the most significant association with type 2 diabetes based on previous studies

Table 1 Clinical characteristics of the study participants

Characteristic	Type 2 diabetes	Controls
Number	1,912	2,041
Men/women (n/n)	785/1,127	635/1,406
Age (years)	63.9±9.5	58.1±9.4
BMI (kg/m^2)	25.3±3.48	24.5±3.24
Waist to hip ratio	0.89±0.06	0.86±0.06
Fasting blood glucose (mmol/l)	7.42 (6.08–9.49)	4.89 (4.51–5.25)
Triacylglycerol (mmol/l)	1.51 (1.07–2.19)	1.34 (0.94–1.91)
Total cholesterol (mmol/l)	4.40 (3.82–5.03)	4.44 (3.9–5.02)
HDL-cholesterol (mmol/l)	1.14 (0.96–1.35)	1.22 (1.03–1.46)
LDL-cholesterol (mmol/l)	2.7 (2.24–3.2)	2.74 (2.33–3.26)
Systolic blood pressure (mmHg)	140 (127–151)	130 (120–141)
Diastolic blood pressure (mmHg)	80 (76–90)	80 (74–89)
HbA$_{1c}$ (%)	7.11 (6.38–8.31)	5.80 (5.46–6.11)
Obesity (%)	20.7	14.1

Data are medians (25–75% range) or means±SD

[18–20]. After considering the linkage disequilibrium (LD) structure based on HapMap Han Chinese and the pairwise linkage disequilibrium D' and r^2 values, we used rs2237892 to represent rs2074196 and rs2283228 ($r^2 = 0.73$ and 0.95, respectively) and thus selected three representative variants (rs2237892, rs2237895 and rs2237897) to be genotyped in our study.

Genotyping High molecular weight genomic DNA was prepared from venous blood using the QuickGene 610L Automatic DNA/RNA Extraction System (Fujifilm, Tokyo, Japan). All the genotyping experiments were done using ligase detection reactions [21]. All genotyping success rates were above 98% and all mismatch rates were below 1% in 1641 duplicate samples.

Statistical analysis We used SHEsis [22] to perform the Hardy–Weinberg equilibrium test, to compare the differences of allele, genotype and haplotype frequencies between cases and controls and to calculate LD coefficients (D' and r^2) in the control group.

To establish the closest best-fit model for each SNP, we carried out the logistic regression analysis by comparing additive, dominant and recessive models with age, sex and $\log_e$ BMI as covariants, and the model that had the lowest Akaike's information criterion value was considered to be the best-fitting model for the respective SNP. In the additive model, homozygotes for the risk allele (1/1), heterozygotes (1/0) and homozygotes for the non-risk allele (0/0) were coded to an ordered categorical variable for the genotype (2, 1 and 0, respectively). The dominant model was defined as 1/1+1/0 vs 0/0 and the recessive model as 1/1 vs 1/0+0/0. The association of the SNPs with type 2 diabetes was assessed by logistic regression after adjusting for sex, age and $\log_e$ BMI. The population attributable risk (PAR) [23] was calculated as:

$$\text{PAR} = 1 - \frac{1}{n_c} \sum_{i \in \text{Case}} \frac{1}{\text{OR}_i}$$

where n_c is the number if individuals in each case group and OR_i is equal to $\beta \times Y$ (the estimated OR of the ith individual in each case group [β is the regression coefficient vector in terms of Y, and Y is the term for the respective SNP in the logistic regression model]). In addition, to analyse the independent effect of each SNP in the *KCNQ1* gene, we carried out a conditional analysis by including the most significant SNP in the region and the SNP being tested, coded according to the most appropriate genetic model, combined with age, sex and $\log_e$ BMI as covariates, in a logistic regression analysis.

For quantitative traits in relation to genotypes, a general linear statistical method was used, applying additive, dominant and recessive models while adjusting for the effect of age and sex (BMI, waist and waist to hip ratio), or age, sex and $\log_e$ BMI (all other traits). The statistical analyses were performed using the SPSS (SPSS, Chicago, IL, USA) program. A p value <0.05 was considered significant.

Results

The allele and genotype distribution are summarised in Table 2. All three variants genotyped were in Hardy–

Table 2 Association of candidate SNPs in *KCNQ1* with type 2 diabetes in participants with type 2 diabetes and in controls

SNP	Group	Allele data			Genotype distribution (%)			Additive model	
Allele		Frequency[a] (%)	OR (95% CI)	p value	C/C	C/R	R/R	OR (95% CI)	p value[b]
rs2237892 T[c], C[d]	Case	69.6	1.19 (1.08–1.31)	3.0×10^{-4}	165 (8.8)	813 (43.2)	902 (48.0)	1.23 (1.11–1.36)[e]	1.1×10^{-4}
	Control	65.8			224 (11.2)	919 (46.0)	853 (42.7)		
rs2237895 C[c,d], A	Case	34.6	1.20 (1.09–1.32)	1.9×10^{-4}	209 (11.1)	886 (47.0)	790 (41.9)	1.23 (1.11–1.37)[f]	7.8×10^{-5}
	Control	30.6			169 (8.5)	883 (44.3)	942 (47.2)		
rs2237897 T[c], C[d]	Case	68.4	1.24 (1.13–1.36)	3.9×10^{-5}	183 (9.7)	822 (43.8)	873 (46.5)	1.28 (1.16–1.41)[g]	2.0×10^{-6}
	Control	63.6			271 (13.6)	912 (45.7)	813 (40.7)		

[a] Risk allele frequency

[b] Adjusted for age, sex and $\log_e$ BMI

[c] Minor allele

[d] Risk allele

PAR (%)=[e] 23, [f] 12.6, [g] 27.3

C/C, homozygous for minor allele; C/R, heterozygous for minor allele; R/R, homozygous for common allele

Weinberg equilibrium in both the case and control groups. Allele frequency ORs of the three SNPs, rs2237892 (OR 1.19, 95% CI 1.08–1.31, $p = 3.0 \times 10^{-4}$), rs2237895 (OR 1.20, 95% CI 1.09–1.32, $p = 1.9 \times 10^{-4}$) and rs2237897 (OR 1.24, 95% CI 1.13–1.36, $p = 3.9 \times 10^{-5}$) were significantly associated with type 2 diabetes in our sample. The risk alleles were in the same direction as in previous studies [18, 19]. The best-fitting genetic model for all three was the additive model (see Electronic supplementary material [ESM] Table 1). Under the additive model with adjustment for age, sex and $\log_e$ BMI, significant association was detected in all three polymorphisms (rs2237892, OR 1.23, 95% CI 1.11–1.36, $p = 1.1 \times 10^{-4}$, PAR=23.9%; rs2237895, OR 1.23, 95% CI 1.11–1.37, $p = 7.8 \times 10^{-5}$, PAR=12.6%; rs2237897, OR 1.28, 95% CI 1.16–1.41, $p = 2.0 \times 10^{-6}$, PAR=27.3%; Table 2).

The LD structure (rs2237892/rs2237895/rs2237897) is shown in Fig. 1. LD coefficients (D' and r^2) among the three variants (see ESM Table 2) suggested that the degree of linkage disequilibrium was relatively high. So haplotypes were constructed with all three variants and the frequencies of haplotypes were then analysed by excluding the rare haplotypes (those below 2% frequency in cases or controls); this revealed a significant difference in the distribution of the global haplotypes between the type 2 diabetes group and the normal controls ($p = 2.6 \times 10^{-5}$). The C-C-C haplotype frequency was significantly higher ($p = 2.1 \times 10^{-3}$) and the T-A-T haplotype frequency was significantly lower ($p = 4.0 \times 10^{-5}$) in the group with type 2 diabetes compared with the control group (see ESM Table 3).

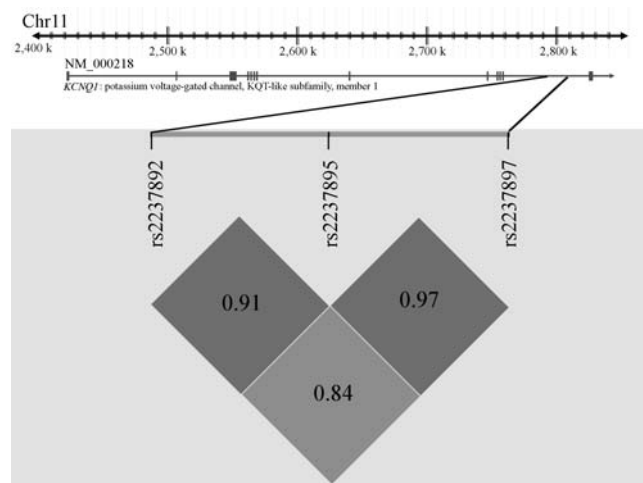As treatment for diabetes may have affected metabolic relationships, only non-diabetic individuals were included

Fig. 1 Linkage disequilibrium structure of the SNPs in *KCNQ1*. Pairwise D' values are colour coded: high D' values are dark, low D' values are light (values were generated by SHEsis software [22]). The numbers shown at the top represent the degrees of the location of the region on chromosome 11 (Chr11)

in the metabolic traits analysis. We found all three variants were associated with BMI and waist measurement, with the homozygous carriers of diabetes-associated allele showing the lowest value. Under the recessive model, rs2237892 and rs2237897 were associated with HbA$_{1c}$ levels and rs2237892 also showed association with fasting plasma glucose levels under the additive model (Table 3). Apart from these associations, the variants were not associated with any other measures in our study.

Discussion

We found the variants located at intron 15 of *KCNQ1*, rs2237892, rs2237895 and rs2237897, to be associated with type 2 diabetes. These results are consistent with previous studies [18–20]. The variant rs2237897 showed the strongest association with type 2 diabetes after testing for independent effects, which was consistent with the study of Tan et al. [20]. In addition, the conditional independent effects test of rs2237892, rs2237895 and rs2237897 confirmed that they were in a linkage disequilibrium block, as the effects of rs2237892 and rs2237895 on type 2 diabetes could be equally attributable to rs2237897 (see ESM Table 4).

KCNQ1, which encompasses 404 kb, is located at chromosome 11p15.5, not far from a candidate region at 11p13–p12 that two independent studies have linked to type 2 diabetes [24, 25]. *KCNQ1* encodes a pore-forming subunit of the voltage-dependent K$^+$ ion channel, which is expressed mainly in the heart and, to a lesser extent, in the brain, adipose tissue and pancreas. The two most important roles of potassium voltage-gated channel, KQT-like (KCNQ1) channels are: (1) repolarisation of the cardiac tissue following an action potential; and (2) water and salt transport in epithelial tissues. Moreover, mutations in *KCNQ1* can lead to dysfunction of the channel and cause the cardiac long QT syndrome LQTS1 that, in turn, may lead to serious arrhythmias, ventricular fibrillation and cardiac arrest. *Kcnq1*-knockout mice have been reported to show cardiac dysfunctions such as prolonged QT interval, hypochlorhydria, hypergastrinaemia, gastric hyperplasia and vacuolation of the parietal cells [26, 27]. For type 2 diabetes, homozygous *Kcnq1*-null mice have been reported not to show hyperglycaemia or glucose intolerance, and the contribution of the *KCNQ1*-encoded protein to the molecular pathogenesis of type 2 diabetes remains unclear [19]. We found that homozygous carriers of diabetes-associated allele showed the lowest BMI in the control group, which contradicted the theory that weight gain may increase the risk of diabetes. This suggests that the *KCNQ1* gene may impact on the pathogenesis of diabetes through pathways other than weight gain. The association of HbA$_{1c}$ levels and

Table 3 Effect of candidate SNP variant genotypes on clinical and biochemical variables in control individuals

SNP	Risk allele	Non-risk allele	Phenotypic characteristic[a]	Genotypes			p value[b]		
				C/C	C/R	R/R	Additive	Dominant	Recessive
rs2237892	C	T	BMI (kg/m^2)	24.3±3.13	24.7±3.30	24.7±3.42	0.039	0.483	0.020
			Waist (cm)	82.9±9.08	83.2±8.79	84.9±16.3	0.043	0.019	0.223
			Waist to hip ratio	0.86±0.06	0.86±0.07	0.86±0.07	0.635	0.492	0.844
			Fasting plasma glucose (mmol/l)	4.85±0.66	4.83±0.60	4.75±0.71	0.051	0.047	0.190
			HbA$_{1c}$ (%)	5.81±0.55	5.75±0.53	5.77±0.69	0.064	0.781	0.012
			Total cholesterol (mmol/l)	4.52±0.90	4.48±0.88	4.53±0.80	0.517	0.583	0.221
			Triacylglycerol (mmol/l)	1.64±1.08	1.58±1.10	1.60±0.85	0.404	0.978	0.255
rs2237895	C	A	BMI (kg/m^2)	23.9±2.86	24.5±3.34	24.6±3.22	0.027	0.200	0.006
			Waist (cm)	82.0±8.47	83.0±9.06	83.8±11.1	0.012	0.036	0.048
			Waist to hip ratio	0.86±0.05	0.86±0.06	0.86±0.06	0.093	0.058	0.655
			Fasting plasma glucose (mmol/l)	4.82±0.69	4.85±0.62	4.81±0.65	0.188	0.081	0.913
			HbA$_{1c}$ (%)	5.75±0.57	5.78±0.55	5.79±0.57	0.651	0.779	0.595
			Total cholesterol (mmol/l)	4.42±0.84	4.51±0.88	4.51±0.88	0.748	0.811	0.245
			Triacylglycerol (mmol/l)	1.59±1.10	1.61±1.03	1.61±1.09	0.986	0.831	0.733
rs2237897	C	T	BMI (kg/m^2)	24.2±3.15	24.7±3.28	24.9±3.36	0.002	0.074	0.002
			Waist (cm)	82.7±9.13	83.5±8.80	84.6±15.2	0.004	0.017	0.018
			Waist to hip ratio	0.86±0.06	0.86±0.06	0.86±0.06	0.576	0.703	0.608
			Fasting plasma glucose (mmol/l)	4.82±0.66	4.85±0.61	4.77±0.68	0.562	0.155	0.854
			HbA$_{1c}$ (%)	5.80±0.55	5.76±0.53	5.77±0.66	0.133	0.662	0.047
			Total cholesterol (mmol/l)	4.52±0.90	4.47±0.87	4.56±0.83	0.630	0.368	0.193
			Triacylglycerol (mmol/l)	1.63±1.11	1.58±1.03	1.67±1.18	0.991	0.332	0.508

Data are means±SD

[a] Multiple linear regression was carried out after logarithmic transformation for data not in normal distribution

[b] Adjusted for age and sex (BMI, waist and waist to hip ratio), or age, sex and log$_e$ BMI (all other traits)

C/C, homozygous for risk allele; C/R, heterozygous for risk allele; R/R, homozygous for non-risk allele

fasting plasma glucose levels in our study, and the association of higher fasting glucose levels and reduced corrected insulin response at 120 min in the study of Tan et al. [20], in conjunction with the lower homeostasis model assessment for beta cell function or corrected insulin response apparent for C-C homozygotes of rs2237892 in the study of Yasuda et al. [18], may reflect a functional role for this channel in beta cell function and the pathogenesis of type 2 diabetes. Thus, further studies will be useful to replicate these promising findings and to fully delineate the role of KCNQ1.

In the present study, the distribution of haplotypes constructed by rs2237892, rs2237895 and rs2237897 showed significant differences between cases and controls, particularly the C-C-C haplotype and the T-A-T haplotype. Thus, it can be seen that the three variants are in an LD block. However, no variant in this region has been detected to have a direct function, so we suggest that there may be one or more other functional variants in this region of KCNQ1. In a recent study, large gene deletions and duplications in KCNQ1 were identified in people with long QT syndrome [28]. This suggests that copy-number variants in KCNQ1 also play a role in associated complex diseases. To clarify the role of KCNQ1 in susceptibility to type 2 diabetes, further research is needed into the SNPs and copy-number variants.

In addition, compared with the controls in previous studies (see ESM Table 5), the minor allele frequencies of all three variants in our population from mainland China were higher or lower than in other populations; for example, the frequency of SNP rs2237897 in our Chinese sample was close to that in the Singapore Chinese

population, higher than that in the Japanese population and completely different from the frequency in the Danish population (63.8%, 65%, 61% and 96%, respectively) [18–20]. These results confirmed the differences in frequencies of some genetic variations among different ethnic groups and different geographic regions. At the same time, these differences also highlight the need to extend genome-wide association scans and subsequent replication studies to different populations.

In summary, we detected the association of *KCNQ1* with type 2 diabetes and some diabetes-related traits in the population of mainland China. In addition, the haplotype distribution was found to be significantly different between cases and controls. These findings may be useful in further research into the pathogenesis of type 2 diabetes, as well as in advancing clinical practice and public health genomics.

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