Chromosome breakpoints contribute to genetic variation

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A new study reveals that - contrary to decades of evolutionary thought - chromosome regions that are prone to breakage when new species are formed are a rich source of genetic variation.

The functions of genes found in these "breakpoint regions" differ significantly from those occurring elsewhere in the chromosomes. This suggests that chromosomal organization plays an important evolutionary role, the researchers report.

The study, published in the journal *Genome Research*, is the first to show that different parts of chromosomes can have very different evolutionary histories, said University of Illinois animal sciences professor Harris Lewin, who led the research. Lewin directs the Institute for Genomic Biology and is part of an international team that sequenced the cow genome.

"Our results demonstrate that chromosome breakage in evolution is non-random and that the breakpoint regions and the more stable regions of chromosomes are evolving in distinctly different ways," he said.

When egg or sperm cells form in animals, maternal and paternal chromosomes first pair up and then recombine. The chromosomes literally break and reattach to one another. In most cases, the new chromosomes have the same arrangement of genes as the parent cells, but with new combinations of maternal and paternal genes.

The "crossing over" of segments of maternal and paternal chromosomes to form hybrid chromosomes has long been acknowledged as a driver of genetic variation.

Sometimes, however, the wrong chromosomes recombine, segments of chromosomes become inverted or complete breakages and fissions occur. These rearrangements may lead to genetic diseases or may contribute to the development of new species.

Until now, scientists have been unable to determine how the organization of genes along chromosomes and variation within the breakpoint regions contribute to the evolution of an organism's genome, Lewin said. Breakages sometimes disrupt genes or gene families that are regulated together, for example. Deletions, insertions and inversions can cause subtle or dramatic changes in how the genes function.

Scientists once hypothesized that chromosomal breakage and recombination occurred randomly along the chromosomes during evolution. But in 2003, a team from the University of California at San Diego and the Lewin laboratory reported that the breakpoints occurred more often in specific chromosomal regions than in others.

In 2004, Lewin and his colleagues reported a surprising finding: Breakpoint regions also contain a higher density of genes than other parts of the chromosome. In 2005, Lewin's team showed that breakpoint regions also have higher numbers of segmental duplications, a type of mutation that increases the copy number of genes and the sequences that flank them.

"To me, this was completely counterintuitive. I thought we would have these breakpoints in gene deserts," Lewin said. "We had to rethink the whole evolutionary hypothesis about what was going on in breakpoints."

In the new study, Denis Larkin, a senior scientist on Lewin's team, compared the chromosomes of nine mammals (human, chimp, macaque, rat, mouse, pig, cattle, dog, opossum) and a chicken. He found that the breakpoint regions contained many more copy number variants, insertions and deletions in their sequences than the other parts of the chromosomes. Such variations appear to make these regions more susceptible to breakage, Lewin said. (The chromosome analysis was facilitated by Evolution Highway, a powerful software tool developed in collaboration with Michael Welge and Loretta Auvil at the National Center for Supercomputing Applications at the University of Illinois.)

The researchers also found that different classes of genes appear in the breakpoint and break-resistant regions of chromosomes. Those in the breakpoint regions code for proteins involved in immunity and muscle contraction, for example. Rearrangements may cause copies of such genes to increase or change the way they are regulated. These new sources of variation may then be subject to natural selection, the mechanism of evolution proposed by Charles Darwin.

The genes in more stable parts of the chromosomes are involved in growth and development, particularly embryonic development. Disruptions to these genes would probably be harmful to the organism as a whole, Lewin said.

"If the chromosome rearrangement is really bad for the organism, it will be eliminated. It won't survive," he said. "So if something persists in the genome, it generally has to either be neutral, or it has to be of some benefit."

Evolutionary biologists have historically focused on small changes in the genome - such as point mutations or the insertion of viral genes - that sometimes lead to the development of new forms, Lewin said.

"But by overlooking the importance of chromosome rearrangements, these earthquakes in the genome, they may have missed a key component of the mechanism for generating the variation used by natural selection," he said.

Source: University of Illinois at Urbana-Champaign (news : web)