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Pharmacogenetics for T2DM
and Anti-Diabetic Drugs

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1. Introduction

1.1 Genes associated with T2DM
1.1.1 Genes associated with ion transport

1.1.1.1 KCNJ11

The potassium inwardly rectifying channel subfamily J member 11 (*KCNJ11*) gene encodes Kir6.2 protein, the inwardly rectifying potassium channel, which is a complex of two subunits [2]. ATP-sensitive K^+ (K_{ATP}) channels critically control insulin secretion by coupling metabolism to electrical activity [3]. The β-cell channels are assembled, with tetradimeric stoichiometry, from two structurally distinct subunits: inwardly rectifying K-channel subunit (KIR6.2) and the regulatory sulfonylurea receptor subunit-1 (SUR1). Some studies showed that the *KCNJ11* E23K (Lys23Glu, 67 G>A, rs5219) polymorphism could affect insulin secretion and T2DM susceptibility by influencing the sensitivity of the K_{ATP} channel to ATP [4-6]. E23K promotes development of T2DM by increasing the threshold ATP concentration, thus inducing over activity of pancreatic β-cell K_{ATP} channels and inhibiting insulin secretion [7]. E23K markedly affected channel gating, significantly reduced the time spent in long inter burst closed states. Meta-analysis of all case-control data showed that the E23K allele was associated with T2DM [8]. The E23K variant was associated with a reduction in estimates of glucose-induced serum insulin levels in middle-aged glucose-tolerant subjects. This result is in accordance with the recent *in vitro* finding that the E23K variant is associated with a reduced ATP sensitivity of the Kir6.2/SUR1channel complex [4, 7]. T2DM patients with one A allele of the *KCNJ11* E23K polymorphism seem to be more sensitive to repaglinide as compared with individuals with the GG genotype [9].

1.1.1.2 KCNQ1

KCNQ1 (potassium voltage-gated channel, KQT-like subfamily, member 1) gene, locates on 11p15.5, encodes a voltage-gated K^+ channel with six transmembrane regions and is expressed in the heart, stomach, small and large intestine, kidney and pancreas [10]. Two independent GWA studies identified that SNPs rs2237892, rs2237895, and rs2237897 located in intron 15 of the *KCNQ1* gene were strongly associated with T2DM [6,7]. The association

of rs2237892, rs2237897, and rs2283228 with T2DM was confirmed in populations of Korean, Singaporean, Chinese, European ancestry and Japanese. The risk allele of rs2237892, rs2237895, and rs2237897 were associated with impairment of insulin secretion according to the homeostasis model assessment of β-cell function or the corrected insulin response [11, 12]. In a Chinese study, SNP rs2237892 was significantly associated with increasing fasting plasma glucose, while rs2237892 and rs2237897 were associated with HbA1c. The SNP rs2237897 was associated with both acute insulin and C-peptide response after arginine stimulation in T2DM group. The SNP rs2237895 was associated with both first- and second-phase insulin secretions in the controls. For rs2237892, rs2237895 and rs2237897 polymorphisms, homozygous carriers of the diabetes-associated allele had significantly decreased BMI (body mass index) and waist circumferences [13]. In German population, the rs2237892, rs2237895 and rs2237897 were nominally associated with OGTT (oral glucose tolerance test)-derived insulin secretion indexes [14]. It has been reported that SNP rs2237892 affected repaglinide and rosiglitazone therapeutic response. Individuals who were rs2237892 TT homozygote carriers treated with repaglinide for 48 weeks exhibited lower 2-h glucose levels and significantly higher cumulative attainment rates of target 2-h glucose levels than the C allele carriers; patients with a greater number of rs2237892 C alleles showed larger augmentations in both fasting insulin and HOMA-IR. The rs2237895 C allele was also associated with greater increments in both fasting insulin and HOMA-IR. SNP rs2237897 associated with decrease in 2-h glucose levels in the rosiglitazone 48-week therapy [15]. The minor C-allele of rs2237895 of *KCNQ1* gene, which had a prevalence of about 42% among Caucasians was associated with reduced measures of insulin release following an oral glucose load suggesting that the increased risk T2DM [16]. Another SNP rs151290 was associated with 30-min C-peptide levels during OGTT, first-phase insulin secretion, and insulinogenic index after adjustment in the dominant model in the population of mainland China [17]. And rs151290 was associated with glucose-stimulated gastric inhibitory polypeptide and GLP-1 increase after adjustment in the dominant model [14]. The molecular mechanism of KCNQ1 SNPs in the intron affects insulin secretion is unclear [6,8,9], suggesting the important role of KCNQ1 in insulin secretion by pancreatic β-cells. The increased risk for T2DM associated with KCNQ1 is likely to be caused by a reduction in insulin secretion. Further studies will be needed to verify these findings and to fully delineate the role of KCNQ1 and its related pathways in disease pathogenesis [18] .

1.1.1.3 SLC30A8

GWA studies also identified that the zinc transporter solute carrier family 30 member 8 gene (*SLC30A8*) polymorphism was a risk of T2DM in several populations [19-25]. The *SLC30A8* gene is an especially interesting candidate gene because of its exclusive expression in the pancreas and major in β-cell [25, 26]. *SLC30A8* gene encodes ion channel zinc transporter protein member 8 (ZnT-8), which is thought to be the β-cell zinc concentration regulator. ZnT-8 is a critical molecule during the insulin maturation and release process that carries zinc from the cytoplasm into insulin secretory vesicles [26]. Therefore, its polymorphisms may affect its activity, which in turns correlates with T2DM susceptibility and therapeutic efficacy. SNP rs13266634 polymorphism (973C>T) in *SLC30A8* gene is a non synonymous SNP that causes an amino acid change from arginine (R) to tryptophan (W) at position 325 (Arg325Trp). This SNP is associated with T2DM onset and development in several populations [19-25]. It has been reported that the genetic polymorphism of *SLC30A8* was associated with impaired proinsulin conversion involved in the production and secretion

pathway [27]. Fu *et al.* found that reduced ZnT-8 expression in cultured pancreatic β cells gives rise to reduced insulin response to hyperglycemia and that *SLC30A8* polymorphism could affect insulin secretion and glycemic response [28]. Another two studies indicated that patients with the rs13266634 C allele showed decreased first-phase insulin release following an intravenously administered glucose load [29, 30]. Furthermore, it has been found that the C alleles of rs13266634 at *SLC30A8* were associated with increased FPG and decreased insulin during the OGTT. An investigation also showed SNP rs13266634 increased the risk for T2DM by 1.24-fold in Chinese Han population [30]. A Chinese population study explored SLC30A8 is one susceptibility gene for T2DM and influences response to repaglinide. T2DM patients with T allele showed a better repaglinide response on FINS and PINS compared with CC wild-type homozygote [31].

1.1.1.4 WSF1

Wolfram syndrome 1 (*WFS1*) gene encodes wolframin, a 100 kDa transmembrane glycoprotein that maintains calcium homeostasis of the endoplasmic reticulum, which is expressed in neurons and pancreatic β-cells and regulates calcium fluxes in the endoplasmic reticulum [32]. *WFS1* is critical for survival and function of insulin-producing pancreatic β-cells [33]. *WFS1* gene polymorphism rs10010131 was confirmed with T2DM in several GWA studies [19-25]. In the Diabetes Prevention Program, it is noted a trend towards increased insulin secretion in carriers of the protective rs10010131 variants [34]. Rare mutations in *WFS1* cause Wolfram syndrome, variation in *WFS1* also predisposes to common T2DM. It has been reported that *WFS1* gene variants were associated with reduced insulin response to oral but not intravenous glucose [35-39]. *WFS1* gene was associated with estimates of a decreased pancreatic β-cell function among middle-aged individuals with abnormal glucose regulation [37]. *WFS1* gene was also associated with impaired incretin signaling, the level of glycemia determines SNP effects on insulin secretion. This indicated the increasing relevance of these SNPs during the progression of prediabetes stages toward clinically overt T2DM [40].

1.1.2 Genes involved in cell cycles

1.1.2.1 CDKAL1

A variant in the cyclin-dependent kinase 5 (CDK5) regulatory subunit associated protein 1-like 1 (*CDKAL1*) gene was associated with T2DM in individuals of European ancestry and individuals from Hong Kong of Han Chinese ancestry [22]. SNP rs7756992 is located in intron 5 of the *CDKAL1*. It resides in a large LD block of 201.7 kb that includes the *CDKAL1* gene exons 1-5 and the minimal promoter region but no other known genes. It has been proposed that polymorphism rs7756992 confers risk of T2DM through reduced insulin secretion because the insulin response for heterozygote was approximately 20% lower than for heterozygote or non carriers. The function of the CDKAL1 gene product is still unknown. But the CDKAL1 gene product is similar to CDK5 regulatory subunit-associated protein 1 (CDK5RAP1) gene product. CDK5RAP1 is expressed in neuronal tissues and inhibits CDK5 activity by binding to the CDK5 regulatory subunit p35. In pancreatic β-cells, CDK5 shows to act in the loss of β-cell function under glucotoxic conditions [41]. Inhibition of the CDK5/p35 complex prevents a decrease of insulin gene expression and glucotoxicity [42]. It is proposed that CDKAL1 may act in the inhibition of the CDK5/p35 complex in β-cells similar to CDK5RAP1 in neuronal tissue. Reduced

CDKAL1 expression or inhibitory function could lead to an impaired response to glucotoxicity. The association of CDKAL1 rs7756992 with T2DM was replicated in Japanese [43], Chinese [30] and Indians populations [44]. And variants in *CDKAL1* were strongly associated with β-cell function estimated by HOMA-β (Homeostasis model assessment for β cell function) [30]. Evidence from previous GWA studies implicating variants in *CDKAL1* and near *CDKN2A/B* implies that cell cycle dysregulation may be a common pathogenetic mechanism in T2DM [19, 20, 24].

1.1.2.2 CDKN2A/B

Cyclin-dependent kinase inhibitor-2A/B (CDKN2A/B) gene encode p15^{INK4b} and p16^{INK4a} protein which are tumor suppressors that inhibit cyclin-dependent kianse 6 (CDK6) and CDK4, respectively. CDKN2B and CDKN2A are expressed in pancreatic islets and adipocytes [19, 20, 24]. CDKN2A/2B (rs10811661) was associated with T2DM [45]. SNP rs10811661 located 125 kb upstream of the CDKN2B and CDKN2A genes, has been associated with T2DM in three of the GWA studies (OR for pooled studies 1.20 [95% CI 1.14–1.25], $P=5\times10^{-15}$) [19, 20, 24]. And the association was confirmed in Danish, Norwegian, French, Korean, Japanese and Chinese participants [10–15]. In murine models studies suggest that the rs10811661 polymorphism located upstream of the CDKN2B and CDKN2A genes may confer increased risk for T2DM by affecting β cell function [46-48].

1.1.2.3 CDC123/CAMK1D

SNP rs12779790 is located ~90 kb from cell division cycle 123 homolog [S. cerevisiae] (*CDC123*) gene and~63.5kb from calcium/calmodulin-dependent protein kinase I delta (*CAMK1D*) gene. *CDC123* gene encodes a protein involved in cell cycle regulation and nutritional control of gene transcription [23, 49]. CAMK1D regulates granulocyte function [50], it is also possible that a causative variant in this region is related to CAMK1D and affects pancreatic β-cell function through increased apoptosis. SNP rs12779790 is found associated with T2DM in several studies. G risk allele of rs12779790 was associated with a lower insulin genic index, corrected insulin response, and area under the insulin/glucose curve during OGTTs and a lower DI in carriers of the G allele [51]. In Asian Indian descent subjects also found the β-cell defect [34]. Trend toward lower β-cell function could be observed in Caucasians population [35, 38, 52]. SNP rs12779790 variation carriers showed a lower insulin response to glucose stimulation and noted a trend toward a reduced insulin response after arginine stimulation. Arginine stimulation during hyperglycemia is a measure of (near) maximal insulin secretion and has been suggested as a proxy for β-cell mass. This gene variant affected β-cell function by causing reduced β-cell mass due to enhanced apoptosis [50].

1.1.3 Genes involved in gene transcription

1.1.3.1 TCF2

The SNPs rs7501939 and rs4430796 on 17q12 are located in the first and second intron of the transcription factor 2 isoform b (*TCF2*) gene, respectively [53]. One of the variants is in *TCF2* (*HNF-1β*), a gene known to be mutated in individuals with maturity-onset diabetes of the young type 5 [54]. SNPs in *TCF2* are also associated with both T2DM and prostate cancer [53, 54]. Three genes with common variants that influence risk of T2DM were first discovered based on rare Mendelian mutations (*KCNJ11*, *WSF1* and *TCF2*). This is

particularly interesting given the recent finding that SNPs in *TCF2* are also associated both with T2DM and prostate cancer [53, 54].

1.3.2 TCF7L2

Transcription factor 7-like 2 (*TCF7L2*) gene encodes a transcription factor (Tcf-4) which involved in the regulation of cellular proliferation and differentiation [55]. TCF7L2 plays an important role in the Wnt signaling pathway. TCF7L2 is involved in the growth, differentiation, proliferation, and insulin secretion of pancreatic β-cells [56]. GWA studies found variants in the *TCF7L2* showed to be associated with an increased risk for T2DM [19, 20, 22, 23, 25, 57]. The strongest associations with T2DM with a clear gene dose effect were reported for the rs7903146 variant [58]. *TCF7L2* was found to be associated with less weight loss in response to lifestyle intervention [59]. Genetic variants in the exon 4 (including rs7903146) block of *TCF7L2* were associated with impaired insulin secretion and incident diabetes in a prospective Chinese cohort [60]. *TCF7L2* gene polymorphism also affected the drug response for T2DM therapy which was the only predictor of sulfonylureas treatment failure [61]. The rs7903146 T-allele conferred a higher risk for sulfonylurea treatment failure [61]. It has been observed that homozygous carriers of the *TCF7L2* risk alleles (rs1225372 and rs7903146) were twice as likely not to respond to sulfonylureas as patients homozygous for the non-risk alleles [62].

1.1.3.3 HHEX

GWA studies identified that the haematopoietically expressed homeobox (*HHEX*) gene polymorphism was a risk of T2DM in several populations [19-25]. *HHEX* encodes the transcription factor hematopoietically expressed homeobox protein, which is expressed in the embryonic ventral-lateral foregut that causes the ventral pancreas and the liver [63]. It has been confirmed the significant association of *HHEX* with T2DM in the Japanese population [64]. *HHEX* was a common T2DM-susceptibility gene across different ethnic groups. The OR values of the three SNPs rs1111875, rs5015480 and rs7923837 genotyped in *HHEX* (1.20–1.46) were higher in Japanese than those of the European population (1.20) [64]. *HHEX* variant was associated with impaired proinsulin conversion [38]. SNP rs1111875 and rs7923837 was associated with T2DM independent of body fat [65]. SNP rs7923837 in the 3'-flanking region of the HHEX locus was associated with altered glucose-stimulated insulin release. This SNP's major allele represented a risk allele for β-cell dysfunction and might confer increased susceptibility of β-cells toward adverse environmental factors [66]. Knockout of *HHEX* gene showed impair proliferation of endodermal epithelial cells, positioning of ventral foregut endoderm cells relative to the mesoderm, and budding and morphogenesis of the ventral pancreas [63]. This genetic manipulation finally provoked lethality during midge station [63].

1.1.3.4 JAZF1

The juxtaposed with another zinc finger gene 1 (*JAZF1*) gene encodes a transcriptional repressor of nuclear receptor subfamily 2, group C, member 2 (NR2C2) with three C2H2-type zinc fingers [67]. Mice deficient in Nr2c2 exhibit growth retardation, low IGF1 serum levels, and perinatal and early [53, 54] stnatal hypoglycaemia [68]. JAZF1 is expressed in pancreas, brain, thalamus, liver, uterus, endometrial and prostate. In a meta-analysis in East Asians, it has been found that the variant of *JAZF1* rs864745 was significantly

associated with T2DM [69]. SNP rs864745 is in intron 1 of the JAZF1 gene. The major T-allele of the rs864745 conferring increased diabetes risk was associated with increased 2nd phase serum insulin release during an IVGTT, and an increased fasting serum insulin level [69]. Carriers of the diabetes-associated T-allele of rs864745 had an allele dependent 3% decrease in BIGTT-AIR. JAZF1 is expressed in the pancreas [67], one might speculate that a gain-of-function variant in JAZF1 may lead to postnatal growth restriction also affecting pancreatic β-cell mass and function [51]. SNP rs864745 in JAZF1 were significantly associated with traits of insulin secretion in a glucose-tolerant Danish population [51].

1.1.4 Others

1.1.4.1 PPAR-γ2

Peroxisome proliferator-activated receptor-γ2 (PPAR-γ2) is one of PPAR-γ isoforms and is a member of the nuclear hormone receptor subfamily of transcription factors, which regulates transcription of various genes [70]. *PPAR-γ* plays an important role in adipocyte differentiation, regulating glucose, and lipid homeostasis [70]. Pro12Ala is one of important polymorphism in codon 12 of exon B causing proline-to-alanine change [71]. The Ala allele reduces the transcriptional activity of PPAR-γ2 and may protect against T2DM compared with the more common Pro/Pro genotype [72, 73]. The effects of the PPAR-γ2 Pro12Ala polymorphism on glucose and insulin metabolism may be modified by prenatal exposure to famine during midge station [74]. Patients with the Pro12Ala genotype had a better therapeutic response to rosiglitazone than the Pro12Pro genotype subjects. The genetic variations in the PPAR-γ2 gene can affect the response to rosiglitazone therapeutic efficacy in T2DM patients [75].

1.1.4.2 IGF2BP2

Insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2) belongs to an mRNA-binding protein family that plays role in RNA localization, stability and translation [76]. IGF2BP2 is highly expressed in pancreatic islets and binds to insulin-like growth factor 2 (IGF-2), which is an important growth and insulin signaling molecule [24]. IGF2BP2 is a homolog of IGF2BP1, which binds to the 5'UTR of IGF2 mRNA and regulates IGF2 translation [77]. Several GWA studies have found that subjects carrying mutant alleles of SNPs rs1470579 and rs4402960 in *IGF2BP2* gene showed a moderately increased risk of T2DM. Several studies have confirmed this result in Asian populations [30, 57, 78, 79]. T2DM patients with different *IGF2BP2* genotypes showed various levels of insulin secretion. It has been demonstrated that variants in *IGF2BP2* gene affect first-phase insulin secretion and the disposition index detected by hyperglycemic clamps [80].

Interactions between genetic variation in *IGF2BP2* and T2DM maybe exerted through this IGF2 pathway and through the insulin pathway. The *IGF2BP2* gene is located at chromosome 3q27.2. Intron 2 is the longest intron among mammalian species. SNPs rs1470579 and rs4402960 are located in a 50-kb region of this intron. Diabetes-predisposing variants may affect regulation of IGF2BP2 expression [20]. The *IGF2BP2* gene variant (rs4402960) was associated with insulin sensitivity, FPG, glucose AUC, and FPG [81]. SNP rs4402960 was also associated with reductions in first-phase insulin secretion and in the disposition index, which reflected the failing adaptive capacity of pancreatic β-cells [80] resulting in hyperglycemia including FPG and PPG. SNP rs4402960 has also been shown to be associated with the

disposition index in Hispanic Americans [82], HOMA-β in non-diabetic Japanese individuals and lower acute insulin release and tolerance [64]. SNP rs4402960 is strongly associated with an increased risk of T2DM and increased AUC of glucose in individuals of Dutch descent [83]. Wu et al observed a significant association of SNPs (rs1470579 and rs4402960) in *IGF2BP2* [1.17 (1.03–1.32); *P*=0.014] with combined IFG (impaired fasting glycemia)/T2DM group. The association of these SNPs with HOMA-β reduction suggested that *IGF2BP2* gene confers T2DM risk through a reduction of β-cell function [30]. Another study in Chinese T2DM population according with these results and found *IGF2BP2* variations effect on the therapeutic efficacy of repaglinide treatment in Chinese T2DM patients. Patients with the rs1470579 AC+CC genotypes had poor responses to repaglinide treatment with respect to FPG and PPG compared with individuals with the AA genotype. Patients with the GT+TT genotypes of rs4402960 also showed a better repaglinide therapeutic effect on PINS compared with individuals with the GG genotype. Replication of this research has indicated that *IGF2BP2* variants were more likely to be associated with reduced β-cell function [80, 84]. IGF2BP2 was shown to affect insulin secretion in a previous study. Understanding the biological mechanism by which variants in *IGF2BP2* could mediate these effects on the biphasic pattern of insulin secretion will require further investigation.

1.1.4.3 FTO

Fat mass and obesity associated (*FTO*) gene was found in a GWA study for T2DM susceptibility genes identified and showed to predispose to diabetes through an effect on BMI [85]. SNPs rs9939609 in the *FTO* gene region on chromosome 16 was strongly associated with T2DM [85]. A number of SNPs in tight linkage disequilibrium with rs9939609, and residing in the first intron of the *FTO* gene, had been associated with obesity in large populations of adults and children. It had been showed that common variation rs9939609 was reproducibly associated with BMI and obesity from childhood into old age [86]. And recently it has been identified T2DM risk variants only the risk variant of the FTO gene (rs8050136) showed statistically significant association with BMI, FMI, and Waist Circumferences [87] .Some data indicated that *FTO* SNP rs9939609 was associated with differences in BMI, with the presence of the A allele linked to a greater risk of increased BMI and increased values for specific measures of adiposity, such as the sum of skin fold values and total body water as assessed by isotope analysis [88].

1.1.4.4 THADA

THADA (thyroid adenoma associated) gene encodes thyroid adenoma–associated protein may involve in the death receptor pathway and apoptosis [89]. Disruption of THADA by chromosomal rearrangements (including fusion with intronic sequence from PPAR-γ) is observed in thyroid adenomas [90]. The function of THADA has not been well-characterized, but there is some evidence to suggest that it may be involved in the death receptor pathway and apoptosis [89, 91]. The THADA gene variant was also associated with lower β-cell response to GLP-1 and arginine, suggested lower β-cell mass as a possible pathogenic mechanism [92]. SNP rs7578597 was a non-synonymous SNP causing threonine to alanine in 1187 position which strongly associated with T2DM (combined OR [95%CI] of 1.15[1.10-1.20], *P*=1.1×10^{-9}) resided in exon 24 of *THADA* gene[23]. Subjects with the rs7578597 (T1187A) gene variant in *THADA* had a reduced β-cell mass due to increased apoptosis [92]. Analyses in the control subjects showed that THADA SNP rs7578597 was association with 2-h insulin during oral glucose tolerance tests [93].

1.1.4.5 TSPAN8/ LGR5

Tetraspanin 8 is a cell-surface glycoprotein, widely expressed cell surface glycoprotein known to form complexes with integrins to regulate cell motility in cancer cell lines [23, 94]. Tetraspanin 8 gene (TSPAN8) polymorphism rs7961581 was one of the strongest statistical signals associated with T2DM. SPAN8/LGR5 rs7961581 was significantly associated with T2DM in a meta-analysis in East Asians [69]. SNP rs7961581 associated with decreased levels of CIR, of AUC-insulin/AUC-glucose ratio, and of the insulinogenic index [51]. SNP rs7961581 resided ~110 kb upstream of *TSPAN8* gene. Because 6-integrin binding to laminin had been shown to negatively affect pancreatic β-cell mass maintenance [95], it was possible that variation in TSPAN8 influenced pancreatic β-cell function.

1.1.4.6 ADAMTS9

ADAMTS9 is a member of the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) protein family which has been implicated in the cleavage of proteoglycans [96], the control of organ maturation, development [97] and inhibition of angiogenesis [98]. ADAMTS9 is a secreted metalloprotease that cleaves the proteoglycans versican and aggrecan, and is expressed in skeletal muscle and pancreas [23]. SNP rs4607103 in *ADAMTS9* gene representing a cluster of associated SNPs, resides ~38 kb upstream of the *ADAMTS9* gene, and also associated with T2DM susceptibility [52]. It has been found common diabetes-related C allele of rs4607103 at chromosome 3p14.3-2 upstream of ADAMTS9 was associated with a decrease in insulin sensitivity of peripheral tissues, as estimated from a euglycemichy perinsulinemic clamp [69]. And impairment of insulin sensitivity occurred in the presence of an increase in serum insulin levels in response to intravenous and oral glucose loads [69]. The major C-risk allele of rs4607103 near ADAMTS9 conferred increased risk of T2DM, associated with increased fasting plasma glucose levels and reduced insulin-stimulated glucose uptake during a euglycemic-hyperinsulinemic clamp. The C-risk allele also showed statistically significant associations with increased levels of serum insulin at 30 min after oral ingestion of glucose as well as with increased first and second phase serum insulin release as estimated from an IVGTT [99].

1.1.4.7 NOTCH2

Notch 2 (Notch homolog 2 [Drosophila]) expresses when pancreatic buds branch and is restricted to embryonic ducts, should be the source for endocrine and exocrine stem cells in mice [23, 100]. Notch pathway plays key role in dictating endocrine differentiation. Activation of this pathway is critical for the maintenance of the progenitor pool between the first and second transitions of pancreatic development [101]. NOTCH2 is a type 1 transmembrane receptor. The SNP rs10923931 residing in intron 5 of the NOTCH2 gene strongly associate with T2DM susceptibility. SNP rs10923931 is near complete linkage disequilibrium with SNP rs2641348 in the ADAM30 gene [23]. Rs2641348, a non-synonymous SNP (L359P) within the neighboring ADAM metallo-peptidase domain 30 gene (ADAM30) represented the same signal (r^2=0.92 based on HapMap CEU data) and was also followed-up.

1.1.4.8 PTPRD

A GWA study in Chinese population identified two genes, PTPRD and SRR, which were not previously described to be involved in diabetes or glucose metabolism [102]. PTPRD is the protein tyrosine phosphatase receptor type D gene and widely expressed in skeletal muscle, pancreas, and brain which belong to the receptor type IIA (R2A) subfamily of protein tyrosine phosphatases (PTPs). The R2A PTP subfamily comprises leukocyte common

antigen-related (LAR), protein tyrosine phosphatase sigma (PTPRS), and PTPRD. The R2A family has been implicated in neural development, cancer, and diabetes [103]. PTPRD-deficient mice exhibited impaired learning and memory, early growth retardation, neonatal mortality, posture and motor defects [104]. LAR- and PTPRS-deficient mice showed defected glucose homeostasis and insulin sensitivity [105-107]. Transgenic mice over expressing LAR in skeletal muscle showed whole-body insulin resistance [108]. R2A subfamily members have similar structure [109]. PTPRD could act in T2DM pathogenesis and affect insulin signaling on its target cells. But it need further

Gene	SNP	Position	Effect	References	Chromosome
KCNJ11	rs5219	Exon	E23K	[25]	11p15.1
PPAR-γ2	rs1801282	Exon B	P12A	[74]	3p25
TCF2	rs7501939	Intron 1	/	[53]	17q12
	rs4430796	Intron 2	/	[53]	
WSF1	rs10010131	Intron	/	[40]	
	rs752854	Intron	/	[37]	4p12
	rs6446482	Intron	/	[37]	
	rs734312	Exon	H61R	[37]	
TCF7L2	rs7903146	Exon 4		[58]	10q25.3
HHEX	rs1111875	3'-UTR	/	[20]	
	rs5015480	?	/	[20]	
	rs7923837	?	/	[20]	
SLC30A8	rs13266634	Exon 8	R325W	[25]	8q24.11
CDKAL1	rs7756992	Intron 5	/	[22]	
	rs7754840	?	/	[118]	6p22.3
	rs9465871	?	/	[30]	
	rs10946398	?	/	[30]	
CDKN2A-2B	rs10811661	?	/	[19]	9p21
IGF2BP2	rs1470579	Intron 2	/	[20]	3q27.2
	rs4402960	Intron 2	/	[20]	
FTO	rs8050136	Intron	/	[87]	16q12.2
	rs9939609	Intron 1		[86]	
JAZF1	rs864745	Intron 1	/	[23]	7p15.2-p15.1
CDC123/CAMK1D	rs12779790	?	/	[23]	10p13
THADA	rs7578597	Exon 24	T1187A	[23]	2p21
TSPAN8	rs7961581	?	/	[23]	12q14.1-q21.1
ADAMTS9	rs4607103	near	/	[23]	3p14.3-2
NOTCH2	rs 10923931	Intron 5	/	[23]	1p13-p11
PTPRD	rs17584499	Intron 10	/	[102]	9p24.1-p23
SRR	rs391300			[102]	17p13.3
	rs4523957			[102]	
KCNQ1	rs2237892	Intron 15	/	[23]	11p15.5
	rs2237895	Intron 15	/	[23]	
	rs2237897	Intron 15	/	[23]	
	rs2283228	Intron 15	/	[11]	
	rs151290	Intron 15	/	[17]	

Table 1.1 Summary of associated genes

characterize. *PTPRD* gene polymorphism rs17584499 showed significant association with T2DM (*P* = 8.54610-10; odds ratio [OR] = 1.57; 95% confidence interval [CI] = 1.36–1.82) [102]. This SNP locates in intron 10.

1.1.4.9 SRR

SRR (serine racemase) gene encodes aserine racemase that synthesizes D-serine from L-serine [110, 111]. D-serine (co-agonist) and the neurotransmitter glutamate bind to the N-methyl Daspartate (NMDA) receptors and trigger excitatory neurotransmission in the brain [102, 112, 113]. NMDA receptor activation requires binding of glutamate and D-serine, which plays a neuromodulatory role in NMDA receptor transmission, synaptic plasticity, cell migration, and neurotoxicity [62]. D-serine and SRR express in the pancreas [114]. Glutamate signaling has function involved in positively regulates insulin and glucagon secretion in pancreatic islets [115-117]. Thus, SRR and D-serine may play roles in the etiology of T2DM. SNPs rs391300 and rs4523957 in the SRR gene were associated with T2DM in a Han Chinese GWA study. SNPs rs391300 and rs4523957 were in tight LD with each other (r^2 = 0.942 in HapMap HCB)[102]. The nearby SNP rs216193 also showed significant association; this SNP resides 3.8 kb upstream from SRR. SNP rs216193 was in tight LD with rs391300 (r^2 = 0.942 in HapMap HCB) [102].

2. Anti-diabetic drugs pharmacogenetics

2.1 Insulin secretagogue agents ------sulfonylureas (SUs)

The sulfonylurea anti-diabetic agents are insulin secretogogues including the first generation sulfonylureas (acetohexomide, chlorpropamide, tolazamide and tolbutamide) and second generation sulfonylureas (glibenclamide (glyburide), glipizide, gliclazide, and glimepiride) which are most widely used for T2DM treatment by closing the pancreatic β-cell potassium channels and stimulation insulin secretion [119].

2.1.1 Cytochrome P450

Sulfonylurea hypoglycemic agents are metabolized by cytochrome P450 2C9 (CYP2C9) enzyme. Genetic polymorphisms Arg144Cys (*CYP2C9*2*) and Ile359Leu (*CYP2C9*3*) could affect the safety and efficacy of sulphanylureas drugs in T2DM patients [120]. *CYP2C9* genotypes significantly affected glyburide pharmacokinetics. Carriers with *CYP2C9* variant **3* had decreased oral clearances [121]. Suzuki *et al* reported the subjects with *CYP2C9*3* alleles showed the metabolic activity decrease of glimepiride hydroxylation and a marked elevation in the plasma concentrations of glimepiride, compared with subjects with a *CYP2C9*1/*1*(wild type). The elevated glimepiride concentrations in subject with *CYP2C9*1/*3* may increase the pharmacological effects [122]. Zhang *et al* reported the pharmacokinetics of gliclazide modified release were affected mainly by *CYP2C19* genetic polymorphism in healthy Chinese subjects [123].

2.1.2 Sulfonylurea receptor

The sulphonylurea receptor is a subunit of the ATP-sensitive potassium channel located in pancreatic β-cell. The variants in the exon 16 -3C/T variant (rs1799854) of *SUR1* (Sulfonylurea Receptor 1) was associated with T2DM and 25% reduction in second-phase insulin secretion in -3T allele carriers in Dutch subjects with normal glucose tolerance (NGT) and impaired glucose tolerance (IGT) [124]. The association also found in Japanese [125] and

Finnish population [126]. A recent publication reported genotyped 25 SNPs from 661 Chinese T2DM patients who received 8 weeks of gliclazide therapy. The subjects with GG genotype in SUR exon 33(S1369A, rs757110) had a 7.7% greater decrease in FPG and 11.9% greater decrease in HbA1c after 8 weeks of gliclazide therapy [127].

2.1.3 Others

It was described that the exon 33 of the ABCC8 (rs757110) and KCNJ11 (rs5210) genes were associated with gliclazide antidiabetic efficacy [127]. SNPs of TCF7L2 had been consistently associated with T2DM in different ethnic descent and also had great impact on the T2DM patients' response to sulfonylureas [128]. The Go-DARTS2 study reported that the T allele of rs7903146 was associated with increased HbA1c in both cases and controls [129]. The same study group revealed that carriers of TCF7L2 variants were more likely to fail sulfonylurea therapy but not metformin (HbA1c > 7 %) within 3-12 months of treatment initiation [62].

Hepatocyte nuclear factor-1α (HNF-1α) is a homeodomain-containing transcription factor that expressed in the pancreatic β-cell and HNF-1α SNPs have been associated with β-cell dysfunction and maturity onset diabetes of the young (MODY) [130]. Variations in HNF-1α polymorphisms of T2DM were reported to be more sensitive to the hypoglycaemic effects of sulfonylureas [131-133]. *Pearson et al* reported that patients with HNF-1α polymorphisms (P129T, E132K, R159W, R229P, W267R and P291fsinsC) had a 5.2-fold greater response to gliclazide than to metformin and 3.9-fold greater response to gliclazide than patients without HNF-1α mutations [134].

2.2 Insulin secretagogue agents ------ Non-sulfonylureas

Meglitinides (repaglinide and nateglinide) represent a new class of insulin secretagogue, structurally unrelated to sulphanylureas by very rapid onset and abbreviated duration of action [135]. Meglitinides stimulate first-phase insulin release in a glucose-sensitive manner and reduce the risk of hypoglycemic events.

2.2.1 Cytochrome P450 and transporters

Repaglinide is metabolized by CYP2C8 and CYP3A4 [136]. The *CYP2C8*3* variant (Arg139Lys, Lys399Arg) allele was associated with reduced plasma concentrations of repaglinide [137]. Repaglinide mean AUC and maximum plasma concentration (C_{max}) were 45 and 39 lower, respectively, in subjects with the *CYP2C8*1/*3* genotype compared with wild-type homozygotes. Repaglinide AUC was also 13% lower in subjects with the *CYP2C8*1/*4* genotype compared with wild-type homozygotes, although this was not statistically significant [137]. Genetic polymorphisms of *CYP3A4*, specifically *CYP3A4*18*, played a major role in contributing to the inter-individual variability in repaglinide's pharmacokinetics [138].

The oral bioavailability of nateglinide is about 73%, and it is rapidly absorbed and extensively metabolized primarily by CYP2C9 in the liver and a smaller fraction by CYP3A4 and CYP2D6 [139]. Nateglinide is confirmed as a substrate of CYP2C9. A previous report showed that the *CYP2C9*3* allele was associated with significantly reduced oral nateglinide clearance and pharmacokinetic parameters, which seemed to be unaffected by *CYP2C9*2* and *CYP2D6*4* or *5* carriers [140].

The meglitinide class drug nateglinide is metabolized by CYP2C9. According to pharmacokinetic data, moderate dose adjustments based on CYP2C9 genotypes may help in reducing interindividual variability in the anti hyperglycemic effects of nateglinide [173]. Carriers of the *CYP2C9*3/*3* genotype may be at a slightly higher risk of hypoglycemia compared to carriers of *CYP2C9*1*, particularly when taking nateglinide doses above 120 mg [140].

Polymorphic organic anion transporting polypeptide 1B1 (SLCO1B1) is a major determinant of repaglinide pharmacokinetics [141]. SLCO1B1 (which codes the *OATP1B1* gene, also known as OATP-C, OATP2) polymorphisms are important predictors of repaglinide pharmacokinetics [141]. Repaglinide AUC was 60–110% greater in participants with the c.521CC genotype than in those with the c.521TT genotype after ingestion of single repaglinide doses ranging from 0.25 to 2mg [142]. Haplotypes of SLCO1B1*1b/*1b (c.388 G–c.521 T) was associated with reduced pharmacokinetic exposure after a single dose oral administration of 2 mg repaglinide, including decreased AUC0-∞ and increased clearance of repaglinide [143].

2.2.2 Others

An association of (*IGF2BP2*) rs1470579 and rs4402960 polymorphisms and development of T2DM and therapeutic efficacy of repaglinide in Chinese T2DM patients was reported. The effects of the repaglinide treatment on FPG (*P*<0.05) and PPG (*P*<0.05) were reduced in patients with the rs1470579 AC+CC genotypes compared with AA genotype carriers. Patients with the rs4402960 GT+TT genotypes exhibited an enhanced effect of repaglinide treatment on PINS (*P*<0.01) compared with GG genotype subjects [144]. *SLC30A8* rs13266634 and rs16889462 polymorphisms were associated with repaglinide therapeutic efficacy in Chinese T2DM patients. There were significantly augmented repaglinide effects in patients with rs13266634 CT+TT genotypes on FINS and PINS compared with rs13266634 CC genotype. And patients with rs16889462 GA genotype showed enhanced repaglinide effects on FPG, PPG, and HbAlc compared with GG genotype [31]. Variations in the neural nitric oxide synthase adaptor protein (NOS1AP) involved in insulin secretion and insulin signal pathway may explain some of the variability in response to anti-diabetic drug. A common variant in rs10494366 was associated with repaglinide monotherapy efficacy on insulin resistance in newly diagnosed Shanghai Chinese T2DM patients [145]. And *sheng et al* study suggested that NAMPT -3186C>T polymorphism was significantly associated with plasma levels of PINS and CHO in Chinese T2DM patients with repaglinide monotherapy [146]. KCNQ1 polymorphism rs2237892 was associated with repaglinide's efficacy on improving insulin sensitivity in Chinese patients with T2DM [15].

2.3 Biguanides

Metformin (a biguanide) is among the most widely prescribed drugs and has a gluco-regulator effect in the presence of endogenous insulin by reducing gastrointestinal glucose absorption, decreasing endogenous glucose production and reducing peripheral resistance to insulin [147].

2.3.1 Transporters

Organic cation transporter 1 (OCT1, gene name SLC22A1) is the major mechanism for metformin entry into hepatocytes and enterocytes [148]. Human OCT1 is highly

polymorphic. Shu' study provided proof of concept that genetic variation in OCT1 may be associated with variation in response to metformin OCT1 Met420del had reduced activity for metformin [149]. Another study in healthy subjects also confirmed polymorphisms in OCT1 were associated with the renal clearance of metformin [150]. Low-function OCT1 amino acid substitutions Arg61Cys, Ser401Gly, Met420del, and Gly465Arg, and the OCT1 promoter-linked variant rs1867351, were associated with an increase in the renal clearance of metformin by~20% and ~30%, respectively. These data suggested that a reduction in OCT1 expression or activity may increase renal excretion of metformin [150]. But in T2DM patients, the OCT1 loss-of-function variants, Arg61Cys and Met420del, did not attenuate the HbA1C reduction achieved by metformin [151].

2.3.2 Others

Recently, serine-threonine kinase 11 (*STK11*), which phosphorylates AMPK, has also been reported to be involved in metformin effects. The *STK11* rs8111699 SNP influenced insulin sensitivity and metformin efficacy [152]. Schroner et al showed that the degree of reduction in HbA1c and FPG after ulphonylurea treatment in addition to previous metformin monotherapy was related to *TCF7L2* gene polymorphisms [153]. ATM, a gene known to be involved in DNA repair and cell cycle control, played a role in the effect of metformin upstream of AMP-activated protein kinase, and variation in this gene altered glycemic response to metformin [154].

2.4 Euglycemic agents

Thiazolidinediones (pioglitazone, rosiglitazone) are insulin sensitizing agents and have glucose and lipid lowering activity. They are selective agonists for the PPAR-γ and decrease insulin resistance and enhance the biological response to endogenously produced insulin.

2.4.1 Cytochrome P450

Both rosiglitazone and pioglitazone are extensively metabolized in the liver by CYP2C8 [155, 156]. Kirchheiner and colleagues considered the influence of the *CYP2C8*3* polymorphism on single dose and multiple-dose rosiglitazone (8 mg) pharmacokinetics in German healthy volunteers [157]. Tornio et al evaluated the effects of the *CYP2C8*3* allele on single-dose pioglitazone (15 mg) pharmacokinetics in healthy volunteers [158]. The weight-adjusted pioglitazone AUC was 34% lower in *CYP2C8*3* homozygotes and 26% lower in heterozygotes compared with wild-type homozygotes ($P < 0.05$, both comparisons). The half-life of pioglitazone was significantly shorter in heterozygotes (3.4 h) and *CYP2C8*3* homozygotes (3.3 h) compared with wild-type homozygotes (4.5 h). Daily et al reported following a single dose of rosiglitazone 4 mg, mean AUC was 29% lower and weight-adjusted oral clearance was 39% higher in heterozygotes compared with wild-type homozygotes [159].

2.4.2 Others

Rosiglitazone improves insulin sensitivity by reducing plasma glucose levels and serum insulin, NEFA and triglyceride and by increasing HDL cholesterol levels [160, 161]. *Vestergaard et al* reported rosiglitazone treatment, in combination with insulin and metformin, of patients with severe primary insulin resistance due to IR mutations and diabetes mellitus, had no impact on the measured estimates of glucose and lipid

metabolism [162]. It was found that variations SNP45 and SNP276 in the *adiponectin* gene could affect the rosiglitazone treatment response to the serum adiponectin level and blood glucose control [158]. *Sun et al* reported that the adiponectin allele 45T/G and -11377C/G polymorphisms were significantly associated with the therapeutic efficacy of multiple-dose rosiglitazone in Chinese patients with T2DM [163]. And *TNF-a* G-308A polymorphism might be associated with the therapeutic efficacy of rosiglitazone in T2DM patients [164]. Genetic variations 11482G/A in the perilipin gene could affect weight gain associated with rosiglitazone treatment in patients with T2DM [165]. *Brunham et al* demonstrated that the ATP-binding cassette transporter subfamily A number 1 (ABCA1) probably had an effect on islet cholesterol homeostasis, and influencing glucose tolerance and insulin secretion [166]. The 219K variant of *ABCA1* gene was associated with the therapeutic effect of rosiglitazone. The RR homozygotes had a better response to rosiglitazone treatment in terms of insulin sensitivity improvement than minor K allele carriers [167]. The genetic variations in the *PPAR-γ2* gene could affect the response to rosiglitazone treatment in patients with T2DM. Patients with the Pro12Ala genotype in the *PPAR-γ2* gene had a better therapeutic response to rosiglitazone than did patients with the Pro12Pro genotype [75]. *LPIN1* genetic variations rs10192566 could affect rosiglitazone treatment response in T2DM [168]. Zhang et al reptored carriers of A allele of Thr394Thr or Ser allele of Gly482Ser in *PGC-1a* gene showed a trend for poor therapeutic efficacy to rosiglitazone for A allele of Thr394Thr but a significant improvement in its effectiveness for Gly482Ser. Variants in PGC-1α gene might impair the therapeutic efficacy of rosiglitazone [169].

Himelfarb et al investigated TNF-α and IL-6 expression in leukocytes and their association with polymorphisms and bone markers in diabetic individuals treated with pioglitazone. *TNF-a* -308G>A polymorphism appeared to be involved in regulation of gene expression independently of hyperglycemia and its interaction with pioglitazone might modify tALP, a important bone marker. *IL6* -174G>C variant was related with reduced risk of postprandial hyperglycemia but not with mRNA expression or bone markers [170]. The *PPAR-γ* Pro12Ala gene polymorphism was associated with the response to pioglitazone in Chinese patients with T2DM [171]. Pioglitazone treatment had significantly beneficial effects on serum lipid profile and blood pressure in S447S genotype carriers. The S447X variant in lipoprotein lipase (LPL) gene might be a cause for therapy modification by pioglitazone [172].

3. Conclusion

The rapidly increasing prevalence of T2DM is becoming a tremendous public health problem that affects more than 170 million patients worldwide. T2DM is a complex metabolic disorder with two major pathophysiological features: insulin resistance and pancreatic β-cell dysfunction. The mechanism of this disease remains unknown; however, environmental factors and genetic variations are considered two major contributors to onset and development of T2DM. In this chapter, we introduced gene associated with T2DM, such as: KCNJ11, KCNQ1, SLC30A8, WSF1, CDKAL1, CDKN2A/B, TCF2, TCF7L2, HHEX, JAZF1, PPAR-γ2, IGF2BP2, FTO, THADA, TSPAN8/ LGR5, ADAMTS9, NOTCH2, PTPRD, and SRR. Meanwhile, we described four anti-diabetic drugs pharmacogenetics, including insulin secretagogue agent sulfonylureas (SUs) and meglitinides, biguanides, and euglycemic agents. Genetic polymorphisms in drug-metabolizing enzymes, transporters, receptors, and other drug targets have been linked to interindividual differences in the

efficacy and toxicity of a number of medications. Mutations in genes important in drug absorption, distribution, metabolism and excretion (ADME) play critical role in pharmacogenetics of diabetes. Numerous genes that influence pharmacogenetics of oral antidiabetics have been described. The investigations of genes associated with T2DM benefits of personalized medicine. And different types of genetic mutations and their influence on the response to therapy with oral antidiabetics are needed future study.

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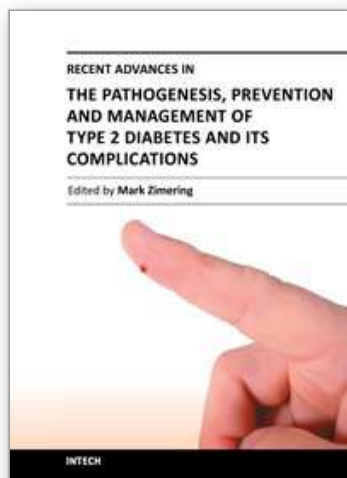
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Type 2 diabetes â€œmellitusâ€ affects nearly 120 million persons worldwide- and according to the World Health Organization this number is expected to double by the year 2030. Owing to a rapidly increasing disease prevalence, the medical, social and economic burdens associated with the microvascular and macrovascular complications of type 2 diabetes are likely to increase dramatically in the coming decades. In this volume, leading contributors to the field review the pathogenesis, treatment and management of type 2 diabetes and its complications. They provide invaluable insight and share their discoveries about potentially important new techniques for the diagnosis, treatment and prevention of diabetic complications.

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