The Association between KCNQ1 Gene Polymorphism and Type 2 Diabetes Risk: A Meta-Analysis

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Abstract

Background: KCNQ1 (potassium voltage-gated channel KQT-like sub-family, member 1) encodes a pore-forming subunit of a voltage-gated K+ channel (KvLQT1) that plays a key role for the repolarization of the cardiac action potential as well as water and salt transport in epithelial tissues. Recently, genome-wide association studies have identified KCNQ1 as a type 2 diabetes (T2D) susceptibility gene in populations of Asian descent. After that, a number of studies reported that the rs2237892 and rs2237895 polymorphism in KCNQ1 has been implicated in T2D risk. However, studies on the association between these polymorphism and T2D remain conflicting. To investigate this inconsistency, we performed this meta-analysis.

Methods: Databases including Pubmed, EMBASE, Web of Science and China National Knowledge Infrastructure (CNKI) were searched to find relevant studies. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association. Potential sources of heterogeneity were also assessed by subgroup analysis and meta-regression.

Results: A total of 25 articles involving 70,577 T2D cases and 99,068 controls were included. Overall, the summary odds ratio of C allele for T2D was 1.32 (95% CI 1.26–1.38; P<0.01) and 1.24 (95% CI: 1.20–1.29; P<0.01–5) for KCNQ1 rs2237892 and rs2237895 polymorphisms, respectively. Significant results were also observed using co-dominant, dominant and recessive genetic models. After stratifying by ethnicity, sample size, and diagnostic criteria, significant associations were also obtained.

Conclusions: This meta-analysis suggests that the rs2237892 and rs2237895 polymorphisms in KCNQ1 are associated with elevated type 2 diabetes susceptibility.

Introduction

Type 2 diabetes (T2D) is a complex metabolic disorder characterized by variable degrees of insulin resistance, impaired insulin secretion and elevated blood glucose. It has become a global major health problem showing worldwide increasing prevalence with an estimated 300 million people predicted to develop the disease by 2025 [1]. Although its exact etiology is unknown, a combination of multiple genetic and environmental factors is considered to contribute to the pathogenesis of the disease. Until recently, few genes identified through the candidate gene approach have been confirmed to be associated with T2D (e.g., PPARG, KCNJ11, CAPN10, and TCF7L2). However, because the pathogenesis of T2D is yet to be elucidated completely, the candidate-gene approach is limited in power to detect novel disease-susceptibility genes.

Recently, spectacular advance was made in identifying susceptible genes involved in T2D through genome-wide association strategy (GWAS) [2]. KCNQ1 (potassium voltage-gated channel KQT-like subfamily, member 1) is a gene encoding the pore-forming subunit of a voltage-gated K+ channel (KvLQT1) that plays a key role for the repolarization of the cardiac action potential as well as water and salt transport in epithelial tissues [3–5]. Mutations in the KCNQ1 gene cause the long QT syndrome and deafness [6]. In addition, KCNQ1 is also expressed in pancreatic islets and the cultured insulin-secreting INS-1 cells and deafness [6]. In addition, KCNQ1 is also expressed in pancreatic islets and the cultured insulin-secreting INS-1 cells [7,8], and blockade of the channel with KCNQ1 inhibitors 293B stimulated insulin secretion [8], suggesting that KCNQ1 channels may play a role in regulation of insulin secretion.

Several important single nucleotide polymorphisms (SNPs) have been identified in the KCNQ1 gene. Two polymorphisms (rs2237892 and rs2237895) which were in moderate linkage disequilibrium (LD) were first identified to be associated with increased T2D risk in Asians through genome wide association approach ($r^2 = 0.30$) [9]. The relationship between KCNQ1 polymorphisms and T2D has been reported in various ethnic groups. However, recent studies [10,11] found no association...
between the two polymorphisms and T2D. These disparate findings may be due partly to insufficient power, false-positive results, and publication biases. The interpretation of these studies has been further complicated by the use of different populations, or different control source. To help clarify the inconsistent findings, we conducted a comprehensive meta-analysis to quantify the overall risk of KCNQ1 polymorphism on developing T2D.

Materials and Methods

Literature Search Strategy

Genetic association studies published before the end of June 2012 on T2D and polymorphisms in the KCNQ1 gene were identified through a search of PubMed, Web of Science, EMBASE and CNKI (Chinese National Knowledge Infrastructure) with keywords “KQT-like subfamily, member 1”, “KCNQ1”, “type 2 diabetes mellitus”, “type 2 diabetes”, “T2D”, “T2DM”. All references cited in these studies and published reviews were examined in order to identify additional work. Eligible studies had to meet all of the following criteria: (a) should have been published in peer-reviewed journal; (b) were independent association studies investigating polymorphism with T2D using original data; (c) should have presented sufficient data to calculate the odds ratio (OR) with confidence interval (CI) and p value, and (d) should have described the genotyping method, equipment, and protocols used or provided reference to them. The major reasons for exclusion of studies were (a) overlapping data, (b) case-only studies and (c) review papers.

Data Extraction

Data extraction was performed independently by two reviewers and differences were resolved by further discussion among all authors. For each included study, the following information was extracted from each report according to a fixed protocol: first author, publication year, definition and numbers of cases and controls, diagnostic criterion, genotype frequency, source of controls, gender, body mass index (BMI), Hardy–Weinberg equilibrium (HWE) status, ethnicity and genotyping method.

Statistical Methods

The strength of association between polymorphisms of KCNQ1 and T2D risk was assessed by odds ratio (OR) with the corresponding 95% confidence interval (CI). The per-allele OR of the risk allele was compared between cases and controls using co-dominant genetic model. Additional pooled estimates were also given with corresponding results under co-dominant, dominant and recessive genetic models. Heterogeneity across individual studies was calculated using the Cochran’s $X^2$ based Q-statistic test followed by subsidiary analysis or by random-effects regression models with restricted maximum likelihood estimation [12–15]. Random-effects and fixed-effect summary measures were calculated as inverse variance-weighted average of the log OR. The results of random-effects summary were reported in the text because it takes into account the variation between studies. Ethnicity, diagnostic criterion (World Health Organization or American Diabetes Association criterion), study size ($\geq 1000$ and $< 1000$ cases) were pre-specified as characteristics for assessment of heterogeneity. Ethnic group was defined as Caucasian (i.e., people of European origin), East Asian, South Asian (i.e., Indian) and others. Ethnicity, BMI, diagnostic criterion, sample size, mean age at test and sex distribution in cases and controls were analyzed as covariates in meta-regression. Funnel plots was used to provide diagnosis of the potential publication bias. Egger’s regression test was also conducted to identify small study effects [15]. Sensitivity analysis, which determines the influence of individual studies on the pooled estimate, was also performed to assess the stability of the result. All P values are two-sided at the $P=0.05$ level. All statistical analyses were carried out with the Stata software version 10.0 (Stata Corporation, College Station, TX).

Results

Characteristics of Studies

The combined search yielded 85 references. 60 articles were excluded because they clearly did not meet the criteria or overlapping references (Figure S1). A total of 25 studies were finally included with 70,577 T2D cases and 99,068 controls [9–11,16–37]. The detailed characteristics of the included studies were shown in Table 1. There are 36 data sets from 22 studies with 63,760 T2D cases and 89,709 controls concerning rs2237892 and 26 data sets from 13 studies involving 37,822 T2D cases and 47,195 controls concerning rs2237895. These two polymorphisms were found to occur in frequencies consistent with Hardy–Weinberg equilibrium in the control populations of the vast majority of the published studies. Of the cases, 69.2% were East Asians, 23.5% were Caucasians, 5.8% were South Asians and 1.5% were of other ethnic origins.

Association of rs2237892 Polymorphism with T2D

Overall, there was evidence of an association between the increased risk of T2D and the variant in different genetic models when all the eligible studies were pooled into the meta-analysis (Figure 1). Using random effect model, the summary per-allele OR of the C variant for T2D was 1.32 [95% CI: 1.26–1.38, $P(Z)<10^{-5}$; $P(Q)<10^{-5}$], with corresponding results under dominant and recessive genetic models of 1.62 [95% CI: 1.51–1.74, $P(Z)<10^{-5}$; $P(Q)=0.0006$] and 1.40 [95% CI: 1.33–1.48, $P(Z)<10^{-5}$; $P(Q)<10^{-4}$], respectively. Similar results were also detected under co-dominant model (Table 2).

When studies were stratified for ethnicity, significantly increased risks were found among East Asian populations (C allele: OR = 1.32, 95% CI: 1.27–1.38; dominant model: OR = 1.63, 95% CI: 1.53–1.74; recessive model: OR = 1.40, 95% CI: 1.33–1.48), and South Asian (C allele: OR = 1.50, 95% CI: 1.15–1.95; dominant model: OR = 1.41, 95% CI: 1.20–1.68; recessive model: OR = 1.30, 95% CI: 1.18–1.44). Similar significant associations were also observed for Caucasians (C allele: OR = 1.18, 95% CI: 1.05–1.32; dominant model: OR = 1.20, 95% CI: 1.06–1.36; recessive model: OR = 1.28, 95% CI: 1.16–1.42). By considering sample size subgroups, the OR was 1.28 (95% CI: 1.22–1.35; $P<10^{-5}$) in large studies compared to 1.40 (95% CI: 1.31–1.49; $P<10^{-5}$) in small studies. In the stratified analysis by diagnostic criterion, significant associations were found for WHO criterion with per-allele OR of 1.31 (95% CI: 1.25–1.37; $P<10^{-5}$) and for ADA criterion of 1.38 (95% CI: 1.20–1.59; $P<10^{-5}$). Subsidiary analyses of HWE status yielded a per-allele OR for controls consistent to HWE of 1.32 (95% CI: 1.27–1.38), while no significant results were detected for studies deviated from HWE. Similar results were also found using co-dominant, dominant or recessive genetic model (Table 2). After adjusting for multiple testing using Bonferroni correction, all significant associations for rs2237892 under the co-dominant, dominant and recessive genetic models remained.

Significant heterogeneity was present among the 36 data sets ($P<0.05$). In meta-regression analysis, diagnostic criterion ($P=0.39$), mean age of cases ($P=0.11$) and controls ($P=0.51$), mean BMI of case ($P=0.65$) and controls ($P=0.39$), sex
Table 1. Characteristics of the studies included in the meta-analysis.

| Study          | Year | Ethnicity                  | No. of cases/controls | Diagnostic criteria | Definition of control | Age of cases/controls | Sex distribution in cases/controls (% male) | Genotyping method                  |
|----------------|------|----------------------------|-----------------------|---------------------|-----------------------|-----------------------|-------------------------------------------|-----------------------------------|
| Yasuda [9]     | 2008 | Japanese, Chinese, Korean  | 9182/9959             | WHO                 | Non-diabetic participants | NA/NA                | NA/NA                                    | GeneChip, PCR-based Invader assay   |
| Unoki [16]     | 2008 | Japanese                   | 3463/1313             | WHO                 | Normoglycemic         | NA/NA                | NA/NA                                    | GeneChip                           |
| Lee [17]       | 2008 | Korean                     | 865/496               | ADA                 | Normal fasting glucose | 58/55                | 4854                                     | TaqMan                             |
| Takeuchi [18]  | 2009 | Japanese                  | 5619/7359             | WHO                 | Non-diabetic participants | 63/65                | 61/48                                     | GeneChip, TaqMan, MassARRAY         |
| Qi [19]        | 2009 | Chinese                    | 424/1908              | WHO                 | Normal fasting glucose | 60/58                | NA/NA                                    | GenomeLab SNPstream                 |
| Jonsson [20]   | 2009 | Swedish                    | 2684/5482             | ADA                 | Normal fasting glucose | 58/58                | 59/38                                     | TaqMan                             |
| Hu [21]        | 2009 | Chinese                    | 1719/1720             | WHO                 | Normal glucose tolerance | 61/57               | 52/41                                     | MassARRAY                          |
| Liu [22]       | 2009 | Chinese                    | 1885/1994             | WHO                 | Normal fasting glucose | 54/58                | 41/31                                     | TaqMan                             |
| Chen [10]      | 2010 | Chinese                    | 57/341                | T2D patient         | Normal fasting glucose | NA/52                | NA/48                                     | TaqMan                             |
| Yamauchi [23]  | 2010 | Japanese                   | 7764/6432             | WHO                 | Non-diabetic participants | 65/58               | NA/NA                                    | GeneChip                           |
| Han [24]       | 2010 | Chinese                    | 990/559               | WHO                 | Normal glucose tolerance | 56/58               | 34/53                                     | SNaPshot                           |
| Tsai [25]      | 2010 | Chinese                    | 2798/2367             | ADA                 | Non-diabetic participants | 60/49               | 52/50                                     | GeneChip                           |
| Tan [26]       | 2010 | Chinese, Malaysian, Indian | 4817/2863             | WHO                 | Normal glucose tolerance | NA/NA               | NA/NA                                    | MassARRAY                          |
| Grallert [27]  | 2010 | German                     | 1186/1405             | ADA                 | Normoglycemic         | 61/61                | 55/55                                     | TaqMan                             |
| Voight [28]    | 2010 | European                   | 8130/38987            | WHO                 | Non-diabetic participants | NA/NA               | NA/NA                                    | GeneChip, TaqMan, KASPar, MassARRAY |
| Xu [29]        | 2010 | Chinese                    | 1891/2852             | WHO                 | Normal glucose regulation | 63/60               | 44/38                                     | SNaPshot                           |
| Zhou [30]      | 2010 | Chinese                    | 537/510               | WHO                 | Normal fasting glucose | 57/56                | 43/37                                     | MassARRAY                          |
| Been [11]      | 2011 | Indian                     | 1428/1593             | WHO                 | Normoglycemic         | NA/NA                | NA/NA                                    | TaqMan                             |
| Saif-Ali [31]  | 2011 | Malaysian                  | 234/177               | T2D patient         | Non-diabetic participants | 48/45               | 45/46                                     | RFLP                               |
| Tabara [32]    | 2011 | Japanese                   | 493/394               | ADA                 | Normal glucose tolerance | 60/59               | 55/53                                     | TaqMan                             |
| Odegere [33]   | 2011 | Mongolian                  | 177/216               | WHO                 | Non-diabetic participants | NA/NA               | NA/NA                                    | TaqMan                             |
| Saif-Ali [34]  | 2011 | Chinese                    | 300/230               | T2D patient         | Non-diabetic participants | 50/53               | 51/61                                     | RFLP                               |
| van Vliet-Ostaptchous [35] | 2012 | Dutch                     | 454/5182              | WHO                 | Healthy participants  | 64/51                | 43/42                                     | TaqMan                             |
| Campbell [36]  | 2012 | Latin American             | 876/399               | WHO                 | Non-diabetic participants | 63/61               | 49/NA                                     | SNPlex                             |
| Yu [37]        | 2012 | Chinese                    | 8509/3930             | WHO                 | Normal glucose tolerance | NA/NA               | 48/41                                     | MassARRAY                          |

NA: Not Available, WHO: World Health Organization, ADA: American Diabetes Association.
distribution in cases ($P = 0.30$) and controls ($P = 0.38$) did not significantly explained such heterogeneity. By contrast, ethnicity ($P = 0.03$) and sample size ($P = 0.03$) were significantly correlated with the magnitude of the genetic effect.

### Association of rs2237895 Polymorphism with T2D

For T2D risk and the rs2237895 polymorphism of KCNQ1, our meta-analysis gave an overall OR of $1.24$ (95% CI: 1.20–1.29; $P < 10^{-5}$; Figure 2) with statistically significant between-study heterogeneity ($P < 10^{-5}$). Significantly increased T2D risks were also found under dominant [OR = 1.32, 95% CI: 1.24–1.39; $P(Z) < 10^{-5}$; $P(Q) < 10^{-4}$] and recessive [OR = 1.35, 95% CI: 1.26–1.45; $P(Z) < 10^{-5}$; $P(Q) = 0.001$] genetic model. Significant associations were also found using co-dominant model (Table 3).

When stratifying for ethnicity, significant risks were found among East Asians in all genetic model (C allele: OR = 1.30, 95%
Table 2. Meta-analysis of the KCNQ1 rs2237892 polymorphism on type 2 diabetes risk.

| Sub-group analysis | No. of data sets | No. of case/ control | C allele | Heterozygote | Homozygote | Dominant model | Recessive model |
|--------------------|------------------|---------------------|----------|--------------|------------|----------------|----------------|
| Overall            | 36               | 63760/89709         | 1.32 (1.26–1.38) | 1.41 (1.31–1.52) | 1.86 (1.71–2.02) | 1.62 (1.51–1.74) | 1.40 (1.33–1.48) |
| Ethnicity          |                  |                     |          |              |            |                |                |
| East Asian         | 26               | 43023/38454         | 1.32 (1.27–1.38) | 1.42 (1.33–1.52) | 1.88 (1.74–2.03) | 1.63 (1.53–1.74) | 1.41 (1.33–1.50) |
| South Asian        | 5                | 4284/3075           | 1.50 (1.15–1.95) | 0.002 0.005 0.004 0.01 0.10 0.22 0.40 0.60 0.82 1.03 1.16 1.28 | 1.27 (1.09–1.30) | 1.50 (1.33–1.50) | 1.41 (1.33–1.50) |
| Caucasian          | 3                | 15400/47565         | 1.18 (1.05–1.33) | 0.006 0.03 0.04 0.07 0.10 0.14 0.20 0.30 0.40 0.50 0.60 | 1.20 (1.06–1.36) | 1.27 (1.11–1.45) | 1.28 (1.16–1.45) |
| Others             | 2                | 1053/615            | 1.50 (1.21–1.85) | 0.0001 0.03 0.06 0.09 0.12 0.15 0.18 0.21 0.24 0.27 0.30 | 1.46 (1.19–1.97) | 1.71 (1.07–1.28) | 1.11 (1.04–1.19) |
| Sample size        |                  |                     |          |              |            |                |                |
| Small              | 16               | 6793/9180           | 1.40 (1.31–1.49) | 1.49 (1.25–1.79) | 2.00 (1.71–2.33) | 1.73 (1.47–2.03) | 1.44 (1.32–1.58) |
| Large              | 20               | 56967/80529         | 1.28 (1.22–1.35) | 1.39 (1.28–1.51) | 1.82 (1.65–2.01) | 1.59 (1.48–1.72) | 1.39 (1.29–1.49) |
| Diagnostic criterion|                 |                     |          |              |            |                |                |
| WHO criterion      | 30               | 59052/84645         | 1.31 (1.25–1.37) | 1.43 (1.31–1.56) | 1.87 (1.70–2.03) | 1.62 (1.50–1.76) | 1.39 (1.31–1.48) |
| ADA criterion      | 3                | 4117/4316           | 1.38 (1.20–1.59) | 0.13 0.03 0.02 0.07 0.10 0.14 0.20 0.30 0.40 0.50 | 1.62 (1.25–2.11) | 1.46 (1.21–1.77) | 1.39 (1.31–1.48) |
| HWE status         |                  |                     |          |              |            |                |                |
| Yes                | 34               | 57987/88849         | 1.32 (1.27–1.38) | 1.40 (1.30–1.52) | 1.88 (1.73–2.05) | 1.63 (1.51–1.75) | 1.43 (1.36–1.49) |
| No                 | 2                | 5773/860            | 1.75 (0.64–4.81) | 0.27 0.02 0.03 0.06 0.10 0.14 0.20 0.30 0.40 0.50 0.60 | 1.86 (0.59–4.97) | 1.55 (0.94–2.17) | 1.01 (0.86–1.21) |

P(Z): Z test used to determine the significance of the overall OR.
P(Q): Cochran's chi-square Q statistic test used to assess the heterogeneity in subgroups.
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CI: 1.26–1.33; dominant model: OR = 1.37, 95% CI: 1.32–1.44; recessive model: OR = 1.47, 95% CI: 1.38–1.57). Similar results were also found in the Caucasian populations (C allele: OR = 1.12, 95% CI: 1.08–1.16; dominant model: OR = 1.18, 95% CI: 1.05–1.33; recessive model: OR = 1.19, 95% CI: 1.10–1.27). Among South Asian populations, only marginally significant results were detected (C allele: OR = 1.20, 95% CI: 1.02–1.40; dominant model: OR = 1.21, 95% CI: 1.05–1.41; recessive model: OR = 1.25, 95% CI: 1.01–1.64). In considering sample size subgroups, the OR was 1.29 (95% CI: 1.21–1.38; P<10^-5) in small studies compared to 1.23 (95% CI: 1.18–1.29; P<10^-5) in large studies. Further stratified according diagnostic criterion, significant results were found for both WHO and ADA criterion in all genetic models (Table 3). After adjusting for multiple testing using Bonferroni correction, all significant associations for rs2237895 under the co-dominant, dominant and recessive genetic models remained.

In meta-regression analysis, neither sample size (P=0.24), diagnostic criterion (P=0.50), mean BMI of cases (P=0.37) and controls (P=0.26), mean age of cases (P=0.05) and controls (P=0.22), nor sex distribution in cases (P=0.64) and controls (P=0.61) were significantly correlated with the magnitude of the genetic effect; while ethnicity (P=0.02) explained a large part of the heterogeneity.

Sensitivity Analyses and Publication Bias
A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data-set to the pooled ORs, and the corresponding pooled ORs were not qualitatively altered. The shape of the funnel plots was symmetrical for these polymorphisms (Figure S2 and S3). The statistical results still did not show small study effects in these studies for rs2237892 (Egger test, P=0.12) and rs2237895 (Egger test, P=0.07).

Discussion
Multiple lines of evidence support an important role for genetics in determining risk for T2D. Two independent GWA studies recently performed in Japanese populations identified KCNQ1 as a T2D susceptibility gene [9,16]. After that, a number of studies reported that common SNPs in KCNQ1 have been implicated in T2D risk. However, studies on the association between these polymorphism and T2D remain conflicting. This is the first meta-analysis involving a total of 169,645 subjects from 25 case-control studies examining the association of two commonly studied polymorphisms (rs2237892 and rs2237895) of KCNQ1 with T2D risk.

Our results demonstrated that the C alleles of rs2237892 and rs2237895 polymorphism of KCNQ1 are a risk factor for developing T2D. In the stratified analysis by ethnicity, significant associations were observed among different populations in all genetic models among East Asian, Caucasian and South Asian populations, which
Table 3. Meta-analysis of the KCNQ1 rs2237895 polymorphism on type 2 diabetes risk.

| Sub-group analysis | No. of data sets | No. of case/control C allele | Heterozygote | Homozygote | Dominant model | Recessive model |
|--------------------|------------------|-----------------------------|--------------|------------|----------------|----------------|
|                    |                  |                             | OR (95%CI)   | P(Z)       | OR (95%CI)     | P(Z)           |
| Overall            | 26               | 37822/47195                 | 1.24 (1.20–1.29) | <10^-5     | 1.25 (1.19–1.32) | <10^-5         |
|                    |                  |                             | 1.009        |            | 1.54 (1.41–1.68) | <10^-5         |
|                    |                  |                             | 0.0004       |            | 1.32 (1.24–1.39) | <10^-5         |
|                    |                  |                             | 0.001        |            | 1.35 (1.26–1.45) | <10^-5         |
| Ethnicity          |                  |                             |              |            |                |                |
| East Asian         | 17               | 25713/20820                 | 1.30 (1.26–1.33) | <10^-5     | 1.69 (1.57–1.81) | <10^-5         |
|                    |                  |                             | 0.68         |            | 1.37 (1.32–1.44) | <10^-5         |
|                    |                  |                             | 0.0004       |            | 1.47 (1.38–1.57) | <10^-5         |
| South Asian        | 3                | 1658/1759                   | 1.20 (1.02–1.40) | 0.03       | 1.18 (1.01–1.38) | 0.04           |
|                    |                  |                             | 0.64         |            | 1.21 (1.05–1.41) | 0.01           |
|                    |                  |                             | 0.01         |            | 1.25 (1.01–1.64) | 0.04           |
| Caucasian          | 5                | 10274/24400                 | 1.12 (1.08–1.16) | <10^-5     | 1.24 (1.15–1.34) | <10^-5         |
|                    |                  |                             | 0.65         |            | 1.19 (1.10–1.27) | <10^-4         |
| Others             | 1                | 876/399                     | 1.26 (0.93–1.70) | 0.13       | 1.14 (0.98–1.33) | 0.08           |
|                    |                  |                             | NA           |            | NA             |                |
|                   |                  |                             | NA           |            | NA             |                |
|                   |                  |                             | NA           |            | 1.14 (0.98–1.33) | 0.08           |
|                   |                  |                             |              |            |                |                |
| Sample size        |                  |                             |              |            |                |                |
| Small              | 11               | 3382/7910                   | 1.29 (1.21–1.38) | <10^-5     | 1.74 (1.42–2.14) | <10^-5         |
|                    |                  |                             | 0.0001       |            | 1.40 (1.23–1.59) | <10^-5         |
|                    |                  |                             | 0.83         |            | 1.51 (1.26–1.81) | <10^-4         |
| Large              | 15               | 34440/39285                 | 1.23 (1.18–1.29) | <10^-5     | 1.25 (1.17–1.33) | <10^-5         |
|                    |                  |                             | 0.0007       |            | 1.51 (1.37–1.67) | <10^-4         |
|                    |                  |                             | 0.003        |            | 1.31 (1.22–1.44) | <10^-3         |
| Diagnostic criterion|                |                             |              |            |                |                |
| WHO criterion      | 17               | 28708/24862                 | 1.26 (1.20–1.33) | <10^-5     | 1.26 (1.17–1.34) | <10^-3         |
|                    |                  |                             | 0.002        |            | 1.59 (1.43–1.76) | <10^-3         |
|                    |                  |                             | 0.0004       |            | 1.33 (1.24–1.42) | <10^-3         |
|                    |                  |                             | 0.0001       |            | 1.40 (1.29–1.51) | <10^-3         |
| ADA criterion      | 6                | 8523/21585                  | 1.18 (1.12–1.24) | <10^-5     | 1.23 (1.11–1.36) | <10^-5         |
|                    |                  |                             | 0.0001       |            | 1.29 (1.16–1.42) | <10^-5         |
|                    |                  |                             | 0.31         |            | 1.22 (1.07–1.35) | <10^-3         |
| NA: Not Available. |                  |                             |              |            |                |                |

P(Z): Z test used to determine the significance of the overall OR.
P(Q): Cochran's chi-square Q statistic test used to assess the heterogeneity in subgroups.
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suggested a similar role of the polymorphism in different ethnicity with different genetic backgrounds and living environment. Meta-analysis is often dominated by a few large studies, which markedly reduces the evidence from smaller studies. By considering sample size, significantly increased T2D susceptibility in KCNQ1 risk allele carriers was also found both in large and small studies for all genetic models. However, our results suggest an overestimation of the true genetic association by small studies. Besides, studies using different diagnostic criterion also get consistent positive results. Furthermore, we explored potential sources of heterogeneity across studies and the possibility of publication bias.

The Kv7 channels are believed to play an important role in the pancreatic β-cells mediating repolarization of the membrane terminating Ca2+-influx and insulin secretion, and a Kv7 channel knock-out in rat islets as well as pharmacological inhibition of Kv7 channels in mouse β-cells have been reported to enhance glucose-stimulated insulin secretion [38–41]. The Kv7.1 channel, encoded by KCNQ1, is expressed in INS-1 cells and has been suggested to play an important role in maintaining the membrane potential in these cells [8]. Based on in vitro data and the association with T2D, there is compelling evidence suggesting an effect also on T2D-related quantitative traits with variation in this gene. The analyzed polymorphism rs2237892 was found to be associated with a fasting parameter of insulin secretion [homo-
estasis model assessment of β-cell function (HOMA-B)] in a Japanese sample and with an oral glucose tolerance test-derived insulin secretion parameter (corrected insulin response) in a European sample [9]. In addition, Qi et al. also confirmed the association of the KCNQ1 variants with impaired β-cell function estimated by HOMA-B [19]. Moreover, Jonsson et al. conducted a prospecptive population based study and found that rs2237895 indeed increases risk of future T2D and that this is due to failing β-cell function [20]. Recently, a variant in the KCNQ1 gene (rs2237892) was reported to be associated with second-phase insulin secretion by hyperglycaemic clamp technique [35]. This observation indicates that KCNQ1 might play a role in second-phase insulin secretion suggesting a novel potential link between KCNQ1 and impaired β-cell function via the decreased release of newly formed insulin following glucose stimulation. These association and functional studies combined with our meta-analysis suggest the KCNQ1 variants may be implicated in the pathogenesis of T2D mainly through impaired insulin secretion of pancreatic β-cells. Since rs2237892 and rs2237895 is located near the outside of a KCNQ1 exon, it does not change the amino acid sequence, indicating that further study of the biological function of this SNP is necessary.

Although it has been known for decades that both type 2 diabetes and obesity have a genetic basis [42], only a few of risk genes with robust and reproducible effects have been identified for these diseases. Unfortunately, almost all the studies included in current meta-analysis did not explore the interaction between KCNQ1 genotype and obesity. Recently, Yu et al. found that rs2237892 was associated with waist circumference, but the association and functional studies combined with our meta-analysis should be taken into consideration. First, although the funnel plot and Egger’s test showed no publication bias and although an exhaustive literature search was done, it is likely that some publications and unpublished data were overlooked. Selection bias for the meta-analysis might have occurred. Second, our results were based on unadjusted estimates, whereas a more precise analysis could be conducted if all individual raw data were available, which would allow for the adjustment by other co-

## Supporting Information

### Figure S1 The flow chart of the included studies.

(FIG)

### Figure S2 Begg’s funnel plot of KCNQ1 rs2237892 polymorphism and type 2 diabetes.

(FIG)

### Figure S3 Begg’s funnel plot of KCNQ1 rs2237895 polymorphism and type 2 diabetes.

(FIG)

### Checklist S1

(DOC)

## Author Contributions

Conceived and designed the experiments: YC. Performed the experiments: QMS KS XZS. Analyzed the data: QMS KS XZS. Contributed reagents/materials/analysis tools: QMS KS XZS. Wrote the paper: QMS KS YC.

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