

# **Facioscapulohumeral muscular dystrophy: The unmet medical need**

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# Facioscapulohumeral Muscular Dystrophy (FSHD)

- Prevalence of ~1:8,000 - 1:20,000
- Autosomal dominant disorder of families
- Extremely disabling
- Can be life shortening for those with respiratory insufficiency



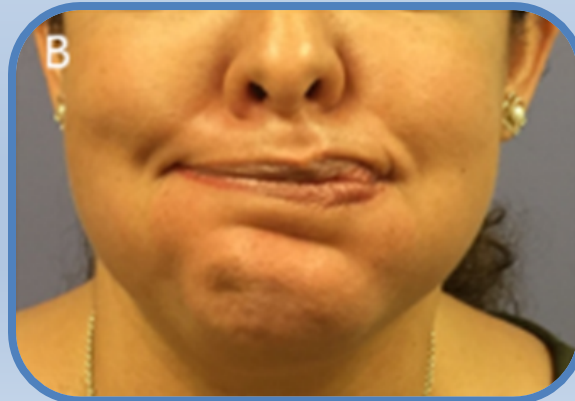
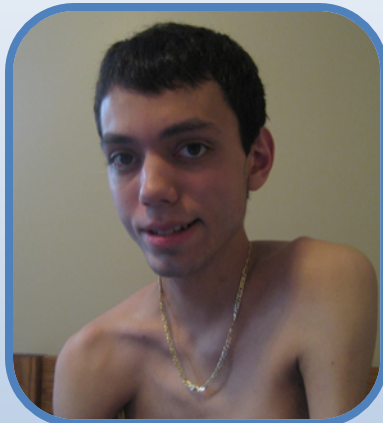
# FSHD Phenotype

- Wide variability of severity
- Asymmetric involvement
- Majority present in adolescence/early adulthood
- Almost pure skeletal muscle disease: Usually no extramuscular symptoms



# FSHD Phenotype

- Weakness of facial muscles: Transverse smile, eyelid closure weakness, buccal muscle weakness





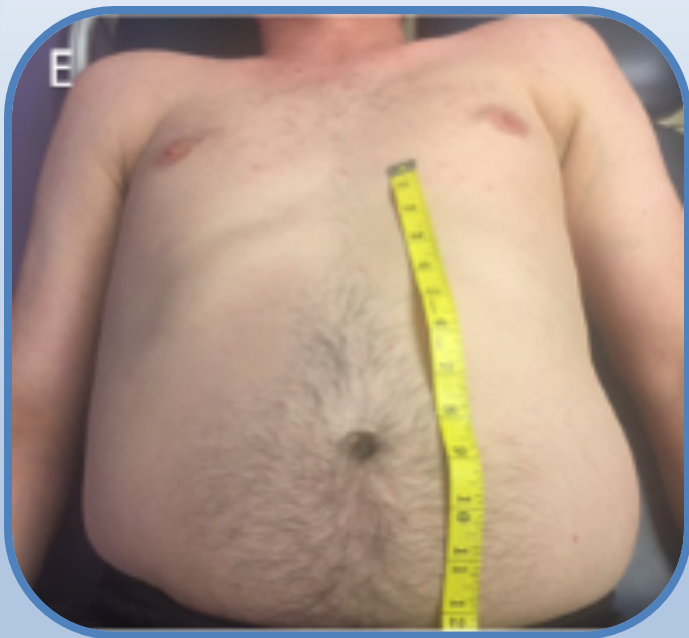
# FSHD Phenotype

- Weakness of muscles of scapular fixation: scapular winging.
- Weakness and wasting and muscles overlying humerus: biceps/triceps



# FSHD Phenotype

- Pelvic girdle, foot dorsiflexor, abdominal muscle weakness may follow



Beevor sign

Wagner, Continuum 2019

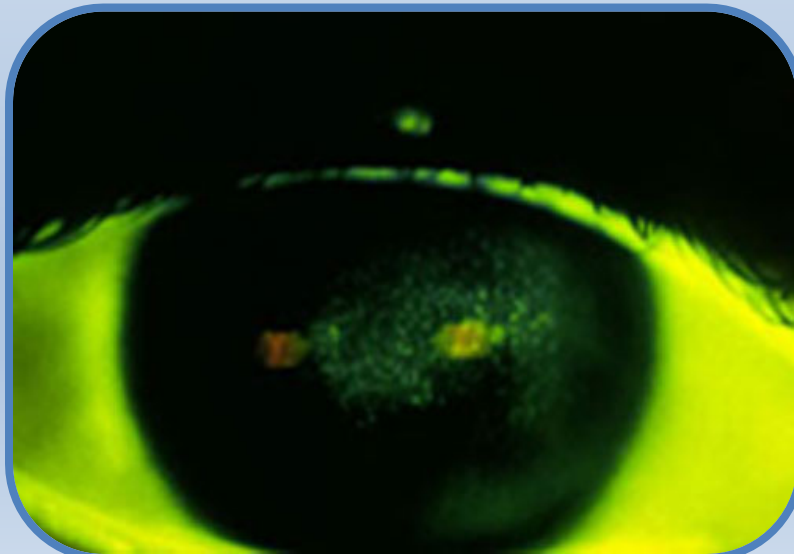
# Early or “Infantile Onset” FSHD

- Rapid progression with loss of ambulation
- Association with retinal vascular abnormalities and high tone hearing loss
- More likely to be associated with respiratory insufficiency



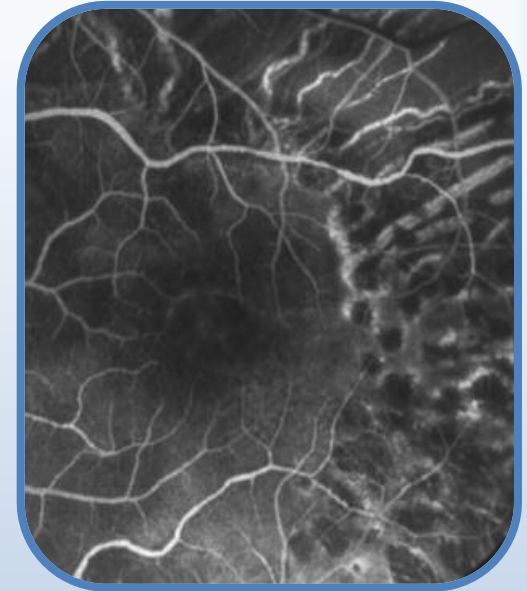
# Current Management

- No good pharmacological agents to prevent muscle wasting and weakness
- Aquatic and physical therapy
  - Olsen et al., Aerobic training improves exercise performance in FSHD, Neurology 2005.
- Bracing
  - Foot drop: ankle foot orthoses
  - Abdominal laxity: abdominal binder
- For prevention of corneal abrasions
  - Lacrilube at night, artificial tears



# Specific Treatments

- Vascular telangiectasia
  - Retinal exam with ophthalmologist
  - Fluorescein angiography if abnormal retinal exam or family history of Coat's syndrome in FSHD
  - Laser treatments
- Scapular Fixation
  - Anticipated benefits: reduced pain, Improved arm abduction/extension, Less “winging”
  - Risks: surgical risks, infection, pain, decreased pulmonary function, long rehab
  - No randomized trials

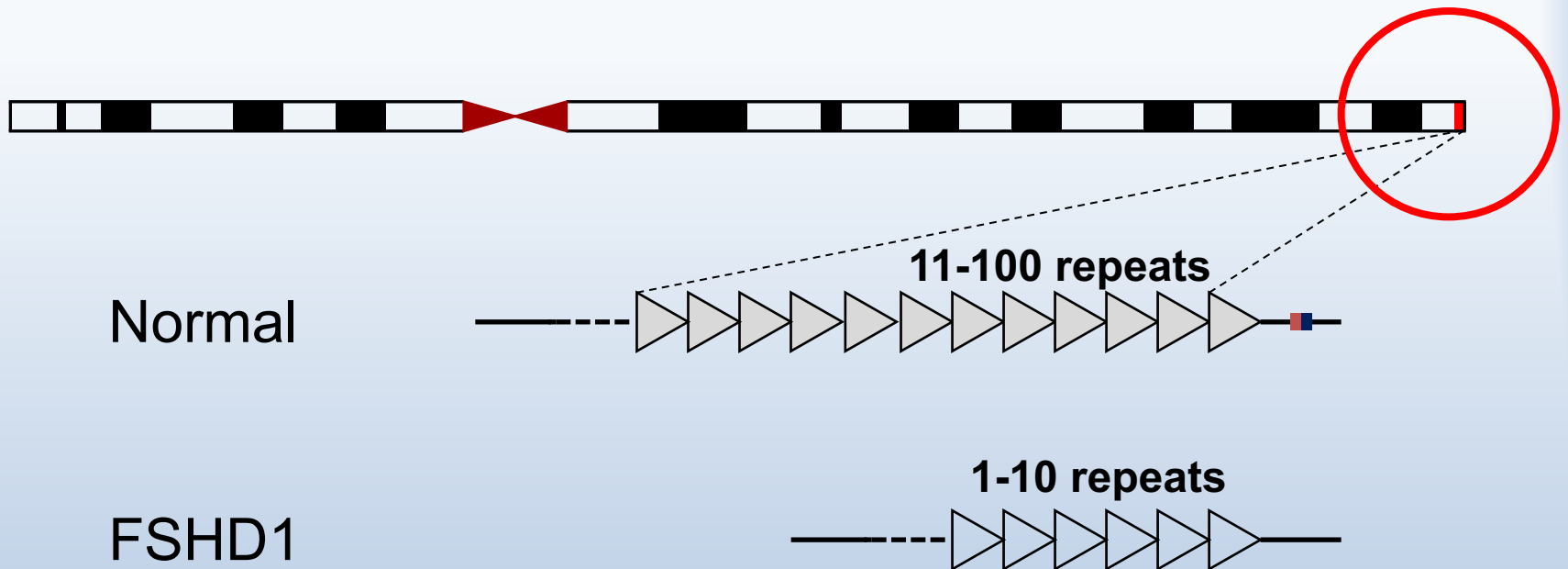




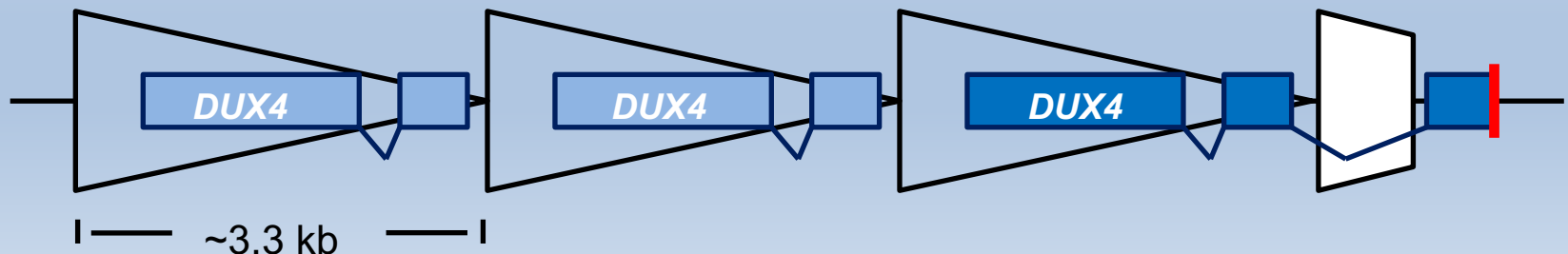


Scapulofixation on the right, winging on the left

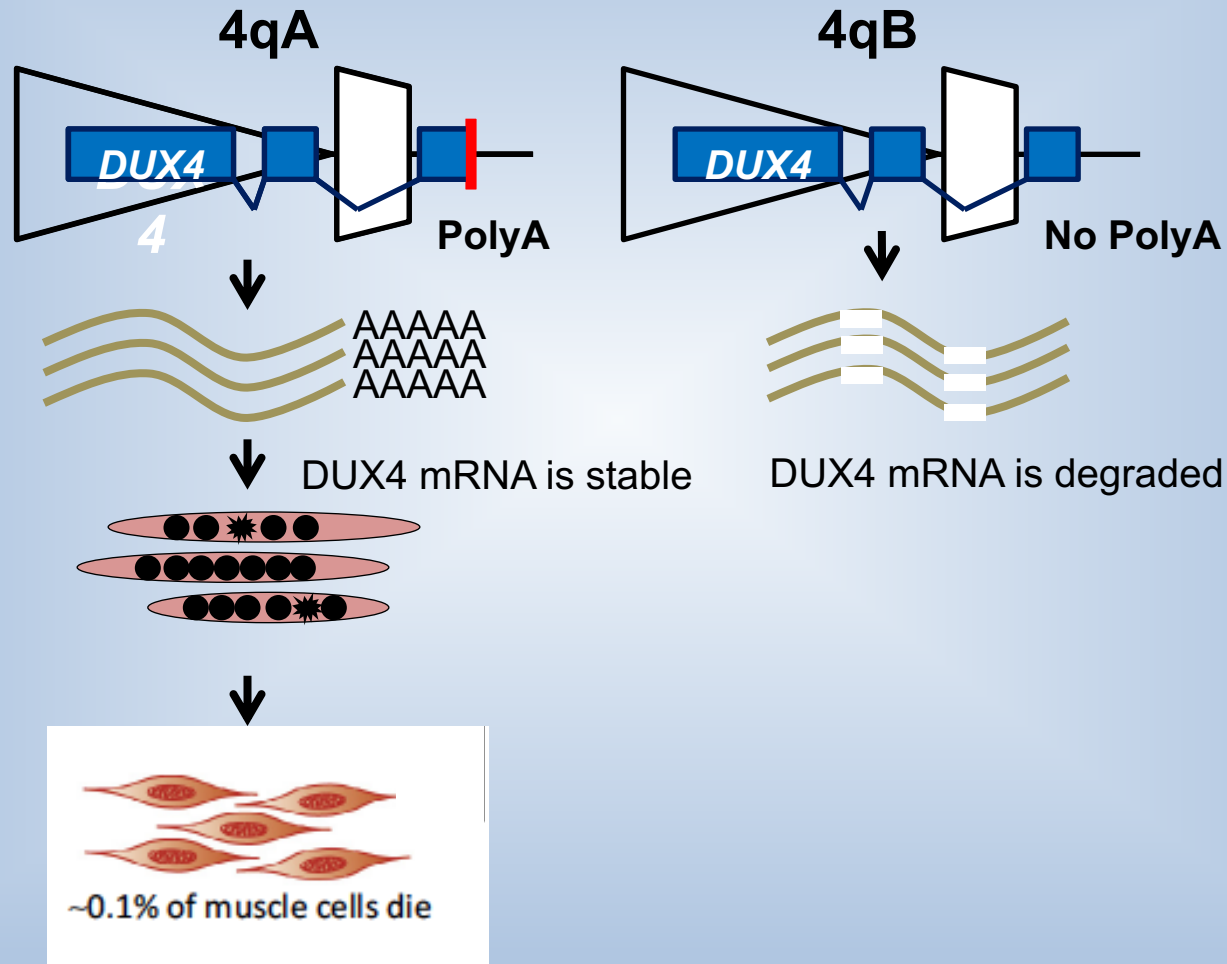
FSHD1 is linked to a truncated repetitive region in the subtelomeric region of chromosome 4



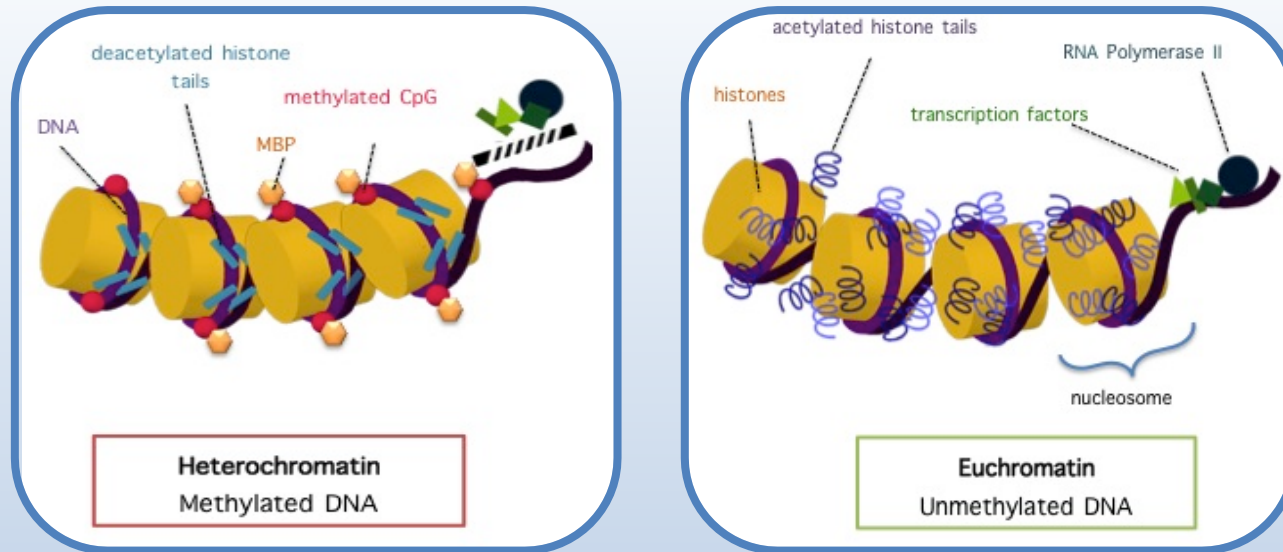
Within each D4Z4 repeat unit is an open reading frame for a gene called **DUX4**



# D4Z4 repeat truncation **AND** a permissive haplotype results in stable DUX4 transcript expression



# D4Z4 repeat truncation leads to changes in epigenetic regulation of the region



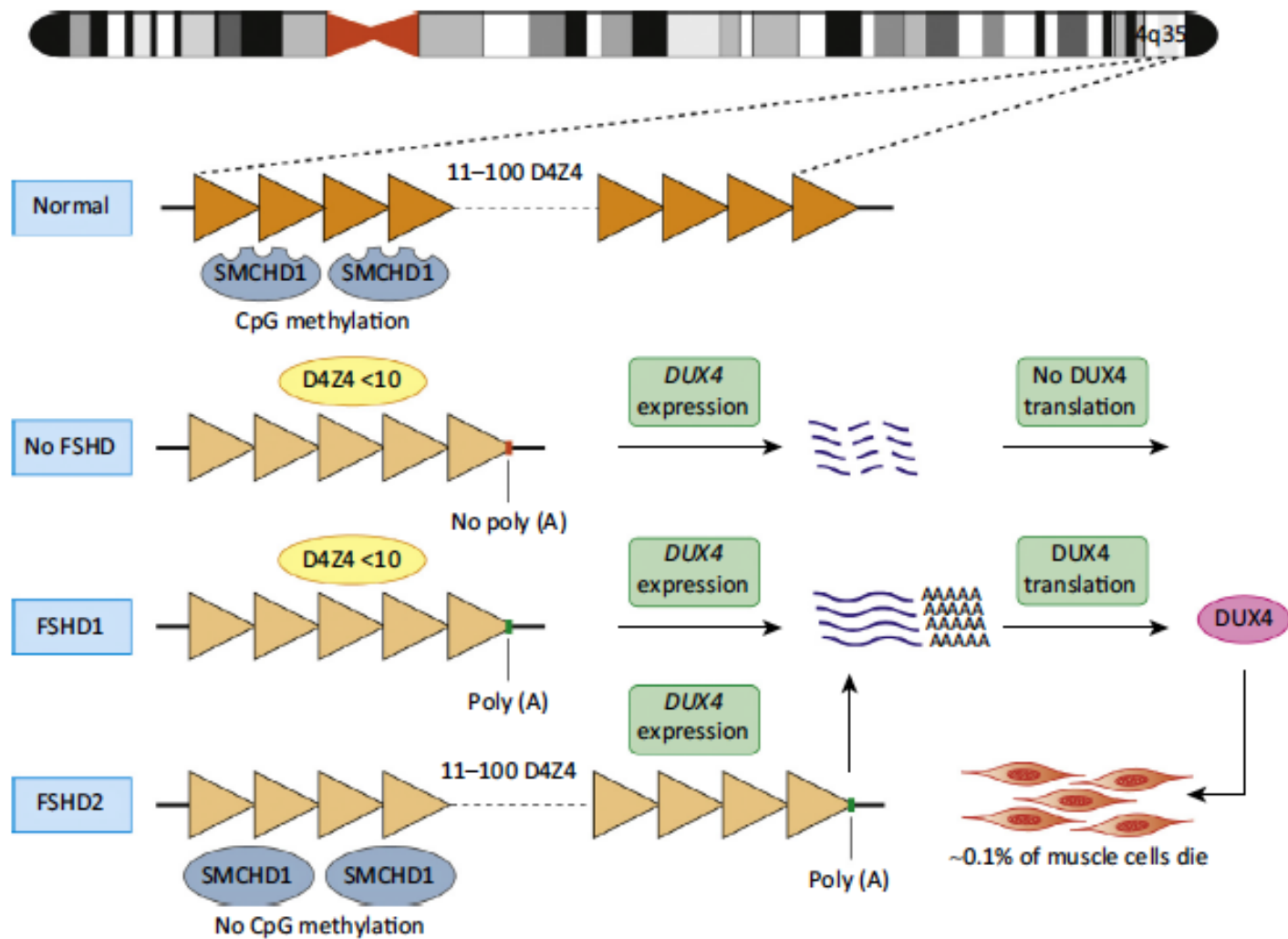
## Normal (11-100 repeats):

Highly methylated, closed chromatin structure → transcriptional repression of DUX4

## FSHD1 (1-10 repeats):

Loss of methylation, open chromatin structure → transcriptional activation of DUX4

# FSHD1 vs FSHD2



TRENDS in Molecular Medicine



# Diagnosis of FSHD

- Clinical phenotype, normal to slightly elevated CK
- Genetic Testing FSHD1:
  - Determination of the number of D4Z4 units on chromosome 4 by Southern blot or genome-wide optical mapping
  - 1 to 10 repeats AND chromosome 4 permissive haplotype 4qA
  - 95% of FSHD patients carries one allele of 1-10 units
  - Early or “Infantile Onset” associated with 1-3 units
  - Mild or reduced penetrance associated with 8-10 units.
- Genetic Testing FSHD2:
  - Chromosome 4 permissive haplotype 4qA
  - Hypomethylation of D4Z4 repeat array
  - Heterozygous pathogenic variant in SMCHD1 or DNMT3B

# Targets for FSHD Therapeutics

- 4q35 subtelomeric D4Z4 locus
  - Overexpression of SMCHD1
  - Modulation of histone acetylation
- DUX4
  - Knock down mRNA expression
  - Inhibit DUX4 protein/binding partners
- DUX4 target genes
- Downstream pathology
  - Inflammation
    - Immunomodulatory drugs
  - Atrophy
    - Anabolic agents

# Conclusions

- FSHD is one of the most common muscular dystrophies
- It is marked by extensive muscle involvement with resulting disabilities
- The genetic cause is complex and the pathophysiology is incompletely understood
- There are insufficient meaningful treatments.



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