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Newly published model of FSHD and a potential gene therapy to improve functional outcomes

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Facioscapulohumeral muscular dystrophy (FSHD) is the most prevalent dominantly inherited muscular dystrophy in the world. To date, there are no pharmacologic treatments available for the more than 850,000 people affected worldwide.

Developing models to use for testing potential therapeutics has been a challenge for the research community.

"Just a little over a decade ago, we didn't know the gene or mechanism responsible for FSHD," says Scott Harper, Ph.D., principal investigator in the Center for Gene Therapy in The Research Institute at Nationwide Children's Hospital. "In a relatively short time, we've seen a lot of big changes that will help move the field forward."

One of those advances comes from the Harper Lab. In a study published [today] in *JCI Insights*, Dr. Harper and his team describe a mouse model of FSHD that can be used for the development of therapeutics.

"We present an extensively characterized model that recapitulates many features of FSHD, and we showed it to be useful in studying the effectiveness of experimental therapeutics," says Dr. Harper. "It's the culmination of nine years of work in our lab, and we are confident that it will aid in the discovery and development of therapeutics for patients with FSHD."

DUX4 is the protein responsible for FSHD. When DUX4 is expressed in a cell, it triggers cellular pathways leading to cell death. In the case of FSHD, this cell death occurs in skeletal muscles. FSHD usually presents sometime in the second decade of life or later, though it can occur at any age.

"One of the reasons that it has been challenging to create animal models for FSHD is that DUX4 is so incredibly toxic," says Dr. Harper. "Even small amounts of 'leaky' production of DUX4 make it difficult to get the animals to develop properly. To produce the mice we wanted, we needed to control when and where DUX4 would be turned on in mice."

So how did they do it? The mouse model they created, called TIC-DUX4 mice, only express DUX4 when they are exposed to the drug Tamoxifen. This means that they can develop normally, without DUX4 production. Then, researchers can turn on the DUX4 gene by giving the mice sunflower oil containing Tamoxifen orally. The result is also dose dependent, meaning that the level of DUX4 gene expression can be fine-tuned by adjusting the Tamoxifen dose.

In the publication, the team goes on to describe how they successfully used the model to test AAV1.Follistatin, a muscle-strengthening gene, as a treatment for the muscle weakness in the TIC-DUX4 mice.

"Follistatin has been shown to be safe when delivered to humans with other muscular dystrophies, such as Becker and Duchenne," says Dr. Harper. "While the effectiveness may be limited in those cases, because they are more aggressive, we think that the typically slower progression of FSHD may make it a better candidate for Follistatin therapy. Our experiment here shows that it can help increase muscle mass and strength in the FSHD mice, even in the presence of DUX4 expression. Although more work needs to be done, we believe our study shows that Follistatin gene therapy may prove to be a promising potential treatment

for FSHD-associated muscle weakness."

More information: Giesige CR, Wallace LM, Heller KN, Eidahl JO, Saad NY, Fowler AM, Pyne NK, Al-Kharsan M, Rashnonejad A, Chermahini GA, Domire JS, Mukweyi D, Garwick-Coppens SE, Gukes SM, McLaughlin J, Meyer K, Rodino-Klapac LR, Harper SQ. AAV-mediated follistatin gene therapy improves functional outcomes in the TIC-DUX4 mouse model of FSHD. *JCI Insight*. 2018 Nov 15. [Epub ahead of print]

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