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REVIEW

Pharmacogenetics of oral antidiabetic treatment

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Abstract: In the majority of patients with type 2 diabetes (T2D), oral antidiabetic drug (OAD) treatment is the first line treatment after lifestyle measures fail. Two major groups of OAD are used in clinical practice – insulin secretagogues and insulin sensitisers.
Sulphonyluea (SU) derivatives are insulin secretagogues and stimulate insulin secretion by inhibiting ATP-sensitive potassium channels. Genes *KCNJ11* and *ABCC8* encode potassium channel proteins. *KCNJ11* gene Glu23Lys polymorphism was associated with an increased risk of SU secondary failure, while Ser1369Ala polymorphism of *ABCC8* gene had influence antidiabetic efficacy of SU drug gliclazide. In addition, the polymorphism of *TCF7L2* gene, which has the strongest association with T2D, also influenced secondary SU drug failure. Insulin sensitisers include both metformin and glitazones. Some drug-genotype associations were observed for metformin in patients with T2D. Several genes influenced the effect of glitazone treatment. Rosiglitazone was more effective in diabetes control in carriers of Pro12Ala polymorphism of *PPARG* gene encoding the PPARg-receptor – the target of this drug. Rosiglitazone treatment had less effect on glycemic control and adiponectin increase in T2D patients with GG-genotypes of adiponectin (*APM1*) polymorphism. Pioglitazone treatment had smaller effect on glycemic control in patients with *LPL* Ser447X polymorphism.
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 "patient-tailored therapy" in T2D *(Tab. 1, Ref. 58)*. Full Text in free PDF *www.bmj.sk.*
Key words: diabetes mellitus type 2, pharmacogenetics, oral antidiabetic drugs.

Abbreviations: AMPK – adenosin monophosphat activated proteinkinase, ATP – adenosin triphosphate, CV – cardiovascular, DPP-4 – depeptidyl peptidase-4, FTO – FaT mass Obesity**,** GIP – glucose-dependent insulinotropic polypepeptide, GLP – 1-glucagon-like peptid-1, GWAS – genome-wide association studies, HbA1c – glycated hemoglobin, HNF1-α – hepatic nuclear factor 1-α, IR – insulin resistance, IRS – insulin receptor substrate, MODY – Maturity Onset Diabetes of the Young, OAD – oral antidiabetic drugs, P-NDM – permanent neonatal diabetes mellitus, SU – sulphonylurea, T2D – type 2 diabetes.

Type 2 diabetes (T2D) is a disease with significant genetic predisposition. In recent years, genome-wide association studies (GWAS) uncovered nearly 20 candidate genes for T2D. In the pathogenesis of T2D factors of internal and external environment play an important role. The most important environmental factor is obesity, as in different populations 50 – 90 % of these patients are overweight or obese. However, the situation is complicated by the fact that obesity itself is genetically determined. The current concept of multiple gene inheritance of DM type 2 is based on the assumption that type 2 diabetic patients are carriers of a mosaic of several gene polymorphisms associated with the disease (1, 2) (Tab. 1). The effects of individual genes are not large, but when interacting with external factors they increase the risk of developing T2D. Among genes whose products affect insulin sensitivity, an association with the gene for peroxisome proliferator-activated receptor g (PPARG) was observed. The *FTO* gene (FaT mass Obesity) is connected to the development of insulin resistance (IR) through the predisposition to obesity (3, 4). Other genes, which have been identified by GWAS, are expected to be related to a disorder of insulin secretion (2, 5–10). Among them, the *TCF7L2* gene is so far the strongest indicator of an increased risk of developing T2D of all identified genes. Carriers of one risk allele have an increased risk of developing T2D by 40 %, homozygotes by more than 100 % (5).

Basic therapeutic interventions in T2D 2 include diet, adequate physical activity and pharmacotherapy by oral antidiabetic drugs (OAD) and/or insulin replacement therapy. Currently, a wide range of OAD with different mechanisms of action is available. Since IR and insulin secretion failure are the major pathogenetic mechanisms involved in the development of T2D, therapeutic approaches have usually focused on the influence of

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Tab. 1. The most significant associations of oral antidiabetic therapy.

Mutation//polymorphism of gene	Effect of SU derivatives
Mutation *KCNJ11*(permanent neonatal diabetes mellitus)	Possibility to change the therapy from the initial insulin treatment to SU derivatives, drug of choice glibenklamid
Mutation *HNF 1á* (MODY3)	High efficacy
Polymorphism *ABCC8* Ser1369Ala	Gliclazide more effective in Ala/Ala genotype vs Ser/Ser genotype
Polymorphism *KCNJ11* Glu23Lys	Increased risk of secondary failure of treatment with SU derivatives
Polymorphism *IRS-1* Gly972Arg	Increased risk of secondary failure of treatment with SU derivatives
Polymorphism *TCF7L2* rs 12255372G/T, rs7903146T/C	Higher rate of SU treatment failure in rs12255372 TT genotype vs GG genotype and higher rate of SU treatment failure in rs 7903146 CC genotype vs TT genotype
Polymorphism *NOS1AP* rs10494366	Glibenclamide less effective in rs10494366 TG or GG genotype vs TT genotype
Mutation/polymorphism of gene	Effect of metformin
Polymorphism *IRS-1* Gly972Arg	Higher effect of metformin in patients with polycystic ovary syndrome
Polymorphism *STK11* rs 741765	Lower likelihood of ovulation induction in patients with polycystic ovary syndrome during metformin treatment
Mutation/polymorphism of gene	Effect of thiazolidinediones
Polymorphism *PPARG* Pro12Ala	Higher effect of rosiglitazone on glycemic control
Polymorphism *APM1* T45G	Reduced effect of rosiglitazone on glycemic control
Polymorphism *APM1*T276G	Reduced effect of rosiglitazone on glycemic control
Polymorphism *LPL* Ser447X	Reduced effect of pioglitazone on glycemic control

one of the two main mechanisms. Insulin sensitizers have the primary goal to reduce the IR. In the clinical practice, first biguanids (currently, only metformin is used in the clinical practice), and later thiazolidinediones were used. Insulin secretagogues (derivatives of sulphonylurea, derivatives of meglitinide, enhancers of the effects of incretins) therapeutically affect the second major defect in DM type 2 – insulin secretion failure (11). Inhibitors of á-glucosidase (acarbose, miglitol) reduce the absorption of glucose from the intestine (12).

Several pharmacogenetic studies have shown the gene polymorphisms affecting basic pathogenetic mechanisms of T2D development (candidate genes) on the effect of treatment with various OAD. Beyond gene variants, affecting directly the mechanisms of insulin secretion and insulin sensitivity, the effect of OAD is also modulated by genetic factors affecting the pharmacokinetics of these therapeutics. These factors include variants of genes encoding isoforms of cytochrome P450 and genes for organic cationic and anionic transporters. Therefore, several studies analyzed the impact of gene polymorphisms affecting the pharmacokinetics of OAD on the effects of these drugs (13).

Genetic factors and the effects of sulphonylurea derivatives

Sulphonylurea derivatives (SU) act as insulin secretagogues through the stimulation of insulin secretion via the sulphonylurea receptor (SUR1) in B-cells of the Langerhans islands, while their effect is independent of food intake (14).

Among genes, whose products affect the secretion of insulin, a relationship was observed between the effects of SU derivatives and the *KCNJ11*, *ABCC8*, *TCF7L2*, *HNF1A* and *NOS1P* genes.

The product of *ABCC8* gene is a SUR1 subunit of an ATP-dependent potassium channel of B cells. SU derivatives, by binding to SUR1 (via an ATP independent mechanism) will lead to a channel closure and depolarization of the cell membrane. Depolarization induces opening of the calcium channel, calcium ion entry into the cell and activation of vesicles followed by insulin secretion. *KCNJ11* gene is located on chromosome 11 near the *ABCC8* gene. Association of KCNJ11 with T2D was confirmed by GWAS. The product of this gene is the subunit Kir6.2 of the ATP-dependent potassium channel of B cells. Under physiological conditions, the binding of ATP to Kir6.2 leads to closure of this channel and to subsequent insulin secretion (15). Mutation of this gene causes permanent neonatal diabetes (P-NDM) in which the sensitivity of this channel to ATP is significantly reduced. The clinical signs of this type of diabetes include severe hyperglycemia and ketoacidosis (17). In most patients with P-NDM it is possible to change the therapy from the initial insulin therapy to SU derivatives. Drug of choice among SU derivatives is glibenclamide because it affects not only SUR1 (pancreas) but also SUR2A (heart, muscle), thus enabling an improvement of neurologic symptoms present in some patients with P-NDM (18).

Pharmacogenetic studies performed so far on the impact of polymorphisms of genes *ABCC8* and *KCNJ11* on the effects of SU derivatives have not shown clear results. Zychma et al and Meirhaeghe et al did not confirm the effects of ABCC8 polymorphism 16T/C on the effects of treatment with SU derivatives (19, 20). Feng et al in a study with 1268 patients with T2D, as

well as Zhang et al in a study with 115 Chinese type 2 diabetics found an effect of a non-synonymic *ABCC8* Ser1369Ala polymorphism on the treatment with SU-derivative gliclazide. Patients with the Ala/Ala genotype responded better to gliclazide (based on the levels of glycated hemoglobin, fasting glycaemia and postprandial glycaemia) compared to the patients with Ser/Ser genotype (21, 22). Sesto et al found that patients with the non-synonymic KCNJ11 polymorphisms Glu23Lys more often fail to respond to treatment with SU derivatives (23). Holstein et al reported that type 2 diabetics with the *KCNJ11* polymorphism Glu23Lys were at significantly lower risk for hypoglycaemia induced by SU derivatives (glibenclamide, glimepiride) compared to the patients without this polymorphism (24).

TCF7L2 gene is located on chromosome 10p. The product of this gene is the transcription factor 7 like 2 (TCF7L2). TCF7L2 is a nuclear factor which binds â-catenin, mediates WNT-signaling, which is important also for normal development of pancreas during embryogenesis and for the secretion of GLP-1 by L-cells of the small intestine (25). In addition to the indirect influence on insulin secretion (through the enteroinsular axis), TCF7L2 has probably also a direct effect on insulin secretion at the level of proinsulin processing (26).

GoDARTs study with 4469 genotyped type 2 diabetics found an effect of *TCF7L2* polymorphisms rs12255372 and rs7903146 on the failure of treatment with SU derivatives. 57 % of patients with the TT genotype of the *TCF7L2* polymorphism rs12255372, compared to the 40 % of patients with the GG genotype after one year of treatment with SU derivatives failed to achieve the primary goal of therapy (HbA1c< 7 %). A similar although weaker relationship was found for the rs7903146 polymorphism. Almost 50% of patients with TT genotype of this polymorphism, compared to the 40% of patients with the CC genotype, achieved the primary goal of treatment after one year of therapy with SU derivatives (27).

HNF1A gene encoding the nuclear receptor hepatic nuclear factor 1-á (HNF1-á) is located on chromosome 12q. Mutation of this gene causes a monogenic type of diabetes- Maturity Onset Diabetes of the Young (MODY) 3. A common feature of MODY is that it is diabetes with a dominant role of genetics in the pathogenesis. For MODY 3 it is typical that it begins in adolescence, clinical picture is similar to type 2 DM. Other characteristics include familiar occurrence with autosomal dominant type of heredity, frequent occurrence of chronic complications and the high sensitivity for SU derivatives. When starting the treatment with SU derivatives in patients with MODY 3 very low doses should be considered due to possible occurrence of post-initiating hypoglycaemia (28).

The product of the *NOS1AP* gene is a protein that influences the level of intracellular calcium. The effect of this gene on the SU derivatives is suggested, given that these drugs induce calcium entry into the cells and subsequent secretion of insulin. Becker et al found that in patients with TG or GG genotype of the rs10494366 polymorphism of *NOS1AP* the SU derivative - glibenclamide was less effective than in carriers of TT genotype of this polymorphism (29).

The product of the *IRS-1* gene is the insulin receptor substrate 1, which is a signaling protein that mediates the signal from the activated insulin receptor into the cell. This gene is thought to be related to insulin sensitivity. In one study, a relationship was observed between the Gly972Arg polymorphism of *IRS-1* and an increased risk of secondary failure of treatment with SU derivatives (30).

The products of genes of the individual cytochrome P450 isoforms – CYP2C9, CYP2C8, CYP2C19, CYP2D6, are microsomal liver enzymes, which play an important role in the oxidative biotransformation of many drugs. It seems that the major role in clearance of SU derivatives plays the CYP2C9 cytochrome P450 isoform. Patients with T2D with the Ile359Leu polymorphism of *CYP2C9* (CYP2C9*3) require lower doses of the SU derivative – tolbutamide and glimepiride to reduce glycaemia compared to the patients without this polymorphism, which indicates that carriers of this polymorphism have a reduced clearance of SU derivatives (31,32). Holstein et al found that patients with CYP2C9 Ile359Leu polymorphisms (CYP2C9 *3) and with CYP2C9 Arg144Cys (CYP2C9*2) were more frequently admitted to urgent medicine department due to severe hypoglycaemia during the treatment with SU derivatives in comparison to patients without these polymorphisms (33).

Genetic factors and the effect of meglitinide derivatives

Meglitinide derivates (glinides) stimulate insulin secretion similarly to SU derivatives, although they bind to another site of the SU receptor (34). Among the genes that affect the pharmacokinetics of meglitinide derivatives, in relation to the effect of these drugs, belong very likely to the most important genes for cytochrome P450 isoforms - *CYP2C9* and *CYP2C8,* as well as the gene encoding the organic anionic-transporter – *SLCO1B1*.

Ile359Leu polymorphism of *CYP2C9* (CYP2C9*3) was associated with a reduced clearance of meglitinide derivatives while Arg139Lys polymorphism of *CYP2C8* (CYP2C8*3) increased the clearance of these drugs. The 521T/C polymorphism of *SLCO1B1* led to a change in the pharmacokinetics meglitinide derivatives. However, all of these studies were performed on healthy volunteers, and so it is difficult to estimate the effect of mentioned polymorphisms on the antidiabetic effect of glinides (13, 35, 36).

Genetic factors and effects of inhibitors of dipeptidyl peptidase-4

Enhancers of the incretin effect – analogues of glucagon like peptide-1 (GLP-1) and inhibitors of dipeptidyl peptidase-4 (DPP-4) are considered to be physiological insulin secretagogues, because they stimulate insulin secretion only in the postprandial period. While GLP-1 analogues are administered parenterally, orally administered DPP-4 inhibitors prevent the degradation of incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). This leads to increased plasma concentrations of these hormones resulting in higher postprandial glucose-in-

duced insulin secretion and a reduction of postprandial levels of glucagon (37).

Among genes identified in association with T2D in GWAS, genes *TCF7L2* and *MTNR1B* may be most likely involved in the effect of inhibitors of dipeptidyl peptidase-4 (DPP-4). *TCF7L2* is a transcription factor that regulates the secretion of preproglucagon, which after cleavage changes into glucagon, as well as GLP-1.

MTNR1B gene product is the melatonin receptor 2, which binds melatonin. *MTNR1B* rs1387153 polymorphism led to a decrease in insulin secretion after stimulation with GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) (38).

The product of the *GLP-1R* gene is a receptor for GLP-1, which mediates the effect of GLP-1. *GLP-1R* polymorphism T149M was detected in 791 Japanese type 2 diabetics in comparison with the control group of 318 non-diabetics where this polymorphism was not found. This polymorphism leads to a reduced GLP-1 receptor function. It might imply that inhibitors of DPP-4 will be less effective in patients with these gene polymorphisms (39, 40). However, pharmacogenetic studies have not yet been published that would monitor the impact of genetic factors on the effect of DPP-4 inhibitors, or the effect of GLP-1 analogues.

Genetic factors and the effect of metformin

Metformin increases the sensitivity to insulin resulting in reduction of hepatic gluconeogenesis and increased glucose uptake in skeletal muscle and in adipose tissue. Metformin acts as an activator of the enzyme adenosinmonophosphate activated proteinkinase (AMPK) (41).

Among genes whose products may influence the effect of insulin genes, *IRS-1* and *STK11* is related to the effect of metformin. Genes affecting the pharmacokinetics of metformin include genes *OCT1*, *OCT2*, *MATE*, *PMAT* and could have a relationship to its effect.

In patients with polycystic ovary syndrome, the polymorphism Gly972Arg in *IRS1* metformin decreased fasting insulin levels and IR (expressed as HOMA-IR) more effective compared to the patients homozygous for the Gly allele (42).

STK11 gene encodes the STK11 kinase. STK11 kinase phosphorylates the threonine residue at position 172 in the polypeptide chain of the enzyme AMPK, what leads to the activation of AMPK and subsequently to its metabolic effect (43). Legro et al applied metformin to patients with polycystic ovary syndrome (PCOS), which is associated with IR. In this study, the C-allele of the gene rs741765 polymorphism of *STK11* was associated with a significantly lower likelihood of ovulation induction in PCOS during metformin treatment (44).

OCT1 gene encodes an organic cationic transporter-1 (OCT-1). OCT-1 is expressed mainly on the membrane of hepatocytes. It is suggested that its main task is metformin uptake in the liver. Products of genes *OCT2*, *MATEs*, and *PMAT* are other organic cationic transporter, which appears to play an important role in metformin uptake in the liver and its renal excretion. Shu et al found that in carriers of 4 non-synonymic *OCT1* polymorphisms (R61C, G401S, M420del and G145R) the effect of metformin was significantly lower compared to the subjects without these polymorphisms (45). In contrast to this study, Shiki et al found that 11 different *OCT1* polymorphisms and two polymorphisms of the *OCT2* gene did not influence the effect of metformin (46).

Genetic factors and the effect of thiazolidinediones

Thiazolidinediones (rosiglitazone and pioglitazone) are selective agonists of nuclear receptors PPAR-ă (peroxisome proliferator-activated receptor ă). They lead to the activation of transcription of the insulin-sensitive genes that are involved in carbohydrate and lipid metabolism. The resulting effect of thiazolidinediones action is an improvement of insulin effects in target tissues (47).

Among the genes that affect the IR, *PPARG*, *PGC-1*, *APM1* and *LPL* are likely to influence thiazolidinediones (TZD). The gene *PLIN* is probably related to adverse effects (increase in body weight) of these drugs.

PPARG gene product is a nuclear receptor PPAR-ă, which is the therapeutic aim of this group of OAD. *PPARG* Pro12Ala polymorphism has a protective effect on the development of DM type 2. The association of *PPARG* with T2D was confirmed also by GWAS. Pro12Ala polymorphism and TZD have opposite effects on adipose tissue. While the presence of Ala allele is associated with a reduction of lipogenesis, TZD stimulate differentiation of adipocytes and their apoptosis. In both cases, there is a reduction of IR (48). Kang et al found that treatment with rosiglitazone led to a significantly larger reduction of fasting glycaemia and HbA1c in 198 Korean patients with DM type 2 who were carriers of the Ala allele in comparison to the patients – carriers of the major allele Pro (49).

The product of *APM1* (*ACDC*) is adiponectin – hormone produced exclusively by adipose tissue. The *APM1* gene is located on chromosome 3q27. Adiponectin increases sensitivity to insulin, it has also antiinflammatory and antiatherogenic effects. The levels of adiponectin are usually reduced in T2D, obesity, cardiovascular (CV) diseases (51). TZD increase adiponectin levels in serum. Kang et al found in 166 type 2 diabetics that in patients with the GG genotype of T45G and T276G polymorphisms of *APM1* the rosiglitazone treatment led to a smaller reduction in fasting glycaemia, HbA1c, and a smaller increase in serum adiponectin levels compared to the patients who were carriers of allele T (52).

PLIN gene encodes 4 isoforms of perilipin. Perilipin A reduces the hydrolysis of triglycerides, thereby increasing their storage in fat cells. *PLIN* gene is located on chromosome 15q26.1 (53). Kang et al in a study of 160 type 2 diabetics found that patients with the AA genotype of the G11482A polymorphism of the *PLIN* gene experienced less weight gain compared to the G allele carriers during treatment with rosiglitazone (54).

The LPL gene product is lipoprotein lipase – the enzyme that plays a key role in the metabolism of lipoproteins and fatty acids. It seems that this gene and its product play an important role in the pathogenesis of IR (55). Wang et al found that treatment with pioglitazone in type 2 diabetics led to lower glycemic effect in patients with Ser447X polymorphism of *LPL*, when compared to the patients without this polymorphism (56).

Genetic factors and the effect of alpha-glucosidase inhibitors

The mechanism of action of these drugs lies in the competitive inhibition of intestinal α-glucosidase enzymes (12). A link to the effect of inhibitors of alpha-glucosidase has been described for genes *PPARG*, *PGC1A* and *APM1*. Women with an impaired glucose tolerance with Pro/Pro genotype of the Pro12Ala polymorphism of *PPRAG* 2.9-times more frequently progressed to manifest T2D compared to the Pro/Ala genotype during treatment with acarbose. Acarbose also led to prevention of T2D in Ser482 allele carriers of Gly482Ser *PGC1A* polymorphism (57). TT genotype of *APM1* polymorphism +276 G/T was in the patients with impaired glucose tolerance treated with acarbose associated with a higher risk of progression to T2D in comparison to the patients with GG genotype of this polymorphism (58).

Conclusion

Results of several studies published in recent years demonstrated the importance of genetic factors in the interindividual variability of glycemic effect of oral anti-diabetic drugs. Currently, several large prospective studies are ongoing that monitor this impact directly in type 2 diabetics. Although the effect of analyzed polymorphisms on the anti-diabetic treatment observed until now was relatively small, it cannot be excluded that in near future gene-drug interactions with a stronger effect will be identified. Practical implication of these studies would be "patient-tailored therapy" for every individual patient with DM depending on its genotype, which should improve the rational choice of oral anti-diabetic drug therapy.

References

1. Barroso I. Genetics of type 2 diabetes. Diabet Med 2005; 22: 517–535.

2. Lyssenko V et al. Clinical risk factors, DNA variants, and the development of type 2 diabetes. N Engl J Med 2008; 359: 2220–2232.

3. Dobríková M, Stančáková A, Javorský M, Tkáč I. Genetic background of type 2 diabetes mellitus. Interná med 2007; 3: 147–152.

4. Frayling TM, Timpson NJ, Weedon MN et al. A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity. Science 2007; 316: 889–894.

5. Lyssenko V. The transcription factor-7 like 2 gene and increased risk of type 2 diabetes: an update. Curr Opin Nutr Metab Care 2008; 1: 385–392.

6. Reis AF, Velho G. Sulfonylurea receptor -1 (SUR1) : genetic and metabolic evidences for a role in the susceptibility to type 2 diabetes mellitus. Diabetes Metab 2002; 28: 14–19.

7. Van Dam RM, Hoebee B, Seidell JC et al. Common variants in the ATP-sensitive K^+ channel genes *KCNJ11* (Kir6.2) and *ABCC8* (SUR1) in relation to glucose intolerance: population –based studies and meta-analyses. Diabetes UK. Diabetic Medicine 2005; 2: 590–598.

8. Yasuda K, Miyake K, Horikawa Y et al. Variants in *KCNQ1* are associated with susceptibility to type 2 diabetes mellitus. Nat Genet 2008; 40 (9): 1092–1097.

9. Lyssenko V, Nagorny CLF, Erdos MR et al. Common variant in *MTNR1B* associated with increased risk of type 2 diabetes and impaired early insulin secretion. Nat Genet 2008; DOI: 10.1038/ng.208.

10. Steinthorsdottir V et al. A variant in *CDKAL1* influences insulin response and risk of type 2 diabetes. Nat Genet 2007; 39: 770–775.

11. Tkáč I. Enhancement of incretin effect as a new therapeutic approach it the treatment of tpye 2 diabetes mellitus. Intern Med 2006; 12: 668–671.

12. Baron AD. Postprandial hyperglycaemia and alpha – glucosidase inhibitors. Diabetes Res Clin Pract 1998; 40: Suppl 1: 51–55.

13. Bozkurt O, De Boer A, Grobbee DE et al. Pharmacogenetics of glucose-lowering drug treatment. Mol Diag Ther 2007; 11: 291–302.

14. Gribble FM, Reimann, F. Sulphonylurea action revisited: the post cloning era. Diabetologia 2003; 46: 875–891.

15. Reis AF, Velho G. Sulfonylurea receptor-1 (SUR 1): genetic and metabolic evidences for a role in the susceptibility to type 2 diabetes mellitus. Diabetes Metab 2002; 28, 14: 14–19.

16. Gloyn AL, Weedon MN, Owen KR et al. Large-scale association studies of variants in genes encoding the pancreatic beta-cell KATP channel subunits Kir6.2 (KCNJ11) nad SUR1 (ABCC8) confirm that the KCNJ11 E23K variant is associated with type 2 diabetes. Diabetes 2003; 52 (2): 568–572.

17. Vaxillaire M, Populaire C, Busiah K et al. Kir6.2 mutations are a common cause of permanent neonatal diabetes in large cohort of French patients. Diabetes 2004; 53: 2719–2722.

18. Staník J, Gašperíková D, Pašková M et al. Prevalence of permanent neonatal diabetes in Slovakia and successful replacement of insulin with sulfonylurea therapy in KCNJ11 and BCC8 mutation carriers. JCEM 2007; 4.

19. Zychma MJ, Gumprecht J, Strojek K et al. Sulfonylurea receptor gene 16-3 polymorphism –association with sulfonylurea or insulin treatment in type 2 diabetes subjects. Med Sci Monit 2002; 8–7: 512–515.

20. Meirhaeghe A, Helbecque N, Cottel D et al. Impact of sulfonylurea receptor 1 genetic variability on non-insulin dependent diabetes mellitus prevalence and treatment : a population study. Am J Med Genet 2001; 101 (1): 4–8.

21. Feng Y, Mao G, Ren X et al. 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.

22. Zhang H, Liu X, Kuang H et al. Association of sulfonylurea receptor 1 genotype with therapeutic response to gliclazide in type 2 diabetes. Diabetes Research and Clinical Practice 2007; 77: 58–61.

23. Sesti G, Laratta E, Cardellini M et al. The E23K variant of KCN11 endcoding the pancreatic beta-cell adenosine 5 triphosphate-sensitive potassium channel subunit Kir6.2 is associated with an increased risk of secondary failure to sulfonylureas in patients with type 2 diabetes. J. Clin Endocrinol Metab 2006; 91: 2334–2339.

24. Holstein A, Hahn M, Stumvoll M et al. The E23K viariant of *KCN11* and the risk for severe sulfonylurea –induced hypoglycemia in patients with type 2 diabetes. Horm Metab Res 2009; DOI 10.1055/s-0029-1192019.

25. Smith U. TCF7L2 and type 2 diabetes – we WNT to know. Diabetologia 2007; 50: 5–7.

26. Hattersley AT. Prime suspect: the TCF7L2 gene and type 2 diabetes risk. J Clin Invest 2007; 17: 2178–236.

27. Pearson ER, Donelly LA, Kimber CH et al. Variation in TCF7L2 influences therapeutic response to sulfonylureas. A GoDARTs Study. Diabetes 2007; 56: 2178–2182.

28. Shepherd M, Pearson ER, Houghton J et al. No deterioration in glycemic control in HNF-1 alpha maturity-onset diabetes of the young following transfer from long-term insulin to sulphonylureas. Diabetes Care 2003; 26 (1): 3191–3192.

29. Becker ML, Aarnoudse AJLHJ, Newton-Cheh CH et al. Common variation in the *NOS1AP* genes is associated with reduced glucose-lowering effect and with increased mortality in users of sulfonylurea. Pharmacogenetics and Genomics 2008; 18: 591–597.

30. Sesti G, Marini MA, Cardellini M et al. The Arg972 variant in insulin receptor substrate-1 is associated with an increased risk of secondary failure to sulfonylurea in patients with type 2 diabetes. Diabetes Care 2004; 27 (6): 1394–1398.

31. Becker ML, Visser LE, Trienekens PH et al. Cytochrome P4502C9 (*)2 and (*)3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes melitus. Clin Pharmacol Ther 2007.

32. Suzuki K, Yanagava T, Shibasaki T et al. Effect of *CYP2C9* genetic polymorphisms on the efficacy and pharmacokinetics of glimepiride in subjects with type 2 diabetes. Diabetes Research and Clinical Practice 2006; 72: 148–154.

33. Holstein A, Plaschke A, Ptak M et al. Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycemic agents. Br J Clin Pharmacol 2005; 60 (1): 103–106.

34. Moorodian AD, Thurman JE. Drug therapy of postprandial hyperglycaemia. Drugs 1999; 57 (1): 19–29.

35. Niemi M, Leathart JB, Neuvonen M et al. Polymorphism in CYP2C8 is associated with reduced plasma concentrations of repaglinide. Clin Pharmacol Ther 2003; 74 (4): 380–387.

36. Niemi M, Backman JT, Kajosaari LE et al. Polymorphic organic anion transporting polypeptide 1B1 is a major determinant of repaglinide pharmacokinetics. Clin Pharmacol Ther 2005; 77 (6): 468–478.

37. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006; 368: 1696–1705.

38. Bouatia-Naji N, Bonnenfond A, Cavalcanti-Proenca Ch et al. A variant near MTNR1B is associated with the increased fasting plasma glucose levels and type 2 diabetes risk. Nat Genet 2008; DOI:10.1038/ng.277.

39. Beinborn M, Worall CHI, McBride EW et al. A human glucagon-like peptide receptor polymorphism results in reduced agonist responsiveness. Regulatory Peptides 2005, 130: 1–6.

40. Tokuyama, Y, Matsui K, Egashira T et al. Five misssence mutations in glucagon-like peptide 1 receptor gene in Japanese population. Diabetes Res Clin Pract 2004; 66: 63–69.

41. Hawley SA, Gadalla AE, Olsen GS et al. The antidiabetic drug metformin activates the AMP-activated protein kinase cascade via an adenine nucleotide-independent mechanism. Diabetes 2002; 51: 2420–2425.

42. Ertrunc D, Tok EC, Aktas A. The importance of IRS-1 Gly972Arg polymorphism in evaluating the response to metformin treatment in polycystic ovary syndrome. Human Reproduction 2005; 20: 1207–1212.

43. Shaw RJ, Lamia KA, Vasquez D et al. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. Science 2005; 310: 1642–1646.

44. Legro RS, Barnhart HX, Schlaff WD et al. Ovulatory response to treatment of polycystic ovary syndrome is associated with a polymorphism in the STK11 gene. J Clin Endocrinol Metab 2008; 93: 792–800.

45. Shu Y, Sheardown SA, Brown C et al. Effect of genetic variation in the organic cation transporter 1(OCT1) on metformin action. J Clin Invest 2007; 117: 1422–1431.

46. Shikata E, Yamamoto R, Takane H et al. Human organic cation transporter (OCT1 and OCT2) gene polymorphisms and therapeutic effects of metformin. J Hum Genet 2007; 52: 117–122.

47. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. Ann Intern Med 1999; 131 (4): 281–303.

48. Yamauchi T, Kamon J, Waki H et al. The mechanisms by which both heterozygous peroxisome proliferaton receptor g (PPARg) deficiency and PPARg agonists improve insulin resistance. The Journal of biological Chemistry 2001; 276 (44): 41245–41254.

49. Kang ES, Park SY, Kim HJ et al. Effects of Pro12Ala polymorphism of peroxisome proliferator –activated receptor gamma 2 gene on rosiglitazone response in type 2 diabetes. Clin Pharmacol Ther 2005; 78, 2: 202–208.

50. Vega RB, Huss JM, Kelly DP. The coactivator PGC-1 cooperates with peroxisome proliferator-activated receptor g in transcriptional control of nuclear genes encoding mitochondrial fatty acid oxidation enzymes. Mol Cell Biol 2000; 20: 1868–1876.

51. Weyer C, Funahashi T, Tanaka S et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001; 86: 1930–1935.

52. Kang ES, Park SY, Kim HJ et al. The influence of adiponectin gene polymorphism on the rosiglitazone response in patients with type 2 diabetes. Diabetes Care 2005; 28 (5): 1139–1144.

53. Mottugai-Tabar S, Ryden M, Lofgren P et al. Evidence for an important role of perilipin in the regulation of human adipocyte lipolysis. Diabetologia 2003; 46: 789–797.

54. Kang ES, Cha SB, Kim HJ et al. The 11482G>A polymorhism in the perilipin genes is associated with weight gain with rosiglitazone treatment in type 2 diabetes. Diabetes Care 2006; 29: 1320–1324.

55. Javorsky M, Kozárová M, Šalagovič J, Tkáč I. Relationship among urinary albumin excretion rate, lipoprotein lipase *PvuII* polymorphism and plasma fibrinogen in type 2 diabetic patients. Physiol Res 2006; 55: 55–62.

56. Wang G, Wang X, Zhang Q et al. 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.

57. Andrulionyte L, Zacharova J, Chiasson JL et al. Common polymorhisms of the PPAR-gamma 2 (Pro12Ala) and PGC-1alpha (Gly482Ser) genes are associated with the conversion from impaired glucoese tolerance to type 2 diabetes in the STOP-NIDDM trial. Diabetologia 2004; 47: 2176–2184.

58. Zacharova J, Chiasson JL, Laakso M. The common polymorphisms (single nucleotid polymorphism /SNP/+45 and SNP+276) of the adiponectin gene predict the conversion from impaired glucose tolerance to type 2 diabetes:the STOP-NIDDM trial. Diabetes 2005; 54: 893–899.

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