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Clinical and research uses of genetic risk scores in type 1 diabetes

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Abstract

Type 1 diabetes (T1D) is a chronic disease of high blood glucose caused by autoimmune destruction of pancreatic beta cells eventually resulting in severe insulin deficiency. T1D has a significant heritable risk. Genetic associations found are particularly strong in the HLA class II region but T1D is a polygenic disease associated with over 60 loci across the genome. Polygenic risk scores are one method of summing these genetic risk elements as a single continuous variable. This review discusses the clinical and research utility of genetic risk scores in T1D particularly in disease prediction and progression. We also explore creative uses of genetic risk scores in big data and the limitations of using a genetic risk score. The increase in publically available genetic data and rapid fall in costs of genotyping mean that a T1D genetic risk score (T1D GRS) is likely to prove useful for disease prediction, discrimination, investigation of unusual cohorts, and investigation of biology in large datasets where genetic data are available.

Introduction

Type 1 diabetes (T1D) is an autoimmune disease caused by destruction of insulin producing pancreatic beta cells leading to severe insulin deficiency [1, 2]. Multiple interacting factors are known to contribute to the development of autoimmunity, beta-cell loss and subsequent development of clinical T1D. These include a background genetic risk, infant and adult diet, environmental exposure, beta-cell stress and immune phenotype.

This review explains how measurable genetic risk for T1D can be combined into a single score using established methods for polygenic disease. This facilitates assessment of T1D genetic risk as a continuous measure in many clinical and research settings. The increase in publically available genetic data and rapid fall in costs of genotyping mean that a T1D

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genetic risk score (T1D GRS) is likely to prove useful for T1D prediction and classification, investigation of atypical diabetes cohorts, and investigation of T1D classification and biology in large datasets where genetic data are available

Type 1 diabetes has a strong heritable genetic component

Twin concordance for T1D is 23%-70% [2, 3] with risk of 6-7% for siblings, 1-4% for maternal and 6-9% for paternal inheritance [4, 5]. The dominant genetic drivers of this risk are Class 2 HLA *DR* and *DQ* genes on chromosome 6 that encode cell surface proteins that present peptides on antigen presenting cells [6-8]. The HLA haplotypes *DRB1*03:01* – *DQA1*05:01* – *DQB1*02:01* (commonly referred to as *DR3*) and *DRB1*04:XX* – *DQA1*03:01* – *DQB1*03:02* (commonly referred to as *DR4-DQ8*) are the two most significant risk haplotypes, with highest genetic risk for T1D occurring in the compound heterozygote (average odds ratio (OR) 17) [9]. Risk is lower for homozygote combinations and again lower for those with a single copy of *DR3* or *DR4-DQ8* [8]. These are common in the white Caucasian population (~4.5% and ~12.5% respectively [9]) and 85% of those with T1D have at least 1 of these haplotypes present. Strong protection from T1D also occurs with certain HLA Class II haplotypes including *DRB1*15:01* – *DQA1*01:02* – *DQB1*06:02* (commonly referred to as *DR15-DQ6.2*) which is common in white Caucasians (12%) and reduces risk of T1D over 20-fold (OR 0.03) [8]. As HLA class II alleles confer 50% of heritable risk in T1D, Class II HLA typing (originally by serology, then by DNA probe technology, now by Sanger sequencing and Next Generation Sequencing) has been the commonest method to assess genetic predisposition to T1D in research studies [10, 11].

HLA class 1 alleles, whose expression can be induced in most cells, and are able to present antigen to T-cell receptors, and several have been independently associated with development of T1D even when adjusting for HLA class II. These include *A*24* that is associated with both T1D risk and progression of beta-cell loss [12-14], *B*3906* that has been shown to modulate risk when present only with specific class 2 haplotypes [15] and *B*57* [16]. Finally, more than 60 common non-HLA T1D risk variants across the genome have been identified in linkage and genome wide association studies (GWAS) in genes including *INS*, *PTPN22*, *CTLA-4* and *IL2RA* [17, 18] (<http://www.immunobase.org/disease/T1D/>) (see Figure 1). The majority of these risk alleles have odds ratios less than 1.3 and although discovery of these variants has helped define important potential mechanisms of T1D, the presence of any one of these variants in individuals has a very modest individual effect on overall risk of T1D.

Progress in genetic research, recently led by large collaborative consortia [19] (T1DGC, <https://www.wtccc.org.uk>, <http://www.t1dbase.org/disease/T1D/>) has led to identification of pathways that are involved in the pathogenesis of T1D and pathways that are important for different stages of disease. Use of the vast accumulated genetic knowledge over the last 40 years of research for direct patient benefit, either by aiding diagnosis, improving disease prediction, or identifying T1D endotypes that may respond to specific treatments, has been modest outside of specific research settings [20]. Genetic testing for T1D risk is not part of routine clinical care. This may in part be due to very modest individual risk effects of non-

HLA SNPs, historic expense in genotyping HLA alleles and SNPs, lack of available working treatments and a lack of widespread understanding of the complex HLA nomenclature.

Polygenic disease risk can be measured using genetic risk scores

Early attempts to use genetics to predict T1D stratified people into broad categories such as high, intermediate and low risk[4, 21]. These attempts essentially ascribed categorical risk based on presence of *DR3* and/or *DR4-DQ8* and did not describe the different T1D risk associated with each allele combination or the presence of any other genetic information. This type of approach underrepresents the discriminative power of genetic information by not quantifying the risk associated with *DR3* and *DR4-DQ8*, not measuring other significant HLA risk, and not including non-HLA alleles. Since the advent of GWAS (e.g. [17, 22, 23]) and the large number of low odds ratio variants associated with common disease that have been discovered, scores that sum polygenic risk have been developed and tested for disease stratification and prediction[24]. These have been used in a wide variety of diseases including type 2 diabetes (T2D) [25] and cardiovascular disease [26] and offer an opportunity to better measure and quantify genetic risk.

There are many ways to generate a genetic risk score ranging from summing the number of risk alleles, log-additive models that consider the sum of alleles adjusted for effect magnitudes to more complex approaches involving gene-gene interaction modelling and genome-wide statistical learning approaches [27]. Where the outcome is binary disease status, logistic regression models can be used to determine the relative effect size of each locus included in the genetic risk score. Receiver operator characteristic area under the curve (ROC AUC) analysis is often used to assess discriminative or predictive power [28] with an AUC close to 1 indicating near perfect sensitivity and specificity and an AUC of 0.5 equivalent to the flip of a coin.

Genetic risk scores are theoretically likely to be useful in HLA linked autoimmune diseases such as T1D as the heritability is high and the disease prevalence modest [29]. The majority of the genetic risk can be often captured with a small number of SNPs [30, 31] that tag high odds ratio HLA alleles. Given that a significant proportion of the genetic variance can be captured with a modest number of SNPs, and the costs of genotyping individual SNPs has fallen dramatically, a genetic score may in the future be an easy and inexpensive tool for assessment of genetic risk and additionally can often be generated from publically available genotype array data without need for new assay design. Additionally, a genetic risk score, weighting for the relative contribution of each locus, allows expression of genetic risk as a continuum and more complete use of genetic information.

Genetic risk scores can be used for T1D prediction: Improved prediction over HLA typing, but require caution in healthy individuals

One method to better understand, predict and in future prevent T1D is to identify people in early life who will go on to develop T1D in the future. This allows study of early life factors such diet, exposure to infections, and the developing infant-maternal immune systems [32] that are implicated in pathogenesis but poorly understood. Initiation of autoimmunity, as

measured by incidence of autoantibodies, most commonly occurs in early life but there is normally a gap of many years (2 to more than 15) prior to clinical presentation of T1D [33]. Once a preventive therapy becomes available this offers a window of opportunity to intervene prior to T1D onset but early identification of those at risk of T1D is necessary [34, 35].

Winkler and colleagues first showed a genetic score of non-HLA risk alleles modestly improved T1D prediction [36] but more recently demonstrated the addition of HLA SNPs offered best prediction of T1D [37]. Steck similarly showed that addition of PTNP22 and UBASH3A typing to HLA typing improved T1D risk prediction in the DAISY cohort [38]. Winkler et al used multivariate logistic regression and Bayesian feature selection to generate a weighted genetic score from 2 HLA and 9 non-HLA SNPs (*DR3/4* status plus *PTPN22*, *INS*, *IL2RA*, *ERBB3*, *ORMDL3*, *BACH2*, *IL27*, *GLIS3*, and *RNLS*) in the type 1 diabetes genetics consortium dataset (T1DGC). They then validated the score as a predictive tool in two additional cohorts [39, 40] and showed that predicted progression to T1D or multiple islet autoantibody positive status with ROC AUC of 0.84-0.87. Their results highlighted a problem with prediction of rare diseases, coined the “prevention paradox” [41], where even those at highest genetic risk of disease are more likely to not develop future disease than develop future disease. Winkler’s study showed that even people with an extremely high-risk score that was 99.5% specific only had a positive predictive value of 19.5% for future T1D. Since Winkler and Steck’s studies, Fronhart and colleagues have used the Winkler 10 factor model in DAISY [42] and shown that differences in predictive power of genetic scores may occur when comparing general population cohorts to first degree relative cohorts. Recent analyses by Bonifacio [43] in TEDDY and in the Trialnet pathway to prevention study (personal communication Redondo / Oram) using scores confirm the utility of genetic scores and underline their likely future role in T1D prediction and birth cohort studies [35].

Genetic risk scores can be used to discriminate type 1 diabetes from type 2 diabetes

Classification of diabetes into the two main subtypes is becoming an increasing problem as increasing obesity means more T2D is presenting in teenagers and young adults, and there are more obese people with T1D in line with increases with the general population. Classification with either clinical features and or autoantibodies alone still does not diagnose all individuals correctly [44, 45]. This matters as individuals with T1D will require insulin treatment whereas those with other forms of diabetes can often be best treated with diet or oral antihyperglycemic agents. There is almost no overlap in the genetics of T1D and T2D and genetic risk could therefore be used as a diagnostic tool. We first tested the discriminatory ability of a 30 SNP T1D GRS containing HLA and non-HLA loci in gold standard T1D and T2D patients from the WTCCC [22, 46]. We used a log additive model weighted for odds ratio in GWA studies, and included the common protective HLA class 2 (*DR15-DQ6.2*) and class 1 HLA risk alleles. The T1D GRS was highly discriminative (ROC AUC 0.87-0.88) of T1D in WTCCC T1D v T2D cases and in a local cohort of cases in the age overlap between T1D and T2D (age 20-40) with T1D defined by insulin deficiency. In contrast, addition of a T2D genetic score of 69 variants added little to the discrimination.

A combined regression model including age of diagnosis, BMI, autoantibodies and the T1D GRS offered near perfect prediction of T1D (ROC AUC 0.96) and showed the most accurate clinical diagnosis in the future may be with a combined model using these features [20] (see Figure 2). Despite a simpler method of calculation, the discriminative power of the T1D GRS was greater than other published scores due to the addition of the common, strongly protective *DR15-DQ6.2* HLA haplotype, additional class 1 HLA alleles, and the weighted use of non-HLA risk SNPs. Similarly to Winkler we showed that the majority of discriminative power is from the top 10 SNPs and this highlights how the inexpensive genotyping of 10 SNPs could be implemented as a diagnostic test in the future.

Genetic risk scores can be used to discriminate type 1 diabetes from controls and can be used to classify unusual groups of patients

Patel et al showed, that the 30 SNP T1D GRS could be used to discriminate monogenic diabetes from T1D [47]. Patel analysed the T1D GRS in 805 patients with MODY and 1963 controls and showed a high T1D GRS (>0.280 , 50th centile of T1D) was indicative of T1D (see Figure 3). Patel additionally studied 242 white Europeans with neonatal diabetes (NDM) and showed that score category predicted a monogenic aetiology with 90%, 59% and 8% of patients in the GRS categories of $<5^{\text{th}}$, 50th-75th and $>75^{\text{th}}$ T1D centile. This analysis highlighted a group of patients diagnosed under the age of 6 months with very high T1D genetic risk and monogenic disease who are likely to have extremely early onset T1D. This study demonstrated the utility of measuring T1D genetic risk as a continuous distribution when assessing unusual cohorts, and this method could be used in other settings to estimate the amount of T1D in other difficult to classify subgroups and to prioritise individuals for more expensive genome sequencing efforts.

Creative use of genetic risk scores in large datasets

The use of SNP array data in large publically available population datasets is beginning to allow the investigation of diabetes aetiology without the requirement for prohibitively expensive biomarker measurement. It has been suggested that T1D presents throughout life [48], but due to an excess of T2D cases in adulthood, the incidence of older onset T1D has been difficult to define and assess [49]. Thomas et al generated the T1D GRS in 379,511 people (13,250 with self-reported diabetes diagnosis before the age of 60) from UK Biobank to address the issue of how much T1D presents in later life [50]. Thomas identified T1D genetically, by calculating the excess of cases in those with high ($>50^{\text{th}}$ centile T1D GRS) compared to low T1D genetic risk ($<50^{\text{th}}$ centile). A survival analysis stratified by T1D GRS (above or below 50th centile) showed that that T1D is common in later life with 42% of genetically defined T1D occurring after the age of 30. As the analysis did not define T1D with clinical criteria, Thomas was able to study phenotype in the genetically defined T1D and show these cases had a very similar clinical presentation to those diagnosed at younger ages. This highlighted the power of studying genetic associations in large population datasets, and that there may be many ways this can help our understanding of disease.

Despite the described benefits and uses of genetic risk scores for diabetes research and clinical testing, there are some important limitations with current methods

Table 1 provides an overview of the advantages and disadvantages of polygenic risk scores in T1D. Thus far, discovery and validation of T1D associated genetic variants has focused mainly on Caucasian populations. Other ethnic groups have different frequencies of key risk and protective alleles, and potentially different SNP associations with HLA alleles [51-53]. The utility of genetic risk scores in non-white Caucasian ethnicities needs to be tested and likely refined according to ethnicity.

It is clear that there are environmental interactions with genetic factors [54] and that odd ratios for individual HLA alleles and SNPs can vary by population irrespective of ethnicity [9]. This raises a question of whether genetic risk scores should be optimised for each population, environment and ethnicity. The answer to this lies in a trade-off between pragmatism and precision. Current T1D GRS models will be improved by increasing precision, per-population, and environmental adjustments, however even with current limitations T1D genetic risk scores are highly predictive and discriminative for T1D. A single validated tool, tested in multiple settings with a single numeric output akin to a T1D probability, may be more translatable into clinical care than multiple scores used for different populations and different settings.

Conclusions

Over the past 10 years large-scale genome-wide association studies have provided a substantial in our understanding of the role of common genetic variation in complex human diseases such as diabetes [18, 19, 22, 55, 56]. These have provided important new insights into disease mechanism, but despite dramatic reductions in the cost of genotyping, direct impact on clinical care and utility for clinically focussed research questions has lagged behind. Genetic risk scores allow summation of T1D genetic risk into a score that can be used to aid diagnosis, the identify those at risk of T1D from birth, and to investigate diabetes aetiology in large cohorts using cheap SNP typing or SNP array data. These exiting translational opportunities are built on the hard groundwork undertaken to discover the genetic associations of T1D over the last 40 years.

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Figure 1. Manhattan plot of variants associated with T1D [19]

Manhattan plot showing associations of genotyped and imputed variants across the autosome in T1DGC. As the logarithmic scale demonstrates the HLA signal is the most dominant association.

Figure 2. ROC-AUC Comparisons [46]

A series of ROC analyses demonstrating that the T1D GRS is an additive and independent predictor of insulin deficiency in young adults with diabetes when compared with known biomarker and clinical discriminators. AAD, age at diagnosis; ABS, autoantibody status for GAD and IA-2; ALL, T1D GRS, BMI, age at diagnosis, and autoantibodies as predictors.

Figure 3. Dot plots of T1D GRS stratified by disease [47]

Those without diabetes, with T2D, and those with maturity onset diabetes of the young (MODY) all have similar and significantly lower T1D GRS than people with T1D.

Table 1

Advantages and Limitations of Polygenic risk scores in T1D

Advantages	Limitations
Simplifies genetic risk into a single number and allows non-HLA familiar to interpret	SNPs alone not accurate enough to replace formal HLA typing for clinical use (e.g. transplantation)
Expresses genetic risk as a continuum thus easier to model or combine with other data	Validation thus far limited mostly to white Caucasians, further validation needed in other ethnicities
More discriminative of T1D than either HLA or non-HLA loci alone	Limited by ability of chip assays to capture highly polymorphic regions such as HLA
As genetic risk is permanent cross-sectional studies can be used to assess utility of assessment in early life	Accuracy limited by study size of discovery data or training data
Cheap to genotype and often data available on SNP array data	
Little/no measurement variation between assays unlike other biomarkers	
Validation across different cohorts possible due to ease of measurement	