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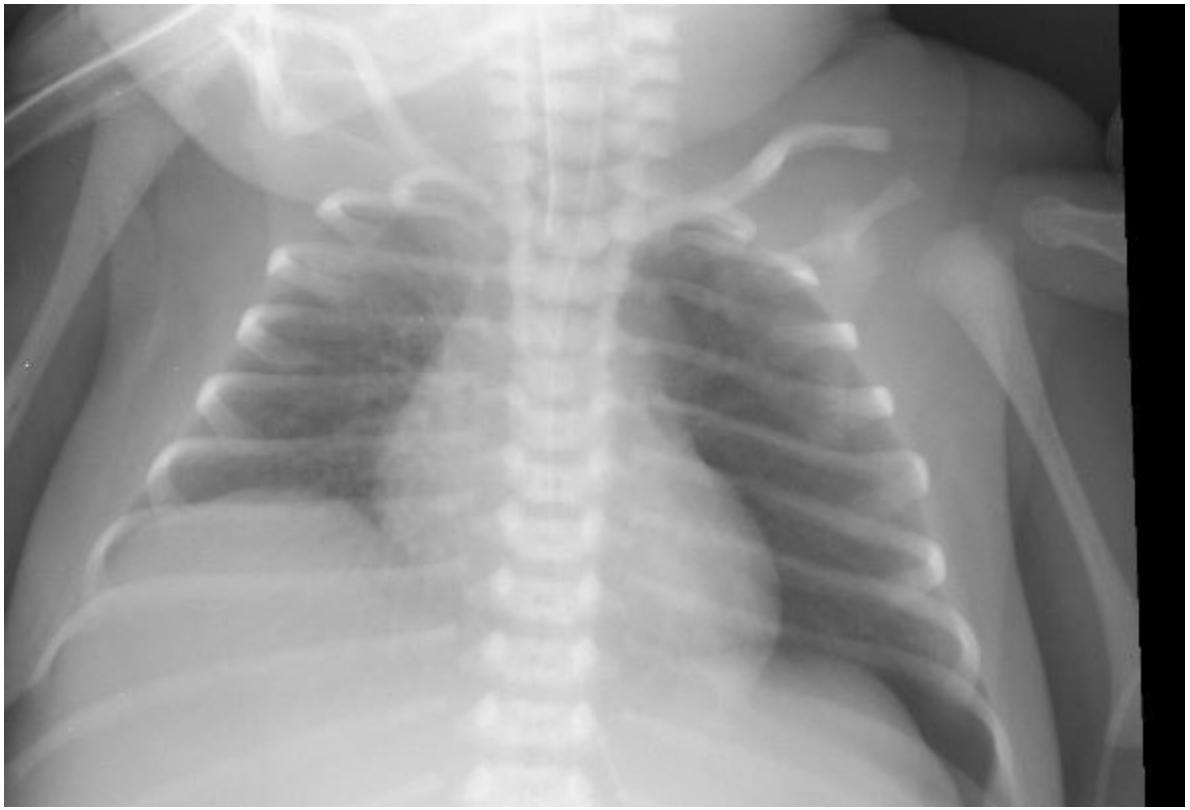
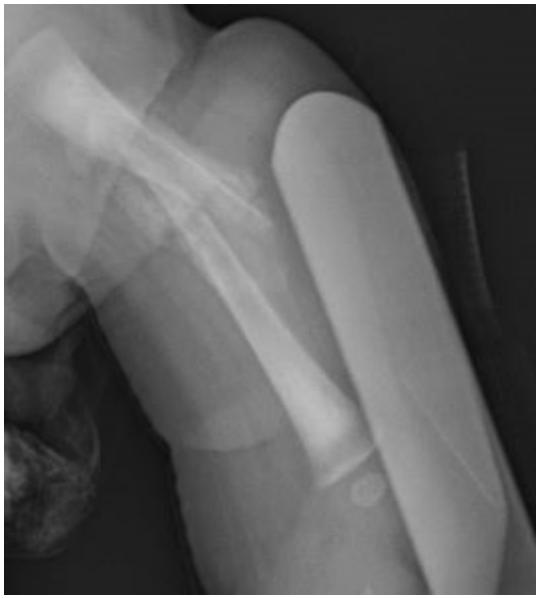
A newborn with multiple anomalies and respiratory failure

Case Presentation

- 36 week C-section delivery due to polyhydramnios, non-reassuring FHT, BW 2194g
- No respiratory effort at birth, intubated and transported; failed extubation day 3-4
- Large PDA and small PFO, RV and LV slightly dilated, R hypertrophic, R diaphragm elevation; no active movement R, limited L, both move with ventilator; thin ribs, micro-retrognathia, small mouth and upturned nose, very little active movement.
- Thrombocytopenia, hypoglycemia, Rx sepsis, cultures negative.
- Tethered cord (sacral tuft, conus at L4-L5), L rocker bottom, R club foot, wide-spaced nipples, clenched hands, small tapered fingers, low set ears
- Femur fracture noted on day 5, splinted, R testis high, L mid canal on US
- Karyotype 46 XY, microarray normal, head ultrasound OK, MRI non-op SDH
- CPK levels 377 on day 6, 98 at 3 1/2 weeks





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Differential Diagnosis

- Genetic consult: Fryns syndrome
  - Not diaphragmatic hernia, eyes and brain OK, no cleft, micro not macrostomia
- Pena Shokeir 1
  - Really a sequence, not an etiology, no pterygia
- SMA, SMARD, XL-SMA
- Congenital myopathy or muscular dystrophy, NMJ

Diagnostic approach

- Edx could have differentiated myopathic vs neuropathic; biopsy was recommended, carnitines, lactate/pyruvate done and WNL
- Rapid WES was available
  - Critically ill newborn infants
  - Early diagnosis is desirable to guide clinical management during
  - Strong single hypothesis cannot be formulated and/or specific non-genetic laboratory tests not available

WES result

p.Gly148Arg (GGC>CGC): c.442 G>C in exon 3 in the ACTA1 gene (NM_001100.3)

De novo, but mosaic

? mother much lower level, 2 unaffected sibs

Not previously reported

Highly conserved across species

Other variants in same part of protein significant

Non-conservative amino acid substitution

G148S also causes disease

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ACTA1

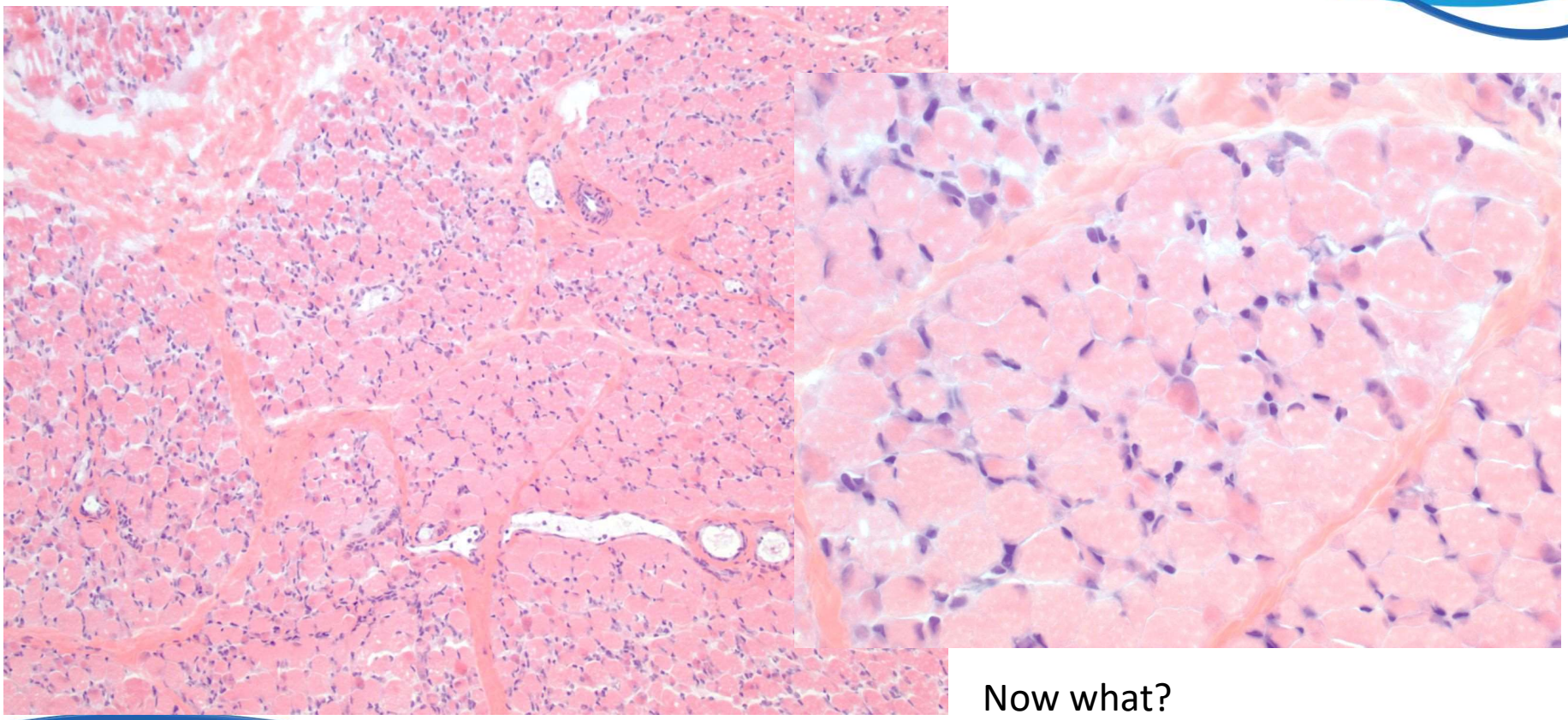
- From Xome Dx:

The ACTA1 gene encodes the skeletal muscle alpha-actin protein, a core component of the sarcomere (North and Ryan, 2012). ACTA1 pathogenic variants are associated with several congenital myopathies including nemaline myopathy (NEM) and myopathy with congenital fiber-type disproportion (CFTDM) (Sparrow et al., 2003). ACTA1 pathogenic variants are the most common cause of nemaline myopathy, accounting for 15-25% of cases (North and Ryan, 2012). ACTA1-associated myopathies result in muscle weakness and hypotonia, ranging from severe congenital-onset weakness and respiratory failure, to a mild childhood-onset myopathy with survival into adulthood. These disorders can be identified by their histological phenotype, which can include accumulation of actin filaments, the presence of nuclear or sarcoplasmic rod bodies, and core lesions without rod bodies (Sparrow et al., 2003). ACTA1-related myopathies are typically inherited in an autosomal dominant manner with many pathogenic variants being de novo, although less severe forms can be familial (DeChene et al., 2013; North and Ryan, 2012). However, both autosomal recessive and dominant inheritance of ACTA1 variants has been documented in NEM (Laing et al., 2009). A homozygous missense pathogenic variant in the ACTA1 gene has been reported in two brothers with infantile-onset congenital muscular dystrophy with rigid spine (O'Grady et al., 2014).

- 7 exons, chr 1
- Nemaline myopathy, variable severity (90%)
- CFTD, rigid spine, SCHP phenotypes possible
- 25% of nemaline cases, but 50% of severe ones

Biopsy findings

- Prominent fiber size variation, with rounded atrophic fibers alternating with scattered hypertrophic fibers.
- Mildly increased endomysial connective tissue.
- Several fibers with irregular internal structure, “granularity” on Gomori trichrome stain.
- No ragged-red fibers, inflammation/vasculitis, perifascicular atrophy, vacuolated fibers, degenerating or regenerating fibers, split fibers, increased internal nuclei or neurogenic changes
- Fascia and epimysial fibroadipose tissue unremarkable.



Now what?

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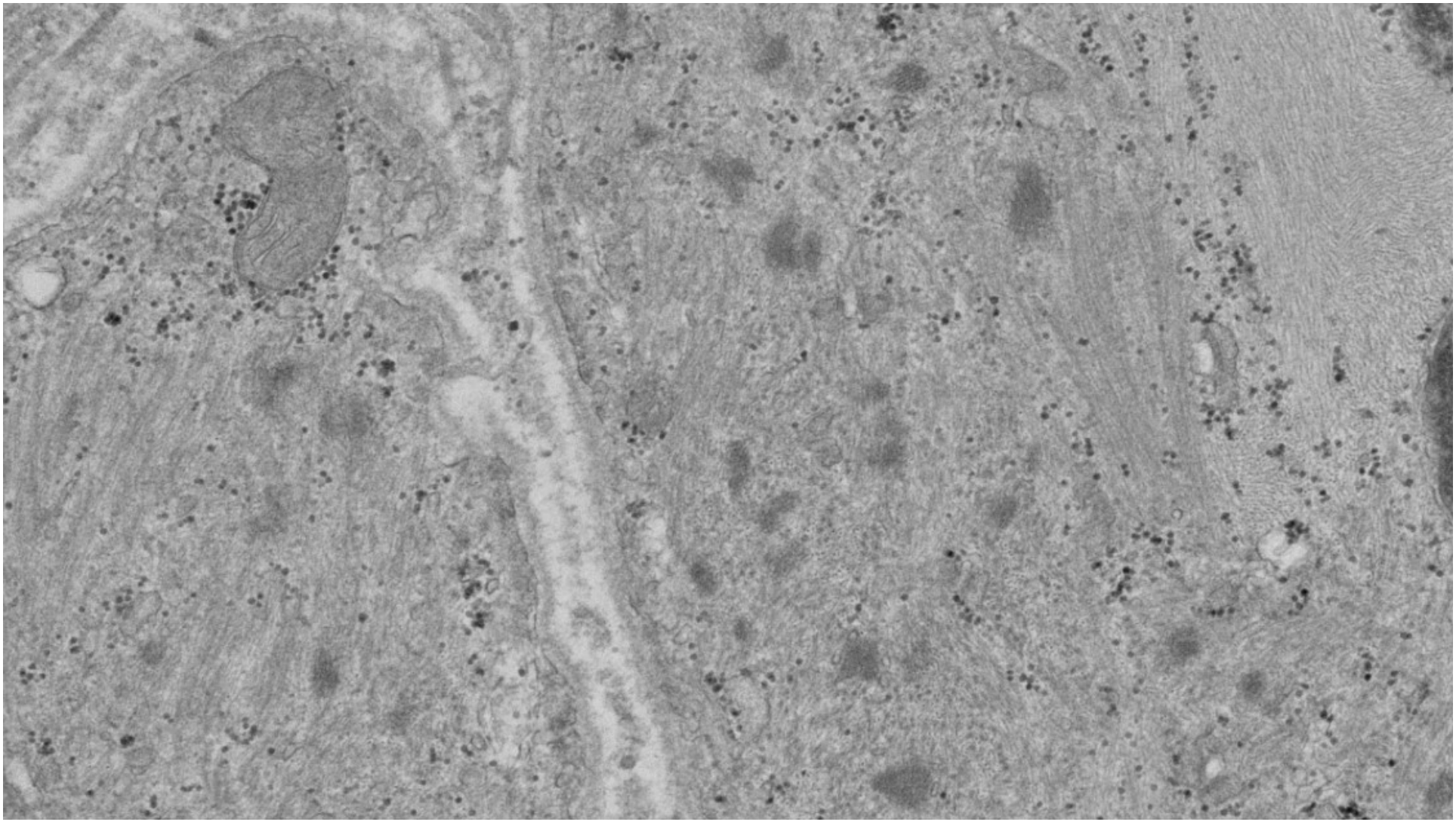
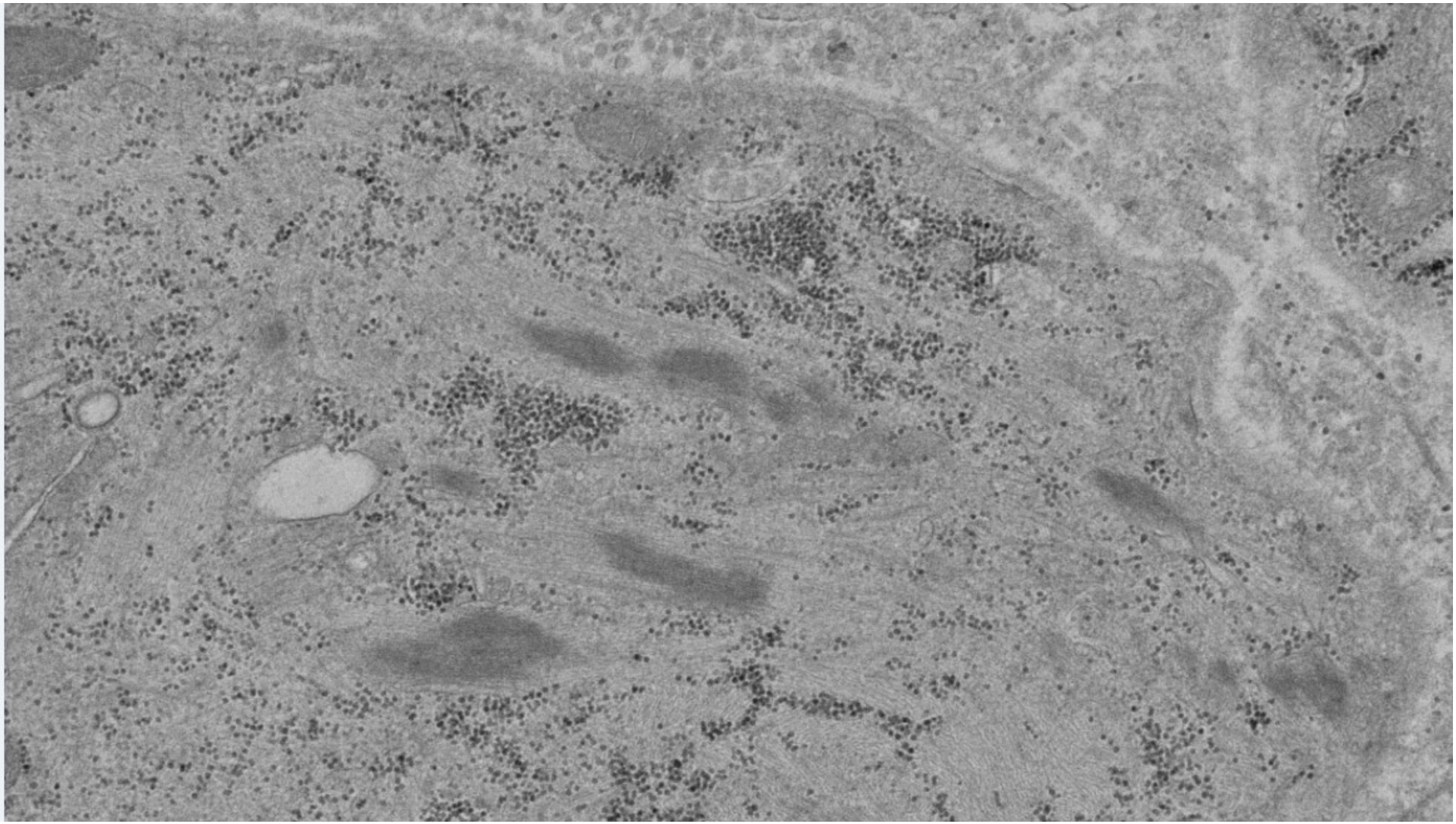
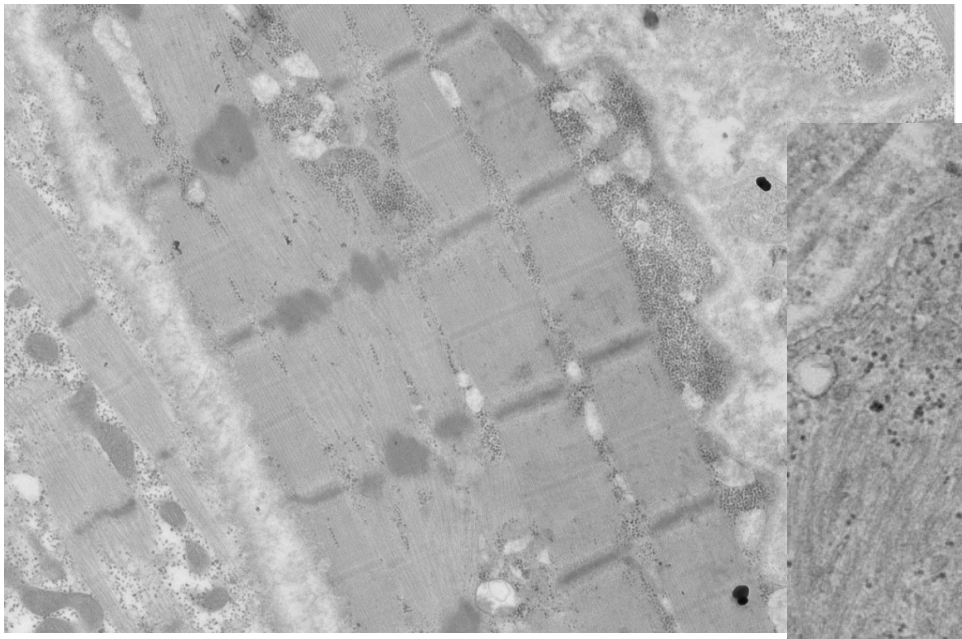
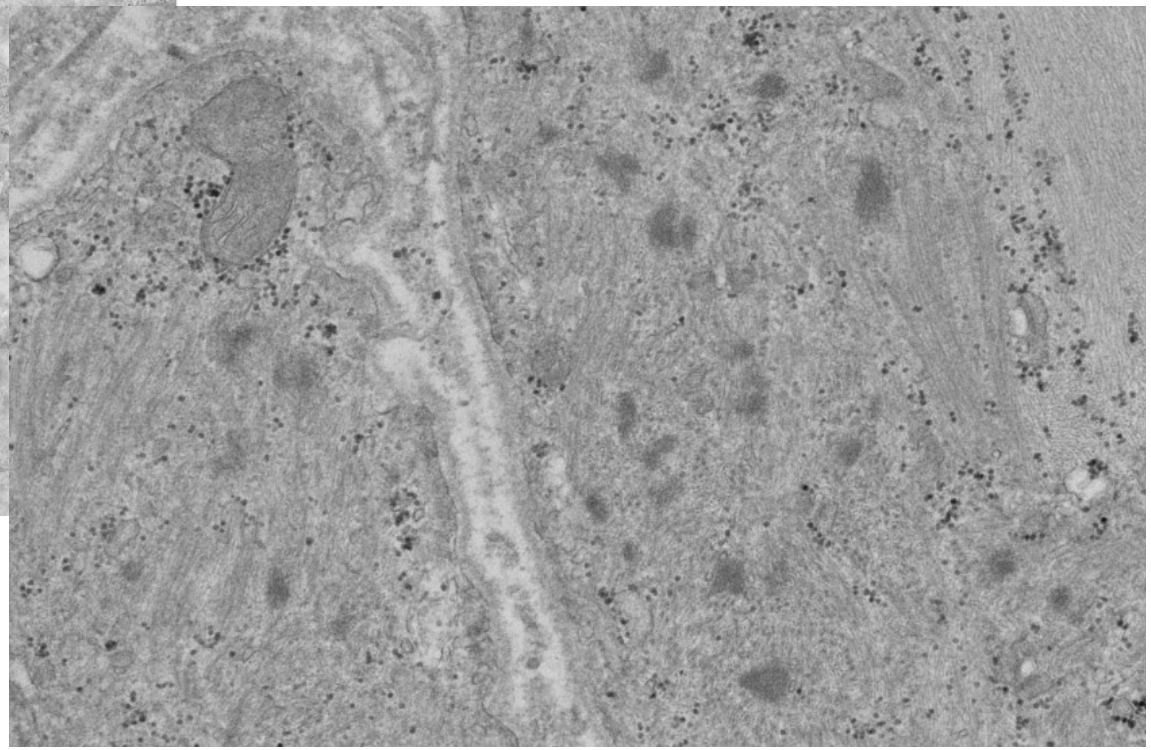




Milder case

- Term baby, no initial problems (questioned by GM, may have always been floppy, mom had some delays and gait changes)
- Hypotonic, FTT after febrile illness, CPK 199 at 2 months, hospitalized at 3 months
- Microarray with 9p24.3(592,076-694,567) x1 includes KANK
- PWS negative, DMPK repeats 10 and 12, SMN OK
- Biopsy done first
- p.G44C due to 130g>t in ACTA1 on WES, maternal





Similar light microscopy findings
Images courtesy of Murat Gokden MD

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Other causes of Nemaline Myopathy

- *NEB* (nebulin) 50% of NM. usually “typical congenital) can be associated with a severe neonatal presentation or in older patents with predominantly distal weakness.
- *TPM3* (slow α-tropomyosin) may have rods are restricted to type 1 slow muscle fibers, or fiber type disproportion alone
- *TPM2 (*beta-tropomyosin) usually mild dominant disease.
- *TNNT1* (low troponin T) common in Old Order Amish
- *CFL2* (muscle-specific cofilin) rare, only three families
- *KBTBD13* associated with slow voluntary movements and relative sparing of the facial and respiratory muscles.
- *KHLH40* rare cause of very severe neonatal phenotype similar to our case 1
- *KHL41* frameshift causes severe phenotype with neonatal death, missense with impaired motor function with survival into late childhood and/or early adulthood
- *LMOD3* (leiomodin 3) severe if frameshift, typical congenital otherwise

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Outcomes

- Case 1 – possible aspiration, pneumothoraces, required Servo vent, nitrous, sildanefil; agreed to withdraw support at nearly 5 months of age
- Case 2 – dysphagia improved, gait delayed but functional, has ongoing pulmonary care

References

- https://ghr.nlm.nih.gov/condition/fryns-syndrome#genes
- https://www.sciencedirect.com/topics/neuroscience/distal-spinal-muscular-atrophy-type-1
- https://ijponline.biomedcentral.com/articles/10.1186/s13052-017-0418-0
- https://bmcgenomics.biomedcentral.com/articles/10.1186/1471-2164-15-1090
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- https://www.ncbi.nlm.nih.gov/books/NBK1288/ re nemaline myopathy causes
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