Open Questions in the Genetic Evolution of Type 2 Diabetes

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Abstract

Common Type 2 Diabetes Mellitus (T2DM) clusters in families, but does not follow Mendelian patterns. Common genetic variants have little isolated effects, but combined genotype scores based on 15 risk alleles predict 5-8 fold increased individual risk of T2DM. Evolution of these risk alleles remains an enigma. Since humans also postreproductively contribute to offspring fitness, there are several explanations: (1) genetic basis of T2DM is well adapted to the hunter-and-gatherer environment with permanent famine interrupted by short food abundance periods. Why are there noncarriers, who even when obese, do not develop T2DM? (2) heterosis: the nonsymptomatic heterocygotes Aa have a higher fitness than wildtype aa, but homocygotes AA develop manifest T2DM. Are nonsymptomatic relatives of manifest T2DM fitter than population average? (3) High spontaneous mutation rates at T2DM relevant loci. Why are there populations with a much higher prevalence of manifest T2DM? Pros and Cons of models will be assessed.

Introduction

James Neel opened his classic 1962 article on the evolution of diabetes by posing a theoretical dilemma:

> For the population geneticist, diabetes mellitus has long presented an enigma. Here is a relatively frequent disease, often interfering with reproduction by virtue of an onset during the reproductive or even pre-reproductive years, with a well-defined genetic basis…If the considerable frequency of the disease is of relatively long duration in the history of our species how can this be accounted for in the face of the obvious and strong genetic selection against the condition?

Neel's solution to this puzzle looked back to our hunter-gatherer ancestors, whose food supply he assumed to be scarce and erratic – feast or famine. He suggested that diabetes mellitus is the result of a "*thrifty genotype*, in the sense of being exceptionally efficient in the intake and/or utilization of food" when it was available, to compensate for times when it was unavailable (1962: 354, italics added). According to Neel, the genotype was functional for hunters and gatherers but became dysfunctional in modern times when the food supply became reliably abundant.

Neel wrote as if he did not understand the distinction between Types 1 and 2 diabetes, although these were known since the 1930s to be different diseases. Type 1, caused by destruction of insulin producing cells in the pancreas, was often called "juvenile onset" diabetes because it occurred in childhood and (until the advent of insulin therapy) was invariably fatal within a few years of diagnosis, foreclosing the possibility of transmitting any susceptibility genes to the next generation. Type 2, characterized by insulin resistance and/or abnormal insulin secretion, was called "adult onset" diabetes because morbidity rarely occurred before middle age,

when reproduction was usually complete. Thus, there is no real enigma. Type 2 genes easily pass from one generation to the next.

Notwithstanding Neel's faulty premise, variants of the "thrifty gene" hypothesis for Type 2 diabetes (T2D) continue to be propounded and debated. No doubt the strongest reason for the continued appeal of this hypothesis is the undoubted heritability of T2D. For at least a century, "adult onset" diabetes has been known to run in families. Today there are several validated T2D- and obesity-susceptible loci. Recently Southam et al. (2009) looked at 17 T2D-susceptible loci and 13 obesity-susceptible loci to assess if they were likely to be derived or ancestral. They found no consistent patterns of selection that provide conclusive confirmation of the thrifty genotype hypothesis.

It is tempting to think that T2D- or obesity-susceptible genes offer some advantage to explain their continuing presence. If there was strong positive selection since the Paleolithic, one might expect everyone to have them, but their frequency differs across different ethnic/racial groups. For example, there is a very high incidence of the susceptibility allele in the PPARGC1A gene among Polynesians, but it is absent in New Guineans (Myles et al. 2007). So the question turns to why they are more prevalent in some populations than others. It has been suggested that Polynesians underwent strong selection pressure for energetic efficiency during their settlement of the Pacific, which required long voyages that encountered cold stress and starvation. Such explanations remain speculative. We cannot exclude the possibility that different frequencies in different populations, especially populations derived fairly recently from a small number of founders, are results of drift and do not involve differential selection.

Another hypothesis, originally offered in contrast to Neel's thrifty genotype, is the "thrifty phenotype" theory. This proposes that the uterine environment, during period of famine,

has an epigenetic effect that increases the fetus's efficiency in the intake and utilization of food, and makes it susceptible in later life to T2D. Corroborative evidence is sketchy because several decades intervene between uterine exposure and the onset of T2D. Also, critics have pointed out that if a relationship is observed between low birth weight and adult illness, this is not inconsistent with the thrifty genotype hypothesis. By this account, fetuses with thrifty genes are most likely to survive stressful pregnancies, and if these surviving infants reach adulthood at a time of abundant food, they would be prone to T2D (Hattersley and Toole 1999).

Obesity and Sedentary Lifestyle

The U.S. Centers for Disease Control estimates that nearly 11% of Americans over age 20 are diabetic (www.cdc.gov/diabetes/pubs/factsheet07.htm). It is impossible to say what the incidence was early 20th century America, but there is a general perception that it was far lower. The situation globally is well summarized by Zimmet, Alberti and Shaw:

> Diabetes mellitus, long considered a disease of minor significance to world health, is now taking its place as one of the main threats to human health in the 21st century. The past two decades have seen an explosive increased in the number of people diagnosed with diabetes worldwide. Pronounced changes in the human environment, and in human behavior and lifestyle, have accompanied globalization, and these have resulted in escalating rates of both obesity and diabetes (2001: 782).

If there is genetic or epigenetic evolution of T2D, it seems insufficient to explain the present rapid increase of the disease. The global number of people with diabetes [90% of it T2D] is about 200 million and is expected to be 300 million in 2025. T2D is typically preceded by impaired glucose tolerance (IGT, or "pre-diabetes"). Of course, part of the increase in cases

of T2D and IGT, especially in developing nations, is because of general population increase, of more people living long enough to show insulin resistance, and of better screening. Apart from these factors, the age-specific increase in T2D and obesity is stunning, a combination recognized by the term "diabesity" (Zimmet et al. 2001).

Rising obesity, first in the U.S. and now widespread, was in 1997 recognized by the World Health Organization as a global epidemic. It is generally attributed to the new Westernized diet -- with excess calories, simple carbohydrates and saturated fats -- and more sedentary work and lifestyles. Therapeutic interventions based on weight loss and exercise forestall the progression from IGT to T2D, suggesting that obesity and sedentarism are not simply correlative but causal factors in the etiology of T2D (e.g., Tuomilehto et al. 2001).

It is a viable hypothesis that the current rise in T2D is primarily caused by rising obesity and sedentarism. This occurred first in the U.S. and other industrial nations. , and after World War II in nonindustrial nations that rapidly adopted the Westernized diet and in which the day's activity became more sedentary, either because of less muscle-intensive jobs or increasing joblessness.

A corollary hypothesis is that the more rapidly this obesity/sedentarism increases in a population, the higher the susceptibility to IGT and full blown T2D, and the earlier the age of onset. The mechanism may be cultural and psychological rather than simply physiological or genetic. People suddenly presented with a cheap cornucopia of tasty starch and fat are psychically impelled to stuff themselves, especially if family and neighbors are eating around them, rather like Americans at the annual Thanksgiving dinner, but now lasting day after day. Also, in cultures that traditionally value corpulence as a sign of beauty, health or status, as among Polynesians, there is no guilt or other emotional inhibition against putting on weight.

The industrialized nations moved toward obesity and sedentarism less abruptly, and their cultural body ideals foster guiltiness about overeating and becoming fat, so their increases in IGT and T2D were slower and have not reached the extremes found among the Polynesians.

Genetic Variation

Any claim that today's T2D epidemic is primarily caused by obesity and sedentarism must address the fact that certain individuals and populations are more (or less) prone to IGT and T2D, even controlling on obesity/sedentarism. Certainly this leaves open the possibility that different groups experienced different selection pressures for thrifty genes, though it does not as easily explain the difference among individuals in the same population.

The reliable association of certain gene loci with T2D or obesity does not imply that they are causal in any direct way. Genetically isolated groups have different gene frequencies, and if the groups have different disease rates, then overall they may show reliable but spurious gene-disease correlations. Alternatively, genes may play a causal role by some indirect route, for example, if there is genetic variance in indolence, that might explain why some individuals, living in a culture of abundant food and high unemployment, eat excessively, gain weight, and increase their risk for T2D.

Alleviation

Leaving aside the theoretical issue of whether or not the present epidemic of T2D is a modern dysfunction of genes that were functional for Paleolithic hunters and gatherers, ameliorative strategies must find other points of attack. Obvious targets are excessive diets and

physical inactivity. This can hardly be seen as overriding personal responsibility because present cultural and structural features make it almost inevitable that obesity will spread. One cannot walk into a Starbuck's for a black coffee without being tempted by an array of delectable pastries. School children are subjected to school lunches, TV ads, and fast food marketers plying them with high-caloric starchy and fatty foods. In the U.S. this diet is based largely on federally-subsidized corn products. In pitting personal freedoms against public health, the fight against diabetes is reminiscent of past public campaigns to require childhood vaccinations.

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