Diagnostic Slide Session: Case 2024-7 100th Annual Meeting of the American Association of Neuropathologists

Submitted by:

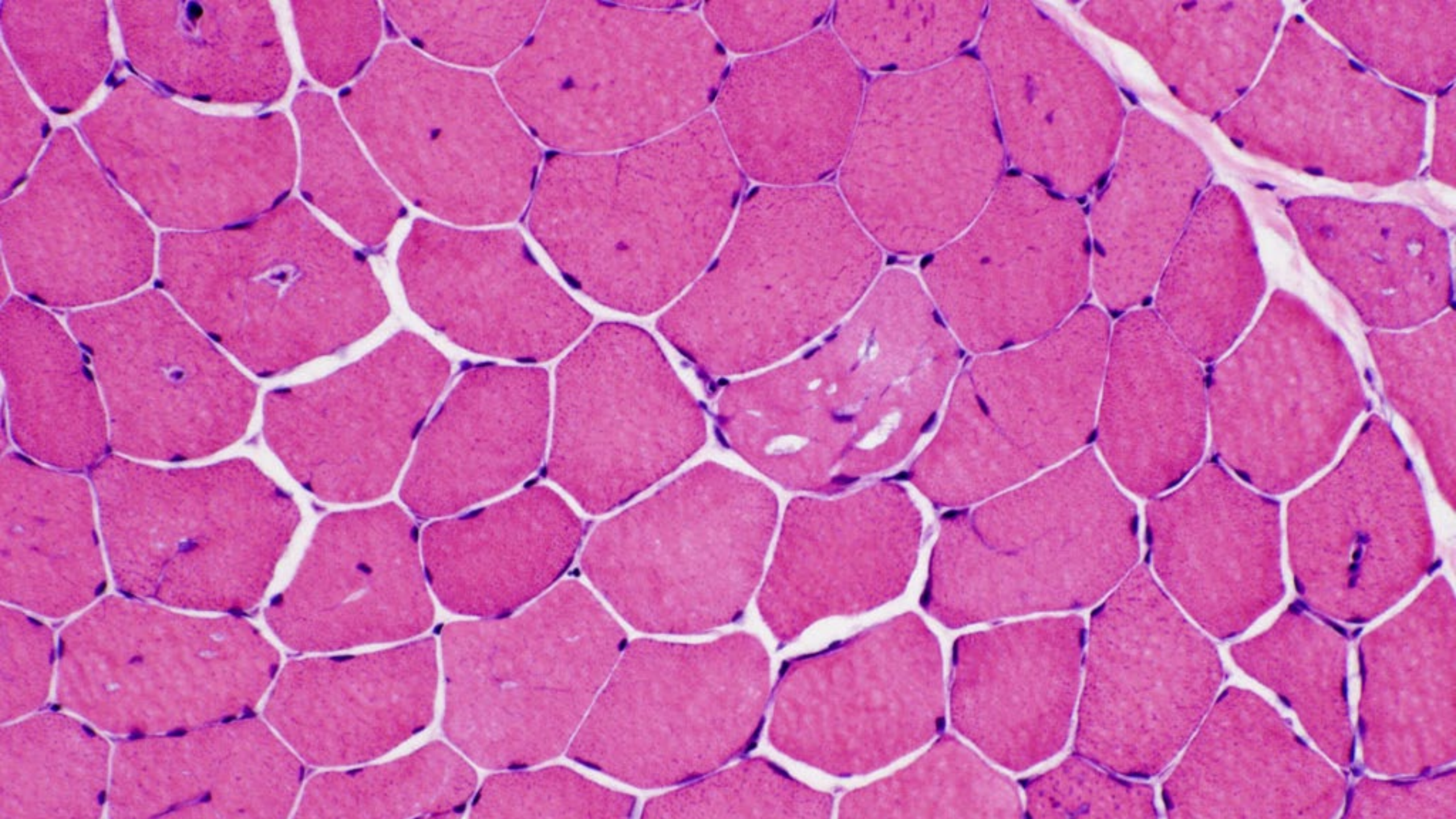
Jane E. Persons, MD, PhD[1]; Kathryn L. Eschbacher, MD[1]; Thomas L. Winder, PhD[1]; Rodney D. McComb, MD[2]; Steven A. Moore, MD, PhD[1]

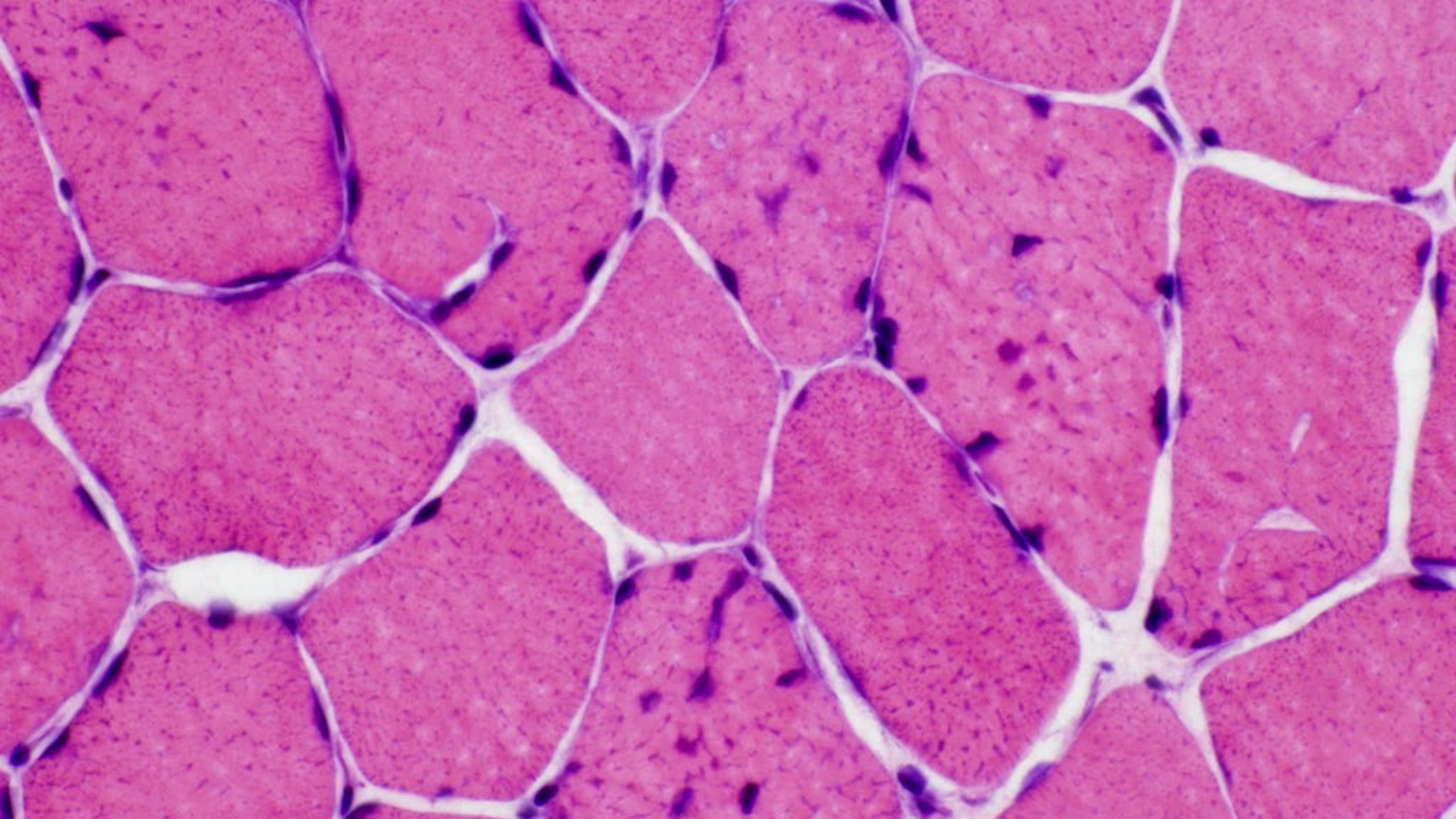
[1]University of Iowa Hospitals and Clinics, Iowa City, IA

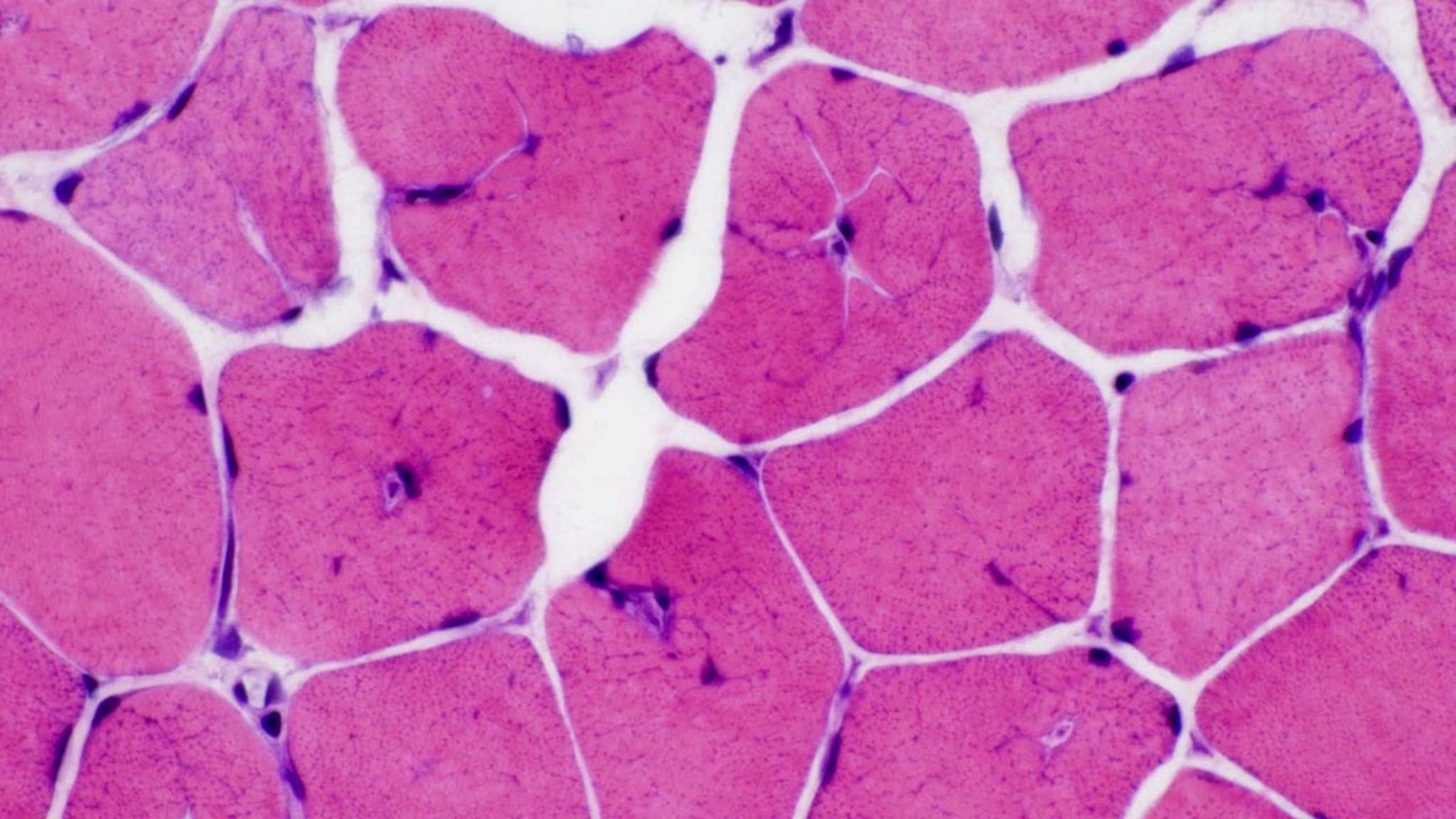
[2]University of Nebraska Medical Center, Omaha, NE

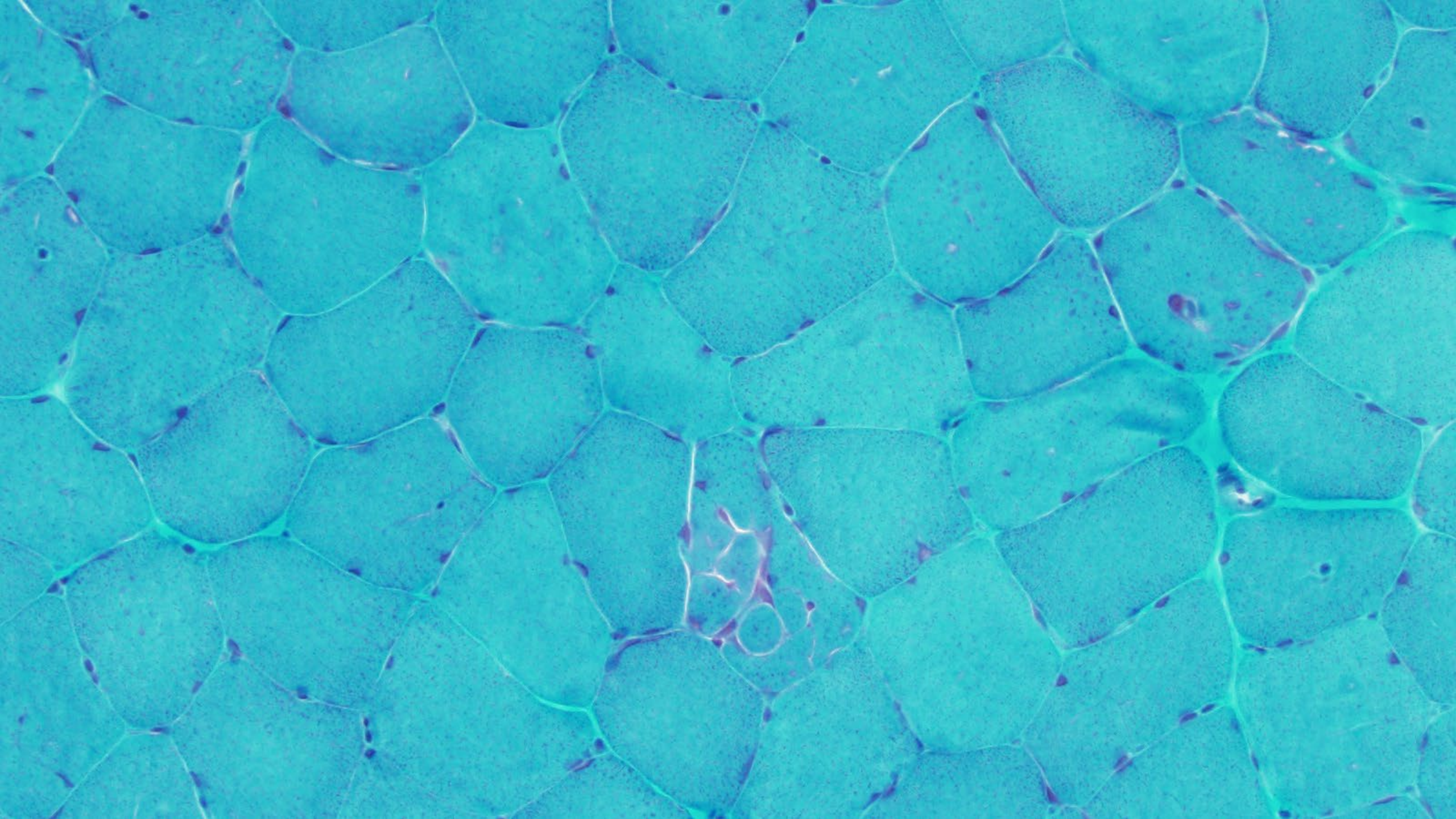
Clinical Summary

- 16-year-old male who initially presented with hypertrophic cardiomyopathy requiring heart transplant
- Two months following heart transplant developed proximal weakness and elevated creatine kinase (2945 U/L)
- Weakness initially interpreted as steroid myopathy → prednisone was stopped
- Persistent weakness and elevated CK prompted muscle biopsy





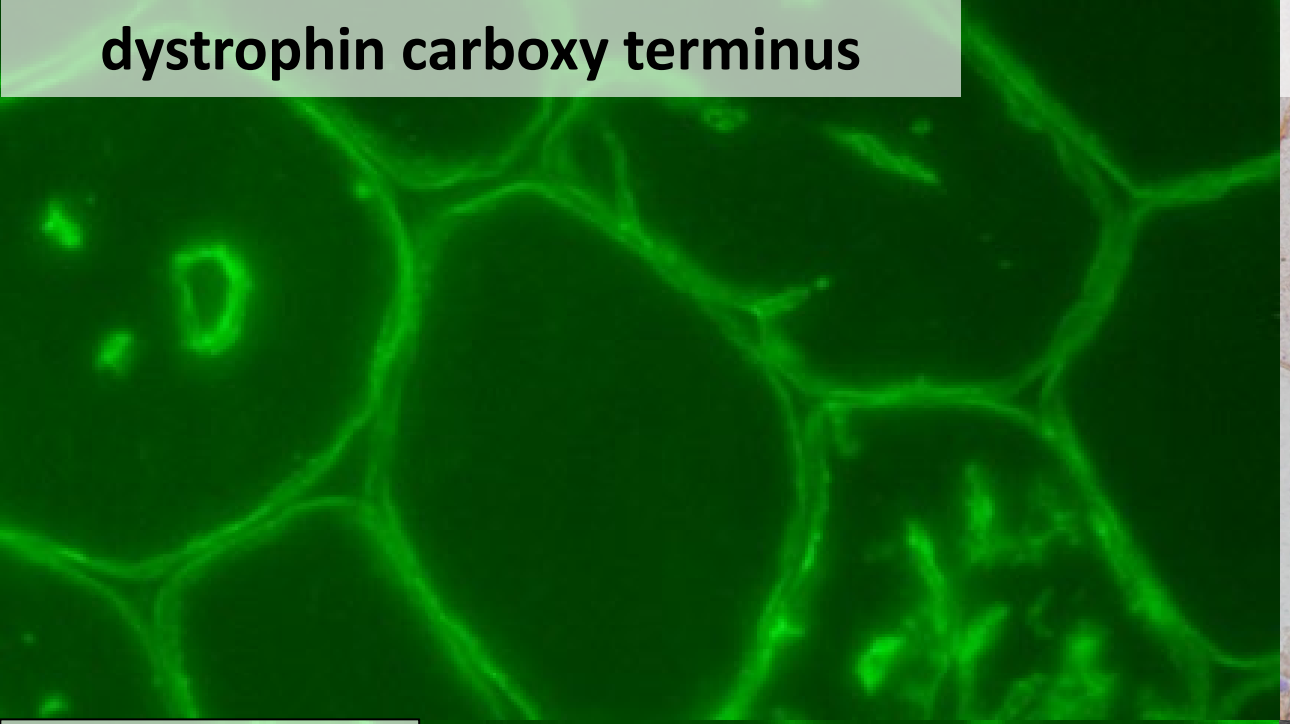


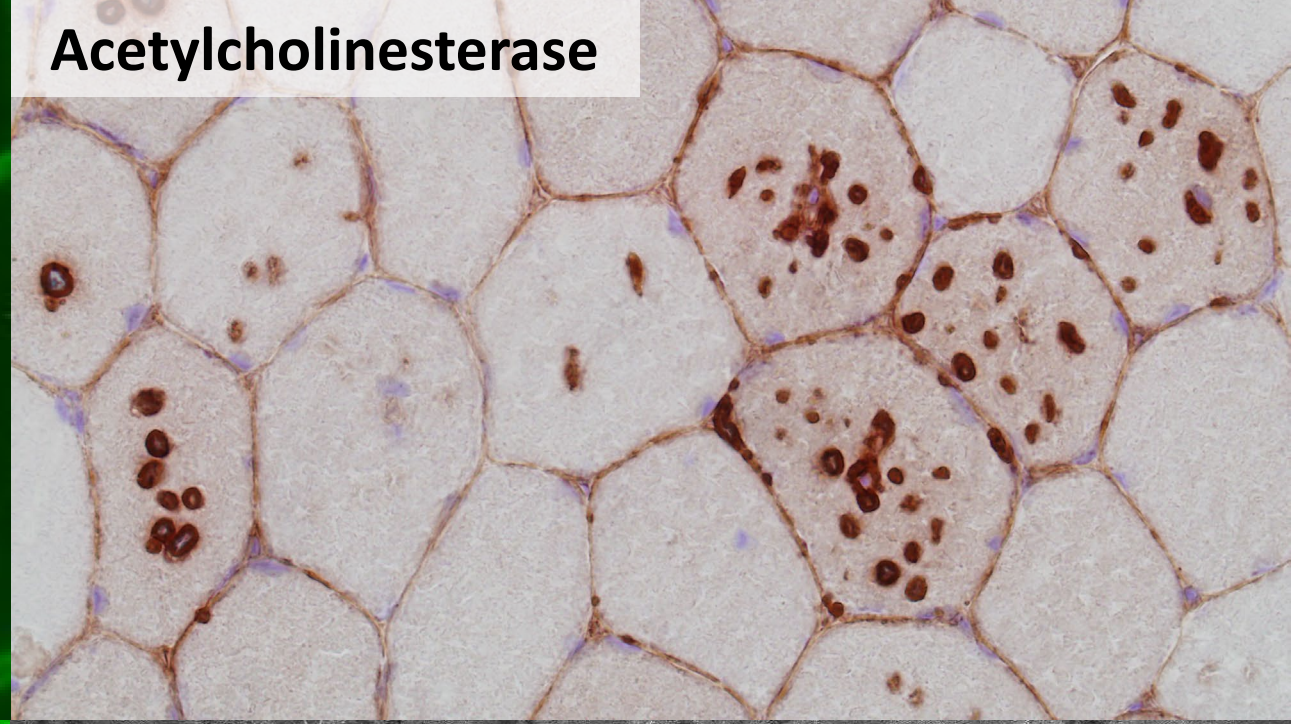


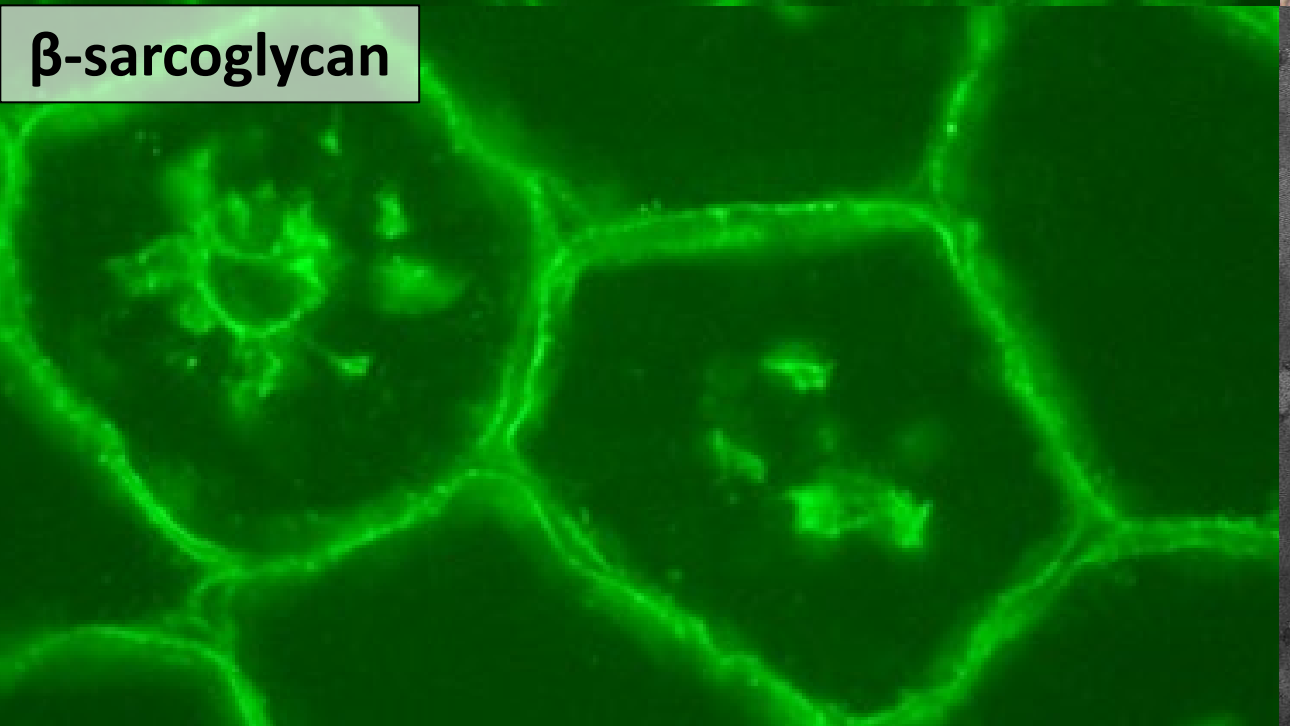
Diagnosis?

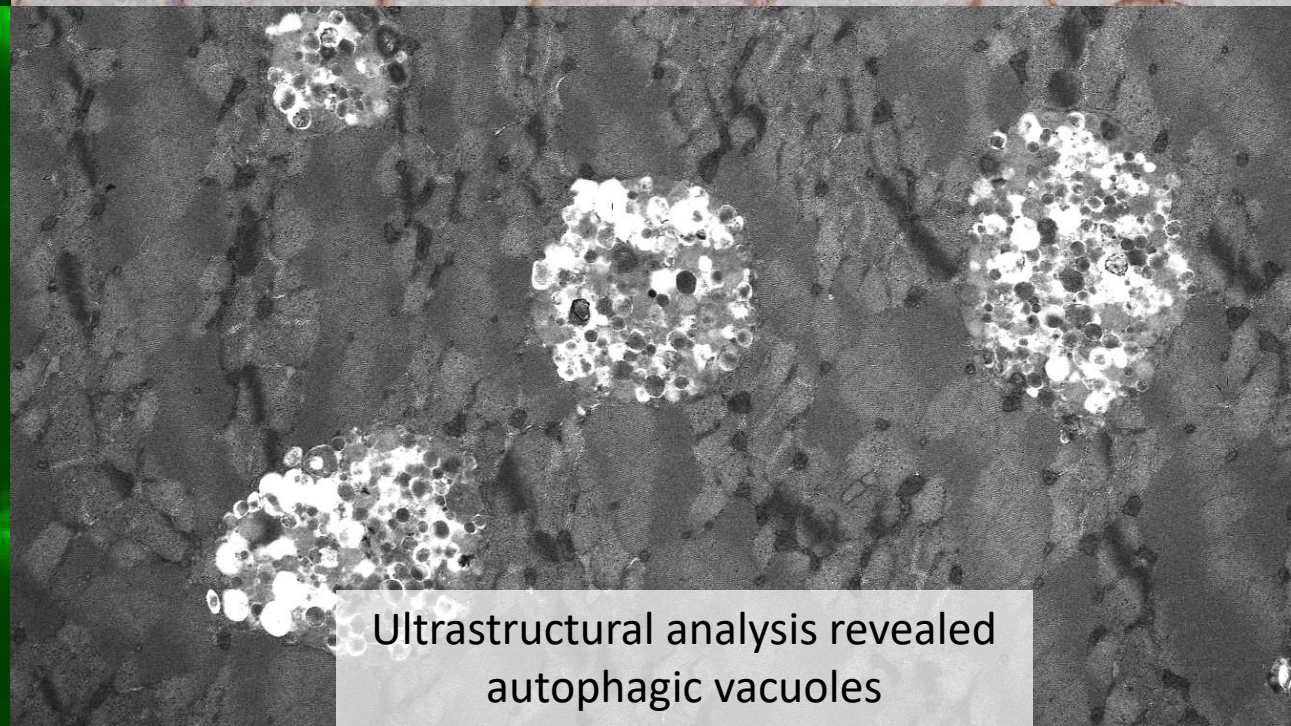
Clinical Differential Diagnosis:
Proximal Muscle Weakness with Cardiomyopathy

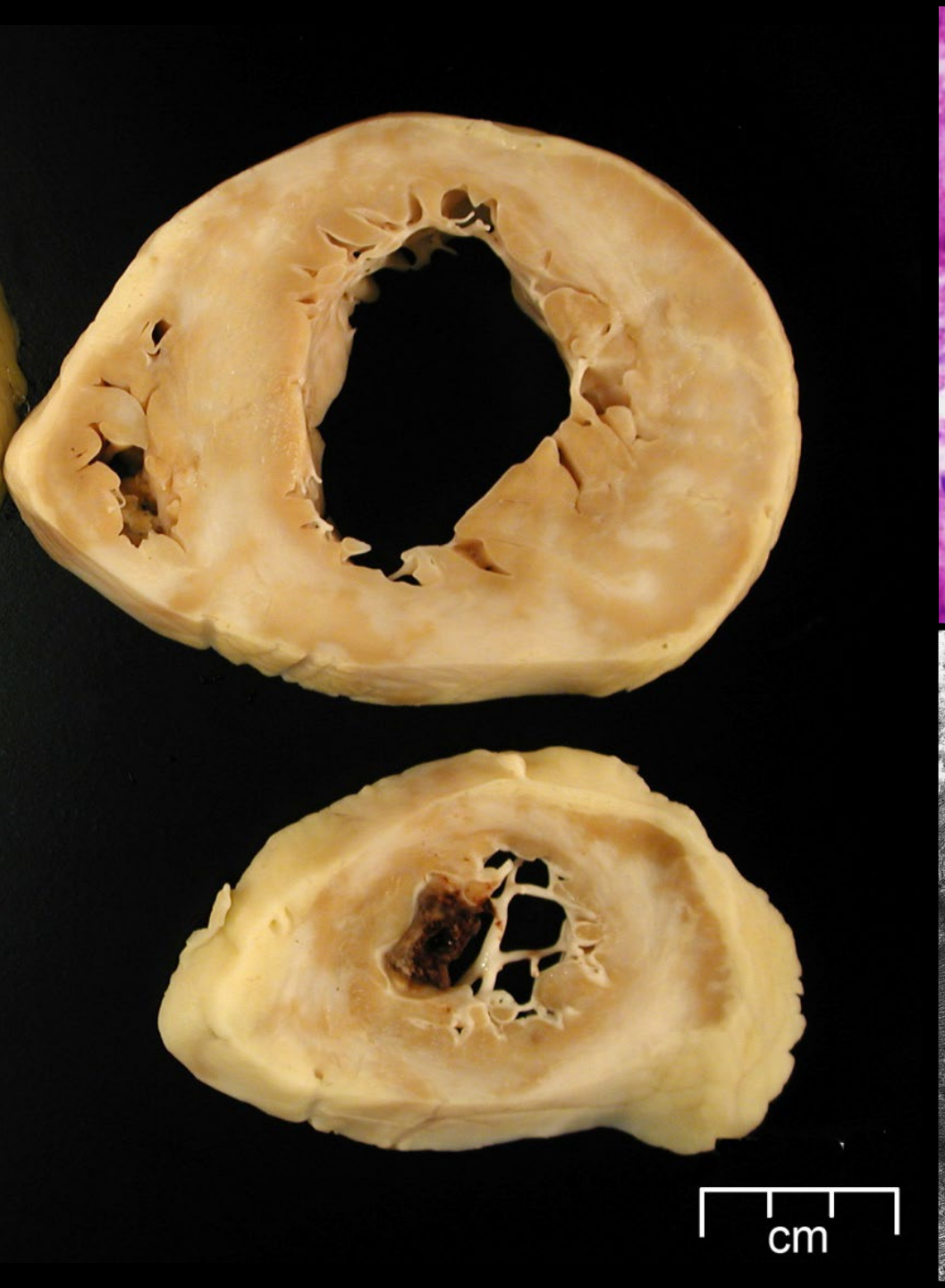
	Other Clinical & Laboratory Features	Mode of Inheritance	Expected Muscle Pathology
Dystrophinopathy (Becker Muscular Dystrophy)	• Onset varies widely (5-60 years of age) • Elevated CK	• X-linked	• Degenerative/regenerative fibers • Fiber size variability • Endomysial fibrosis • Increased internally placed nuclei
Limb-Girdle Muscular Dystrophy (Dystroglycanopathies, Sarcoglycanopathies)	• Onset typically in childhood, but varies by mode of inheritance • Elevated CK	• Autosomal recessive	• Degenerative/regenerative fibers • Fiber size variability • Endomysial fibrosis • Increased internally placed nuclei
Emery-Dreifuss Muscular Dystrophy	• Onset in 1st-2nd decade • Contractures • Elevated CK	• X-linked (types 1 & 6) • Autosomal dominant (types 2, 4, 5, 7) • Autosomal recessive (type 3)	• Degenerative/regenerative fibers • Fiber size variability • Endomysial fibrosis • Increased internally placed nuclei
Pompe Disease	• Onset classically in infancy, but also milder late-onset phenotypes • Hypotonia • Respiratory distress • Hepatosplenomegaly • Elevated CK	• Autosomal recessive	• Autophagic vacuoles, some with sarcolemmal features
Danon Disease	• Onset in 1st-2nd decade • Elevated CK • Mild intellectual disability	• X-linked	• Autophagic vacuoles with sarcolemmal features

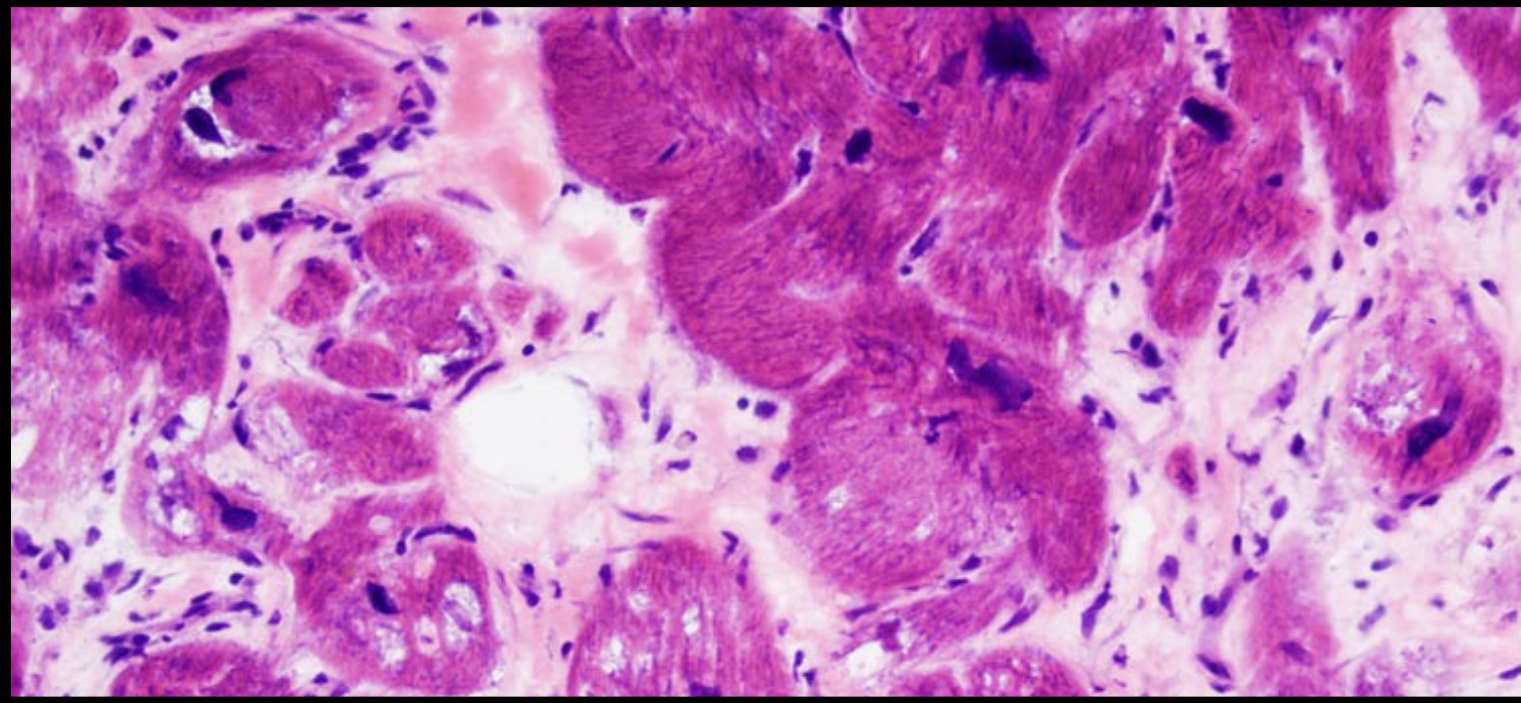

dystrophin carboxy terminus

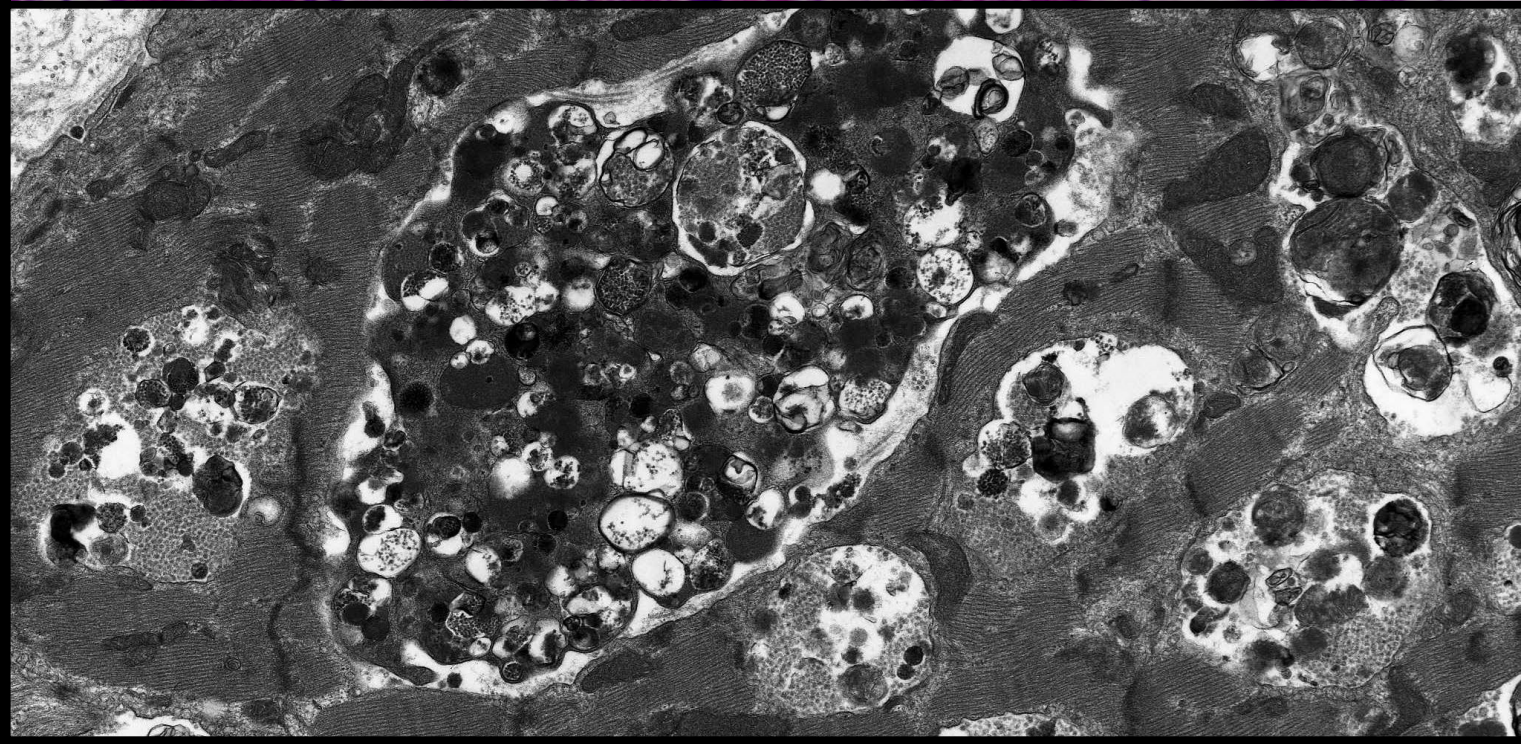

Acetylcholinesterase


β-sarcoglycan


Ultrastructural analysis revealed
autophagic vacuoles

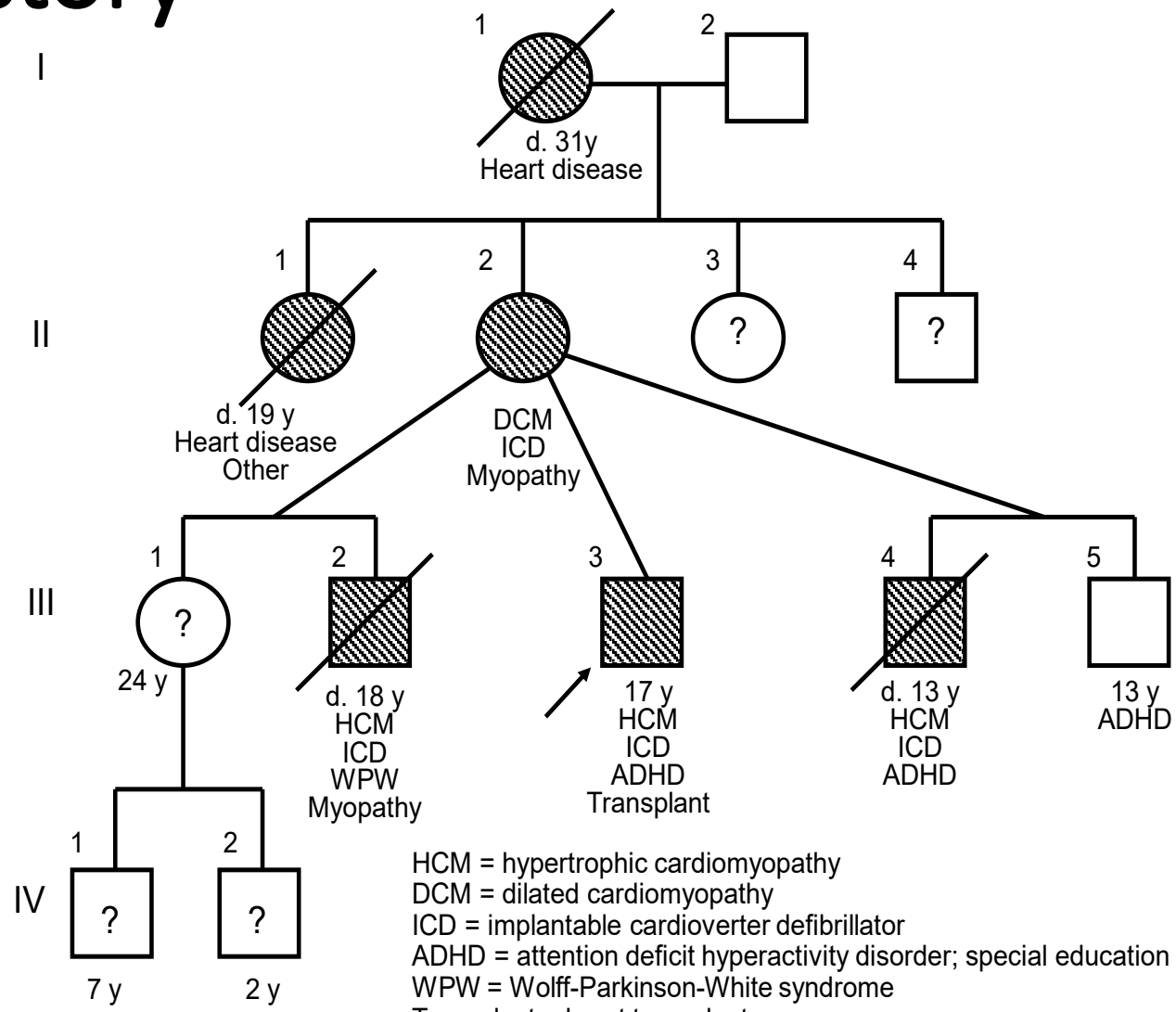

cm





Additional Family History

- Two half-brothers with hypertrophic cardiomyopathy who died at ages 13 and 18 years
- Mother: dilated cardiomyopathy and proximal myopathy in early 30s

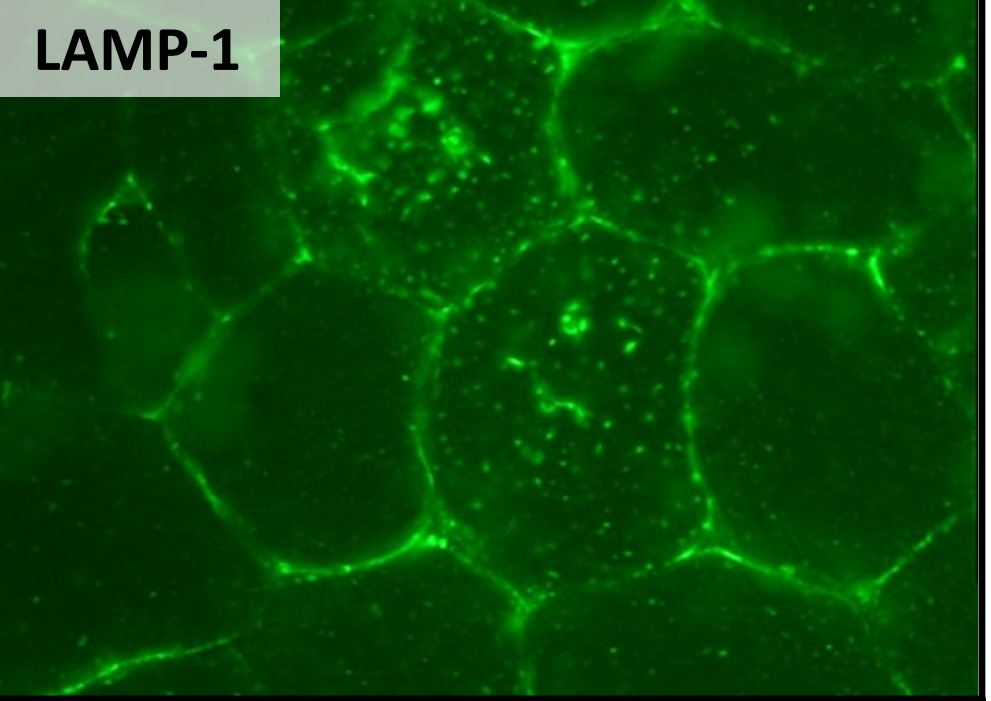


HCM = hypertrophic cardiomyopathy
DCM = dilated cardiomyopathy
ICD = implantable cardioverter defibrillator
ADHD = attention deficit hyperactivity disorder; special education
WPW = Wolff-Parkinson-White syndrome
Transplant = heart transplant
Other = short stature, thick neck, endocrine dysfunction (Turner syndrome?)

Differential Diagnosis:

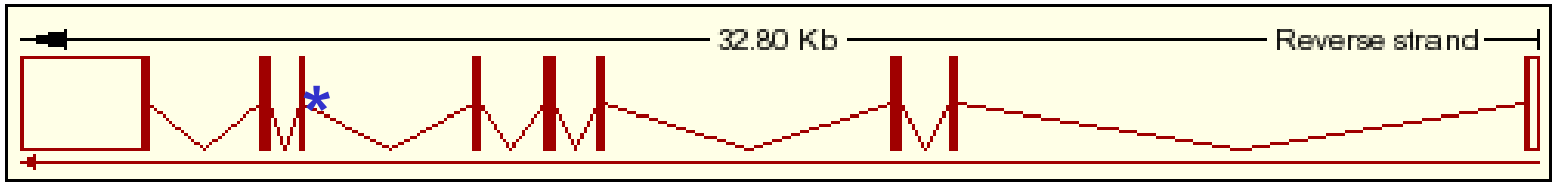
Autophagic Vacuolar Myopathies with Proximal Muscle Weakness

	Pompe Disease	X-linked Myopathy with Excessive Autophagy	Danon Disease	Congenital Myasthenic Syndrome	Hydroxychloroquine/ Chloroquine-related Autophagic Vacuolar Myopathy
Muscle Pathology	• Autophagic vacuoles, some with sarcolemmal features Increased LAMP2 immunoreactivity • Lysosomal glycogen accumulation	• Autophagic vacuoles with sarcolemmal features • Increased LAMP2 immunoreactivity • Extensive complement C5b-9 deposition	• Autophagic vacuoles with sarcolemmal features • Absence of LAMP2 immunoreactivity	• Autophagic vacuoles, some with sarcolemmal features • Tubular aggregates	• Autophagic vacuoles, some with sarcolemmal features • Myeloid and curvilinear bodies identified by EM
Cardiac Involvement	• Severe hypertrophic cardiomyopathy • Conduction abnormalities	• None	• Severe hypertrophic cardiomyopathy • Conduction abnormalities	• None	• Cardiomyopathy sometimes observed
Other Clinical & Laboratory Features	• Onset classically in infancy, but also milder late-onset phenotypes • Hypotonia • Respiratory distress • Hepatosplenomegaly • Elevated CK • Acid maltase deficiency	• Onset in 1st-2nd decade • Normal acid maltase levels • Elevated CK	• Onset in 1st-2nd decade • Normal acid maltase levels • Elevated CK • Mild intellectual disability	• Onset in 1st decade • Fatigable muscle weakness • EMG shows motor action potential decrement upon repetitive stimulus • Normal or mildly elevated CK	• Elevated CK • Peripheral neuropathy • Extended use of hydroxychloroquine/ chloroquine
Mutant Gene	• *GAA*	• *VMA21*	• *LAMP2*	• *GFPT1* • *DPAGT1*	• None
Mode of Inheritance	• Autosomal recessive	• X-linked	• X-linked	• Autosomal recessive	• Acquired

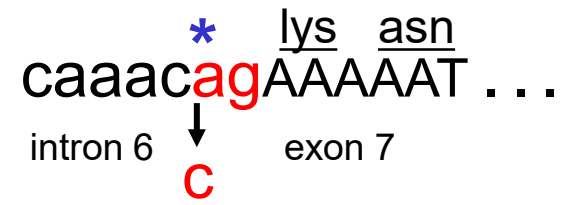


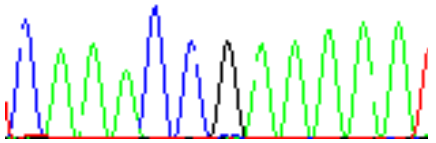
Ancillary Testing

- Molecular genetic testing identified *LAMP2* c.865-2A>C mutation
- Mother was confirmed to be a carrier

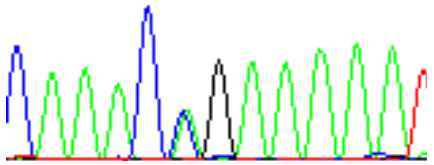


c.865-2A>C





male proband, III-3



mother, II-2

Final Diagnosis – Danon disease

- X-linked vacuolar myopathy caused by mutation of *LAMP2* gene
  - *LAMP2* = Lysosome-Associated Membrane Protein 2
    - Location: Xq24
  - >100 different disease-causing mutations have been reported
    - Most commonly c.926G>A
- LAMP2
  - Component of lysosomal membrane
  - Mediates lysosome-autophagosome fusion
  - Deficiency leads to defective autophagy and accumulation of autophagic vacuoles
- Clinical features
  - Cardiac involvement (100% penetrance)
  - Proximal muscle weakness with elevated CK (80-90% penetrance)
  - Mild cognitive impairment and/or developmental delay (70-80% penetrance)
- Female carriers have milder features and/or later onset (typically 30s-40s)

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