# Scientists identify abnormal disease pathway in dystonia

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Scientists tried creating a laboratory model of idiopathic torsion dystonia, a neurological condition marked by uncontrolled movements, particularly twisting and abnormal postures. But the genetic defect that causes dystonia in humans didn't seem to work in the laboratory models that showed no symptoms whatsoever.

Now, a team of scientists at The Feinstein Institute for Medical Research have figured out why and the finding could lead to ways to test novel treatments. Aziz M. Ulug, PhD, and his colleagues at the Feinstein's Center for Neurosciences wanted to understand why some people with a gene that causes dystonia never get symptoms and others with the same mutation are disabled by the abnormal movements. Since the first dystonia gene was identified in the 1990s, scientists have observed that most people who carry this mutation never develop symptoms.

Last year, a team led by David Eidelberg, MD, head of the Feinstein Institute's Center for Neuroscience, figured out why the majority of these mutation carriers are protected from symptoms – they have an additional lesion that evens the score. In an article published in the Journal of Neuroscience, the team described two separate areas along the brain pathway that links the cerebellum to the motor cortex. The integrity of the pathway in these two regions together determines whether a mutation carrier will display clinical manifestations of the disease.

New advances in diffusion imaging in humans led to the discovery that

there were two places along the motor pathway that seemed to stop the flow of neural signals from one part of the circuit to the other. Those with only one lesion in the circuit developed the debilitating movements and those with two lesions did not. "We found a consistent cerebellar pathway problem in all DYT1 carriers. When we went back and looked at those without symptoms, we saw that they had an additional lesion downstream in the portion of the pathway connecting directly to the motor cortex," said Dr. Eidelberg. "This second area of pathway disruption abrogated the effects of the first lesion."

Normally, the cerebellum (a region that controls movement) puts the breaks on the motor cortex by potentiating inhibition at the cortical level. It is likely that mutation carriers have a developmental problem in the flow of neural signals along this circuit such that the brain cannot inhibit an unwanted movement. With the second pathway lesion, Dr. Eidelberg explained, "the flow is shut off and the abnormal activity stops."

The Feinstein team has since looked at laboratory models to try to figure out why this second lesion is protective. Since the identification of the DYT1 gene, scientists have been trying to create a genetic model of the movement disorder. But when they placed the same mutation in an experimental mouse model, there was a major problem: no symptoms. Dr. Ulug's team used a novel magnetic resonance approach to understand why the mutant animals were clinically normal. They found that the mutant mice displayed the same two pathway abnormalities that were found in the human gene carriers. However, the animals had dual lesions across the board, resembling the 70 percent of carriers who fail to display clinical manifestations of the disease. The study was published in the *Proceedings of the National Academy of Sciences.*

Knowing this critical piece of the puzzle may enable scientists to create true laboratory models of the disease – with symptoms that mimic what is seen in patients. These findings may help to design treatments to make

the symptomatic carriers of dystonia genes more like their unaffected counterparts with the same genetic mutation.

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