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Team identifies genetic defect that may cause rare movement disorder

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A Massachusetts General Hospital (MGH)-led research team has found that a defect in transcription of the TAF1 gene may be the cause of X-linked dystonia parkinsonism (XDP), a rare and severe neurodegenerative disease. The study, published in the February 22 issue of *Cell*, is a collaboration between the laboratories of Michael Talkowski, PhD, and Cristopher Bragg, PhD, both of the MGH

Department of Neurology and the Collaborative Center for X-linked Dystonia Parkinsonism (CCXDP).

"Even though the first clinical descriptions of this disease were published more than 40 years ago, it has been difficult to determine its cause or what might be done to treat it," says Talkowski, who is also a member of the MGH Center for Genomic Medicine. "Perhaps the biggest challenge with XDP has been understanding its genetic basis, and without knowing the causative gene defect, it has been hard to hypothesize about the underlying disease mechanisms."

Occurring only among individuals with ancestry from the Philippines island of Panay, XDP causes the death of certain cells within the brain. Symptoms begin around age 40 with dystonia - involuntary muscle contractions that can force the body into abnormal, sometimes twisted positions - and eventually proceed to Parkinson's-like symptoms, such as slowness of movement and a shuffling gait. Patients become progressively more disabled as the disease progresses and often die from complications such as infections or pneumonia.

Prior to this study, it had been reported that all individuals with XDP share seven DNA sequence changes, which cluster within a region of the X-chromosome that includes the TAF1 gene. Bragg explains, "These sequence changes have always appeared to be inherited together; in other words, all reported patients had all seven sequence variants, and none have ever been found in unaffected people. Because of this pattern, it had not been possible to determine which, if any, of these changes may be pathogenic."

To address that question, Talkowski and Bragg worked with CCXDP Director, Nutan Sharma, MD, PhD, to mount the largest genomics study ever performed for XDP, analyzing a total of 792 DNA samples from individuals with XDP and their unaffected relatives, as well as historical

samples from studies dating back to the initial descriptions of the disease. The analysis of these samples revealed a far greater genetic diversity among XDP patients than was previously known. While most shared a total of 54 unique sequence changes in a collection of variants known as a haplotype, in some individuals the haplotype had been broken apart due to genetic recombination. By comparing these recombination events, it was possible to narrow the disease-causing genomic segment to a smaller region that contained only the TAF1 gene.

To further pinpoint any altered functions associated with these variants, the Bragg laboratory reprogramed skin cells from patients with XDP and their healthy relatives back into stem cells, which differentiated into neural progenitor cells and then mature neurons. Talkowski's team used RNA sequencing to characterize TAF1 expression patterns and found a defect in how the DNA sequence is transcribed into RNA in neural cells from XDP patients. In those cells, a portion of the TAF1 RNA appeared to terminate prematurely, which reduced expression of the full-length RNA. The truncated TAF1 RNA ended close to a known XDP-specific sequence variants - a large DNA insertion known as a retrotransposon. To determine whether the retrotransposon caused the transcriptional defect, the Bragg lab used genome editing tools to remove the sequence, which restored RNA transcription and normalized TAF1 expression.

In a separate study published last December in *PNAS*, Bragg and colleague, Laurie Ozelius, PhD, also of MGH Neurology, had analyzed the sequence of the retrotransposon in patients with XDP and found that it contained a segment of repetitive DNA that was longer in patients who developed symptoms at an earlier age and shorter in those whose symptoms appeared later. Bragg says, "The combined results of these two studies provide the strongest evidence to date that this retrotransposon is the most likely cause of XDP."

Talkowski adds, "We cannot say definitively that this mechanism is the

sole cause of XDP. There is still much work to do. However, it is a major step forward in understanding the defects that occur in patients' cells, and the integrated genomic approaches we have used might be applicable to other unsolved disorders. This finding in XDP is particularly exciting given the tremendous advances that have occurred in recent years with RNA-based therapeutics. The possibility that XDP may result from defective transcription means there may be ways to treat it, and that is certainly cause for hope."

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