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Genetic risk scores in type 1 diabetes: from genetic risk to personalized medicine



ABSTRACT

Type 1 diabetes mellitus (T1DM) is a complex autoimmune disease with an estimated heritability of 65%-88%, in which genetics plays a fundamental role. Advances in genetics in recent years have made it possible to identify multiple T1DM risk variants, driving the development of so-called genetic risk scores, tools that integrate information from numerous genes to estimate an individual's probability of developing the disease. These tools have evolved from simple models comprising dozens of variants focused exclusively on the HLA system to high-resolution scores analyzing thousands or millions of genetic variants—known as *polygenic risk scores* (PRS), although in clinical and research practice both terms are often used interchangeably. These genetic scores have now demonstrated usefulness in different clinical and research settings. Their potential applications include early identification of individuals at higher risk of developing pancreatic autoimmunity, prediction of progression through the different preclinical stages of T1DM, diagnostic classification of complex cases of diabetes, and estimation of the risk of certain complications or patterns of clinical progression. Nevertheless, despite their potential, they still have important limitations (1). This article reviews the technological evolution of these scores and their direct impact on personalized care for people with diabetes.



» WHAT IS T1DM REALLY, AND WHY DOES IT DEVELOP?

T1DM is a chronic disorder in which the immune system mistakenly attacks the pancreatic beta cells responsible for producing insulin. As a result, the body progressively loses its ability to regulate blood glucose levels, and insulin treatment becomes necessary. We now know that its onset occurs long before blood glucose levels increase and symptoms appear. Thus, a silent autoimmune response may persist for years, detectable only through autoantibodies directed against the pancreas, while beta cells are progressively destroyed (1). (Figure 1). Therefore, identifying individuals in presymptomatic stages or those at greater risk of developing this autoimmune response would allow preventive measures to be implemented before clinical disease develops. In this context, genetics has become a fundamental tool because we now know that disease onset depends on a complex combination of genetic predisposition and certain environmental factors that remain incompletely understood.

WHY IS GENETICS SO IMPORTANT IN T1DM?

T1DM is one of the autoimmune diseases in which the influence of genetics has been most clearly demonstrated. There is no single “diabetes gene,” but there are genetic variants that significantly increase the probability of developing the disease. The importance of genetics was initially observed in family studies: first-degree relatives of a person with T1DM have a risk up to 10 times higher than that of the general population. Furthermore, among identical twins, if one develops T1DM, the other may have a risk of

up to 60%, confirming that genetic predisposition is fundamental (1).

Currently, more than 90 genetic regions associated with T1DM risk have been identified. The most relevant is located within the HLA system on chromosome 6, which is involved in the immune response and accounts for up to 50% of the total risk of T1DM. In particular, the HLA DR3-DQ2 and HLA DR4-DQ8 haplotypes markedly increase risk, whereas other variants may be protective. In addition to the HLA system, many other genes are involved, although each of these variants generally has only a very small individual effect. The combination of all these genetic variants can substantially modify individual risk.¹ This has made genetic risk scores possible: tools that integrate multiple variants to estimate the probability of developing T1DM. Indeed, in several studies these scores have enabled identification of up to 85%-90% of patients who will develop the disease, even in the absence of a family history.² Although they are not routinely used in clinical practice, they represent a highly promising pathway toward more preventive and personalized medicine.

GENETIC RISK SCORES: WHAT DOES HAVING A PREDISPOSITION REALLY MEAN?

Having a genetic predisposition does not mean that a person will develop the disease. Most individuals with genetic risk will never develop it because genetics does not act alone; environmental factors that are still not well defined also play a role. Therefore, predisposition should be understood as an »

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STAGE	CLINICAL/METABOLIC CHARACTERISTICS	CLINICAL RELEVANCE
Stage 1	Presence of at least 2 autoantibodies with normal glucose levels.	Enables identification of individuals in the presymptomatic phase.
Stage 2	Presence of at least 2 autoantibodies with mild glucose abnormalities.	Critical phase for intervention before clinical progression.
Stage 3	Presence of at least 1 autoantibody with elevated glucose levels.	Represents overt clinical disease.

Figure 1. Clinical stages of autoimmune diabetes progression.

GRS model	No. of variants	Main population/setting	Key utility	Reported performance
Winkler Score (10)	41 SNPs	General population	Initial prediction of T1DM	87%
Exeter T1DM-GRS (3, 4)	30 SNPs	Mainly European populations	T1DM vs monogenic diabetes; T1DM vs T2DM	87% and 88%
Combined GRS (Winkler + T1DM-GRS) (5)	Combination of both models	Children with high-risk HLA and no family history	Prediction of presymptomatic autoimmunity	Identifies 10% at risk in this subpopulation
T1DM-GRS2 (6)	67 SNPs	European populations	Population screening, detection of autoantibodies, and presymptomatic T1DM	92% (population screening)
Virginia PrIMeD (7) (8)	74 SNPs	Diverse populations	Pediatric screening using saliva samples	~89%
GenProb-T1DM (8)	Based on PGST1DM and PGST2DM	Atypical or ambiguous phenotypes	T1DM vs T2DM	91%
T1DM MAPS (9)	38 HLA haplotypes + 1 million non-HLA variants	Multi-ancestry populations	Prediction in non-European and European populations	90% in non-European populations; 89% in European populations

Figure 2. Genetic risk score models.

Abbreviations: GRS, genetic risk score; SNP, single nucleotide polymorphism. Reported performance cannot be directly compared across studies because of differences in cohorts, study design, and clinical objectives. From the initial models based on common variants, such as the Winkler Score, which was based on 41 SNPs and was able to predict T1DM in the general population with a performance of 87% (10), or the Exeter T1DM-GRS model, based on 30 SNPs and focused mainly on the highest-risk HLA haplotypes and several non-HLA genes, with a discriminatory performance of 87% for distinguishing T1DM from monogenic diabetes and 88% for distinguishing T1DM from T2DM (3,4), GRS models have progressively evolved toward more refined approaches. Bonifacio et al. combined the Winkler Score and T1DM-GRS, improving prediction of T1DM in children with high-risk HLA and no family history by identifying individuals with a risk >10% of developing presymptomatic autoimmunity, doubling the performance achieved with HLA alone (5). Subsequently, the Exeter model was optimized into T1DM-GRS2, based on 67 common variants, which more comprehensively incorporates HLA alleles through interactions together with new non-HLA alleles and currently represents the standard in European populations, with a discriminatory performance of 92% for population screening. It is also useful for distinguishing T1DM from T2DM and for detecting autoantibodies and presymptomatic T1DM in adults during preclinical stages (2, 6). However, its performance decreases in other ethnic groups, with a reported performance of 82% in non-European populations. Other models, such as Virginia PrIMeD, have attempted to reduce this bias through a 74-SNP score designed for diverse populations, including individuals of European and African ancestry, and applicable to pediatric screening using saliva samples, with predictive performance close to 89% (7). More recently, GenProb-T1DM incorporated extended genetic risk scores based on millions of variants to distinguish T1DM from T2DM in atypical or ambiguous phenotypes, achieving a performance of 91% and maintaining similar performance across different ethnic groups, although with lower performance in external validations (8). Finally, T1DM MAPS represents a multi-ancestry approach incorporating 38 HLA haplotypes and 1 million non-HLA variants, with improved prediction in non-European populations and high performance in European populations after adjustment for ancestry (9).

» increased probability rather than an inevitable outcome (1).

To estimate this risk, researchers have developed genetic risk scores (GRS), which combine the effects of multiple genetic variants. These tools have evolved from simple models to more complex and precise systems useful for classification, prediction, and selection of populations for surveillance (Figure 2). However, most have been developed in populations of European ancestry, and their performance may be reduced in other ancestry groups. Although more advanced GRS improve prediction and early detection, none can determine with absolute certainty who will develop

T1DM. Their main value lies in identifying individuals with a higher probability of developing the disease who could benefit from closer follow-up or early-detection programs (1, 2).

USEFULNESS OF GENETIC RISK SCORES FOR PREDICTING THE RISK OF DEVELOPING T1DM

T1DM does not begin when symptoms appear, but much earlier, with a silent autoimmune process in which autoantibodies can already be detected even though glucose levels remain normal. In this context, genetic risk scores make it

possible to identify individuals with a higher probability of developing the disease even years before clinical diagnosis. Several studies have shown that these scores help predict who will develop autoantibodies, who will progress to T1DM, or who may develop it at younger ages (2, 3, 9). This information has important clinical value because it enables the selection of candidates for autoantibody surveillance programs or metabolic monitoring, reduces the risk of diagnosis presenting with diabetic ketoacidosis—a potentially serious and frequent complication at diagnosis—and facilitates early preparation of families, as well as access to diabetes education and future preventive therapies (1).

» USEFULNESS FOR PREDICTING PROGRESSION BETWEEN THE PRECLINICAL STAGES OF T1DM

Not all individuals with T1DM progress at the same rate once the autoimmune process has begun. Some remain in early stages for years without glucose abnormalities, whereas others progress more rapidly toward clinical diabetes (1). Genetics can help identify individuals with a greater genetic risk burden and therefore a higher probability of developing multiple autoantibodies and progressing earlier to clinical disease (2). This information is useful for determining who requires closer follow-up and more frequent monitoring. In addition, this predictive capacity may be particularly valuable for selecting candidates for new immunomodulatory therapies designed to delay the onset of clinical T1DM (1).

USEFULNESS FOR CORRECTLY CLASSIFYING COMPLEX CASES

Although diabetes is generally divided into categories, distinguishing between T1DM, type 2 diabetes (T2DM), and other less common forms can be difficult in clinical practice, particularly in adults. Some cases have atypical courses, such as adults with slowly progressive T1DM and persistent insulin production, or patients with T2DM who experience weight loss or require insulin early. These cases may also be confused with monogenic diabetes, LADA, or ketosis-prone forms of diabetes, potentially leading to diagnostic errors and delays in appropriate treatment, increasing the risk of metabolic decompensation and complicating clinical follow-up. In this context, T1DM genetic risk scores are proving useful for more accurately distinguishing between T1DM and T2DM, particularly in patients with an ambiguous clinical presentation. In general, T1DM is associated with a greater genetic burden related to autoimmunity, whereas in T2DM this predisposition is considerably lower. These tools are particularly useful in young adults with characteristics intermediate between T1DM and T2DM, suspected cases of LADA, patients initially diagnosed with T2DM who progress rapidly to insulin dependence, and children or adults with suspected monogenic diabetes or unclear clinical presentations (1, 3, 4, 6, 8).

USEFULNESS FOR PREDICTING CLINICAL PROGRESSION AND DEVELOPMENT OF COMPLICATIONS

In addition to estimating the risk of developing T1DM and its progression, genetics could provide information on how the disease will evolve once diagnosed. Some studies have described associations between genetic variants and parameters such as glycemic control, loss of insulin production, and the risk of long-term complications, suggesting that genetics may help explain part of the clinical variability among patients with T1DM. Associations have been observed between certain variants and HbA1c levels, as well as with microvascular complications such as retinopathy and nephropathy.¹ However, these findings should be interpreted with caution because factors such as disease duration, glycemic control, and cardiovascular risk remain the main determinants. Genetics probably acts as an additional modifier but does not replace the importance of metabolic control and healthy lifestyle habits. Genetic risk scores could also be useful for identifying individuals at greater risk of diabetic ketoacidosis at diagnosis, facilitating targeted early-surveillance programs.

INTEGRATION OF DATA FOR MORE ACCURATE PREDICTION IN T1DM

Overall, combining genetic information with autoantibodies, family history, metabolic parameters, and clinical data will enable the generation of models that substantially enhance the predictive capacity of genetic risk scores and represents one of the most promising strategies for understanding the individual course of T1DM and providing more individualized follow-up. Nevertheless, although these advances are highly promising, their use remains focused mainly on research and they are not yet part of routine management in most health care systems.

CURRENT LIMITATIONS OF GENETIC RISK SCORES FOR T1DM

Although genetic risk scores have advanced considerably in the study of T1DM, they still »

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» have important limitations that hinder their routine use in clinical practice. Their main limitation is that they cannot predict with absolute certainty who will develop the disease; having a high genetic risk burden increases the probability, but many individuals at high risk never develop T1DM, whereas many diagnosed individuals have a relatively low genetic predisposition. For this reason, they should be combined with other clinical biomarkers or environmental factors such as age, family history, BMI, and others to increase their usefulness (1).

Another important limitation is that most genetic risk scores have been developed in populations of European ancestry, reducing their accuracy in other ethnic groups because of differences in the structure and frequency of genetic variants across populations and limiting the universal applicability of some current models. Although some researchers have attempted to overcome this limitation using more complex or extended models, there remains considerable room for improvement because large cohort studies in populations of non-European ancestry

are still lacking (8, 9). In addition, these extended models, although generally highly accurate, require costly genetic and bioinformatic techniques and are not widely available across all health care systems.

Furthermore, there are interpretative barriers because specialists in genetics and bioinformatic analysis are required to obtain and interpret the results, involving professionals with specific training in a specialty that is not yet officially recognized within our healthcare system. In addition, there are ethical and psycho-»

» logical barriers because the use of genetic information raises important ethical issues, and communicating a high level of risk may generate anxiety for patients and their families if it is not accompanied by appropriate medical counseling, par-

ticularly when no definitive preventive strategies are yet available that can completely prevent the disease.

Nevertheless, these tools have considerable potential and could become a key

component of prevention, early diagnosis, and personalized medicine in T1DM. The major challenge will be ensuring that these advances can be incorporated safely, equitably, and effectively into real-world clinical practice. **D**

CONCLUSIONS

- T1DM is a complex autoimmune disease in which genetics plays an important role but does not, by itself, determine whether the disease will develop. Genetic risk scores integrate multiple variants to estimate individual risk and represent a highly promising tool for more personalized medicine.
- These scores could help identify individuals at higher risk at an early stage, predict disease progression, and reduce serious complications through surveillance and early detection. They may also be useful for classifying complex cases of diabetes and improving the differential diagnosis between T1DM, T2DM, and other less common forms of diabetes.
- Although technical, economic, and ethical limitations remain, advances in genetics are progressively changing the way T1DM is understood, predicted, and managed.

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