Introduction to FSHD: FSHD2 Genetics (Pt 1)

The FSHD region is on chromosome 4q35.

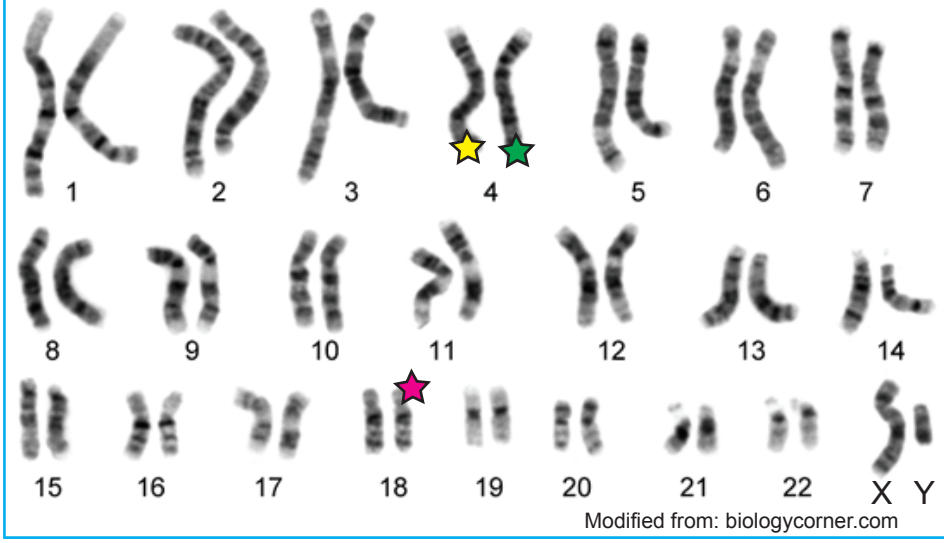
You have 23 pairs of chromosomes (#1-22 + X/X or X/Y), one of each from Mom and one from Dad.
FSHD is associated with chromosome 4.

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

FSHD2 is caused by a mutation in one of the FSHD2 genes (*SMCHD1, DNMT3B*, or two mutations on *LRIF1*).
The most common (>80% of the cases) gene mutated in FSHD2 is *SMCHD1* on chromosome 18p11★.

However, FSHD2 still requires a specific sized D4Z4 array on chromosome 4q35 (11 - 20RUs), as indicated ★ .

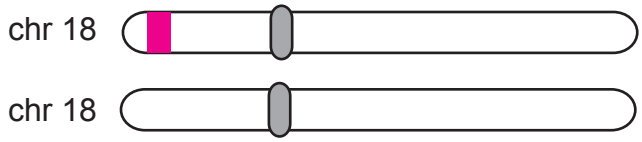
The 23 pairs of human chromosomes, with FSHD2



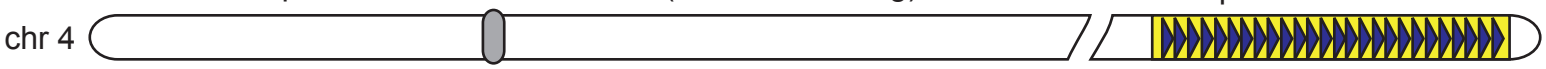
Modified from: biologycorner.com

FSHD2

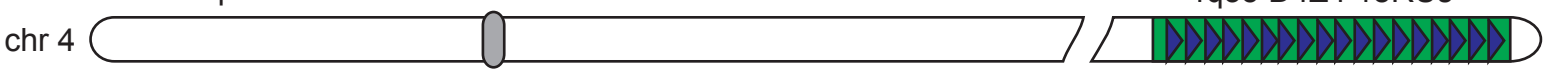
FSHD2 *SMCHD1* mutation in one copy of chromosome 18p



FSHD2 nonpermissive chromosome 4 (D4Z4 is too long)



FSHD2 permissive chromosome 4



FSHD2 is caused by mutations in FSHD2 genes such as *SMCHD1* combined with an FSHD2 permissive chromosome 4q35 D4Z4 array ▶▶▶▶▶ between 11-20RUs).

SMCHD1: *Nature Genetics* (2012) 44:1370-4
DNMT3B: *American Journal of Human Genetics* (2016) 98:1020-9
LRIF1: *Neurology* (2020) 94:e2441-e2447

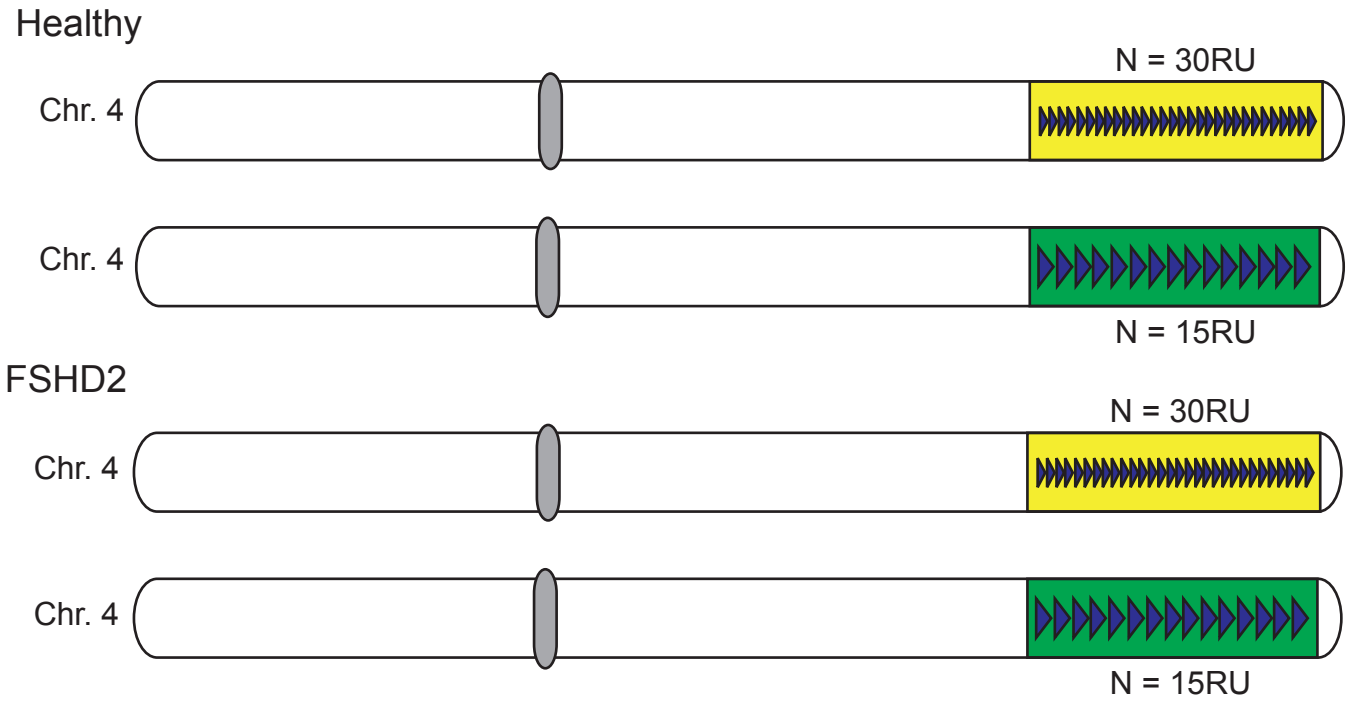
Introduction to FSHD: FSHD2 Genetics (Pt 2)

FSHD2 is digenic. It requires:
1) a mutation in an FSHD2 gene (*SMCHD1* or *DNMT3B*),
+
2) a specific range of 4q35 D4Z4 repeat units (<21RUs).

The FSHD region is located at chromosome 4q35 and is also required for FSHD2.
It is marked below with a ▭ for the healthy state and a ▭ for the FSHD2 permissive state.

FSHD2 requires a pathogenic mutation in one of the FSHD2 genes AND a 4q35 D4Z4 array 11-21RUs.
Either condition on its own does not result in FSHD2.

The size of the 4q35 D4Z4 array is important, but not diagnostic or pathogenic.



There must also be an FSHD2 mutation in either *SMCHD1, DNMT3B*, or mutations in both copies of *LRIF1.*

SMCHD1: *Nature Genetics* (2012) 44:1370-4
DNMT3B: *American Journal of Human Genetics* (2016) 98:1020-9
LRIF1: *Neurology* (2020) 94:e2441-e2447

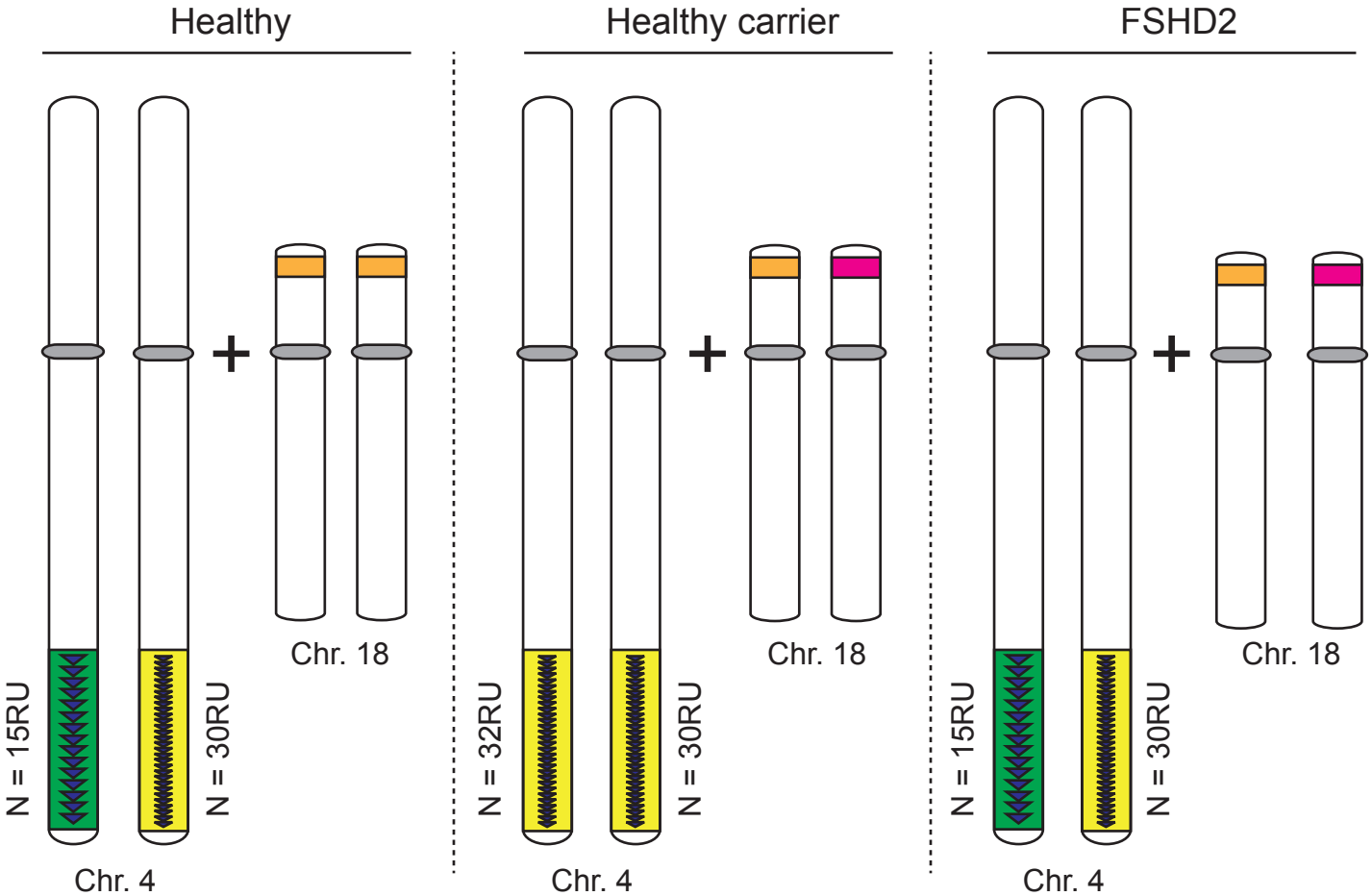
Introduction to FSHD: FSHD2 Genetics (Pt 3)

FSHD2 is digenic. It requires:
1) a mutation in an FSHD2 gene (*SMCHD1* or *DNMT3B*),
+
2) a specific range of 4q35 D4Z4 repeat units (<21RUs).

The FSHD region is located at chromosome 4q35 and is also required for FSHD2.
It is marked below with a ▭ for the healthy state and a ▭ for the FSHD2 permissive state.

FSHD2 is primarily caused by mutations in the *SMCHD1* gene on chromosome 18p11.32.
It is marked below with a ▭ for the healthy state and a ▭ for an FSHD2 mutation.

FSHD2 requires a pathogenic mutation in one of the FSHD2 genes AND a 4q35 D4Z4 array 11-21RUs. Either condition on its own does not result in FSHD2. Thus, one can be a carrier of an FSHD2 mutation while being healthy.



FSHD2 appropriate array but no FSHD2 mutation

FSHD2 mutation but the D4Z4 arrays are too large

FSHD2 appropriate array and an FSHD2 mutation

Introduction to FSHD: FSHD2 Genetics (Pt 4)

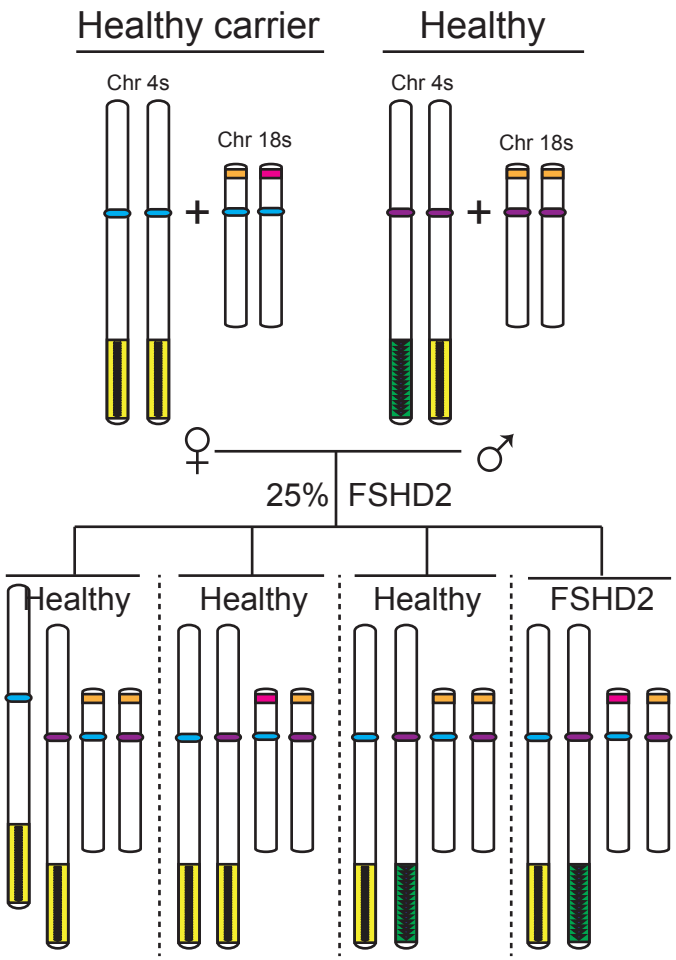
FSHD2 is digenic and has autosomal dominant inheritance.

The FSHD region is located at chromosome 4q35 and is also required for FSHD2.
It is marked below with a [yellow] for the healthy state and a [green] for the FSHD2 permissive state.

FSHD2 is primarily caused by mutations in the *SMCHD1* gene on chromosome 18p11.32.
It is marked below with a [orange] for the healthy state and a [pink] for an FSHD2 mutation.

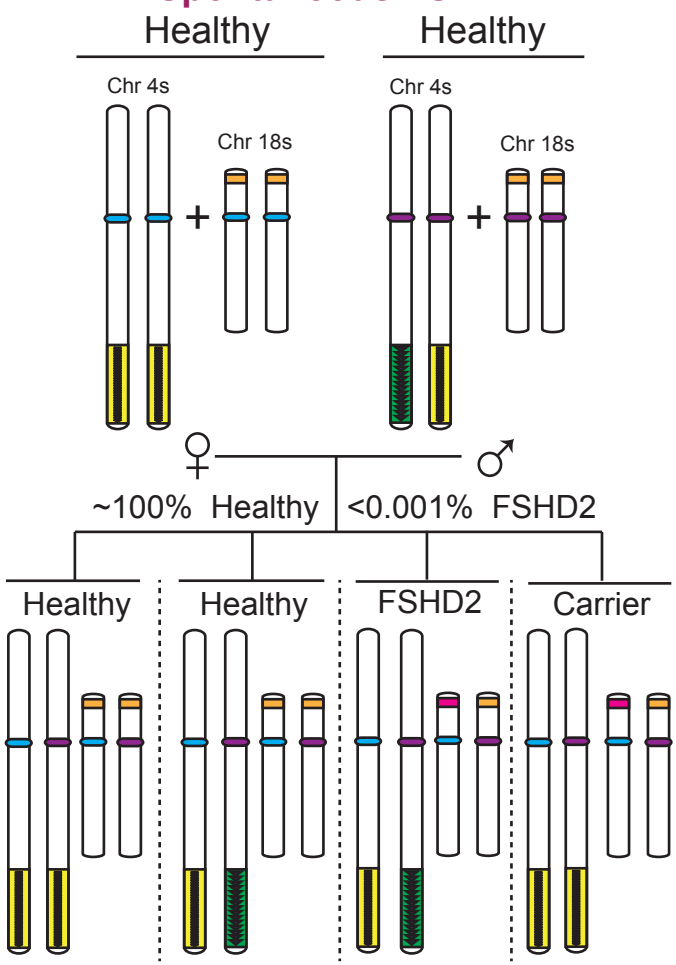
FSHD2 requires a pathogenic mutation in one of the FSHD2 genes AND a 4q35 D4Z4 array 11-21RUs. Either condition on its own does not result in FSHD2. Thus, one can be a carrier of an FSHD2 mutation while being healthy and FSHD2 can appear to skip a generation.

Familial FSHD2



One chr. 4 from Mom, one from Dad
One chr. 18 from Mom, one from Dad

Spontaneous FSHD2



One chr. 4 from Mom, one from Dad
One chr. 18 from Mom, one from Dad
Spontaneous mutation in an egg or sperm may produce an FSHD2 mutation. Would still need an appropriate 4q35 D4Z4.

Introduction to FSHD: FSHD2 Genetics (Pt 5)

So, FSHD2 is digenic. What do these two mutations do?

1) a mutation in an FSHD2 gene (*SMCHD1* or *DNMT3B*),

+

2) a specific range of 4q35 D4Z4 repeat units (<21RUs).

The FSHD region is located at chromosome 4q35 and is also required for FSHD2.
It is marked below with a ▭ for the healthy state and a ▭ for the FSHD2 permissive state.

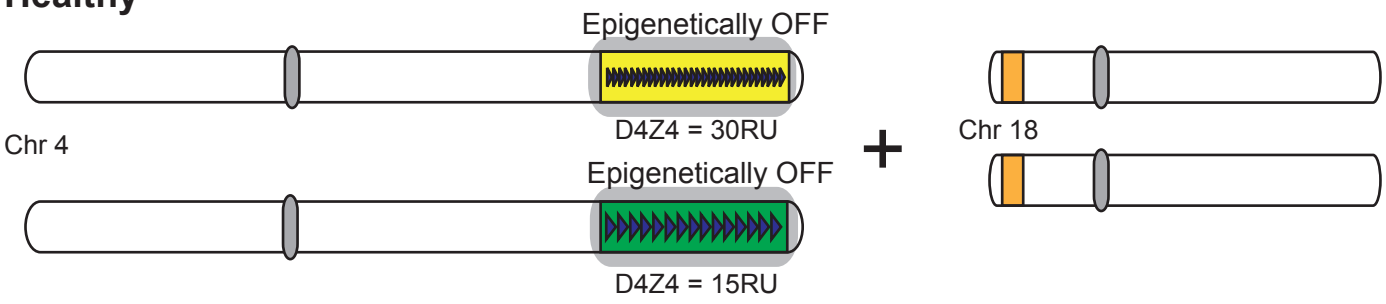
FSHD2 is primarily caused by mutations in the *SMCHD1* gene on chromosome 18p11.32.
It is marked below with a ▭ for the healthy state and a ▭ for an FSHD2 mutation.

FSHD2 requires a pathogenic mutation in one of the FSHD2 genes AND a 4q35 D4Z4 array 11-21RUs. Either condition on its own does not result in FSHD2. Thus, one can be a carrier of an FSHD2 mutation while being healthy.

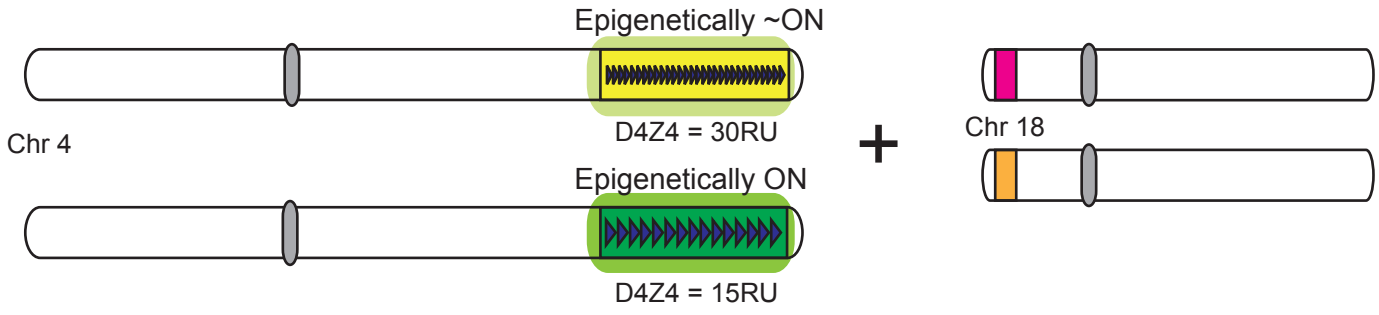
As is the case with FSHD1, FSHD2 is caused by altering the epigenetic state of 4q35.2

Nature Genetics (2003) 35:315-7 and *Human Mutation* (2009) 30:1449-59.

Healthy



FSHD2



FSHD1