

Discovery of new form of dystrophin protein could lead to therapy for some DMD patients

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Scientists have discovered a new form of dystrophin, a protein critical to normal muscle function, and identified the genetic mechanism responsible for its production. Studies of the new protein isoform, published online Aug. 10 in *Nature Medicine* and led by a team in The Research Institute at Nationwide Children's Hospital, suggest it may offer a novel therapeutic approach for some patients with Duchenne muscular dystrophy, a debilitating neuromuscular condition that usually leaves patients unable to walk on their own by age 12.

Duchenne muscular dystrophy, or DMD, is caused by mutations in the gene that encodes [dystrophin](#), which plays a role in stabilizing the membrane of muscle fibers. Without sufficient quantities of the protein, muscle fibers are particularly susceptible to injury during contraction. Over time, the muscle degenerates and [muscle fibers](#) are slowly replaced by fat and scar tissue. Many different types of mutations can lead to DMD, some of which block dystrophin production altogether and others that result in a protein that doesn't function normally.

In 2009, a team led by Kevin Flanigan, MD, a principal investigator in the Center for Gene Therapy at Nationwide Children's, published two studies describing patients whose genetic mutation was located in an exon 1, at the beginning of the gene. This mutation should have made natural production of functioning dystrophin impossible, resulting in severe disease. However, the patients had only minimal symptoms and relatives carrying the same mutations were identified who were walking well into their 70s. Muscle biopsies revealed that, despite the genetic mutations, the patients were producing significant amounts of a slightly smaller yet functioning dystrophin. In the 2009 studies, Dr. Flanigan's group demonstrated that translation of this dystrophin did not begin in exon 1, as usual, but instead began later in the gene in exon 6, although the mechanism controlling this alternate translation remained

unknown.

In their latest study, Dr. Flanigan's team has found the explanation. In order to utilize the protein-building instructions they carry, exons are first transcribed into a final genetic blueprint called messenger RNA. Under normal conditions, the messenger RNA is marked at its very beginning by a special molecular cap that is critical for recruiting ribosomes, the cellular structures responsible for translation of the gene into a protein. Most cases of DMD are due to mutations that interrupt the translational activity of ribosomes.

In explaining the mild symptoms seen in many patients with mutations in the first exons of the dystrophin gene—including the group of patients they first described in 2009—the researchers have now demonstrated that dystrophin can be produced by an alternate cellular mechanism in which capping of the messenger RNA is not required. This newly described mechanism makes use of an internal ribosome entry site, or IRES, found within exon 5 in the dystrophin gene, allowing initiation of protein translation within exon 6 that can then proceed in the normal fashion along the rest of the gene.

"This alternate translational control element is encoded within the dystrophin gene itself, in a region of the gene that evolution has highly conserved," Dr. Flanigan said. "This suggests that the dystrophin protein that results from its activation plays an important but as of yet unknown role in cell function—perhaps when muscle is under cell stress, one of the conditions under which IRES elements are typically activated."

Although clinical trials are currently investigating drugs to treat the more common gene mutations found in the middle of the dystrophin gene, no current therapies are specifically directed toward the approximately 6 percent of patients with mutations affecting the first four exons. Although

many of these patients have relatively mild disease, many others have much more severe symptoms. If scientists could figure out a way to activate IRES in those patients, they may be able to produce enough dystrophin to lessen muscle degeneration, Dr. Flanigan said.

To study that possibility, his team is developing different approaches to trigger the IRES, using a new DMD mouse model they have developed. One of these approaches, called exon skipping, is based on the removal of an exon early in the gene in order to mimic the IRES-activating [mutations](#) found in minimally affected patients.

"Rather than intending this as a personalized therapy, we are developing this as a tool that could be used for all patients harboring a mutation within the first few exons of dystrophin," said Nicolas Wein, PhD, lead author of the new study and a postdoctoral scientist in the Center for Gene Therapy at Nationwide Children's. "Using this approach, we have already shown that we are able to restore running ability in our new mouse model of DMD. We hope to translate this into clinical trials in DMD [patients](#) in the future."

More information: Wein N, Vulin A, Falzarano MS, Szigyarto CA, Maiti B, Findlay A, Heller KN, Uhlén M, Bakthavachalu B, Messina S, Vita G, Passarelli C, Gualandi F, Wilton SD, Rodino-Klapac LR, Yang L, Dunn DM, Schoenberg DR, Weiss RB, Howard MR, Ferlini A, Flanigan KM. Translation from a DMD exon 5 IRES results in a functional dystrophin isoform that attenuates dystrophinopathy in humans and mice. *Nature Medicine*. [Epub 2014 Aug 10] [DOI: 10.1038/nm.3628](#)

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