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. Genetic factors play a significant role in the development of T2DM, particularly in individuals with a family history of diabetes. It is estimated that between 35% and 70% of T2DM cases have a genetic predisposition.

The healthcare field is experiencing the rise of "personalized medicine" as a promising direction. 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. 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. This innovative strategy shows great potential in transforming diabetes management and enhancing patient outcomes.

Metformin is commonly prescribed as the first-line pharmacotherapy for T2DM. In cases where patients are unable to tolerate metformin, sulfonylurea (SU), is used as the first-line drug of choice. SU is a class of oral hypoglycemic medications, with first-generation drugs including tolbutamide, acetohexamide, tolamazide, and chlorpropamide, and second-generation drugs including glimepiride, gliclazide, glipizide, and glyburide. Both generations of SUs have shown significant reductions in glycosylated hemoglobin levels.

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 SU response, SU-induced hypoglycemia, and the development of secondary failure to this drug among T2DM patients.

**METHODS**


**Mechanism of action of SUs:**

It is widely accepted that chronic hyperglycemia, the main diagnostic marker of T2DM, results from the failure of pancreatic β-cell, leading to a gradual decrease in beta-cell mass and insulin production in response to glucose. 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. 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. Structurally, Kir6.2 and SUR1 consists of four pore-forming subunits surrounding the pore of the KATP channel on the plasma membrane of pancreatic β-cell. The closure of these channels initiates insulin secretion, while their opening inhibits it.

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. 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.

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

**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.

**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. Genetic factors account for 20%–95% of the differences in drug responses between individuals, as genetic variations can influence drug absorption, distribution, metabolism, targeting, and efficacy.
Genomic differences arise from genetic variations like single nucleotide polymorphisms (SNPs), insertions and deletions, or copy number variations. In the field of pharmacogenomics, studies on SU have highlighted several gene variants associated with treatment outcomes, such as CYP2C9, KCNJ1, 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. It is the predominant isoform of CYP2C in the liver, constituting approximately 20% of hepatic CYP proteins. The CYP2C9 gene, located on chromosomal region 10q23.33, spans about 55 kb with nine exons encoding a protein comprising 490 amino acids. 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.

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

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. Similarly, in Khyber Pakhtunkhwa Pakistan, a modest non-significant impact of this polymorphism on T2DM susceptibility was reported. 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. Another study in Chinese patients revealed that the CYP2C9*3 rs1057910 polymorphism significantly influenced the therapeutic response to gliclazide in T2DM patients. Furthermore, Lebanese individuals with the CYP2C9*3 variant exhibited maximum glycemic control when treated with a combination of metformin and SU.

Regarding the CYP2C9*2 (rs1799853) variant, Egyptian T2DM patients with the CYP2C9*2/*3 genotype demonstrated improved glycemic control with glibenclamide treatment. Conversely, a study in Poland did not find any association between the CYP2C9*2 variant and the therapeutic response to SUs in T2DM patients. 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.
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 K\textsuperscript{v}7.1.\textsuperscript{53} KCNQ1 is predominantly expressed in cardiac tissues and pancreatic islets, which plays a crucial role in regulating insulin secretion.\textsuperscript{28} The KCNQ1 gene has been linked to the development of type 2 diabetes mellitus (T2DM) and its vascular complications.\textsuperscript{54} Genetic variations in KCNQ1 have been associated with fasting glucose levels and \( \beta \)-cell function.\textsuperscript{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.\textsuperscript{55} The rs2237895 polymorphism in KCNQ1 gene was found to influence the therapeutic response to SUs in Iranian and Chinese patients.\textsuperscript{24,56} Whereas KCNQ1 rs2237892 polymorphism was associated with SU response in Chinese patients,\textsuperscript{56} but not in Iranian patients.\textsuperscript{24} A common variant of KCNQ1, rs2237897, showed association with the efficacy of gliclazide in newly diagnosed Chinese T2DM patients.\textsuperscript{57}

ATP-binding cassette 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.\textsuperscript{58} ABCC8 comprises 39 exons encode for the 1,582 amino acids of SUR, which is crucial for insulin secretion regulation.\textsuperscript{60} KCNJ11, located 4.5 Kb away from ABCC8, has a single exon encodes for the 390 amino acids of Kir6.2 protein.\textsuperscript{26} SUR-1 and Kir6.2 proteins are important for KATP channel function, and mutations in ABCC8 and KCNJ11 genes can disrupt their activity.\textsuperscript{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.\textsuperscript{33} However, a previous study in Iran found no association between the ABCC8 rs757110 variant and response to SU.\textsuperscript{61} Another study indicated that the rs757110 variant did not influence the response to SUs in Iranian patients.\textsuperscript{62}
metformin and glimepiride combination therapy in Egyptian T2DM patients. The ABCB8 rs1799854 variant also did not significantly impact the response to SU treatment in Iranian and Indonesian T2DM patients.

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

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. It plays a role in regulating of biosynthesis, the secretion of insulin in pancreatic beta cells. TCF7L2 is considered the most significant genetic locus associated with the risk of developing T2DM, and has been consistently identified in diverse populations. Numerous studies have shown that polymorphisms in the TCF7L2 gene are associated with increased susceptibility to T2DM. Specifically, the intronic single nucleotide polymorphisms (SNPs) rs7903146 (C/T) and rs12255372 (G/T) within the TCF7L2 gene are strongly associated with T2DM risk. Furthermore, variants of TCF7L2 have been shown to impact the initial response to SUs.

The TCF7L2 rs12255372 SNP was linked to poor response to SU in Egyptian patients, and also correlated with therapeutic success with SUs in Indian T2DM patients. Additionally, the TCF7L2 rs7903146 polymorphism influenced response to SU in German and Slovakian patients, but not in Indian patients. Moreover, genotype may influence the response to SU. TT homozygotes of rs4506565 showed association with increased treatment failure in Indian patients receiving SUs.

Insulin receptor substrate-1 (IRS1)

The IRS1 is located on the chromosome 2p36.3. It encodes a protein, that is phosphorylated by the insulin receptor tyrosine kinase. IRS plays a pivotal role in insulin signaling, and is essential for maintaining fundamental cellular functions such as, survival, development, and digestion system.

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. However, no significant association was found between this variant and the response of Egyptian patients to SUs.

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

The human Cdkal1 gene is located on chromosome 6p22.3. 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. CDKAL1 has been associated with the development of T2DM, and may be targeted for therapeutic purposes. It plays an important role in regulation of insulin secretion by pancreatic beta cells.

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. Another study from Iran found a significant association between the CDKAL1 rs7754840 variant and the response to SU therapy.

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, that encodes the proteins p16INK4A and p14ARF. These proteins play a crucial role in regulating cell cycle pathways. Similarly, the CDKN2B gene, located on human chromosome 9p21.3, encodes p15INK4B, which acts as a cell-cycle regulator inhibiting cyclin-dependent kinases CDK4 and CDK6.

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.

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. Furthermore, CDKN2A has been identified as a critical regulator of glucose homeostasis in humans.

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 β-cell function has been observed among carriers of different genotypes of rs10811661.

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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 34.

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.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Polymorphism</th>
<th>Rs number</th>
<th>Patient</th>
<th>Age</th>
<th>SEX</th>
<th>Duration of treatment</th>
<th>Population</th>
<th>Outcome</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td>CYP2C9</td>
<td>C/A</td>
<td>Rs 1067910</td>
<td>30</td>
<td>From 30 to 60 years</td>
<td>15 females, 15 males</td>
<td>33.1 ± 22.9 months</td>
<td>Iran</td>
<td>The therapeutic response to SU was not significantly related to of CYP2C2 rs 1057910 genetic variant</td>
<td>(22)</td>
</tr>
<tr>
<td>KCNQ1</td>
<td>BWRT</td>
<td>C/A</td>
<td>Rs 2237895</td>
<td>100</td>
<td>Between 20 to 60 years</td>
<td>68 Females, 32 Males</td>
<td>6 months</td>
<td>Iran</td>
<td>The KCNQ1 rs2237895 polymorphism is associated with the response to SU in Iranian T2DM patients</td>
<td>(24)</td>
</tr>
<tr>
<td>ABCC8</td>
<td>SUR1</td>
<td>G/A, C/A</td>
<td>Rs 1799854, Rs 757110</td>
<td>61</td>
<td>Between 35 to 80 years</td>
<td>31 Males, 30 Females</td>
<td>-</td>
<td>Iran</td>
<td>The rs 1799854 and rs 757110 variants in the ABCC8 gene had no significant influence on response to SUs treatment</td>
<td>(41)</td>
</tr>
<tr>
<td>TCF7L2</td>
<td>TCF7L2</td>
<td>G/T</td>
<td>Rs 12255372</td>
<td>47</td>
<td>Between 53 to 66 years</td>
<td>13 Male, 34 Female</td>
<td>3 months</td>
<td>Egypt</td>
<td>The TCF7L2 rs 12255372 gene polymorphism is associated with poor therapeutic response to oral antidiabetic agents</td>
<td>(68)</td>
</tr>
<tr>
<td>KCNQ1</td>
<td>BWRT</td>
<td>C/T, A/C</td>
<td>Rs 2237892, Rs 2237895</td>
<td>44</td>
<td>-</td>
<td>31 Male, 13 Female, 19 Male, 14 Female</td>
<td>16 Weeks</td>
<td>China</td>
<td>The KCNQ1 polymorphism is associated with gliclazide efficacy</td>
<td>(68)</td>
</tr>
<tr>
<td>IRS-1</td>
<td>PHP 9</td>
<td>G/A</td>
<td>Rs 1801278</td>
<td>81</td>
<td>Between 40 to 70 years</td>
<td>-</td>
<td>-</td>
<td>Egypt</td>
<td>The ISR-1 gene did not have a significant positive effect on patient response to SUs</td>
<td>(75)</td>
</tr>
<tr>
<td>CDKN2A/CDKN2B</td>
<td>CDK4A/CDK4B</td>
<td>T/C</td>
<td>Rs 10811661</td>
<td>747</td>
<td>-</td>
<td>-</td>
<td>48 Weeks</td>
<td>China</td>
<td>Participants with the minor allele C of rs10811661 in CDKN2A/CDKN2B showed a significantly greater reduction in fasting blood glucose</td>
<td>(65)</td>
</tr>
<tr>
<td>TCF7L2</td>
<td>TCF-4</td>
<td>T/C</td>
<td>Rs 7903146</td>
<td>92</td>
<td>-</td>
<td>45 Male, 47 Female</td>
<td>6 Months</td>
<td>Germany</td>
<td>The TCF7L2 rs7903146 variant is associated with an altered hypoglycemic response to SUs</td>
<td>(71)</td>
</tr>
<tr>
<td>CDKAL1</td>
<td>CDK5</td>
<td>A/G</td>
<td>Rs 7756992</td>
<td>101</td>
<td>-</td>
<td>50 Males, 51 Female</td>
<td>6 Months</td>
<td>Slovensko</td>
<td>The reduction of fasting plasma glucose after six months of SU treatment is related to the variation in CDKAL1 in T2DM patients</td>
<td>(78)</td>
</tr>
<tr>
<td>CDKAL1</td>
<td>CDK5</td>
<td>C/G</td>
<td>Rs 7754840</td>
<td>102</td>
<td>(51 sensitive, 51 resistant)</td>
<td>-</td>
<td>-</td>
<td>12 Months</td>
<td>Iran</td>
<td>The genotypes of rs7754840 are significantly associated with response to SU treatment</td>
</tr>
<tr>
<td>SLCO1B3</td>
<td>Ber-1b3</td>
<td>T/G</td>
<td>Rs 4149117</td>
<td>184</td>
<td>-</td>
<td>-</td>
<td>48 Week</td>
<td>China</td>
<td>The rs 4149117 in the gene SLCO1B3 is not associated with SU efficacy</td>
<td>(80)</td>
</tr>
<tr>
<td>TCF7L2</td>
<td>TCF7L2</td>
<td>G/T</td>
<td>Rs 12255372</td>
<td>250</td>
<td>-</td>
<td>110 Males, 140 Females</td>
<td>-</td>
<td>India</td>
<td>The rs 12255372 has a direct correlation with response to SU</td>
<td>(98)</td>
</tr>
</tbody>
</table>
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.  

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

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. 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.

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

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

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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