2022 AANP DIAGNOSTIC SLIDE SESSION CASE 5

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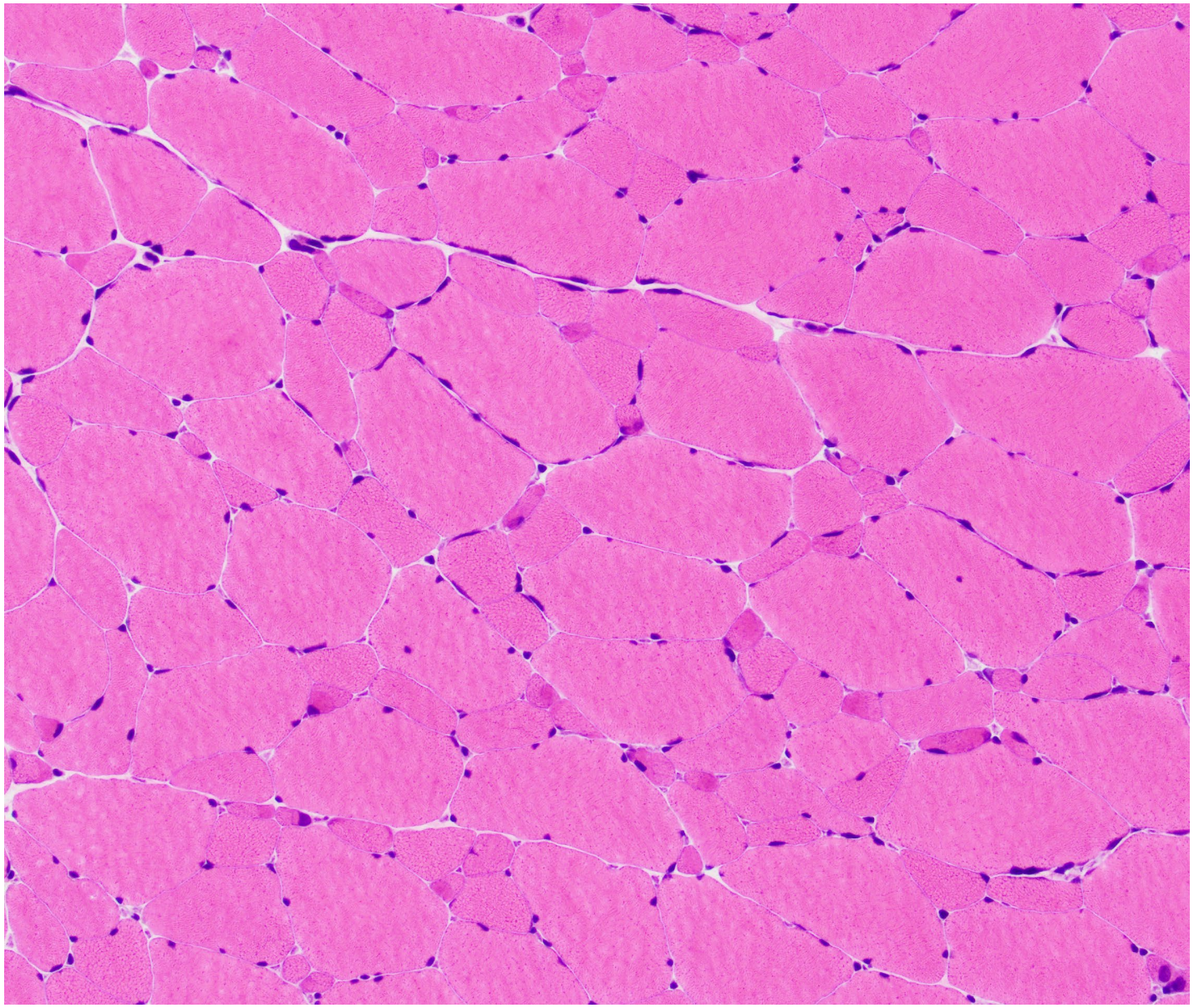
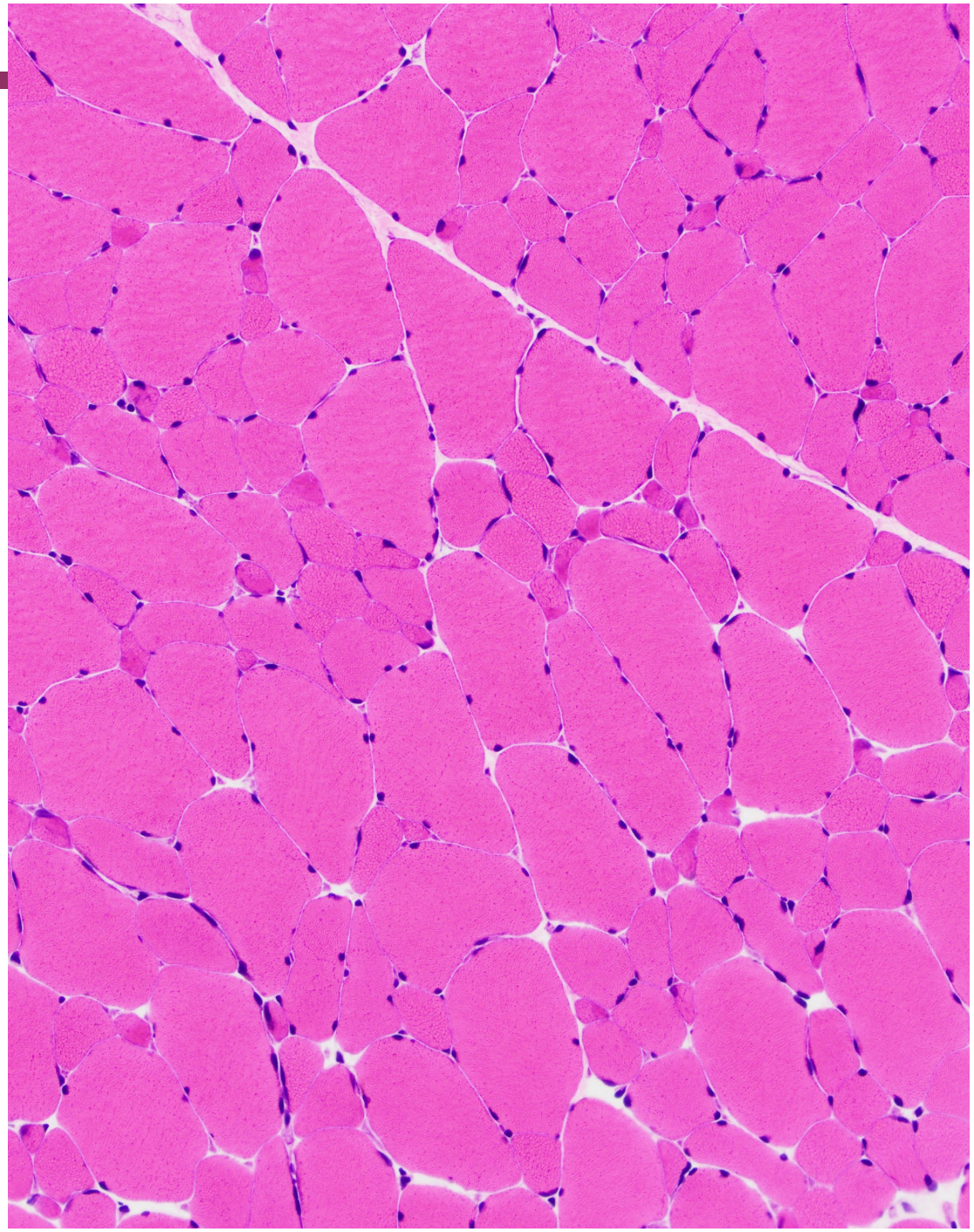
CLINICAL PRESENTATION

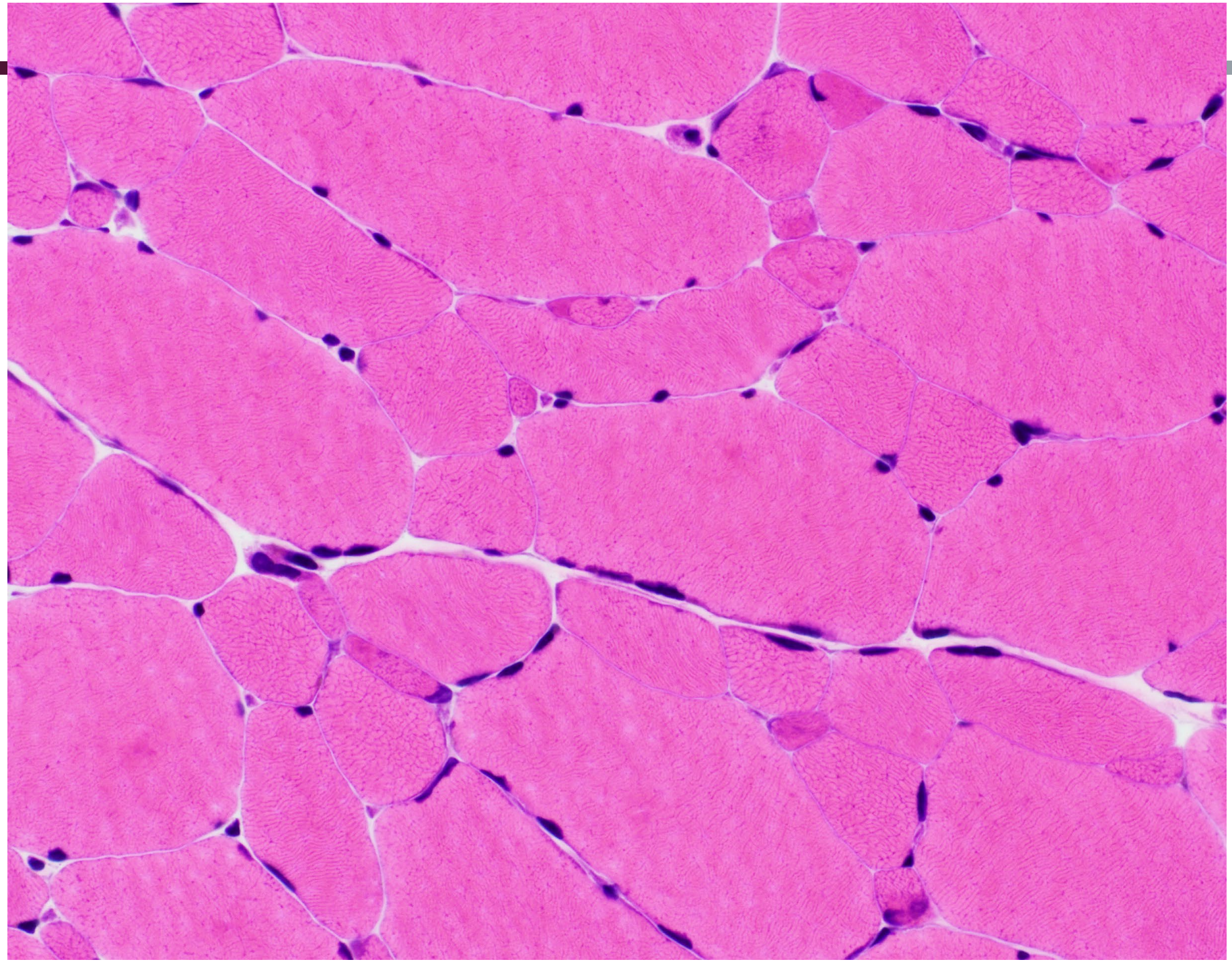
- 60-year-old woman
- Admitted to the hospital with severe generalized weakness and progressive dyspnea leading to acute respiratory failure requiring intubation
- History of delayed motor milestones and scoliosis since childhood
- Physical exam
  - Facial and neck flexor weakness
  - Limb weakness: proximal in the upper limbs and both proximal and distal in the lower limbs
  - Pes cavus
  - Contractures of wrists and ankles
- EMG showed evidence of a severe diffuse myopathy with fibrillation potentials only in the vastus medialis
- CK value was normal
- Left biceps muscle biopsy performed

- H&E





- H&E

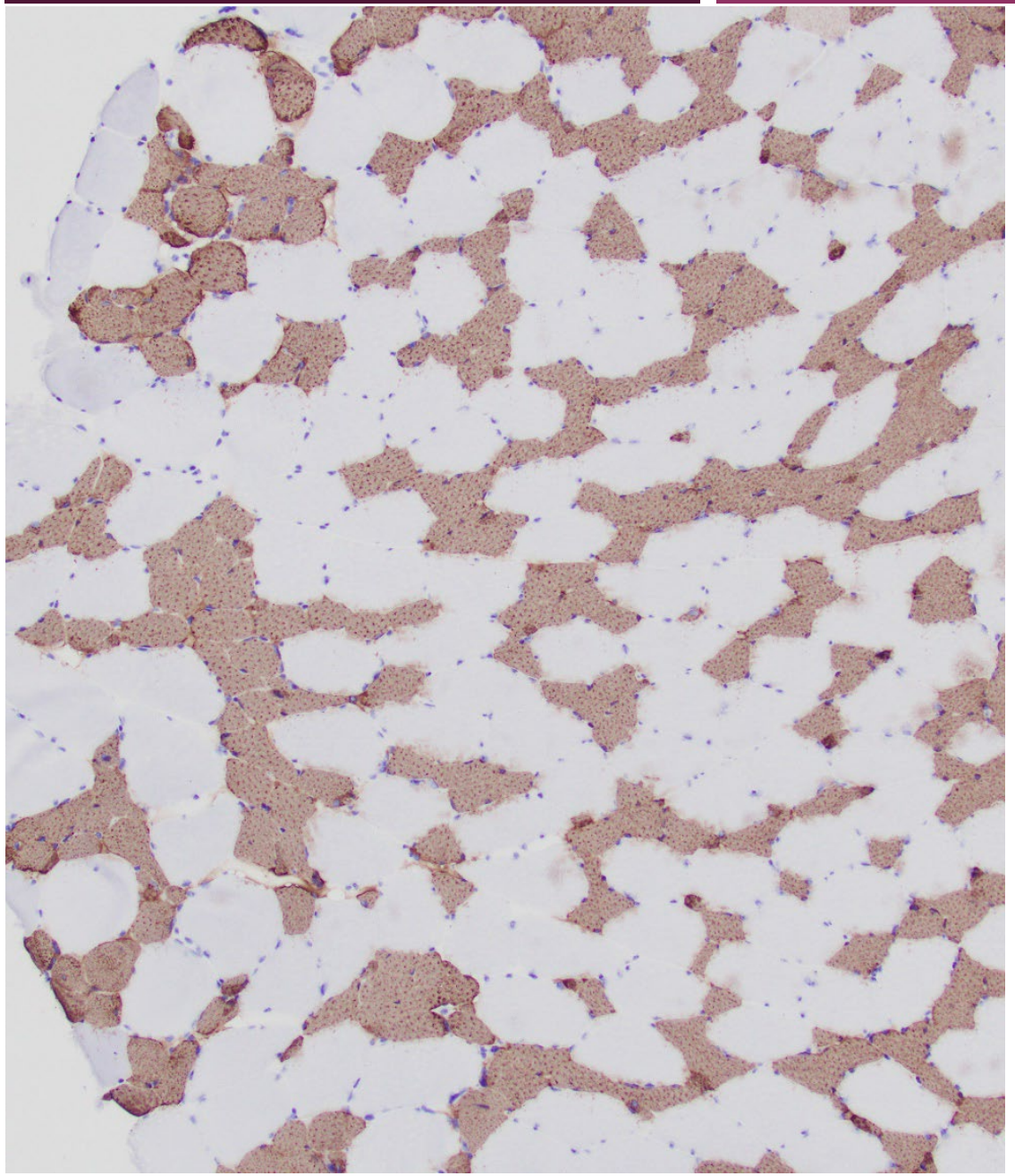


DISCUSSION

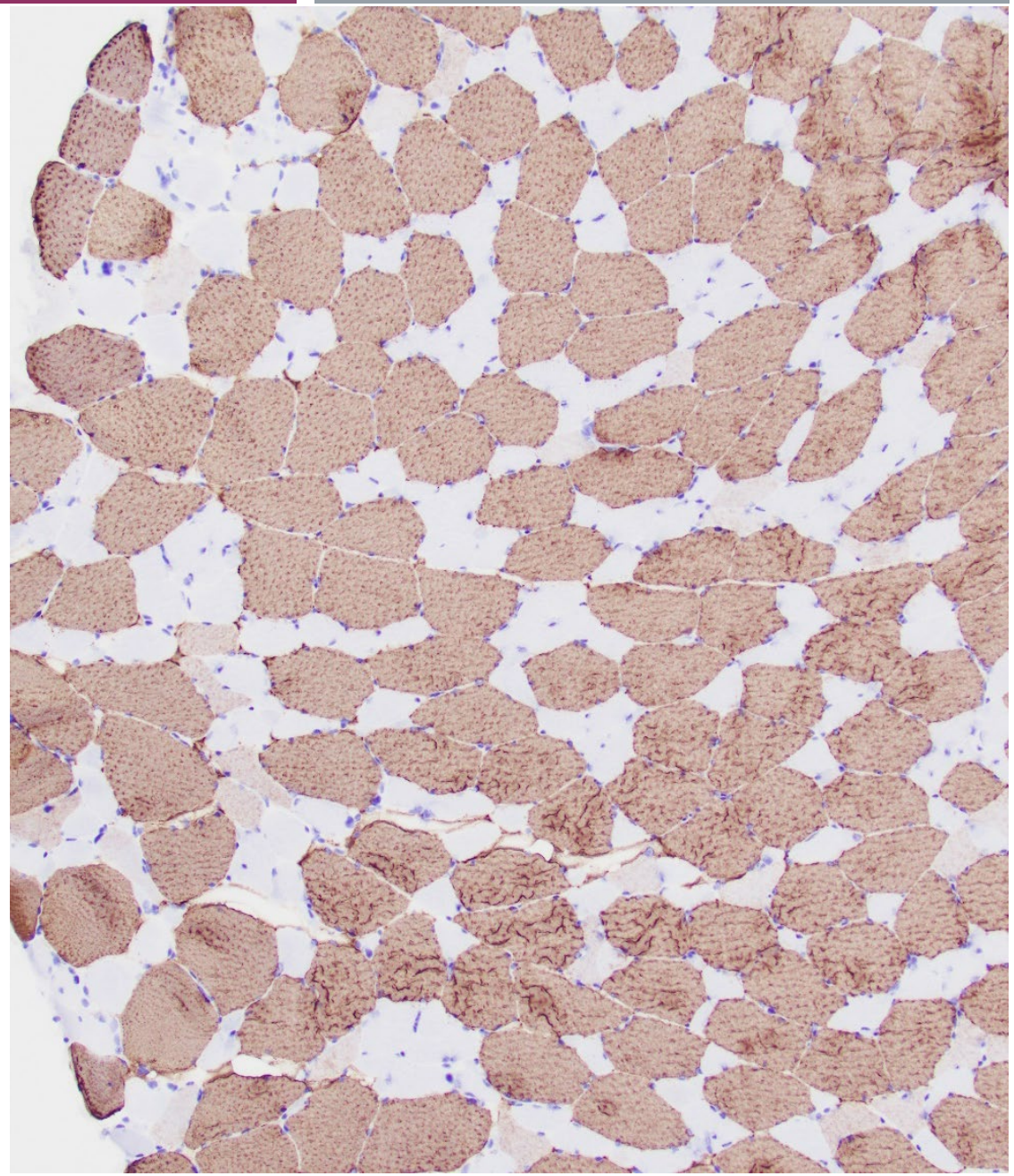
DIFFERENTIAL DIAGNOSIS?

ADDITIONAL STUDIES?

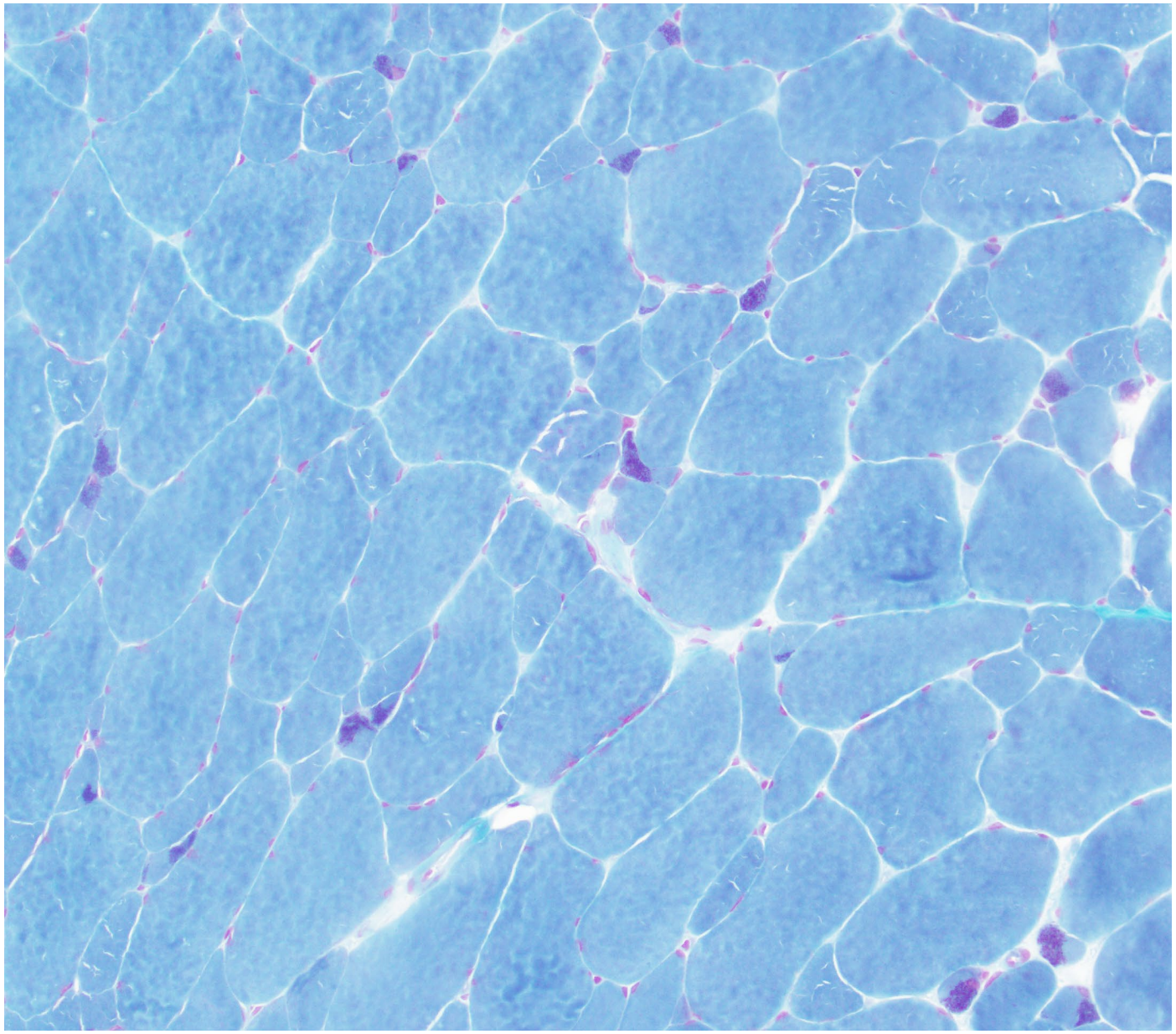
- Slow myosin (type 1 fibers)

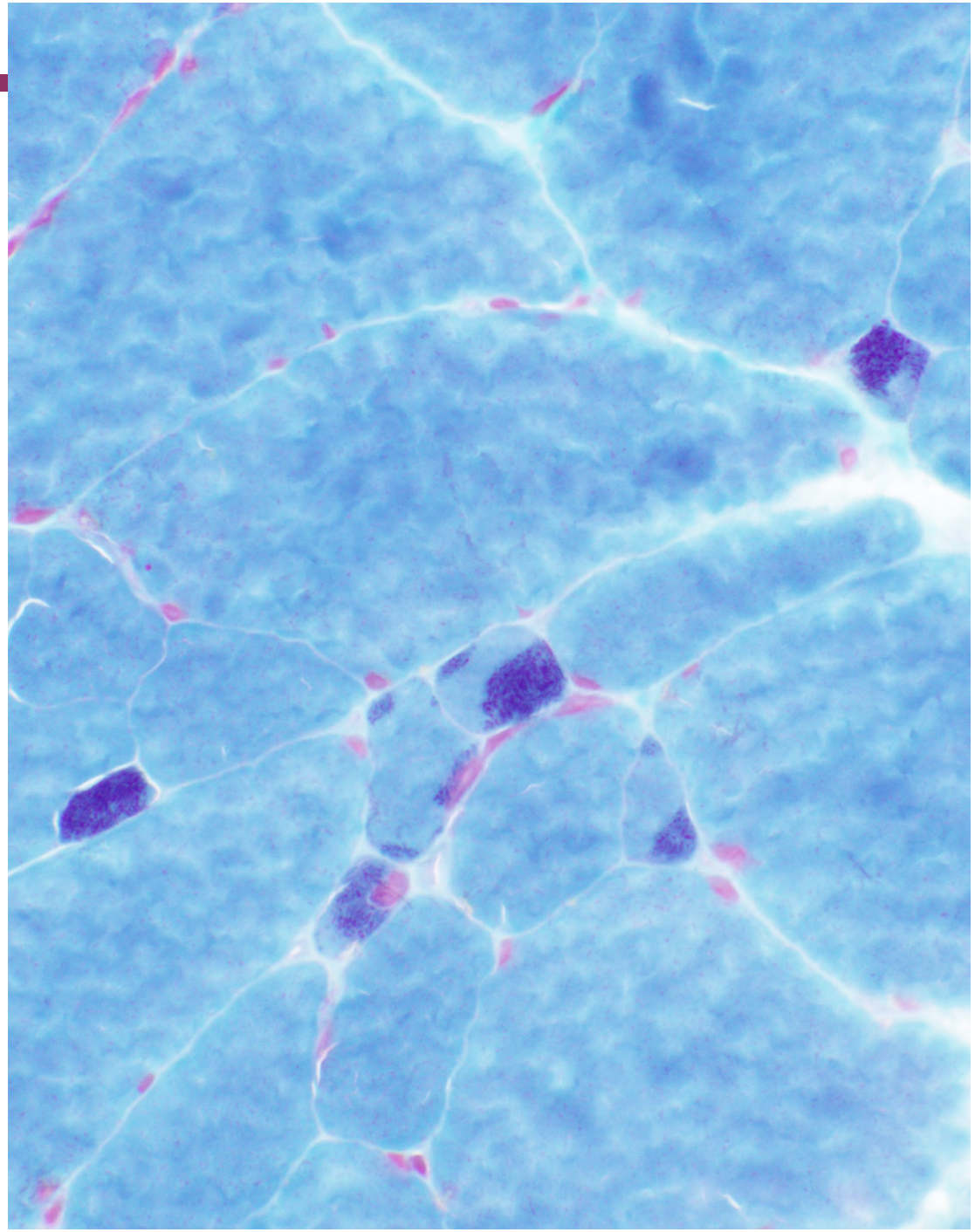


- Fast myosin (type 2 fibers)

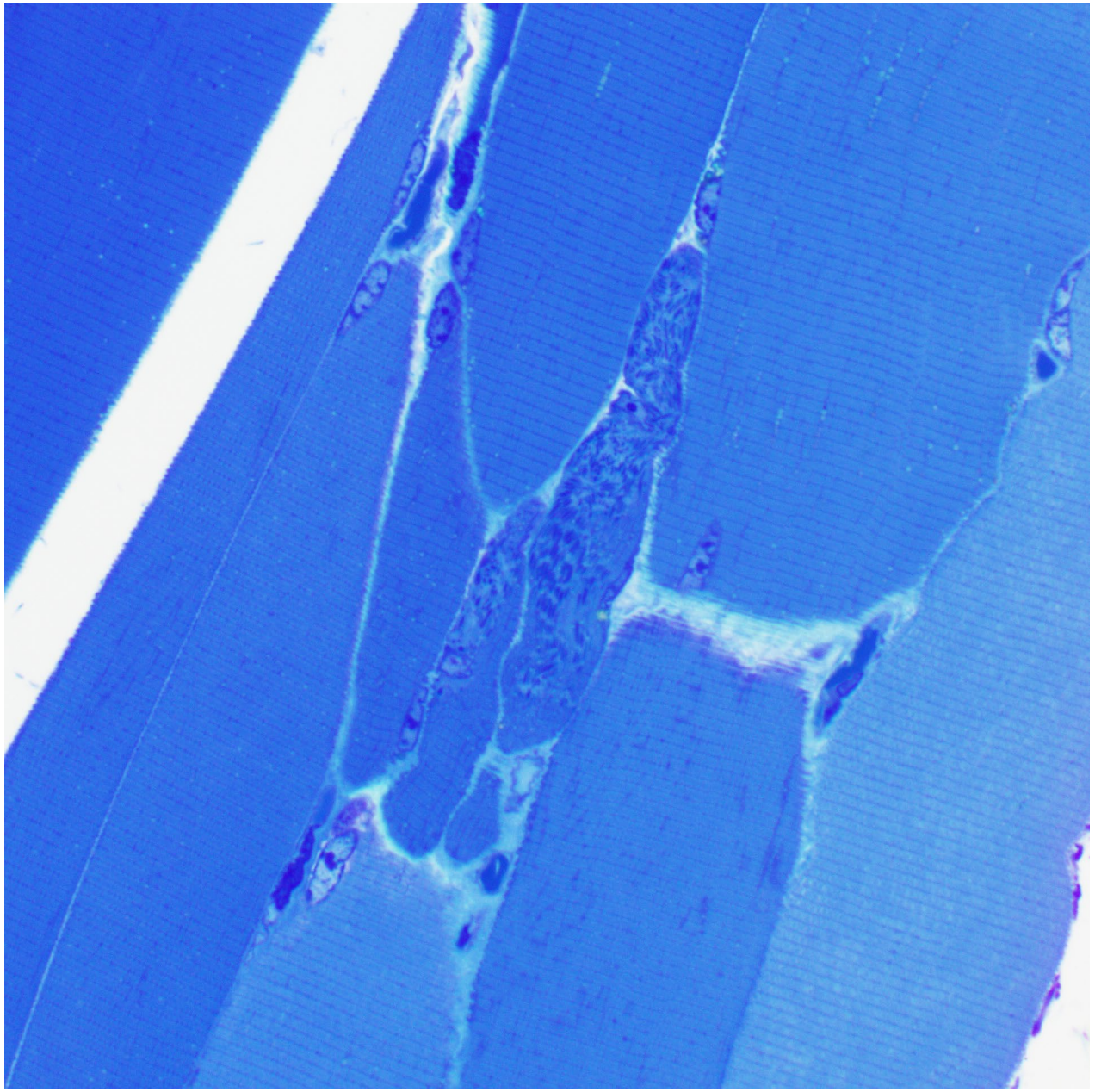


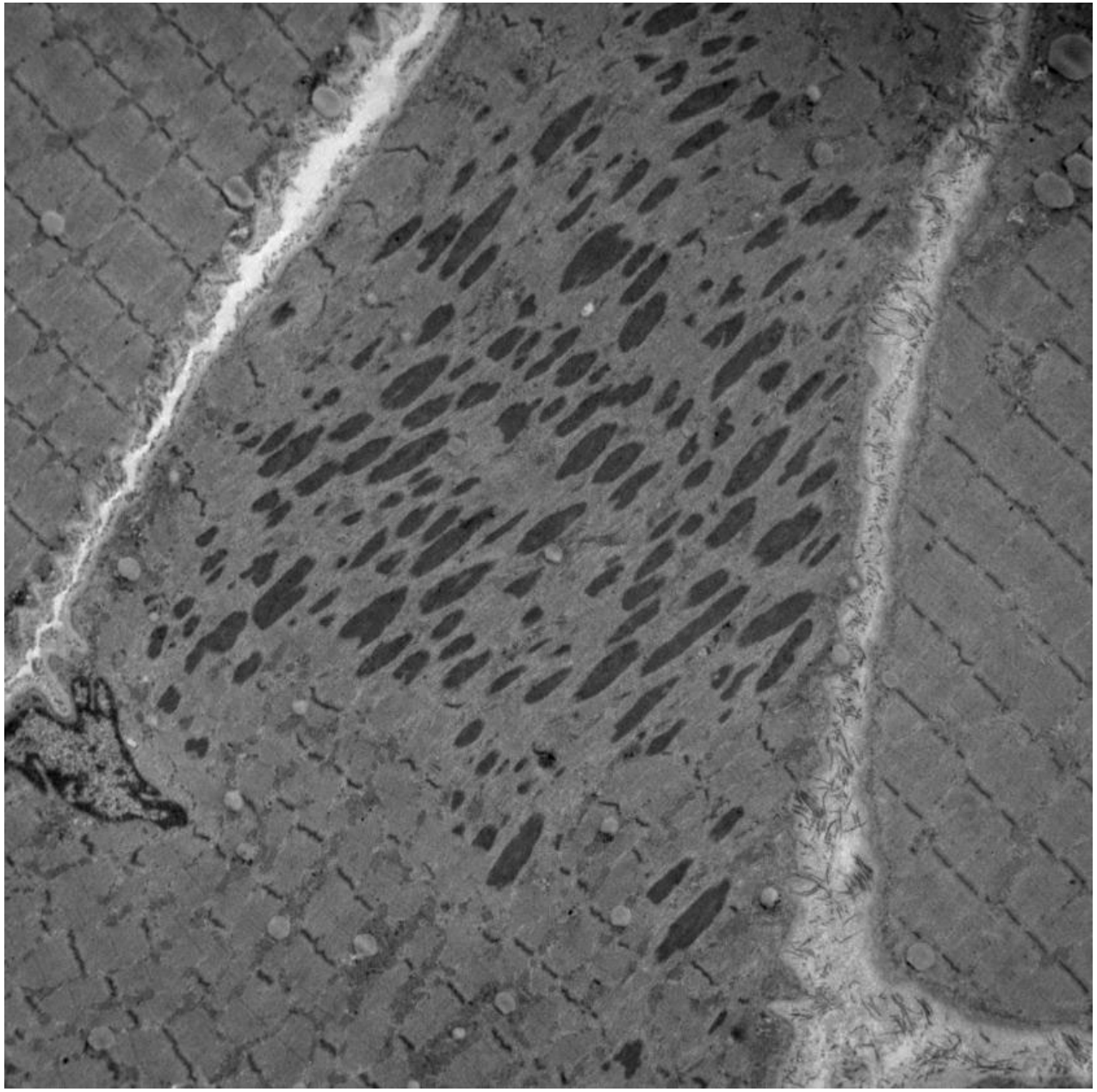
- **Modified Gomori Trichrome**



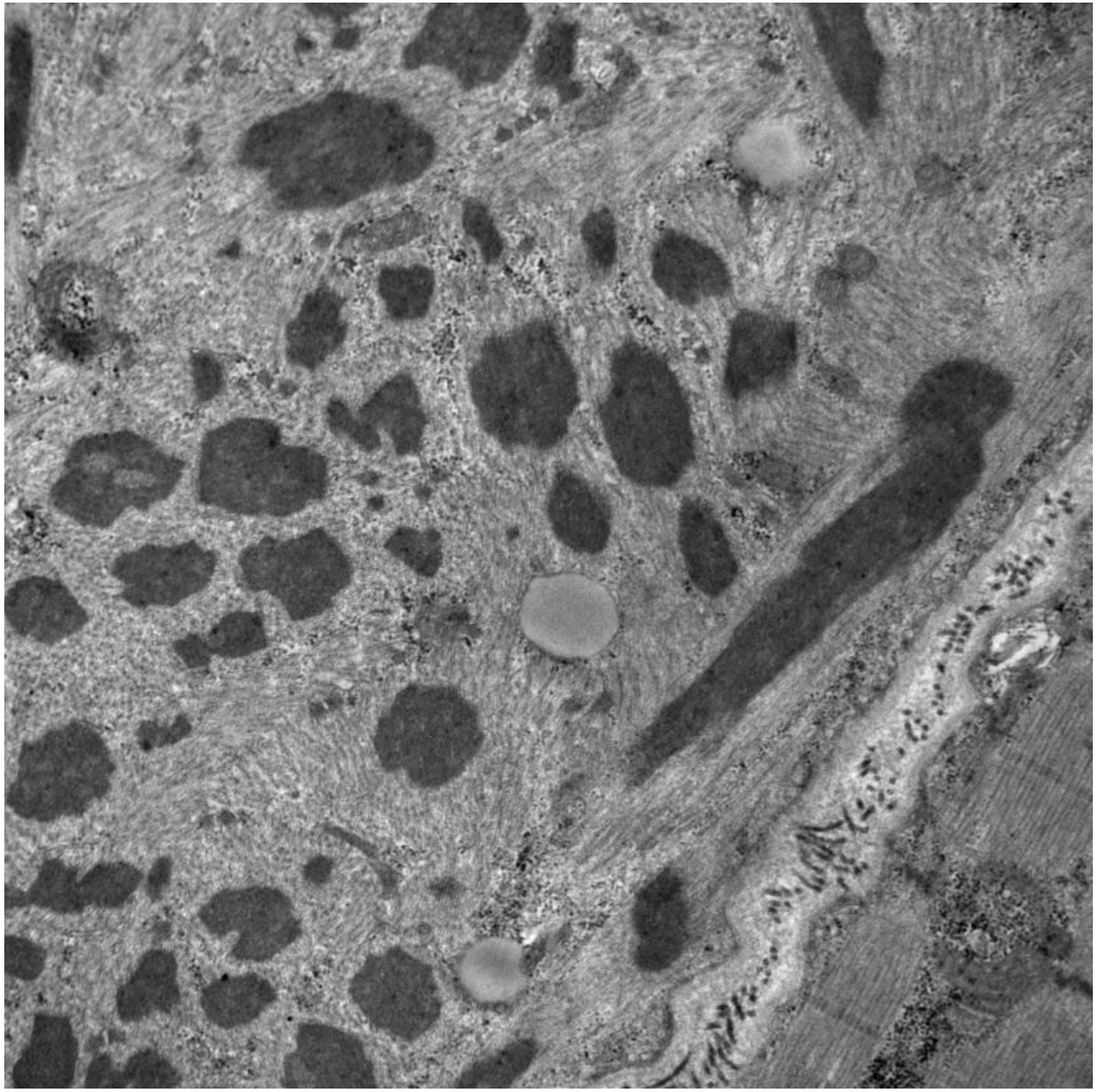


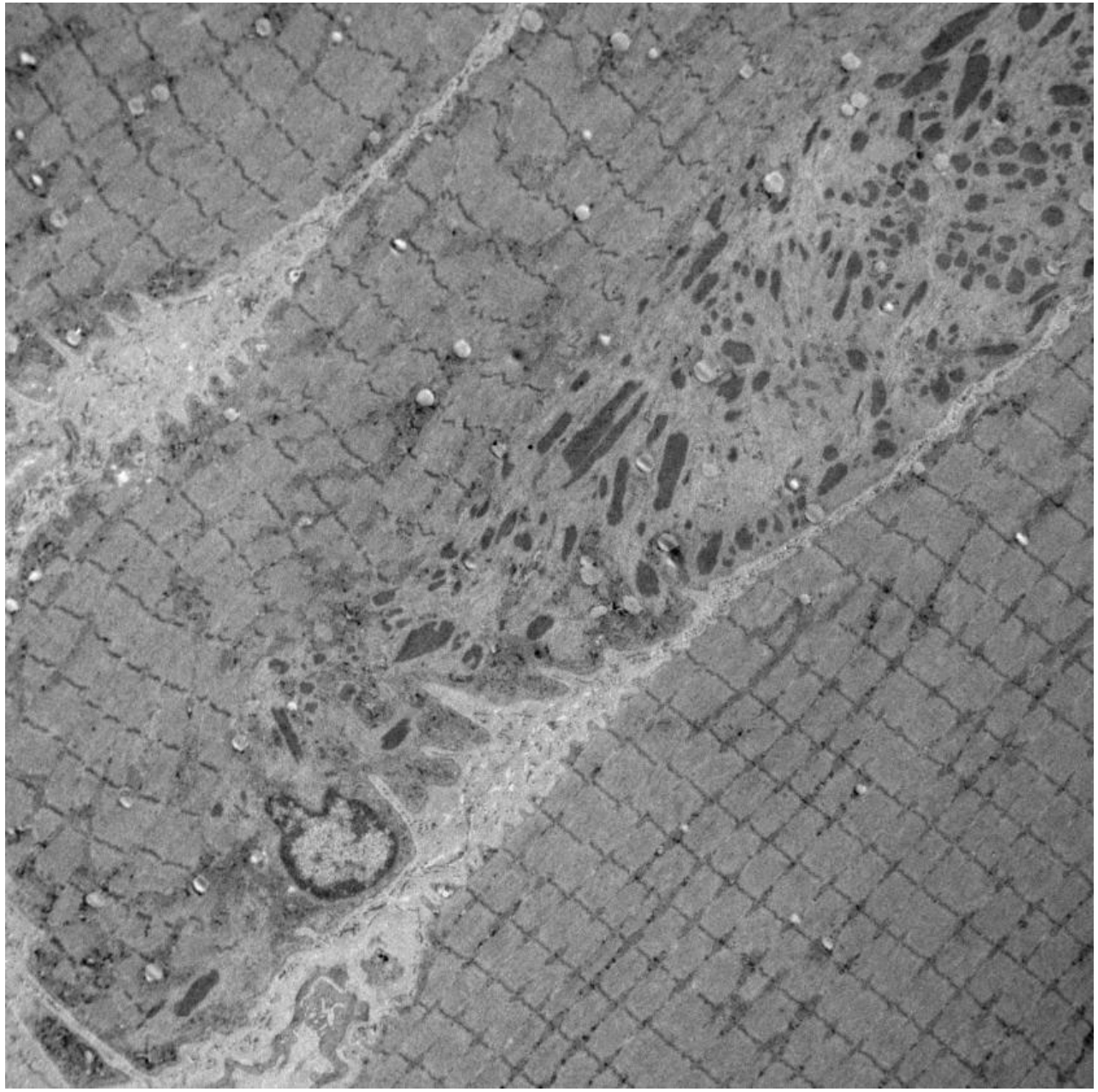
- Toluidine blue, Epon thick sections
- Electron microscopy





Electron microscopy





ADDITIONAL HISTORY

- Genetic testing performed after the muscle biopsy identified a heterozygous pathogenic missense variant in *TPM3*

DIAGNOSIS

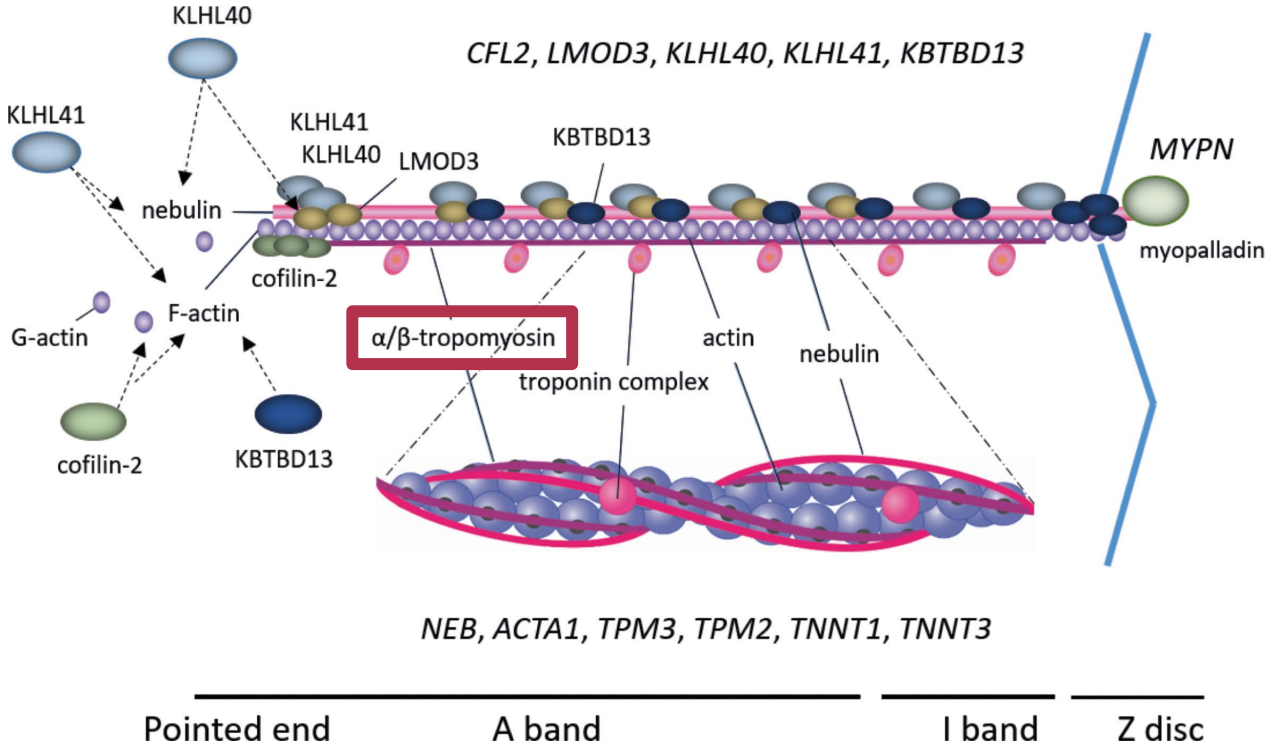
- **Congenital nemaline myopathy due to pathogenic missense variant in *TPM3***

CONGENITAL NEMALINE MYOPATHY

- One of the most common forms of congenital myopathy
  - Most common presentations: typical (infantile) and severe (neonatal) onset
- Typical/infantile onset presents with hypotonia, muscle hypotrophy, and generalized weakness of neck flexors and proximal limb muscles in infancy
  - Muscle weakness causes feeding and breathing difficulties
  - Disease course is typically mildly progressive or non-progressive
- Severe/neonatal onset presents in utero or at birth with inability to move or breathe
  - Also presents with joint contractures and fractures
- Mild onset is a less common presentation and presents in childhood or adulthood
  - Adult presentation must be distinguished from HIV-associated or sporadic late onset nemaline myopathy (SLONM)

CONGENITAL NEMALINE MYOPATHY

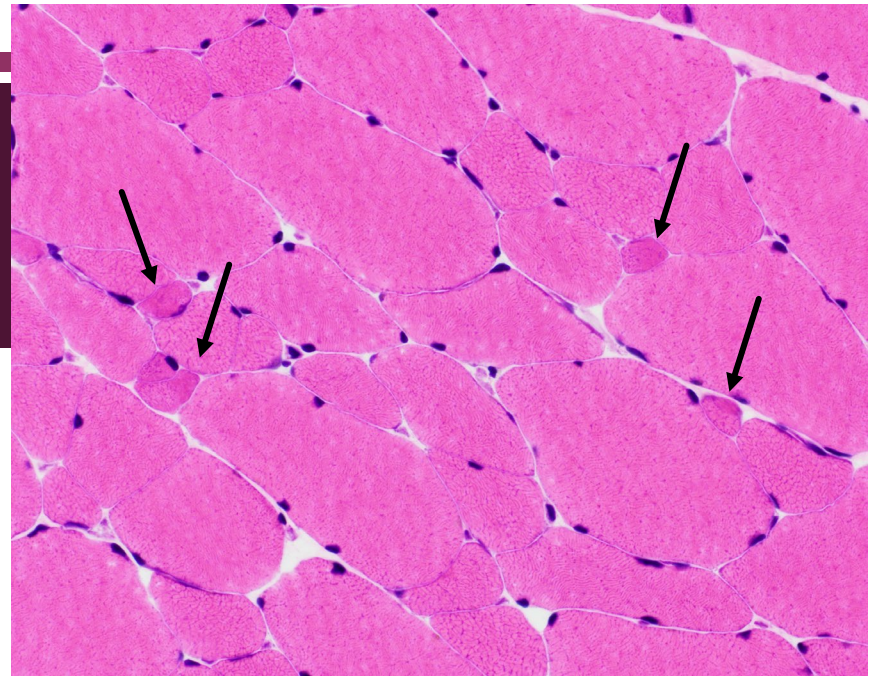
- Pathogenic variants in 12 genes identified as causes of nemaline myopathy
  - Involved with formation and regulation of the thin filament in the sarcomere
- *NEB* (nebulin) and *ACTA1* (skeletal muscle alpha actin) are most commonly mutated genes
  - Other structural genes: *TPM3* (alpha tropomyosin), *TPM2* (beta tropomyosin), *MYPN* (myopalladin), *TNNT1* (troponin T1), and *TNNT3* (troponin T3)
  - Regulatory genes: *KLHL40, KLHL41, LMOD3, KBTBD13,* and *CFL2*

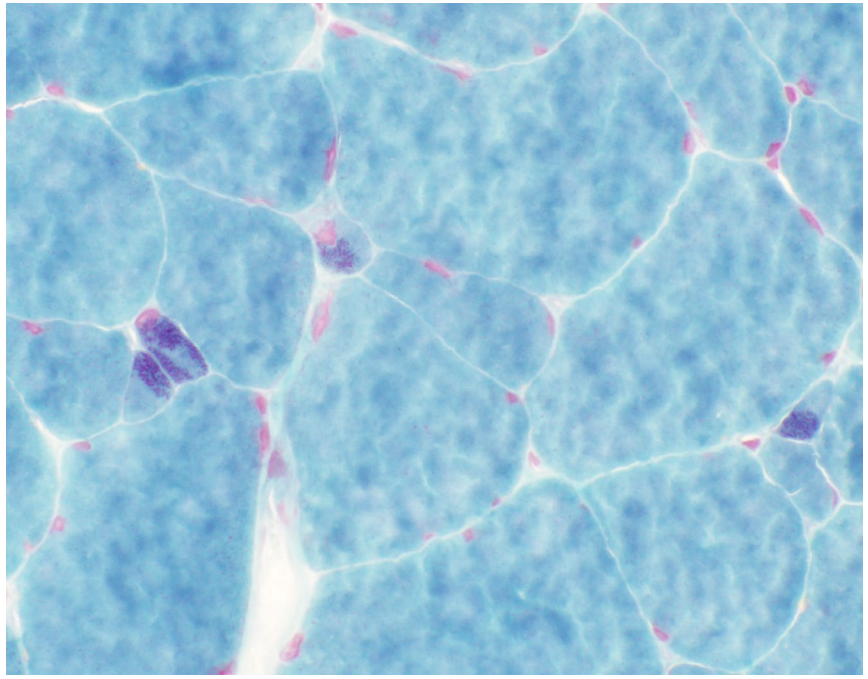


Laitila J, Wallgren-Pettersson C. Recent advances in nemaline myopathy. Neuromuscul Disord. 2021 Oct;31(10):955-967. PMID: 34561123.

CONGENITAL NEMALINE MYOPATHY

- Histopathologic examination demonstrates nemaline rods aggregating in the cytoplasm
  - Rods commonly directly beneath the sarcolemma
  - Intranuclear rods less common
  - May have cap-like appearance on H&E stain
  - Rods most frequently aggregate in type 1 fibers
  - Presence in type 1 and type 2 fibers suggest pathogenic variants in *NEB* or *TNNT3*
- Rods appear red/purple on modified Gomori trichrome stain
- They immunoreact for alpha-actinin
- Electron microscopy demonstrates electron dense rods or ovoid structures in parallel with longitudinal sarcomeres with internal honeycomb structure





TPM3-RELATED NEMALINE MYOPATHY

- *TPM3* encodes alpha-tropomyosin
  - Expressed in skeletal muscle, but only type 1 fibers
  - Involved in actin filament coating and reveal of myosin binding sites
- *TPM3* pathogenic variants can cause autosomal dominant or more rarely autosomal recessive congenital myopathy
- *TPM3*-related congenital myopathy can lead to nemaline myopathy, cap myopathy, congenital fiber type disproportion or have overlapping pathologic features
- <10% of nemaline myopathy cases are due to pathogenic variants in *TPM3* or *TPM2*
  - *TPM3* pathogenic variants have been identified in both severe/neonatal onset and mild/childhood onset types

ACQUIRED NEMALINE MYOPATHY

- Associated with underlying monoclonal protein (SLONM) or HIV infection
- Most common presentation is dyspnea, proximal limb and axial muscle weakness, and muscle atrophy
- Progression to respiratory failure is a common cause of death
- Muscle biopsy demonstrates nemaline rods filling atrophic type 1 and 2 fibers without a type 1 fiber predominance
- Inflammatory component consisting of macrophages, T-lymphocytes, and MHC Class I expression on the sarcolemma has been observed in some SLONM cases
- Important to distinguish from congenital nemaline myopathy as SLONM has treatment options, including IVIg, chemotherapy, and autologous stem cell transplant

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