DNA template could explain evolutionary shifts

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Rearrangements of all sizes in genomes, genes and exons can result from a glitch in DNA copying that occurs when the process stalls at a critical point and then shifts to a different genetic template, duplicating and even triplicating genes or just shuffling or deleting part of the code within them, said researchers from Baylor College of Medicine in a recent report in the journal *Nature Genetics*. The report further elucidated the effect of the fork stalling and template switching mechanism involved in some forms of copy number variation.

"I think this is going to make people think very hard about copy number variation with respect to genome evolution, gene evolution and exon shuffling," said Dr. James R. Lupski, vice chair of molecular and human genetics at BCM and senior author of the report.

The mechanism not only represents a newly discovered method by which the genome generates copy number variation among genes, but it also demonstrates that copy number variation can occur at a different time in the life of a cell. DNA replication takes place as the cell is dividing and becoming two - a process known as mitosis.

Copy number variation involves structural changes in the human genome that result in the deletion of genes or parts of them or extra copies of genes. Often, this process is associated with disease or with evolution of the genome itself.

DNA (deoxyribonucleic acid) exists as two complementary strands that

remain together because of the attraction between nucleotides. A, or adenine, is always attracted to T, or thymine. C, or cytosine, is always attracted to G, or guanine.

When a cell divides, it must reproduce its DNA so that each cell that results from the division has the same genetic code. That means it must replicate its DNA. During this process, an enzyme called a helicase separates the two strands, breaking the hydrogen bonds between the A - T and G - C base pairs. The two separating strands become the replication fork. On one strand, an enzyme called DNA polymerase reads the genetic material in the strand as a template and makes a strand of complementary DNA to pair to it. Again, the code is A to T and C to G. This process is continuous. On the lagging strand, the complementary strand is made in short, separated segments by a process that involves RNA and a series of enzymes.

Until the 1990s, researchers studying reasons for genetic mutations or changes looked at molecular "typos" in this process, tiny changes in the As, Ts, Cs or Gs called single nucleotide polymorphism (SNPs). They changed the message of the gene. However, in the early 1990s, Lupski was one of the early champions of a newly discovered mechanism in which the structure of the DNA itself was grossly duplicated or deleted to change numbers of copies of a gene that occurred in the genetic material. This "copy number variation" wrote a new chapter in the understanding of human genetic variation.

In a previous report (www.bcm.edu/news/item.cfm?newsID=1038) , Lupski and colleagues described how the process that copies DNA during cell division stalls when there is a problem with the genetic material. In some cases, the process seeks a different template, often copying another similar but significantly different stretch of DNA before it switches back to the appropriate area.

In this newer report, Lupski and colleagues describe how this process - called fork stalling and template switching (FoSTeS) in humans or microhomology-mediated break-induced replication (MMBIR) in simpler models - generated genomic rearrangements ranging in size from several megabases to a few hundred base pair during normal cell division, resulting in the duplication or even triplications of individual genes or the rearrangements of single exons (the coding region of genes).

"This phenomenon occurs throughout the genome," said Dr. Feng Zhang, a postdoctoral associate in Lupski's laboratory and the first author of the report.

In studies of subjects with abnormalities in the gene associated with Charcot-MarieTooth type 1A (PMP22), the researchers found that the fork stalling, template switching phenomenon explained the changes, from those that involved triplication of a gene to others that resulted from shuffling within an exon.

Studies of one family - two children and a mother - demonstrated that the event occurred during mitosis or cell division, a significant finding that further confirms the significance of the event.

The researchers noted that finding this mitotic rearrangement of the gene in the mother, who did not have the disorder, of two children with a neuropathy suggests that the mechanism might be considered in genetic counseling about the risk of having another child with the disorder.

The scientists wrote, "We propose that FoSTeS/MMBIR may be a key mechanism for generating structural variation, particularly nonrecurrent CNV (copy number variation), of the human genome. "

The observation of mosaicism for an apparent mitotically generated, FoSTeS/MMBIR-mediated complex PMP22 rearrangement in the

unaffected mother of two children with neuropathy suggests this mechanism can have
implications for genetic counseling regarding recurrence risk.

More information: www.nature.com/ng/index.html

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