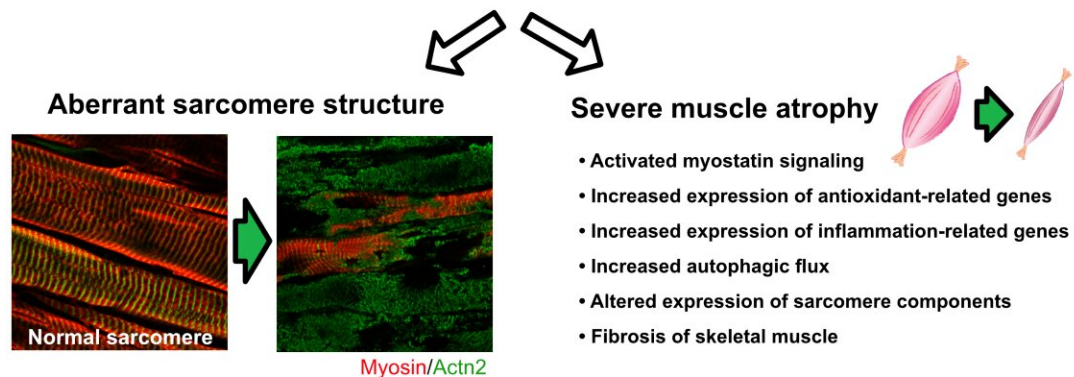


Scientists demonstrate severe muscle atrophy in postnatal mice lacking two critical myosins

December 14 2022

Double knockout mice of skeletal muscle myosins (IIX and IIb) A new animal model for human muscle atrophy



The model mice will promote the development of therapeutic agents for human muscle atrophy

Double myosin knockout mice show anomalous sarcomere structures and exhibit severe muscle atrophy, thus serving as a useful disease model and potentially aiding the development of therapies against human muscle atrophy. Credit: Keisuke Hitachi from Fujita Health University

Muscles are made up of proteins. Myosin, a fibrous protein, serves as a molecular motor and converts the chemical energy stored inside our body into mechanical energy. The synergistic association between the

muscle proteins myosin and actin gives rise to skeletal muscle contraction and relaxation, thus allowing the body to move. Therefore, a decrease in muscle mass (i.e., skeletal muscle atrophy) results in reduced motor function.

Patients with skeletal muscle atrophy suffer from weak and shrinking muscles. However, the genetic underpinnings of human skeletal muscle atrophy disorders are not fully clear. In a recent study published in *The FASEB Journal*, a group of researchers has discovered an association between skeletal muscle atrophy in a mouse model and the simultaneous absence of two types of myosin.

The skeletal muscle myosin heavy chain or "MyHC" is a fundamental component of the sarcomere—the basic contractile unit of a muscle fiber. The corresponding proteins "MyHC-IIx" and "MyHC-IIb," are encoded by the genes *Myh1* and *Myh4*, respectively. Using mice that were simultaneously deficient for MyHC-IIx and MyHC-IIb, the research team delineated—for the first time—the role of MyHC-IIx and MyHC-IIb in skeletal muscle atrophy.

"MyHC-IIx and MyHC-IIb are abundant in fast muscles and produce abundant instantaneous power. MyHC-IIb is barely detectable in human skeletal muscles. We produced genetically modified mice with the simultaneous loss of MyHC-IIx and MyHC-IIb by introducing nonsense frameshift mutations into the *Myh1* and *Myh4* genes, mimicking the loss of MYH1 in human skeletal muscle. Mice deficient in these two types of MyHCs showed very severe muscle atrophy symptoms and died within the first four weeks of life," says Dr. Keisuke Hitachi of Fujita Health University, who planned the overall experimental design.

The researchers made a series of key observations during their detailed double knockout (dKO; knockout of both MyHC-IIx and MyHC-IIb) analyses. For instance, they recorded a drastic reduction in skeletal

[muscle mass](#) in the dKO mice at the weaning phase of 2–3 weeks of age. Although the dKO mice appeared normal after birth and until 2 weeks of age, they started showing severe skeletal muscle atrophy after 2 weeks. Interestingly, the dKO mice also showed low glucose and high cholesterol levels—a sign of impaired nutrition.

In 3-week-old dKO mice, the production of other skeletal muscle MyHCs, such as MyHC-I, MyHC-IIa, MyHC-neo, and MyHC-emb, was elevated. However, this increase could not compensate for the loss of MyHC-IIx and MyHC-IIb. The deficiencies in motor function were further evinced by the abnormal sarcomere structures observed in dKO mice. Overall, the findings indicate that the simultaneous loss of these two key skeletal muscle MyHCs is significantly detrimental to postnatal skeletal muscle function in mice.

Senior author Dr. Kunihiro Tsuchida, a Professor at the Institute for Comprehensive Medical Science, Fujita Health University, says, "The double MyHC knockout experiments indicated that myosin deficiency causes the activation of various signaling pathways that trigger skeletal muscle atrophy. In amyotrophic mice, the microstructures necessary for muscle contraction collapse."

He adds, "The phenotype of the dKO mice was similar to that seen in humans with cancer-induced muscle atrophy. Thus, these dKO mice could serve as a useful animal model and provide insights for developing therapeutics to combat muscle atrophy and muscle-related diseases in humans."

Quite interestingly, skeletal muscle disorders have not yet been linked to the Myh1 and Myh4 genes in humans. However, this study clearly establishes a link between the simultaneous loss of MyHC-IIx and MyHC-IIb and skeletal muscle atrophy in a [mouse model](#), and the linkages could now be explored in humans.

Given that skeletal muscles constitute 30–40% of our body weight and are critical for muscular movement, this study has enormous implications from a translational point of view. It could help elucidate the molecular mechanisms of skeletal muscle wasting disorders caused by the loss of skeletal muscle MyHCs in human [muscle](#) atrophy and potentially aid in the exploration of treatment strategies.

More information: Keisuke Hitachi et al, Simultaneous loss of skeletal muscle myosin heavy chain IIx and IIb causes severe skeletal muscle hypoplasia in postnatal mice, *The FASEB Journal* (2022). [DOI: 10.1096/fj.202200581R](https://doi.org/10.1096/fj.202200581R)

Provided by Fujita Health University

Citation: Scientists demonstrate severe muscle atrophy in postnatal mice lacking two critical myosins (2022, December 14) retrieved 26 April 2024 from <https://medicalxpress.com/news/2022-12-scientists-severe-muscle-atrophy-postnatal.html>

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