COMMENTARY

Teasing Diabetes Apart, One Locus at a Time

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Diabetes Care 2018;41:224–226 | https://doi.org/10.2337/dci17-0046

Although most organ-specific autoimmune diseases show middle-age onset and a range of severity, type 1 diabetes appears to be relatively atypical given its striking severity and childhood onset. But the discovery of islet cell antibodies (ICA) as a disease hallmark by the recently deceased Franco Bottazzo in 1974 posed interesting conundrums (1). Not everyone with type 1 diabetes had ICA, and not everyone with ICA had diabetes; indeed, they were also found in a fraction of patients with type 2 diabetes. Further, the higher the ICA titer, the more likely one was to get the disease and to get it early. It followed that individuals with low-titer ICA could develop diabetes in adulthood, while others escaped diabetes altogether (2,3). The passing years have illuminated these points, with tracking of multiple autoantibodies with disease progression (4).

Type 1 diabetes is a classic example of a complex trait with a strong genetic basis. However, a differential impact of genetic and nongenetic factors is encapsulated in the "threshold hypothesis"—more of one, less of the other, and vice versa (2). In children, diabetes has a high heritability, but data suggests it declines with increasing age of onset (5), reflecting declining HLA impact. The appearance of multiple high-titer diabetes autoantibodies, likely secondary to environmental events around birth, presage early-onset type 1 diabetes (2,6) (Fig. 1). But a second wave of serum autoantibodies, which appear in subjects for up to 10 more years, presents with different immunogenetic characteristics (Fig. 1). In those cases, autoantibodies are often single, low-titer, and raised to glutamic acid decarboxylase, with enrichment of HLA DR3/DQ2 without depletion of protective HLA genotypes (6). We do not know how these "second-wave" autoantibodies in children relate to adult-onset autoimmune diabetes, but many immunogenetic characteristics are shared, including their HLA genetic susceptibility and the frequency of single autoantibodies, usually GADA (3,6). Given that older patients typically have less severe loss of insulin secretory capacity, their tipping point for hyperglycemia could be achieved through a range of adverse effects, just as for type 2 diabetes. Such effects would include insulin-secreting cell stress by altering insulin secretory demands and enhancing β-cell fragility (2,7).

Certainly there has been a coincident global epidemic of obesity and type 2 diabetes; there has also been a general increase in type 1 diabetes worldwide, and increased body weight and insulin demand are associated with more rapid disease progression in adolescents (8–10). In looking at patients with type 1 diabetes for genetic factors associated with type 2 diabetes, an obvious approach would be to seek major type 2 diabetes–associated genetic loci in those type 1 diabetes cases with modest immunogenetic features. Recent studies have done just that, with fascinating results, as outlined below.

One of us (S.F.A.G.) first reported the association of the *TCF7L2* locus with type 2 diabetes while working on an extensive family-based study in Iceland (11). The subsequent flood of genome-wide association studies revealed the *TCF7L2* locus as the most statistically significant type 2 diabetes signal (12,13). This locus has a worldwide effect, although it is not always the "top hit" (14). One single nucleotide polymorphism (SNP), rs7903146, is considered the optimal SNP to capture that disease association (15), and many believe it is the actual causal variant. Intriguingly, the *TCF7L2* locus markedly increases the risk of cystic fibrosis–related diabetes (16) and likely also plays a role in those patients with adult-onset type 1 diabetes who do not initially need insulin treatment, so-called latent autoimmune

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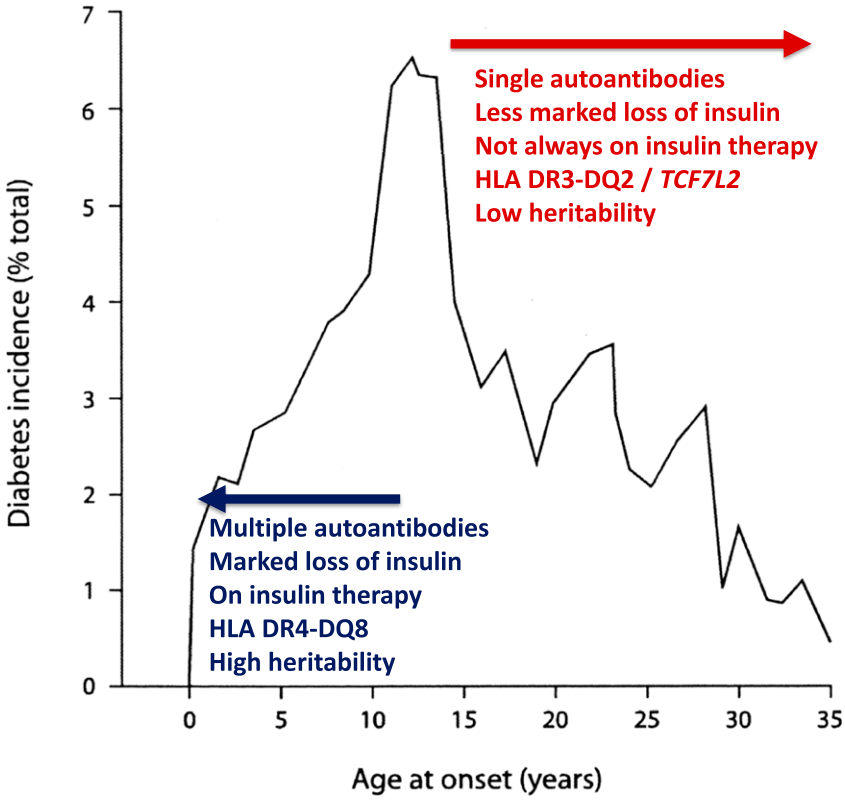

Figure 1—The incidence of insulin-treated type 1 diabetes in the first 35 years of life. Patients diagnosed before age 12 have different features (as illustrated) than those diagnosed later. The majority of that latter group do not require insulin treatment initially, especially when diagnosed after 25 years of age. Redondo et al. (19) now find that subjects with type 1 diabetes aged ≥12 years at diagnosis, as with older patients who do not initially require insulin, are enriched for the *TCF7L2* locus previously associated with type 2 diabetes.

diabetes in adults (LADA) (3,17,18). While it might be argued that LADA is simply a heterogeneous disease, an admixture of both type 1 and type 2 diabetes in which shared genes alter the threshold for diabetes, i.e., the "tipping point," an article in this issue of *Diabetes Care* hints at an alternative explanation.

Redondo et al. (19) sought to partition type 1 diabetes to explore this variant by leveraging newly diagnosed participants in Type 1 Diabetes TrialNet, a well-characterized cohort of 810 patients, offering substantial statistical power, crucially with extensive autoantibody and HLA data. By analyzing just this one variant, already strongly implicated from LADA studies, they eliminated issues of multiple statistical testing. The frequency of the risk allele within *TCF7L2* was markedly higher among patients with type 1 diabetes, specifically those with single, but not multiple, autoantibodies. In other words, this risk variant was associated with the "second-wave" cohort described earlier, but here in patients with typical type 1 diabetes as opposed to LADA. There was no correlation with obvious comorbidities and HLA haplotype; indeed, the variant appeared to be more predictive than HLA. Importantly, this association was only significant in adolescents; it was not seen in children aged <12 years old (19). Allied with results from larger LADA studies, this suggests common genetic ground between people with type 2 diabetes and those with type 1 diabetes with single autoantibodies diagnosed after age 12, irrespective of whether they do or do not initially require insulin therapy (17,18). Such an effect would be consistent with the "threshold hypothesis" outlined earlier (i.e., the smaller the HLA load, the more marked the *TCF7L2* association) and would argue against older patients with either LADA or type 1 diabetes having distinct disease causes (2,3,20,21).

The cross-sectional nature of the study does not allow the authors to assess the impact of this key variant with time. In addition, given that rs7903146 is the optimal SNP to work with, it is unfortunate that the authors did not leverage that marker, or computationally impute it given the highly informative genotyping array they used, in their transethnic cohort. The two SNPs employed are not necessarily in linkage disequilibrium with this key variant beyond European ancestry, especially in African ancestry, although we accept that they are reasonable proxies for that variant in European ancestral populations (the leveraged cohort was largely non-Hispanic white). Extending such efforts to additional ethnicities would add further context to these observations.

Looking forward, applying a genetic risk score approach with the remaining established type 2 diabetes loci is warranted to investigate whether the effect Redondo et al. (19) have identified can be extended to other key loci. Such an effect could be important as we seek to define type 1 diabetes, which at one end of a spectrum is associated with a potent immunogenetic mix that leads to severe diabetic ketoacidosis and, at the other end, with modest immunogenetic features and limited metabolic damage not requiring insulin treatment (3,21). That said, while many of the type 2 diabetes loci uncovered to date have a clear and unequivocal primary role in the islet β-cell, this is less clear for the *TCF7L2* locus. A pleiotropic role for that locus in many cells has been reported (22–24), with contradictory effects depending on the physiological setting, and other genes in this genomic neighborhood may also be relevant, such as *ACSL5* (25). Nevertheless, from the striking link with diabetes in both cystic fibrosis and autoimmune diabetes, we infer a direct role for the *TCF7L2* locus in diabetes risk.

These present results (19), allied to other reports, clearly implicate genes other than HLA in the heterogeneity of type 1 diabetes. They offer us a glimpse into a future in which genetics can be used to partition component parts of diabetes, with fundamental implications for a more tailored approach leading toward precision medicine.

Funding. S.F.A.G. is supported by the National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases (R01 DK085212) and the Children's Hospital of Philadelphia Daniel B. Burke Endowed Chair for Diabetes Research.

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

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