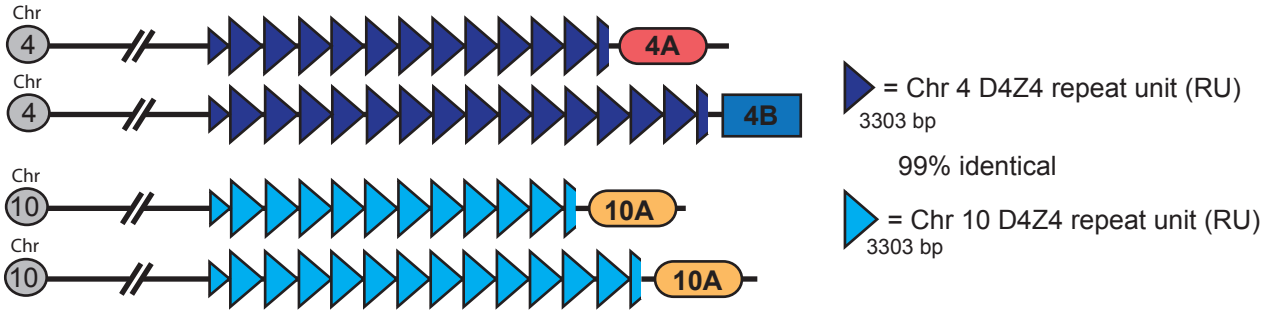
# Types of FSHD: FSHD1 Genetics (Pt 1)

## All forms of FSHD are associated with the chromosome 4 D4Z4 array. FSHD1 is caused by deletions in this D4Z4 array.

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; specifically, a region called a D4Z4 repeat array located at 4q35.
A D4Z4 repeat unit (RU) is 3303 base pairs of DNA. The arrays consist of D4Z4 RUs arranged head-to-tail.
A very similar D4Z4 array is found on chromosome 10q26. The chr 10 array is not associated with FSHD.
All four D4Z4 arrays (2 on chr 4 and 2 on chr 10) typically have different numbers of RUs that can reach ~100.




Complicating matters, the 4q35 region is duplicated on 10q26.

Bakker *et al.* (1995) *Muscle Nerve* 2:S39-44
Deidda *et al.* (1995) *Eur J Hum Gene* 3:155-67.

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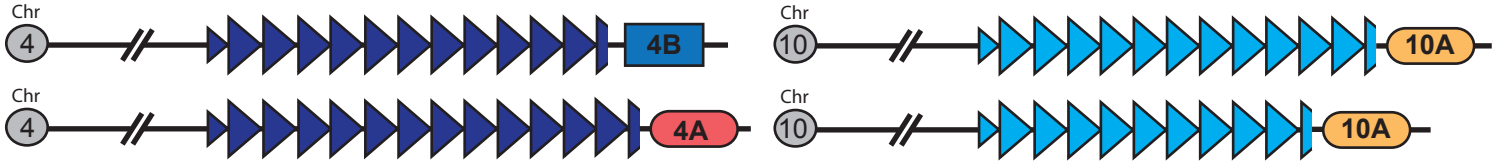
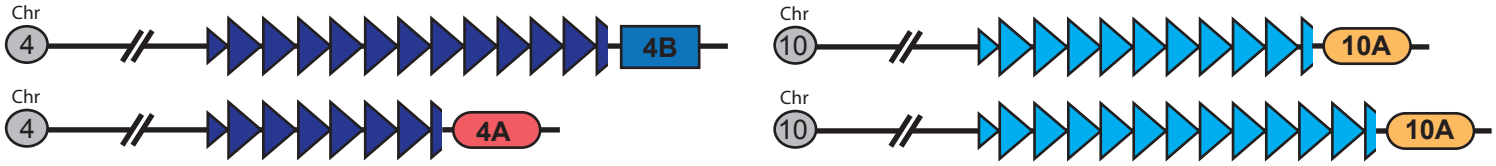
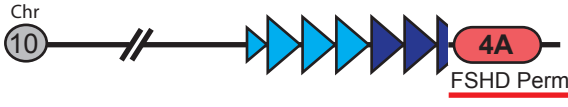
Individuals that are not genetically FSHD1 have >10 D4Z4 RUs on both chromosome 4s; the number of D4Z4 RUs on chromosome 10 do not matter for this determination.



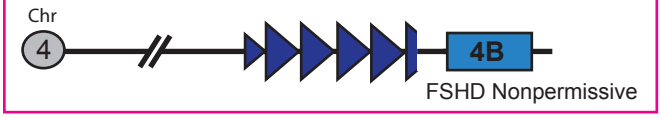

Genetically FSHD1 individuals have <11 D4Z4 RUs on one chromosome 4 combined with a 4A subtelomere; again, the number of D4Z4 RUs on chromosome 10 do not matter for this determination.




Rare chromosome 10-linked FSHD1 is caused by translocation of chromosome 4 D4Z4 and 4qA.




D4Z4 contractions on chromosome 4B are NOT genetically FSHD1.



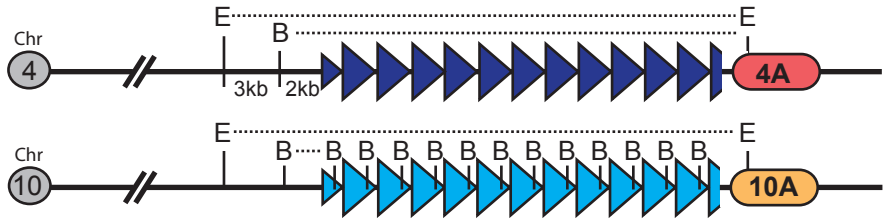


Wijmenga *et al.* (1992) *Nature Genetics* 2:26-30
van Deutekom *et al.* (1993) *Hum Mol Genet* 2:2037-42.
Lemmers *et al.* (2002) *Nature Genetics* 32:235-6.
Lemmers *et al.* (2004) *Am J Hum Genet* 75:1124-30.
Lemmers *et al.* (2010) *Science* 329:1650-3.

# Types of FSHD: FSHD1 Genetics (Pt 2)

## All forms of FSHD are associated with the chromosome 4 D4Z4 array. FSHD1 is caused by deletions in the D4Z4 array.

Determining the size of your chromosome 4 D4Z4 arrays

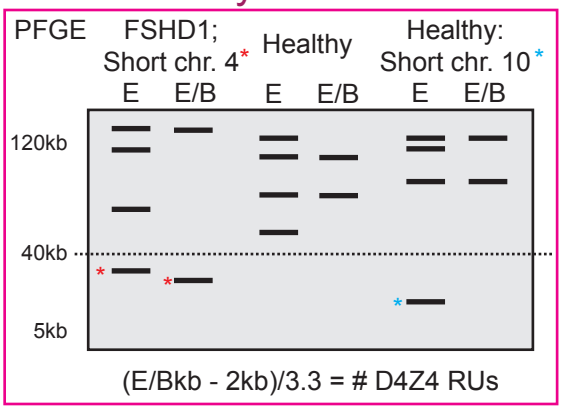



E = EcoRI
B = BlnI

These enzymes cut the DNA at specific sequences resulting in specific sizes.

Lemmers *et al.* (2012) *Neuromuscular Disorders* 22:463-70.

1 D4Z4 = 3.3kb

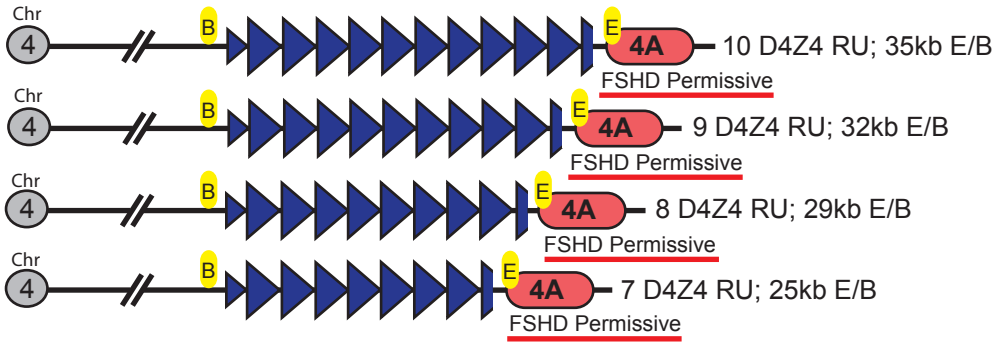



(E/Bkb - 2kb)/3.3 = # D4Z4 RUs

There is an imperfect correlation between FSHD severity and size of deletion, with the largest deletions (shortest arrays) being more severe and the smaller deletions (larger arrays) being less severe.

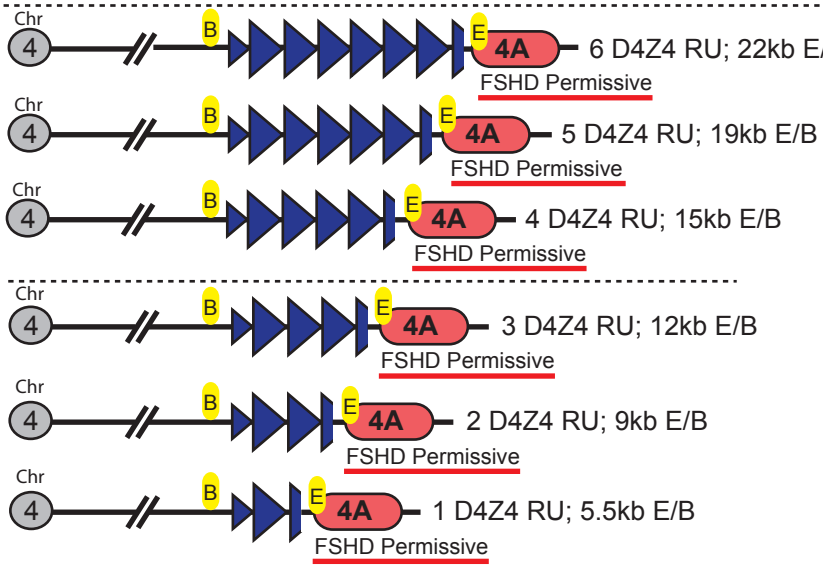
Lunt *et al.* (1995) *Hum Mol Genet* 4:951-8.
Goselink *et al.* (2019) *Neurology* 92:e378-385.

There are, of course, exceptions. Nikolic *et al.* (2016) *BMJ Open* 6:e007798




The genetic FSHD1 range of 7-10 RUs is often clinically mild to asymptomatic.

Statland *et al.* (2015) *Neurology* 85:2147-50.

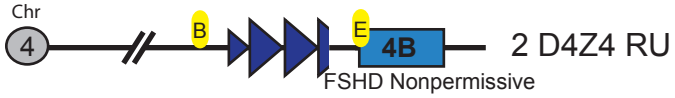



The genetic FSHD1 range of 1-3 RUs is often clinically severe with early onset.

Klinge *et al.* (2006) *Neuromuscular Disord* 16:553-8.
Chen *et al.* (2013) *Neuromuscular Disord* 23:298-305.

Healthy: Genetic FSHD1 requires at least 1 D4Z4 RU on a 4qA chromosome.

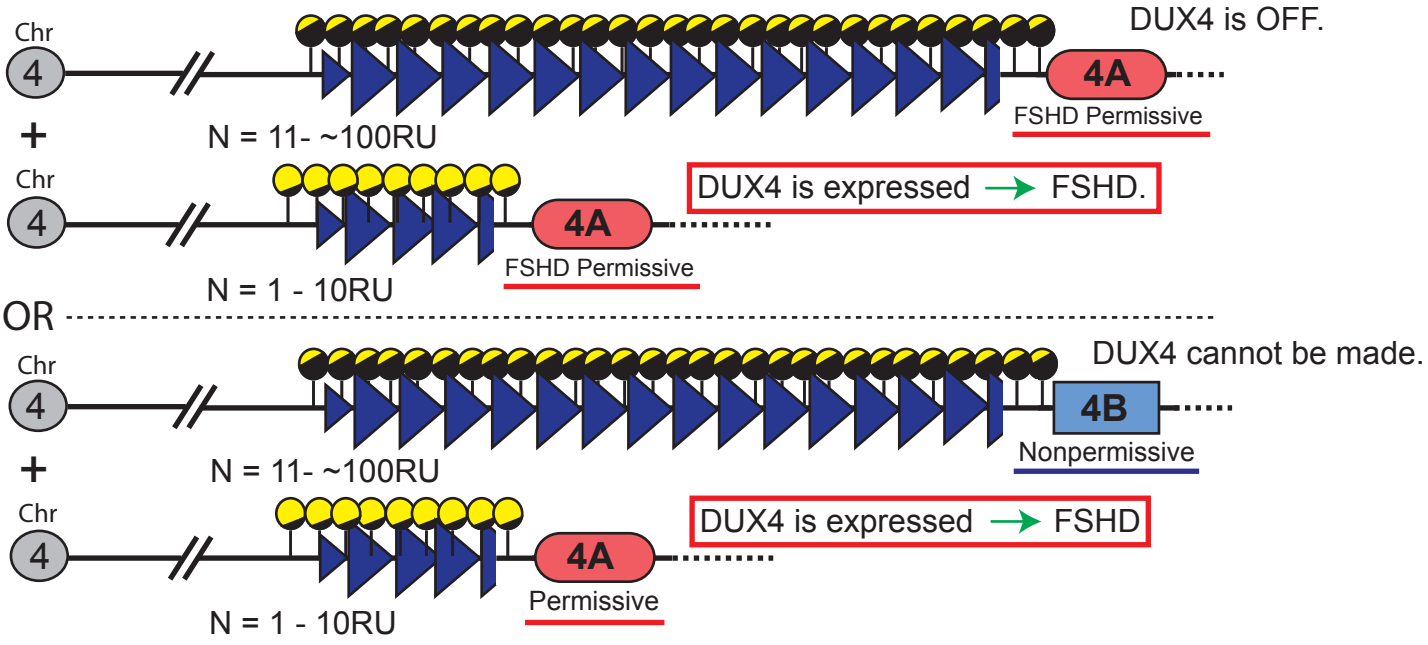

Tupler *et al.* (1996) *J Med Genet* 33:366-70.



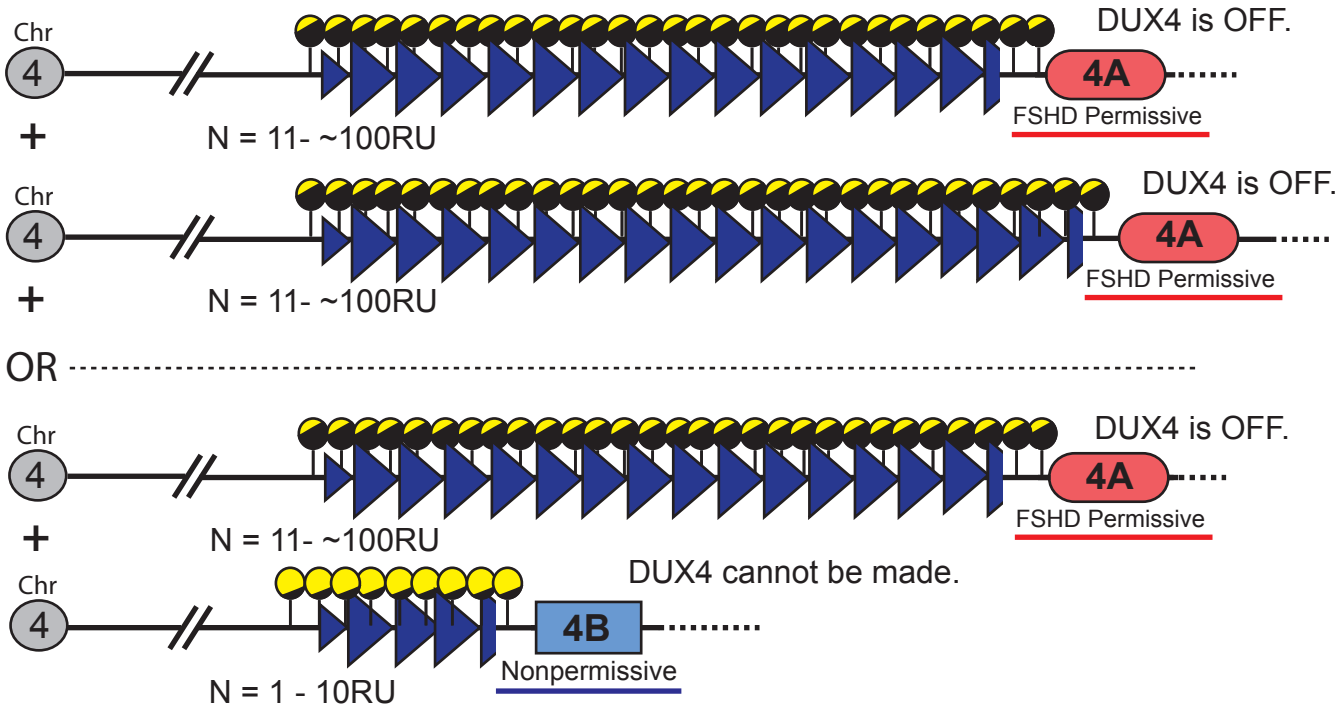

Lemmers *et al.* (2004) *Am J Hum Genet* 75:1124-30.

# Types of FSHD: FSHD1 vs Healthy

## FSHD1: One FSHD permissive chr. 4 is contracted to between 1-10RUs.




## Healthy/Not FSHD1: One or more of the genetic requirements for FSHD are not met.



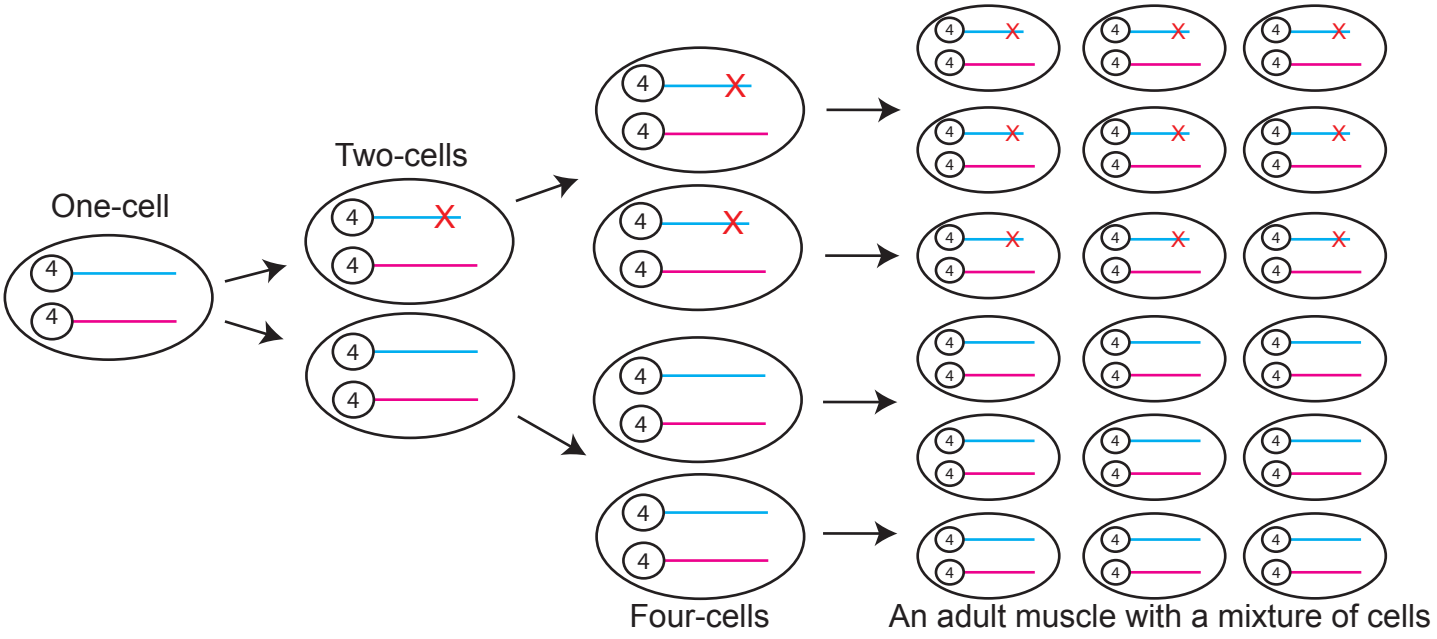

= D4Z4 repeat unit (RU)

= Low levels of DNA methylation, epigenetics → ON

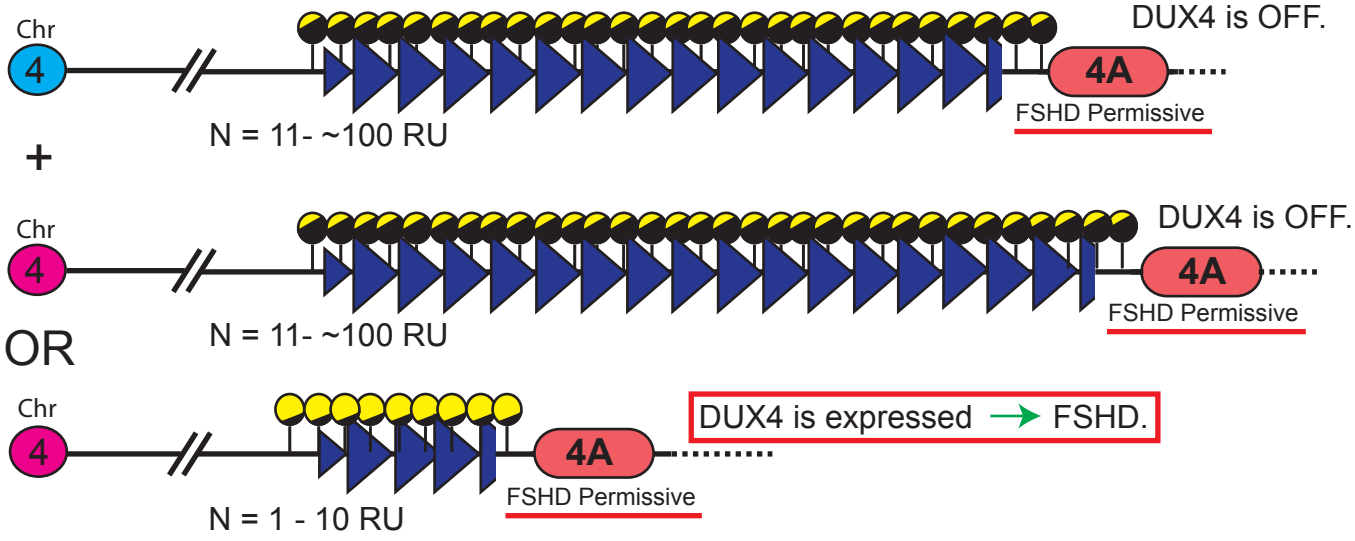
= High levels of DNA methylation, epigenetics → OFF

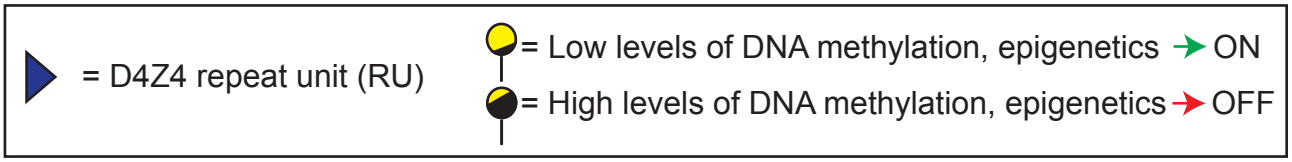
# Types of FSHD: Mosaic for FSHD1

Mosaic FSHD1: A spontaneous contraction that occurs after fertilization such that only some cells have a contracted chromosome 4. Thus, one's body is a mixture of healthy cells and genetically FSHD1 cells.




Mosaic FSHD1: An individual with two different genetic populations of cells at the FSHD locus; one population has two healthy chromosome 4s and a second population has one healthy chromosome 4 and one FSHD1 chromosome 4.



# Types of FSHD: Infantile (early-onset) FSHD1

Infantile/early-onset FSHD is found in subjects with 1-3RUs and is characterized clinically by facial weakness before age 5yrs and scapulohumeral weakness before age 10yrs. Weakness can be accompanied by hearing loss and retinopathy.

**Some key papers describing early-onset FSHD:**

ORIGINAL CONTRIBUTION

**Facioscapulohumeral Muscular Dystrophy in Early Childhood**

*Arch Neurol* (1994) 51:387-94.

*Oebele F. Brouwer, MD, PhD; George W. Padberg, MD, PhD; Ciska Wijmenga, PhD; Rune R. Frants, PhD*

**Severe phenotype in infantile facioscapulohumeral muscular dystrophy**

Lars Klinge *, Michelle Eagle, Irene D. Haggerty, Catherine E. Roberts, Volker Straub, Kate M. Bushby

*Neuromuscular Disorders* (2006) 16:553-8.

**Early onset as a marker for disease severity in facioscapulohumeral muscular dystrophy**

Rianne J.M. Goselink, MD, Karlien Mul, MD, Caroline R. van Kernebeek, MD, Richard J.L.F. Lemmers, PhD, Silvère M. van der Maarel, PhD, Tim H.A. Schreuder, PhD, Corrie E. Erasmus, MD, PhD, George W. Padberg, MD, PhD, Jeffrey M. Statland, MD, Nicol C. Voermans, MD, PhD, and Baziel G.M. van Engelen, MD, PhD

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*Neurology* (2019) 92:e378-85.

## Typically, FSHD1 with 1-3 D4Z4 RUs