IL-6 gene rs1800795 polymorphism and diabetes mellitus: a comprehensive analysis involving 42,150 participants from a meta-analysis

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Abstract

Background: Over the past two decades, several studies have focused on the association between a common polymorphism (rs1800795) from interleukin-6 (IL-6) gene and Diabetes Mellitus (DM) risk. However, the results remain ambiguous and indefinite.

Methods: A comprehensive analysis was performed to explore this relationship. A search was conducted in the PubMed, Embase, Chinese (CNKI and Wanfang), and GWAS Catalog databases, covering all publications until February 10, 2022. Odds ratios (OR) with 95% confidence intervals (CI) were used to evaluate the strength of the association. Publication bias was assessed using both Begg and Egger tests.

Results: Overall, 34 case–control studies with 7257 T2DM patients and 15,598 controls, and 12 case–control studies (10,264 T1DM patients and 9031 health controls) were included in the analysis. A significantly lower association was observed between the rs1800795 polymorphism and T2DM risk in Asians, mixed population, and hospital-based (HB) subgroups (C-allele vs. G-allele: OR = 0.76, 95% CI 0.58–0.99, P = 0.039 for Asians; CG vs. GG: OR = 0.74, 95% CI 0.58–0.94, P = 0.014 for mixed population; CC vs. GG: OR = 0.61, 95% CI 0.41–0.90, P = 0.014 for HB). However, increased associations were found from total, mixed population, and HB subgroups between rs1800795 polymorphism and T1DM susceptibility (CG vs. GG: OR = 1.32, 95% CI 1.01–1.74, P = 0.043 for total population, CC vs. GG: OR = 2.45, 95% CI 1.18–5.07, P = 0.016 for mixed individuals; C-allele vs. G-allele: OR = 1.29, 95% CI 1.07–1.56, P = 0.0009 for HB subgroup).

Conclusions: In summary, there is definite evidence to confirm that IL-6 rs1800795 polymorphism is associated with susceptibility to decreased T2DM and increased T1DM.

Keywords: Interleukin-6, Type 2 diabetes mellitus, Type 1 diabetes mellitus, Polymorphism, Risk, Meta-analysis

Background

Diabetes mellitus (DM) is a chronic medical condition in which the body either produces too little insulin from pancreatic islets or lacks effective access to insulin [1]. Type 1 DM (T1DM) is most often diagnosed in children and adolescents with respect to islet function development. Type 2 DM (T2DM) is caused by insulin resistance, and the body cannot use insulin effectively...
and may gradually lose its production capacity [2–4]. To the best of our knowledge, age, obesity, and family history are the major risk factors of developing DM [5]. However, the exact pathogenesis of DM is not fully understood. Past genome-wide association studies (GWAS) have identified over 100 genetic sites, which suggests that there are significant associations between different sites and susceptibility to DM, indicating that genetic factors may be crucial for its occurrence and development [6, 7].

Interleukin-6 (IL-6), a classic proinflammatory cytokine, plays a prominent role in the inflammatory response and is associated with insulin resistance and T2DM [8]. In addition, chronic low-grade inflammation and activation of the innate immune system are closely associated with the pathogenesis of T1DM and its complications. Inflammatory cytokines such as IL-6 are determinants of these pathogenic processes [9, 10].

The IL-6 gene is located on chromosome 7p21. The gene, which includes seven exons, covers approximately 12.8 kb of genomic DNA [11]. A common single nucleotide polymorphism (SNP) in the IL-6 promoter in T2DM has been named rs1800795 (also named –174G/C) [12]. The rs1800795 polymorphism functionally affects IL-6 promoter activity, indicating that the carried CC genotype individual is associated with lower plasma levels of IL-6 compared with individuals with the GG genotype [13]. In addition, the G-allele in homozygotes (GG genotype) was associated with higher concentrations of IL-6, increasing the immune response [14, 15], demonstrating

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**Fig. 1** A flowchart illustrating the search strategy used to identify association studies for IL-6 rs1800795 polymorphism and DM risk
| Author          | Year  | Country | Ethnicity | Type       | Cases | Controls | SOC | Genotype | NOS |
|----------------|-------|---------|-----------|------------|-------|----------|-----|----------|-----|
| Campos         | 2019  | Brasil  | Mixed     | T1DM       | 141   | 150      | HB  | 9        | 69  | 63       | 7   | 68       | 75  | 0.084 PCR–RFLP | 6   |
| Mysliwiec      | 2008  | Poland  | Caucasian | T1DM       | 200   | 172      | HB  | 59       | 105 | 36       | 43  | 75       | 54  | 0.103 PCR–RFLP | 8   |
| Siekiera       | 2002  | Poland  | Caucasian | T1DM       | 36    | 36       | HB  | 5        | 24  | 7        | 12  | 18       | 6   | 0.684 PCR–SSP | 6   |
| Ururahy        | 2015  | Brazil  | Mixed     | T1DM       | 120   | 152      | HB  | 9        | 41  | 70       | 4   | 45       | 103 | 0.727 TaqMan | 8   |
| Settin         | 2009  | Egypt   | African   | T1DM       | 50    | 98       | PB  | 9        | 38  | 3        | 6   | 87       | 5   | <0.05 PCR–SSP | 7   |
| Javor          | 2010  | Slovakia| Caucasian | T1DM       | 151   | 140      | PB  | 31       | 85  | 35       | 21  | 66       | 53  | 0.951 PCR–SSP | 7   |
| Cooper         | 2007  | USA     | Caucasian | T1DM       | 8852  | 7785     | PB  | 1612     | 4312 | 2928     | 1515| 3814     | 2456| 0.0619 MALDI-TOF | 9   |
| Jahromi        | 2000  | England | Caucasian | T1DM       | 257   | 120      | PB  | 32       | 95  | 130      | 29  | 51       | 40  | 0.118 sequence | 7   |
| Tsavou         | 2004  | Greece  | Caucasian | T1DM       | 31    | 39       | PB  | 3        | 11  | 17       | 3   | 11       | 25  | 0.281 PCR–SSP | 8   |
| Mysliwska      | 2009  | Poland  | Caucasian | T1DM       | 210   | 170      | PB  | 69       | 110 | 31       | 51  | 68       | 51  | <0.05 PCR–RFLP | 8   |
| Perez-Bravo    | 2011  | Chile   | Mixed     | T1DM       | 145   | 103      | PB  | 6        | 49  | 90       | 1   | 27       | 75  | 0.396 PCR–RFLP | 7   |
| Mukhopadhyaya  | 2010  | India   | Asian     | T2DM       | 40    | 40       | PB  | 6        | 11  | 23       | 15  | 13       | 12  | 0.029 PCR–RFLP | 8   |
| Hamid          | 2005  | Denmark | Caucasian | T2DM       | 1389  | 4401     | PB  | 328      | 659 | 402      | 1022| 2133     | 1246| 0.062 MALDI-TOF | 9   |
| Plataski       | 2018  | Greece  | Caucasian | T2DM       | 144   | 180      | HB  | 12       | 64  | 68       | 12  | 54       | 114 | 0.119 PCR–RFLP | 6   |
| Vozarova       | 2003  | Spain   | Caucasian | T2DM       | 211   | 118      | PB  | 17       | 110 | 84       | 19  | 65       | 34  | 0.193 PCR–RFLP | 8   |
| Buraczynska    | 2016  | Poland  | Caucasian | T2DM       | 1090  | 612      | PB  | 240      | 534 | 316      | 129 | 288      | 195 | 0.237 sequence | 9   |
| Chen           | 2002  | China   | Asian     | T2DM       | 196   | 130      | PB  | 40       | 84  | 72       | 42  | 58       | 30  | 0.254 PCR–RFLP | 7   |
| Tsavou         | 2004  | Greece  | Caucasian | T2DM       | 31    | 39       | HB  | 3        | 11  | 17       | 3   | 11       | 25  | 0.281 PCR–SSP | 6   |
| Eze            | 2016  | Switzerland | Caucasian | T2DM       | 286   | 5560     | PB  | 40       | 135 | 111      | 865 | 2614     | 2081| 0.352 TaqMan | 7   |
| Bouhaha        | 2010  | Tunisia | African   | T2DM       | 169   | 281      | PB  | 4        | 40  | 125      | 7   | 64       | 210 | 0.428 Sequencing | 8   |
| Ghavimi        | 2016  | Iran    | Asian     | T2DM       | 120   | 120      | HB  | 18       | 62  | 40       | 27  | 64       | 29  | 0.463 PCR–RFLP | 7   |
| Fathy          | 2018  | Kuwait  | Asian     | T2DM       | 50    | 42       | HB  | 1        | 13  | 36       | 2   | 11       | 29  | 0.487 TaqMan | 8   |
| Lara-Gómez     | 2019  | Mexico  | Mixed     | T2DM       | 31    | 30       | HB  | 1        | 11  | 19       | 0   | 5        | 25  | 0.618 Sequencing | 7   |
| Dhamodharan    | 2015  | India   | Asian     | T2DM       | 139   | 106      | HB  | 1        | 46  | 92       | 12  | 44       | 50  | 0.626 PCR–RFLP | 7   |
| Danielsson     | 2005  | Sweden  | Caucasian | T2DM       | 20    | 20       | HB  | 6        | 12  | 2        | 6   | 9        | 5   | 0.662 Sequencing | 7   |
| Vozarova       | 2003  | Spain   | Caucasian | T2DM       | 143   | 145      | PB  | 0        | 1    | 142      | 0   | 9        | 136 | 0.699 PCR–RFLP | 9   |
| Neelofar       | 2017  | India   | Asian     | T2DM       | 50    | 50       | HB  | 3        | 19  | 28       | 3   | 20       | 27  | 0.78 sequence | 7   |
| Kavitha        | 2016  | India   | Asian     | T2DM       | 30    | 30       | HB  | 0        | 0    | 30       | 0   | 1        | 29  | 0.926 PCR–RFLP | 6   |
| Kong           | 2010  | China   | Asian     | T2DM       | 107   | 121      | PB  | 0        | 2    | 105      | 0   | 2        | 119 | 0.927 PCR–SSP | 6   |
| Zhang          | 2011  | China   | Asian     | T2DM       | 512   | 483      | HB  | 0        | 2    | 510      | 0   | 1        | 482 | 0.982 PCR–RFLP | 7   |
| Saxena         | 2014  | India   | Asian     | T2DM       | 213   | 145      | HB  | 4        | 46  | 163      | 19  | 21       | 105 | <0.05 PCR–RFLP | 6   |
| Xiao           | 2009  | China   | Asian     | T2DM       | 85    | 132      | HB  | 0        | 0    | 85       | 0   | 0        | 132 | <0.05 PCR–RFLP | 7   |
| Nadeem         | 2017  | Pakistan| Asian     | T2DM       | 539   | 250      | HB  | 37       | 267 | 235      | 48  | 74       | 128 | <0.05 PCR–RFLP | 6   |
| Karadeniz      | 2014  | Turkey  | Caucasian | T2DM       | 86    | 340      | HB  | 6        | 27  | 53       | 26  | 171      | 143 | <0.05 PCR–RFLP | 6   |
Table 1 (continued)

| Author  | Year | Country  | Ethnicity | Type   | Case | Control | SOC    | Cases   | Controls | HWE   | Genotype       | NOS |
|---------|------|----------|-----------|--------|------|---------|--------|---------|----------|-------|----------------|-----|
| Erdogan | 2017 | Turkey   | Caucasian | T2DM   | 35   | 119     | HB     | 1       | 16       | 18    | <0.05          | PCR–RFLP | 8 |
| Helaly  | 2013 | Egypt    | African   | T2DM   | 69   | 98      | PB     | 18      | 49       | 2     | <0.05          | an allele–specific PCR | 8 |
| Mohlig  | 2004 | Germany  | Caucasian | T2DM   | 188  | 376     | PB     | 32      | 103      | 53    | <0.05          | SNuPE    | 8 |

*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; *NOS* Newcastle–Ottawa Scale
that this polymorphism is functional, or that it defined a difference in IL-6 expression levels according to the genotype of the polymorphism.

Several epidemiological studies have observed associations between genetic variants of IL-6 and the risk of DM. For instance, Saxena et al. observed that the rs1800795 polymorphism showed a highly significant association with T2DM [16]. In contrast, Dhamodharan et al. determined that the C allele conferred significant protection against T2DM [17]. In addition, Fathy et al. [18] demonstrated a lack of significant association between rs1800795 polymorphism and T2DM. For T1DM, an increased association was observed between T1DM and the polymorphism by Cooper et al. [19]. However, Tsiavou et al. observed no significant differences [20]. Two meta-analyses (Yin and Xu et al.) showed that rs1800795 is not associated with T1DM risk [21, 22]. On the other hand, Huth and Xia et al. performed a meta-analysis and concluded that this polymorphism could be associated with a decreased risk of T2DM [23, 24]. In the last 10 years, some larger and more comprehensive studies have been conducted on this association. Therefore, it is

![Fig. 2](image)

**Fig. 2**  
A The MAF of minor-allele (mutant-allele) for IL-6 rs1800795 polymorphism from the 1000 Genomes online database.  
B The frequency about C-allele or G-allele both in case and control groups.  
C The risk frequency of rs1800795 polymorphism to several disease from TCGA database

| Study          | Population     | Group | Sample size | Ref. allele (C) | Alt. allele (G) |
|----------------|----------------|-------|-------------|----------------|----------------|
| 1000Genomes    | African        | Sub   | 1322        | 0.0182         | 0.9818         |
| 1000Genomes    | East Asian     | Sub   | 1008        | 0.0010         | 0.9990         |
| 1000Genomes    | European       | Sub   | 1006        | 0.4155         | 0.5845         |
| 1000Genomes    | South Asian    | Sub   | 978         | 0.139          | 0.861          |
| 1000Genomes    | American       | Sub   | 694         | 0.184          | 0.816          |
| Current study  | Total          | Case  | 17,520      | 0.3817         | 0.6183         |
| Current study  | Total          | Control | 24,629     | 0.394          | 0.606          |
Table 3  Stratified analyses of IL-6 rs1800795 polymorphism and T2DM and T1DM risk

| Variables          | N0. | Case/Control | C-allele vs. G-allele | CG vs. GG |
|--------------------|-----|--------------|-----------------------|-----------|
|                    |     |              | OR (95% CI)           | Ph  | P     | OR (95% CI)           | Ph  | P     |
| T2DM               |     |              | Ph                    |     |       | Ph                    |     |       |
| Total              | 34  | 7257/15598   | 0.88 (0.76–1.01)      | 0.000 | 0.075 | 0.91 (0.77–1.08)      | 0.000 | 0.281 |
| HWE                | 25  | 5927/14023   | 0.98 (0.84–1.15)      | 0.000 | 0.832 | 0.97 (0.83–1.13)      | 0.000 | 0.687 |
| Ethnicity          |     |              | Ph                    |     |       | Ph                    |     |       |
| Asian              | 14  | 2595/2208    | 0.76 (0.58–0.99)      | 0.000 | 0.039 | 0.99 (0.73–1.32)      | 0.002 | 0.925 |
| Caucasian          | 12  | 3767/12090   | 0.96 (0.81–1.12)      | 0.000 | 0.579 | 0.95 (0.73–1.22)      | 0.000 | 0.683 |
| Mixed              | 5   | 582/846      | 1.09 (0.55–2.19)      | 0.000 | 0.804 | 0.74 (0.58–0.94)      | 0.154 | 0.014 |
| African            | 3   | 313/454      | 0.83 (0.37–1.89)      | 0.000 | 0.665 | 0.91 (0.77–1.08)      | 0.041 | 0.486 |
| SOC                |     |              | Ph                    |     |       | Ph                    |     |       |
| HB                 | 23  | 3546/9186    | 0.83 (0.68–1.01)      | 0.000 | 0.059 | 0.95 (0.73–1.23)      | 0.000 | 0.706 |
| PB                 | 11  | 3711/6412    | 0.98 (0.79–1.22)      | 0.000 | 0.874 | 0.89 (0.75–1.05)      | 0.100 | 0.166 |
| T1DM               |     |              | Ph                    |     |       | Ph                    |     |       |
| Total              | 12  | 10,264/9031  | 1.17 (0.96–1.42)      | 0.000 | 0.120 | 1.32 (1.01–1.74)      | 0.000 | 0.043 |
| HWE                | 10  | 10,004/8763  | 1.13 (0.91–1.41)      | 0.000 | 0.268 | 1.24 (0.96–1.61)      | 0.002 | 0.100 |
| Ethnicity          |     |              | Ph                    |     |       | Ph                    |     |       |
| Caucasian          | 7   | 9737/8462    | 1.06 (0.81–1.38)      | 0.000 | 0.682 | 1.37 (0.90–2.11)      | 0.000 | 0.146 |
| Mixed              | 3   | 406/405      | 1.39 (1.10–1.77)      | 0.497 | 0.006 | 1.33 (0.99–1.79)      | 0.835 | 0.059 |
| SOC                |     |              | Ph                    |     |       | Ph                    |     |       |
| HB                 | 4   | 497/510      | 1.29 (1.07–1.56)      | 0.122 | 0.009 | 1.47 (1.11–1.94)      | 0.428 | 0.008 |
| PB                 | 8   | 9767/8521    | 1.15 (0.89–1.48)      | 0.000 | 0.276 | 1.27 (0.88–1.82)      | 0.000 | 0.195 |
| Ethnicity (with HWE) |   |              | Ph                    |     |       | Ph                    |     |       |
| Caucasian          | 6   | 9527/8292    | 0.99 (0.74–1.34)      | 0.000 | 0.971 | 1.21 (0.80–1.82)      | 0.001 | 0.368 |
| Mixed              | 3   | 406/405      | 1.39 (1.10–1.77)      | 0.497 | 0.006 | 1.33 (0.99–1.79)      | 0.835 | 0.059 |
| SOC (with HWE)     |     |              | Ph                    |     |       | Ph                    |     |       |
| HB                 | 4   | 497/510      | 1.29 (1.07–1.56)      | 0.122 | 0.009 | 1.47 (1.11–1.94)      | 0.428 | 0.008 |
| PB                 | 6   | 9507/8253    | 1.09 (0.80–1.49)      | 0.000 | 0.578 | 1.13 (0.81–1.58)      | 0.010 | 0.460 |

Variables: CC vs. GG, CC vs. GG, CC vs. CG + GG

| Variables          | CC vs. GG | CC vs. GG | CC vs. CG + GG |
|--------------------|-----------|-----------|----------------|
|                    | OR (95% CI) | Ph | P | OR (95% CI) | Ph | P | OR (95% CI) | Ph | P |
| T2DM               |           |     |   |           |     |   |           |     |   |
| Total              | 0.87 (0.73–1.03) | 0.000 | 0.039 | 0.76 (0.57–1.02) | 0.000 | 0.039 | 0.82 (0.63–1.07) | 0.000 | 0.039 |
| HWE                | 0.98 (0.82–1.16) | 0.000 | 0.786 | 0.98 (0.72–1.33) | 0.000 | 0.905 | 0.99 (0.76–1.29) | 0.000 | 0.962 |
| Ethnicity          |           |     |   |           |     |   |           |     |   |
| Asian              | 0.82 (0.61–1.11) | 0.000 | 0.208 | 0.45 (0.24–0.85) | 0.000 | 0.014 | 0.48 (0.27–0.86) | 0.000 | 0.014 |
| Caucasian          | 0.93 (0.72–1.20) | 0.000 | 0.569 | 0.94 (0.74–1.19) | 0.043 | 0.595 | 0.98 (0.89–1.10) | 0.513 | 0.778 |
| Mixed              | 0.94 (0.53–1.67) | 0.000 | 0.833 | 1.25 (0.30–5.19) | 0.000 | 0.759 | 1.38 (0.35–5.64) | 0.000 | 0.645 |
| African            | 0.71 (0.23–2.13) | 0.003 | 0.536 | 0.99 (0.15–6.34) | 0.002 | 0.991 | 1.22 (0.22–6.67) | 0.000 | 0.818 |
| SOC                |           |     |   |           |     |   |           |     |   |
| HB                 | 0.85 (0.66–1.10) | 0.000 | 0.227 | 0.61 (0.41–0.90) | 0.000 | 0.014 | 0.64 (0.46–0.90) | 0.000 | 0.011 |
| PB                 | 0.92 (0.73–1.14) | 0.001 | 0.430 | 1.08 (0.68–1.71) | 0.000 | 0.751 | 1.21 (0.79–1.85) | 0.000 | 0.373 |
| Ethnicity (with HWE) |       |     |   |           |     |   |           |     |   |
### Table 3 (continued)

| Variables            | CC vs. CG vs. GG | Ph | P     | CC vs. GG | Ph | P     | CC vs. CG + GG | Ph | P     |
|----------------------|------------------|----|-------|-----------|----|-------|----------------|----|-------|
| **Asian**           |                  |    |       |           |    |       |                |    |       |
| CO                   | 0.82 (0.56–1.20) | 0.002 | 0.303 | 0.62 (0.28–1.38) | 0.000 | 0.241 | 0.72 (0.38–1.35) | 0.004 | 0.305 |
| Caucasian            | 1.13 (0.89–1.44) | 0.000 | 0.316 | 1.01 (0.80–1.28) | 0.098 | 0.918 | 1.00 (0.90–1.12) | 0.495 | 0.979 |
| Mixed                | 0.94 (0.53–1.67) | 0.000 | 0.833 | 1.25 (0.30–5.19) | 0.000 | 0.759 | 1.38 (0.35–5.54) | 0.000 | 0.645 |
| **SOC (with HWE)**   |                  |    |       |           |    |       |                |    |       |
| HB                   | 1.01 (0.75–1.37) | 0.000 | 0.932 | 0.85 (0.53–1.36) | 0.000 | 0.493 | 0.85 (0.60–1.21) | 0.026 | 0.369 |
| PB                   | 0.96 (0.77–1.18) | 0.003 | 0.677 | 1.13 (0.72–1.79) | 0.000 | 0.590 | 0.99 (0.78–1.30) | 0.000 | 0.426 |
| **T1DM**            |                  |    |       |           |    |       |                |    |       |
| Total                | 1.32 (0.99–1.76) | 0.000 | 0.060 | 1.40 (0.90–2.18) | 0.000 | 0.134 | 1.12 (0.83–1.50) | 0.005 | 0.463 |
| HWE                  | 1.25 (0.94–1.67) | 0.000 | 0.131 | 1.27 (0.78–2.05) | 0.000 | 0.331 | 1.04 (0.74–1.45) | 0.014 | 0.839 |
| Ethnicity            |                  |    |       |           |    |       |                |    |       |
| Caucasian            | 1.30 (0.83–2.01) | 0.000 | 0.249 | 1.31 (0.67–2.92) | 0.000 | 0.645 | 0.93 (0.69–1.23) | 0.024 | 0.598 |
| Mixed                | 1.43 (1.07–1.90) | 0.724 | 0.015 | 2.45 (1.18–5.07) | 0.486 | 0.016 | 2.20 (1.08–4.48) | 0.487 | 0.031 |
| **SOC**             |                  |    |       |           |    |       |                |    |       |
| HB                   | 1.51 (1.15–1.98) | 0.337 | 0.003 | 1.77 (1.14–2.74) | 0.128 | 0.010 | 1.16 (0.57–2.35) | 0.066 |
| PB                   | 1.27 (0.86–1.86) | 0.000 | 0.229 | 1.33 (0.77–2.32) | 0.000 | 0.312 | 1.10 (0.77–1.57) | 0.013 | 0.611 |
| Ethnicity (with HWE) |                  |    |       |           |    |       |                |    |       |
| Caucasian            | 1.15 (0.74–1.78) | 0.00 | 0.540 | 0.99 (0.56–1.75) | 0.000 | 0.968 | 0.88 (0.61–1.25) | 0.018 | 0.465 |
| Mixed                | 1.43 (1.07–1.90) | 0.724 | 0.015 | 2.45 (1.18–5.07) | 0.486 | 0.016 | 2.20 (1.08–4.48) | 0.487 | 0.031 |
| **SOC (with HWE)**   |                  |    |       |           |    |       |                |    |       |
| HB                   | 1.51 (1.15–1.98) | 0.337 | 0.003 | 1.77 (1.14–2.74) | 0.128 | 0.010 | 1.16 (0.57–2.35) | 0.066 | 0.680 |
| PB                   | 1.14 (0.78–1.68) | 0.000 | 0.494 | 1.11 (0.59–2.10) | 0.001 | 0.746 | 0.97 (0.62–1.50) | 0.041 | 0.887 |

P<sub>h</sub> value of Q-test for heterogeneity test; P<sub>Z</sub> value 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

#### Egger’s test

| Genetic type | Coefficient | Standard error | t   | P value | 95% CI of intercept | z   | P value |
|--------------|-------------|----------------|-----|---------|---------------------|-----|---------|
| **T2DM**     |             |                |     |         |                     |     |         |
| C-allele vs. G-allele | −0.842 | 0.636 | −1.32 | 0.195 | (−2.139–0.555) | 1.02 | 0.306  |
| CG vs. GG    | −0.688 | 0.469 | −1.47 | 0.152 | (−1.645–0.268) | 1.18 | 0.239  |
| CC + CG vs. GG | −0.756 | 0.511 | −1.48 | 0.149 | (−1.799–0.278) | 1.05 | 0.292  |
| CC vs. GG    | −0.318 | 0.301 | −1.06 | 0.301 | (−0.636–0.005) | 0.34 | 0.736  |
| CC vs. CG + GG | −0.304 | 0.32 | −0.95 | 0.351 | (−0.961–0.303) | 0.45 | 0.653  |
| **T1DM**     |             |                |     |         |                     |     |         |
| C-allele vs. G-allele | 1.268 | 0.697 | 1.82 | 0.099 | (−0.286–2.235) | 1.17 | 0.244  |
| CG vs. GG    | 0.858 | 0.454 | 1.89 | 0.088 | (−0.152–1.869) | 0.07 | 1      |
| CC + CG vs. GG | 0.894 | 0.481 | 1.86 | 0.093 | (−0.178–1.967) | 0.21 | 0.837  |
| CC vs. GG    | 0.455 | 0.323 | 1.41 | 0.189 | (−0.265–1.174) | 0.75 | 0.451  |
| CC vs. CG + GG | 0.523 | 0.384 | 1.36 | 0.202 | (−0.331–1.379) | 0.34 | 0.732  |
necessary to perform an updated meta-analysis to understand the associations between rs1800795 polymorphism and T1DM/T2DM [12, 15–20, 25–60].

Materials and methods
Document retrieval and data extraction
We used online databases, including PubMed, Embase, CNKI, Wanfang, and GWAS Catalog (https://www.ebi.ac.uk/gwas/) until on Feb 10, 2022, with keywords including ‘Interleukin-6/IL-6’, ‘polymorphism/variant’, and ‘Diabetes Mellitus/DM/T1DM/T2DM’. Two researchers (Zhiying Cheng, Chunmin Zhang) evaluated the articles to identify the stages through the abstract and then the full article. Systematic analysis/meta-analysis, case studies, other polymorphisms, insufficient data for each genotype, and duplications were identified and removed from further analysis. In addition, our meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Additional file 1: Table S1) and Meta-analysis of Observational Studies in Epidemiology. This study was registered at PROSPERO (number 329822; https://www.crd.york.ac.uk/prospero/). Eligible studies were selected based on the following criteria: @) studies assessing the
association between TIDM or T2DM. Additional file: As per journal requirements, every additional file must have a corresponding caption. In this regard, please be informed that the caption was taken from the Additional file 1 itself. Please advise if action taken appropriate and amend if necessary, and rs1800795 variants; @) case/control studies; and @) age-and sex-matched control subjects. The exclusion criteria were: @) not case/control studies; @) insufficient genotype frequency; @) duplicate studies; and @) significantly biased articles. Information including the name of the first author, year of publication, origin, race, DM type, genotype methods, and Hardy–Weinberg equilibrium (HWE) was collected.

**Quality assessment**
Quality was assessed using the Newcastle–Ottawa Scale (NOS) for cross-sectional study quality assessment. The methodological quality of each study (sampling strategy, response rate, and representativeness), comparability, and outcomes were assessed using the NOS tool. Studies with a score of more than 7 out of 10 were considered suitable. This cutoff point was determined after reviewing relevant meta-analyses from the literature [61–63].

**Statistical analyses**
The correlation between IL-6 rs1800795 polymorphism and the risk of TIDM/T2DM was measured using 95%

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**Fig. 4** Forest plot of T2DM risk associated with IL-6 rs1800795 polymorphism (CG vs. GG) in the subgroup of Mixed subgroup
confidence interval (CI) and odds-ratio (OR) according to the genotype frequencies of the case and control groups. Ethnic groups were divided into African, mixed, Caucasian, and Asian groups. Population-based (PB) and hospital-based (HB) control subgroups were also identified.

The statistical significance of the results was calculated using the Z-test. In these studies, the heterogeneity hypothesis was assessed using the Q-test based on the chi-squared test [64]. If significant heterogeneity ($<0.1$) was detected, the random effects model was used, else the fixed effects model was selected [65, 66]. For IL-6 rs1800795, we studied the relationship between variation and the risk of T2DM in the 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 T1DM risk. The asymmetry of the funnel plot was evaluated using Begg’s test, and publication bias was evaluated using Egger’s test. Statistical significance was set at $P<0.05$ [67]. Pearson’s chi-squared test was used in the control group (P<0.05), and the $\chi^2$ test was used to evaluate the deviation of rs1800795 polymorphism from the expected frequency of HWE [68]. All statistical tests were conducted using Stata (version 11.0; StataCorp LP, College Station, Texas, USA). The power of our meta-analysis was calculated online using the website http://www.power-analysis.com/.

Gene interaction network analysis of the IL-6 gene
To fully understand the role of IL-6 and its potential functional partners in DM, we used the STRING online server (http://string-db.org/) to construct an IL-6 gene–gene interaction network.
Results

Study selection and characteristics

A total of 1356 articles were identified from the four main databases (PubMed, Embase, CNKI, and Wanfang). 1260 papers were excluded after reading the abstract, and 96 articles were used for a complete evaluation. Among them, 50 articles were excluded for the following reasons: systematic analysis/meta-analysis (10), only case studies (9), other polymorphisms in the IL-6 gene (15), insufficient data for each genotype (8), and duplication (8) (Fig. 1). Thus, 46 papers [13–18] accounting for a total of 17,521 DM patients and 24,629 healthy controls were included in our meta-analysis (34 case–control studies including 7257 T2DM patients and 15,598 controls, and 12 case–control studies including 17,521 T1DM and 9031 controls) [12, 15–20, 25–60] (Table 1). We checked the minor allele frequency (MAF) reported for the five main populations worldwide in the 1000 Genomes Browser (https://www.ncbi.nlm.nih.gov/snp/rs1800795#frequency_tab) (Fig. 2A). In addition, the C-allele frequency was significantly lower in both cases and controls (Fig. 2B) (Table 2). The relationship between this polymorphism and several organs is shown in Fig. 2C (https://www.gtexportal.org/home/). The distribution of genotypes in controls was not consistent with the HWE in T2DM (9 case–control studies) [15, 26, 32, 38, 41, 42, 51, 53, 60] and T1DM (2 case–control studies) [44, 48] (Table 1). Genotyping of the SNPs of IL-6 gene rs1800795 polymorphism was conducted using the genotyping methods listed in Table 1.

IL-6 rs1800795 polymorphism and T2DM risk

The results of the meta-analysis suggested no associations between IL-6 rs1800795 polymorphism and T2DM risk (Table 3). If studies that were not consistent with HWE were excluded, no significant results were detected in any of the three models. Analysis of ethnicity subgroups showed a statistically significant association in Asians (OR_C-allele vs. G-allele = 0.76, 95% CI 0.58–0.99, \(P = 0.039\), random effect model; OR_CC vs. GG = 0.45, 95% CI 0.24–0.85, \(P = 0.014\), random effect model, OR_CC vs. CG+GG = 0.48, 95% CI 0.27–0.86, \(P = 0.014\), random effect model, Fig. 3) and mixed populations (OR_CC vs. GG = 0.74, 95% CI 0.58–0.94, \(P = 0.014\), fixed effect model, Fig. 4). Surprisingly, a marginal and poorly significant difference was found in the HB sources of the control subgroup (OR_CC vs. GG = 0.61, 95% CI 0.41–0.90, \(P < 0.011\), random
effect model, \( OR_{CC \text{ vs. } CG+GG} = 0.64, 95\% \ CI 0.46–0.90, \ P=0.011, \) random effect model, Fig. 5). Furthermore, if studies that were not consistent with HWE were included, no significant association was found between Asians and HB subgroups (Table 3).

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

There was a significant positive association between rs1800795 polymorphism and T1DM susceptibility in the total analysis (\( OR_{CC \text{ vs. } GG} = 1.32, 95\% \ CI 1.01–1.74, \ P=0.043, \) random effect model, Fig. 6) (Table 3). Additionally, a risk association was observed between this polymorphism in the mixed population (\( OR_{C\text{-alle} \text{ vs. } G\text{-alle}} = 1.39, 95\% \ CI 1.10–1.77, \ P=0.006, \) fixed effect model, \( OR_{CC \text{ vs. } GG} = 2.45, 95\% \ CI 1.18–5.07, \ P=0.016, \) fixed effect model, \( OR_{CC+CG \text{ vs. } GG} = 1.43, 95\% \ CI 1.07–1.90, \ P=0.015, \) fixed effect model, \( OR_{CC \text{ vs. } GG+GG} = 2.20, 95\% \ CI 1.08–4.48, \ P=0.031, \) fixed effect model, Fig. 7). Similar relationships were observed for the sources of the HB subgroup (\( OR_{C\text{-alle} \text{ vs. } G\text{-alle}} = 1.29, 95\% \ CI 1.07–1.56, \ P=0.009, \) fixed effect model, \( OR_{CG \text{ vs. } GG} = 1.47, 95\% \ CI 1.11–1.94, \ P=0.008, \) fixed effect model, Fig. 8). Furthermore, when we excluded studies that were not consistent with HWE, the results remain the same as above (Table 3).

**Publication bias and sensitive analysis**

Begg’s and Egger’s tests were performed to assess publication bias, which was not found for T2DM or T1DM analyses (T2DM: \( t_{C\text{-alle} \text{ vs. } G\text{-alle}} = −1.32, \ P=0.195 \) for Egger’s test, \( z=1.02, \ P=0.306 \) for Begg’s test, Fig. 9a, b; T1DM: \( t_{C\text{-alle} \text{ vs. } G\text{-alle}} = 1.82, \ P=0.099 \) for Egger’s test, \( z=1.17, \ P=0.244 \) for Begg’s test, Fig. 10a,b, Table 4). To delete studies that may influence the power and stability of the whole study, we applied a sensitivity analysis, and no sensitive case–control studies were found (Figs. 9c, 10c, Table 4).
Gene–gene network diagram and interactions

Our analysis using the STRING online server indicated that IL-6 interacts with several genes. The ten most significant genes from the network of gene–gene interactions are shown in Fig. 11. These ten genes are: interleukin-6 receptor (IL6R); interleukin-6 receptor subunit beta (IL6ST); interleukin-1 beta (IL1B); interleukin-8 (CXCL8); growth-regulated alpha protein (CXCL1); C-X-C motif chemokine 2 (CXCL2); C–C motif chemokine 2 (CCL2); interleukin-17A (IL17A); tumor necrosis factor (TNF); and interleukin-1 alpha (IL1A).

Discussion

Diabetes has reached pandemic dimensions, and is becoming relevant in both developed and developing countries, affecting over 400 million people worldwide [69]. To date, several studies have focused on the relationship between IL-6 rs1800795 polymorphism and DM risk [26, 29, 30, 38]. A few meta-analysis-based studies have also indicated similar associations [21–24]. However, there is a lack of robust conclusions. Therefore, it is necessary to recombine previously published studies to perform a comprehensive meta-analysis to understand the above-mentioned association in further detail. To the best of our knowledge, meta-analysis is a powerful method when the results are based on a large number of samples and are inconsistent, including different ethnicities or countries [24]. The conclusion obtained from the meta-analysis is more robust than that of a single study [24]. To investigate the association between IL-6 rs1800795 and DM, our comprehensive study included 42,150 individuals. Our results indicate that IL-6 rs1800795 acts as a protective factor in T2DM. In other words, individuals carrying the C-allele may have a decreased association with T2DM, particularly among Asians, mixed populations, and HB source studies. However, IL-6 rs1800795 was found to be a risk factor for T1DM, and there was a significantly increased association between this polymorphism and T1DM risk in four genetic models in mixed-population and HB source studies.

Therefore, IL-6 rs1800795 polymorphism may have different effects in different types of DM, and also have different influences on different ethnicities, such as Asians and mixed populations. This could be due to the
following: the pathogenic mechanisms of T2DM and T1DM are different, with differences in several significantly expressed genes. Further studies should focus on the functions and mechanisms of mutation or wild-type IL-6 rs1800795 polymorphism to define the dissimilarity between T2DM and T1DM. On the other hand, the same gene may have different effects, even opposite, and the IL-6 gene may behave differently for T2DM and T1DM. Therefore, rs1800795 polymorphism affecting the expression of IL-6 may also differ in its roles in T2DM and T1DM. Different races have heterogeneity, and the same gene may also have different roles in different ethnicities [70, 71]. Third, heterogeneity in the selection strategy may exist, which may have affected our results. To evaluate the stability and validity of the current study, we performed a power analysis. The power in T2DM was 1 and that in T1DM was 0.166, indicating that the conclusions from T2DM were more powerful and persuasive than those for T1DM. This suggests that more studies on rs1800795 and T1DM risk should be conducted in future to obtain a robust conclusion.

The development and outcome of DM are complex and multifactorial. Focusing only on each gene or polymorphism provides a limited understanding of the same. Hence, we attempted to detect other potential genes related to DM using the online STRING server. The other ten most probable genes were obtained from the network. Among them, six genes belonged to the interleukin family and three were in the front. Four genes were related to the chemokine (C–X–C motif) ligand family. For example, the first related gene is IL-6R, which is the receptor of the IL-6 gene. Qi et al. reported that the IL6R rs8192284 variant was significantly associated with plasma CRP level and could predict diabetes risk [72]. Jiao et al. performed a meta-analysis and suggested that the IL-1B (-511) T-allele polymorphism is associated with a decreased T2DM
risk in East Asians [73]. Silva et al. concluded that functional CXCL8 rs4073, rs2227307, and rs2227306 SNPs are relevant genetic factors for T2DM [74]. Trapali et al. indicated that the TNF-α308G/A polymorphism is significantly associated with T2DM susceptibility [75]. In summary, there is a need to explore these partners of the IL-6 gene and gene–gene interactions in the development and treatment of DM.

Although we performed a comprehensive meta-analysis, this study has several limitations. First, studies from mixed populations and Africans are limited, which leads to missing or insufficient results and may influence the conclusion. Second, one single 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 interactions, and further studies should pay close attention to the same. Third, four databases were included, and some valuable studies from other databases or languages could not be identified, which should have an impact on the current conclusions. Finally, most of the studies were selected using the PCR–RFLP technique in current publications, and the authors may apply to duplicate selected samples for the second time at least 10% of the total samples to confirm the genotypes detected by PCR–RFLP, as real-time PCR is a reference method which can verify the genotyping in PCR–RFLP technique to avoid false positives.

**Conclusions**

In summary, our meta-analysis provided evidence that the IL-6 rs1800795 polymorphism was associated with significantly increased T1DM risk in a mixed population. In contrast, a decreased association was found in T2DM susceptibility in Asians. Consequently, further well-designed large-scale studies, particularly those related to gene–gene and gene–environment interactions, are warranted.
Abbreviations
DM: Diabetes mellitus; GWAS: Genome-wide association studies; IL-6: Interleukin-6; SNP: Single nucleotide polymorphism; 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.

Supplementary Information
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Author contributions
CZ conceived of the study, CZ prepared the data, ZC were involved in the data analyses, ZC and MY prepared the figures. All the authors agreed to the submission of the present work. All the authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed in this study are included in this published article.

Additional file 1: PRISMA 2019 checklist.

Fig. 11 Human IL-6 interactions network with other genes obtained from String server. At least 10 genes have been indicated to correlate with IL-6 gene. A the gene–gene interaction, B the detail of relative ten core genes.
Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors proclaims that they have no competing interests.

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