Association of *KCNQ1* gene polymorphism with gestational diabetes mellitus in a Chinese population

Q. Zhou · K. Zhang · W. Li · J. T. Liu · J. Hong ·
S. W. Qin · F. Ping · M. L. Sun · M. Nie

Received: 2 June 2009 / Accepted: 28 July 2009 / Published online: 28 August 2009
© Springer-Verlag 2009

Keywords Gestational diabetes mellitus · *KCNQ1* · Polymorphism

p_c p value corrected for multiple testing
SNP Single nucleotide polymorphism

Abbreviations

GCT	Glucose challenge test
GDM	Gestational diabetes mellitus
HOMA-B	Homeostasis model assessment of beta cell function
HOMA-IR	Homeostasis model assessment of insulin resistance
OR _a	Adjusted OR
p_a	Adjusted p value

Electronic supplementary material The online version of this article (doi:10.1007/s00125-009-1500-y) contains supplementary material, which is available to authorized users.

Q. Zhou · K. Zhang · W. Li · J. Hong · S. W. Qin · F. Ping ·
M. L. Sun · M. Nie (✉)
Key Laboratory of Endocrinology, Ministry of Health,
Department of Endocrinology, Peking Union Medical College
Hospital, Peking Union Medical College,
Chinese Academy of Medical Sciences,
Shuai Fuyuan 1#, Dongcheng District,
Beijing 100730, People's Republic of China
e-mail: nm_pumch@yahoo.com.cn

J. T. Liu
Department of Obstetrics & Gynecology, Peking Union Medical
College Hospital, Peking Union Medical College,
Chinese Academy of Medical Sciences,
Beijing, People's Republic of China

Present Address:

Q. Zhou · J. Hong
Department of Endocrinology,
First Affiliated Hospital of Wenzhou Medical College,
Wenzhou, People's Republic of China

To the Editor: Epidemiological study has confirmed that women with a history of gestational diabetes mellitus (GDM) are at increased risk of developing type 2 diabetes mellitus later in life [1]. Women with a family history of diabetes also have a significantly increased risk of GDM [2]. Some researchers consider that GDM may share some risk factors and genetic susceptibility with type 2 diabetes mellitus.

KCNQ1, located at chromosome 11p15.5, encodes the pore-forming K⁺ channel alpha-subunit, which is produced in a wide variety of tissues including the pancreas. Recent evidence has revealed a strong association of *KCNQ1* with susceptibility to type 2 diabetes [3, 4]. However, no studies have focused on the association between *KCNQ1* gene polymorphism and GDM. Our aim in this study was to investigate the correlation between *KCNQ1* variants and GDM in a Chinese population.

All pregnant women were screened for GDM between 24 and 28 weeks with a 50 g glucose challenge test (GCT). Plasma glucose 1 h after intake of glucose less than 7.8 mmol/l was defined as GCT negative (GCT⁻), but otherwise a participant was diagnosed as GCT positive (GCT⁺). GCT⁺ women then had a 100 g oral glucose tolerance test. The glucose threshold values were: fasting, 5.3 mmol/l; 1 h, 10.0 mmol/l; 2 h, 8.6 mmol/l; and 3 h, 7.8 mmol/l. If two or more of the glucose values met or exceeded the threshold value, GDM was diagnosed; normal glucose tolerance was diagnosed when all plasma glucose values were below the threshold values.

Based on the above definitions, 1,436 pregnant women were included in the study: 520 with GDM; 275 who were GCT–; and 641 with normal glucose tolerance (the last two groups served as controls). Informed written consent was obtained from all participants, and the study was approved by the Institutional Review Board of our hospital.

Clinical and biochemical data of all participants, including age, blood pressure, plasma glucose, serum insulin, triacylglycerol and high-sensitivity C-reactive protein levels were collected at 24–28 weeks' gestation. The homeostasis model assessment (HOMA) index was calculated and used to assess beta cell function (HOMA-B) and insulin resistance (HOMA-IR). The details are presented in Electronic supplementary material (ESM) Table 1.

KCNQ1 polymorphisms were genotyped by PCR and restriction fragment length polymorphism methods (ESM Tables 2 and 3). The statistical analyses were performed using SPSS 11.0 (SPSS, Chicago, IL, USA). Continuous data were analysed by *t* test or ANOVA. Non-parametric tests were performed when variables did not have a Gaussian distribution. The χ^2 test was used for comparisons between categorical variables. Bonferroni correction was used to correct for multiple testing. A two-sided *p* value <0.05 was considered statistically significant.

In order to calculate power, the following assumptions were made: a prevalence of GDM equal to 3%, a high-risk allele frequency of 0.15 and an effect size of 1.3. Under these assumptions, our sample of 520 cases and 916 controls would have >80% power with a type I error rate of 0.05. Power calculations were performed using the Genetic Power Calculator, available at <http://ibgwww.colorado.edu/~pshaun/gpc/> (accessed 15 April 2009) [5].

All single nucleotide polymorphisms (SNPs) were in Hardy–Weinberg equilibrium ($p>0.05$), except for rs2237895 ($p=3.5 \times 10^{-5}$) in the GDM group. Compared with controls, we found that the risk allele in rs2237896 was moderately associated with GDM (OR 1.228 [95% CI 1.045–1.442], $p=0.012$, corrected p value [p_c] for multiple testing $p_c=0.037$). And, under a recessive model (AA vs AG+GG), the OR value increased further (OR and p values were adjusted for age, BMI, triacylglycerol and high-sensitivity C-reactive protein, [OR_a and p_a , respectively] OR_a 1.585 [1.088–2.308], $p_a=0.016$ [$p_c=0.049$]). In addition, we found a positive association between the C allele and genotype in rs2237895 and GDM (OR 1.200 [1.020–1.411], $p=0.028$; $p_a=0.016$ [$p_c=0.047$], respectively), but the significance in the C allele disappeared after correcting for multiple testing ($p_c=0.083$). The allele and genotype in SNP rs2237892 had no significant association with GDM (ESM Table 4).

Next, we investigated the association of the three SNPs with beta cell function and insulin resistance

(ESM Table 5). Among all participants, the SNP rs2237895 variant was nominally associated with impairment of beta cell function, having a lower value for HOMA-B ($p=0.021$), but the significance was not seen after correcting for multiple testing ($p_c=0.062$). Using the dominant model, the association was significant ($p=0.005$ [$p_c=0.016$]) (HOMA-B was 140.25 ± 142.15 [AC+CC] vs 158.15 ± 99.66 [AA]). However, we did not detect an association between the SNPs and insulin resistance based on HOMA.

In this study, our results were not entirely in accordance with previous studies on type 2 diabetes, in which the association of type 2 diabetes with three SNPs (rs2237892, rs2237895 and rs2237896) in *KCNQ* has been found to be strong ($p<0.0001$) [3, 4]. Here, we demonstrated that the SNP rs2237896 was the risk allele for GDM with moderate p values, the rs2237895 variant might predispose to GDM because of the diminished p_c value, and we failed to show a statistical association between rs2237892 and GDM in a Chinese population. Given that our study was adequately powered, we believe these differences may be due to: (1) the diagnostic criteria and glucose threshold values adopted in our study; (2) the genetic background of our population and the heterogeneous nature of these disorders; (3) limited sample sizes; and (4) a smaller effect size (OR <1.3) of rs2237892.

In addition, we investigated the association of the three SNPs with beta cell function and insulin resistance using HOMA-B and HOMA-IR. Apart from a dominant model in rs2237895 variant, we did not find other genetic models associated with impairment of beta cell function after correcting the p value, but the homozygote of the risk allele had the lowest HOMA-B value, also suggesting beta cell dysfunction. Moreover, we did not detect any association between the SNPs and insulin resistance based on HOMA-IR values. Thus, we infer that *KCNQ1* variants affect glucose metabolism, possibly through impairment of insulin secretion, in line with results from other studies in different populations [6, 7].

In conclusion, our present study demonstrates a close link between SNPs in *KCNQ1* and GDM. These effects may be through the impairment of beta cell function, but the precise mechanism remains unknown and further studies are needed for clarification.

Acknowledgements This study was supported by grants from the Project of National Natural Science Foundation of China (no. 30672210). We thank all individuals for their participation in the research.

Duality of interest The authors declare that there is no duality of interest associated with this study.

References

1. Linne Y, Barkeling B, Rossner S (2002) Natural course of gestational diabetes mellitus: long term follow up of women in the SPAWN study. *BJOG* 109:1227–1231
2. Williams MA, Qiu C, Dempsey JC, Luthy DA (2003) Familial aggregation of type 2 diabetes and chronic hypertension in women with gestational diabetes mellitus. *J Reprod Med* 48:955–962
3. Yasuda K, Miyake K, Horikawa Y et al (2008) Variants in *KCNQ1* are associated with susceptibility to type 2 diabetes mellitus. *Nat Genet* 40:1092–1097
4. Unoki H, Takahashi A, Kawaguchi T et al (2008) SNPs in *KCNQ1* are associated with susceptibility to type 2 diabetes in East Asian and European populations. *Nat Genet* 40:1098–1102
5. Purcell S, Cherny SS, Sham PC (2003) Genetic Power Calculator: design of linkage and association genetic mapping studies of complex traits. *Bioinformatics* 19:149–150
6. Müssig K, Staiger H, Machicao F et al (2009) Association of type 2 diabetes candidate polymorphisms in *KCNQ1* with incretin and insulin secretion. *Diabetes* 58:1715–1720
7. Tan JT, Nurbaya S, Gardner D, Sandra Y, Tai ES, Ng DP (2009) Genetic variation in *KCNQ1* associates with fasting glucose and beta-cell function: a study of 3734 subjects comprising three ethnicities living in Singapore. *Diabetes* 58:1445–1449