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Modification of 4q35 and muscular gene expression in fetuses carrying a shortened D4Z4 array linked to FSHD

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muscle-specific expression pattern in FSHD patients. The mechanism precluding onset and progression of FSHD remains highly controversial and still debated. Our work is the first to uncover changes in gene expression in fetuses carrying a D4Z4-linked 4q35 defect. These results are important for understanding FSHD but also in general, to understand how epigenetic mechanism modulate the transcription of repetitive DNA sequences in the human genome especially in the human diseases.

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Modification of 4q35 and muscular gene expression in fetuses carrying a shortened D4Z4 array linked to FSHD

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Facio-Scapulo-Humeral Dystrophy (FSHD) is an enigmatic pathology. This autosomal dominant disorder is linked to deletion within a D4Z4 macrosatellite in the subtelomeric 4q35 region. The gene product leading to the disease has not been clearly identified and epigenetic changes are likely key players in the disease since beside reduction in the number of repeats, D4Z4 is hypomethylated in FSHD. Within D4Z4, DUX4 has been found upregulated in patients. Different DUX4 transcripts have been described. Production of a long transcript encompassing the DUX4 sequence and a region distal to D4Z4 encoding a toxic protein has been proposed as the cause of disease. A causal link between DUX4 expression and D4Z4 hypomethylation subsequent to array shortening has been proposed but never firmly established. We analyzed DUX4 expression as well as the expression of 4q35 genes and muscular markers in FSHD and non-FSHD biopsies during fetal development and in adults in a large cohort of samples. We highlight several genes whose expression differs between control and FSHD samples. Furthermore, we detected DUX4 transcripts in both groups, in muscle but also in other tissues indicating that expression of the long transcript is not restricted to FSHD muscles. Using FSHD and control myoblasts, we showed that DUX4 expression is induced by hypomethylation after knock-down of DNA methyltransferases, independently of D4Z4 array shortening. Our result tends toward a stochastic activation DUX4 transcription rather than a