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An Overview of the Pharmacogenetics of Sulfonylurea in Type 2 Diabetes Mellitus

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ABSTRACT

Background and Objective: Diabetes mellitus (DM) is a prevalent disease, with its prevalence increasing over the past few decades, posing a significant public health challenge. Type 2 diabetes mellitus (T2DM) is a chronic condition characterized by abnormal blood glucose levels due to insulin deficiency or resistance. This review delves into the pharmacogenetic implications of sulfonylurea (SU) therapy, elucidating the impact of genetic variations on SUs response, SU-induced hypoglycemia, and the development of secondary failure to this drug among T2DM patients. **Methods:** The data was obtained through a search on Pubmed and Google Scholar using the following keywords: 'Sulfonylurea', 'Type 2 diabetes mellitus', 'genetic', 'polymorphism', 'SNP', 'drug response', 'pharmacogenomics', and "precision medicine". **Results:** Our analysis suggests that genetic variations could significantly influence the response to SU therapy, the risk of hypoglycemia associated with SUs, and the occurrence of secondary failure. However, this review reveals conflicting outcomes for different genes/variants that may be due to the heterogeneity among previous studies. **Conclusions:** Translating these findings into clinical practice remains a major challenge, underscoring the critical need for more extensive and standardized research to generate precise data. Such data can then be used to develop precision medicine for T2DM and improving patient outcomes.

***Keywords**: Type 2 diabetes mellitus, sulfonylureas, pharmacogenetics, hypoglycemia, secondary failure, SNP, genetic variation.*

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder that occurs as a result of decreased insulin activity [1]. It is a prevalent disease in the modern world [2], with its prevalence increasing over the past few decades, posing a significant public health challenge [3]. According to the latest edition of the authoritative resource on global impact of diabetes (IDF Diabetes Atlas), more than 537 million people worldwide suffer from diabetes, and this number is projected to reach 643 million by 2030 [4].

DM is categorized into type 1 diabetes, type 2 diabetes, other types of diabetes mellitus, and gestational diabetes mellitus.[5] Type 2 diabetes mellitus (T2DM) is a chronic condition characterized by abnormal blood glucose levels due to insulin deficiency or resistance [6] The pathogenesis of T2DM involves various factors, including environmental factors, unhealthy eating habits,

high dietary glucose intake, obesity, smoking, alcohol consumption, and genetic factors [7]. Genetic factors play a significant role in the development of T2DM, particularly in individuals with a family history of diabetes [8]. It is estimated that between 35% and 70% of T2DM cases have a genetic predisposition [4].

The healthcare field is experiencing the rise of "personalized medicine" as a promising direction [9]. Precision medicine, also known as personalized medicine, is envisioned as a novel medical approach that aims to enhance prevention, diagnosis, and treatment effectiveness by gaining a comprehensive understanding of patients' genetic and genomic information, moving away from the current standard "one-size-fits-all" treatment [10]. T2DM presents an appealing opportunity for a precision medicine approach due to its diverse nature with varying underlying pathophysiology and the availability of multiple glucose-lowering treatment options with different mechanisms of action [11]. This innovative strategy shows great potential in transforming diabetes management and enhancing patient outcomes [9]. Metformin is commonly prescribed as the first-line pharmacotherapy for T2DM [12]. In cases where patients are unable to tolerate metformin, sulfonylurea (SU), is used as the first-line drug of choice [13].

SU is a class of oral hypoglycemic medications [12], with first-generation drugs including tolbutamide, acetohexamide, tolazamide, and chlorpropamide, and second-generation drugs including glimepiride, gliclazide, glipizide, and glyburide [14]. Both generations of SUs have shown significant reductions in glycosylated hemoglobin levels [13].

Understanding the pharmacogenetics of SUs is crucial for evaluating individual differences in drug response and potential side effects, leading to valuable insights for personalized treatment approaches in T2DM patients.

This review focuses on the pharmacogenetic aspects of sulfonylurea therapy, elucidating the impact of genetic variations on SUs response, SU-induced hypoglycemia, and the development of secondary failure to this drug among T2DM patients.

METHODS

Data was obtained by searching PubMed and Google Scholar, using the keywords: 'Sulfonylurea', 'Type 2 diabetes mellitus', 'genetic', 'polymorphism', 'SNP', 'drug response', 'pharmacogenomics', "precision medicine".

Mechanism of action of SUs:

It is widely accepted that chronic hyperglycemia, the main diagnostic marker of T2DM, results from the failure of pancreatic ß-cell, leading to a gradual decrease in beta-cell mass and insulin production in response to glucose [4]. ATP-sensitive potassium (KATP) channels are potassium channels regulated by adenosine triphosphate (ATP) and adenosine diphosphate (ADP), control membrane potential-dependent processes to meet metabolic needs [15]. These channels are composed of octameric protein complexes, with major subunit of the ATP-sensitive K+ channel KIR6.1 or major subunit of the ATP-sensitive K+ channel (KIR6.2) protein assembly encoded by *KCNJ8* and *KCNJ11* genes, respectively, surrounded by sulfonylurea receptor 1 (SUR1) or SUR2A/B proteins encoded by *ABCC8* and *ABCC9* genes, respectively [16]. Structurally kir6.2 and SUR1 consists of four pore-forming subunits surrounding the pore of the KATP channel on the plasma membrane of pancreatic ß-cell. The closure of these channels initiates insulin secretion, while their opening inhibits it [17].

Loss-of-function mutations in *KCNJ11* and *ABCC8* genes have been associated with congenital forms of hyperinsulinemia and hypoglycemia, indicating the crucial role of the pancreatic β-cell KATP channel in regulation of insulin secretion [15].

Effective SU therapy involves inhibiting KATP in the membranes of pancreatic β-cell through direct and indirect interactions with the SUR subunits. This enhances the ATP sensitivity of the KIR6.2 subunits, leading to channel closure at lower intracellular ATP levels [16].

Consequently, intracellular potassium levels rise, causing depolarization and subsequent calcium influx through voltage-gated calcium channels [18,19]. This influx of calcium triggers the controlled release of insulin from beta cell [20], and thus reducing blood glucose levels[13].

Pharmacogenetics of sulfonylurea

Pharmacogenetics explores how variations in the human genome can impact individual responses to drugs, including their efficacy and potential side effects. Identifying genetic factors that influence glycemic response could offer insights into the treatment mechanisms of T2DM and pave the way for personalized treatment approaches [21].

The effect of genetic variants on the response to SUs therapy

Various medications for T2DM may not yield the same results for all patients or may lead to diverse side effects that restrict their use. Factors such as age, gender, and genetic makeup contribute to the variability in treatment responses. Pharmacogenomics aims to address why oral antidiabetic drugs exhibit varying effectiveness in treating T2DM among different individuals [22]. Genetic factors account for 20%–95% of the differences in drug responses between individuals [23], as genetic variations can influence drug absorption, distribution, metabolism, targeting, and efficacy [24].

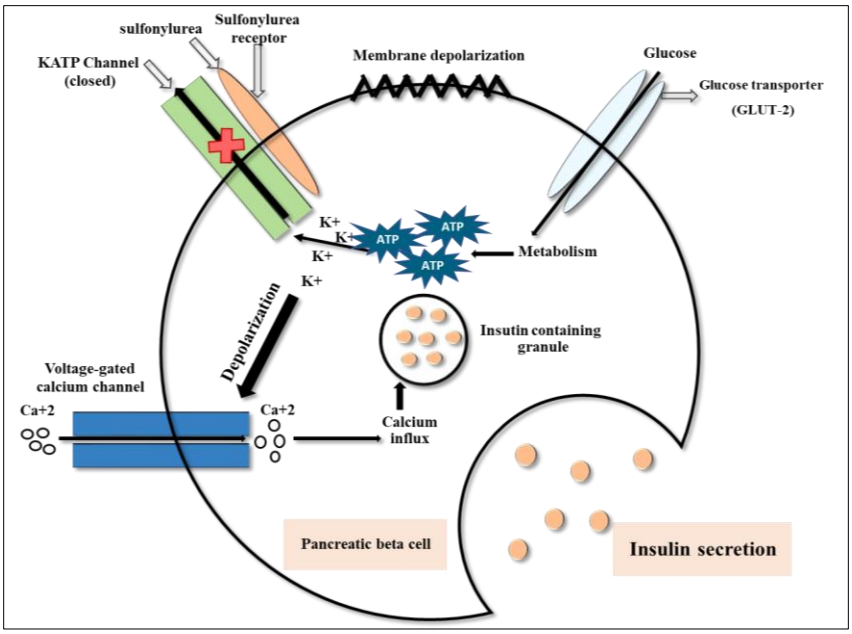

Figure 1. Schematic representation of the mechanism of action of SU drugs

Genomic differences arise from genetic variations like single nucleotide polymorphisms (SNPs), insertions and deletions, or copy number variations [25].

In the field of pharmacogenomics, studies on SU have highlighted several gene variants associated with treatment outcomes, such as *CYP2C9*, *KCNQ1*, *KCNJ11*, *TCF7L2*, *IRS-1*, *CDKAL1*, and *SLCO1B3*, with variable results among the different ethnic population. Genes associated with therapeutic responses to SUs are shown in **Table 1**.

Cytochrome P450 (*CYP2C9*):

CYP2C9 plays a pivotal role in the metabolism of SUs [42]. It is the predominant isoform of CYP2C in the liver, constituting approximately 20% of hepatic CYP proteins [43].

The *CYP2C9* gene, located on chromosomal region 10q23.33, spans about 55 kb with nine exons encoding a protein comprising 490 amino acids [44]. The distribution of polymorphic alleles of *CYP2C9* varies significantly across populations, with many allelic variants showing altered drug metabolic activities compared to the wild type protein. To date, pharmacogenetic studies has identified 85 allelic variants of the *CYP2C9* gene [42].

The interaction between variants in *CYP2C9* and P450 oxidoreductase genes is crucial in determining the efficacy of SU treatment [45]. Notably, *CYP2C9*2* (Arg144Cys) and *CYP2C9*3* (Ile359Leu) are key genetic variants of the *CYP2C9* gene [46].

The association between *CYP2C9* genetic polymorphisms and SU treatment outcomes remains inconclusive. In Iranian patients, no significant correlation was observed between the therapeutic response to SUs and the *CYP2C9*3* (rs1057910) variant [22]. Similarly, in Khyber Pakhtunkhwa Pakistan, a modest non-significant impact of this polymorphism on T2DM susceptibility was reported [46]. Conversely, a study in Mexican patients suggested that the *CYP2C9*3* genetic variant independently contributes to good glycemic control in T2DM patients treated with glibenclamide [47]. Another study in Chinese patients revealed that the *CYP2C9*3* rs1057910 polymorphism significantly influenced the therapeutic response to gliclazide in T2DM patients [48]. Furthermore, Lebanese individuals with the *CYP2C9*3* variant exhibited maximum glycemic control when treated with a combination of metformin and SU [49].

Regarding the *CYP2C9*2* (rs1799853) variant, Egyptian T2DM patients with the *CYP2C9*2/*3* genotype demonstrated improved glycemic control with glibenclamide treatment [50]. Conversely, a study in Poland did not find any association between the CYP2C9*2 variant and the therapeutic response to SUs in T2DM patients [51]. Similarly, a study in the Netherlands indicated that genotyping for *CYP2C9*2* and *CYP2C9*3* alleles did not have clinical implications for dosing SUs in primary care T2DM patients [52].

Table 1. Genes involved in pharmacokinetics or pharmacodynamics of SU

Gene	Location/ Exon count	Tissue expression	Protein encoded by gene	Reference
CYP2C9	10q23.33 (9 Exon)	It is mainly expressed in the liver, but other organs are also involved: kindly, placenta, adrenal gland, gastrointestinal tract, and skin	CYP2C9	[26,27]
KCNQ1	11p15.5 (19 Exon)	It is mainly expressed in the tissues or cells of the heart, as well as in pancreas islets, which plays an important role in the regulation of insulin secretion	KvLQ1	[26,28]
ABCC8	11p15.1 (38 Exon)	It is expressed in the brain as well as in the pancreas.	SUR1	[26,29]
TCF7L2	10p25.2 (20 Exon)	It is expressed in epithelial tissues including the mammary glands, skin, and gastrointestinal tract.	TCF7L2\ TCF-4	[26,30]
IRS-1	2p36.3 (4 Exon)	It predominates in skeletal muscle	Insulin receptor substrate 1 (IRS-1)	[26,31,32]
KCNJ11	11p15.1 (4 Exon)	It is mainly expressed in tissues such as the heart and pancreas	Kir6.2	[26,33]
CDKN2A	9p21.3 (10 Exon)	In many tissues	$p16^{INK4A}$ and $p14^{ARF}$ proteins	[26,34,35]
CDKN2B	9p21.3 (2 Exon)	It is highly expressed in subcutaneous adipose tissue (SAT)	$p15^{INK4B}$	[26,36,37]
CDKAL1	6p22.3 (23 Exon)	its spatial expression includes skeletal muscles, pancreas and brain	CDKAL1	[26,38]
SLCO1B3	12p12.2 (17 Exon)	It is mainly expressed in liver cells, and also expressed in pancreas	OATP1B3 (OATP8)	[26,39,40,41]

Potassium voltage-gated channel KQT-like subfamily, member 1 (*KCNQ1*)

The human gene *KCNQ1*, located on chromosome 11p15.5, spans 404 kb and comprises 16 exons, encoding the pore-forming subunit of a voltage-gated potassium (K+) channel (KVLQT1), known as Kv7.1 [53].

KCNQ1 is predominantly expressed in cardiac tissues and pancreatic islets, which plays a crucial role in regulating insulin secretion [28]. The *KCNJ11* gene has been linked to the development of type 2 diabetes mellitus (T2DM) and its vascular complications [54]. Genetic variations in *KCNQ1* have been associated with fasting glucose levels and β-cell function [55].

Recent studies have highlighted a significant correlation between polymorphisms in the *KCNQ1* gene and the therapeutic response to SUs, including variants such as rs2237897, rs2237895, rs2237892, and rs163184. Variations in the *KCNQ1* gene have been shown to impact the response to SU treatment in addition to metformin in T2DM patients [55].

The rs2237895 polymorphism in *KCNQ1* gene was found to influence the therapeutic response to SUs in Iranian and Chinese patients [24,56]. Whereas *KCNQ1* rs2237892 polymorphism was associated with SU response in Chinese patients [56], but not in Iranian patients[24]. A common variant of *KCNQ1*, rs2237897, showed association with the efficacy of gliclazide in newly diagnosed Chinese T2DM patients [57].

ATP-binding cassette transporter sub-family C member 8 (*ABCC8*), Potassium Inwardly Rectifying Channel Subfamily J Member 11 (*KCNJ11*)

The *KCNJ11* and *ABCC8* genes are located on chromosome 11p15.1, and encode the Kir6.2 subunit and the sulfonylurea receptor 1 (SUR1) regulatory subunit of the KATP channel, respectively [58]. *ABCC8* comprises 39 exons encode for the 1,582 amino acids of SUR [59], which is crucial for insulin secretion regulation [60]. *KCNJ11*, located 4.5 Kb away from *ABCC8*, has a single exon encodes for the 390 amino acids of Kir6.2 protein [59].
SUR-1 and Kir6.2 proteins are important for KATP channel function, and mutations in *ABCC8* and *KCNJ11* genes can disrupt their activity [17]. Mutations in these genes impact K-ATP channel dynamics in beta cells' membranes, leading to impaired insulin secretion, and affecting response to SUs through the SU binding region in SUR [23].

However, a previous study in Iran found no association between the *ABCC8* rs757110 variant and response to SU [61]. Another study indicated that the rs757110 variant did not influence the response to

metformin and glimepiride combination therapy in Egyptian T2DM patients [62]. The *ABBC8* rs1799854 variant also did not significantly impact the response to SU treatment in Iranian and Indonesian T2DM patients [61,63].

Various SNPs of the *KCNJ11* gene have been identified, with the rs5219 polymorphism being particularly noteworthy for glycemia regulation [17]. This rs5219 variant was identified as a key SNP associated with an increased risk of developing T2DM in the Kinh Vietnamese population [64]. The rs5219 variant in the *KCNJ11* gene was linked to therapeutic response to SU in Slovakian patients [65], while another study found no association between this polymorphism and response to SU in Indonesian patients [66].

Transcription factor 7-like 2 (*TCF7L2*):

The human *TCF7L2* gene, located on chromosome 10q25.3, consists of 18 exons with a complex splicing pattern across various tissues [67]. It plays a role in regulating of biosynthesis, the secretion of insulin in pancreatic beta cells [68].

TCF7L2 is considered the most significant genetic locus associated with the risk of developing T2DM, and has been consistently identified in diverse populations [67].

Numerous studies have shown that polymorphisms in the *TCF7L2* gene are associated with increased susceptibility to T2DM [68]. Specifically, the intronic single nucleotide polymorphisms (SNPs) rs7903146 (C/T) and rs12255372 (G/T) within the *TCF7L2* gene are strongly associated with T2DM risk [68]. Furthermore, variants of *TCF7L2* have been shown to impact the initial response to SUs [67].

The *TCF7L2* rs12255372 SNP was linked to poor response to SU in Egyptian patients [69], and also correlated with therapeutic success with SUs in Indian T2DM patients [70].

Additionally, the *TCF7L2* rs7903146 polymorphism influenced response to SU in German [71] and Slovakian patients [72], but not in Indian patients [70]. Moreover, genotype may influence the response to SU. TT homozygotes of rs4506565 showed association with increased treatment failure in Indian patients receiving SUs [70].

Insulin receptor substrate-1 (*IRS1*)

The *IRS1* is located on the chromosome 2p36.3 [31]. It encodes a protein, that is phosphorylated by the insulin receptor tyrosine kinase [73].

IRS plays a pivotal role in insulin signaling, and is essential for maintaining fundamental cellular functions such as, survival, development, and digestion system [73].

Dysfunction of *IRS-1* can lead to impaired insulin signaling. Genetic variations in *IRS-1*, such as the glycine to arginine change at codon 972 (rs1801278), may contribute to the development of insulin resistance [74]. However, no significant association was found between this variant and the response of Egyptian patients to SUs [75].

Cdk5 regulatory associated protein 1-like 1 (*CDKAL1*):

The human *Cdkal1* gene is located on chromosome 6p22.3 [38]. The *CDKAL1* gene encodes cyclin-dependent kinase 5 regulatory subunit-associated protein 1 (CDK5RAP1)-like 1. CDK5 is involved in the glucose-dependent regulation of insulin secretion [76].

CDKAL1 has been associated with the development of T2DM, and may be targeted for therapeutic purposes [38]. It plays an important role in regulation of insulin secretion by pancreatic beta cells [77].

Research from Slovakia showed association between the *CDKAL1* rs7756992 polymorphism, and the response of Slovakian patients with T2DM to SU treatment, showing a correlation with the reduction in fasting plasma glucose levels after six months of SU treatment [78]. Another study from Iran found a significant association between the *CDKAL1* rs7754840 variant and the response to SU therapy [79].

Cyclin-dependent kinase inhibitor 2A (*CDKN2A*), and Cyclin-Dependent Kinase Inhibitor 2B (*CDKN2B*):

The *CDKN2A* gene, located on chromosome 9p21.3, is a tumor suppressor gene [34], that encodes the proteins $p16^{INK4A}$ and $p14^{ARF}$ [35]. These proteins play a crucial role in regulating cell cycle pathways [80]. Similarly, the *CDKN2B* gene, located on human chromosome 9p21.3, encodes $p15^{INK4B}$, which acts as a cell-cycle regulator inhibiting cyclin-dependent kinases CDK4 and CDK6 [36].

These proteins function as cyclin-dependent kinase inhibitors involved in various cellular processes such as inflammation, cell cycle regulation, apoptosis, senescence, aging, DNA damage response, and extracellular matrix remodeling [81].

Specific gene polymorphisms within the *CDKN2A/B* genes have been associated with an increased predisposition to T2DM. For instance, the *CDKN2A/B* rs10811661 was shown to be associated with the pathogenesis of T2DM in the Iraqi population. It also affected insulin level in those patients [35]. Furthermore, *CDKN2A* has been identified as a critical regulator of glucose homeostasis in humans [82].

Previous studies have suggested that the *CDKN2A/CDKN2B* genes may be linked to the efficacy of glibenclamide. Participants carrying the minor allele C of rs10811661 in *CDKN2A/CDKN2B* exhibited a significantly greater reduction in fasting blood glucose levels. Additionally, a significant difference in ß-cell function has been observed among carriers of different genotypes of rs10811661 [83].

Solute carrier organic anion transporter family member 1B1 (SLCO1B1**)/ 1B3 (*SLCO1B3*):**

The *SLCO1B3* gene, also known as organic anion transporting polypeptide (OATP) 1B3 [39], is located on human chromosome 12p12-31.7 to 12p12-37.2, and encodes a transmembrane protein composed of 702 residues [39]. It is mainly expressed in the liver cells' basement membrane around the central vein [40]. It is also expressed in pancreas, the SU target organ, and it enhances the insulinotropic effect of SU [41].

Similarly, the *SLCO1B1* gene, located on the short arm of chromosome 12, encodes the OATP1B1 protein comprising 691 amino acids [84.]

The hepatic transporters, OATP1B1 and OATP1B3, play a crucial role in drug disposition by facilitating the uptake of various drugs from blood into hepatocytes [85]. Genetic variations affecting transport activity may impact the efficacy of SU [86].

Research has indicated a potential interaction between SU and rosuvastatin, a common substrate of OATP1B1 and OATP1B3 often used in combination with SUs, mediated by these transporters [85].

Previous studies have shown that glibenclamide and glipizide are substrates of OATP1B3, while gliclazide and glimepiride are substrates of OATP1B1[87]. The OATP1B3 variant (699G > A) significantly influences the transport and metabolism of glibenclamide and glipizide [87].

Recent research highlighted SLCO1B3 as a key determinant of the insulinotropic effect of glibenclamide at the tissue level [88]. However, a study from China found no association between the SLCO1B3 variant rs4149117 and SU effectiveness [88].

Polymorphisms in the SLCO1B1 gene can lead to complete or partial loss of OATP1B1 function, altering the pharmacokinetic profile of substrates [89]. The C allele of rs10770791 in an intronic region of SLCO1B1 was linked to a 0.11% greater reduction in HbA1c following glipizide treatment [90].

In (**Table 2**), we compiled several studies conducted to detect the association between the gene polymorphism, and SU response in T2DM patients. Inconsistent results for different variants may be attributed to factors such as insufficient sample size, and differences in study design, gender, age, lifestyle, ethnicity, concomitant use of other medications, etc **[91]**.

Pharmacogenetics of sulfonylurea-induced hypoglycemia in T2DM:

Hypoglycemia is a common complication of antidiabetic medications, such as SUs [91]. The United Kingdom Prospective Diabetes Study reported that 17% of patients taking SUs experienced at least one hypoglycemic event annually [93].

Some individuals metabolize the drug slowly, leading to higher levels of the drug in their bloodstream over time, which can result in prolonged hypoglycemic effects [94]. SU acts by lowering the level of blood glucose by increasing insulin secretion in the pancreas, and by blocking the ATP-sensitive potassium channels [92]. Consequently, patients with T2DM receiving SU therapy are at risk for hypoglycemia [95].

Several patient characteristics, including sex, age, food interactions, and comorbidities, have been reported to influence hypoglycemia risk. Other established risk factors for SU-induced hypoglycemia are low hemoglobin level, polypharmacy, and the use of long-acting SU [93].

Since the increased risk of hypoglycemia with SU therapy increases with higher drug concentrations, genetic variations impacting drug clearance and effectiveness, can lead to interindividual variability in risk [95].

Specifically, common variants such as *CYP2C9*2* (Arg144Cys, rs1799853) and *CYP2C9*3* (Ile359Leu, rs1057910) are known to impair the catalytic function of the *CYP2C9* enzyme, affecting the metabolism of SUs, and potentially elevating the likelihood of SU-induced hypoglycemia [93]. A study conducted in Pakistan further supported the association between the *CYP2C9*2* variant and hypoglycemia induced by SUs [94].

However, findings regarding the association between *CYP2C9*2* genotypes and SU-induced hypoglycemia are inconsistent. A Greek study found no association between the *CYP2C9*2* variant and SU-induced hypoglycemia in T2DM patients treated with SUs [96].

Similarly, a study in European American T2DM patients did not detect association between reduced-function *CYP2C9* alleles and SU-related hypoglycemia [95].

These discrepancies in results may be attributed to differences in study design, including variations in hypoglycemia definitions, the age of participants, specific SUs analyzed, and limited statistical power due to small sample sizes [94].

The *SLCO1B1* c.521C variant was shown to have a protective effect on SU-related hypoglycemia risk independently and in interaction with *CYP2C9* phenotypes [41].

On the other hand, variants like *TCF7L2* rs7903146 and *KCNJ11* E23K were shown to be not associated with SU-induced hypoglycemia in T2DM([97],[98]).

The effect of genetic polymorphisms on the development of secondary failure to SUs

Treatment with SUs is initially successful in T2DM **[99]**. However, it has been observed that each year 5–7% of diabetic patients undergoing SU therapy convert to insulin treatment progressively as SU fails. This clinical phenomenon is known as "secondary failure to SU", posing a significant challenge in the management

Table 2. Genetic variants that have been tested for association with response to SU therapy in T2DM patients.

Gene	Protein	Polymorphism	Rs number	Patient	Age	SEX	Duration of treatment	Population	outcome	Ref
CYP2C9	CYP2C9	C\A	Rs 1067910	30	From 30 to 60 years	15 females 15 males	33.1 ± 22.9 months	Iran	The therapeutic response to SU was not significantly related to of CYP2C2 rs 1057910 genetic variant	[22]
KCNQ1	BWRT	C\A	Rs 2237895	100 patient (50 responder, 50 non-responder)	Between 20 to 60 years.	68 Females, 32 Males	6 months	Iran	The KCNQ1 rs2237895 polymorphism is associated with the response to SU in Iranian T2DM patients	[24]
ABCC8	SUR1	G\A C\A	Rs 1799854 Rs 757110	61	Between 35 to 80 years	31 Males 30 Females	-	Iran	The rs 1799854 and rs 757110 variants in the ABCC8 gene had no significant influence on response to SUs treatment	[61]
TCF7L2	TCF7L2	G\T	Rs 12255372	47	Between 53 to 66 years	13 Male 34 Female	3 months	Egypt	The TCF7L2 rs 12255372 gene polymorphism is associated with poor therapeutic response to oral antidiabetic agents	[69]
KCNQ1	BWRT	C\T A\C	Rs 2237892 Rs 2237895	44 33	-	31 Male 13 Female 19 Male 14 Female	16 Weeks	China	The KCNQ1 polymorphism is associated with gliclazide efficacy	[56]
IRS-1	PHIP 9	G\A	Rs 1801278	81 49) Non responder, 32 Responder)	Between 40 to 70 years	-	-	Egypt	The ISR-1 gene did not have a significant positive effect on patient response to SUs	[75]
CDKN2A\ CDKN2B	CDK4\ CDK4B	T\C	Rs 10811661	747	-	-	48 Weeks	China	Participants with the minor allele C of rs10811661 in CDKN2A/CDKN2B showed a significantly greater reduction in fasting blood glucose	[83]
TCF7L2	TCF-4	T\C	Rs 7903146	92	-	45 Male 47 Female	6 Months	Germany	The TCF7L2 rs7903146 variant is associated with an altered hypoglycemic response to SUs	[71]
CDKAL1	CDK5	A\G	Rs 7756992	101	-	50 Males 51 Female	6 Months	Slovensko	The reduction of fasting plasma glucose after six months of SU treatment is related to the variation in CDKAL1 in T2DM patients	[78]
CDKAL1	CDK5	C\G	Rs 7754840	102 (51 sensitive, 51 resistant)	-	-	12 Months	Iran	The genotypes of rs7754840 are significantly associated with response to SU treatment	[79]
SLCO1B3	Ber-1b3	T\G	Rr 4149117	184	-	-	48 Week	China	The rs 4149117 in the gene SLCO1B3 is not associated with SU efficacy	[88]
TCF7L2	TCF-4\ TCF7L2	G\T	Rs 12255372	250	-	110 Males, 140 Females	-	India	The rs 12255372 has a direct correlation with response to SU	[70]

of T2DM patients. Various factors have been linked to secondary failure to SUs, including changes in body weight, inadequate dietary control, young age at diagnosis, deteriorating insulin sensitivity, and the presence of anti-islet cell and antibodies to glutamic acid decarboxylase (anti-GAD) antibodies [100].

The deterioration of beta-cell function due to prolonged overstimulation is believed to be a contributing factor to secondary SU failure [101].

Cyb5r3, involved in regulating glucose utilization in β-cells by enhancing the stability of glucokinase, the key enzyme in glycolysis, has been implicated in the mechanism of secondary SU failure. Studies have shown that the functional loss of oxidoreductase Cyb5r3 affects SU failure through its interactions with glucokinase [102].

Genetic variants have also been associated with an increased risk of secondary failure to SUs. For instance, the common polymorphism in the pore-forming KATP channel subunit (E23K) variant of the Kir6.2 gene and the Arg972 *IRS-1* variants have been linked to increased risk of secondary failure to SUs [99].

The Arg972 *IRS-1* variant is shown to be associated with increased risk for secondary failure to SU [100]. Additionally, the Kir6.2 E23K polymorphism has been suggested to accelerate secondary SU failure in non-obese Japanese T2DM patients [101].

A previous study showed that the *TCF7L2* rs7903146 variant is associated with hypoglycemic response to SUs, resulting in earlier secondary failure [71]. Furthermore, the rs757110 *ABCC8* gene polymorphism has been identified as an independent predictor of secondary SU failure [103].

CONCLUSION

In the current review, we explore recent advancements in research on the pharmacogenetics of SUs. Our analysis suggests that genetic variations could significantly influence the response to SU therapy, the risk of hypoglycemia associated with SUs, and the occurrence of secondary failure. However, the review reveals conflicting outcomes for different genes/variants that may be due to the heterogeneity among previous studies. Consequently, translating these findings into clinical practice presents a substantial challenge, underscoring the critical need for more extensive and standardized investigations to generate precise data. Such data can then be leveraged to advance precision medicine for T2DM, ultimately improving patient outcomes.

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Conflict of interest

The author declares that there isn't any conflict of interest regarding the publication of this paper.

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