UPDATES IN FSHD

MD NSW NIRD 5/8/23

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NeuRA/POWH & CRGH

OVERVIEW

FSHD background

Updates

- Genetic testing in FSHD
- Disease progression
- Disease severity & prognosis

Current & upcoming clinical trials

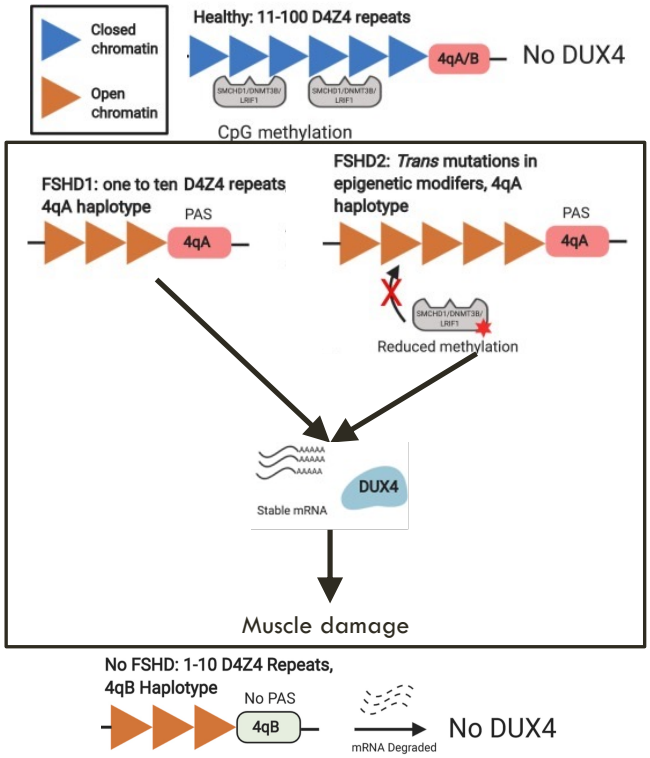
FSHD BACKGROUND

Third most common muscular dystrophy
- Prevalence 1/8000 - 20000

Asymmetric weakness (face, periscapular, upper arm, lower leg, abdominal, etc.)
- Severity is extremely variable

Hearing loss, retinal vasculopathy, etc.

DUX4 gene expression → muscle damage
- Reduced D4Z4 methylation → open chromatin
  - **AND**
- 4qA allele

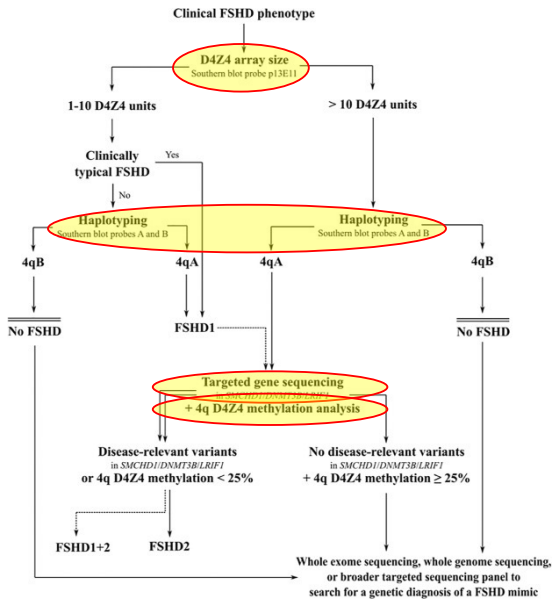


Cohen J, DeSimone A, Lek M, et al. *Trends Mol Med*. 2021;27:123-137.

FSHD GENETIC TESTING

Current genetic testing algorithm

- May involve multiple tests
  - Particularly for FSHD2 or patients with atypical features
- May have long turnaround time
  - Especially haplotyping
- May need 'large' quantity of DNA
  - Difficulty applying to prenatal genetic diagnosis
- May still produce inconclusive results



Jia FF, Drew AP, Nicholson GA, et al. *Neuromusc Disord*. 2021;31:1101-1112.

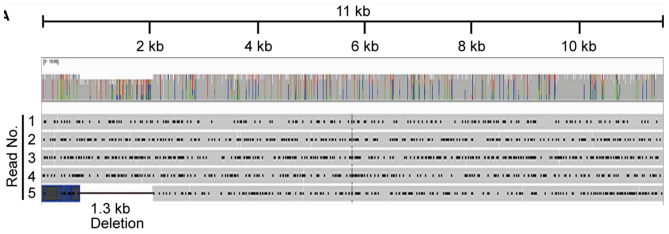
GENETIC TESTING UPDATE-1

Newer genetic technologies

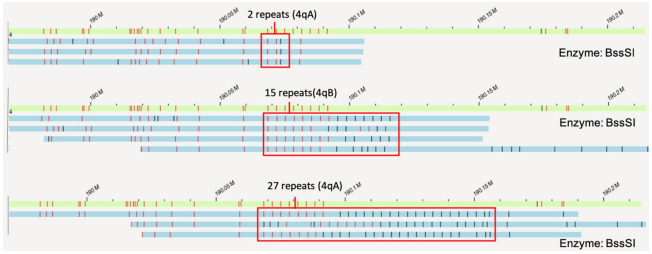
- Long-read sequencing (e.g. Oxford nanopore)
- Single molecule optical genome mapping (e.g. BioNano)
- Molecular combing

Advantages

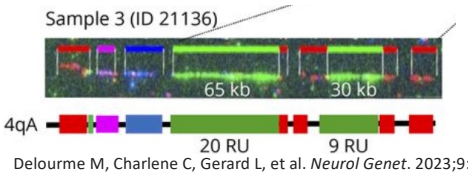
- Simplify diagnostic algorithm
- Decreased turnaround time
- Increase overall rate of diagnosis
  - Identify novel genetic contributors to FSHD that could not be detected by previous technologies
- Potentially need 'less' DNA → simplified prenatal testing



Hiramuki Y, Kure Y, Saito Y, et al. *J Transl Med*. 2022;20:517.



Dai Y, Li P, Wang Z, Liang F, et al. *J Med Genet*. 2020;57:109-120.



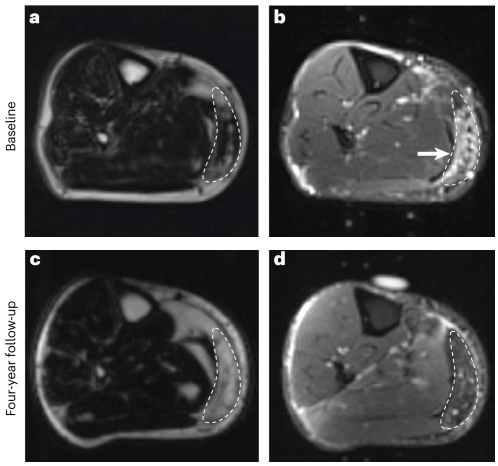
Delourme M, Charlene C, Gerard L, et al. *Neurol Genet*. 2023;9:e200076.

GENETIC TESTING UPDATE-2

New MBS item number for FSHD genetic testing in Australia

- MBS item number 73422 (introduced 1st Nov 2022)
  - Neuromuscular gene panel: can potentially include FSHD2 genes (*SMCHD1*, *DNMT3B*, *LRIF1*)
- MBS item number 73435 (introduced 1st July 2023)
  - Assessment of D4Z4 array/*DUX4* gene

FSHD DISEASE PROGRESSION



Tihaya MS, Mul K, Balog J, et al. *Nat Rev Neurol*. 2023;19:91-108.

Non-linear progression

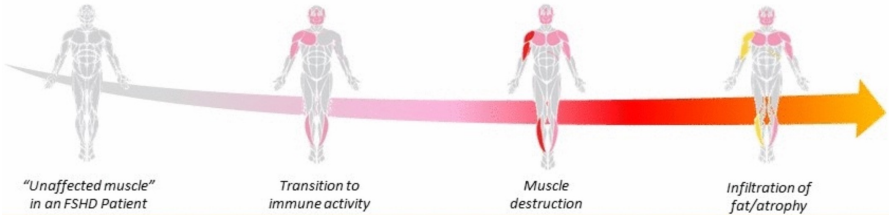
- Long periods of stability + short periods of rapid deterioration

Stepwise **muscle-by-muscle** involvement

- Supported by MRI and muscle biopsy studies

Likely due to short "**bursts**" of *DUX4* expression in individual muscles

- DUX4 expression → muscle inflammation → muscle destruction & replacement by fat

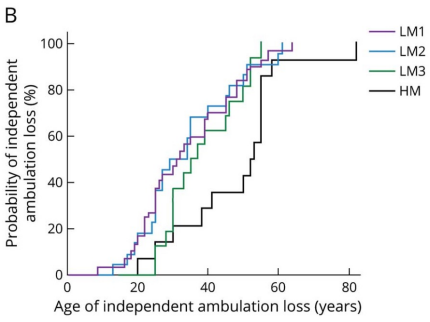


https://investors.atyrpharma.com/static-files/d200d9bb-6d16-4a6a-8c07-18f9e398a36c

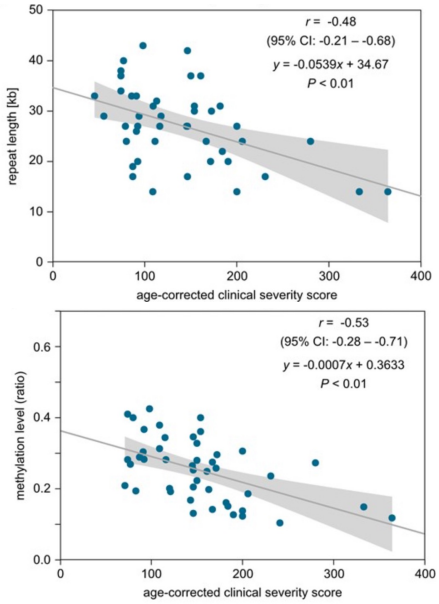
DISEASE SEVERITY & PROGNOSIS

Multiple contributors to disease severity

- D4Z4 repeat length
- Mosaicism
- Gender
- D4Z4/*DUX4* methylation levels



Zheng F, Qiu L, Chen L, et al. *Neurology.* 2023;101:e225-e237.



Erdmann H, Scharf F, Gehling S, et al. *Brain*. 2023;146:1388-1402.

- Other (e.g. environmental factors, etc.)

CURRENT & UPCOMING CLINICAL TRIALS

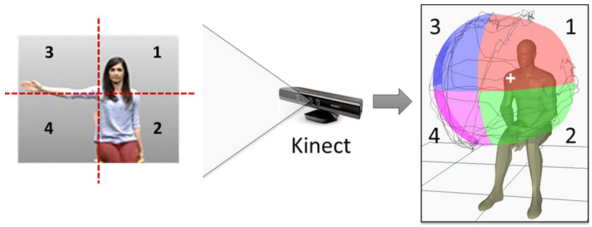
*Many of the results not yet published in peer-reviewed journals yet

Table 2. Description and comparison of drug based FSHD clinical trials started over years.

Drug/ ClinicalTrials.gov Identifier	Action	Responsible	Phase	Status	Start	End	Participants (n)
Losmapimod/ NCT05397470	P38 MAPK inhibitor	Fulcrum Therapeutics	PHASE 3	Recruiting	Jun 2022	Est. 2024	230
RO7204239/ GYM329/ NCT05548556	antimyostatin antibody	Hoffmann-La Roche	PHASE2	Recruiting	Feb 2023	Est. 2025	48
Losmapimod/ NCT04264442 NCT04004000	P38 MAPK inhibitor	Fulcrum Therapeutics	PHASE2	Active- Not Recruiting	2022 2019	Est. 2025 2024	76 14
Testosterone+ Somatropin/ NCT03123913	Hormone	University of Rochester	PHASE1	Completed	Feb 2019	Feb 2023	20
Losmapimod/ NCT04003974	P38 MAPK inhibitor	Fulcrum Therapeutics	PHASE2	Completed	Aug 2019	Jan 2021	80
ATYR1940 Resolaris/ NCT02603562 NCT02836418 NCT02531217 NCT02579239 NCT02239224	T-cells activation inhibitor	aTyr Pharma, Inc.	PHASE1/2 PHASE1/2 PHASE1/2 PHASE2 PHASE1/2	Completed	2016 2016 2015 2015 2014	2017 2017 2017 2017 2015	8 8 9 18 20
ACE-083/ NCT02927080 NCT03943290	Activins and myostatin inhibitor	Acceleron Pharma Inc.	PHASE2	Terminated Not achieving secondary endpoints	2020 2019	2022 2020	95 62

Salsia V, Vattemi GNA, Tupler RG. *Curr Opin Neurol*. 2023.

FTX-1821 (LOSMAPIMOD)

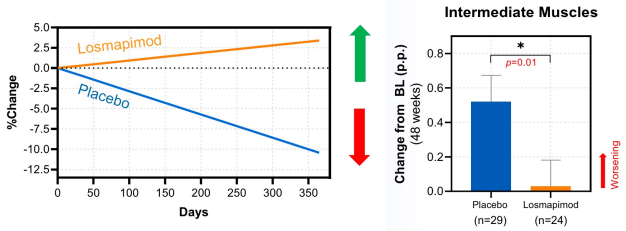


Han JJ, De Bie E, Nicorici A, et al. *Muscle Nerve*. 2015;52:948-55.

Blocks p38 MAPK → reduce *DUX4* expression

Phase 2b trial (ReDUX4) results

- 48 weeks of losmapimod vs. placebo
  - Did **not** reduce *DUX4* expression in muscle biopsy
  - Downstream benefits **were** shown
    - **Slower rate of decline** in Reachable Workspace (RWS)
    - **Less fat infiltration in muscle**
- 96 week open label extension results*
  - Maintenance/stabilisation in RWS



https://ir.fulcrumtx.com/static-files/0a6f0ec1-def9-4350-b741-1cecd62f103d

Phase 3 trial (REACH) currently recruiting

- US, Canada, Europe

Fulcrum Therapeutics

Reach

Phase 3 clinical trial of losmapimod

Wang L, Han J, Shoskes J, et al. *Neurology*. 2023;100(17 S2):3896.

AOC 1020

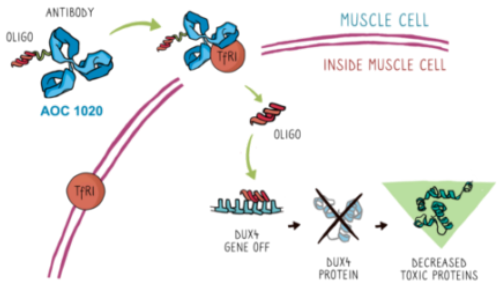
Anti-TfR1 antibody + siRNA conjugate

- Targets siRNA into muscle cells to reduce *DUX4* expression

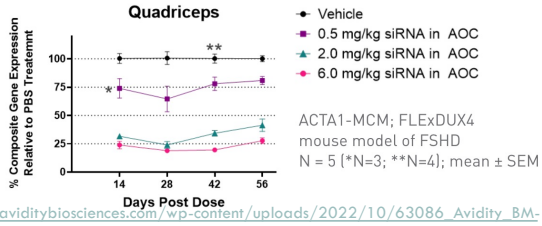
Use in FSHD mouse models: reduces *DUX4* expression signature

Phase 1/2 trial (FORTITUDE) currently recruiting

- USA



https://www.fshdsociety.org/2022/09/29/avidity-biosciences-announces-phase-1-2-trial-for-fshd/



ACTA1-MCM; FLExDUX4 mouse model of FSHD
N = 5 (*N=3; **N=4); mean ± SEM

https://www.aviditybiosciences.com/wp-content/uploads/2022/10/63086_Avidity_BM-FSHD-AOC-1020-WMS_Poster-36x42in-05FB_FINAL-LSVP.08.pdf

AVIDITY BIOSCIENCES

FORTITUDE™

Phase 1/2 clinical trial of AOC 1020

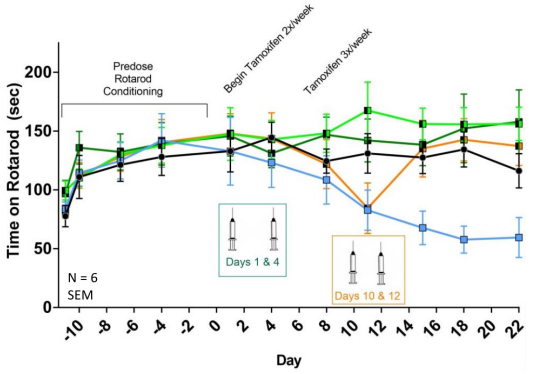
ARO-DUX4

RNA interference molecule targeting *DUX4* mRNA → block DUX4 production

Use in FSHD mouse model: reduced *DUX4* expression, reversed weight loss, reversed loss of function on rotating rod test

Under regulatory review by NZ Medicines and Medical Devices Safety Authority

- ?upcoming phase 1/2a trial (ARODUX4-1001)



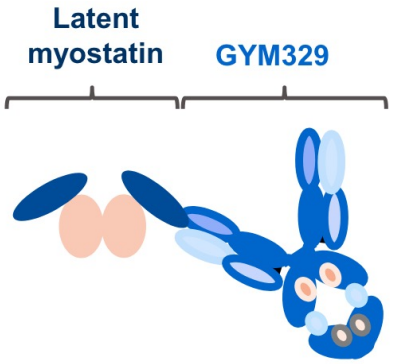
https://ir.arrowheadpharma.com/static-files/010912ca-0571-4009-962c-b0e2eae09e03

arrowhead pharmaceuticals

Press Release

Arrowhead Pharmaceuticals Files for Regulatory Clearance to Initiate a Phase 1/2 Study of ARO-DUX4 for Facioscapulohumeral Muscular Dystrophy

GYM329 / RO7204239



Antibody against myostatin, which normally blocks muscle growth

Use in mouse models: increase in muscle size & grip strength

https://medically.gene.com/content/dam/pdmahub/restricted/neurology/aan-2023/AAN-2023-presentation-statland-MANOEUVRE-study-design-a-study-of-GYM329-RO7204239-in-patients.pdf

Phase 2 trial (MANOEUVRE) currently recruiting

- USA, Denmark, Italy

Roche

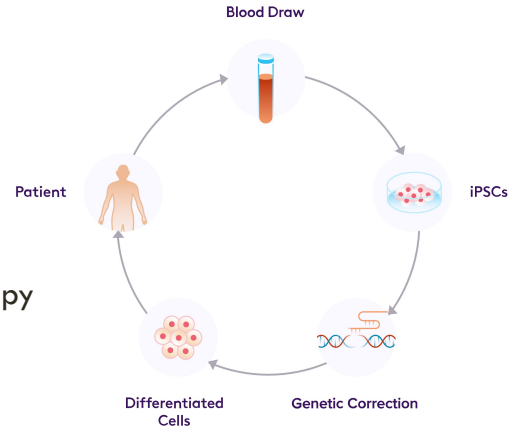
MANOEUVRE

A Study to Evaluate RO7204239 in Participants with Facioscapulohumeral Muscular Dystrophy

VTA-120

Autologous, genetically engineered iPSC-derived cell therapy

Currently in preclinical stages



Program		Cell Type	Indication	Discovery	Preclinical	Phase 1/2
Neuromuscular Platform						
VTA-100	Autologous	Satellite Cell	Limb-Girdle Muscular Dystrophy (LGMD2A)			
VTA-120	Autologous	Satellite Cell	Facioscapulohumeral Muscular Dystrophy (FSHD)			

VITA Therapeutics

https://www.vitatx.com/

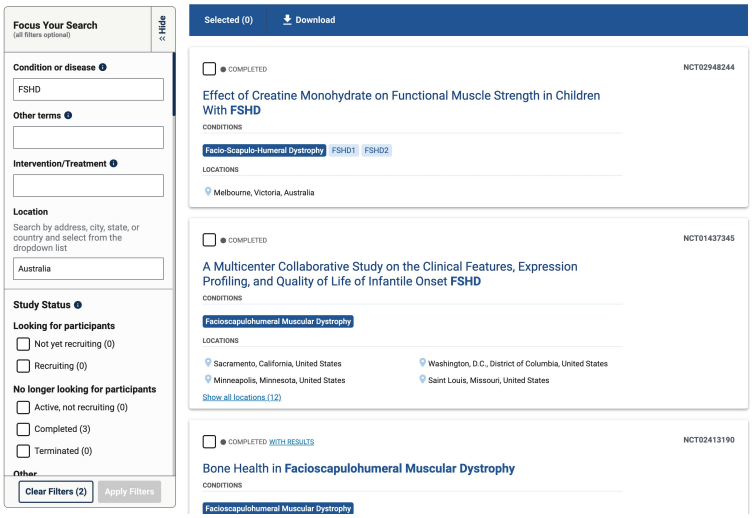
FINDING MORE INFORMATION

General

- https://mdnsw.org.au
- Https://fshdglobal.org
- https://www.australiannmdregistry.org.au/

Clinical Trial Registries

- https://clinicaltrials.gov
- https://anzctr.org.au
- https://www.ausnmd.org/clinical-trial-finder/



SUMMARY OF FSHD UPDATES

Diagnosis

- New genetic technologies → improve diagnosis of FSHD
- New MBS item number → improve access to FSHD genetic testing

Progression

- Longitudinal muscle MRI → monitor disease progression (particularly in clinical trial setting)

Prognosis

- D4Z4/*DUX4* methylation testing → improve prognostication

Treatment

- Multiple clinical trials recruiting or upcoming → reason for optimism/hope
- Patient enrolment in Australian neuromuscular registry → ↑'trial readiness' & ↑chance of trials coming to Australia