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A meta-analysis about the association between −1082G/A and −819C/T polymorphisms of *IL-10* gene and risk of type 2 diabetes

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ABSTRACT

The present meta-analysis was conducted to investigate the association between the −1082G/A and −819C/T polymorphisms of the *IL-10* gene and risk of type 2 diabetes mellitus (T2DM). Relevant articles were identified by searching PubMed, Embase, and Web of Science. Pooled odds ratios (ORs) were used to assess the strength of the association between target polymorphisms and the risk of T2DM. Significant associations between the −1082G/A polymorphism and T2DM were found for the allele contrast (OR = 0.90, 95% CI: [0.83, 0.98], $P = 0.02$), homozygote contrast (OR = 0.82, 95% CI: [0.69, 0.97], $P = 0.02$), and recessive genetic model (OR = 0.85, 95% CI: [0.74, 0.96], $P = 0.01$). However, no significant association was found for the dominant genetic model (OR = 0.91, 95% CI: [0.80, 1.05], $P = 0.08$). The association between −819C/T polymorphism and T2DM was significant for the allele contrast (OR = 0.73, 95% CI: [0.64, 0.84], $P < 0.01$); however, no significant associations were found for −819C/T in the homozygote contrast (OR = 1.01, 95% CI: [0.38, 2.67], $P = 0.99$), dominant genetic model (OR = 0.94, 95% CI: [0.50, 1.77], $P = 0.86$), and recessive genetic model (OR = 0.92, 95% CI: [0.50, 1.68], $P = 0.78$). No significant publication bias was detected. This meta-analysis suggests that allele A of −1082G/A and allele C of −819C/T in the *IL-10* gene have potentially protective effects in terms of risk of T2DM.

1. Introduction

Type 2 diabetes mellitus (T2DM) is becoming increasingly prevalent worldwide. It is expected that this latent disorder affected 200 million people in 2010 and will affect 300 million in 2025. The majority of this increase will occur in developing countries where medical resources are limited [1,2]. T2DM accounts for approximately 90% of all diabetes cases and is referred to as non-insulin dependent diabetes mellitus or adult-onset diabetes [3]. Recent studies have shown that several genetic and environmental factors are associated with T2DM.

Cytokines play a crucial role in different immunopathological conditions, and cytokine secretion is determined by polymorphisms in the cytokine genes [4]. Interleukin-10 (*IL-10*) is involved in regulation of inflammation and *IL-10* demonstrates broad-spectrum anti-inflammatory activity; its circulating level can therefore serve as an indicator of many diseases including T2DM [5]. The *IL-10* gene has been mapped to chromosome 1q and three biallelic polymorphisms in the *IL-10* promoter region, the −1082G/A (rs1800896), −819C/T (rs1800871), and −592C/A (rs1800872) single nucleotide polymorphisms (SNPs), were shown to affect the level of *IL-10* production [6]. However, the association between these SNPs and T2DM remains widely disputed. A recent meta-analysis [7] suggested that the −1082G/A polymorphism of the *IL-10* gene might be associated with increased risk of coronary artery disease, especially in Caucasian populations. While it is known that diabetes is one of the most important risk factors of coronary artery disease, a recent meta-analysis [8] showed that the −592C/A polymorphism of the *IL-10* gene is not associated with the risk of T2DM. Therefore, we hypothesized that at least one of the remaining two SNPs, the −1082G/A polymorphism and −819C/T polymorphism of *IL-10*, may be associated with T2DM. In order to overcome the limitations of individual studies, this meta-analysis was performed to find a more robust association between the −1082G/A and −819C/T polymorphisms and risk of T2DM. To the best of

Abbreviations: FEM, fixed effect model; HWE, Hardy–Weinberg equilibrium; PRISMA, preferred reporting items for systematic reviews and meta-analyses; REM, random effect model; SNP, single nucleotide polymorphism; T2DM, Type 2 diabetes mellitus.

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the authors' knowledge, this is the first meta-analysis assessing the relationship between the −1082G/A and −819C/T polymorphisms of *IL-10* gene and risk of T2DM.

2. Methods

2.1. Search strategy

To identify all relevant studies, a computerized literature search was conducted using the electronic databases PubMed, Embase, and Web of Science. The search was based on the following keywords: "*IL-10*" or "interleukin-10", "gene" or "polymorphism" or "variant," and "diabetes". Reference sections of the retrieved articles were also screened for relevant studies. This search strategy was performed iteratively until no new relevant articles were found. All articles identified through this search strategy were published on or before August 27, 2012. This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [9].

2.2. Selection criteria

First, titles and abstracts of all relevant papers were reviewed. Then, full-texts were reviewed as a second screening. The studies ultimately chosen for inclusion in the analysis met the following criteria: (i) the study design was a case-control study; (ii) the −1082G/A polymorphism of the *IL-10* gene was tested in T2DM patients and non-T2DM controls; (iii) the papers identified sample size, distribution of alleles, genotypes, or other information that can help to infer the results; (iv) when multiple publications reported on the same or overlapping data, the most recent article or the article based on the largest study population was selected [10]; and (v) the publication language was limited to English and Chinese. A study was excluded if it did not meet the inclusion criteria. In addition, reviews, editorials, meeting abstracts, and commentaries were excluded from our analysis.

2.3. Data extraction

Data were extracted independently by two reviewers (Zhang F. and Yang Y.). Consensus was reached by discussion and a third party (Wang Y.) was involved when necessary. The following information was extracted from each article: first author, year of publication, country where study was conducted, ethnicity of subjects, source of control group (population-based or hospital-based), demographic characteristics of case and control groups (including age and gender), ascertainment of diagnosis of diabetes, method of genotype assay, deviation from HWE (Hardy–Weinberg Equilibrium) of the control group, and distributions of alleles and genotypes in the case and control groups.

2.4. Risk of bias in individual studies

According to the PRISMA Statement, risk of bias in individual studies should be thoroughly assessed and described based on both "study level" (e.g., adequacy of allocation concealment) and "outcome level" (e.g., reliability and validity of the data). Quality scoring criteria (see Appendix Table) were modified from previous meta-analyses of observational studies [11–13]; these criteria are specifically intended for use in assessing the risk of bias in individual studies independently by the same two reviewers. For the present study, Zhang F. and Yang Y. scored each included study, and total scores ranged from 0 (worst) to 11 (best).

2.5. Statistical analyses

Crude ORs with their 95% confidence intervals (CIs) for alleles and genotypes were used to assess the strength of association between the −1082G/A and −819C/T polymorphisms of the *IL-10* gene and risk of T2DM. The pooled ORs were performed for the allele contrast, homozygote contrast, dominant genetic model, and recessive genetic model. The heterogeneity assumption was assessed using an *I*-squared test. Study heterogeneity was not considered significant when $I^2 < 50\%$. When no significant heterogeneity was found, the pooled OR of all studies was calculated by the fixed effects model (FEM), more specifically the Mantel–Haenszel method [14]. Otherwise, the random effects model (REM), specifically the DerSimonian and Laird method, was used. Subgroup analyses were conducted on the basis of subject ethnicity. Sensitivity analyses were performed by removal of individual studies that deviated from the HWE assumption in controls. If the original article did not mention HWE in controls, we calculated it by using online HWE software provided through the Online Encyclopedia for Genetic Epidemiology Studies (website: http://www.oege.org/software/hwe-mr-calc.shtml) [15].

Potential publication bias was assessed by visual inspection of a funnel plot. Moreover, the Begg's rank correlation test [16] and Egger's linear regression test [17] were performed (significance level of 0.10). All statistical tests were conducted with STATA Version 11.0 and the Cochrane Collaboration meta-analysis software, Review Manager 5.1. A *P* value of 0.05 for any test or model was considered to be statistically significant unless otherwise specified.

3. Results

3.1. Literature search

Initially, a total of 855 citations were retrieved. The majority of these were excluded after the first screening of titles and abstracts, mainly because the studies were duplicates, were conducted with type 1 or gestational diabetes populations, or were based on animal experiments. During the full-text review, another one relevant publication was found through reference screening. Ultimately, 14 additional studies were excluded and 10 studies [18–27] remained for final data synthesis. The details of the retrieval and exclusion process are shown in Fig. 1.

3.2. Eligible studies

Nine studies with 2369 cases and 2720 controls were included in the analysis of the −1082G/A polymorphism and four studies with 1397 cases and 987 controls were included in the analysis of the −819C/T polymorphism. Each of the included studies was published between 2004 and 2012. The overall study characteristics are shown in Table 1 and Table 2. All of the included studies were case-control studies. Five studies were conducted with Caucasian samples, four with Asian samples, and one with an African sample. The cases were diagnosed with T2DM based on World Health Organization (WHO) criteria or the American Diabetes Association (ADA) guidelines using oral glucose tolerance test or fasting blood glucose. All controls were sampled from a healthy or non-diabetic population. Only three studies described whether the allele distributions of controls were in HWE [18,21,24]. When it was not explicitly mentioned, we determined HWE. It was found that the allele distributions of only two studies' controls [21,26] deviated from HWE. Finally, the source of controls was population-based in five studies and hospital-based in all other included studies.