A Newborn with Hypotonia and Weakness

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NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

History

- 41 weeks GA, induced vaginal delivery
- G2 mother, no reports of decreased fetal movements
- BW 3171g (39th%ile), HC 33.5cm (79th%ile)
- Apgars 3, 8 requiring PPV & CPAP
- Unable to feed by mouth or wean off ventilator

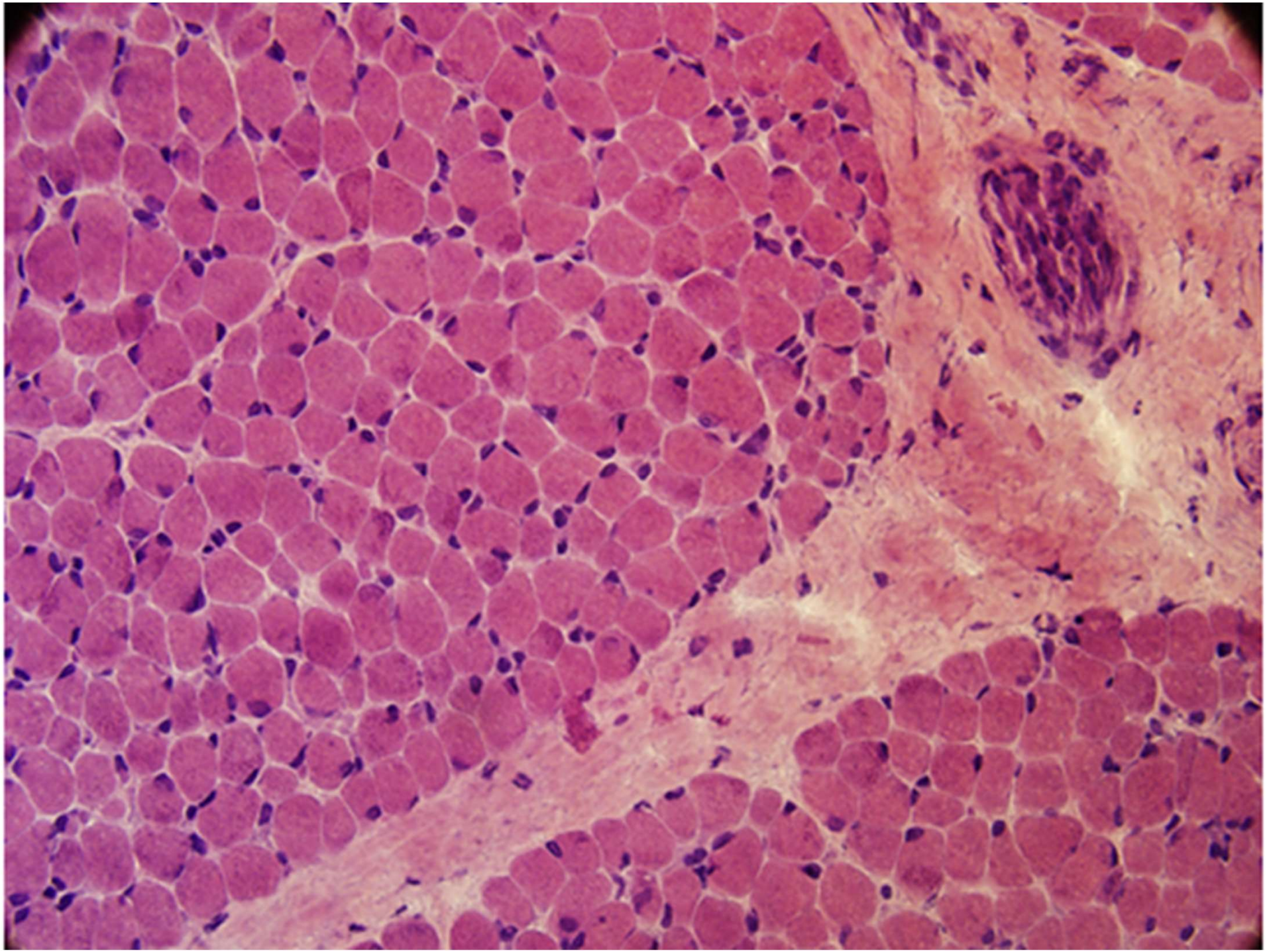
- Family: + consanguinity

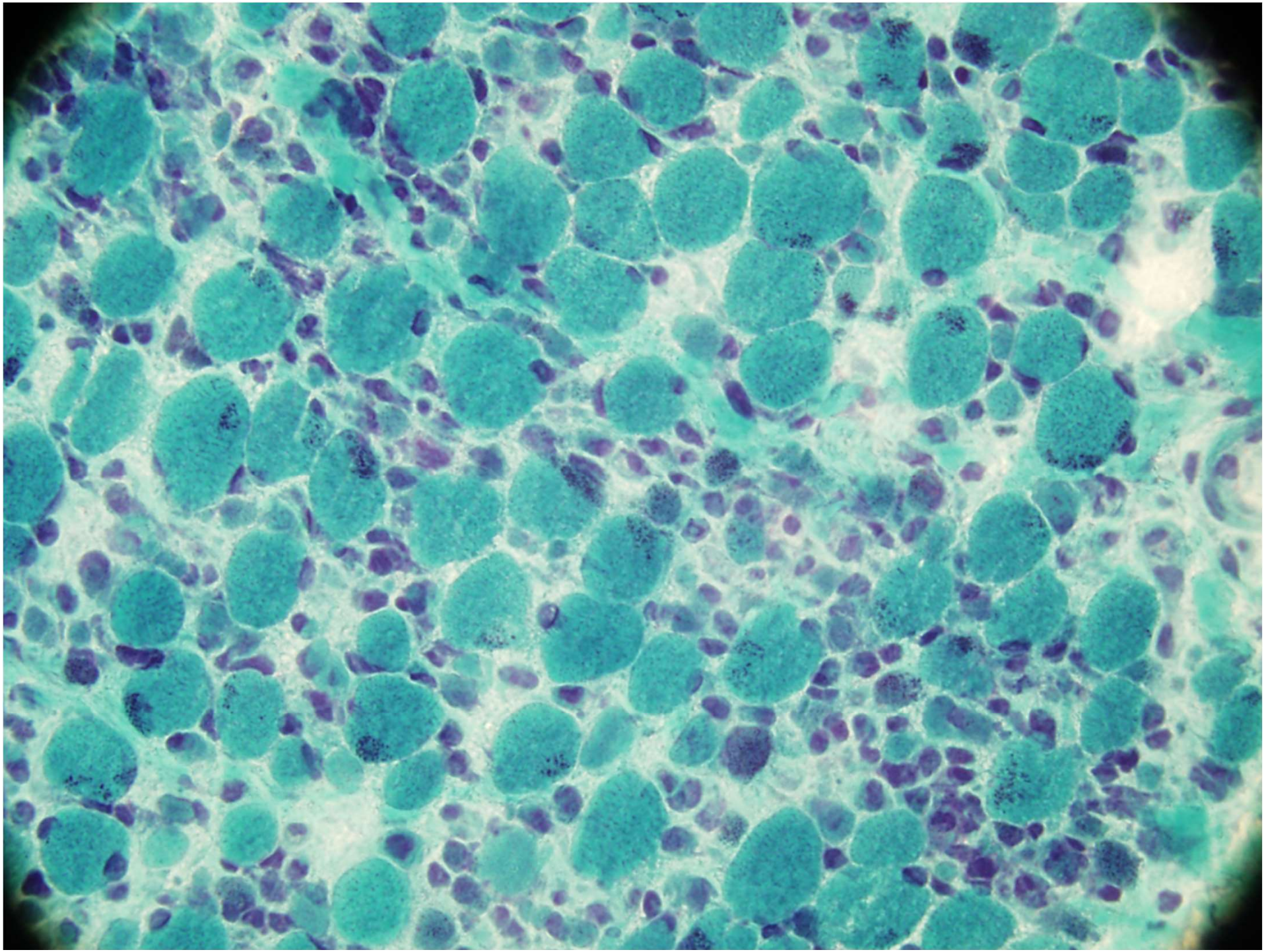
Physical Exam

- Slightly down slanting palpebral fissures
- Long fingers
- Dimpling at elbows
- Distal joint laxity, no contractures
- Undescended testes
- Bifacial weakness, poor suck, absent gag, hypotonia, weakness, areflexia
- No ophthalmoplegia

Diagnostic Process

- MRI Brain
  - Left posterior fossa extra-axial blood products
- SMA, Prader-Willi, microarray testing
  - Negative except region of homozygosity 3p22.3-3p21.33
- CK 220 --> 39
- EMG
  - NCVs, RNS, EMG within normal limits
- GeneDx Congenital Myopathy/Muscular Dystrophy panel
  - 22 genes, unrevealing *LAMA2* variant
- WES
- Left quadriceps Muscle Biopsy





WES

- c.931C>A, p.R311S
- homozygous variant in *KLHL40*
- located in the region of homozygosity noted on microarray

KLHL40

- Kelch like family member 40[1]
  - Chromosome 3p22.1
  - Contains BACK, BTB/POZ domains and 5 kelch repeats
  - Exact function unknown
    - Binds NEB and LMOD3
    - Essentially for maintenance of sarcomere/contractility

- Studies in zebrafish and mice have shown it is required for muscle development/function[1,2]

Nemaline Myopathy 8[2,3]

- Autosomal recessive inheritance
- In utero akinesia/hypokinesia
- Severe weakness
  - Respiratory failure 96%
  - Facial weakness 100%
  - Dysphagia 95%
  - Contractures 89%
- Average age of death 5 months

Nemaline Myopathy 8[4,5,6]

- c.1405G>T homozygous – locked in state
- c.1498C>T homozygous -- NG feeds, walks at 20 months
- C.604delG, c.1513G>C – response to mestinon

References

1. Garg et al. KLHL40 deficiency destabilizes the think filament proteins and promotes nemaline myopathy. J Clin Invest 2014; 124(8):3529-39.

2. Ravenscroft et al. Mutations in *KLHL40* are a frequent cause of severe autosomal-recessive nemaline myopathy. Am J Hum Genet 2013; 93:6-18.

3. Colombo et al. Congenital myopathies: Natural history of a large cohort. Neurol. 2015; 84:28-35.

4. Kawase et al. Nemaline myopathy with *KLHL40* mutation presenting as congenital totally locked-in state. Brain Devel 2015; 37:887-90.

5. Seferian et al. Mild clinical presentation in *KLHL40*-related nemaline myopathy. Neuromuscul Disord 2016; 26:712-6.

6. Natera-de Benito et al. KLHL40-related nemaline myopathy with a sustained positive response to treatment with acetylcholinesterase inhibitors. J Neurol 2016; 263:517-23.