Where we are in FSHD and how did we get here?

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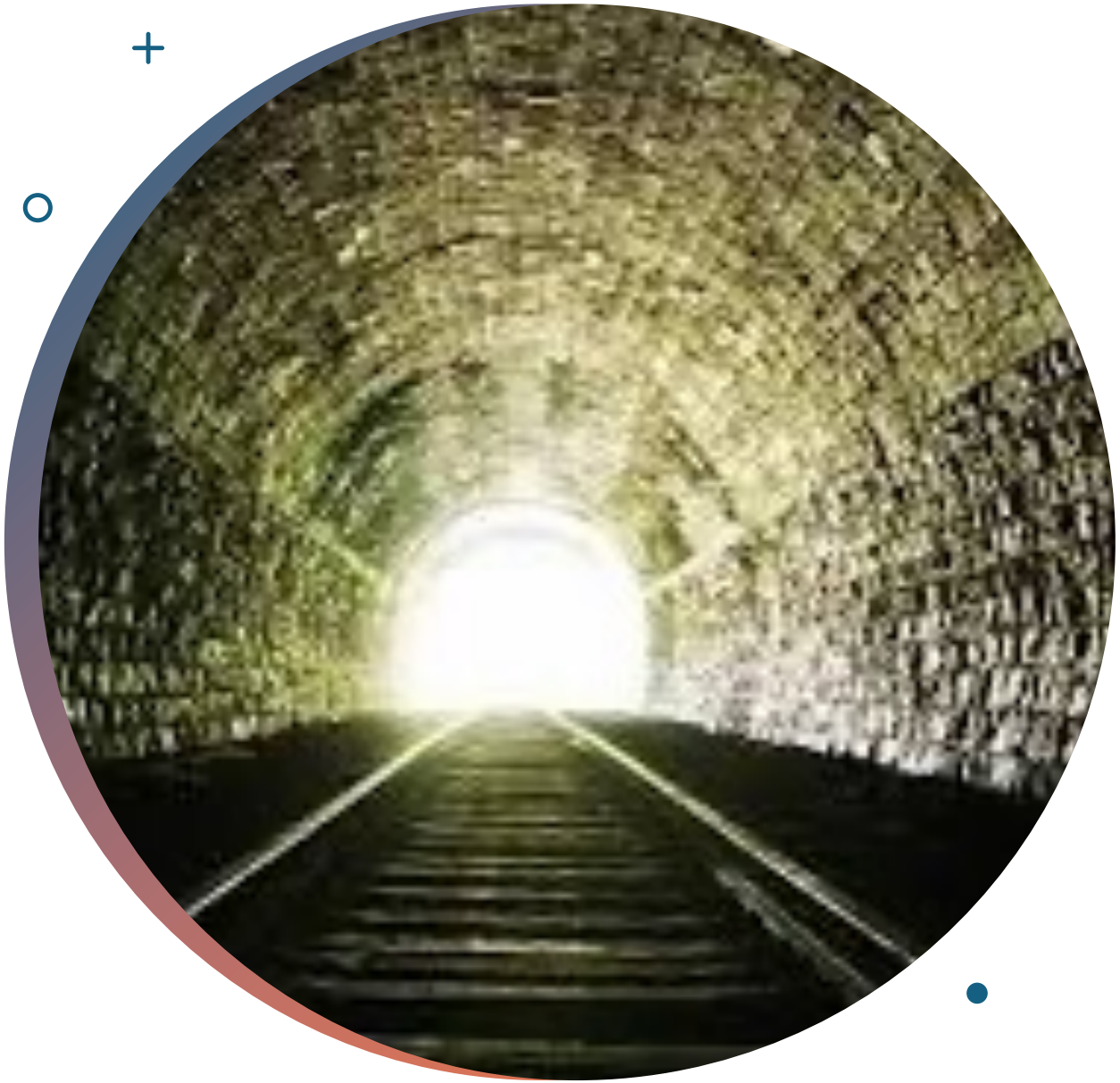
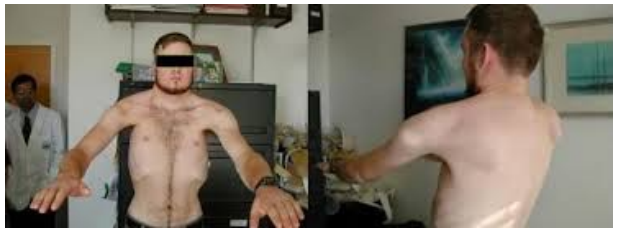
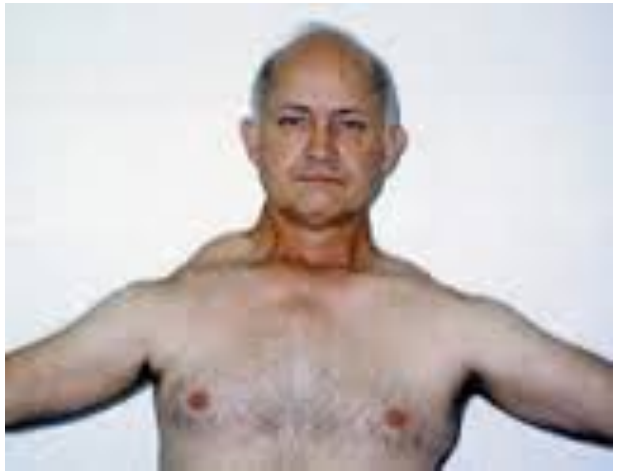


Amazing progress!

- FSHD described in the 1880s
- Family inheritance described in 1950
- Hunt for the genetic cause from 1982-2010
- 3 active clinical trials
- Multiple more in pipeline

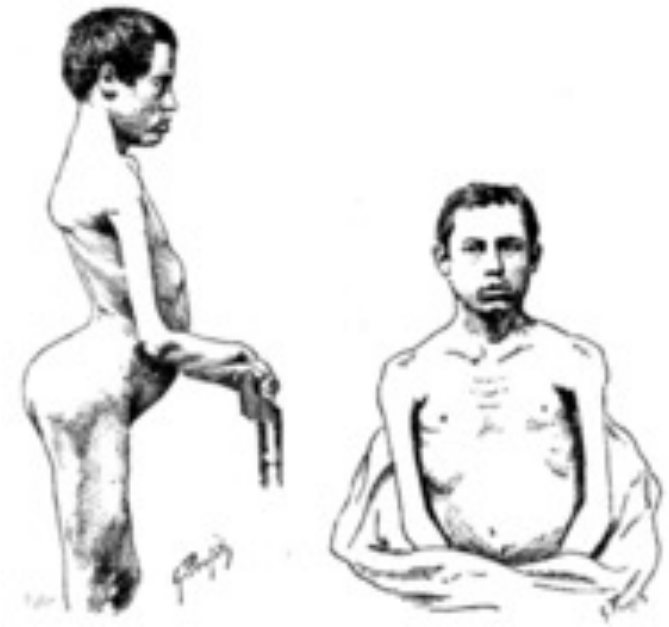
Background





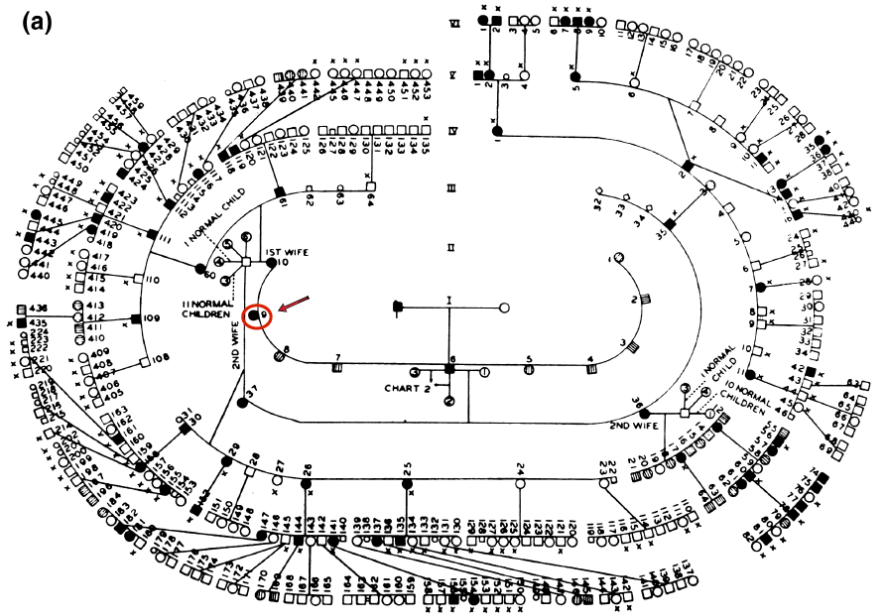
- Asymmetric, regional, and highly variable
- Face
- Scapular muscles
- Humeral muscles
- Peroneal
- Quadriceps
- Abdominal/core muscles

Original description of FSHD



- Landouzy and Dejerine (1884)
- Two brothers with a childhood progressive muscle atrophy affecting facial muscles

The Utah cohort and finding the gene



- Tyler and Stephens (1950) describe 1249 individuals from a single kindred
- Establishes autosomal dominant inheritance
- Demonstrates stable mutation between generations
- Padberg performs linkage studies (1982)
- Multiple groups narrow location in 1990s

Unifying genetic model

Multiple decades of work

Early funding by FSHD Society

Highlighted the ability to target the mechanism

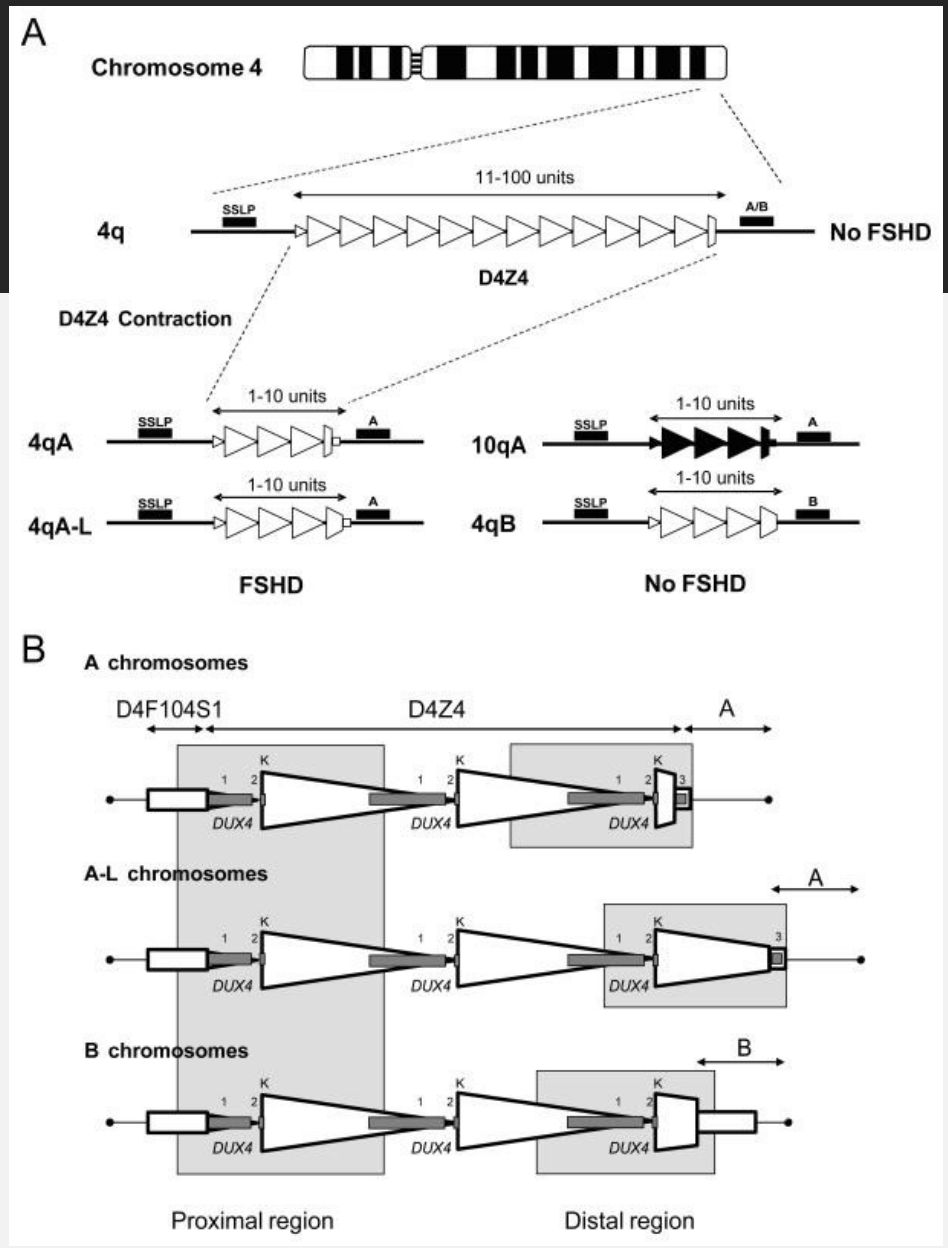
Allows for disease modifying therapies!

Shortened D4Z4 + 4qA + hypomethylation of D4Z4 = FSHD Type 1

chromosome 4

SMCHD1 mutation + 4qA + hypomethylation of D4Z4 = FSHD Type 2

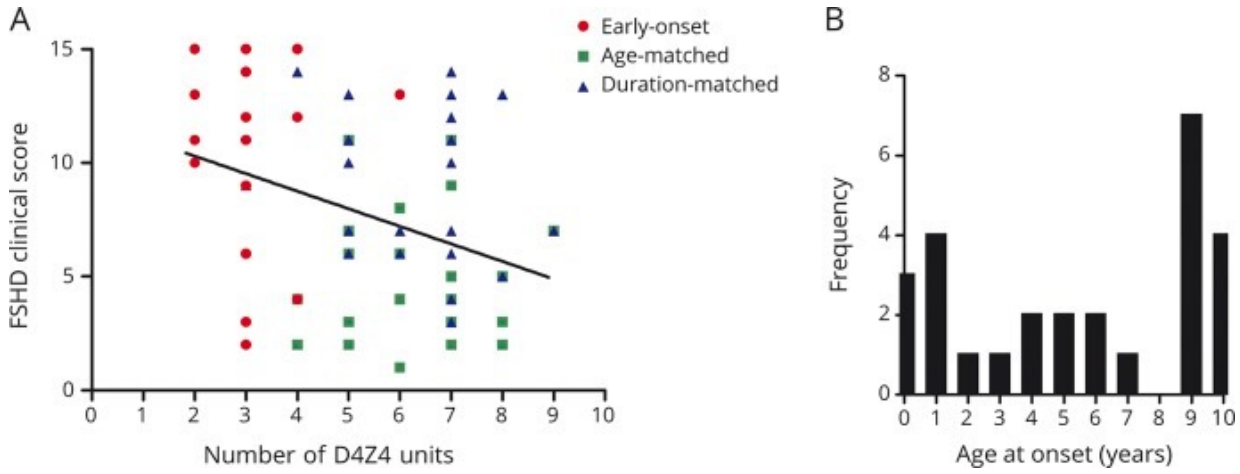
chromosome 18 **chromosome 4**



Lemmers, et al, 2010

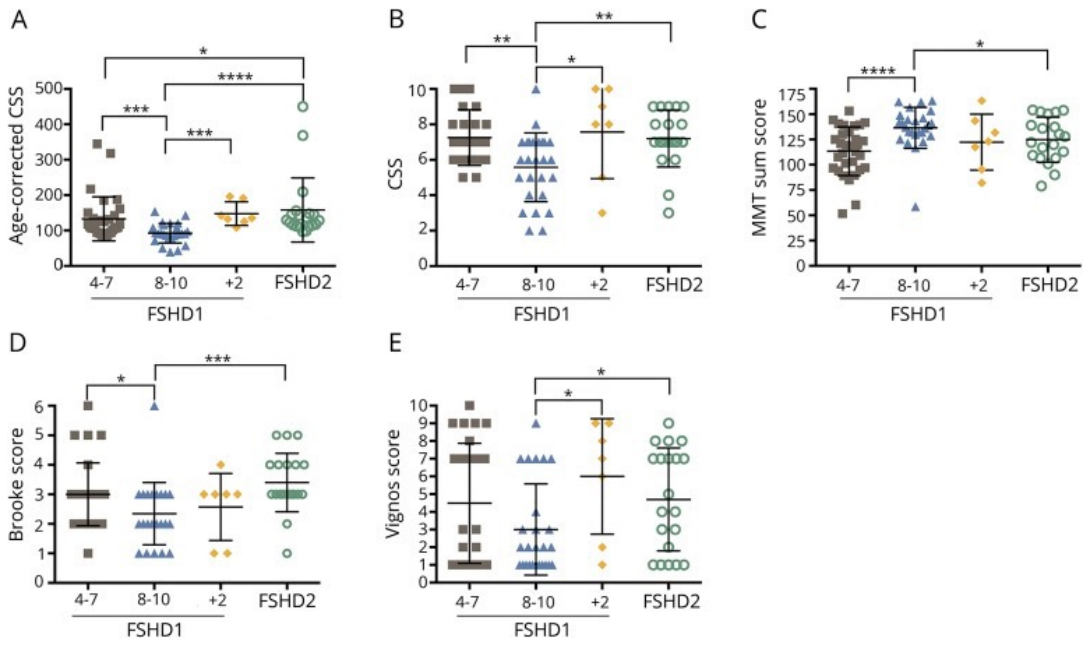
How important is the repeat length in FSHD1?

- Key natural history finding
- Likely predictive of a more severe phenotype (1-3 repeat units)
- Over 4 is less predictive
- May be affected by modifiers in methylation genes



Goselink, et al., 2019

FSHD1 or 2: What is the difference?



- Genetically distinct
- Increases diagnostic complexity
- Clinically no identified difference

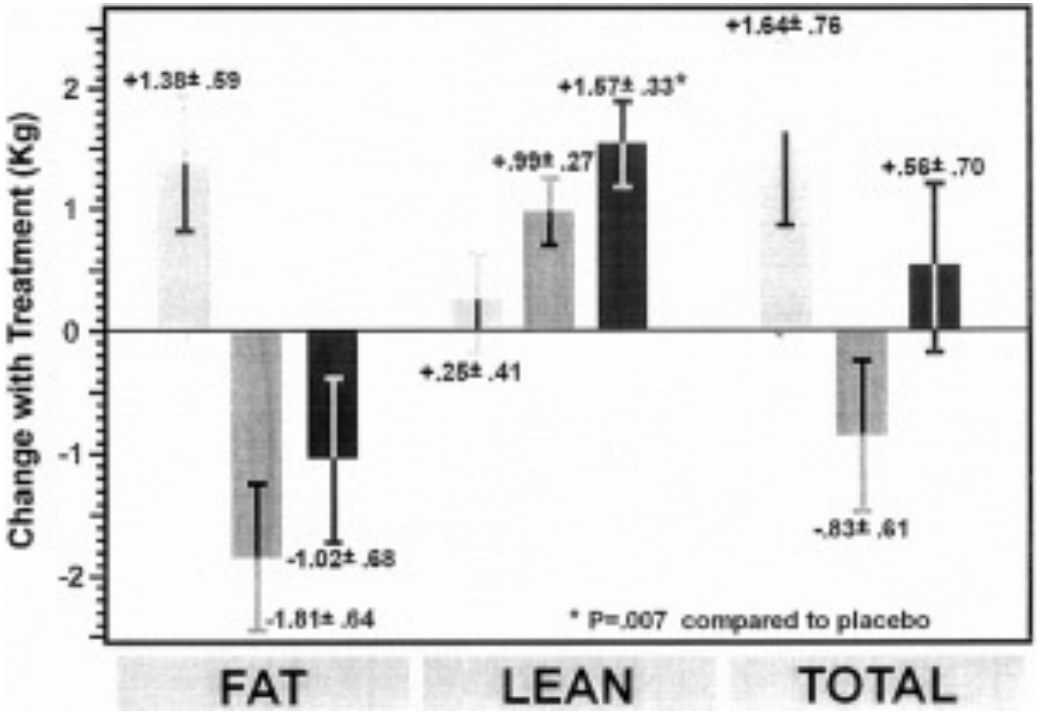
Sacconi, et al., 2019

Early trials

Trial of albuterol by Rochester and Ohio state ultimately negative but established early focus on muscle strength and showed muscle mass could increase (2000s)

Two myostatin inhibitors subsequently failed (2007, 2016)

FSHD society recruited patients



Kissel, et al, 2001

FSHD CTRN:

- The Goal: hasten therapeutic development for FSHD by:
  - Training sites / streamlining regulatory and data management / patient engagement
  - Refining trial strategies / Developing outcome measures / Clinical Trials
  - Understanding the patient reported disease impact
  - Training the next generation of FSHD researchers
  - Resources for industry

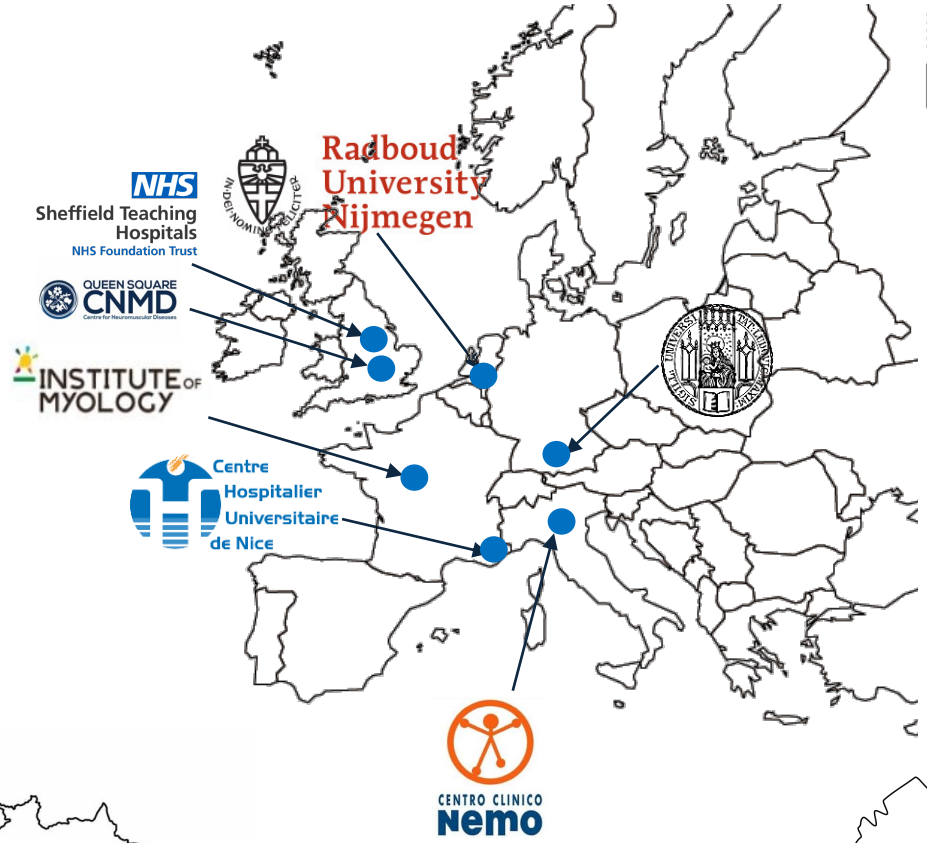
- Funding: NINDS, MDA, FSHD Society, Friends of FSH Research, FSHD Canada / SOLVE FSHD, AFM, industry partners (Fulcrum, Dyne, Avidity, more), and private donors
  - It takes a village to raise a child

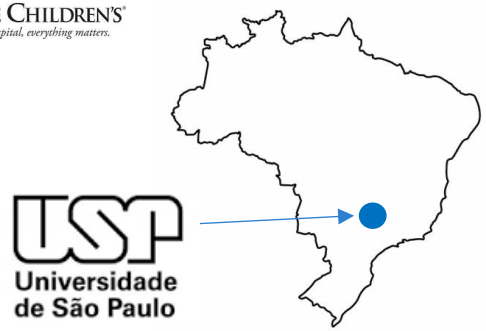
Courtesy of J. Statland, FSHD CTRN

FSHD CTRN
FSHD CLINICAL TRIAL RESEARCH NETWORK

Current FSHD CTRN Members

FSHD CTRN Website





Courtesy of J. Statland, FSHD CTRN

FSHD CTRN Active Studies

- ReSolve FSHD: ~240 enrolled, completing last visits (+RWS Fulcrum)
- DYNE Extension:
  - ReSolve protocol + muscle biopsies in 30 patients; Includes only EU sites
  - Total recruited to date: 58 / 80
- MOVE (**open for enrollment**):
  - Minimal assessments, includes adults and children
  - 272 participants so far
  - Remote assessment sub-study (URMC, KUMC): 20 subjects (2 televisits, 14 days apart)
- MOVE+ (**open for enrollment**):
  - Muscle biopsy and MRI added to MOVE protocol (up to n=200)
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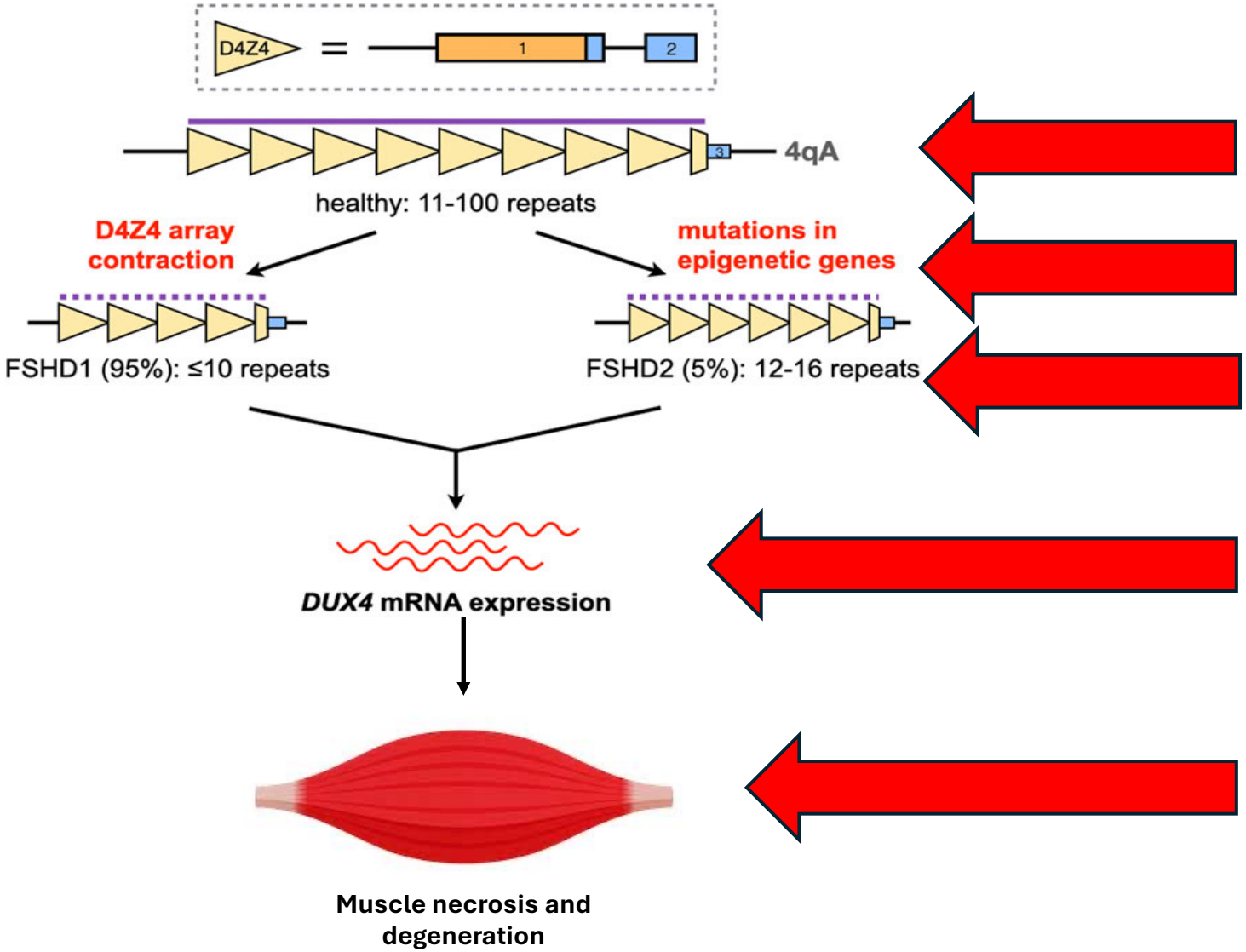
Courtesy of J. Statland, FSHD CTRN

How could you treat FSHD?



1. Gene editing to restore D4Z4 repeat
2. Epigenetic silencing of locus
3. Modulation of epigenetic methylation*
4. Knockdown or silencing of DUX4 expression*
5. Modulation of muscle atrophy*

*In active clinical trials

The role and growth of the foundation

- FSH(D) society founded in 1991
- Advocated for including MDs beyond DMD in federal programs (MD Care Act)
- World FSHD day established
- FSHD local chapters
- ICD-10 code for FSHD
- World FSHD Alliance
- International care guideline
- Brought FSHD awareness and supported drug development

FSHD Society's role in drug development

- Brought FSHD awareness
- Financially supported research to find cause and support clinical readiness projects
- Supported recruitment
- Voice of the patient/ FDA interactions
- Project Mercury

PROJECT MERCURY

The Global Initiative to Speed the Delivery of Therapies for FSHD

Just the beginning

- Need approved therapies
- Improve access to these therapies
- Further engage the community to improve the quality of life for individuals living with FSHD

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