Review Article

Association between Genetic Polymorphisms and Risk of Kidney Posttransplant Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Objectives. The purpose of this study was to clarify the role of genetic factors on posttransplant diabetes mellitus (PTDM) risk.

Methods. Relevant publications were systematically retrieved from PubMed, EMBASE, and the Cochrane Library up to December 2020. Data from eligible case-control and cohort studies were extracted for qualitative and quantitative analyses. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to estimate the association between gene polymorphisms and PTDM in the quantitative meta-analysis.

Results. A total of 43 eligible articles were identified, and 16 studies on 9 DNA variants from 8 genes were included in the meta-analysis. TCF7L2 rs7903146 was significantly associated with PTDM risk in 5 genetic models (OR (95% CI): allelic: 1.59 (1.17–2.16), \( P \leq 0.003 \); dominant recessive: 1.62 (1.14, 2.31), \( P \leq 0.007 \); recessive: 1.87 (1.18, 2.94), \( P \leq 0.007 \); homozygote: 2.21 (1.23, 3.94), \( P \leq 0.008 \); and heterozygote 1.50 (1.08, 2.10), \( P \leq 0.017 \)). KCNQ1 rs2237892 was significantly correlated with PTDM risk in 3 genetic models (allelic: 0.68 (0.58, 0.81), \( P \leq 0.001 \); dominant: 0.60 (0.49, 0.74), \( P \leq 0.001 \); and heterozygote: 0.61 (0.48, 0.76), \( P \leq 0.001 \)). KCNJ11 rs5219 was significantly linked with PTDM in the recessive genetic model (1.59 (1.01, 2.50), \( P \leq 0.047 \)). No significant correlations of PTDM with TCF7L2 rs7903146, KCNQ1 rs2237892, and KCNJ11 rs5219 polymorphisms were found.

Conclusions. The gene polymorphisms of TCF7L2 rs7903146, KCNQ1 rs2237892, and KCNJ11 rs5219 may predispose kidney transplant recipients to PTDM. Large sample size studies on diverse ethnic populations were warranted to confirm our findings.

1. Introduction

PTDM is a common serious complication after kidney transplantation, which is often associated with increased risk of graft failure, cardiovascular disease, and mortality [1]. Approximately 5.5% to 60.2% of kidney transplant patients develop PTDM in the first year after surgery [2]. A large retrospective study involving 11,659 kidney recipients from the United States Renal Data System (USRDS) demonstrated that the cumulative incidence of PTDM was 9.1%, 16%, and 24% at 3 months, 12 months, and 36 months, respectively [3]. Its etiopathogenesis is multifactorial, and transplant-related risk factors for PTDM include immunosuppressants, ethnicity, age, sex, body mass index, genetic factors, hepatitis C and cytomegalovirus infections, and family history of diabetes [2]. Immunosuppressive drugs consisting of corticosteroids and calcineurin inhibitors are important risk factors of PTDM, contributing to the development of hyperglycemia and diabetes [4]. Tacrolimus (TAC) and cyclosporin (CsA) are two major calcineurin inhibitors required after transplantation to prevent acute or chronic graft rejections [1]. The mechanisms underlying the diabeticogenic effect of immunosuppressive regimen include enhancing insulin resistance, reducing insulin secretion, and direct toxic effects on pancreatic \( \beta \)-cells [4]. It has also been suggested that glucocorticoid-induced hyperglycemia is
partially reversible through avoidance or early withdrawal of the drugs [5].

More evidence suggests that genetic risk factors play a significant role in the development of PTDM. Many genes associated with diabetes mellitus (DM) have also been correlated with PTDM risk. Gene mutations such as single nucleotide polymorphisms (SNPs) are the most common type of genetic variation. SNPs of TCF7L2 rs7903146, TCF7L2 rs12255372, KCNQ1 rs2237892, KCNJ11 rs5219, SLC30A8 rs13266634, PPARY rs1801282, CDKN2A/B rs10811661, HHEX rs1111875, and IGF2BP2 rs4402960 have recently been detected and shown to affect PTDM occurrence. Among them, TCF7L2 rs7903146 had an established strong effect across different populations and is the most common susceptible gene for PTDM [6–12]. One previous meta-analysis assessed the potential association between TCF7L2 rs7903146 polymorphism and PTDM [13]. However, there was a lack of systematic review on the correlation between other genes polymorphisms and PTDM. The meta-analysis by Benson et al. evaluated the allelic distribution of 18 gene polymorphisms in PTDM development [14]. In this study, we included several updated articles and comprehensively examined the association of nine SNPs from eight genes including TCF7L2, KCNQ1, KCNJ11, SLC30A8, PPARY, CDKN2A/B, HHEX, and IGF2BP2 with PTDM risk in all allelic and genotype models. Moreover, we reviewed the literature on genetic SNP markers susceptible to PTDM, which might help predict the risk of PTDM and facilitate the early prevention of this disease.

2. Materials and Methods

2.1. Literature Search. According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (see Supplementary Materials), we systematically searched PubMed, EMBASE, and the Cochrane Library for studies published up to December 2020.

2.2. Eligibility Criteria. The inclusion criteria included (1) kidney transplant recipients diagnosed with new-onset diabetes after transplantation (NODAT) or PTDM according to ADA or WHO guideline, (2) original studies examining the relationship between the gene polymorphism and NODAT or PTDM in patients after kidney transplantation, (3) study type: cohort or case-control studies, and (4) language restricted to English.

2.3. Search Strategy. When searching for possible eligible studies in the PubMed, EMBASE, and Cochrane Library databases, we used the mesh term of “kidney transplantation,” “polymorphism, genetic,” “posttransplant diabetes mellitus,” and “new-onset diabetes mellitus after transplantation,” as well as relevant keywords.

2.4. Data Extraction and Quality Assessment. The selection and inclusion of studies were performed in two stages by two independent reviewers, which included the analysis of titles/abstracts followed by the full texts. Disagreements were resolved by a third reviewer. Data retrieved from the eligible studies consisted of main demographical and clinical variables, including names of authors, publication year, study design, country, ethnicity, mean age, mean BMI, female percentage, genetic risk factors for PTDM, genotyping method and genotypes, diagnosis of PTDM, immunosuppressive therapy, time of PTDM diagnosis after transplantation, and age at transplant. We selected SNPs that showed significant associations with PTDM in allelic and/or genotype models from individual studies. The outcome was the evaluation of the impact of SNPs on the development of PTDM. Excel spreadsheet was used for the collection of extracted data. The methodological quality of included studies was evaluated by NOS. The base information was shown in Supplementary Table 1, and data used for all analyses were shown in Supplementary Table 2.

2.5. Statistical Analysis. Crude ORs with their 95% CIs were estimated and used to assess the strength of correlations of PTDM with TCF7L2 (rs7903146) C/T, TCF7L2 (rs12255372) G/T, SLC30A8 (rs13266634) C/T, KCNQ1 (rs2237892) C/T, PPARY (rs1801282) C/G, CDKN2A/B (rs10811661) C/T, HHEX (rs1111875) C/T, IGF2BP2 (rs4402960) G/T, and KCNJ11 (rs5219) C/T polymorphism. The pooled OR was calculated for allelic effect of C/T, G/T, or C/G; dominant model of CC/CT + TT, GG/GT + TT, or CC/GG + GG; recessive model of TT/CT + CT, TT/GG + GT, or GG/CC + GC; homozygote model of CC/TT, GG/TT, or GG/CC; and heterozygote model of CT/CC, GT/ GG, or GC/GG. The significance of the pooled OR was determined by the Z-test ($P \leq 0.05$).

Cochran’s Q statistic was used to assess the heterogeneity among studies ($P < 0.10$ indicated evidence of heterogeneity; https://doi.org/10.1136/bmj.327.7414.557). When significant heterogeneity ($P < 0.10$) was achieved, the random-effects model was used to combine the effect sizes of the included studies; otherwise, the fixed-effects model was adopted [15]. In addition, sensitivity analyses were performed to identify the effects of individual studies on pooled results and test the reliability of the estimates. All statistical analyses were performed using the STATA SE 14.0 software (StataCorp, College Station, Texas, USA).

3. Results

3.1. Study Selection and Characteristics of Included Studies. A total of 173 relevant publications were identified through searching the databases and other resources. After initial screening, duplicated documents; conference abstracts; reviews; publications on unrelated diseases, transplants, and interventions; and articles without full text were removed. The remaining 62 publications were assessed carefully; then 19 articles were excluded due to insufficient data. Finally, 43 eligible studies were included for the qualitative analysis. Among them, the data from 16 studies were used for the quantitative meta-analysis. The study screening flow chart was shown in Figure 1. The characteristics of the selected
3.2. Quality Assessment. The quality assessment of included studies using NOS was shown in Table 2, with the maximum of 9 points representing the least risk of bias. Overall, the methodological quality scores were 9 for 24 studies, 8 for 13 studies, 7 for 4 studies, and 6 for the other 2 studies, suggesting moderate to low risk of bias. The majority of the studies in the meta-analysis had a very low bias. Among them, 12 studies were assigned 9 points; 3 studies received 8 points; and only 1 study got 7 points.

3.3. Meta-Analysis of the Association between Nine Genetic Polymorphisms and PTDM Risk after Renal Transplantation.

In this meta-analysis, the TCF7L2 rs7903146 polymorphism was found to be significantly associated with the risk of PTDM in five genetic models (OR (95% CI): all: 1.59 (1.17–2.16), P = 0.003; dominant: 1.62 (1.14, 2.31), P = 0.007; recessive: 1.87 (1.18, 2.94), P = 0.007; heterozygote: 2.21 (1.23, 3.94), P = 0.008; and heterozygote 1.50 (1.08, 2.10), P = 0.017; Figure 2(a) and Table 3).

The pooled analysis did not observe the susceptibility of TCF7L2 rs12255372 polymorphism to PTDM in five genetic models (OR (95% CI): all: 1.06 (0.87, 1.54), P = 0.314; dominant: 1.18 (0.78, 1.79), P = 0.424; recessive: 1.36 (0.67, 2.76), P = 0.401; homozygote: 1.45 (0.70, 3.00), P = 0.317; and heterozygote 1.15 (0.74, 1.81), P = 0.529; Figure 2(b) and Table 3).

SLC30A8 rs13266634 polymorphism was not found to be significantly correlated with PTDM in five genetic models (OR (95% CI): all: 1.28 (0.70, 2.32), P = 0.421; dominant: 1.29 (0.68, 2.44), P = 0.442; recessive: 1.43 (0.55, 3.72), P = 0.467; homozygote: 1.66 (0.52, 5.30), P = 0.396; and heterozygote 1.16 (0.68, 1.97), P = 0.593; Figure 3(a) and Table 3).

There was a linkage between KCNQ1 rs2237892 polymorphism with PTDM in three genetic models (OR (95% CI): all: 0.68 (0.58, 0.81), P < 0.001; dominant: 0.6 (0.49, 0.74), P < 0.001; and heterozygote: 0.61 (0.48, 0.76), P < 0.001), but the association was not observed in other two genetic models (OR (95% CI): recessive: 0.87 (0.44, 1.69), P = 0.672, and homozygote: 0.75 (0.35, 1.58), P = 0.444; Figure 3(b) and Table 3).

Regarding PPARγ rs1801282 polymorphism, no significant correlation was found in all five genetic models (OR (95% CI): all: 0.98 (0.75, 1.28), P = 0.885; dominant: 1.04 (0.78, 1.40), P = 0.772; recessive: 0.44 (0.12, 1.60), P = 0.213; homozygote: 0.44 (0.12, 1.61), P = 0.217; and heterozygote: 1.11 (0.82, 1.48), P = 0.505; Figure 4(a) and Table 3).

CDKNA2A/B rs10811661 polymorphism was also not shown to be related with PTDM risk in all five genetic models (OR (95% CI): all: 1.10 (0.79, 1.52), P = 0.588; dominant: 1.51 (0.95, 2.38), P = 0.079; recessive: 1.06 (0.71, 1.57), P = 0.778; homozygote: 1.52 (0.93, 2.49), P = 0.092; and heterozygote: 1.54 (0.96, 2.48), P = 0.075; Figure 4(b) and Table 3).

With regard to HHEX rs1111875 polymorphism, no significant correlation with PTDM risk was demonstrated in all five genetic models (OR (95% CI): all: 1.15 (0.89, 1.50), P = 0.283; dominant: 1.35 (0.98, 1.86), P = 0.067; recessive: 1.09 (0.65, 1.83), P = 0.735; homozygote: 1.30 (0.74, 2.30), P = 0.357; and heterozygote: 1.35 (1.00, 1.84), P = 0.051; Figure 4(c) and Table 3).

Similarly, the IGF2BP2 rs4402960 polymorphism was not significantly associated with PTDM in all five genetic models (OR (95% CI): all: 0.97 (0.78, 1.21), P = 0.801; dominant: 0.92 (0.63, 1.34), P = 0.670; recessive: 0.23 (0.83, 1.82), P = 0.292; homozygote: 1.14 (0.76, 1.71), P = 0.532; and heterozygote: 0.88 (0.57, 1.36), P = 0.559; Figure 5(a) and Table 3).

In addition, the overall analysis revealed that KCNJ11 rs5219 polymorphism was significantly associated with PTDM risk in the recessive genetic model (OR (95% CI): 1.59 (1.01, 2.50), P = 0.047), though no association was found in the other genetic models (OR (95% CI): all: 1.10 (0.74, 1.63), P = 0.651; dominant: 0.98 (0.57, 1.66), P = 0.929; heterozygote: 0.90 (0.58, 1.40), P = 0.641; and homozygote: 1.45 (0.79, 2.66), P = 0.228; Figure 5(b) and Table 3).

3.4. Sensitivity Analysis. For meta-analyses on the association of three gene polymorphisms including TCF7L2 rs7903146, SLC30A8 rs13266634, and PPARγ rs1801282 with PTDM risk, the sensitivity analysis results showed that in all five genetic models, the reestimated ORs were all similar to the overall effects when excluding any individual study and assessing the remaining ones (Supplementary Figures 1–3).

4. Discussion

Genetic factors have been increasingly considered to play an important role in the pathogenesis of PTDM. This meta-analysis showed that gene polymorphisms of TCF7L2 rs7903146, KCNQ1 rs2237892, and KCNJ11 rs5219 contributed to PTDM occurrence and development. The genetic variations of TCF7L2 rs12255372, SLC30A8 rs13266634, PPARγ rs1801282, CDKNA2A/B rs10811661, HHEX rs1111875, and IGF2BP2 rs4402960 SNPs were not found to be associated with PTDM risk.

Previous studies indicated that these nine gene SNPs were associated with T2DM. Many genes associated with
T2DM have also been associated with an increased risk of PTDM. T2DM and PTDM were thought to share certain common pathophysiological processes. Impaired insulin secretion and increased insulin resistance have been suggested as mechanisms underlying the development of PTDM. One of the most intensively studied genes was TCF7L2. TCF7L2, a key component of the Wnt signaling pathway, is involved in the regulation of pancreatic β-cell proliferation, differentiation, and insulin secretion [6, 10]. Two common SNPs, rs7903146 and rs12255372, were located in TCF7L2 introns 3 and 4, respectively. TCF7L2 rs7903146 C/T emerged as the most common susceptible gene for T2DM in genome-wide association studies (GWAS) [2, 51]. Its association with PTDM has been well demonstrated in Asian (Indian and Korean), White, and Caucasian populations [6–12]. The T allele mutation at TCF7L2 rs7903146 loci has been linked with impaired insulin secretion and hepatic insulin resistance. The results of the association between TCF7L2 rs12255372G/T and PTDM remained conflicting [6, 11, 12]. TCF7L2 rs7903146 and rs12255372 haplotype analyses did not reveal any significant association with PTDM [11].

KCNQ1 encodes a subunit of the voltage-gated K+ channel. It is expressed in the pancreas and may help regulate the membrane potential of insulin-secreting cells and is involved in triggering and maintaining glucose-stimulated insulin secretion [25, 43]. Although this meta-analysis suggested the susceptibility of the most common KCNQ1 rs2237892 SNP to PTDM, opposite effects of KCNQ1 rs2237892 polymorphism have been discussed. Hwang et al. showed that KCNQ1 rs2237892C/T, located in intron 15, was significantly associated with decreased risk of PTDM in both allelic and genotype models, suggesting a protective effect on the development of PTDM [20]. Kang et al. reported that the T allele of KCNQ1 rs2237892 was correlated with a high risk of PTDM in an allele-specific manner [8].

The pooled analysis of KCNJ11 genes suggested its role in the pathogenesis of PTDM. ATP-sensitive potassium channel KCNJ11 plays an important role in the regulation of insulin secretion by pancreatic β cells, as well as glucose metabolism. KCNJ11 rs5219 glutamic acid to lysine amino acid substitution reduces potassium channels’ sensitivity to ATP molecules, resulting in overactivity of the channel and subsequent inhibition of

Figure 1: Flowchart of the search process of our study.
Table 1: Characteristics of the included studies.

| Study ID     | Country/Ethnicity                      | Design                        | Genotyping methods | Immunosuppressive treatment | Diagnostic criteria of cases | Time of PTDM diagnosis after transplantation (months) | Sample size PTDM/ non-PTDM | Age at transplantation (mean ± SD), y | Gender female (%) PTDM/ non-PTDM |
|--------------|----------------------------------------|-------------------------------|--------------------|-------------------------------|-------------------------------|------------------------------------------------------|-----------------------------|-------------------------------------|-------------------------------------|
| Van der Burgh [17] | Netherlands                             | Prospective cohort           | PCR                | TAC                           | ADA criteria                  | 12                                                   | 29/138                      | 60.7 ± 51.1                          | 34.5/41.3                           |
| Guad [18]     | Malaysia/Malay, Chinese, Indian         | Cohort                        | PCR                | CSA/TAC/both                  | ADA criteria                  | 12                                                   | 29/139                      | 39.3 ± 13.4/33.9 ± 11.8             | 44.8/40                             |
| Mota-Zamorano [19] | Spain/Caucasian                        | Cohort                        | RT-PCR             | CSA/TAC                       | ADA criteria                  | 12                                                   | 57/238                      | —                                    | —                                   |
| Hwang [20]    | Korean/                                 | Case-control, multicenter,   | PCR                | TAC/steroid                   | ADA criteria                  | 12                                                   | 254/848                     | 52.2 ± 10.4/45.1 ± 12.0            | 40.2/47.5                           |
| Zhang [21]    | China/Chinese, Han                      | Cohort                        | PCR-RFLP           | Triple-therapy/TAG, MMF, ster| ADA criteria                  | 6                                                    | 17/112                      | 49.35 ± 9.06/46.56 ± 9.91           | 29.4/23.2                           |
| Yokoyama [22] | Japan/Japanese                          | Cohort                        | PCR                | CSA/TAC                       | ADA criteria                  | 12                                                   | 11/27                       | 37.3 ± 9.0/44.6 ± 15.0             | 27.2/44.4                           |
| Shi [23]      | China/Chinese, Han                      | Case-control                  | PCR                | TAC                           | ADA criteria                  | 3                                                    | 57/112                      | 43.1 ± 9.0/38.6 ± 11.8             | —                                   |
| Yalin [24]    | Turkey                                  | Monocenter case-control       | PCR-RFLP           | CSA + AZA + PRED/ CSA + MMF + PRED/ TAC + MMF + PRED Standard triple-therapy TAC, MMF, and steroids | ADA criteria                  | —                                                    | 58/60                       | 47.2 ± 11.0/38.5 ± 10.1            | 31/36.7                             |
| Dabrowska-Zamojcin [25] | Poland                                 | Cohort                        | RT-PCR             | TAC                           | ADA criteria                  | 8.6                                                   | 35/166                      | 45.11 ± 9.90/38.26 ± 11.17          | 46.4/39.2                           |
| Alagbe [6]    | South Africa                            | Cohort                        | PCR                | TAC/MMF, MMF, steroids CSA/TAC | ADA criteria                  | 12 (TAC)/36 (CSA)                                     | 20/91                       | 44/37                              | 37.4/50                             |
| Ong [26]      | Korea                                   | Cohort                        | PCR                | TAC/others                    | ADA criteria                  | 3                                                    | 52/257                      | 45.56 ± 1.28/38.28 ± 0.71           | 47.1/39.4                           |
| Kim [27]      | Korea                                   | Cohort                        | PCR                | CSA/TAC/others                | ADA criteria                  | 3                                                    | 51/254                      | —                                    | —                                   |
| Dabrowska-Zamojcin [28] | Poland                                 | Cohort                        | RT-PCR             | Triple-drug therapy, CSA/TAC, AZA or MMF, and steroids | ADA criteria                  | 3                                                    | 23/146                      | —                                    | —                                   |
| Romanowski [29] | Poland/Caucasian                       | Cohort                        | RT-PCR             | TAC/CSA                       | ADA criteria                  | 3                                                    | 43/272                      | 39.57 ± 11.8/39.48 ± 10.39          | 28.6/23.5                           |
| Romanowski [30] | Poland/Caucasian                       | Cohort                        | RT-PCR             | Triple-therapy TAC, MMF, and steroids | ADA criteria                  | 3                                                    | 23/146                      | 40.4 ± 9.4/38.7 ± 6.2              | 25.6/26.3                           |
| Khan [10]     | India                                   | Cohort                        | PCR-RFLP           | CSA/TAC                       | ADA criteria                  | 3                                                    | 42/98                       | 39.57 ± 11.8/39.48 ± 10.39          | 28.6/23.5                           |
| Chen [31]     | China/Chinese                           | Cohort                        | PCR                | TAC                           | WHO guidelines                | 1                                                    | 78/80                       | 78.0 ± 7.8/38.7 ± 6.2              | 25.6/26.3                           |
| Kurzawski [32] | Poland/White                           | Cohort                        | RT-PCR             | TAC                           | ADA criteria                  | 12                                                   | 48/176                      | —                                    | —                                   |
| Study ID | Country/Ethnicity               | Design | Genotyping methods | Immunosuppressive treatment | Diagnostic criteria of cases | Time of PTDM diagnosis after transplantation (months) | Sample size | Age at transplantation (mean ± SD), y | Gender female (%) PTDM/ non-PTDM |
|----------|---------------------------------|--------|-------------------|----------------------------|-----------------------------|-----------------------------------------------------|------------|---------------------------------|---------------------------------|
| Yao [33] | China/Chinese                   | Cohort | PCR-RFLP          | MMF and corticosteroids    | ADA criteria                | 6                                                   | 16/89      | 47.81 ± 15.54/36.62 ± 11.43   | 37.5/34.8                       |
| Nicoletto [34] | Brazil/Caucasian               | Cohort | RT-PCR            | CSA/TAC                    | ADA criteria                | 12                                                  | 83/187     | 48.1 ± 11.0/39.8 ± 11.9        | 39.6/39.8                       |
| Lee [35]  | Korea                           | Cohort | PCR               | TAC/others                 | ADA criteria                | 3                                                   | 49/253     | 45.18 ± 9.39/38.1 ± 11.21      | 46.9/38.7                       |
| Elens [36] | Belgium                         | Cohort | RT-PCR            | TAC                        | —                           | —                                                   | 9/76       | —                              | —                              |
| Weng [37] | China/Taiwan                    | Cohort | PCR-RFLP          | CSA/TAC                    | International consensus guidelines | —                                                  | 27/251     | 47.6 ± 9.8/41.7 ± 11.5         | 44.6/22.2                       |
| Kurzawski [38] | Poland/Caucasian                 | Cohort | RT-PCR            | TAC                        | ADA criteria                | 12                                                  | 67/168     | 47.7 ± 10.6/43.2 ± 13.0        | 45.5/46.4                       |
| Kim [39]  | Korea                           | Cohort | PCR               | TAC/others                 | ADA criteria                | 3                                                   | 53/253     | 44.91 ± 1.33/38.34 ± 0.71      | 47.2/39.5                       |
| Kang [39] | Korea                           | Cohort | PCR               | CSA/TAC                    | The International Consensus Guidelines | 12                                                  | 154/421    | 42.3 ± 9.2/37.3 ± 9.4          | 37.7/35.6                       |
| Yu [40]   | China/Chinese                   | Cohort | PCR               | CSA or TAC, mycophenolate or AZA, and steroid, CSA or TAC, mycophenolic acid derivatives, sirolimus, and PED | ADA criteria | 24                                | 97/301     | 45.55 ± 10.78/40.26 ± 11.47   | 19.6/33.9                       |
| Yang [12] | USA                             | Cohort | RT-PCR            | TAC and MMF                | ADA criteria                | 133/170                                             | 51/72      | 44.30 ± 13.79/41.01 ± 13.11   | 43.6/43.5                       |
| Wang [41] | UAS/White, African American, Hispanic, Asian | Case-control | PCR             | TAC and MMF                | ADA criteria                | 3                                                   | 51/72      | 49.02 ± 13.04/47.22 ± 12.83   | 45.1/37.5                       |
| Tsai [42] | China/Taiwan                    | Cohort | PCR-RFLP          | TAC                        | ADA criteria                | 19.27 ± 26.3                                         | 85/198     | 54.9 ± 9.36/50.6 ± 11          | 45.9/50                         |
| Tavira [43] | Spain/Caucasian                 | Cohort | PCR-RFLP          | Standard triple TAC, MMF, and PED | ADA criteria                | 12                                                  | 145/260    | 49 ± 11/44 ± 13                | 40/38                           |
| Özdemir [44] | Turkey                        | Cohort | PCR               | Standard triple therapy with TAC, MMF, and PED | ADA criteria/WHO guidelines | 12                                                  | 23/27      | 37.9 ± 10.5/38.3 ± 10.9        | 33.3/35                         |
| Kurzawski [11] | Poland                        | Cohort | RT-PCR            | TAC, MMF, and steroids      | ADA criteria                | 12                                                  | 66/168     | 47.7 ± 10.6/43.2 ± 13.0        | 45.5/46.4                       |
| Fougeray [45] | France/Caucasians, Black, Asiatics, Other/unknown | Cohort | PCR             | TAC and MMF                | ADA criteria                | 3                                                   | 21/248     | —                              | —                              |
| Study ID  | Country/Ethnicity       | Design | Genotyping methods | Immunosuppressive treatment                           | Diagnostic criteria of cases | Time of PTDM diagnosis after transplantation (months) | Sample size | Age at transplantation (mean ± SD), y | Gender female (%) PTDM/non-PTDM |
|-----------|-------------------------|--------|--------------------|------------------------------------------------------|-------------------------------|------------------------------------------------------|-------------|--------------------------------------|-----------------------------|
| Chang [46]| China/Taiwan Cohort    | PCR-RFLP | CSA or TAC, MMF, or mycophenolic acid with or without PED | ADA criteria                     | Any time in follow-up             | 81/259                                               | 55.3 ± 10.0/52.6 ± 11.3 | 43.2/48.4                           |
| Kurzawski [47]| Poland Cohort PCR | TAC, MMF, and steroids | ADA criteria | 12                         | 56/158                           | 47.3 ± 9.9/43.0 ± 13.2 | 51.8/52.5               |
| Kao [16]  | China/Taiwan Cohort    | PCR-RFLP | CsA/FK506          | ADA criteria                     | Any time in follow-up             | 73/241                                               | 49.4 ± 9.37/47 ± 10.85 | 42.5/47.3                           |
| Jeong [48] | Korea Cohort PCR       | TAC/others | ADA criteria       | 3                                | 56/255                           | 45.11 ± 9.90/38.26 ± 11.17 | 46.4/39.2               |
| Dutkiewicz [49]| Poland/Caucasian Cohort PCR-RFLP | TAC, MMF, and steroids | ADA criteria       | 3                                | 21/138                           | 46.8 ± 8.8/42.0 ± 13.6 | 33.3/43.5               |
| Kang [8]   | Korea Cohort PCR       | Calcineurin inhibitors and GC | International consensus guidelines | 12                              | 145/444                          | 42.6 ± 9.1/37.4 ± 9.3  | 35.2/34.7               |
| Ghisdal [7] | France Cohort RT-PCR  | CSA/TAC/mTOR inhibitor | ADA criteria       | 6                                | 118/958                          | 52.8/46.7                                            | 42.4/37.1               |
| Kang [9]   | Korea Cohort PCR       | CSA/TAC | ADA criteria       | 3                                | 174/450                          | 42.1 ± 8.99/35.42 ± 9.43 | 35.1/35.6               |
| Kang [50]  | Korea Cohort RT-PCR    | CSA/TAC and GC | ADA criteria       | 3                                | 119/391                          | 41.10 ± 9.33/35.64 ± 10.8 | 34.5/36.5               |

PCR: polymerase chain reaction; RT-PCR: real-time polymerase chain reaction; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; ADA: American Diabetes Association; WHO: World Health Organization; CSA: cyclosporine A; AZA: azathioprine; PRED: prednol; MMF: mycofenolat mophetil; TAC: tacrolimus; PED: prednisone; PTDM: posttransplant diabetes mellitus; and GC: glucocorticoids.
| Study                  | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at the start of the study | Comparability of cohorts on the basis of the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts | Total quality scores |
|-----------------------|------------------------------------------|------------------------------------|---------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------|---------------------|-----------------------------------------------|-----------------------------------|----------------------|
| Van der Burgh [17]    | *                                        | *                                  | *                         | *                                                                                | **                                                              | *                   | *                                                             | *                                  | 9                    |
| Guad [18]             | *                                        | *                                  | *                         | *                                                                                | **                                                              | *                   | *                                                             | *                                  | 9                    |
| Mota-Zamorano [19]    | *                                        | *                                  | *                         | *                                                                                | **                                                              | *                   | *                                                             | *                                  | 8                    |
| Hwang [20]            | *                                        | *                                  | *                         | *                                                                                | **                                                              | *                   | *                                                             | *                                  | 9                    |
| Zhang [21]            | *                                        | *                                  | *                         | *                                                                                | **                                                              | *                   | *                                                             | *                                  | 9                    |
| Yokoyama [22]         | *                                        | *                                  | *                         | **                                                                               | *                                                               | *                   | *                                                             | *                                  | 9                    |
| Shi [23]              | *                                        | *                                  | *                         | *                                                                                | *                                                               | *                   | *                                                             | *                                  | 8                    |
| Dabrowska-Zamojcin [25]| *                                        | *                                  | *                         | *                                                                                | *                                                               | *                   | *                                                             | *                                  | 8                    |
| Alagbe [6]            | *                                        | *                                  | *                         | —                                                                                | **                                                              | *                   | *                                                             | *                                  | 8                    |
| Ong [26]              | *                                        | *                                  | *                         | *                                                                                | *                                                               | —                   | —                                                             | —                                  | 6                    |
| Kim [27]              | *                                        | *                                  | *                         | *                                                                                | *                                                               | *                   | *                                                             | *                                  | 8                    |
| Dabrowska-Zamojcin [28]| *                                        | *                                  | *                         | —                                                                                | *                                                               | *                   | *                                                             | *                                  | 7                    |
| Romanowski [29]       | *                                        | *                                  | *                         | —                                                                                | *                                                               | *                   | *                                                             | *                                  | 7                    |
| Romanowski [30]       | *                                        | *                                  | *                         | *                                                                                | *                                                               | *                   | *                                                             | *                                  | 8                    |
| Khan [10]             | *                                        | *                                  | *                         | *                                                                                | **                                                              | *                   | —                                                             | —                                  | 7                    |
| Chen [31]             | *                                        | *                                  | *                         | **                                                                               | *                                                               | *                   | *                                                             | *                                  | 9                    |
| Kurzawski [32]        | *                                        | *                                  | *                         | *                                                                                | **                                                              | *                   | *                                                             | *                                  | 9                    |
| Yao [33]              | *                                        | *                                  | *                         | *                                                                                | *                                                               | *                   | *                                                             | *                                  | 8                    |
| Nicoletto [34]        | *                                        | *                                  | *                         | *                                                                                | *                                                               | *                   | *                                                             | *                                  | 8                    |
| Lee [35]              | *                                        | *                                  | *                         | *                                                                                | *                                                               | *                   | *                                                             | *                                  | 8                    |
| Elens [36]            | *                                        | *                                  | *                         | *                                                                                | *                                                               | *                   | *                                                             | *                                  | 9                    |
| Weng [37]             | *                                        | *                                  | *                         | *                                                                                | *                                                               | *                   | *                                                             | *                                  | 8                    |
| Kurzawski [38]        | *                                        | *                                  | *                         | *                                                                                | **                                                              | *                   | *                                                             | *                                  | 9                    |
| Kim [39]              | *                                        | *                                  | *                         | *                                                                                | **                                                              | *                   | *                                                             | *                                  | 9                    |
| Kang [8]              | *                                        | *                                  | *                         | *                                                                                | **                                                              | *                   | *                                                             | *                                  | 9                    |
| Yu [40]               | *                                        | *                                  | *                         | *                                                                                | **                                                              | *                   | *                                                             | *                                  | 9                    |
| Yang [12]             | *                                        | *                                  | *                         | *                                                                                | **                                                              | *                   | *                                                             | *                                  | 9                    |
| Tsai [42]             | *                                        | *                                  | *                         | *                                                                                | *                                                               | *                   | *                                                             | *                                  | 8                    |
| Tavira [43]           | *                                        | *                                  | *                         | *                                                                                | **                                                              | *                   | *                                                             | *                                  | 9                    |
| Ozdemir [44]          | *                                        | *                                  | *                         | *                                                                                | **                                                              | *                   | *                                                             | *                                  | 9                    |
TABLE 2: Continued.

| Study       | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at the start of the study | Comparability of cohorts on the basis of the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts | Total quality scores |
|-------------|----------------------------------------|------------------------------------|--------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------|----------------------|---------------------------------------------|---------------------------------|----------------------|
| Kurzawski [11] | *                                      | *                                  | *                        | *                                                                               | *                                                              | *                    | *                                          | *                               | 8                    |
| Fougeray [45]  | *                                      | *                                  | *                        | *                                                                               | —                                                              | *                    | *                                          | *                               | 7                    |
| Chang [46]     | *                                      | *                                  | *                        | *                                                                               | *                                                              | *                    | *                                          | *                               | 8                    |
| Kurzawski [47] | *                                      | *                                  | *                        | *                                                                               | +                                                              | *                    | *                                          | *                               | 9                    |
| Kao [16]       | *                                      | *                                  | *                        | *                                                                               | +                                                              | *                    | *                                          | *                               | 9                    |
| Jeong [48]     | *                                      | *                                  | *                        | *                                                                               | +                                                              | *                    | *                                          | *                               | 9                    |
| Dutkiewicz [49] | *                                      | *                                  | *                        | *                                                                               | +                                                              | *                    | *                                          | *                               | 9                    |
| Kang [8]       | *                                      | *                                  | *                        | *                                                                               | +                                                              | *                    | *                                          | *                               | 9                    |
| Ghisdal [7]    | *                                      | *                                  | *                        | *                                                                               | +                                                              | *                    | *                                          | *                               | 9                    |
| Kang [9]       | *                                      | *                                  | *                        | *                                                                               | +                                                              | *                    | *                                          | *                               | 9                    |
| Kang [50]      | *                                      | *                                  | *                        | *                                                                               | +                                                              | *                    | *                                          | *                               | 9                    |
| Case-control   |                                        |                                    |                          |                                                                                 |                                                                 |                      |                                             |                                 |                      |

| Study       | Is the case definition adequate? | Representativeness of the cases | Selection of controls | Definition of controls | Comparability of cases and controls on the basis of the design or analysis | Ascertainment of intervention | Same method of ascertainment for cases and controls | Non-response rate | Total quality scores |
|-------------|---------------------------------|---------------------------------|-----------------------|------------------------|--------------------------------------------------------------------------------|------------------------------|----------------------------------------------------|----------------------|----------------------|
| Yalin [24]  | *                               | *                               | *                     | *                      | +                                                                             | *                           | *                                                  | *                    | 9                    |
| Wang [41]   | *                               | *                               | *                     | *                      | +                                                                             | *                           | *                                                  | *                    | 9                    |

*One point; **two points.
NOTE: Weights and between-subgroup heterogeneity test are from random-effects model.

**Figure 2: Continued.**
insulin secretion [12, 24, 25]. The meta-analysis of the Asian Indian population showed no significant association of KCNJ11 rs5219 polymorphism with risk of T2DM [52]. However, other meta-analyses demonstrated a significant effect of KCNJ11 rs5219 in susceptibility to T2DM in East Asians, Caucasians, and North Africans [53].

Controversial results have been reported for the association of SLC30A8, PPARc, CDKN2A/B, HHEX, and IGF2BP gene polymorphisms with PTDM. In this overall analysis, these extensively evaluated genes were not found to contribute to the development of PTDM. SLC30A8 belongs to the zinc transporter family, which plays a major role in transporting zinc from the cytoplasm to intracellular vesicles for insulin maturation, storage, and secretion from \( \beta \)-cells [7, 8, 10, 22, 38, 50]. The SLC30A8 rs13266634 arginine to tryptophan variant, associated with impaired \( \beta \)-cell function, has been proposed as important genetic markers of T2DM in Europeans and East Asians but not the African population [54, 55]. PPARc gene belongs to the nuclear hormone receptor subfamily that controls the expression of genes involved in glucose and lipid homeostasis. The SNP rs1801282 (C/G) is the most common variant located in exon-2 of PPARc, and the substitution of proline to alanine of PPARc reduces its transcriptional activity and insulin sensitivity [7, 12, 21, 38, 41]. One meta-analysis suggested that PPARc rs1801282 was significantly associated with T2DM under the heterozygote genetic model in Asian and Caucasian populations [56]. CDKN2A/B, which encodes two kinase inhibitors p16INK4a and p15INK4b, regulates pancreatic \( \beta \)-cell regeneration. The locus rs10811661 locates \(-100\) kb upstream of CDKN2A/B gene-coding sequence, but the mechanism by which this SNP affects T2DM and PTDM susceptibility remains to be investigated [7, 8, 22, 38]. HHEX gene encodes a

| model and author (year) | Odds Ratio (95% CI) | Weight (%) |
|-------------------------|---------------------|------------|
| Allele model            |                     |            |
| Alagbe (2017)           | 1.73 [0.70, 4.28]   | 9.91       |
| Yang (2011)             | 0.97 [0.64, 1.45]   | 49.28      |
| Kurzawski (2011)        | 1.30 [0.84, 2.04]   | 40.81      |
| Subgroup, DL (I² = 0.0%, \( p = 0.407 \)) | 1.16 [0.87, 1.54] | 100.00     |
| Dominant model          |                     |            |
| Alagbe (2017)           | 2.17 [0.69, 6.86]   | 11.81      |
| Yang (2011)             | 0.91 [0.56, 1.46]   | 49.55      |
| Kurzawski (2011)        | 1.38 [0.78, 2.45]   | 38.63      |
| Subgroup, DL (I² = 20.7%, \( p = 0.283 \)) | 1.18 [0.78, 1.79] | 100.00     |
| Recessive model         |                     |            |
| Alagbe (2017)           | 1.31 [0.13, 13.57]  | 9.24       |
| Yang (2011)             | 1.29 [0.44, 3.78]   | 43.88      |
| Kurzawski (2011)        | 1.43 [0.51, 4.03]   | 46.88      |
| Subgroup, DL (I² = 0.0%, \( p = 0.991 \)) | 1.36 [0.67, 2.76] | 100.00     |
| Homozygote model        |                     |            |
| Alagbe (2017)           | 1.81 [0.16, 20.00]  | 9.15       |
| Yang (2011)             | 1.24 [0.42, 3.66]   | 44.92      |
| Kurzawski (2011)        | 1.62 [0.55, 4.73]   | 45.93      |
| Subgroup, DL (I² = 0.0%, \( p = 0.925 \)) | 1.45 [0.70, 3.00] | 100.00     |
| Heterozygote model      |                     |            |
| Alagbe (2017)           | 2.24 [0.68, 7.37]   | 12.64      |
| Yang (2011)             | 0.86 [0.52, 1.43]   | 48.64      |
| Kurzawski (2011)        | 1.34 [0.74, 2.44]   | 38.72      |
| Subgroup, DL (I² = 24.8%, \( p = 0.264 \)) | 1.15 [0.74, 1.80] | 100.00     |

NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

![Figure 2: Forest plots of (a) TCF7L2 (rs7903146) C/T and (b) TCF7L2 (rs12255372) G/T polymorphism and PTDM risk in five genetic models: allele, dominant, recessive, homozygote, and heterozygote genetic model.](image)
transcription factor involved in hepatic and pancreatic development via the Wnt signal pathway [7, 8, 22, 38]. The SNP rs1111875 at the 3′-flanking region of the HHEX gene, which may decrease pancreatic beta-cell function, is reported to be associated with T2DM risk as lead SNP in Chinese Han and European populations [57]. A meta-analysis of IGF2BP2 rs4402960 suggested a significant association with T2DM in Asian populations [58]. The mRNA-binding protein IGF2BP2 is highly expressed in pancreatic islets and participates in a spectrum of the biological process including cellular metabolism.

McCaughan et al. examined in GWAS the association between PTDM and 26 gene SNPs in the White population [59]. This association was validated for eight SNPs, and KCNJ11 rs5219, PPARγ rs1801282, SLC30A8 rs13266634, and TCF7L2 rs7903146 polymorphisms were included, whereas the genetic variants of TCF7L2 rs12255372, KCNQ1 rs2237892, CDKN2A/B rs10811661, HHEX rs1111875, and IGF2BP2 rs4402960 were not studied.

### Table 3: Genetic polymorphisms and risk of PTDM after renal transplantation.

| Gene       | Model       | No. of paper | OR    | 95% CI | P value | I² (%) | P value (Heterogeneity) |
|------------|-------------|--------------|-------|--------|---------|--------|------------------------|
| TCF7L2 (rs7903146) | Allele model | 7            | 1.59  | 1.17–2.16 | 0.003   | 60.8   | 0.018                  |
|            | Dominant model | 7            | 1.62  | 1.14–2.31 | 0.007   | 54.6   | 0.040                  |
|            | Heterozygote model | 7            | 1.50  | 1.08–2.10 | 0.017   | 45.9   | 0.085                  |
|            | Homozygote model | 5            | 2.21  | 1.23–3.94 | 0.008   | 35.3   | 0.186                  |
|            | Recessive model | 5            | 1.87  | 1.18–2.94 | 0.007   | 12.8   | 0.332                  |
| TCF7L2 (rs12255372) | Allele model | 3            | 0.16  | 0.87–1.54 | 0.314   | 0      | 0.407                  |
|            | Dominant model | 3            | 1.18  | 0.78–1.79 | 0.424   | 20.7   | 0.283                  |
|            | Heterozygote model | 3            | 1.15  | 0.74–1.81 | 0.529   | 24.8   | 0.991                  |
|            | Homozygote model | 3            | 1.45  | 0.70–3.00 | 0.317   | 0      | 0.925                  |
|            | Recessive model | 3            | 1.36  | 0.67–2.76 | 0.401   | 0      | 0.264                  |
| SLC30A8 (rs13266634) | Allele model | 6            | 1.28  | 0.70–2.32 | 0.421   | 93.4   | <0.001                 |
|            | Dominant model | 6            | 1.29  | 0.68–2.44 | 0.442   | 87.4   | <0.001                 |
|            | Heterozygote model | 6            | 1.16  | 0.68–1.97 | 0.593   | 79.0   | <0.001                 |
|            | Homozygote model | 6            | 1.66  | 0.52–5.30 | 0.396   | 90.9   | <0.001                 |
|            | Recessive model | 6            | 1.43  | 0.55–3.72 | 0.467   | 89.6   | <0.001                 |
| KCNQ1 (rs2237892) | Allele model | 4            | 0.68  | 0.58–0.81 | <0.001 | 0      | 0.473                  |
|            | Dominant model | 4            | 1.29  | 0.49–0.74 | <0.001 | 0      | 0.717                  |
|            | Heterozygote model | 4            | 0.61  | 0.48–0.76 | <0.001 | 0      | 0.890                  |
|            | Homozygote model | 4            | 0.75  | 0.35–1.58 | 0.444   | 59.6   | 0.059                  |
|            | Recessive model | 4            | 0.87  | 0.44–1.69 | 0.672   | 53.4   | 0.092                  |
| PPARγ (rs1801282) | Allele model | 5            | 0.98  | 0.75–1.28 | 0.885   | 0      | 0.642                  |
|            | Dominant model | 5            | 1.04  | 0.78–1.40 | 0.772   | 0      | 0.665                  |
|            | Heterozygote model | 5            | 1.11  | 0.82–1.48 | 0.505   | 0      | 0.713                  |
|            | Homozygote model | 5            | 0.44  | 0.12–1.61 | 0.217   | 0      | 0.93                   |
|            | Recessive model | 5            | 0.44  | 0.12–1.60 | 0.213   | 0      | 0.936                  |
| CDKN2A/B (rs10811661) | Allele model | 4            | 1.10  | 0.79–1.52 | 0.588   | 52.8   | 0.095                  |
|            | Dominant model | 4            | 1.51  | 0.95–2.38 | 0.079   | 0      | 0.641                  |
|            | Heterozygote model | 4            | 1.54  | 0.96–2.48 | 0.075   | 0      | 0.877                  |
|            | Homozygote model | 5            | 1.52  | 0.93–2.49 | 0.092   | 0      | 0.462                  |
|            | Recessive model | 4            | 1.06  | 0.71–1.57 | 0.778   | 46.6   | 0.132                  |
| HHEX (rs1111875) | Allele model | 4            | 1.15  | 0.89–1.50 | 0.283   | 45.3   | 0.139                  |
|            | Dominant model | 4            | 1.35  | 0.98–1.86 | 0.067   | 19.2   | 0.294                  |
|            | Heterozygote model | 4            | 1.35  | 1.00–1.84 | 0.051   | 7.2    | 0.357                  |
|            | Homozygote model | 4            | 1.30  | 0.74–2.30 | 0.357   | 46.8   | 0.130                  |
|            | Recessive model | 4            | 1.09  | 0.65–1.83 | 0.735   | 53.5   | 0.092                  |
| IGF2BP2 (rs4402960) | Allele model | 4            | 0.97  | 0.78–1.21 | 0.801   | 20.0   | 0.290                  |
|            | Dominant model | 4            | 0.92  | 0.63–1.34 | 0.670   | 49.3   | 0.116                  |
|            | Heterozygote model | 4            | 0.88  | 0.57–1.36 | 0.559   | 55.5   | 0.081                  |
|            | Homozygote model | 4            | 1.14  | 0.76–1.71 | 0.532   | 0      | 0.663                  |
|            | Recessive model | 4            | 0.23  | 0.83–1.82 | 0.292   | 0      | 0.692                  |
| KCNJ11 (rs5219) | Allele model | 3            | 1.10  | 0.74–1.63 | 0.651   | 56.3   | 0.102                  |
|            | Dominant model | 3            | 0.98  | 0.57–1.66 | 0.929   | 50.1   | 0.135                  |
|            | Heterozygote model | 3            | 0.90  | 0.58–1.40 | 0.641   | 20.1   | 0.286                  |
|            | Homozygote model | 3            | 1.45  | 0.79–2.66 | 0.228   | 21.5   | 0.280                  |
|            | Recessive model | 3            | 1.59  | 1.01–2.50 | 0.047   | 0      | 0.575                  |
### Allele model

| Model and Author (Year) | Odds Ratio (95% CI) | Weight (%) |
|-------------------------|---------------------|------------|
| Yokoyama (2018)         | 1.05 [0.37, 2.96]   | 12.08      |
| Khan (2015)             | 2.01 [1.16, 3.48]   | 16.29      |
| Kurzawski (2012)        | 5.12 [3.30, 7.94]   | 17.15      |
| Kang (2009)             | 0.66 [0.50, 0.87]   | 18.17      |
| Ghisdal (2009)          | 0.92 [0.68, 1.25]   | 18.04      |
| Kang (2008a)            | 0.70 [0.54, 0.91]   | 18.27      |
| Subgroup, DL (I² = 78.8%, p = 0.000) | 1.28 [0.70, 2.32] | 100.00    |

### Dominant model

| Model and Author (Year) | Odds Ratio (95% CI) | Weight (%) |
|-------------------------|---------------------|------------|
| Yokoyama (2018)         | 0.83 [0.20, 3.39]   | 10.34      |
| Khan (2015)             | 2.46 [1.17, 5.17]   | 16.54      |
| Kurzawski (2012)        | 12.10 [4.21, 34.78] | 13.41      |
| Kang (2009)             | 0.57 [0.39, 0.84]   | 19.83      |
| Ghisdal (2009)          | 0.92 [0.63, 1.34]   | 19.87      |
| Kang (2008a)            | 0.65 [0.45, 0.94]   | 20.01      |
| Subgroup, DL (I² = 87.0%, p = 0.000) | 1.28 [0.68, 2.41] | 100.00    |

### Recessive model

| Model and Author (Year) | Odds Ratio (95% CI) | Weight (%) |
|-------------------------|---------------------|------------|
| Yokoyama (2018)         | 1.78 [0.25, 12.45]  | 10.94      |
| Khan (2015)             | 2.17 [0.68, 6.89]   | 15.46      |
| Kurzawski (2012)        | 9.22 [4.56, 18.63]  | 18.01      |
| Kang (2009)             | 0.58 [0.34, 1.00]   | 18.73      |
| Ghisdal (2009)          | 0.87 [0.42, 1.78]   | 17.95      |
| Kang (2008a)            | 0.59 [0.35, 0.97]   | 18.91      |
| Subgroup, DL (I² = 89.6%, p = 0.000) | 1.43 [0.55, 3.72] | 100.00    |

### Homozygote model

| Model and Author (Year) | Odds Ratio (95% CI) | Weight (%) |
|-------------------------|---------------------|------------|
| Yokoyama (2018)         | 1.47 [0.18, 11.72]  | 11.98      |
| Khan (2015)             | 3.16 [0.93, 10.73]  | 16.08      |
| Kurzawski (2012)        | 37.64 [11.68, 121.31] | 16.32     |
| Kang (2009)             | 0.44 [0.24, 0.80]   | 18.66      |
| Ghisdal (2009)          | 0.84 [0.40, 1.76]   | 18.16      |
| Kang (2008a)            | 0.48 [0.28, 0.84]   | 18.79      |
| Subgroup, DL (I² = 90.7%, p = 0.000) | 1.65 [0.52, 5.24] | 100.00    |

### Heterozygote model

| Model and Author (Year) | Odds Ratio (95% CI) | Weight (%) |
|-------------------------|---------------------|------------|
| Yokoyama (2018)         | 0.68 [0.15, 3.16]   | 7.95       |
| Khan (2015)             | 2.30 [1.05, 5.06]   | 15.85      |
| Kurzawski (2012)        | 6.93 [2.33, 20.63]  | 11.97      |
| Kang (2009)             | 0.62 [0.41, 0.93]   | 21.26      |
| Ghisdal (2009)          | 0.93 [0.62, 1.39]   | 21.37      |
| Kang (2008a)            | 0.72 [0.49, 1.05]   | 21.60      |
| Subgroup, DL (I² = 78.8%, p = 0.000) | 1.16 [0.68, 1.96] | 100.00    |

NOTE: Weights and between-subgroup heterogeneity test are from random-effects model.

(a) 

**Figure 3: Continued.**
The most significantly associated pathway of β-cell apoptosis and dysfunction in the pathogenesis of PTDM.

The previous meta-analysis by Benson et al. collected case-control kidney transplant studies that were carried out in Asian, Caucasian, and mixed ethnicity populations up to 2015 and investigated the association between 18 genetic variants across 12 genes and PTDM in the allele model [14]. They found TCF7L2 rs7903146 and KCNQ1 rs2237892 were correlated with higher PTDM risk, whereas the allelic distribution of TCF7L2 rs12255372, SLC30A8 rs13266634, PPARγ rs1801282, CDKN2A/B rs10811661, HHEX rs1111875, IGF2BP2 rs4402960, and KCNJ11 rs5219 was not linked with PTDM. Our meta-analysis included a number of updated publications till 2019, covering Asian, Caucasian, White, and African populations from both cohort and case-control studies. We comprehensively analyzed nine SNPs of eight genes in five allelic and genotype models, each model containing a minimum of three publications with complete data information, which would provide better power to identify alleles associated with PTDM susceptibility robustly. However, our study suggested KCNQ1 rs2237892 was correlated with lower PTDM risk in the allele model. Furthermore, significant associations with PTDM were found for TCF7L2 rs7903146 in the dominant, recessive, homozygote, and heterozygote genotype models; for KCNQ1 rs2237892 in the dominant and heterozygote models; and for KCNJ11 rs5219 in the recessive model. The meta-analysis by Quaglia et al. focused on TCF7L2 rs7903146 studies published from 2009 to 2014 and showed that TCF7L2 rs7903146 was strongly associated with PTDM in the dominant and recessive models, which was similar to our findings [13]. Moreover, both previous meta-analyses retrieved data from
| model and author (year) | Odds Ratio (95% CI) | Weight (%) |
|------------------------|---------------------|------------|
| Allele model           |                     |            |
| Zhang (2019)           | 1.86 [0.58, 5.97]   | 5.30       |
| Kurzawski (2012)       | 0.78 [0.42, 1.44]   | 18.84      |
| Wang (2011)            | 0.76 [0.27, 2.11]   | 6.82       |
| Yang (2011)            | 0.90 [0.55, 1.46]   | 30.76      |
| Ghisdal (2009)         | 1.13 [0.73, 1.75]   | 38.28      |
| Subgroup, DL ($I^2 = 0.0\%$, $p = 0.642$) | 0.98 [0.75, 1.28] | 100.00     |
| Dominant model         |                     |            |
| Zhang (2019)           | 1.99 [0.57, 6.91]   | 5.45       |
| Kurzawski (2012)       | 0.84 [0.43, 1.64]   | 18.80      |
| Wang (2011)            | 0.74 [0.25, 2.15]   | 7.44       |
| Yang (2011)            | 0.95 [0.55, 1.62]   | 29.09      |
| Ghisdal (2009)         | 1.22 [0.76, 1.94]   | 39.22      |
| Subgroup, DL ($I^2 = 0.0\%$, $p = 0.665$) | 1.04 [0.78, 1.40] | 100.00     |
| Recessive model        |                     |            |
| Kurzawski (2012)       | 0.27 [0.01, 5.10]   | 19.24      |
| Yang (2011)            | 0.50 [0.10, 2.64]   | 60.47      |
| Ghisdal (2009)         | 0.47 [0.03, 8.20]   | 20.29      |
| Subgroup, DL ($I^2 = 0.0\%$, $p = 0.936$) | 0.44 [0.12, 1.60] | 100.00     |
| Homozygote model       |                     |            |
| Kurzawski (2012)       | 0.27 [0.01, 5.02]   | 19.26      |
| Yang (2011)            | 0.50 [0.10, 2.66]   | 60.39      |
| Ghisdal (2009)         | 0.49 [0.03, 8.61]   | 20.34      |
| Subgroup, DL ($I^2 = 0.0\%$, $p = 0.930$) | 0.44 [0.12, 1.61] | 100.00     |
| Heterozygote model     |                     |            |
| Zhang (2019)           | 1.99 [0.57, 6.91]   | 5.60       |
| Kurzawski (2012)       | 0.92 [0.47, 1.82]   | 18.94      |
| Wang (2011)            | 0.74 [0.25, 2.15]   | 7.64       |
| Yang (2011)            | 1.01 [0.58, 1.77]   | 27.71      |
| Ghisdal (2009)         | 1.27 [0.80, 2.03]   | 40.11      |
| Subgroup, DL ($I^2 = 0.0\%$, $p = 0.713$) | 1.11 [0.82, 1.48] | 100.00     |

Heterogeneity between groups: $p = 0.462$

NOTE: Weights and between-subgroup heterogeneity test are from random-effects model; continuity correction applied to studies with zero cells.

(a)

Figure 4: Continued.
| model and author (year)          | Odds Ratio (95% CI) | Weight (%) |
|---------------------------------|---------------------|------------|
| **Allele model**                |                     |            |
| Yokoyama (2018)                 | 0.86 [0.32, 2.33]   | 9.13       |
| Kurzawski (2012)                | 1.46 [0.78, 2.75]   | 17.94      |
| Kang (2009)                     | 1.33 [1.01, 1.75]   | 38.36      |
| Ghisdal (2009)                  | 0.81 [0.58, 1.12]   | 34.57      |
| Subgroup, DL ($I^2 = 52.8\%$, $p = 0.095$) | 1.10 [0.79, 1.52]   | 100.00     |

| **Dominant model**              |                     |            |
| Yokoyama (2018)                 | 0.78 [0.12, 5.05]   | 6.02       |
| Kurzawski (2012)                | 2.03 [0.10, 42.78]  | 2.25       |
| Kang (2009)                     | 1.85 [1.05, 3.28]   | 64.01      |
| Ghisdal (2009)                  | 1.05 [0.44, 2.50]   | 27.72      |
| Subgroup, DL ($I^2 = 0.0\%$, $p = 0.641$) | 1.51 [0.95, 2.38]   | 100.00     |

| **Recessive model**             |                     |            |
| Yokoyama (2018)                 | 0.78 [0.13, 4.62]   | 4.56       |
| Kurzawski (2012)                | 1.47 [0.75, 2.90]   | 21.49      |
| Kang (2009)                     | 1.32 [0.89, 1.96]   | 36.91      |
| Ghisdal (2009)                  | 0.73 [0.49, 1.08]   | 37.03      |
| Subgroup, DL ($I^2 = 46.6\%$, $p = 0.132$) | 1.06 [0.71, 1.57]   | 100.00     |

| **Homozygote model**            |                     |            |
| Yokoyama (2018)                 | 0.67 [0.06, 6.87]   | 4.42       |
| Kurzawski (2012)                | 2.20 [0.10, 46.64]  | 2.58       |
| Kang (2009)                     | 2.04 [1.09, 3.79]   | 62.07      |
| Ghisdal (2009)                  | 0.93 [0.39, 2.25]   | 30.93      |
| Subgroup, DL ($I^2 = 0.0\%$, $p = 0.462$) | 1.52 [0.93, 2.49]   | 100.00     |

| **Heterozygote model**          |                     |            |
| Yokoyama (2018)                 | 0.82 [0.12, 5.57]   | 6.19       |
| Kurzawski (2012)                | 1.59 [0.07, 35.14]  | 2.36       |
| Kang (2009)                     | 1.74 [0.96, 3.16]   | 63.91      |
| Ghisdal (2009)                  | 1.33 [0.54, 3.28]   | 27.54      |
| Subgroup, DL ($I^2 = 0.0\%$, $p = 0.877$) | 1.54 [0.96, 2.48]   | 100.00     |

Heterogeneity between groups: $p = 0.512$

NOTE: Weights and between-subgroup heterogeneity test are from random-effects model; continuity correction applied to studies with zero cells

(b) Figure 4: Continued.
both candidate gene and GWAS on PTDM, whereas our study only incorporated studies based on the candidate gene method.

GWAS have identified more than 120 genetic loci associated with T2DM susceptibility [60]. In addition, many SNPs have been reported in candidate gene studies with T1DM and T2DM. Vhe genetic variants predisposing to DM were commonly evaluated in PTDM development. Transcription factor encoding gene HNF4A [12], genes encoding renin-angiotensin system (RAS) including ACE and AGT [35, 44]; insulin-resistance genes of VDR (Fox1) [33], adiponectin [34, 40], and PAI-1 [46]; insulin-sensitive gene IRS [12, 31]; glucose homeostasis genes CAPN10 [47], PPARα, and POR [32, 36]; and inflammatory factor genes such as CCL5 [34, 48], IL-6 [37], IL-1B, IL-2, IL-4, IL-17, IL-7R, and IL-17R [18, 29, 39] have been shown to contribute to the pathogenesis of PTDM. Lower GPX1 enzyme activity, caused by GPX1 599C to T mutation, increases the exposure
| Allele model                  | Odds Ratio (95% CI) | Weight (%) |
|------------------------------|---------------------|------------|
| Yokoyama (2018)              | 1.82 [0.60, 5.56]   | 3.66       |
| Kurzawski (2012)             | 1.20 [0.79, 1.83]   | 21.88      |
| Kang (2009)                  | 0.80 [0.60, 1.08]   | 36.57      |
| Ghisdal (2009)               | 0.98 [0.73, 1.31]   | 37.88      |
| Subgroup, DL (I² = 20.0%, p = 0.290) | 0.97 [0.78, 1.21] | 100.00     |

| Dominant model               |                      |            |
|------------------------------|----------------------|------------|
| Yokoyama (2018)              | 1.75 [0.42, 7.17]    | 6.27       |
| Kurzawski (2012)             | 1.40 [0.79, 2.49]    | 23.87      |
| Kang (2009)                  | 0.65 [0.44, 0.94]    | 35.11      |
| Ghisdal (2009)               | 0.88 [0.60, 1.30]    | 34.75      |
| Subgroup, DL (I² = 0.0%, p = 0.692) | 0.92 [0.63, 1.34] | 100.00     |

| Recessive model              |                      |            |
|------------------------------|----------------------|------------|
| Yokoyama (2018)              | 7.86 [0.30, 208.52]  | 1.42       |
| Kurzawski (2012)             | 1.00 [0.42, 2.40]    | 19.99      |
| Kang (2009)                  | 1.29 [0.67, 2.48]    | 35.81      |
| Ghisdal (2009)               | 1.23 [0.68, 2.24]    | 42.79      |
| Subgroup, DL (I² = 0.0%, p = 0.692) | 1.23 [0.83, 1.82] | 100.00     |

| Homozygote model             |                      |            |
|------------------------------|----------------------|------------|
| Yokoyama (2018)              | 9.00 [0.32, 254.72]  | 1.49       |
| Kurzawski (2012)             | 1.22 [0.48, 3.09]    | 19.15      |
| Kang (2009)                  | 1.02 [0.52, 2.01]    | 36.84      |
| Ghisdal (2009)               | 1.13 [0.60, 2.11]    | 42.53      |
| Subgroup, DL (I² = 0.0%, p = 0.663) | 1.14 [0.76, 1.71] | 100.00     |

| Heterozygote model           |                      |            |
|------------------------------|----------------------|------------|
| Yokoyama (2018)              | 1.45 [0.34, 6.25]    | 7.37       |
| Kurzawski (2012)             | 1.45 [0.79, 2.67]    | 24.75      |
| Kang (2009)                  | 0.58 [0.39, 0.87]    | 34.06      |
| Ghisdal (2009)               | 0.83 [0.55, 1.25]    | 33.82      |
| Subgroup, DL (I² = 55.5%, p = 0.081) | 0.88 [0.57, 1.35] | 100.00     |

Heterogeneity between groups: p = 0.721

NOTE: Weights and between-subgroup heterogeneity test are from random-effects model; continuity correction applied to studies with zero cells.
of pancreatic β cells to oxidative stress and development of PTDM [24, 49]. Additionally, ATF6, GST (SOD and CAT), INFγ and (TGFβ1, TNFα, and STAT4) polymorphisms, which play important roles in endoplasmic reticulum stress, oxidative stress, and inflammation respectively, were not found to be associated with PTDM [16, 28, 41, 42, 45, 49]. In recent studies, new evidence have suggested that genetic variants of TAC metabolizing enzymes including CYP3A4 and CYP24A1 were associated with increased risk of PTDM [21, 23]. GCK, LEP, LEPR, and PCK2 SNPs may contribute to PTDM by influencing glucose and lipid homeostasis [19, 22, 23, 30]. Another ATP-sensitive potassium channel gene ABCC8 encoding SUR1 was implicated to be associated with a high prevalence of PTDM. Moreover, other inflammation genes including TLR4, TLR6 [27], MBL2 [18], transcription factor HNF1β [17], and matrix metalloproteinase gene MMP-2 SNPs may also predispose transplant recipients to the development of PTDM. The effect size of several genetic variants, such as GPX1 599TT, CYP24A1 rs2296241 AA, IL-17F rs763780TC, LEP rs2167270 AA, PCK2 rs4982856TT, TLR6 rs1039559 CC, and MMP-2 rs1132896 CC are relatively large (ORs between 3.5 and 10) [21, 22, 26, 27, 29, 30, 49]. Furthermore, IL-1β rs3136558, IL-2 rs2069762, IL-7R rs1494558, IL-7R rs2172749, IL-17R rs2229151, IL-17F rs4819554 [39], MMP-2 rs243849 [26], IL-6 174 [37], TLR4 rs1927914 [27], PAI-1 −675 5G5G [46], and CAPN10 SNP-63 rs5030952 [47] were reported to confer protective effects for the development of
PTDM. However, the number of studies for these reported gene polymorphisms was limited. There were only one or two relevant articles available, which could not provide enough statistical power to detect differences in the incidence of PTDM between different genotype groups. The association between these gene SNPs and PTDM susceptibility was still inconclusive and further exploration was needed.

This study had several limitations. First, the etiopathogenesis of PTDM was multifactorial. Immunosuppressive regimen, ethnicity, older age, sex, BMI, and other related clinical characteristics contributed significantly to the risk of PTDM. However, crude estimates of effect were often used to evaluate the association between genes polymorphisms and PTDM without adjustments for other confounding variables. Second, PTDM in kidney recipients occurred mainly during the first months. Additionally, there could be a reversible phenotype change from PTDM to non-PTDM. In this study, there was high heterogeneity regarding the observational follow-up time after renal transplantation, which varied from 3 to 12 months among the studies. Third, treatment modality varied greatly for different studies, which may substantially influence the overall incidence of PTDM. Fourth, certain minor allele frequencies (MAF) differed greatly in different races. The sample size in some studies might be too small to detect minor effects, and some study populations presented with various genetic backgrounds. Furthermore, for most studies, it is unclear whether there was preexisting impaired glucose tolerance, which may affect the estimated incidence of PTDM.

Our meta-analysis revealed a significant association between PTDM and gene polymorphisms of TCFL7L2 rs7903146, KCNQ1 rs2237892, and KCNJ11 rs5219. Furthermore, we reviewed the literature on available gene SNPs that were susceptible to PTDM. The regulatory mechanism of relevant genes SNPs in the occurrence and development of PTDM was worthy of further exploration. SNPs showing association may serve as genetic markers for the prediction of the development of PTDM, combined with other risk factors of PTDM. Alternate medication of diabetogenic drugs may be considered for early prevention of PTDM based on risk assessment. Further large sample studies with diverse race populations are necessary to confirm our findings.

Data Availability

Since it is a meta-analysis, all data were extracted from public databases, and all data were available in Supplementary Materials.

Disclosure

All authors have completed the ICMJE uniform disclosure form.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors’ Contributions

Shan Xu conceptualized and designed the study. Zhenwei Jiang and Nan Hu contributed to the collection and assembly of data. Shan Xu and Nan Hu had done the data analysis and interpretation. Shan Xu and Nan Hu wrote the manuscript. All authors approved the final version of the manuscript.

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Supplementary Materials

The supplementary materials contain supplementary figures and tables and PRISMA checklist. (Supplementary Materials)

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