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Triggering Typical Nemaline Myopathy With Compound Heterozygous Nebulin Mutations Reveals Myofilament Structural Changes as Pathomechanism

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Abstract
Nebulin is a giant protein that winds around the actin filaments in the skeletal muscle sarcomere. Compound-heterozygous mutations in the nebulin gene (NEB) cause typical nemaline myopathy (NM), a muscle disorder characterized by muscle weakness with limited treatment options. We created a mouse model with a missense mutation p.Ser6366Ile and a deletion of NEB exon 55, the Compound-Het model that resembles typical NM. We show that Compound-Het mice are growth-retarded and have muscle weakness. Muscles have a reduced myofibrillar fractional-area and sarcomeres are disorganized, contain rod bodies, and have longer thin filaments. In contrast to nebulin-based severe NM where haplo-insufficiency is the disease driver, Compound-Het mice express normal amounts of nebulin. X-ray diffraction revealed that the actin filament is twisted with a larger radius, that tropomyosin and troponin behavior is altered, and that the myofilament spacing is increased. The unique disease mechanism of nebulin-based typical NM reveals novel therapeutic targets.

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