

SEPTEMBER 01, 2005

A New View of Human-Chimpanzee Genome Differences

Comparisons of the human genome and the newly completed draft of the chimpanzee genome have unearthed major differences between the patterns of large duplicated segments of DNA in the two species. These segmental duplications—which straddle large stretches of DNA—appear to have had a significant impact in altering the genomic landscape of apes and humans.

The popular understanding of the genetic differences between chimpanzees and humans should be recast in light of the findings of major differences in segmental duplications, said the senior author of the study, Evan Eichler of the Howard Hughes Medical Institute at the University of Washington School of Medicine.

"So when we talk about how similar chimps and humans are, we really need to be careful that we are referring to variation in the whole genome as opposed to just those single-base-pair changes."

— **Evan E. Eichler**

The traditional comparison cited in textbooks is that the difference is 1.2 percent, based on variations in single base-pairs in gene sequences. "But our data on these duplications shows a 2.7 percent difference, base per base, between chimps and humans," said Eichler. "So when we talk about how similar chimps and humans are, we really need to be careful that we are referring to variation in the whole genome as opposed to just those single-base-pair changes."

Eichler led the research team which published the comparative genome analysis in the September 1, 2005, issue of the journal *Nature*. Their research article was one of several analyses that accompanied a report on the draft sequence of the chimpanzee genome. Eichler also participated in the chimpanzee genome project.

Eichler and his colleagues in Seattle collaborated with researchers from the University of Bari in Italy, the Max Planck Institute for Evolutionary

Anthropology, the Washington University School of Medicine in St. Louis, Children's Hospital of Oakland Research Institute and the National Library of Medicine.

Duplications of extensive segments of DNA occur during the production of sperm or eggs because of a predisposition of certain sites along the chromosomes to undergo breakage and rearrangements, Eichler explained. The resulting segmental duplications are evolutionarily important because they give rise to extra copies of genes that allow evolution to more freely "experiment" with mutations that could give rise to new traits, said Eichler. However, they can also lead to some two dozen genetic diseases.

Comparative analysis of segmental duplications in humans and chimpanzees could give important insights into why such specific abnormalities tend to occur and when these events arose. "The chimp can provide us historical information about ancestral states of disease," said Eichler. "We know that there are some disease 'architectures' that are shared between chimp and human, so we know that is the ancestral state. But other predisposing structures have arisen only in the human lineage, so such comparisons can provide important information on the genetic histories of disorders and disease susceptibilities of the human species."

In their analysis, the researchers mapped the draft chimpanzee sequence data onto the human genome sequence as a reference. With their comparative map, they used sophisticated computational analysis to distinguish three categories of segmental duplications—those found in humans but not in chimpanzees; those found in chimpanzees but not in humans; and those shared between humans and chimpanzees. The researchers looked for duplications greater than about 20,000 base pairs in length.

Their analysis revealed that about a third of the duplications were found in humans but not in chimpanzees. "This was surprising, because it tells us that there is a high frequency of *de novo* duplications that arose over the time of human and great ape evolution," said Eichler. "In contrast there are a lot of theories out there that duplications emerge and are maintained through selection or other processes such as gene conversion."

In analyzing the chimpanzee-only duplications, the researchers found that chimpanzees showed fewer sites of duplication than humans, but they did have a great number of copies of the duplicated segments. Of particular interest to the scientists, was that a few of the shared duplications were often "hyperexpanded" in the chimpanzee.

In one of the more extreme cases, while the human genome showed four copies of one segment, the chimpanzee genome showed some 400 copies. "Such hyperexpansions are interesting because they occur on the ends of chromosomes," said Eichler. "In the case of the segment that showed such massive duplication, it occurred near a region that in the great apes is broken into two chromosomes, but in humans is the fused chromosome two." Such a difference hints at some chromosomal instability in both species that resolved

itself differently in humans than in chimpanzees, he said.

Eichler was also intrigued by the data indicating that chimpanzee-only or human-only duplications tended to occur near regions of shared human-chimpanzee duplications—a phenomenon the researchers dubbed “duplication shadowing.” Discovery of this phenomenon, he said, could lead to greater understanding of the properties of chromosomal regions that tend to experience instabilities. “Such regions are pretty important from an evolutionary perspective, because a lot of people operate under the assumption that these types of mutational processes are randomly distributed,” said Eichler. “But in essence, they are not. There is probably something about these regions that has made them particularly hot in terms of change over the course of evolutionary time.”

The next major project the researchers will tackle is trying to understand what the differences in segmental duplication mean for the species in terms of the evolution of genes embedded in those segments. “At the top of our list is to work out which of the genes in the duplications show signatures of natural selection,” said Eichler. “This is a big question, because our hypothesis is that the big differences in structure between humans and chimps arose or might be tolerated because of important adaptations in the genes themselves.” There are a few examples of such rapidly evolving duplicated genes, but these genes have not been systematically analyzed due to the difficulties in characterizing genes in these regions of the genome.

When the genome of another great ape, the orangutan, is completely sequenced, the data should provide researchers with the opportunity to gain even more insight into evolutionarily important genetic differences between humans and other primates, he said.