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Review

THE ROLE OF GENETIC FACTORS IN LIKELIHOOD OF TYPE 2 DIABETES MELLITUS

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Type 2 diabetes mellitus (DM2) is the ninth leading cause of worldwide mortality. To predict likelihood of the disease and its unfavorable clinical course with developing complications, it is necessary to consider genetic and molecular factors of DM2 pathogenesis. Therefore, the aim of this review was to analyze the role that belongs to genetic factors in molecular mechanisms of DM2 development and to establish the most significant single nucleotide polymorphisms (SNP) in DM2 pathogenesis.

The authors have analyzed literature sources found in such databases as CYBERLENINKA, E-library, and National Center for Biotechnology Information over the last 10 years as well as the integrated database GeneCards.

By now, Genome-Wide Association Studies (GWAS) have identified about 100 genes and more than 700 polymorphisms that influence DM2 risks and its likelihood. Classifications of candidate genes with their effects and expression being limited by external and internal transcription factors are rather tentative. Literature analysis has established certain ambiguousness of the role that belongs to genetic markers in DM2 pathogenesis. It is advisable to add new genetic markers of the PPARγ, TLR4, IRS and IL-6 genes to the existing test-systems. This will increase the likelihood of detecting hereditary predisposition to diabetes mellitus according to the key molecular-genetic mechanisms of its development and ensure implementation of relevant measures aimed at preventing the disease and early identification of genetic risk groups.

Keywords: *diabetes mellitus, hereditary predisposition analysis, genetic markers, single nucleotide polymorphisms, signaling pathways.*

Type 2 diabetes mellitus (T2DM) is a polycomponent disease primarily caused by insulin resistance (IR) [1]. Worldwide, it is estimated that 425 million adults (20–79 years) have diabetes, projected to reach 629 million by 2045. Also, DM is the ninth leading cause of worldwide mortality [2]. Personal human genome (individual allele combinations, single nucleotide polymorphisms or SNP included) and impacts of various risk factors are combined in T2DM pathogenesis [3–5]. By now, genome-wide association studies (GWAS) have identified approximately 100 genes and more than 700 polymorphisms able to modify T2DM risk [6]:

1. Genes associated with β-cell function: *ABCC8, IGF2BP2, IRS1, CDKAL1, KCNJ11,*

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KCNQ1, SLC30A8, C2CD4A, WFS1, TCF7L2, GCK [5].

2. Genes that participate in formation of insulin resistance: *PPARG*, *IRS1*, *ADIPOQ*, *ADIPOR2* [6].

3. Genes associated with glucose metabolism and participating in glucose level regulation: *G6PC2*, *GCK*, *GCKR*, *OCT3* [6].

4. Genes that have some associations with T2DM but their exact molecular pathways have not been established yet: *ACHE*, *PLS1*, *PCNXL2*, *PAPL*, *CR2*, *LPIN2* [7, 8].

There are only tentative classifications of candidate genes, action and expression of which are limited by external and internal transcription factors. Therefore, **the aim of this review** was to analyze significance of certain genes and their SNPs with an important pathogenetic role in basic molecular mechanisms of T2DM development.

Materials and methods. The authors analyzed relevant databases including CYBERLENINKA, Elibrary, National Center for Biotechnology Information, as well as the integrated database GeneCards[1].

Genes associated with β-cell function. Most identified variants of the genes from this group influence insulin secretion by pancreatic β-cells and not insulin effects [9].

Human sirtuin SIRT1, NAD^+ histone deacetylase, modulates insulin secretion and regulates activity of transcription factors and their co-regulators [10, 11]. A study conducted on a Chinese population investigated 5 SNPs that cover 100 % of common genetic variations (minor allele frequency ≥ 0.05) within the SIRT1 gene. A subsequent analysis of insulin resistance risk and T2DM risk in the examined population established their different roles [12]. The homozygous combination per the allele A of *SIRT1* gene polymorphism rs10509291 was associated with high T2DM risk in a Chinese Han population [p = 0.002; OR (odds ratio), 95 % CI (confidence interval) = 1.551 (1.179–2.04)]. Linear regression analyses adjusting for age, gender, and body mass index (BMI) showed that HbA1c and HOMA-IR in subjects with rs10509291 AA genotype were higher than those with TT genotype in T2DM group (p = 0.045, p = 0.035, respectively).

GCK (Glucokinase). The *GCK* gene plays an important role in glucose metabolism and glucose-stimulated insulin secretion. It makes for glucose absorption and its transformation into glycogen in the liver [13]. Rare mutations in GCK cause Maturity-Onset Diabetes of the Young 2 (MODY 2). This 3'UTR SNP was also established to be associated with diabetes (OR = 1.36, 95 % CI = [1.11–1.65], p = 0.002), where the allele A (allele frequency 0.05) was associated with the highest T2DM risk [14].

HNF1A and *HNF4A (Hepatic nuclear factor)* encode a transcription factor that participates in the development and functioning of pancreatic β-cells. Heterozygous mutations lead to *HNF* function loss and induce a decrease in glucose phosphorilation into glucoso-6-phosphate (G6P). The reaction blocks G6P from entering the glycolytic pathway thereby leading to non-progressing fasting hyperglycemia [15]. Family inheritance of diabetes was significantly more common in patients with the p.I27L TT genotype in a Turkish population (β = 1.45; 95 % CI = [1.2–4.2]; p = 0.036) [16].

Mutations rs757110 of the *ABCC8 gene (ATP Binding Cassette Subfamily C Member 8)*, which encodes the sulfonylurea receptor, might be associated with hyperinsulinemia [15].

SLC30A8 (solute carrier family 30 member 8, encodes the zinc efflux transporter protein). The protein that is encoded by this gene is a zinc transporter. *SLC30A8* is expressed in the pancreas, namely, pancreatic islets. The encoded protein is co-localized with insulin in granules of INS-1 cells secretory pathway. Mice with zero *SLC30A8* levels have lower insulin secretion (GSI) and glycemia. Homo-

[1] GeneCards®: The Human Gene Database. Available at: https://www.genecards.org/ (March 14, 2024).

zygous rs13266634 TT genotype of the *SLC30A8* gene, according to E.S. Melnikova with colleagues, is associated with T2DM risk for women in all age groups in a Novosibirsk population (OR = 1.51; 95 % CI = [1.11–2.05]; p = 0.008). In contrast, rs13266634CC genotype of the *SLC30A8* gene is associated with protector effect as regards T2DM (OR = 0.57; 95 % CI = [0.35–0.92]; p = 0.026) [17].

PAM (*Peptidylglycine Alpha-Amidating Monooxygenase*) encodes α-amidase, which is localized on secretory granule membranes and participates in wrapping insulin granules and their release from β-cells [18]. Two GWAS-identified SNPs in the *PAM* gene (rs78408340, c.1616C>G, OR = 1.47, MAF = 7.3) and (rs35658696, c.1688A>G, OR = 1.23, MAF = 0.045), influence T2DM risk [19]. Both polymorphisms are associated with decreased insulinogenic index (which reflects glucose-stimulated insulin secretion) and this allows assuming their effects to be mediated by changes in β-cell functioning and associated with T2DM risk [18, 19]. H.J. Yoo with colleagues [20] compared glucose levels in carriers of various allele combinations of rs13175330 polymorphisms of the *PAM* gene. They established that rs13175330 allele G carriers in the hypertension without therapy group had significantly increased levels of insulin, insulin resistance, and oxidized low-density lipoproteins (LDL) and significantly decreased LDL-cholesterol levels and LDL particle sizes compared to the AA carriers (OR = 1.607; 95 % CI = [1.220–2.116]; p = 0.001).

C2CD4A and *C2CD4B (Calcium Dependent Domain C2, Containing 4A, B).* This is a locus present on the 15q chromosome and identified by GWAS [21]. It is associated with proinsulin levels and T2DM risk. The allele A (rs7172432 *VPS13C/C2CD4A/C2CD4B*) associated with T2DM disrupted glucose-mediated insulin secretion GSI in a diabetes-free Danish population (n = 5722) [22]. The fasting glucose lead SNP (rs11071657) is located between the C2CD4A and C2CD4B genes that are located near the VPS13C gene encoding the lipid transportation protein [22]. The risky allele is associated with lower glucose-stimulated insulin reaction and changes in the insulinogenic index, which gives evidence of its relationship with T2DM risk.

KCNQ1 gene *(potassium voltage-gated channel KQT-like subfamily, member 1)*. The *KCNQ1* gene product is expressed in pancreatic islets and participates in regulating insulin secretion by pancreatic β-cells. The rs2237892 polymorphism is associated with T2DM risk. Iranian patients with the CC genotype (rs2237892) had 30 % lower T2DM risk against healthy donors and those differences were trend-like (p = 0.475).

Adenosine triphosphate-sensitive potassium channel (K_{ATP}) plays an important role in regulating glucose-mediated insulin secretion by pancreatic β-cells through the connection between the cellular membrane potential and cellular metabolism. A K_{ATP}-channel pore is a heterodimer that consists of four tetramers of the (Kir6.2) potassium channel and highly affine sulfonylurea receptor 1 (SUR1). SUR1 is encoded by the *ABCC8*, which is located next to *KCNJ11*. *KCNJ11* has 219 SNPs; of them, six have been paid more attention due to their association with diabetes. The polymorphism (rs2237892 allele 23Lys OR = 1.62; p = 0.019) of the *KCNJ11* gene is believed to be associated with elevated T2DM risk in a Kyrgyz population [23]. The authors analyzed the relationship of this gene in combinations with other genes and then assumed the *KCNJ11* gene to be significant for T2DM risk in various populations with different likelihood (Mauritanian population: OR = 2.08, 95 % CI = [1.09–3.97], p = 0.026; Chinese Han population: OR = 1.25, 95 % CI = [1.04–1.50], p = 0.017) predominantly through IR formation [24].

A strong correlation was found between the rs5219 polymorphism and T2DM susceptibility in Caucasians and in some Asian populations (OR = 1.376 (1.085–1.745), p = 0.008) [24]. The allele A (valine to isoleucine substitution in position 250) reduces K_{ATP} sensiti-

vity, which makes the channel hyperactive and results in subsequent inhibition of insulin secretion. Insulin secretion is influenced more significantly in AA genotype carriers against GA genotype carriers. The rs5210 and rs5215 polymorphisms of the *KCNJ11* gene can also cause neonatal diabetes and inborn hyperinsulinemia [24].

TCF7L2 (*transcription factor 7 like 2*) encodes a transcription factor, which, as a Wnt signal pathway component, participates in expression of certain genes. Their products are involved in growth and development of pancreatic β-cells. IVS3C>T (rs7903146), which is located in the 3rd intron, has two alternative allele variants, C and T. The allele combination C/T (rs7903146) is known to impair the capability of pancreatic islets to produce insulin as a response to being stimulated by the insulinotropic intestinal hormone or glucose. Its frequency and associations with T2DM risks differ between various populations. Thus, for example, in Caucasians, the minor allele T was found more frequently, in 22–36 %, and was associated with high T2DM risk. But it was much less frequent in Asians (3–6 %) and was not associated with the disease. However, the gene was shown to have pathogenic influence in combinations with other genes. In a Kyrgyz population, IVS3C>T of the *TCF7L2* gene was not significantly independently associated with T2DM risk; however, its predisposing influence was found in combinations with some genotypes of the *ADIPOQ* (G276T/CC OR = 1.97 at 95 % CI between 1.07 and 3.61; p = 0.04) and *KCNJ11* genes (Lys23Lys/CC OR = 2.65 at 95 % CI between 1.12 and 6.28; p = 0.042 and Glu23Lys/ CT OR = 3.88 at 95 % CI between 1.27 and 11.91; p = 0.027) [23].

WSF1 (*Wolfram syndrome 1)* is a wolframin gene. It participates in regulating homeostasis of calcium channels. GWAS established not less than 19 polymorphisms of the *WFS1* gene to be associated with T2DM risk. The heterozygous TC genotype (rs1801214) in a Saudi Arabia population was authentically associated with pre-diabetes susceptibility (OR = 0.60; 95 % CI = [0.44–0.80]; p < 0.01) [25]. Another most important SNP, rs1046322 WFS1, is significantly associated with BMI and waist circumference in South-Eastern Asian population. Quantitative deficiency of the *WFS1* gene makes carriers of the single functional WFS1 column susceptible to diabetes and metabolic syndrome as well as to environmental exposures. However, frequency of this SNP varies in different populations, from 7.2 % in Chileans to 50 % in Siberians [26].

IGF2BP2 (*insulin like growth factor 2 mRNA binding protein 2*) belongs to a protein family binding to the insulin-like growth factor 2 (IGF-2) for further transfer of insulin signals. GWAS established the *IGF2BP2* rs4402960 and rs1470579 polymorphisms to be associated with T2DM risk in Asians. In the case-control study, the carriers of TT genotype at rs4402960 had a higher T2DM risk than the G carriers (TG + GG) (adjusted odd ratio (AOR) = 1.962, 95 % CI = [1.065–3.612], p = 0.031); CC carriers at rs1470579 were more susceptible to T2DM than A carriers (CA + AA) (AOR = 2.014, 95 % CI = [1.114–3.642], p = 0.021) [27].

IRS-1 is Insulin Receptor Substrate-1. The *IRS-1* gene is located in the 2q36-37 locus and has several known polymorphisms. This gene encodes a protein, which is phosphorylated by insulin receptor tyrosine kinase and thus plays a critical role in the insulin signaling pathway. Such polymorphisms as Gly972Arg, Pro170Arg, Ala513Pro and Met209Thr of the *IRS-1* gene make for the inhibited activity of phosphatidylinositol 3-kinase (PI3K) and developing insulin resistance and obesity. Among all examined mutations, glycine-to-arginine substitution in the codon 972 (2963G>A, p.Gly972Arg, rs1801278, G972R) is most frequently considered in relation to T2DM risk. This polymorphism reduces levels of IRS-1 phosphorilation and stimulates its inhibiting impacts on tyrosine kinase thereby reducing the speed of

the insulin signaling pathway in glucose transportation, translocation of glucose and glycogen transporter [28, 29], especially in obese patients [30]. The GA, GA+AA genotypes increase IR in patients with T2DM with severe hyperglycemia (OR = 2.536; 95 % CI = [1.030–6.249]; p = 0.043) [31]. Marked reduction in IRS-1 expression was observed in visceral as compared to subcutaneous adipose tissue of morbidly obese patients [32].

IRS-2 participates in insulin-stimulated glucose absorption, metabolic regulation in the liver, and lipid metabolism [33]. Glycine-to-aspartate substitution in the locus 1057 of the gene (Gly1057Asp) is a commonly known polymorphism of the *IRS-2*, which is associated with lower sensitivity to insulin and impaired glucose tolerance as well as with elevated obesity risk [34]. People with BMI < 27 kg/m^2 tended to have GD and DD genotypes more frequently in the control group against the cases. However, allele D carriers prevailed in the group of T2DM patients with BMI > 27 kg/m^2. Therefore, the authors concluded that the minor allele D was associated with T2DM risk although the difference in allele frequency was not significant (OR = 1.55, 95 % CI = [0.961–1.41]; p = 0.108). The combined genotype analysis showed that the difference in the allele and genotype frequencies reached statistical difference between the cases and the controls as well as the odds ratio substantially increased when the R allele (G972R) was present together with D allele (G1057D) in any combination. The GG genotype was much more frequent among obese patients, especially against the control group. This may indicate that having the allele D protects people with normal body weight from T2DM [34].

CDKAL1 is an inhibitor of the cyclin-dependent kinase (CDK5) [35]. It influences β-cells functioning by inhibiting the activity of CDK5 and tRNA-modifying enzymes. An association between multiple polymorphisms of the *CDKAL1* gene (rs7754840, rs4712524, rs10946398, rs7756992) and T2DM in various populations was confirmed by several studies. Thus, rs10440833, rs10946398, rs4712523, rs4712524 and rs7754840 of the *CDKAL1* were associated with susceptibility to GDM in Central China [36] and Pakistan population [37]. The strongest association was revealed between T2DM risk and the rs10946398 polymorphism of the *CDKAL1* gene [38], which was established by the authors of this meta-analysis in various populations. In an Asian population, the differences were statistically significant (p < 0.01) for dominant genetic model of the rs10946398 *CDKAL1* (AA against AC+CC) (OR = 0.75, 95 % CI = [0.64–0.88], p = 0.0003); this was not detected for non-Asian populations [38].

HHEX gene *(hematopoietically expressed homeobox)* is responsible for somatostatin secretion in pancreatic δ-cells. A study accomplished on a population sample from southeastern Iran (n = 250) aimed to estimate possible correlations between polymorphisms of the *HHEX* gene and T2DM risks. The finding revealed the all measured inheritance models of rs1111875G/A and of rs5015480C/T variants dramatically increased the risk of T2D while another polymorphism (rs7923837A/G) was not associated with risk/protective role in T2D [39].

The MTNR1B gene (melatonin receptor 1B) is associated with risk of gestational DM; however, findings are rather controversial. Allele G combinations of the rs10830963 polymorphism of the *MTNR1B* gene were established to be associated with fasting hyperglycemia, disrupted insulin secretion and T2DM. Risk analysis established risky genotypes in Caucasians: CG (OR = 1.40; 95 % CI = [1.16–1.70]; p < 0.001) and GG (OR = 2.21; 95 % CI = [1.54–3.17]; p < 0.001) and Asians: CG (OR = 1.15; 95 % CI = [1.02–1.28]; p = 0.020) and GG (OR = 1.52; 95 % CI = [1.23–1.89]; p < 0.001) [40].

The *UCP2* and *UCP3* (*uncoupling protein 2, 3*) genes. They uncouple oxidation and oxidative phosphorilation in mitochondria of skeletal muscles, cardiac muscle and brown

adipose tissue; disrupt insulin production; inhibit fatty acids metabolism. In the *UCP2* gene, the Ala55Val polymorphism in the 4th exon has been studied most profoundly (rs660339, with C to T substitution in the position 164 of the transcript). This leads to a substitution in amino acid sequence from alanine to valine. This substitution is associated with elevated obesity risk and higher obesity and T2DM prevalence [41]. However, this risk is population-dependent: the SNP is associated with elevated insulin secretion in Caucasians and lower T2DM risk in Asians. The mutation -866G/A (*rs659366*) of the *UCP2* gene disrupts normal insulin production by pancreatic cells. In Asians, the allele combinations AA (OR = 1.254; 95 % CI = [1.022–1.540]; $p = 0.031$) and AG (OR = 1.198; 95 % CI = [1.047–1.371]; $p = 0.009$) play the key role in T2DM pathogenesis [42].

Genetic variants in genes of *glutathione synthetize (GSS)* and gamma-*glutamyl transferase 7 (GGT7)* are markers of T2DM susceptibility. They potentially increase the disease risk by disrupting glutathione metabolism and contribute to the disease pathogenesis through intracellular glutathione deficiency. I. Azarova with colleagues believe [43] the *GSS* G/A-A/A genotypes per rs13041792 to be authentically associated with elevated T2DM risk (OR = 1.21; 95 % CI = [1.04–1.42]; $p = 0.046$). Meanwhile, the SNP rs6119534 (OR = 0.73; 95 % CI = [0.53–0.99]) and rs11546155 (OR = 0.42; 95 % CI = [0.22–0.80]) of the *GGT7* gene were established to have significant associations with reduced T2DM risk.

Genes that participate in formation of insulin resistance. *ADIPOQ (the adiponectin gene).* Several SNPs of the adiponectin gene including rs17300539, rs1501299, rs266729, and rs2241766 are the most significant concerning diabetes pathogenesis [44, 45]. These polymorphisms have been established to be associated with insulin resistance, dyslipidemia and atherogenesis. Some studies also established associations between alleles of the rs17366743 locus and hypoadiponectinemia in people with disrupted tolerance to carbohydrates [45–48].

Associations between polymorphic locuses of the *ADIPOQ* gene and T2 DM have been established in various ethnic and geographic groups across the globe [45]. Thus, as association between rs1501299 and obesity was revealed in a Spanish population [49]. D.L. Brovin with colleagues [50] established a relationship between rs2441766 and rs266729 and levels of total and high-molecular serum adiponectin in females with abdominal obesity and metabolic syndrome in Saint Petersburg. H. Kaur and others [51] showed *ADIPOQ*-3971A>G (rs822396) and +276G>T (rs1501299) polymorphisms to be risk factors of obesity and metabolic syndrome in a North Indian Punjabi population. Frequency of the GG (-3971A>G) and TT (+276G>T) genotypes was higher among patients with obesity ($p = 0.008$ and $p = 0.035$ respectively). Both genotype variants (-3971GG and +276TT) created authentically elevated obesity risk (OR = 1.52; $p = 0.03$ and OR = 1.58, $p = 0.04$ respectively). The G-T haplotype model (possessing -3971G and +276T alleles) was shown to provide approximately 3-fold risk towards the obesity susceptibility (OR = 2.69, $p = 0.009$) and metabolic syndrome risk (OR = 2.73, $p = 0.009$) [51].

Some polymorphisms of 45 T>G (rs2241766) of the *ADIPOQ* gene have been investigated in a Russian population. They are associated with risks of obesity, insulin resistance and T2DM[2]. The allele combinations TG and GG (rs2241766) increase T2DM risk (OR = 3.81; 95 % CI = [1.79–8.09] and OR = 10.0; 95 % CI = [2.25–44.7]).

It is noteworthy that studies with their focus on associations between the given polymorphisms and T2DM have yielded

[2] Vakhromeeva K.A. Polimorfnye geneticheskie markery sakharnogo diabeta 2-go tipa i ikh assotsiatsii s kliniko–metabolicheskimi pokazatelyami v russkoi populyatsii [Polymorphic genetic markers of type 2 diabetes mellitus and their associations with clinical metabolic indicators in a Russian population]: the abstract of the dissertation … for Candidate of Medical Sciences degree. Tyumen, 2015, 23 p. (in Russian).

somewhat controversial results in several populations [52, 53].

ADIPOR1, ADIPOR2. The ADIPOR1 and ADIPOR2 receptors located in various tissues bind to adiponectin and thus support its biological functions. The receptor to adiponectin 1 (*ADIPOR1*, located on the 1q32 chromosome) is synthesized in the human body predominantly in skeletal muscles whereas the receptor to adiponectin 2 (*ADIPOR2*, located on the 12p13.33 chromosome) is predominantly expressed in the liver. D.S. Khodyrev and others [54] established an association between the polymorphic marker rs11061971 of the *ADIPOR2* gene and T2DM in a Russian population ($p = 0.004$ when comparing allele frequencies, $p = 0.011$ when comparing genotype frequencies). According to their findings, the allele A and AA genotype reduced T2DM risk (OR = 0.76 and 0.75 respectively) whereas the allele T and TT genotype increased T2DM risk (OR = 1.31 and 1.63 respectively). A study [55] established the allele GA of the +795 G/A (rs16928751) polymorphism of the *ADIPOR2* gene to be associated with high BMI in T2DM patients in a Crimea population. Carriers of the TG genotype of the −102 T/G (rs2275737) polymorphism of the *ADIPOR1* gene had higher risk of elevated HbA1c levels (1.36 higher against TT carriers TT, $p < 0.05$). Carriers of the TT genotype of −106 T/C (rs2275738) polymorphism of the *ADIPOR1* gene were found to have higher glucose levels in blood (1.14 times higher against CC carriers, $p < 0.05$).

LEP (the leptin gene) encodes a protein that is secreted by white adipocytes into the circulation and plays a major role in the regulation of energy homeostasis. Circulating leptin binds to the leptin receptor (*LEPR* gene) in the brain, activates lower signaling pathways that prevent excessive food intake and makes for energy consumption. Several mutations associated with T2DM were registered for the leptin gene *LEP* (rs7799039 (-2548 G/A)) and the leptin receptor *LEPR* (rs1137101 (Gln223Arg)) [56–58]. Special attention is paid to influence exerted by the SNP rs1137101 of the *LEPR* gene on obesity. C.O. Mărginean and others [59] showed AG+GG for the *LEPR* 223 gene ($p = 0.0001$) and GA+AA for the *LEPR* 1019 gene ($p = 0.0001$) to be the most frequent genotypes of polymorphisms of the *LEPR* 223, 1019, 492 and 976 genes in obese children. Such polymorphisms of the *LEP* gene as rs7799039 and rs2167270 were associated with obesity in a Taiwanese [60] and Arabian [61] population (OR = 1.85; 95 % CI = [1.37–2.5]). At the same time, some studies dispute impacts of combined polymorphisms of adiponectin and leptin receptor genes [62, 63]. The allele combination GG of the polymorphism (rs7799039) of the *LEP* gene was shown to be associated with high systolic blood pressure in Crimean T2DM patients [64].

PPARγ (PPARG) encodes the protein PPARG, a nuclear receptor that regulates gene transcription (*LPL*, *FATP* and others). The *PPARγ* gene is closely involved in lipid metabolism regulation, mostly due to being expressed in adipose tissues and the liver [65]. Mutations of the *PPARG* gene can disrupt these regulatory mechanisms thereby resulting in metabolic disruptions and elevated cardiovascular risk [66]. E. Pokushalov with colleagues [67] revealed specific polymorphisms in the PPARG promoter, in particular, rs10865710 and rs3856806, which have significant associations with glucose levels in DM patients. Analysis in sub-groups established considerable differences in lipid profiles that were associated with the PPARG- polymorphism. A decrease in levels of low density lipoproteins was 11.7 % higher in people with *PPARG* polymorphisms than in their peers without them (95 % CI from -19.3 to -4.0 %; $p < 0.01$).

The Pparg2 Pro12Ala and IL6-174G>C polymorphisms regulate body weight and potentially have a role in obesity risk worldwide [68]. Bearing this in mind, we can consider them promising for associative investigations of obesity phenotypes.

FTO (fat mass and obesity) encodes 2-oxoglutarate-dependent dioxygenase of nucleic

acid, which may be associated with growing fat depots resulting in obesity. The gene is located in the 16q12.2 chromosome and can have variations in its intron areas. In a study [69], mRNA FTO expression was established to be lower in obese patients and patients with T2DM against the controls ($r = 0.401$, $p < 0.001$). The role of several polymorphisms of the *FTO* gene including rs9939609, rs141115189, rs9926289, rs11075990, rs1121980, rs17817449, rs3751812, rs9939609, rs9940128, rs9941349 and rs9939609 was investigated as regards risks of T2DM associated with obesity and other components of metabolic syndrome (high fasting levels of glucose and triglycerides, low levels of high density lipoproteins) [70–76]. Minor homozygous genotypes of the rs11075990, rs1121980, rs17817449, rs3751812, rs9939609, rs9940128, rs9941349 polymorphisms of the *FTO* gene were shown to be associated with T2DM risk (OR = 2.20–2.78; $p < 0.05$) [75].

IL-6 (interleukin-6) is a pro-inflammatory cytokine, which is mostly synthesized by macrophages. Its role in insulin resistance development is basically determined by a possibility to increase glucose absorption during physical activity with occurrence of muscle hypertrophy, myogenesis and oxidation of fatty acids in skeletal muscles [77, 78]. The *IL-6* gene is located on the 7p21 chromosome and includes seven exons. The most widely spread SNP is located in the promoter zone –174 of the IL-6 gene and is associated with G-C substitution (rs1800795) [79]. Homozygotes per the allele C tend to have a lower plasma IL-6 level associated with a lower concentration of glycated hemoglobin in blood and fasting insulin against the allele G carriers. At the same time, some studies report absence of any association between the allele combinations CC and GC and T2DM risk ($p = 0.039$) [79].

AKT encodes a protein, which consists of 480 amino acid residuals and includes three domains. AKTs are divided into three isoforms (AKT1, AKT2 and AKT3) based on differences in amino acid residuals of serine / threonine. AKT2 is found in tissues sensitive to insulin (liver, muscles and adipose tissue) and is encoded by a gene located on the 19q13.1 chromosome. Serine / threonine kinase AKT2 is an effector protein in the insulin signaling pathway and is associated with metabolic impacts of insulin [80]. Variations of the *AKT2* gene are associated with T2DM, fasting hyperglycemia and postprandial hyperinsulinemia. The *AKT2* mutation p.Pro50Thr related to a rare allele was associated with peculiarities of metabolic syndrome, lipodystrophy and T2DM risk in a Finnish population (OR = 1.05; 95 % CI = [1.0–1.1]; $p < 0.001$) [81]. The p.Pro50Thr mutation of the *AKT2* gene causes a reduction in glucose absorption in insulin-sensitive tissues and is associated with elevated fasting insulin levels in blood and T2DM risk ($p = 0.038$). The (p.E17K) mutation of the *AKT2* gene may disrupt the insulin signaling pathway, which results in lower levels of insulin in plasma, ketone bodies, fatty acids and glucose [81–83].

Genes associated with glucose metabolism. *GCKR* (glucokinase) determines the threshold of glucose-stimulated insulin secretion (GSI), controls gluconeogenesis and glycogen synthesis in hepatocytes. There are two known polymorphisms of the *GCKR* gene, rs780094 and rs1260326. The AA genotype (rs780094) was shown to be associated with hypertriglyceridemia in DM patients (OR = 5.335; 95 % CI = [1.779–15.99]; $p = 0.003$). The TT genotype (rs1260326) is associated with levels of HOMA-IR, FPG and triglycerides (OR = 4.523; 95 % CI = [1.458–14.03], $p = 0.009$). At C-T substitution, proline is replaced with leucine in the amino acid sequence of the encoded protein. Protein structure modification changes its function and is associated with decreasing glucose-6-phosphatase levels and growing levels of GCK, phosphofructokinase and fatty acid synthase. These metabolic changes can potentially explain lower glucose levels in plasma and higher levels of triglycerides [84, 85].

G6PC2. Glucose-6-Phosphatase Catalytic Subunit 2 (G*6PC2*) competes with pancreatic

GCK activity for glucose use. Two SNPs, rs560887 and rs563694, are associated with hyperglycemia in European populations. Any significant sex- and age-dependent differences have not been established among dominant and recessive models of the *G6PC2* gene polymorphisms ($p > 0.05$) [85].

The role that belongs to genotype in molecular mechanisms of T2DM development. Defects of the insulin signaling pathway are a probable common mechanism that explains elevated insulin resistance as well as glucose and insulin levels. This fact is confirmed by accumulated data [86], which are also supported by our findings [55, 64].

Insulin-stimulated glucose transport goes by the *PI3K/AKT-dependent signaling pathway* (phosphatidylinositol 3-kinase /protein kinase B), which results in GLUT4 (glucose transporter 4) moving onto the plasmatic membrane to attach glucose and activate glycogen synthase. Being stimulated by insulin, *PI3K* phosphorilates membrane phospholipids and turns PIP2 (phosphatidylinositol 4,5-bisphosphate) into PIP3 (phosphatidylinositol (3,4,5)-trisphosphate). This complex phosphorilates / activates *PDK1* and *PDK2* (phosphoinositide-dependent kinases), which, in its turn, activates *AKT/PKB* and *PKC* (protein kinase C) phosphorilation for moving *GLUT4* onto the plasmatic membrane from the intracellular space. Carriers of rs2494746 CG/GG or rs2494738 GA/GG genotypes in AKT1 have higher T2DM risk against homozygous carriers [87].

Insulin resistance in T2DM patients is characterized by several defects in the cascade of insulin signaling transfer. This is confirmed by changes in expression of genes that encode metabolic pathways in T2DM patients (*IR*, *IRS*, *PI3K*, *AKT* and *GLUT4)* [88].

In addition to insulin signal transfer by PI3K, insulin can activate the *mitogen-activated protein kinase (MAP) ERK*, which results in expression of kB (IkB) and NF-kB and inhibitors of the *Janus kinase/signal transducers and activators of transcription (JAK/STAT)* thereby initiating transcription of pro-inflammatory genes, in particular *IL-6* [89]. In addition, phosphorilated STAT3 induces expression of SOCS3, which acts as a feedback inhibitor for the leptin signaling pathway thus influencing appetite [90]. Alimentary hyperglycemia reinforces fatty acid synthesis, which activates *PPARγ* genes inducing a descending cascade of expression of genes that reinforce lipogenesis. As a result, a new cycle of *PPARγ* expression starts and *TLR4* expression occurs as well [91]. This activates genes encoding multiple inflammation mediators, including the CRP gene promoter that interacts with IL-1 and IL-6 [92]. Pro-inflammatory mediators enhance lipolysis by direct and indirect damage to cellular membranes thereby increasing levels of free fatty acids. This creates the final loop in genetically determined vicious circles of T2DM pathogenesis [93].

Genetic information can be used in practice to predict T2DM risk using the Cambridge Risk Score (CRS) and Framingham Diabetes Risk Model (FDRM). They both consider age, sex, sugar-reducing therapy, family history of T2DM, BMI, smoking, as well as levels of high density lipoproteins, triglycerides and fasting glycemia [94]. Investigation of a genetic status, including such key genes as *PPARγ, TLR4, IRS* and *IL6*, can become a marker eligible for early T2DM detection, especially in patients who have family history of the disease.

Conclusion. Multiple polymorphisms associated with T2DM development have been established in various geographic and ethnical groups across the globe. SNP markers of gene involved into key molecular-genetic T2DM mechanisms, in particular *PPARγ, TLR4, IRS* and *IL6*. This will increase the likelihood of detecting hereditary predisposition to diabetes mellitus and ensure early identification of genetic risk groups aimed at developing targeted prevention activities.

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