J Human Gen Genom. 2025 May;9(1): A-10-389-4 doi: 10.6118/jhgg.9.1.122
Published online 2026 Jan 11 **Review Article**

Bridging Genetics and Diagnosis in Type 1 and Type 2 Diabetes: The Role of Polymorphisms

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Received: 2026/01/10 **Accepted:** 2026/04/07

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Diabetes mellitus, encompassing type 1 (T1D) and type 2 diabetes (T2D), is a major global health burden with rapidly increasing prevalence. T1D is characterized by autoimmune destruction of pancreatic β-cells, whereas T2D primarily involves insulin resistance and β-cell dysfunction. Despite advances in clinical and molecular research, gaps remain in understanding the genetic architecture and gene–environment interactions driving disease onset and progression. This review summarizes current evidence on genetic polymorphisms associated with T1D and T2D, with a focus on their roles in disease susceptibility, complications, and potential therapeutic implications. In T1D, variants in the HLA region, INS, and PTPN22 have been strongly linked to autoimmunity and β-cell vulnerability. In T2D, genes such as TCF7L2, KCNJ11, SLC30A8, and EPO influence insulin secretion, glucose homeostasis, and risk modulation, with loss-of-function mutations in SLC30A8 showing protective effects. Emerging data highlight how genetic variants interact with zinc metabolism, inflammatory pathways, and environmental factors to shape disease heterogeneity. Additionally, polymorphisms in both T1D- and T2D-associated genes contribute to the risk of long-term complications, including nephropathy, retinopathy, and cardiovascular disease. By integrating evidence from genome-wide association studies, next-generation sequencing, and functional analyses, this review emphasizes the diagnostic and prognostic value of genetic markers. Understanding these genetic insights not only enhances risk prediction and early diagnosis but also supports the development of precision medicine approaches tailored to individual genetic backgrounds.

Keywords: Polymorphism, Genetic, Diabetes Mellitus, Type 1, Diabetes Mellitus, Type 2, Insulin-Secreting Cells, Precision Medicine.

1. Introduction

Diabetes mellitus, encompassing both Type 1 diabetes (T1D) and Type 2 diabetes (T2D), affected approximately 537 million people globally in 2021, with the projection of a surge in diabetes cases to 783 million by 2045 (1). It also significantly increases the risk of cardiovascular diseases, hypertension, and other complications, contributing substantially to global morbidity and mortality (2, 3). T1D is an autoimmune disorder where the body's immune system targets and destroys the insulin-producing β-cells in the pancreas, while T2D is primarily characterized by insulin resistance and β-cell dysfunction (4, 5). Despite significant advances in understanding the pathophysiology of both conditions, there remain substantial gaps in our understanding of the genetic factors that contribute to their development and progression (6). While various genetic loci have been identified, the complex interactions between genetic variations and

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environmental factors are still not fully elucidated. These gaps limit our ability to predict risk, diagnose early, and tailor individualized treatments for affected individuals.

Recent advancements in genomics, including genome-wide association studies (GWAS) and next-generation sequencing (NGS), have provided substantial insights into the genetic factors associated with both T1D and T2D (7). For T1D, the human leukocyte antigen (HLA) region has been well-established as a major genetic determinant, while T2D research has focused on genes involved in insulin secretion, β-cell function, and glucose homeostasis (8-10). Despite these findings, many identified genetic variants show modest effects on disease risk, and the full spectrum of relevant genetic variations, particularly in diverse populations, remains incompletely characterized (11).

In this study, we aim to review the current literature on genetic polymorphisms in T1D and T2D, with a focus on their role in disease susceptibility, progression, and diagnosis. By the findings of latest studies, we aim to provide a comprehensive understanding of how specific genetic variants contribute to the pathogenesis of T1D and T2D. Moreover, we will explore the implications of these findings for improving genetic screening, risk prediction, and the development of personalized treatment strategies.

2. HLA Gene Polymorphisms in Type 1 Diabetes

HLA region has been reported the most important genetic risk factor to T1D susceptibility (8). Several studies found specific alleles such as HLA-DR3 and HLA-DR4 to significantly increase the risk of developing T1D (12, 13). Approximately 90% of patients with T1D carry either DR4-DQ8 or DR3-DQ2, compared to 40% of the general population that do not have either of the haplotypes (14). Similarly, Ludvigsson et al. found HLA-DR 3 and/or DR 4 in 91% of 745 young T1D patients, while DR 2 without DR 3/4 was rare. DR 3-only cases had milder disease, more partial remissions, and no seasonal incidence peaks, unlike DR 3/4 cases (15). In another study on Korean children with T1D, Jung et al. found that HLA-DRB104, DRB109, and DQB104 were significantly increased, while HLA-DRB114, DRB115, DQB105, and DQB1*06 were decreased, indicating susceptibility and protective roles respectively (16). In a similar study, Soetjipto et al. reported that Indonesian children with T1DM most frequently carried HLA-DQA1 0101/0102 and HLA-DQB1 0301, with 01/03 and 02/03 detected only in T1DM cases (17). Additionally, HLA-G 14-bp deletion polymorphism was found to be strongly associated with T1DM age of onset in Cypriot patients (18).

3. PTPN22 Gene and Its Role in Type 1 Diabetes

The PTPN22 gene encodes lymphoid tyrosine phosphatase, a protein involved in T cell receptor (TCR) signaling (19). In a study by Sarmiento et al., the R620W variant of PTPN22 was associated with multiple autoimmune diseases, including T1D (20). This variant was shown to alter TCR regulation T cell activation, potentially leading to defective immune regulation and increased autoimmunity (21). In another study, Zaid et al. reported that carrying the R620W polymorphism may lower the threshold for T-cell activation, and potentially increase the risk of autoimmune and infectious diseases (22). The PTPN22 C1858T polymorphism has been reported in numerous studies in the context of T1D. For instance, Giza et al. found that the PTPN22 C1858T polymorphism occurred more frequently in Greek T1D patients than controls, but the difference was not statistically significant, likely due to the low minor allele frequency in this population (23). In a similar study on Iranian patients with T1D, Almasi et al. found no significant difference in genotype or allele frequencies of the PTPN22 C1858T polymorphism between 144 Azeri T1D patients and 197 controls (24).

4. TCF7L2 Gene and Its Link to Type 2 Diabetes

The Transcription Factor 7-like 2 (TCF7L2) gene is involved in regulating the production of proglucagon, which serves as the precursor of the glucagon-like peptide-1 (GLP-1) hormone (25). The TCF7L2 gene has been identified as a major genetic determinant of T2D (26). Several studies have investigated the functional impact of TCF7L2 variants on insulin secretion and glucose metabolism. For example, Jainandunsing et al. demonstrated that the rs7903146 variant of TCF7L2 exhibits a gene-dose effect on insulin synthesis and glucose tolerance status (27). Similarly, Cropano et al. reported that carriers of the rs7903146 variant had impaired β-cell function and altered insulin secretion (28). These findings suggest that TCF7L2 variants can directly modulate pancreatic function and contribute to T2D pathophysiology. Huang et al. further observed that TCF7L2 polymorphisms regulate the transcription of the proglucagon gene, affecting GLP-1 production and, consequently, glucose homeostasis (29).

Studies have also evaluated the association of TCF7L2 polymorphisms with T2D and its complications. In a case-control study, Aboelkhair et al. investigated 180 subjects to assess the relationship between the rs7903146 variant and T2D, as well as microvascular complications. They found that the TT and CT genotypes, as well as the T allele, were significantly more frequent in diabetic patients compared to controls, indicating increased susceptibility to T2D. However, no significant association was observed between this variant and microvascular complications, suggesting that the T allele specifically influences disease onset rather than its sequelae (30). Complementing this, Ferreira et al. explored the functional effects of the rs7903146 variant on postprandial hormone responses in T2D patients treated with the GLP-1 agonist exenatide. They observed that CT/TT had higher insulin levels during a mixed-meal test and demonstrated a significant reduction in postprandial insulin after exenatide treatment, whereas noncarriers (CC) showed no change. Glucagon responses were similarly reduced in both groups, highlighting the specific effect of the T allele on insulin regulation (31).

Haplotype analysis has provided further insights into the genetic influence of TCF7L2. Verma et al. evaluated multiple variants and found that the haplotype GC was associated with increased risk of T2D, while the GCG and GTA haplotypes were protective. Although individual SNPs alone were not strongly informative, haplotype-based analysis revealed clear associations with T2D susceptibility, emphasizing the importance of considering variant combinations rather than single loci (32).

Meta-analyses have confirmed these associations across diverse populations. Stephen et al. performed a meta-analysis of 15 case-control studies to evaluate rs12255372 and rs7903146 in Asian and Caucasian populations. They reported that rs12255372 was consistently associated with T2D across allelic, recessive, dominant, and over-dominant models, while rs7903146 did not show significant associations under these models, highlighting potential population-specific effects (33).

Similarly, Dou et al. conducted a meta-analysis of 20 case-control studies in the Chinese Han population. Their analysis confirmed that the rs7903146 C/T variant was significantly associated with increased T2D risk in both northern and southern regions of China, whereas rs12255372 G/T and rs290487 T/C variants showed no significant associations. The effect of rs290487 was influenced by body mass index, while associations for rs7903146 were independent of age and sex (34). Muruganantham et al. also performed a meta-analysis on SLC30A8 and TCF7L2 variants, confirming that TCF7L2 variants (rs7903146, rs12255372) were significantly associated with T2D across all genetic models, whereas SLC30A8 rs13266634 showed significance only in the recessive model (35). Together, these studies underscore the robust association of TCF7L2 polymorphisms, particularly rs7903146 and rs12255372, with T2D susceptibility in multiple populations.

5. EPO Gene Polymorphisms: Associations with Diabetic Retinopathy

Several studies have investigated the association between erythropoietin (EPO) gene polymorphisms and diabetic retinopathy (DR) in patients with T2D. These studies highlight both population-specific effects and variability across different EPO variants.

Kaur et al. examined a cohort of 302 T2D patients with retinopathy and 312 diabetic controls from northern India. They found that two variants, rs507392 and rs1617640, were significantly associated with increased DR risk, while rs551238 showed no clear link (36). Similarly, Li et al. performed a meta-analysis of eight studies including 2,861 cases and 2,136 controls to assess the association between EPO polymorphisms and diabetic microvascular complications. They reported that rs1617640 was linked to increased susceptibility overall, although no significant association was observed with diabetic retinopathy specifically. In contrast, rs551238 showed a significant association with higher DR risk across multiple genetic models, suggesting that EPO variants may influence vulnerability to microvascular complications in diabetes (37).

In a Northern Chinese cohort, Liu et al. found that the EPO rs551238 A allele and AA genotype were associated with increased DR risk, whereas the C allele and CC genotype were protective. For rs1617640, the T allele and TT genotype conferred higher risk, while the G allele and GT genotype were protective. These findings reinforce that EPO variants, particularly rs551238 and rs1617640, contribute to DR susceptibility, although their effects may vary across populations (38). In addition, Sesti et al. examined EPO polymorphisms in 1,042 Southern Brazilians with T2D through a case–control study and meta-analysis. In the case–control analysis, no significant association was observed between rs1617640, rs507392, or rs551238 and DR. However, the meta-analysis (14 datasets, 9,117 subjects for rs1617640) suggested that the G allele of rs1617640 conferred a protective effect under dominant, heterozygous additive, and overdominant models. Subgroup analyses indicated that this protective effect was particularly evident in T1D patients and non-Asian populations, and remained significant for NPDR and overall DR after correction for multiple testing. No associations were detected for rs507392 or rs551238 (39).

In another study, rs1617640 polymorphism in the EPO gene was compared between 150 T2D patients and150 healthy controls. Genotype analysis using ARMS-PCR showed that the GG genotype occurred in 8% of patients versus 1.3% of controls, GT in 51.3% versus 86.7%, and TT in 40.7% versus 12%. Among diabetic patients, the TT genotype was observed in 37.6% of those with retinopathy and 42.6% of those without retinopathy. These results suggest that although rs1617640 distribution differs significantly between diabetic patients and healthy individuals, there is no significant association between this polymorphism and diabetic complications in this cohort (40).

Beyond diabetic complications, Montesanto et al. investigated the impact of EPO variants on mortality. In 542 elderly Italian T2D patients followed for 12 years, three EPO variants (rs1617640-T/G, rs507392-T/C, rs551238-A/C) were significantly associated with all-cause mortality. Haplotype analysis showed that carriers of the G-C-C haplotype had increased survival, whereas carriers of the T-T-A haplotype had reduced survival. This study highlights the potential role of EPO genetic variability not only in diabetic complications but also in long-term outcomes such as mortality (41).

6. KCNJ11 and ABCC8: Genes Involved in β-Cell Function

The primary genetic contributors to diabetes and hyperinsulinism are variants in the ABCC8 and KCNJ11 genes. These genes encode the subunits of the β-cell ATP-sensitive potassium channel, a critical regulator of insulin secretion in response to glucose. Mutations in these genes disrupt normal insulin regulation: inactivating mutations lead to excessive insulin release, resulting in congenital hyperinsulinism, while activating mutations produce the opposite effect, causing diabetes (42).

Several studies have investigated the role of ABCC8 and KCNJ11 variants in T1D. Reddy et al. conducted a case-control study with 60 T1D patients and 60 healthy controls and found that the ABCC8 rs1799854 (3C>T) variant was significantly associated with T1D, with the CT genotype conferring a threefold increased risk. The ABCC8 rs1801261 (C>T) variant showed no significant association. For KCNJ11, the rs5219 (C>T) variant was significantly associated with T1D, with the TT genotype more frequent in patients, while rs5215 (G>A) was not linked to the disease (43).

In T2D, Chistiakov et al. studied 127 Russian T2D patients and 117 controls to assess the KCNJ11 E23K and ABCC8 exon 31 variants. The KCNJ11 E23 allele and ABCC8 exon 31 A allele were linked to increased T2D risk. Carriers of the KCNJ11 EE genotype exhibited higher 2-hour serum insulin, while ABCC8 G/G homozygotes had lower 2-hour glucose and elevated fasting and postprandial insulin. In non-diabetic subjects, G/G carriers showed higher β-cell function (HOMA-β), indicating that these variants influence both susceptibility to T2D and β-cell insulin secretionn (44). Additionally, Hashemian et al. investigated the genetic basis of congenital hyperinsulinism (CHI) in the Iranian population, focusing on the ABCC8, KCNJ11, and HADH genes. Over an 11-year period, 20 pediatric patients with confirmed CHI were enrolled, and gene variants were analyzed using PCR and sequencing. Among these patients, 16 carried variants in the studied genes. Notable findings included a homozygous missense mutation in ABCC8 observed in three infants, frameshift variants in ABCC8, and a missense variant in KCNJ11. Most variants were classified as of unknown significance, with only seven identified as pathogenic. The majority of detected variants were in ABCC8, highlighting the need for functional studies to clarify their roles in CHI within this population (45).

Functional studies using animal models further elucidate the role of KCNJ11 in T2D. Sachse et al.

demonstrated that the KCNJ11 E23K (K23) variant impairs glucose-stimulated insulin secretion by reducing ATP sensitivity of the KATP channel. Mice with two K23 alleles (KK) showed elevated glucose thresholds for insulin release, impaired glycemic control, and accelerated β-cell failure, particularly under a high-fat diet. This study indicates that the K23 variant increases diabetes risk by diminishing insulin secretion at threshold glucose levels (46).

Pharmacogenetic studies have linked KCNJ11 and ABCC8 variants to therapeutic response in T2D. He et al. evaluated the effects of KCNJ11 E23K and ABCC8 exon16–3T/C variants on repaglinide treatment in 100 Chinese patients. Carriers of the KCNJ11 E/K and K/K genotypes exhibited greater reductions in HbA1c and 2-hour postprandial glucose, and a higher treatment response rate compared with E/E homozygotes. Similarly, ABCC8 exon16–3 C/C homozygotes showed greater improvements in fasting insulin and insulin resistance than T/C or T/T carriers (47). Song et al. extended this pharmacogenetic insight through a review, identifying KCNJ11 rs5219, ABCC8 rs757110, rs1799854, and other variants as influencing sulfonylurea response, supporting a personalized medicine approach based on patient genotypes (48).

Large population-based studies have further clarified the association of these variants with T2D. Gloyn et al. studied 2,486 UK subjects and found that the KCNJ11 E23K allele was associated with T2D in case-control analysis and confirmed by meta-analysis, whereas ABCC8 exon16–3T/C and exon18 T/C variants showed no association (49). Laukkanen et al. also reported that the ABCC8 1273AGA allele and a high-risk promoter haplotype increased T2D risk twofold, and the combination with KCNJ11 E23K raised the risk sixfold, highlighting additive effects of these genes on disease susceptibility (50).

Population-specific studies have provided further insights. Moazzam-Jazi et al. found no significant association of common KCNJ11 variants with T2D among Iranian adults. However, a meta-analysis of 72 studies confirmed that rs5219 and rs5215 increase T2D risk across multiple populations, with ethnicity-specific effects and sample size influencing effect estimates (51). In addition, Viji et al. investigated ABCC8 rs757110 in South Indian subjects, showing significant associations with T2D for both heterozygous and homozygous recessive genotypes (52). Meta-analysis across Asian and Caucasian populations confirmed the association under multiple genetic models (51).

7. Insulin Gene Variants and Type 1 Diabetes Susceptibility

Variation in the Insulin gene (INS) is strongly associated with T1D susceptibility and beta-cell dysfunction (53). DNA methylation at the INS locus may influence disease risk by modulating gene expression. Carry et al. identified three methylation probes upstream of the INS transcription start site (cg03366382, cg21574853, and cg25336198) that were significantly associated with T1D, highlighting a potential role of INS-related DNA methylation in disease development (54).

In addition to epigenetic effects, specific INS variants can impact long-term complications in T1D. Tienhoven et al. reported that patients carrying a protective INS variant had markedly lower risk of developing proliferative diabetic retinopathy (PDR) and diabetic kidney disease (DKD) under intensive insulin therapy. In long-term follow-up (~20 years), PDR and DKD were absent in carriers within 1–5 years post-diagnosis, while 4.3% of non-carriers developed complications. In the secondary intervention group (1–15 years), PDR was significantly less frequent in carriers versus non-carriers, whereas DKD rates were similar (55). These findings suggest that INS variants can define disease endotypes with preserved beta-cell function and superior glycemic control.

Mutations in the INS coding region can also cause early-onset diabetes. Fu et al. identified one novel mutation (p.I99_C100insSI) and three previously reported variants (p.G32S, p.R89C, and p.C96R) in four Chinese infants with permanent neonatal diabetes. All mutations were de novo. The R89C mutation disrupts the cleavage site between the A chain and C-peptide, while the other three interfere with disulfide bond formation, emphasizing the critical role of INS structure in beta-cell function (56).

Common INS polymorphisms also contribute to T1D susceptibility in diverse populations. Saatov et al. studied the rs689 polymorphism in 94 Uzbek patients with a familial history of T1D and 66 controls. The T risk allele and the AT heterozygous genotype were significantly more frequent in patients, while the A allele conferred protection. These results highlight that both allelic variation and heterozygosity at INS influence disease risk (57).

Regulatory variants such as the variable number of tandem repeats (INS-VNTR) further modulate diabetes susceptibility and gene expression. Pela et al. investigated INS-VNTR in 348 Brazilian diabetic patients and 339 controls. They found that the I:I genotype increased T1D risk, the III:III genotype was protective, and the I:III genotype associated with T2D. Gene and miRNA expression profiles differed according to genotype, demonstrating that INS-VNTR variants influence both disease susceptibility and gene regulation across diabetes types (58). Together, these studies illustrate that INS variation, ranging from structural mutations to regulatory polymorphisms and epigenetic modifications, critically affects T1D onset, progression, and complications.

8. Role of SLC30A8 Gene in Glucose Regulation

The SLC30A8 gene encodes the zinc efflux transporter SLC30A8 (ZNT8), which supplies zinc necessary for the formation of insulin hexamers. Variations at amino acid position 325 in human ZnT8 are linked to differences in T2D risk and can alter the specificity of ZnT8 autoantibody epitopes in T1D (59).

Several studies have examined the interaction between SLC30A8 polymorphisms and zinc in modulating T2D risk. Shan et al. assessed the combined effects of plasma zinc levels and the rs13266634 polymorphism on impaired glucose regulation (IGR) and T2D in 1,796 participants. They found that the CC genotype was associated with higher T2D risk compared with TT, while higher plasma zinc levels were inversely associated with disease risk. Notably, the protective effect of zinc varied by genotype: each 10 μg/dL increase in zinc corresponded to a 22% lower T2D risk in TT carriers, 17% in CT carriers, and only 7% in CC carriers, indicating a significant gene–zinc interaction (60). Similarly, Sirivarasay et al. found that individuals carrying the CC genotype with low serum zinc had increased susceptibility to T2D, and proteomic profiling revealed differentially expressed proteins linked to zinc transport, ZnT8, and insulin processing pathways in prediabetic/diabetic subjects (61). Collectively, these studies suggest that both genetic variation and zinc status influence T2D susceptibility through effects on insulin metabolism.

experimental models. Mitchell et al. used mouse models to show that β-cell–specific ZnT8 deletion (Ins1CreZnT8KO) impaired glucose tolerance and inhibited glucose-induced insulin secretion in vivo, while Zn^{2+} release from islets was severely reduced. Conversely, transgenic overexpression of ZnT8 in adult β-cells (ZnT8Tg) enhanced glucose tolerance and Zn^{2+} secretion, despite impaired insulin release in vitro, demonstrating that ZnT8 activity directly regulates glucose homeostasis (62).

Human genetic studies of SLC30A8 loss-of-function (LoF) variants provide further evidence for its role in T2D. Lamarche et al. analyzed 100,814 South Asian participants and identified 15 homozygous and 615 heterozygous LoF carriers, including a Gln174Ter variant enriched in this population. T2D risk was reduced in a gene dose-dependent manner, and oral glucose tolerance tests showed lower glucose levels and higher glucose-stimulated insulin secretion with preserved β-cell function in LoF carriers (63). Flannick et al. examined ~150,000 individuals across five ancestries, identifying 12 rare protein-truncating variants of SLC30A8. Carriers had a 65% reduced T2D risk, and Icelandic carriers of a frameshift variant also demonstrated lower glucose levels, confirming the protective effect of reduced ZnT8 activity (64).

The association of the SLC30A8 rs13266634 polymorphism with T2D has been widely replicated. Dong et al. conducted a meta-analysis of 28 case-control studies in the Chinese population (25,912 T2D cases, 26,975 controls), finding that the C risk allele was more frequent in T2D patients, with CC and CT genotypes conferring 1.51- and 1.23-fold higher T2D risk than TT carriers, while no association was observed for IGR (65). Mitu et al. examined 163 T2D patients and 75 controls in Bangladesh, confirming a significant association of rs13266634 with T2D but not with cardiovascular disease, hypertension, or early-onset T2D (66). Jin et al. performed a meta-analysis of 27 studies (42,609 cases, 69,564 controls), demonstrating that the C allele significantly increased T2D risk in both European and Asian populations, without differences between hospital-based and population-based studies (67).

SLC30A8 polymorphisms also influence gestational diabetes mellitus (GDM). Zeng et al. studied 500 GDM patients and 502 controls, finding that rs2466293 increased GDM risk, whereas rs13266634 was associated with decreased risk in individuals aged ≥30 years. However, CC and CT carriers of rs13266634 had higher mean blood glucose levels than TT carriers, and haplotype CG increased GDM risk, suggesting age- and genotype-dependent effects on glucose regulation (68). A comprehensive overview of the associated genetic polymorphisms is presented in Table 1.

Table 1. Comprehensive Summary of Genetic Polymorphisms Associated with Type 1 and Type 2 Diabetes.

Gene	Variant	Population	Diabetes Type	Functional / Clinical Effect	Ref.
HLA-DRB1 / DQA1 / DQB1	*HLA-DRB1*03*, **04*, **15*, *DQA1*0101/0102*, *DQB1*0301/0602*	European, Asian	T1D	Modulates antigen presentation; DR3/DR4 increased risk; DR2 and DQB1*0602 protective	(12–17)
CTLA4	+49A/G (rs231775)	Korean children	T1D	Affects T-cell costimulatory signaling; G allele linked to increased susceptibility	(16)
PTPN22	C1858T (rs2476601)	European, Iranian, Greek	T1D	Alters TCR regulation and autoimmunity threshold; T allele increases risk	(19–24)
TCF7L2	rs7903146 (C>T), rs12255372 (G>T)	Multiethnic	T2D	Impairs GLP-1 signaling and insulin synthesis; strong predictor of T2D	(25–35)
EPO	rs1617640 (T/G), rs551238 (A/C), rs507392	Indian, Chinese, Brazilian	T2D (Retinopathy)	Regulates hypoxia-induced angiogenesis via HIF-1α and VEGF signaling; risk alleles increase retinopathy	(36–41)
KCNJ11	E23K (rs5219), rs5215	Multiethnic	T2D, T1D	Reduces KATP sensitivity, impairs insulin secretion; affects sulfonylurea response	(43–46, 49, 51)
ABCC8 (SUR1)	rs757110, exon16–3T/C	Indian, European	T2D	Modulates insulin secretion; certain alleles linked to enhanced response to repaglinide	(47, 48, 52)
INS	VNTR, rs689	Multiethnic	T1D	Influences insulin gene expression and β-cell antigenicity; VNTR III/III protective	(53–58)
SLC30A8 (ZnT8)	rs13266634 (C/T), LoF mutations	European, Asian	T2D	Regulates zinc transport in β-cells; LoF mutations protective	(59–67)

T1D, Type 1 diabetes; T2D, Type 2 diabetes, TCR, T cell receptor; GLP-1, Glucagon-like peptide-1; LoF, Loss of function; VEGF, Vascular endothelial growth factor

9. Implications for Diagnostic and Therapeutic Strategies

The identification of genetic polymorphisms has profound implications for both the diagnosis and treatment of diabetes. In T1D, genetic testing, particularly HLA genotyping, can aid in early detection, especially in at-risk populations (69). In addition to genetic testing, biomarkers, such as islet autoantibodies, can enhance the precision of diagnostic tools (70). For T2D, genetic testing for polymorphisms in TCF7L2, KCNJ11, and SLC30A8 could help identify individuals at risk for β-cell dysfunction and insulin resistance, enabling early intervention to prevent disease onset. The use of polygenic risk scores (PRS), which aggregate multiple genetic variants, holds promise for improving risk prediction in both T1D and T2D (71, 72). For example, Dornbos et al. developed a rare variant polygenic score (PGS) including 21,293 mostly ultra-rare variants to improve T2D diagnosis. This PGS identified significantly more undiagnosed T2D cases and, combined with common variants, could detect 4.9 million misdiagnosed cases in the United States, 1.5 times more than common variants alone (73). However, the complexity of gene-environment interactions remains a challenge, as environmental factors such as diet, exercise, and infections can modify genetic risk.

10. Discussion

The genetic architecture of diabetes reflects a complex interplay between inherited susceptibility, environmental exposures, and molecular pathways regulating immune function, β-cell integrity, and metabolic homeostasis. Findings from this review reinforce that heterogeneity in genetic associations arises not only from population differences but also from context-dependent gene–environment interactions and functional diversity among polymorphisms. For example, discrepancies reported for PTPN22 C1858T across Greek and Iranian cohorts can be attributed to variation in minor allele frequencies, differing linkage disequilibrium structures, and environmental factors such as pathogen exposure or dietary patterns influencing immune regulation (23, 24). Meta-analytic evidence further supports that the penetrance of PTPN22 variants is modulated by environmental triggers, emphasizing that autoimmune risk in T1D cannot be understood solely through genetic determinants (19).

Beyond immune-related loci, polymorphisms regulating tissue-specific responses contribute to diabetes complications. EPO variants such as rs1617640 and rs551238 exemplify this complexity. These polymorphisms may alter transcription factor binding, particularly HIF-1α-mediated signaling, thereby influencing erythropoietin expression during hypoxic stress in retinal tissues (36). Dysregulated EPO activity may intensify VEGF-driven angiogenesis and oxidative damage, providing a mechanistic explanation for genotype-specific differences in microvascular outcomes (74). Although some studies demonstrate strong associations of these variants with diabetic retinopathy, others report no significant relationship, suggesting that specific genetic variations in the EPO locus may play a critical role in the susceptibility to diabetic retinopathy (75).

In T2D, pharmacogenomic insights into KCNJ11 and ABCC8 highlight how β-cell ion channel variants shape therapeutic response. Carriers of the KCNJ11 E23K and ABCC8 exon16–3C alleles exhibit enhanced glycemic improvement with sulfonylureas, likely due to altered KATP channel conformation that improves drug responsiveness and improved insulin secretion following therapy (47, 48).

Conversely, individuals harboring the TCF7L2 rs7903146 T allele often show reduced sulfonylurea effectiveness but demonstrate superior outcomes with incretin-based therapies (31). The contrast between these pharmacogenetic profiles underscores the molecular specificity of treatment response and supports the integration of genotyping into precise therapeutic decisions.

These findings demonstrate that genetic polymorphisms not only influence susceptibility to T1D and T2D but also modulate disease presentation and pharmacologic outcomes. However, variability across studies underscores the importance of considering ancestry, sample size, and methodological differences when interpreting genetic associations. Furthermore, the biological pathways implicated, from T-cell signaling and hypoxia-regulated angiogenesis to β-cell ion channel physiology, highlight that diabetes is not a uniform disease entity but a spectrum of endotypes driven by distinct molecular networks.

11. Future Research Directions

Despite the advances in genetic research, several questions remain unanswered. Future studies should focus on identifying rare variants and exploring the interactions between genetic and environmental factors in diabetes pathogenesis. Longitudinal studies are particularly important to understand how genetic risk factors, in combination with environmental exposures, influence the onset and progression of diabetes over time. Additionally, expanding research to include diverse populations will help identify genetic variants that may be specific to certain ethnic groups and improve the generalizability of genetic findings. Gene therapy and precision medicine approaches are rapidly advancing and may hold the key to future diabetes treatment. The identification of novel genetic targets for therapeutic intervention could provide new avenues for treating both T1D and T2D. Furthermore, the development of genetic-based prevention strategies, such as early genetic screening in high-risk individuals, could reduce the global burden of diabetes by enabling earlier interventions before the onset of clinical symptoms.

12. Conclusion

Genetic polymorphisms are important in influencing the susceptibility and progression of both T1D and T2D. While advances in genomic research have provided significant insights, particularly through studies identifying key loci such as HLA, PTPN22, INS in T1D, and TCF7L2, KCNJ11, SLC30A8 in T2D, challenges remain in understanding gene-environment interactions and extending findings to diverse populations. Future research must integrate genetic and environmental data and enhance representation across populations. These efforts will be essential for translating genetic discoveries into clinical applications, facilitating earlier diagnosis, improved risk prediction, and the development of personalized treatment strategies to optimize patient outcomes.

Declaration of Statements

Consent to Participate/Ethical Approval

Not required.

CRediT Author Contribution

Supervision, F.A.; Conceptualization and Study Design, F.A.; Methodology, D.T.R., A.M., M.M., N.R.; Search Strategy, D.T.R., A.M., and M.M.; Investigation, D.T.R., A.M., and M.M.; Literature Review, D.T.R., A.M., and M.M.; Data Acquisition, D.T.R., A.M., and M.M.; Academic, Scientific, and Grammatical Revision, F.A., and M.M.; Definition of Intellectual Content, F.A.; Investigation of the Clinical and Experimental Studies, F.A. and M.M.; Formal Analysis, F.A.; Preparation of the first draft of the manuscript, D.T.R., A.M., M.M., and F.A.; Preparation of the last draft of the manuscript, F.A. and M.M.

All authors named on the title page confirm that they have read and approved the final version of the manuscript and have received an electronic copy. The criteria for authorship have been satisfied, and each author asserts that the manuscript reflects genuine work. Additionally, they confirm the accuracy and legitimacy of the data and agree to submit the manuscript to this journal.

Conflicts of Interests

The authors declare that they have no conflicts of interest.

Funding

No grant is received from any financial organizations or funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgement

Not applicable.

Data Availability Statement

The authors confirm that the data supporting of this study are available within the article.

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