A Newborn with Hypotonia and Weakness

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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 8,3

- 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 84,5,6

- 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