Pharmacogenetics and personalized treatment of type 2 diabetes

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Abstract

Type 2 diabetes mellitus (T2DM) is a worldwide epidemic with considerable health and economic consequences. T2DM patients are often treated with more than one drug, including oral antidiabetic drugs (OAD) and drugs used to treat diabetic complications, such as dyslipidemia and hypertension. If genetic testing could be employed to predict treatment outcome, appropriate measures could be taken to treat T2DM more efficiently. Here we provide a review of pharmacogenetic studies focused on OAD and a role of common drug-metabolizing enzymes (DME) and drug-transporters (DT) variants in therapy outcomes. For example, genetic variations of several membrane transporters, including *SLC22A1/2* and *SLC47A1/2* genes, are implicated in the highly variable glycemic response to metformin, a first-line drug used to treat newly diagnosed T2DM. Furthermore, cytochrome P450 (CYP) enzymes are implicated in variation of sulphonylurea and meglitinide metabolism. Additional variants related to drug target and diabetes risk genes have been also linked to interindividual differences in the efficacy and toxicity of OAD. Thus, in addition to promoting safe and cost-effective individualized diabetes treatment, pharmacogenomics has a great potential to complement current efforts to optimize treatment of diabetes and lead towards its effective and personalized care.

Key words: type 2 diabetes mellitus; pharmacogenomics; pharmacogenetics; oral antidiabetic drugs; personalized medicine

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Introduction

It has been estimated that around 285 million people suffer from type 2 diabetes mellitus (T2DM) with projected rise to 438 million in the next 20 years (1). Current therapies for T2DM include lifestyle modification and use of oral antidiabetic drugs (OAD). Several OAD classes are currently available to treat T2DM patients, with sulphonylureas (SU), biguanides, thiazolidinediones (TZDs), and meglitnides being the most frequently used. Effects of these drugs depend on the extent of drug absorption from the gut lumen, uptake and metabolism of the drug in the liver, the extent of its transport back into the systemic circulation for extrahepatic effects, and for drugs with substantial renal secretory clearance (e.g., metformin) on active renal tubular secretion into the urine. Drug-metabolizing enzymes (DME) and drug transporters (DT) have a crucial role in the fate of drugs in human body. Information regarding the incidence of cytochrome P450 (CYP) gene polymorphisms is increasing (2-4), although the level of detail such as in the case of other DME, including UDP-glucuronosyltransferases and N-acetyltransferases, is not as extensive. In addition, recent studies identified genetic variations of DT associated with the altered treatment outcomes (5,6) and revealed an important role of the transporter-mediated OAD uptake in their disposition and effects (4).

Furthermore, recent data showed that epigenetic changes in response to environmental stimuli may play an important role in the diabetes development (7). In addition to the role of DNA methylation and histone modifications, recent studies also indicated that microRNAs (miRNAs), a class of

small, single-stranded non-protein coding gene products that post-transcriptionally suppress mRNA target expression, could serve as a new generation of biomarkers for diabetes. Strikingly, a recent analysis of the specific miRNAs provided sufficient data to diagnose and predict the T2DM development in normoglycemic patients (8). Thus, characterization of the miRNAs pattern together with the analysis of specific pharmacogenetic variants could facilitate the design of a therapy tailored to the individual patient, contributing to the current efforts in the personalized medicine (9,10). Here we aim to summarize the pharmacogenomics data related to the T2DM therapy, particularly the associations of SU, TZDs, biguanides, and meglitinides treatment outcomes with polymorphisms of DME, DT, drug target and diabetes risk genes that might lead to the promotion of personalized T2DM treatment.

Sulphonylureas

In addition to insulin resistance (IR), insufficient pancreatic β-cell function plays an important role in the pathogenesis of T2DM. The insufficient production and secretion of insulin can be increased by secretagogue drugs, like SU that bind to sulphonylurea receptor (SUR) leading to the cell depolarization and stimulation of insulin release. Potassium inwardly rectifier 6.2 subunit (Kir6.2) of pancreatic islet ATP-sensitive K+ (KATP) channels are hetero-octamers assembled from Kir6.2 and the sulphonylurea receptor 1 (SUR1), encoded by the *KCNJ11* and *ABCC8* gene, respectively. This channel is essential for glucose-stimulated insulin secretion from pancreatic β-cells, modulates glucose uptake into skeletal muscle, glucose production and release from the liver (11). Physiologically, decreased plasma glucose levels lead to lower metabolic rate which opens KATP channels, suppressing electrical activity and insulin release. In contrast, KATP channels close when metabolism increases, ATP rises and MgADP falls, leading to membrane depolarization, opening of voltage-gated Ca2+ channels, Ca2+ influx, and insulin secretion.

In recent years single nucleotide polymorphisms (SNPs) of the genes encoding KATP channel have been related to the efficacy of secretagogue drugs (Table 1). Loss-of-function (LOF) mutations of these genes are the most common cause of congenital hyperinsulinism, with over 150 mutations characterized in SUR1 (*ABCC8*) and 24 in Kir6.2 (*KCNJ11*) (12). On the other hand, gain-of-function (GOF) mutations in Kir6.2 or SUR1 cause neonatal diabetes (ND). A similar number of over 40 different ND mutations have been characterized in Kir6.2 and in SUR1 (12). All Kir6.2 mutations cause dominant ND by reducing the ability of ATP to block KATP channel (13), hyperpolarizing the β-cells, and preventing insulin secretion. Thus, the mutated KATP channel does not close in response to increased ATP concentrations. However, it could be closed when SU bind to SUR1 by an ATP-independent route. The discovery of the causal role of KATP channels has enabled ND patients to switch from insulin to SU therapy that significantly improved glycemic control and reduced the risk of diabetic complications (14,15).

A common Glu23Lys polymorphism (also known as E23K) in *KCNJ11* (potassium inwardly-rectifying channel, subfamily J, member 11) gene encoding Kir6.2, is associated with T2DM development (16,17), as well as an increased risk of SU therapeutic failure (18). The functional effects of the E23K variant on insulin secretion and insulin sensitivity in humans are controversial, although recent larger studies demonstrate a significantly reduced insulin secretion, lower insulin levels, and improved insulin sensitivity (19), consistent with enhanced KATP activity in pancreatic β-cells. Furthermore, a recent study found that the carriers of the *KCNJ11* K-allele had better therapeutic response to gliclazide (20). *KCNJ11* variations have been also associated with altered response to glibenclamide therapy and misdiagnosis of Type 1 diabetes (14). Importantly, recent evidence demonstrated that patients with *KCNJ11* mutations could be treated more efficiently with SU than with insulin (14,21,22).

The *ABCC8* gene encodes the SUR1 subunit which regulates KATP channel activity. *ABCC8* mutations are genetically more heterogeneous, with homozygous, heterozygous and compound hetero-

Table 1. Summary of the gene polymorphisms involved in the pharmacogenetics of sulphonylureas.

SNP	Study population	Associated response phenotype	Reference
KCNJ11			
E23K (Glu23Lys) (rs5219)	T2DM patients (N = 525) with secondary SU failure.	Carriers of the K allele showed a tendency toward shorter duration of therapy before failure as compared with EE homozygotes; pancreatic islets from K allele carriers showed a significantly lower glibenclamide-stimulated insulin release.	Sesti et al, 2006 (18)
	Patients with T2DM (N = 101) treated with gliclazide for 6 months.	K-allele carriers had significantly higher decrease in HbA1c compared with EE homozygotes.	Javorsky et al, 2012 (20)
3p + 215 G>A (rs5210)	Patients with T2DM (N = 1.268), 8 weeks of gliclazide therapy.	Significantly associated with decrease in FPG.	Feng et al, 2008 (25)
ABCC8			
Ser1369Ala (rs757110)	Patients with T2DM (N = 1.268), 8 weeks of gliclazide therapy.	Associated with significant decrease in FPG.	Feng et al, 2008 (25)
exon 16-3C>T (rs1799854)	Patients with T2DM (N = 228) on SU therapy.	Carriers of wild-type CC genotype had significantly lower HbA1c compared to the patients with TT genotype.	Nikolac et al, 2009. (28)
Arg1273Arg (rs1799859)	Patients with T2DM (N = 228) on SU therapy.	Patients with wild-type GG genotype had significantly higher HbA1c levels compared to the patients with AA genotype.	Nikolac et al, 2009 (28)
	Patients with T2DM (N = 251) on SU therapy.	Patients with GG genotype had significantly higher triglyceride levels compared to the patients with AA genotype.	Nikolac et al, 2012 (29)
KCNQ1			
rs163184 T>G	T2DM patients (N = 87) who failed to achieve glycemic control on metformin therapy, treated 6 months with SU.	Carriers of the T-allele (TT+TG) achieved significantly lower FPG levels compared to the patients with the risk GG genotype.	Schroner et al, 2011 (34)
TCF7L2			
rs7903146 C>T	T2DM patients (N = 87) 6-month sulphonylurea in addition to metformin.	Significantly higher reduction in HbA1c and FPG in patients with CC genotype compared to the CT+TT genotype.	Schroner et al, 2011 (39)
	T2DM patients (N = 189), 6-month SU treatment.	T allele was significantly more frequent in patients who failed to respond to SU than in the control subjects.	Holstein et al, 2011 (41)
rs12255372 G>T rs7903146 C>T	Population-based GoDARTS study: T2DM patients, incident SU users (N = 901).	2-fold greater likelihood of SU failure (not to achieve target HbA1c<7% (53 mmol/mol)) in the 12% of the TT homozygotes at rs1225372 than in the GG group.	Pearson et al, 2007 (40)
CYP2C9			
*3 (Ile359Leu) (rs1057910)	Healthy volunteers (N = 21), a single oral dose of glyburide.	In *3/*3 homozygotes total drug clearance was less than half, while insulin secretion was higher as compared to the wild-type *1/*1 genotype.	Kirchheiner et al, 2002 (48)
	Healthy volunteers (N = 29).	In *3 allele heterozygotes higher the median total AUC of glyburide and glimepiride, compared to subjects with the *1/*1 genotype.	Niemi et al, 2002 (49)
	A population-based cohort Rotterdam Study (N = 7.983).	Carriers of *3 allele required lower doses of tolbutamide to regulate glucose levels as compared to the *1/*1 genotype.	Becker et al, 2008 (42)
*2 (Arg144Cys) (rs1799853) *3 (Ile359Leu) (rs1057910)	Population-based GoDARTS study: T2D patients, incident users of SU (N = 1.073).	More likely to achieve a treatment HbA1c<7% (53 mmol/mol) than patients with the wild-type genotype.	Zhou et al, 2010 (51)

FPG - fasting plasma glucose; AUC - area under the curve.

zygous mutations being described (23). Heterozygous activating mutations in the *ABCC8* gene have been characterized as a cause of permanent and transient ND that may present as T2DM (24). Interestingly, a common Ser1369Ala SNP of *ABCC8* influenced antidiabetic efficacy of SU in Chinese (25), but not in German population (26). In addition, this same Ser1369Ala variant of *ABCC8* appeared not to be associated with the risk for severe SU-induced hypoglycemia in German (26) and Japanese (27) T2DM patients. Additional polymorphisms of *ABCC8* gene, including SNP in exon 16 (-3C/T) and exon 31 (Arg1273Arg) have been also reported to be associated with the SU efficacy in European Caucasians (28-30).

Importantly, two common ATP-sensitive potassium (KATP) channel variants, E23K and S1369A, of the *KCNJ11* and *ABCC8* genes respectively, are in strong linkage disequilibrium (LD) and form a haplotype that appears to be associated with an increased T2DM risk (31). A recent analysis of structure-activity relationships in KATP channels containing either the E23/S1369 non-risk or K23/A1369 risk haplotypes, demonstrated that KATP channels containing the K23/A1369 risk haplotype were significantly less sensitive to inhibition by tolbutamide, chlorpropamide, and glimepiride (32). Glibenclamide and glipizide demonstrated similar inhibitory effects on KATP channels in patients with either haplotype. Based on these data, the authors suggested that it would be possible to design novel OAD with an increased efficacy in patients homozygous for these common KATP channel haplotypes.

Patients with deficient hepatic nuclear factor-1--alpha (HNF1-alpha), a transcription factor vital for correct β-cell development and function, have progressive β-cell deterioration and are more sensitive to SU than matched T2DM patients (33). Furthermore, a recent study has suggested that the magnitude of fasting plasma glucose (FPG) levels reduction after 6-month SU treatment in addition to metformin in T2DM patients was related to the rs163184 (T>G) SNP in *KCNQ1* gene (34). *KCNQ1* encodes a voltage-gated potassium channel expressed in the heart, stomach, small and large intestine, kidney, and pancreas. However, its role in insulin secretion by pancreatic β-cells is not completely understood. Importantly, the FPG response to SU was significantly lower in carriers of the risk GG genotype of rs163184 variation in *KCNQ1* (34). In addition, the Arg(972) variant of *IRS-1* gene encoding the insulin receptor substrate (IRS)-1 that is an important component of the insulin signaling cascade, was also associated with an increased risk for secondary SU failure (35).

The most promising gene variants affecting the SU response are those involved in drug pharmacodynamics, such as the transcription factor 7-like 2 *(TCF7L2*) that encodes a transcription factor (Tcf-4), involved in the regulation of cellular proliferation and differentiation (36). *TCF7L2* gene has the strongest association with T2DM reported to date (37,38). A recent study demonstrated that the degree of reduction in HbA1c and FPG levels following a combined SU and metformin treatment was related to *TCF7L2* rs7903146 (C>T) SNP (39). Interestingly, individuals with the T2DM-associated homozygous TT genotype were less likely to respond to SU therapy (39-41).

Sulphonylureas are mainly metabolized by the enzyme cytochrome P450 (CYP) isoform CYP2C9. A recent population-based Rotterdam study showed that polymorphisms in *CYP2C9* gene affected the patient sensitivity to SU (42). The carriers of *CYP2C9*3* (Ile359Leu) polymorphism appeared to be protected against development of T2DM (43), while *CYP2C9*2* (Arg144Cys) polymorphism was not associated with diabetes susceptibility (44). Although these two allelic variants, *CYP2C9*2* and *CYP2C9*3*, have been associated with elevated SU serum levels, the tolbutamide dose was lower in *CYP2C9*3* allele carriers as compared to patients with the wild-type *CYP2C9* genotype, while similar effect was not observed for the *CYP2C9*2* genotype (42). Furthermore, *CYP2C9*3* increased the risk of hypoglycemia in T2DM patients treated with SU (43,45) and multiple studies indicated that the *CYP2C9*3* allele was associated with decreased SU clearance (46,47). Homozygous carriers of the *CYP2C9*3/*3* genotypes had reduced clearance of glyburide and increased insulin secretion following glyburide administration (48, 49). Furthermore, diabetic patients with a *CYP2C9*3* variant required

lower doses of tolbutamide for glucose control than patients with the wild-type genotype (42). Recently, Swen *et al*. (50) demonstrated no significant effects of the *CYP2C9*2* and *CYP2C9*3* alleles on prescribed dose in incident SU users. However, a large population-based GoDARTS (Genetics of Diabetes Audit and Research in Tayside Scotland) study performed in 1,073 incident SU users demonstrated that patients with two copies of the *2 or *3 alleles were three times more likely to achieve treatment target of HbA1C levels under 7% (53 mmol/mol) than patients with two wild-type *CYP2C9*1* alleles (51).

Thiazolidinediones

Thiazolidinediones, also known as glitazones, act by activating their molecular target, PPARs (peroxisome proliferator-activated receptors). TZDs bind with greatest specificity for PPARγ, a nuclear transcription factor expressed diffusely in humans, including adipocytes, to promote adipogenesis and fatty acid uptake. By reducing circulating fatty acid concentrations and lipid availability in liver and muscle, these drugs improve the patients' sensitivity to insulin and reduce hyperglycemia. In addition, TZDs have a multitude of other therapeutic effects including anti-inflammatory effects and amelioration of hypertension, microalbuminuria and hepatic steatosis (52).

Rosiglitazone and pioglitazone are TZDs that have been shown to improve glycemic control and may act to slow the progression of β-cell failure. However, recent studies demonstrated that use of rosiglitazone could cause serious side effects, including an increased risk of myocardial infarction and death from cardiovascular causes as compared to pioglitazone (53,54). Due to these serious side effects, the European Medicines Agency (EMA) has recommended the suspension of the marketing authorizations for the rosiglitazone, while US Food and Drug Administration (FDA) has decided that rosiglitazone can remain available, but only under a very stringent restricted access program. Thus, the only TZD that is still available on market is pioglitazone, which appears to have more favorable effects on cardiovascular system in T2DM patients as compared to rosiglitazone (55,56). The mechanism of the antidiabetic action of pioglitazone involves activation of PPARγ, while its direct antioxidant action may also contribute to its effect on IR (57). However, the treatment with pioglitazone for more than one year may be associated with an increased risk of bladder cancer (58-60).

Recently, as shown in Table 2, several gene variants have been also associated with the TZDs therapy outcomes (61). Adipokinins, including adiponectin, leptin, resistin, peroxisome proliferator-activated receptor γ (PPARγ) and tumor necrosis factor (TNF)-α, are of a particular interest due to their important role in IR. Loss-of-function mutations in PPARγ are associated with severe IR and diabetes mellitus (62). Variants in *PPARG* or *ADIPOQ* (adiponectin) have been variably associated with TZDs response. Strikingly, rosiglitazone was significantly more effective in diabetic patients with Pro12Ala polymorphism of *PPARG*, who consequently had a significantly greater decrease in FPG and HbA1c levels than carriers of the wild-type genotype (63). A recent study reported that Thr394Thr and Gly482Ser SNPs of the peroxisome proliferator activated receptor-γ coactivator-1α (PGC-1α), which is a transcriptional coactivator of PPARγ, were also associated with rosiglitazone efficacy in Chinese T2DM patients (64). In addition, a pilot study suggested that the G/G genotype of resistin SNP-420 may be an independent predictor of the reduction of FPG and HOMA-IR (Homeostasis Model of Assessment-Insulin Resistance) by pioglitazone (65). Furthermore, recent studies demonstrated that the genetic variations of –11377C/G and T45G in adiponectin gene (66) and leptin G-2548A (67), as well as TNF-α G-308A (67) appeared to affect rosiglitazone efficacy and reversed IR in Chinese diabetic patients.

Treatment with TZDs has been particularly associated with high rates of developing fluid retention and peripheral edema, leading to congestive heart failure (52). Interestingly, a recent study done by Chang *et al*. (68) have suggested that rs296766 polymorphism of *AQP2* gene coding aquaporin-2 (the vasopressin-regulated water channel), and rs12904216 polymorphism of *SLC12A1* (the solute carrier protein family 12 group A, member one) gene coding the sodium-potassium-2 chloride

Table 2. Summary of the gene polymorphisms involved in the pharmacogenetics of thiazolidinediones.

SNP	Study population	Associated response phenotype	Reference
PPARG			
Pro12Ala (rs1801282)	Patients with T2DM (N = 198), 12-week rosiglitazone therapy.	The decrease in FPG and HbA1c levels was significantly greater in subjects with the Pro12Ala genotype, who had a significantly better drug response.	Kang et al, 2005 (63)
PGC-1α			
+1302G>A (Thr394Thr) (rs2970847) +1564G>A (Gly482Ser) (rs8192678)	Patients with T2DM (N = 41), 12-week rosiglitazone therapy.	Patients with the A or Ser variant were more likely to have a negative response; patients with Gly482Gly genotype had decreased FPG and PINS to a greater degree compared with Gly482Ser + Ser482Ser genotype.	Zhang et al, 2010 (64)
Resistin			
-420 C>G (rs1862513)	Prospective study: T2DM patients treated with pioglitazone (N = 121) Retrospective study: T2DM patients treated with pioglitazone (N = 63)	The reduction of HbA1c correlated with the G/G genotype.	Makino et al, 2009 (65)
Adiponectin			
45T>G (Gly15Gly) (rs2241766) -11377C>G (rs266729)	Patients with T2DM (N = 42) treated 12 weeks with rosiglitazone.	Attenuated effect in -11377CG +GG heterozygotes on FPG, PPG, HOMA-IR compared with CC genotype; enhanced effect in patients with -11377/45 CGTT diplotype on FPG and PPG.	Sun et al, 2008 (66)
Leptin			
-2548G>A (rs7799039)	Patients with T2DM (N = 42) treated 12 weeks with rosiglitazone.	Patients with G allele had significantly lower BMI and serum leptin levels and increased FPG than patients with AA genotype.	Liu et al, 2008 (67)
TNF-alpha			
-308G>A (rs1800629)	Patients with T2DM (N = 42) treated 12 weeks with rosiglitazone.	Attenuated effect in patients with GA+AA genotype on FINS compared with GG genotype.	Liu et al, 2008 (67)
CYP2C8			
*3 (Arg139Lys and Lys399Arg) (rs10509681)	Healthy volunteers (N = 31); a single-dose rosiglitazone.	Decreased mean total clearance, elimination half-lives, and plasma glucose AUC; *3 allele confers higher in vivo metabolic capacity than the wild-type *1 allele.	Kirchheiner et al, 2006 (71)

FPG - fasting plasma glucose; PINS - postprandial insulin; PPG - postprandial glucose; HOMA-IR - homeostasis model of assessment - insulin resistance; BMI - body mass index; FINS - fasting insulin; AUC - area under the curve.

transporter (NKCC2) with a key role in electrolyte movement across epithelia, represented risk factors for TZDs-associated edema. In addition to these genetic factors, the same study demonstrated that female gender and older age were also contributing factors to the edema development following TZDs treatment.

A recent study showed a diminished effect of pioglitazone treatment on glycemic control in patients with Ser447X polymorphism of gene encoding lipoprotein lipase (LPL), the enzyme responsible for the lipolytic processing of triglyceride-rich lipoproteins (61). CYP2C8 and CYP3A4 are the main DME catalyzing biotransformation of the pioglitazone (69), whereas rosiglitazone is metabolized by CYP2C8 and CYP2C9 (70). Genetic variation in *CYP2C8* was found to be associated with altered clearance of rosiglitazone, with higher drug clearance in carriers of *CYP2C8*3* allele coding for Arg139-Lys and Lys399Arg amino acid substitutions (71).

Biguanides

The biguanide drug metformin is recommended as the first-line therapy for T2DM (72). A main action of metformin is suppression of hepatic gluconeogenesis (73). Other antihyperglycemic effects include an increase of glucose uptake and utilization, improvement of insulin sensitivity, and reduction of intestinal glucose absorption (73). The molecular mechanisms of metformin action are not fully elucidated. It is believed that metformin increases the AMP/ATP ratio by specific inhibition of mitochondrial respiratory-chain complex 1, which leads to the activation of adenosine monophosphate-activated protein kinase (AMPK) (74-77). Potential mechanism of AMPK phosphorylation by metformin includes the upstream serine-threonine kinase11 (STK11/LKB1) (78). However, a recent study showed that metformin could also inhibit gluconeogenesis in an AMPK-independent way (79).

Metformin is not metabolized but is excreted unchanged in urine by active tubular secretion (80). There is large variation in metformin renal clearance, and genetic factors contribute to this by more than 90% (81,82). Its oral absorption, hepatic uptake and renal elimination are mediated by carrier proteins (83). The intestinal absorption of metformin is probably mediated by plasma membrane monoamine transporter (PMAT, encoded by *SLC29A4* gene), expressed on the luminal side of enterocytes (84). Organic cation transporter 1 (OCT1, encoded by *SLC22A1* gene), expressed in the basolateral membrane of hepatocytes, mediates hepatic metformin uptake (85). OCT2 (encoded by *SLC22A2*), expressed primarily at the basolateral membrane in the kidney tubular cells, facilitates uptake of metformin into proximal tubule cells (86). The multidrug and toxin extrusion transporter 1 (MATE1, encoded by *SLC47A1*) and MATE2-K (encoded by *SLC47A2*), located in the apical membrane of the renal proximal tubule cells, facilitate metformin excretion from tubular cells into urine (87-89).

The therapeutic response to metformin is highly variable. In patients receiving metformin as an initial treatment for T2DM, less than two-thirds achieve desired glycemic control or the HbA_{1c} goal of < 7% (< 53 mmol/mol) (90). This implies that identification of genetic factors associated with treatment effectiveness could be relevant. The majority of pharmacogenetic studies of metformin response have investigated the effects of polymorphisms in the gene encoding OCT1, *SLC22A1* (Table 3). OCT1 is necessary for metformin transport into the liver and subsequent metformin activity. Human *SLC22A1* gene is highly polymorphic. Reduced-function polymorphisms of the *SLC22A1* gene, such as R61C (rs12208357), G401S (rs34130495), 420del (rs72552763), and G465R (rs34059508) have been associated with lower effects of metformin in the oral glucose tolerance test (91). These same SNPs were also associated with a significantly higher metformin AUC, higher maximal plasma concentration and lower oral volume of distribution (92). However, a subsequent study demonstrated an additive increase in renal clearance of metformin with increasing number of reduced-function alleles (93). In a large population-based GoDARTS study the effects of R61C and 420del variants on initial glycemic response to metformin, the mid-term HbA_{1c} control, and the rate of metformin monotherapy failure were not found (94). Another study analyzed the effects of 11 tagging SNPs in the *SLC22A1* gene on HbA1c reduction, in a smaller cohort of incident users of metformin (95). A significant association of intronic rs622342 A>C SNP and lower HbA1c reduction was found (95).

A recent prospective study investigated the effects of variations in genes encoding OCT1, OCT2, MATE1, MATE2, and PMAT, on the trough steady-state plasma concentration (Css) of metformin and HbA1c change in T2DM patients treated with metformin (96). The mean trough Css of metformin, as well as the absolute decrease in HbA1c levels after 6 and 24 months, correlated conversely with the number of reduced-function *SLC22A1* alleles (R61C, G401S, M420del and G465R) (96). It is hypothesized that in patients with reduced function OCT1 variants, less metformin is transported into hepatocytes and the volume of distribution decreases, resulting in a shorter half-life and lower trough Css of metformin (96). These results are in accordance

Table 3. Summary of the gene polymorphisms involved in the pharmacogenetics of biguanides.

SNP	Study population	Associated response phenotype	Reference
SLC22A1			
R61C (Arg61Cys) (rs12208357) G401S (Gly401Ser) (rs34130495) 420del (rs72552763) G465R (Gly465Arg) (rs34059508)	Healthy volunteers (N = 21).	Lower effects of metformin in the oral glucose tolerance test.	Shu et al, 2007 (91)
	Healthy volunteers (N = 20).	Higher metformin AUC, higher maximal plasma concentration and lower oral volume of distribution.	Shu et al, 2008 (92)
	Healthy men (N = 103).	Additive increase in renal clearance of metformin with increasing number of reduced-function alleles.	Tzvetkov et al, 2009 (93)
	Prospective study: T2DM patients treated with metformin (N = 159).	Inverse correlation of metformin trough Css and reduction of HbA1c levels with the number of reduced-function SLC22A1 alleles.	Christensen et al, 2011 (96)
R61C (Arg61Cys) (rs12208357) 420del (rs72552763)	Population-based GoDARTS study: T2DM patients, incident users of metformin (N = 1.531).	No effects on initial glycemic response to metformin, the mid-term HbA1c control, and the rate of metformin monotherapy failure.	Zhou et al, 2009 (94)
rs622342 A>C	Population-based study: T2DM patients, incident users of metformin (N = 102).	Lower HbA1c reduction.	Becker et al, 2009 (95)
SLC22A2			
T199I (Thr199Ile) (rs201919874) T201M (Thr201Met) (rs145450955) A270S (Ala270Ser) (rs316019)	Healthy subjects (N = 26).	Increased metformin Cmax and AUC and reduced renal clearance of metformin.	Song et al, 2008 (100)
A270S (Ala270Ser) (rs316019)	Healthy subjects (N = 15).	Reduced renal clearance of metformin.	Wang et al, 2008 (101)
	Healthy subjects (N = 23).	Increased metformin renal clearance.	Chen et al, 2009 (102)
SLC47A1			
rs2289669 G>A	Population-based study: T2DM patients, incident users of metformin (N = 116).	Greater reduction of HbA1c levels.	Becker et al, 2009 (103)
rs8065082 C>T	DPP study: individulas at high risk for T2DM randomized to placebo (N = 1.000), metformin (N = 990) or lifestyle intervention program (N = 1.004).	Lower diabetes incidence in subjects treated with metformin.	Jablonski et al, 2010 (104)
SLC47A2			
rs12943590 G>A	Retrospective study: T2DM patients initially treated with metformin (N = 253).	Lower HbA1c reduction.	Choi et al, 2011 (105)
ATM			
rs11212617 A>C	GWA study (N = 1.024) and two replication cohorts (N = 1.783 and N = 1.113) of T2D patients, incident users of metformin.	Association with treatment success (achieving an HbA1c below 7% (53 mmol/mol)), the combined odds ratio = 1.35.	Zhou et al, 2011 (107)

AUC - area under the curve; C_{ss} - steady-state plasma concentration; C_{max} – peak plasma concentration.

with previous studies (91,93). Replication of results regarding influence of OCT1 low-activity alleles on metformin pharmacokinetics and response, indicated that those variants could be useful pharmacogenetic markers for metformin therapy.

The first study on the association of genetic variations of OCT1, OCT2, and MATE1 transporters with gastrointestinal side effects of metformin therapy has been recently published (97). The minor alleles of rs628031 (M408V) and rs36056065 (8 bp insertion), which are two variants of the *SLC22A1* gene in strong LD, were significantly associated with the presence of side effects (97). The local increase of drug concentration in the intestinal tissue is proposed as a mechanism of metformin intolerance (98). OCT1 and OCT3 (encoded by *SLC22A3* gene) are also expressed in enterocytes (99), and although their role in the intestinal transport of metformin is not yet defined, authors suggest that SNPs in these genes may influence the intestinal metformin uptake and thus induce gastrointestinal side effects (97).

The results of the studies exploring the effect of the only common coding variant in the gene encoding OCT2 (*SLC22A2*), A270S (rs316019), on metformin clearance, have been contradictory. Two studies found significantly reduced renal clearance of metformin in homozygous variant carriers compared to wild-type homozygotes (100,101). Interestingly, a separate study reported the opposite effect in individuals heterozygous for A270S variant who had higher metformin renal clearance as compared to the reference group (102). Christensen *et al*. (96) did not find the association between A270S and metformin trough Css or therapeutic response. However, given the importance of OCT2 in metformin pharmacokinetics, further pharmacogenetic studies are needed.

A preliminary study in the incident metformin users from the population-based Rotterdam study cohort assessed the influence of variations in MATE1-encoding gene, *SLC47A1*, on the HbA1c-lowering effect of metformin (103). From 12 tagging SNPs analyzed, the rs2289669 G>A in intron 10 was associated with greater reduction in HbA1c levels (103). In a latter large-scale prospective clinical study (Diabetes Prevention Program, DPP) an association of rs8065082 SNP in the *SLC47A1* gene and lower diabetes incidence in subjects treated with metformin was found (104). This SNP was in high LD with rs2289669 G>A and thus, the DPP study confirmed the findings from a small preliminary study of Becker *et al*. (103). However, rs2289669 G>A was not associated with metformin renal clearance (93), nor with metformin trough Css (96), and the mechanism underlying the impact of this *SLC47A1* SNP remained unclear.

A recent study analyzed the effect of the MATE2-K gene (*SLC47A2*) polymorphism on glycemic response to metformin in newly diagnosed T2DM patients (105). A common 5'-UTR variant, g.-130-G>A (rs12943590), was associated with enhanced promoter activity and weaker response to metformin, assessed by the relative HbA1c change (105). The study also explored the impact of OCT1, OCT2, and MATE1 variants on the initial metformin response. In line with previous studies (103,104), the intronic rs2289669 G>A SNP in MATE1 gene was associated with higher HbA1c relative change, almost at the level of statistical significance (105).

In addition, other candidate genes which are likely to modulate metformin pharmacokinetics and response are genes encoding OCT3 (*SLC22A3*) and PMAT (*SLC29A4*) transporters. Recent *in vitro* study suggested that OCT3 is implicated in the uptake of metformin in muscle cells and its genetic variants may modulate metformin action (106). Genetic polymorphisms in PMAT showed a tendency of association with lower metformin trough concentration, and could be associated with decreased metformin absorption (96).

Recently, the first genome-wide association study (GWAS) on glycemic response to metformin in T2DM was performed. The study identified a common rs11212617 A>C SNP associated with treatment success in the large GWAS cohort (107), which was replicated in the two additional cohorts (107). The authors proposed that *ATM* (the ataxia telangiectasia mutated) gene, encoding a serine/threonine protein kinase of the phosphoinositide 3-kinase-related protein kinase (PIKK) family, was the causative gene due to its association with IR, increased T2DM risk, and its role in AMPK activation (107). In general, additional studies are re-

quired to identify genes involved in mechanisms of metformin pharmacological action.

Meglitinides

This class of short-acting insulin secretagogues acts by binding to β-cells and inhibiting KATP channel to stimulate insulin release. This is similar to the mechanism of action of the sulphonylureas and both, meglitinides (glinides) and SU, bind at two sites of the SUR1 subunit to inhibit channel activity (108). These two sites are thought to overlap to accommodate the negative charge and the central phenyl ring present in both, SU and meglitinides (109). Repaglinide is specifically designed to stimulate early insulin secretion in the postprandial period after binding to a distinct site on the β-cell (110). Similarly, nateglinide is an amino acid derivative that also induces an early insulin response to meals decreasing postprandial blood glucose levels. Due to their short action, meglitinides have a lower risk to induce hypoglycemia than SU. Furthermore, meglitinides offer an alternative OAD agent of similar potency to metformin, and may be indicated where side effects of metformin are intolerable or where metformin is contraindicated.

Gene polymorphisms associated with the variable meglitinides response are summarized in Table 4. A recent study showed that *SLCO1B1* gene, which encodes the organic anion-transporting polypeptide 1B1 (OATP1B1), is a major determinant that markedly affects the repaglinide pharmacokinetics (111), consistent with an enhanced hepatic uptake by OATP1B1. *SLCO1B1* 521T>C SNP appeared to play an important role in the nateglinide pharmacokinetics (112). However, a study done by Kalliokoski *et al*. (113) found that, in contrast to repaglinide, the nateglinide disposition was not affected by the *SLCO1B1* 521T>C SNP. Furthermore, the same research group demonstrated that the *SLCO1B1*1B/*1B* genotype was associated with reduced plasma levels of repaglinide, but had limited effects on the nateglinide disposition (114). A very recent study performed in healthy Chinese population have demonstrated that both, the *521T>C* SNP of *SLCO1B1 and CYP2C9*3* polymorphism, could significantly affect the nateglinide pharmacokinetics (115). However, these variants were not significantly associated with variations in its glucose-lowering effects and could only partially explain the interindividual variability of nateglinide plasma concentration (115).

Nateglinide is metabolized by CYP2C9 and moderate dose adjustments based on *CYP2C9* genotypes may affect its pharmacokinetics (115) and interindividual variability in its antihyperglycemic effects (70). Repaglinide is metabolized by CYP2C8 and CYP3A4 (116) and, according to clinical studies, *CYP2C8*3* carriers have higher clearance than carriers of the wild-type genotypes (70). However, recent study demonstrated that *CYP2C8*3* did not appear to affect the repaglinide pharmacokinetics (117).

A recent pharmacogenetic study done in the Chinese population showed that the G2677T/A SNPs of *MDR1* gene, encoding P-glycoprotein transporter, were associated with the variability in the repaglinide pharmacokinetics, suggesting that carriers of the *MDR1* 2677GT and TT allele might be exposed to higher levels of repaglinide (118).

Furthermore, Dai *et al*. (119) found that rs2237892 (C>T) and rs2237895 (C>A) SNPs, both located in intron 15 of *KCNQ1* gene (120), encoding a voltage-gated K+channel expressed in the various tissues including pancreas, were associated with the repaglinide efficacy in Chinese T2DM patients. Diabetic patients carrying the rs2237892 risk C allele had lower fasting insulin levels and HOMA-IR than those carrying the T allele. Furthermore, FPG and HOMA-IR levels were higher in T2DM patients with the rs2237895 risk C allele compared with the carriers of the A allele. Interestingly, following repaglinide treatment, T2DM patients with the rs2237892 T allele and the rs2237895 C allele were more likely to have a positive effect on postprandial glucose levels than patients with the rs2237892 CC and rs2237895 AA genotype (119). In addition, a recent study performed by Yu *et al*. (121) demonstrated that Chinese T2DM patients, who were rs2237892 TT homozygotes, had lower glucose levels following repaglinide treatment, while the rs2237895 C risk allele in those patients was associated with greater increments in both, fasting insulin and HOMA-IR levels.

Table 4. Summary of the gene polymorphisms involved in the pharmacogenetics of meglitinides.

SNP	Study population	Associated response phenotype	Reference
SLCO1B1			
521T>C (Val174Ala) (rs4149056)	Healthy volunteers (N = 17); a single-dose of nateglinide.	The Cmax and AUC of nateglinide were higher in the subjects with the TC and CC genotype compared to the TT genotype; the t1/2 of nateglinide in CC subjects was longer than in subjects with TT genotype.	Zhang et al, 2006 (112)
	Healthy volunteers (N = 31); a single-dose of nateglinide.	Significant predictor of the AUC of nateglinide (a combined effect with the CYP2C9*3).	Cheng et al, 2012 (115)
	Healthy volunteers in two studies (N = 12) and (N = 32); a single-dose of repaglinide.	AUC of repaglinide was larger in participants with the CC genotype than in those with the TT genotype.	Kalliokoski et al, 2008 (111, 113)
SLC30A8			
973C>T (Arg325Trp) (rs13266634) 974G>A (Arg325Gln) (rs16889462)	Patients with T2DM (N = 48) treated 8 weeks with repaglinide.	Better response on FINS and PINS in patients with rs13266634 CT+TT genotypes compared with CC genotype. In patients with rs16889462 GA genotype an enhanced repaglinide efficacy on FPG, PPG, and HbA1c compared with GG genotype.	Huang et al, 2010 (122)
MDR1			
2677G>T/A (Ala893Ser/Thr) (rs2032582)	Healthy volunteers (N = 24); a single-dose of repaglinide.	AUC of repaglinide was significantly higher in subjects with the GT and TT alleles than in those with the GG and TA alleles.	Xiang et al, 2012 (118)
KCNQ1			
rs2237892 C>T rs2237895 A>C	Patients with T2DM (N = 40) treated 8 weeks with repaglinide.	T2DM patients with the rs2237892 T allele and rs2237895 C allele were more likely to have a positive response in terms of PPG levels than T2DM patients with the rs2237892 CC and rs2237895 AA genotypes.	Dai et al, 2012 (119)
	Patients with T2DM (N = 209) treated 8 weeks with repaglinide.	rs2237892 TT homozygotes exhibited lower 2-h glucose levels than the C allele carriers; rs2237892 C and rs2237895 C alleles were associated with larger increase in FINS and HOMA-IR.	Yu et al, 2011 (121)
KCNJ11			
67 A>G (Lys23Glu) (rs5219)	Patients with T2DM (N = 40) treated 8 weeks with repaglinide.	Patients with the GA or AA genotype showed higher levels of FPG, PPG, and HbA1c compared with patients with GG genotype.	Yu et al, 2010 (123)
TCF7L2			
rs290487 C>T	Patients with T2DM (N = 40) treated 8 weeks with repaglinide.	In patients with the TT genotype, a better efficacy with respect to FINS, triglycerides, and LDL-c compared to the CC or CT genotype.	Yu et al, 2010 (123)
NAMPT			
-3186 C>T (rs11977021)	Patients with T2DM (N = 35) treated 8 weeks with repaglinide.	The elevated PINS in patients with CT genotypes of -3186 C/T were significantly lower than that in patients with the CC and TT genotypes.	Sheng et al, 2011 (124)
CYP2C9			
*3 (Ile359Leu) (rs1057910)	Healthy volunteers (N = 31); a single-dose of nateglinide.	Significant predictor of the AUC of nateglinide (a combined effect with the SLCO1B1 521T>C).	Cheng et al, 2012 (115)

C_{max} – maximum plasma concentration; AUC - area under the curve; $t_{1/2}$ - elimination half-life; FINS - fasting insulin; PINS - postprandial insulin; FPG - fasting plasma glucose; PPG - postprandial glucose; HOMA-IR - homeostasis model of assessment - insulin resistance; LDL-c - low-density lipoprotein cholesterol.

Polymorphisms of the zinc transporter solute carrier family 30 member 8 gene (*SLC30A8*), including rs13266634 (973C>T, Arg325Trp) and rs16889462 (974G>A, Arg325Gln) SNPs, were recently reported to be related to T2DM development and importantly, to the repaglinide efficacy in Chinese T2DM patients (122). Patients with rs13266634 CT+TT genotypes showed decreased fasting and postprandial insulin levels compared to patients with CC genotype, while a significant differences in the decreased fasting and postprandial glucose and HbA1c levels were found between T2DM patients with GA and GG genotype of *SLC30A8* rs16888462 SNP. Since *SLC30A8* is mainly expressed in the pancreatic β-cells and appears to play a critical role during insulin maturation and release, the authors have speculated that *SLC30A8* variations influence the zinc disposition and that KATP function, affecting the therapeutic efficacy of repaglinide (122).

Furthermore, the *KCNJ11* and *TCF7L2* polymorphisms seemed also to be associated with repaglinide efficacy in Chinese T2DM patients (123). Diabetic patients with the GA or AA genotype of the *KCNJ11* Lys23Glu SNP showed higher levels of fasting and postprandial glucose and HbA1c following repaglinide treatment than in patients with the GG genotype. On the other hand, in T2DM patients with the TT genotype of *TCF7L2* rs290487 (C/T), the drug showed better efficacy with respect to levels of fasting insulin, triglycerides, and low-density lipoprotein cholesterol as compared to carriers of the CC or CT genotype (123).

A recent study performed by Sheng *et al*. (124) suggested that the -3186C>T SNP of gene encoding nicotinamide phosphoribosyltransferase (NAMPT) was significantly associated with postprandial insulin and total cholesterol levels in Chinese T2DM patients treated with repaglinide. Following the drug treatment, the elevated postprandial insulin levels as well as the total cholesterol levels in patients with CT genotype were significantly lower than in T2DM patients with the CC and TT genotype of the -3186C>T polymorphism (124).

Conclusions

In conclusion, the evidence has been accumulating to show that pharmacogenetics/pharmacogenomics has the potential to improve the management of T2DM and the effective OAD prescribing. Several variants related to drug-metabolizing enzymes, drug-transporters, drug target, and diabetes risk genes have been linked to interindividual differences in the OAD treatment outcomes. As summarized here, significant pharmacogenetic evidence has demonstrated an association between specific gene polymorphisms and interindividual variability in OAD therapeutic and side effects. Identification of drug-genotype interactions in pharmacogenetic studies of the OAD treatment might have clinical implications in the near future resulting in selection of more specific personalized therapy in T2DM. Although benefits from a personalized diabetes care are well established in patients with certain monogenic forms of diabetes, individualized treatment options in the more common polygenic forms of diabetes are also anticipated. However, it is also well understood that the diversity in drug effects cannot be explained by studying the genomic variations only and there are many potential barriers to the translation of pharmacogenetic findings to the antidiabetic treatment. Particularly, epigenomic research that focuses on nongenomic modifications influencing gene expression, may expand the scope of pharmacogenomics towards optimization of drug therapy. Recently introduced "miRNA-pharmacogenomics" that analyzes the polymorphisms in the miRNA regulatory pathway and its association with drug response, would also provide useful information for personalized medicine. Since the pharmacogenetic associations in diabetes that have been reported to date have had limited impact on the individual treatments choice, the value of genetic information in guiding therapeutic decisions in T2DM treatment must be further tested in adequately designed and rigorously conducted clinical trials. With recent scientific and technological advances, pharmacogenomics has a great potential to yield therapeutic advances leading the way towards personalized diabetes care.

Potential conflict of interest

None declared.

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