



FSHD Permissive vs Nonpermissive (Pt 1)

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.

Key research papers identifying the requirement for 4qA to develop FSHD:

Facioscapulohumeral muscular dystrophy is uniquely associated with one of the two variants of the 4q subtelomere

Nature Genetics (2002) 32:235-6

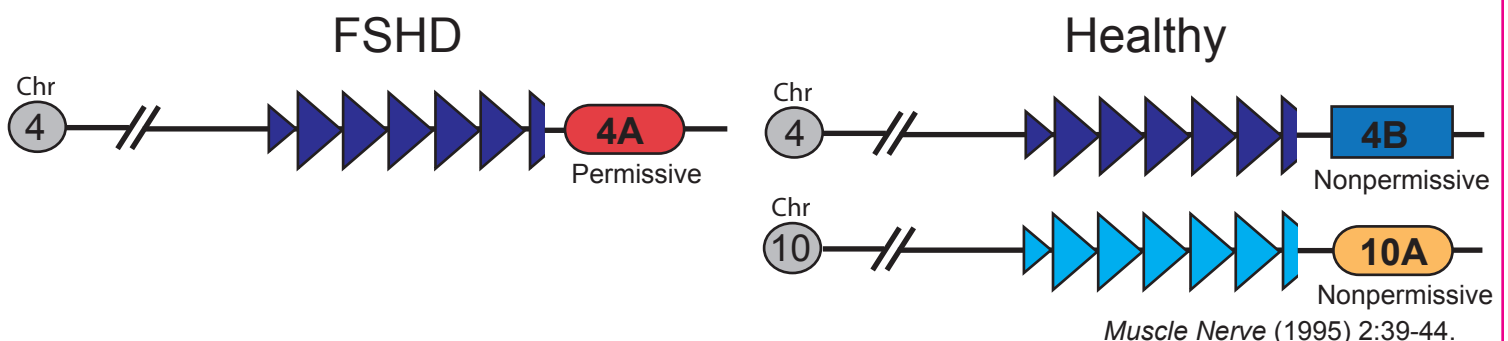
Richard J.L.F. Lemmers¹, Peggy de Kievit¹, Lodewijk Sandkuijl^{1,2}, George W. Padberg³, Gert-Jan B. van Ommen¹, Rune R. Frants¹ & Silvere M. van der Maarel¹

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Contractions of D4Z4 on 4qB Subtelomeres Do Not Cause Facioscapulohumeral Muscular Dystrophy

Richard J. F. L. Lemmers,¹ Mariëlle Wohlgenuth,² Rune R. Frants,¹ George W. Padberg,² Eva Morava,^{3,4} and Silvere M. van der Maarel¹ *Am J Hum Genet* (2004) 75:1124-30

Also: Thomas *et al.* *J Med Genetics* (2007) 44:215-8.



We learned:

- 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 10 do not result in FSHD.
- FSHD is only associated with 4A chromosomes.
- Chromosome 4A is permissive for FSHD, not pathogenic.
- Chromosome 4A-L is also permissive for FSHD.



FSHD Permissive vs Nonpermissive (Pt 2)

ScienceExpress

Report

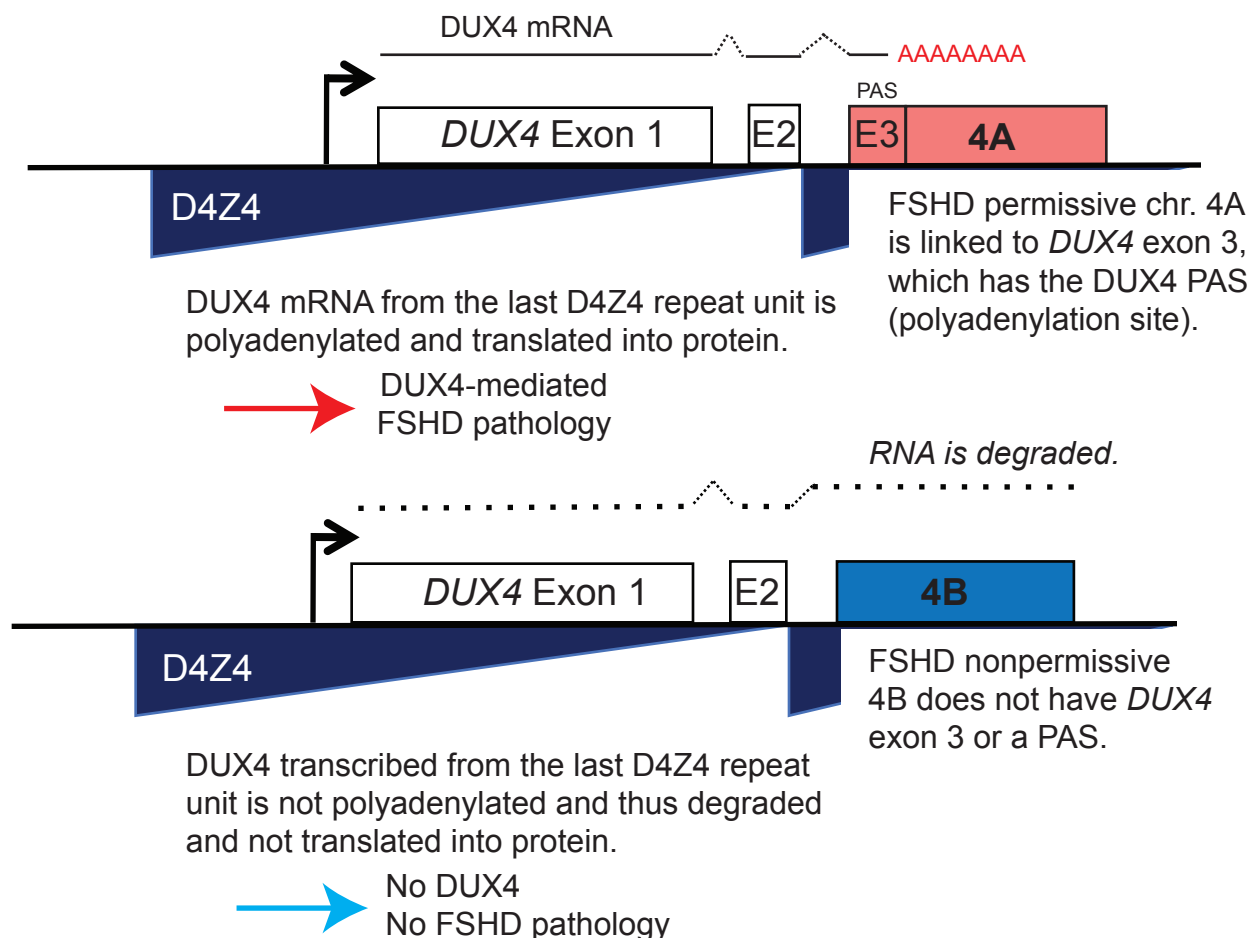
A Unifying Genetic Model for Facioscapulohumeral Muscular Dystrophy

Richard J.L.F. Lemmers, Patrick J. van der Vliet, Rinse Klooster, Sabrina Sacconi, Pilar Camañó, Johannes G. Dauwerse, Lauren Snider, Kirsten R. Straasheijm, Gert Jan van Ommen, George W. Padberg, Daniel G. Miller, Stephen J. Tapscott, Rabi Tawil, Rune R. Frants, Silvère M. van der Maarel*
Science (2010) 329:1650-3.

The complete *DUX4* gene has 3 exons (the part of the gene that becomes the mature mRNA). Exons 1 and 2 are found in every D4Z4 repeat. However, exon 3, which contains the PAS (or polyadenylation site) is distal to the D4Z4 repeat and linked to the 4A region (or subtelomere). The exon 3 PAS/4A region is necessary for *DUX4* expression and thus to develop FSHD. Thus, 4A, due to the linked exon 3 PAS, is permissive for FSHD.

The 4B region (or subtelomere) is not linked to exon 3. Thus, if a chromosome is 4B, a critical part of the *DUX4* gene --- the *DUX4* PAS --- is missing and this cannot result in FSHD. Thus, 4B chromosomes, due to the inability to make polyadenylated *DUX4* mRNA, is FSHD nonpermissive.

A permissive 4A chromosome is required for BOTH FSHD1 and FSHD2.

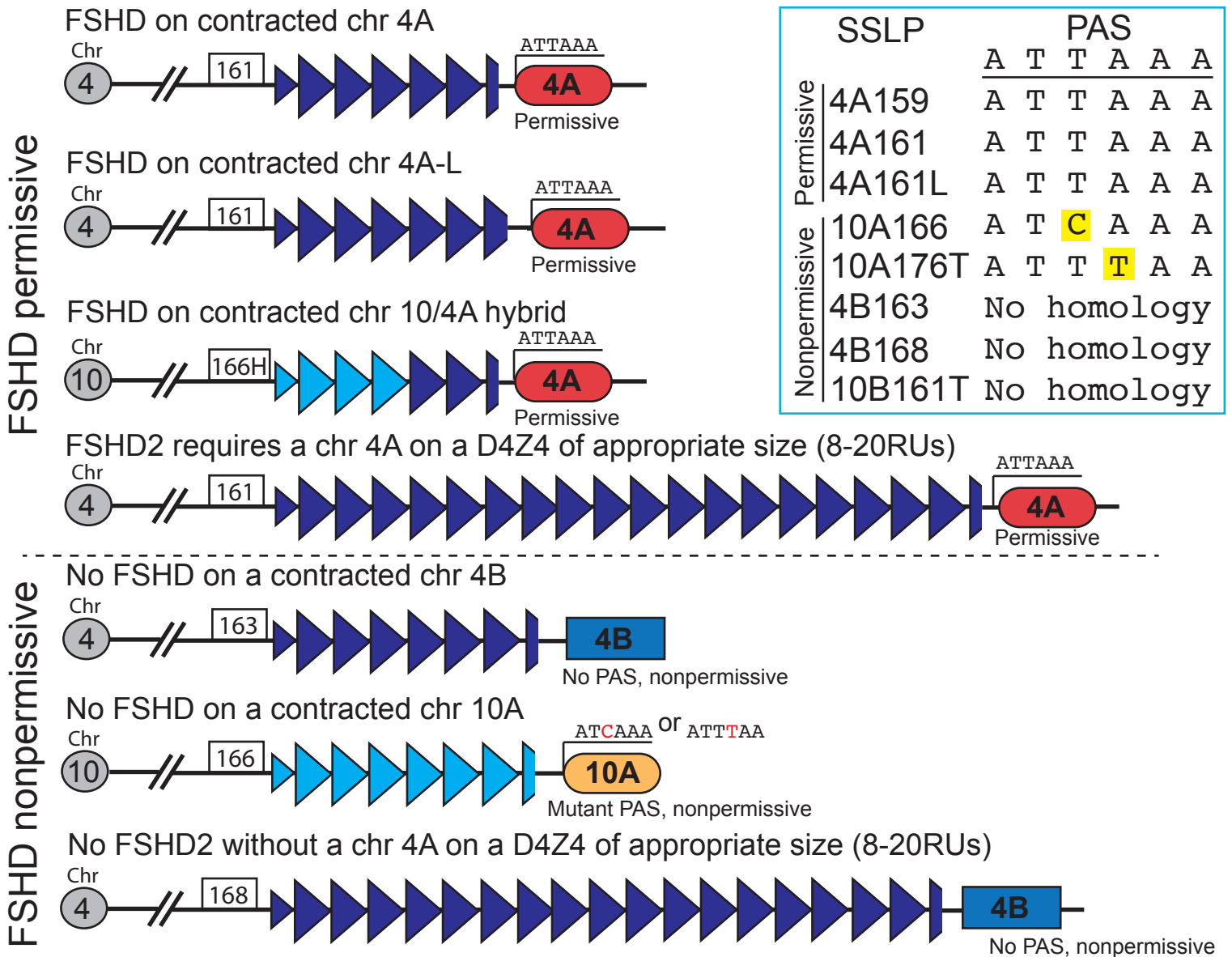


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All messenger RNAs (mRNAs) require polyadenylation to terminate transcription and stabilize the transcript for export from the nucleus and translation into protein. This is dictated by a polyadenylation signal (PAS). In FSHD, permissive chromosomes have a *DUX4* PAS; nonpermissive don't.

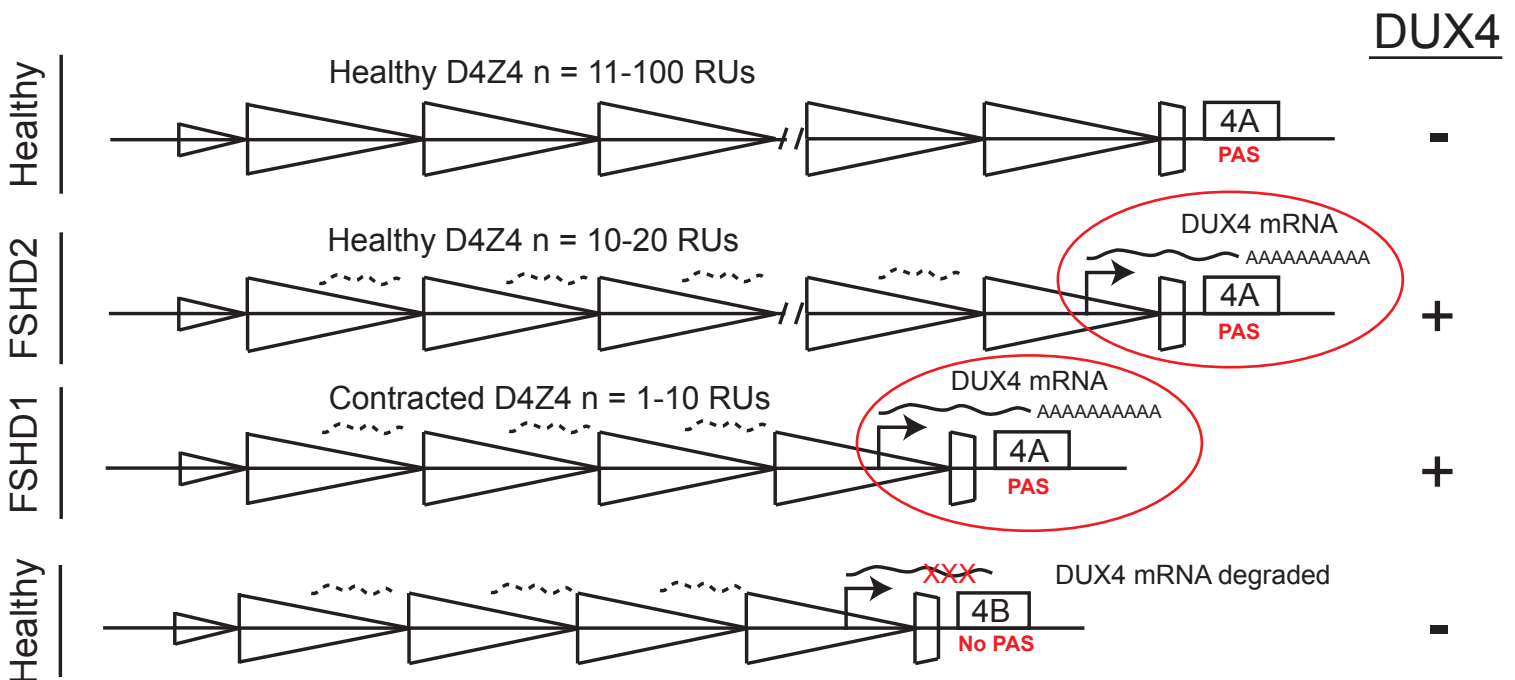


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Science (2010) 329:1650-3.

Aberrant expression of the pathogenic *DUX4* gene requires a permissive 4qA subtelomere with a PAS and proper *DUX4* mRNA splicing.



We learned:

- The 4A subtelomere, with a PAS is permissive, not pathogenic.
- Healthy chromosome 4s are also 4A with a PAS.
- The 4A PAS is necessary for FSHD, but not sufficient.
- Both FSHD1 and FSHD2 require a 4A PAS.
- The PAS stabilizes the *DUX4* mRNA.
- This conclusively shows that *DUX4* is the FSHD pathogenic gene.



FSHD Permissive vs Nonpermissive (Pt 5)

What about 4A-L and 4A166?

- ▶ Both the 4A161L and 4A166 haplotypes are permissive since they both have an exon 3 and DUX4 PAS. However, only the 4A161L is linked to FSHD.
- ▶ The 4A-L refers to “long” due to an extra long sequence in the last partial D4Z4 that makes up inton 2. Regardless, the DUX4 mRNA is polyadenylated and made into DUX4 protein.
- ▶ The 4A166 haplotype, for reasons currently under investigation, is very inefficient at making polyadenylated DUX4 mRNA and thus is not linked to FSHD despite technically being qualified as FSHD permissive.

