

Genetic Variation in *KCNQ1* Associates With Fasting Glucose and β -Cell Function

A Study of 3,734 Subjects Comprising Three Ethnicities Living in Singapore

Jonathan T. Tan,¹ Siti Nurbaya,² Daphne Gardner,¹ Sandra Ye,² E. Shyong Tai,¹ and Daniel P.K. Ng²

OBJECTIVE—The potassium voltage-gated channel, KQT-like subfamily, member 1 (*KCNQ1*) has been found through a genome-wide association study to be a strong candidate for conferring susceptibility to type 2 diabetes in East Asian and European populations. Our objective was to describe the association between polymorphisms at the *KCNQ1* locus with insulin resistance, β -cell function, and other type 2 diabetes-related traits in a sample of Chinese, Malays, and Asian Indians living in Singapore.

RESEARCH DESIGN AND METHODS—We examined the associations between four previously reported *KCNQ1* single-nucleotide polymorphisms (SNPs) with type 2 diabetes-related traits in 3,734 participants from the population-based 1998 Singapore National Health Survey cohort (2,520 Chinese, 693 Malay, and 521 Asian Indians). Insulin resistance was calculated from fasting insulin and glucose using the homeostasis model assessment method, whereas pancreatic β -cell function was assessed using the corrected insulin response at 120 min (CIR_{120}).

RESULTS—SNPs rs2237897, rs2237892, and rs2283228 were significantly associated with type 2 diabetes (odds ratio [OR] 1.48, $P = 3 \times 10^{-4}$; OR 1.38, $P = 0.002$; OR 1.31, $P = 0.012$, respectively). Within the Chinese population, the risk alleles for rs2237897, rs2237892, and rs2283228 were significantly associated with higher fasting glucose levels ($P = 0.014$, 0.011, and 0.034, respectively) and reduced CIR_{120} ($P = 0.007$, 0.013, and 0.014, respectively). A similar trend was observed among the Malay and Asian Indian minority groups, although this did not reach statistical significance because of limited sample sizes.

CONCLUSIONS—The increased risk for type 2 diabetes associated with *KCNQ1* is likely to be caused by a reduction in insulin secretion. Further studies will be useful to replicate these findings and to fully delineate the role of *KCNQ1* and its related pathways in disease pathogenesis. *Diabetes* 58:1445–1449, 2009

From the ¹Department of Endocrinology, Singapore General Hospital, Singapore; and the ²Department of Community, Occupational and Family Medicine, National University of Singapore, Singapore.

Corresponding author: Daniel P.K. Ng, cofnpkd@nus.edu.sg.

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The prevalence of type 2 diabetes has increased dramatically over the last 2 decades and is predicted to double in a generation from 150 million in 2000 to 300 million by 2025 (1). The majority of this increase is taking place in developing countries undergoing nutritional transition and has a major impact on morbidity and health care resources (2,3). Although the precise pathophysiology of type 2 diabetes remains unclear, it is largely thought to be caused by a combination of the interaction between multiple genes and environmental factors (4).

Single-nucleotide polymorphism (SNP) analysis of genome variation in large cohorts have led to the identification of several genes being implicated in the pathogenesis of type 2 diabetes, of which *TCF7L2* has been considered to be the most important to date (5). More recently, the first genome-wide association study using 207,097 SNP markers in Asian (Japanese) patients with type 2 diabetes and unrelated control subjects was conducted. This led to the finding that polymorphisms (rs2237895, rs2237897, and rs2283228) within a novel diabetes susceptibility gene, *KCNQ1*, were strongly associated with type 2 diabetes in the Japanese population (6,7). Importantly, both studies corroborated these novel findings in populations of European and East Asian ancestry, including Chinese subjects living in Singapore (6). Notwithstanding these promising findings, it is unclear whether these polymorphisms are associated with quantitative traits relevant to the pathogenesis of type 2 diabetes, primarily impaired β -cell function and insulin resistance (8). Unoki et al. (6) did not report any association with β -cell function or insulin resistance, whereas only Yasuda et al. (7) found an association with β -cell function in Japanese ($P = 0.021$) and Finnish subjects ($P = 0.024$). To fill this knowledge gap, we aimed to investigate the association of these polymorphisms with 1) insulin resistance and β -cell function and 2) other quantitative metabolic risk phenotypes associated with type 2 diabetes within three different ethnicities (Chinese, Malay, and Asian Indian) living in Singapore.

RESEARCH DESIGN AND METHODS

The study used data from the cross-sectional population-based 1998 Singapore National Health Survey (NHS98; $n = 4,723$). Genotype data were available for 3,734 subjects comprising 2,520 Chinese, 693 Malay, and 521 Asian Indians. A total of 1,881 Chinese subjects with normal glucose tolerance (NGT) had previously served as the control subjects for the Singapore replication arm in our original report (6), whereas type 2 diabetes case subjects were from a separate study (the Singapore Diabetes Cohort Study). In this present study, all subjects (including subjects with NGT, impaired fasting glucose, impaired

TABLE 1
Clinical characteristics of the NHS98 study population by ethnicity

	Chinese	Malay	Asian Indian
<i>n</i>	2,520	693	521
Age	37.9 ± 12.2	38.8 ± 12.7	40.5 ± 12
% male	54.5	52.4	52.5
BMI (kg/m ²)	22.7 ± 3.7	25.6 ± 5	25.2 ± 4.8
Waist-to-hip ratio	0.82 ± 0.07	0.83 ± 0.08	0.86 ± 0.08
Waist circumference (cm)	78.1 ± 10.6	82.6 ± 12	85.2 ± 11.8
Fasting glucose (mmol/l)*†	5.53 (0–17.9)	5.89 (3.5–30)	6.01 (4.1–21.5)
Fasting insulin (mmol/l)*†	6.13 (0.2–576)	7.38 (0.7–83.4)	8.81 (1–119)
HOMA-IR*†	1.47 (0.05–19.68)	1.86 (0.11–22.24)	2.2 (0.23–31.2)
CIR ₁₂₀ *†	0.79 (0.001–9.2)	0.76 (0.002–10.9)	0.84 (0.003–11.1)
Glucose tolerance (%)			
NGT	75.2	60	60.7
IFG/IGT	17.2	25.6	19.9
Type 2 diabetes	7.6	14.4	19.4

Data are means ± SD unless otherwise stated. CIR₁₂₀: $100 \times I_{120} / [G_{120} \times (G_{120} - 70)]$. Units for insulin₁₂₀ (*I*₁₂₀) are given in mmol/l and for glucose₁₂₀ (*G*₁₂₀) in mg/dl. *Geometric mean (range) shown, due to skewed nature of data. †Subjects taking diabetes medication were excluded (59 Chinese, 35 Malays, and 44 Asian Indians).

glucose tolerance [IGT], and type 2 diabetes) were derived from the NHS98 study. Details of the NHS98 survey have been previously described in greater detail (9). Briefly, this was a population-based, cross-sectional survey conducted between September and November in 1998. The reference population was 2.16 million Chinese, Malay, and Asian Indian Singapore residents aged between 18 and 69 years. The survey was based on the World Health Organization (WHO)-recommended model for field surveys of diabetes and other noncommunicable diseases and the WHO MONICA protocol for population surveys. The research protocol for NHS98 was approved by the Singapore General Hospital Institutional Review Board (#54/2001).

Biological measures. Fasting blood samples were collected for glucose and insulin after an overnight fast of 10 h. All subjects underwent a 75-g oral glucose tolerance test except those taking oral hypoglycemic agents or insulin. Subjects were classified as having diabetes if they gave a history of diabetes or if their fasting glucose was >7 mmol/l or 2-h post-challenge glucose >11.1 mmol/l. Impaired fasting glycemia was defined as fasting glucose of 6–7 mmol/l and impaired glucose tolerance as 2-h post-challenge glucose of 7.8–11.1 mmol/l. Other measurements included the following: BMI and waist and hip circumference. Insulin resistance was estimated using the homeostasis model assessment method (HOMA-IR) (10). β-Cell function was assessed using the corrected insulin response at 120 min (CIR₁₂₀) (11).

SNP genotyping. Genotyping of four SNPs in intron 15 of *KCNQ1* rs2237897 (C>T), rs2237895 (A>C), rs2237892 (C>T), and rs2283228 (A>C) was performed using the TaqMan SNP genotyping assay (Applied Biosystems, Foster City, CA). Genotyping success rate for rs2237897, rs2237895, rs2237892, and rs2283228 was 92, 99, 92, and 87%, respectively. To assess reproducibility, 1% of samples were analyzed in duplicate; genotyping was 100% concordant for these samples.

Statistical analysis. Minor allele frequency, Hardy-Weinberg equilibrium, and linkage disequilibrium (LD; reported using *r*²) were estimated using Haploview (12). The distribution of glucose and insulin measures were skewed and therefore normalized by natural logarithmic transformation. Means were subsequently back transformed for presentation. Quantitative traits are presented as means and SDs. Linear regression analyses were performed to study the associations between diabetes-related traits with genotypic groups. Individuals were assigned as 0/1/2 according to their number of minor alleles under an additive model of inheritance. There was no significant heterogeneity between the sexes (*P* > 0.05), and subsequent analyses were performed with the sexes combined and adjusted for sex. Linear regression with adjustment for ethnicity was used to estimate the summary effect size of the SNPs in the combined sample from the three ethnic groups. Logistic regression was used to estimate the association between *KCNQ1* SNPs and type 2 diabetes. All analyses were stratified by ethnic group and adjusted for age, sex, and BMI (where appropriate). Analysis of association with β-cell function was further adjusted for insulin resistance (13). Analyses were performed using STATA (version 9.1 for Windows) (14).

RESULTS

The anthropometric and biochemical characteristics of the participants are detailed in Table 1. Among these individ-

uals, there was a higher prevalence of type 2 diabetes among the Malay and Asian Indian populations and a lower mean BMI and fasting glucose level among the Chinese population.

Allele frequency for rs2237897, rs2237895, rs2237892, and rs2283228 were similar between the Chinese and Malays but different in Asian Indians (Table 2). rs2237895 was in weak LD with rs2237897, rs2237892, and rs2283228 (*r*² < 0.25), whereas moderate LD was observed between rs2237897, rs2237892, and rs2283228 (Chinese: *r*² = 0.56–0.79 Malay: *r*² = 0.74–0.86, Asian Indian: *r*² = 0.39–0.62) (Supplemental Fig. 1, found in an online-only appendix at <http://diabetes.diabetesjournals.org/cgi/content/full/db08-1138/DC1>). All SNPs in the Chinese and Malays were in Hardy-Weinberg equilibrium (*P* > 0.05). In the Asian Indians,

TABLE 2
Association of *KCNQ1* genetic variants with type 2 diabetes in the Chinese, Malay, and Asian Indian population in Singapore

	Risk allele frequency	OR (95% CI)	<i>P</i> *
rs2237897 (C>T)			
Chinese	0.65	1.50 (1.15–1.96)	0.003
Malay	0.67	1.32 (0.88–1.98)	0.183
Asian Indians	0.95	2.61 (1.01–6.74)	0.047
Combined		1.48 (1.20–1.83)	3 × 10 ⁻⁴
rs2237895 (A>C)			
Chinese	0.35	1.09 (0.85–1.39)	0.496
Malay	0.32	1.39 (0.90–2.14)	0.14
Asian Indians	0.39	1.17 (0.81–1.70)	0.394
Combined		1.16 (0.97–1.4)	0.111
rs2237892 (C>T)			
Chinese	0.67	1.39 (1.08–1.79)	0.011
Malay	0.68	1.28 (0.85–1.93)	0.245
Asian Indians	0.95	2.32 (0.87–6.22)	0.094
Combined		1.38 (1.12–1.70)	0.002
rs2283228 (A>C)			
Chinese	0.63	1.22 (0.94–1.58)	0.135
Malay	0.66	1.39 (0.91–2.11)	0.124
Asian Indians	0.92	2.16 (0.98–4.74)	0.055
Combined		1.31 (1.06–1.61)	0.012

Risk allele denoted in bold. **P* values adjusted for age, sex, BMI, and ethnicity (for combined analysis).

three of the SNPs that had low minor allele frequency (rs2237897, rs2237892, and rs2283228) were not in the Hardy-Weinberg equilibrium. Consequently, the results for the Asian Indians should be interpreted with caution.

Table 2 shows the association between *KCNQ1* SNPs with type 2 diabetes in the Chinese, Malay, and Asian Indian population in Singapore. Significant associations were observed in the Chinese, with rs2237897 showing the strongest effect: odds ratio (OR) 1.50 (1.15–1.96), $P = 0.003$. In the combined sample of the three ethnic groups, the risk alleles of rs2237897 (C), rs2237892 (C), and rs2283228 (A) were also associated with type 2 diabetes in our study, consistent with previous reports (6,7). Of these, rs2237897 showed the strongest association (OR 1.48 [1.20–1.83], $P = 0.0003$). In the combined sample of only Chinese and Malays subjects, the association with rs2237897 remained significant (OR 1.45 [1.16–1.81], $P = 0.001$).

Table 3 shows the association between *KCNQ1* SNPs with diabetes-related traits. The risk alleles for rs2237897, rs2237892, and rs2283228 showed statistically significant association with higher fasting glucose levels ($P = 0.014$, 0.011, and 0.034, respectively) and reduced CIR₁₂₀ ($P = 0.007$, 0.013, and 0.014, respectively) in the Chinese population. After restricting to subjects without diabetes, the association remained significant with CIR₁₂₀ ($P = 0.011$, 0.020, and 0.015, respectively; online appendix Table 1). A similar trend was observed among the Malays and Asian Indians, although the associations did not reach statistical significance, possibly because of the limited sample sizes for these minority ethnic groups. In the combined analysis, rs2237897 and rs2237892 were significantly associated with fasting glucose levels ($P = 0.029$ and $P = 0.021$, respectively), whereas rs2237897, rs2237892, and rs2283228 were significantly associated with lower β -cell function (CIR₁₂₀) ($P = 0.013$, 0.021, and 0.020, respectively). These SNPs also showed associations with BMI in the Malay population and waist-to-hip ratio in Asian Indians. However, these associations were no longer statistically significant in the combined analysis. Based on a risk allele frequency of between 0.3 and 0.6, power calculations estimate that the combined sample provided 90% power to detect a 10% change in the examined traits.

DISCUSSION

Polymorphisms within *KCNQ1* have recently been shown to be strongly associated with an increased risk of type 2 diabetes in the East Asian and European populations (6,7). Of the three polymorphisms within *KCNQ1* previously described, rs2237897 appeared to have the strongest association with type 2 diabetes (6), whereas another study reported the strongest association with rs2237892 (7). Consistent with these findings, we found that both these SNPs were significantly associated with type 2 diabetes in the combined analysis of three ethnic groups. In addition, the presence of the risk allele for *KCNQ1* variants rs2237897, rs2237892, and rs2283228 were associated with increased fasting glucose level and decreased β -cell function in the Chinese population and combined sample. This is in agreement with the study by Yasuda et al. (7), which reported an association of these *KCNQ1* variants with β -cell function. Together, these findings corroborate the hypothesis that the role of this protein in the pathogenesis of type 2 diabetes is likely mediated through its effects on the pancreatic β -cell, although there is still a possibility

that these polymorphisms may increase the risk of type 2 diabetes through regulation of nearby genes. In contrast, there was no association between rs2237895 with any diabetes-related traits, specifically highlighting the importance of the polymorphisms rs2237897, rs2237892, and rs2283228 (which are in moderate LD) in increasing the risk of developing type 2 diabetes. Further fine mapping of SNPs in *KCNQ1*, especially within the LD block containing rs2237897 and rs2237892, may allow the identification of the causal variant.

KCNQ1 is located on 11p15.5, which encodes the pore-forming α -subunit of the I_{Ks}K⁺ channel, which is expressed mainly in the heart and, to a lesser extent, the inner ear, stomach, small and large intestine, liver, and kidney. *KCNQ1* is also expressed in the pancreas, where it is coexpressed with products of other regulators such as *KCNE1*, which may alter its biophysical characteristics and role (15). As such, it is plausible that polymorphisms within the *KCNQ1* gene alter the properties and role of the I_{Ks}K⁺ channel, causing decreased pancreatic β -cell function and insulin production, leading eventually to hyperglycemia.

Whereas we do appreciate that the associations observed in the Chinese do not represent an independent replication, since the controls used are largely the same as those in the study by Unoki et al. (6), we have provided data on Malays and Indians and, in our opinion, it was reassuring that similar trends for an effect of these three polymorphisms on association with type 2 diabetes, fasting glucose, and β -cell function were also observed in the Malay and Asian Indian subjects, even though their limited numbers certainly resulted in a reduction of study power. Although associations with BMI in Malays and waist-to-hip ratio in Asian Indians were found, the smaller sample sizes for these ethnic groups, together with the fact that these observations were not found in other ethnic groups, inevitably led us to be cautious in interpreting these findings. One caveat of this study is that we only examined the SNPs, which showed the strongest association, identified by Unoki et al. (6) and Yasuda et al. (7). Although the Chinese show strong and consistent associations with these SNPs, the association among Malays and Asian Indians is less clear. Further fine mapping of the *KCNQ1* locus, for instance, through deep DNA resequencing may allow the identification of population-specific causative variants.

The use of CIR₁₂₀ represented a limitation of our study, since it only served as an approximate measure of β -cell function, which may be better assessed using the CIR₃₀. Thus, if CIR₃₀ measurements were available, the positive associations that had been observed in our study may be further strengthened. It has also been suggested that CIR₁₂₀ could inadvertently capture information on additional aspects of glucose intolerance instead of insulin secretion alone. The previous finding of the association between CIR₃₀ with *KCNQ1* SNPs, in nondiabetic European subjects of the Botnia prospective study during their follow-up visit ($P = 0.024$) (7), however, appeared to corroborate our hypothesis that these SNPs may exert their effect on type 2 diabetes through an effect on insulin secretion.

In conclusion, the risk alleles of rs2237897, rs2237892, and rs2283228 within the *KCNQ1* gene are associated with decreased pancreatic β -cell function and fasting glucose levels, suggesting that the impact of these polymorphisms on the risk of type 2 diabetes may be mediated through an

TABLE 3
Association with *KCNQ1* with diabetes-related traits

Number of risk alleles	Chinese		Malay		Asian Indian		P (adjusted for age and sex)	Combined Δ Trait	P (adjusted for age and sex)
	0	1	0	1	0	1			
rs2237897 (C>T)	<i>n</i> = 2,291		<i>n</i> = 638		<i>n</i> = 489				
BMI (kg/m ²)	23.5	23.4	26.4	25.4	23.4	23.9	24.3	0.477	0.568
WHR	0.87	0.87	0.88	0.88	0.86	0.86	0.90	0.036	0.400
Fasting glucose (mmol/l)*‡	5.58	5.68	5.76	5.80	5.37	5.57	5.78	0.209	0.029
Fasting insulin (mmol/l)*‡	6.45	6.43	7.25	6.83	6.49	7.44	8.52	0.290	0.576
HOMA-IR*‡	1.60	1.62	1.87	1.77	1.55	1.84	2.17	0.211	0.280
Cumulative insulin response*†‡	0.83	0.76	0.80	0.76	0.71	1.08	0.99	0.820	0.013
rs2237895 (A>C)	<i>n</i> = 2,520		<i>n</i> = 693		<i>n</i> = 521				
BMI (kg/m ²)	23.4	23.6	25.4	25.0	24.7	24.6	24.5	0.786	0.359
WHR	0.87	0.87	0.88	0.87	0.87	0.90	0.90	0.562	0.146
Fasting glucose (mmol/l)*‡	5.61	5.67	5.78	5.80	5.63	5.71	5.80	0.160	0.271
Fasting insulin (mmol/l)*‡	6.45	6.34	6.86	6.76	6.66	8.72	8.87	0.474	0.259
HOMA-IR*‡	1.61	1.59	1.77	1.75	1.74	2.20	2.27	0.297	0.400
Cumulative insulin response*†‡	0.76	0.73	0.84	0.76	0.69	1.07	0.94	0.071	0.218
rs2237892 (C>T)	<i>n</i> = 2,327		<i>n</i> = 642		<i>n</i> = 474				
BMI (kg/m ²)	23.6	23.4	26.2	25.4	23.9	24.1	24.3	0.619	0.731
WHR	0.87	0.87	0.88	0.87	0.87	0.88	0.89	0.064	0.623
Fasting glucose (mmol/l)*‡	5.55	5.66	5.72	5.74	5.49	5.61	5.73	0.460	0.021
Fasting insulin (mmol/l)*‡	6.42	6.42	7.42	6.92	6.81	7.58	8.44	0.342	0.514
HOMA-IR*‡	1.58	1.60	1.90	1.77	1.66	1.84	2.13	0.310	0.244
Cumulative insulin response*†‡	0.85	0.78	0.88	0.84	0.80	1.13	1.05	0.937	0.021
rs2283228 (A>C)	<i>n</i> = 2,215		<i>n</i> = 586		<i>n</i> = 450				
BMI (kg/m ²)	23.4	23.4	25.8	25.2	23.2	24.1	24.9	0.078	0.800
WHR	0.87	0.87	0.88	0.88	0.87	0.88	0.90	0.011	0.863
Fasting glucose (mmol/l)*‡	5.57	5.65	5.66	5.73	5.60	5.69	5.79	0.672	0.056
Fasting insulin (mmol/l)*‡	6.26	6.35	7.31	6.83	6.38	7.78	8.93	0.257	0.216
HOMA-IR*‡	1.55	1.58	1.86	1.75	1.65	1.96	2.28	0.284	0.095
Cumulative insulin response*†‡	0.83	0.77	0.90	0.82	0.76	1.13	0.99	0.809	0.020

Risk allele is shown in bold. Combined estimates were obtained using linear regression with adjustment for ethnicity. *Additionally adjusted for BMI and excluding subjects taking diabetic medication (59 Chinese, 35 Malays, and 44 Asian Indians). †Additionally adjusted for insulin resistance (HOMA-IR). ‡Values were log-transformed to improve normality in regression analysis, and adjusted means were subsequently back-transformed. WHR, waist-to-hip ratio.

impact on β -cell function rather than insulin resistance. Further studies will be useful to replicate these promising findings and to fully delineate the role of *KCNQ1* and its related pathways in the pathogenesis of type 2 diabetes.

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