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MINIREVIEWS

Genetics of type 2 diabetes

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Abstract

Type 2 diabetes (T2D) is the result of interaction between environmental factors and a strong hereditary component. We review the heritability of T2D as well as the history of genetic and genomic research in this area. Very few T2D risk genes were identified using candidate gene and linkage-based studies, but the advent of genome-wide association studies has led to the identification of multiple genes, including several that were not previously known to play any role in T2D. Highly replicated genes, for example TCF7L2, KCNQ1 and KCNJ11, are discussed in greater detail. Taken together, the genetic loci discovered to date explain only a small proportion of the observed heritability. We discuss possible explanations for this "missing heritability", including the role of rare variants, gene-environment interactions and epigenetics. The clinical utility of current findings and avenues of future research are also discussed.

Key words: Type 2 diabetes; Genetics; TCF7L2; Genome-wide association studies; Heritability

Core tip: We review the history and the current state of knowledge regarding the genetic component of type 2 diabetes risk. Genes like TCF7L2 that have been replicated in multiple studies are discussed in detail. The significance of these findings is discussed and gaps in our knowledge are identified, as are avenues for future research.

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INTRODUCTION

Diabetes has been recognized as a distinct disease for over 2000 years[1] but it was not until 1935 that Hinsworth established that there were two district types of diabetes[2]. While both common types of diabetes are characterized by sustained elevations of plasma glucose levels, type 1 diabetes is an autoimmune disease that results in complete loss of the insulin-producing β-cells in the pancreatic islets, while type 2 diabetes (T2D) typically results when insulin secretion from the islets fails to keep pace with increasing insensitivity to the action of circulating insulin on its target tissues (particularly muscle, liver, and fat).

The development of T2D is the result of interaction between environmental factors and a strong hereditary component. Environmental risks factors known to impact the development of T2D include obesity, sedentary lifestyle, small or large birth weight and stress. Other nutritional factors and toxins may also play a role[3]. These environmental factors clearly play a major role in the development of diabetes, but they do not impact everyone in the same way. Even with the same environmental exposures, some people are more susceptible to developing diabetes than others, and this increased risk appears to be inherited. But while hereditary factors clearly play a role in the development of diabetes, the actual genetic variants involved in this inherited risk were completely unknown prior to the advent of modern genetic technologies. The advance of human genetic studies in the 1980s finally made it possible to try and identify genetic loci that underlie this hereditary component. Here, we will re-

view the heritability of T2D and the various genetic loci identified to date as contributing to this heritability.

HERITABILITY OF T2D

Estimates for the heritability of T2DM range from 20%-80% and evidence for heritability comes from a variety of population, family, and twin-based studies[4,5]. The lifetime risk of developing T2D is 40% for individuals who have one parent with T2D and 70% if both parents are affected[6]. First degree relatives of individuals with T2D are about 3 times more likely to develop the disease than individuals without a positive family history of the disease[7]. The concordance rate in monozygotic twins is about 70% whereas the concordance in dizygotic twins has been observed to be only 20%-30%[8]. The observed familial risk is higher when studies are restricted to parents in the 35-60 year age range, indicating the greater role played by environmental factors in those who develop diabetes late in life[9]. It should be noted that a significant proportion of this heritability reflects heritability of obesity rather than diabetes, obesity being a major driver of T2D in every population.

This familial clustering of T2DM risk found in various family studies is not entirely due to genetic factors. Epigenetic processes can produce inherited risk over one or several generations, intrauterine and pregnancy related factors can impact the risk of siblings, and shared environment can be hard to control for in many such studies. Thus the genetic component of T2D may turn out to be less than what was estimated in older studies.

GENETIC ARCHITECTURE OF T2DM DISEASE RISK

The detailed genetic architecture of T2D risk has not yet been precisely defined. A relatively small percentage (5% or less) of non-autoimmune diabetes is due to monogenic causes and is classified as monogenic diabetes of the young or MODY (previously referred to as maturity onset diabetes of the young). These cases are understood to be caused by single genes of high penetrance, of which mutations in the Hepatocyte nuclear factor-1A (HNF1A) and the glucokinase (GCK) gene are the most common[10]. These forms of diabetes are sometimes misdiagnosed as T2D but clinically they are distinct diseases. They will not be considered further in this review but it should be kept in mind that the boundaries between polygenic and monogenic forms are not always sharply defined at the genetic level. Polymorphisms in genes involved in monogenic forms of diabetes also play a role in polygenic T2D[11].

T2D itself is thought to be a polygenic disorder that develops due to complex interaction between multiple genes and environmental factors. How these genes interact with each other and with the environment to produce T2D is still poorly understood. Unlike T1D, where the genetic risk is mostly concentrated in the HLA region, the genetic component of T2D risk is not concentrated in one region and appears to be the result of the interaction of multiple genes scattered all across the genome. It is possible; even likely, that the genetic component of T2D is due to multiple common genetic variants of small effect (common disease common variant hypothesis) but this is by no means certain and it may turn out that the effect is due to multiple rare variants or even a few rare variants of large effect[12-14].

IDENTIFICATION OF DIABETES RISK GENES

Linkage studies

Linkage is the tendency for genes and other genetic markers to be inherited together because of their location near one another on the same chromosome. While linkage analysis is simple in principle, it has relatively poor resolution as only a few hundred markers were usually genotyped across the genome, and the regions identified by linkage could include millions of base pairs and hundreds of genes. While these methods were quite successful in detecting rare variants of large effect (*e.g.*, classical single gene disorders), they proved relatively unsuccessful in identifying genes that are involved in complex polygenic disorders. These studies only revealed two genes, calpain 10 (*CAPN10*) and transcription factor 7-like 2 (T-cell specific, HMG-box) (*TCF7L2*) that were reliably identified as being associated with T2D.

***CAPN10*:** *CAPN10* encodes a cysteine protease that is part of the calpain family, a large family of ubiquitously expressed genes that play multiple roles in intracellular remodeling, post-receptor signaling and other intracellular functions. It became the first *T2D* gene to be discovered by linkage analysis when a locus on chromosome 2 was associated with T2D in 1996[15]. Initially the locus was labeled NIDDM1 but the gene (or genes) involved were not identified. In 2000 the causative gene was finally identified as *CAPN10*[16]. Subsequent studies did not always confirm this finding but larger meta-analyses have shown that variants in *CAPN10* are likely to be truly associated with T2D[17]. At this time the function of this gene in glucose metabolism remains unknown and its link to T2D, while confirmed in several populations, is not always consistent[18-20].

***TCF7L2*:** *TCF7L2* was discovered as a T2D susceptibility gene after a strong linkage signal was mapped to chromosome 10q in a Mexican-American population[21]. This region was later fine-mapped in the Icelandic population and confirmed in United States and Danish cohorts, where the risk locus was found to be located in intron 3 of the *TCF7L2* gene[22]. The association between T2D and a number of single-nucleotide polymorphisms (SNPs) in the *TCF7L2* gene has since been strongly confirmed in multiple Genome-wide association studies (GWAS) in different ethnic groups and this gene remains the most

replicated and most strongly associated T2D risk gene at this time[23]. We will discuss this gene further in the GWAS section of this review.

Candidate gene studies

In candidate gene studies, genes already suspected of playing a role in the pathogenesis of T2D were studied through focused sequencing efforts. The usual strategy was to focus on genes already known to be involved in glucose metabolism, insulin secretion, insulin receptors, post-receptor signaling and lipid metabolism. Somewhat to the surprise of investigators, most of the genes known to be involved in insulin secretion and action were not found to be associated with T2D in the population. The relatively few genes that were found to be associated with T2D include peroxisome proliferator-activated receptor gamma (*PPARG*), insulin receptor substrate 1 (*IRS1*) and *IRS-2*, potassium inwardly-rectifying channel, subfamily J, member 11 (*KCNJ11*), Wolfram syndrome 1 (wolframin) (*WFS1*), HNF1 homeobox A (*HNF1A*), HNF1 homeobox B (*HNF1B*) and *HNF4A*. Other genes including *RAPGEF1* and *TP53* were identified using an algorithm that prioritizes candidate genes for complex human traits based on trait-relevant functional annotation but have not been consistently replicated in later studies[24].

PPARG: *PPARG* gene was an attractive candidate gene for T2D because it encodes the molecular target of thiazolidenediones, a commonly used class of anti-diabetic medications. It was found that a proline to arginine change at position 12 in the *PPARG* gene led to a 20% increase in the risk of diabetes. This finding has since been confirmed in some other populations and other polymorphisms in this gene have been found to play a role in some cases of diabetes[25]. Even so, the significance of these mutations was not replicated in all populations and the contribution of these polymorphisms to the worldwide prevalence of diabetes remains low[26,27].

IRS1* and *IRS-2: Insulin receptor substrate *IRS-1* and *IRS-2* genes encode peptides that play an important role in insulin signal transduction. Polymorphisms in these genes were found to be associated with decreased insulin sensitivity in some populations[28,29] but as with other candidate genes, the role played by these polymorphisms in the global burden of diabetes and related insulin-resistance disorders like PCOS remains small.

KCNJ11: *KCNJ11* gene encodes the Kir6.2 ATP-sensitive potassium channel that plays an important role in the regulation of insulin secretion by beta cells. Activating mutations in this gene are a well-established cause of neonatal diabetes. A missense polymorphism in KCNJ11 was found to be associated with T2D and confirmed in subsequent studies[30]. The odds ratio of developing T2D is about 1.2 in carriers of the risk allele and this allele was also found to be associated with decreased insulin secretion in different populations[31-33].

WFS-1: *WFS-1* gene encodes Wolframin, a protein that is defective in individuals suffering from the Wolfram syndrome (characterized by diabetes insipidus, juvenile diabetes, optic atrophy, and deafness). *WFS1* gene appears to be involved in beta cell function and 2 SNPs in WFS-1 were found to be significantly associated with T2D in a large case-control study involving about 24000 samples[34]. This was subsequently confirmed in other studies in different populations[35]. These studies provided evidence that beta cell dysfunction plays a critical role in the development of T2D and pointed out novel genes that play a previously unknown role in beta cell survival and function, but their role in the global burden of diabetes remains minor.

HNF1A*, *HNF1B* and *HNF4A: *HNF1A*, *HNF1B* and *HNF4A* are all known MODY genes (*i.e.,* genes that harbor rare high penetrance mutations that cause monogenic diabetes of the young). These genes play a role in the development of the liver, in the regulation of hepatic metabolic functions, and in the development and functioning of beta cells. Variants in these genes that do not lead to MODY have been found to be associated with decreased insulin secretion and an increase in the risk of T2D in various populations, but as with other candidate genes, their role in worldwide diabetes prevalence appears to be relatively small[36-38].

Genome wide association studies

Candidate gene studies and linkage analysis identified a few T2D risk genes, but their overall contribution to the observed heritability of T2D remained small and it was clear that other techniques were needed to look for variants that were not easily identified by these methods. With the development of high-throughput SNP genotyping technology and the availability of Hapmap data, it became possible to scan hundreds of thousands of SNPs that were in linkage disequilibrium with millions of SNPs across the genome. TCF7L2, already identified *via* linkage studies, was the most significant and most replicated signal found in GWAS studies, but these studies also helped to identify scores of other genetic loci that appear to be linked to T2D[39]. Over the last 6 years, the number of known T2D variants has risen to over 60; including confirmation of variants identified earlier by candidate gene and linkage studies. While most studies have focused on Europid populations, this is being rectified as more studies of Asian, African and other populations become available.

Since obesity is a major contributor to the development of T2D, genes that increase the risk of obesity also show up in GWAS for T2D. These include some frequently replicated genes include like FTO and MC4R; these genes seem to primarily impact obesity risk and effect T2D risk mostly *via* their effect on obesity (though FTO may have a small but detectable influence on T2D risk independent of the risk of obesity). Here we will focus on genes that specifically increase the risk of T2D,

independent of obesity. The most important of these include

TCF7L2: This remains the most significant and consistently replicated gene linked to T2D. It was initially discovered by linkage studies, then confirmed in the very first large-scale GWAS study conducted in a French population by Sladek *et al*[40]. This publication was followed in quick succession by several other major GWAS paper, including the landmark Welcome Trust study that genotyped 2000 individuals with T2D along with 3000 controls and found that TCF7L2 was the most robust T2D signal, with an odds ratio of 1.36 for carriers heterozygous for the risk allele[41]. This finding was then replicated in almost every human population studied[42-48] and remains the most robust T2D risk gene identified to date. Carriers of the various identified risk alleles have an OR of 1.4[49] and homozygotes may have an OR of 2.5.

TCF7L2 encodes a transcription factor that is a member of the Wnt signaling pathway and is known to be active in the beta cells. Studies in multiple ethnicities indicate that the risk allele is present in intron 3 of the *TCF7L2* gene. An early investigation by Lyssenko *et al*[50] revealed that the risk alleles increased the level of TCF7L2 protein in beta cells and was associated with impaired insulin secretion, incretin effects and enhanced rate of hepatic glucose production. *TCF7L2* expression in human islets was increased 5-fold in T2D, particularly in homozygotes and overexpression of *TCF7L2* in human islets reduced glucose-stimulated insulin secretion. These findings were replicated in several subsequent studies, indicating that TCF7L2 probably plays a role in causation of T2D by decreasing insulin secretion from beta cells, perhaps by altering the action of incretins that modulate the insulin response to meals[51,52]. Other studies indicate that alternative splicing of this gene can lead to the production of different isoforms in different tissues and the presence of specific isoforms in adipose tissue may be related to insulin sensitivity in that tissue[53,54]. It is also possible that T2D risk is conferred by multiple mechanisms, including decreased beta cell insulin response and decreased insulin sensitivity in target tissues like adipose tissue. A recent murine study shows that, at least in mice, when *TCF7L2* is knocked out in liver cells it leads to hypoglycemia and when it is overexpressed it causes hyperglycemia, but there is no effect when it is knocked out in the beta cells[55]. This indicates that the liver may also be an important site where *TCF7L2* variants influence glucose metabolism. Finally, there are indications that this gene may play a role in cancer as well as in diabetes[56,57]. Thus, the discovery of its association with diabetes has opened up several new avenues of research and should eventually lead to the characterization of previously unknown physiological mechanisms that play a role in both diabetes and cancer.

HHEX: hematopoietically expressed homeobox (*HHEX*) While TCF7L2 remains the strongest T2D signal in GWAS studies from across the globe, several other genes have been repeatedly identified in different populations as being associated with T2D. *HHEX* was identified as one such gene in multiple studies in both Caucasian and Asian populations[58]. Located on chromosome 10q, this gene is also a member of the homeobox family and encodes a transcription factor involved in Wnt signaling. Risk alleles appear to confer an OR of developing T2D of 1.5. The mechanism by which this gene confers diabetes risk remains poorly understood.

SLC30A8: Solute carrier family 30 (zinc transporter), member 8 (*SLC30A8*). This gene encodes for a protein that is involved in the storage and secretion of insulin granules and that is expressed at a high level only in the pancreas, particularly in the islets of Langerhans[59]. This provides an obvious mechanism by which it may be involved in conferring T2D risk and this association has been replicated in multiple studies in different populations[60-62]. Interestingly, this gene has also been found to be associated with the development and progression of type 1 diabetes[63] though this has not been confirmed in all studies[64].

CDKN2A/B: Cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*). SNPs located upstream of the *CDKN2A2B* genes have been associated with the risk of T2D in multiple large GWAS. These genes are located on chromosome 9p21 and generate several transcript variants. At least three alternatively spliced variants of *CDKN2A* encoding distinct proteins have been reported, two of which are known to function as inhibitors of *CDK4* kinase. *CDKN2B* is also located in the same region and generates at least 2 splice variants. Both genes are important cell cycle regulators with a role in tumor suppression. This region was found to be associated with T2D in multiple GWAS studies in different populations and it is estimated that the risk alleles confer an odds ratio for development of T2D of between 1.2 and 1.5[65]. How variations in these genes alter diabetes risk remains unclear but recent research points to a role in insulin secretion rather than insulin action[66]. These variants also show up in GWAS for cardiovascular disease, in particular for atherosclerosis, but the mechanism underlying this association remains unknown[67].

IGF2BP2: insulin-like growth factor 2 mRNA binding protein 2 (*IGF2BP2*) encodes a protein that binds to the 5' UTR of the insulin-like growth factor 2 (IGF2) mRNA and thereby regulates IGF2 translation. Alternate transcriptional splice variants, encoding different isoforms, have been characterized[68]. This gene has been found to be associated with T2D risk in multiple GWAS[69,70]. As with other variants like HHEX and CDKN2A/B, it may play a role in beta cell function[65] but the mechanism by which it influences T2D risk remains largely unknown.

Other genes linked to T2D risk include *CDKAL1* (CDK5 regulatory subunit associated protein 1-like 1),

Table 1 Thirty-eight genetic variants associated with type 2 diabetes at genome-wide significance

Locus	Chr	Risk allele frequency	OR (95%CI)
NOTCH2	1	0.11	1.13 (1.08-1.17)
PROX1	1	0.5	1.07 (1.05-1.09)
IRS1	2	0.61	1.19 (1.13-1.25)
THADA	2	0.92	1.15 (1.10-1.20)
RBMS1/ITGB6	2	0.57	1.11 (1.08-1.16)
BCL11A	2	0.46	1.08 (1.06-1.10)
GCKR	2	0.62	1.06 (1.04-1.08)
IGF2BP2	3	0.29	1.17 (1.10-1.25)
PPARG	3	0.92	1.14 (1.08-1.20)
ADCY5	3	0.78	1.12 (1.09-1.15)
ADAMTS9	3	0.81	1.09 (1.06-1.12)
WFS1	4	0.27	1.13 (1.07-1.18)
ZBED3	5	0.26	1.08 (1.06-1.11)
CDKAL1	6	0.31	1.12 (1.08-1.16)
JAZF1	7	0.52	1.10 (1.07-1.13)
GCK	7	0.2	1.07 (1.05-1.10)
KLF14	7	0.55	1.07 (1.05-1.10)
DGKB/TMEM195	7	0.47	1.06 (1.04-1.08)
SLC30A8	8	0.75	1.12 (1.07-1.16)
TP53INP1	8	0.48	1.06 (1.04-1.09)
CDKN2A/B	9	0.79	1.20 (1.14-1.25)
TLE4	9	0.93	1.11 (1.07-1.15)
TCF7L2	10	0.25	1.37 (1.28-1.47)
HHEX	10	0.56	1.13 (1.08-1.17)
CDC123/CAMK1D	10	0.23	1.11 (1.07-1.14)
KCNQ1	11	0.61	1.40 (1.34-1.47)
KCNJ11/ABCC8	11	0.5	1.15 (1.09-1.21)
CENTD2	11	0.88	1.14 (1.11-1.17)
MTNR1B	11	0.3	1.09 (1.06-1.12)
KCNQ1	11	0.52	1.08 (1.06-1.10)
HMGA2	12	0.1	1.10 (1.07-1.14)
TSPAN8/LGR5	12	0.23	1.09 (1.06-1.12)
OASL/HNF1A	12	0.85	1.07 (1.05-1.10)
PRC1	15	0.22	1.07 (1.05-1.09)
ZFAND6	15	0.56	1.06 (1.04-1.08)
FTO	16	0.45	1.15 (1.09-1.22)
HNF1B	17	0.43	1.12 (1.07-1.18)
DUSP9	X	0.12	1.27 (1.18-1.37)

Modified from Florez *et al*[71].

HMGA2 (high mobility group AT-hook 2), *KCNQ11* (potassium voltage gated channel, KQT like subfamily, member 1) and *NOTCH2-ADAM30* (Notch 2-ADAM metallopeptidase domain 30). Their exact role in the pathophysiology of T2D remains mostly unknown. A list of these and other variants is given below in Table 1.

As can be seen in Table 1, the odds ratios for individual risk alleles are generally less than 1.3 (TCF7L2 and KCNQ1 being the most prominent exceptions) and it has been estimated that all the risk alleles identified to date can only explain about 10% of the observed heritability of T2D. Thus these alleles cannot be used to estimate the genetic risk of developing T2D in an individual patient with any degree of certainty since a simple family history will be much more informative than a detailed genotype at this point. But the discovery of these genes has opened entirely new avenues in our quest to understand the regulation of glucose metabolism and the development of T2D. For example, prior to these genetic studies, no one could have predicted that *TCF7L2* plays any role in glucose regulation. But initially *via* linkage studies, and then in multiple GWAS, it has been shown to be the single most significantly associated diabetes risk gene in the world. This has led to intensive investigation of its physiological role and though those investigations are at an early stage, it is hoped that they will eventually yield a new and more complete understanding of the mechanisms that regulate insulin secretion and action and whose alteration may lead to an increased risk for T2D. That in turn may lead to the identification of new drug targets, diagnostic tests, and targeted therapies (pharmacogenomics).

What do these genes do?

The fact that many of these genes are active in beta cells or may be involved in insulin secretion support the notion that beta cell dysfunction is a crucial final step on the path to diabetes[72,73]. Very few of these genes seem to play a role in insulin sensitivity (though that may change as more information becomes available) and genes involved in the insulin signaling pathway rarely show up in T2D GWAS studies. When indices of beta-cell function (HOMA-B) and insulin sensitivity (HOMA-IR) derived from paired fasting glucose and insulin measures from 37000 individuals were used to try and identify the function most affected by various T2D risk genes, it was found that risk alleles at ten loci (*MTNR1B*, *SLC30A8*, *THADA*, *TCF7L2*, *KCNQ1*, *CAMK1D*, *CDKAL1*, *IGF2BP2*, *HNF1B* and *CENTD2*) were associated ($P < 0.05$) with reduced beta-cell function, and only three loci (*PPARG*, *FTO* and *KLF14*) were associated with reduced insulin sensitivity[74].

It is possible that this may be because rare variants have a greater impact on insulin sensitivity or because environmental factors play a greater role in altering insulin sensitivity and thus swamp underlying genetic variation in risk. Still, this finding was not expected when candidate gene studies were initiated and shows how agnostic high throughput methods like GWAS can help to generate novel hypotheses and illuminate new aspects of biology. Some of the genes found to be associated with T2D also appear to be linked to dyslipidemia, atherosclerotic heart disease and cancer and it is possible that as we learn more about the role of these genes, we may be able to understand more about the relationship between T2D and other components of the metabolic syndrome as well as cancer[71].

Gene-environment interactions: It is abundantly clear that the risk of developing T2D is heavily influenced by environmental factors. Since our genetic code does not change significantly in one or two generations, the recent secular trend in diabetes must be due mostly to changes in the environment. Increased adiposity is the single most significant factor in the development of T2D and the epidemics of obesity and T2D largely parallel one another. The increasing prevalence of obesity is thought

to be related primarily to changes in dietary habits and our increasingly sedentary lifestyle, though other factors (including toxins and infectious agents) may play a role. Genes may influence the risk of diabetes not only by directly altering insulin action or secretion, but also by altering how any given individual interacts with these environmental factors. Even within the same broad environment, individuals vary greatly in their adoption of unhealthy lifestyles and their willingness to change such lifestyles. By influencing who adopts a more unhealthy diet (this includes genetic influence on taste and food preferences), who exhibits greater willingness to change unhealthy behaviors[75], who burns more calories at rest, who exhibits greater activity levels when not actively exercising, what kind of microbiome an individual carries, and who opts for a more sedentary lifestyle, genetic factors can play a role in determining who becomes obese or develops diabetes in any given environment[76]. These gene-environment interactions may be extremely complex and may be one reason why such a small proportion of the heritability of T2D has been explained at this time[77].

Epigenetics

Epigenetics refers to heritable changes in gene function that occur without a change in nucleotide sequence. Mechanisms like DNA-methylation, histone acetylation and non-coding RNAs are used by the cell to regulate gene expression in response to environmental cues and can persist for an individual's lifetime and can be passed on over 2-3 generations[78]. It is well known that the maternal environment and early infancy can alter the lifelong risk of chronic diseases. For example, infants who are born small for gestational age are at an increased risk for the development of obesity and T2D as adults. Some or most of this risk may be due to epigenetic changes in critical genes and animal experiments[79] and initial human studies suggest that such mechanisms may indeed explain the impact of intrauterine nutrition and birth weight of future risk of diabetes, obesity and metabolic syndrome[80]. It is thus possible that some of the observed heritability of T2D is due to epigenetic changes during intra-uterine life that are the result of maternal environmental influences, rather than inherited variations in the DNA sequence. As our understanding of epigenetics advances and as the ability to profile genome-wide DNA methylation and other epigenetic mechanisms becomes more widely used, we are likely to see important discoveries regarding the epigenetic changes that alter the risk of T2D. Epigenetic profiling may also help to identify novel genes that play a role in the pathogenesis of T2D just as GWAS led to the identification of multiple genes that were previously unsuspected of having a role in diabetes.

Risk prediction based on genetic information

While we know that a person's future risk of developing T2D has a significant heritable component and believe that most of this inherited risk is associated with particular genotypic features (in most cases, multiple variants of small effect?), and have identified several risk variants in genome-wide association studies, these variants still explain a relatively small proportion of the observed heritability. Several studies have found that a risk score based on traditional risk factors (BMI, family history, age, sex, HDL, triglycerides, *etc.*) consistently outperforms any set of genetic markers and the addition of known genetic markers does not significantly improve prediction based on traditional risk factors[81-83].

This indicates that our current state of knowledge regarding specific genetic markers is still incomplete and fails to explain most of the inherited risk. But as more data becomes available and better statistical techniques are applied to analyze gene-gene and gene-environment interactions, this predictive ability is likely to improve[84]. Even before that happens, these genetic discoveries have already provided important new insights into the pathophysiology of T2D and as the physiologic role of these genes in glucose regulation becomes clearer, these discoveries can be expected to lead to better diagnostic and therapeutic tools. Potential applications are not limited to better risk prediction, new drug targets and better targeted drug therapy; some time in the future when our technologies have improved far beyond current levels, they may include the ability to alter the risk of diabetes using gene-therapy or epigenetic reprogramming.

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