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Digenic inheritance of an SMCHD1 mutation and an FSHD-permissive D4Z4 allele causes facioscapulohumeral muscular dystrophy type 2.

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Abstract: Facioscapulohumeral dystrophy (FSHD) is characterized by chromatin relaxation of the D4Z4 macrosatellite array on chromosome 4 and expression of the D4Z4-encoded DUX4 gene in skeletal muscle. The more common form, autosomal dominant FSHD1, is caused by contraction of the D4Z4 array, whereas the genetic determinants and inheritance of D4Z4 array contraction-independent FSHD2 are unclear. Here, we show that mutations in SMCHD1 (encoding structural maintenance of chromosomes flexible hinge domain containing 1) on chromosome 18 reduce SMCHD1 protein levels and segregate with genome-wide D4Z4 CpG hypomethylation in human kindreds. FSHD2 occurs in individuals who inherited both the SMCHD1 mutation and a normal-sized D4Z4 array on a chromosome 4 haplotype permissive for DUX4 expression. Reducing SMCHD1 levels in skeletal muscle results in D4Z4 contraction-independent DUX4 expression. Our study identifies SMCHD1 as an epigenetic modifier of the D4Z4 metastable epiallele and as a causal genetic determinant of FSHD2 and possibly other human diseases subject to epigenetic regulation.