FSHD Genetics:
Introduction (Pt 1)

All forms of FSHD are associated with the chromosome 4q35.2 D4Z4 array.

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.

Chromosomes are numbered according to their size, with #1 being the largest. Chromosomes have a structure used during replication, called a centromere, that separates the chromosome into two parts (called arms); the shorter of the two arms is called “p”, for petite, and the longer is called “q”, just because.

You will notice in the figure below that there is a banding pattern of the chromosomes. The bands reflect different chromosome staining due to different composition and structure of the region. The numbers after the “p” or “q” refer to banding regions along the chromosome and ultimately to a specific band and sub-band.

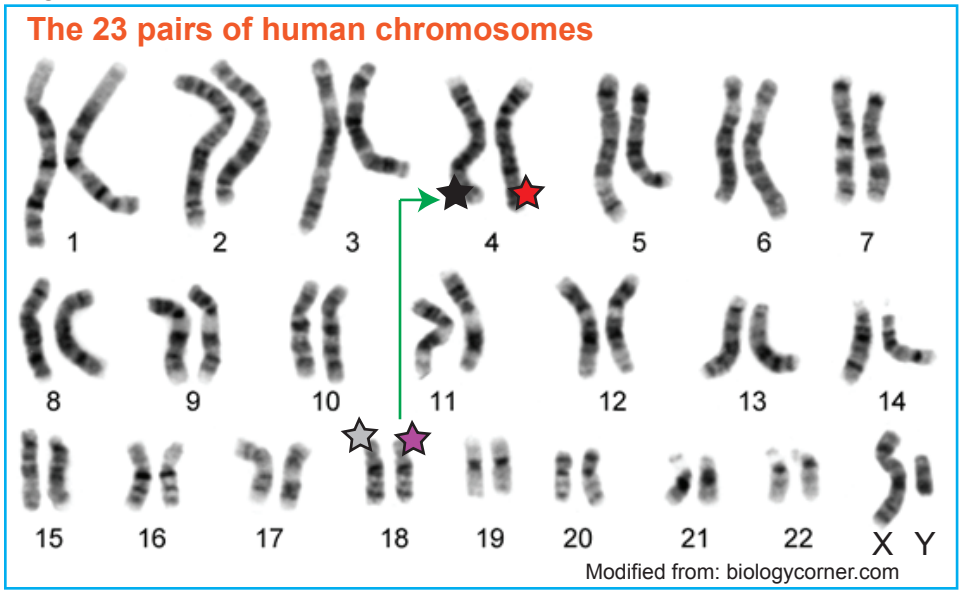
The FSHD region is located at chromosome 4q35.2, on the long arm (q) of chromosome 4, (4q) at band region 3, band number 5, sub-band number 2 (4q35.2), which is essentially near the very tip. It is marked with a ★.

FSHD1 is autosomal (meaning not a sex chromosome X or Y) dominant, so you only need a mutation ★ on one of your copies (either Mom’s or Dad’s) of chromosome 4 for FSHD1.

Since you only need one mutant chromosome 4q35.2 for FSHD1, if you are FSHD1 (male or female) it will be passed on to your children at a chance of 50%.

The gene most commonly mutated in FSHD2 (*SMCHD1*) is located at chromosome 18p11 ☆. As with FSHD1, you only need to have a mutation ★ in one of your copies to have FSHD2. However, FSHD2 still works through the FSHD locus on chromosome 4q35 so there are additional genetic requirements for FSHD2 (discussed later).

Because of the extra genetic requirements, FSHD2 inheritance is more complicated (discussed later).



FSHD1 is caused by deletions within the chromosome 4q35.2 D4Z4 array.
This leads to epigenetic changes at 4q35.2 and expression of the pathogenic *DUX4* gene from within the array.

FSHD2 is caused by mutations in genes encoding regulators of the 4q35.2 D4Z4 array.
This leads to epigenetic changes at 4q35.2 and expression of the pathogenic *DUX4* gene from within the array.

FSHD Genetics:
Introduction (Pt 2)

All forms of FSHD are associated with the chromosome 4q35.2 D4Z4 array.

FSHD1 is caused by deletions in the D4Z4 array on chromosome 4q35*.

Key research papers identifying the common mutation in FSHD1:

Chromosome 4q DNA rearrangements associated with facioscapulohumeral muscular dystrophy

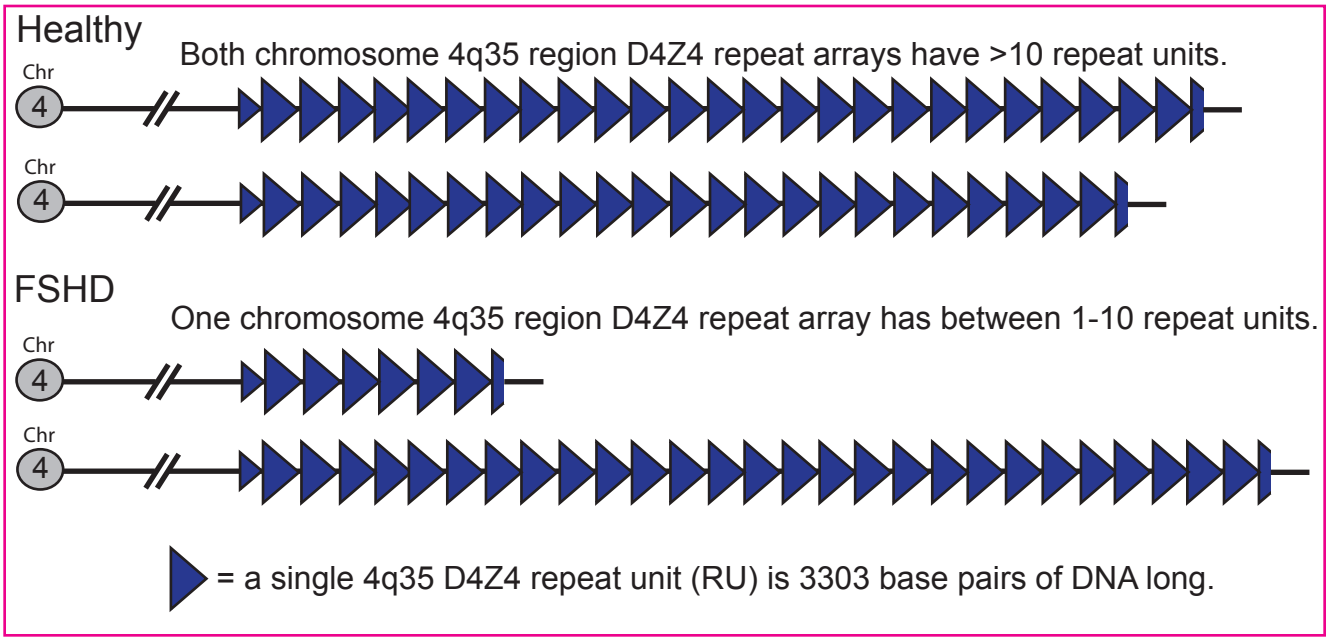
Nature Genetics (1992) 2:26-30.

Cisca Wijmenga[1,2], Jane E. Hewitt[3], Lodewijk A. Sandkuijl[1], Lorraine N. Clark[3], Tracy J. Wright[3], Hans G. Dauwerse[1], Anne-Marie Gruter[1,2], Marten H. Hofker[1], Petra Moerer[1,2], Robert Williamson[3], Gert-Jan B. van Ommen[1], George W. Padberg[2] & Rune R. Frants[1]

FSHD associated DNA rearrangements are due to deletions of integral copies of a 3.2 kb tandemly repeated unit

Judith C.T.Van Deutekom, Cisca Wijmenga, Esther A.E.Van Tlenhoven, Anne-Marie Gruter, Jane E. Hewitt, George W. Padberg ✉, Gert-Jan. B.van Ommen, Marten H. Hofker, Rune R. Fronts ✉

Human Molecular Genetics, Volume 2, Issue 12, December 1993, Pages 2037–2042,



* The field typically refers to the FSHD region as chromosome 4q35