

Type 2 Diabetes-Associated Genetic Polymorphisms as Potential Disease Predictors

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Abstract: Diabetes is a major cause of mortality worldwide. There are several types of diabetes, with type 2 diabetes mellitus (T2DM) being the most common. Many factors, including environmental and genetic factors, are involved in the etiology of the disease. Numerous studies have reported the role of genetic polymorphisms in the initiation and development of T2DM. While genome-wide association studies have identified around more than 200 susceptibility loci, it remains unclear whether these loci are correlated with the pathophysiology of the disease. The present review aimed to elucidate the potential genetic mechanisms underlying T2DM. We found that some genetic polymorphisms were related to T2DM, either in the form of single-nucleotide polymorphisms or direct amino acid changes in proteins. These polymorphisms are potential predictors for the management of T2DM.

Keywords: type 2 diabetes, genetic polymorphisms, susceptibility prediction

Introduction

Diabetes is a chronic disease that can lead to serious complications. It is classified into two main types: type 1 diabetes mellitus and type 2 diabetes mellitus (T2DM). T2DM is a metabolic disorder that is characterized by peripheral insulin resistance and impaired insulin secretion.¹ During the period from 1980 to 2008, the number of people worldwide with T2DM has more than doubled.² Studies on the prevalence of diabetes in the adult population aged 20–79 years estimated that the worldwide prevalence of people with T2DM was 6.4% in 2010, where 285 million adults had T2DM. By 2030, 439 million adults are predicted to have T2DM, accounting for 7.7% of the adult population worldwide.³

Environmental and genetic factors are involved in the pathogenesis of T2DM.⁴ The majority of genes involved play a role in β -cell function. Genetic polymorphisms that have impacts on important proteins that participate in glucose metabolism and insulin secretion may also affect susceptibility to T2DM.⁵ Genome-wide association studies (GWASs), the candidate gene approach, and linkage analysis have identified various genes that contribute to T2DM susceptibility.^{6–8} The development of genetic risk scores using combined analysis of loci has significantly contributed to predicting the incidence of T2DM.^{9–11} Therefore, it is possible to facilitate early diagnosis and determine preventative strategies to reduce the incidence of the disease.^{12–15}

T2DM has a strong genetic basis, and individuals with a first-degree family history are at increased risk of developing the disease, and this risk is increased twofold if both parents have diabetes.¹⁶ Several risk factors for T2DM have been

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identified, including obesity and central obesity, ethnicity, family history of diabetes, elevated blood pressure, dyslipidemia, lifestyle factors and dietary intake.^{17–19} Some of these risk factors are associated with functional metabolism; therefore, genetic-based diagnoses may provide a more promising diagnostic tool. More than 200 genetic loci have been detected to be associated with T2DM risk,⁶ the genes elaborated in this review represent only a selected subset of T2DM-associated genes.

Methodology

The present review included studies published in the PubMed database obtained using the keywords “gene prediction”, “gene association”, and “type 2 diabetes”. Reviews, non-English studies, unrelated studies, such as non-human studies and reporting T2DM complications, were excluded. A flowchart of the literature search is shown in Figure 1.

Of the 6129 articles obtained in June 2019, we included 41 studies that focused specifically on the association between genetics and the prediction of T2DM (Table 1), where several genes have been associated with T2DM and can be used as predictors of the disease, including KLF14, KCNQ1, DUSP9, FTO, HNF4A, IGFBP2, CDKN2A/B, TCF7L2, KCNJ11, antioxidant genes, DNAJC3, PGC-1 α , ADIPOQ, CDKAL1, POMC, PPAR γ 2, and SLC30A8.^{20–61}

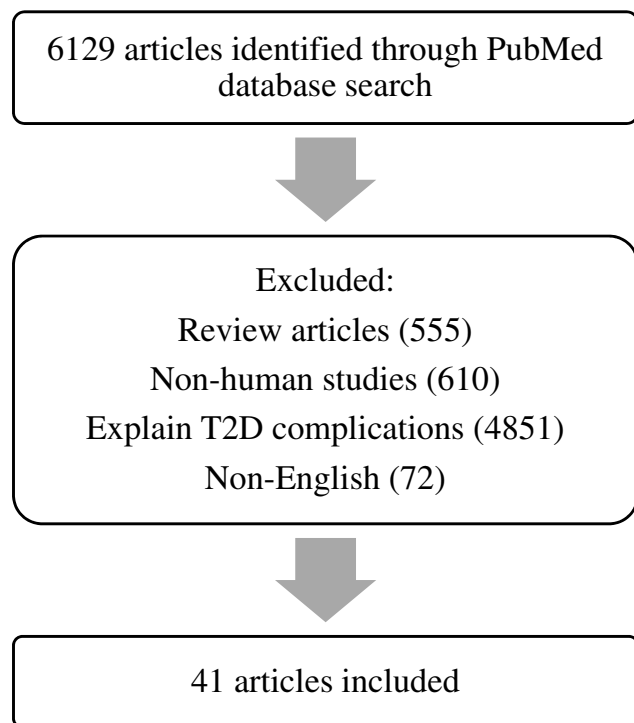


Figure 1 Flowchart outlining the literature search process.

KLF14

The transcription factor, KLF14, is located on chromosome 7q32.3. Variations in this gene are associated with high-density lipoprotein (HDL)-cholesterol and T2DM.^{62,63} A previous study showed that KLF14 is involved in metabolism as a transcriptional activator as it regulates the gene networks that participate in lipid metabolism.⁶⁴ KLF14 gene is assumed to be an ancient retrotransposed copy of KLF16 gene, presumably after the divergence between eutherians and marsupials^{65,66} due to its lack of introns and a high sequence homology with KLF16 gene. The maternal expression of KLF14 was associated with an increased risk of T2DM when carried on the maternal chromosome.⁶⁷

The expression of KLF14 in adipose tissue was shown to be associated with a combined insulin resistance phenotype. It is characterized by increased fasting insulin and triglyceride levels and decreased HDL-cholesterol levels.⁶⁸ Higher fasting insulin levels are manifested in the risk allele of rs4731702,⁶⁷ such that the risk allele of this non-coding genetic variant could play a role in insulin resistance. Furthermore, it may act to influence the expression of genes associated with the body mass index (BMI) and the homeostasis model assessment for insulin resistance (HOMA-IR) due to its primary effects on insulin sensitivity, fasting glucose, and adiponectin.⁶⁹ Moreover, rs4731702 was reported to be associated with gene expression in subcutaneous adipose tissue biopsies.⁶⁸ Hence, it was suggested that KLF14 is the master transregulator of adipose tissue gene expression.⁷⁰ One study also revealed that the G allele of KLF14 (rs972283) contributes to elevated blood pressure. Therefore, patients with metabolic syndrome have a greater risk of cardiovascular disease.²⁰

KCNQ1

The KCNQ1 gene, which encodes the alpha-subunit of voltage-gated potassium channel Kv7.1, is a member of the Kv channel superfamily, and is located on chromosome 11p15.5.^{71,72} The protein that KCNQ1 gene encodes is the pore-forming alpha subunit of KCNQ1/KCNE1, KCNQ1/KCNE2 and KCNQ1/KCNE3 potassium channels.⁷³ The expression of KvLQT1 repolarizes the action potential in cardiac muscles.²⁰ KCNQ1 is also expressed in other tissues such as adipose tissue, the pancreas, and the brain.⁷⁴

Mutations in KCN genes are associated with the development of diabetes. Variants in the KCNQ1 gene have been associated with reduced depolarization-evoked insulin exocytosis.²⁴ The variant allele (C allele) of the rs2283228 [an intron variant according to National Center for

Table I Association Between Genetic and Prediction of T2DM

| Probable Mechanism | Genes | Chromosome Position | SNPs | Population | Allele (Risk/Other) | Ref. No. | | | | |
|--------------------|----------|---------------------|-------------|---------------------------|---------------------|-----------|---------------------------|-----------------|------|------|
| Insulin action | KLF14 | 7q32.3 | rs972283 | Han Chinese | G/A | [11] | | | | |
| | | | | Northern Germany | G/A | [12] | | | | |
| | DUSP9 | Xq28 | rs5945326 | Northern Germany | A/G | [12] | | | | |
| | | | | Japanese | A/G | [16] | | | | |
| | | | | Pakistani | A/G | [17] | | | | |
| | | | Han Chinese | A/G | [18] | | | | | |
| β-cell function | KCNQ1 | 11p15.5 | rs2237895 | Han Chinese | C/A | [11] | | | | |
| | | | | Japanese, Asian, European | C | [13] | | | | |
| | | | | | | rs2237892 | Japanese, Asian, European | C | [13] | |
| | | | | | | rs2074196 | Japanese, Asian, European | G | [13] | |
| | | | | | | rs2283228 | Eastern Finland | A/C | [14] | |
| | | | | | | | Asian Indian | A/C | [15] | |
| | | | | rs231362 | Northern Germany | G/A | [12] | | | |
| | SLC30A8 | 8q24.11 | rs13266634 | Japanese | C/T | [23] | | | | |
| | | | | Lebanese | – | [24] | | | | |
| | | | | Tunisian Arabs | – | [24] | | | | |
| | HNF4A | 20q13.12 | rs2425637 | Finnish | G/T | [25] | | | | |
| | | | | | | | rs6130608 | French-Canadian | T/C | [26] |
| | | | | | | | rs736824 | French-Canadian | T/C | [26] |
| | | | | | | | rs745975 | French-Canadian | C/T | [26] |
| | | | | | | | rs3212183 | French-Canadian | C/T | [26] |
| | | | | | | | rs4812829 | South Asian | A/G | [27] |
| | IGFBP2 | 3q27 | rs4402960 | Northern Han Chinese | T/G | [28] | | | | |
| | | | | Tunisian | T/G | [29] | | | | |
| | | | rs1470579 | Tunisian Arabs | – | [24] | | | | |
| | | | | Lebanese | – | [24] | | | | |
| | CDKN2A/B | 9p21.3 | rs10811661 | Indian | T/C | [30] | | | | |
| | | | | Pakistani | T/C | [17] | | | | |
| | | | | Mexican | T/C | [31] | | | | |
| | | | | Chinese She | T/C | [32] | | | | |
| | | | | Chinese | T/C | [33] | | | | |
| | | | | Uyghur | T/C | [34] | | | | |
| | | | | Han Chinese | T/C | [35] | | | | |

(Continued)

Table 1 (Continued).

| Probable Mechanism | Genes | Chromosome Position | SNPs | Population | Allele (Risk/Other) | Ref. No. | |
|--|-----------------|---------------------|--------------------------|------------------|---------------------|----------|------|
| | TCF7L2 | 10q.25.2–25.3 | rs7903146 | Spaniards | T/C | [36] | |
| | | | | Austrians | T/C | [37] | |
| | | | | Lebanese | – | [24] | |
| | | | | Tunisian Arabs | – | [24] | |
| | | | rs7901695 | African-American | C/T | [38] | |
| | | | | Italian | C/T | [39] | |
| | | | rs7903146 | African-American | T/C | [38] | |
| | | | | rs12255372 | European Caucasians | T | [40] |
| | | | | | Cameroonian | T/G | [41] |
| | | | | French | T/G | [37] | |
| | KCNJ11 | 11p15.1 | rs2285676 | Han Chinese | – | [42] | |
| | | | | rs5215 | South Indian | C/T | [43] |
| | | | | rs5219 | Mauritanian | – | [44] |
| | | | | | Chinese She | – | [32] |
| | | | | | Chinese | T/C | [33] |
| | | | | | Lebanese | – | [24] |
| | | | | | Tunisian Arabs | – | [24] |
| | DNAJC3 | 13q32.1 | – | Turkish | – | [45] | |
| | CDKAL1 | 6p22.3 | rs10946398 | Han Chinese | C/A | [47] | |
| rs775480 | | | Alaska Native | C/A | [48] | | |
| SLC30A8 | 8q24.11 | rs13266634 | Chinese | C/T | [51] | | |
| | | | Asian, European, African | C/T | [52] | | |
| Obesity | FTO | 16q12.2 | rs1558902 | Japanese | A/T | [19] | |
| | | | rs9939609 | Scandinavian | A/T | [20] | |
| | | | | Spaniards | A/T | [21] | |
| | | | rs8050136 | Finnish | A/C | [22] | |
| Regulated insulin sensitivity in muscle and liver | ADIPOQ | 3q27 | rs1501299 | Chinese | – | [46] | |
| | | | rs7627128 | Chinese | – | [46] | |
| | | | rs182052 | Chinese | – | [46] | |
| Regulated insulin sensitivity in peripheral tissue | POMC | 2p23.3 | – | – | A/G | [49] | |
| Insulin sensitivity | PPAR γ 2 | 3p25.2 | rs1801282 | Caucasian | – | [50] | |

(Continued)

Table 1 (Continued).

| Probable Mechanism | Genes | Chromosome Position | SNPs | Population | Allele (Risk/Other) | Ref. No. |
|---|-------------------|---------------------|-------------------------|------------|---------------------|----------|
| Induced oxidative stress via ROS generation | Antioxidant genes | 1p13.3 | GSTM1 del | – | – | [138] |
| | | 22q11.23 | GSTT1 del | – | – | [138] |
| | | 11q13.2 | GSTP1 105I/V (+313A/G) | – | – | [138] |
| | | 11p13, 6q25.3 | CAT-21A/T, SOD2 + 47C/T | – | – | [138] |
| | | 3p21.31 | GPx1 + 599C/T | – | – | [138] |

Abbreviations: Ref, Reference; SNP, single-nucleotide polymorphism; T2DM, type 2 diabetes mellitus.

Biotechnology Information (NCBI) dbSNP database: <https://www.ncbi.nlm.nih.gov/snp/rs2283228>] was shown to be associated with increased fasting glucose levels and impaired β -cell function in Asians.⁷⁵ Moreover, previous studies showed that a vast majority of the genomic loci detected to date were associated with β -cell dysfunction in patients with T2DM.^{76–78} *KCNQ1* is expressed in pancreatic islets and plays an essential role in glucose homeostasis as it functions as a regulator of insulin secretion.^{71,72} The *KCNQ1* protein was shown to be expressed in insulin-secreting INS-1 cells.⁷⁹ A study showed that the C allele of the intronic rs2237895 in *KCNQ1* was associated with a decreased risk of abdominal obesity in patients with T2DM. These findings indicated that the C allele of rs2237895 is correlated with a decreased BMI and waist circumference in a Chinese population.^{80–82}

DUSP9

DUSP9 encodes dual-specificity phosphatase 9 [also known as map kinase phosphatase 4 (MKP4)], mapped on chromosome X, with a cytogenetic location at Xq28. It is expressed in various tissues such as adipose tissue, muscles, insulin-responsive tissues, and the liver. DUSP9 plays important roles in regulating cell cycle and insulin action, and also has protective effects against the development of insulin resistance due to its ability to inactivate extracellular signal-regulated kinase and c-Jun N-terminal kinase. Therefore, DUSP9 was considered as a stress-induced insulin resistance mediator.^{83,84} While the effects of DUSP9 on insulin metabolism may differ depending on conditions and tissues, it is considered an important regulator of insulin sensitivity.²⁵

The study of Voight et al⁶² first discovered an association of DUSP9 rs5945326 and T2DM risk in population of

European descent. Then, the study of Fukuda et al²⁵ replicated such an association in a Japanese population. A study of Rees et al²⁶ showed that SNPs in or near *DUSP9* and 12 other genomic loci showed significant associations with T2DM in Pakistani populations, with similar effect sizes to those seen in European populations.

FTO

Biological function of *FTO* (fat-mass and obesity associated) modulates the gene expression through methylation–demethylation modification since *FTO* is part of Fe(II)- and 2-oxoglutarate-dependent dioxygenases superfamily. Therefore, ubiquitously expressed hepatic *FTO* showed an important role in the homeostasis of glucose and lipid.^{85–89}

Many studies have demonstrated a strong association between the *FTO* gene and the incidence of obesity, which is a major risk factor for T2DM.^{90–96} The majority of people with T2DM, particularly those of East Asian ethnicities, achieve their maximum lifetime BMI (BMI_{max}) at the time of or before the onset of disease, and after T2DM diagnosis. The BMI_{max} may also be reached after lifestyle interventions such as diet and exercise, and/or treatment with various antidiabetic medicines that may affect their obesity-related measurements, such as the BMI.^{97,98}

A previous study has reported that the BMI_{max} was strongly associated with an increased risk of T2DM. *FTO* SNPs were significantly correlated with the BMI_{max} in a sex-stratified analysis.²⁸ The study also found that rs1558902 was correlated with the incidence of T2DM in humans, and the correlations between SNPs and T2DM remained significant after the adjustment for the current age and BMI. Furthermore, Hertel et al also reported that adjusting the *FTO* variant for the waist-to-hip ratio and waist circumference conferred an

increased risk of T2DM.²⁹ Decreased mitochondrial oxidative capacities, oxidative stress, and lipid accumulation are suggested to increase the expression of FTO in patients with T2DM. Furthermore, the rs9939609 SNP may alter the risk of T2DM independent of the BMI by affecting other genes in the region.⁹⁹ The increased FTO expression can stimulate *de novo* lipogenesis, inhibit lipolysis and fatty acid oxidation, and increase gluconeogenesis, which can lead to abnormally increased triglyceride deposition and the production of hepatic glucose (Figure 2).

HNF4A

The HNF4A gene is a member of the steroid hormone receptor superfamily that is mainly expressed in the kidney, liver, pancreas (including β -cells), and small intestine, and influences metabolism and lipid transport.^{100,101} It also plays roles in liver function and hepatocyte differentiation.^{102,103} The HNF4A gene is composed of 13 exons and two promoters, known as P1 and P2.¹⁰⁴ The P1 promoter is active mainly in liver cells,^{104–106} while the P2 promoter is the major splice variant in pancreatic β -cells.^{107–109}

Approximately 1–2% of all diabetes cases are the monogenic form, known as maturity-onset diabetes of the young (MODY).¹¹⁰ It is characterized by an early age of onset (usually during adolescence or childhood), dominant inheritance, and defects in β -cell function. MODY resulting from mutations in the HNF4A transcription factor are known as MODY1.¹¹¹ Studies on the genetic linkage have demonstrated

that MODY1 is closely related to markers near HNF4A on chromosome 20.¹¹²

The non-coding variants of HNF4A gene rs6017317¹¹³ and rs4812829³⁶ and a coding missense variant rs1800961 (T130I)¹¹⁴ have been shown to play a role in the development of T2DM. In pancreatic β -cells (Figure 3), HNF4A is required for glucose metabolism and the expression and secretion of the normal insulin gene,¹¹⁵ while in the liver, HNF4A is required for hepatic gluconeogenesis.¹¹⁶ Yamagata et al screened for mutations in HNF4A in patients with MODY1 and reported that MODY1 is encoded by HNF4A.¹¹¹ Clinical studies reported that MODY1 can be caused by impaired insulin secretion by pancreatic β -cells. Loss of or decreased HNF4A can lead to β -cell dysfunction.¹¹⁷ Based on these findings, HNF4A may participate in insulin secretion disorders, as seen in patients with T2DM and MODY1.

IGF2BP2

IGF2BP2 (insulin-like growth factor 2 mRNA-binding protein 2) was identified as an important T2DM candidate gene.^{31,118,119} It is located on chromosome 3q27 (<https://www.genecards.org/cgi-bin/carddisp.pl?gene=IGF2BP2>), and is highly expressed in pancreatic islet cells.³¹ In adipose tissue and the pancreas, IGF2BP2 can reduce the expression of IGF2, which is a growth factor that plays a crucial role in controlling pancreatic development and adipogenesis.^{120,121} IGF2BP2 plays roles in normal embryonic growth and development.¹²²

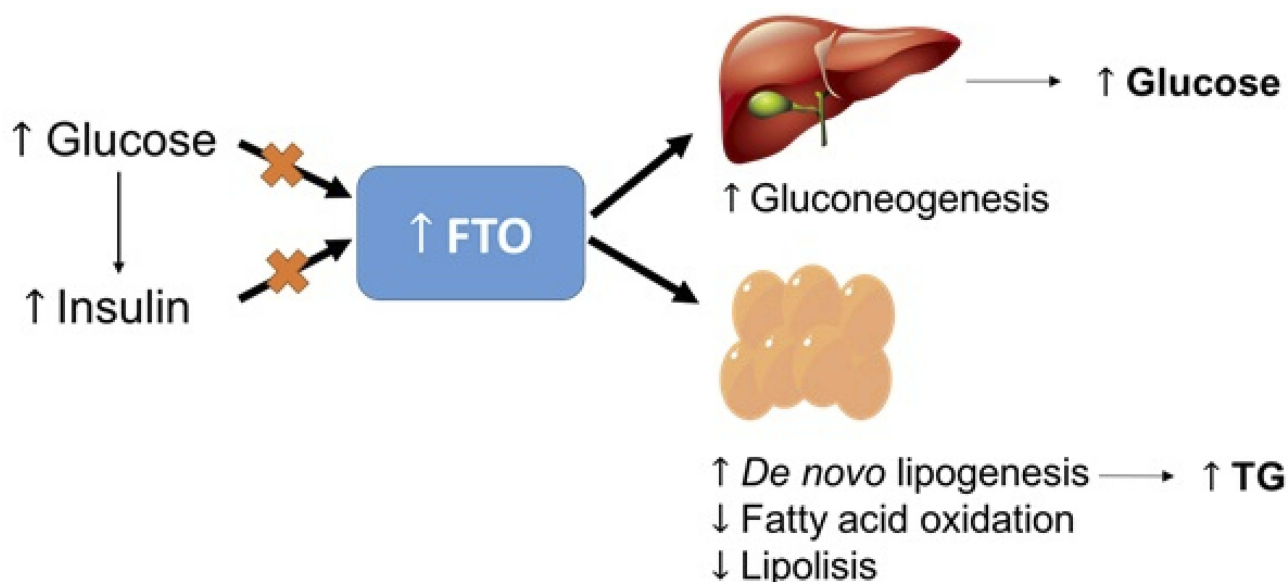


Figure 2 Impairments in the regulation of insulin and glucose may cause an increase in hepatic FTO expression.

Abbreviation: TG, triglyceride.

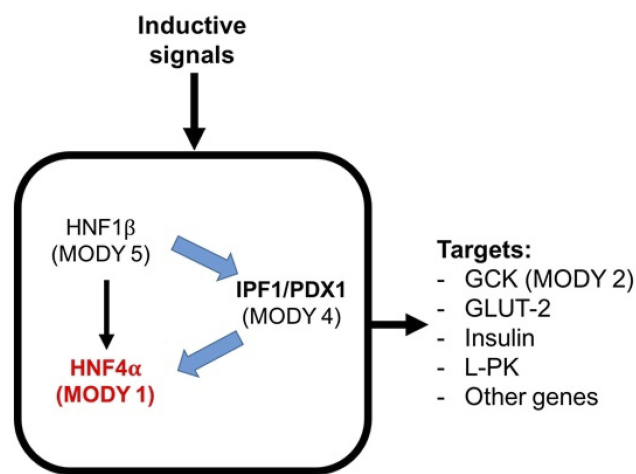


Figure 3 Transcription factor network in the pancreatic β -cell.

Abbreviations: GCK, glucokinase; GLUT-2, glucose transporter-2; L-PK, liver pyruvate kinase.

It also plays a role in T2DM, which is associated with decreased insulin secretion.¹²³ Hence, IGF2BP2 may support T2DM development via changes in adipose tissue or impaired β -cell function.

Duesing et al conducted a comprehensive genetic association study on French Caucasians and showed that IGF2BP2 rs4402960 and rs1470579 were associated with T2DM susceptibility.¹²⁴ Another study reported higher levels of fasting plasma glucose, total cholesterol, and postprandial serum insulin in patients with T2DM who carried the C allele of rs1470579 compared with patients with T2DM who were AA carriers. IGF2BP2 polymorphisms play a role in the regulation of pancreatic β -cell function.¹²⁵ Studies have also demonstrated that IGF2BP2 is strongly associated with overweight and obesity.³⁸ Obesity is associated with T2DM; hence, it is hypothesized that the association between IGF2BP2 and T2DM may be modified by obesity. This is also known as the interplay between IGF2BP2 and obesity with T2DM.¹²⁶ In keeping with this hypothesis, Chistiakov and co-workers,¹²⁷ reported that patients with T2DM have a more than twofold increase in IGF2BP2 expression levels in adipose tissue compared with healthy individuals. Associations between IGF2BP2 and visceral/abdominal total fat were also demonstrated in Mexican Americans and Canadian Caucasians, proposing a possible role of IGF2BP2 in insulin resistance.¹²⁸

CDKN2A/B

The CDKN2A/B locus is located on chromosome 9p21.3, such that the CDKN2A gene encodes both the p16 inhibitor of cyclin-dependent kinase p16INK4A and p14ARF, and the CDKN2B gene encodes p15INK4B,¹²⁹ respectively, and this

locus has been associated with T2DM risk.^{43,118} Further, the 9p21 SNP rs10811661, which was associated with the expression of a long non-coding RNA known as antisense noncoding RNA in the INK4 locus [ANRIL; also called CDKN2B antisense RNA 1 (CDKN2B-AS1)],¹³⁰ was linked with the risk of human diabetes in a GWAS.¹¹⁸ Polymorphisms in CDKN2A/B affect metabolic health related to proteins that contribute to the regulation of β -cell mass, insulin secretory function, and proliferation.⁴³ Additional studies in Asia and Europe have also confirmed that CDKN2A/B is associated with T2DM risk.^{40–42,44,56,131–133} CDKN2A/B is highly expressed in adipocytes and islet cells, as well as in brain cells. Both CDKN2A and CDKN2B are tumor suppressor genes involved in cell apoptosis, tumorigenesis, and proliferation.¹³⁴

Alterations to the phenotype of immune cells influence systemic and peripheral insulin resistance and lead to T2DM. Especially in obesity condition, macrophage infiltrates into adipose tissue and lead to develop a chronic low-grade inflammation. These adipose tissue macrophages (ATMs) stimulate pro-inflammatory cytokines secretion and further will contribute to insulin resistance.¹³⁵ Additionally, CDKN2A/B-ANRIL gene products control glucose homeostasis, in part, via the control of insulin secretion and β -cell function (Figure 4).

TCF7L2

TCF7L2 (transcription factor 7-like 2) is a transcription factor that plays a role in the Wnt-signaling pathway,

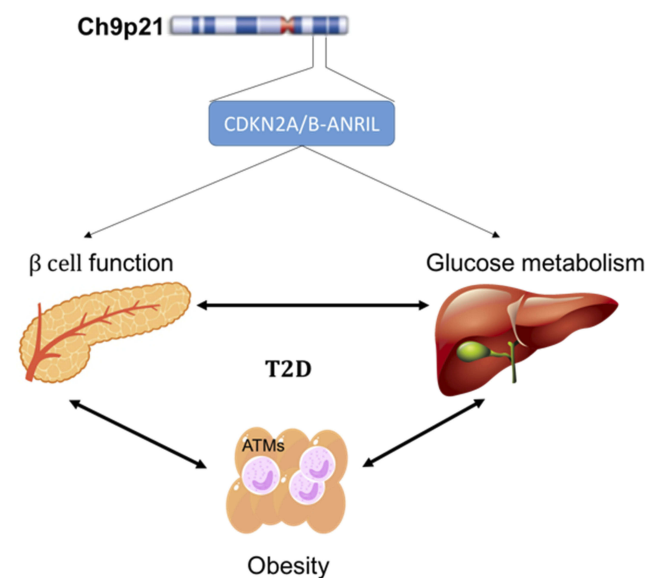


Figure 4 Probable mechanism of CDKN2A/B-antisense noncoding RNA in the INK4 locus (ANRIL) gene product.

Abbreviation: ATM, adipose tissue macrophage.

which regulates pancreatic islet cell functions, such as proliferation and cell survival.¹³⁶ A previous study showed that increased β -cell apoptosis was associated with decreased *TCF7L2* activity, resulting in the downregulation of insulin secretion.^{137,138}

The *TCF7L2* gene is located on chromosome 10q.25.2–25.3, also known as the *TCF4* locus. Previous studies have indicated that people with T2DM are more likely to carry the genetic variant (rs7903146) of this gene.^{139–141} Furthermore, studies on various ethnic populations have shown that mutations of this gene are associated with *TCF7L2* in a self-regulating manner via transcriptional protein complex binding across rs7903146.^{142–144}

The Wnt-signaling pathway also controls the transcription of the proglucagon gene, which regulates incretin hormones such as glucagon-like peptide-1 that inhibits glucagon activity and maintains food mobility from the stomach to the duodenum, and gastric inhibitory polypeptide that is produced by

intestinal K cells. Mutations in *TCF7L2* also result in reduced expression of the proglucagon gene and, consequently, reduced glucagon-like peptide-1 production.^{145–147}

TCF7L2 is expressed in other organs, such as skeletal muscle, gut, fat, and liver, which are all also involved in mediating metabolic homeostasis.¹⁴⁸ The overexpression of β -catalsase produced reciprocal effects on hepatic gluconeogenesis.¹⁴⁹ On the other hand, the Wnt-signaling pathway negatively regulates adipogenesis, and Wnt ligands produced by adipocytes may also function as endocrine and paracrine factors.¹⁵⁰ Based on those studies, the possible roles of *TCF7L2* in the pathogenesis of T2DM are summarized in Figure 5.

KCNJ11

The *KCNJ11* gene (potassium channel, inwardly rectifying, subfamily J, member 11) encodes the Kir6.2 protein (inward-rectifier potassium ion channel), which is

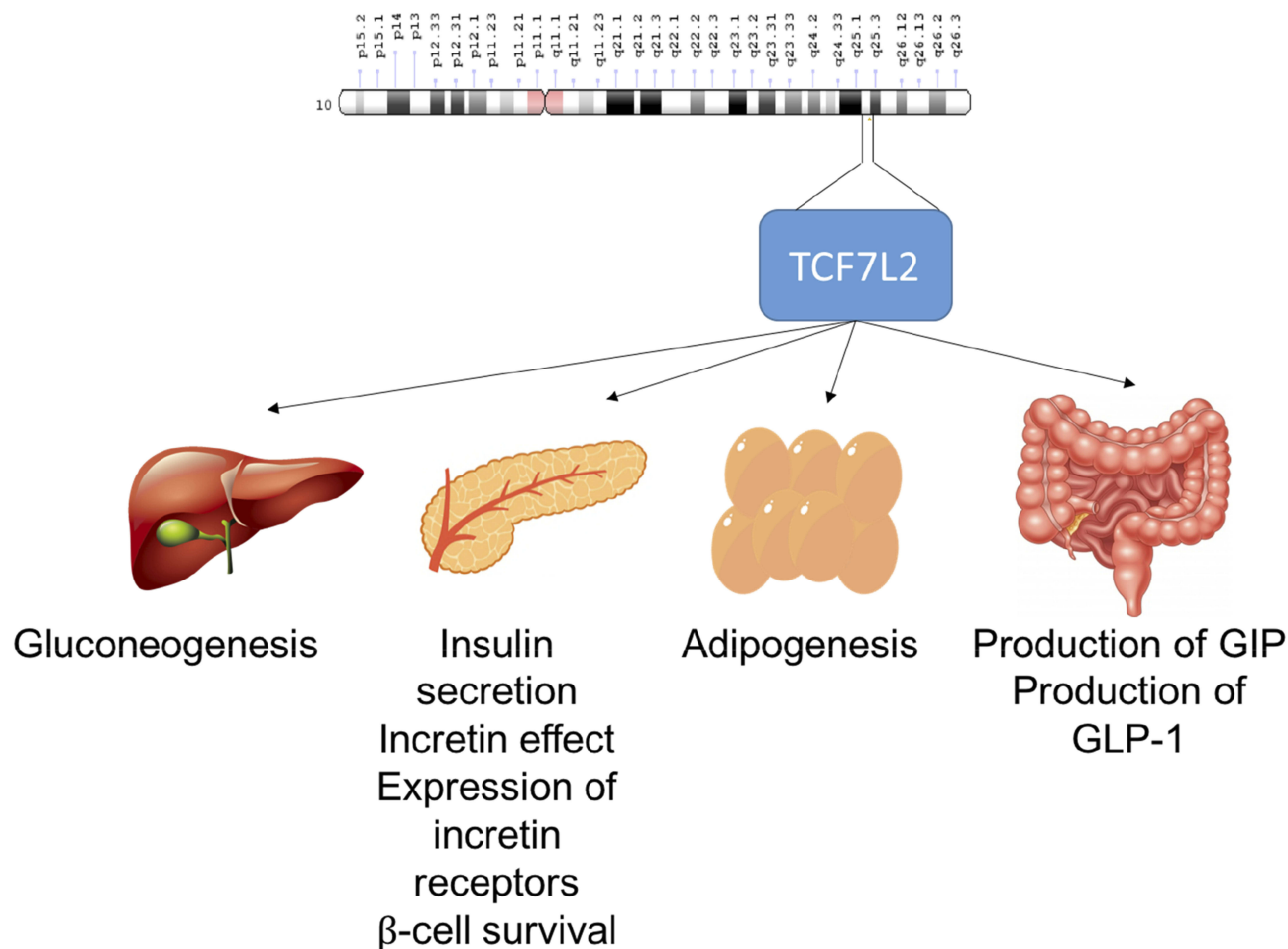


Figure 5 Possible role of *TCF7L2* in the pathogenesis of T2DM.

Abbreviations: GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1.

important for insulin secretion via the ATP-sensitive potassium (K_{ATP}) channel. It has no intron region and is located on chromosome 11p15.1.¹⁵¹ As described in Figure 6, when the body demands insulin, Kir6.2 couples itself to SUR1 (sulfonylurea receptor-1) and binds to a K_{ATP} channel on the pancreatic β -cell membrane, leading to insulin production. Increased glucose levels stimulate the K_{ATP} channel to open and allow the entry of K^+ ions. Increasing levels of K^+ ions depolarize the cell membrane and induce Ca^{2+} channels to increase levels of free intracellular Ca^{2+} . The Ca^{2+} ions trigger other components of the insulin secretion pathway to release granules.^{152,153} Therefore, mutations in KCNJ11 result in reduced insulin production due to reduced or absent Kir6.2 protein expression.¹⁵⁴ The variant allele of KCNJ11 gene rs5219 may decrease channel sensitivity to ATP and alter the charge of the ATP-binding region.⁵¹ A recent meta-analysis showed a strong relationship between polymorphisms of rs5219 and susceptibility to T2DM in East Asian and Caucasian populations.¹⁵⁵ Kir6.2 is also expressed in neurons, the brain, and muscles.¹⁵⁶

Antioxidant Genes

Disruption to the balance of antioxidants and reactive oxygen species (ROS) results in increased oxidative stress, which may lead to diabetes. The generation and accumulation of ROS in β -cells can cause β -cell dysfunction, defects in

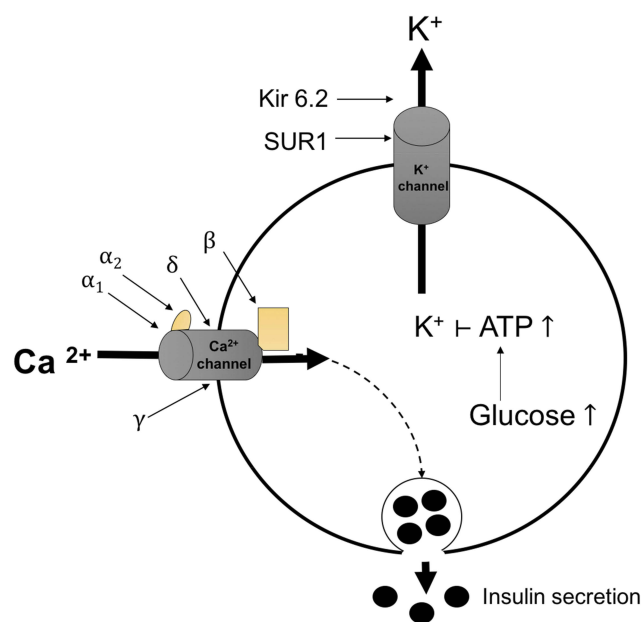


Figure 6 Mechanism of insulin secretion by the K_{ATP} channel in pancreatic β -cells. SUR1 and Kir6.2 proteins in the K_{ATP} channel mediate insulin secretion.

Abbreviations: ATP, adenosine triphosphate; Ca^{2+} , calcium ion (composed of α_1 , α_2 , β , γ , and δ subunits); K^+ , potassium ion; K_{ATP} , ATP-sensitive potassium channel; Kir6.2, inward rectifier potassium ion channel; SUR1, sulfonylurea receptor-1.

insulin production, and impaired function, which result in diabetes.¹⁵⁷ However, the impact of oxidative stress can be reduced or modified by enzymatic antioxidants, including catalase (CAT), glutathione-S-transferase (GST), glutathione peroxidase (GPx), superoxide dismutase (SOD), nitric oxide synthase, and nicotinamide adenine dinucleotide phosphate oxidase.^{158–160} Banerjee et al reported that individuals with a polymorphism affecting the genetic regulation of these six enzymes were at increased risk of developing T2DM. Known polymorphisms in these genes include GSTM1del, GSTT1del, GSTP1 105I/V(+313A/G), CAT-21A/T, SOD2 +47C/T, and GPx1 +599C/T.¹⁶¹ Banerjee and co-workers also concluded that the risk of developing T2DM increases as the variation of the genes that regulate antioxidant enzyme increases.¹⁶¹

DNAJC3

As explained by DNAJC3 is an endoplasmic reticulum (ER) lumen protein and a member of the HSP70 family. It is located in all tissues in humans (predominantly the liver and pancreas), and plays a role in maintaining homeostasis in the ER.⁵⁴ It serves as co-chaperone of binding immunoglobulin protein (BiP) during the unfolded protein response (UPR), which is an ER adaptive signaling pathway. Normally, the ER regulates membrane homeostasis by synthesizing and modifying secretory and membrane proteins.⁵⁴ However, when cells are exposed to abnormal conditions, such as infection, homeostasis imbalance, glucose deprivation, or stimulation that leads to ER protein overproduction, the proteins undergo incomplete or abnormal processes that form unfolded or misfolded proteins. The accumulation of these proteins increases stress in the ER lumen, eventually triggering the UPR in the ER.⁵⁴

Three pathways were reported to generate the UPR signaling pathway, including activation of transcription factor-6;¹⁶² activation of inositol-requiring transmembrane kinase/endoribonuclease 1;¹⁶³ and double-stranded RNA-dependent protein kinase-like eukaryotic initiation factor 2 α kinase (PERK).¹⁶⁴

The UPR pathways will reduce the ER stress and maintain the cell survival by correcting the misinterpreted protein. This can be carried out by the SIL1 protein, which interacts with BiP and binds the misinterpreted protein. DNAJC3 acts prior to protein correction. It binds reversibly to hydrophobic segments of the protein and delivers it to the chaperone, BiP.⁵⁴ DNAJC3 is involved in the PERK pathway, collaborating with the chaperone, BiP, and SIL1 protein, a nucleotide exchange factor.⁵⁴ DNAJC3 mutations, such as deletions and

stop mutations, result in reduced or absent binding between BiP and unfolded or misfolded proteins.⁵⁴ In summary, adaptive response failure leads to unsuccessful pancreatic ER homeostasis and cell death; and in pancreatic cell death, particularly in the pancreatic islet, this will reduce insulin production. Therefore, mutations in the DNAJC3 gene are correlated with diabetes.⁵⁴

PGC-1 α

PGC-1 α (peroxisome proliferator-activated receptor (PPAR)- γ coactivator-1 α) is a transcription coactivator that is involved in various biological responses, such as temperature adaptation, energy homeostasis in the mitochondria, glucose metabolism, triglyceride homeostasis, and heart development.¹⁶⁵

In humans, the PPARGC1A gene is located on chromosome 4 and encodes a 798-amino acid protein PGC-1 α , which is expressed in most tissues with highly active mitochondria and oxidative metabolism, such as the heart, skeletal muscle, and brown adipose tissue.¹⁶⁶

The PGC-1 α gene can convert muscle fiber type and stimulate fatty acid oxidation, thus may lead to a decreased fatty acid concentration in muscles.¹⁶⁷ In contrast, a recent study showed that insulin-resistant skeletal muscle and the liver were associated with increased levels of triglycerides.¹⁶⁸

A previous study by Kelley and co-workers suggested that a decrease in mitochondrial oxidative enzymes leads to defects in the mitochondrial fatty acid oxidation pathway and, ultimately, diabetes. Furthermore, the study also observed that patients with T2DM showed downregulated expression of PPARGC1A gene.¹⁶⁹

ADIPOQ

The ADIPOQ gene encodes adiponectin, which is an adipocytokine. The adipose tissue plays an important role in the development of diabetes mellitus and obesity.¹⁷⁰ Adiponectin, a major adipocyte secretory protein in human plasma, functions as a regulator of energy and is involved in glucose tolerance.¹⁷¹ The ADIPOQ gene is located on human chromosome 3q27 and is reported to be a susceptibility locus for T2DM.^{172,173}

Adiponectin is associated with increased insulin sensitivity, reduced ER stress, and increased fatty acid oxidation.¹⁷⁴ Its functions are mediated by its receptors, AdipoR1 and AdipoR2. The binding of adiponectin to its receptor activates intracellular signaling molecules that play important roles in lipid and carbohydrate metabolism.¹⁷⁵

Li et al reported ADIPOQ gene polymorphisms in rs1501299, rs182052, and rs7627128 in a Chinese population, and showed a significant association with T2DM. Furthermore, a haplotype-based case-control study on the association between T2DM and the ADIPOQ gene found that the haplotypes A–A–T and G–A–T were correlated with increased potency and decreased risk of T2DM, respectively.⁵⁵

CDKAL1

Klimentidis et al reported that variations in CDKAL1 rs775480 were associated with hemoglobin A1c, which is related to T2DM. The rs775480 polymorphism is located at intron 5 of the CDKAL1 gene.⁵⁷ This SNP is associated with decreased glucose sensitivity and insulin secretion in β -cells.^{176,177} Furthermore, the rs10946398 polymorphism of the CDKAL1 gene was proposed as a marker of impaired insulin secretion, as the CC/CA genotypes and C allele contribute to T2DM susceptibility in obese individuals.^{56,178,179}

POMC

Mutations in the POMC (pro-opiomelanocortin) gene are reportedly associated with overweight and obesity as well as the phenotype of early-onset T2DM.^{58,180,181} POMC is a precursor polypeptide hormone that is produced in the neurons of the arcuate nucleus of the hypothalamus and plays an important role as a controller of homeostasis, as well as energy balance, food intake, and glucose metabolism.^{182–184}

Mencarelli et al reported that patients with T2DM and obesity related to mutations in the POMC genes showed a missense mutation in the signal peptide.⁵⁸ This mutation led to a heterozygous substitution of arginine for glycine at A15G–POMC (codon 15), which inhibited the production and secretion of the POMC protein. In humans, POMC deficiency can cause insulin resistance (hyperinsulinemia) since POMC-derived peptides have local effects on the central melanocortin pathway, and intact neuronal melanocortin signaling regulates insulin sensitivity in peripheral tissues.^{185,186}

PPAR γ 2

PPAR γ 2 (peroxisome proliferator-activated receptor-gamma 2) is a ligand-activated transcription factor of the nuclear hormone receptor superfamily.¹⁸⁷ The PPAR γ 2 gene plays roles in glucose homeostasis, lipid metabolism, obesity, insulin sensitivity, T2DM, and various adipocyte-specific genes.^{59,188–190}

Based on several case-control and family-based studies, estimated that Pro12 allele (ie, the major allele) of PPAR γ was associated with a 1.25-fold elevated risk of T2DM.¹⁹¹ Further, the study of Chan et al showed that the Pro12Ala polymorphism was associated with T2DM risk in the multiethnic Women's Health Initiative (WHI) Observational Study at a nominal significance level (Pro12 allele is the risk-increasing allele, $p=0.01$, additive model). The study was replicated in the WHI SNP Health Association Resource (WHI-SHARe) Hispanic American case-control sample (Pro12 allele is the risk-increasing allele, $p=0.02$, additive model).¹⁹²

Phani et al reported that the PPAR γ 2 gene was associated with T2DM in an obese diabetic Indian population ($BMI \geq 25 \text{ kg/m}^2$).¹⁹³ The rs1801282 polymorphism in the PPAR γ 2 gene has been associated with adiposity and regulation of the BMI. Furthermore, the Ala12 variant allele of rs1801282 has been shown to exhibit a decreased binding affinity to the cognate DNA element and therefore could reduce PPAR γ 2 transcriptional activity.¹⁹⁴ Based on the study of Valve et al, the Ala12 variant allele was associated with a lower BMI and a higher insulin sensitivity among normal weight and mildly obese individuals.¹⁹⁵ This polymorphism has also been linked to increased insulin sensitivity and protects from T2DM in Caucasian populations.^{59,193}

Motavallian et al compared the allele distributions of Pro12Ala polymorphism between healthy individuals and those with diabetes.¹⁸⁸ They found a higher frequency of the Ala allele12 in healthy individuals than in patients with diabetes. Another study found a protective role of high Ala frequency against T2DM as it was associated with increased insulin sensitivity, while low frequency of the Ala12 allele was associated with decreased insulin sensitivity (insulin resistance), which may lead to diabetes. These findings suggest that polymorphisms in the PPAR γ 2 gene are associated with T2DM.

SLC30A8

Previous studies have reported that the SLC30A8 (solute carrier family 30 member 8) rs13266634 polymorphism in the major C allele was strongly associated with the risk of T2DM.^{60,61} In addition, Chang et al also reported that the SLC30A8 rs13266634 SNP was associated with age as a T2DM risk factor.¹⁹⁶

SLC30A8 is expressed in pancreatic β -cells and encodes a zinc transporter.¹⁹⁶ Zinc is an important element for insulin secretion and storage.¹⁹⁷ Low ZnT8 (zinc transporter-protein

member 8) expression leads to decreased insulin production by β -cells. Low Zn^{2+} production facilitates hormone clearance by the liver (Figure 7). The study using ZnT8KO mice had low peripheral blood insulin levels despite hypersecretion from β cells pancreas, whilst reduced Zn^{2+} production favors clearance of the hormone by liver.³² Furthermore, ZnT8 overexpression increasing Zn^{2+} accumulation, the Zn^{2+} that secreted with insulin suppressed hepatic insulin clearance via the inhibition of clathrin-dependent insulin endocytosis.^{32,198} The SLC30A8 gene encodes ZnT8, which forms a solid hexamer from binding with insulin in β -cells, matures, and is stored in secretory vesicles.¹⁹⁹

Zn^{2+} plays a crucial role in insulin release and regulates the homeostasis of insulin concentration between pancreas and body. When blood glucose level is low, Zn^{2+} binds insulin in pancreas for storage purpose and an increase in blood glucose level will liberate insulin from Zn^{2+} . High level of ZnT8 means there is a lot of Zn^{2+} available for bind and hold insulin in pancreas. In other words, insulin secretion will be limited to an increase in blood glucose and this is a normal physiology of body in maintaining the glucose homeostasis. Besides, a low level of ZnT8 indicates a small concentration of Zn^{2+} which means there is inadequate insulin depositor and thus, insulin hypersecretion will occur.²⁰⁰ The hypersecretion of insulin will impact the insulin sensitivity, liver clearance, and blood glucose level as the following statement, first liver will intoxicate an excessive amount of insulin. In other words, hepatic clearance will increase and liver takes more energy to function, resulting in glycogen breakdown to glucose.²⁰¹ Second, Zn^{2+} also presents in insulin

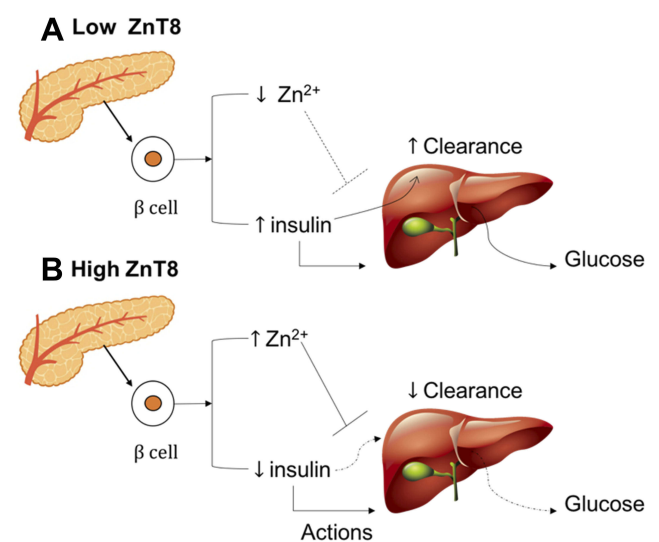


Figure 7 Interaction between ZnT8 expression (A) low ZnT8 and (B) high ZnT8, hormone action, and hepatic insulin clearance.

targeted cells to improve the sensitivity for insulin-receptor bind. A lack of Zn^{2+} will reduce the insulin sensitivity and decrease insulin-receptor bind affinity.²⁰² These mechanisms will lead to an increase in blood glucose level or T2DM event.

The SLC30A8 rs13266634 polymorphism is a non-synonymous SNP that causes an amino acid change from arginine, encoded by the C-allele, to tryptophan, encoded by the T-allele, at position 325 (Arg325Trp). This polymorphism has been linked with the development of T2DM in several populations.^{31,118,119,139,140,203,204}

T2DM risk is influenced by both genetic and environmental risk factors. Therefore, gene–environment interaction studies in T2DM could be more explored as indicated by other studies showed that a significant interaction between SLC30A8 gene rs13266634 and age in T2DM risk ($p < 0.0001$).^{196,205}

Conclusion and Future Prospects

Some genetic polymorphisms are associated with T2DM, either in the form of regulatory non-coding SNPs or as missense coding SNPs that cause direct changes to amino acids within a protein. Genes that are considered to predict or be associated with T2DM disrupt homeostasis, including insulin action and sensitivity, β -cell function and proliferation, and obesity. We realized that this review might use an incomplete searching method and some relevant papers have not been included, but it summarized genes that might be related to the development of T2DM. Moreover, studies show that different SNPs and mechanisms lead to diabetes in different ethnic groups.

Despite remarkable progress, the results from these genetic studies remain inconclusive. Therefore, future studies are required using different ethnic groups to confirm these findings globally, to determine correlations between gene expression and the mechanisms involved to confirm the suggested pathways, and to ensure that treatment of a specific gene will not have knock-on adverse effects on other genes. Thus, further intensive studies are necessary to identify more T2DM-associated genes. The evaluation and confirmation of the currently identified genes are also necessary due to conflicting findings. These polymorphisms may help to reduce the incidence and predict the risk of T2DM. Early identification may increase the prevention efficacy and increase prediabetic prognosis significantly.

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Disclosure

All authors declare that there is no conflict of interest related to this study.

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