UNRAVELING THE HUMAN GENOME

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Scientists track ‘stealth’ DNA elements in primate evolution

Scientists in the Department of Biological Sciences have unraveled the details of a 25 million-year-old evolutionary process in the human genome. Specific DNA sequences that appear to have persisted in a latent state for long periods of time may not be simply lying dormant. Instead, the researchers say that these elements have played a crucial role in human evolution by surreptitiously spawning hyperactive progeny copies, giving rise to the most abundant family of DNA elements in the human genome: Alu elements.

The study, which was led by LSU scientist Dr. Mark A. Batzer, provides the first strong mechanistic evidence for the evolution of Alu elements to date. It appeared in the May issue of the journal Genome Research. Batzer has garnered much national attention for his work tracing the genetic history of the Acadian people of South Louisiana.

Alu elements are short, 300 nucleotide-long DNA sequences capable of copying themselves, mobilizing through an RNA intermediate, and inserting into another location in the genome. Over evolutionary time, this retrotransposition activity has led to the generation of over one million copies of Alu elements in the human genome, making them the most abundant type of sequence present. Because Alu elements are so abundant, comprising approximately 10% of the total human genome, they have been thoroughly characterized in terms of their origin and sequence composition. What has remained elusive to scientists, however, are the actual mechanisms by which these elements persist and propagate over time to influence human evolution.

In an attempt to understand these mechanisms, Dr. Batzer and his colleagues examined a subfamily of Alu elements in the human genome known as the AluYb lineage, and compared these elements to those in the genomes of other primate species, including chimpanzees, bonobos, gorillas, orangutans, gibbons and siamangs. The AluYb subfamily accounts for approximately 40% of all human-specific Alu elements and is currently one of the most active Alu lineages in the human genome. Some AluYb elements are still actively mobilizing in the human genome, causing insertion mutations that have led to the development of a number of heritable diseases.

Dr. Batzer’s team demonstrated that some AluYb subfamily members have orthologs in all primate genomes tested, which dates the AluYb lineage to an origin approximately 18-25 million years ago. Their results also indicated that the AluYb subfamily underwent a major species-specific expansion in the human genome during the past 3-4 million years. This apparent 20 million-year stretch of retrotranspositional quiescence, followed by a sudden outburst of human-specific retrotransposition activity in the past few million years, led Dr. Batzer and colleagues to formulate a new theory for the evolution of Alu elements, termed the “stealth driver” model.

To date, the most widely accepted theory of Alu retrotransposition is called the “master gene” theory, which asserts that the majority of Alu retrotransposition activity is driven by a small number of hyperactive “master” sequences. In this model, mutations occurring in the “master” copies have rendered themselves capable of substantial propagation and persistence over time. However, prior evidence from the Ya5 subfamily indicated that at least some “master” Alu elements may persist in low-copy numbers for long periods of evolutionary time without retrotranspositional activity, suggesting that the mechanisms of Alu expansion may be much more complex. The new paper by Han et al., provides evidence that a second large family of human Alu

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Dr. Mark Batzer
George C. Kent Professor of Biological Sciences

My laboratory is interested in the study of genetic variation, genome structure, and the identification of the genes responsible for several genetic disorders. The insertion of mobile elements into the genome represents a novel class of nuclear markers for the study of human genomic diversity.

The Alu family of mobile elements comprise approximately 10% of the human genome. Initial research on these elements demonstrated that, although these elements exist at a very high copy number, individual subfamilies of the elements of different genetic ages exist within the genome. Most members of the recently integrated Alu subfamilies are restricted to the human genome and absent from non-human primates. Many of these “young” Alu repeats have inserted so recently within the human genome that individuals can be polymorphic for the presence or absence of an Alu element at a particular chromosomal location.

Alu insertion polymorphisms offer two important advantages over other nuclear-based polymorphisms for human evolution studies. First, the presence of an Alu element represents identity by descent, since the probability that two different young Alu repeats would integrate independently in the same chromosomal location is negligible.

Second, the ancestral state of each Alu insertion polymorphism is known to be the absence of the Alu element, which can be used to root trees of population relationships. The research within my laboratory is focused around the characterization of mobile element based genetic variation.

There are currently five major research projects within the laboratory. Human population genetics & genomic diversity, non-human primate comparative genomics, forensic genomics, the genetic basis of healthy aging in humans, and the development of low cost high throughput technology for DNA sequencing and genotyping.

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elements termed Yb has a similar evolutionary pattern to that of AluYa5.

In their manuscript, Dr. Batzer and his co-workers describe a “stealth driver” model for Alu retrotransposition in the human genome, where low-activity Alu elements are maintained in low-copy number for long periods of time and occasionally produce short-lived hyperactive progeny that contribute to the formation and expansion of Alu elements in the human genome. “In contrast to ‘master’ genes, ‘stealth drivers’ are not responsible for generating the majority of new Alu copies, but rather for maintaining genomic retrotransposition capacity over extended periods of time,” Batzer explains. “By generating new Alu copies at a slow rate, a ‘stealth driver’ may occasionally spawn progeny elements that are capable of much higher retrotransposition rates. These hyperactive progeny elements may act as ‘master’ genes for the amplification of Alu subfamilies and are responsible for producing the majority of the subfamily members. Due to their high retrotransposition levels, however, they are likely to be rapidly purged from human populations through natural selection.”

Honoring their Excellence—New Professorships Awarded

Eight distinguished professorships were awarded at a reception in April. Front row: Dr. Mark Batzer, George C. Kent Professor; Dr. Jim Moroney, Streva Memorial LSU Alumni Professor; Dr. Graça Vicente, Barré Professor of Chemistry standing next to donor Mr. Charles Barré; Dr. Mark Hafner, DeSoto Parish Alumni Chapter Professor; Dean Kevin Carman. Back row: Dr. Rob Strongin, Webster Parish Alumni Professor; Philip & Foymae West Professor of Chemistry; and Dr. John Battista, Mary Lou Applewite Professor of Biological Sciences. Not in attendance was Dr. Roy Goodrich, Ball Family Professor of Physics.

Leaving the Nest—Five students from Dr. Mark Batzer’s research group graduated with their PhDs in May 2005. Seen here is Dr. Batzer (green shirt) with Drs. Pauline Callinan, Dale Hedges, Anthony Oieno, Anthony Carter and Jinchuan Xing.