# Juvenile onset FSHD
# Clinical features and management

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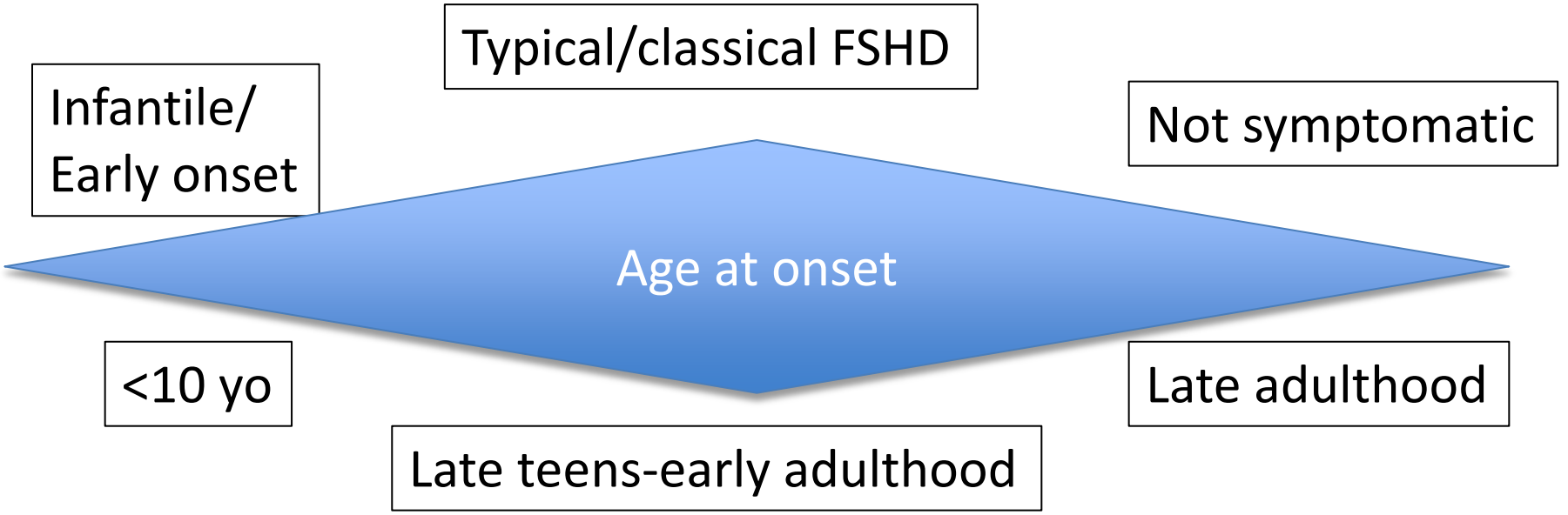
# Goals

- Review the clinical spectrum
- Introduce the clinical features at the youngest end of the spectrum
- Discuss monitoring and management

# Clinical spectrum in FSHD



# FSHD: Typical Onset and Progression

- Clinical weakness starts in teens or early adulthood
  - Mild facial weakness since childhood
  - Sleep with whites of eye showing
- ~95% of affected people will have weakness on examination by age 20 years
  - Rochester Registry: mean age at reported onset of symptoms 21.5 yrs
- Severity can be quite variable within families
- 61% of 238 patients had classic disease
  - Tonin et al, Neuromuscul Disord. 2004 Jan;14(1):33-8

# Early onset FSHD

- Wide phenotypic variation
- Often more severe disease
- Multiple organ system involvement is more common

# Early onset FSHD (Infantile FSHD)

- 1970s and 1980s-single patient reports
  - Association between Coats disease (severe eye disease) and FSHD
  - Association between hearing loss and FSHD
- 1991
  - Brouwer et al demonstrated with genetic testing that early onset FSHD has same molecular basis as typical FSHD

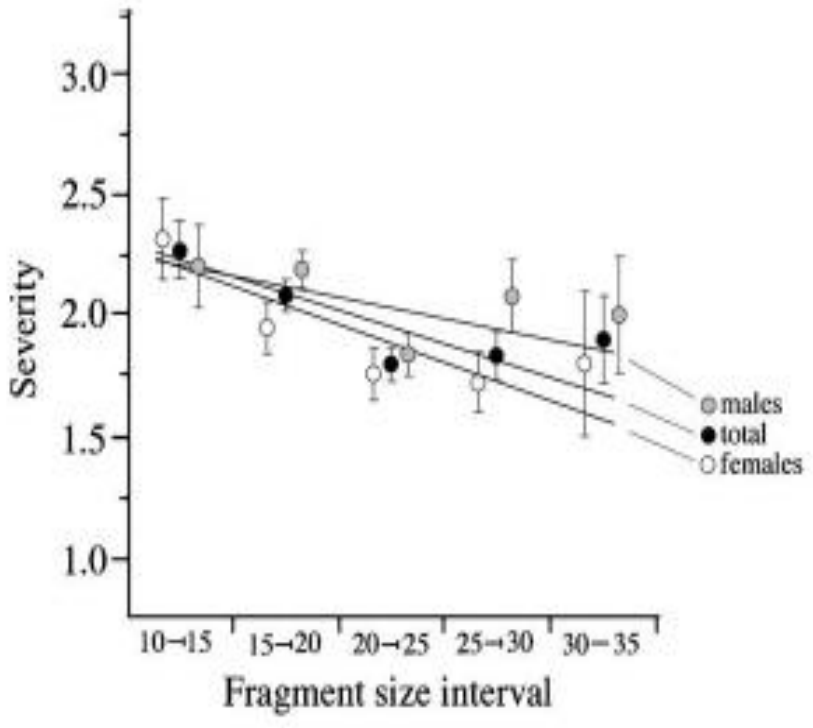
# Early onset FSHD

- 10-20% of patients have early onset disease in clinical series
  - EcoR1 fragments generally <20kb
  - 9% of 522 abnormal DNA samples tested at U of Iowa had EcoRI <15kb

# Relationship between severity and D4Z4 deletion size

- 1990s--Genotype phenotype studies show relationship between deletion size and severity

Larger deletion
→More severe disease

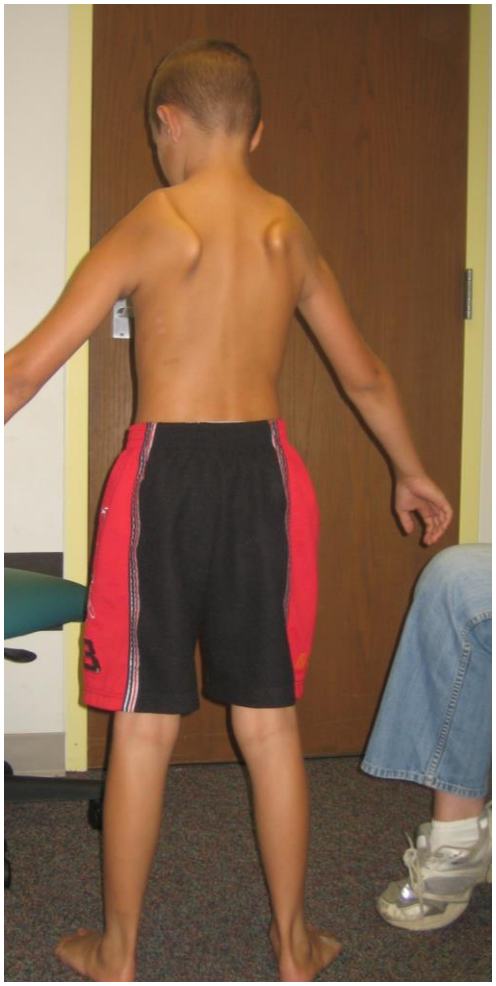


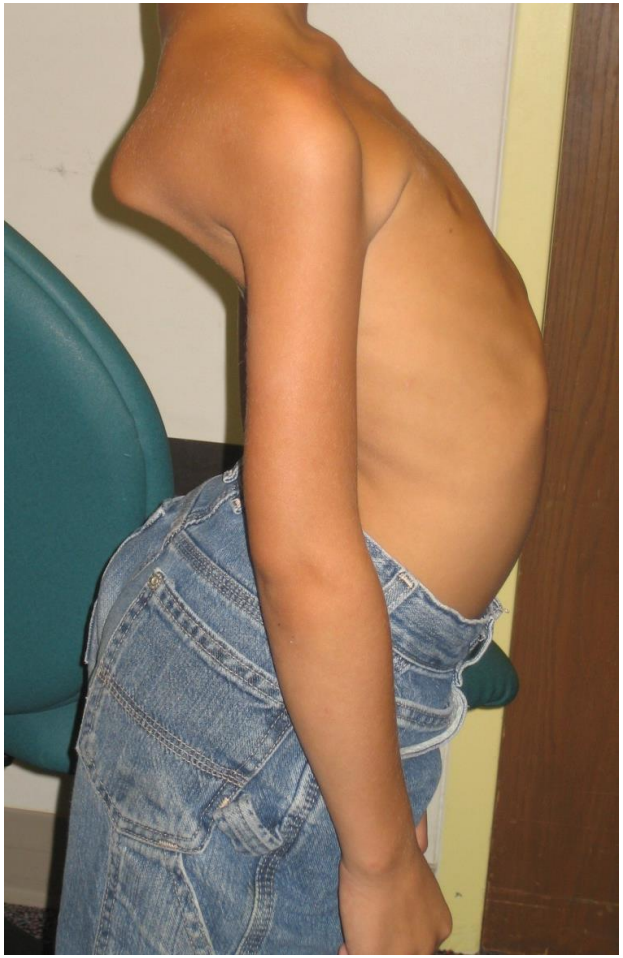

Tonin et al, Neuromuscul Disord. 2004 Jan;14(1):33-8.

# Inheritance

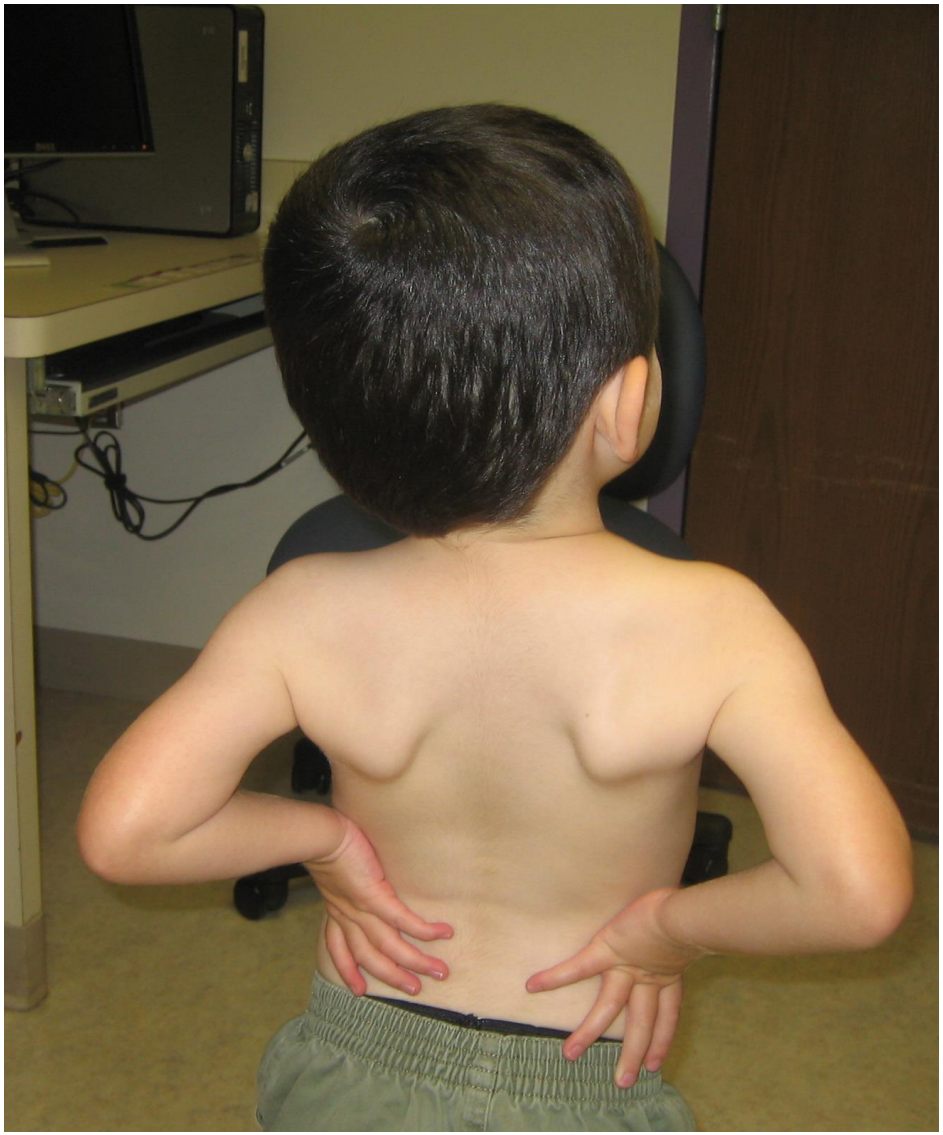
- Autosomal dominant, but often the severely affected child is the first person with FSHD in the family
- New mutation in child OR
- Parent could be mosaic
  - Usual situation: all cells in the body have the same genetic make-up
  - Mosiac: 2 populations of cells in the body, some with the FSHD-related variant, some without
    - If germ cells involved, can have multiple affected children despite no symptoms in the parent.
- Mangement: genetic counseling

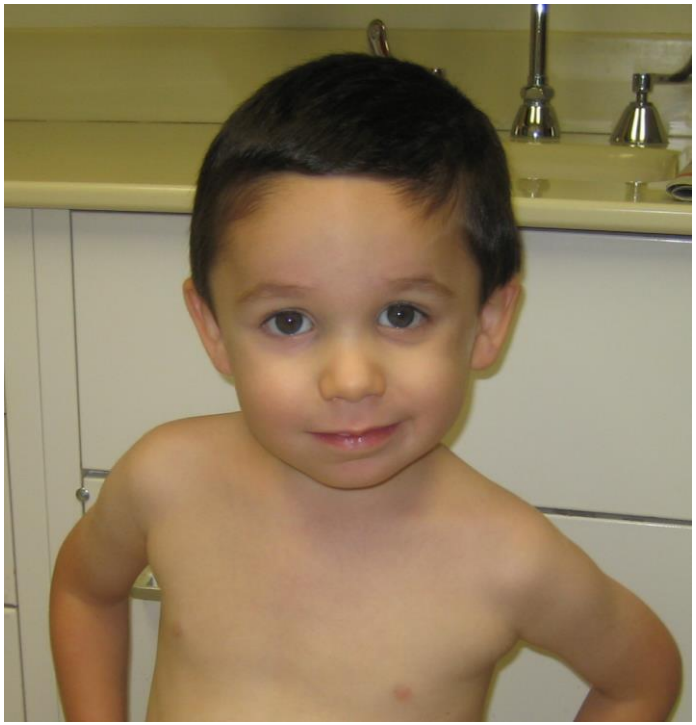
# Intermediate onset FSHD





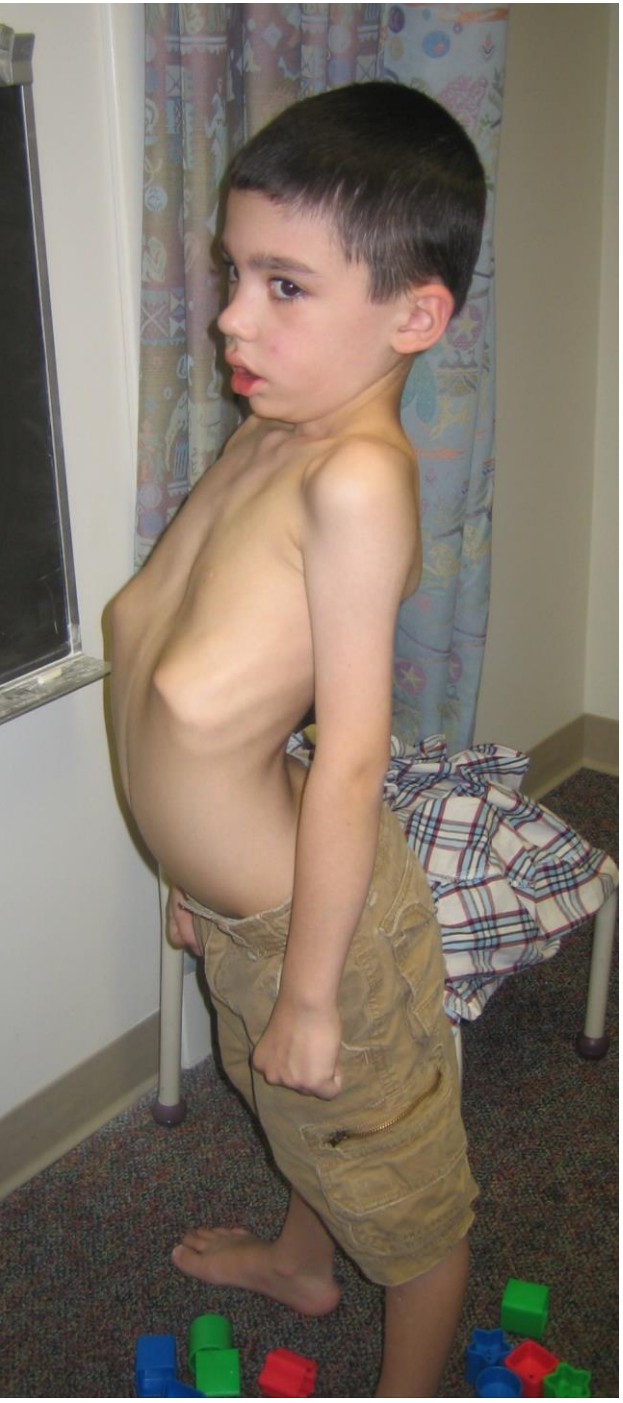
# Mild childhood onset FSHD





# Possible contributors to disease severity

- Very small fragments
- Double mutations:
  - FSHD 2 variants as modifiers of FSHD1
- Other modifiers?

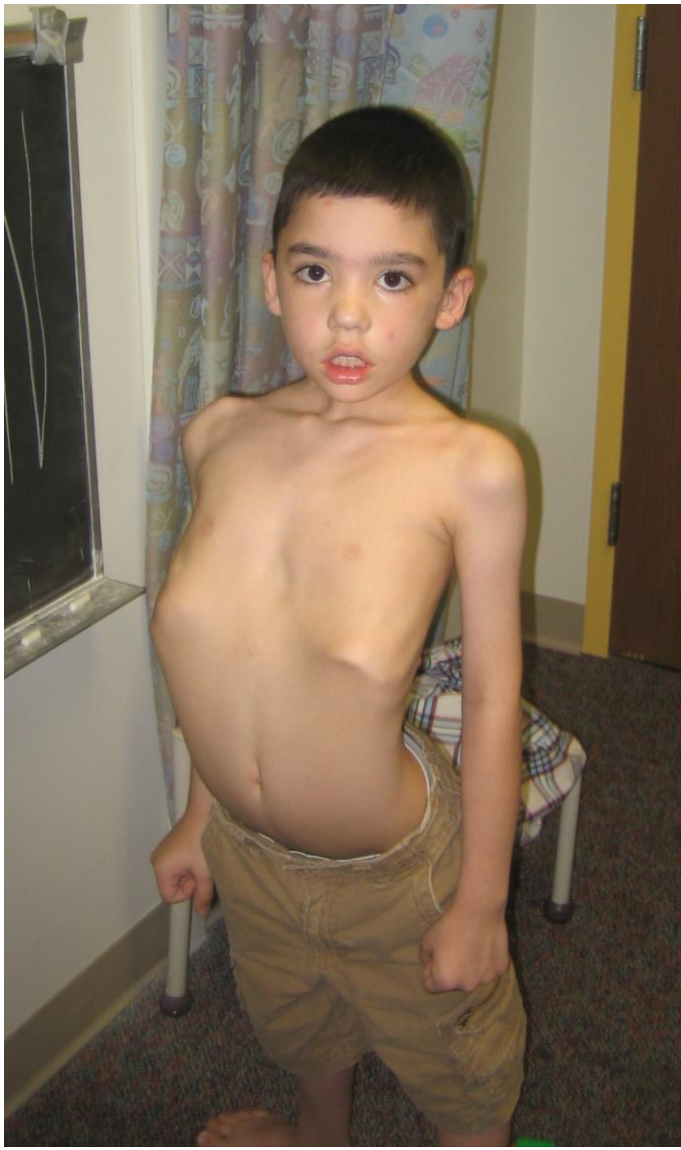


# Early Onset (or infantile) FSHD

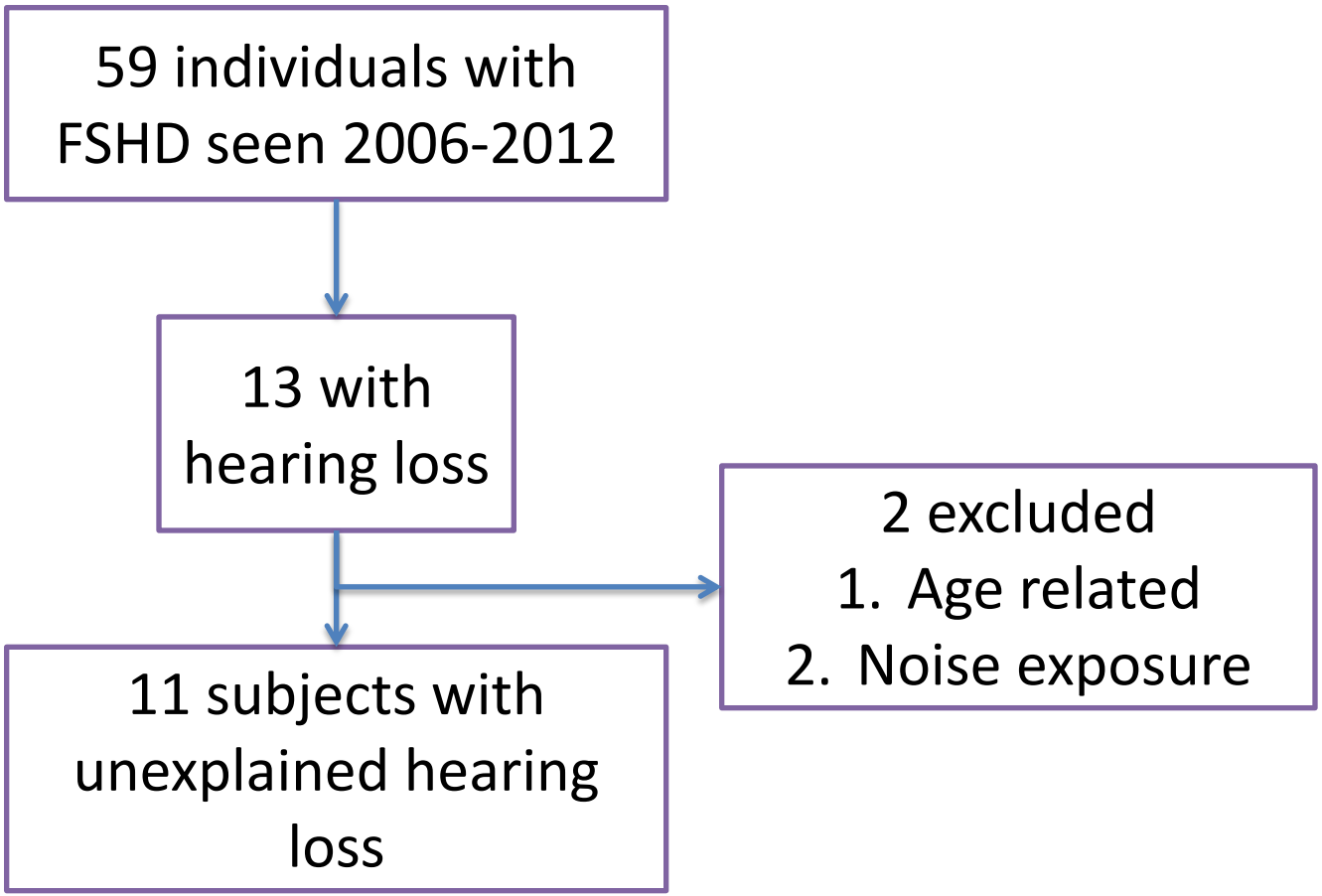
- Systems to consider
  - Hearing
  - Eyes
  - Brain
  - Breathing
  - ?heart

# Hearing loss

- Facial weakness since infancy.  At 2 yo, parents concerned about facial weakness.
- First spoke at 2 years.
- Abnormal gait with lordosis.
- Dx = autism.
- 7 yo, Dx FSHD
  - EcoRI/BlnI fragment size of 15kb.
- Seen by us and failed hearing screening.
- Follow up evaluation: mild to moderate high frequency hearing loss bilaterally and was fitted for hearing aids.



# Retrospective review of hearing loss in FSHD




Lutz, Neurology. 2013 Oct 15;81(16):1374-7.

# Clinical characteristics of participants with hearing loss.

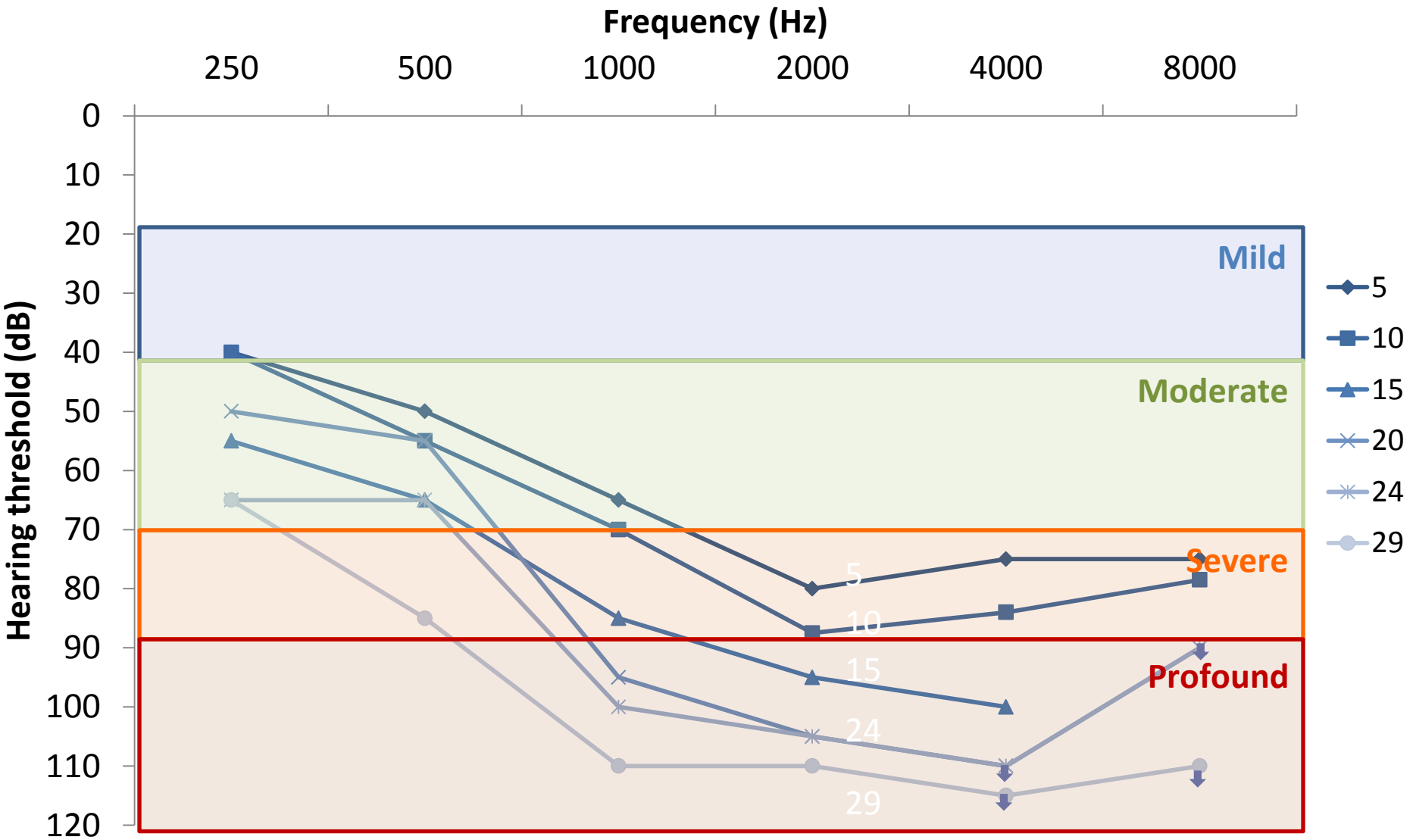
| Clinical characteristics | |
|---|---|
| Patients | 11 |
| EcoRI/BlnI fragment size | 9-18 kb |
| Family history of FSHD | 2 patients |
| Age of onset of facial weakness | 0-5 years |
| Age of onset of shoulder girdle weakness | 3-15 years |
| Age at last exam | 7-50 years |

# Hearing loss was detected between birth and 7 years of age.

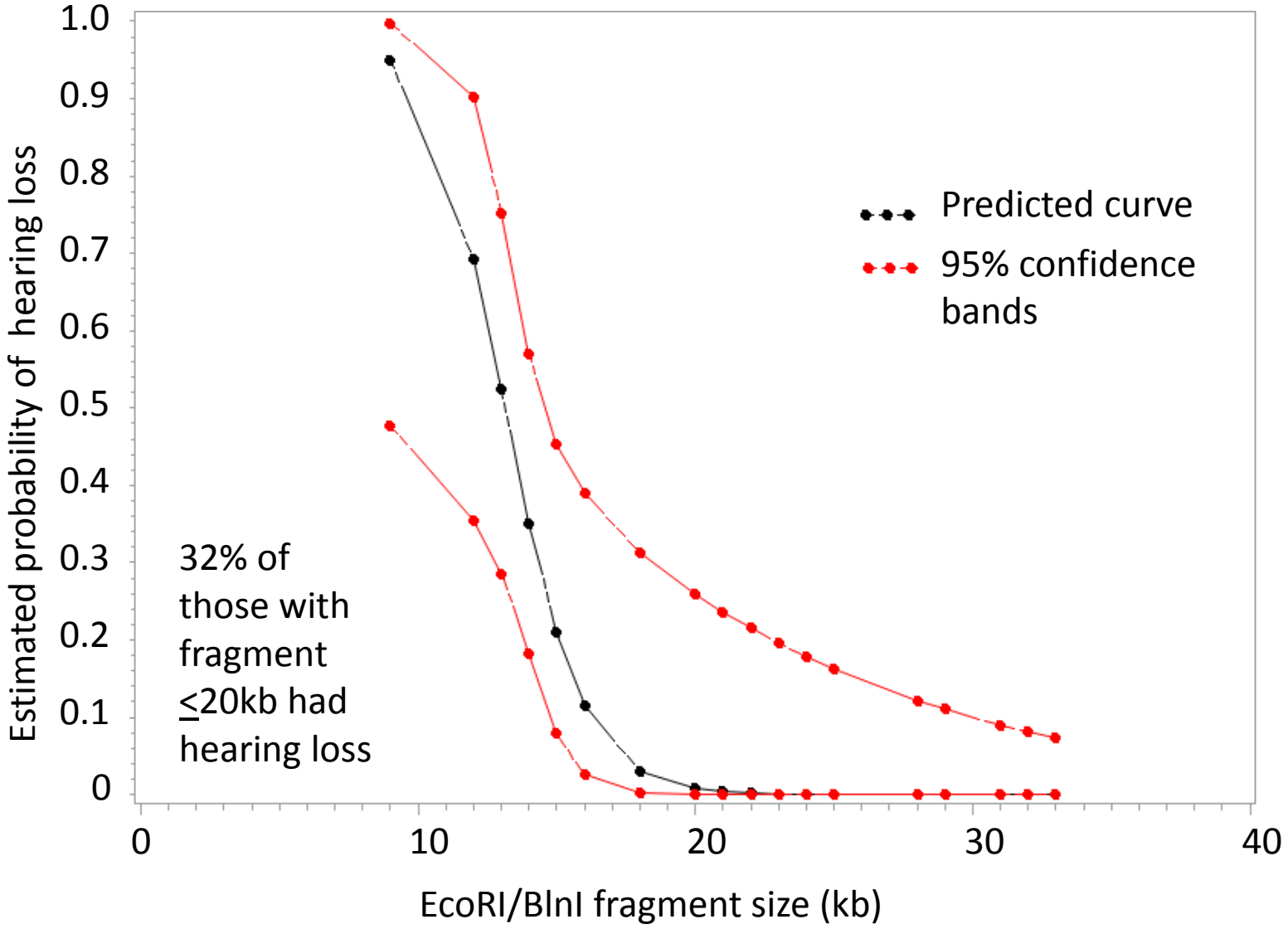
| Age of detection of hearing loss | |
|---|---|
| Newborn Hearing Screening | 3 tested |
| Failed | 2 |
| Passed | 1 |
| Age of detection of hearing loss | 1.5-7 years |

Lutz, Neurology. 2013 Oct 15;81(16):1374-7.

# Hearing loss is progressive.



# Probability of hearing loss is higher with shorter EcoRI/BlnI 4q35 fragment.



# FSHD: Hearing loss

- Patients with early onset FSHD often have hearing loss, which can affect normal social function.
  - In general, FSHD allele <17-20kb (EcoRI)
- Patients with typical onset FSHD
  - Frequency of adult-onset hearing loss similar to controls


- Brower et al Neurology. 1991 Dec;41(12):1878-81
- Voit, et al. Eur J Pediatr. 1986 Sep;145(4):280-5.
- Trevisan et al. Audiol Neurootol. 2008;13(1):1-6.
- Lutz, Neurology. 2013 Oct 15;81(16):1374-7.

# Recommendations: Hearing

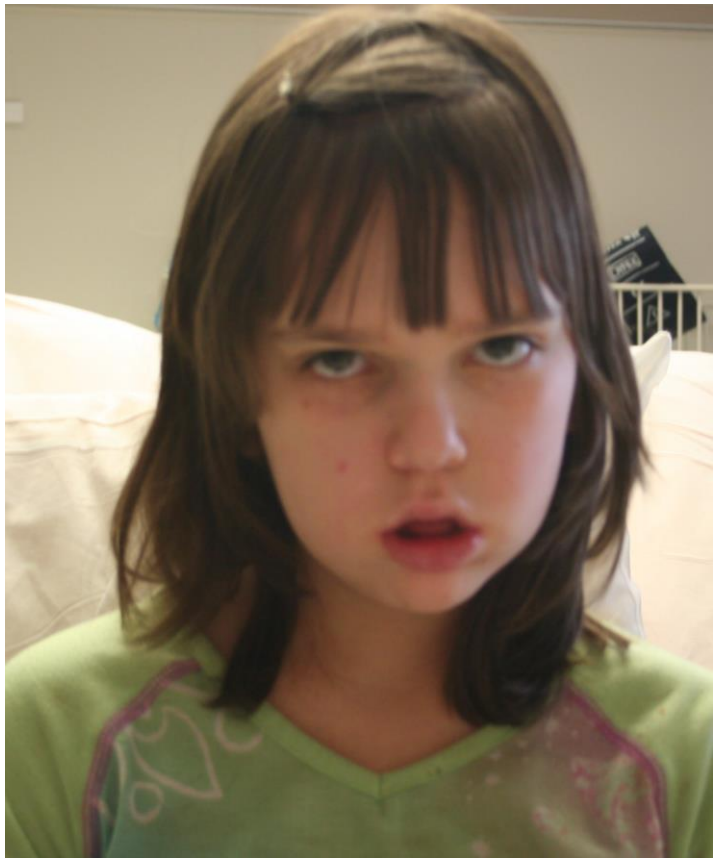
- Hearing evaluation if preschool, pre-language
  - Newborn screening alone is not adequate
  - Older patients with normal language and no symptoms don't need formal hearing evaluation due to FSHD
- Hearing testing if there is concern about language or social development in early childhood
- Repeated screening if hearing loss identified as it can be progressive

# FSHD: Retinal vasculopathy

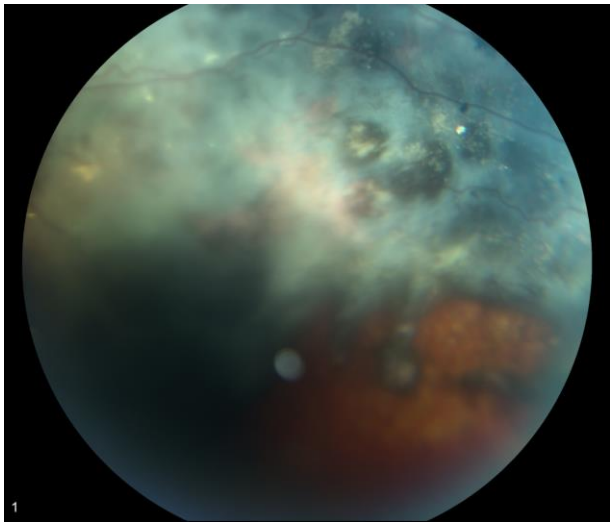
- Patients with early onset FSHD may have a severe form of retinal vascular disease (Coat's disease).
  - Vessel irregularity, narrowing, microaneurysms
  - May progress to retinal detachment and blindness.
- ≤ 75% of all patients with FSHD have some retinal vessel abnormality.
  - No effect on vision.


- Fitzsimmons, et al. Brain. 1987 Jun;110 ( Pt 3):631-48
- Padberg et al. Muscle Nerve. 1995;2:S73-80.

# Retinal vasculopathy



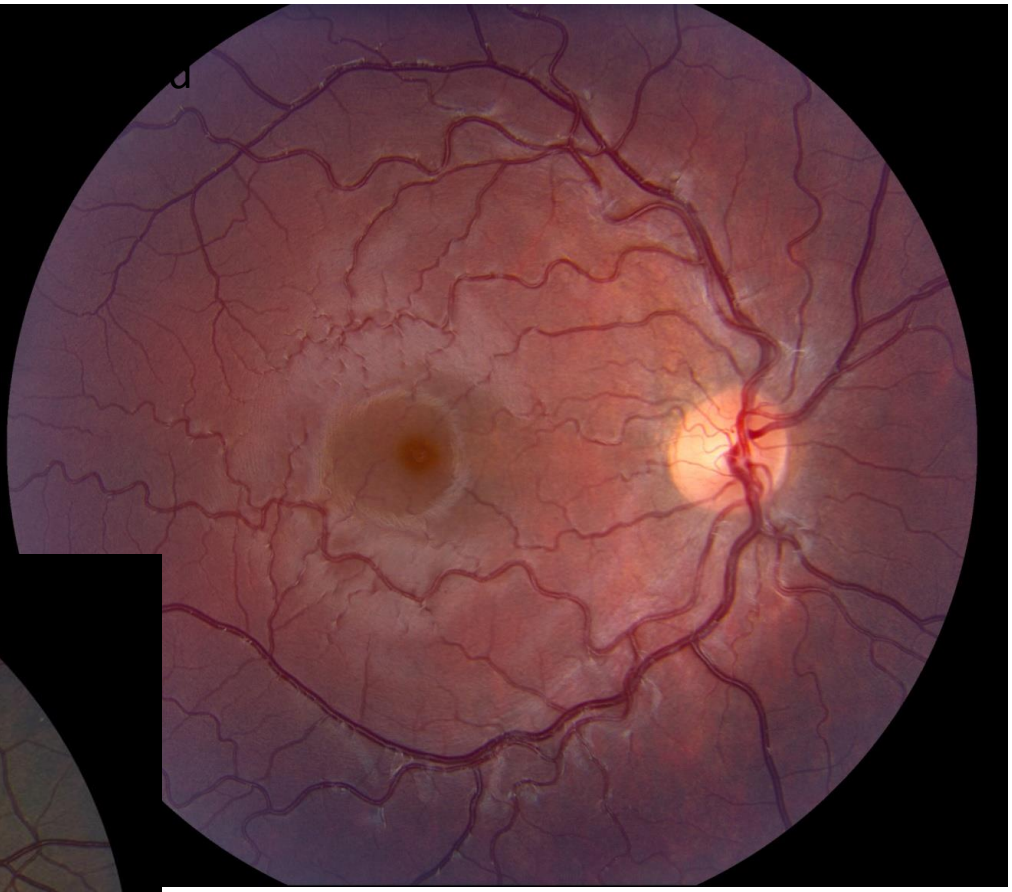
- First concern at 15 months, funny glare in eye
  - Retinal detachment, started on laser therapy
- 18 mo: not talking
  - Moderate sensorineural hearing loss
- Diagnosis: FSHD ~2 yo
- EcoRI/BlnI fragment 13kb

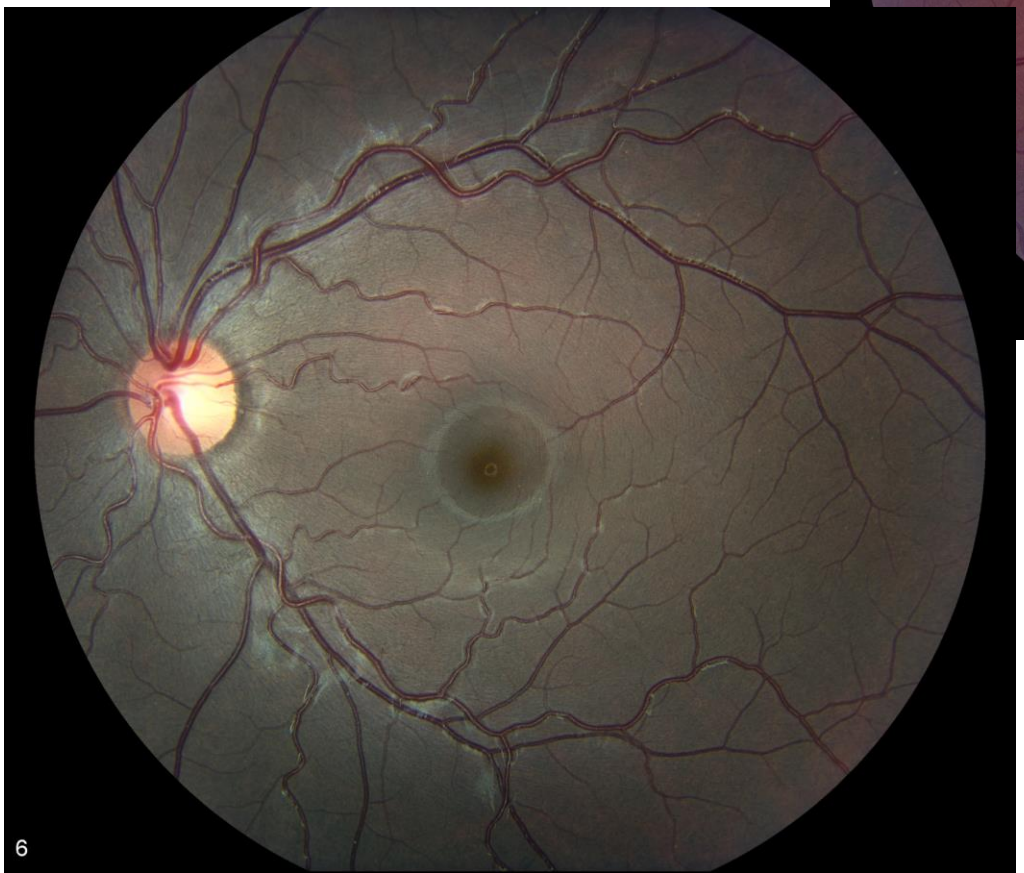


# Coats Syndrome in FSHD

- Exhaustive review of literature, Rochester registry, survey of FSHD clinics
- 10 patients from registry, clinics; 4 from literature
- Coats disease prevalence in FSHD = 0.8% (95% CI 0.2%–2.2%).
- Age at onset of Coats disease infant-53 yrs
- 57% also had hearing loss
- Median FSHD allele size 13kb
    - Statland, et al. Neurology 2013;80:1247–1250

# Retinal tortuosity without vision loss





Arterial (not venous) tortuosity correlated with clinical disease severity (r=0.78 to 0.9)

Longmuir, J AAPOS. 2010 Jun;14(3):240-3.

# Recommendations
# Retina/vision

- Everyone with FSHD should have at least one dilated eye exam
  - Eye doctor should be told of risk of retinal blood vessel abnormality
  - If there is a significant abnormality, referral to a retina specialist

# FSHD: Brain

- The most severely affected children can have abnormal brain function
  - Cognitive impairment and learning disability
  - Seizures/epilepsy
  - Possibly more common in Asian populations

- Funakoshi,et al, Neurology. 1998 Jun;50(6):1791-4.

# FSHD: Cardiac involvement

- There may be subtle heart problems in some patients with FSHD
  - Most commonly tendency to rhythm disturbance
  - 10/83 (12%) with rhythm disturbance by symptoms or Holter
- Cardiac dysfunction is rarely/never clinically significant or symptomatic in FSHD
- No clinical monitoring is recommended


- Galetta, et al Neuromuscul Disord. 2005 Jun;15(6):403-8
- Laforet et al, Neurology. 1998 Nov;51(5):1454-6
- Stevenson et al, J Am Coll Cardiol. 1990 Feb;15(2):292-9
- Trevisan et al. Eur Neurol. 2006;56(1):1-5.

# FSHD: Respiratory involvement

- Respiratory difficulty is possible in FSHD, most severely affected are at greatest risk
- Annual FVC is recommended for some patients
  - wheelchair bound
  - superimposed pulmonary disease
  - moderate to severe kyphoscoliosis or other chest wall deformity

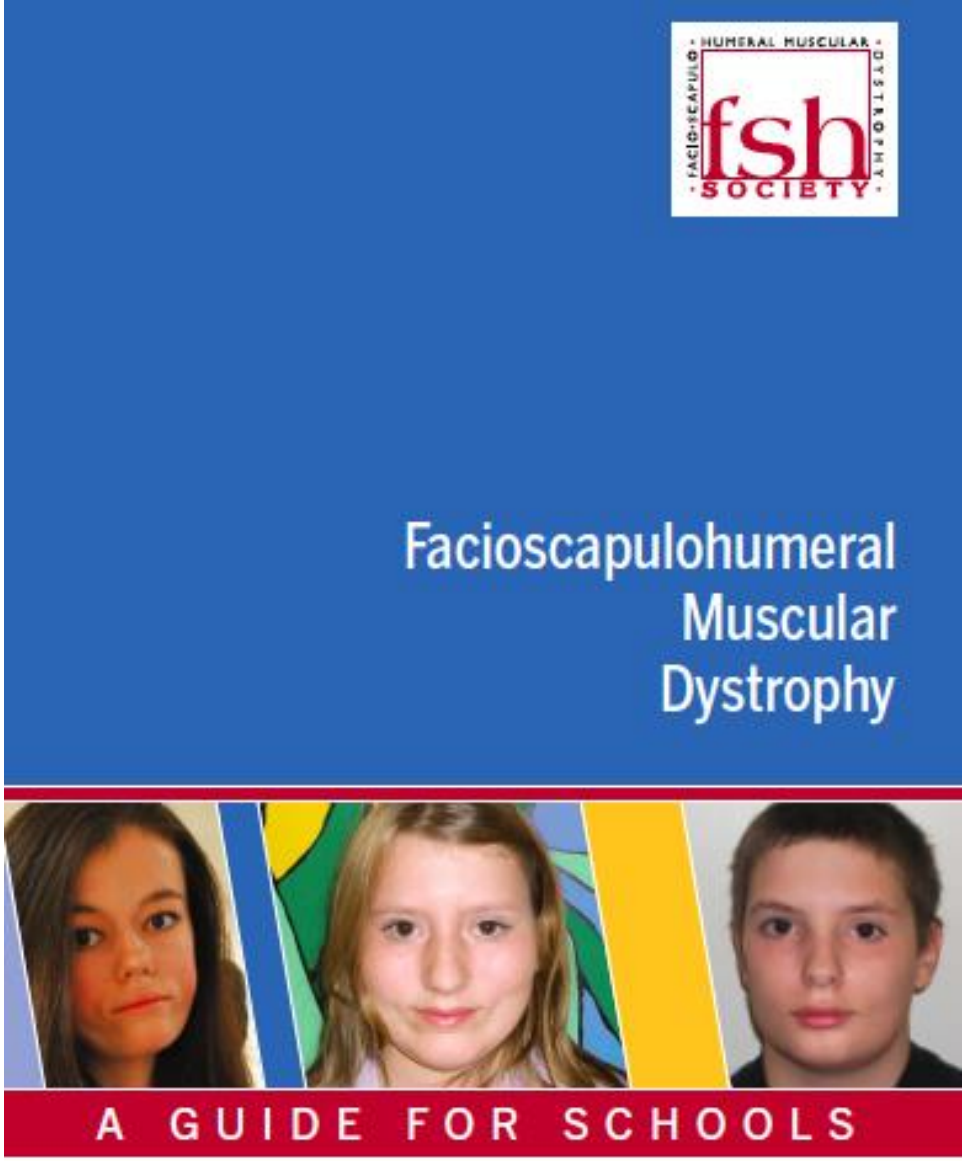
# Guide for Schools

Web search:

"FSHD guide for schools" and download the pdf

- Funded by the FSH Society
- Developed with the assistance of young people with FSHD

- General principles
  - Young person should be involved in educational plans and strategies
  - Avoid decreased academic expectations
  - Insure transfer of plans between grades, schools and districts



# Potential difficulties in the classroom

- Raising hand to respond/ask questions
  - Establish an alternative cue at the beginning of the year
- Sitting in a standard chair
- Writing on wall mounted white/chalk boards
  - Use alternative technology
- Fatigue with handwriting
- Special case of PE class

# Potential problems with mobility

- Establish an emergency plan if speed/stairs/mobility is a problem
- Use elevator if appropriate
- Avoid classroom floor activities
- Carrying books
  - 2 sets of books so student doesn't carry between classes/home and school
  - Electronic media
- Bus steps, fatigue with long trips to school

# Potential problems with communication

- Limited facial expression
  - Teachers/others need to be conscious of listening to words rather than interpreting facial expression
    - Particularly when student is reporting an emotion
- Unclear speech
  - Specific comments for speech therapy
  - Teachers can allow pre-recorded presentations, visual aids for classroom presentations
- Low speech volume
- Hearing impairment

# Potential problems with mealtime

- Carrying lunch tray
- Difficulty closing mouth, social difficulties
  - Attention to food texture/consistency
  - If desired, offer smaller lunch room to share with friends

# Potential social/emotional concerns

- Low self-confidence, lack of self-advocacy
  - Involve student in decisions and plans
- Connecting with peers
- Expressing emotions

# Management of early onset FSHD summary

- Attention to all the usual medical issues and be alert for possible problems
  - Vision, hearing, learning
  - Genetic counseling, possible mosaicism
- Attention to managing the environment with attention to
  - Safety
  - Motor function
  - Social and emotional function

# Thank you

The families and patients who continue to educate me
Katie Lutz, Wellstone fellow 2012
My colleagues
Shelly Mockler
NIH, CDC for research support