Novel Insights Into the Etiology of Diabetes From Genome-Wide Association Studies

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The flood of confirmed genes for type 2 diabetes arising from genome-wide association (GWA) studies has started to raise questions as to the value of such research. Objections stem from the low individual allelic effect sizes (1.1–1.5) and from the recent observations that allele-counting summaries of the current known variants do not add much to the predictive models for type 2 diabetes (1). It has also been suggested that such a large number of variants of this effect size would be required to explain the known heritable component for diabetes that almost every gene could eventually be identified as a type 2 diabetes gene. If this did turn out to be the case, what would be the value of this knowledge (2)? These grumbles come despite the fact that prior to 2007, genetic research in common complex disease had made very little substantive progress either in the realms of candidate gene studies or in the previous generation of genome-wide studies that used microsatellite markers in a linkage paradigm. As noted by Rich, Norris, and Rotter in a commentary last year (3), the results from GWA studies have quickly turned from a trickle to a flood (4–16), and the most immediate advances from this are not disease prediction but, rather, in leading to a better understanding of etiopathogenesis together with identification of novel gene products and pathways as targets for intervention (17).

While the road to drug discovery on such a basis is undoubtedly long and rocky, in terms of disease etiology per se, we are uncovering a wealth of additional knowledge regarding the pathoetioloogy of type 2 diabetes. First, we are finding that the majority of genetic loci involved in type 2 diabetes are firmly rooted in the biology of the pancreatic β-cell and only associated with insulin resistance to a minor degree (18). This is epitomized by the seminal discovery of variants in the SLC30A8 gene, which appears to be involved in the uptake of zinc, which is in this case required for the production of insulin (13). This clearly may have an important role in determining some of the priorities in future diabetic research. While some genetic loci are very elusive to further study and point the finger at multiple genes encoding poorly understood gene products, many of these gene loci implicate the involvement of known pathways that may or may not have been greatly appreciated as important in type 2 diabetes. Obviously, the discovery that an obesity gene, FTO, also predisposes individuals to type 2 diabetes was a gratifying and sensible observation (5); however, the discovery that this gene is predominantly a behavioral gene involved in appetite/food choice has major implications for future pathways for weight reduction/diabetes prevention interventions (19).

In a less obvious fashion, the characterization of the melatonin receptor (MNTR1B) as a modulator of glycemic control and type 2 diabetes susceptibility has brought to the fore previous epidemiological observations regarding sleep patterns/melatonin levels and their role in type 2 diabetes (4,10,20,21). In this case, the genetic effect provides a logical anchor point to suggest the direct causality of poor sleep, melatonin levels, and disease susceptibility (22). In type 1 diabetes, a focus on a viral trigger for this disease has been strengthened by the discovery of a key viral defense gene, IFIHI, as playing a role in susceptibility to type 1 diabetes (23). In contrast, a novel uric acid transporter has been identified from GWA study approaches that harbors variants that predispose to gout (24). These variants have no associations with type 2 diabetes susceptibility or other features of the metabolic syndrome, suggesting that high uric acid levels seen in type 2 diabetes and the metabolic syndrome are not disease causing but may arise as a result of the metabolic disturbances apparent in type 2 diabetes. The use of GWA studies has also highlighted a common etiology of different diseases/phenotypes, with certain genes being involved in both cancer and diabetes—most interestingly, the opposing roles of TCF2 polymorphisms in prostate cancer and type 2 diabetes lend further support to previous epidemiology suggesting that type 2 diabetes confers protection from prostate cancer (6). In addition, JAZF1, a known oncogene (25), has also been shown to harbor variants that modulate susceptibility to prostate cancer and diabetes (15,26,27). It is well established that shorter stature is associated with type 2 diabetes; however, the potential environmental/socioeconomic confounders limit the interpretation of this data. There is now a convergence between the list of genes associated with height in GWA studies and those affecting type 2 diabetes risk, with the JAZF1 locus associated with height, type 2 diabetes susceptibility, and fasting glucose in nondiabetic individuals, thus confirming a causal role for stature/growth phenotypes in type 2 diabetes susceptibility (28). In a similar fashion, a gene widely studied as a drug target for metabolic disease, PPARD, has also recently been shown to contain variants that modulate height (29).

Another interesting finding from GWA studies further changes our understanding of the way we view A1C as a measure of glycemic control. Recent studies from the Women’s Health Study have identified common genetic variation in hexokinase 1 as a robust modifier of A1C in...
glycemic control, reminds us of the widespread nature of such glucose levels through such anemic mechanism, rather than by systemic results in hemolytic anemia. The finding that HK1 variants modulate nondiabetic populations (9). In this issue of Diabetes, Bonnefond et al. (30) have shown that modulation of A1C levels by variants in the HK1 gene is not via a role in systemic glucose homeostasis or, thus, in type 2 diabetes etiology and remind us that A1C is also modulated by anemia independently of glucose control. It would appear that this may be due to local glucose handling in the erythrocyte, potentially affecting erythrocyte turnover. Importantly, HK1 is the predominant hexokinase in the erythrocyte that provides phosphorylated glucose as a precursor for both glycolysis and the pentose shunt in the erythrocyte. Mutations in HK1 (31) and in downstream activities involved in both glycolysis (pyruvate kinase) and the pentose shunt (glucose-6-phosphate dehydrogenase) are common causes of inherited hemolytic anemia and are known to affect A1C levels (32,33). Erythrocytes rely on glycolysis exclusively for ATP production, and the pentose shunt is the only mechanism by which erythrocytes can provide NADH for the reduction of glutathione, the major defense against oxidative stress in these cells. Genetic defects in this pathway are generally seen in the next step, glucose-6-phosphate dehydrogenase, which results in extreme sensitivity to environmental insults, leading to hemolytic anemia (32). Environmental stressors, which provoke anemia in individuals with a defective pentose shunt, include Fava beans (famism) or drugs such as primaquine. These genetic defects are highly prevalent in populations that have historically been highly exposed to malarial infection, such as Africa, India, the Middle East, and southern Europe; therefore, in studies of A1C, it will be very important to control for these defects (or indeed other hemoglobinopathies such as sickle cell) if study populations have a significant proportion of ancestry from these regions (Fig. 1).

So, despite the grumbles regarding GWA studies and disease prediction, it is clear that these insights demonstrate the immense value of the GWA studies performed during the last 3 years to diabetes research. We also have to realize that this is only the start of the genomic revolution. Indeed, the current reports are based on genotyping chips that query only the most common variation in the genome and represent a mere scratch on the surface of the genetic architecture of human complex disease. The use of new genotyping platforms with increased genetic content, the completion of the 1,000 genome project, and widespread adoption of whole-genome sequencing should provide another quantum jump in our understanding of interindividuality in disease processes and will hopefully allow us to provide truly personalized medicine in type 2 diabetes.

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FIG. 1. Fava beans: Individuals with defective erythrocyte glucose handling (generally G6PD mutations) are sensitive to Fava beans, resulting in hemolytic anemia. The finding that HK1 variants modulate A1C levels through such an anemic mechanism, rather than by systemic glycemian control, reminds us of the widespread nature of such glucose handling defects in malarial endemic countries.
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