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# Ape Genomes Assembled without Human Fillers

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Humans may be less inclined to read themselves into the genomes of great apes, now that less “humanized” ape genomes have been assembled. The newly assembled genomes, one

for the chimpanzee and one for the orangutan, are “all ape,” that is, they do not rely on human fillers. In previously assembled ape genomes, genetic information from the human genome was used to fill in thousands of gaps, potentially skewing answers to the popular question, “What distinguishes humans from apes?”

To ensure that each of the new genomic assemblies would yield the whole magilla, a multi-institutional team of scientists exploited long-read PacBio sequencing and long-range mapping technology. The new assemblies, the scientists estimate, improve chimpanzee and orangutan gene annotation and genomic contiguity by 32- to 533-fold, respectively.

Details about the newly assembled genomes appeared June 8 in the journal *Science*, in an article entitled “High-Resolution Comparative Analysis of Great Ape Genomes.” This article not only describes the comprehensive search for genomic information—the use of single-molecule, real-time (SMRT) sequencing technology and the analysis of more than 500,000 full-length complementary DNA samples from induced pluripotent stem cells—it also offers early comparative deliberations.

For example, the article highlights the identification of 17,789 DNA variants in humans—each representing changes in gene regulation—that may have emerged since humans’ divergence from their ape relatives. Intriguingly, these variants were enriched near genes involved in brain morphology that were decreased in expression in humans, relative to chimpanzees—highlighting these DNA regions as potential candidates for investigation of gene-linked functional differences between humans and their primate cousins.

“Of the 17,789 fixed human-specific insertions and deletions, we focus on those of potential functional effect,” wrote the article’s authors. “We identify 90 that are predicted to disrupt genes and an additional 643 that likely affect regulatory regions, more than doubling the number of human-specific deletions that remove regulatory sequence in the human lineage.”

The researchers also studied brain organoids—laboratory-grown tissues coaxed from stem cells of apes or humans and forming a simplified version of organ parts. These brain proxies were examined to shed light on how differences in gene expression during brain development in humans and chimps might account for chimps' smaller brain volume, which is three times less than human brain volume. There are also significant dissimilarities in cortical structures in human and chimp brains.

"We investigate the association of structural variation with changes in human-chimpanzee brain gene expression using cerebral organoids as a proxy for expression differences," the *Science* article indicated. "Genes associated with fixed structural variants show a pattern of down-regulation in human radial glial neural progenitors, whereas human-specific duplications are associated with up-regulated genes in human radial glial and excitatory neurons."

The downregulated genes are more likely to have lost segments of DNA specifically in the human branch important in regulating their expression. This finding is consistent with a "less is more" hypothesis proposed in the 1990s by now-retired University of Washington School of Medicine genome sciences professor Maynard Olson, Ph.D., and his colleagues. The hypothesis proposes that the loss of functional elements contributes to critical aspects of human evolution.

On the other hand, certain human genes appear to be linked to upregulation for neural progenitors and excitatory neurons in the nervous system. These genes are more likely to have gained additional copies in the human species, compared to other apes, through a process of gene duplication.

The researchers, led by University of Washington's Zev N. Kronenberg, Ph.D., and Evan Eichler, Ph.D., predict that more advanced, long-range sequencing and mapping technologies, and even longer-read sequencing, will assist in increasing knowledge on the evolutionary journey taken by the great apes and our human ancestors. The scientists caution that the ape genomes and their work on them are not yet complete because the genome assemblies are still missing other larger, more complex structural variations that cannot yet be assembled.

"Our goal," said Eichler, "is to generate multiple ape genomes with as high quality as the human genome. Only then will we be able to truly understand the genetic differences that make us uniquely human."

"The improved ape genome assemblies provide the most comprehensive view to date of intermediate-size structural variation and highlight several dozen genes associated with structural variation and brain-expression differences between humans and chimpanzees," the *Science* article concluded. "These new references will provide a stepping stone for the completion of great ape genomes at a quality commensurate with the human reference genome and, ultimately, an understanding of the genetic differences that make us human."