FSHD Patient Day 2014!
What we know, what we think we know, what we have left to learn

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Overview

- Clinical Features
- Natural History
- Future Directions

Facioscapulohumeral Muscular Dystrophy (FSHD)

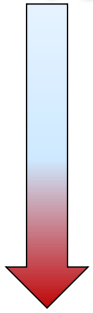
- One of the most common muscular dystrophies
  - Prevalence 1:15,000 to 1:20,000
  - or ~ 21,000 in US
- Slowly progressive
- *Facio* = face, *Scapulo* = scapular girdle, *Humeral* = upper arms
- Diagnosis is based on characteristic clinical presentation and genetic testing

FSHD: there are 2 types

- Two genetically distinct forms
  - Clinically identical
- Type 1: ~95%
  - Deletion of repeated DNA sequence on chromosome 4 (normal >10 repeats, FSH 1-10 repeats)
  - Autosomal dominant inheritance, but up to 1/3 spontaneous
- Type 2: ~5%
  - No deletion on chromosome 4
  - ~80% associated with mutations in SMCHD1
  - Digenic inheritance

Patterns of Muscle Involvement

- Typically descending pattern



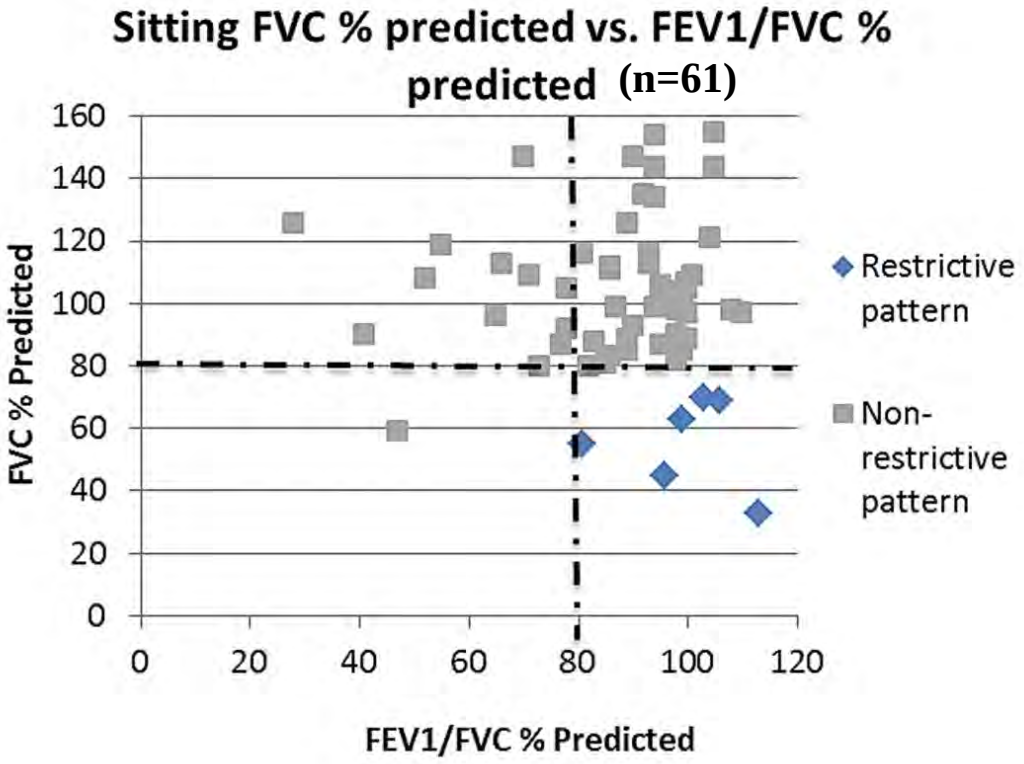
  - First affecting the face, shoulders, and upper arms
  - Followed by distal legs (e.g. tibialis anterior), quads and hamstrings
  - Hip muscles
- Can have marked axial and abdominal weakness
- Striking side to side asymmetry
- No or minimal contractures
- Often presence of pectus excavatum (hollowed chest)
- Other initial presentations have been described

FSHD: Respiratory Involvement

- Estimates of lung involvement have varied greatly (0-25%)
- Review of Dutch registry of ventilator dependent patients
  - Estimated 1% of Dutch FSHD population requiring mechanical ventilation (researchers took the number of ventilator dependent patients with FSHD, and compared to Dutch FSHD prevalence)

Wohlgemuth M, et al. Neurology. 2004;63(1):176-8

Reduced Lung Capacity in ~10%: Who is at Risk?



- Associated with higher disease severity score and lower extremity/ pelvic girdle involvement

Scully M, et al. Muscle and Nerve (2014) In press.

FSHD: Cardiac Involvement

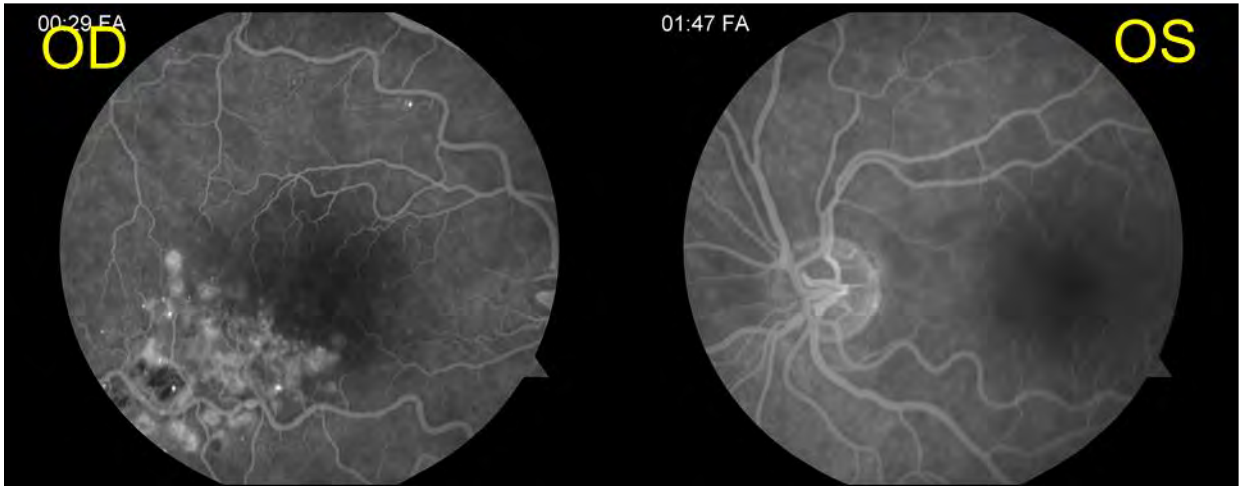
- No association with structural changes
  - No cardiomyopathy
- Cardiac (mainly atrial) arrhythmias ~ 5-10%?
- Typically not symptomatic
  - Most common symptom palpitations
- Severe cardiac conduction deficit or cardiomyopathy = revisit diagnosis

Extramuscular manifestations

- Retinal vascular changes
- Hearing changes

Retinal Disease

- Although retinal vascular changes can be seen in over half of patients (peripheral telangiectasias)
  - Coats disease = Sympomatic retinal vasculopathy
  - quite rare <1% (aneurysmal dilations, exudates, retinal detachment, blindness)



Coats Disease in FSHD

- Idiopathic Coats disease tends to be:
  - Unilateral
  - Mostly male
- In FSHD
  - Often bilateral
  - Mostly women
  - Small residual D4Z4 fragments
  - Typically the more severe infantile onset disease
- Who do we screen?

FSHD	Total
Case No.	n=14
Age Coats	10 (1, 15)
FSHD Dx years	12 (5, 18)
D4Z4 Fragment Kb	13 (12, 13)
Gender Female	92.9%
Bilateral	64.3%

Statland JM, et al. Neurology. 2013;80(13):1247-50.

FSHD: Hearing Loss

- Older studies suggested high frequency hearing loss in up to 60% of patients; however more recent studies suggest may not be different than general population
  - Largely asymptomatic
- However symptomatic hearing loss in small proportion of FSHD
  - Typically infantile onset, more severe disease
  - Smallest residual D4Z4 fragments (1-3 repeats)
- May affect language development if not detected early in childhood onset disease

Lutz KL, et al. Neurology. 2013;81(16):1374-7.

Natural History: Data from a large US Registry of FSHD Patients

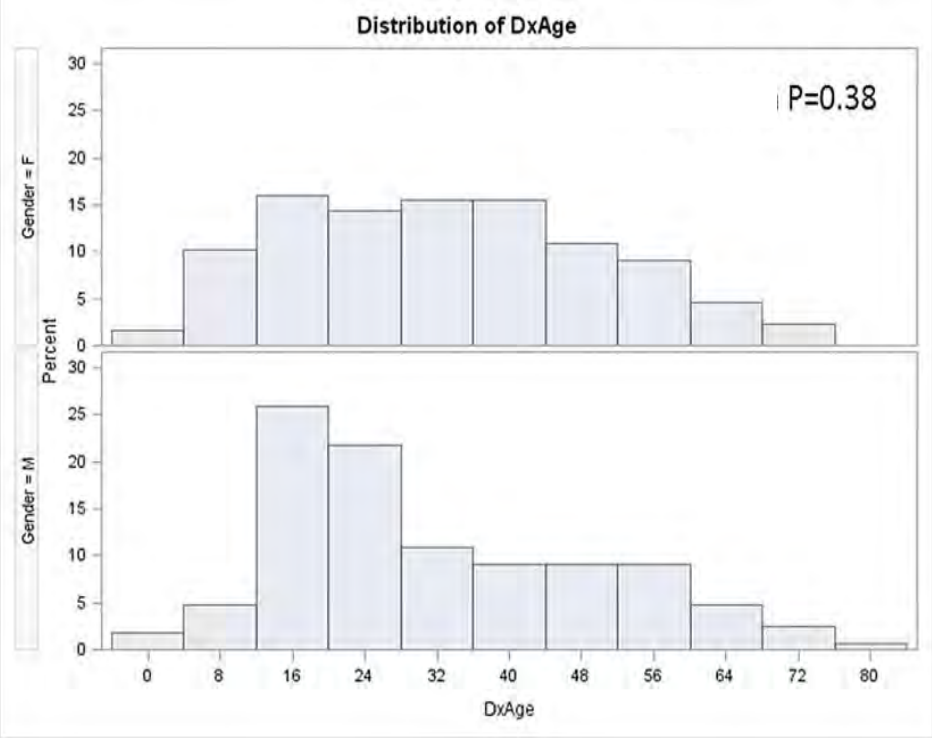
US Registry of FSHD Patients and Family Members

- Limited data about progression of functional impairment in FSHD
- 313 genetically confirmed and clinically affected FSHD1 participants
  - An average of 6 years of follow up
- Mean age 51.5 years, range 9-91 years
- Roughly equal number men and women
- Geographically distributed across the US
- Mostly well educated (>60% some college or beyond)

Statland JM, Tawil R. Muscle Nerve. 2013. Epub 2013/07/23

Disease Characteristic	Value
Age initial symptom (SD)	21.1 (15.0)
Age diagnosed (SD)	31.3 (17.3)
D4Z4 contraction (kb)	24.8 (5.7)
Facial weakness (%)	282 (90.1%)
Scapular weakness (%)	303 (96.8%)
Functional Burden	
Dry or irritated eyes (%)	152 (48.6%)
Difficulty whistling or drinking through a straw (%)	188 (60.1%)
Difficulty raising arms above shoulder height (%)	228 (72.8%)
Difficulty getting out of a chair (%)	108 (34.5%)

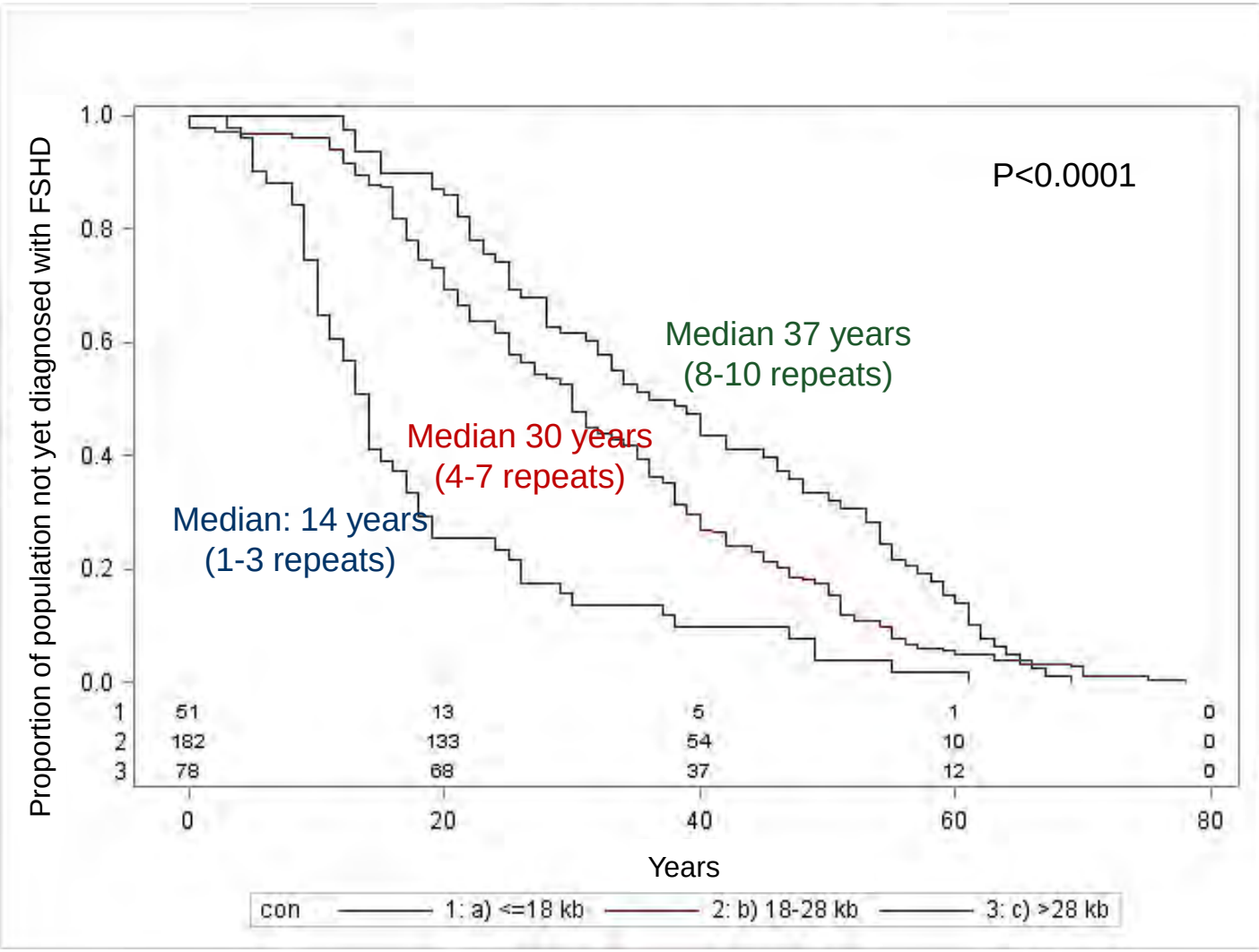
FSHD: Age at diagnosis



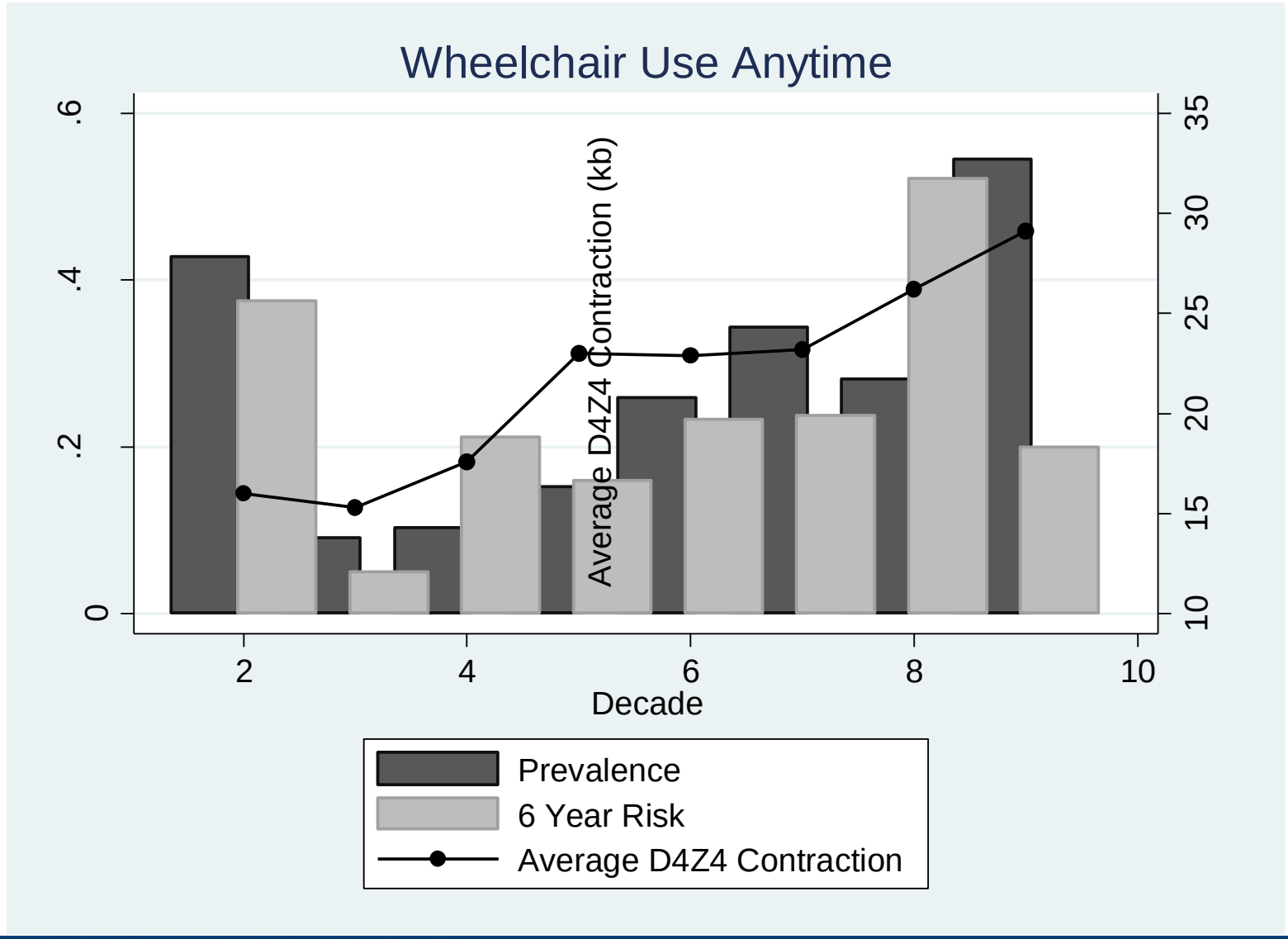
- Men show peak in diagnosis around 20 years of age, women diagnosed on average older

Statland JM, Tawil R. Muscle Nerve. 2013. Epub 2013/07/23

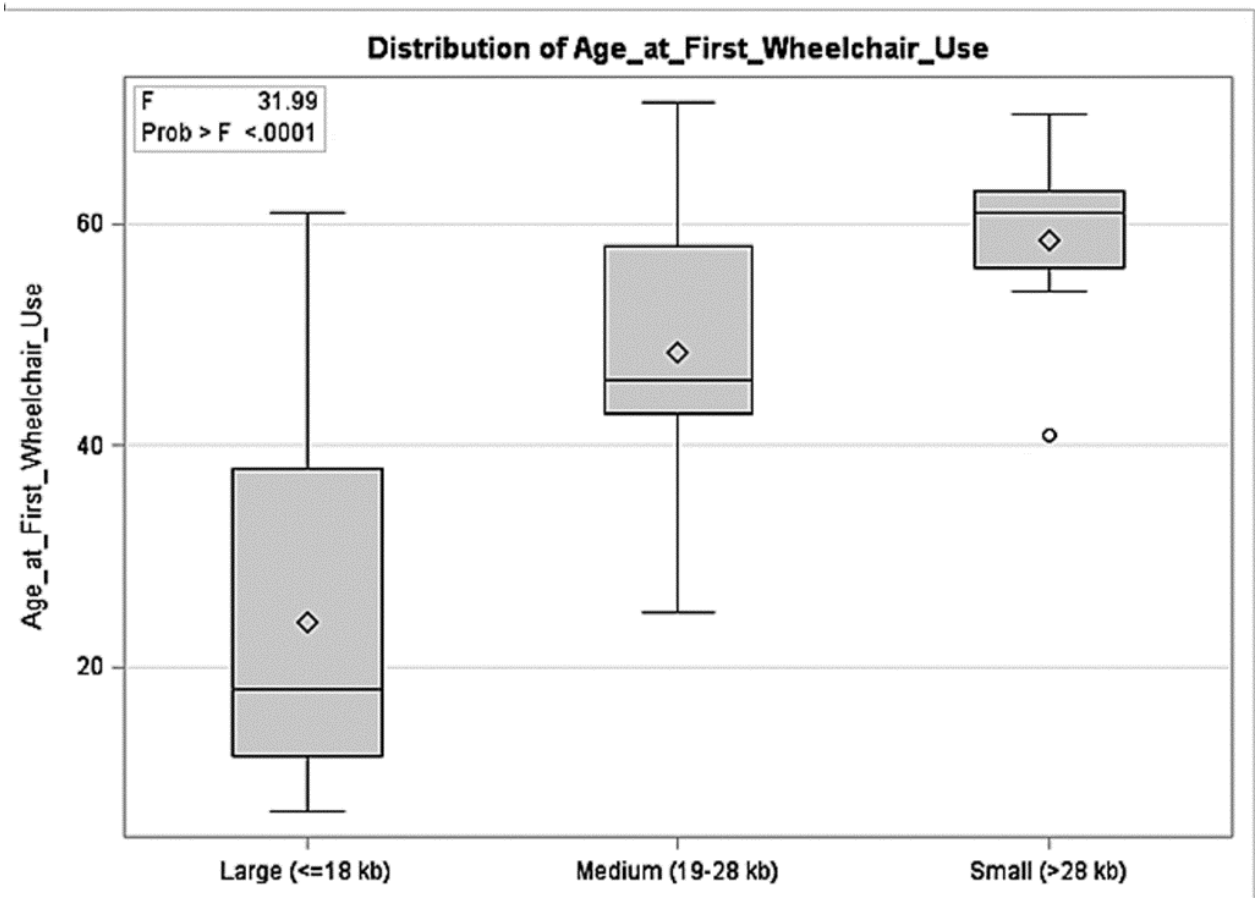
Dx Age: Relationship to contraction



WC Use by Decade and D4Z4 Deletion



Relationship of Age to First WC Use



1-3 repeats 4-7 repeats 8-10 repeats

Linear Relationship to Age for Other Assistive Devices

Age at First Use for Assistive Devices in Years	
Ankle Foot Orthotic (SD) n=91	40.2 (15.2)
Ankle Knee Orthotic (SD) n=48	43.2 (14.6)
Cane (SD) n=124	49.1 (14.1)
Walker (SD) n=79	56.8 (15.5)

Registry Summary

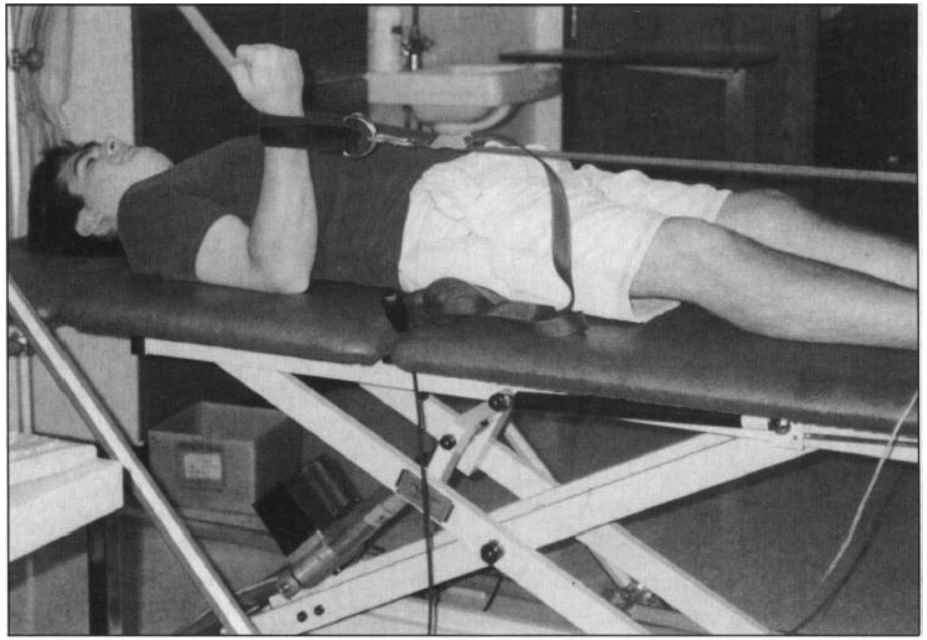
- This risk of using a WC is not distributed evenly across the FSHD population
  - Higher risk in people with small residual fragments
  - And older people
- Risk for other assistive devices related to age
- Unless we can find other markers to determine who is most at risk
  - The ability to use WC use as endpoint in study will be limited due to the long time needed for such studies

Natural History: outcomes

- What have we learned about the Natural History of FSHD as measured by clinical trial outcome measures?
- Natural history study 3 year prospective longitudinal study (1997) n=81

FSH-DY Group. (1997) Neurology 48: 38-46

Background: QMT



- Technique for testing strength against fixed resistance
- Uses a digital force transducer
- Connected by an inelastic strap to metal frame
- Standardized positions for different muscles

Personius et al. (1994) Phys Ther 74: 253-63

Background: QMT

- Reliable: What you measure one day you measure the next
- Can be standardized to normal expected strength based on gender, height, and age
  - E.g. Create percent predicted of normal
  - Advantages: makes changes in individual muscles comparable
- Standardized scores can be averaged across muscle groups to create combined score to follow progression over time

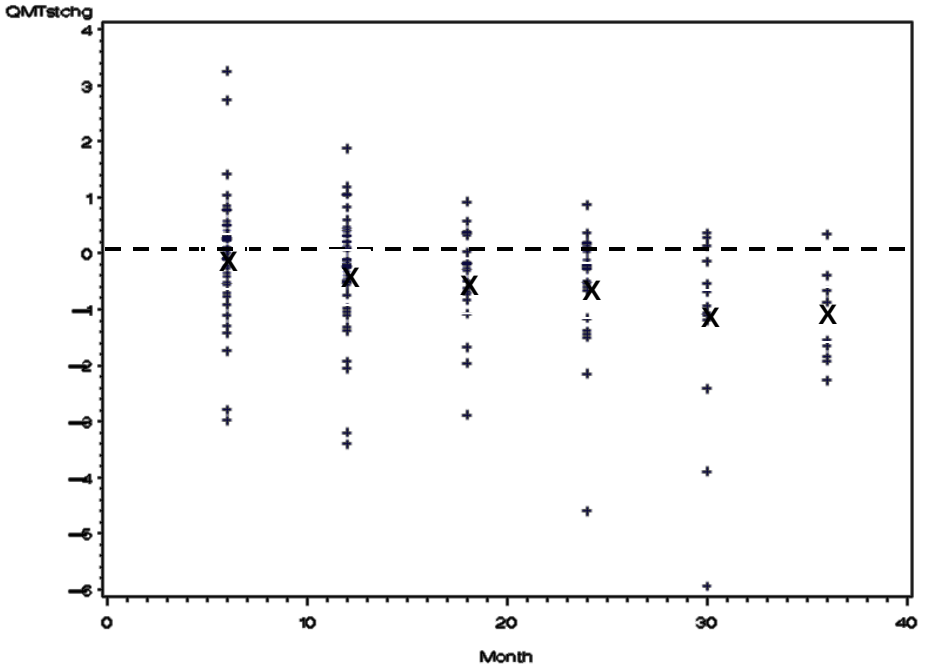
Background: MMT

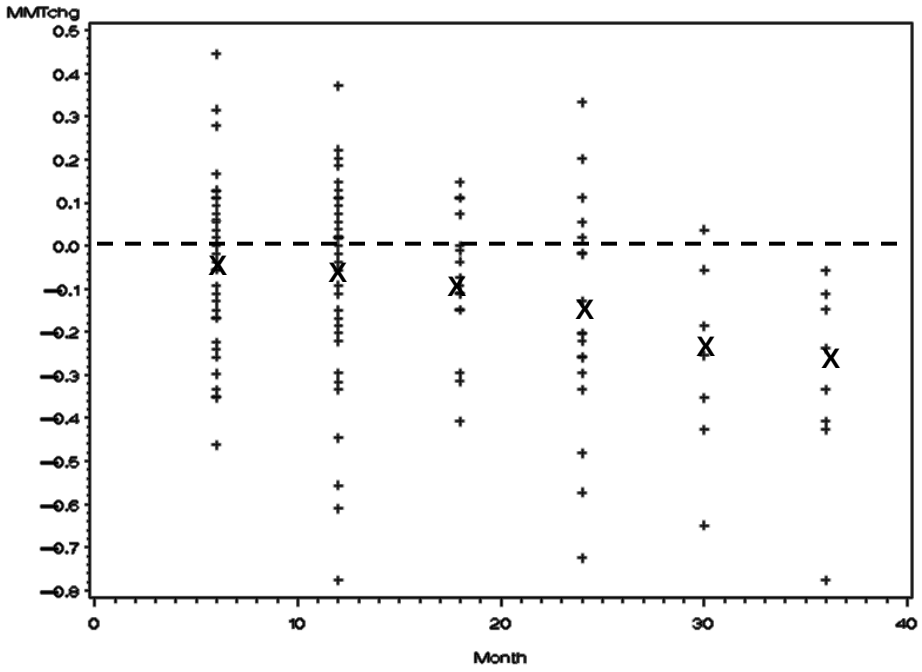
MMT Grade	Description
5	Normal strength
5−	Uncertain muscle weakness
4+	Inability to resist against maximal pressure throughout range of motion
4	Ability to resist against moderate pressure throughout range of motion
4−	Ability to resist against minimal pressure throughout range of motion
3+	Ability to move through full range of motion against gravity and to resist against minimal pressure through partial range of motion, then contraction breaks abruptly
3	Ability to move through full range of motion against gravity
3−	Ability to move through greater than one half range of motion against gravity
2+	Ability to move through less than one half range of motion against gravity
2	Ability to move through full range of motion with gravity eliminated
2−	Ability to move in any arc of motion with gravity eliminated
1	A flicker of movement is seen or felt in the muscle
0	No contraction palpable

- Also reliable
- Standardized procedure for positioning
- Uses standard strength scale
  - Range: 0 = no strength; 3= strength against gravity but no resistance; 5= normal strength
- Scores averaged across muscles to create combined score

Natural History Combined Scores

- Followed subjects at 6 months intervals for 3 years
- Most responsive to disease progression: compared to functional measures, functional grades, and muscle mass





Extension of Natural History

- Extending natural history in 15 subjects who subsequently enrolled in albuterol trial
  - Confirmed slow but steady loss of strength over 2-7 years follow up (~ 2-4% per year)

Statland JM, et al. Neuromuscul Disord. 2013;23(4):306-12.

How Many For Clinical Trial?

- How many people needed to show a difference in strength depends on how big an effect you think you're going to see with a treatment?
  - For example to show halt of progression would need ~160 people per treatment arm
  - On the other hand for an effect twice as large would only need ~40 per treatment arm

The FSH-DY Group. Neurology. 1997;48(1):38-46.

Summary – Measures of Strength

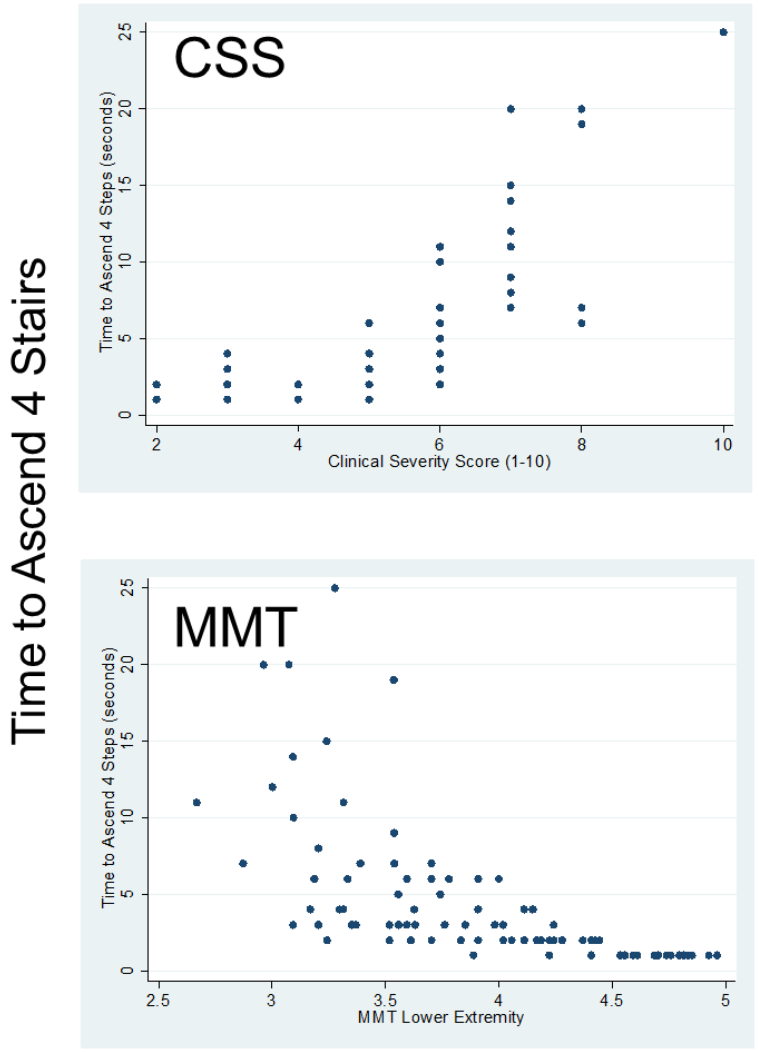
- QMT and MMT are reliable measures of strength
- Both showed significant disease progression at 1 year
  - However the 'clinical importance' of this change is not known
- Variability measurements can be used for power and sample size estimates
  - But ~160 people per group to demonstrate halt of disease progression a large number for rare disease
- The ability to identify specific people or 'muscles at risk' for progression would increase the sensitivity of strength outcomes in future trials

Functional Measures

- Include measures like:
  - Time to ascend 4 stairs
  - walk 30 feet
  - get up from a chair
  - Drink 6 ounces of water
  - Brooks and Vignos functional scales
- Good face validity
  - A change in a functional activity would intuitively seem meaningful

Functional Measures in FSHD

- Reliable
- Typically moderate to strong linear relationship to disease severity or measures of strength
- But do not change over periods of time as long as 3 years



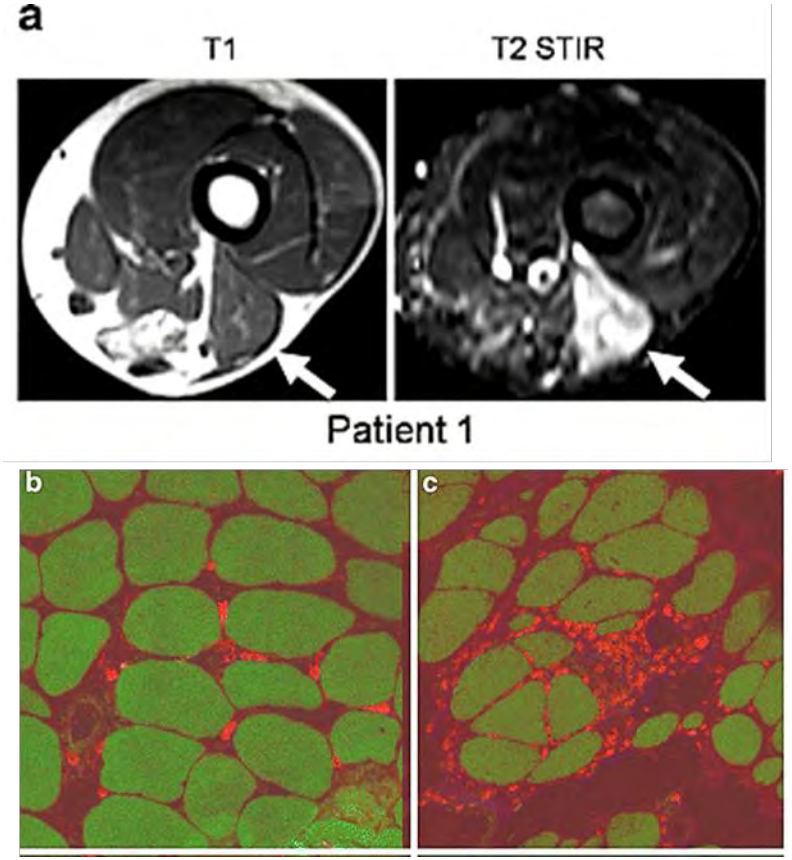
Future Challenges for the Design of Therapeutic Trials

Challenges: Biomarkers

- Biomarkers are things like gene expression, or levels of proteins in your blood which can predict changes in the disease
- Biomarkers are important for proof of concept studies, or as an early signal a drug is working
- DUX4 is hard to measure directly
- Targets of DUX4 may be easier to measure
  - Downstream changes appear to be more persistent
- However more work is needed to determine which biomarkers will work best in FSHD

MRI: non-invasive biomarker of disease progression?

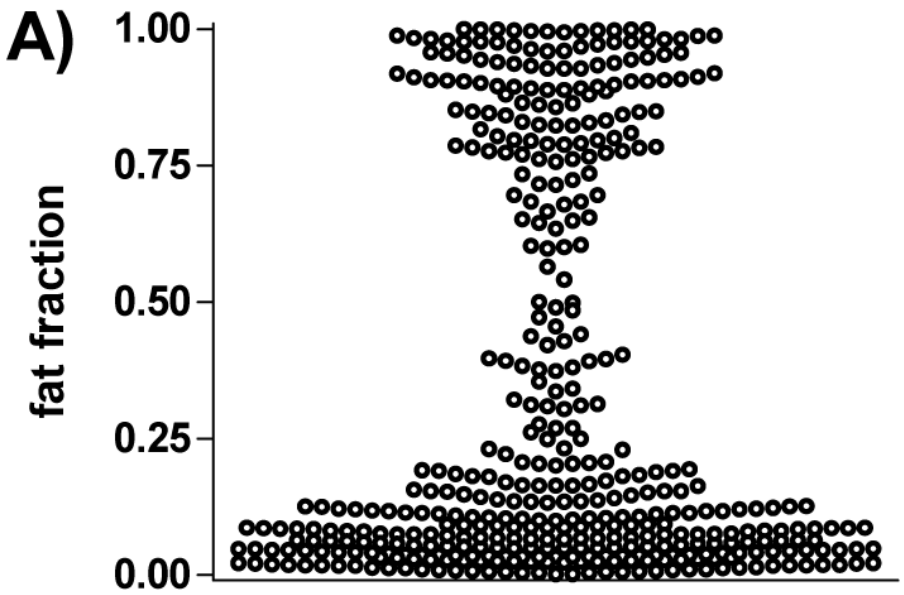
- MRI uses magnetic fields and radio waves to look at muscle
- Changes on MRI might indicate active disease
  - May help target muscles at risk for progression
- Relationship between DUX4 expression and inflammation seen on MRI?



Frisullo, G., et al. (2011) J Clin Immunol 31(2): 155-166.
Tasca, G., et al. (2012). PLoS One 7(6): e38779.

Non-invasive Biomarkers: MRI

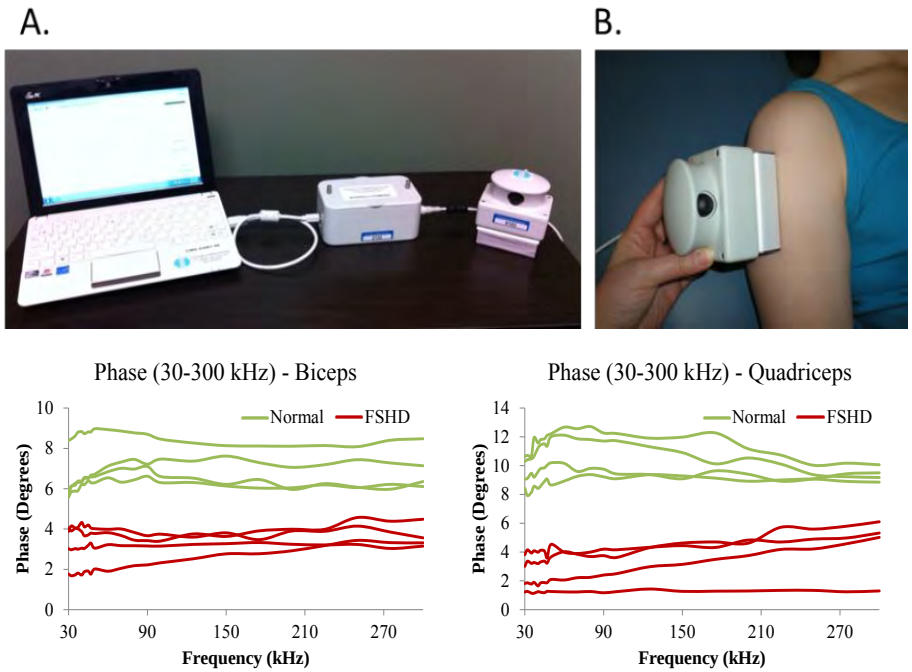
- Alternatively can also use MRI to measure muscle mass and fat content in muscle
- As muscles become weaker the fat content goes up
- Changes in fat content might identify muscles at risk for progression



Janssen, B. H., et al. (2014). PLoS One 9(1): e85416.

Other Non-Invasive Biomarkers

- Electrical impedance myography found to be a useful biomarker in motor neuron disease
  - Impedance is resistance to current flow
  - Largely determined by muscle structure

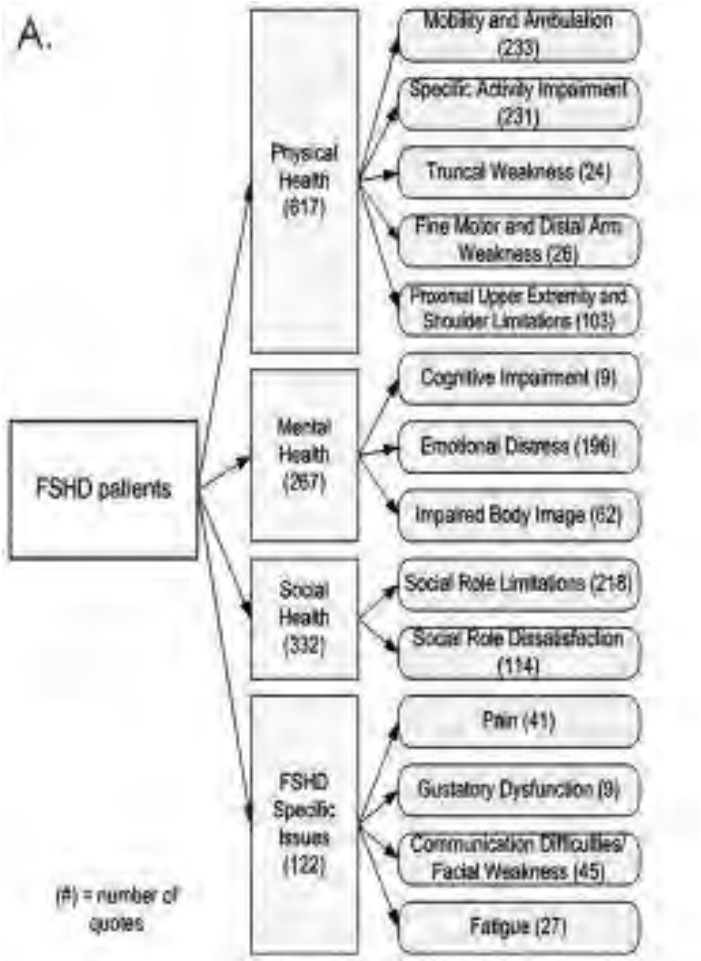


Current Studies

- Prospective 12 month longitudinal study
- To test: reliability, relationship to other measures of FSHD, and changes over time:
  - Disease specific health inventory
  - Disease specific functional rating scale
  - Electrical Impedance Myography

FSHD Health Inventory

- Developed by Chad Heatwole, MD
  - using FDA Guidance
- Patient interviews (1375 quotes) used to identify relevant symptoms
- National cross-sectional study of 328 FSHD patients
  - Rank importance of different symptoms identified in interviews
- Final questionnaire 116 questions in 14 subdomains



Johnson, N. E., et al. Muscle Nerve 46(6): 951-953.

FSHD-Functional Outcome

- Evaluator administered functional tasks
- Chosen to represent areas of body affected by FSHD
- Combined to create a 72 point scale for use in clinical trials
- Preliminary data:
  - Reliable
  - Associations with other measures of disease (strength, clinical severity scores)

Leg Function	Sit to stand without hands
	6 Minute Walk Test
	Self-selected gait speed
	Go' 30 feet
	Timed ascend/descend stairs
Arm Function	Shoulder abduction
	Shoulder forward flexion
	Elbow flexion
	Time to don/doff coat
Trunk Function	Time to pick penny up from floor
	Sit up with feet held
	Timed supine to sit
Hand Function	Grip dynamometry (M/F)
Balance/Mobility	Timed Up and Go

Clinical Trials: Opportunities

- FSHD is one of the most common muscular dystrophies
  - Patient recruitment should not be an issue
- Established outcome measures and natural history using these outcome measures
- Current efforts to build networks of FSHD clinical trial sites
  - Standardizing protocols for biomarkers, imaging, strength and functional measures, and quality of life measures
  - If studies will be done at different sites at least they will be done the same way

Summary

- Recent advances have elucidated a unified genetic model for FSHD1 and 2
- Identifies potential disease-directed therapeutic targets
- The slow disease progression and individual to individual variability present challenges when developing outcomes for future trials
  - Identifying markers of disease activity to help stratify people will be key
- International cooperation and standardization of procedures will be necessary for comparing interventions across studies

Thanks: everyone who came today

- Organizations
  - Experimental Therapeutics Program
  - MDA Clinical Research Training Program
  - FSH Society
  - Registry of FSH Patients and Family Members
- URMC
  - Rabi Tawil, MD – mentor
  - Robert Griggs, MD – mentor
  - Chad Heatwole, MD – collaborator
  - Kate Eichinger – PT
  - Shree Pandya – PT
  - Colleen Donlin-Smith – coordinator
  - Bharati Shah – Lab
  - Don Henderson – Lab
- KUMC
  - Richard Barohn, MD – mentor
- LUMC – the Netherlands
  - Silvere van der Maarel - collaborator
- Fred Hutchinson Cancer Center – Seattle
  - Stephen Tapscott - collaborator