International Bioinformatics Effort Reveals Evolutionary Hotspots And Link To Cancers

UC San Diego Professors' Theory Vindicated

July 21, 2005

Doug Ramsey

Comparing the genomes of humans and seven other mammals, an international team of evolutionary sleuths has confirmed a theory put forward by scientists at UCSD two years ago: that fragile regions exist in the human genome that break over and over again in the course of evolution.

The UCSD researchers who advanced that theory of 'fragile' rather than 'random' breakage - Jacobs School of Engineering professor Pavel Pevzner, and mathematics professor Glenn Tesler - were among the team of 25 scientists involved in the new study, reported in the July 22 issue of the journal Science.

The publication appears to put an end to a debate that has raged in the field of bioinformatics. For thirty years before Pevzner and Tesler's 2003 paper in the Proceedings of the National Academy of Sciences, scientists widely agreed that evolutionary changes happened at random locations along the genome. After the UCSD paper disputed that long-held belief, one of the field's pioneers, David Sankoff from the University of Ottawa, claimed to have found a mistake in their logic.

In a keynote to the 13th annual conference on Intelligent Systems for Molecular Biology in late June, Pevzner argued that Sankoff used a flawed algorithm in his analysis, and he says the Science article confirms it.

"We have been waiting to see whether we were right about evolutionary hotspots existing somewhere in the genome," said Pevzner, who holds the Ronald R. Taylor Chair in the Jacobs School's Computer Science and Engineering department. "With this new study, we clearly see the position in these mammalian genomes where rearrangements happen repeatedly, just as earthquakes tend to happen more frequently along geological fault zones."

Among other findings of the study based on computational comparisons of the human, mouse, rat, cow, pig, dog, cat and horse genomes:

Chromosomal evolution has accelerated since the extinction of dinosaurs 65 million years ago; and
Many of the 'preferred' sites of genome rearrangement are also involved in human cancers.

"This study has revealed many hidden secrets on the nature and timing of genome evolution in mammals, and it demonstrates how the study of basic evolutionary processes can lead to new insights into the origin of human diseases," said Harris Lewin, director of the Institute for Genomic Biology at the University of Illinois, Urbana-Champaign (UIUC), who led the study with William J. Murphy of Texas A&M University.

"The goal of this study was to put together a unified view of genomic architecture of all mammals whose genomes are known to a sufficient degree of resolution," said Tesler. "This allows us to infer common ancestors

of the various creatures. We also looked at common features and came up with long regions that never were broken in the course of evolution."

In all, 1,159 pair-wise breakpoints were found among the genomes of human and six non-primate species. Using a bioinformatics tool, researchers aligned and compared the breakpoints across species and constructed an evolutionary scenario for chromosomal rearrangements among all genomes and ancestors.

According to the study, one of the most gene-dense regions of the human genome is characterized by recurrent breaks in different mammalian lineages, notably dog, cat, cattle, and rodents. "Nobody yet understands why certain locations are fragile," said UCSD's Pevzner. "Many people are trying to answer this question, but I suspect it will take another couple of years to find an answer."

Cancer Connection?

Chromosomal breakpoints have been implicated as potentially major triggers for cancers and many other human diseases. The multi-species comparison showed significant overlapping with breakpoints that occur in a variety of human cancers. The researchers theorize that chromosome rearrangements that result in the activation of cancer-causing genes are related to the propensity of chromosomes to break and form new combinations as new mammalian species evolve.

"This is probably the first large-scale demonstration that certain recurrent cancer breakpoints happen around areas where evolutionary rearrangement occur," said Pevzner, whose lab is collaborating separately with UC San Francisco medical researchers on a study of chromosomal rearrangements in cancer. "But it will require much higher-resolution data to prove convincingly that there is a correlation between evolutionary fragility and cancer fragility."

Speed of Evolution

Rates of evolutionary change were obtained by analyzing the placements of breakpoints in the genomes of the species studied. The study estimates that since a massive comet or asteroid struck Earth 65 million years ago and triggered the extinction that killed off the dinosaur, rates of chromosomal evolution among the species have increased from two- to five-fold.

"The widespread origin and diversification of most mammalian orders after the dinosaur extinction, due to exploitation of new ecological niches, may have facilitated isolation and opportunities for the fixation of chromosomal differences," said Texas A&M's Murphy.

For his part, UCSD's Pevzner notes that the speed of discovery in genomics is also accelerating. "Just two years after we predicted the existence of these evolutionary hotspots, this international team was able to identify the regions of the human genome where rearrangements are more likely to occur," said Pevzner. "This pace of discovery is phenomenal if you consider that it took more than 14 years for someone to photograph Pluto after astronomer Percival Lowell first predicted the existence of 'Planet X.'"

Media Contact: Doug Ramsey, Jacobs School of Engineering (858) 822-5825


HUMAN
FERUNGULATE ANCESTOR
BOREOEUTHERIAN ANCESTOR
HUMAN/MOUSE/RAT ANCESTOR