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Short Communication

The lack of association between interleukin-6 gene −174 G/C polymorphism and the risk of type 1 diabetes mellitus: A meta-analysis of 18,152 subjects

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ABSTRACT

Epidemiological studies have evaluated the association between interleukin-6 (IL-6) gene −174 G/C polymorphism and type 1 diabetes mellitus (T1DM) risk, but results of different studies have been inconsistent. The present meta-analysis was therefore designed to clarify these controversies. PubMed, Embase and Web of Science were searched from the first available year to March 25, 2012, as well as hand searching of the references of identified articles were performed. All studies investigating the association between IL-6 gene −174 G/C polymorphism and T1DM risk were included. Data analyses were carried out by Review Manager 5.1.2 and Stata 11.0. Seven studies were included in the final meta-analysis, covering a total of 9697 T1DM cases and 8455 controls. The results showed no evidence for significant association between IL-6 gene −174 G/C polymorphism and T1DM risk (for C/C + C/G vs. G/G: OR = 1.30, 95% CI = 0.84–2.00, p = 0.24; for C/C vs. C/G + G/G: OR = 1.10, 95% CI = 0.75–1.60, p = 0.63; for C/C vs. G/G: OR = 1.34, 95% CI = 0.75–2.42, p = 0.33; for C allele vs. G allele: OR = 1.16, 95% CI = 0.88–1.53, p = 0.30). In addition, the similar results were obtained in the subgroup analysis based on ethnicity. In summary, the present meta-analysis suggests that IL-6 gene −174 G/C polymorphism is not associated with T1DM risk. However, due to the small sample size in most of the included studies and the selection bias existed in some studies, the results should be interpreted with caution.

1. Introduction

Type 1 diabetes mellitus (T1DM) is a multifactorial autoimmune disorder characterized by the destruction of β cells in Langerhans islets of the pancreas (Settin et al., 2009). T1DM seriously affects the quality of life for patients and national healthcare systems, and its prevalence in the general population has been evaluated to be approximately 2–3% (Frisk et al., 2008; Van den Driessche et al., 2009). Despite its results from synthetically action involving environmental and genetic factors, a detailed etiology underlying T1DM is still unclear. It is well known that inflammatory response is an essential part of the pathogenesis of T1DM (Rabinovitch and Suarez-Pinzon, 1998), suggesting that the cytokines involved in inflammatory response may play an important role in the development of T1DM.

Interleukin-6 (IL-6), as a multifunctional cytokine, plays a key role in the inflammatory response that is associated with insulin-resistant states (Pickup et al., 1997). The gene encoding IL-6 is located on chromosome 7p21 and the single-nucleotide polymorphism at the 50 flanking region of the IL-6 gene promoter (−174 G/C) has been identified in 1998 (Fishman et al., 1998). Previous studies have reported that the G-to-C mutation in this promoter region could affect IL-6 gene transcription and its serum levels (Brull et al., 2001; Fishman et al., 1998; Nauck et al., 2002), thus influencing the inflammatory process of T1DM. Recently a variety of epidemiological studies have focused on the association between IL-6 gene −174 G/C polymorphism and T1DM. However, results of different studies have been inconsistent. To comprehensively evaluate the genetic risk of −174 G/C polymorphism in IL-6 gene for T1DM, we performed a meta-analysis by collecting and sorting the previous published studies.

2. Materials and methods

2.1. Data sources

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria (Moher et al., 2009). We carried out a search, collecting all published studies on humans up to March 25, 2012. The following electronic databases were systematically searched for relevant studies: PubMed, Embase

Abbreviations: T1DM, type 1 diabetes mellitus; IL-6, interleukin-6; PRISMA, Systematic Reviews and Meta-analyses; MeSH, medical subject headings; OR, odds ratio; CI, confidence interval; HWE, Hardy–Weinberg equilibrium; NOS, Newcastle–Ottawa Scale; PB, population-based.

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and Web of Science. The text word terms and medical subject headings (MeSH) used were: ("interleukin-6" or "IL-6") and ("polymorphism" or "mutation" or "variant" or "genotype") and ("type 1 diabetes mellitus" or "type 1 diabetes" or "diabetes mellitus" or "diabetic patients"). Furthermore, hand searching of the references of identified articles was performed.

2.2. Inclusion criteria

Studies were included if they met the following five inclusion criteria: (1) evaluation of the association between IL-6 gene −174 G/C polymorphism and T1DM risk; (2) published case-control studies; (3) studies with full text articles; (4) not republished data, and (5) sufficient data for calculation of odds ratio (OR) with 95% confidence interval (CI).

2.3. Data extraction

Two authors (Yin YW and Sun QQ) independently screened the title and abstract of each potentially eligible article by the search strategy and inclusion criteria. Any disagreement in opinion was resolved by discussion with a third investigator (Zhang BB). The following data were collected from each study: (1) name of the first author; (2) year of publication; (3) country of origin; (4) ethnicity of the studied population; (5) source of controls; (6) number of cases and controls, and (7) available allele and genotype frequency information. Furthermore, evidence of Hardy–Weinberg equilibrium was collected (HWE, $p<0.05$ of HWE was considered significant).

2.4. Quality score assessment

The quality of included studies was evaluated independently by two authors (Hu AM and Liu HL) of this article according to the Newcastle–Ottawa Scale (NOS) (Wells et al., 2011). The NOS ranges between zero (worst) and nine stars (best). Studies with a score equal to or higher than seven were considered to be of high quality. Disagreement was resolved by discussion.

2.5. Statistical methods

Crude OR with their 95% CI was estimated and used to assess the strength of association between IL-6 gene −174 G/C polymorphism and T1DM risk. The pooled OR was calculated respectively for dominant model (C/C + C/G vs. G/G), recessive model (C/C vs. C/G + G/G), additive model (C/C vs. G/G) and allelic model (C allele vs. G allele).

Heterogeneity among studies was examined using Cochran's Q statistic and the I^2 statistic ($p<0.10$ and $I^2>50\%$ indicated the evidence of heterogeneity) (Berkey et al., 1995; Higgins et al., 2003). If there was no statistical heterogeneity among studies, the fixed-effect model was used; otherwise the random-effect model was used (DerSimonian and Laird, 1986; Mantel and Haenszel, 1959). Subgroup analysis was performed by ethnicity. Sensitivity analyses were carried out by limiting the meta-analysis to studies conforming to HWE and the high quality studies (according to the NOS score). An estimate of potential publication bias was carried out by Begg's funnel plot and Egger's regression test ($p<0.05$ was considered representative of statistically significant publication bias) (Egger et al., 1997). All the statistical tests were performed using the software Review Manager 5.1.2 and Stata 11.0.

3. Results

3.1. Characteristics of included studies

The study selection process is detailed in Fig. 1. Based on our search strategy, 793 potentially eligible articles were identified in our initial search. Of these, 786 articles were excluded based on the inclusion criteria. Finally, seven articles met the inclusion criteria and were included in the meta-analysis (Cooper et al., 2007; Jahromi et al., 2000; Javor et al., 2010; Myśliwiec et al., 2008; Myśliwska et al., 2009; Pérez-Bravo et al., 2011; Settin et al., 2009; Tsiavou et al., 2004), which contained 9697 T1MD cases and 8455 controls. Table 1 shows the studies included in the meta-analysis and their main characteristics. Six studies were performed in Caucasians, and one study was performed in mixed populations. The countries of these studies included Chile, Egypt, England, Greece, Poland, Slovakia and UK. Two studies did not follow the HWE ($P<0.05$) (Myśliwska et al., 2009; Settin et al., 2009). The NOS results showed that the average score was 7.3, which indicated that the methodological quality was generally good.

3.2. Quantitative synthesis

The association between IL-6 gene −174 G/C polymorphism and T1DM risk was investigated in eight studies with a total of 9697 T1MD cases and 8455 controls. Given that significance between-study heterogeneity existed in overall comparisons (for C/C + C/G vs. G/G: $P_Q<0.00001$, $I^2=84\%$; for C/C vs. C/G + G/G: $P_Q=0.007$, $I^2=66\%$; for C/C vs. G/G: $P_Q<0.0001$, $I^2=80\%$; for C allele vs. G allele: $P_Q<0.00001$, $I^2=84\%$), we used the random-effect model. Overall, there was no significant association found between IL-6 gene −174 G/C polymorphism and T1DM risk (for C/C + C/G vs. G/G: OR = 1.30, 95% CI = 0.84–2.00, $p=0.24$; for C/C vs. C/G + G/G: OR = 1.10, 95% CI = 0.75–1.60, $p=0.63$; for C/C vs. G/G: OR = 1.34, 95% CI = 0.75–2.42, $p=0.33$; for C allele vs. G allele: OR = 1.16, 95% CI = 0.88–1.53, $p=0.30$). The main results of meta-analysis were shown in Table 2 and Fig. 2, respectively.

In the subgroup analysis by ethnicity, we only analyzed the Caucasians as just one study involved in mixed populations. We obtained similar results that no significant association was found in all genetic models. The results of subgroup analysis quantitatively illustrated that IL-6 gene −174 G/C polymorphism was not associated with T1DM risk. The main results of subgroup analysis were shown in Table 2.

3.3. Sensitivity analysis

Sensitivity analyses were performed to assess the stability of the results. The included studies of sensitivity analyses were limited to those conforming to HWE and those with high NOS score (≥7). Two studies without HWE ($p<0.05$) (Myśliwska et al., 2009; Settin et al., 2009) and one study with relatively low NOS score (<7) (Cooper et al., 2007) were excluded from the sensitivity analyses. All the results were not materially altered, which suggested that our results were statistically robust. The results of sensitivity analyses were shown in Table 2.

3.4. Publication bias

The shapes of the funnel plots did not reveal any evidence of obvious asymmetry in all genetic models (Fig. 3). Meanwhile, the results of Egger's regression test still did not provide any evidence of publication bias ($p=0.277$ for dominant model, $p=0.313$ for recessive model, $p=0.287$ for additive model, and $p=0.764$ for allelic model, respectively).

4. Discussion

T1DM is a complex disease which severely affects human health. Epidemiological studies indicate that the incidence of T1DM is rising worldwide (Onkamo et al., 1999), especially in childhood. Recently, the association between IL-6 gene −174 G/C polymorphism and T1DM risk has been intensively studied. However, results in different studies have been inconsistent. Most studies reported that IL-6 gene −174 C allele was associated with the risk of T1DM (Cooper et al., 2007; Pérez-Bravo et al., 2011; Settin et al., 2009). Several other studies demonstrated that G allele was associated with the development of T1DM (Jahromi et al., 2000; Myśliwiec et al., 2008). However, the studies of Myśliwska et al. and Javor et al. suggested that IL-6 gene