Jurnal Biologi Tropis

Review Paper

From Genes to Therapy: The Role of Candidate Gene SNP Polymorphisms in the Implementation of Personalized Medicine for Type 2 Diabetes Mellitus

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Article History
Received : November 17th,2025
Revised : December 17th,,2025
Accepted : Decenber 23th,2025

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Abstract: Type 2 diabetes mellitus is a long-term metabolic disorder shaped by genetic, environmental, and lifestyle influences. Research in genomics reveals that single nucleotide polymorphisms (SNPs) in specific genes can elevate the risk of this condition and may lead to differences in how individuals react to diabetes medications, potentially positioning them as indicators for risk and treatment outcomes in personalized healthcare. This review aims to explore the contributions of SNPs in candidate genes, particularly TCF7L2 rs7903146, KCNJ11 rs5219, KCNQ1 rs2237892, SLC30A8 rs11558471, IRS1 rs1801278, CDKAL1 rs7754840, and MTNR1B rs10830963, contributes to the development of type 2 diabetes. responses to therapy, and their possible roles as clinical markers. A narrative review was carried out by searching literature on PubMed, SpringerLink, and Google Scholar using keywords like “type 2 diabetes mellitus,” “SNP,” and “pharmacogenomics.” English-language articles from 2015 to 2025 that examined connections between genetic variations and either disease risk or treatment responses in humans were included. The findings suggest that these polymorphisms largely impair beta-cell function or disrupt insulin signaling, increasing the likelihood of type 2 diabetes mellitus. Some SNPs are also tied to varied reactions to insulin-based drugs, although metformin typically demonstrates more uniform effectiveness across different genotypes. In summary, SNPs in candidate genes hold promise as tools for risk assessment and personalized treatment choices, but extensive, multi-ethnic prospective studies are essential before they can be integrated into standard clinical practice.

Keywords: Genes sNPs, Type-2 DM, Personalized Medicine, Pharmacogenomic.

Introduction

Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disorder whose global prevalence continues to rise (Zhou et al., 2016). According to data from the International Diabetes Federation (IDF) in 2023, more than 500 million individuals worldwide are living with diabetes, and approximately 90 percent of these cases are classified as T2DM, with this figure projected to exceed 640 million by 2030 (International Diabetes Federation, 2023). This disease is associated with substantial morbidity and mortality and imposes a considerable economic burden on healthcare systems globally (Bommer et al., 2018). The heterogeneity in clinical manifestations and variation in treatment response indicate that T2DM has a complex biological background in which genetic determinants act alongside lifestyle and environmental factors (Mahajan et al. 2024).

Genomic research has fundamentally advanced our understanding of Type 2 Diabetes Mellitus (T2DM) by elucidating the role of single

nucleotide polymorphisms (SNPs), the most abundant class of genetic variation in the human genome (Cirillo et al., 2018). These polymorphisms can modulate gene expression and protein function involved in homeostasis, including metabolic pathways, β-cell functionality, and insulin sensitivity (Prasadet Type 2 diabetes mellitus (T2DM) is a complex metabolic condition influenced by multiple factors, with its worldwide occurrence steadily increasing (Zhou et al., 2016). According to the International Diabetes Federation (IDF) data from 2023, over 500 million people globally have diabetes, and about 90 percent of these cases are T2DM, with projections indicating this number could surpass 640 million by 2030 (International Diabetes Federation, 2023). The condition contributes significantly to illness and death rates and places a heavy financial strain on global healthcare systems (Bommer et al., 2018). The diversity in symptoms and differences in how treatments work suggest that T2DM involves intricate biological processes where genetic factors interact with lifestyle and environmental elements (Mahajan et al., 2024).

Progress in genomics has offered fresh insights into the mechanisms behind T2DM, especially through the discovery of single nucleotide polymorphisms (SNPs) as the most common type of genetic variation in people (Cirillo et al., 2018). These variations can affect gene activity and protein roles related to glucose processing, pancreatic β-cell performance, and insulin responsiveness (Prasad et al., 2021). Various candidate genes, such as TCF7L2, PPARG, KCNJ11, SLC30A8, and IRS1, have been associated with a higher T2DM risk in diverse groups. Research across ethnicities shows variations in allele frequencies and impact levels, highlighting that genetic influences on T2DM vulnerability and treatment outcomes are not consistent worldwide (Mahajan et al., 2024).

Extensive genomic research has pinpointed single nucleotide polymorphisms (SNPs) linked to both the risk and outcomes of Type 2 Diabetes Mellitus (T2DM) (DeForest et al., 2022). These genetic differences affect gene control and essential pathways that regulate glucose metabolism, β-cell function, and insulin sensitivity (Mahajan et al., 2024). Some studies also indicate that the effects of specific SNPs may vary by ethnic background, pointing to a connection between genetics and environmental factors in determining T2DM's clinical features (Vujkovic et al., 2020).

This review seeks to compile the most recent scientific findings on the involvement of SNP variations in candidate genes in T2DM's development and their influence on treatment responses, with a focus on their importance for advancing personalized medicine. The discussion examines how genetic differences relate to underlying molecular processes and how these connections impact the success of diabetes therapies. By adopting a comprehensive, multi-population viewpoint, this article aims to explain gene-therapy interactions and support the adoption of personalized medicine as an approach to more accurate, effective, and fair T2DM management for varied human groups.

Material and Methode

This article review uses the narrative review method to collect and explain various research results on the link between genetic polymorphisms (Single Nucleotide Polymorphism/SNP) in candidate genes and the risk and effectiveness of type 2 diabetes mellitus (T2DM) therapy. Literature searches were conducted using several databases, namely PubMed, SpringerLink, and Google Scholar, using the keywords: “Type 2 Diabetes Mellitus,” “SNP,” “genetic polymorphism,” “pharmacogenomics,” and “personalized medicine.” The articles used were English-language studies published between 2015 and 2025 that had undergone peer review. Only studies conducted on humans and describing the relationship between SNPs and diabetes risk or therapy were included. Meanwhile, studies using animal models, irrelevant to humans, or not in English were excluded from this review. Each eligible article was then read and analyzed. The research results were grouped based on the function of the gene and the biological pathways involved in diabetes. Through this method, it is hoped that a clearer picture of the role of genetic variation in the disease process and response to antidiabetic drugs can be obtained, as well as supporting the direction of more personalized therapy development in the future.

Result and Discussion

Molecular Mechanisms & Pathophysiology of DMT2

In normal physiological states, an increase in blood glucose levels is detected by pancreatic beta cells, prompting a precisely controlled release of insulin (Galicia et al., 2020). Glucose enters the cells through the GLUT2 transporter and is metabolized, raising the intracellular ATP/ADP ratio (Galicia et al., 2020 The rise in intracellular ATP concentration leads to the closure of ATP-sensitive potassium (KATP) channels. This action induces membrane depolarization, which in turn activates voltage-gated calcium channels. The subsequent influx of Ca^{2+} ions acts as the stimulus for the exocytosis of insulin-containing granules. Once secreted, insulin attaches to receptors in peripheral tissues and stimulates the PI3K-Akt pathway, boosting glucose uptake in cells and reducing glucose production in the liver (Galicia et al., 2020). In Type 2 Diabetes Mellitus, several stages of this process are disrupted, affecting both the beta cells' capacity to release insulin properly and the responsiveness of peripheral tissues to insulin (Ojo et al., 2023).

At the molecular level, many of these pathophysiological issues are influenced or altered by genetic variations in genes that control essential glucose metabolism pathways (Zeggini et al., 2024). This review examines seven T2DM candidate genes, grouped by their functions in pancreatic beta cell activity, insulin release, insulin responsiveness, and glucose and lipid metabolism. Single nucleotide polymorphisms (SNPs) In these candidate genes not only heighten the risk of T2DM but also contribute to variations in individual responses to diabetes treatments, making them key elements in personalized medicine approaches. A comparative overview of the seven SNPs covered in this review is presented in Table 1.

Table 1. Summary of candidate gene SNPs linked to type 2 diabetes mellitus. and their therapeutic relevance

Functional Pathway	Candidat Genes	SNP	Risk Allele	Population	Association Results	Therapeutic Relevance	References
Insulin secretion and Wnt/β-catenin signaling pathway	TCF7L2	rs7903146	C > T	European descent population (n = 898,130)	The T risk allele is strongly associated with an increased risk of DMT2. This variant affects insulin secretion through the regulation of gene expression in pancreatic β cells and the incretin signaling pathway.	Increases efficacy of metformin and decreases efficacy of sulfonylurea drugs	Mahajan *et al*., 2018; Dhawan., 2016; Dujic *et al*., 2019; Plata *et al*., 2021
Regulation of insulin secretion through ATP-sensitive K^+ channels (KATP channels)	KCNJ11	rs5219	G>A	Vietnamese Kinth Population (N = 202 Cases / 202 Controls)	The A allele is significantly associated with an increased risk of T2DM in both the codominant and recessive models. This variant affects the sensitivity of KATP channels to ATP, thereby reducing insulin secretion.	Lower response to glibenclamide and better response to metformin	(Tran *et al*., 2022; Haghvirdizadeh, 2015; Phani *et al*., 2017; Makhzoom *et al*., 2019)

Functional Pathway	Candidat Genes	SNP	Risk Allele	Population	Association Results	Therapeutic Relevance	References
Glucose-stimulated Insulin Secretion	KCNQ1	rs2237892	T>C	Asia (China, Korea, Malaysia; total N= 15,736 patients from 10 studies)	The C allele is significantly associated with an increased risk of T2DM by affecting insulin secretion through dysfunction of the K^+ channel in pancreatic β cells, which reduces insulin	Therapeutic response to gliclazide MR (sulfonylure a class)	Li *et al*., 2015; Ao *et al*., 2015; Zou *et al*., 2016
Zn^{2+} ion transport in pancreatic β cells (ZnT8) that plays a role in insulin secretion	SLC30A8	rs11558471	G>A	Malay – Malaysia (N = 992: 476 NGT / 516 T2DM)	The A allele is significantly associated with an increased risk of T2DM The G>A variant reduces ZnT8 transporter function → decreased insulin secretion	Nutritional intervention with zinc supplement ation has the potential to improve ZnT8 function	Seman *et al*., 2015; Davidson *et al*., 2014; Drake *et al*., 2017
Insulin signaling pathway	IRS1	rs1801278 (Gly972Ar g)	G > A	Lahore, Pakistan (161 cases vs. 161 controls)	The A allele (Arg972) is associated with an increased risk of T2DM by reducing IRS-1 phosphorylation, thereby decreasing PI3K/Akt activation → increased insulin resistance.	Reduces respons to OAD therapy (metformin, sulfonylurea).	Albegali 2019; Prudente 2018; Hou *et al*., 2024; Ijaz *et al*., 2019
Insulin secretion	CDKAL1	rs7754840	C>G	Iran (Isfahan Province); Case–control: 140 T2DM patients, 140 healthy controls	The C allele is associated with an increased risk of T2DM The C risk allele reduces tRNA translation efficiency in pancreatic β cells, leading to decreased insulin secretion	Responds well to DPP-4 inhibitor therapy	Osada 2016; Mansori 2015; Soltani., 2018
Regulation of circadian rhythm and insulin secretion	MTNR1B	rs10830963	G	Europe, N= 283,531,	Increased risk of T2DM by decreasing early-phase insulin secretion and edisrupts circadian rhythm regulation of glucose.	Reduced response to nateglinide**;**	*Huang et al., 2025; Song et al., 2021., Tuomi et al., 2016; Tan et al., 2021*
TCF7L2 rs7903146					The TCF7L2 gene produces a transcription		

factor vital to growth and operation of pancreatic β cells via the Wnt/β-catenin signaling pathway. As illustrated in Figure 1 (left panel) under normal conditions, this pathway's activation sustains the activity of genes crucial for insulin release, including ISL1 and GLP1R, which helps β cells react to rising glucose levels (del Bosque-Plata et al., 2021). As illustrated in Figure 1 (right panel), the rs7903146 (C>T) variant, where the risk allele T is in a regulatory area (enhancer), links to alterations in TCF7L2 expression control and interference with Wnt/β-catenin pathway function. This results in less formation of the β-catenin–TCF7L2 complex in the cell nucleus and reduced activity of Wnt target genes that manage insulin secretion (del Bosque-Plata et al., 2021).

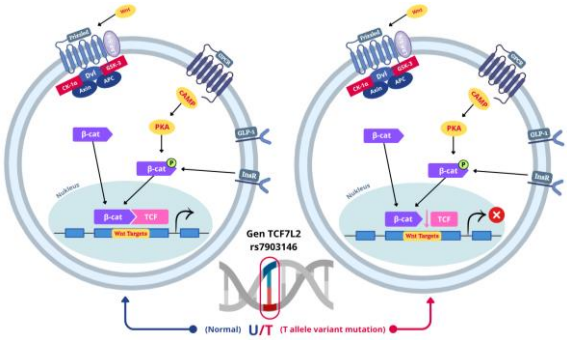

Figure 1. Proposed role of TCF7L2 rs7903146 in Wnt signaling and β-cell dysfunction in type 2 diabetes. Adapted from Chiang et al., 2014

Consequently, β cells' ability to detect glucose and produce initial insulin release is compromised, heightening vulnerability to Type 2 Diabetes Mellitus (T2DM) (Mahajan et al., 2018). Disruptions in insulin secretion tied to the T risk allele in rs7903146 affect treatment outcomes, especially in personalized medicine. Some research indicates that carriers of the T allele show a weaker reaction to sulfonylureas, seen in inadequate blood sugar management or higher chances of treatment not working (Dhawan & Padh, 2016). In contrast, for metformin treatment, the rs7903146 variant has been linked in certain studies to varied blood sugar responses, with some risk allele carriers potentially experiencing better results (Dujic et al., 2019; del Bosque-Plata et al., 2021). Thus, for those with the TCF7L2 rs7903146 (C>T) variant, metformin might be a more suitable choice than sulfonylureas based on underlying mechanisms. Nonetheless, since findings on the link between TCF7L2 and drug responses are not always uniform, applying this genetic data in clinical settings demands careful evaluation and additional research.

KCNJ11 rs5219

The KCNJ11 gene produces the Kir6.2 subunit, a core component of the ATP-sensitive potassium (KATP) channel vital for managing insulin release in pancreatic β cells. As illustrated in Figure 2 (upper panel) under typical physiological conditions, glucose processing boosts the intracellular ATP/ADP ratio, shutting KATP channels, depolarizing the membrane, activating voltage-dependent calcium channels, and prompting insulin secretion (Makhzoom et al., 2019). In contrast, Figure 2 (lower panel) the rs5219 (E23K, G>A) polymorphism leads to a glutamate-to-lysine replacement at position 23 of the Kir6.2 subunit (Makhzoom et al., 2019). This shift reportedly decreases the KATP channels' responsiveness to ATP, causing them to stay open more often despite elevated ATP levels.

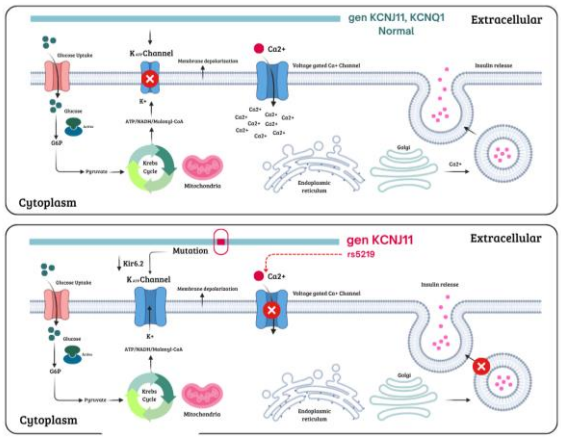

Figure 2. Proposed role of the KCNJ11 rs5219 (E23K) variant in KATP channel regulation and insulin secretion in pancreatic β-cells. Adopted from Assad et al., 2025

This reduces membrane depolarization and calcium entry, disrupting glucose-triggered insulin release and contributing to the elevated Type 2 Diabetes Mellitus (T2DM) risk in those with the risk allele (Tran et al., 2022). Modifications in KATP channel activity linked to the KCNJ11 rs5219 (E23K) variant also influence treatment results in Type 2 Diabetes Mellitus (T2DM), particularly within personalized medicine. For carriers of the risk

allele, this variant associates with a diminished response to sulfonylureas, as seen in higher glibenclamide failure rates among newly diagnosed T2DM patients (Phani et al., 2017). On the other hand, the rs5219 polymorphism connects to more significant decreases in fasting glucose and HbA1c following a six-month course of metformin therapy in newly diagnosed T2DM patients, pointing to a better metformin outcome (Shorokhova & Baranov, 2021). This variation in drug reactions suggests that testing for KCNJ11 rs5219 could aid in selecting antidiabetic treatments that align with a person's genetic traits, promoting personalized medicine for T2DM.

KCNQ1 rs2237892

The KCNQ1 gene produces the voltage-gated potassium channel essential for repolarizing the pancreatic β-cell membrane and fine-tuning insulin secretion (Ao et al., 2015). In typical conditions, KCNQ1 supports the β-cell membrane potential balance, enabling glucose-driven depolarization to activate calcium channels, facilitate Ca^{2+} entry, and promote insulin release. As illustrated in Figure 3, the rs2237892 (T>C) polymorphism involves a single nucleotide shift from thymine (T) to cytosine (C), modifying KCNQ1 expression control (Ao et al., 2015).

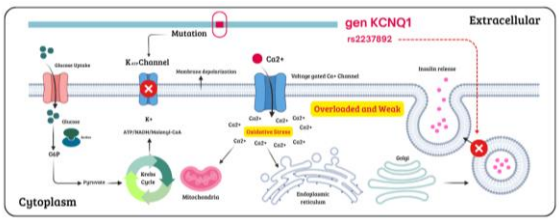

Figure 3. Proposed role of the KCNQ1 rs2237892 variant in β-cell membrane repolarization and impaired insulin secretion in type 2 diabetes. Adopted from Assad et al., 2025

This change boosts K^+ channel activity and hastens membrane repolarization, shortening depolarization and impairing insulin secretion. As a result, KCNQ1 variations connect to a greater Type 2 Diabetes Mellitus (T2DM) risk via reduced β-cell glucose response and lower insulin production (Li et al., 2018). In the context of personalized medicine, those with the KCNQ1 rs2237892 C allele often display a diminished response to sulfonylurea medications, matching their weakened insulin secretory function (Zou et al., 2015). Because this mutation affects potassium channel operation in β cells, metformin is viewed as a preferable initial treatment for these individuals, focusing on improving peripheral insulin sensitivity and reducing liver glucose output instead of depending on boosted insulin secretion (Meng et al., 2015).

SLC30A8 rs11558471

The ZnT8 protein, which is encoded by the SLC30A8 gene, functions as a zinc transporter that is predominantly localized in pancreatic β cells. As illustrated in Figure 4 (upper panel), under physiological conditions, ZnT8 facilitates the transport of zinc ions into insulin-containing secretory granules. Within these granules, zinc is essential for the proper crystallization, stable storage, and rapid availability of insulin for secretion in response to elevated blood glucose levels (Davidson et al., 2014). As illustrated in Figure 4 (lower panel), the rs11558471 (G>A) polymorphism in SLC30A8 is situated within the 3′ UTR region; consequently, it does not alter the amino acid sequence of the ZnT8 protein but can influence its expression levels and the efficacy of zinc transport into insulin granules (Davidson et al., 2014).

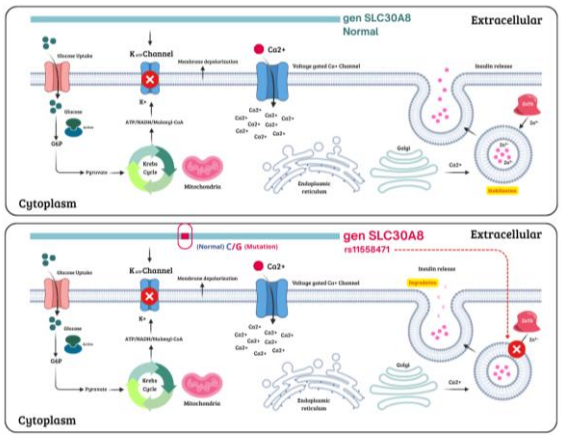

Figure 4. Proposed role of the SLC30A8 rs11558471 variant in ZnT8 mediated zinc transport insulin granule maturation and increased risk of type 2 diabetes Mellitus. Adapted from Assad et al., 2025.

A reduction in granular zinc content impairs insulin maturation and storage, leading to a diminished insulin secretory response to

hyperglycemia. Over time, this dysfunction can contribute to impairments in glucose homeostasis and elevate the risk for Type 2 Diabetes Mellitus in individuals carrying the rs11558471 variant (Tran et al., 2022). Furthermore, genetic variation in SLC30A8, particularly the rs11558471 polymorphism, has been associated with interindividual variability in the metabolic response to dietary zinc. Research indicates that higher zinc intake, from both dietary sources and supplements, is correlated with reduced fasting glucose concentrations, an effect that is more pronounced in carriers of the rs11558471 variant compared to non-carriers (Kanoni et al., 2011). Therefore, the modulation of ZnT8 expression and function represents a promising future target for precision medicine strategies aimed at augmenting pancreatic β-cell performance in patients with a genetic predisposition to Type 2 Diabetes Mellitus.

IRS1 rs1801278

The IRS1 (Insulin Receptor Substrate-1) gene encodes a critical intracellular adaptor protein that mediates signaling between the insulin receptor and the phosphatidylinositol 3-kinase (PI3K)-Akt cascade, a pathway fundamental for stimulating glucose uptake in peripheral tissues (Ijaz et al., 2019). As illustrated in Figure 5 under physiological conditions, insulin binding triggers the autophosphorylation of tyrosine residues on its receptor, which in turn promotes the phosphorylation of IRS proteins (Ijaz et al., 2019).

Phosphorylated IRS1 then recruits the p85 regulatory subunit of PI3K, initiating the PI3K-Akt signaling axis. This sequence of events culminates in the translocation of GLUT4 transporters to the plasma membrane, thereby facilitating cellular glucose uptake (Ijaz et al., 2019). As illustrated in Figure 4, a missense polymorphism in IRS1, rs1801278 (Gly972Arg), introduces an amino acid substitution from glycine to arginine at codon 972, a position flanking key tyrosine phosphorylation sites (Ijaz et al., 2019). This substitution alters the local protein conformation of IRS1, impairing its phosphorylation and reducing its affinity for PI3K binding (Ijaz et al., 2019).

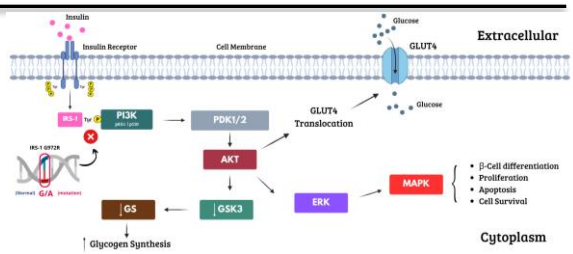

Figure 5. Proposed role of the IRS1 rs1801278 (Gly972Arg) variant in PI3K/Akt signaling and insulin resistance in type 2 diabetes. Adapted from Ibadurrahman et al., 2022.

The consequent attenuation of PI3K-Akt pathway activation compromises insulin signal transduction, leading to impaired insulin sensitivity, which elevates the susceptibility to insulin resistance and, ultimately, Type 2 Diabetes. Mellitus (Albegali et al., 2019). From a pharmacogenomic perspective, the Gly972Arg variant is associated with a reduced therapeutic response to oral antidiabetic agents whose mechanism of action relies on enhancing insulin sensitivity (Prudente et al., 2018). Consequently, carriers of the Arg972 allele may derive greater benefit from therapeutic strategies that function independently of the insulin signaling pathway. For instance, SGLT2 inhibitors, which lower plasma glucose levels by promoting its renal excretion, represent a viable alternative (Hou et al., 2024). This approach aligns with the principles of personalized medicine, offering a tailored treatment strategy for Type 2 Diabetes Mellitus patients carrying the IRS1 Gly972Arg polymorphism.

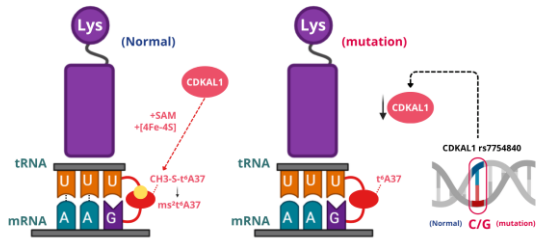

Figure 6. Proposed role of the CDKAL1 rs7754840 variant in impaired proinsulin processing and β-cell function in type 2 diabetes. Adapted from Wei & Tomizawa, 2012

The CDKAL1 gene plays a critical role in maintaining pancreatic β-cell function by facilitating the accurate biosynthesis of insulin. It encodes an enzyme responsible for a specific

post-transcriptional modification of tRNA Lys(UUU), which is indispensable for the precise translation of proinsulin mRNA (Mansoori et al., 2015). As illustrated in Figure 6 under conditions of normal CDKAL1 activity, this process ensures the correct synthesis and folding of proinsulin into its biologically active form, enabling its subsequent secretion. However, in carriers of the rs7754840 (C>G) variant, particularly the C allele, CDKAL1 enzymatic function is diminished, leading to impaired tRNA modification. As illustrated in Figure this defect compromises the fidelity of proinsulin translation, resulting in the production of misfolded peptides.

The accumulation of these aberrant proteins within the β-cell triggers endoplasmic reticulum (ER) stress, a key factor that disrupts normal β-cell function. This dysfunction manifests as a reduced capacity for insulin production and secretion, thereby contributing to hyperglycemia and an elevated risk for type 2 diabetes mellitus (T2DM) (Mansoori et al., 2015). From a clinical pharmacogenomic standpoint, this genetic variant influences interindividual variability in responses to antidiabetic drugs. For instance, a study by Soltani et al. (2018) demonstrated that carriers of the C allele exhibit a diminished glycemic response to sulfonylureas. This is likely due to the pre-existing impairment in insulin secretory capacity, which limits the efficacy of drugs that act primarily by stimulating insulin release via KATP channel blockade (Soltani et al., 2018).

Conversely, research by Osada et al. (2016) indicated that patients with this same variant may derive greater benefit from DPP-4 inhibitors. The mechanism of these agents, which involves enhancing endogenous incretin activity to potentiate glucose-stimulated insulin secretion, appears to be more compatible with the underlying pathophysiology in these individuals (Osada et al., 2016). The differential impact of the rs7754840 genotype on drug efficacy not only elucidates its role in T2DM susceptibility but also underscores its potential utility in guiding therapeutic decisions, aligning with the principles of personalized medicine for the management of T2DM.

MTNR1B rs10830963

The MTNR1B gene encodes the MT1B melatonin receptor, which is expressed in pancreatic β-cells and plays a role in the circadian regulation of insulin secretion. As illustrated in Figure 7 (left panel) shows that receptor activation lowers intracellular cAMP, reduces PKA activity, and limits calcium entry, which slightly suppresses glucose-stimulated insulin secretion. (Tuomi et al., 2016). As illustrated in Figure 7 (right panel) the rs10830963 polymorphism in MTNR1B, where the G allele is the risk variant, is associated with increased receptor expression in β-cells.

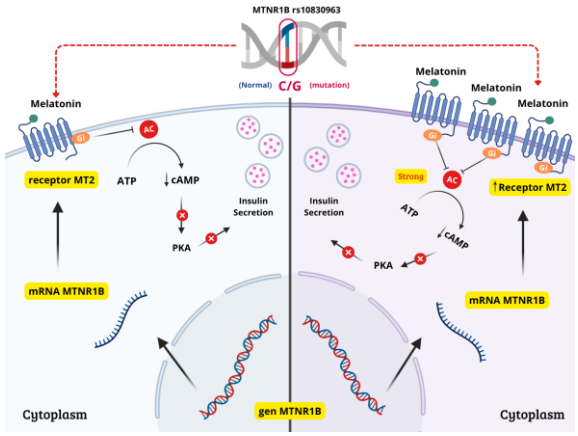

Figure 7. Proposed role of the MTNR1B rs10830963 variant in melatonin receptor mediated beta cell dysfunction and increased risk of type 2 diabetes. Adapted from Phatel et al., 2022

This amplifies melatonin-mediated inhibition of insulin secretion, leading to impaired first-phase insulin release, elevated fasting glucose, and an increased risk of developing type 2 diabetes (Tuomi et al., 2016; Huang et al., 2025). From a therapeutic perspective, carriers of the G allele exhibit a blunted reduction in fasting glucose and less pronounced improvement in glycemic parameters following nateglinide treatment, indicating a reduced response to insulin secretagogues that require preserved β-cell function (Song et al., 2021). In contrast, research that evaluated commonly used glucose-lowering treatments, including metformin, has not demonstrated a consistent effect of the rs10830963 variant on measures of glycemic control. These findings indicate that this polymorphism does not reliably modify the therapeutic performance of widely prescribed antidiabetic medications. (Tan and Benedict,

2021). These findings highlight the potential relevance of MTNR1B genotyping for individualized treatment selection in type 2 diabetes, in line with the principles of precision medicine.

In summary, polymorphisms in genes such as TCF7L2, KCNJ11, KCNQ1, SLC30A8, CDKAL1, and MTNR1B predominantly impair pancreatic β-cell function through diverse mechanisms including defective proinsulin synthesis, disrupted insulin granule maturation, altered ion channel activity, and dysregulated transcriptional and circadian signaling. In contrast, variants in IRS1 mainly reduce insulin sensitivity in peripheral tissues by disrupting insulin receptor signaling pathways. This dual pathophysiology β-cell dysfunction and insulin resistancereflects the polygenic and heterogeneous nature of type 2 diabetes and helps explain the considerable interindividual variation in disease severity and treatment response. Pharmacogenomic evidence further indicates that specific variants in TCF7L2, KCNJ11, KCNQ1, CDKAL1, and MTNR1B not only increase disease susceptibility but also influence response to certain glucose-lowering agents, particularly sulfonylureas and other insulin secretagogues. In comparison, metformin generally exhibits a more consistent efficacy profile across these genetic backgrounds.

Limitations of Evidence and Challenges in Implementing Personalized Medicine

Although numerous studies have demonstrated associations between specific candidate gene polymorphisms and both Type 2 Diabetes Mellitus (T2DM) risk and interindividual variation in antidiabetic drug response, the existing body of evidence possesses several limitations. Many findings are derived from observational studies characterized by restricted sample sizes, heterogeneous designs, and diverse participant cohorts, leading to inconsistencies in results and necessitating cautious extrapolation to other populations (Suzuki et al., 2024). Although numerous genetic associations for type 2 diabetes have been identified, most large scale studies have been conducted in European ancestry cohorts so their direct applicability to Southeast Asian populations remains uncertain and requires further validation (Ju et al., 2022).

From an implementation standpoint, additional challenges include the financial cost and accessibility of genetic testing, the requisite laboratory infrastructure, the preparedness of healthcare providers to interpret genetic findings, and ethical concerns regarding the storage and use of patients' genetic (Zhang et al., 2019)). These factors collectively explain why, despite the compelling theoretical promise of pharmacogenomics in T2DM, international clinical guidelines continue to prioritize traditional clinical factors such as glycemic levels, comorbidities, hypoglycemia risk, and patient preference over routine genetic profiling for therapeutic decision-making.

Future Directions

Future research should not only aim to verify the associations between candidate gene single nucleotide polymorphisms and both type 2 diabetes mellitus risk and therapeutic outcomes but also assess their potential to serve as clinically meaningful biomarkers. There is an urgent need for prospective and well controlled clinical studies that directly compare treatment approaches guided by genetic information with standard therapeutic strategies based on empirical decision making. Such studies are necessary to determine whether genetic data derived from variants including TCF7L2 rs7903146, KCNJ11 rs5219, KCNQ1 rs2237892, SLC30A8 rs11558471, IRS1 rs1801278, CDKAL1 rs7754840, and MTNR1B rs10830963 can truly enhance glycemic control, lower the risk of therapeutic failure, or minimize adverse drug reactions.

Recent findings also highlight additional variants that show meaningful associations with increased susceptibility to type 2 diabetes, such as IGF2BP2 rs4402960, PPARG rs1801282, FTO rs9939609, and MTNR1B rs10830962. The accumulation of evidence from these variants supports the development of a multigene biomarker panel, since each polymorphism contributes only a modest individual effect. Combining these variants into a single predictive tool may improve accuracy in estimating disease risk and anticipating individual responses to antidiabetic therapy.Large and ethnically diverse studies are needed to confirm whether these genetic markers function consistently across different populations, particularly those in Asian

regions. Variations in allele frequency and gene–environment interactions make cross population validation an essential step before any biomarker can be reliably implemented in clinical practice.

The integration of these genetic markers with clinical factors such as body mass index, age, baseline HbA1c, and lifestyle components including dietary patterns and physical activity into predictive models embedded within electronic health record systems is expected to support the practical application of personalized treatment in type 2 diabetes. With sufficient validation, the variants that show consistent associations with disease progression and drug response can be incorporated into a biomarker panel designed for early detection, risk stratification, and individualized therapy selection.

Conclusion

Type 2 Diabetes Mellitus is a complex condition influenced by a multitude of factors, including genetic variation. Several candidate genes—including TCF7L2, KCNJ11, KCNQ1, SLC30A8, IRS1, CDKAL1, and MTNR1B—play critical roles in regulating pancreatic β-cell function and insulin sensitivity. Polymorphisms in these genes can disrupt insulin production, secretion, or tissue responsiveness, thereby elevating the risk of T2DM. Evidence indicates that some of these polymorphisms are also associated with differential responses to certain antidiabetic drug classes, particularly those that stimulate insulin secretion, whereas metformin generally exhibits a more consistent efficacy profile across different genetic backgrounds.This evidence suggests that genetic information holds potential for guiding more tailored drug selection for individual patients, aligning with the principles of personalized medicine. However, the current evidence base remains insufficient to recommend genetic testing as a primary guide for routine therapy, as existing studies often report conflicting results and are frequently conducted in limited, specific populations. Consequently, the application of genetic polymorphism data in T2DM management is presently best viewed as a promising avenue for future development. Its widespread integration into clinical practice awaits further validation through large-scale, robustly designed research.

Acknowledgments

The author wishes to convey sincere appreciation to the supervising lecturer for the guidance and encouragement offered during the completion of this research and manuscript. The author also extends gratitude to Universitas Singaperbangsa Karawang for the support and facilities that made this work possible. Heartfelt thanks are also given to family members and close relatives whose constant support and understanding greatly contributed to the accomplishment of this study.

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