How hot spots of genetic variation evolved in human DNA

March 19 2019, by Charlotte Hsu

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What makes one person different from one another, and how did these differences evolve?

A study by University at Buffalo biologists is illuminating one aspect of this complicated question. The research examines hot spots of genetic variation within the human genome, examiining the sections of our DNA that are most likely to differ significantly from one person to another.

The findings uncover a complex evolutionary history, shedding light on the malleability of human DNA and pointing to just how adaptable—yet delicate—we are as a species.

"We have made some headway into understanding how variations in the genome occur," says Omer Gokcumen, Ph.D., assistant professor of biological sciences in the UB College of Arts and Sciences. "Which parts of the genome are protected and conserved through evolution? Which parts are not protected, and why?

"There is previous work showing that structural variations—deletions, duplications, other alterations of DNA—they're not distributed uniformly throughout the genome. There are deserts and there are hot spots. The big question is whether this clustering has biological meaning, whether it is random or driven by evolutionary forces. Our research addresses this question."

The study, published online on March 18 in the journal *Genome Biology and Evolution*, was conducted by Gokcumen and UB biological sciences Ph.D. candidate Yen-Lung Lin, who has since graduated and will soon begin a new job as a postdoctoral researcher at the University of Chicago.

Exploring the architecture of thousands of genomes

The human genome is the entirety of a person's DNA. Genes—the fragments of DNA that influence traits such as eye color and risk for disease by telling our bodies how to build important proteins—make up about 1.5 percent of our genomes. The rest consists of noncoding DNA, whose function (or lack thereof) is a topic of debate among scientists.

Every person's genome is different, and the new study compared the DNA of more than 2,500 individuals.

Scientists zeroed in on the sections of the genome that differ most between people, identifying 1,148 areas that harbor unusually high numbers of structural variants, including chunks of duplicated, deleted, inserted, inverted or repeated sections of DNA.

New insights on the malleability of human DNA

An examination of these "hot spots" revealed a complex evolutionary story.

Most are found in gene-poor regions of the genome, as expected. (Altering genes can lead to devastating health problems, so it makes sense that gene-rich areas would tend to be more heavily conserved through evolution, Gokcumen explains.)

However, a small subset of structural variant hot spots is found in parts of the genome that harbor important genes. In these hubs, genes linked to our sense of smell, blood and skin function, and immunity to disease are overrepresented, according to the study.

Balancing selection—in which dueling evolutionary forces drive a species to preserve an array of traits—may help to explain why these gene-heavy hot spots exist.

One example: In the study, a DNA deletion that increases a person's risk for a blood disorder called thalassemia was found in about 16 percent of genes in sub-Saharan African populations. While evolution mostly weeded this genetic variation out of human societies in other parts of the world, the variation persists in sub-Saharan Africa because it's valuable there, Gokcumen says: The deletion may confer resistance to malaria, a major disease in the region.

"There's an evolutionary reason why this mutation is lingering, despite its

ill effects," he says. "It's actually beneficial too, at least for some populations. Balancing selection is important for adaptation, and we think it contributes to the development of some structural variant hot spots."

If the findings on balancing selection showcase humanity's adaptability, a second result from the study hints at just how delicate we are—at how easily problems can arise.

The conclusion has to do with the malleability of human DNA, and the possibility that some hot spots of variation may be located in sections of the genome that are, for biochemical reasons, more susceptible to being altered.

In most people, genetic mutations in these regions are not devastating. But in some cases, large genetic deletions that begin in one hotspot and end in another may result in the erasure of entire genes in between, leading to health complications, Gokcumen says.

One example: The study found that a number of consecutive structural variant hot spots lie on either side of the short stature homeobox (SHOX) gene, whose deletion can lead to a severe bone growth disorder that causes very short stature. In some people who are missing the SHOX gene, deletions of DNA began in one hotspot, spanned the entire SHOX gene, and ended in a second hotspot.

When Gokcumen and Lin ran statistical tests, they found that the start and end points of large genetic mutations with known medical relevance were found in structural variant hot spots more often than would be expected.

More information: *Genome Biology and Evolution* (2019). DOI: 10.1093/gbe/evz058

Provided by University at Buffalo