

Humans riddled with rare genetic variants

Blossoming of variation followed explosion in population size.

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By sequencing more people more thoroughly than ever before, researchers have affirmed that rare genetic variants — those carried by fewer than five people in a thousand — are widespread and likely to have an important role in human health.

Two studies^{1,2} published today in *Science* find that most human genetic variants are rare, and that rare variants are more likely than common ones to affect the structure or function of proteins, and therefore to have biological or medical consequences. The papers, along with another study³ published last week in *Science*, all conclude that humans carry such a high load of rare variants because the species experienced a population growth spurt that began a few millennia after the adoption of agriculture, which occurred about 10,000 years ago.

The three studies add to a growing body of knowledge that has profound implications for researchers investigating the genetic roots of disease.

For the past decade, researchers have looked for links between genes and disease by scanning the genome for common genetic variants. But these [common variants have failed to explain most of the genetic contribution to disease](#), prompting researchers to speculate that either individual common variants must have very small impacts on complex traits⁴, or that rare variants might be more important.

The two studies published today used deep sequencing — in one case sequencing each base in the sampled genes an average of more than 100 times¹ — to find a trove of rare variation in humans.

In a project sponsored by the US National Heart, Lung and Blood Institute in Bethesda, Maryland, researchers led by Joshua Akey and Michael Bamshad at the University of Washington in Seattle sequenced 15,585 genes in 2,440 people, and found that 86% of the variants discovered in the subjects were rare. More than 95% of the variants that were predicted to have a medical or biological consequence were rare variants¹.

The second project was led by John Novembre of the University of California Los Angeles and Vincent Mooser of UK-based drug company GlaxoSmithKline. It reports that more than 95% of variants found by sequencing 202 genes in 14,002 people were rare, and that 74% of the variants were carried by only one or two people in the study².

Today's papers come on the heels of a study published last week by Andy Clark and Alon Keinan of Cornell University in Ithaca, New York, that used data from sequencing studies to show that "explosive" growth of the human population beginning around 1,400 years ago helped to seed the human genome with variants that have not yet been weeded out by the process of natural selection³.

Jonathan Pritchard, a population geneticist at the University of Chicago in Illinois, says that previous studies hadn't been able to detect the excess of rare variation that would be expected to accompany the relatively recent surge in human population growth. "We've known that human populations are growing, but haven't been able to see a clear signal of that" in genetic data, Pritchard says. "Now, with this very large sample size, it's become easy to see the signal of recent population growth that has been difficult to find."

This widespread rare variation means that it will be very complicated to follow through on the promise of initiatives such as the Human Genome Project: to find the genes that, when mutated, cause human disease, and to predict disease risk for an individual on the basis of his or her unique genetic profile. Akey and Bamshad, for instance, estimated that each person in their study carried between 25 and 31 genetic variants that were shared by no one else in the study. Predicting the effects of these rare variants will not be easy.

The papers also indicate that researchers will need to study the genetic sequences of thousands of people — as many as 20,000 in some cases — to find enough of the variants to connect them to particular illnesses.

And, because many of the rare variants found in the studies were unique to specific populations with different geographic origins, variants linked to a particular disease risk in some groups won't explain the same disease in others.

The findings suggest that researchers will need to revamp their current methods for deciphering gene function, Akey says. Genetics researchers will need to devise new tools for linking rare variation to complex traits and for evaluating the functions of thousands of rare variants much faster than is now possible.

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References

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