Selection Analysis Suggests Modern Melanesians Carry Adaptive Archaic Hominin CNVs

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NEW YORK – At least some of the large copy number variants (CNVs) subjected to positive selection in the genomes of individuals in Melanesia originated in archaic hominins, according to a new study from investigators in the US, Italy, and France, hinting that their modern humans ancestors may have acquired CNVs that helped them adapt to new environments as they moved out of Africa and mixed with Neanderthals or Denisovans.

"Our results collectively suggest that large CNVs originating in archaic hominins and introgressed into modern humans have played an important role in local population adaptation and represent an insufficiently studied source of large-scale genetic variation," senior and corresponding author Evan Eichler, a genome sciences researcher at the University of Washington, and his colleagues wrote.

As they reported online today in *Science*, the researchers tallied archaic hominin CNVs from a handful of Neanderthal or Denisovan genomes, before analyzing structural variant patterns in genome sequences for hundreds of participants in the Simons Genome Diversity Project (SGDP). With this strategy, they narrowed in on large chromosome 8 and 16 CNVs that not only showed signs of positive selection in modern Melanesian individuals, but also appeared to have their roots in modern human admixture with Denisovans or Neanderthals.

"Although larger CNVs are generally deleterious and associated with disease, examples of adaptive CNVs in humans have been documented," the authors explained. "However, relatively little is known about the extent to which CNVs contribute to the genetic basis of local adaptation and, more importantly, whether CNVs introgressed from other hominins may have been targets of adaptive selection."

The team reasoned that Melanesian island populations may be particularly prone to carrying adaptive structural variants stemming from archaic introgression, since prior studies indicate that individuals in this part of Oceania have higher-than-usual proportions of ancestry from archaic hominins, on average, particularly ancestry from Denisovans.

For the analysis, the investigators analyzed sequences for one Denisovan representative, as well as Neanderthals from Croatia and the Altai Mountains. Across the three archaic hominin genomes, they identified more than 5,100 archaic CNVs, which they subsequently genotyped in 249 SGDP genomes and genome sequences for 72 non-human great apes.

The approach made it possible to distinguish between CNVs that are found in both modern humans and non-human primates and those that are specific to one or more modern human lineages. After tracking down almost 2,700 modern human CNVs that also appeared to be polymorphic in one or more of the archaic hominins, for example, the group focused in on the CNVs that did not turn up in the African population.

From there, the researchers incorporated population-specific CNV clues from SGDP to find the archaic hominin-related CNVs in Melanesians, weeding out potential *de novo* structural variants with statistical analyses, and refining their gaze with positive selection signals. They followed up on suspicious chromosome 8 and 16 CNVs with PCR assays on blood or cell line samples from hundreds more Melanesians.

"Although each of these loci will require more detailed investigation, we focus here on two of the largest and most complex copy number polymorphisms discovered among the Melanesians," the authors noted.

At a chromosome 8 site linked to skeletal muscle regulation, for example, the researchers identified an apparent Melanesian-specific duplication neighboring a deletion suspected of originating in Neanderthals. On the other hand, a Denisovan-derived duplication turned up at a chromosome 16 locus previously implicated in everything from human embryonic development to autism spectrum disorder.

"[T]his study highlights the substantial large-scale genetic variation that remains to be characterized in the human population and the need for development of additional reference genomes that better capture the diversity of our species and complete our understanding of human genes," the authors concluded.