IL-6 gene rs1800795 polymorphism and diabetes mellitus: a comprehensive analysis involving 39099 participants

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Abstract
Background Over the past two decades, many studies concentrated the association between a common polymorphism (rs1800795) from interleukin-6 (IL-6) gene and Diabetes Mellitus (DM) risk have been published, however, the results remain ambiguous and indefinite. Methods In current, we performed a comprehensive analysis to explore above relationship. A search was conducted in the PubMed, Embase, Chinese (CNKI and Wanfang) databases, covering all papers published until Sep 20, 2019. Odds ratios (OR) with 95% confidence intervals (CI) was applied to evaluate the strength of this association. Publication bias was assessed with both Begg and Egger’s tests. Results Overall, 26 case-control studies with 5973 T2DM patients and 13968 controls, and 11 case-control studies (10193 T1DM patients and 8965 health controls) were included for analysis in our study. Finally, significant decreased association was observed between the rs1800795 polymorphism and T2DM risk in overall sample, Asians and hospital-based subgroup (for example: C-allele vs. G-allele: OR = 0.65, 95%CI = 0.53-0.81, P < 0.05), however, increased associations were found from Mixed population and hospital-based subgroup between rs1800795 polymorphism and T1DM susceptibility (for example: CC vs. GG: OR = 2.45, 95%CI = 1.18-5.07, P = 0.016 for Mixed individuals). Conclusions In summary, there had a definite evidence to confirm that IL-6 rs1800795 polymorphism was associated with susceptibility of decreased T2DM and increased T1DM.

Background
Diabetes Mellitus (DM) is a chronic medical condition in which the body either produces too little insulin from pancreatic islet or has a lack of effective access to insulin [1]. Type 1 DM (T1DM) is most often diagnosed in children and adolescents about the development of islet function. Type 2 DM (T2DM) is due to insulin resistance, that the body can’t use insulin effectively and may gradually mislay the production capacity [2-4]. To our current knowledge, age, obesity and a family history are risk factors for developing of DM [5]. However, the exact pathogenesis of DM is still not fully understood. Past genome-wide association studies (GWAS) already identified over 100 genetic sites, which supported that there have significantly associations between different sites and susceptibility of DM, it also means genetic factors may be crucial for its occurrence and development [6, 7].
Interleukin-6 (IL-6), as a classic proinflammatory cytokine, plays a prominent role in inflammatory response, which is associated with insulin-resistant states and T2DM [8]. In addition, chronic low-grade inflammation and activation of the innate immune system are closely involved in the pathogenesis of T1DM and its complications. Inflammatory cytokines, such as IL-6, are shown to be determinant in these pathogenic processes [9, 10].

The IL-6 gene is located at chromosome 7p21. The gene including seven exons covers approximately 12.8 kb of genomic DNA [11]. A common single nucleotide polymorphism (SNP) in the IL-6 promoter was first discovered and identified, named rs1800795 (also named -174G/C) in T2DM [12]. The rs1800795 polymorphism has been suggested to functionally affect IL-6 promoter activity, which showed the carried CC genotype individual is associated with lower plasma levels of IL-6 compared with individuals with GG genotype [13], in addition, whose G-allele in homozygous (GG genotype) was associated with higher concentrations of IL-6 increasing the immune response [14, 15].

Several epidemiological studies have supported the associations between genetic variants of IL-6 and risk of DM. For instance, Saxena et al. suggested rs1800795 polymorphism showed a highly significant association with T2DM [16]. On the contrary, Dhamodharan et al. determined C-allele conferred significant protection against T2DM [17]. Besides, Fathy et al. [18] demonstrated that the lack of significant association between rs1800795 polymorphism and T2DM was detected. For T1DM, increased association was found between T1DM and this polymorphism from Cooper et al. [19], however, Tsiavou et al. observed no significant differences were existed [20]. Two meta-analyses (Yin and Xu et al.) both showed that rs1800795 was not associated with T1DM risk [21, 22]. Although, Huth and Xia et al. both made meta-analysis and had a conclusion that this polymorphism could be associated with the decreased risk of T2DM [23, 24], little aspects had significant results. In the last ten years, some larger and comprehensive research on the association has been carried out and published. For the controversial conclusions between rs1800795 polymorphism and T1DM/T2DM, it is necessary to perform an updated meta-analysis to clarify the association [12, 15-20, 25-52].

Methods

Document retrieval and data extraction
We made use of searches on databases, including Pubmed, Embase, CNKI and Wanfang, until on Sep 20, 2019, with keywords including ‘Interleukin-6/IL-6’, ‘polymorphism/variant’ and ‘Diabetes Mellitus/DM/TIDM/T2DM’. Eligible studies must be according with the following criteria: @) the studies assess the association between TIDM or T2DM and rs1800795 variants; @) case/control studies; @) age-and gender-matched control subjects. The criteria for exclusion were @) not case/control studies; @) insufficient genotype frequency; @) duplicated studies and @) significantly biased articles. The information including name of first author, year of publication, origin, race, DM type, genotype methods, Hardy-Weinberg equilibrium (HWE) were collected.

**Statistic analysis**

The correlation between *IL-6 rs1800795* polymorphism and the risk of TIDM/T2DM was measured by 95%CI and OR according to the genotype frequencies of cases and control groups. Ethnic group are divided into African, Mixed, Caucasian and Asian. Population-based (PB) and hospital-based (HB) control subgroups were collected.

The statistical significance of the summary is calculated by Z-test. In these studies, the heterogeneity hypothesis was assessed by Q-test based on chi-square [53]. If significant heterogeneity (< 0.1) is detected, the random model is carried out, otherwise the fixed effect model is selected [54, 55]. For *IL-6 rs1800795*, we studied the relationship between variation and the risk of T2DM in C-allele vs. G-allele, CG vs. GG and CC+CG vs. GG models; and C-allele vs. G-allele, CC vs. GG, CC vs. CG+GG, CG vs. GG and CC+CG vs. GG models for TIDM risk. The asymmetry of funnel plot was evaluated by Begg’s test, and the publication bias was evaluated by Egger’s test, whose *P*-value < 0.05 was considered significant [56]. Pearson chi-square test was used in the control group (*P* < 0.05), and $\chi^2$ test was used to evaluate the deviation of *rs1800795* polymorphism from the expected frequency of HWE [57]. All above statistical tests were conducted using Stata (Version 11.0; Statacorp LP, College Station of Texas). The power of our meta-analysis was calculated online using the website [http://www.power-analysis.com/](http://www.power-analysis.com/).
Results

Study selection and characteristics

A total of 1134 articles were identified from main four databases (Pubmed, Embase, CNKI and Wanfang) based on above search criteria. Among them, 35 articles were excluded because of following reasons: systematic analysis/meta-analysis (8), just only case study (6), other polymorphisms in IL-6 gene (12), not sufficient data of each genotype (5) and duplication (4) (Figure 1). Thus, a total of 40 different articles [13-18] accounting for a total of 16581 DM patients and 23799 healthy controls were included in our meta-analysis (29 case-control studies including 6388 T2DM patients and 10193 controls, and 11 case-control studies including 14834 T1DM and 8965 controls, respectively) (Table 1). Additionally, we tried to compare the minor allele frequency (MAF) between our current study and data from 1000Genomes (https://www.ncbi.nlm.nih.gov/snp/rs1800795#frequency_tab). Five types of ethnicity are listed from 1000Genomes: African:0.018, East Asian: 0.001, Europe: 0.416, South Asian:0.14, American:0.18 (Figure 2). The MAF of T2DM subjects and controls was 0.331 and 0.387, respectively; of T1DM patients and controls was 0.331 and 0.43, respectively. The distribution of genotypes in controls was not consistent with the HWE in T2DM (9 case-controls) and T1DM (2 case-controls), respectively (Table 1). Genotyping of the SNPs of IL-6 gene rs1800795 polymorphism was conducted using some different genotype methods in Table 1.

IL-6 rs1800795 polymorphism and T2DM risk.

The results of the overall meta-analysis suggested negative associations between this polymorphism and T2DM susceptibility in two genetic models (OR_{C-allele vs. G-allele} = 0.85, 95% CI = 0.75–0.96, $P_{\text{heterogeneity}} < 0.001$, $P = 0.008$; OR_{CC+CG vs. GG} = 0.84, 95% CI = 0.70–0.99, $P_{\text{heterogeneity}} < 0.001$, $P = 0.039$) (Table 2, Figure 3a). If these studies not consistent with HWE were excluded, no significant result were detected in all three models. Analysis of ethnicity subgroups showed statistically significant association in Asians (OR_{C-allele vs. G-allele} = 0.65, 95% CI = 0.53–0.81, $P_{\text{heterogeneity}} = 0.060$, $P < 0.001$; OR_{CC+CG vs. GG} = 0.72, 95% CI = 0.51–1.00, $P_{\text{heterogeneity}} = 0.006$, $P$
= 0.053, **Figure 3b**). To our surprise, a marginally and poorly significant difference was found in the HB sources of control subgroup (OR\textsubscript{C-allele vs. G-allele} = 0.82, 95% CI = 0.69–0.97, \(P_{\text{heterogeneity}} < 0.001\), \(P < 0.022\), **Figure 4**) (**Table 2**).

**IL-6 rs1800795 polymorphism and T1DM risk.**

There was no significantly positive association between rs1800795 polymorphism and T1DM susceptibility in both total and subgroup consistent with HWE (for example: OR\textsubscript{C-allele vs. G-allele} = 1.16, 95% CI = 0.94–1.42, \(P_{\text{heterogeneity}} < 0.001\), \(P = 0.162\), OR\textsubscript{CC vs. GG} = 1.38, 95% CI = 0.87–2.17, \(P_{\text{heterogeneity}} < 0.001\), \(P = 0.169\); studies consistent with HWE: OR\textsubscript{CG vs. GG} = 1.19, 95% CI = 0.89–1.58, \(P_{\text{heterogeneity}} = 0.003\), \(P = 0.235\), OR\textsubscript{CC+CG vs. GG} = 1.18, 95% CI = 0.86–1.62, \(P_{\text{heterogeneity}} < 0.001\), \(P = 0.306\)) (**Table 3**). The important finding was that there had a risk association between this polymorphism in Mixed population (OR\textsubscript{C-allele vs. G-allele} = 1.39, 95% CI = 1.10–1.77, \(P_{\text{heterogeneity}} = 0.497\), \(P = 0.006\), OR\textsubscript{CC vs. GG} = 2.45, 95% CI = 1.18–5.07, \(P_{\text{heterogeneity}} = 0.486\), \(P = 0.016\), OR\textsubscript{CC+CG vs. GG} = 1.43, 95% CI = 1.07–1.90, \(P_{\text{heterogeneity}} = 0.724\), \(P = 0.015\), OR\textsubscript{CG vs. CG+GG} = 2.20, 95% CI = 1.08–4.48, \(P_{\text{heterogeneity}} = 0.487\), \(P = 0.031\), **Figure 5a,b,c,d**). Similar relationships were observed for sources of HB subgroup (for example: OR\textsubscript{C-allele vs. G-allele} = 1.29, 95% CI = 1.07–1.56, \(P_{\text{heterogeneity}} = 0.122\), \(P = 0.009\), OR\textsubscript{CG vs. GG} = 1.47, 95% CI = 1.11–1.94, \(P_{\text{heterogeneity}} = 0.428\), \(P = 0.008\), **Figure 6a,b,c,d** (**Table 3**).

**Publication bias and sensitive analysis**

Begg’s and Egger’s test were performed to assess publication bias, which was not found both for T2DM and T1DM analysis (for example: T2DM: \(t\textsubscript{C-allele vs. G-allele} = -1.66\), \(P = 0.108\) for Egger’s test, \(z= 0.77\), \(P = 0.441\) for Begg’s test, **Figure 7a,b**; T1DM: \(t\textsubscript{C-allele vs. G-allele} = 1.64\), \(P = 0.136\) for Egger’s test, \(z= 1.25\), \(P = 0.213\) for Begg’s test, **Figure 8a,b, Table 4**). To delete studies which may influence the power and stability of whole study, we applied the sensitive analysis, finally, also no
sensitive case-control studies were found (Figure 9, 10, Table 4).

Discussion

Diabetes had reached pandemic dimensions, which is becoming relevant both in developed and developing countries and affecting over 400 million people worldwide [58]. T2DM represents the most prevalent form because of the huge and heterogeneous number of patients [59]. Diabetes can cause long-term damage, dysfunction and failure of different organs, such as the eyes (blindness/retinopathy), kidneys (renal failure), nerves (diabetes peripheral neuropathy), heart (cardiovascular diseases) and blood vessels (diabetic foot disorders) [2, 4, 60]. Based on above data, prevention and treatment to DM, especially T2DM could be a key strategy to reduce the global impact of DM. Currently, there is growing evidence on the efficacy of the use of genetic susceptibility for DM prevention and management [5].

IL-6 is a key anti- and pro-inflammatory cytokine produced mainly by T-cells and macrophages [11], which plays significant roles in the regulation of the autoimmune disease such as T2DM, because elevated levels of IL-6 can be used to predict the development. A common polymorphism (rs1800795) in the promoter of IL-6 gene has been widely reported, and been considered as a risk factor for T2DM based on the change of expression of IL-6 [13]. To data, a number of studies have been focused on the relationship between IL-6 rs1800795 polymorphism and DM risk [26, 29, 30, 38]. In addition, some articles about meta-analysis also shown the conclusions above association [21-24], However, lack of powerful and convincing conclusions remain exist. So, it is necessary to re-combine previous published studies to make a comprehensive meta-analysis to solve above association.

To our best knowledge, meta-analysis is a powerful method to carry out inconsistent results based on large number of samples including different ethnicities or countries [24]. The conclusion obtained from meta-analysis is more reliable and persuasive than one single study [24]. To investigate the association between IL-6 rs1800795 and DM, our studies is a timely and comprehensive study including 39099 individuals. Our results indicated that IL-6 rs1800795 acted as a protective factor in T2DM, in other words, individuals carrying C-allele may have decreased association with T2DM, especially for Asians and HB source studies. However, IL-6 rs1800795 was a risk factor in T1DM, there
had a significantly increased association between this polymorphism and T1DM risk in four genetic models in Mixed population and HB source studies.

Above information indicated *IL-6 rs1800795* polymorphism may have different effect in different types of DM, and also exist different influences for different ethnicities, such as Asians and Mixed population. Some potential reasons may be explained: the pathogenic mechanisms about T2DM and T1DM is different, many significant expressed genes are not exactly the same, on the other hand, the same gene may have different effects, even the opposite results, based on current results, IL-6 gene may have different way between T2DM and T1DM, so *rs1800795* polymorphism affecting expression of IL-6 also have different roles between T2DM and T1DM. Different races includes heterogeneity, the same gene also may have different roles in different ethnicities [61, 62]. Third, the heterogeneity about selection strategy also maybe exist, which should affect our results. Furthermore, to evaluate the stable and convince of current study, we applied the Power analysis. Finally, the power in T2DM was 1, however, in T1DM was 0.166, which means the conclusions from T2DM was powerful and persuasive, rather than for T1DM. That suggested more studies about *rs1800795* and T1DM risk should be added in the future to obtain a trustworthy conclusion.

Although we made a comprehensive meta-analysis, several limitations also should be considered. First of all, the studies from Mixed population and Africans are limited, which lead to missing or insufficient results, finally may influence the whole conclusion. Second, one signal gene or one polymorphism may not have the power to result in the development of DM, which is a complex process including gene-gene or gene-environment interaction, further studies should pay close attention above content. Third, four databases were included, some valuable studies from other databases or other languages may not be identified, which should have an impact to current conclusions.

**Conclusions**

In summary, our present meta-analysis provided evidence that the *IL-6 rs1800795* polymorphism was associated with significantly increased T1DM risk in Mixed population, in opposite, decreased
association were found in T2DM susceptibility in Asians. Consequently, further well-designed large studies, particularly those related to gene-gene and gene-environment interactions, are warranted.

Declarations

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Not applicable.

Authors’ contributions

ZC and CZ designed and conceived this study. CZ contributed to literature searching. CZ were involved in data extraction. CZ analyzed the data. ZC wrote the manuscript. ZC revised the paper. All authors have approved the final edition of the manuscript.

Availability of data and materials

All the data generated in the present research is contained in this manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Characteristics of studies of IL-6 rs1800795 polymorphism and T2DM and T1DM risk included in our meta-analysis

| Author            | Year | Country     | Ethnicity | Type  | Case | Control | SOC |
|-------------------|------|-------------|-----------|-------|------|---------|-----|
| Mukhopadhyaya     | 2010 | India       | Asian     | T2DM  | 40   | 40      | PB  |
| Hamid             | 2005 | Denmark     | Caucasian | T2DM  | 1389 | 4401    | PB  |
| Plataki           | 2018 | Greece      | Caucasian | T2DM  | 144  | 180     | HB  |
| Vozarova          | 2003 | Spain       | Caucasian | T2DM  | 211  | 118     | PB  |
| Buraczynska       | 2016 | Poland      | Caucasian | T2DM  | 1090 | 612     | PB  |
| Chen              | 2002 | China       | Asian     | T2DM  | 196  | 130     | HB  |
| Tsiavou           | 2004 | Greece      | Caucasian | T2DM  | 31   | 39      | HB  |
| Eze               | 2016 | Switzerland | Caucasian | T2DM  | 286  | 5560    | HB  |
| Bouhaha           | 2010 | Tunisia     | African   | T2DM  | 169  | 281     | PB  |
| Ghavimi           | 2016 | Iran        | Asian     | T2DM  | 120  | 120     | HB  |
| Fathy             | 2018 | Kuwait      | Asian     | T2DM  | 50   | 42      | HB  |
| Lara-Gómez        | 2019 | Mexico      | Mixed     | T2DM  | 31   | 30      | HB  |
| Dhamodharan       | 2015 | India       | Asian     | T2DM  | 139  | 106     | HB  |
| Danielsson        | 2005 | Sweden      | Caucasian | T2DM  | 20   | 20      | HB  |
| Study                | Year | Country | Ethnicity | Disease | Cases | Controls | Type |
|----------------------|------|---------|-----------|---------|-------|----------|------|
| Vozarova             | 2003 | Spain   | Caucasian | T2DM    | 143   | 145      | PB   |
| Neelofar             | 2017 | India   | Asian     | T2DM    | 50    | 50       | HB   |
| Kavitha              | 2016 | India   | Asian     | T2DM    | 30    | 30       | HB   |
| Kong                 | 2010 | China   | Asian     | T2DM    | 107   | 121      | HB   |
| Zhang                | 2011 | China   | Asian     | T2DM    | 512   | 483      | HB   |
| Saxena               | 2014 | India   | Asian     | T2DM    | 213   | 145      | HB   |
| Xiao                 | 2009 | China   | Asian     | T2DM    | 85    | 132      | HB   |
| Nadeem               | 2017 | Pakistan| Asian     | T2DM    | 539   | 250      | HB   |
| Mohlig               | 2004 | Germany | Caucasian | T2DM    | 188   | 376      | HB   |
| Karadeniz            | 2014 | Turkey  | Caucasian | T2DM    | 86    | 340      | HB   |
| Erdogan              | 2017 | Turkey  | Caucasian | T2DM    | 35    | 119      | HB   |
| Helaly               | 2013 | Egypt   | African   | T2DM    | 69    | 98       | PB   |
| Mysliwiec            | 2008 | Poland  | Caucasian | T1DM    | 200   | 172      | HB   |
| Siekiera             | 2002 | Poland  | Caucasian | T1DM    | 36    | 36       | HB   |
| Ururahy              | 2015 | Brazil  | Mixed     | T1DM    | 120   | 152      | HB   |
| Settin               | 2009 | Egypt   | African   | T1DM    | 50    | 98       | PB   |
| Javor                | 2010 | Slovakia| Caucasian | T1DM    | 151   | 140      | PB   |
| Campos               | 2019 | Brasil  | Mixed     | T1DM    | 141   | 150      | HB   |
| Cooper               | 2007 | USA     | Caucasian | T1DM    | 8852  | 7785     | PB   |
| Jahromi              | 2000 | England | Caucasian | T1DM    | 257   | 120      | PB   |
| Tsiavou              | 2004 | Greece  | Caucasian | T1DM    | 31    | 39       | PB   |
| Mysliwska            | 2009 | Poland  | Caucasian | T1DM    | 210   | 170      | PB   |
| Perez-Bravo          | 2011 | Chile   | Mixed     | T1DM    | 145   | 103      | PB   |

HB: hospital-based; PB: population-based; SOC: source of control; PCR-RFLP: polymerase chain reaction followed by restriction fragment length polymorphism; PCR-SSP: polymerase chain reaction followed with sequence specific primers; MALDI-TOF: a chip-based matrix-assisted laser-desorption/ionization time-of-flight; HWE: Hardy-Weinberg equilibrium of control group.

Table 2 Stratified analyses of IL-6 rs1800795 polymorphism and T2DM risk.
**T2DM**

| Variables | N     | Case/Control | C-allele vs. G-allele | CG vs. GG |
|-----------|-------|--------------|----------------------|-----------|
|           |       |              | OR(95%CI) P<sub>h</sub> P | OR(95%CI) P<sub>h</sub> P |
| **Total** | 26793/13968 | 0.85(0.75-0.96) 0.000 0.008 | 0.91(0.76-1.08) 0.000 0.281 |
| **HWE**   | 19475/12508 | 0.89(0.76-1.03) 0.000 0.125 | 0.97(0.82-1.14) 0.017 0.683 |
| **Ethnicity** |       |              |                      |           |
| Asian     | 12208/1649 | 0.65(0.53-0.81) 0.060 0.000 | 0.90(0.60-1.33) 0.001 0.590 |
| Caucasian | 113623/11910 | 0.89(0.77-1.02) 0.000 0.103 | 0.83(0.66-1.05) 0.000 0.124 |
| Mixed     | 131/30    | ——           | ——                   | ——        |
| African   | 2238/379  | 1.24(0.93-1.25) 0.157 0.151 | 1.07(0.69-1.66) 0.741 0.753 |
| **SOC**   |       |              |                      |           |
| HB        | 192862/8273 | 0.82(0.69-0.97) 0.000 0.022 | 0.93(0.70-1.22) 0.000 0.580 |
| PB        | 73111/5695 | 0.92(0.77-1.10) 0.001 0.368 | 0.96(0.87-1.07) 0.150 0.512 |

<sup>P<sub>h</sub></sup>: value of Q-test for heterogeneity test; <sup>P</sup>: Z-test for the statistical significance of the OR, SOC:

source of control; HB: hospital-based; PB: population-based

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**Table 3 Stratified analyses of IL-6 rs1800795 polymorphism and T1DM risk.**

**T1DM**

| Variables | N     | Case/Control | C-allele vs. G-allele | CG vs. GG |
|-----------|-------|--------------|----------------------|-----------|
|           |       |              | OR(95%CI) P<sub>h</sub> P | OR(95%CI) P<sub>h</sub> P |
| **Total** | 1110193/8965 | 1.16(0.94-1.42) 0.000 0.162 | 1.33(0.99-1.77) 0.000 0.056 |
| **HWE**   | 99933/8697  | 1.09(0.87-1.36) 0.000 0.461 | 1.19(0.89-1.58) 0.003 0.235 |
| **Ethnicity** |       |              |                      |           |
| Caucasian | 79737/8462 | 1.06(0.81-1.38) 0.000 0.682 | 1.37(0.90-2.11) 0.000 0.146 |
| Mixed     | 3406/405   | 1.39(1.10-1.77) 0.497 0.006 | 1.33(0.99-1.79) 0.835 0.059 |
| African   | 150/98     | -            | -                    | -         |
| **SOC**   |       |              |                      |           |
| HB        | 4497/510   | 1.29(1.07-1.56) 0.122 0.009 | 1.47(1.11-1.94) 0.428 0.008 |
| PB        | 79696/8455 | 1.13(0.86-1.48) 0.000 0.367 | 1.27(0.85-1.90) 0.000 0.248 |

<sup>P<sub>h</sub></sup>: value of Q-test for heterogeneity test; <sup>P</sup>: Z-test for the statistical significance of the OR, SOC:

source of control; HB: hospital-based; PB: population-based
Table 4 Publication bias tests (Begg’s funnel plot and Egger’s test for publication bias test) for IL-6 rs1800795 polymorphism and T2DM and T1DM risk

| Genetic type          | Coefficient | Standard error | t    | P value |
|-----------------------|-------------|----------------|------|---------|
| **T2DM**              |             |                |      |         |
| C-allele vs. G-allele | -0.87       | 0.523          | -1.66| 0.108   |
| CG vs. GG             | -0.652      | 0.396          | -1.65| 0.112   |
| CC+CG vs. GG          | -0.683      | 0.416          | -1.64| 0.113   |
| **T1DM**              |             |                |      |         |
| C-allele vs. G-allele | 1.265       | 0.773          | 1.64 | 0.136   |
| CG vs. GG             | 0.835       | 0.499          | 1.67 | 0.129   |
| CC+CG vs. GG          | 0.87        | 0.53           | 1.64 | 0.135   |
| CC vs. GG             | 0.458       | 0.358          | 1.28 | 0.234   |
| CC vs. CG+GG          | 0.535       | 0.426          | 1.25 | 0.241   |

**Figures**
A flowchart illustrating the search strategy used to identify association studies for IL-6 rs1800795 polymorphism and DM risk.
Figure 2

T-allele frequencies for the IL-6 rs1800795 polymorphism among cases/controls stratified by ethnicity. Horizontal line: T-allele frequency; Vertical line: ethnicity type. EAS: East Asian; EUR: European; AFR: African; AMR: American; SAS: South Asian.
Figure 3

Forest plot of T2DM risk associated with IL-6 rs1800795 polymorphism (A: C-allele vs. G-allele, B: CC+CG vs. GG) in the subgroup of ethnicity analysis. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.
Figure 4

Forest plot of T2DM risk associated with IL-6 rs1800795 polymorphism (C-allele vs. G-allele) in the source of control subgroup. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.
Figure 5

Forest plot of T1DM risk associated with IL-6 rs1800795 polymorphism (A: C-allele vs. G-allele, B: CC+CG vs. GG, C: CC vs. GG, D: CC vs. CG+GG) in the subgroup of ethnicity analysis. The squares and horizontal lines correspond to the study-specific OR and 95% CI.

The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.
Figure 6

Forest plot of T1DM risk associated with IL-6 rs1800795 polymorphism (A: C-allele vs. G-allele, B: CG vs. GG, C: CC+CG vs. GG, D: CC vs. GG) in the source of control subgroup. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.
Figure 7
A: Begg’s funnel plot for publication bias test (C-allele vs. G-allele). B: Egger’s publication bias plot (T-allele vs. G-allele) for T2DM.

Figure 8
A: Begg’s funnel plot for publication bias test (C-allele vs. G-allele). B: Egger’s publication bias plot (T-allele vs. G-allele) for T1DM.
Figure 9

Sensitivity analysis between IL-6 rs1800795 polymorphism and T2DM risk (C-allele vs. G-allele).
Figure 10

Sensitivity analysis between IL-6 rs1800795 polymorphism and T1DM risk (C-allele vs. G-allele).