Mapping a clan of mobile selfish genes

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Much of human DNA is the genetic equivalent of e-mail spam: short repeated sequences that have no obvious function other than making more of themselves.

After starting out in our primate ancestors 65 million years ago, one type of repetitive DNA called an Alu retrotransposon now takes up 10 percent of our genome, with about one million copies. Roughly every 20th newborn baby has a new Alu retrotransposon somewhere in its DNA, scientists have estimated.

"I think of them as molecular machines that can copy themselves and move around the genome, says Scott Devine, PhD, assistant professor of biochemistry at Emory University School of Medicine. "These elements pose a major threat to our genetic information, because they can damage genes when they jump into them, leading to altered traits or diseases such as cancers."

As mutations gradually blur the features of older Alu elements, some become unable to make copies of themselves. To identify the Alu retrotransposons that are still capable of moving around, Devine and graduate student E. Andrew Bennett, who is first author, divided them into families and tested a representative of each family in the laboratory.

The results are published online and are scheduled to appear in the December issue of the journal *Genome Research*. Laboratories at Emory, the University of Michigan and the Max Planck Institute for Developmental Biology contributed to the study.

"We wanted to see what dictates whether an Alu element will be mobile," Devine says. "That way we could predict which Alu copies are more likely to damage our genetic information. This information will become very useful as we enter the age of personalized genomics, allowing us to make predictions about the future health of individuals."

Alu elements get their name because they usually include the recognition site for the enzyme Alu I (AGCT), a common laboratory tool for cutting DNA into pieces. Geneticists have already identified over 40 Alu elements that interrupt genes and cause human diseases, including neurofibromatosis, hemophilia and breast cancer, Devine says.

Bennett and Devine tested Alu elements by putting each of 89 family representatives on a small circle of DNA next to a gene that allows human cells to resist a poisonous drug. They then introduced the DNA circles into cells in culture dishes.

If the Alu element could jump, carrying the drug-resistance gene onto the cells' chromosomes, the cells survived the drug. The authors conclude that around 10,000 Alu elements are still capable of jumping around, with 37,000 having at least a low level of activity. The youngest ones were all capable of moving around, and the oldest ones were all inactive.

"These results mean that Alu is by far the most abundant class of jumping genes and poses the greatest transposon-mediated threat to our genomes," Devine says.

The term retrotransposons comes from how they replicate: first, the DNA is transcribed (copied) into RNA, and the RNA is reverse-transcribed into DNA again. Depending on the type of cell, if an Alu element is located near genes that have been shut off, the Alu element is less likely to get transcribed.

That means the number of Alu elements that do move around is probably slightly lower. The team has constructed a database of Alu elements to compile additional information about each family.

Devine says an enzyme that is part of the normal machinery of the cell transcribes Alu elements, but they actually depend on another type of repetitive element, called L1, to make the enzyme that can reverse-transcribe them.

Scientists think Alu elements "hijack" part of the cell during the copying process. In the cell, Alu RNA is thought to resemble another type of RNA that guides protein production. The team's tests indicate that Alu elements that can best mimic that RNA, called the signal recognition particle, are more likely to be active.

"Alus are really parasites of a parasite," Devine says. "They've cleverly taken advantage of another element's machinery to survive."

Reference: Bennett, E.A. et al. Active Alu retrotransposons in the human genome. Genome Res. Published October 3, 2008, 10.1101/gr.081737.108

Source: Emory University