Phenotypic variability of siblings with proximal weakness

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Objective

- Here we present two brothers with proximal muscle weakness.

Case-1 HPI

36 year old male

- Slowly progressive proximal muscle weakness which began when he was 10 years of age.
- Always lagged his peers in motor tasks.
- Mild muscle cramping with activity.
- Patient states he was told he has LGMD based on muscle biopsy (Records were unavailable to review).

ROS: Dyspnea on exertion. No swallowing issues, double vision, or droopy eyes.

FH: Older brother has similar issues

PMH: Schizophrenia, sleep apnea

Meds: Latuda, Adderall, valproic acid

Case-1 Physical examination

- **Cranial nerves- normal**

	R	L		R	L
O.Occuli	5	5	O.Oris	5	5
Neck flexion	**4**		Neck extension	5	
Shoulder abductors	**4**	**4**			
Elbow extensors	5	5	Elbow flexors	5	5
Wrist flexion	5	5	Wrist Extension	5	5
Finger flexion	5	5	Finger extension	5	5
Hip flexion	**4**	**4**	**Hip abduction**	**4**	**4**
Knee flexion	5	5	Knee extension	5	5
Plantar flexion	5	5	Dorsiflexion	5	5

- **Sensation**: Intact ; **Normal DTR and downgoing plantars**
- **Normal coordination and gait**

Case-2 HPI

38 year old male:

- Limb girdle pattern weakness since age of 13 yrs.
- He has ptosis and extra ocular movement restriction since childhood.
- He had surgery for tight Achilles issues.

ROS: Dyspnea on exertion.

PMH: Sleep apnea, depression

Meds: Sertraline

Case-2 Physical examination

- **Bilateral ptosis, abduction restriction of both eyes. Slight down gaze restriction.**

	R	L		R	L
O.Occuli	**4**	**4**	**O.Oris**	**4**	**4**
Neck flexion	**4**		Neck extension	5	
Shoulder abductors	**4**	**4**			
Elbow extensors	5	5	**Elbow flexors**	**4**	**4**
Wrist flexion	5	5	Wrist Extension	5	5
Finger flexion	5	5	Finger extension	5	5
Hip adduction	**4**	**4**	**Hip abduction.**	**4-**	**4-**
Hip flexion	**4-**	**4-**	Hip extension		
Knee flexion	**4+**	**4+**	Knee extension	5	5
Plantar flexion	5	5	**Dorsiflexion**	**4+**	**4+**

- **Sensation:** Vibration(15 sec fingers, 7 sec-Toes). Other -normal.
- **Reflexes (R/L)**: Reflexes 1 except in ankle. Normal coordination.
- **Gait and Station**: Could not do toe walk, heel walk or tandem gait.
- He could not get up from squat position without assistance.

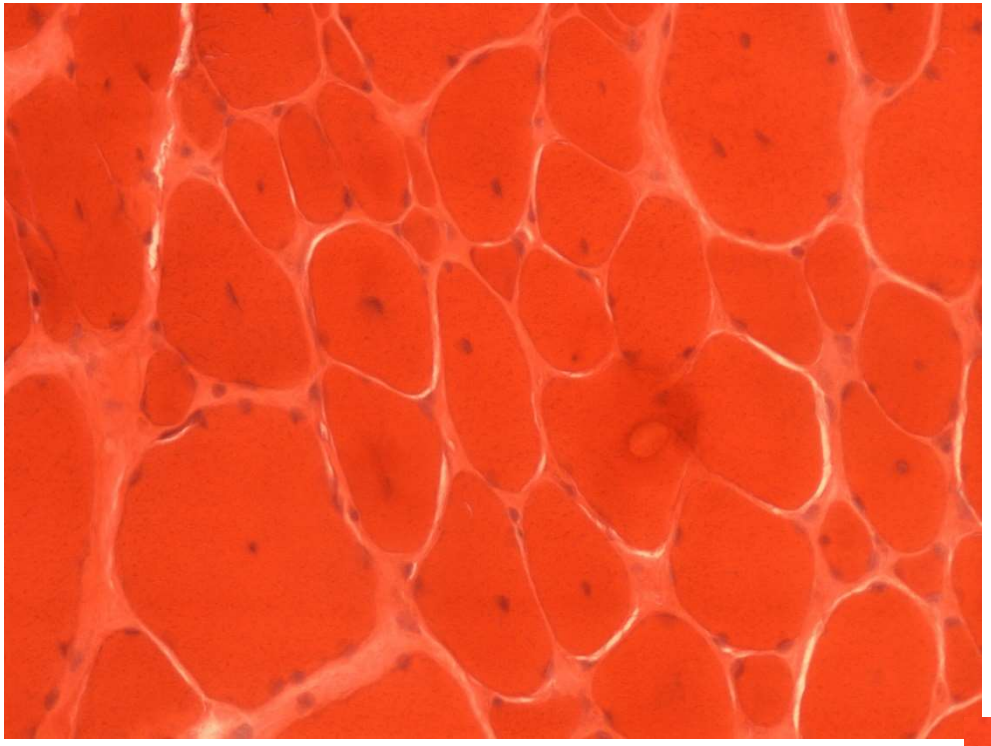
Results

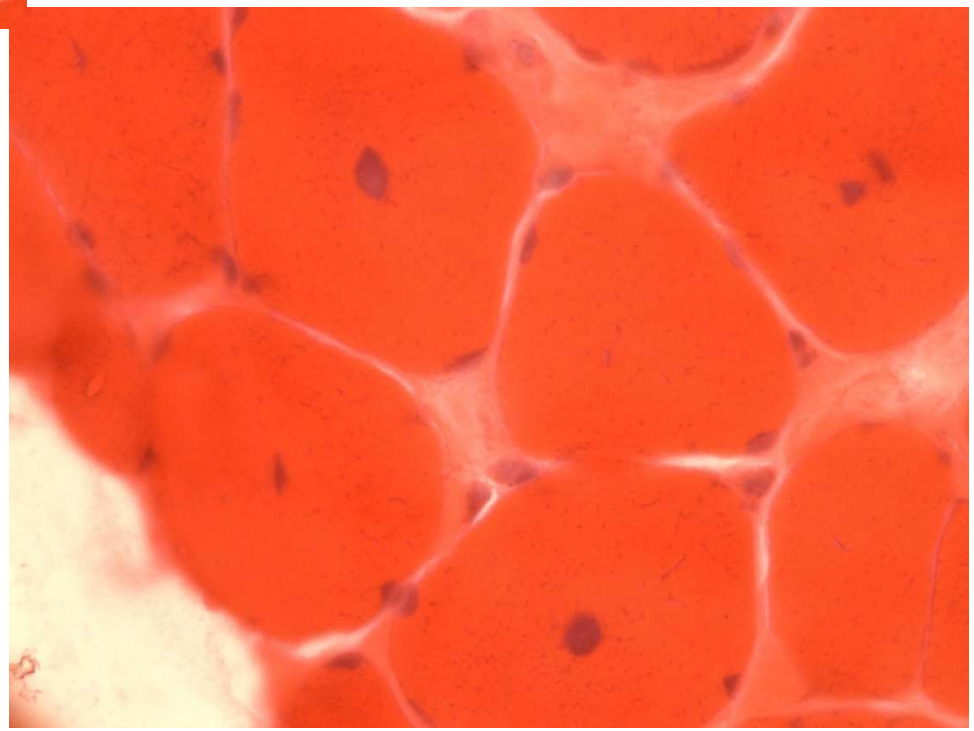
- CPK, SPEP, TSH were normal in both cases.
- PFT - FVC 53% pred in case 1 and 45% pred in case 2
- Genetic testing using a LGMD panel (including 35 genes) was negative in case 1.

EMG findings in;

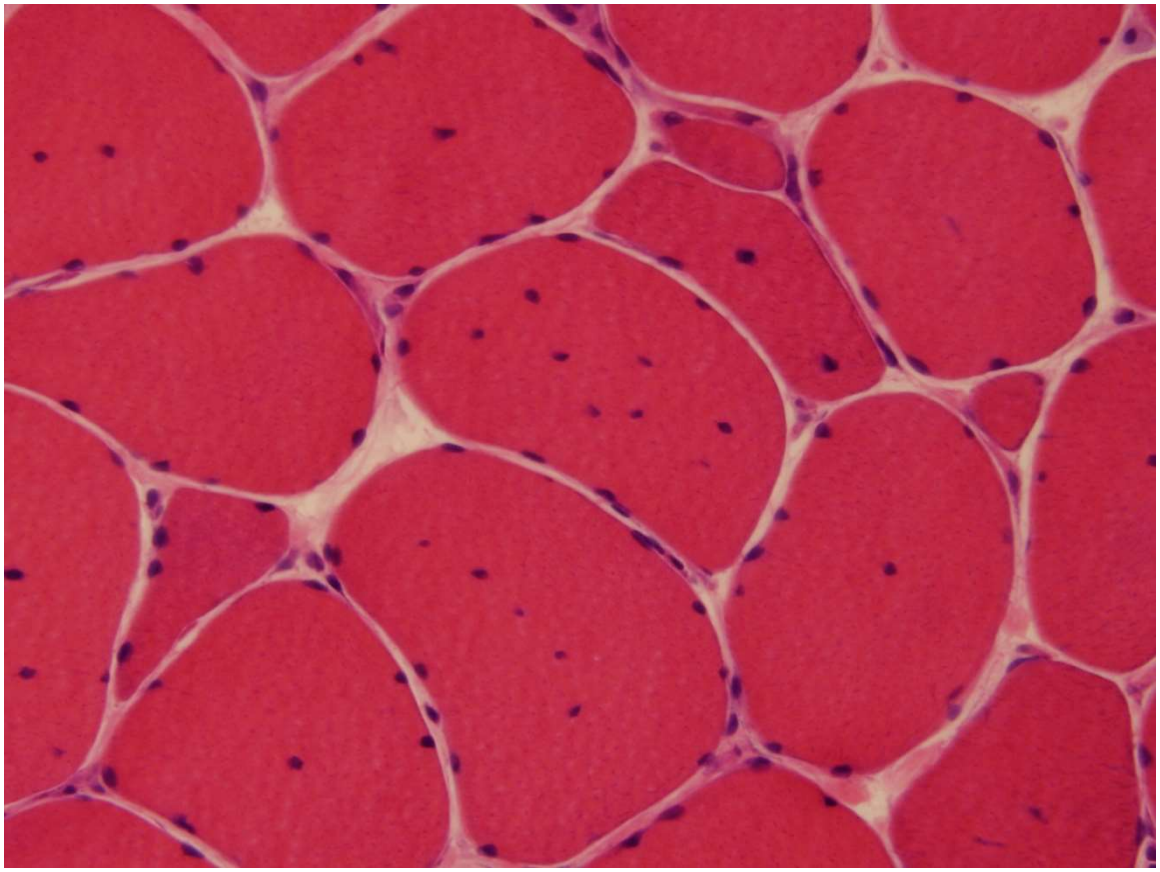
- **Case 1**- showed nonirritative myopathy , distal sensorimotor polyneuropathy, axonal, mild to moderate.
- **Case 2** - showed irritative myopathy and absent sural response.

Case 1 Muscle biopsy (H&E)

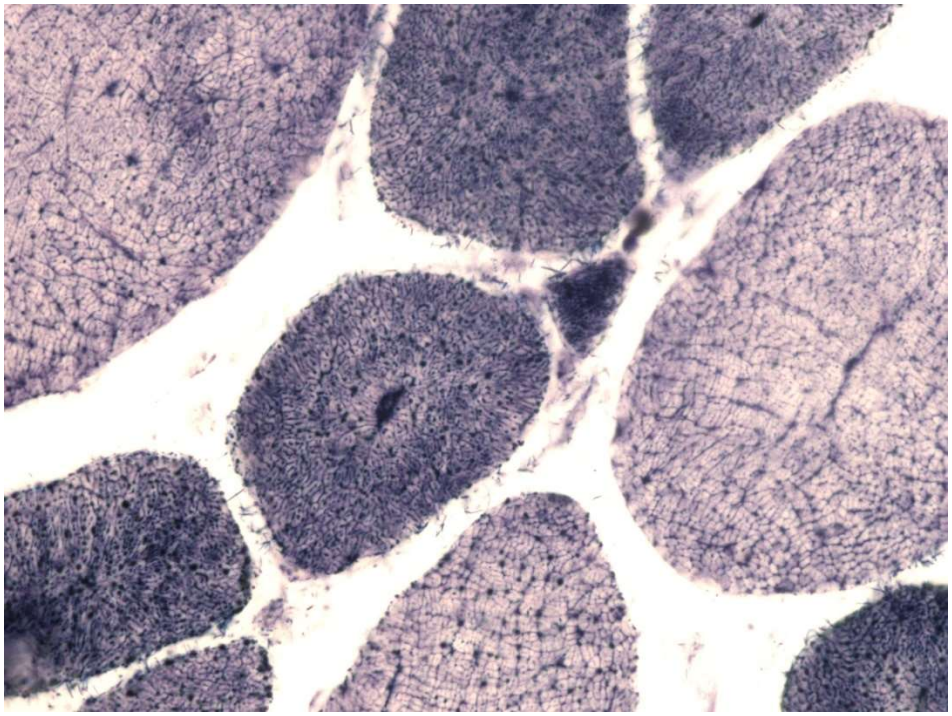




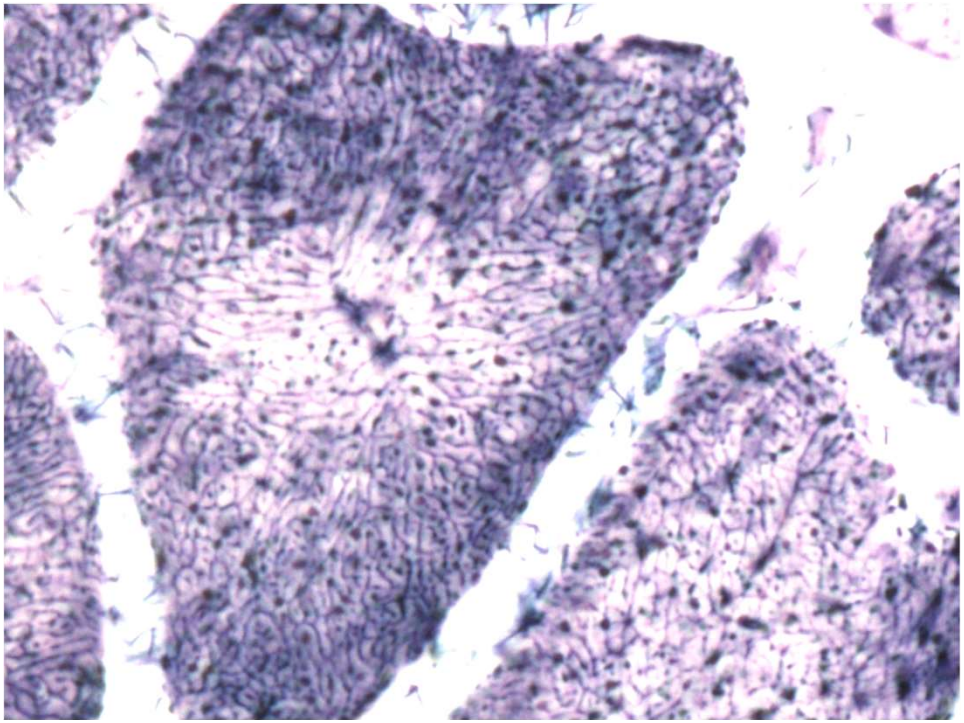
Case 2 Muscle biopsy



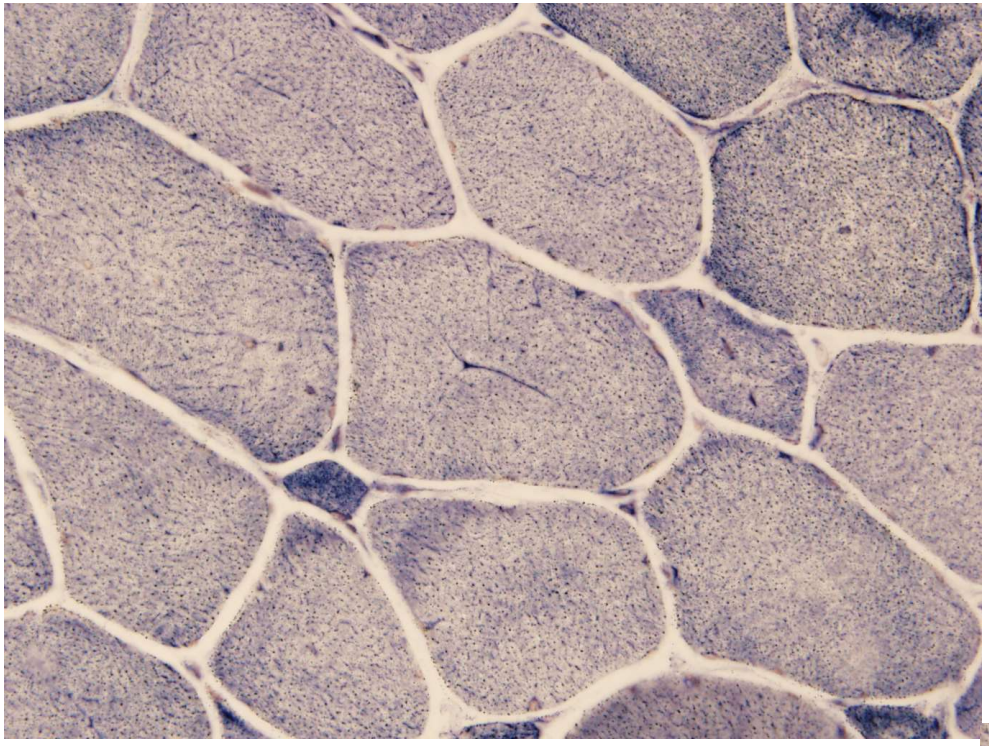
Diagnosis

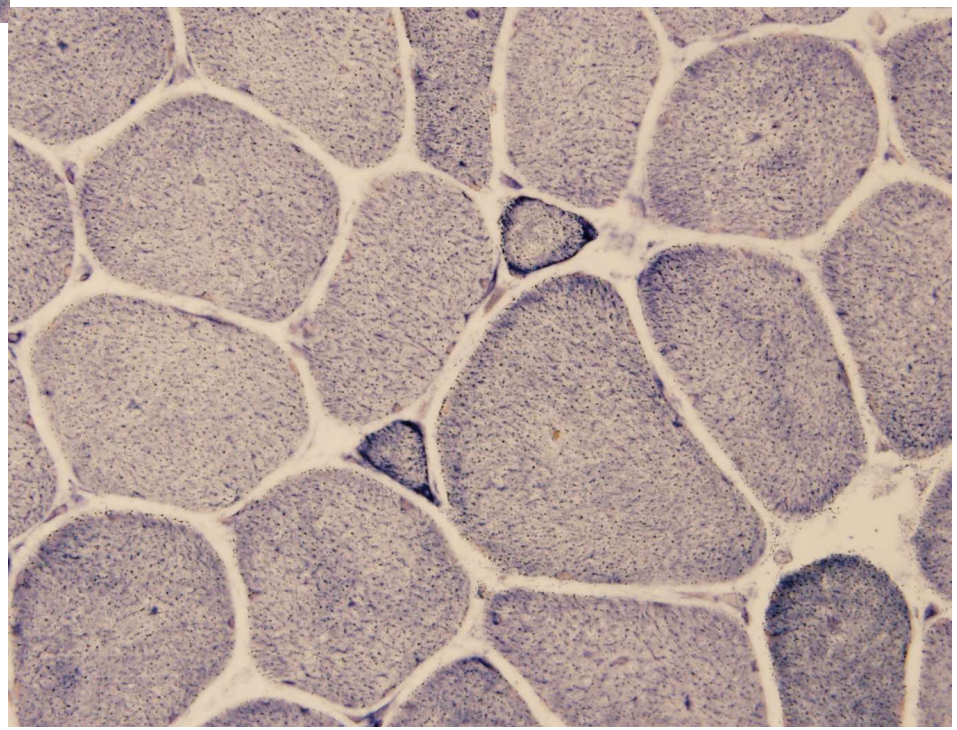


Case 1 Muscle biopsy



Case 2 Muscle biopsy





Genetics

- The impression was **Centro nuclear myopathy (CNM)**.

- **Case 1:** An expanded next generation NM genetic panel which included CNM genes (117 genes: DNM2, MYF6, BIN1, RYR1, TTN, MTM1) revealed: variant of unknown significance (VOUS) **in MTM1 and PLEC.**
  - **Case 2:** targeted testing + **VOUS in MTM1**

- **MTM1: hemizygous VOUS, Exon 9, c.734C>T, p.Pro245Leu**
  - Missense mutation in highly conserved region
  - Not present in population databases (ExAC)
  - 2 out of 3 algorithms predicted to be harmful.

Centronuclear myopathy

- (CNM) is a group of rare genetic muscle disorders characterized by muscle fibers with centrally located nuclei.

- **<u>The most common forms of CNM have been attributed to:</u>**

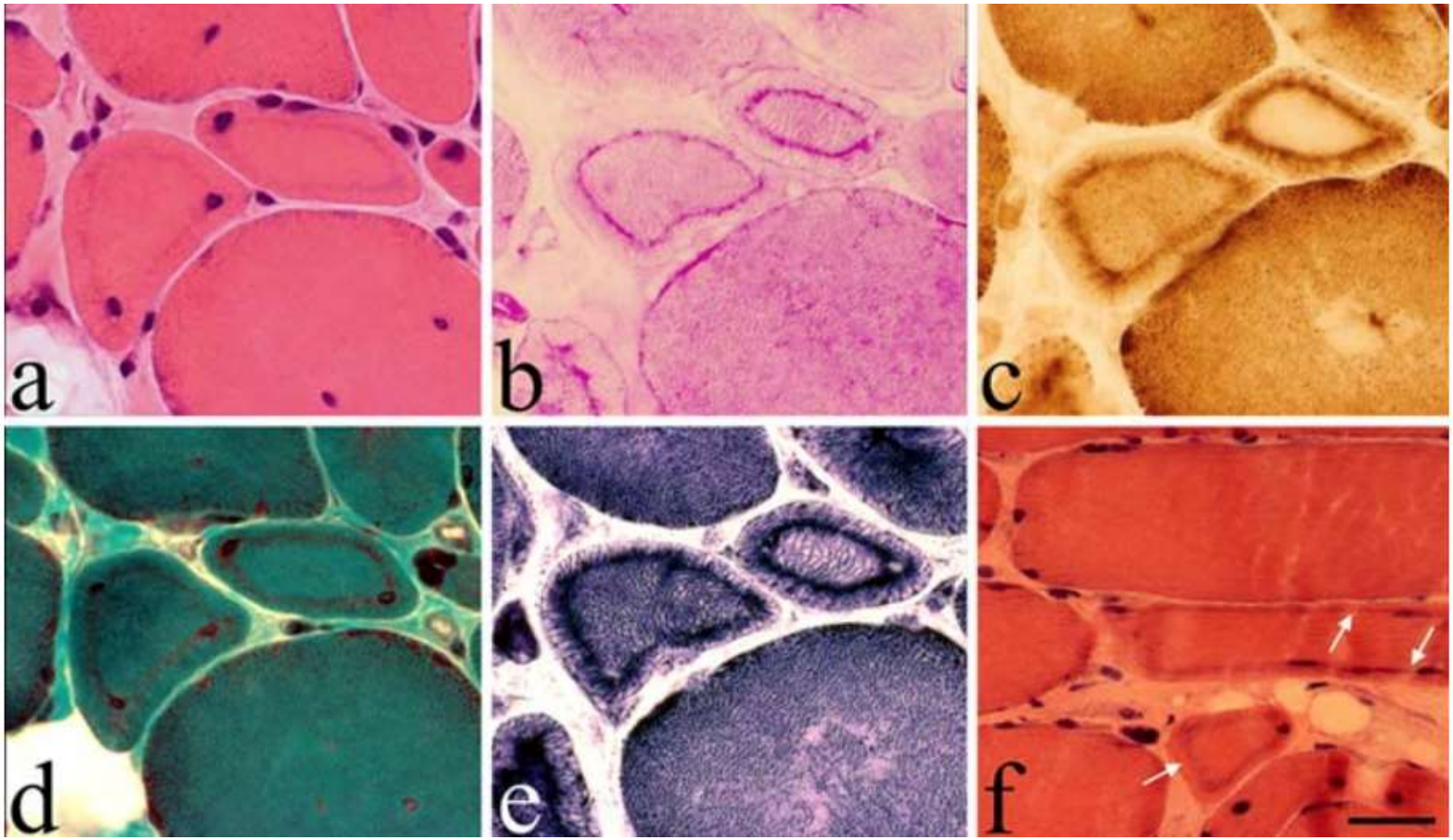
  - X-linked recessive mutations in the MTM1 gene(46.1%)
  - AD mutations in the DNM2 gene-encoding dynamin-2 (7.9%)
  - AR mutations in BIN1(0.9%) , RYR1(2.2%) , TTN(0.4%) genes

MTM1 myopathy (Myotubular myopathy)

- A rare X linked congenital myopathy
  - **In males:** characterized by marked neonatal hypotonia and respiratory insufficiency, facial and ocular involvement.
  - **In females:** phenotypic diversity from unaffected to disease similar to males; also hemiface, hemibody atrophy, and unilateral diaphragm weakness (Hemi-hemi syndrome) described previously at CK meeting

- Muscle biopsy with prominent central nuclei in the majority of muscle fibers
  - In the classic infantile form there is " Classic perinuclear halo" on muscle biopsy
  - A late onset form described with 'necklace fibers' (Basophilic ring underneath sarcolemma)

H&E staining, some small fibers showed, underneath the sarcolemma, a **basophilic ring or "necklace"** that followed the contour of the cell.



Necklace fibers are smaller and show a strongly reactive necklace with H&E (a, f) and GT (d), with oxidative techniques (c, e) and for PAS (b), thus indicating the presence of SR, mitochondria and glycogen.

MTM1 myopathy

Severe (Classic) 80 %	• Characteristic facies • Ventilator dependence • Inability to ambulate independently • High incidence of death in infancy • **25% of boys with severe X-MTM die in the first year of life** • Associated with truncating mutations
Moderate	• Less severe delay of motor milestones • Prolonged periods of ventilatory support
Mild	• Minimal delay in motor milestones • Ventilator support not required • No /limited impact on life span • Associated with missense or splice site mutations

MTM1 Natural History

- Survey and 1 year study (n=50)
  - 86% non-ambulant
  - 75% require ventilator (>16 hours/day)
  - Mortality 10%/year typically due to respiratory cause
  - Only 2 did not require WC, ventilator, or feeding tube

Discussion/Conclusion

- A review of literature for majority of CNM cases with MTM1 mutations revealed primarily infantile onset with significant hypotonia, abnormal extraocular motility, ptosis and respiratory failure.
  - Milder phenotypes associated with missense mutations like our case

- Increased access to inexpensive next generation sequencing panels can help expand the phenotype of CNM.

- Muscle biopsy important to help guide genetic testing and understand the potential relevance of VOUS.

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