MedicalXpress

Length of flanking repeat region and timing affect genetic material

October 6 2011

In children with genomic disorders, often a gamete – egg or sperm – has gone disastrously awry with either a duplication or deletion of genetic material that results in physical and neurological problems for the subsequent child.

Previous studies have identified a procedure called nonallelic homologous recombination, which occurs during meiosis or sexual cell division, as the event that most commonly occurs and results in this mistake in DNA.

Researchers from Baylor College of Medicine, studying large groups or cohorts of families in which a child has a genomic disorder, propose that many of these disorders occur during a period in meiosis called the synapse, when homologous (similar in length and containing genes for the same biological feature) chromosomes pair. One of the pair (an allele) comes from the mother; the other from the father. When these chromosomes do not pair with the proper partner or in the proper place, the DNA may cross over, resulting in the loss or duplication of genetic material.

In a report published online in the *American Journal of Human Genetics*, Dr. James R. Lupski, vice chair of molecular and human genetics at BCM, graduate student Pengfei Liu and colleagues studied the deletions of genetic material in 131 patients with a genomic disorder called Smith-Magenis syndrome and the duplication of genetic material in 79 patients with Potocki-Lupski syndrome.

"They are reciprocals in terms of molecular characteristics," said Liu, who is first author of the report. "That means that one set of patients has a duplication in a region of the human genome where the other set has a deletion. Thus their diseases are different."

Even some of the physical characteristics are mirrors. "We see obesity in people with the deletion and a leanness in those with the duplication," said Lupski.

All these genetic changes are de novo, which means they are recognized first in the patients with syndrome, neither parent has the event or the disease. However, the change actually occurred during production of the sperm or egg from a parent.

Lupski compares what happens in the genome to what occurs when a person tries to type material from a book on a computer screen. Sometimes, the person's eyes skip over part of the sentence to an identical word or repeat, leaving out the words in between and creating an entire new and wrong thought. At other times, the person types and retypes a portion of the sentence, resulting in a nonsensical paragraph.

In Smith-Magenis syndrome, children have developmental delay, low muscle tone and a host of behavioral and physical characteristics that help define the syndrome clinically. The disorder occurs when a piece of chromosome 17 is missing or deleted.

In Potocki-Lupski syndrome, a duplication of genetic material occurs at the same place on the same chromosome. The children also have developmental delay, speech and learning problems, low muscle tone and autism.

In this study, Lupski and Liu, in collaboration with Dr. Phil Hastings, professor of molecular and human genetics at BCM, worked out the

mechanism by which the rearrangements occur during meiosis.

"We counted the frequency of the six different types of rearrangement and tried to correlate why some occur more frequently than others," said Liu. "Whenever the flanking homology is longer, this ectopic (wrongly placed) recombination occurs more easily."

Many times, in genomic disorders caused by deletion or duplication of genetic material, the rearranged segments of the genome are flanked by large homologous low copy repeat (repeated sequences of DNA) structures. When non-allelic (out of sync) or ectopic recombination occurs in these flanking regions, the intervening segment of DNA is duplicated or deleted.

"This was a surprising result to us," said Liu. "Before now, most people thought that homologous recombination at allelic positions suggests that the search for homology (sections of DNA with which to pair) is restricted to a very short DNA segment. Our results indicate that the length of segment that participates is much longer when recombination occurs at non-allelic positions. We postulate that this pairing precedes recombination, probably during synapsis (when maternal and paternal chromosomes associate side-by-side during sexual cell division called meiosis). This may give an explanation as to why many of the genomic disorders arise – because chromosomes misalign during synapsis."

"We think this means there may be ectopic synapsis (mispairing of the chromosomes) that occurs first and then the ectopic recombination," he said.

"The interesting thing is that we are not actually looking at synapsis, but instead at patient numbers," said Lupski. "We can infer from these patient numbers what is going on in meiosis in the sperm and eggs."

"This could represent an example wherein results from studying our 'model organism', Homo sapiens, can provide insights into the workings of the other organisms," said Liu.

Provided by Baylor College of Medicine