FSHD Genetics:
Introduction (Pt 3)

All forms of FSHD are associated with the chromosome 4q35 D4Z4 array.

FSHD2 is historically “contraction-independent”.

After discovery of the FSHD deletion on 4q35, there were still some clinical FSHD cases that did not have that deletion.

This suggested there were other genes unlinked to 4q35 that, in rare cases, could cause clinical FSHD when mutated.

Now, roughly 5% of confirmed FSHD cases are known to be FSHD2.

First reports of contraction-independent FSHD.

Workshop report
44th ENMC International Workshop:
Facioscapulohumeral Muscular Dystrophy: Molecular Studies
19-21 July 1996, Naarden, The Netherlands

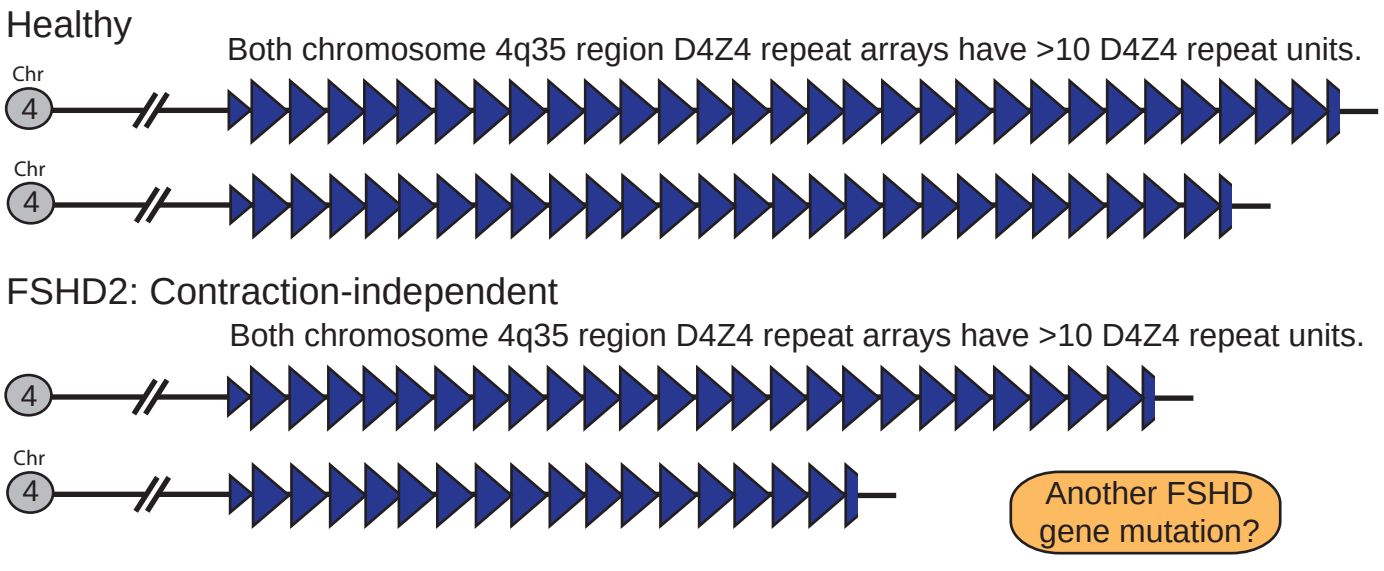
3.1.5. Non-linkage and recombination

From 523 familes with clinical FSHD, there were 11 at most, and yet possibly zero (0-2%) which could be unlinked to 4q35;

Hypomethylation of D4Z4 in 4q-linked and non-4q-linked facioscapulohumeral muscular dystrophy *Nature Genetics* (2003) 35:315.

Petra G M van Overveld[1], Richard J F L Lemmers[1], Lodewijk A Sandkuijl[1,5], Leo Enthoven[2], Sara T Winokur[3], Floor Bakels[1], George W Padberg[4], Gert-Jan B van Ommen[1], Rune R Frants[1] & Silvère M van der Maarel[1]

Suggested a connection between FSHD2 and the 4q35 region



FSHD Genetics:
Introduction (Pt 4)

All forms of FSHD are associated with the chromosome 4q35 D4Z4 array.

It turns out that FSHD2 is, in fact, linked to the 4q35 D4Z4 array in several ways. FSHD2 requires an FSHD permissive 4A, a specific range of D4Z4 RUs, and causes the same epigenetic changes as FSHD1.

Despite FSHD2 being characterized as "contraction-independent" FSHD, it is not totally independent of D4Z4 array size; requires a range of 8* - 20 D4Z4 RUs on a permissive 4qA.

*traditionally, FSHD1 has been 1-10RUs and FSHD2 as >10RUs; more recently, FSHD2 has been refined to 8 - 20 as we learn more about the prevalence of FSHD2 mutations. You will see variable ranges in the literature depending on the group.

Key research papers showing additional FSHD2 requirements:

As with FSHD1, FSHD2 also requires a permissive chromosome 4A.

Sciencexpress Report

A Unifying Genetic Model for Facioscapulohumeral Muscular Dystrophy

Richard J.L.F. Lemmers, Patrick J. van der Vliet, Rinse Klooster, Sabrina Sacconi, Pilar Camaño, 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.

FSHD2 requires a D4Z4 array between 8 - 20RUs on a permissive chromosome 4A.

Digenic inheritance of an *SMCHD1* mutation and an FSHD-permissive D4Z4 allele causes facioscapulohumeral muscular dystrophy type 2

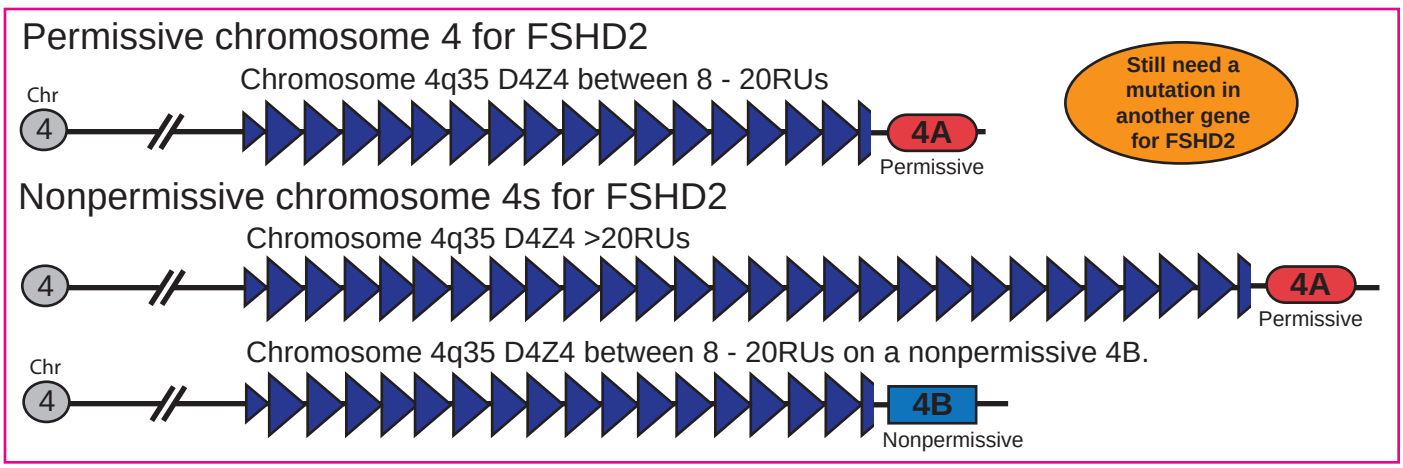
Richard J L F Lemmers[1,13], Rabi Tawil[2,13], Lisa M Petek[3], Judit Balog[1], Gregory J Block[3], Gijs W E Santen[4], Amanda M Amell[3], Patrick J van der Vliet[1], Rowida Almomani[4], Kirsten R Straasheijm[1], Yvonne D Krom[1], Rinse Klooster[1], Yu Sun[1], Johan T den Dunnen[1,4], Quinta Helmer[5], Colleen M Donlin-Smith[2], George W Padberg[6], Baziel G M van Engelen[6], Jessica C de Greef[1,12], Annemieke M Aartsma-Rus[1], Rune R Frants[1], Marianne de Visser[7], Claude Desnuelle[8,9], Sabrina Sacconi[8,9], Galina N Filippova[10], Bert Bakker[4], Michael J Bamshad[3,11], Stephen J Tapscott[10], Daniel G Miller[3,11] & Silvère M van der Maarel[1]

Nature Genetics (2012) 44:1370-4.

Cis D4Z4 repeat duplications associated with facioscapulohumeral muscular dystrophy type 2

Richard J.L.F. Lemmers[1,*], Patrick J. van der Vliet[1], Jeroen P. Vreijling[2], Don Henderson[3], Nienke van der Stoep[2], Nicol Voermans[4], Baziel van Engelen[4], Frank Baas[2], Sabrina Sacconi[5], Rabi Tawil[3] and Silvère M. van der Maarel[1]

Human Molecular Genetics (2018) 27:3488-97.



FSHD Genetics:
Introduction (Pt 5)

All forms of FSHD are associated with the chromosome 4q35 D4Z4 array.

FSHD2 is caused by mutations in genes that encode repressors of the 4q35 D4Z4 array, when combined with FSHD2 permissive 4q35 genetics.

FSHD2 requires a range of 8 - 20 D4Z4 RUs on a permissive 4qA chromosome.

Current FSHD2 genes are *SMCHD1*, *DNMT3B*, and *LRIF1*.

Key research papers identifying the genes mutated in FSHD2:

Digenic inheritance of an *SMCHD1* mutation and an FSHD-permissive D4Z4 allele causes facioscapulohumeral muscular dystrophy type 2

Richard J L F Lemmers[1,13], Rabi Tawil[2,13], Lisa M Petek[3], Judit Balog[1], Gregory J Block[3], Gijs W E Santen[4], Amanda M Amell[3], Patrick J van der Vliet[1], Rowida Almomani[4], Kirsten R Straasheijm[1], Yvonne D Krom[1], Rinse Klooster[1], Yu Sun[1], Johan T den Dunnen[1,4], Quinta Helmer[5], Colleen M Donlin-Smith[2], George W Padberg[6], Baziel G M van Engelen[6], Jessica C de Greef[1,12], Annemieke M Aartsma-Rus[1], Rune R Frants[1], Marianne de Visser[7], Claude Desnuelle[8,9], Sabrina Sacconi[8,9], Galina N Filippova[10], Bert Bakker[4], Michael J Bamshad[3,11], Stephen J Tapscott[10], Daniel G Miller[3,11] & Silvère M van der Maarel[1]

Nature Genetics (2012) 44:1370-4.

Mutations in *DNMT3B* Modify Epigenetic Repression of the D4Z4 Repeat and the Penetrance of Facioscapulohumeral Dystrophy

Mari Auranen,[3] Satomi Mitsuhashi,[4] Patrick J. van der Vliet,[1] Kirsten R. Straasheijm,[1] Rob F.P. van den Akker,[1] Marjolein Kriek,[1,5] Marlies E.Y. Laurense-Bik,[5] Vered Raz,[1] Monique M. van Ostaijen-ten Dam,[6] Kerstin B.M. Hansson,[5] Elly L. van der Kooi,[7] Sari Kiuru-Enari,[3] Bjarne Udd,[8] Maarten J.D. van Tol,[6] Ichizo Nishino,[4] Rabi Tawil,[9] Stephen J. Tapscott,[10] Baziel G.M. van Engelen,[2] and Silvère M. van der Maarel[1,*]

Am J Human Genetics (2016) 98:1020-9.

Homozygous nonsense variant in *LRIF1* associated with facioscapulohumeral muscular dystrophy

Kohei Hamanaka, Darina Sikrova, Satomi Mitsuhashi, Hiroki Masuda, Yukari Sekiguchi, Atsuhiko Sugiyama, Richard J.L.F. Lemmers, Remko Goossers, Megumu Ogawa, Koji Nagao, Chikashi Obuse, Satoru Noguchi, Yukiko K. Hayashi, Stoshi Kuwabara, Judit Balog, Ichizo Nishimo*, Silvere van der Maarel*

Neurology (2020) 94:e2441-7.

We learned:

- Both FSHD1 and FSHD2 have genetic requirements on 4q35.
- Both FSHD1 and FSHD2 require an FSHD permissive 4A.
- FSHD1 contractions result in arrays between 1-10 D4Z4 RUs.
- FSHD2 is not truly contraction-independent, requires D4Z4 arrays of 8-20RUs.
- FSHD2 requires a mutation in another gene not located at 4q35.
- Genes mutated in FSHD2 encode proteins that function at 4q35.
- FSHD2 gene mutations require FSHD2 permissive genetics at 4q35.
- FSHD2 gene mutations themselves are not pathogenic for FSHD.