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Potential treatment for most common form of muscular dystrophy

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Dr. Mani S. Mahadevan first identified the gene responsible for myotonic muscular dystrophy and now has come up with a potential new treatment for the

disease.

A doctor who was one of the discoverers of the gene responsible for myotonic muscular dystrophy has now identified a drug that could slow the progression of muscle damage and muscle dysfunction associated with the disease – issues that cause patients significant disability and deterioration in quality of life.

The potential treatment is an experimental drug currently being evaluated for treating other conditions, such as rheumatoid arthritis. In lab tests, mice with myotonic dystrophy that were given the treatment had better muscle function in tests such as running on a treadmill and had improved grip strength. In addition, their muscles became healthier and, notably, many even lived longer. While more testing needs to be done, Dr. Mani S. Mahadevan of the University of Virginia School of Medicine, is hopeful about the drug's potential in humans as well.

"The nice thing about this therapy is that we know that it's already been shown to be safe, because clinical trials have already been done with it for other conditions. That's a big, big hurdle that's been overcome," he said. "With a lot of drugs, the problem is that once you do these proof-of-concept studies, the drugs need to be developed a lot further, refined and tested for safety and efficacy. But a lot of that work has been done, so therefore we can leapfrog the development of this therapy so that it can be moved into clinical trials sooner."

Mahadevan, of U.Va.'s Department of Pathology, has been conducting pioneering research into the causes of myotonic dystrophy, the most common form of muscular dystrophy, for more than two decades. His work revealed that the condition is caused by an expanding piece of DNA – a mutation that grows worse with each generation. Many people,

he noted, do not even realize they have the mutation until a child or grandchild is born with a severe form of the disease.

In his latest discovery, Mahadevan and his team determined that in both mice and people with myotonic dystrophy, their muscles exhibit excessive activity of a cellular protein called TWEAK and its receptor, Fn14. And not only are the activity levels high in these tissues, they correlate with the severity of the disease symptoms.

With that discovery, Mahadevan approached the biotech company Biogen Idec, which had a longstanding interest in the TWEAK pathway, to see if the company had a therapy that could block the activity. Biogen Idec had just such a drug in development. After a multi-year collaboration with the company, Mahadevan and his team were able to show that this drug reduced the symptoms of myotonic dystrophy in mice – thus illuminating a path toward the first potential treatment for the debilitating muscle wasting seen in humans.

The drug has not yet been approved by the Food and Drug Administration, and therefore is not available to patients. The next steps would be for the drug to be tested in myotonic dystrophy patients as part of a clinical trial to determine if it is effective. Mahadevan isn't sure when such a trial might begin.

He notes that the drug might be used as a treatment for myotonic dystrophy on its own or possibly in conjunction with other approaches that are in the pipeline. "There's a lot of excitement within the patient community and within the field of researchers who are working on myotonic dystrophy right now," Mahadevan said. "There's a lot of hope."

A paper outlining the findings has been published online by the journal *Human Molecular Genetics*.

More information: "TWEAK/Fn14, a pathway and novel therapeutic target in myotonic dystrophy" *Hum. Mol. Genet.* (2015) 24 (7): 2035-2048 first published online December 11, 2014 DOI: 10.1093/hmg/ddu617