

# Researchers trace effects of genetic defect in myotonic muscular dystrophy

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Research on the genetic defect that causes myotonic muscular dystrophy has revealed that the mutation disrupts an array of metabolic pathways in muscle cells through its effects on two key proteins. A study published in *Nature Structural & Molecular Biology* shows that the loss of a single protein accounts for most of the molecular abnormalities associated with the disease, while loss of a second protein also seems to play an important role.

Each of the affected proteins interacts with an array of genes that are active in [muscle cells](#) and other tissues, said coauthor Manuel Ares, professor of molecular, cell, and developmental biology at the University of California, Santa Cruz. The study reveals a cascading sequence of molecular events in which a mutation in one gene ends up affecting hundreds of other genes and the physiological processes that depend on them.

"This is a genetic disease in which there isn't just one gene that is affected," Ares said. "Our hope is that by chasing down more of the affected genes we might be able to figure out how to address more of the symptoms."

Myotonic dystrophy involves difficulty relaxing muscles (myotonia) and, as in other muscular dystrophies, progressive muscle weakness and wasting. The most common type of myotonic dystrophy (type 1) is caused by changes in a gene that has a repeating sequence of three DNA building blocks. This sequence is repeated five to 35 times in the normal

gene, but an excessive number of repeats (50 to 5,000) leads to disease. When the defective gene is transcribed into a messenger RNA molecule, the expanded repeat section causes the RNA to bind tightly to certain proteins, forming clumps within the [muscle cells](#).

"Previous studies have shown that two proteins called Mbnl1 and Mbnl2 are bound up by the repeat RNA and create an aggregate inside the nucleus of the muscle cell," Ares said.

By binding these proteins in clumps, the abnormal RNA prevents them from carrying out their normal functions in the cell. Mbnl1 is involved in a process called RNA splicing, in which the messenger RNA copied from a gene gets "edited" before it can direct the synthesis of proteins.

"When a gene is turned on, its DNA sequence gets copied into a messenger RNA molecule. But that direct copy needs to be processed to make a functional message that can be translated into a protein," Ares said. "Splicing factors like Mbnl1 tell the splicing machinery where to do the cutting and pasting. Without Mbnl1, incorrect splicing can affect lots of different genes."

Ares has pioneered the use of microarray technology to detect changes in RNA splicing caused by genetic [mutations](#) and other perturbations. UCSC graduate student Hongqing Du, the first author of the paper, earned her M.D. from Harbin Medical University in China and was eager to apply this technology to a human disease. So Ares and Du teamed up with leading investigators of myotonic dystrophy who had developed animal models of the disease.

Charles Thornton's lab at the University of Rochester School of Medicine developed a mouse strain that expresses large amounts of the abnormal repeat RNA in muscle cells. Maurice Swanson's lab at the University of Florida College of Medicine developed a mouse strain that

is unable to make the Mbnl1 protein. Both strains of mice show symptoms similar to myotonic dystrophy.

Ares's lab used splicing-sensitive microarrays developed in collaboration with Affymetrix to show that the RNA splicing defects in muscle cells from these two mouse strains are nearly the same. This indicates that the vast majority of the splicing problems are due to the loss of the Mbnl1 protein as a result of binding to the abnormal repeat RNA. Earlier studies had associated several splicing defects with the disease, but the microarrays revealed effects on a much larger number of genes.

"Our microarray methods detected hundreds of splicing events that were being affected, giving us a broader picture of what's going on in cells as the disease is taking hold," Ares said.

Tests for some of the newly identified splicing defects in human patients with myotonic dystrophy confirmed that the same changes occur in both mouse and human cells. More extensive testing in humans will enable the researchers to identify which RNA splicing changes might be clinically useful for diagnosing or monitoring the disease, Ares said.

The researchers also found another set of changes that were seen only in the mouse strain that makes the abnormal repeat RNA and not in the mice lacking Mbnl1. These effects were not splicing errors, but changes in gene expression detected by microarrays that measured the amounts of messenger RNA being transcribed from different genes.

"We suspect that the loss of Mbnl2 is responsible for those gene expression defects," Ares said.

Many of the genes with altered expression levels are involved in making the extracellular matrix, a [protein](#) coat that binds muscle cells together and enables muscle tissue to generate a coherent force when it contracts.

"We're excited by this finding because the group of genes affected is rich in these structural components operating outside the cell to hold the tissue together, and that might explain some aspects of the disease," Ares said. "Some of the genes in this class have been implicated in other kinds of genetically inherited muscular dystrophy and connective tissue diseases, revealing unanticipated links with the myotonic form of muscular dystrophy."

A recent grant from the Muscular Dystrophy Association will enable Ares and his collaborators to investigate how these findings might be used to help patients with myotonic dystrophy. The researchers may be able to develop methods for early detection of the disease or for predicting how the disease will progress in individual patients. Further research could also yield molecular markers of the disease for use in developing and evaluating new treatments.

"Right now we have a bewildering list of splicing events that are going wrong, as well as gene expression defects, and we have a lot of work to do to figure out which are the key events that might be used as reliable markers of the disease," Ares said.

Provided by University of California - Santa Cruz

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