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Unscrambling the Gibbon Genome

The arboreal, branch-swinging antics of the gibbon are nothing compared to the acrobatics its genome has undergone during evolution. While the genomes of humans and other primates still resemble that of their common ancestor, the massive genomic scrambling of the gibbon genome has rendered it a complex puzzle. Solving that puzzle, scientists believe, could help reveal how evolution experiments with genomic rearrangement, as well as how chromosomes can become unstable in cancer and other genetic diseases.

Now, a research team has mapped in the finest detail yet the many chromosomal breaks and rearrangements that have reshaped the white-cheeked gibbon's genome as it evolved. The research team was led by Howard Hughes Medical Institute investigator Evan Eichler at the University of Washington and Mariano Rocchi of the University of Bari in Italy. The joint first authors of their research paper, published in the February 2007 issue of the journal *Genome Research*, were Roberta Roberto and Oronzo Capozzi, both in Rocchi's laboratory. Other co-authors were from the Washington University School of Medicine in St. Louis and the Gibbon Conservation Center in Santa Clarita, California.

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— **Evan E. Eichler**

One of the big questions in genome evolution for at least 30 years has been why certain karyotypes seem to evolve much more rapidly, said Eichler. A karyotype is a particular arrangement of chromosomes. Why do some lineages show excessive rearrangements, while sibling species do not? In the primate line, the amount of rearrangement between species is relatively minor, but the gibbon has always been an outlier, with a rapidly evolving genome.

Part of the motivation for studying the gibbon genome has been that—because we have such a high-quality reference human genome—it should be possible to identify not only the rearrangements that have occurred,

but the breakpoints and the sequences in those areas, he said. With that information, we should begin to understand the mechanism by which such breakages occur.

Rocchi, Eichler, and their colleagues used two complementary techniques to compare in detail the gibbon and human genomes, so they could zero in on where rearrangements have occurred in the gibbon genome. Using a technique called fluorescence in-situ hybridization (FISH), Rocchi's group attached fluorescent tags to hundreds of pieces of human DNA and watched as those snippets of DNA sought out and attached to similar DNA sequences on gibbon chromosomes. This enabled the scientists to locate corresponding, or syntenic, genomic blocks between the two species. The location of the syntenic blocks gave the researchers a low-resolution map of breakpoints between the human and gibbon genomes.

In a complementary analysis, Eichler and his colleagues used computational techniques to construct a map that compares known gibbon DNA sequences to the known sequence of the human genome. The approach identified several hundred sites of potential rearrangement. They then combined the data from the two approaches and performed additional FISH experiments to refine their analyses and narrow down the location of the breakpoints.

The combination of the techniques yielded the first detailed map of the gibbon genome's basic framework. The researchers identified and narrowed down 86 evolutionary breakpoints at high resolution, and a dozen more at lower resolution. Additionally, they isolated 49 DNA segments that span breakpoints.

According to Eichler, this detailed map of the breakpoints could help scientists understand why the gibbon's chromosome structure has been so unstable in evolutionary terms. The implications of the studies, however, go far beyond what researchers may learn about the genetic makeup of this particular ape. By permitting researchers to identify properties characteristic of regions of the genome that are predisposed to break, Eichler said the new data could help scientists understand why some genomic regions in general are unstable during evolution. Chromosomal instability and breakages are also frequently associated with cancer and other genetic diseases, he pointed out.

Eichler said the detailed map of genomic rearrangements could offer insight into how gibbons evolved into such successful, specialized arboreal primates.

In terms of primate evolution, gibbons show some remarkable adaptations, he said. Their morphology is very different from other apes, with their extremely long limbs giving them an extraordinary ability to brachiate [swing from branch to branch]. It may be—and this is very speculative—that these large-scale genomic rearrangements altered the expression pattern of genes that relate to these adaptive characteristics. Particularly intriguing, noted the researchers, is that several of the genes found in regions of chromosomes that have undergone rearrangement are associated with skeletal development.

Eichler said the framework map will aid in sequencing the entire gibbon genome. Part of the problem with the gibbon genome is that it is so rearranged that you really can't use the human chromosome organization to build a large-scale assembly, he said. So we would like to use this framework to help direct the assembly of the gibbon genome.