MedicalXpress

RNA editing technique treats severe form of muscular dystrophy

October 12 2015

An RNA editing technique called "exon skipping" has shown preliminary success in treating a rare and severe form of muscular dystrophy that currently has no treatment, based on a new study from Northwestern Medicine and the University of Chicago. Children with the disease lose significant muscle strength early in life.

The discovery stems from the persistence of a father—Scott Frewing—whose two sons were diagnosed with a rare and severe form of muscular dystrophy and his search for and partnership with the genetic scientist—Dr. Elizabeth McNally—who studies the disease. The rare form of the disease is Limb Girdle Muscular Dystrophy Type 2C.

McNally is director of the Center for Genetic Medicine at Northwestern University Feinberg School of Medicine and the former director of the Institute of Cardiovascular Research at UChicago, which is where she began the research. She also is a physician at Northwestern Medicine.

The new therapy has been licensed to the Kurt+Peter Foundation, which supports Limb Girdle Muscular Dystrophy 2C research and is being developed with the goal of clinical trials and eventual commercial treatments. The boys' family and friends started the foundation in 2010 to apply promising research to Limb Girdle Muscular Dystrophy Type 2C.

The finding will be published Oct. 12 in the *Journal of Clinical Investigation*.

Originally developed to treat Duchenne Muscular Dystrophy, another form of muscle disease, exon skipping coaxes cells to "skip" over abnormal sections of the genetic code, so that the body can make a functional protein, which in this case, governs muscle function and development.

In the paper, lead investigator McNally summarizes her research in fruit flies and mouse models. Her team, which included Quan Gao a University of Chicago graduate student and Dr. Eugene Wyatt, a postdoctoral fellow at Northwestern, demonstrated that protein made from exon skipping was functional to stabilize and slow progress of the disease. Working with human cells obtained from individuals with the disease, the team showed that exon skipping can be successfully induced with antisense compounds.

"We recognize that this is version 1.0," McNally said. "But if this can stabilize individuals with this disease, even if it gave them 10 more years of walking, that's huge. That would also mean 20 to 30 more years of breathing, and that is hugely beneficial for the patients and for their parents who are caring for them. And, of course, we're interested in developing version 2.0 that will be even better."

Limb Girdle Muscular Dystrophy is caused by mutations in any of at least 15 different genes and affects 1 in 14,500 to 1 in 123,000 annually. Individuals with Limb Girdle Muscular Dystrophy Type 2C have detrimental mutations in a key protein, gamma sarcoglycan, which is necessary for normal muscle development and function. The disease is an inherited disorder that is found in patients around the world and is prevalent in France, northern Africa and parts of South America.

Although children with the disease are able to live normally at young ages, over time their deteriorating muscles prevent them from engaging in a number of typical childhood activities. Many of the children with

the disease are in a wheelchair in their mid-to-late teenage years. Scott Frewing's sons, Kurt and Peter, were diagnosed with the disease in 2009 and 2010 respectively. The boys' family and friends started the Kurt+Peter Foundation in 2010 to apply promising research to Limb Girdle Muscular Dystrophy Type 2C.

In 2010, Frewing, president of the Kurt+Peter Foundation, began proactively looking for scientists researching Limb Girdle Muscular Dystrophy Type 2C and similar forms of muscular dystrophy, with hope of supporting research to find a treatment. When Frewing approached McNally in 2010, she was one of the only researchers worldwide working on the disease. Frewing had heard of exon skipping and wondered if it would work for his boys. McNally didn't think that exon skipping would make the tiny relevant protein in the disease functional. But, after Frewing persisted, she did a predictive analysis, which showed that that less than half of the protein would be left, but that three key parts of the protein remained. The Kurt+Peter Foundation has provided annual grants to fund further evaluation and development of this potential therapy.

"There are always new ways to treat a disease, and sometimes it is the patients and families who push us to think of these," McNally said. "This partnership is a perfect example of how precision medicine can help address very rare diseases."

A new partnership among the University of Chicago, Northwestern University and The Kurt+Peter Foundation will support the development of therapies for Limb Girdle Muscular Dystrophy Type 2C.

The Kurt+Peter Foundation is licensing McNally's research and hopes to turn her discoveries in the laboratory into treatments that could help to slow the decline in muscle function. The Foundation will continue to partner with McNally to further test exon skipping in Limb Girdle

Muscular Dystrophy Type 2C and develop the therapy.

McNally and Frewing are looking to clear the hurdles necessary to begin clinical trials. Obstacles remain to commercialize the treatment, including the high cost of manufacturing the antisense oligonucleotides, the molecules that function to regulate gene expression that are necessary to make the treatment.

"We are thrilled to be able to continue development of this promising treatment technique," Frewing said. "This is a terrible disease affecting children worldwide, and we hope to soon be able to provide families with treatment techniques that can lessen the disease's severity."

The agreement among the Kurt+Peter Foundation, UChicago and Northwestern is the first license UChicago has executed with a foundation.

"This arrangement is a great example of how research institutions and foundations can bring their respective strengths and resources to the table and work together to develop new therapeutics for small groups of patients," said Thelma Tennant, assistant director at UChicagoTech, the University of Chicago's Center for Technology Development & Ventures, the organization that negotiated the agreement between the foundation and institutions. "In a purely market-driven world, these patients would have very few options."

Provided by Northwestern University