**Name of journal: World Journal of Translational Medicine**

**ESPS Manuscript NO: 12821**

**Columns: MINIREVIEWS**

**Pharmacogenetics of type 2 diabetes mellitus: An example of success in clinical and translational medicine**

Brunetti A *et al*. Pharmacogenetics of type 2 diabetes

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**Received:** July 27, 2014 **Revised:** September 25, 2014

**Accepted:** October 31, 2014

**Published online:**

**Abstract**

The pharmacological interventions currently available to control type 2 diabetes mellitus (T2DM) show a wide interindividual variability in drug response, emphasizing the importance of a personalized, more effective medical treatment for each individual patient. In this context, a growing interest has emerged in recent years and has focused on pharmacogenetics, a discipline aimed at understanding the variability in patients’ drug response, making it possible to predict which drug is best for each patient and at what doses. Recent pharmacological and clinical evidences indicate that genetic polymorphisms (or genetic variations) of certain genes can adversely affect drug response and therapeutic efficacy of oral hypoglycemic agents in patients with T2DM, through pharmacokinetic- and/or pharmacodynamic-based mechanisms that may reduce the therapeutic effects or increase toxicity. For example, genetic variants in genes encoding enzymes of the cytochrome P-450 superfamily, or proteins of the ATP-sensitive potassium channel on the beta-cell of the pancreas, are responsible for the interindividual variability of drug response to sulfonylureas in patients with T2DM. Instead, genetic variants in the genes that encode for the organic cation transporters of metformin have been related to changes in both pharmacodynamic and pharmacokinetic responses to metformin in metformin-treated patients. Thus, based on the individual’s genotype, the possibility, in these subjects, of a personalized therapy constitutes the main goal of pharmacogenetics, directly leading to the development of the right medicine for the right patient. Undoubtedly, this represents an integral part of the translational medicine network.

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**Key words:** Type 2 diabetes; Anti-diabetic drugs;Personalized therapy; Genetic variants; Genome-wide association study

**Core tip:** Type 2 diabetes mellitus (T2DM) is a heterogeneous complex disorder, in which predisposing genetic variants (polymorphisms) and precipitating environmental factors interact synergistically in the development of the disease. Besides being useful in identifying individuals at risk for T2DM, knowledge of the polymorphisms associated with T2DM is also useful in pharmacogenetics for correlating individual variants with individual responses to anti-diabetic drugs. To date, a wide variety of genes that influence pharmacogenetics of anti-diabetic drugs have been identified. However, with few exceptions, drug therapy has not taken into account the individual genetic diversity of treated patients, representing, this, a substantial limitation of pharmacogenetics. This review focuses on clinically important polymorphisms affecting a patient’s response to diabetic medications.

Brunetti A, Brunetti FS, Chiefari E. Pharmacogenetics of type 2 diabetes mellitus: An example of success in clinical and translational medicine. *World J Transl Med* 2014, In press

**INTRODUCTION**

The common observation that patients with type 2 diabetes mellitus (T2DM) show a great variability in the individual response to the same drug treatment suggests the importance of a personalized care approach, in which the most appropriate treatment is indicated by the genetic peculiarities of each individual[1]. The introduction, in 2007, of genome-wide association study (GWAS) has greatly enhanced the number of genes that are known to be associated with common diseases. Applied to millions of people, this method has allowed the identification of several genetic variants which are associated with T2DM[2]. However, similarly to other complex diseases, none of the individual variants identified so far is in itself sufficient to cause the disease, but most of the genetic risk for T2DM is mediated by the combined influence of more genetic variants that individually have only a small degree of risk[3,4]. This combination (haplotype) defines the genetic profile of the individual. The fact that the pathogenesis of T2DM requires the involvement of multiple genes in different combination is in line with the assumption that T2DM, far from being a disease genetically identifiable in a few specific forms, actually consists of a large number of rather different disorders[3,4], each of which is associated with a specific disease phenotype only apparently identical to one another, and in which inter-individual variability in drug response can be identified both in terms of drug efficacy and undesired drug reactions.

Therefore, clarifying the molecular mechanisms by which genetic variations may cause differences in phenotypic traits and in individual drug response is essential not only to determine the etiological role of gene variants, but also to identify new personalized medical solutions. Personalized therapy, based on the genetic diversity of each individual, is one of the most fascinating challenges of modern medicine, representing an integral part of the translational medicine effort, whose ultimate goal is to translate advances in biomedical research into new medical treatments and improvements in patient care (Figure 1). Herein, we provide an overview of this area and its relevance to clinical practice in T2DM.

**PHARMACOGENETICS AND GENE POLYMORPHISMS**

Pharmacogenetics is defined as the influence of variations in DNA sequence on drug response (www.ema.europa.eu). Its relevance arises from the clinical observation that patients suffering from the same disease do not necessarily respond to the same drug treatment in terms of therapeutic efficacy as well as adverse effects. The principal aim of pharmacogenetics is to provide personalized medicine, tailored to an individual’s genetic makeup, in order to optimize the effectiveness and safety of drug treatment. Although elements of pharmacogenetics can be traced back to ancient Greece (510 years BC), when it was already known the risk of hemolytic anemia in certain individuals in response to the ingestion of uncooked fava beans[5], the term “pharmacogenetics” was first coined by Friedrich Vogel in 1959[6] to indicate the importance of genetic polymorphisms on the disposition and action of drugs. The first evidence on the role of genetic variants in drug response back to the ‘70s and refers to cytochrome P-450 2D6 (CYP2D6), an enzyme of the hepatic P-450 microsomal enzyme system, which is involved in the metabolism of numerous drugs. Studies of the genetic variations within the P-450 family of enzymes provided the first direct evidence for the genetic contributions to drug therapy and efficacy, and these studies continue to be an active part of the basic and clinical research performed today. In fact, numerous other genetic variations have been identified in subsequent years, within the P-450 family of enzymes, including the biotransformation enzymes CYP3A4/5 and the cytochrome P-450 2C9 enzyme (CYP2C9). It has been shown that individuals carrying genetic variants of *CYP2D6* (and other P-450 isoforms resulting in poor enzymatic activity), who are concomitantly taking medications that are influenced by these enzymes, are at risk for increased or prolonged drug effect, influencing the speed and effectiveness of drug metabolism[7]. However, there is no doubt that the greatest contribution to pharmacogenetics has come from the sequencing of the entire human genome in 2003, showing that over 99% of DNA is identical in all humans and that, therefore, phenotypic differences among individuals, as well as differences in disease susceptibility and the inter-individual variability in drug response, are the result of sequence polymorphisms that affect less than 1% of 3 billion bases of human DNA. In most cases, these variants consist of the exchange of single nucleotides in both coding and noncoding DNA regions and are defined as single nucleotide polymorphisms (SNPs) (Figure 2). The ability of the SNP to influence drug response and therapeutic efficacy may rely on the capacity of the variant to induce changes in the expression of proteins that may influence either the pharmacokinetic and/or pharmacodynamic profile and hence the clinical efficacy of the drug. On the basis of these acquisitions, recent GWAS have identified several SNPs that can affect both the therapeutic efficacy and the occurrence of adverse reactions after drug intake[8-10].

**PHARMACOGENETICS IN T2DM TREATMENT**

***Pharmacogenetics of sulfonylureas***

In Caucasians, sulfonylureas are metabolized primarily in the liver by CYP2C9 to active metabolites, which are ultimately excreted by the kidney[11]. In previous work, it was demonstrated that polymorphisms of the *CYP2C9* gene significantly affect the pharmacological response of diabetic patients to sulfonylureas[12], due to the reduction of the catalytic activity in the metabolism of these drugs[13-16], with a consequent increase in drug bioavailability. In particular, in certain diabetic patients with the variants Ile359Leu (isoleucine changes to leucine in exon 7 position 359) and Arg144Cys (arginine changes to cysteine in exon 3 position 144) in the *CYP2C9* gene, the clearance of glibenclamide was reduced by 30-80%, allowingthe use of lower doses of this drug to limit the risk of hypoglycemia[12,17-20]. The risk of hypoglycemia in sulphonylurea treated patients was confirmed in a study with a larger population, in which the simultaneous presence (or the presence in homozygosity) of the variants Ile359Leu and Arg144Cys in the *CYP2C9* gene was associated with the improvement in markers of glycemic control, including glycated hemoglobin A1c (HbA1c)[21]. Therefore, genotyping of the *CYP2C9* gene may provide important additional information in predicting the adverse effects of these drugs and to assist physicians in prescribing oral hypoglycemic agents.

The ATP-sensitive potassium (K-ATP) channel plays a central role in mediating glucose-stimulated insulin release from pancreatic beta-cells (Figure 3). In physiological conditions, the rapid entry of glucose into the beta-cell results in an increase in the intracellular concentration of ATP, which promotes the closure of the ATP-sensitive K+ channel (K-ATP channel) with consequent opening of the voltage-dependent calcium channel, elevation of intracellular calcium ion concentration and insulin secretion. The K-ATP channel is composed of two subunits: the sulphonylurea receptor (SUR1) and the pore-forming inward rectifier K+ channel Kir6.2[22,23]. Genetic variants inactivating the *KCNJ11* (potassium inwardly-rectifying channel, subfamily J, member 11) gene, which encodes for the protein Kir6.2, and the *ABCC8* [ATP-binding cassette, sub-family C (CFTR/MRP), member 8] gene, which encodes the SUR1 protein, are responsible for neonatal diabetes mellitus; conversely, activating mutations of these two genes lead to hyperinsulinism and neonatal hypoglycemia[24]. As an example of pharmacogenetics with important clinical implications, recent studies have found that diabetic patients carrying mutations in the *KCNJ11* gene respond better to treatment with sulfonylureas than to treatment with insulin[25-27].

Association of the polymorphism Ser1369Ala (serine 1369 to alanine substitution) in *ABCC8* with the antidiabetic efficacy of gliclazide was found in patients with T2DM, after two months of treatment[28]. In particular, patients with the genotype alanine/alanine had a greater reduction in either fasting plasma glucose or 2 hours postload plasma glucose during oral glucose tolerance test, and a greater decrease in HbA1c levels compared to patients with the Serine/Serine genotype[28]. The variant Ser1369Ala in *ABCC8* is often associated in linkage disequilibrium with a variant, Glu23Lys (glutamine to lysine variant at position 23), in the *KCNJ11* gene, forming a haplotype that increases the risk of developing T2DM[29]. It has been observed that this haplotype displays large differences to the therapeutic effects of various sulfonylureas: greater to gliclazide, less apparent to tolbutamide, chlorpropamide and glimepiride, invariable in the glipizide and glibenclamide treatment group[30].

Interesting results, in this context, have been obtained from the study of the transcription factor 7-like 2 (*TCF7L2*) gene, which encodes a nuclear transcription factor that appears to play a role in beta-cell function. Genetic variants of *TCF7L2* are associated with increased risk of T2DM[3]. Recently, two variants of the *TCF7L2* gene, rs7903146 (G > T), and rs7903146 (C > T), have been shown to influence the therapeutic efficacy of sulfonylureas[31-33]. In particular, the reduction in both HbA1c and fasting plasma glucose was higher in diabetic patients carrying either GG or CC genotypes[31-33]. In contrast, diabetic patients with the TT genotype in both the rs7903146 (G > T) and the rs7903146 (C > T) variants showed a lower response to sulfonylureas and appeared to be more prone to therapeutic failure[31-33].

***Pharmacogenetics of metformin***

Metformin, in use for control of diabetes since 1950s, is the first-line pharmacological therapy for T2DM. After oral administration, the drug is absorbed into the blood via the gastrointestinal tract, rapidly distributed in body tissues by travelling through specific transport proteins (including the organic cation transporters OCT1 and OCT2, the multidrug and toxin extrusion transporters MATE1 and MATE2-K, and the plasma membrane monoamine transporter PMAT) located on the cytoplasmic membrane of many cells, especially intestinal cells, liver cells and kidney cells[34], and excreted in the urine almost unchanged from the original drug. The individual’s response to metformin is highly variable with less than 2/3 of treated patients achieving glycemic control[35]. Thus, identification of genetic variants that may influence the interindividual variability to metformin would be of major importance for the effective treatment of these patients. However, studies on the pharmacogenetics of metformin are relatively limited, mainly because its mechanism of action is still poorly defined. So far, most of the studies on this topic have involved the solute carrier family 22A1 (*SLC22A1*) gene, which by coding for the OCT1 transport protein, plays a key role in the cell absorption of the drug[36], and is essential for the anti-gluconeogenic effect of metformin into the liver[37] (Figure 4). It has been shown that polymorphisms of this gene (rs12208357; rs34130495; rs72552763; rs34059508), by reducing the functional capacity of OCT1, can alter the bioavailability of metformin and mitigate its hypoglycemic response in healthy people carrying these gene variants[37-39]. Recently, two polymorphisms of *SLC22A1* (rs628031 and rs36056065) have been associated with gastrointestinal side effects in diabetic patients treated with metformin[40]. At the same time, other authors[41,42] have also reported that the bioavailability of metformin was increased in healthy individuals carrying mutations of the *SLC22A2* gene, which encodes for the OCT2 transport protein. Variants of this gene, by adversely affecting OCT2 function, may decrease the renal clearance of metformin, and may contribute to increased plasma metformin levels with increased risk of hypoglycemic events.

Interindividual variation in metformin response has been recently reported in subjects with genetic variations in *SLC47A1* and *SLC47A2* genes coding for MATE1 and MATE2-K, respectively, which play important roles in the urine excretion of metformin. A better glycemic response to metformin, with lower HbA1c levels, has been reported in association with the *SLC47A1* gene variant rs2252281[43-46]. In contrast, the therapeutic response to metformin was reduced in diabetic patients carriers of the variant rs12943590 in the *SLC47A2* gene[45,46]. Therefore, these observations imply that genetic variants of MATE1 and MATE2-K are important determinants of the therapeutic efficacy of metformin in patients treated with this drug. The first GWAS on the efficacy of metformin on glycemic control in diabetic patients resulted in the demonstration that a gene variant near ataxia telangiectasia mutated (*ATM*), rs11212617, is significantly associated with metformin treatment response in T2DM, more frequently with HbA1c levels < 7%[47]. The explanation of this phenomenon lies in the role ATM, the protein product of the *ATM* gene, plays in the context of insulin signaling and insulin action[48].

Thus, genetic variants of *SLC22A1* and *SLC22A2* may be determinant in the therapeutic efficacy of metformin. Furthermore, genotyping of *SLC22A1* and *SLC22A2* is useful in the management of diabetic patients under metformin theraphy.

***Pharmacogenetics of thiazolidinediones***

Genetic variants that can influence the pharmacogenetics of oral antidiabetic medications were also assessed in diabetic patients treated with pharmacogenetics of thiazolidinediones (TZDs) (pioglitazone and rosiglitazone). As agonists of PPAR-γ (peroxisome proliferator-activated receptor gamma), TZDs act as insulin-sensitizing, thus reducing the release of glucose from the liver and increasing glucose uptake in muscle[49]. The *PPAR-γ* gene has been extensively investigated in pharmacogenetic studies of TZDs, especially because genetic variants of this gene have been associated with an increased risk of T2DM[3]. However, pharmacogenetic studies with TZDs have shown conflicting results, probably due to insufficient sample size and low levels of statistical power[50]. Furthermore, it is worthy noting that the retrospective study design used in the majority of studies on pharmacogenetics has its own drawbacks, being able to expose to a variety of confounding and bias, including age, gender, ethnicity, lifestyle, concomitant use of other medications, etc. A similar discrepancy has emerged from studies on the genetic variants of the *CYP2C8* gene, which is responsible for metabolizing pioglitazone[50]. A reduction in the blood glucose-lowering effect of pioglitazone was recently observed in diabetic patients carriers of the truncation variant, Ser447X, of the *LPL* (lipoprotein lipase) gene[51]. Another study has reported that the -420 C/G variant of the *resistin* gene promoter can also be used as an independent predictor of the reduction of fasting plasma glucose and insulin resistance by pioglitazone in T2DM[52]. As it is known, side effects of TZDs therapy include fluid retention and peripheral edema, worsening heart failure[53]. In this context, various genetic variations have been discovered in genes known to be involved in sodium and water reabsorption. Among these, the aquaporin 2 (*AQP2*) rs296766 variant and the *SLC12A1* rs12904216 variant, both of which have been associated with edema in T2DM patients treated with a TZD[54]. *AQP2* gene codes aquaporin-2, which function as a water channel in the collecting duct of the kidney[55]. *SLC12A1* encodes the kidney-specific sodium-potassium-chloride cotransporter, NKCC2, which plays an important role in both urine concentration and NaCl reabsorption[54,56]. Therefore, it is quite evident that these variants may represent both a risk factor for the development of edema in diabetic patients during treatment with TZDs.

***Pharmacogenetics of metiglinides***

Metiglinides (repaglinide and nateglinide) are a class of rapid-acting, short duration insulin secretagogues that act in a manner similar to that of the sulfonylureas[57]. Nateglinide is also metabolized by the CYP2C9 enzyme of the cytochrome P-450 system, and gene variants of *CYP2C9* are associated with variability in glucose-lowering effect of nateglinide[58]. Repaglinide is metabolized by CYP2C8 and to a lesser degree by CYP3A4[59]. Also in this case, gene variants of *CYP2C8* have been associated with increased clearance of repaglinide, although with contradictory results[60]. The solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) gene encodes for the organic anion transporting polypeptide, OATP1B1, which regulates cellular uptake of various drugs, including statins by the liver. Recent studies have reported the role of some variants of *SLCO1B1* in the pharmacokinetics of metiglinides[61-64]. For example, a more effective hypoglycemic effect of repaglinide was observed in diabetic patients carrying the Glu23Lys (E23K) polymorphism in the *KCNJ11* gene[65], and the rs13266634 variant in the *SLC30A8* gene[66]. Similarly, polymorphisms of neurogenic differentiation 1 (*NeuroD1*), also called beta2 (*NEUROD1/BETA2*), paired box gene 4 (*PAX4*)[67] and uptake control 2 (*UPC2*)[68] genes were also found to be associated with the hypoglycemic efficacy of repaglinide. An association of the variant G2677 T/A in the multidrug resistance (*MDR1*) gene, which encodes a multidrug efflux pump, with the variability in the pharmacokinetics of repaglinide was found recently in a Chinese study in healthy volunteers[69].

***Pharmacogenetics of incretins***

Glucagon-like peptide-1 (GLP-1) is part of the group of incretin hormones that are secreted from endocrine cells in the intestinal mucosa in response to meals. It mediates insulin secretion in a glucose-dependent manner and is easily inactivated after being secreted by the enzyme dipeptidyl peptidase-IV (DPP-IV). Recent pharmacological research has led to the development and synthesis of medications that are capable of acting at this level as both GLP-1 agonists (exenatide and liraglutide) and DPP-IV inhibitors (gliptins)[70]. Variants of the GLP-1 receptor (*GLP-1R*) gene have been shown to be associated with altered sensitivity to GLP-1[71]. Furthermore, whereas variants in the *TCF7L2* (rs7903146) and *WFS1* (wolfram syndrome 1) (rs10010131) genes have been associated with a reduced response to exogenous GLP-1, variations in the *KCNQ1* (rs151290, rs2237892, and rs2237895) gene appear to alter the secretion of endogenous GLP-1[72]. The only significant study on the pharmacogenetics of gliptins showed that three novel genetic loci [transmembrane protein 114 (*TMEM114*), carbohydrate sulfotransferase 3 (*CHST3*) and Chymotrypsinogen B1 (*CTRB1/2*)] were identified, which affect GLP-1-induced insulin release during hyperglycemic clamp in nondiabetic Caucasian subjects[73].

**CONCLUSION**

Pharmacogenetics is an expanding area of research which seeks to understand how variations in the genome influence medication response. Pharmacogenetics has gained increasing attention in the context of translational medicine, providing an opportunity for personalized treatment strategies based on an individual’s genetic makeup. The results obtained so far with the study of genetic variants in patients with T2DM (and other common diseases) may be used for the realization of a pharmacogenetic test, which can assist in making treatment decisions on the basis of each patient’s genetic profile, thus improving the overall management of the disease and ensuring better results in terms of safety and therapeutic efficacy. The clinical use of pharmacogenetics, through the identification of individual genetic variants (genetic polymorphisms), can contribute to move to a more evidence-based and less empiric clinical management of patients, thereby avoiding treatment failures, while reducing the incidence of adverse drug reactions (Figure 5).

**REFERENCES**

1 **Hamburg MA**, Collins FS. The path to personalized medicine. *N Engl J Med* 2010; **363**: 301-304 [PMID: 20551152 DOI: 10.1056/NEJMP1006304]

2 **McCarthy MI**, Zeggini E. Genome-wide association studies in type 2 diabetes. *Curr Diab Rep* 2009; **9**: 164-171 [PMID: 19323962 DOI: 10.1007/s11892-009-0027-4]

3 **Brunetti A**, Chiefari E, Foti D. Recent advances in the molecular genetics of type 2 diabetes mellitus. *World J Diabetes* 2014; **5**: 128-140 [PMID: 24748926 DOI: 10.4239/WJD.V5.I2.128]

4 **Doria A**, Patti ME, Kahn CR. The emerging genetic architecture of type 2 diabetes. *Cell Metab* 2008; **8**: 186-200 [PMID: 18762020 DOI: 10.1016/J.Cmet.2008.08.006]

5 **Ingelman-Sundberg M**. Pharmacogenetics of cytochrome P450 and its applications in drug therapy: the past, present and future. *Trends Pharmacol Sci* 2004; **25**: 193-200 [PMID: 15063083 DOI: [10.1016/j.tips.2004.02.007](http://dx.doi.org/10.1016/j.tips.2004.02.007)]

6 **Vogel F**. Moderne Probleme der Humangenetik. *Ergeb Inn Med Kinderheilkd* 1959; **12**: 52-125 [DOI: 10.1007/978-3-642-94744-5\_2]

7 **Mahgoub A**, Idle JR, Dring LG, Lancaster R, Smith RL. Polymorphic hydroxylation of Debrisoquine in man. *Lancet* 1977; **2**: 584-586 [PMID: 71400 DOI: 10.1016/S0140-6736(77)91430-1]

8 **Crowley JJ**, Sullivan PF, McLeod HL. Pharmacogenomic genome-wide association studies: lessons learned thus far. *Pharmacogenomics* 2009; **10**: 161-163 [PMID: 19207016 DOI: 10.2217/14622416.10.2.161]

9 **Daly AK**. Genome-wide association studies in pharmacogenomics. *Nat Rev Genet* 2010; **11**: 241-246 [PMID: 20300088 DOI: 10.1038/Nrg2751]

10 **Motsinger-Reif AA**, Jorgenson E, Relling MV, Kroetz DL, Weinshilboum R, Cox NJ, Roden DM. Genome-wide association studies in pharmacogenomics: successes and lessons. *Pharmacogenet Genomics* 2013; **23**: 383-394 [PMID: 20639796 DOI: 10.1097/FPC.0B013E32833D7B45]

11. **Kirchheiner J**, Bauer S, Meineke I, Rohde W, Prang V, Meisel C, Meisel C, Roots I, Brockmöller J. Impact of CYP2C9 and CYP2C19 polymorphisms on tolbutamide kinetics and the insulin and glucose response in healthy volunteers. *Pharmacogenetics* 2002; **12**: 101-109 [PMID: 11875364]

12 **Becker ML**, Visser LE, Trienekens PH, Hofman A, van Schaik RH, Stricker BH. Cytochrome P450 2C9 \*2 and \*3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. *Clin Pharmacol Ther* 2008; **83**: 288-292 [PMID: 17597710 DOI: 10.1038/sj.clpt.6100273]

13 **Kirchheiner J**, Brockmöller J, Meineke I, Bauer S, Rohde W, Roots I. Impact of CYP2C9 amino acid polymorphisms on glyburide kinetics and on the insulin and glucose response in healthy volunteers. *Clin Pharmacol Ther* 2002; **71**: 286-296 [PMID: 11956512 DOI: 10.1067/mcp.2002.122476]

14 **Elliot DJ**, Suharjono BC, Gillam EM, Birkett DJ, Gross AS, Miners JO. Identification of the human cytochromes P450 catalysing the rate-limiting pathways of gliclazide elimination. *Br J Clin Pharmacol* 2007; **64**: 450-457 [PMID: 17517049 DOI: 10.1111/j.1365-2125.2007.02943.x]

15 **Kidd RS**, Curry TB, Gallagher S, Edeki T, Blaisdell J, Goldstein JA. Identification of a null allele of CYP2C9 in an African- American exhibiting toxicity to phenytoin. *Pharmacogenetics* 2001; **11**: 803-808 [PMID: 11740344]

16 **Wang R**, Chen K, Wen SY, Li J, Wang SQ. Pharmacokinetics of glimepiride and cytochrome P450 2C9 genetic polymorphisms. *Clin Pharmacol Ther* 2005; **78**: 90-92 [PMID: 16003298 DOI: 10.1016/j.clpt.2005.03.008]

17 **Ragia G**, Petridis I, Tavridou A, Christakidis D, Manolopoulos VG. Presence of CYP2C9\*3 allele increases risk for hypoglycemia in Type 2 diabetic patients treated with sulfonylureas. *Pharmacogenomics* 2009; **10**: 1781-1787 [PMID: 19891554 DOI: 10.2217/Pgs.09.96]

18 **Holstein A**, Plaschke A, Ptak M, Egberts EH, El-Din J, Brockmöller J, Kirchheiner J. Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. *Br J Clin Pharmacol* 2005; **60**: 103-106 [PMID: 15963101 DOI: 10.1111/j.1365-2125.2005.02379.x]

19 **Bozkurt O**, de Boer A, Grobbee DE, Heerdink ER, Burger H, Klungel OH. Pharmacogenetics of glucose-lowering drug treatment: a systematic review. *Mol Diagn Ther* 2007; **11**: 291-302 [PMID: 17963417]

20 **Distefano JK**, Watanabe RM. Pharmacogenetics of Anti-Diabetes Drugs. *Pharmaceuticals* (Basel) 2010; **3**: 2610-2646 [PMID: 20936101 DOI: 10.3390/ph3082610]

21 **Zhou K**, Donnelly L, Burch L, Tavendale R, Doney AS, Leese G, Hattersley AT, McCarthy MI, Morris AD, Lang CC, Palmer CN, Pearson ER. Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a Go-DARTS study. *Clin Pharmacol Ther* 2010; **87**: 52-56 [PMID: 19794412 DOI: 10.1038/Clpt.2009.176]

22 **Shyng S**, Nichols CG. Octameric stoichiometry of the KATP channel complex. *J Gen Physiol* 1997; **110**: 655-664 [PMID: 9382894 DOI: 10.1085/Jgp.110.6.655]

23 **Winkler M**, Stephan D, Bieger S, Kühner P, Wolff F, Quast U. Testing the bipartite model of the sulfonylurea receptor binding site: binding of A-, B-, and A + B- site ligands. *J Pharmacol Exp Ther* 2007; **322**: 701-708 [PMID: 17495126 DOI: 10.1124/Jpet.107.123224]

24 **Flanagan SE**, Clauin S, Bellann**é**-Chantelot C, de Lonlay P, Harries LW, Gloyn AL, Ellard S. Update of mutations in the genes encoding the pancreatic beta-cell K(ATP) channel subunits Kir6.2 (KCNJ11) and sulfonylurea receptor 1 (ABCC8) in diabetes mellitus and hyperinsulinism. *Hum Mutat* 2009; **30**: 170-180 [PMID: 18767144 DOI: 10.1002/Humu.20838]

25 **Pearson ER**, Flechtner I, Njølstad PR, Malecki MT, Flanagan SE, Larkin B, Ashcroft FM, Klimes I, Codner E, Iotova V, Slingerland AS, Shield J, Robert JJ, Holst JJ, Clark PM, Ellard S, Søvik O, Polak M, Hattersley AT. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med* 2006; **355**: 467-477 [PMID: 16885550 DOI: 10.1056/NEJMOA061759]

26 **Siklar Z**, Ellard S, Okulu E, Berberoğlu M, Young E, Savaş Erdeve S, Mungan IA, Hacihamdioğlu B, Erdeve O, Arsan S, Oçal G. Transient neonatal diabetes with two novel mutations in the KCNJ11 gene and response to sulfonylurea treatment in a preterm infant. *J Pediatr Endocrinol Metab* 2011; **24**: 1077-1080 [PMID: 22308870]

27 **Dupont J**, Pereira C, Medeira A, Duarte R, Ellard S, Sampaio L. Permanent neonatal diabetes mellitus due to KCNJ11 mutation in a Portuguese family: transition from insulin to oral sulfonylureas. *J Pediatr Endocrinol Metab* 2012; **25**: 367-370 [PMID: 22768671]

28 **Feng Y**, Mao G, Ren X, Xing H, Tang G, Li Q, Li X, Sun L, Yang J, Ma W, Wang X, Xu X. Ser1369Ala variant in sulfonylurea receptor gene ABCC8 is associated with antidiabetic efficacy of gliclazide in Chinese type 2 diabetic patients. *Diabetes Care* 2008; **31**: 1939-1944 [PMID: 18599530 DOI: 10.2337/Dc07-2248]

29 **Fatehi M**, Raja M, Carter C, Soliman D, Holt A, Light PE. The ATP-sensitive K(+) channel ABCC8 S1369A type 2 diabetes risk variant increases MgATPase activity. *Diabetes* 2012; **61**: 241-249 [PMID: 22187380 DOI: 10.2337/Db11-0371]

30 **Lang VY**, Fatehi M, Light PE. Pharmacogenomic analysis of ATP-sensitive potassium channels coexpressing the common type 2 diabetes risk variants E23K and S1369A. *Pharmacogenet Genomics* 2012; **22**: 206-214 [PMID: 22209866 DOI: 10.1097/FPC.0B013E32835001E7]

31 **Schroner Z**, Javorsky M, Tkacova R, Klimcakova L, Dobrikova M, Habalova V, Kozarova M, Zidzik J, Rudikova M, Tkac I. Effect of sulphonylurea treatment on glycaemic control is related to TCF7L2 genotype in patients with type 2 diabetes. *Diabetes Obes Metab* 2011; **13**: 89-91 [PMID: 21114608 DOI: 10.1111/J.1463-1326.2010.01324.X]

32 **Pearson ER**, Donnelly LA, Kimber C, Whitley A, Doney AS, McCarthy MI, Hattersley AT, Morris AD, Palmer CN. Variation in TCF7L2 influences therapeutic response to sulfonylureas: a GoDARTs study. *Diabetes*2007; **56**: 2178-2182 [PMID: 17519421 DOI: 10.2337/Db07-0440]

33 **Holstein A**, Hahn M, **Körner A**, Stumvoll M, Kovacs P. TCF7L2 and therapeutic response to sulfonylureas in patients with type 2 diabetes. *BMC Med Genet* 2011; **12**: 30 [PMID: 21349175 DOI: 10.1186/1471-2350-12-30]

34 **Viollet B**, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. *Clin Sci* (Lond) 2012; **122**: 253-270 [PMID: 22117616 DOI: 10.1042/CS20110386]

35 **Kahn SE**, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O’Neill MC, Zinman B, Viberti G, ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006; **355**: 2427-2443 [PMID: 17145742 DOI: 10.1056/NEJMOA066224]

36 **Wang DS**, Jonker JW, Kato Y, Kusuhara H, Schinkel AH, Sugiyama Y. Involvement of organic cation transporter 1 in hepatic and intestinal distribution of metformin. *J Pharmacol Exp Ther* 2002; **302**: 510-515 [PMID: 12130709 DOI: 10.1124/Jpet.102.034140]

37 **Shu Y**, Sheardown SA, Brown C, Owen RP, Zhang S, Castro RA, Ianculescu AG, Yue L, Lo JC, Burchard EG, Brett CM, Giacomini KM. Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action. *J Clin Invest* 2007; **117:** 1422-1431 [PMID: 17476361 DOI: 10.1172/JCI30558]

38 **Shu Y**, Brown C, Castro RA, Shi RJ, Lin ET, Owen RP, Sheardown SA, Yue L, Burchard EG, Brett CM, Giacomini KM. Effect of genetic variation in the organic cation transporter 1, OCT1, on metformin pharmacokinetics. *Clin Pharmacol Ther* 2008; **83:** 273-280 [PMID: 17609683 DOI: 10.1038/sj.clpt.6100275]

39 **Christensen MM**, Brasch-Andersen C, Green H, Nielsen F, Damkier P, Beck-Nielsen H, Brosen K. The pharmacogenetics of metformin and its impact on plasma metformin steady-state levels and glycosylated hemoglobin A1c. *Pharmacogenet Genomics* 2011; **21**: 837-850 [PMID: 21989078 DOI: 10.1097/FPC.0B013E32834C0010]

40 **Tarasova L**, Kalnina I, Geldnere K, Bumbure A, Ritenberga R, Nikitina-Zake L, Fridmanis D, **Vaivade** I, Pirags V, Klovins J. Association of genetic variation in the organic cation transporters OCT1, OCT2 and multidrug and toxin extrusion 1 transporter protein genes with the gastrointestinal side eff ects and lower BMI in metformin- treated type 2 diabetes patients. *Pharmacogenet Genomics* 2012; **22**: 659-666 [PMID: 22735389 DOI: 10.1097/FPC.0B013E3283561666]

41 **Song IS**, Shin HJ, Shim EJ, Jung IS, Kim WY, Shon JH, Shin JG. Genetic variants of the organic cation transporter 2 influence the disposition of metformin. *Clin Pharmacol Ther* 2008; **84**: 559-562 [PMID: 18401339 DOI: 10.1038/CLPT.2008.61]

42 **Wang ZJ**, Yin OQ, Tomlinson B, Chow MS. OCT2 polymorphisms and in-vivo renal functional consequence: studies with metformin and cimetidine. *Pharmacogenet Genomics* 2008; **18**: 637-645 [PMID: 18551044 DOI: 10.1097/FPC.0B013E328302CD41]

43 **Becker ML**, Visser LE, van Schaik RH, Hofman A, Uitterlinden AG, Stricker BH. Genetic variation in the multidrug and toxin extrusion 1 transporter protein influences the glucose-lowering effect of metformin in patients with diabetes: a preliminary study. *Diabetes* 2009; **58** :745-749 [PMID: 19228809 DOI: 10.2337/DB08-1028]

44 **Jablonski KA**, McAteer JB, de Bakker PI, Franks PW, Pollin TI, Hanson RL, Saxena R, Fowler S, Shuldiner AR, Knowler WC, Altshuler D, Florez JC, Diabetes Prevention Program Research Group. Common variants in 40 genes assessed for diabetes incidence and response to metformin and lifestyle intervention in the diabetes prevention program. *Diabetes* 2010; **59**: 2672-2681 [PMID: 20682687 DOI: 10.2337/DB10-0543]

45 **Choi JH**, Yee SW, Ramirez AH, Morrissey KM, Jang GH, Joski PJ, Mefford JA, Hesselson SE, Schlessinger A, Jenkins G, Castro RA, Johns SJ, Stryke D, Sali A, Ferrin TE, Witte JS, Kwok PY, Roden DM, Wilke RA, McCarty CA, Davis RL, Giacomini KM. A common 5’-UTR variant in MATE2-K is associated with poor response to metformin. *Clin Pharmacol Ther* 2011; **90**: 674-684 [PMID: 21956618 DOI: 10.1038/CLPT.2011.165]

46 **Stocker SL**, Morrissey KM, Yee SW, Castro RA, Xu L, Dahlin A, Ramirez AH, Roden DM, Wilke RA, McCarty CA, Davis RL, Brett CM, Giacomini KM. The effect of novel promoter variants in MATE1 and MATE2 on the pharmacokinetics and pharmacodynamics of metformin. *Clin Pharmacol Ther* 2013; **93:** 186-194 [PMID: 23267855 DOI: 10.1038/CLPT.2012.210]

47 **Zhou K**, Bellenguez C, Spencer CC, Bennett AJ, Coleman RL, Tavendale R, Hawley SA, Donnelly LA, Schofield C, Groves CJ, Burch L, Carr F, Strange A, Freeman C, Blackwell JM, Bramon E, Brown MA, Casas JP, Corvin A, Craddock N, Deloukas P, Dronov S, Duncanson A, Edkins S, Gray E, Hunt S, Jankowski J, Langford C, Markus HS, Mathew CG, Plomin R, Rautanen A, Sawcer SJ, Samani NJ, Trembath R, Viswanathan AC, Wood NW, Harries LW, Hattersley AT, Doney AS, Colhoun H, Morris AD, Sutherland C, Hardie DG, Peltonen L, McCarthy MI, Holman RR, Palmer CN, Donnelly P, Pearson ER, The GoDARTS and UKPDS Diabetes Pharmacogenetics Study Group, The Wellcome Trust Case Control Consortium. Common variants near ATM are associated with glycemic response to metformin in type 2 diabetes. *Nat Genet* 2011; **43**: 117-120 [PMID: 21186350 DOI: 10.1038/NG.735]

48 **Yang DQ**, Kastan MB. Participation of ATM in insulin signalling through phosphorylation of eIF-4E-binding protein 1. *Nat Cell Biol* 2000; **2**: 893-898 [PMID: 11146653 DOI: 10.1038/35046542]

49 **Chen L**, Yang G. PPARs Integrate the Mammalian Clock and Energy Metabolism. *PPAR Res* 2014; **2014:** 653017 [PMID: 24693278 DOI: 10.1155/2014/653017]

50 **Becker ML**, Pearson ER, Tkáč I. Pharmacogenetics of Oral Antidiabetic Drugs. *Int J Endocrinol* 2013; **2013:** 686315 [PMID: 24324494 DOI: 10.1155/2013/686315]

51 **Wang G**, Wang X, Zhang Q, Ma Z. Response to pioglitazone treatment is associated with the lipoprotein lipase S447X variant in subjects with type 2 diabetes mellitus. *Int J Clin Pract* 2007; **61**: 552-557 [PMID: 17394430 DOI: 10.1111/J.1742-1241.2006.01242.X]

52 **Makino H**, Shimizu I, Murao S, Kondo S, Tabara Y, Fujiyama M, Fujii Y, Takada Y, Nakai K, Izumi K, Ohashi J, Kawamura R, Yamauchi J, Takata Y, Nishida W, Hashiramoto M, Onuma H, Osawa H. A pilot study suggests that the G/G genotype of resistin single nucleotide polymorphism at -420 may be an independent predictor of a reduction in fasting plasma glucose and insulin resistance by pioglitazone in type 2 diabetes. *Endocr J* 2009; **56**: 1049-1058 [PMID: 19738363 DOI: HTTP://DX.DOI.ORG/10.1507/ENDOCRJ.K08E-320]

53 **Karalliedde J**, Buckingham RE. Thiazolidinediones and their fluid-related adverse effects: facts, fiction and putative management strategies. *Drug Saf* 2007; **30**: 741-753 [PMID: 17722967]

54 **Chang TJ**, Liu PH, Liang YC, Chang YC, Jiang YD, Li HY, Lo MT, Chen HS, Chuang LM. Genetic predisposition and nongenetic risk factors of thiazolidinedione- related edema in patients with type 2 diabetes. *Pharmacogenet Genomics* 2011; **21**: 829-836 [PMID: 21934636 DOI: 10.1097/FPC.0B013E32834BFFF1]

55 **Knepper MA**, Wade JB, Terris J, Ecelbarger CA, Marples D, Mandon B, Chou CL, Kishore BK, Nielsen S. Renal aquaporins. *Kidney Int* 1996; **49**: 1712-1717 [PMID: 8743483]

56 **Ji W**, Foo JN, O’Roak BJ, Zhao H, Larson MG, Simon DB, Newton-Cheh C, State MW, Levy D, Lifton RP. Rare independent mutations in renal salt handling genes contribute to blood pressure variation. *Nat Genet* 2008; **40**: 592-599 [PMID: 18391953 DOI: 10.1038/NG.118]

57 **Yan FF**, Casey J, Shyng SL. Sulfonylureas correct trafficking defects of disease-causing ATP-sensitive potassium channels by binding to the channel complex. *J Biol Chem* 2006; **281**: 33403-33413 [PMID: 16956886 DOI: 10.1074/JBC.M605195200]

58 **Kirchheiner J**, Roots I, Goldammer M, Rosenkranz B, **Brockmöller** J. Effect of genetic polymorphisms in cytochrome p450 (CYP) 2C9 and CYP2C8 on the pharmacokinetics of oral antidiabetic drugs: clinical relevance. *Clin Pharmacokinet* 2005; **44**: 1209-1225 [PMID: 16372821 DOI: 10.2165/00003088-200544120-00002]

59 **Bidstrup TB**, **Bjørnsdottir** I, Sidelmann UG, Thomsen MS, Hansen KT. CYP2C8 and CYP3A4 are the principal enzymes involved in the human in vitro biotransformation of the insulin secretagogue repaglinide. *Br J Clin Pharmacol* 2003; **56**: 305-314 [PMID: 12919179 DOI: [10.1046/J.0306-5251.2003.01862.X](http://dx.doi.org/10.1046/j.0306-5251.2003.01862.x)]

60 **Tomalik-Scharte D**, Fuhr U, Hellmich M, Frank D, Doroshyenko O, Jetter A, Stingl JC. Effect of the CYP2C8 genotype on the pharmacokinetics and pharmacodynamics of repaglinide. *Drug Metab Dispos* 2011; **39**: 927-932 [PMID: 21270106 DOI: 10.1124/DMD.110.036921]

61 **Kalliokoski A**, Neuvonen M, Neuvonen PJ, Niemi M. The effect of SLCO1B1 polymorphism on repaglinide pharmacokinetics persists over a wide dose range. *Br J Clin Pharmacol*2008; **66**: 818-825 [PMID: 18823304 DOI: 10.1111/J.1365-2125.2008.03287.X]

62 **Zhang W**, He YJ, Han CT, Liu ZQ, Li Q, Fan L, Tan ZR, Zhang WX, Yu BN, Wang D, Hu DL, Zhou HH. Effect of SLCO1B1 genetic polymorphism on the pharmacokinetics of nateglinide. *Br J Clin Pharmacol* 2006; **62**: 567-572 [PMID: 16796707 DOI: 10.1111/j.1365-2125.2006.02686.x]

63 **Kalliokoski A**, Neuvonen M, Neuvonen PJ, Niemi M. Different effects of SLCO1B1 polymorphism on the pharmacokinetics and pharmacodynamics of repaglinide and nateglinide. *J Clin Pharmacol* 2008; **48**: 311-321 [PMID: 18187595 DOI: 10.1177/0091270007311569]

64 **Kalliokoski A**, Backman JT, Neuvonen PJ, Niemi M. Eff ects of the SLCO1B1\*1B haplotype on the pharmacokinetics and pharmacodynamics of repaglinide and nateglinide. *Pharmacogenet Genomics* 2008; **18**: 937-942 [PMID: 18854776 DOI: 10.1097/FPC.0B013E32830D733E]

65 **He YY**, Zhang R, Shao XY, Hu C, Wang CR, Lu JX, Bao YQ, Jia WP, Xiang KS.. Association of KCNJ11 and ABCC8 genetic polymorphisms with response to repaglinide in Chinese diabetic patients. *Acta Pharmacol Sin* 2008; **29**: 983-989 [PMID: 18664331 DOI: 10.1111/J.1745-7254.2008.00840.X]

66 **Huang Q**, Yin JY, Dai XP, Wu J, Chen X, Deng CS, Yu M, Gong ZC, Zhou HH, Liu ZQ. Association analysis of SLC30A8 rs13266634 and rs16889462 polymorphisms with type 2 diabetes mellitus and repaglinide response in Chinese patients. *Eur J Clin Pharmacol* 2010; **66**: 1207-1215 [PMID: 20809084 DOI: 10.1007/S00228-010-0882-6]

67 **Gong ZC**, Huang Q, Dai XP, Lei GH, Lu HB, Yin JY, Xu XJ, Qu J, Pei Q, Dong M, Zhou BT, Shen J, Zhou G, Zhou HH, Liu ZQ. NeuroD1 A45T and PAX4 R121W polymorphisms are associated with plasma glucose level of repaglinide monotherapy in Chinese patients with type 2 diabetes. *Br J Clin Pharmacol* 2012; **74**: 501-509 [PMID: 22296034 DOI: 10.1111/J.1365-2125.2012.04202.X]

68 **Wang S**, Se YM, Liu ZQ, Lei MX, Hao-BoYang ZX, Nie SD, Zeng XM, Wu J. Effect of genetic polymorphism of UCP2-866 G/A on repaglinide response in Chinese patients with type 2 diabetes. *Pharmazie* 2012; **67**: 74-79 [PMID: 22393835]

69 **Xiang Q**, Cui YM, Zhao X, Yan L, Zhou Y. The Influence of MDR1 G2677T/a genetic polymorphisms on the pharmacokinetics of repaglinide in healthy Chinese volunteers. *Pharmacology* 2012; **89**: 105-110 [PMID: 22398664 DOI: 10.1159/000336345]

70 **Umpierrez GE**, Meneghini L. Reshaping diabetes care: the fundamental role of dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists in clinical practice. *Endocr Pract* 2013; **19**: 718-728 [PMID: 23512382 DOI: 10.4158/EP12292.RA]

71 **Sathananthan A**, Man CD, Micheletto F, Zinsmeister AR, Camilleri M, Giesler PD, Laugen JM, Toffolo G, Rizza RA, Cobelli C, Vella A. Common genetic variation in GLP1R and insulin secretion in response to exogenous GLP-1 in nondiabetic subjects: a pilot study. *Diabetes Care* 2010; **33**: 2074-2076 [PMID: 20805279 DOI: 10.2337/DC10-0200]

72 **Smushkin G**, Sathananthan M, Sathananthan A, Dalla Man C, Micheletto F, Zinsmeister AR, Cobelli C, Vella A. Diabetes-associated common genetic variation and its association with GLP-1 concentrations and response to exogenous GLP-1. *Diabetes* 2012; **61**: 1082-1089 [PMID: 22461567 DOI: 10.2337/DB11-1732]

73 **'t Hart LM**, Fritsche A, Nijpels G, van Leeuwen N, Donnelly LA, Dekker JM, Alssema M, Fadista J, Carlotti F, Gjesing AP, Palmer CN, van Haeften TW, Herzberg-Schäfer SA, Simonis-Bik AM, Houwing-Duistermaat JJ, Helmer Q, Deelen J, Guigas B, Hansen T, Machicao F, Willemsen G, Heine RJ, Kramer MH, Holst JJ, de Koning EJ, Häring HU, Pedersen O, Groop L, de Geus EJ, Slagboom PE, Boomsma DI, Eekhoff EM, Pearson ER, Diamant M. The CTRB1/2 locus affects diabetes susceptibility and treatment via the incretin pathway. *Diabetes* 2013; **62**: 3275-3281 [PMID: 23674605 DOI: 10.2337/DB13-0227]

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**P-Reviewer:** Fang Y, Guarneri F, Jia JH **S-Editor:** Tian YL

**L-Editor: E-Editor:**



**Figure 1** **From bench to bedside.** Translational medicine is a discipline of biomedical research that attempts to connect basic research with clinical care.



**Figure 2** **Single nucleotide polymorphism.** As the most common type of variant, a single nucleotide polymorphism is characterized by a single DNA base pair substitution at a specific location in a gene. SNP: Single nucleotide polymorphism.



**Figure 3** **The ATP-sensitive K+ channels** **regulate insulin release in beta-cells.** Single nucleotide polymorphism in *SUR1* and/or *Kir6.2* genes may cause functional abnormalities of the ATP-sensitive K+ channel (K-ATP channel)on the pancreatic β-cell membrane, leading to abnormalities in insulin secretion.



**Figure 4** **Organic cation transporter 1 plays a major role in drug uptake across the liver cell membrane.** Single nucleotide polymorphism associated with organic cation transporter 1 may contribute to variation in response to metformin. AMPK: Adenosine 5'-monophosphate (AMP)-activated protein kinase.



**Figure 5** **Pharmacogenetic testing.** The pharmacogenetic test has the potential to provide personalized therapy based on individual genetic variability.