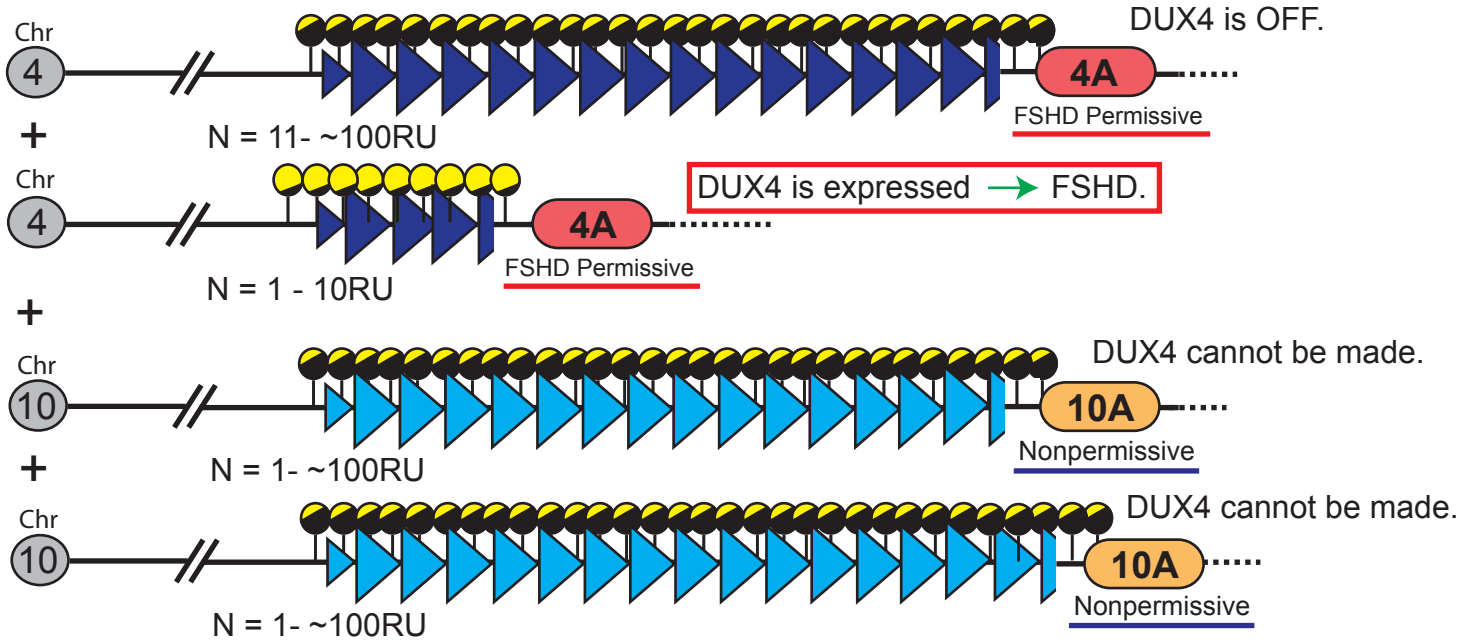
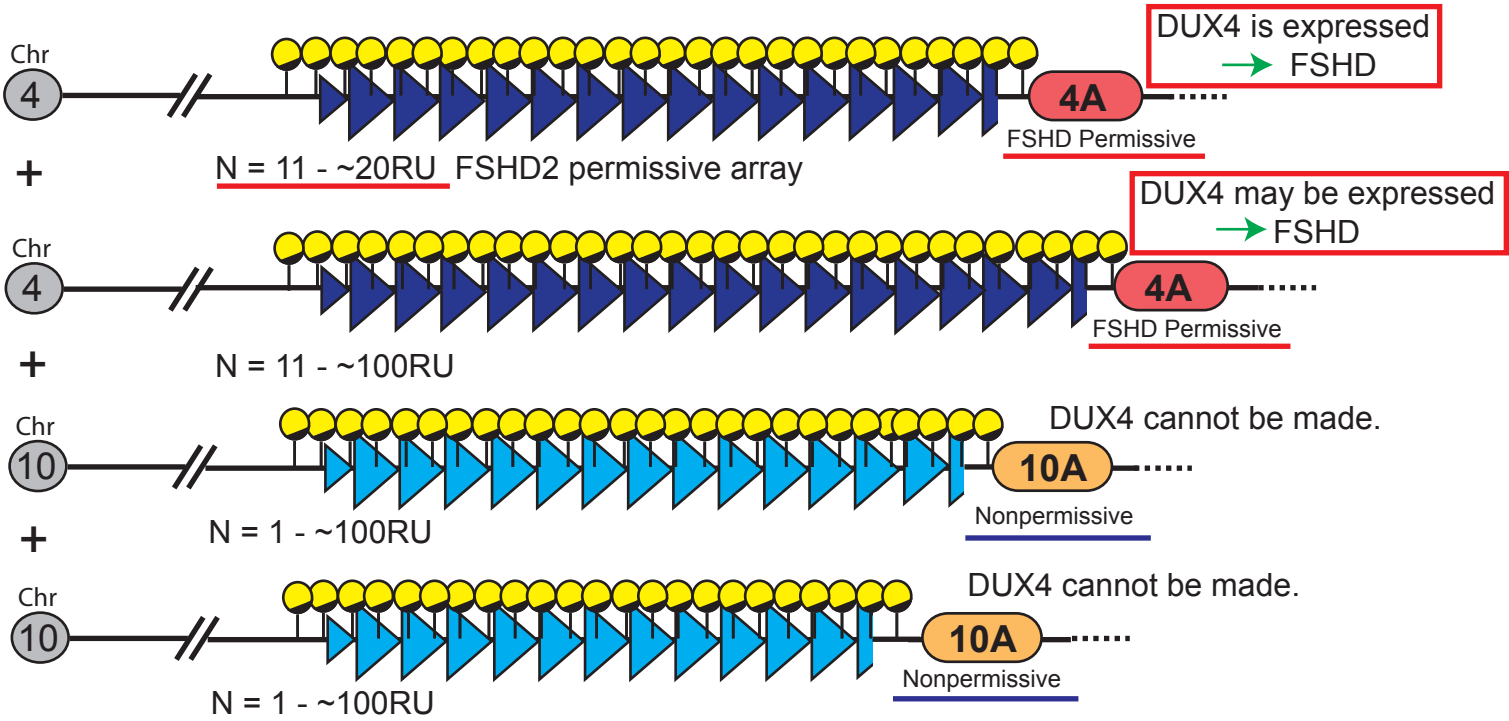
Types of FSHD: FSHD1 vs FSHD2

FSHD1: One FSHD permissive chr. 4 is contracted to between 1-10RUs.



FSHD2: Both chr. 4s and both chr. 10s are affected. At least one chr 4 must be FSHD permissive (4A) AND between 11-20 D4Z4 RUs long.



= Chr 4 D4Z4 repeat unit (RU)

= Chr 10 D4Z4 repeat unit (RU)

= Low levels of DNA methylation, epigenetics → ON

= High levels of DNA methylation, epigenetics → OFF

Types of FSHD: FSHD1+2

Some FSHD1 cases are more severe than one might predict based on the size of the D4Z4 deletion (i.e., small deletions are typically mild but sometimes they can present as clinically very severe). These can be indications of an FSHD2 mutation combined with the FSHD1 contraction. This can also explain some high variability in FSHD clinical severity within families.

Key paper identifying FSHD2 mutations as disease modifiers for FSHD1

REPORT

Am J Hum Genet (2013) 93:744-51.

The FSHD2 Gene *SMCHD1* Is a Modifier of Disease Severity in Families Affected by FSHD1

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FSHD1+2:

FSHD1 = One FSHD permissive chr. 4 is contracted to between 1-10 RUs.

FSHD2 = Mutation in SMCHD1 (or DNMT3B). *The size of the noncontracted array is not so important. The key is the FSHD2 mutation.