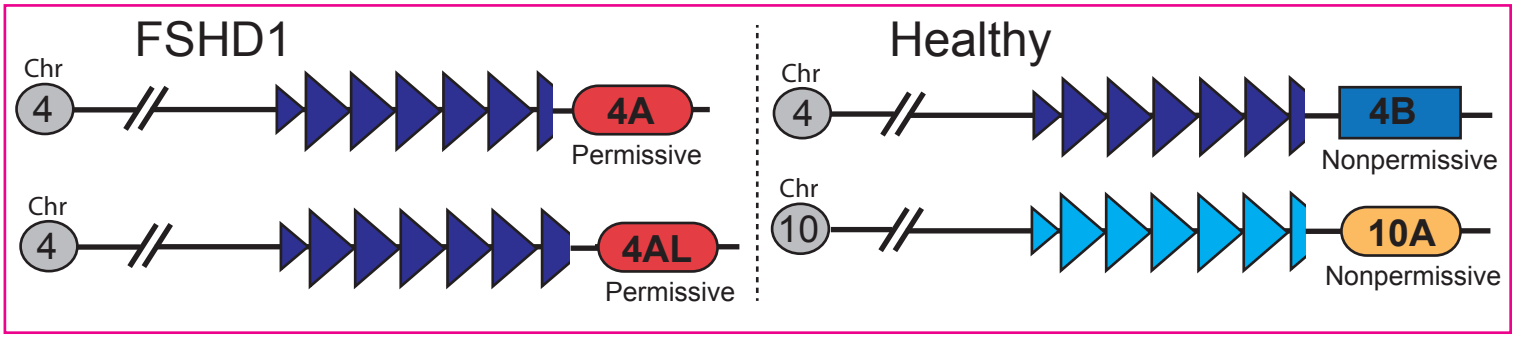
Introduction to FSHD: Permissive Genetics (Pt 1)

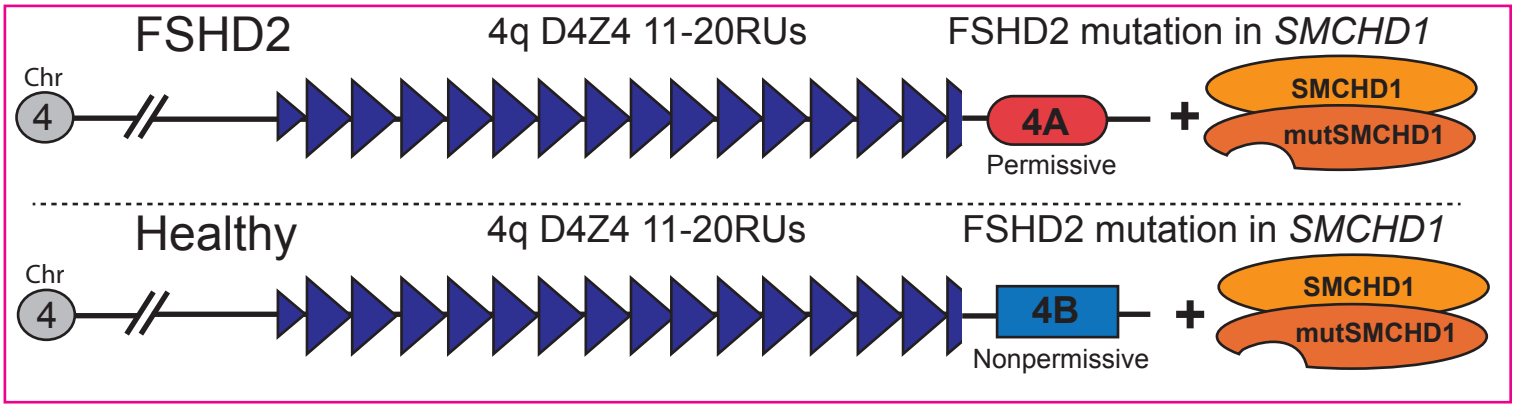
We know that:

- **FSHD1 is caused by contractions of the chromosome 4q35 D4Z4 repeat array to 1-10RUs.**
- **FSHD2 is caused by mutations in FSHD2 genes combined with a chromosome 4q35 D4Z4 array 11-20RUs.**

Now it gets a little more complicated!

All forms of FSHD require a specific type of DNA sequence distal to the chromosome 4 D4Z4 array. The sequence (termed "4A") is "permissive" for FSHD because it is required to develop FSHD, but in and of itself, it does not cause FSHD; it is not pathogenic.



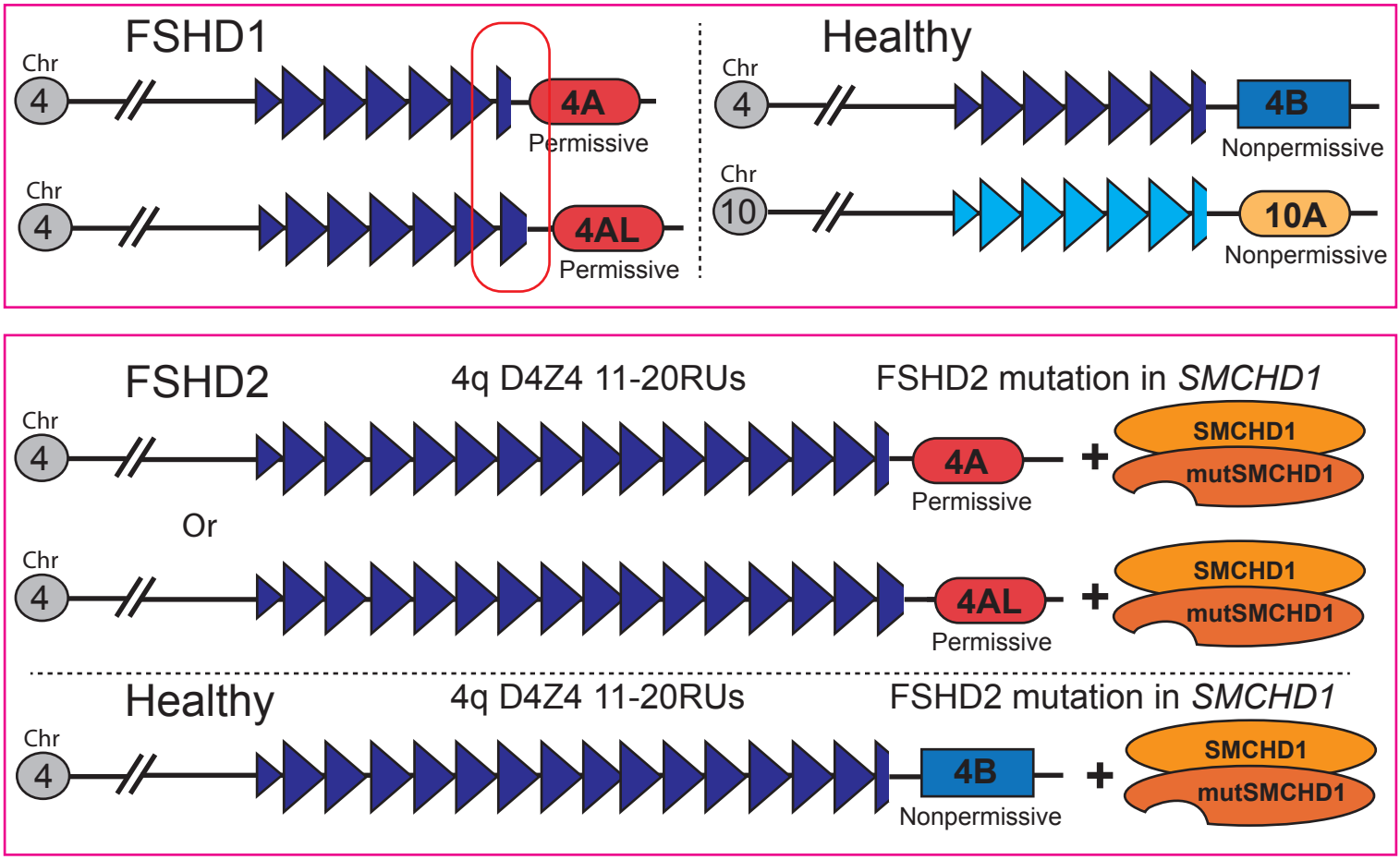


Muscle Nerve (1995) 2:39-44. *Nature Genetics* (2002) 32:235-6. *American J of Human Genetics* (2004) 75:1124-30.
Science (2010) 329:1650-3. *Nature Genetics* (2012) 44:1370-4.

Introduction to FSHD: Permissive Genetics (Pt 2)

All forms of FSHD require chromosome 4qA (or AL).

Chromosome 4qAL is a variant where the last partial RU (circled in red) is slightly longer. It is a bit of a misnomer in that the "A" part is the same for 4A and 4AL.



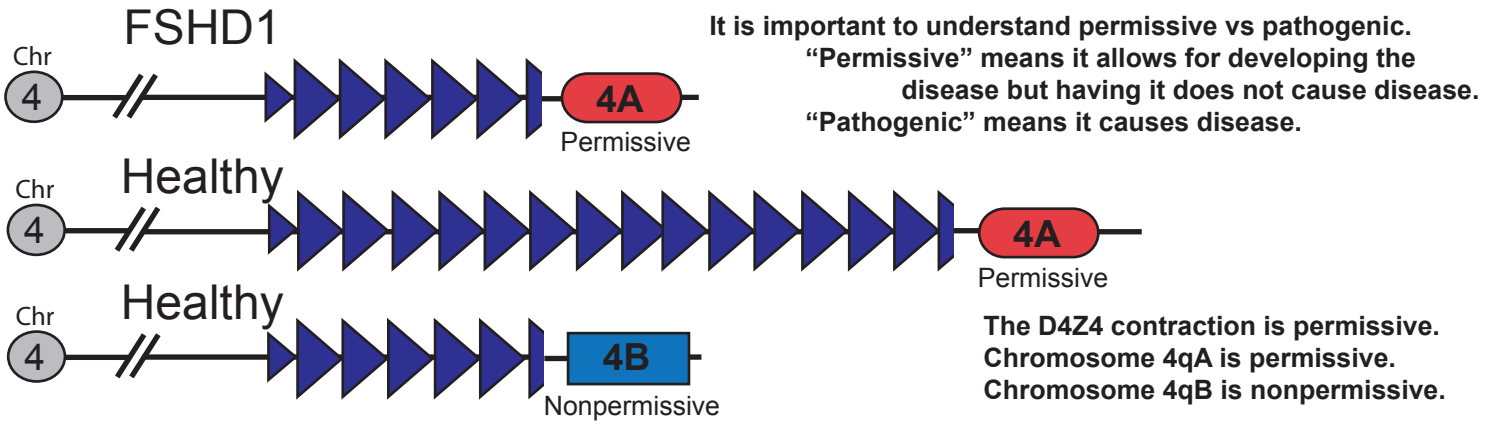
Muscle Nerve (1995) 2:39-44. *Nature Genetics* (2002) 32:235-6. *American J of Human Genetics* (2004) 75:1124-30. *Science* (2010) 329:1650-3. *Nature Genetics* (2012) 44:1370-4.

Key points to know:

- The D4Z4 deletion, alone, is NOT pathogenic!
- The region distal to the D4Z4 array is important.
- There are two variants: 4A and 4B (also 10A and 10B).
- Contractions on 4B or chromosome 10A do not result in FSHD.
- FSHD is only associated with 4A chromosomes.
- Both FSHD1 and FSHD2 require 4A chromosomes.
- Chromosome 4A is permissive for FSHD, not pathogenic.
- Chromosome 4AL is also permissive for FSHD, not pathogenic.

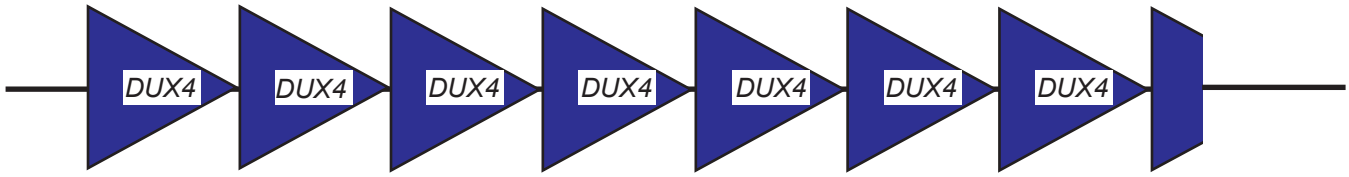
Introduction to FSHD: Permissive Genetics (Pt 3)

The chromosome 4qA (or AL) is "permissive" for FSHD. It is a special DNA sequence that is missing from the 4qB and 10qA regions that is required to develop FSHD, although it does not cause FSHD.



American J of Human Genetics (2007) 81:884-94. *Science* (2010) 329:1650-3.

A copy of a gene called *DUX4* resides in each 4q35 D4Z4 RU.



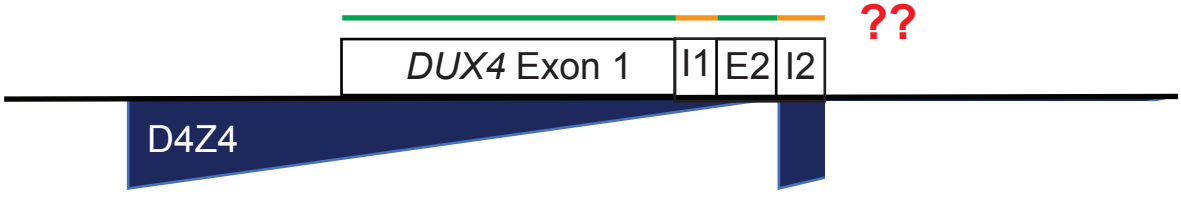
Gene (1999) 236:25-32.

In general, genes are DNA sequences that encode the information for making a protein.

The DNA is copied (transcribed) into RNA, which is then decoded (translated) and assembled into protein.

Genes have several parts, including regulatory elements (help determine ON or OFF), exons (encode the information for making a protein - green), which are interrupted by noncoding introns (- orange), and RNA processing signals for stability and transport.

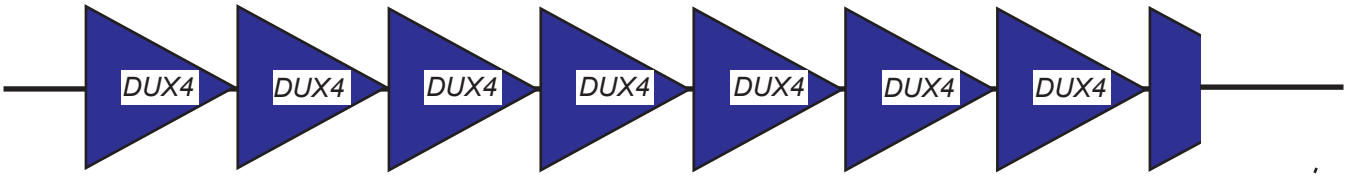
The *DUX4* genes in each D4Z4 RU have two exons and two introns but no processing signals and thus cannot be made into mature RNAs or DUX4 proteins.



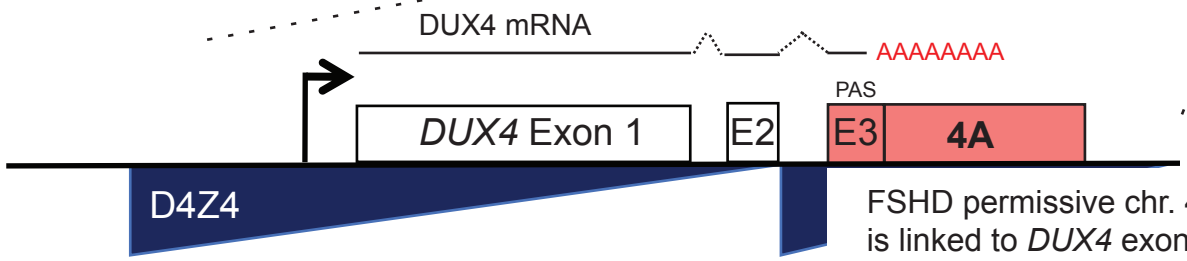
Introduction to FSHD: Permissive Genetics (Pt 4)

The chromosome 4qA (or AL) is "permissive" for FSHD. It has a special DNA sequence that is missing from the 4qB and 10qA regions that is required to develop FSHD, although it does not cause FSHD.

A copy of a gene called *DUX4* resides in each 4q35 D4Z4 RU. *Gene* (1999) 236:25-32.



DUX4 encodes a toxic protein.
Neuromuscular Disorders (2007) 17:611-23.



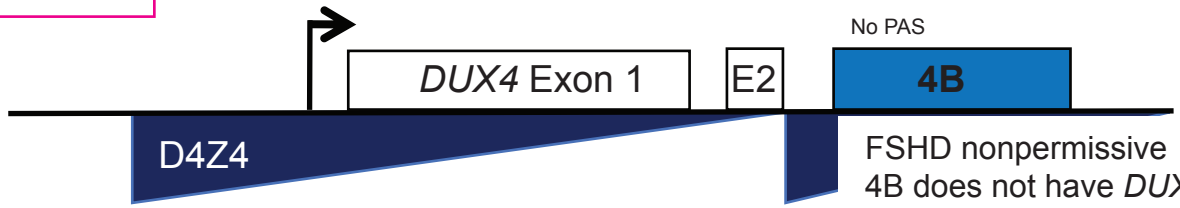
FSHD permissive chr. 4A is linked to *DUX4* exon 3, which has the DUX4 PAS (polyadenylation signal).

DUX4 mRNA from the last D4Z4 repeat unit is polyadenylated and translated into protein.

→ DUX4-mediated FSHD pathology

RNA polyadenylation (via PAS) is required for the mRNA to be translated into protein.

RNA is degraded.



FSHD nonpermissive 4B does not have *DUX4* exon 3 or a PAS.

DUX4 transcribed from the last D4Z4 repeat unit is not polyadenylated and thus degraded and not translated into protein.

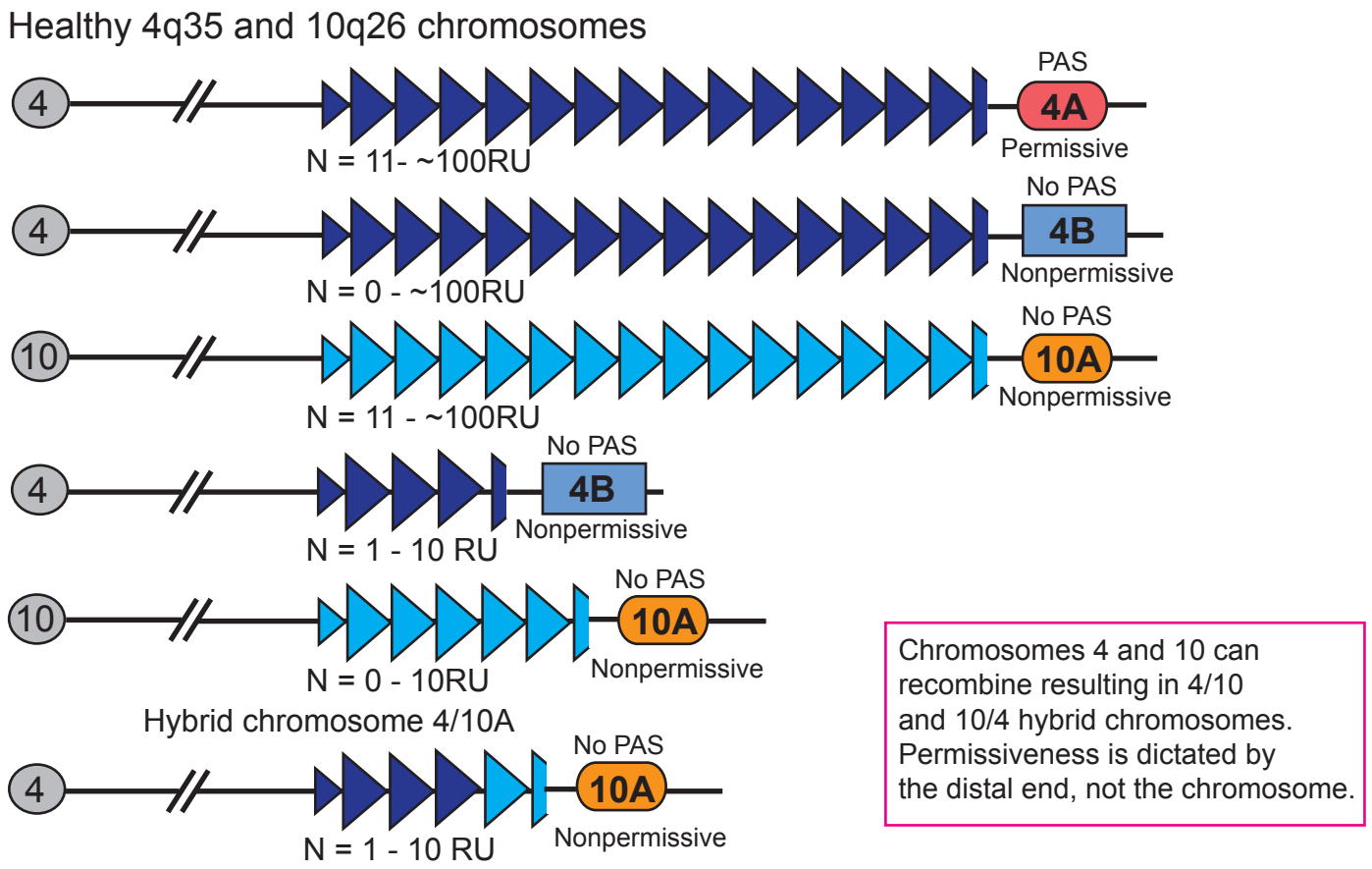
→ No DUX4
No FSHD pathology

A permissive 4A chromosome is required for BOTH FSHD1 and FSHD2.
Expression of the *DUX4* gene is required for FSHD1 and FSHD2.

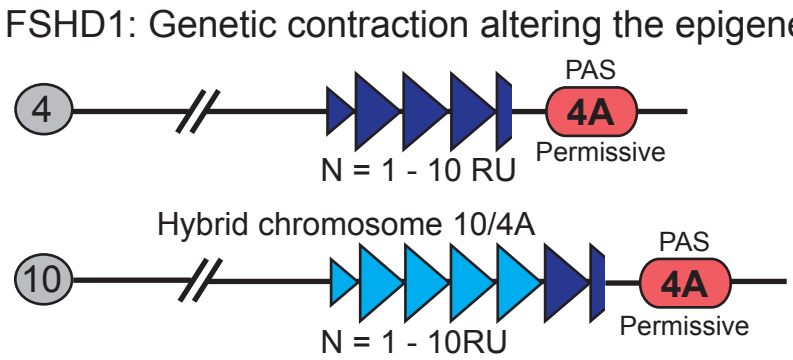
Science (2010) 329:1650-3. *PLoS Genetics* (2010) 10:e1001181.

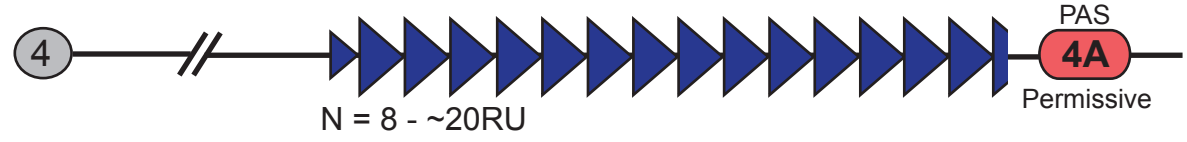
Introduction to FSHD: Permissive Genetics (Pt 5)

Summary of 4q and 10q healthy and FSHD genetics.



Chromosomes 4 and 10 can recombine resulting in 4/10 and 10/4 hybrid chromosomes. Permissiveness is dictated by the distal end, not the chromosome.





= Chromosome 4 D4Z4 repeat unit

= Chromosome 10 D4Z4 repeat unit