Review Article

Genetics of T2DM and Its Chronic Complications: Are We Any Closer to the Individual Prediction of Genetic Risk?

(diabetes mellitus / diabetes complication / polymorphism / Central European population / genetic / GWAS / diabetic neuropathy / diabetic kidney disease / diabetic retinopathy / cardiovascular disease)

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Abstract. Type 2 diabetes mellitus (T2DM) is a complex disease that has risen in global prevalence over recent decades, resulting in concomitant and enormous socio-economic impacts. In addition to the well-documented risk factors of obesity, poor dietary habits and sedentary lifestyles, genetic background plays a key role in the aetiopathogenesis of diabetes and the development of associated micro- and macrovascular complications. Recent advances in genomic research, notably next-generation sequencing and genome-wide association studies, have greatly improved the efficiency with which genetic backgrounds to complex diseases are analysed. To date, several hundred single-nucleotide polymorphisms have been associated with T2DM or its complications. Given the polygenic background to T2DM (and numerous other complex diseases), the degree of genetic predisposition can be treated as a "continuous trait" quantified by a genetic risk score. Focusing mainly on the Central European population, this review summarizes recent state-of-the-art methods that have enabled us to better determine the genetic architecture of T2DM and the utility of genetic risk scores in disease prediction.

Introduction to type 2 diabetes mellitus

The first known reference to diabetes appears in the ancient Egyptian scroll, the Ebers Papyrus, written around 1550 BCE. In modern times, the role of the pancreas in the pathogenesis of diabetes was first described by Joseph von Mering and Oskar Minkowski in 1889 (Karamanou et al., 2016). Representing another landmark moment for diabetes research, Frederick Banting and John Macleod (Banting et al., 1922) discovered the insulin hormone, for which they received the Nobel Prize in Physiology or Medicine in 1923. Paul Langerhans was the first to describe the insulin-producing cell mass in the pancreas that bears his name (Langerhans and Morrison, 1937). But it was not until 1940 that diabetes was differentiated into the two forms we know today (Himsworth, 1940): type 1 diabetes mellitus (T1DM), which is an autoimmune disease comprising the loss of insulin-producing beta cells in the pancreatic islets of Langerhans; and type 2 diabetes mellitus (T2DM), which is characterised by insensitivity to insulin in target tissues, principally the muscles, liver and fat (Ali, 2013). In 1953, Frederick Sanger and E.O.P. Thompson were awarded the Nobel Prize in Chemistry for describing the sequence of the insulin molecule, a springboard

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Abbreviations: ACR – albumin-to-creatinine ratio, AGE – advanced glycation end-products, BMI – body mass index, CAC – coronary artery calcification, CAD – coronary artery disease, CE – Central European, CKD – chronic kidney disease, CVD – cardiovascular disease, DKD – diabetic kidney disease, DN – diabetic neuropathy, DPN – diabetic peripheral neuropathy, DR – diabetic retinopathy, eGFR – estimated glomerular filtration rate, ESRD – end-stage renal disease, EWAS – epigenome-wide association study, GRS – genetic risk score, GWAS – genome-wide association study, IDF – International Diabetes Federation, IGT – impaired glucose tolerance, MI – myocardial infarction, MODY – maturity-onset diabetes of the young, NO – nitric oxide, RAGE – receptor for advanced glycation end-products, SNP – single-nucleotide polymorphism, T1DM – type 1 diabetes mellitus, T2DM – type 2 diabetes mellitus.

for the subsequent mutagenesis and development of insulin analogues.

According to the World Health Organization (2019), T2DM is the "most common type" of diabetes, characterized by "various degrees of β-cell dysfunction and insulin resistance" and "commonly associated with overweight and obesity." T2DM is typically asymptomatic for a long period and diagnosed accidentally. Later, as the glucose metabolism becomes more impaired, it can manifest with symptoms such as thirst, polyuria, weight loss and blurred vision starting to occur. Hyperglycaemia can cause pathological changes in tissues long before a clinical diagnosis of T2DM is made.

Epidemiology

Worldwide, 463 million adults aged 20–79 have T2DM (Williams et al., 2020), representing 9.3 % of the population in this age group. The greatest rise in prevalence (since 1980) is attributed to the Eastern Mediterranean region (from 5.9 % to 13.7 % in 2014) (WHO, 2019). The International Diabetes Federation (IDF) estimates that there will be 642 million diabetes patients worldwide in 2040 (10.4 % of the global population), while another 7.8 % of the population will have impaired glucose tolerance (IGT) (Williams et al., 2020).

Epidemiological data for the Czech Republic (total population 10.7 million) indicate that approximately 1,045 thousand patients had diabetes in 2019 (ÚZIS, 2020). Of these, 85 % had T2DM, 7.4 % had IGT and 6.5 % had T1DM, while the remaining had secondary types of diabetes. Furthermore, 38,000 diabetics died from complications associated with diabetes in 2019 (ÚZIS, 2020). The burden of the disease has resulted in rising financial costs for healthcare systems in the form of direct medical costs, indirect costs associated with productivity loss, morbidity, and premature mortality (Williams et al., 2020).

Most diabetic patients die of some form of vascular complications. Up to 65 % of all deaths in people with diabetes are caused by cardiovascular complications (mostly stroke and coronary heart disease). Another serious complication of diabetes is diabetic kidney disease (DKD), which accounts for up to 44 % of all new cases of end-stage renal disease (ESRD) worldwide. Notably, many patients with DKD die of cardiovascular complications, with the cardiovascular system affecting the kidneys and vice versa. DKD patients are also at increased risk of other diabetic complications such as diabetic retinopathy (DR). Renal-retinal syndrome, a condition characterized by the presence of both complications at the same time, has been known for some time (Deshpande et al., 2008).

Aetiology

T2DM develops as a result of the complex interplay between (i) environmental risk factors (obesity, sedentary lifestyles, age, nutrition, stress, etc.), which augment insulin resistance, and (ii) genetic predisposition (Adeghate et al., 2006). The role of the latter is supported by three key findings that link T2DM to hereditary factors. Firstly, when individuals with a comparable degree of insulin resistance are exposed to the same environmental risk factors, some develop diabetes while others do not. Secondly, the heritability of T2DM is 40–70 % according to the population and family background. For instance, individuals with one parent diagnosed with T2DM have a 40 % lifetime risk of developing T2DM, while in individuals where both parents are diabetic, this risk increases to 70 % (Tillil and Köbberling, 1987). Finally, manifestation of T2DM in monozygotic twins is 70 % (Kaprio et al., 1992).

Genetic contribution to type 2 diabetes mellitus

The genetic architecture of T2DM is polygenic, considering that Mendelian inheritance has been historically apparent only in a fraction of cases later reclassified into forms of maturity onset diabetes of the young (MODY) (Ali, 2013). Many of the genes/loci that contribute to an individual's genetic susceptibility to T2DM usually have a small effect size. The discovery of common and rare variants depends on the methodology applied (GWAS vs. next-generation sequencing).

The most common genetic variants are single-nucleotide polymorphisms (SNP), which take the form of single base substitution or insertion/deletion with an occurrence > 1 % in any given population (Conway and Maxwell, 2009). Identifying candidate genes for a disease as common as diabetes and/or its complications is complex (Tanaka and Babazono, 2005; Ahlqvist et al., 2015; Ma, 2016). Genes associated with T2DM are understood to play a role in glucose metabolism, insulin secretion, insulin receptor activity, post-receptor signalling and lipid metabolism (Ali, 2013).

Genome-wide association studies

Genome-wide association studies (GWAS) facilitate a more complex and systematic approach unburdened by prior biological assumptions. A combination of association and epidemiological studies, GWAS scan hundreds of thousands of SNPs across the genome to identify differences in genotype distribution between defined groups (McKnight et al., 2015; Uitterlinden, 2016). In 2007, the International HapMap Project identified approximately three million SNPs in the human genome. Albeit representing only 0.1 % of the genome, taken together this figure accounts for over 90 % of its total variability (Frazer et al., 2007). Sample size and ethnic origin are the most important criteria when designing an association study, with origin affecting the distribution of alleles in respective populations (Iles, 2008).

Gaulton et al. (2008) found an association between T2DM and several genes, including *PPARG* (peroxisome proliferator-activated receptor gamma), *IRS1* and *IRS2* (insulin receptor substrate 1 and 2), *KCNJ11* (potassium inwardly rectifying channel, subfamily J, member 11) and *WFS1* (Wolfram syndrome 1). Other studies

have identified T2DM associations with *TCF7L2* (transcription factor 7-like 2) (Lyssenko et al., 2007) and *IGF2BP2* (insulin-like growth factor-2 mRNA-binding protein 2) (Jia et al., 2011).

Various diabetes-genetics consortia have found dozens of SNPs associated with T2DM. In the present study, we highlight a few SNPs that have been widely repeated across these studies, such as *FTO* (alpha-ketoglutarate-dependent dioxygenase), *TCF7L2* (transcription factor 7-like 2), *IRS1* (insulin receptor substrate 1), *GCKR* (glucokinase regulatory protein), *SLC30A8* (solute carrier family 30 member 8), *RREB1* (ras-responsive element-binding protein 1), among many others (Salonen et al., 2007; Morris et al., 2012; Talmud et al., 2015; Fuchsberger et al., 2016; Mahajan et al., 2018; Polfus et al., 2021; Srinivasan et al., 2021).

GWAS are adept at identifying loci that would otherwise be inaccessible using the classical candidate gene approach. To date, hundreds of SNPs have been associated with T2DM (Talmud et al., 2015; Wood et al., 2017; Xu et al., 2018; Vujkovic et al., 2020; Ustinova et al., 2021). In this review, we focus primarily on the Central European (CE) population, defined as Germany, Austria, Czech Republic, Slovenia, Slovakia, Poland and Hungary.

Chronic T2DM complications

Complications associated with T2DM can be divided into chronic and acute. Acute complications are caused by a sudden fluctuation in blood glucose levels. In contrast, chronic complications develop gradually and only typically manifest after several years of the disease. In general, the prevalence of complications rises in tandem with the duration of T1DM or T2DM and with exposure to, and poor management of, modifiable risk factors such as hyperglycaemia, blood pressure, overweight/obesity and lipid levels (Ting et al., 2016). Genetics is also understood to play a role. Significant inter-individual variability in the extent and severity of complications among diabetic patients has been observed. Identification of genetic susceptibility to diabetic complications together with early detection and treatment of T2DM patients (in an existing pre-diabetes state) can be effective in preventing the onset and progression of complications such as cardiovascular disease (Henning, 2018).

Cardiovascular disease (CVD) in T2DM

Macrovascular complications in the form of coronary artery disease (CAD), heart attack, or stroke are the most common causes of death in T2DM patients (Deshpande et al., 2008). The rate of CVD is two to three times higher in T2DM patients than in adults without diabetes. Patients with T2DM without previous history of CVD have the same risk for acute coronary syndrome as adults without T2DM but with previous myocardial infarction (MI). Diabetes has also been strongly related to fatal rather than non-fatal MI, with hazard ratios for these events higher in women than in men (Sarwar et al., 2010).

Risk factors associated with increased risk of CVD include, but are not limited to, the following: insufficient glycaemic compensation, increased glycated haemoglobin, increased concentration of LDL cholesterol, decreased concentration of HDL cholesterol, hypertension, smoking, physical inactivity, and increased BMI (Henning, 2018). Physically inactive adults with diabetes have a 2.8-increased risk of cardiovascular mortality compared to physically active T2DM patients. Furthermore, T2DM patients who engaged in more than three hours per week of light physical activity (i.e., no sweating/not being out of breath) had a similar risk of death from cardiovascular disease as the healthy population (Moe et al., 2013).

Diabetic kidney disease (DKD)

DKD, previously known as diabetic nephropathy, is a severe microvascular complication that progresses gradually over the life span of 30–40 % of both T1DM and T2DM patients (Williams et al., 2020). Clinically, DKD is characterized as a variably progressive decline in kidney function accompanied by a variable degree of albuminuria, eventual proteinuria, and hypertension (Ahlqvist et al., 2015; Williams et al., 2020). Morphological correlations in its clinical course manifest as structural and functional changes in the glomerulus, such as thickening of the glomerular basement membrane, mesangial cell expansion, capillary injury, reduced podocyte numbers, extracellular matrix accumulation, among other changes (Gu, 2019). In developed countries, DKD is a leading cause of ESRD requiring dialysis and transplantation (Williams et al., 2020).

The striking feature of DKD is its inter-individual variability. Not all patients who develop DKD disregard the optimal recommendations for the management of glycaemia and other risk factors. On the other hand, some diabetic patients develop DKD despite tight diabetes control (Gu, 2019). However, proper glycaemic control is associated with slower DKD progression in diabetic patients (Brownlee, 2005; Barrera-Chimal and Jaisser, 2020). Further, evidence of the heritability of DKD has been observed in the family aggregation of DKD between various ethnic groups (Williams et al., 2020). Taken together, these data suggest that genetics plays a crucial role in DKD manifestation and progression.

Diabetic retinopathy (DR)

In the majority of high-income countries, diabetic retinopathy (DR) is a leading cause of acquired vision loss in the working-age population and is attended by devastating socio-economic and human impacts (Williams et al., 2020). DR prevalence increases in tandem with the duration of both T1DM and T2DM and with exposure to, and poor management of, modifiable risk factors such as hyperglycaemia, hypertension, hyperlipidaemia and BMI (Ting et al., 2016). Screening, early

detection and timely treatment can prevent or halt the progression of DR. However, implementing these three principles remains a challenge, especially in poor and middle-income countries (Williams et al., 2020). Evidence relating to the importance of genetic predisposition in DR has accumulated over recent decades. For example, in monozygotic twin studies, the concordance of a degree of DR between twins with T2DM was 95 % compared to 68 % in monozygotic twins with T1DM (Leslie and Pyke, 1982). Some DR-focused GWAS will be discussed further in this review.

Diabetic neuropathy (DN)

DN is a neurodegenerative disorder primarily affecting the peripheral nervous system (Feldman et al., 2019; Patel et al., 2021). The most common form of DN is distal symmetric polyneuropathy, accounting for 75 % of all neuropathies across the diabetic population (Patel et al., 2021).

Symptoms usually first manifest in the legs before progressing to more proximal parts of the limbs (Said, 2007; Williams et al., 2020). Symptoms referred to as "positive" include tingling, dysesthesia, burning feelings, the sensation of electricity, or shooting pains that tend to occur predominantly at night. Symptoms referred to as "negative" include loss of sensation, an unsteady gait, or numbness. These latter symptoms can result in numbness in the legs, causing patients to be less aware of injury and increasing the risk of foot ulcers (Zakin et al., 2019).

DN occurs in approximately 25 % of adults with diabetes. Limb amputation (in whole or in part) is 10–20 times more common in diabetics than in healthy individuals. These complications are more common in people with T2DM compared to T1DM. Maintaining a HbA1c level under 7 % can lead to a 35 % reduction in limb amputation compared to poorer diabetic control (Williams et al., 2020).

Considering that genetic factors can explain inter-individual variability, some patients may develop severe forms of DN despite satisfactory T2DM management, and vice versa (Said, 2007). The few DN-focused GWAS performed to date will be discussed further in this review.

For a summary of the major diabetes complications, see Table 1.

Genetic contribution to T2DM complications

Since T1DM and T2DM share some characteristics, it is not surprising that genetic overlaps have been reported (Maeda et al., 2010). On the other hand, it should be noted that T1DM and T2DM are distinguished by many characteristics and pathological mechanisms. Therefore, most of the genes associated with T1DM are not associated with T2DM, and vice versa (Anders et al., 2018).

Providing a summary of all known SNPs associated with T2DM, cardiovascular disease, diabetic kidney disease, diabetic retinopathy and diabetic neuropathy is beyond the scope of this review. Instead, we have chosen to highlight a few of the key, widely discussed SNPs associated with the above-mentioned comorbidities in T2DM patients, predominantly in the Central European population.

Table 1. Basic information on the most common diabetic complications

	Prevalence	**Symptoms**	**Estimated genetic background**	**Source**
Diabetic retinopathy	44 % in Caucasians; data differs across ethnic groups	Gradually worsening vision Sudden vision loss Floating shapes in the field of vision Blurred or patchy vision Eye pain or redness Difficulty seeing in the dark	25 %	(Arar et al., 2008; Williams et al., 2020)
Diabetic kidney disease	25 % and 36 % of people in the UK and US, respectively	Poor appetite Weight loss Muscle cramps Fluid retention Need to pass urine more often than usual Feeling sick (nausea)	30–75 %	(Williams et al., 2020; Ma, 2016)
Diabetic foot	28–40 % in Caucasians	Changes in skin colour Swelling in the foot or ankle Pain in the legs Open foot sores that are slow to heal or drain Corns or calluses Dry cracks in the skin	6 %	(Meng et al., 2017; Williams et al., 2020)
Cardiovascular disease	32 % in high- and middle-income countries	Chest pain, feelings of chest tightness or pressure Shortness of breath Fainting or near-fainting Heart palpitations	50 %	(Williams et al., 2020; Ma, 2016)

Cardiovascular disease in T2DM

It is well established that patients with T2DM are at increased risk of CVD compared to the healthy population and, moreover, that these two diseases have a number of risk factors in common (Herder et al., 2011). A revealing study found an association between rs10911021, near the *GLUL* (glutamate-ammonia ligase) gene, and increased risk of CAD in T2DM patients compared to subjects without T2DM (Qi et al., 2013). Unfortunately, this finding was not replicated in another study involving a larger cohort of patients (van Zuydam et al., 2018). The same study did, however, report a significant, genome-wide association between rs11072811, near the *ADAMTS7* (ADAM metallopeptidase with thrombospondin type 1 motif 7) gene, and CAD in T2DM patients compared to the non-diabetes population.

Diabetic kidney disease

More than two hundred SNPs associated with kidney function have been identified thus far (Cañadas-Garre et al., 2019; Gu, 2019; Wuttke et al., 2019). The biological mechanisms behind these SNPs and how they contribute to diabetic kidney disease remains elusive in many cases, since approximately 90 % of identified variants lie within the non-coding region of DNA (Xu et al., 2018).

One product of the *PPARG2* (peroxisome proliferator-activated receptor gamma type 2) gene is a ligand-activated nuclear transcription factor, which plays a central role in coordinating various gene expression responses to exogenous ligands (Herrmann et al., 2002; Ding and Choi, 2015). The rs1801282 SNP has been associated with decreased risk of DKD (e.g., Herrmann et al., 2002), but also with increased risk of DKD (e.g., Liu et al., 2010), a discrepancy possibly caused by ethnic variability. For example, a recent meta-analysis found an association between rs1801282 and decreased risk of DKD in Caucasians (OR = 0.63) but not in Asians (Ding and Choi, 2015).

Renin-angiotensin system disruption is involved in cardiovascular and renal health complications (Crowley and Coffman, 2012). An SNP in *AGTR1* (angiotensin II receptor type 1) involved in water-sodium retention and elevated blood pressure has been associated with T2DM microvascular complications (Crowley and Coffman, 2012). One GWAS found an association between rs12695897 (another *AGTR1* SNP) and DKD in Americans with both European and African ancestry (Palmer et al., 2014).

Another gene of note is *CUBN*, which encodes cubilin, a transmembrane-transporting protein expressed in many tissues, including the kidneys. The rs141640975 polymorphism has been associated with albuminuria in the European population (Ahluwalia et al., 2019). In addition to confirming this association, a GWAS by Casanova and colleagues found that two SNPs in the *CUBN* gene (rs45551835 and rs45619139) were associated with albumin-creatinine ratio (ACR) in a diabetic population. The same authors also associated ACR with other 56 loci, 20 of which had not been previously reported in patients from the UK Biobank (Casanova et al., 2019).

Diabetic retinopathy

Only a few GWAS have focused on DR-associated SNPs, and particularly in non-European populations. A GWAS from 2018 associated NADPH oxidase 4 (*NOX4*) and its polymorphism rs3913535 with severe DR, and another two nearby SNPs (rs10765219 and rs11018670) with promising P values. Conversely, a meta-analysis using multiple Caucasian cohorts found that rs10765219 and rs11018670, but not rs391353, were associated with DR (Meng et al., 2018).

Another GWAS involving multi-ethnic cohorts (both European and African Americans) and replicated in other European, Asian and Hispanic cohorts found the C allele of rs142293996 in the *NVL* (nuclear VCP-like) gene to be associated with DR in European discovery cohorts (Pollack et al., 2019). However, a replication cohort failed to confirm this result.

Han et al. (2019) and Cho and Sobrin (2014) have provided several reasons as to why DR-focused GWAS have been unsuccessful in yielding significant SNPs. First, the sample size used in discovery cohorts is often low compared to GWAS standards. Second, some DR-focused GWAS enrol patients with modest degrees of retinopathy.

Diabetic neuropathy

Of the few GWAS to examine DN predisposition, all have used the Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) cohort. The first of these identified rs17428041 on chromosome 8 next to the *GFRA2* gene (GDNF family receptor alpha 2) as being associated with neuropathic pain (Meng et al., 2015). The second GWAS defined patients with neuropathic pain based on multiple prescriptions for pain-relieving drugs, with controls defined as those not using any of the pain medications defined in the paper (3,260 patients). The authors of this study found associations with the rs71647933 polymorphism in females and with rs6986153, next to the *HMGB1P46* gene, in males. In the third GWAS, patients were defined as T1DM or T2DM with a history of at least one foot ulcer, while controls were defined as T1DM or T2DM in the absence of any known history of foot ulcers. Only rs80028505 was associated with diabetic foot ulcers (Meng et al., 2015).

For a summary of the above-mentioned SNPs associated with T2DM and its complications, see Table 2.

Genetics of T2DM in the Central European populations

The next part of this review focuses on the genetic predisposition of T2DM and its complications in the CE populations.

TCF7L2 is a gene that encodes transcription factor TCF4, a protein in the Wnt pathway that is important for

Table 2. Summary of SNPs (cited in this review) in the general population

Gene	Name of gene	Polymorphism	Associated allele	OR	Association	More information
AGTR1	Angiotensin II receptor type 1	rs12695897	T	0.58	DKD, CVD	(Palmer et al., 2014)
PPARG2	Peroxisome proliferator-activated receptor gamma type 2	rs1801282	G	0.63	DKD	(Herrmann et al., 2002)
GFRA2	GDNF family receptor alpha 2	rs17428041	C	0.67	DN	(Meng et al., 2015)
ADAMTS7	ADAM metallopeptidase with thrombospondin type 1 motif 7	rs11072811	A	1.05	CAD	(Ahlqvist et al., 2015)
GCKR	Glucokinase regulatory protein	rs1260326	T	1.07	T2DM	(Fuchsberger et al., 2016)
IRS2	Insulin receptor substrate 2	rs11843936	C	1.10	Diabetes	(Gaulton et al., 2008)
RREB1	RAS-responsive element binding protein 1	rs9379084	A	1.12	T2DM	(Fuchsberger et al., 2016)
IGF2B2	Insulin-like growth factor-2 mRNA-binding protein 2	rs4402960	T	1.13	T2DM	(Jia et al., 2011)
PPARG	Peroxisome proliferator-activated receptor gamma	rs1801282	C	1.14	Diabetes	(Saxena et al., 2007)
SLC30A8	Solute carrier family 30 member 8	rs13266634	T	1.14	T2DM	(Fuchsberger et al., 2016)
IRS1	Insulin receptor substrate 1	rs1560251	A	1.16	Diabetes	(Gaulton et al., 2008)
WFS1	Wolfram syndrome 1	rs12511742	T	1.32	Diabetes	(Gaulton et al., 2008)
GLUL	Glutamate-ammonia ligase	rs10911021	C	1.36	CAD	(Qi et al., 2013)
NOX4	NADPH oxidase 4	rs3913535	C	1.55	DR	(Meng et al., 2018)
TCF7L2	Transcription factor TCF4	rs7903146	T	1.58	T2DM	(Lyssenko et al., 2007)
HMGB1P46	High-mobility group box 1 pseudogene 46	rs6986153	G	1.67	DN	(Meng et al., 2015)
NVL	Nuclear VCP-like	rs142293996	C	2.38	DR	(Pollack et al., 2019)
KCNJ11	Potassium inwardly rectifying channel, subfamily J, member 11	rs5219	T	2.50	Diabetes	(Gaulton et al., 2008)
CUBN	Cubilin	rs141640975	A	No data	Albuminuria	(Ahluwalia et al., 2019)

the development and proper functioning of beta cells in pancreatic tissue. The rs7903146 polymorphism is one of the most commonly analysed variants in association studies. A change in the nucleotide sequence increases the amount of TCF4 in beta cells, leading to proliferation of these cells and long-term activation of the signal that precipitates cell death by exhaustion (Kang et al., 2008). TT homozygotes are associated with defective insulin secretion, resulting in T2DM manifestation. In the Czech Republic, the TT genotype has been linked to the development of T2DM (OR = 2.05) (Vcelak et al., 2012), a finding replicated in a Hungarian meta-analysis (OR = 1.49) (Lukacs et al., 2012). In the Slovakian population, TT homozygotes have been associated with an increased risk of T2DM development before the age of 40 (OR = 3.02) (Kozarova et al., 2010).

The *FTO* (alpha-ketoglutarate dependent dioxygenase FTO) gene is associated with T2DM and familial obesity. The product of the *FTO* gene is a nuclear protein important in epigenetic regulation (Wu et al., 2010). Frayling et al. (2007) associated the A allele of the rs9939609 polymorphism with increased BMI as well as elevated risk of diabetes. In the Czech population, genotype GG (rs17817449) has been associated with the development of T2DM (OR = 1.86) (Hubacek et al., 2018).

In the Czech population, a study by Lukasova et al. (2008) identified an association between the glucokinase (*GCK*) gene and T2DM, but found no differences in frequencies between T2DM patients and healthy controls. Similarly, another study detected no association between the rs10811661 SNP within the *CDKN2A/2B* locus and T2DM (Hubacek et al., 2013).

IGF2BP2 (insulin-like growth factor 2 mRNA binding-protein 2) encodes a protein with affinity to the mRNA of growth factor IGF2 and regulates its translation. This gene is expressed in beta cells in pancreatic tissue (Christiansen et al., 2009). In the Czech population, the T allele of rs4402960 has been associated with T2DM (OR = 1.26) (Gu et al., 2012).

The rs1801282 polymorphism in the *PPARG2* gene has been examined in the Czech population. Fasting serum insulin levels in T2DM patients were higher in CC homozygotes compared to G-allele carriers (Sramkova

et al., 2002). However, in one Slovenian study, the association with T2DM was not found (Kruzliak et al., 2015). A Hungarian study analysed the same polymorphism in obese adolescents. After a glucose tolerance test, plasma glucose and insulin levels were significantly lower in G-allele carriers compared to the CC genotype. Further, there were no significant differences between the groups in age, BMI, waist circumference, blood pressure, serum lipids, uric acid levels, or TNF-α (Jermendy et al., 2011).

Vedralová et al. (2012) focused on four genetic variants in the vitamin D receptor (*VDR*) gene and two in the parathyroid hormone (*PTH*) gene, found associations between DKD and specific genotypes, namely, rs2228570 (TT genotype) in the *VDR* gene, and rs6254 (GG genotype) and rs6256 (AA genotype) in the *PTH* gene.

In the West-Austrian population, Drexel et al. (2019) analysed three polymorphisms (rs9934336, rs3813008 and rs3116150) within the *SCL5A2* gene (solute carrier family 5 member 2), detecting an association between the rs9934336 AA genotype and T2DM.

Another controversial SNP in the CE population is rs8192673 (peroxisome proliferator-activated receptor-gamma coactivator-1-alpha; PGC-1α). One study found this SNP to be a significant risk factor for T2DM in the Slovenian population (Kunej et al., 2004), but the result was not confirmed in another, later Slovenian study (Kruzliak et al., 2015). Further, this SNP was not found to be statistically significant in association with age of T2DM onset (Kozarova et al., 2010).

A recent German study by Pitchika et al. (2022) examined the *APOE* polymorphism in association with T2DM and metabolic syndrome. Although *APOE4* carriers had a significantly lower risk of developing T2DM (OR = 0.47), both *APOE2* and *APOE4* carriers were found to be at increased risk of developing metabolic syndrome (OR = 1.45 and 1.56, respectively). APOE is known to be involved in lipid metabolism, thus increasing the risk of metabolic syndrome. On the other hand, APOE4 protects against T2DM development, probably due to its effect on inflammation.

In the Czech population, *KCNJ11* (potassium inwardly rectifying channel subfamily J member 11) variant rs5219 has not been associated with T2DM (Cejková et al., 2007). The association between one *KCNJ11* SNP and its response to sulphonylurea has also been investigated. Results show that for each T allele, HbA1c decreased by 0.16 % after six months of sulphonylurea treatment (Javorsky et al., 2012). In a study of Slovakian patients, *KCNJ11* was not associated with age of T2DM diagnosis (Kozarova et al., 2010).

The *ENPP1* (ectonucleotide pyrophosphatase/phosphodiesterase 1) gene and its two polymorphisms rs1044498 (C allele) and rs997509 (T allele) have been associated with T2DM in the presence of obesity in Polish subjects (Bochenski et al., 2006). A recent German study found an association between the rs4987105 polymorphism in the *ALOX5* (arachidonate 5-lipoxygenase) gene and T2DM, where the C allele was significantly more common. The CC genotype was also associated with increased levels of C-reactive protein in T2DM compared to healthy controls (Nejatian et al., 2019).

In the German population, the rs13266634 polymorphism in the *SLC30A8* (solute carrier family 30 member 8) gene and its TT genotype were associated with decreased proinsulin-to-insulin conversion (Kirchhoff et al., 2008). Another report found an association between the TT genotype and decreased insulin secretion in the same population (Staiger et al., 2007).

A Hungarian study, focusing on several variants in the *WFS1* (wolframin ER transmembrane glycoprotein) gene, found T2DM to be associated with rs6824720 (G allele), rs10010131 (G allele), rs13147655 (G allele), rs1046320 (A allele) and rs9457 (C allele) (Elek et al., 2015).

Finally, the frequencies of T2DM-associated alleles in most (within *FTO*, *IGF2BP2*, *ARAP1* and *CDKN2A/2B*) but not all (*TCF7L2*) genes have been shown to be elevated in the Roma population in the Czech Republic (Hubacek et al., 2020).

Genetics of diabetic complications in the Central European population

Several studies have attempted to detect SNPs associated with DKD in the CE population. Makuc et al. (2017) found that SNPs rs699 and rs4762 in the *AGT* (angiotensinogen) gene were not associated with risk of DKD or its progression. Angiotensin-converting enzyme (the *ACE* gene) is known to be involved in regulating blood pressure (impaired blood pressure regulation is a known risk factor for DKD and other kidney diseases). A Czech study aimed at finding an association between an *ACE* polymorphism and increased risk of DKD in diabetic patients found no differences between the groups examined (Demova et al., 2012).

A Slovenian study focusing on the CE population genotyped the *ACE* rs4340 polymorphism but found no association between it and DKD (Seruga et al., 2016). Another Slovenian study genotyped *PECAM1* (rs688; platelet and endothelial cell adhesion molecule 1) in T2DM patients with or without DKD. Again, this polymorphism was not associated with an increased risk of DKD (Zavrsnik et al., 2016).

In contrast, still another Slovenian study detected the relationship between two genes encoding antioxidant proteins: the *CAT* gene (catalase) and rs1138272 in the *GSTP1* gene (glutathione s-transferase p1) and ESRD in T2DM patients (Klen et al., 2015). In Slovenian patients with T2DM, it has been demonstrated that C-allele carriers (rs3803278 in *ALOX5AP*; arachidonate 5-lipoxygenase-activating protein) are at increased risk of developing DKD (Cilensek et al., 2020).

A study from Austria found *TCF7L2* SNPs (rs7903146, rs12255372 and rs11196205) to be significantly associated with CAD in T2DM patients (OR = 1.91, 1.9 and 1.75, respectively) (Muendlein et al., 2011).

Tanhäuserová et al. (2014) found that the rs1056534 C allele within *FN3K* is associated with faster DKD progression. However, another Czech study did not confirm this association (Skrha et al., 2014).

Several genes have been associated with diabetic retinopathy and diabetic neuropathy in the CE population. For example, in the Slovenian population, an association was drawn between variable number tandem repeats (VNTR) in two genes – *EDNRB* (rs10507875; endothelin receptor type B) and *NOS3* (rs869109213; nitric oxide synthase 3) – and diabetic retinopathy. Logistic regression analysis found that the combined effect of rs10507875 and rs869109213 on DR risk was greater than the separate effect of each SNP individually (Bregar et al., 2017). Interestingly, the 4a4b genotype (rs869109213) was not associated with DR in another study of the Slovenian population with T2DM (Petrovic et al., 2008). However, a subsequent study associated 4a4a (rs869109213) with a 3.4-fold increase in DR (Cilensek et al., 2012).

Endothelial variant of nitric oxide synthase (eNOS), which is encoded by the *NOS3* gene, is an enzyme that catalyses nitric oxide (NO) production. NO plays a crucial role in regulating vascular tone. Extensive data highlight its roles in the pathogenesis of DKD (Kuricova et al., 2012) and DR (Bregar et al., 2017) in the Czech population and DN in the Romanian population (Manea et al., 2008). A small study detected an increased frequency in the T allele of the G894T polymorphism in patients with T2DM without metabolic syndrome (OR = 0.66) compared to both T2DM patients with metabolic syndrome and healthy controls (Manea et al., 2008). Kuricova et al. (2013) found an association between TT homozygotes in the G849T polymorphism and an increased major cardiovascular event in T2DM patients with DKD (OR = 2).

A German study found glyoxylase 1 (*GLO1*, rs2736654) and its CC genotype to be significantly associated with DN compared to CA and AA genotypes (OR = 1.49) (Groener et al., 2013).

The rs4880 SNP in manganese superoxide dismutase (MnSOD) and its TT genotype were found to be potential risk factors for DR (OR = 2.1) in the Slovenian population with T2DM (Petrovic et al., 2008).

A Slovenian study described an increased risk of DR (OR = 2.2) for CC homozygotes (rs2073618 in the osteoprotegerin (*OPG*) gene) vs. G-allele carriers in T2DM patients. The combined effect of the rs2073618 CC genotype and the rs3134069 (located in promotor region of the *OPG* gene) AA genotype compared to CG/GG + AA resulted in an OR = 2.54 for DR (Mankoc Ramus et al., 2013).

Klen et al. (2015) investigated rs9934336 in *SLC5A2* in the Slovenian population and found that carriers of at least one A allele are at an increased risk of DR compared to non-carriers among T2DM patients (OR = 7.62). The previously mentioned study by Drexel et al. (2019) tried to find an association between SNPs in gene *SLC5A2* and CAD, but no statistically significant association has been found. Interestingly, the authors found rs9934336 (genotype AA) to be protective against T2DM. Importantly, this variant encodes protein SGLT2, which is a target for gliflozins, the newest form of antidiabetic drugs. Therefore, this SNP is particularly deserving of further research.

In the Slovenian T2DM population, the PlA1/A2 polymorphism of glycoprotein IIIa (GPIIIa), specifically its A2A2 genotype, was associated with lower risk of DR (Nikolajevic-Starcevic et al., 2011) but not with risk of MI (Nikolajevic-Starcevic and Petrovic, 2013). Another study found that rs8192678 in *PPARG* and its AA genotype increased the risk of DR (OR = 2.7) in Slovenian patients (Petrovic et al., 2005). The association of *PPARG* with the age of T2DM diagnosis has also been investigated, albeit unsuccessfully (Kozarova et al., 2010). A recent study from Slovenia found that a genetic variant in erythropoietin (*EPO*) rs1617640 and its GG genotype were associated with a 1.6-fold increased risk of proliferative DR compared to T-allele carriers (Mankoc Ramus et al., 2021).

The *APOE4* variant in the apolipoprotein E gene had a protective effect on DR development in Czech T2DM female patients but not in Czech T2DM male patients (Dlouha et al., 2021).

One Slovenian study investigated the influence of two polymorphisms (rs2107595 and rs11984041) in the histone deacetylase 9 (*HDAC9*) gene in patients with T2DM. The TT genotype in rs11984041 increased the probability of DR development by 3.76 compared to the CC genotype. However, rs2107595 was not found to be significant (Cilensek et al., 2021).

A Slovenian study focusing on the CE population analysed the endothelin-1 (*EDN1*) gene as well as its rs5370, rs1476046 and rs3087459 polymorphisms in association with DKD. There were no significant results between patients with T2DM and DKD compared to T2DM patients without DKD (Seruga et al., 2017). A more recent study from Slovenia found that the CC genotype of the rs7069102 polymorphism in sirtuin 1 (*SIRT1*) was associated with DKD (OR = 2.39) (Letonja et al., 2021). A further Slovenian study found that the arachidonate 5-lipoxygenase-activating protein (*ALOXA5AP*) gene as well as its rs38022789 polymorphism were associated with DKD in T2DM subjects. Here, the CC genotype was associated with a 3.14-increased risk compared to the TT genotype (Cilensek et al., 2020).

A study from Germany examined polymorphisms in *MMP9* (matrix metalloproteinase 9; rs17576) and *CUBN* (cubilin; rs1801239) in association with DKD, ESRD and CVD. The authors found that the GG genotype (rs17576) was more frequent in patients with DKD using a multivariate model (OR = 6.07). Interestingly, AA homozygotes proved a protective factor for onset of proteinuria (OR = 0.87). Carriers of the C allele in *CUBN* had increased proteinuria compared to the AA genotype. However, none of these SNPs was associated with CVD (Albert et al., 2019).

A recent study involving the Slovenian population found that the CC genotype allele of the rs1333049 polymorphism of cyclin-dependent kinase inhibitor 2B antisense RNA1 (CDKN2B-AS1) was associated with MI (OR adjusted for BMI) (Tibaut et al., 2022). A Slovenian study investigating the risk of CAD in T2DM patients reported that the thioredoxin reductase 2 (*TXNRD2*) rs1548357 polymorphism may represent a risk factor for myocardial infarction. The prevalence of MI was lower in C-allele carriers compared to the TT genotype (Kariz et al., 2015).

In the Polish population, Mrozikiewicz-Rakowska et al. (2017) found an association between three SNPs and DR in T2DM patients. More specifically, in *AKR1B1* (rs759853; aldo-keto reductase family 1 member B), G-allele carriers were at greater risk (OR = 3.0) than non-carriers. Another two SNPs in *TNFRSF11B* (TNF receptor superfamily member 11b) were significantly associated with DR. In T2DM patients, the A allele in rs3134069 was associated with an increased, while the C allele in rs2073618 was associated with a lower risk of DR.

Buraczynska et al. (2010) investigated the C5507G polymorphism in the complement receptor 1 (*CR1*) gene, finding that the GG genotype was more frequent in patients with ESRD and CVD compared to ESRD patients without CVD and healthy controls. They also found that the T allele of rs11614913 in the mRNA-196a2 gene was protective against T2DM development. On the other hand, TT homozygotes were at increased risk of CVD.

The same authors also explored the effect of the G-174C polymorphism in the *IL6* gene. No significant differences in genotypes between T2DM groups and healthy controls were observed. On the other hand, a greater frequency of C alleles was observed in patients with CVD history compared to patients without CVD, where HR = 2.4 and 4.55 for the C genotype and CC genotype, respectively (Buraczynska et al., 2016). Buraczynska et al. (2017) also described an association between the TT genotype of glutathione peroxidase 1 (*GPX1*) (rs1050450) and increased risk of diabetic peripheral neuropathy (DPN).

To our knowledge, no GWAS has examined the risk of DN in the CE population.

For a summary of the SNPs mentioned in association with the CE population in this review, see Table 3.

Genetic risk score

Almost 40 years ago, it was proposed that *"a large number of people at a small risk may give rise to more*

Table 3. Summary of SNPs (cited in this review) associated with T2DM or its complications in the CE population

Association	Gene	Name of gene	Polymorphism	Associated allele	OR	Further information
T2DM	*APOE*	Apolipoprotein E	rs429358, rs7412	C, C	0.47	(Pitchika et al., 2022)
	ALOX5AP	5-Lipoxygenase-activating protein	rs4987105	C	1.44	(Nejatian et al., 2019)
	WFS1	Wolfram syndrome 1	rs10010131	G	1.42	(Elek et al., 2015)
			rs9457	C	1.42	
			rs13147655	G	1.44	
			rs6824720	G	1.50	
			rs1046320	A	1.55	
	SLC5A2	Solute carrier family 5 member 2	rs9934336	A	0.86	(Drexel et al., 2019)
	IGF2BP2	Insulin-like growth factor 2 mRNA-binding protein 2	rs4402960	T	1.26	(Gu et al., 2012)
	FTO	Alpha-ketoglutarate-dependent dioxygenase	rs17817449	G	1.30	(Hubacek et al., 2018)
	TCF7L2	Transcription factor TCF4	rs7903146	T	2.10	(Lyssenko et al., 2007)
	ENPP1	Ectonucleotide pyrophosphatase/ phosphodiesterase 1	rs1044498	C	1.70	(Bochenski et al., 2006)
			rs997509	T	4.70	
CAD	*TCF7L2*	Transcription factor TCF4	rs11196205	G	1.75	(Muendlein et al., 2011)
			rs12255372	G	1.90	
			rs7903146	C	1.91	
MI	*TXNRD2*	Thioredoxin reductase 2	rs1548357	T	0.60	(Kariz et al., 2015)
	CDKN2B-AS1	Cyclin-dependent kinase inhibitor 2B antisense RNA1	Rs1333049	C	1.50	(Tibaut et al., 2022)

Association	Gene	Name of gene	Polymorphism	Associated allele	OR	Further information
DKD	*PTH*	Parathyroid hormone	rs6254	G	1.70	(Vedralová et al., 2012)
	VDR	Vitamin D receptor	rs2228570	T	1.82	(Vedralová et al., 2012)
	PTH	Parathyroid hormone	rs6256	A	2.01	(Vedralová et al., 2012)
	FN3K	Fructosamine-3-kinase	rs1056534	C	No data	(Tanhäuserová et al., 2014)
	SIRT1	Sirtuin 1	rs7069102	C	2.40	(Letonja et al., 2021)
	ALOX5AP	Arachidonate 5-lipoxygenase-activating protein	rs3803278	C	3.14	(Cilensek et al., 2020)
			rs38022789	C	3.14	
	MMP9	Matrix metalloproteinase 9	rs17576	G	6.07	(Albert et al., 2019)
ESRD	*CAT*	Catalase	rs1001179	T	5.43	(Klen et al., 2015)
	GSTP1	Glutathione S-transferase pi 1	rs1138272	T	3.68	(Klen et al., 2015)
ESRD; CVD	*CR1*	Complement receptor 1	C5507G	G	3.44	(Buraczynska et al., 2010)
DR	*APOE*	Apolipoprotein E	rs429358, rs7412	CC	0.65	(Dlouha et al., 2021)
	AKR1B1	Aldo-keto reductase family 1 member B	rs759853	G	3.00	(Mrozikiewicz-Rakowska et al., 2017)
	TNFRSF11B	TNF receptor superfamily member 11b	rs3134069	A	3.33	(Mrozikiewicz-Rakowska et al., 2017)
	GPIIIa	Glycoprotein IIIa	PlA1/A2	A2A2	0.60	(Nikolajevic-Starcevic et al., 2011)
	EPO	Erythropoietin	rs1617640	G	1.60	(Mankoc Ramus et al., 2021)
	EDNRB	Endothelin receptor type B	rs10507875	G	1.88	(Bregar et al., 2017)
	NOS3	Nitric oxide synthase 3	rs869109213	4a4a genotype	1.99	(Bregar et al., 2017)
	Mn-SOD	Manganese superoxide dismutase	rs4880	T	2.10	(Petrovic et al., 2008)
	OPG	Osteoprotegerin	rs2073618	C	2.20	(Mankoc Ramus et al., 2013)
	PGC1a	Peroxisome proliferator-activated receptor-gamma coactivator-1	rs8192673	A	2.70	(Kunej et al., 2004)
	PPARG	Peroxisome proliferator-activated receptor gamma	rs8192678	A	2.70	(Petrovic et al., 2005)
	HDAC9	Histone deacetylase 9	rs11984041	T	3.76	(Cilensek et al., 2021)
	SLC5A2	Solute carrier family 5 member 2	rs9934336	A	7.62	(Klen et al., 2015)
DN	*GLO1*	Glyoxylase 1	rs2736654	C	1.49	(Groener et al., 2013)
Insulin levels	*PPARG2*	Peroxisome proliferator-activated receptor gamma 2	rs1801282	G	No data	(Sramkova et al., 2002)
Sulphonylurea treatment	*KCNJ11*	Potassium inwardly rectifying channel subfamily J member 11	rs5219	T	No data	(Javorsky et al., 2012)
Decreased insulin secretion	*SLC30A8*	Solute carrier family 30-member 8	rs13266634	T	No data	(Kirchhoff et al., 2008)
Proteinuria	*CUBN*	Cubilin	rs1801239	A	0.87	(Albert et al., 2019)

cases of disease than the small number who are at a high risk" (Rose, 1985). But what is the most apt method for identifying these large numbers of people at a small risk? Genetic scores could be the answer.

Genetic scores are calculated based on the presence of individual risk alleles to a particular complex disease. The two most used genetic scores are the genetic risk score (GRS) and the polygenic risk score (PRS).

A GRS determines the level of risk of someone developing, or progressing to, a given disease based on selected SNPs. It can be determined in two ways: either as an unweighted GRS (uGRS), which is calculated based on the number of risk alleles, or, since not all SNPs contribute equally to the disease, as a weighted GRS (wGRS), determined based on an odds ratio or hazard ratio for each SNP (Zusi et al., 2018; Igo et al., 2019).

A PRS represents the estimated effect of the total number of genetic variants (including SNPs without significant genome-wide associations) on the phenotype of a given individual (Igo et al., 2019). For the purposes of this review, we will focus on GRS in the context of T2DM and its complications.

One of the first genetic risk scores was designed by a Scandinavian study group. Examining 16 SNPs based on weighted and unweighted models, the authors found a slight improvement in T2DM prediction when compared with clinical risk factors alone (Lyssenko et al., 2008). Meigs et al. (2008) calculated their GRS from 18 SNPs (13 SNPs overlapping with the Lyssenko study) associated with T2DM, involving over 2000 subjects from the Framingham Offspring Study (Meigs et al., 2008). However, the GRS for these 18 risk alleles was only slightly better (12 %) at predicting new patients with T2DM compared to the knowledge of common risk factors alone and family history.

A study from Poland, which calculated both wGRS and uGRS, separated patients based on the amount of physical activity (PA) performed during a week. T2DM prevalence was higher in individuals with low physical activity compared to those with high physical activity. The T2DM prevalence was not significantly different between individuals with high uGRS and wGRS compared to low u/wGRS in both low PA and high PA subgroups (Szczerbiński et al., 2019). In this study, 9/19 SNPs overlapped with the Lyssenko et al. (2008) study, 5/19 overlapped with the Meigs et al. (2008) study, and 5/19 SNPs overlapped with both studies.

From an array comprising almost 200,000 SNPs associated with cardio-metabolic diseases, Talmud et al. (2015) identified 65 polymorphisms that influence the development of T2DM. Despite some of these selected SNPs exhibiting low OR values, the GRS predicted new onset of T2DM over a median follow-up period of 10 years.

A large Czech study (Hubacek et al., 2023) screened 21 SNPs selected from a list described previously (Talmud et al., 2015). Of these, only six SNPs (within *FTO*, *IGF2BP2*, *TCF7L2*, *THADA*, *ARAP1*, and *KCNQ1*) were associated with T2DM, and only three (*FTO*, *TCF7L2* and *IGF2BP2*) with both T2DM risk and increased risk of at least one complication. The calculated GRS clearly distinguished (for adjusted and unadjusted ORs) between controls and T2DM patients. Subjects with a GRS > 6 had double the risk of T2DM in three independent groups of patients. The GRS also predicted the development of neuropathy, nephropathy, and leg ischaemia.

An Italian study calculated an unweighted GRS composed of 39 SNPs associated with CKD and/or kidney function. After correcting for multiple comparisons, ACR was not found to be significantly associated with GRS (Zusi et al., 2018).

In another study (Ma et al., 2017), a weighted GRS composed of 53 SNPs (17 SNPs overlapping with a study by Zusi et al., 2018) was calculated to examine whether a higher GRS may predict progression to stage 3 CKD independently of common clinical risk factors in a Caucasian population. Although the authors demonstrated that a higher GRS may predict progression to stage 3 CKD, the improvement in prediction was weak compared to common clinical risk factors.

Using data on 452,000 individuals from the UK Biobank, lower GRS (representing lower eGFR outcomes) composed of 147 SNPs associated with eGFR (less than a dozen SNPs overlapped with studies by Zusi et al. (2018) and Ma et al. (2017)) was statistically significantly associated with a higher risk of chronic renal failure, glomerular disease, acute kidney injury, and hypertensive disease (Wuttke et al., 2019).

Contrary to that, some studies have failed to associate GRS with predicted CKD/DKD progression or its development (O'Seaghdha et al., 2012; Thio et al., 2018). The differences observed across GRS studies could be caused by a variance in SNP selection and between ethnic groups. More rare variants with greater heritability effects need to be identified in order to increase the predictive power of GRS (O'Seaghdha et al., 2012; Thio et al., 2018; Zusi et al., 2018).

Adams et al. (2014) calculated two GRSs. The first included 12 SNPs associated with coronary artery calcified plaque (CAC), while the second consisted of 8 SNPs associated with CAC and MI. Both weighted and unweighted GRSs were calculated for each set of SNPs in patients from the Diabetes Heart Study. Only the unweighted GRS containing SNPs associated with CAC and the weighted GRS composed of CAC- and MI-risk SNPs were associated with CVD and MI, respectively.

Another study calculated a CVD-associated GRS using data from the Look AHEAD cohort. One hundred and fifty-three SNPs have been genotyped in a total of 4,322 patients (median follow-up period of 9.6 years) with T2DM, and weighted GRS has been calculated. Participants in the highest GRS quartile had a 51 % greater incidence of CVD compared to the lowest quartile. Also, GRS was statistically significantly associated with deaths from cardiovascular causes, non-fatal MI, non-fatal stroke, and hospitalization due to angina (HR, 95 % CI per 1 SD increase in GRS: 1.19 [1.10, 1.28]) (Look AHEAD Research Group, 2015). In this study,

4/153 SNPs overlapped with a study by Adams et al. (2014).

Zusi et al. (2018) determined a GRS from 42 SNPs associated with CVD risk phenotypes. No significance was observed between GRS and serum lipids or electrocardiogram abnormalities. Sixteen out of 153 SNPs overlapped with the Look AHEAD study (2015), 8/12 SNPs with Adams et al. (2014), and three (rs1333049, rs12526453 and rs4773144) with both studies.

There are insufficient data on GRS in relation to DR. One recent GWAS calculated a PRS in 6,079 individuals with T2DM. They found that patients in the highest PRS decile had a 1.8 higher risk of DR compared to the lowest decile of patients. Among individuals without DR, the highest decile of patients displayed significantly more symptoms of DR compared to the lowest decile (Forrest et al., 2021). Given the scarcity of data on GRS and DR, further research is required.

Conclusion

To date, numerous GWAS have associated hundreds of SNPs with T2DM and/or its complications. Given, however, that most of these studies have sampled European-American (Caucasian) populations, approximating these results to other ethnicities is a considerable challenge. To our current knowledge, none has been performed in a CE population.

On the other hand, several SNPs associated with T2DM by previous consortia have also been associated with T2DM and/or its complications in CE populations, including *TCF7L2*, *IGF2BP2*, *PPARG*, *SLC30A8*, *KCNJ11*, *WFS1*, and *FTO*. We were not able to find any information on associations between the *GCKR* and *RREB1* genes and T2DM in CE populations.

GRS is a potentially powerful tool for predicting which individuals may be at increased risk of a particular disease. The two biggest issues with regard to SNPs associated with the observed traits are which ones to select and in what quantity. As observed by Keaton et al. (2014), considering that ethnic-specific differences in the genetic architecture exist, any given GRS must necessarily be calculated for each ethnic group or population separately.

We believe that a suitably designed GRS, i.e., one that is adept at predicting which individuals may be at increased risk of a particular phenotype, would result in more frequent screening as well as targeted lifestyle/diet interventions in these at-risk individuals, thus reducing or preventing the risk of developing disease.

In the context of current genetic research on T2DM and its complications, numerous potential pitfalls need to be addressed. Firstly, the widely discussed gene-environment interaction posits that diabetes manifestation is not only caused by an individual's genetic predisposition, but also by environmental factors. Particularly in the West, lifestyles have changed dramatically over the past 50 years, during which time the diabetes epidemic has unfolded.

Secondly, epigenetic factors that are commonly acknowledged to be influenced by environmental factors must also be considered (Amrom et al., 2022). Epigenetic factors can change over a human lifespan and, furthermore, are inherited by an individual's offspring. Epigenetic regulation includes DNA methylation, histone modifications and RNA interferace. Non-coding RNAs, more specifically micro-RNAs (miRNAs), have recently emerged as important regulators of gene expression and function, the alteration of which has been shown to contribute to human disease. Promisingly, therapeutic approaches based on the modification of miRNA expression have been explored in recent years (Weale et al., 2021).

Thirdly, alternative splicing of gene products is another phenomenon deserving further analysis.

In summary, considering the differences in natural selection, environmental exposure and epigenetic background, the effect and interaction of a given gene will vary from one ethnic group to the next. Inevitably, given the complexity of a disease such as diabetes, its development also comes under the influence of the above factors. In a general context, additional research and investment are required if we are to enhance our understanding of the interplay between hereditary susceptibility and GRS calculation.

Conflict of interest

The authors declare no conflicts of interest.

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