Introduction to FSHD: FSHD1 Genetics (Pt 1)

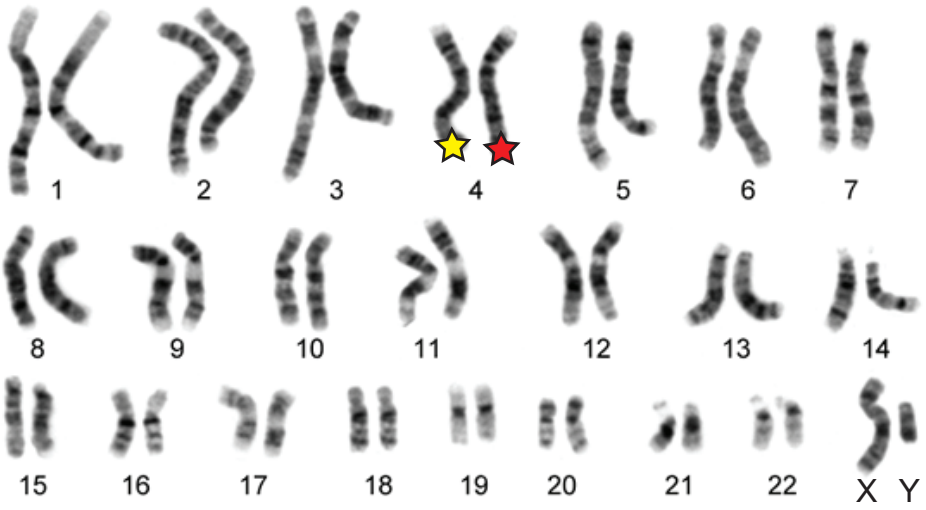
The FSHD region is on chromosome 4q35.

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.

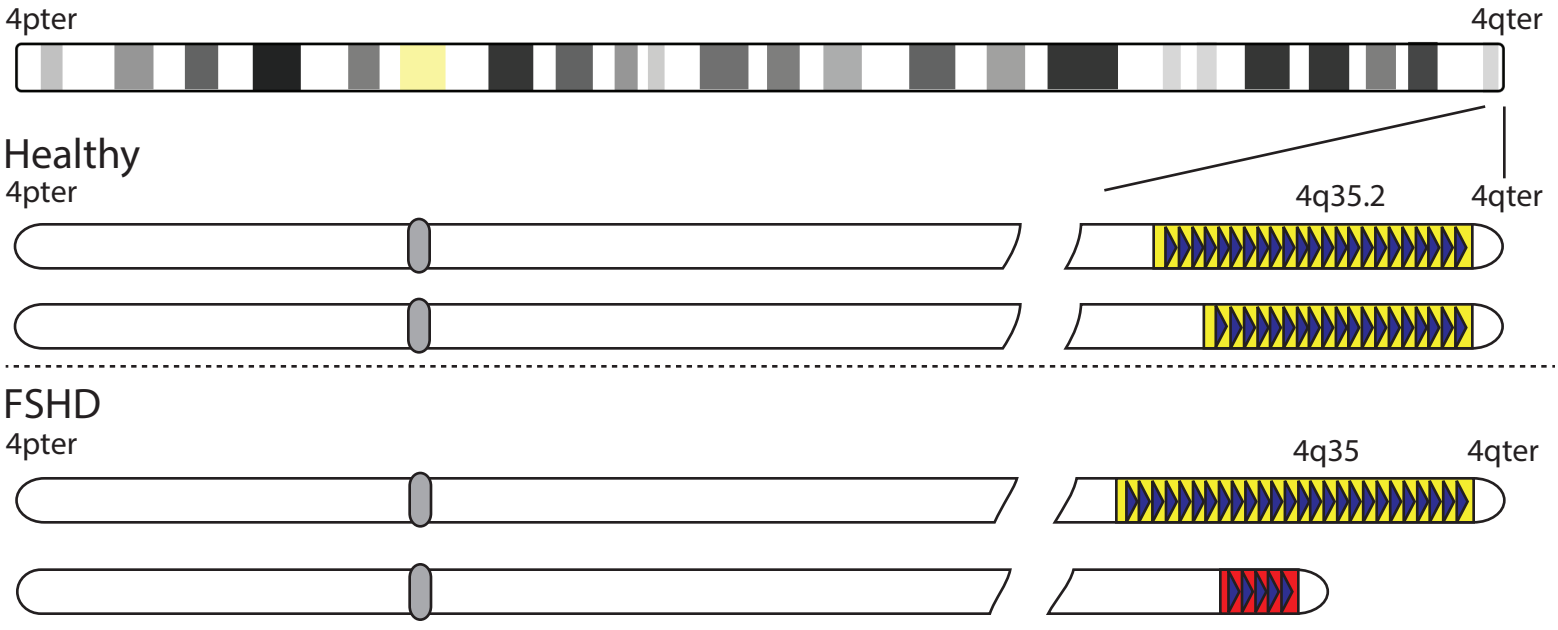
The FSHD region is located at chromosome 4q35. It is marked with a ☆.

FSHD1 is caused by a deletion of DNA repeat sequence (called D4Z4) at 4q35 ★ on one of your two chromosomes.

The 23 pairs of human chromosomes, with FSHD1



Modified from: biologycorner.com



FSHD1 is caused by deletions within the chromosome 4q35 D4Z4 array.
A D4Z4 unit (illustrated as ▶) is composed of 3,303 base pairs (bp) of DNA sequence.
These 3,303 bp are repeated many times, thus it is called a D4Z4 repeat or array (▶▶▶▶▶).

Key references:

Human Molecular Genetics (1993) 2:2037-42 and *Neuromuscular Disorders* (1993) 3:487-91.

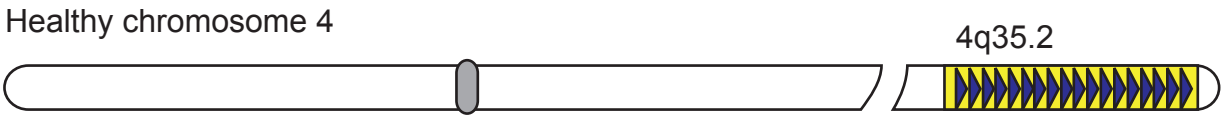
Introduction to FSHD: FSHD1 Genetics (Pt 2)

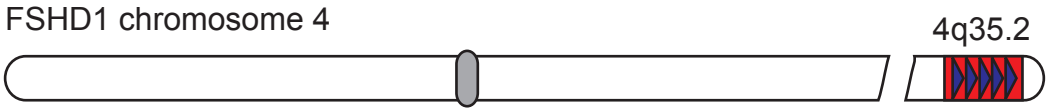
The FSHD region is on chromosome 4q35.

The FSHD region is located at chromosome 4q35; therefore, it is on the long arm of chromosome 4. It is marked below with a ▭ for the healthy state and a ▭ for the FSHD state.

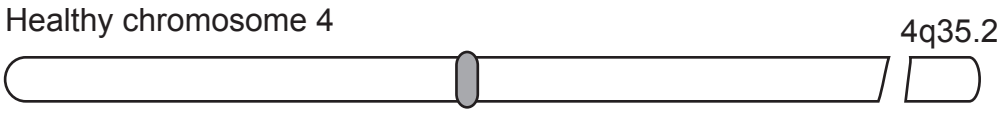
FSHD1 is caused by a deletion within a DNA repeat sequence, termed a D4Z4 repeat (illustrated as ▶) at 4q35 on one of your two chromosome 4s.

Thus, in FSHD, you do not really lose genetic information; each D4Z4 repeat has the same sequence. Instead, you have a decrease in the number of the D4Z4 repeats but maintain the DNA sequence data.





In fact, if the entire 4q35 D4Z4 array is lost, you do NOT get FSHD! Thus, the D4Z4 is required for FSHD, but only when in a particular context. *Journal of Medical Genetics* (1996) 33:366-70.



You need the genetic information in the D4Z4 to develop FSHD.

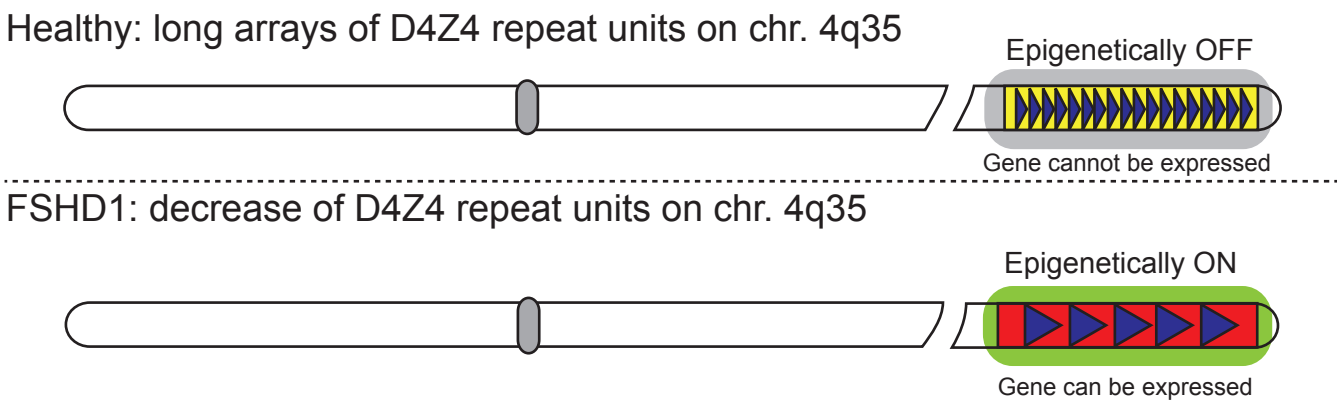
So, lots of repeats are good, a few repeats are bad, and no repeats are good again. What is going on?

It comes down to how your cells deal with DNA repeats. Most of your genes are 1 copy per chromosome. D4Z4s are present in hundreds of copies.

DNA repeats are generally silenced by the cellular machinery as a genome defense mechanism (e.g., invasive viruses are repetitive and silenced). Thus, when you lose D4Z4 repeats on chromosome 4, they are no longer "viewed" as repeats by the silencing machinery and are not turned off.

FSHD is caused by a loss of this (epigenetic) silencing of repeats.

Loss of repression (the OFF switch) leads to aberrant expression of the contracted D4Z4 repeat units (now ON).



Introduction to FSHD: FSHD1 Genetics (Pt 3)

The FSHD region is on chromosome 4q35.

The FSHD region is located at chromosome 4q35; therefore, it is on the long arm of chromosome 4. It is marked below with a ▭ for the healthy state and a ▭ for the FSHD state.

FSHD1 is caused by a deletion within a DNA repeat sequence, termed a D4Z4 repeat (illustrated as ◗) at 4q35 on one of your two chromosome 4s resulting in a loss of repressive repeat structure.

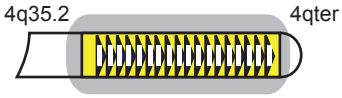
DNA repeats are generally silenced by the cellular machinery as a genome defense mechanism (e.g., invasive viruses are repetitive sequences and silenced). This silencing is via repressive epigenetic regulation.

◗ and ▶ represent the same 3,303 bp of DNA, but packed differently; they are epigenetically different.

"Epigenetics" refers to 1) context-dependent and sequence-independent regulation; and 2) cellular memory. It's complicated, but essentially, the same DNA sequence (such as a D4Z4 RU) can exist in two states: an expressed state (ON) or a repressed state (OFF), and this state, once established, is very stable and remembered or maintained through generations.

Healthy state

Epigenetically OFF



18 D4Z4 RU = ~60,000 bp DNA
Very compressed, tightly packed
The *DUX4* gene inside the ◗
cannot be expressed

FSHD state

Epigenetically ON

5 D4Z4 RU = ~16,500 bp DNA
Expanded, dynamic, loosely packed
The *DUX4* gene inside the DUX4
can be expressed.

Nature Genetics (2003) 35:315-7.

In FSHD1, you lose many D4Z4 repeats on chromosome 4, and the remaining small number of repeats are no longer "recognized" as repeats and are thus not epigenetically silenced.

FSHD is caused by a loss of epigenetic silencing of repeats leading to expression of the pathogenic gene (*DUX4*) from within the contracted (and no longer silenced) distal D4Z4 unit.

Once your epigenetic status is established very early in human development (way before birth), it stays that way for life. More on epigenetics later....

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

Reviewed in: Himeda and Jones (2019) *Ann Rev Genomics Human Genetics* 20:265-91.
Gatica and Rosa (2016) *Neuromuscular Disorders* 26:844-852.
Tawil, van der Maarel and Tapscott (2014) *Skeletal Muscle* 4:12.

Introduction to FSHD: FSHD1 Genetics (Pt 4)

FSHD1 has autosomal dominant inheritance.

The FSHD region is located at chromosome 4q35; therefore, it is on the long arm of chromosome 4. It is marked below with a ▭ for the healthy state and a ▭ for the FSHD state.

FSHD1 is caused by a deletion of DNA repeat sequence, termed a D4Z4 repeat (illustrated as ▶) at 4q35 on one of your two chromosome 4s.

You have 23 pairs of chromosomes, 22 pairs are called autosomes, 1 pair (XX or XY) are sex chromosomes. Thus, chromosome 4 is an autosome. Since FSHD is linked to chromosome 4, it is an autosomal disease and occurs equally in females and males.

FSHD is a dominant disease. Thus, you only need an FSHD1 mutation on one of your chromosome 4s. In contrast, many neuromuscular diseases are recessive, meaning you need both copies of a gene to be mutated.

Since FSHD1 is autosomal dominant, if you are FSHD1 there is a 50% chance of passing FSHD1 to each child.

However, someone has to be the first in a family to get FSHD1. There is ~1:20,000 (0.005%) chance that two healthy parents have a child with FSHD1 due to a spontaneous (new) mutation in either the sperm or egg.