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Review article

Possible clinical applications of knowledge about the genetics of type 2 diabetes

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Abstract
Type 2 diabetes mellitus (T2DM) is a polygenic disease that develops as a result of the interaction of hereditary predisposition and environmental factors. The predisposition to develop T2DM is associated with the inheritance of certain alleles of "healthy" genes. More than 100 polymorphic variants of genes that increase the risk of developing T2DM have already been described. Today, genes predisposing to the development of β-cell dysfunction and insulin resistance (IR) are the most well studied. In addition, genes that affect lipid metabolism and eating behavior and genes of some cytokines can participate in the formation of a genetic predisposition to the development of T2DM. Our article reviews the most promising potential areas of application of knowledge about the genetics of T2DM in clinical practice. The first direction is to specify the classification and stratification of T2DM into subclasses/clasters. The second one is an individual assessment of the risk of developing T2DM and its complications. Today, predictive models of the risk of developing type 2 diabetes are not accurate enough for widespread use in clinical practice, but now researchers are actively working to improve their accuracy and effectiveness. And finally, knowledge about the genetics of T2DM can help predict the effectiveness of glucose-lowering therapy. In this review, we also discuss the topic of metabolic disease endophenotypes. The concept of endophenotypes suggests the presence of certain pathogenic common links in the pathogenesis of IR, obesity, T2DM, cardiovascular diseases, non-alcoholic fatty liver disease and chronic kidney disease, which are based on certain polymorphic gene variants. The results of research in the field of genetics of T2DM give us new possibilities for a personalized approach to the management of this complex disease.

Keywords: genetics of diabetes, genetic risk assessment, classification, endophenotypes, pharmacogenomics

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a polygenic multifactorial disease, unlike, for example, maturity-onset diabetes of the young (MODY). The cause of multifactorial disease isn't DNA changes in one particular gene, but the presence of a genetic predisposition. It can be realized under the influence of environmental factors. Genetic predisposition to the development of polygenic diseases, including T2DM, is associated with the inheritance of specific alleles of "healthy" genes. These alleles are called etiological variants. These gene variants are widely distributed in a population, and each of them does not lead to the development of the disease on its own. Only the presence of a combination of etiological variants can lead to physiological changes. The modifications are part of the pathogenesis of a particular disease. It should be noted that a polygenic disease develops in individuals with a genetic predisposition only as a result of the interaction between genetic factors and various environmental factors. Therefore, T2DM can be called not only a polygenic, but also a multifactorial disease [1]. The multifactorial nature of T2DM has been demonstrated in many studies. The first studies devoted to the molecular genetic mechanisms of T2DM were carried out on the basis of the research of linkage disequilibrium and the results of the search for candidate genes [2]. Discovery of polymorphic markers in candidate genes, whose products are involved in the pathogenesis of T2DM, made it possible to identify genes associated with insulin resistance (IR), obesity, β-cell dysfunction, and decreased incretin response [3]. But the greatest progress in identifying genetic markers for the development T2DM was achieved with the advent of GWAS (Genome-Wide Association Study). This method detects relatively weak associations of genetic variations with the development of a particular disease. However, the genetic predisposition to multifactorial diseases is not always explained by common polymorphisms. Therefore, the etiological variants are clarified during further studies on sequencing of the genome regions of interest, which were previously identified in genome-wide studies [3, 4].

TYPE 2 DIABETES-ASSOCIATED GENETIC POLYMORPHISMS

More than 100 common genetic variants increasing the risk of T2DM have already been described. And most of them are polymorphisms in genes belonging to the system associated with β-cell function. For example, *ABCC8 (rs757110, rs1799859), IGF2BP2 (rs4402960, rs11705701, rs1470579),*

CDKAL1 (rs7754840, rs10946398), KCNJ11 (rs5219, rs5129), KCNQ1 (rs2283228, rs2237895, rs2237897, rs2237892, rs231362, rs163184), SLC30A8 (rs11924032, rs13266634), C2CD4A/B (rs10811661, rs7172432, rs1436955), WFS1 (rs1801214, rs10010131), TCF7L2 (rs7903146, rs12255372, rs12243326*), GCK (rs4607517)* and some other genes [2, 3, 5, 6]. Genetic variants involved in the formation of IR are also well studied. There are genetic changes in *PPARG (*rs18012824, rs1801282, rs1801284*), IRS1 (*rs2943634, rs2943641*), ADIPOQ (*rs16861194, rs266729, rs2241766, rs1501299, rs17366743, rs17300539), *ADIPOR2 (*rs11061971, rs16928751*), PPARGC1A (*rs8192678*), FTO (*rs8050136, rs9939609, rs17817449, rs1421085, rs11642841*)* [2, 3, 5–8].

Chronic inflammation and impaired angiogenesis play an important role in the development of T2DM and its complications. Therefore, associations of gene polymorphisms of various cytokines and growth factors with T2DM have also been studied. According to some authors, individuals with certain combinations of genetic variants of *VEGF*, *IL1B, IL4, IL6, IL10* and *TNFA* may have a higher risk of developing T2DM. The association of polymorphic loci of the chemokine genes *CCL20 (rs6749704)* and *CCL5 (rs2107538)* with T2DM was also shown in some studies [2, 9].

Some gene polymorphisms associated with lipid metabolism disorders are also considered as candidate genes for T2DM by some authors – *LPL, FABP2* and *LRP 5* [2]. In addition, some studies have shown the association of polymorphic markers of xenobiotic biotransformation genes with the risk of developing T2DM. There are *GCLC (rs17883901), GPX2 (rs4602346), GSTP1 (rs1695), GSTT1 (type I/D polymorphism; rs17856119)* and *NOS2 (rs2297518)*. The mechanism of this relationship is possibly associated with an increased concentration of reactive oxygen species (ROS) in patient's blood. And increased oxidative stress leads to a decrease in the activity and mass of β-cells, because they are very vulnerable to the action of ROS due to their extremely low antioxidant capacity [2, 3, 10]. Association T2DM with single-nucleotide polymorphisms (SNP) of the *MC4R (rs17782313)* and the *FTO (rs8050136, rs9939609, rs17817449, rs1421085, rs11642841)* genes is no less interesting, because the products of these genes affect eating behavior [2, 3, 5].

T2DM-associated genetic polymorphisms with unknown mechanism of participation in the pathogenesis of carbohydrate metabolism disorders have also been identified by genome-wide studies in recent years. For example, *ACHE, PLS1, TCERG1L, PCNXL2, PAPL, CR2 GALNTL4, LOC729013, LPIN2, RBM43, RND3, PEX5L, SRR, DUSP9, ZPLD1, TMEM45B, BARX2, KIF11, HUNK, SPRY2, SYN2, PPARG, CENTD2, NOTCH2, ADAM30, C2CD4B, NOTCH2, MAEA, ZFAND3, SLC30A8, ADCY5, GCC1, PAX4, TLE4/CHCHD9, GLIS3, PEPD, HMGA2, ADAMTS9* and some other genes [3].

It should be noted, that different polymorphisms associated with T2DM have been identified in genome-wide studies in European and Asian populations [6]. It also was found, that ethnicity and gender also affect the distribution of polymorphisms and their association with T2DM [7]. The discovery of new susceptibility loci of T2DM using GWAS in various ethnic groups confirms the need for more genome-wide studies among people of different countries and nationalities. New genetic risk loci have been successfully explored recently not only in Asian and European populations, but also in Pima Indians and Mexican Americans. [6]. At the moment, we also have data from large studies of prevalence of various polymorphic markers associated with T2DM among different peoples living in Russia [2, 3, 5, 11–17].

POSSIBLE CLINICAL APPLICATIONS OF KNOWLEDGE ABOUT THE GENETICS OF TYPE 2 DIABETES

The development of genomic technologies opens up new possibilities for personalized prevention and treatment of T2DM. There are several areas in which the results of molecular genetic studies can bring a significant help:

- a detailed study of the molecular mechanisms of the pathogenesis of T2DM;
- an assessment of the contribution of genetic predisposition and environmental factors to the development of T2DM;
- an assessment of the individual genetic risk of developing T2DM and the susceptibility of a particular person to the effects of lifestyle changes;
- stratification of T2DM into subclasses to predict the course and outcomes of the disease, to assess the risk of developing complications of diabetes and to determine the most effective individualized treatment strategies;
- a prediction the timing and intensity of progression of T2DM and its complications;
- predicting the clinical response to therapeutic agents and assessing the risk of early need for insulin therapy in patients with T2DM;
- a support in the development and validation of new drugs or the potential use of already existing off-label drugs [18–20].

Further in the article, we will take a closer look at the application of advances in the study of the genetics of T2DM to stratify the disease into subclasses, to assess the risk of developing carbohydrate metabolism disorders and complications of diabetes, and also to predict the effectiveness of glucose-lowering therapy.

SUBCLASSIFICATION OF T2DM

The phenotypes of patients with T2DM are significantly heterogeneous and they have an unequal risk of developing complications of diabetes. The rate of the disease progression varies from very fast in some patients to slow in others. The need for insulin therapy develops in some patients already in the first years after the manifestation of the disease, while other patients have effective glycemic control and a stable course of diabetes for decades on metformin monotherapy. In addition, the complications associated with hyperglycemia are also heterogeneous in different patients with T2DM. These facts suggest that many subgroups with different clinical course of the disease exist within a single

nosology. It prompted researchers to identify patients with T2DM into clusters [19, 21].

In 2015 L. Li et al. made one of the first major attempts to cluster patients using clinical and laboratory features. They analyzed data from electronic health records of 11,210 people of different nationalities using machine learning methodology and identified 3 subtypes of patients with T2DM [22]. Then E. Ahlqvist et al. studied a cohort of 8,980 Swedish patients with newly diagnosed T2DM based on this work. They selected the following clinical characteristics for their cluster analysis: anti-glutamic acid decarboxylase (GAD) autoantibodies, age at diagnosis of T2DM, body mass index (BMI), glycated hemoglobin (HbA1c) and the homeostatic model assessments of β-cell function and IR (HOMA2-b and HOMA2-IR, respectively). Five clusters with different prognosis of disease progression and risk of complications were identified by the authors of the study after clustering: Severe Autoimmune Diabetes (SAID), Severe Insulin Deficient Diabetes (SIDD), Severe Insulin Resistant Diabetes (SIRD), Mild Obesity-related Diabetes (MOD) and Mild Age-Related Diabetes (MARD) [19, 23]. This method showed high reproducibility and proved predictive value in studies on a variety of populations, including European, American, Hispanic, Chinese cohorts. In addition, this method of covariant selection has demonstrated its reproducibility and fundamentality in patient cohorts of large randomized clinical trials, for example, ADOPT, RECORD, LEADER, DEVOTE, SUSTAIN-6 and ORIGIN [19, 24–29]. It is interesting, that E. Ahlqvist et al. also performed a molecular genetic study to identify a possible genetic predisposition to a particular course of T2DM. And the results of the study showed that the genetic associations in the clusters were really different. It supports the significance of the clustering method.

According to the study, no one genetic variant was associated with all clusters simultaneously. For example, gene variant *TCF7L2 (rs7903146)* was associated with SIDD, MOD and MARD, but not with SIRD. The *TM6SF2* gene polymorphism *(rs10401969)* was associated with SIRD, but not with MOD. This genetic polymorphism has a known association with non-alcoholic fatty liver disease (NAFLD). These results suggest that SIRD is characterized by more metabolically unhealthy obesity than MOD, and this feature is probably genetically determined. SNP *rs4402960* in *IGF2BP2* and *rs10811661* in *CDKN2B* was associated with development of SIDD and MARD. And the products of these genes affect the survival of pancreatic β-cell. Also, the association between the genetic variants of *HHEX/IDE (rs1111875*) and the development T2DM with signs of the SIDD cluster was found. While a variant of *KCNJ11 (rs5219)* has been identified in a group of patients with MOD [23].

Recently, R. Wagner et al. have applied clustering methods with complex clinical variables on a longitudinal cohort of patients without T2DM and identified 6 clusters. Three of these new clusters corresponded to very low-risk, low-risk, and obese but low-risk groups. The remaining 3 clusters were associated with an increased risk of T2DM and were determined by β-cell failure (4 cluster), IR / NAFLD (5 cluster) and visceral fat / nephropathy (6 cluster). Patients in clusters 4 and 5 had a high risk of T2DM, while patients in cluster 6 had a moderate risk of diabetes, but an increased risk of chronic kidney disease (CKD) and high rates of all-cause mortality. R. Wagner et al. also applied the genetic risk score in the study cohort of patients and found that the 2 highest-risk clusters (β-cell and IR / NAFLD) had concurrently increased genetic risk. These results highlight the role of nonmodifiable genetic risk in development of T2DM [19, 30].

It should be noted, that clustering approaches based on clinical data have their limitations despite the high reproducibility. First, clinical signs are not static indicators and they are highly dependent on environmental factors. For example, a patient with newly diagnosed T2DM has changed his lifestyle after consulting a doctor. And lifestyle modification led to a decrease his body weight, BMI and IR, and the patient may be assigned to another cluster in the future. Also, the list of universal clinical variables for clustering isn't clearly described at the moment. And the variables chosen for cluster analysis have a significant impact on which subgroups will be identified [19].

In this regard, the researchers proposed to cluster patients with T2DM based on the results of a molecular genetic study. A significant number of polymorphic markers associated with T2DM have been identified using GWAS, and these genetic data are more stable than clinical indicators. They don't change over time and can be used to assess the risk of developing the disease at any point in patient's life, regardless of changes of clinical parameters [19].

Currently, we have 2 hierarchical clustering of etiological variants – «hard» и «soft». In «hard» hierarchical clustering each genetic variant can only belong to one specific cluster or subgroup. And «soft» clustering means that each genetic variant can belong to more than one cluster or phenotype. Such approach allows modeling pleiotropic effects of genes / loci. Therefore, such clustering seems more appropriate in study of a polygenic multifactorial diseases, such as T2DM. For example, one person may have both genetic variants that affect the risk of developing obesity and insulin secretion. And both of these factors will simultaneously contribute to the risk of developing T2DM [19, 31].

The method of "soft" hierarchical clustering was developed by M.S. Udler et al. The researchers used 94 genetic variants and 47 clinical features associated with high risk of T2DM to subclassify the disease. As a result, they identified and reproduced 5 partially overlapping genetic clusters (table). The first two clusters were associated with impaired insulin processing/secretion, and all patients in these subgroups have genes connected with β-cell deficiency. The remaining 3 clusters were related to tissue-specific response to insulin. Cluster 3 ("obesity/adiposity") was characterized by increased waist circumference (WC), BMI, body fat and fasting insulin. According to these parameters cluster 3 represented classic obesity mediated T2DM. Cluster 4 ("lipodystrophy") was determined by elevated IR, high triglycerides levels, increased waist-to-hip ratio (in women only) and

Table. Comparison of subgroups of T2DM identified by clustering based on clinical features and with genetic clustering methods (adapted from [19])

Possible pathogenic defect	Clinical and Biochemical Clustering (E. Ahlqvist et al.)			Genetic Clustering (M.S. Udler et al., A. Mahajan et al.)			
	Cluster	Characteristics	Outcomes	Cluster	Characteristics	Outcomes	Example Genes Captured in Cluster
β-cell failure	SAID	GADA+ ↓insulin	↑ insulin dependence	β-cell	↑proinsulin ↓ insulin	↑ CAD ↑stroke	HNF1A, SLC30A8
	SIDD	↓ insulin	↑ retinopathy ↑ insulin dependence	Proinsulin	↓proinsulin ↓ insulin	-	KCNJ11
Mixed β-cell failure + IR	–	–	–	Mixed	↓proinsulin ↓ insulin ↑HOMA2-IR	–	PAM, RREB1
IR	SIRD	↑HOMA2-IR ↑HOMA2-b ↑ BMI	↑ CKD ↑ NAFLD	Lipodystrophy	↓ BMI ↑ TG ↑ insulin	↑ CAD ↑ CKD ↑ hypertension	KLF14, FAM13A
				NAFLD/lipid	↓ TG	↓ CKD	TM6SF2, GCKR
	MOD	↑ BMI, mild T2DM	–	Obesity/adiposity	↑ BMI ↑ insulin	–	FTO/IRX, MCR4
?	MARD	↑ age, normal BMI, mild T2DM	–	–	–	–	–

SAID – Severe autoimmune diabetes mellitus; SIDD – Severe insulin-deficient diabetes mellitus; SIRD – Severe insulin-resistant diabetes mellitus; MOD – Mild obesity-related diabetes mellitus; MARD – Mild age-related diabetes mellitus; GADA – anti-glutamic acid decarboxylase autoantibodies; TG – triglycerides; CAD – coronary artery disease, CKD – chronic kidney disease; BMI – body index mass; NAFLD - non-alcoholic fatty liver disease; T2DM – type 2 diabetes mellitus

concomitant decrease in BMI. Identification of this cluster draws our attention to the significant role of visceral fat both in the development of IR and T2DM. Cluster 5 («liver/lipid») was associated with decreased serum triglycerides levels, but increased NAFLD risk. And we can assume that the main role in the development of T2DM in patients in cluster 5 play impaired hepatic metabolism of glucose and lipids. It is worth noting that these five genetic clusters were similar in many aspects to previously identified clinical clusters [19, 32, 33].

Another example of the application of the "soft" hierarchical clustering is the study by A. Mahajan et al. In the research authors identified one more cluster, characterized by both impaired insulin secretion and the presence of IR [19, 32, 34].

Application of the "soft" hierarchical clustering technique to independent replication cohorts demonstrated that 1/3 of patients was in the top 10% of genetic risk for a single cluster. The comparison of mean characteristics in individuals with the highest genetic risk identified specific clinical profiles defining each genetic cluster. For example, patients with the highest genetic risk in the «obesity / adiposity» cluster had significantly higher BMI, body fat and WC, than other persons in this cluster. Conversely, individuals at the highest genetic risk for the "lipodystrophy" cluster had significantly lower levels of BMI, body fat mass and HDL cholesterol. Thus, based on these results we can presume that each genetic cluster represented a specific pathophysiology through which intermediate phenotypes affect the risk of T2DM [19, 33].

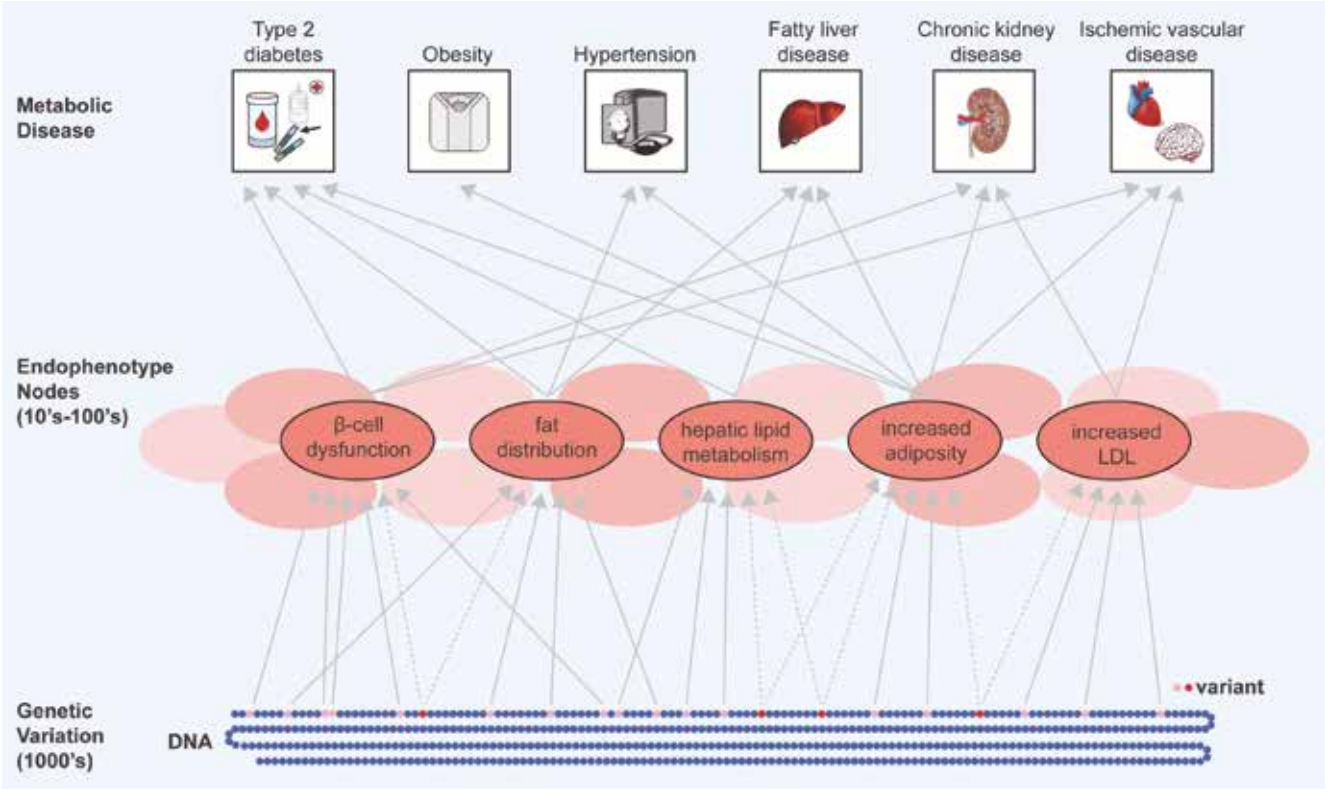
In summary, at least 5 groups representing pathophysiological mechanisms, that may help explain the heterogeneity of T2DM, have been identified using clustering of genetic loci. But further researches are needed to determine the clinical applicability of these clusters. It is possible that new approaches combining clinical and genetic characteristics into a single model will be developed in the near future. Creating models of subclasses of T2DM that take into account the influence of environmental factors (such as dietary habits and physical activity) is also a promising direction. It is clear that the inclusion of genetic knowledge in the classification of T2DM will require more research. But it could potentially expand our understanding of the pathogenesis of the disease and improve the treatment of T2DM as a separate disease, and as part of an integrated network of metabolic diseases [35].

THE CONCEPT OF METABOLIC DISEASE ENDOPHENOTYPES

Certain pathological pathways that belong to some cluster and lead to an increased risk of T2DM can also affect the risk of developing other metabolic disorders, such as obesity, NAFLD, hypertension, atherosclerotic cardiovascular diseases (CVD) and CKD. Some authors propose to use the term "endophenotypes" to refer to common pathological processes that underlie metabolic diseases. Endophenotypes are based on a certain set of genetic variations (*Fig.*) [35].

Understanding the molecular basis of the overall risk of metabolic diseases highlights the close relationship between these disorders. And it can help improve screening for these diseases in healthy people and preventive measures to reduce the risk of complications in people with T2DM.

● ***Figure.*** The concept of endophenotypes underlying the development of metabolic diseases (adapted from [35])



GENETIC RISK ASSESSMENT FOR THE DEVELOPMENT OF T2DM

One of the most important clinical applications of genetic information is to predict the risk of developing T2DM in patients without carbohydrate metabolism disorders. It will allow the development of early intervention strategies to prevent or delay the onset of the disease. In recent studies, genetic risk scoring models have been created by summation of multiple independently inherited polygenic variants associated with T2DM to assess predictive power based on current genetic information [6]. In practice, genetic information may allow health care providers to predict an individual's risk of developing the disease.

In recent years, researchers have proposed several concepts for assessing genetic risk:

- partitioned polygenic risk scores (pPRS) to detect patients with high risk for T2DM by identifying an intermediate pathway (for example, insulin deficiency) for early intervention;
- restricted polygenic risk score (rPRS) based on the study of polygenic variants in candidate genes;
- global polygenic risk scores (gPRS) [19, 34].

Early attempts to combine T2DM risk alleles using well-known candidate genes had limited predictive benefit. The creation of new rPRS models using GWAS has increased their predictive value. However, they were still no better than models based on assessment of clinical parameters [19]. For example, PJ. Talmud et al. found that predictive models based on the patient's phenotypic characteristics (Cambridge Diabetes Risk Score and Framingham Risk Score) determine 10 year risk of developing diabetes more accurately, than genetic scores for 20 polymorphisms associated with T2DM. Adding genetic risk assessment to phenotyping-based risk models slightly improved the accuracy of T2DM risk rating. Thus, the inclusion of a genetic component in existing prognostic scales or the development of new ones that take into account the clinical and genetic characteristics of patients is one of the ways to improve predictive risk models for T2DM [7, 36].

The researchers recognized the limited predictive value of rPRS for assessing the risk of developing a polygenic disease and proposed a different approach – gPRS. This model uses polygenic variants of the whole genome to calculate genetic risk, while rPRS takes into account only a few dozen variants [19]. According to A.V. Khera et al. those 5% of patients who were classified as at high genetic risk on the basis of gPRS results had a 2.75-fold increased risk of developing T2DM compared with the remaining 95% of individuals included in the study [37]. A. Mahajan et al. created a similar gPRS model using the updated GWAS for T2DM in nearly 1 million people and applied it to the entire UK Biobank data. According to the results of this study, the risk of developing T2DM in individuals with a high genetic risk (top 2.5%) was increased by 3.4 times compared with those who had an average (50%) risk [34]. Further M. Vujkovic et al. used gPRS developed by A. Mahajan et al. in them study on a cohort of patients enrolled in the Million Veteran Program. And they found that individuals at the highest genetic risk for T2DM had a significantly higher incidence of microvascular complications (CKD, diabetic neuropathy, diabetic retinopathy) than other patients [38].

Recently, a number of research groups have proposed the use of pPRS in addition to the rPRS and gPRS models. When the researchers use this risk assessment model for a polygenic disorder, he isn't interested in the final phenotype of the disease, but rather in various intermediate phenotypes that reflect various links in its pathogenesis. For example, take intermediate phenotypes that play a significant role in the development of T2DM. This may be the presence of obesity or lipodystrophy, the identification of insulin deficiency or IR, the development of NAFLD and dyslipidemia. The pPRS calculation data for each intermediate phenotype can be used to determine the overall genetic risk of T2DM across known genetic clusters / pathological pathways. Each intermediate phenotype can be visualized as a color. These risks / "colors" can then be combined, and the presentation of the individual risk for T2DM combined with the visualization of the different contributions of individual pathways to development of the disease. This color differentiation helps faster interpretation of genetic testing data and can be used in patient counseling. Health care providers can also choose a personalized therapeutic strategy for patients at very high risk for a particular intermediate phenotype / pathological pathway based on pPRS results. That strategy will focus on the prevention or treatment of identified disorders to prevent the development of T2DM [19].

Unfortunately, today the clinical use of various polygenic risk assessments for T2DM is limited. But we already have the results of several clinical studies using genetic risk assessment models in the management of patients with diabetes. For example, J.H. Li et al. showed that individuals with T2DM and a high genetic risk for rPRS had a more significant decrease in HbA1c in response to sulfonylurea therapy, but not to metformin at 1 year of follow-up [39]. In turn, G. Jiang et al. demonstrated that each increase in the standard deviation in their rPRS model elevated the risk of needing insulin therapy in a patient with T2DM by 7% [40]. R. Wagner et al. used in their study gPRS and found that increased pancreatic steatosis impairs β-cell function with reduced insulin secretion only in individuals with high genetic risk for T2DM [41]. And in a recent study by S. Srinivasan et al. genetic risk assessment using pPRS showed that patients with the highest risk for the intermediate phenotype with lipodystrophy had significantly higher IR and LDL levels despite of lower BMI and WC. These results predispose to an evaluated risk of cardiovascular events in this subgroup of patients [42]. Thus, currently we have limited data on the benefits of using polygenic risk assessment models in real practice. But this direction of application of genetic information is quite relevant and promising. Further research is needed to determine the relationship between different PRS models and stratification of the risk of developing T2DM and its complications and prediction the course the disease and response to therapy in the clinical context [19].

Some authors consider that genetic prediction models can be improved by identifying and including the low-frequency and rare genetic variants or studying polymorphic risk markers for T2DM in populations of non-European origin. It is also necessary to do research aimed at increasing knowledge about the structural features of epigenetic changes in genes. Because of epigenetic factors (DNA methylation, histone modification) can mediate the influence of environmental exposure on the risk of developing T2DM [33, 43]. The development of statistical methods for assessing gene-gene and gene-environment interactions may be also a promising direction in the near future [44].

AN ALTERNATIVE WAY TO USE THE RESULTS OF T2DM GENETIC RISK ASSESSMENT

An alternative clinical direction could be the use of genetic information as a tool to motivate patients to modify their lifestyle to change the increased risk of T2DM. It is well known that proactive lifestyle interventions reduce the risk of T2DM, including in people with prediabetes. Some clinical studies show that lifestyle modification reduces the risk of developing T2DM, even in individuals with genetic variants associated with a high risk of diabetes. For example, in the DPP (Diabetes Prevention Program) study, homozygous carriers of the T allele of the *rs7903146* in *TCF7L2* were randomized to placebo or active lifestyle modification. According to results, patients in the placebo group had an 80% higher risk of developing T2DM than patients in the lifestyle intervention group. So, patients in the intervention group didn't have an increased risk, despite the presence of polymorphism associated with T2DM. The authors of the study concluded that lifestyle changes may outweigh the genetic risk, at least in cases of inheritance of a polygenic variant of *TCF7L2* [45, 46].

Speaking about the benefits of using genetic testing data to motivate patients to change their lifestyle, we can refer to the recently published results of the research by R.W. Grant et al. They studied how knowledge of the genetic risk of a disease can influence a person's desire and willingness to make lifestyle changes. According to a survey of 211 patients about how they would react to the results of genetic testing, containing information about an increased genetic risk of developing T2DM, 71% of respondents answered, that this information would motivate them to change their lifestyle. Thus, genetic information may be useful in persuading the patient to change their behavior and help influence modifiable risk factors for T2DM to prevent the realization of a genetic predisposition [47]. However, further studies involving a larger number of respondents and prospective studies are required to confirm this hypothesis.

ASSESSING GENETIC VARIATION IN PREDICTING INDIVIDUAL RESPONSE TO TREATMENT

Conducting molecular genetic studies among patients with already diagnosed T2DM may also be useful in order to predict individual response to treatment. Genetic information can be used to identify subgroups that have similar responses to various preventive intervention and

treatments to develop personalized therapeutic strategy for patients with T2DM [18].

It is known, that the same glucose-lowering therapy regimen may have different efficacy even in 2 phenotypically similar patients. This individual variability may be related to specific polymorphisms of genes involved in the metabolism and transport of antidiabetic drugs in the human body, as well as influencing the strength of the pharmacological effect [6]. Thus, a decrease in the effectiveness of oral glucose-lowering agents in carriers of certain mutated alleles of genes involved in the pharmacokinetics and pharmacogenomics of medications was demonstrated in the GoDART (Genetics of Diabetes Audit and Research in Tayside) study, in the genetic parts of UKPDS (The UK Prospective Diabetes Study) and DPP [7].

Today, the question of the influence of genetics on the efficacy and tolerability of antihyperglycemic therapy is well studied in relation to the most studied and widely used classes of oral antidiabetic medications – metformin and sulfonylureas (SU). Unfortunately, metformin (a first-line treatment for T2DM) has a high variability in efficacy in different patients. And the endocrinologist should supplement the treatment regimen with other hypoglycemic drugs to achieve optimal glycemic control. According to clinical studies, some polymorphisms in genes *SLC22A1, SLC22A2, SLC47A1, SLC47A2* and *ATM* affect the effectiveness of metformin. For example, SNP *rs12208357, rs34130495, rs34059508, rs72552763, rs622342* variants in *SLT22A1* were associated with a decrease in the effectiveness of the metfofmin hypoglycemic effect, as well as with an increase in its renal clearance. It is interesting, that SNP *rs683369* variant in *SLC22A1* correlated with a 31% reduction in the risk of diabetes in participants taking metformin compared with placebo in DPP study. The researchers also studied the effect of gene polymorphisms of the MATE (multidrug and toxin extrusion) family proteins on the effectiveness of metformin. They chose these proteins, because MATE1 (gene *SLC47A1*) and MATE2 (gene *SLC47A2*) they carry out transmembrane transport of metformin molecules from the cells of the renal epithelium into the lumen of the renal tubules. And they found that SNP *rs2289669* and *rs8065082* variants in *SLC47A1* were associated with increased therapeutic effect of metformin. The Finnish DPP study also showed a decrease in the incidence of transformation of impaired glucose tolerance into T2DM in obese individuals with the minor allele of the SNP *rs8065082* C>T in *SLC47A1* [6, 7, 18]. Thus, genetic variants associated with the response to metformin therapy can be used to predict the effectiveness of treatment in patients with T2DM, including already at the onset of the disease, as well as in patients with prediabetes.

Some polymorphic variants also affect the pharmacokinetics and/or pharmacodynamics of SU, for example polymorphisms of *KCNJ11*, *ABCC8*, *IRIS1*, *TCF7L2*, *KCNQ1*, *CDKAL1* and *CAPN10*. Thus, carriage of SNP in *TCF7L2 (rs7903146)* was a predictor of a less effective response to treatment with SU. Conversely, genetic variants of *ABCC8* and *KCNJ11* are associated with a stronger therapeutic response to SU. It is well known, that SU act through binding to the SUR1 subunit (coding by gene *ABCC8*), which promotes the closure of ATP-sensitive potassium channels and membrane depolarization. Then it leads to an increase in calcium influx into the pancreatic β-cells and an increase in insulin secretion. Another subunit of ATP-sensitive potassium channels is Kir6.2, which is encoded by the *KCNJ11* gene. This gene is located in close proximity to *ABCC8* on chromosome 11. The study of the polymorphism of these genes found a common haplotype E23K in *KCNJ11* and S1369A in *ABCC8*, which was associated with T2DM. This haplotype is less sensitive to the action of SU. The carriage of specific polymorphic variants of *IRS-1* and *NOS1AP* are also associated with a decrease in the effectiveness of SU. It should be taken into account in choosing glucose-lowering therapy [6, 7, 18, 48].

The variability of enzymes that metabolize SU can also change their effectiveness and the risk of developing adverse effects of therapy. SU is metabolized in the liver by the cytochrome P450 system (isoenzyme 2C9), which is encoded by *CYP2C9*. This gene has the major allele *CYP2C9*1* and 2 minor variants Arg144Cys (*CYP2C9*2*) and Ile359Leu (*CYP2C9*3*). GoDARTS demonstrated, that carriers of minor variants of *CYP2C9* had a greater decrease in HbA1c level compared with homozygous carriers of the major allele *CYP2C9*1*. Carriers of minor SNP of *CYP2C9* were 3.4 times more likely to reach the target level of HbA1c <7%. This association was confirmed by genetic analysis of the database of the Rotterdam Study and the Dutch DCS West Friesland Study. It is important that *CYP2C9*2* and *CYP2C9*3* polymorphisms are associated with increased serum sulfonylurea levels, which leads to an increased risk of hypoglycemia in carriers of minor variants of this gene. In this regard, SU should be administered with caution and at a lower dosage if the patient is a known carrier of polymorphic variants of *CYP2C9*2 (I359L)* or *CYP2C9*3 (R114C)* [6, 7, 18, 48].

The influence of various genetic variants on the efficacy and tolerability of thiazolidinediones (TZD) has also been well studied. It was shown that the effectiveness of the action of TZD is mainly genetically mediated by the polymorphism of *PPARγ*. A well-studied Pro12Ala polymorphic variant in PPAR-γ has been associated with decreased fasting blood glucose and HbA1c levels in response to rosiglitazone in several studies. In addition, the carriage of certain polymorphisms in *CYP2C8, SLCO1B1, TCF7L2, CYP3A4, IGF2BP2, SLC30A8, KCNQ1, KCNJ11, NAMPT, UCP2, MDR1, NeuroD1*, *Pax4* affects the effectiveness of TZD therapy. Recent studies have also reported about several significant mutations in genes whose products are involved in the pharmacogenetics of thiazolidinediones (PGC-1α, resistin, adiponectin, leptin, TNF-alpha and CYP2C8). And according to other researchers, the carriage of the A1196G (*CYP2C8*3*) allele in the gene encoding cytochrome P4502C8 is associated with a lower level of TZD in blood plasma. Because of this, there is a weaker therapeutic response, but a lower risk of developing edema during therapy at the same time. When we talk about adverse

events with TZD, it's worth mentioning that the risk of fluid retention and worsening symptoms of heart failure limit their widespread use. And recently, genetic variants that predispose to the development of these side effects have been identified. So, *AQP2 (aquaporin 2) rs296766* allele T and *SLC12A1* (sodium/potassium/chloride transporter) *rs12904216* allele G were associated with a high risk of edema in patients taking glitazones [6, 7, 18, 46, 48].

There are only limited data on the pharmacogenetics of innovative hypoglycemic drugs. But, there are already active researches in this area, and the results of several of them have already been published. So, L. Hart et al. studied the effect of *CTRB1/2*, which determines the effect of chymotrypsin on the effectiveness of incretin based treatment. They found that the SNP rs7202877 in *CTRB1/2* is associated with an absolute decrease in HbA1c by 0.51 ± 0.16% in homozygotes for the minor G allele when they taking DPP-4 inhibitors. This effect was not determine, when GLP-1 agonists were administered. In addition, polymorphism of *GLP1R,* encoding the GLP-1 receptor , has a effect on the effectiveness of therapy with GLP-1 agonists. Carrying allele A in rs10423928 is associated with a statistically significant decrease in insulin secretion and a decrease in the incretin effect of the therapy [7, 48].

CONCLUSION

The discovery of new knowledge in the field of T2DM genetics contributes to the emergence of new opportunities for a personalized approach in the management of this complex disease. One of the perspective directions is the use of the results of genome-wide studies to clarify the etiology and pathological metabolic pathways underlying the development of T2DM. In addition, genetic testing can be used to separate patients with T2DM into specific clusters and / or endophenotypes. It will improve our understanding of the pathogenesis of this disease and allow the development of personalized preventive measures, aimed at reducing the risk of implementing a genetic predisposition to T2DM by influencing certain "critical" pathological pathways. Researchers also have high hopes for improving the accuracy of predictive models of metabolic risk disorders using genetic risk assessment. Advances in pharmacogenomics will allow clinicians to administer personalized therapy regimens to increase its effectiveness and reduce the risk of adverse events.

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