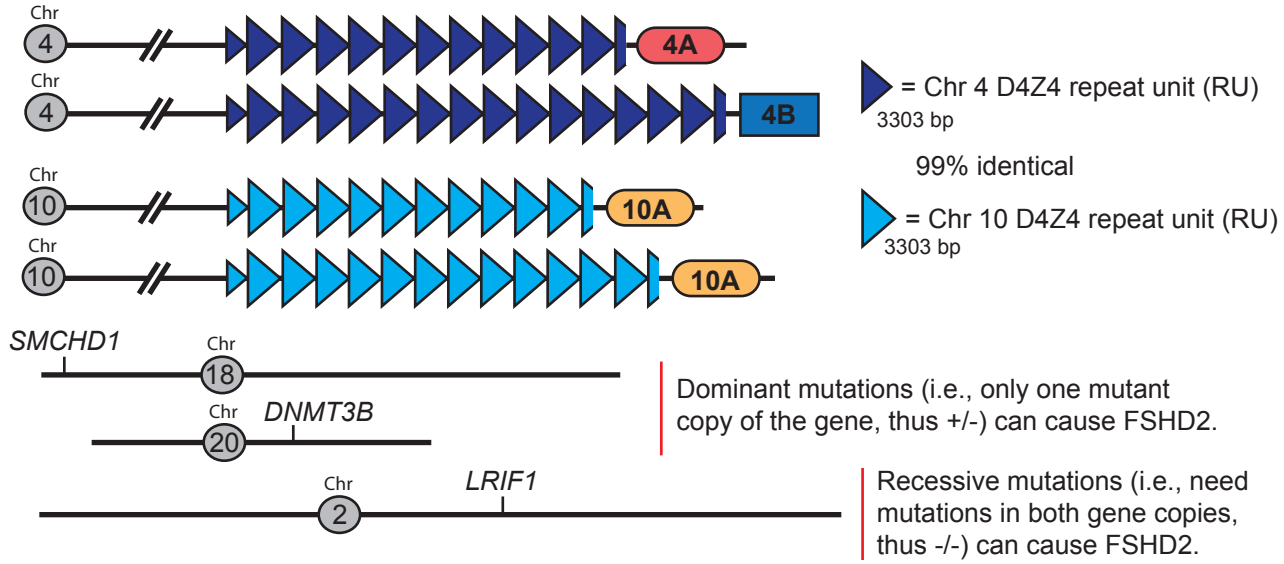
Types of FSHD: FSHD2 Genetics (Pt 1)

All forms of FSHD are associated with the chromosome 4 D4Z4 array
FSHD2 is caused by mutations in other genomic loci.

You have 23 pairs of chromosomes (#1-22 + X/X or X/Y), one of each from Mom and one from Dad. FSHD is associated with chromosome 4; specifically, a region called a D4Z4 repeat array located at 4q35. A D4Z4 repeat unit (RU) is 3303 base pairs of DNA. The array consists of D4Z4 RUs arranged head-to-tail.



FSHD2 always involves another genetic locus, and thus is considered digenic.

FSHD2 mutations affect the epigenetics of the chromosome 4 and 10 D4Z4 arrays.

The most common FSHD2 mutations are in the *SMCHD1* gene on chromosome 18p.
SMCHD1 is a protein the functions in transcriptional repression of D4Z4.

A second FSHD2 gene, *DNMT3B*, was recently identified.
DNMT3B is a DNA methyltransferase that adds DNA methylation to the D4Z4.

The third FSHD2 gene, *LRIF1*, encodes a protein that interacts with SMCHD1 to repress expression from D4Z4. *LRIF1* FSHD2 mutations are recessive; therefore, you need to have mutations in both copies to get FSHD2.

FSHD2 has multiple genetic requirements. FSHD2 requires 1) an FSHD permissive chromosome 4A, 2) a chromosome 4 D4Z4 array with between 11 - 24 RUs, and 3) a single mutation in either the *SMCHD1* gene or the *DNMT3B* gene, or mutations in both copies of the *LRIF1* gene.

FSHD2 can appear to skip generations!
Since the FSHD region is on chromosome 4 and the FSHD2 genes are on different chromosomes (chr. 2, 18, and 20), you can pass on an FSHD2 mutation to a child (50% chance) that does not meet the other genetic criteria for FSHD2 and they will be healthy. They can pass the FSHD2 mutation (50% chance) on to their children (your grandchildren) and if they do have the other genetic criteria inherited from their mother, they will be FSHD2.

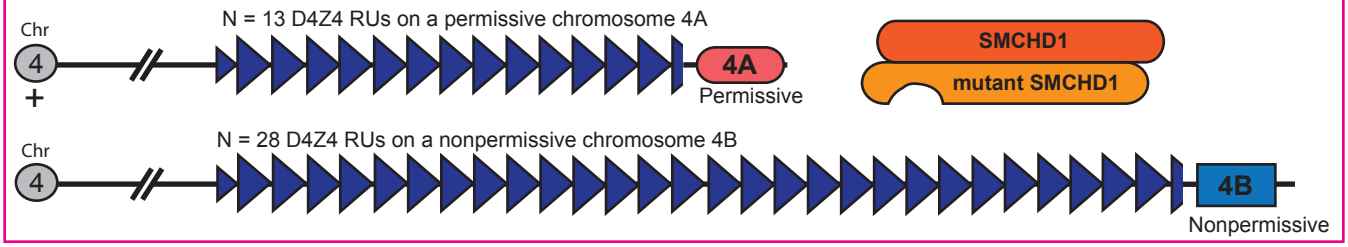
Types of FSHD: FSHD2 Genetics (Pt 2)

All forms of FSHD are associated with the chromosome 4 D4Z4 array.

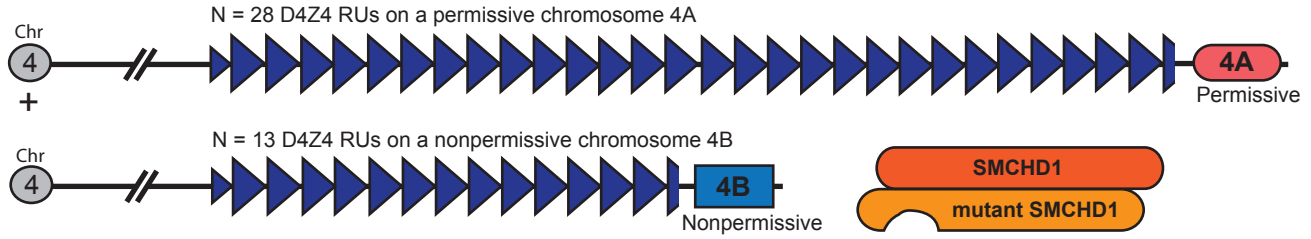
FSHD2 is caused by mutations in genes that encode proteins involved in transcriptional repression of the D4Z4 array.

FSHD2 has 3 genetic requirements: 1) a D4Z4 array between 11-20RUs on 2) an FSHD permissive 4A chromosome with 3) a pathogenic mutation in either *SMCHD1* (most common), *DNMT3B*, or two inactivating mutations in *LRIF1*.

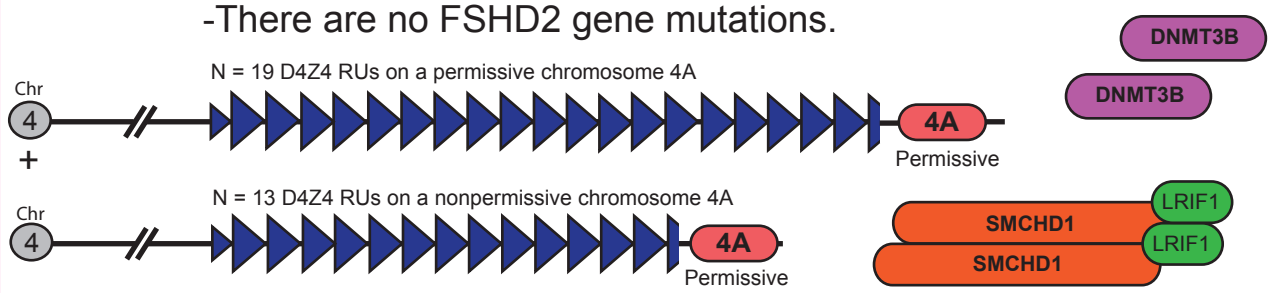
FSHD2: This individual meets all the genetic criteria for FSHD2.



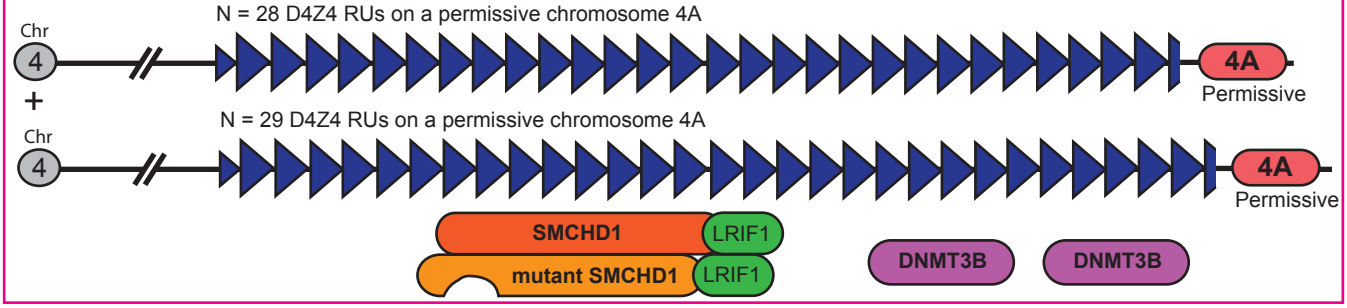
Healthy: This individual does not meet all the genetic criteria.
-The FSHD2-sized chromosome 4 D4Z4 is on a nonpermissive 4B.



Healthy: This individual does not meet all the genetic criteria.
-There are no FSHD2 gene mutations.

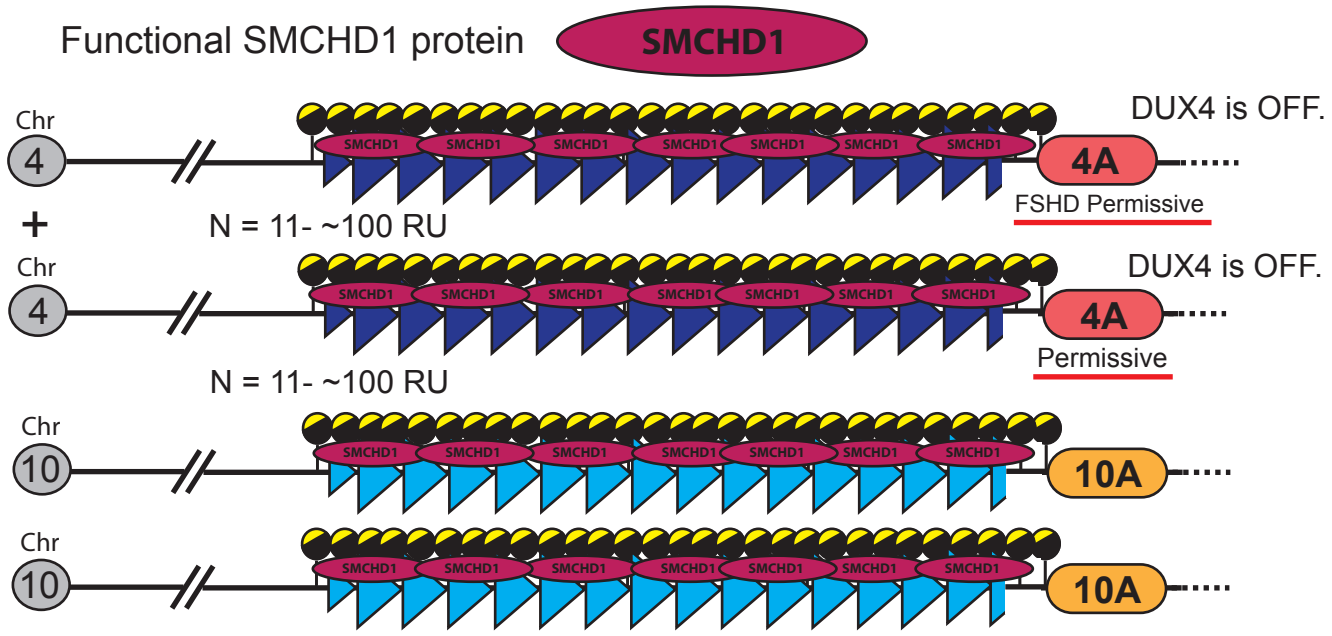


Healthy: This individual does not meet all the genetic criteria.
-They do not have any FSHD2-sized chromosome 4A D4Z4s.

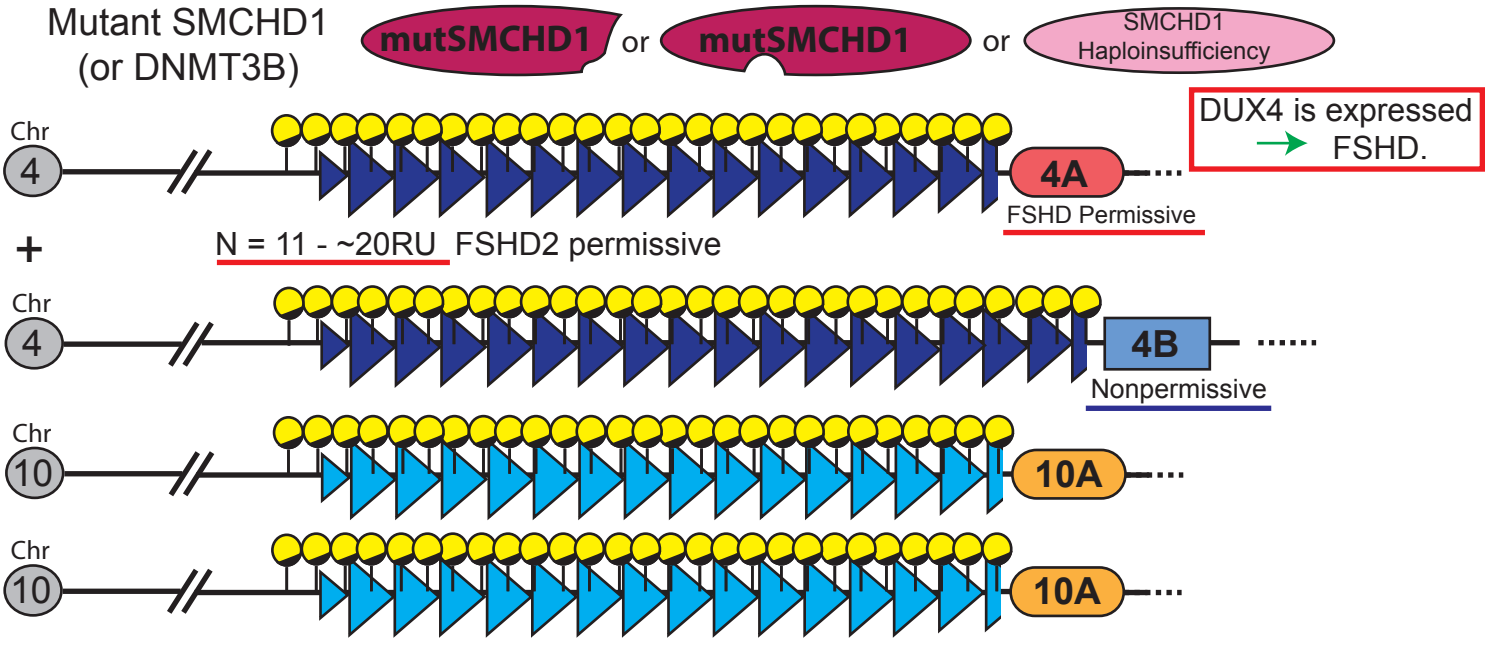


Types of FSHD: FSHD2 vs Healthy

Healthy/Not FSHD: Both chr. 4s are >11 RUs, no *SMCHD1* mutation.



FSHD2: One (or more) chr 4 needs to be FSHD permissive AND between 11-20 D4Z4 RUs long AND an *SMCHD1* or *DNMT3B* mutation.



= 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