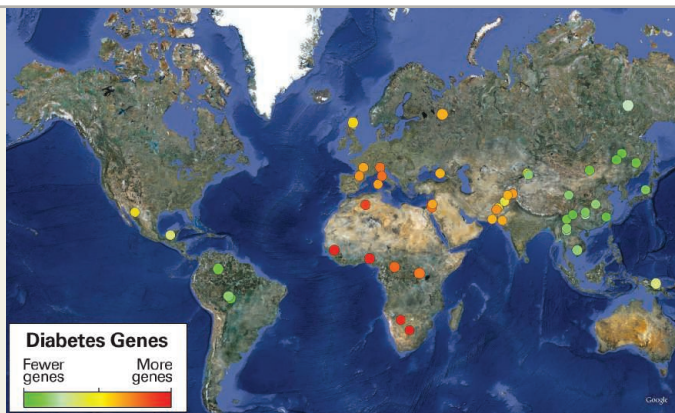


Diabetes Genes Decline Out of Africa

Ask a physician which ethnic group is most at risk for type 2 diabetes, and he might cite Native Americans or African-Americans. But now a thorough analysis of all known genetic variants associated with the disease reveals a surprising pattern: It's Africans themselves who face the highest known genetic risk from this epidemic, according to a new report at the meeting. In 2010, only 3% of sub-Saharan Africans had any kind of diabetes, compared with 12% of Americans, but type 2 diabetes has a big environmental component and is only now beginning to show up in African city dwellers who have adopted a Western diet and lifestyle. As that lifestyle spreads in the future, Africans may face a serious threat, according to a talk and poster from a Stanford University team.

At the poster session, Stanford graduate student Erik Corona stood in front of a Google Earth map of the world that he finds surprising. On this map he had plotted the frequency of 12 gene variants known to be associated with type 2 diabetes in 51 populations from Australia to Zaire. It shows "a clear gradient of red to green from west to east, from Africa to Asia," Corona says (see map). "Something strange is going on with type 2 diabetes."

Corona and Stanford bioinformaticist Rong Chen say the map shows that the genetic risk of diabetes decreased the farther modern humans had migrated out of Africa, especially into Asia—although the risk rose again in Native Americans, perhaps due to adaptations to diet or the northern climate around the Bering Strait. This suggests that as modern humans spread around the world in the past 60,000 years, they lost the single-nucleotide polymorphisms (SNPs) that are known to be linked to diabetes, a pattern that has not been described before, Stanford team leader Atul Butte



Diabetes alert. Genes associated with type 2 diabetes are common (red dots) in Africa and rarer (green dots) in Asia.

says. Perhaps, Butte speculates, some or all of those 12 variants were once beneficial, helping Africans maximize their use of sugar to create energy. Until now, few people lived long enough or ate enough sugar and fat to develop diabetes, so in prehistory the disease probably had little effect on fitness.

Stanford population geneticist Carlos Bustamante finds the pattern intriguing but points out that the challenge now is to find out how much disease the associated gene variants actually cause. "Diabetes is a complex disease," he says. "We have to know if these variants are causative, or do they increase your risk by [a mere] 1.5%?"

The Stanford team argues that their genetic maps are a first step. In his talk, Chen showed that diabetes is just one of 100 diseases for which they have plotted risk, using two new databases, Verimed and Geneworld (<http://geneworld.stanford.edu/>), that will eventually be available to doctors. **—A.G.**

less diverse than autosomes in populations. So the chromosome has been a low priority for sequencers interested in disease risk, and published sequences have been of poor quality. But interest was piqued 3 years ago when teams studying frequencies of different alleles on the X got different results: One group found the X was less diverse in non-Africans, but another group didn't.

Then last year, the 1000 Genomes Project (*Science*, 29 October 2010, p. 574) posted its pilot data, including sequences of the complete genomes of 69 women from Africa and Europe. These data provide a much sharper view of the X, including single-nucleotide

polymorphisms (SNPs). "The 1000 Genomes data rides to the rescue," Clark quipped.

Researchers have long known that Africans have more diverse genomes overall, presumably because the small bands of ancestors traveling out of Africa passed through a genetic bottleneck and lost many variants. Cornell's Alon Keinan, Clark, and their colleagues devised a clever method to compare the amount of variation in SNPs on the X with that on the autosomes and applied it to 36 Yoruba women from West Africa. They found the X had about 73% of the diversity of the autosomes, as expected. But when Keinan examined the genomes of 33 European women, he found that their X chromosomes had only about 61% of the diversity of their autosomes. Because the European genomes were already less diverse overall, this

On the X trail. The X chromosome is less diverse outside Africa (faded pink), whereas the Y chromosome's diversity (blue) does not change.

extra effect meant that the Africans' X chromosomes were twice as diverse as those of the Europeans.

Because of the X's pattern of inheritance, the reduction in diversity out of Africa is likely due to some sex-linked demographic process, Keinan says. One likely explanation is that more men than women were members of the bands who moved out of Africa, a gender imbalance also seen on the front line of some other migrations.

Other researchers find the work convincing. "We are converging on an answer," says computer scientist August Woerner, who works with geneticist Michael Hammer at the University of Arizona in Tucson. Hammer's lab was the one that saw more diversity on the X of non-Africans, but with whole genome sequences, they, too, have now found more diversity in Africans, resolving the debate. "The simplest explanation is waves of male migrations or a few males disproportionately passing on their X chromosomes" by having many children, says geneticist Joshua Akey of the University of Washington, Seattle.

—A.G.

