

Diabetes Genes: How Many Needles in the Haystack?



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Genetics or environment? Nature or nurture? People have long debated which is more important in type 2 diabetes and obesity. It is now clear that the argument is irrelevant--both genetics and environment contribute to adult diabetes, and understanding one without the other only tells you part of the story. Previous editions of *Viewpoint* have focused on some of the lifestyle changes that can reduce the risk of diabetes, such as diet, exercise, and certain medications. What about the other part of the equation--our genes? Well, we know from studies in twins and first-degree relatives of diabetics that genetics accounts for at least 50% of the risk of developing diabetes. With the rapid advances in our knowledge of the human genome, there has been a lot of speculation we would soon know the identity of the genes that play in role in diabetes.

In fact, diabetes geneticists have had a tough row to hoe. There has been success in tracking down the roots of "monogenic" disorders (diseases caused by mutations in a single gene, like cystic fibrosis or sickle cell anemia), but monogenic forms of diabetes account for only 5% of diabetes. We now realize that type 2 diabetes, like most other common diseases, is "polygenic" in nature. Trying to figure out which handful of the 30,000 genes that humans possess is important has proven to be a rather daunting task.

There are two basic approaches to looking for diabetes (or any disease) genes. The first is to identify genes whose function is already known to have an effect on the metabolic pathways that control body weight and blood sugar levels. There are, in fact, a plethora of studies pointing to variations in several such genes that seem to track with diabetes in certain populations. Unfortunately, the vast majority of these studies are underpowered--a geneticist's way of saying that not enough patients were examined to prove that any association seen is not merely the result of chance. Also, many studies have

been criticized for problems with ethnic admixture. Different ethnic backgrounds are believed to contain different diabetes susceptibility genes, and studies in ethnically diverse populations (like the United States) can be confounded by this problem. One way to avoid this is to look in very limited populations of people who are ethnically uniform; hence, a large number of diabetes studies are done in groups like Finns, the Pima Indians of Arizona, and the Amish.

The other way to look for disease genes is to identify markers on the human gene map that track with the disease in large populations or large families. The idea is that if you have a big family where half the members have type 2 diabetes, and you can show that every diabetic in that family has a certain marker on chromosome 12, then you can say that there might be a diabetes gene near that marker on chromosome 12. By collecting more and more markers that are closer and closer together, researchers can pinpoint a putative diabetes gene to within a million or so base pairs--a short distance as far as the genome is concerned. Researchers then poke around the million base pairs near that marker and see if there's a plausible diabetes gene in the vicinity. This approach was used in a large population of Mexican-Americans to identify a gene called calpain 10 as a possible diabetes gene, for example.

I say "possible" diabetes gene because, several years after the initial discovery, there is still debate about whether calpain 10 is the culprit, and not some other gene lurking nearby. To make matters more confusing, it now appears that a least one other gene on a different chromosome needs to be altered in order for the effects of the calpain 10 gene to occur.

One of the more intriguing findings in diabetes genetics centers on a gene called PPAR γ , which encodes a protein that plays numerous roles in biology, from regulation of cholesterol levels to the development of fat cells. The antidiabetic thiazolidinedione (TZD) class of drugs, which includes AvandiaTM and ActosTM, acts by directly activating this protein in fat cells (and possibly other sites as well), although exactly why this improves insulin resistance is not clear. There is a common variation in the PPAR γ gene such that amino acid 12 can be either a proline (Pro) or an alanine (Ala). Most of us have the Pro form of PPAR γ , but about 10% of caucasians have an Ala. As it turns out, having an Ala is a good thing, as it protects from type 2 diabetes. The effect on the risk of diabetes in any given person with a Pro is very small, but because so many of us have a Pro, this may account for as much as 25% of all type 2 diabetes in this country.

A new study also points to a different mutation in PPARG as a cause of diabetes in humans. A group of researchers in the United Kingdom have looked at people with the most severe insulin resistance they could find, with the notion that such folks may have more easily discovered mutations. Normally, we all have two copies of PPARG. In at least one family in the U.K. they found mutations that destroy one of these two copies of PPARG that. Interestingly, this mutation alone does not seem to account for the diabetes in this family, as another mutation was also discovered in affected members. This second mutation was in a gene called PPP1R3A, which affects how glucose is metabolized in muscle cells. Thus, it appears that in this one family at least, two distinct genes expressed in two distinct tissues (muscle and fat) need to be altered for the severe diabetes to appear.

Such a "digenic" (two gene) model is unlikely to account for very many cases of diabetes, but it does illustrate what can happen when you move up one level of complexity from a monogenic disorder. Keep this in mind as you read headlines claiming that the "gene for diabetes has been discovered". There is no single gene for diabetes. What we are really looking for are all the many genes that conspire together to create the pathologic disturbance we call type 2 diabetes.

References:

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