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A Closer Look at the Genome's 'Black Holes'

The centromeres of chromosomes — considered by some to be the genomic equivalent of black holes — may hold the answers to many scientific questions, according to Howard Hughes Medical Institute investigator Steven Henikoff. For example, studies of the centromere may help in understanding the paradox that while centromeric DNA is evolving with extraordinary rapidity, it is still stable enough to perform its job during cell division.

In a review article published in the August 10, 2001, issue of the journal *Science*, Henikoff and colleagues Kami Ahmad and Harmit S. Malik at the Fred Hutchinson Cancer Research Center theorize that the rapid evolution of centromeric DNA may provide a mechanism by which newly evolving species rapidly become genetically incompatible with one another.

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— **Steven Henikoff**

Each chromosome possesses a centromere, which is the site at which sister chromatids are held together. During mitosis and meiosis, the chromatid pair separates, and the centromere is the point of attachment of spindle fibers that pull each chromosome to opposite poles of the dividing cell. "While the centromere is a locus on the chromosome, it is different than a gene, because it is a locus that is acted upon by the apparatus of cell division," said Henikoff.

And unlike genes, which are amenable to mapping and sequencing, probing the genetic makeup of the centromere has proved to be a dead end because of the centromere's unusual structure. "The centromere has remained enigmatic ever since it was discovered that centromeric DNA is highly repetitive," said

Henikoff. "Current methodology really doesn't allow the sequencing of centromeric DNA. Thus, nobody has sequenced the centromeres of the human genome, the fly genome, or that of any other complex organism. They remain big black holes often millions of bases in length in every chromosome."

The wide variability of centromeric DNA across different species has led some researchers to dismiss its importance. According to Henikoff, the centromere shouldn't be dismissed so casually. "Some believe that centromeric DNA sequence is not all that important, because it is not conserved in evolution," said Henikoff. "That lack of conservation has led to the centromere paradox where stable inheritance occurs despite rapidly evolving DNA. Normally, the elements of the mitotic segregation machinery would be expected to be highly conserved, as are other essential cellular machines, such as ribosomes. But the central question with centromeric DNA is why it hasn't found some optimal sequence and just stayed there."

A key to stable centromere inheritance might be found in the proteins called histones, with which all DNA in the nucleus must associate in order for it to form beadlike structures called nucleosomes that bind DNA into compact packages. In the *Science* article, Henikoff and his colleagues suggest that the uniqueness of the centromeric histone H3 may teach researchers some interesting lessons about evolution.

"While histones are crucial, they are thought to be boring, because they are so highly conserved," said Henikoff. "Because the histones must interact reliably with the entire genome, there are few amino acid differences in these proteins between plants and animals." Centromeric histones, however, have evolved to be profoundly different among organisms.

"The idea that we explore in the *Science* review is that the centromeric histone and centromeric DNA are evolving rapidly, but in step, since the histone must interact with the centromeric DNA," said Henikoff.

Analysis of centromeric histones has revealed that they seem to be adapting constantly to the changing centromeric DNA. These evolutionary changes are occurring in parts of the histone that interact with DNA, Henikoff says, "so that tells us that it's the interaction with the DNA that's driving the evolution of the protein."

Henikoff and his colleagues theorize that this continuous evolution is being driven by a sort of competition among centromeric DNA that occurs during meiosis in the egg. Three of the four products of meiosis are discarded, and only one survives to become the oocyte nucleus. The "winning" centromeres are those whose chromosomes may show even a slight advantage in orienting themselves during meiosis, said Henikoff.

"What's important about this competitive process among centromeres is that it can result in fixation of winning centromeres. This process can be deleterious to the host genome, and so centromeric histones would evolve to restore parity between competing centromeres," Henikoff said. Bringing

together incompatible centromeres and histones in hybrids would lead to their sterility or inviability. "Understanding the basis of the sterility of cross-species breeding has been a huge problem in evolution ever since Darwin," he said. "The rapidly evolving centromeric DNA and histones and their incompatibility with their counterparts in another species might account for this phenomenon. We can test these ideas by analyzing the centromeric histones in emerging species."