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DUPLICATION IN GENOMES MAY SEPARATE HUMANS FROM AP

A sudden peak in copying and rearranging of DNA shaped great ape species

By Tina Hesman Saey
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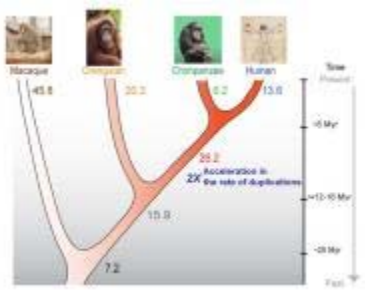

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DUPLICATION DIFFERENCE

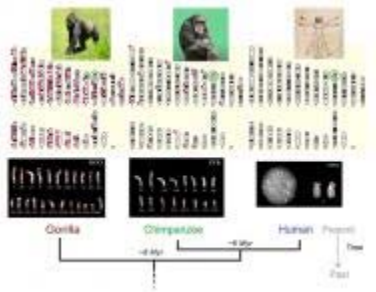
View Larger Version | A burst of duplications happened in the genome of the common ancestor of humans and African great apes between 8 million and 12 million years ago. The numbers closest to the pictures indicate millions of duplicated bases that are unique to each species. For example, 13.6 million bases duplicated in the human genome are not duplicated in the genomes of the other species.
Marques-Bonet et al., Nature, Feb. 12, 2009

Although it may not be as dramatic as the Big Bang birthing the universe, an explosion of DNA duplication in the common ancestor of humans, chimpanzees and gorillas may be responsible for many of the differences among the species, a new study suggests. The big blowup happened 8 million to 12 million years ago, but its effects are still apparent today.

Human and great ape genes are notoriously similar, with few differences in the genetic letters that make up the instruction manual for building each of the primates. But gorillas, orangutans, chimpanzees and humans are obviously different. A new analysis of the entire genomes of humans and their ape cousins, published in the Feb. 11 *Nature*, suggests the differences may have roots in DNA duplications.

Researchers led by Evan Eichler, a Howard Hughes Medical Institute investigator at the University of Washington in Seattle, compared the genomes of macaques, orangutans, gorillas, chimpanzees, bonobos and humans. The scientists found that chunks of the genomes had been copied and rearranged, sometimes multiple times, within each of the lineages.

After orangutans branched off the primate family tree, duplication rates accelerated dramatically in the common ancestor of gorillas, chimpanzees and humans.The burst continued in the common ancestor of humans and chimps, but then slowed again. At the same time that duplication rates were heating up, other types of mutation — such as single letters changes in the genetic sequence — slowed down.



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NOT LIKE THE OTHERS

View Larger Version | Duplication could make the difference: A segment of DNA found only once in the human genome (green circle) has been duplicated in chimpanzees and gorillas multiple times (pink arrows). Some segments duplicated once in chimpanzees are multiplied in humans (not shown).

Marques-Bonet et al., Nature, Feb. 12, 2009

All the duplication activity resulted in structural differences in the architecture of the genome among the species on a scale not previously appreciated. Because earlier studies had only looked at single genes or small parts of the genome, these larger-scale changes were not apparent.

"This paper suggests that the real variation leading to the human lineage is structural," says Mark Gerstein, a bioinformatician at Yale University. "I think it's plausible that copy number or structural variation can affect things even more than mutation – single base changes – can."

Changing a single base, or DNA letter, is likely to have a limited effect because such mutations alter only a single gene. But large duplications containing 20,000 bases or more, such as the ones mapped in the new study, may contain more than one gene or parts of genes and regulatory regions.

Doubling, tripling or quadrupling the number of copies of a piece of DNA in the genome can potentially increase activity of genes contained in the chunks by a corresponding amount. A duplication might contain some parts of a gene, but not all of it, which could change the gene's function. And duplications might contain control panels for genes, Gerstein says. Copying those control panels, in full or in part, and inserting them somewhere else in the genome could change the activity of genes adjacent to the insertion point.

Duplications don't appear to happen randomly, the researchers found. Most duplications occurred next to more ancient duplications, creating hot spots in the genome susceptible to copying and rearranging. These slippery parts of the genome provide flexibility for adaptation to new environments, but they have a downside as well.

Instability has been linked to disease in humans. Cancer cells notoriously have duplications, rearrangements and deletions in their genomes. Unstable DNA also predisposes people to disorders such as autism, mental retardation and schizophrenia. Because duplications linked to autism and schizophrenia are so recent, it is likely that these neurodevelopmental disorders are also quite young, the researchers say.

About 20 percent of the duplications identified in the study are found only in humans. Most of the replicated chunks contain genes with unknown function, so the next step of the project is to figure out how the duplications happen and how the genes inside them contribute to making humans human.

But humans aren't the only ones with extra DNA specific to their species, says Jeff Kidd, a genomics researcher in Eichler's lab.

"If you and I were two chimpanzees talking, we'd be talking about how 20 percent of duplications are unique to chimps," Kidd says. "It's all a matter of perspective."