Researchers replicate FSH muscular dystrophy in mice

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A new study published in the journal *Nature Communications* describes a breakthrough in research related to facioscapulohumeral muscular dystrophy (FSHD). The debilitating genetic disease - which has no approved treatment - affects an estimated 38,000 Americans and causes degeneration and wasting of the skeletal muscles.

Scientists from the University of Minnesota Medical School inserted into mice a gene called DUX4, which is believed to cause FSHD in humans. When they activated the gene in the mice skeletal muscle cells, the animals developed a slow progressive muscular dystrophy with key features of the human disease. Previous attempts to generate a mouse model for FSHD have not shown FSHD-like muscle disease.

"In genetic diseases for which therapies have been developed, like Duchenne muscular dystrophy, mouse models like the one we discovered were essential to the development and testing of potential therapies," said principal investigator Michael Kyba, Ph.D., professor within the University of Minnesota Medical School and member of the Masonic Cancer Center, University of Minnesota, "Now that this hurdle has been overcome for FSHD, we have great hope for therapy development.

In addition to providing a way to test therapies for FSHD, the mouse model allows scientists to understand why muscle degenerates in FSHD patients. According to the study's lead author Darko Bosnakovski, Ph.D., "FSHD is a very unusual muscular dystrophy with a completely different and poorly understood mechanism of muscle damage compared to the

more well-known muscular dystrophies. We really do not know why muscle disappears in these patients."

The researchers were surprised to find that when the DUX4 gene was turned on in muscle cells, the mice muscle became inflamed and other cells in the tissue responded by proliferating and overproducing collagen. This led to muscle fibrosis, a condition where contractile muscle cells become replaced by matrix, leading to loss of muscle strength. The involvement of these matrix-producing cells, known as fibroadipogenic progentiors (FAPs), was previously unknown, and suggests that drugs targeting FAPs or fibrosis might be candidates for slowing down the progression of FSHD.

"This study already points to some targets for future drugs, which is very exciting," Kyba added. "With this mouse model, I'm hopeful we'll make progress in our pursuit for a cure."

More information: Darko Bosnakovski et al, Muscle pathology from stochastic low level DUX4 expression in an FSHD mouse model, *Nature Communications* (2017). DOI: 10.1038/s41467-017-00730-1

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