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Current Opinion in Genetics & Development

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

Seth A Sharp[1], Michael N Weedon[1], William A Hagopian[3] and Richard A Oram[1,2]

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.

Addresses
[1] Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, UK
[2] The Renal Unit, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK
[3] Pacific Northwest Research Institute, Seattle, WA, USA

Corresponding author: Oram, Richard A (r.oram@exeter.ac.uk)

Current Opinion in Genetics & Development 2018, **50**:96–102

This review comes from a themed issue on **Molecular and genetic basis of disease**

Edited by **Ines Barroso** and **Jose Florez**

https://doi.org/10.1016/j.gde.2018.03.009

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, other environmental exposures, 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 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 most common 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. Several have been independently associated

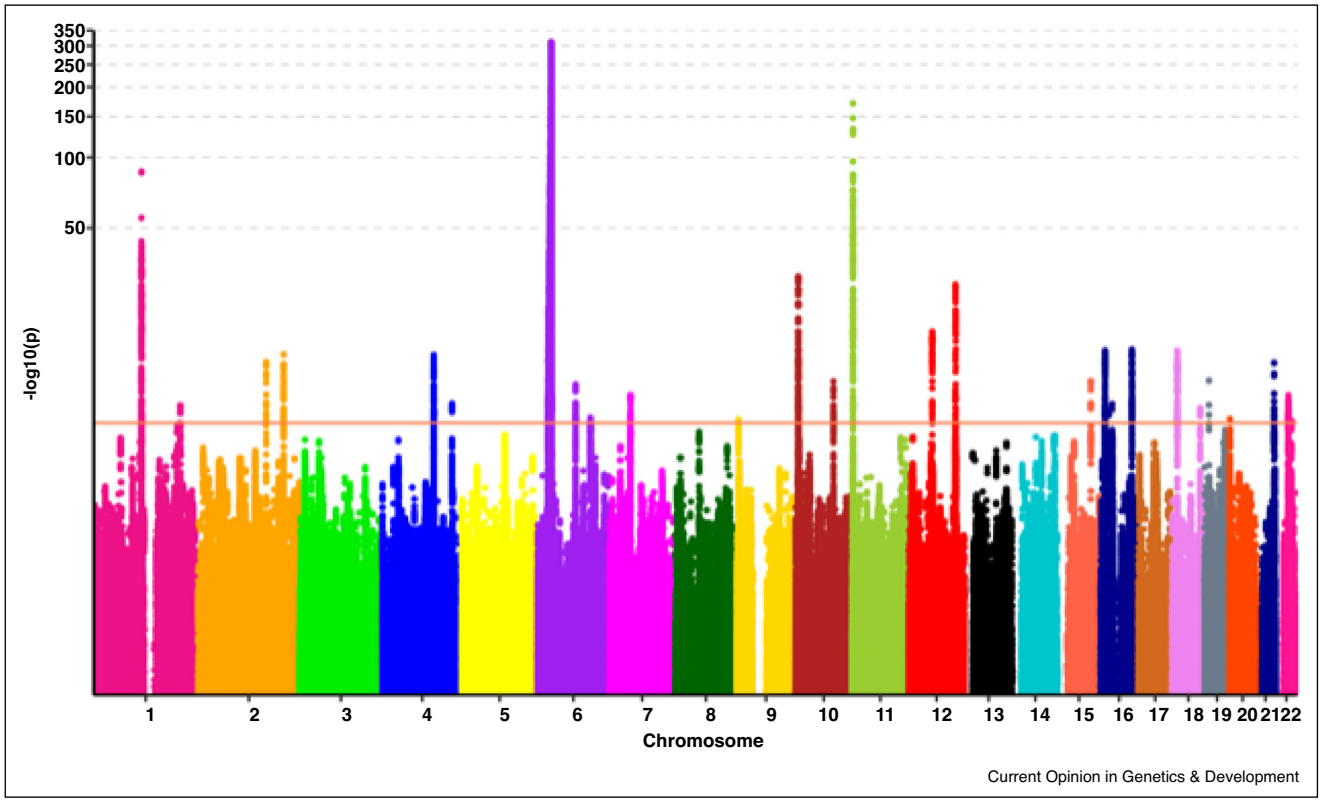
with development of T1D even when adjusting for linkage disequilibrium with HLA class II. These include *A*24* that is associated with both T1D risk and progression of beta-cell loss [12–14], *B*3906* that has been shown to modulate risk when present only with specific class 2 haplotypes [15] and *B*57* [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. 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

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.