Scientists pinpoint earliest steps of common form of muscular dystrophy

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Nearly two decades after they identified the specific genetic flaw that causes a common type of muscular dystrophy, scientists believe they have figured out how that flaw brings about the disease. The finding by an international team of researchers, including scientists at the University of Rochester Medical Center, settles a longstanding question about the roots of facioscapulohumeral muscular dystrophy or FSHD. The work is published in the August 20 issue of *Science*.

Unraveling how the genetic defect causes FSHD has been especially challenging for scientists. Unlike with many genetic diseases, their identification of the mutation that is the basis of FSHD did not quickly lead to a deeper understanding of how the disease actually comes about. The lack of clarity has posed a significant barrier to researchers hoping to turn the knowledge of the genetic flaw into significant progress for patients.

The latest findings clarify the picture significantly. Scientists have discovered that several deleted versions of a gene trigger the remaining copies of that gene to be much more active than usual. That's because the DNA that codes for the gene is not as tightly coiled or elusive to the body's molecular machinery as usual when some copies are missing, and so the gene - known as DUX4, which makes a protein harmful to muscle cells - is more active than it should be.

The work offers up a new therapeutic target to scientists aiming to develop a treatment or cure for the disease.

The research was led by genetics researchers at the University of Leiden in the Netherlands, working together with scientists at the University of Rochester Medical Center, the Fred Hutchinson Cancer Research Center in Seattle, and other investigators. The research was funded by several organizations, including the Fields Center for FSHD and Neuromuscular Research, based at Rochester and at Leiden.

"It is amazing to realize that a long and frustrating journey of almost two decades now culminates in the identification of a single small DNA variant that differs between patients and people without the disease. We finally have a target that we can go after," said Silv?re van der Maarel, Ph.D., professor of medical epigenetics at Leiden and the corresponding author of the paper. Working closely with van der Maarel was the first author of the paper, Richard Lemmers of Leiden.

FSHD is an inherited disorder that usually makes its presence felt in the teen years. First symptoms usually are weakness in the upper body; a person might have trouble lifting the arms, for example. Weakness of the facial muscles is also common, for instance, difficulty smiling or whistling, closing the eyelids completely, or even sipping through a straw. Later on, the condition affects the lower body - the muscles of the feet, legs, and hips. Patients usually live a normal life span, but around 20 percent of patients end up using a wheelchair.

Doctors estimate that about 1 in 20,000 people worldwide, including about 15,000 Americans, have FSHD, which is the third most common type of muscular dystrophy.

It was 18 years ago, in 1992, that a team from the same laboratory in Leiden identified the genetic defect at the root of the disease. The scientists found that in healthy people there are 11 or more copies of a certain DNA sequence dubbed D4Z4 near the tip on chromosome 4. Nearly all FSHD patients have too-few copies - 10 or fewer of the D4Z4 repeat.

Since then the team has worked to understand how that defect translates into the disease. Meanwhile, the University of Rochester built on its history as a

powerhouse of leading muscular dystrophy research and treatment worldwide; Rochester's studies of FSHD were wide ranging and included both clinical and translational research. The University created the National Registry of Myotonic and FSHD Patients and Family Members, which includes information on hundreds of patients who volunteer for research. The FSHD team at Rochester has also established the world's largest repository of biological samples, such as blood, skin and muscle specimens, from individuals with FSHD, a resource that has proven to be crucial in advancing knowledge of the disease.

The groups began collaborating, and their interactions accelerated three years ago, thanks to a gift from New York developer and philanthropist Richard T. Fields.

Now, the team has worked out a crucial step in how the defect leads to disease. The finding draws on the genetics expertise at Leiden, the clinical research experience with FSHD patients at Rochester, and epigenetics knowledge in Seattle.

"In most patients with FSHD, a piece of DNA is missing," said Rabi Tawil, M.D., an author of the Science paper and the neurologist who leads Rochester's FSHD team and the Fields Center. "For a long time it was thought that this was simply junk DNA that was missing, and that the missing material must affect the function of a nearby gene on chromosome 4."

It turns out that each of the D4Z4 repeats contains a copy of a gene known as DUX4, but scientists have not known until recently that DUX4 is a functional gene. When a critical number of copies are missing, the structure of the tip of chromosome 4 becomes more open, making the DUX4 gene more accessible for transcription.

When crucial pieces of DNA that introduce and conclude the repetitive string are composed of certain sequences, the ingredients for molecular mischief are in place, making the remaining copies of DUX4 much more stable than they normally are.

"This provides a new and unifying model for FSHD because it will focus future research on determining whether the DUX4 protein causes FSHD, as indicated by our consortium's genetic analysis," said Stephen Tapscott, M.D., Ph.D., a member of the Human Biology Division at the Fred Hutchinson Cancer Research Center and one of the authors of the Science paper. The team is currently studying how active DUX4 is in patients in FSHD compared to people who do not have the disease.

In previous research, other investigators had identified a nearby gene known as FRG1 as central to the development of FSHD. The teams in Leiden, Rochester and Seattle teams were unable to reproduce those results and instead point to DUX4.

Currently there is no treatment for FSHD that slows the disease or addresses the underlying problem. Typically patients are treated with medications to alleviate their pain, and are given supportive treatment, such as braces and other aids for their arms and legs to help them deal with weakness. There have been a few studies investigating possible treatments - drugs on the market for other conditions - but those haven't turned up anything that works in FSHD patients.

"Interventions tried thus far haven't been based on the science underlying the disease," said Tawil, a professor in the Department of Neurology. "That's why this is such an exciting step. Instead of guesswork, we now have one unified hypothesis, and one target. This marks the first time we can work solidly from basic science to seek a treatment for FSHD."

The team plans to screen existing compounds in a search for one that inhibits DUX4. The group also plans to develop rigorous techniques for measuring the effects of test medications on FSHD patients, and to continue to try to understand how DUX4 damages muscles. Early research indicates that DUX4 hinders the body's ability to regenerate muscle and makes muscles more susceptible to oxidative stress.

More information: *Science* paper: “A Unifying Genetic Model for Facioscapulohumeral Muscular Dystrophy.”

Provided by University of Rochester Medical Center