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Pearson, Ewan R.

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Ewan R. Pearson

Dissecting the Etiology of Type 2 Diabetes in the Pima Indian Population

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The Pima Indian population of Arizona has one of the highest prevalence of diabetes of any population in the world, and the Pima Indians of the Gila River Indian Community have probably been the most studied group for the causes and consequences of diabetes. They develop what would be considered to be classic type 2 diabetes, characterized by obesity and insulin resistance with progression to diabetes characterized by progressive β-cell dysfunction (1).

Given the low degree of admixture and high heritability of type 2 diabetes in the Pima Indians (2), the population should also represent a honeypot for genetic discovery. While in recent years there has been progress in identifying type 2 diabetes risk variants in this population (3,4), the understanding of the genetic contribution to diabetes risk remains far from complete. Like many initiatives in genetics, whole-genome/exome sequencing is now being applied in the hope that rare/low-frequency variants with large effects on diabetes risk will be found.

In this issue of *Diabetes*, Baier et al. (5) report on the results of a targeted sequencing project focusing on the genes encoding the two subunits of the β-cell K_{ATP} channel. Variants identified by whole-genome sequencing in *ABCC8* and *KCNJ11* in 335 Pima Indians are genotyped in 7,710 individuals of full Pima Indian heritage or mixed American Indian heritage (~4/8th Pima Indian). They identify an R1420H variant present in 3.3% of the population that is associated with a doubling of the risk for type 2 diabetes, with diabetes developing, on average, 7 years earlier in those heterozygous for the variant. Baier et al. show that this variant, which appears to be private to the Pima Indian population, is functionally inactivating, similar to the R1420C mutation that is known to cause hyperinsulinemic hypoglycemia of infancy. In keeping with this, they report the R1420H variant is associated with a 170-g increase in birth weight consistent with fetal hyperinsulinemia (Fig. 1). Thus, in a beautiful parallel of the monogenic disease, the diabetes risk variant is associated with increased insulin secretion in utero but decreased β-cell function in adult life (6). This scenario of hyperinsulinism in utero followed by early failure of β-cell function is also described in maturity-onset diabetes of the young owing to *HNF4A* mutations (7), and the mechanism for this switch from over- to undersecretion remains poorly understood.

In addition to reporting the association of the *ABCC8* 1420H variant with increased diabetes risk and increased birth weight, Baier et al. (5) also report that this variant is associated with low adult BMI (Fig. 1). To avoid confounding that could occur in a cross-sectional analysis, whereby those genetically at risk for diabetes develop diabetes at a younger age and lower BMI, the authors use the comprehensive longitudinal data available to establish that this effect is seen consistently over time in both those who develop diabetes and those who do not. This result certainly suggests a role for variation in *ABCC8* function outside of the pancreatic β-cell. K_{ATP} channels are present in the hypothalamus, where they are involved in glucose sensing and appetite regulation. While, to my knowledge, patients with congenital hyperinsulinism are not reported to have low BMI in adulthood, there are two mouse models that support this finding. In one model, Kir6.2 knockout mice that were fed a high-fat diet were resistant to weight gain (8). In a second model, activation of K_{ATP} specifically in proopiomelanocortin neurons drove hyperphagia and an obese phenotype in mice (9). It would be certainly interesting, if challenging, to investigate appetite and leptin regulation in the Pima Indian subgroup with the 1420H variant.

Baier et al. (5) highlight how the carrier frequency for this inactivating *ABCC8* variant will result in a clinically important risk of homozygous infants with severe hyperinsulinism. While this is undoubtedly true and raises the possibility of prepregnancy genetic testing, the finding of this variant present at 3% that has a clear impact on diabetes phenotype has an important implication for our understanding of "type 2 diabetes." There is a tendency to think of type 2 diabetes as one disease characterized by obesity and insulin resistance, as is typically seen in the Pima Indians. Yet, now we can begin to see how genetics can

Division of Cardiovascular & Diabetes Medicine, School of Medicine, University of Dundee, Dundee, Scotland

Corresponding author: Ewan R. Pearson, e.z.pearson@dundee.ac.uk.

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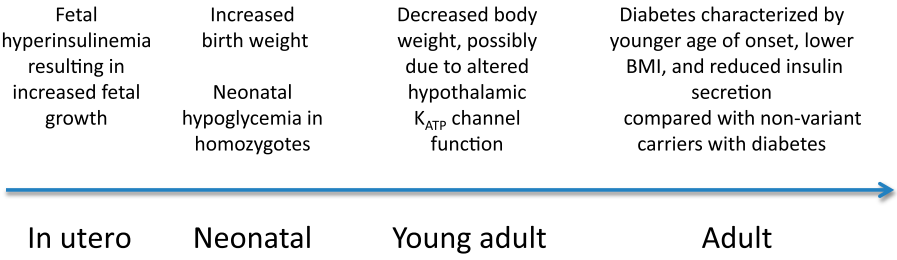

Figure 1—The effect of carrying the 1420H variant in *ABCC8* in the Pima Indian population at different life stages. Data are for heterozygous carriers unless stated.

unravel the pathophysiology of diabetes, identifying subgroups of distinct etiology, even in this population with classic type 2 diabetes. The key step that is required is to establish the clinical utility of this finding in this genetically defined subgroup. The mouse models of hyperinsulinism have reduced β-cell insulin content and poor response to incretin stimulation (10,11). It would be interesting to see how this genetically defined subgroup would respond to sulfonylureas, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide 1 receptor agonists and to see how quickly they would progress to insulin requirement following the diagnosis of diabetes. Knowing the genetic etiology here may be helpful in deciding on treatment choice and advising the patient on the likely disease trajectory.

The past 18 months have seen a number of articles published that report a large genetic risk for diabetes in different ethnic groups or isolated populations. For some, these are population-specific variants in genes associated with monogenic diabetes. A recent example is the finding of a low-frequency variant in *HNF1A* in a Latino population that was associated with a fivefold increased risk for diabetes, with the risk variant present at 2.1% in those with diabetes (12). Similarly, a private G319S variant in *HNF1A* in the Oji-Cree tribe was reported in 1999, with homozygous variant carriers having fourfold risk of diabetes (13). It seems likely that these patient groups will respond well to sulfonylurea therapy, in keeping with the monogenic diabetes caused by *HNF1A* mutations (14), although these studies have yet to be done. Some large effect variants have also been described in genes not linked to monogenic diabetes. The most striking of these is in the Greenlandic population, where the 3% of the population who are homozygous for a variant in *TBC1D4*, which causes muscle insulin resistance, has a 10-fold increased risk for developing type 2 diabetes (15). Finally, and more generalizable across a number of populations, a low-frequency variant with a minor allele frequency of 1.5% in *CCND2* is associated with a 50% reduction in diabetes risk (16,17). These studies and the report of *ABCC8* variants in the Pima Indian population (5) reveal that while some diabetes risk variants of modest effect, such as in *TCF7L2* and *CCND2*, are seen across populations, it is likely that many more large effect variants will be identified by appropriately designed studies in defined populations. These exciting findings and likely future discoveries will increasingly dissect out subgroups of type 2 diabetes and will increase the likelihood of using genetics to guide a stratified approach to diabetes management, but the stratification approach used will need to be population specific.

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