Team identifies DNA element that may cause rare movement disorder

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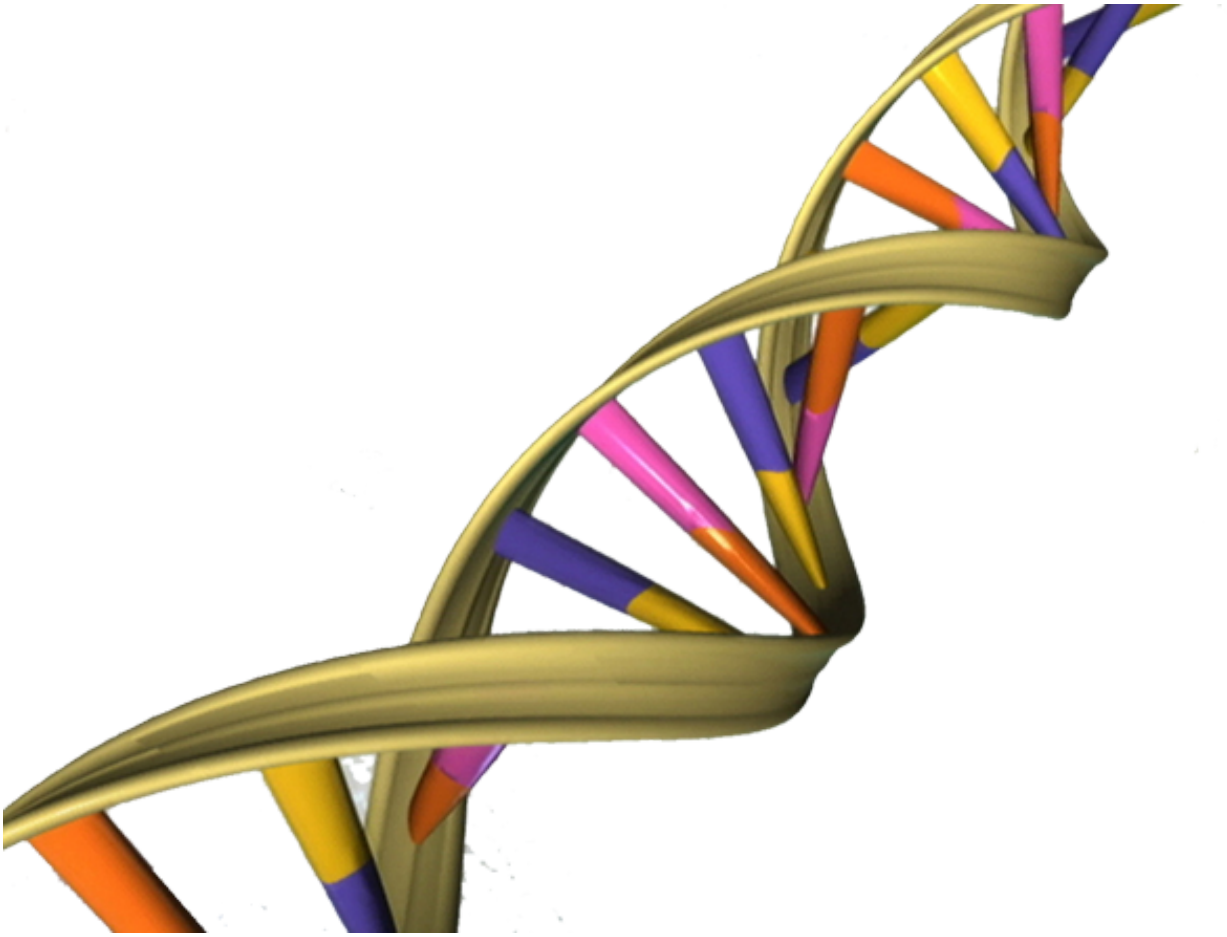

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

A team of Massachusetts General Hospital (MGH) researchers has identified a specific genetic change that may be the cause of a rare but severe neurological disorder called X-linked dystonia parkinsonism (XDP). Occurring only among individuals with ancestry from the Philippines island of Panay, XDP combines features of two common movement disorders, dystonia and Parkinson's disease, in an unusual pattern and significantly shortens the life of affected individuals.

This discovery, which is receiving online publication in *PNAS Early Edition*, represents the work of the Collaborative Center for X-linked Dystonia Parkinsonism in the MGH Department of Neurology, directed by Nutan Sharma, MD, PhD, and Cristopher Bragg, PhD, who with Laurie Ozelius, PhD, is a co-senior author of the report.

"XDP causes certain nerve cells within the brain to progressively die, and its cause has been difficult to understand," explains Bragg. "Before our study it had been reported that all XDP patients share seven changes in their DNA in an identical pattern known as a haplotype, but it was not known which, if any, of these changes might be responsible for the disease. We have now shown that the pattern in patients is actually not identical and that variation in one of these sequence changes strongly determines the age at which symptoms first appear."

These initial symptoms most often involve dystonia - involuntary muscle contractions that can force body parts into abnormal, sometimes twisted positions. Symptoms appear most commonly around the age of 40 and may affect multiple muscle groups - particularly the head and neck, which can interfere with the ability to speak and swallow. Over time patients also develop Parkinson's-like symptoms, such as slowness of movement and a shuffling gait, and become more disabled as the disease progresses. In many cases, patients die from complications, including infections and pneumonia.

The DNA sequence changes associated with XDP are all located on the X chromosome, clustering around a gene called TAF1, which regulates how genes are expressed within cells. One of these sequence changes is an insertion of a large fragment of DNA known as a retrotransposon, a type of DNA element that can move from one site in the genome to another. While the majority of retrotransposons in the human genome are benign, some are inserted at sites that disrupt the normal function of surrounding genes and cause disease. The team led by Ozelius and Bragg analyzed the sequence of the XDP retrotransposon in 140 patients from the Philippines and North America and discovered significant differences between patients in the length of a segment consisting of repetitive DNA sequences. The number of repeats was correlated with the age at which symptoms first appears - patients with longer repeat tracts developed XDP at earlier ages, while those with shorter repeat lengths did not exhibit symptoms until later in life.

"These are the first data directly linking a DNA sequence in XDP to a clinical disease manifestation, which is the strongest evidence to date that this retrotransposon is the likely cause of this disease," says Bragg.

Ozelius adds, "It further reveals that XDP is another example of what are called DNA repeat expansion diseases, many of which affect the brain such as Huntington's disease and some forms of amyotrophic lateral sclerosis. A major question now is whether therapies being developed for those disorders may have similar benefits for patients with XDP."

Sharma, also a co-author of the *PNAS* report, explains, "Currently available treatments for XDP are extremely limited, consisting of only a few oral medications, injections of botulinum toxin into affected muscles to relieve painful muscle contractions, and deep brain stimulation, which is a complex neurosurgical procedure. But the vast majority of XDP patients live on Panay, where such treatments are not

readily available. Part of the mission of our center, in addition to the research we perform, is to improve delivery of care in those regions, which we are working hard to do in partnership with affiliated organizations in the Philippines."

More information: D. Cristopher Bragg el al., "Disease onset in X-linked dystonia-parkinsonism correlates with expansion of a hexameric repeat within an SVA retrotransposon in TAF1," *PNAS* (2017). www.pnas.org/cgi/doi/10.1073/pnas.1712526114

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