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Sulfonylurea pharmacogenomics in Type 2 diabetes: the influence of drug target and diabetes risk polymorphisms

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Abstract

The sulfonylureas stimulate insulin release from pancreatic β cells, and have been a cornerstone of Type 2 diabetes pharmacotherapy for over 50 years. Although sulfonylureas are effective antihyperglycemic agents, interindividual variability exists in drug response (i.e., pharmacodynamics), disposition (i.e., pharmacokinetics) and adverse effects. The field of pharmacogenomics has been applied to sulfonylurea clinical studies in order to elucidate the genetic underpinnings of this response variability. Historically, most studies have sought to determine the influence of polymorphisms in drug-metabolizing enzyme genes on sulfonylurea pharmacokinetics in humans. More recently, polymorphisms in sulfonylurea drug target genes and diabetes risk genes have been implicated as important determinants of sulfonylurea pharmacodynamics in patients with Type 2 diabetes. As such, the purpose of this review is to discuss sulfonylurea pharmacogenomics in the setting of Type 2 diabetes, specifically focusing on polymorphisms in drug target and diabetes risk genes, and their relationship with interindividual variability in sulfonylurea response and adverse effects.

Keywords

drug target; *KCNJ11*; pharmacogenomic; sulfonylurea; SUR1; *TCF7L2*; Type 2 diabetes

Overview of Type 2 diabetes pharmacotherapy

The prevalence of diabetes is increasing at an alarming rate, affecting over 250 million individuals worldwide [101]. In adults, Type 2 diabetes is the most prevalent form, accounting for 90–95% of the worldwide cases of diabetes [101]. In terms of pathophysiology, Type 2 diabetes is characterized by decreased insulin secretion from pancreatic β cells and decreased tissue responsiveness to the normal action of insulin (i.e., insulin resistance). Over time, declining β -cell function and insulin resistance lead to the inability to maintain normoglycemia, and hyperglycemia ensues [1].

Chronic hyperglycemia, as a result of Type 2 diabetes, has many long-term adverse consequences. Chronic hyperglycemia results in microvascular complications such as

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retinopathy, nephropathy and neuropathy, and macrovascular complications such as cardiovascular disease, stroke and peripheral vascular disease. Given these long-term complications, the goal of Type 2 diabetes treatment in men and nonpregnant women is to obviate periods of poor glycemic control and maintain glycated hemo globin (Hb_{A1c}) levels of less than 7% [2]. Lowering glucose to near-nondiabetic levels in patients with Type 2 diabetes has been shown to reduce the risk of microvascular complications [3-5]. In terms of the prevention of macrovascular complications, the United Kingdom Prospective Diabetes Study (UKPDS) showed a nonsignificant 16% reduction in the risk of myocardial infarction in the group of Type 2 diabetes patients receiving intensive glucose control [3]. Furthermore, in the intensive glucose control group, 10-year follow-up showed a reduction in the risk of myocardial infarction and death from any cause over time [6]. Recently, some trials have investigated the effect of more intensive glucose control (e.g., Hb_{A1c} ≤6.0 or ≤6.5%) on cardiovascular events in patients with Type 2 diabetes [7-9]. However, the results have largely shown no benefit on major cardiovascular end points, and in the case of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, an increased risk of mortality associated with intensive glucose control [7-9]. By contrast, two recently published meta-analyses showed that, compared with conventional glucose control, intensive glucose control reduced the risk of some cardiovascular end points (e.g., nonfatal myocardial infarction) [10,11]. However, intensive glucose control was also associated with a higher incidence of weight gain and severe hypoglycemia compared with the conventional glucose control groups [10,11].

Based on existing data at the time regarding the association between glucose control and the prevention of microvascular and macrovascular complications, the 2009 American Diabetes Association Standards for Medical Care in Diabetes recommends a Hb_{A1c} goal of less than 7% in most patients with Type 2 diabetes. There are numerous nonpharmacologic and pharmacologic treatment modalities to achieve and maintain normoglycemia. Lifestyle interventions, such as diet and exercise, are effective; however, long-term adherence is typically poor. Furthermore, lifestyle interventions have a modest durability in the face of worsening glycemia over time [12]. As such, most patients with Type 2 diabetes will require one or more antidiabetic drug therapies to manage their hyperglycemia. Available pharmacologic agents are listed in Table 1 and include biguanides, insulin, sulfonylureas, thiazolidinediones, glucagon-like peptide 1 analogs, α -glucosidase inhibitors, nonsulfonylurea insulin secretagogues, amylin agonists and dipeptidyl peptidase (DPP)-4 inhibitors [12].

Given the variety of pharmacologic treatment options, the American Diabetes Association and the European Association for the Study of Diabetes recently published a consensus statement providing guidance on the management of hyperglycemia in adults with Type 2 diabetes [12]. In this consensus statement, therapies are divided into tiers, and the tiers are further divided into steps. Tier 1 represents well-validated core therapies that are established, clinically effective and cost effective. Tier 1 therapies include lifestyle interventions to decrease weight and increase physical activity, metformin, sulfonylureas and insulin. Tier 2 represents less well-validated therapies such as thiazolidinediones, pioglitazone and the glucagon-like peptide 1 analog, exenatide. Medications that fall into the 'other therapy' category are those not recommended in tier 1 or 2 approaches, and include α -glucosidase inhibitors, nonsulfonylurea insulin secretagogues, pramlintide and DPP-4 inhibitors.

The tiered drug treatment approach serves as a useful guidance for the pharmacotherapeutic management of Type 2 diabetes. However, it does not solve the problem that substantial interindividual variability exists in antidiabetic drug disposition and response. As such, the field of pharmacogenomics has recently been applied to the treatment of Type 2 diabetes.

The goal of pharmacogenomics is to elucidate the relationship between variants in the human genome (i.e., polymorphisms) and variability in the effects of drugs [13]. It is anticipated that pharmacogenomics will improve the use of drug therapy in Type 2 diabetes by identifying genetic predictors of metabolic response, clinical outcomes and adverse effects (Figure 1). Sulfonylureas are in the tier 1 category and have been a mainstay of Type 2 diabetes pharmacotherapy for over 50 years. It is well recognized that interindividual variability exists in sulfonylurea response (i.e., pharmacodynamics), disposition (i.e., pharmacokinetics) and adverse effects. The field of pharmacogenomics has been applied to sulfonylurea clinical studies in order to elucidate the genetic underpinnings of this response variability. Historically, most studies have sought to determine the influence of polymorphisms in drug-metabolizing enzyme genes on sulfonylurea pharmacokinetics in humans. More recently, polymorphisms in sulfonylurea drug target genes and diabetes risk genes have been implicated as important determinants of sulfonylurea pharmacodynamics in patients with Type 2 diabetes. As such, the purpose of this article is to discuss sulfonylurea pharmacogenomics in the setting of Type 2 diabetes, specifically focusing on polymorphisms in drug target and diabetes risk genes, and their relationship with interindividual variability in sulfonylurea response and adverse effects. For comprehensive reviews of the influence of drug-metabolizing enzyme and drug-transporter polymorphisms on variability in sulfonylurea pharmacokinetics, the reader is referred to previous articles by Kirchheiner and colleagues [14] and Pacanowski and colleagues, respectively [15]. In addition, the focus of this present review is on sulfonylurea response in polygenic Type 2 diabetes. For a comprehensive discussion of the use and efficacy of sulfonylureas in patients who possess mutations that cause monogenic forms of diabetes, the reader is referred to articles by Murphy and colleagues [16] and Gloyn and colleagues [17].

Sulfonylurea clinical pharmacology

Mechanistically, the sulfonylureas bind to ATP-sensitive potassium (K_{ATP}) channels on pancreatic β cells. The K_{ATP} channel exists as a complex comprised of the sulfonylurea receptor 1 (SUR1), which is the regulatory subunit, and the inward-rectifier potassium ion channel (Kir6.2), which forms the pore of the channel. Four SUR1 subunits and four Kir6.2 subunits make up the K_{ATP} channel. The binding of sulfonylureas to SUR1 results in closure of the K_{ATP} channel, increased concentrations of intracellular potassium, depolarization of the β -cell membrane, and the subsequent opening of voltage-gated calcium channels. As calcium moves into the β cell, it stimulates the movement of insulin-containing secretory granules to the cell surface. These insulin-containing secretory granules are ultimately released from the β cell and into the circulation [18]. In short, sulfonylureas stimulate insulin release from pancreatic β cells in a glucose-independent manner.

The sulfonylurea drug class has evolved as different generations of agents. The first-generation sulfonylureas are the oldest, and include tolbutamide, tolazamide, chlorpropamide and acetohexamide. The second-generation sulfonylureas include glyburide (also known as glibenclamide), glipizide, gliclazide and glimepiride. All sulfonylureas have the same mechanism of action; however, the second-generation agents are more potent than the first-generation agents on a weight basis. Most sulfonylureas are extensively metabolized in the liver, primarily by the cytochrome P450 (CYP) 2C9 isoenzyme. The half-life of most sulfonylureas is relatively short, with the exception of chlorpropamide, which has a half-life of 24–48 h [19]. In terms of clinical response, the sulfonylureas, on average, lower HbA_{1c} by 1–2% [12]. As insulin secretagogues, the pharmacodynamic effects of sulfonylureas are dependent on functioning β cells; thus they are typically used earlier in the course of the disease process. In later stages of the disease, when β -cell dysfunction becomes most prevalent, sulfonylurea efficacy may decline and may necessitate an increase in drug dosage or the switch to other non-insulin secretagogue therapy. More recently,

studies in isolated rodent and human islets showed that sulfonylureas induce β -cell apoptosis [20–23]. As such, concern has been raised as to whether sulfonylureas may exacerbate the pathogenesis of Type 2 diabetes, particularly β -cell dysfunction in the later stages of the disease. However, at this time, no definitive *in vivo* conclusions have been drawn [23].

Given their mechanism of action, the most common adverse effect of sulfonylureas is hypoglycemia. Sulfonylurea-induced hypoglycemia is more likely to occur with the longer acting agents (e.g., chlorpropamide and glibenclamide), in patients with irregular eating habits, and in those who consume alcohol excessively [24]. Sulfonylureas should also be used with caution in patients who are unable to recognize the symptoms of hypoglycemia (e.g., those on concomitant β -blocker therapy or elderly patients). Weight gain, which is typically 1–4 kg, is another concern of sulfonylurea therapy, particularly given that many Type 2 diabetes patients are already overweight or obese [12,24]. Rare adverse effects include: cholestatic jaundice, skin rash, hemolytic anemia, thrombocytopenia, agranulocytosis, flushing (chlorpropamide) and hyponatremia (chlorpropamide) [24]. Sulfonylureas are susceptible to drug–drug interactions. Pharmacological interactions that may increase sulfonylurea plasma concentrations and glucose-lowering effects include drugs that displace sulfonylureas from plasma proteins (e.g., salicylates, sulfonamides, warfarin, phenylbutazone and fibric acid derivatives), decrease the hepatic metabolism of sulfonylureas (e.g., warfarin, monoamine oxidase inhibitors, chloramphenicol and phenylbutazone) and decrease the renal excretion of sulfonylureas (e.g., salicylates, probenecid and allopurinol) [24]. In addition, inducers of hepatic drug metabolism (e.g., rifampin) may decrease sulfonylurea plasma concentrations and efficacy.

There has been a long-standing debate regarding the potential of sulfonylureas to increase cardiovascular risk. This debate was spurred by the results of the University Group Diabetes Program study, which showed a higher incidence of cardiovascular mortality in patients treated with tolbutamide as compared with patients treated with insulin or placebo [25]. By binding to and closing pancreatic K_{ATP} channels, sulfonylureas promote insulin release. However, sulfonylureas also close myocardial K_{ATP} channels, which is proposed to abolish the protective effects of myocardial ischemic preconditioning [26]. Further complicating this issue, sulfonylureas are thought to have different selectivities for pancreatic versus cardiac K_{ATP} channels, which may confer differing effects on cardiovascular pathophysiology and risk [27]. Despite these mechanistic hypotheses, an increase in cardiovascular risk was not observed in UKPDS, where the myocardial infarction case–fatality rate was similar between sulfonylurea users and nonusers [28]. Along the same lines, there was no evidence of increased cardiovascular risk in the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial, which included an intensive glucose control strategy involving gliclazide (modified release) and other drugs as required [8]. Thus, while it has been documented that sulfonylureas have negative effects on the myocardium, these mechanistic findings have not consistently translated into an increased cardiovascular risk in large-scale clinical trials.

Interindividual variability in sulfonylurea response

Although the sulfonylureas are effective antihyperglycemic agents, interindividual variability exists in drug response. Definitions of sulfonylurea failure vary between clinical studies. However, it is estimated that 10–20% of patients will have less than a 20-mg/dl reduction in fasting plasma glucose following the initiation of sulfonylurea therapy (i.e., primary sulfonylurea failure) [29]. Approximately 50–60% of patients will initially have a greater than 30 mg/dl reduction in fasting plasma glucose, but will fail to reach the desired glycemic treatment goals [29]. For patients who have a good initial response to therapy, the rate of secondary sulfonylurea failure is approximately 5–7% per year [29]. Variability in

sulfonylurea response has also been demonstrated in large-scale randomized trials. For example, A Diabetes Outcome Progression Trial (ADOPT) showed that the incidence of sulfonylurea monotherapy failure (as defined by a fasting plasma glucose >180 mg/dl) at 5 years was 34% compared with 15% for rosiglitazone and 21% for metformin [30]. While some patients fail sulfonylurea therapy, other patients appear to be uniquely sensitive to the hypoglycemic effects of these agents. In the UKPDS study, 31% of patients experienced mild hypoglycemia during the first year of glibenclamide treatment [3]. Severe hypoglycemia with sulfonylurea therapy is less common, with a reported incidence of 1% per year in UKPDS [3]. Clinical factors, such as declining β -cell function, long-standing diabetes, high baseline glucose levels and a high degree of insulin resistance are known to predispose patients to sulfonylurea failure. Along the same lines, sulfonylurea-induced hypoglycemia may result from the duration of sulfonylurea action (e.g., the incidence of hypoglycemia is higher with chlorpropamide and glyburide), mild baseline hyperglycemia, irregular eating patterns, excessive alcohol intake and age.

Beyond these clinical variables, data suggest that genetic polymorphisms may contribute to the observed interindividual variability in sulfonylurea response, disposition and side effects. In terms of drug-metabolizing enzyme polymorphisms, *CYP2C9**3 (Ile359Leu) and to a lesser extent *CYP2C9**2 (Arg144Cys), influence the pharmacokinetics of many sulfonylureas [14]. Oral clearance of tolbutamide, glyburide (glibenclamide), glipizide and glimepiride is reduced in patients carrying a *CYP2C9**3 allele, resulting in decreased clearance and increased plasma drug exposure of most of these agents. For example, the oral clearance of tolbutamide was approximately 6.5-fold lower in *CYP2C9**3 homozygotes compared with wild-type homozygotes [31]. Similarly, glimepiride oral clearance in *CYP2C9**3 homozygotes was only half that of *CYP2C9* wild-type homozygotes [32]. The majority of *CYP2C9* sulfonylurea pharmacogenomic studies have been conducted in healthy volunteers; therefore, the extent to which changes in plasma sulfonylurea exposure, as a result of *CYP2C9* polymorphisms, affect sulfonylurea response and adverse effects in patients with Type 2 diabetes has not been comprehensively studied. However, one study in Type 2 diabetes patients showed that carriers of a *CYP2C9**3 allele required significantly lower tolbutamide doses than wild-type homozygotes [33]. A recent population-based study of incident sulfonylurea users found that Type 2 diabetes patients with *CYP2C9**2/*2, *2/*3 or *3/*3 genotypes were 3.4-times more likely to achieve a treatment Hb_{A1c} of less than 7% compared with *CYP2C9* wild-type homozygotes [34]. Furthermore, patients with at least one copy of the *CYP2C9**2 or *3 allele were less likely to experience sulfonylurea monotherapy treatment failure. *CYP2C9* polymorphisms may also serve as useful predictors of adverse effects. For example, a different study showed that sulfonylurea-treated patients who possessed the *CYP2C9**3/*3 or *2/*3 genotype had 5.2-times the odds of a severe hypoglycemic event than the other *CYP2C9* genotype groups [35]. While the findings that *CYP2C9* polymorphisms influence sulfonylurea response and adverse effects are intriguing, the utility of *CYP2C9* genotyping prior to initiating sulfonylurea therapy is unclear. Prospective studies in patients with Type 2 diabetes are warranted in order to discern whether *CYP2C9* genotyping is a useful tool to guide sulfonylurea dosing and treatment. In recent years, the field of sulfonylurea pharmacogenomics has expanded beyond just variation in drug-metabolism genes and now includes polymorphisms in drug target and diabetes risk genes, which will be the focus of this review hereafter.

Sulfonylurea drug target pharmacogenomics

As previously discussed, SUR1 and Kir6.2 are subunits that make up K_{ATP} channels. The SUR1 regulatory subunit is encoded by the ATP-binding cassette, subfamily C, member 8 (*ABCC8*) gene, while the Kir6.2 pore subunit is encoded by the potassium inwardly-rectifying channel, subfamily J, member 11 (*KCNJ11*) gene. The *ABCC8* and *KCNJ11* genes

are located in 4.5-kb proximity to each other on chromosome 11 [36]. Interest in *ABCC8* and *KCNJ11* as candidate pharmacogenomic genes in polygenic Type 2 diabetes has evolved from clinical experience with monogenic forms of diabetes [16,17]. In transient and permanent neonatal diabetes mellitus, activating mutations in *KCNJ11* and *ABCC8* cause an open K_{ATP} channel state, which promotes membrane hyperpolarization and impaired insulin release [37]. Sulfonylureas are useful in patients with some of these activating mutations as they promote K_{ATP} channel closure, which leads to calcium influx and insulin release [38,39]. By contrast, loss-of-function mutations in *KCNJ11* and *ABCC8* promote channel closure and insulin hypersecretion, and are associated with hyperinsulinemic hypoglycemia of infancy [37]. Mutations causing monogenic forms of diabetes are rare; thus, the search for common polymorphisms that explain variability in sulfonylurea response in polygenic Type 2 diabetes has been an emerging area of research in the field of Type 2 diabetes pharmacogenomics. Given that sulfonylureas interact with K_{ATP} channels, both *ABCC8* and *KCNJ11* are logical candidate drug-target genes to investigate in terms of drug response. A summary of the published *ABCC8* and *KCNJ11* sulfonylurea pharmacogenomic studies in patients with Type 2 diabetes is shown in Table 2.

SUR1 (ABCC8)

Some of the first data to suggest that the polymorphisms in *ABCC8* may alter the mechanism of action of sulfonylureas in patients with Type 2 diabetes came from a healthy volunteer study. Following mutational analysis of *ABCC8*, the combination of a synonymous polymorphism in exon 18 (Thr759Thr) and a C>T polymorphism at position -3 of the intron/exon 16 splice acceptor was associated with a 40% decrease in insulin secretion and a 50% decrease in serum C-peptide secretion following tolbutamide injection. There were no genotype differences in insulin or C-peptide secretion following intravenous glucose administration, which suggested that the observed diminished β -cell response following tolbutamide administration was possibly due to altered interactions of the ligand with its drug target [40]. When this hypothesis was tested in patients with Type 2 diabetes, the intron/exon 16 -3 polymorphism was not associated with differences in plasma glucose or insulin concentrations in patients receiving sulfonylureas compared with those on other therapies [41]. This population-based study did have limitations, with only one fasting blood sample drawn per patient. Thus, pre- and postglucose and insulin concentrations following sulfonylurea therapy were not available. Another observational study evaluated whether the frequency of the intron/exon 16 -3T allele differed in patients who had early sulfonylurea failure versus patients who had diabetes for at least 15 years and who were treated with sulfonylureas alone or in combination with metformin or acarbose [42]. No significant differences in intron/exon 16 -3 C>T genotype distributions or allele frequencies were observed between groups. Potential limitations of this study were a small sample size and the lack of a uniform definition of sulfonylurea failure. In summary, these two published studies in patients with Type 2 diabetes suggest that the intron/exon 16 -3 polymorphism does not influence sulfonylurea response. However, given the limitations of these study designs, this polymorphism merits investigation in additional cohorts of Type 2 diabetes patients receiving sulfonylurea therapy. Other polymorphisms in *ABCC8*, namely Ser1369Ala (T>G, exon 33), have been more consistently associated with differences in sulfonylurea response in patients with Type 2 diabetes. In terms of functional significance, the Ser1389Ala polymorphism is located in the second nucleotide-binding fold, and the Ala/Ala genotype is associated with decreased insulin secretion [43]. Zhang and colleagues prospectively evaluated the effects of the Ser1369Ala polymorphism on response to glimepiride 40 mg twice daily for 8 weeks in 115 patients with Type 2 diabetes [44]. The decrease in Hb_{A1c} from baseline to week 8 was greater in Ala allele carriers (-1.6%) compared with Ser/Ser homozygotes (-0.76%; $p = 0.044$). Of note, the change in fasting plasma glucose did not differ significantly between genotype groups. The authors

hypothesized that the Ala allele conferred hypersensitivity to sulfonylurea therapy, resulting in more efficacious Hb_{A1c} reductions. The reason for the discrepancy between the Hb_{A1c} and fasting plasma glucose results is unclear, but is possibly due to differences in postprandial glucose levels between groups, which is captured by Hb_{A1c} measurements.

The *ABCC8* Ser1369Ala polymorphism was also identified as an important determinant of sulfonylurea response in a large prospective study. Feng and colleagues investigated whether Type 2 diabetes candidate gene variants influenced response to gliclazide 40 mg twice daily following 8 weeks of therapy [45]. A total of 25 polymorphisms in 11 candidate genes were studied (Table 2). The study population (n = 1268) consisted of two cohorts based on the geographic location of the hospitals. In a pooled analysis of both cohorts, patients with the Ser/Ala and Ala/Ala genotypes had 2.8 and 7.7% greater decreases in fasting plasma glucose than Ser/Ser homozygotes. Decreases in 2-h glucose following an oral glucose tolerance test were also greater in the Ser/Ala (−10.8%) and Ala/Ala (−11.9%) genotype groups compared with Ser/Ser. Reductions in Hb_{A1c} from baseline to week 8 were 1.2, 1.5 and 1.7% in the Ser/Ser, Ser/Ala and Ala/Ala genotype groups, respectively, although these differences were not significant between groups. The odds of responding to gliclazide therapy were higher in the Ser/Ala (OR: 1.4, 95% CI: 1.0–2.1) and Ala/Ala groups (OR: 2.2; 95% CI: 1.4–3.6) compared with the Ser/Ser genotype. There was no association between genotype and change in insulin levels. Of note, only one other polymorphism of the 25 studied was significantly associated with the percent reduction in fasting plasma glucose. This SNP, rs5210, is located in the 3' untranslated region of the *KCNJ11* gene.

Although this prospective study had a large sample size, well-defined phenotypic end points and a replication cohort, there were some limitations that merit consideration. The treatment duration was short and the study excluded obese patients and patients who had diabetes for more than 5 years. Furthermore, it is unclear if these results can be applied to other racial groups, as this population was solely comprised of Chinese patients.

KCNJ11

As the pore of the K_{ATP} channel, polymorphisms in *KCNJ11* have been studied regarding their relationship with sulfonylurea response in patients with Type 2 diabetes. The most widely studied polymorphism has been Glu23Lys (E23K). *KCNJ11* E23K has emerged as a Type 2 diabetes risk allele [46–48]. Furthermore, *in vitro* studies have demonstrated that the variant K23 allele is associated with K_{ATP} channel overactivity (i.e., decreased ATP inhibitory sensitivity) and in some clinical studies, the variant K allele is associated with decreased insulin secretion in humans [47–49]. Of note, E23K is in strong linkage disequilibrium with the *ABCC8* Ser1389Ala polymorphism; therefore, most carriers of a *KCNJ11* K23 risk allele also carry an *ABCC8* Ala1369 risk allele [47,50,51]. Thus, like *ABCC8* Ala1369, it has been hypothesized that the *KCNJ11* variant K23 allele may be associated with interindividual variability in sulfonylurea response.

This hypothesis was tested in a group of newly diagnosed diabetes patients treated with sulfonylureas who were participating in the UKPDS study [46]. In this study, the *KCNJ11* E23K variant was not significantly associated with response to sulfonylurea therapy. In another study, Sesti and colleagues investigated whether the E23K variant was associated with an increased risk of secondary sulfonylurea failure in patients with Type 2 diabetes [52]. The study group was comprised of 525 Caucasian patients with Type 2 diabetes who were treated with glibenclamide up to 15 mg per day. The frequency of the K23 allele was 66.8% in patients with secondary sulfonylurea failure compared with 58% in patients who did not fail sulfonylurea therapy (OR: 1.45; 95% CI: 1.01–2.09). After adjusting for potential covariates, the odds of secondary sulfonylurea failure in K allele carriers were

higher than in E/E homozygotes (OR: 1.69; 95% CI: 1.02–2.78). Of note, in the patient group without secondary sulfonylurea failure, the age of diabetes onset was lower and glucose levels were higher in patients who carried a K allele. However, there were no significant genotype differences in age of diabetes onset or glucose levels in the secondary sulfonylurea failure group. The reasons for an increased risk of secondary sulfonylurea failure with the E23K variant in the face of similar diabetes duration and glucose levels are unclear. Also, the reason why the K23 allele was associated with increased sulfonylurea failure in this study, whereas previous studies have shown improved sulfonylurea response with the linked *ABCC8* Ala1369 allele, is unclear. The investigators also studied the effects of the E23K genotype on *ex vivo* human pancreatic islet cell function. Islets of carriers of the K allele demonstrated reduced insulin secretion following glibenclamide administration, although this did not reach statistical significance. Following 24 h of high glucose exposure, islets of carriers of the K allele had significantly lower glibenclamide-stimulated insulin secretion than E23 homozygotes.

Recently, the *KCNJ11* E23K variant has been evaluated for its association with severe sulfonylurea-induced hypoglycemia [53]. Holstein and colleagues hypothesized that Type 2 diabetes patients who possess the variant K allele would have a decreased risk of severe hypoglycemia following sulfonylurea therapy. They conducted a case–control study of 43 patients with Type 2 diabetes taking sulfonylurea therapy (either glimepiride or glibenclamide) who were admitted to the hospital owing to severe hypoglycemia. The study included 54 matched control patients who also had Type 2 diabetes and who were also treated with sulfonylurea therapy, but who had not experienced severe hypoglycemia. The doses of sulfonylureas and the use of metformin were comparable between the case and control groups. The frequency of the K variant allele was higher in the control group compared with cases (46 vs 31%; OR: 0.54; 95% CI: 0.30–0.98; $p = 0.04$). In univariate logistic regression analysis, the presence of the K variant was associated with a decreased risk of sulfonylurea-induced hypoglycemia. However, after controlling for covariates, this genotype association was no longer significant. Additional analyses revealed that K/K homozygotes had significantly higher Hb_{A1c} than patients with the E/K or E/E genotypes (7.57, 6.89 and 6.77%, respectively; $p = 0.04$). The major limitation of this small observational study was that it was probably underpowered to assess the primary end point.

It is important to note that none of the *KCNJ11* clinical studies prospectively set out to determine the influence of the E23K variant on sulfonylurea response. Thus, variability exists in the definition of sulfonylurea failure, choice and dose of sulfonylurea used, and the baseline demographics of the respective populations. In addition, most studies focused exclusively on the E23K polymorphism. Recently, a large, prospective study showed that another *KCNJ11* polymorphism, rs5210, located in the 3' untranslated region, was significantly associated with the percentage decrease in fasting glucose after 8 weeks of gliclazide therapy [45]. However, replication of this finding in other study populations has yet to be performed. Last, the strong linkage disequilibrium between the *KCNJ11* K23 and *ABCC8* Ala1369 risk alleles has prompted investigators to determine the functional consequences of this risk haplotype (i.e., K23/A1369). Using recombinant human K_{ATP} channels, Hamming and colleagues found that variant K23/A1369 K_{ATP} channels have increased sensitivity to gliclazide as compared with wild-type E23/S1369 K_{ATP} channels [54]. Furthermore, they found that the increased sensitivity to gliclazide with the K23/A1369 haplotype was a result of the *ABCC8* A1369 risk allele. These data provide intriguing mechanistic hypotheses regarding the K23/A1369 risk haplotype and merit further investigation in prospective clinical trials of sulfonylurea response in patients with Type 2 diabetes.

Disease-risk polymorphisms & sulfonylurea response

Type 2 diabetes is a polygenic disease, and the biological pathways underlying the pathophysiology of Type 2 diabetes are numerous and complex. Genes hypothesized to predispose individuals to Type 2 diabetes are those involved in pancreatic β -cell function and development, insulin secretion, signaling and resistance, and glucose transport [55]. To date, candidate gene-association studies and genome-wide association studies have identified over 15 Type 2 diabetes risk genes [55]. In terms of sulfonylurea response, polymorphisms in genes that influence insulin, glucose or β -cell physiology could potentially confer differential responses to these agents in Type 2 diabetes. A summary of published studies evaluating the associations between Type 2 diabetes disease risk polymorphisms and sulfonylurea response is shown in Table 3.

TCF7L2

TCF7L2 is a key transcription factor in the WNT signaling pathway that is involved in glucose homeostasis and lipid metabolism, proliferation and function of pancreatic β cells, and the production of glucagon-like peptide 1 [56]. Altered regulation of this signaling pathway has been implicated in the development of Type 2 diabetes, and *TCF7L2* has emerged as a Type 2 diabetes susceptibility gene. Two intronic *TCF7L2* polymorphisms, rs7903146 C>T and rs12255372 G>T, have been the strongest and most consistent predictors of increased Type 2 diabetes risk [56–59]. Meta-analysis data reveal that homozygosity for these variant alleles is associated with an approximately twofold increase in the risk for Type 2 diabetes compared with wild-type homozygotes [58]. These risk alleles were also associated with a fivefold increase in *TCF7L2* protein expression in pancreatic islets from patients with Type 2 diabetes, which, in turn, was associated with reduced insulin secretion from these cells *in vivo* and *in vitro* [60,61]. Other hypothesized mechanisms by which *TCF7L2* polymorphisms confer an increased risk of Type 2 diabetes include decreased β -cell mass, impaired insulin processing or release, impaired GLP-1 signaling in pancreatic β cells, decreased glucagon secretion and hepatic insulin resistance [59].

Given the putative role of *TCF7L2* polymorphisms in β -cell function, Pearson and colleagues set out to determine the impact of *TCF7L2* rs12255372 G>T and rs7903146 C>T on early response to sulfonylurea therapy in Scottish patients with Type 2 diabetes [62]. Using the Genetics of Diabetes Audit and Research Tayside (GoDARTS) database, the investigators identified 901 incident sulfonylurea users. The primary outcome of this study was the failure to attain an Hb_{A1c} 7% or less in the 3–12 months following the index sulfonylurea prescription. For rs1225372, 57% of patients with the T/T genotype failed to attain an Hb_{A1c} of 7% or less, compared with 41 and 40% of patients with the G/T and G/G genotypes, respectively ($p = 0.006$). For rs7903146, 53% of patients with the variant T/T genotype failed to attain an Hb_{A1c} of 7% or less compared with 42 and 40% of patients with the C/T and C/C genotypes, respectively ($p = 0.035$). In logistic regression analysis, the odds of sulfonylurea failure were higher in patients with the rs12255372 T/T genotype compared with the G/G genotype (OR: 1.94; 95% CI: 1.23–3.06; $p = 0.005$) and higher in patients with the rs7903146 T/T genotype compared with the C/C genotype (OR: 1.73; 95% CI: 1.11–2.70; $p = 0.015$). When baseline Hb_{A1c} was included as a covariate in the regression models, the associations between *TCF7L2* genotype and sulfonylurea failure were strengthened. The odds of sulfonylurea failure for rs12255372 T/T vs G/G were 2.16 (95% CI: 1.21–3.86; $p = 0.009$), and for rs7903146, 1.90 (95% CI: 1.09–3.33; $p = 0.024$).

This study also investigated whether *TCF7L2* polymorphisms influenced metformin response in incident metformin users in the GoDARTS database. Unlike the sulfonylurea findings, *TCF7L2* polymorphisms were not associated with metformin treatment failure in

this population. The finding that sulfonylurea, but not metformin response, was affected by *TCF7L2* polymorphism lends indirect support to the hypothesis that the functional consequences of *TCF7L2* polymorphisms are to alter β -cell function. To date, this is the only study that has investigated the association between *TCF7L2* polymorphisms and sulfonylurea response, and there are limitations associated with observational studies (e.g., nonrandomized design, lack of rigorous compliance assessment measures and potential prescriber bias). Nonetheless, these findings are intriguing, particularly since the frequency of variant homozygotes is common in the population (i.e., genotype frequency of 12%).

Insulin receptor substrate-1—Insulin receptor substrate (IRS)-1 is an important signal-transduction protein that mediates the metabolic effects of insulin. A common polymorphism, Gly972Arg, in the *IRS-1* gene was associated with an increased risk of Type 2 diabetes in one meta-analysis [63], but these results were not replicated by other large-scale genetic association studies [64,65]. The variant Arg allele has been associated with decreased glucose-stimulated insulin secretion and decreased insulin response to sulfonylureas in *ex vivo* and *in vitro* studies [66,67]. Sesti and colleagues investigated whether the *IRS-1* Gly972Arg polymorphism was associated with an increased risk of secondary sulfonylurea failure in patients with Type 2 diabetes ($n = 477$) [68]. The frequency of the Arg972 allele was higher in patients with secondary sulfonylurea failure compared with those well controlled on sulfonylurea therapy (16.7 vs 8.7%, respectively). In logistic regression analysis, Arg972 allele carriers had two-times the risk of secondary sulfonylurea failure as compared with noncarriers. This finding was independent of age, sex, BMI, metabolic control, age at diagnosis, duration of diabetes and the *PPAR γ* Pro12Ala genotype.

Nitric oxide synthase 1 adaptor protein—Nitric oxide synthase 1 adaptor protein (*NOS1AP*) binds to and regulates neuronal nitric oxide synthase. Neuronal nitric oxide synthase is hypothesized to reduce intracellular calcium levels through its effects on voltage-gated calcium channels. Subsequently, this enzyme plays a role in the electrical current of the heart and in insulin release from pancreatic β cells [69-72]. Given the relationship between *NOS1AP* and insulin release, Becker and colleagues set out to determine if *NOS1AP* polymorphisms are associated with efficacy and mortality risk in sulfonylurea-treated patients with Type 2 diabetes [73]. In this population-based cohort study of incident sulfonylurea users, patients with the rs10494366 T/G genotype had a greater change in the prescribed dose of glibenclamide compared with the wildtype T/T genotype. However, rs10494366 genotype was not associated with differences in prescribed doses of tolbutamide, gliclazide or glimepiride. In glibenclamide users, variant G allele carriers had an increased risk of mortality compared with the T/T genotype (HR: 2.8; 95% CI: 1.09–7.22). By contrast, mortality risk was lower in tolbutamide and glimepiride users who carried a G allele compared with the T/T genotype (tolbutamide, HR: 0.30; glimepiride, HR: 0.18). Of note, no genotype differences in mortality were observed in metformin or insulin users. The mechanisms through which this polymorphism influenced mortality risk and the reason why this association differed based on the type of sulfonylurea used are unclear. The authors hypothesized that it may be due to differences in the effect of sulfonylureas on other potassium channels, such as calcium-dependent potassium channels, or other sulfonylurea receptor subtypes, such as SUR2A.

Expert commentary

Sulfonylurea efficacy is intrinsically linked to β -cell physiology; therefore, the future study of sulfonylurea pharmacogenomics will be a challenging and complex process. Genes encoding the direct targets of sulfonylurea action (i.e., *ABCC8* and *KCNJ11*) are the most logical candidate genes for investigation. To date, the *ABCC8* Ser1369Ala polymorphism

has been significantly associated with gliclazide response in two prospective studies. Both of these studies were conducted in Asian populations, therefore the applicability of these findings to patients of other races is unclear. Furthermore, both of these studies included only an 8-week treatment period. Therefore, the impact of these polymorphisms on long-term sulfonylurea response and durability outcomes is not known. The *KCNJ11* polymorphism E23K is in strong linkage disequilibrium with the *ABCC8* Ser1369Ala polymorphism. Recent data suggest that the K23/A1369 risk haplotype confers increased sensitivity to gliclazide *in vitro*, and this effect is primarily governed by the A1369 risk allele. In terms of Type 2 diabetes risk genes, polymorphisms in *TCF7L2* and *IRS-1* have been implicated as predictors of sulfonylurea response in two studies. However, to date, neither of these findings have been investigated in replication cohorts. Recently, a polymorphism in *NOS1AP* has been associated with changes in prescribed glibenclamide doses. Interestingly, this polymorphism also conferred differences in mortality risk based on the type of sulfonylurea used. These findings have also yet to be investigated in additional cohorts. Taken together, a number of notable drug target and Type 2 diabetes disease risk polymorphisms have been implicated as important determinants of sulfonylurea response; however, the clinical utility of this information is uncertain as most of these findings have yet to be replicated.

Currently, there are some limitations associated with sulfonylurea pharmacogenomic data. Published studies differ substantially in their designs (e.g., prospective vs population-based cohorts), inclusion criteria, choice of sulfonylurea, treatment duration and outcomes of interest. With the exception of a few investigations, most of the existing sulfonylurea pharmacogenomic studies have been retrospective. In addition, some studies have failed to exclude patients who potentially have monogenic forms of diabetes, such as maturity-onset diabetes of the young, or Type 1.5 diabetes. This is important, as mutations causing monogenic forms of diabetes (e.g., hepatocyte nuclear factor-1 α) have been shown to influence response to sulfonylurea therapy [74]. Another challenge with interpreting the sulfonylurea pharmacogenomic literature is the lack of formal definitions of sulfonylurea failure. Heterogeneity in the definitions of sulfonylurea response and failure may lead to inconsistencies in the observed findings between studies for a given polymorphism. Last, while many studies have identified genetic associations with sulfonylurea response, none of the studies have been designed to elucidate how this genetic information can be used to select therapy and guide sulfonylurea dosing. It is not known whether *a priori* genetic knowledge will decrease the chance of long-term adverse clinical outcomes, particularly microvascular complications, in patients with Type 2 diabetes.

Five-year view

To date, only a limited number of polymorphisms in sulfonylurea drug target genes and Type 2 disease risk genes have been studied, and most of the results have been limited to small, observational studies. Given the complex pathophysiology of Type 2 diabetes and the role of the sulfonylureas in modulating this disease process (i.e., promoting insulin secretion), future studies will likely need to take a genome-wide association approach, or be conducted as association studies with hundreds of biologically relevant genes in order to identify the polymorphisms that are most predictive of sulfonylurea response. Future studies will also need to differentiate between the influence of polymorphisms on early sulfonylurea response and secondary sulfonylurea failure, as different genes are likely to affect sulfonylurea response as Type 2 diabetes progresses. In conclusion, the field of sulfonylurea pharmacogenomics has made some notable findings in recent years. In the coming years, more comprehensive assessments of these existing sulfonylurea pharmacogenomic associations will be necessary in order to determine if genetic information has clinical utility in improving the pharmacotherapeutic management of Type 2 diabetes.

Key issues

- The sulfonylureas are oral agents used in the treatment of Type 2 diabetes. Sulfonylureas lower glycated hemoglobin levels by 1–2%.
- Sulfonylureas bind to ATP-sensitive potassium channels on pancreatic β cells and stimulate insulin release in a glucose-independent manner.
- Although the sulfonylureas are effective antihyperglycemic agents, interindividual variability exists in drug response and disposition.
- Recently, polymorphisms in drug target genes (i.e., ATP-binding cassette, subfamily C, member 8 [*ABCC8*] and potassium inwardly-rectifying channel, subfamily J, member 11 [*KCNJ11*]) and diabetes risk genes (e.g., *TCF7L2* and insulin receptor substrate [*IRS-1*]) have been associated with variability in sulfonylurea response in patients with Type 2 diabetes.
- *ABCC8* encodes the regulatory subunit of the sulfonylurea receptor, and the *ABCC8* Ser1369Ala polymorphism has been associated with differential response to sulfonylurea therapy in patients with Type 2 diabetes. Clinical studies have shown that patients carrying the variant Ala allele have greater sulfonylurea-mediated reductions in fasting plasma glucose and glycated hemoglobin levels than wild-type homozygotes.
- *KCNJ11* encodes Kir6.2, the pore subunit of the sulfonylurea receptor, and the *KCNJ11* E23K polymorphism is associated with interindividual variability in sulfonylurea response and adverse effects in patients with Type 2 diabetes.
- The *KCNJ11* E23K and *ABCC8* Ser1369Ala polymorphisms are in strong linkage disequilibrium. Recent data suggest that the K23/Ala1369 risk haplotype confers increased sensitivity to gliclazide *in vitro*. This finding is primarily governed by the effects of the Ala1369 risk allele.
- *TCF7L2* is a transcription factor in the WNT signaling pathway and it is a Type 2 diabetes risk gene. Polymorphisms in *TCF7L2* have been associated with differential response to sulfonylurea therapy in patients with Type 2 diabetes.
- *IRS-1* is a signal transduction protein that mediates the metabolic effects of insulin. The *IRS-1* Gly972Arg polymorphism is associated with an increased risk of Type 2 diabetes and an increased risk of secondary sulfonylurea failure in patients with Type 2 diabetes.
- While the field of sulfonylurea pharmacogenomics has made some notable findings in recent years, few replication studies have been conducted. In the future, additional studies are also needed to determine how this genetic information can be used to select therapy and guide dosing, or if *a priori* genetic knowledge can be used to decrease the chance of long-term clinical outcomes, particularly microvascular complications, in patients with Type 2 diabetes.

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Figure 1. Application of pharmacogenomics to sulfonylurea therapy
Adapted and reprinted with permission from [15].

Table 1
Available pharmacologic agents for the treatment of Type 2 diabetes

Drug class	Role in Type 2 diabetes therapy
Biguanides (metformin)	Tier 1, step 1
Insulin	Tier 1, step 2
Sulfonylureas (tolbutamide, tolazamide, chlorpropamide, acetohexamide, glyburide [also known as glibenzclamide], glipizide, glimepiride and gliclazide)	Tier 1, step 2
Thiazolidinediones [†] (pioglitazone and rosiglitazone)	Tier 2
Glucagon-like peptide 1 analogs (exenatide)	Tier 2
α-glucosidase inhibitors (acarbose and miglitol)	Other therapy
Nonsulfonylurea insulin secretagogues (repaglinide and nateglinide)	Other therapy
Amylin agonists (pramlintide)	Other therapy
DPP-4 inhibitors (sitagliptin)	Other therapy

DPP-4: Dipeptidyl peptidase-4.

Data taken from [12].

[†]The American Diabetes Association and the European Association for the Study of Diabetes currently recommend pioglitazone if thiazolidinedione therapy is needed.

Table 2
Summary of sulfonylurea drug target Type 2 diabetes pharmacogenomic studies

Study author (year)	Study population	Sulfonylurea	Primary response phenotype	Polymorphism(s) studied	Primary results	Ref.
Meirhaeghe <i>et al.</i> (2001)	Population-based French study; 122 Type 2 diabetes patients were selected based on medical diagnosis and treatment (n = 70, sulfonylurea; n = 52, other treatments excluding insulin)	Various	Single fasting blood sample for glucose, insulin, total cholesterol and triglycerides	ABCC8 intron/exon 16 -3 C>T	No influence of the intron/exon 16 -3 C>T polymorphism on glucose or insulin levels, regardless of treatment. In the sulfonylurea group, the -3C allele was associated with lower triglyceride levels than the T/T genotype	[41]
Zychma <i>et al.</i> (2002)	Type 2 diabetes ≤ 5 years and treated with insulin (n = 68); or Type 2 diabetes for at least 15 years and treated with oral agents (sulfonylurea alone or in combination with metformin or acarbose, n = 99). Patients were selected from two previous cohort studies	Various	Differences in genotype and allele frequencies between the two patient groups	ABCC8 intron/exon 16 -3 C>T	No significant differences in genotype distributions or allele frequencies between groups	[42]
Zhang <i>et al.</i> (2007)	Type 2 diabetes with FPG ≥ 7.8 mmol/l and treated with diet and exercise, but no hypoglycemic agents for 2 months before the study (n = 115)	Gliclazide 40 mg twice daily for 8 weeks Dosage adjustments at weeks 2 and 4 were allowed based on FPG	FPG, Hb _{A1c}	ABCC8 Ser1369Ala	Greater decrease in Hb _{A1c} in Ala allele carriers compared with Ser homozygotes	[44]
Feng <i>et al.</i> (2008)	Type 2 diabetes with onset after the age of 35 and all of the following (n = 1268): diabetes diagnosed within the past 5 years and no antidiabetic treatment within the past 2 months; BMI < 28 kg/m ² ; and FPG between 7.8 and 15 mmol/l	Gliclazide 40 mg twice daily for 8 weeks Dosage adjustments were allowed based on FPG at weeks 2 and 4	Continuous variables: FPG, 2-h glucose post 75 g OGTT, Hb _{A1c} Logistic regression: gliclazide response as defined by week 8 FPG < 7.8 mmol/l	25 SNPs in 11 candidate genes, including ABCC8 and KCNJ11	ABCC8 variant Ala1389 carriers had greater decreases in FPG and 2-h glucose compared with Ser homozygotes Reductions in Hb _{A1c} were greater in Ala/Ala (-1.7%) and Ser/Ala (-1.5%) compared with Ser/Ser (-1.2%), although this was not significant The odds of gliclazide response were 1.4-times greater in Ser/Ala and 2.2-times greater in Ala/Ala compared with Ser/Ser KCNJ11 rs5210 was also associated with the percent reduction in FPG	[45]
Gloyn <i>et al.</i> (2001)	Patients from the UKPDS study who were randomly allocated to sulfonylurea therapy (n = 364)	Chlorpropamide or glipizide	Change in FPG in the first year from randomization; patients on sulfonylurea therapy at 1 year post-randomization were classified as 'successes', while patients who required	KCNJ11 E23K and L270V	The E23K and L270V polymorphisms were not significantly associated with sulfonylurea response	[46]

Study author (year)	Study population	Sulfonylurea	Primary response phenotype	Polymorphism(s) studied	Primary results	Ref.
Sesti <i>et al.</i> (2006)	Type 2 diabetes patients (n = 525) recruited consecutively with the following criteria: onset of diabetes >35 years of age, absence of ketonuria at diagnosis and negative for antigitamic acid decarboxylase antibody	Glibenclamide 15 mg per day. Metformin was added if FPG was >300 mg/dl on two separate occasions	Secondary sulfonylurea failure: those requiring insulin due to FPG >300 mg/dl despite sulfonylurea and metformin therapy, appropriate diet, and absence of conditions that cause hyperglycemia	KCNJ11 E23K	The odds of secondary sulfonylurea failure were 1.69-times higher in variant K23 carriers compared with E/E	[52]
Holstein <i>et al.</i> (2009)	Case-control study of 43 Type 2 diabetes patients admitted to the emergency department owing to severe hypoglycemia (patients treated with insulin were excluded) and 54 Type 2 diabetes control patients without a history of severe hypoglycemia	Glibenclamide and glimepiride	Severe hypoglycemia defined as a symptomatic event requiring treatment with intravenous glucose and confirmed by a glucose measurement <50 mg/dl	KCNJ11 E23K	The frequency of the variant K23 allele was higher in the control group (46%) versus the case group (31%). K/K homozygotes had higher HbA _{1c} than the E/K or E/E genotypes	[53]

ABCC8: ATP-binding cassette, subfamily C, member 8; FPG: Fasting plasma glucose; HbA_{1c}: Glycated hemoglobin; OGTT: Oral glucose-tolerance test; KCNJ11: Potassium inwardly rectifying channel, subfamily J, member 11; SNP: Single-nucleotide polymorphism; UKPDS: United Kingdom Prospective Diabetes Study.

Table 3
Summary of association studies evaluating polygenic Type 2 diabetes risk polymorphisms and sulfonylurea response in patients with Type 2 diabetes

Study author (year)	Study population	Sulfonylurea	Primary response phenotype	Polymorphism(s) studied	Primary results	Ref.
Pearson <i>et al.</i> (2007)	Type 2 diabetes (with age of diagnosis >40 years and no use of insulin within 6 months of diagnosis) and incident sulfonylurea use (n = 901) in the GoDARTS database. Incident sulfonylurea use was defined as no previous diabetes treatment for at least 6 months prior to index sulfonylurea prescription. In addition, incident users were required to have at least one HbA _{1c} recorded in the 3–12 months following sulfonylurea initiation	Various	Failure to attain HbA _{1c} ≤7% in the 3–12 months following the index sulfonylurea prescription	<i>TCF7L2</i> rs12255372 G>T and rs7903146 C>T	The odds of sulfonylurea failure were 2.16-times higher in rs12255372 T/T vs wild-type G/G, and 1.9-times higher in rs7903146 T/T vs wild-type C/C	[62]
Sesti <i>et al.</i> (2004)	Type 2 diabetes patients (n = 477) recruited consecutively with the following criteria: onset of diabetes >35 years of age, absence of ketonuria at diagnosis and negative for antidiabetic acid decarboxylase antibody	In most patients, glibenclamide 15 mg per day Metformin was added if FPG was >300 mg/dl on two separate occasions	Secondary sulfonylurea failure: those requiring insulin due to FPG >300 mg/dl despite sulfonylurea and metformin therapy, appropriate diet and the absence of conditions that cause hyperglycemia	<i>IRS1</i> Gly972Arg	Arg972 variant carriers had two-times the risk of secondary sulfonylurea failure compared with wild-type Gly homozygotes	[68]
Becker <i>et al.</i> (2008)	Population-based cohort study (Rotterdam). Incident sulfonylurea users (n = 619) during 1 January 1991 and 1 January 2005 were included in the analysis	Glibenclamide, tolbutamide, gliclazide and glimepiride	Change in prescribed daily dose; mortality	<i>NOS1AP</i> rs10494366 T>G	T/G genotype was associated with a greater change in prescribed glibenclamide dose than the T/T genotype. In glibenclamide users, G allele carriers had 2.8-times increased risk of mortality compared with T/T. In tolbutamide or glimepiride users, G allele carriers had 0.3-times the risk of mortality compared with T/T	[73]

FPG; Fasting plasma glucose; GoDARTS: Genetics of Diabetes Audit and Research Tayside; HbA_{1c}: Glycated hemoglobin; *IRS-1*: Insulin receptor substrate-1; *NOS1AP*: Nitric oxide synthase 1 adaptor protein; *TCF7L2*: Transcription factor 7-like 2.