Researchers gain insight into mechanism underlying Huntington's

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Researchers at the University of Kentucky Markey Cancer Center and Graduate Center for Toxicology (GCT) have gained new insight into the genetic mechanisms underlying Huntington's disease and other neurodegenerative or neuromuscular disorders caused by trinucleotide repeats (or TNRs) in DNA.

The research, performed in the laboratory of Dr. Guo-Min Li, UK professor of toxicology and biochemistry and the Madeline James & Edith Gardner Distinguished Chair in Cancer Research, examined the mechanisms involved in the development of a specific type of genetic mutation known as trinucleotide repeat expansions. Diseases associated with these mutations, including Huntington's disease, are called trinucleotide repeat disorders.

Findings were published today in *Nature Structural & Molecular Biology*. GCT research scientist Caixia Hou, student Nelson Chan, and professor Liya Gu are coauthors of the study.

"Mutations - the genetic changes in DNA - can lead to many different types of disease, depending on where and in what manner they occur," Li said. "How these genetic changes escape normal DNA repair systems and become ingrained in an affected gene pool leading to familial disorders has been a longstanding subject of study in my laboratory at the UK Medical Center."

The expansion of TNRs at unique sites in the human genome is

associated with at least 15 familial, neurodegenerative or neuromuscular disorders. The mechanism of TNR instability is poorly understood. However, because DNA expansions require DNA synthesis, DNA replication and/or DNA repair must be involved.

Two key TNRs, CAG and CTG repeats - associated with Huntington's disease and myotonic dystrophy, respectively - tend to form hairpin structures via strand slippage in the newly synthesized or "nicked" DNA strand during DNA synthesis associated with DNA replication and/or repair. These hairpin structures are highly thermo-stable and do not "melt" under normal physiologic conditions, and thus they are perceived as "fixed" in the DNA once formed, thereby leading to TNR expansions.

Using an extract of human cells, Li and his colleagues identified a novel DNA repair pathway referred to as DNA hairpin repair (HPR), which specifically targets TNR hairpin removal in the daughter DNA strand, ensuring the fidelity of the TNR sequences in the parental strand. It is proposed that defects or inadequacies in the HPR system may be responsible for TNR instability in the disease state.

More information: http://www.nature.com/nsmb/index.html

Source: University of Kentucky