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Facioscapulohumeral syndromes: New therapeutic trends

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Facioscapulohumeral muscular dystrophy is the third most common myopathy characterized by a progressive and irreversible weakness and wasting of the facial, shoulder and upper arm muscles. The onset is typically in the second decade, but the severity and disease progression are highly variable: while 20% of gene carriers are becoming wheelchair-bound by mid life, an equal proportion of gene carriers remain asymptomatic.

The common form, FSHD1, is caused by contraction of the D4Z4 macrosatellite repeat to 1-10 units leading to chromatin relaxation of the heterochromatic D4Z4 repeat and somatic derepression of the germ line transcription factor DUX4. A variegated pattern of DUX4 immunopositivemyonuclei can only be observed when DUX4 transcripts are stabilized by a polymorphic DUX4 polyadenylation signal immediately distal to the repeat.

A rare form, FSHD2, is associated with D4Z4 contraction-independent chromatin relaxation and derepression of DUX4 in skeletal muscle. In the majority of FSHD2 patients, mutations in a chromatin modifier have recently been mechanistically linked to D4Z4 chromatin relaxation and DUX4 derepression.

With the recent advances identifying DUX4 derepression as a uniform pathogenic mechanism in FSHD, therapeutic approaches acting on the chromatin, RNA or protein level to neutralize DUX4 activity are currently being developed. In parallel activities are ongoing to create new or improve existing cell and animal models, to establish registries, to identify biomarkers and meaningful outcome measures in an effort to initiate evidence-based clinical trials in the coming years.