Genetics Coming of Age in Type 1 Diabetes

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Decades of studies demonstrate that ~50% of risk for type 1 diabetes (T1D) is heritable (1). The first loci linked to T1D were the HLA genes that have the largest effect size of any T1D susceptibility locus, followed by linkage of the insulin VNTR to T1D (2,3). Linkage studies have given way to genome-wide association studies (GWAS) that have identified >50 loci that contribute risk for developing T1D (4). Most of these loci impart modest relative risk for T1D (odds ratio ≤2.0) and together with HLA account for ~80% of the heritability of T1D (5). The question remains: have GWAS delivered in terms of our ability to understand the causes of T1D and thus identify therapeutic targets or predict disease course?

GWAS have revealed several important aspects of T1D disease etiology. First, the majority of genes associated with T1D function in the immune system, underscoring the immune basis of disease initiation and progression (6). Second, GWAS have identified pathways that are important in disease pathogenesis, such as variants in the interleukin-2 (IL-2) signaling pathway (*IL2*, *IL2RA*, and *PTPN2* loci) that are associated with disease (4,7,8). Third, T1D GWAS studies have identified a shared genetic architecture with other autoimmune diseases (e.g., *PTPN22*, *CTLA4*, *SH2B3*, *TYK2*, and *CLEC16A* loci), indicating common pathogenic mechanisms and the possibility of repurposing therapies for T1D that are in use for other autoimmune diseases. Additionally, genotype-phenotype studies have provided important windows into disease pathogenesis by revealing alterations in B-cell and T-cell development, tolerance checkpoints, regulatory T-cell fitness, and cytokine signaling (9–15).

Several recent articles in *Diabetes Care* describe the use of genetics to improve diagnosis and prediction of disease progression in T1D as well as progression to insulin use in type 2 diabetes (T2D).

Using data from the TrialNet Pathway to Prevention Study, Triolo et al. (16) evaluated genetic risk for islet autoimmunity and T1D based on twin and sibling analysis. They report that 62–69% of identical twins with at least one autoantibody (AAb) will develop clinical T1D within 3 years. Accumulated data from multiple studies suggest that essentially all individuals with confirmed ≥2 AAb will eventually develop clinical disease (17), yet there remains a need to better identify those who progress rapidly. Triolo et al. describe a higher-than-expected 3-year risk among those with ≥2 AAb in both nonidentical twins (72%) and full siblings (47%). With the caveat that zygosity was self-reported, the authors found no effect of shared environment on progression. While the small numbers of subjects in certain groups and relatively short follow-up time could skew 3-year risk estimates, the study emphasizes that current approaches testing family members for antibodies accurately identify a population that would most benefit from clinical trials to delay or prevent further progression.

In the September 2018 issue of *Diabetes Care*, Redondo et al. (18) also investigated disease progression by applying a genetic risk score (GRS) developed from 30 T1D risk loci, HLA and non-HLA, to AAb-positive at-risk subjects in the TrialNet Pathway to Prevention Study. GRS significantly improved prediction of progression rate from single to multiple AAb positivity and was a weaker but independent predictor for progression to T1D in multiple AAb–positive subjects. GRS in combination with clinical and metabolic variables was a more accurate predictor of progression to T1D than HLA plus clinical variables alone. An important point, however, is that GRS was predictive only in those individuals without significant metabolic abnormalities, indicating that genetics captured with this GRS plays less of a role once metabolic dysfunction develops. These observations are consistent with previous studies indicating that HLA's greatest effect is on

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development of AAb (19,20). While these analyses were applied to AAb-positive family members, recent work by the TEDDY (The Environmental Determinants of Diabetes in the Young) consortium highlights that a GRS is better than HLA typing alone in identifying individuals without a family history who will develop autoimmunity (21).

Sharp et al. (22) developed an improved T1D GRS (T1D GRS2) with 67 single nucleotide polymorphisms (SNPs) for T1D risk loci including extended HLA and non-HLA region variants. Initial testing was performed in case and control subjects from the Type 1 Diabetes Genetics Consortium (T1DGC) and validated in a UK Biobank cohort. T1D GRS2 significantly improved the receiver operating characteristic area under the curve (0.927) versus the previous 30-SNP GRS (0.886) as well as other published GRS (23). In addition, T1D GRS2 was useful for classifying adult diabetes subtypes and improving newborn screening for T1D. A T1D GRS2 >90th centile had twofold better predictive performance than HLA DR-DQ methods for newborn screening. The limitation of all of the above studies is the use of primarily Caucasian cohorts, as race has been shown to clearly influence the predictive value of this approach (24).

A similar T1D GRS approach was used by Grubb et al. (25) to predict time to insulin use in T2D. Predicting time to insulin use based on GAD65 AAb (GADA) alone is highly variable (26,27). The authors studied a large cohort of participants with T2D aged ≥35 years who were treated without insulin for 6 months after diagnosis and followed for at least 5 years. High T1D GRS was significantly predictive for rapid progression to insulin use in GADA-positive but not GADA-negative T2D patients. The positive predictive value of a high T1D GRS was modest at 48% in GADA-positive subjects, but a low T1D GRS had a high negative predictive value of 82%. Limitations of this study were self-reported time to insulin use and the use of a white European study cohort. These findings indicate that T1D GRS in combination with GAD testing has some clinical value to distinguish different phenotypes of T2D. While this observation does not yet translate into any change in diabetes treatment, such stratification of T2D individuals could be very useful in clinical trials.

In contrast, identification of individuals with monogenic diabetes as compared with T1D or T2D has important clinical implications; the challenge has been to develop a cost-effective algorithm for screening. A combination of AAb screening and T1D GRS was used by Patel et al. (28) to improve prediction of patients with T1D with the aim of excluding them from testing for monogenic diabetes. Extending previous work (29), the authors evaluated the impact of testing for ZnT8, GAD, and IA-2 AAb combined with the use of the T1D GRS in 212 individuals diagnosed with diabetes at a very young age. They found that 45% of patients likely had T1D and thus did not require testing for monogenic disease. None of the patients with ZnT8 AAb alone or with T1D GRS >50th centile (AAb-negative subjects) had monogenic diabetes. Thus, testing for AAb and T1D GRS for relatively low cost can effectively exclude patients with probable T1D from expensive genetic testing of 35 genes for diagnosis of monogenic diabetes.

Taken together, these articles show that a combination of clinical variables and genetic risk load can improve disease prediction. This supports the concept of "composite biomarkers" in predicting rate of disease progression, stratifying patients for therapy, and timing of therapy. It remains to be seen whether this approach is useful in predicting response to disease-modifying therapy. Further testing of T1D GRS in non-Caucasian cohorts is needed to make GRS more widely applicable. Collectively, however, a T1D GRS seems to be coming of age, and it is likely that its first clinical application will involve screening for monogenic diabetes.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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