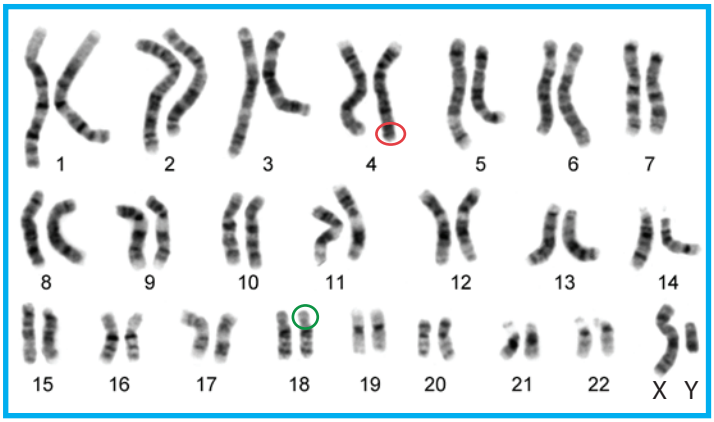
Testing for FSHD
Genetic Analysis (Pt 1):
Chromosomes 4 and 10

You have 23 pairs of chromosomes (46 total); one each from Mom and one from Dad



- The FSHD region is on chromosome 4.
- It is called a D4Z4 repeat and encodes the pathogenic *DUX4* gene.
- There is a similar region on chromosome 10 that is not pathogenic.
- You only need 1 of your chromosome 4s to have a mutation/deletion to develop FSHD1.
- FSHD2 is caused primarily by mutations in the *SMCHD1* gene on chromosome 18; however, the SMCHD1 protein functions at chromosome 4.
- Thus, the mutations that cause either FSHD1 or FSHD2 both affect chromosome 4 and *DUX4*.

The first part of your report analyzes the genetics of your two chromosome 4s and 10s.

Chromosome 4 can either be FSHD permissive or nonpermissive (See section on permissive vs nonpermissive). The critical question being answered in this initial analysis is:

Do you have a chromosome 4 that is FSHD permissive?

There are two types of FSHD permissive chromosome 4s: 4A and 4AL

Chromosome 4B types are FSHD nonpermissive

Because chromosome 4 and 10 are very similar, we assess all 4 chromosomes (both 4s and both 10s) to answer this question. The important part for FSHD is the chromosome 4 analysis.

There are three possibilities for your two chromosome 4s:

Permissive/Permissive: 4A/4A or 4A/4AL or 4AL/4AL.

Permissive/Nonpermissive: 4A/4B or 4AL/4B.

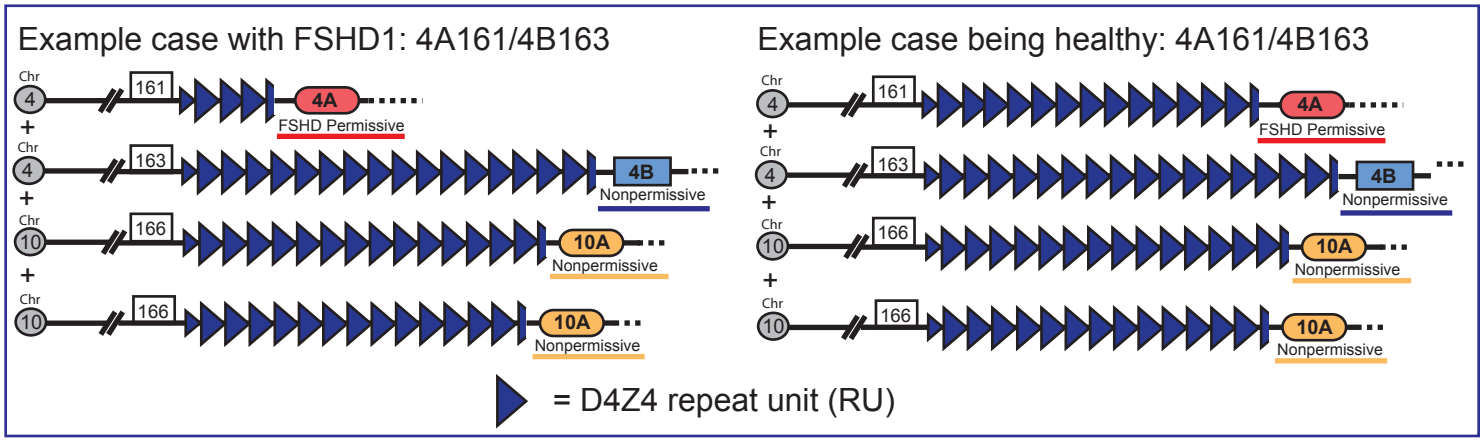
Nonpermissive/Nonpermissive = 4B/4B, and you cannot develop FSHD.

The 4A166 is a special case of an FSHD permissive chromosome that is not associated with FSHD.

The numbers associated with your chromosomes 4 and 10 (e.g., 161, 163, 166) refer to DNA sequences outside of the D4Z4 array that help inform us about a chromosome being FSHD permissive or FSHD nonpermissive (e.g., 4A161 is permissive).

Testing for FSHD
Genetic analysis (Pt 2):
Chromosomes 4 and 10

Haplotypes, SSLPs, and subtelomeres



The numbers associated with your chromosomes 4 and 10 (e.g., 161, 163, 166) refer to sequences (SSLP = simple sequence length polymorphism) that help inform us about a chromosome haplotype being FSHD permissive or nonpermissive (e.g., 4A161 is permissive, 4B163 in nonpermissive).

This SSLP sequence (number) found on the centromeric side of the D4Z4 array, when combined with the A or B subtelomere (the end of a chromosome is called a telomere; A and B are adjacent to the telomere or subtelomeric) distal to the D4Z4 array, is called a haplotype.

Haplotypes are DNA sequences that tend to be inherited together as a group. For example, 4161 and 4A go together (4A161), and 4163 and 4B go together (4B163).

There are specific haplotypes that inform about chromosomes 4 and 10 and help with the genetic analysis.

Above are examples of two different individuals with the same haplotype of 4A161/4B163, 10A166/10A166. Both have one FSHD permissive 4A161 chromosome and one FSHD nonpermissive 4B163 chromosome. The individual on the left is FSHD1; the individual on the right is healthy. Thus, this haplotype does NOT determine if you have FSHD or not; it merely indicates if you are FSHD permissive (See section on permissive vs nonpermissive chromosomes).

Just because you are FSHD permissive does not mean you have FSHD! Roughly 75% of the human population has at least 1 FSHD permissive chromosome; ~25% have two nonpermissive chromosomes.

Two FSHD permissive chromosomes (e.g., 4A161/4A161) are not worse than one FSHD permissive chromosome.

If you have no FSHD permissive chromosomes (e.g., 4B163/4B163), you do not have FSHD and you cannot pass FSHD to your child.