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Association of $K_{ir}6.2$ gene *rs5219* variation with type 2 diabetes: A meta-analysis of 21,464 individuals

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ABSTRACT

Aims: *rs5219* is in *Potassium inwardly-rectifying channel, subfamily J, member 11 (KCNJ11) E23K* gene, located at 11p15.1. Researches on the association between *rs5219* gene polymorphism with type 2 diabetes mellitus (T2DM) were performed extensively, but the results remain controversial. To investigate the relationship, a meta-analysis involving 21,464 individuals was conducted.

Methods: Odds ratios (OR) and 95% confidence intervals (CI) were used to assess the strength of this association. Publication bias was evaluated with Begg's test. Our research includes three gene models: allelic genetic model (K-allele *vs.* E-allele), recessive genetic model (KK *vs.* EK + EE) and dominant genetic model (EE *vs.* EK + KK).

Results: In allelic genetic model, subgroup analysis demonstrated *rs5219* K-allele was relevant to T2DM risk in Caucasian (OR: 1.16, 95% CI: 1.09–1.24, P = 0.000) and East Asian (OR: 1.19, 95% CI: 1.13–1.26, P = 0.000), recessive genetic model indicated *rs5219* KK genotype was related to T2DM risk in Caucasian, East Asian, South Asian, and North African (OR: 1.27, 95% CI: 1.17–1.38, P = 0.000), dominant genetic model pointed out *rs5219* EE genotype was an opposite association with T2DM risk in Caucasian (OR: 0.86, 95% CI: 0.78–0.94, P = 0.001). No obvious evidence of publication bias was found.

Conclusions: There was a believable evidence to verify that *rs5219* variation was associated with T2DM.

1. Introduction

Diabetes mellitus (DM) is a kind of severe disorder since it strongly increases the risk of cardiovascular complications, such as coronary artery disease, myocardial infarction, hyper-

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tension, and dyslipidemia [1–3]. In 2015 it was estimated that there were 415 million (uncertainty interval: 340–536 million) people with diabetes aged 20-79 years, 5.0 million deaths attributable to diabetes, and the total global health expenditure due to diabetes was estimated at 673 billion US dollars. Three quarters (75%) of those with diabetes were living in low-and middle-income countries, lacking of primary care. The number of people with diabetes aged 20–79 years was predicted to rise to 642 million (uncertainty interval: 521–829 million) by 2040 [4]. Among all diabetic cases, approximately 90% are patients with type 2 diabetes mellitus (T2DM). T2DM is caused by a plethora of lifestyle and genetic factors [5,6]. In the past two decades, numerous T2DM susceptibility genes have been distinguished by a candidate gene approach, family linkage studies, and gene expression profiling [7–10].

Adenosine triphosphate (ATP)-sensitive potassium ion channel (K_{ATP}) plays a pivotal role in insulin secretion by glucose-stimulated pancreatic β-cells [11]. *Potassium inwardly-rectifying channel, subfamily J, member 11(KCNJ11)*, which encodes the subunit protein of K_{ATP} (Kir6.2), is highly expressed in the pancreas. Mutation in the *KCNJ11 E23K* gene could set the stage for the descending sensitivity of the ion channel to ATP, which makes the channel consume more ATP until it is closed. As a result, insulin release is damaged and the the risk of T2DM is increased [12]. Located at 11p15.1, *KCNJ11* gene spans 2 kb and contains 1 exon that encodes 390 amino acids [13]. *KCNJ11 E23K* genovariation is located in the 1st exon and formed by missense mutation of the 23rd codon. The substitution variation of adenine (A base) for guanine (G base) in the 23rd codon displaces glutamine (E) with lysine (K) in the corresponding amino acid sequence.

Although studies on *E23K* gene *rs5219* has been shown to be associated with T2DM in many populations [14–30], but the results remain controversial. Thus, our meta-analysis, which included 10,163 T2DM patients and 11,301 control individuals from 17 separate studies, was carried out to ascertain the association between *KCNJ11 E23K* gene *rs5219* polymorphism and T2DM.

2. Methods

2.1. Search strategy

PubMed and Web of Science search up to July 7, 2017, using keywords containing "*Kir6.2*" or "*E23K*" or "*KCNJ11*" or "*rs5219*"; "polymorphism" or "variant" or "mutation" and "type 2 diabetes mullitus" or "type 2 diabetes" or "T2DM" or "T2D".

The search was performed in duplicate by two independent reviewers (*Dongdong Wang and Xiao Chen*). Only the studies with complete genotype data were selected. Articles with incomplete data were not included in our meta-analysis.

2.2. Inclusion criteria and exclusion criteria

The selected studies had to conform with the major criteria as follows: (I) Evaluation of the *KCNJ11 E23K* gene *rs5219* polymorphism and T2DM. (II) the study was a case-control study. (III) the study included sufficient genotype numbers for cases and controls. Accordingly, the following exclusion criteria were also used: (I) the control population was absent from the study. (II) the genotype frequency was not specified in the study. (III) the study was a duplicate of previous publications. (IV) Deviation from Hardy–Weinberg equilibrium (HWE)

2.3. Data extraction

The following items were collected: first author, publication year, country, ethnicity, case number, control number, all genotype frequencies of case and control groups, mutant-allele frequency and HWE of controls.

2.4. Statistical analysis

Odds ratios (OR) with 95% confidence intervals (CI) were used to measure the strength of association of *rs5219* mutation with T2DM. Subgroup analysis was executed on four different portions, where necessary: Caucasian, East Asian, South Asian, North African. The summary OR was determined with the Z-test and $P < 0.05$ was considered statistically significant. Heterogeneity assumption was evaluated with the chi-square-based Q-test and a P value <0.05 for the Q-test or I-squared >50% indicated that heterogeneity may exist. In case significant heterogeneity was detected, the subgroups analysis was used. Otherwise, the fixed effects model (Mantel–Haenszel method) was chosen. For *rs5219* gene polymorphism, we investigated the relationship between genetic variant and T2DM risk using allelic genetic model (K-allele *vs.* E-allele), recessive genetic model (KK *vs.* EK + EE), dominant genetic model (EE *vs.* EK + KK). Publication bias was evaluated with Begg's test and Begg's funnel plot, $P < 0.05$ was considered statistically significant. The Fisher's exact test was used to assess the Hardy–Weinberg equilibrium with the significance set at $P < 0.05$. All statistical tests for the meta-analysis were performed with RevMan software (*version 5.30; the Nordic Cochrane Centre, Copenhagen, Denmark*) and STATA software (*version 12.0; Stata Corp LP, College Station, TX, USA*).

3. Results

3.1. Eligible studies

We found 52 published articles, but only 17 articles with genotype frequency information were used in our meta-analysis. Of the 35 excluded researches, 11 papers were reviews, 20 studies were not involved with the *rs5219* gene polymorphism, and 4 studies were disregarded for deviating from the HWE (Fig. 1). The complete data were collected from 10,163 T2DM patients and 11,301 controls (Table 1) from Caucasian, East Asian, South Asian and North African, respectively.

3.2. Allelic genetic model

Heterogeneity was significant for the allelic genetic model ($P_{heter} = 0.002$, $I^2 = 56.7\%$) (Table 2). Analysis of ethnicity subgroups showed statistically significant association in Caucasians (OR: 1.16, 95% CI: 1.09–1.24, $P = 0.000$) and East Asian (OR: 1.19, 95% CI: 1.13–1.26, $P = 0.000$) and no significant heterogeneity were observed for Caucasians ($P_{heter} = 0.513$, $I^2 = 0.0\%$)

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