The Promise and Practice of Genetics on Diabetes Care: The Fog Rises to Reveal a Field of Genetic Complexity in *HNF1B*

Stephen S. Rich

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Diabetes is a common disease characterized by the disruption of glucose homeostasis that results when insulin, the hormone that converts glucose from the blood into energy used by the body's cellular machinery, is absent (through autoimmune destruction of the pancreatic β-cells in type 1 diabetes) or inefficient (increased insulin resistance or reduced insulin sensitivity in type 2 diabetes). There are multiple pathways to developing diabetes, yet practically all involve an underlying genetic etiology with an environmental trigger.

The extent of knowledge of genetic factors and environmental factors differs across the forms of diabetes. In the case of type 1 diabetes, the concordance in monozygotic twins (genetically identical) is ∼50%, with familial aggregation and modeling suggesting a major impact of genetics on risk (1). The genetic contribution to type 1 diabetes is well described, with HLA genes accounting for one-half of the genetic risk (2) and ∼50 other sites in the genome contributing the majority of the remaining genetic risk (3). The familial (heritable) contribution to type 2 diabetes has also been estimated through twin studies, with monozygotic twin concordance rising from ∼50% in middle age to nearly 80% later in life (4). Complexity in assessment of the contribution of genetic factors to type 2 diabetes arises from the impact of other familial and behavioral factors that are associated with risk, including obesity, reduced physical activity, and dietary habits. Although the overall risk of type 2 diabetes appears "more heritable" than type 1 diabetes, the estimated effects of ∼100 sites across the genome account for ∼10% of the risk (5). Similar investigations have shown other types of diabetes to be heritable, including neonatal diabetes (6), maturity-onset diabetes of the young (MODY) (7), gestational diabetes mellitus (8), and latent autoimmune diabetes in adults (LADA) (9), and numerous studies have shown diabetes complications to be heritable as well (10).

Despite the differences in presumed etiologies and nearly complete nonoverlap of genetic risk factors in multiple forms of diabetes, there is growing recognition that genetic effects on DNA regulation may play an important role in disease initiation and progression. Multiple loci associated with diabetes risk have single nucleotide polymorphisms in/near transcription factor binding sites that could alter the chromatin landscape in relevant tissues. These single nucleotide polymorphisms could either alter the ability to regulate a target gene, transcription factor, or protein or modulate the competitive binding of the regulatory machinery, effectively "silencing" the target gene (3,11–13). While research is just beginning in the areas of type 1 diabetes and type 2 diabetes related to transcription factor binding and its effects on disease and intermediate traits (e.g., production of autoantibodies in type 1 diabetes, insulin sensitivity and resistance in type 2 diabetes), there has been greater progress made for a form of diabetes that is caused by genetic alterations in genes encoding transcription factors—namely, MODY.

MODY is a monogenic form of diabetes (due to defects in a single gene) that usually occurs in adolescence or early adulthood, although it is typically not diagnosed until later in life, as the genetic defect limits (but not blocks) the ability of the pancreas to produce insulin (14). Individuals with MODY are typically not overweight, have normal blood pressure, and often have a strong family history of MODY in an autosomal dominant pattern of transmission. Prolonged exposure to hyperglycemia over decades prior to detection often results in individuals with MODY having high rates of diabetes complications at diagnosis. Although individual forms of MODY appear rare, the prevalence of MODY collectively is estimated at 1–5% of all forms of diabetes. The majority of MODY cases derive from mutations in *GCK* (MODY2) and hepatocyte nuclear factor 1B (*HNF1B*) (MODY3), with many of the causal genes identified as transcription factors.

In this issue of *Diabetes Care*, Dubois-Laforgue et al. (15) provide a critical view of the genetic basis of MODY5 as a transcription factor–driven, monogenic form

Center for Public Health Genomics, University of Virginia, Charlottesville, VA

Corresponding author: Stephen S. Rich, ssr4n@virginia.edu.

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of diabetes. Important insights are obtained into the genetic spectrum of causal mutations in (or deletion of) *HNF1B* associated with MODY5. These gene alterations impact the diagnosis of this form of diabetes, its treatment, the prediction of diabetes risk in carriers currently unaffected, and the likelihood of complications in those with MODY5. The article by Dubois-Laforgue et al. has several strengths, including the multicenter design that enabled the ascertainment of a large sample of 201 individuals, a period of clinical follow-up in subjects over 18 years of age, and the collection of data from those with *HNF1B* mutations (n = 101) or larger deletions that include *HNF1B* (n = 100). The focus on the defects in *HNF1B* (mutation and deletion) rather than diabetes per se provides the opportunity to characterize *1*) the mutational spectrum of *HNF1B* mutations leading to diabetes, *2*) the effect of deletion of *HNF1B* on development of diabetes, and *3*) clinical differences in those with *HNF1B* mutations compared with those with *HNF1B* deletion.

It is sometimes not appreciated that mutations in a single gene associated with a monogenic form of disease do not occur only at a single site. The most obvious examples are the thousands of recognized mutations in *BRCA1* that account for risk of early-onset breast/ovarian cancer (16) and the hundreds of mutations in *CTFR* that, together with the classical ΔF508 deletion, lead to cystic fibrosis (17). Thus, it should not be surprising that in the 154 case subjects with *HNF1B* alterations, ~50% (n = 87) had the entire *HNF1B* gene deleted, while in the remaining 67 subjects with *HNF1B* changes, there were missense mutations (n = 37), nonsense mutations (n = 7), splicing variants (n = 8), insertion/deletions (n = 11), deletion of protein-coding regions (exons, n = 3, all different), and a duplication of an exon. This array of *HNF1B* change suggests many pathways to MODY5 and that gene sequencing rather than genotyping will be required to screen for this genetic effect on disease risk.

Among those with *HNF1B* mutations, there were no differences in the clinical characteristics by type of mutation (missense, nonsense, etc.), although the failure to detect differences could be due to small sample size and low statistical power. A comparison of those subjects with an *HNF1B* deletion and those with an *HNF1B* mutation found that those with the deletion were more often diagnosed as having diabetes, had a lower BMI at diabetes diagnosis, maintained a lower BMI at follow-up, were more often treated with insulin, had a higher estimated glomerular filtration rate at diagnosis and at follow-up, and had a lower frequency of kidney transplantation. These data suggest that having the entire *HNF1B* gene deleted was associated with a better clinical profile and prognosis than having *HNF1B* mutations. This could be due to the greater number of deletion cases treated with insulin at diagnosis and throughout the follow-up period, providing greater glucose control and lessening complication rates. In the absence of insulin treatment, an individual with the loss of a gene (*HNF1B*) would be expected to have earlier and more significant clinical effects than those with single mutations (18). These data may also reflect the relatively limited impact of loss of a gene encoding a transcription factor that is not necessary for survival, given the large number of such factors and overlap in function.

An interesting outcome of this study was that diabetes was not present in all subjects with *HNF1B* mutations/deletions. Only 159 of the 201 subjects developed diabetes, with only 67/144 having clinical symptoms of diabetes at diagnosis. The presence of "causal genetic variants" in people with no apparent disease is now becoming the rule rather than the exception, as other factors may "overcome" genetic risk (19). Even among those with *HNF1B*-mediated diabetes, the clinical presentation at diabetes diagnosis was highly variable with respect to age at onset, clinical symptoms, BMI, HbA_{1c}, and basal and stimulated C-peptide levels. Residual insulin secretion was typically present at diagnosis and follow-up, and the extent of insulin secretion did not correlate with either diabetes duration or kidney function (estimated glomerular filtration rate). There was a general absence of coronary artery disease (~10%) with relatively few risk factors, which may be the impact of low levels of hyperglycemia, insulin and sulfonylurea treatment, and low BMI in those with *HNF1B* mutations and deletions.

While the retrospective cohort design has some limitations (such as a survival bias that could reduce the effect of the *HNF1B* deletion), the study benefits from the large number of participants and careful clinical evaluation. Because of its retrospective design, some data were missing, but the study is the largest of *HNF1B*-related outcomes. Although the study cannot provide accurate frequency of diabetes in those with *HNF1B* alterations or the clinical outcomes, the impact of the genetic heterogeneity, even within a "homogeneous MODY subtype," should provide insights as to the difficulty in applying this information in a public health setting. The MODY5–*HNF1B* relationship is difficult to diagnose, has variable clinical presentation, and has only characteristic renal outcomes to aid in diagnosis. Perhaps members of a family with a history of MODY also consciously (or subconsciously) alter their lifestyle to one that is "diabetes-protective" (diet, exercise, weight loss).

The findings of this study provide insights related to *HNF1B* effects on diabetes development, treatment, and downstream complications. At the same time, the study highlights the future difficulty in translating genomic information into the clinical setting and the implementation of precision public health to reduce the burden of diabetes and its associated increased mortality in the population.

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