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Flipped Genetic Sequences Illuminate Human Evolution and Disease

By comparing the human genome with that of the chimpanzee, man's closest living relative, researchers have discovered that chunks of similar DNA that have been flipped in orientation and reinserted into chromosomes are hundreds of times more common in primates than previously thought. These large structural changes in the genome, called inversions, may account for much of the evolutionary difference between the two species. They may also shed light on genetic changes that lead to human diseases.

Although humans and chimpanzees diverged from one another genetically about six million years ago, the DNA sequences of the two species are approximately 98 percent identical. Given the 2005 publication of the draft chimpanzee genome sequence, researchers can now readily identify the differences between the human and chimp genomes. These differences lend insight into how primates evolved, including traits specific to humans.

The researchers published their findings in the October 28, 2005, issue of the journal *Public Library of Science Genetics (PLoS Genetics)*. The paper was published early online. Senior author Stephen W. Scherer is a HHMI international research scholar, a senior scientist in the Genetics and Genomic Biology Program at the Hospital for Sick Children in Toronto, Canada, and an associate professor of molecular and medical genetics at the University of Toronto.

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This research expands on a *Nature* paper published on September 1, 2005, by HHMI investigator Evan E. Eichler at the University of Washington. Eichler's group determined that novel duplications of genetic material within humans also significantly contribute to differences between the species.

Instead of identifying sequence changes between the two genomes at the base-pair level, Scherer focused his research on large structural variations in chromosomes between humans and chimps, specifically genetic inversions. Inversions can disrupt the expression of genes at the point where the chromosome breaks, as well as genes adjacent to breakpoints.

“From a medical genetics perspective, there are probably hundreds of disease genes that have not yet been characterized,” said Scherer. “The vast majority of disease gene discovery has been based on gene sequencing, but this is not a comprehensive view of chromosomes. We are using an evolutionary approach to identify mutations that may predispose people to disease.”

According to Scherer, prior to this research, only nine inversions between humans and chimps had been identified. Using a computational approach, Scherer's group identified 1,576 presumed inversions between the two species, 33 of which span regions larger than 100,000 base pairs—a sizeable chunk of DNA. The average human gene is smaller, only about 60,000 bases in length.

Scherer's team experimentally confirmed 23 out of 27 inversions tested so far. Moreover, by comparing the chimp genome with its ancestor, the gorilla genome, they determined that more than half of the validated inversions flipped sometime during human evolution.

Perhaps even more interesting than the abundance of inversions that Scherer's group unveiled was their discovery that a subset of the inversions are polymorphic—taking different forms—within humans, meaning that the human genome is still evolving. When the 23 experimentally confirmed inversions were tested against a panel of human samples, the scientists found three inversions with two alleles or pairs of genes displaying the human inversion in some people, whereas others had one allele of the human inverted sequence and one allele of the normal sequence in chimps.

Having one allele with an inversion and one allele without represents a ticking time bomb in genetic terms, Scherer said, since these alleles may improperly align and recombine during replication, ultimately causing DNA deletions or a loss of DNA that subsequent generations inherit. Scherer's prior research on Williams-Beuren syndrome, a disease caused by DNA micro-deletions, identified a significantly higher incidence of inversions among the parents of afflicted patients.

Interestingly, one of the inversions that Scherer identified as polymorphic in his current paper includes a gene known to be involved in colorectal cancer. Whether individuals polymorphic for this inversion are at increased risk for the development of colorectal cancer is not yet known.

Scherer said that his group looked at only a very small subset of the human population when assessing the prevalence of polymorphisms. He suspects

that polymorphisms, and structural variations in general, may be much more common than his preliminary analyses suggest.

“These findings may cause people to rethink their ideas about how species evolved,” Scherer said. “They also highlight how the mechanisms of evolution may be associated with disease.”

Scherer determined that about 10 percent of the presumed inversions either contain a complete gene within the flipped region, constitute a flipped region within a gene, or cause a breakpoint somewhere within a gene. These inversions represent prime targets for disease gene discovery, which Scherer's team is exploring further.