Metabolic & Toxic Myopathies

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AMERICAN ASSOCIATION
OF NEUROPATHOLOGISTS

Disclosures

- I have the following relevant financial relationships to disclose
  - Research Support from Astellas Gene Therapies (formerly known as Audentes Therapeutics, Inc.)

- I write annual neuromuscular disease updates for Free Neuropathology (diamond open-access neuropathology journal, launched in Jan 2020)

Learning Objectives

- Compare and contrast clinicopathologic features of mitochondrial myopathies, glycogen storage myopathies, and acquired / toxic autophagic vacuolar myopathies
- Explain how block of autophagic flux leads to autophagic vacuolar myopathy phenotype
- Outline the role of electron microscopy and ancillary immunohistochemical studies in pathologic diagnosis of metabolic and toxic myopathies

Outline: Select Metabolic and Toxic Disorders

- Mitochondrial myopathies
- Glycogen storage myopathies
- Autophagic vacuolar myopathies (AVMs)

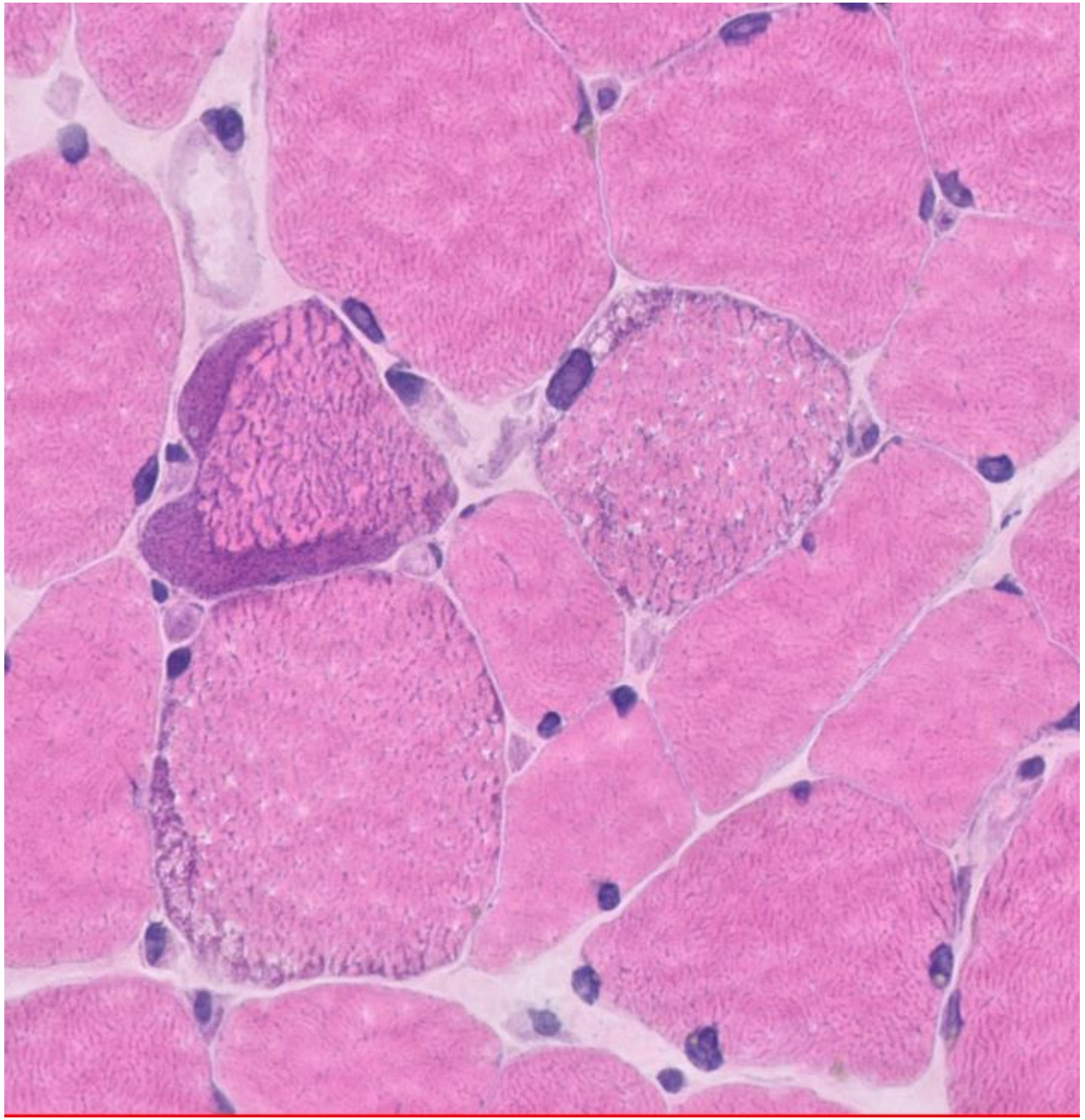
MITOCHONDRIAL MYOPATHIES

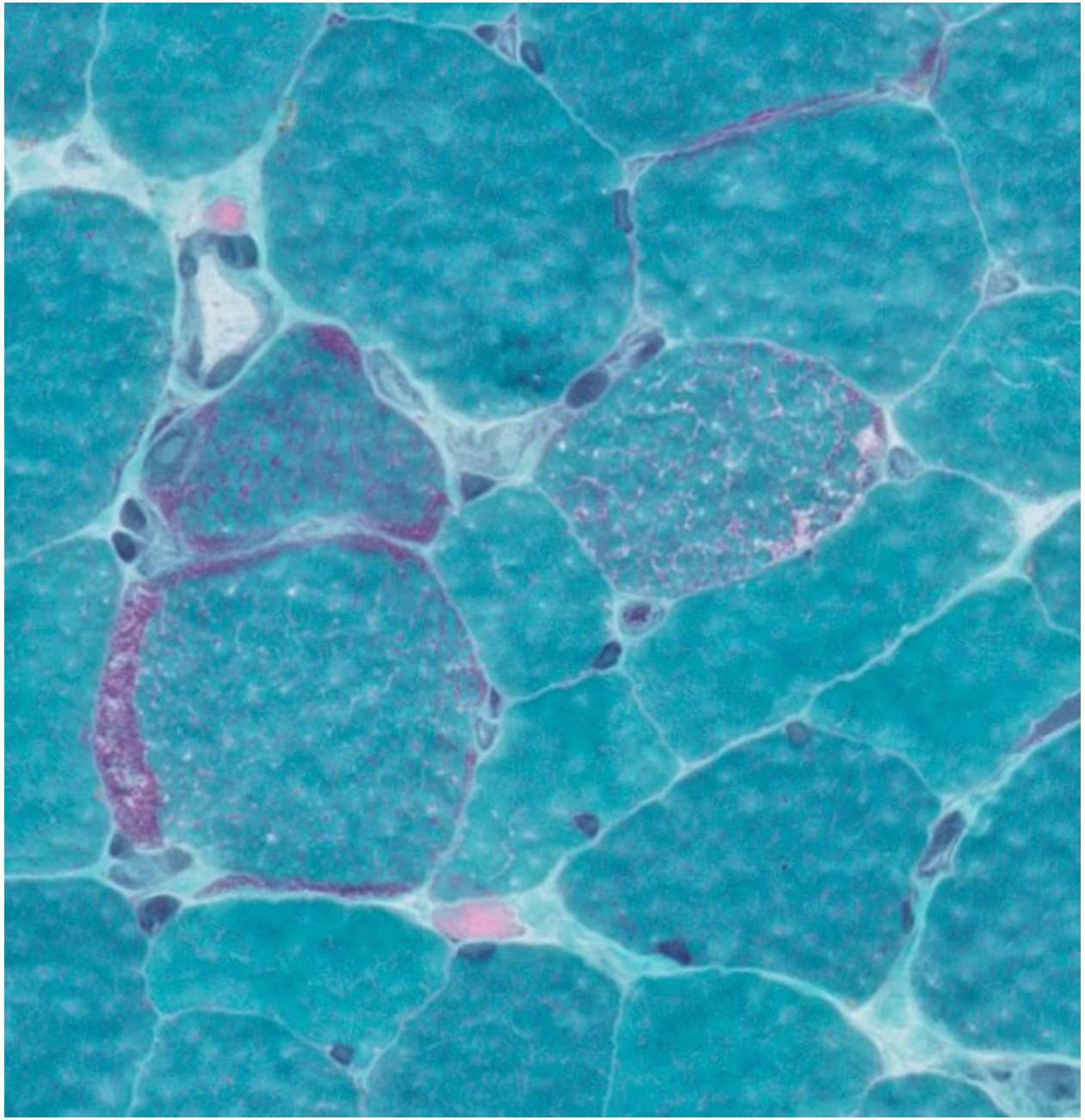
Clinical Findings

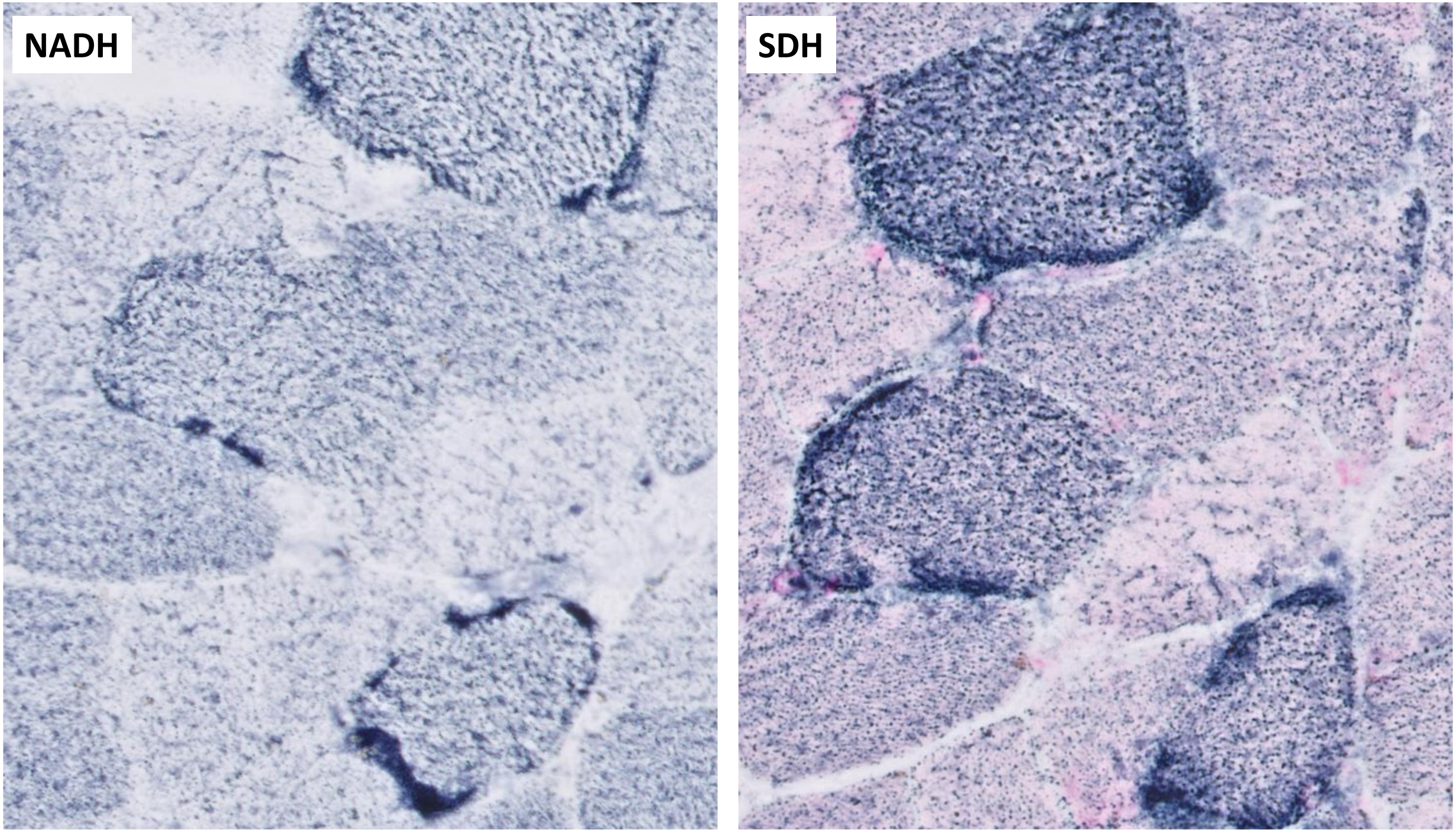
- Variable clinical presentations with regard to age of onset, organ system involvement, severity of symptoms, and prognosis
- Typical clinical syndromes:
  - Chronic progressive external ophthalmoplegia (CPEO)
  - Sensorineural hearing loss
  - Short stature
  - Cardiomyopathy with conduction deficits
  - Peripheral neuropathy (including optic neuropathy)
  - Encephalopathy with or without seizures
  - Diabetes

Molecular Genetics

- Underlying genetic alterations:
  - mtDNA point mutations (most commonly in 1 of 22 tRNAs); maternally inherited or sporadic
  - mtDNA deletions; maternally inherited or sporadic
  - mutations in nuclear genes required for mtDNA replication and maintenance; autosomal dominant or autosomal recessive
- Complex genotype/phenotype relationship: a single mutation can cause different clinical syndromes, while each syndrome can be caused by different genetic alterations
- **Heteroplasmy**: mutant and wild-type mtDNA can coexist in a single cell, with proportion of functional and dysfunctional mitochondria differing among different cells and tissues
- Muscle biopsy is a test of choice even if there is no weakness



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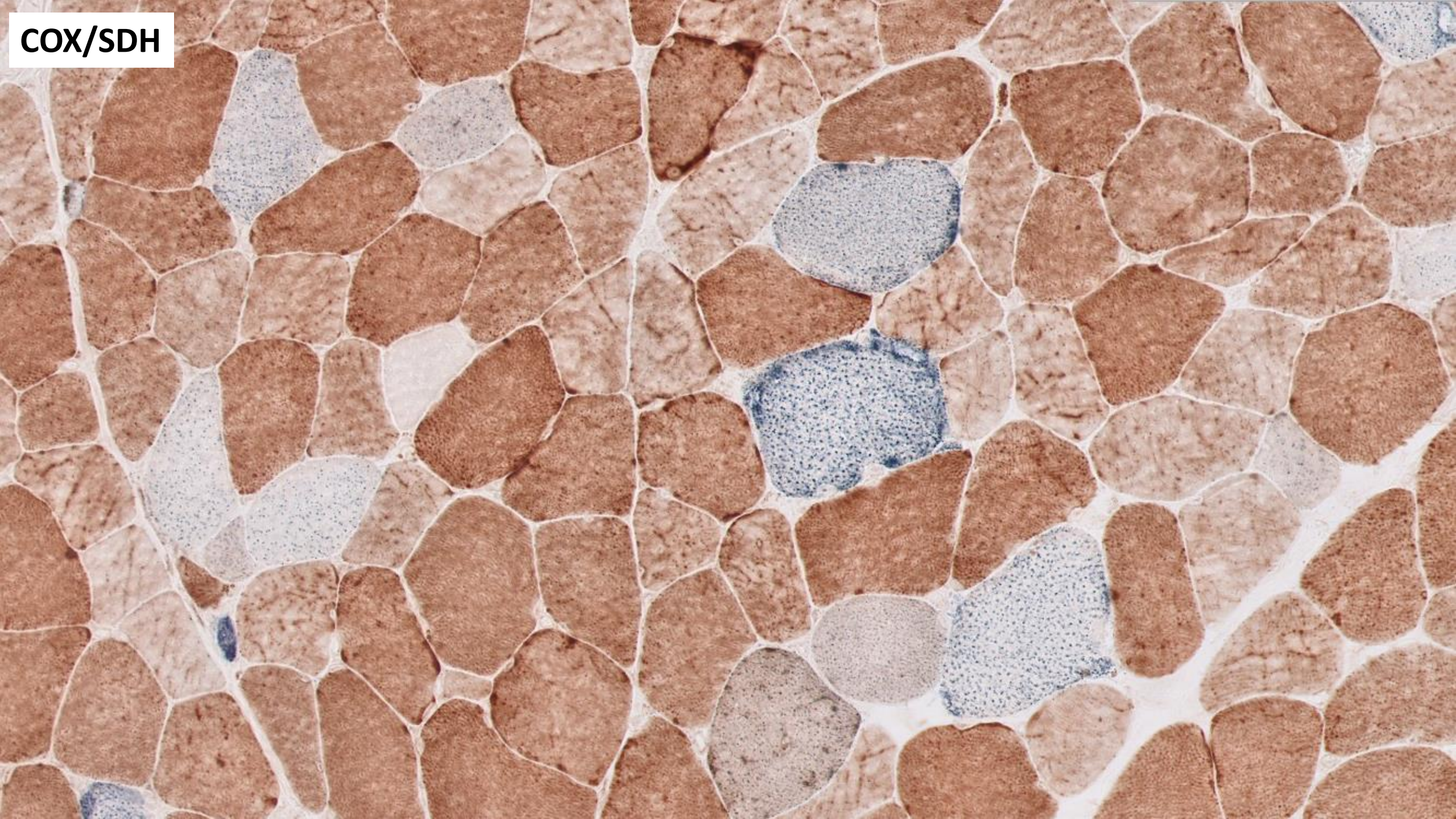
SDH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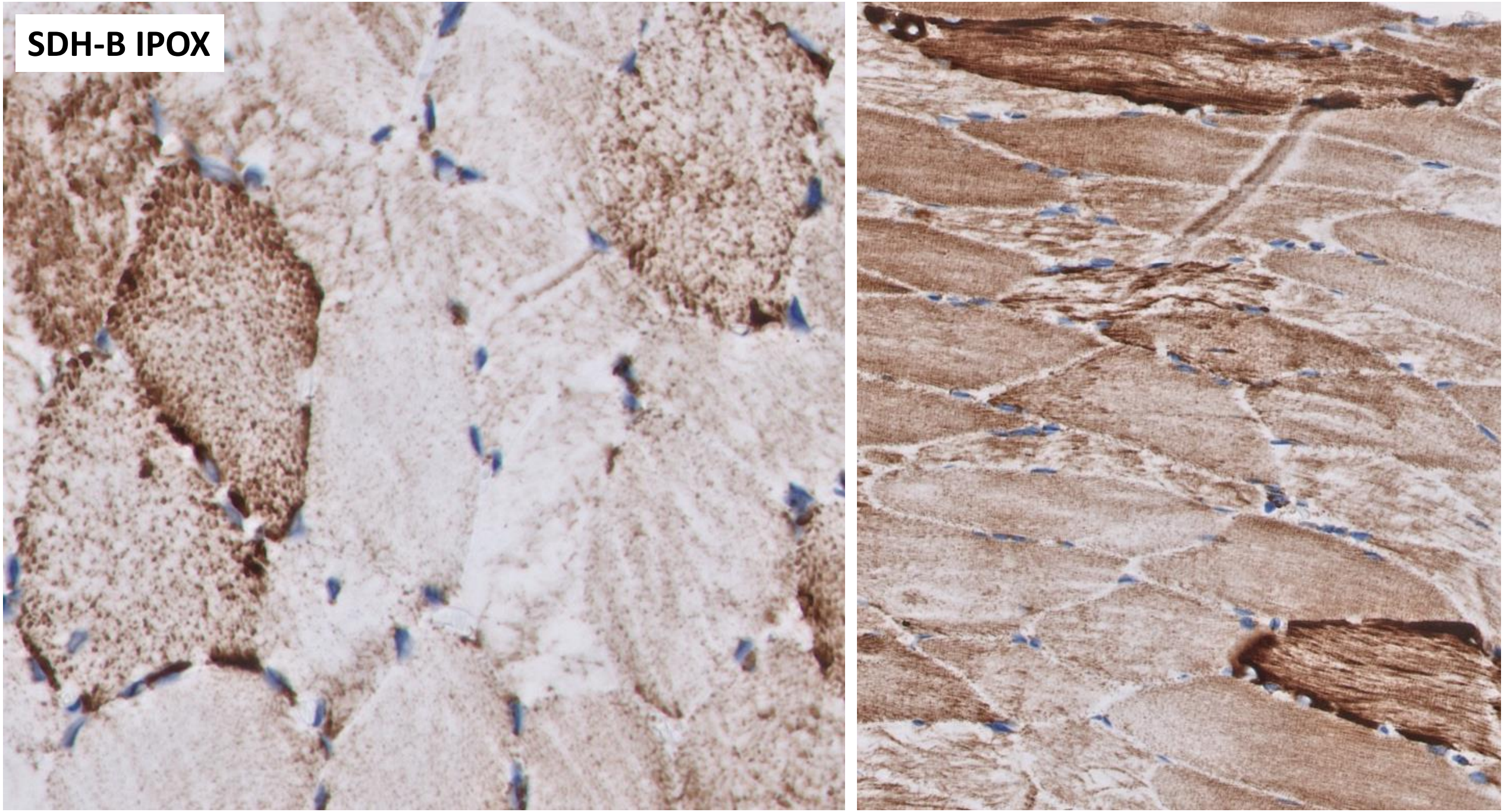
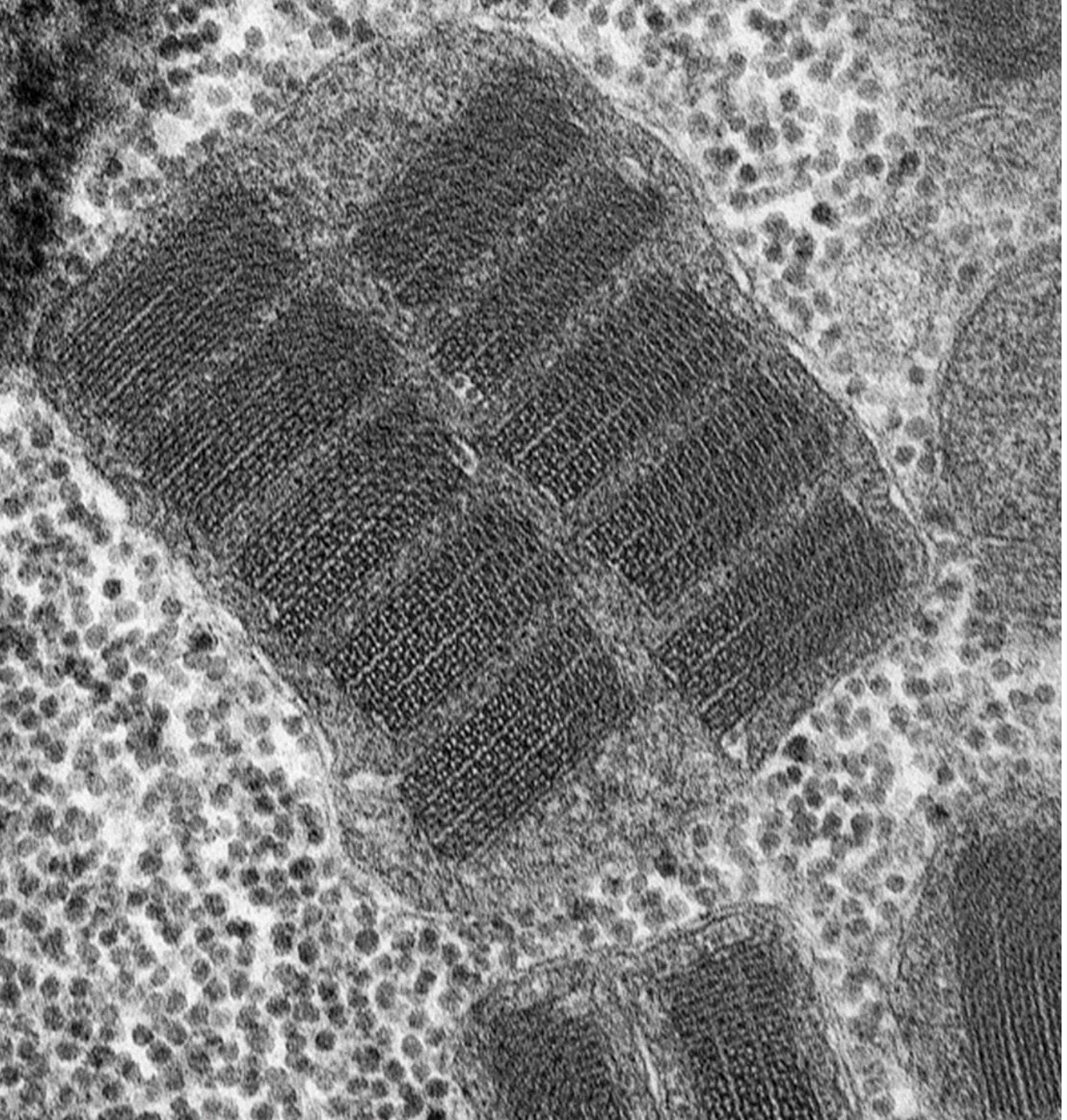
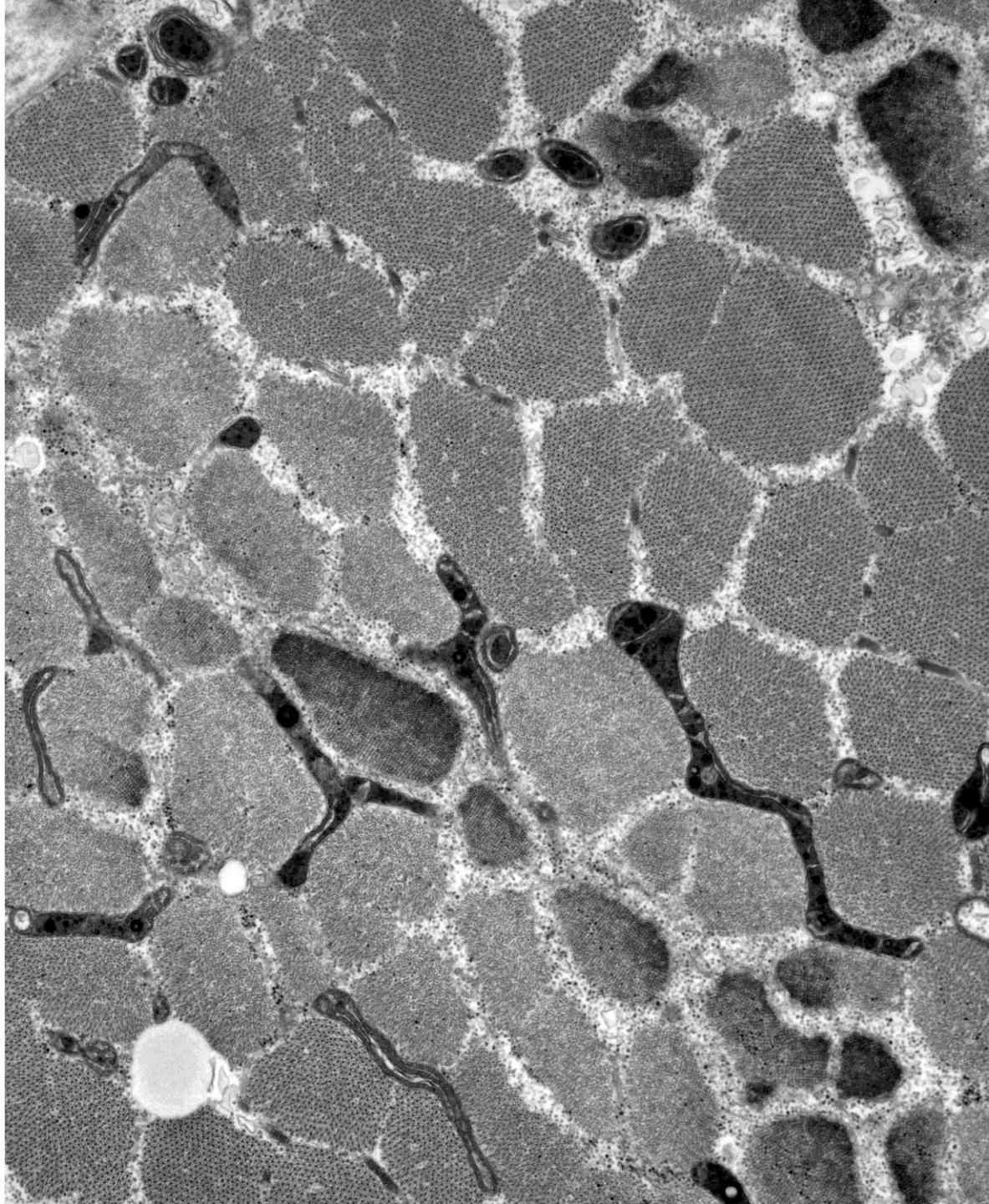

SDH-B IPOX





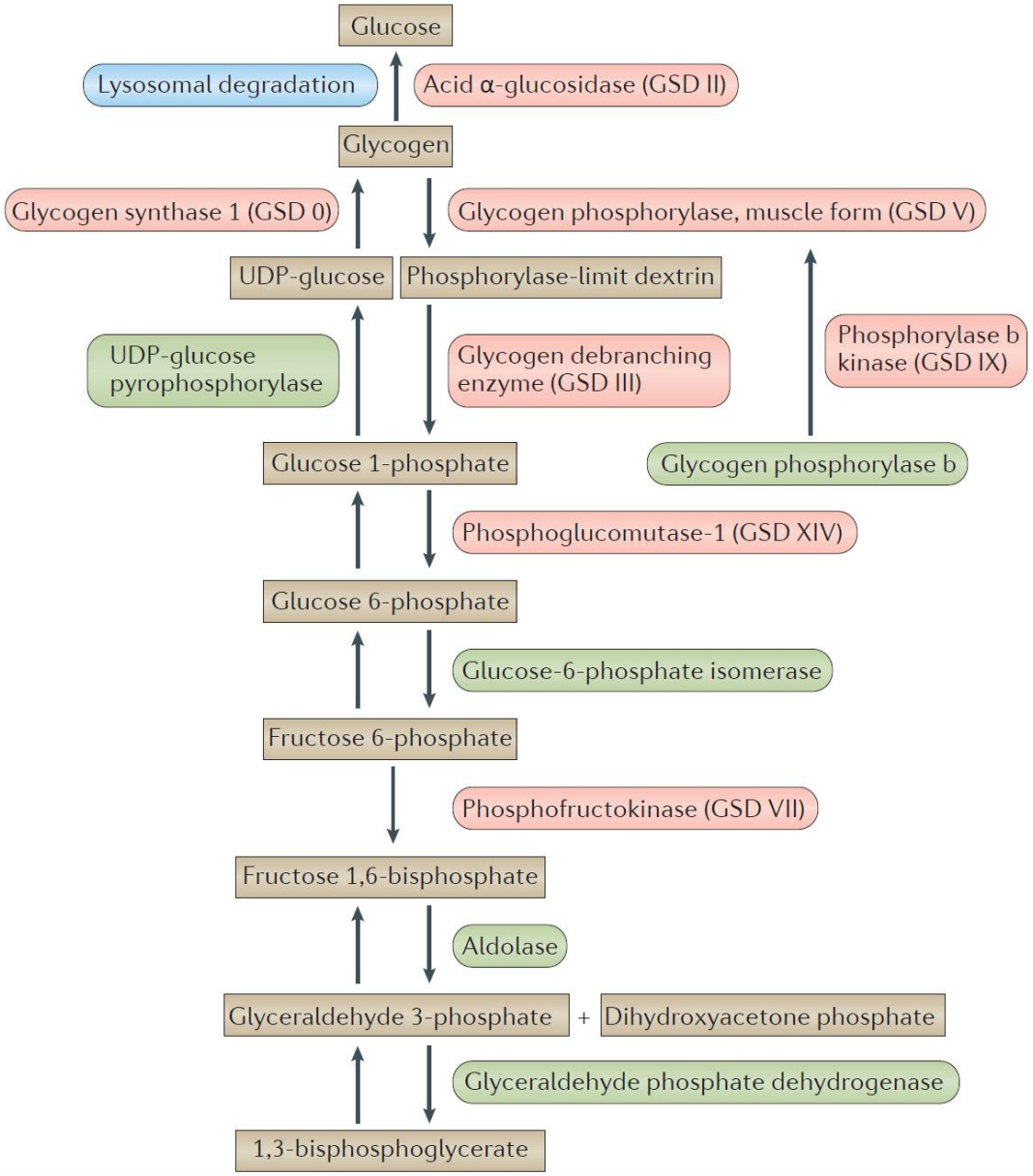
GLYCOGEN STORAGE MYOPATHIES

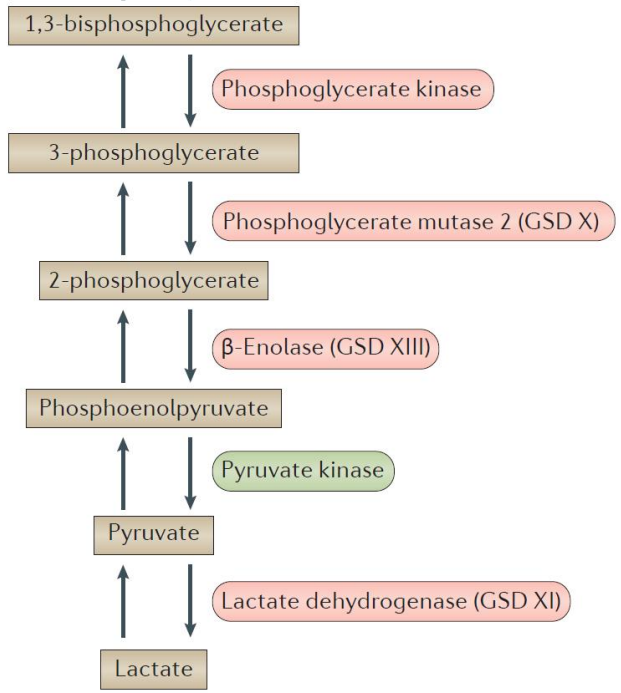
Disorders of Glycogen/Glucose Utilization

- Many subtypes; single gene defects resulting in impaired carbohydrate metabolism (AR or X-linked)
- Clinical presentation:
  - **Exercise intolerance**: exercise-induced pain; rhabdomyolysis
  - Exercise avoidance leads to secondary health issues
  - Additional features (gene defect-specific): dysmorphic features, hemolysis, liver disease, neurologic findings, skin lesions, cardiomyopathy
- Muscle pathology: accumulation of free intersarcomeric and subsarcolemmal glycogen

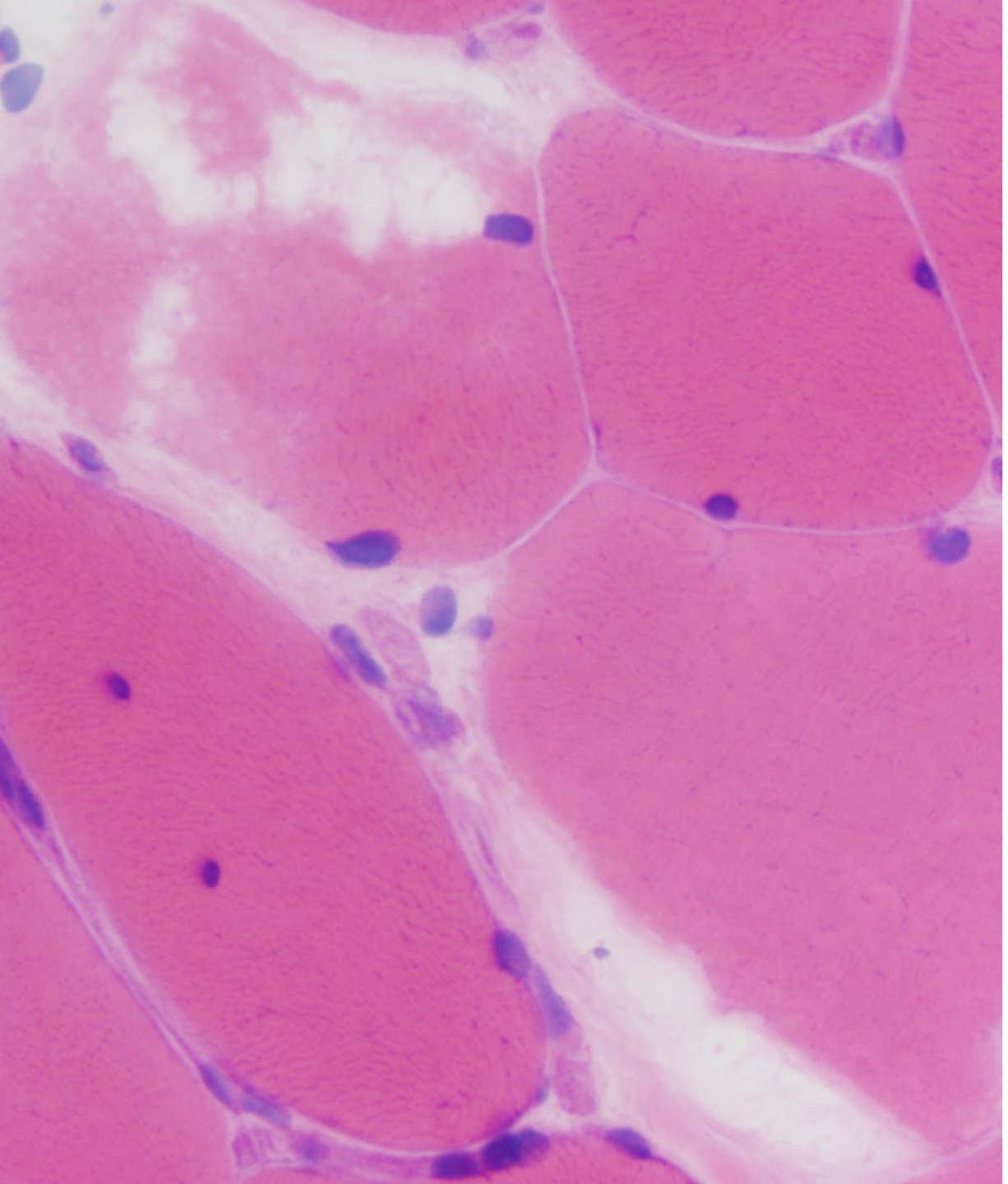
Disorder of Lysosomal Glycogen Degradation

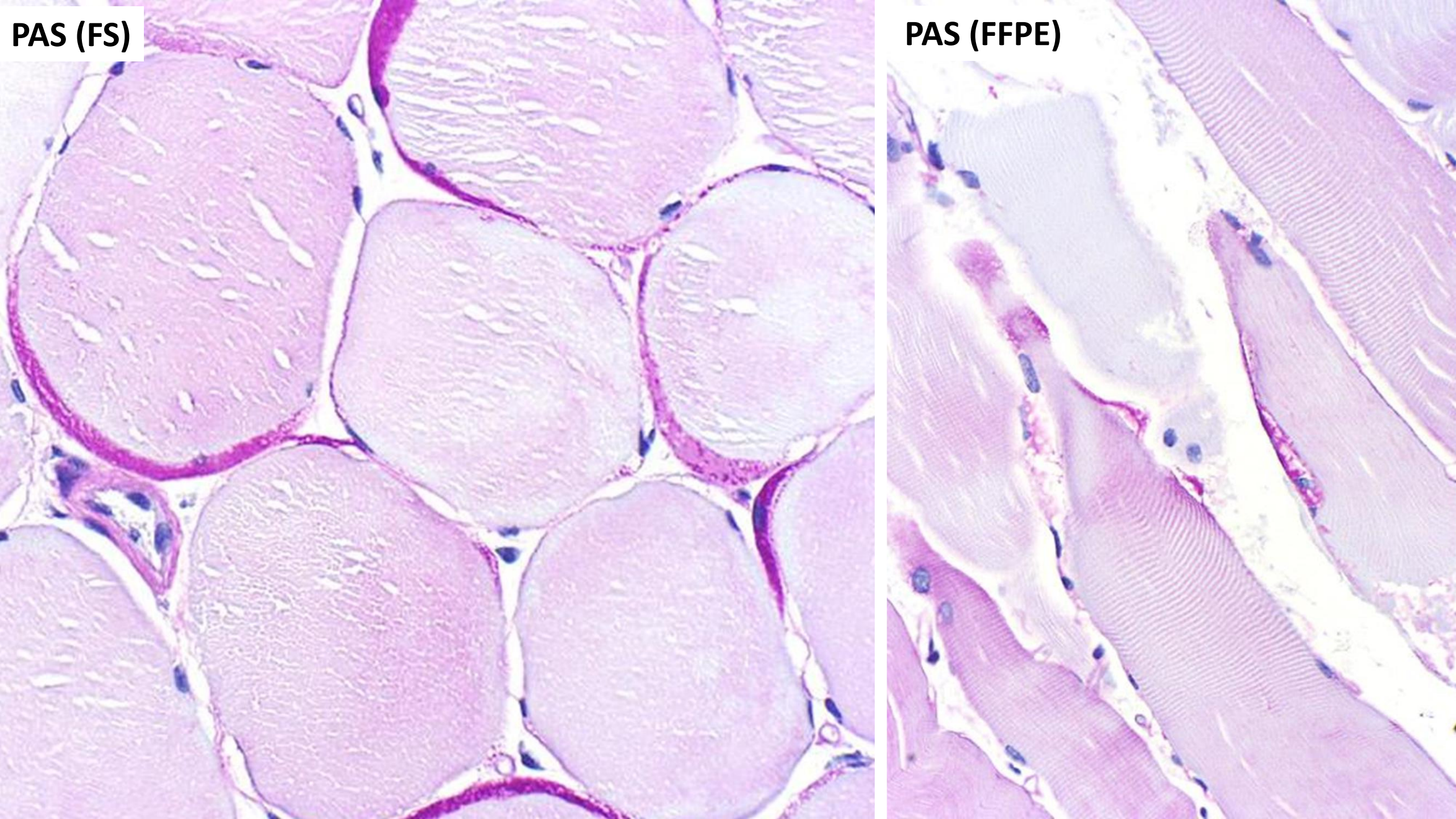
- Acid α-glucosidase (acid maltase) deficiency: GSD II (AR)
  - Infantile onset Pompe disease (IOPD; <1% of residual enzyme activity)
  - Late onset Pompe disease (LOPD; up to 30% of residual enzyme activity)
- Clinical presentation:
  - Hypertrophic cardiomyopathy and hypotonia (IOPD)
  - **Weakness** and muscle atrophy; respiratory insufficiency; scoliosis (LOPD)
  - Cramps, elevated CK
  - Other organ system involvement: CNS, PNS, GI, urinary tract, bones
- Muscle pathology: autophagic vacuolar myopathy; lysosomal glycogen

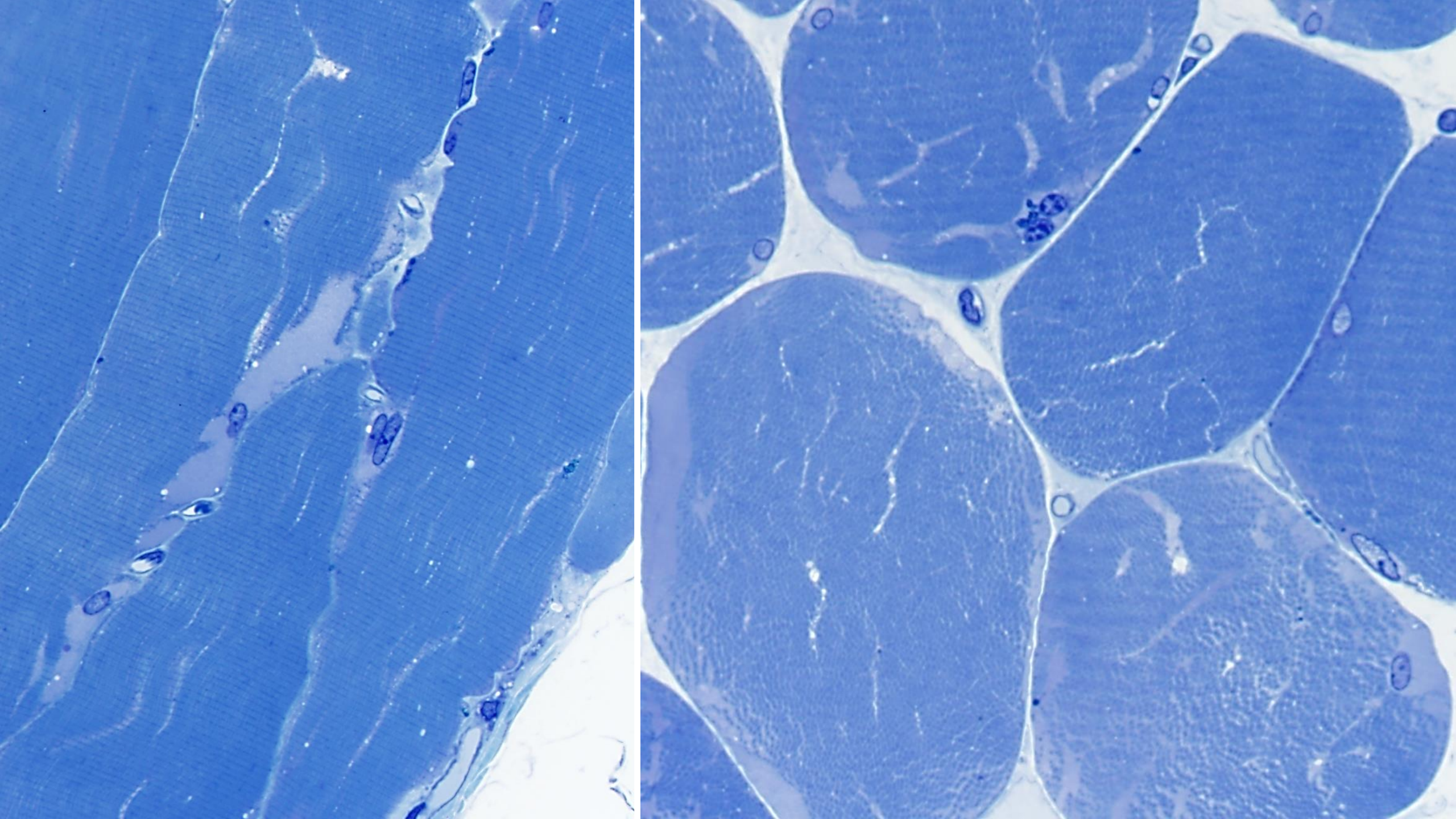


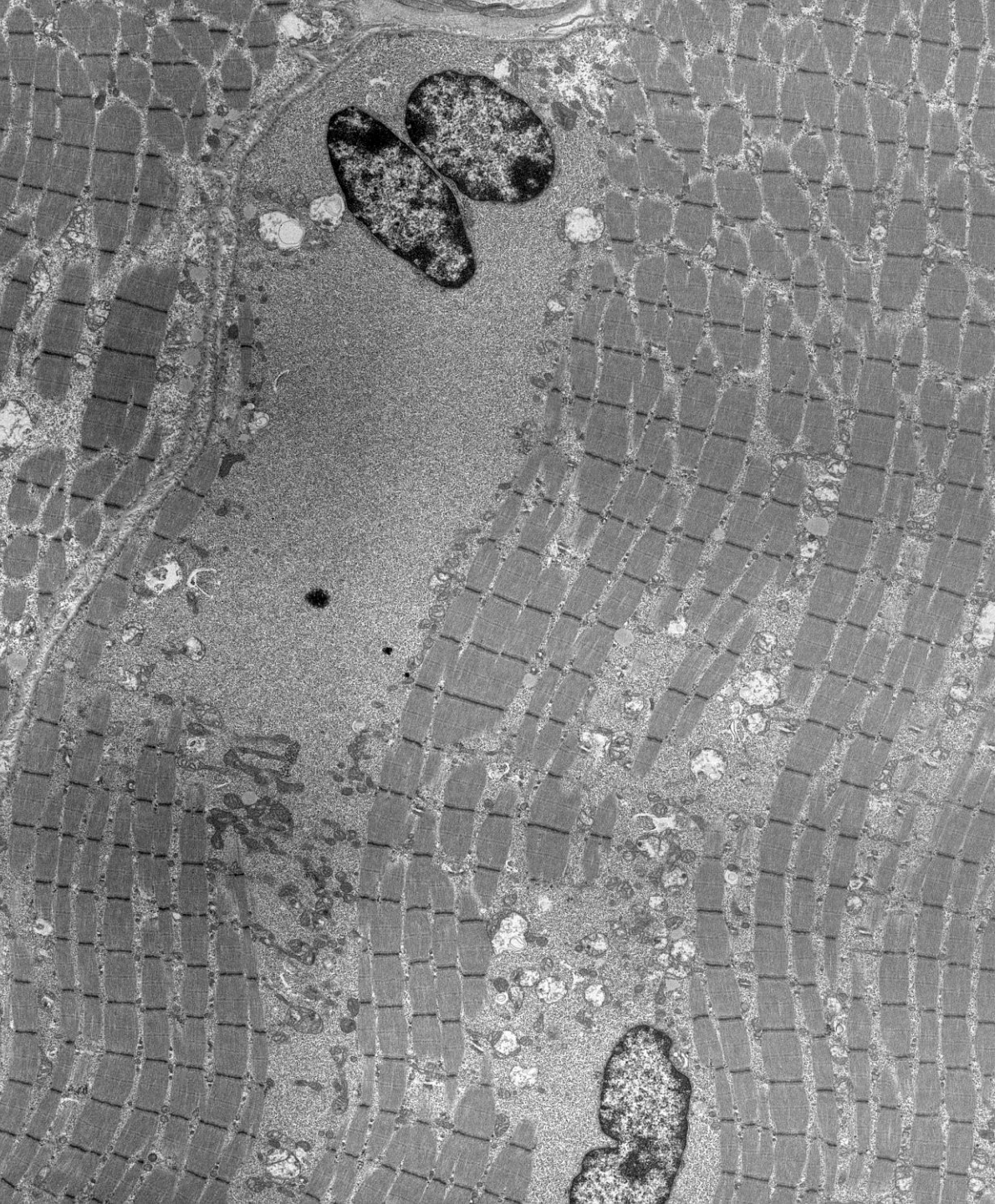


From Godfrey R, Quinlivan R. Skeletal muscle disorders of glycogenolysis and glycolysis. Nat Rev Neurol. 2016 Jul;12(7):393-402

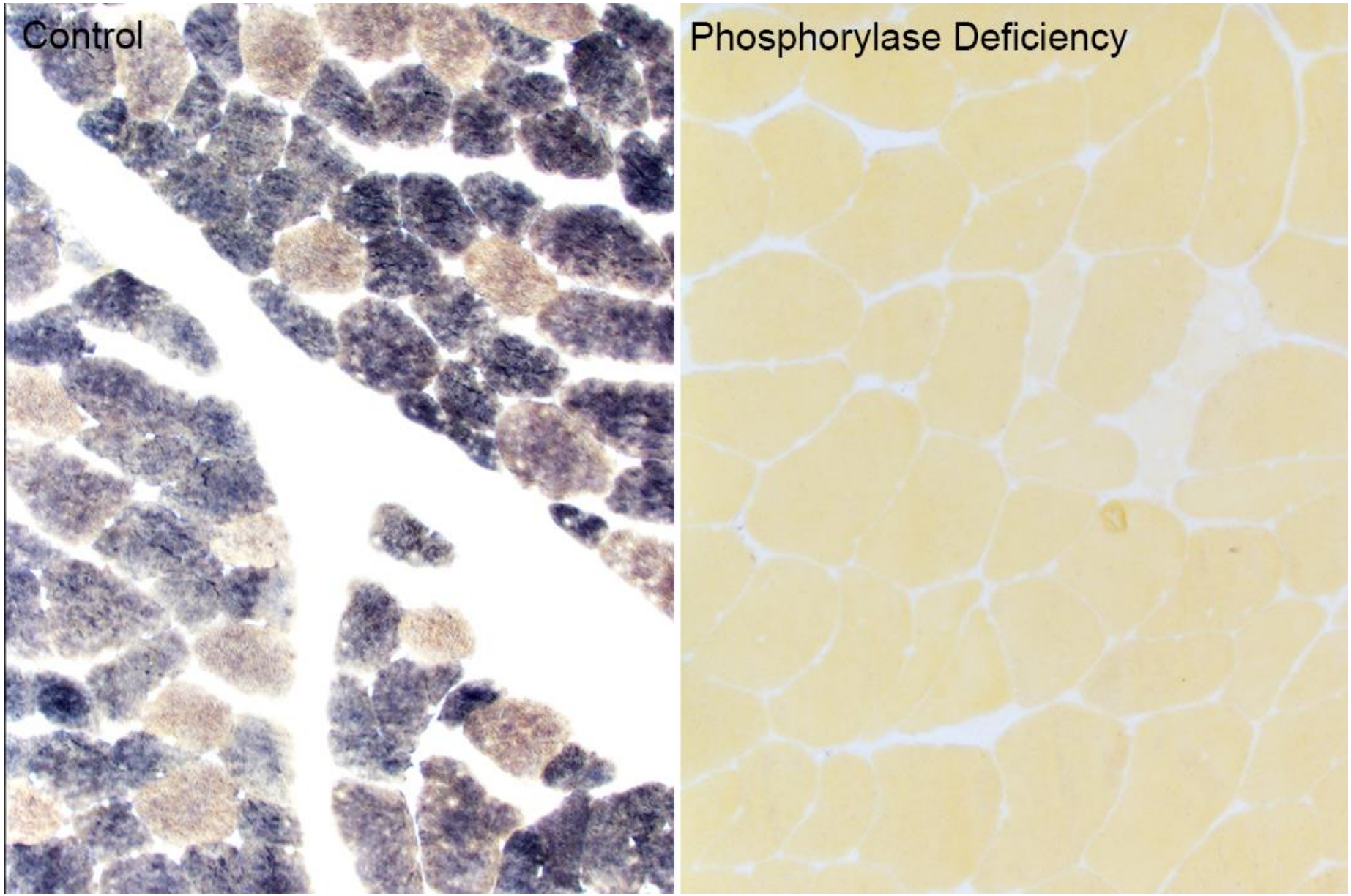



PAS (FS)
PAS (FFPE)





GSD V (McArdle's Disease): muscle glycogen phosphorylase (myophosporylase deficiency)



https://neuromuscular.wustl.edu/pathol/phosphorylase.htm

AUTOPHAGIC VACUOLAR MYOPATHIES

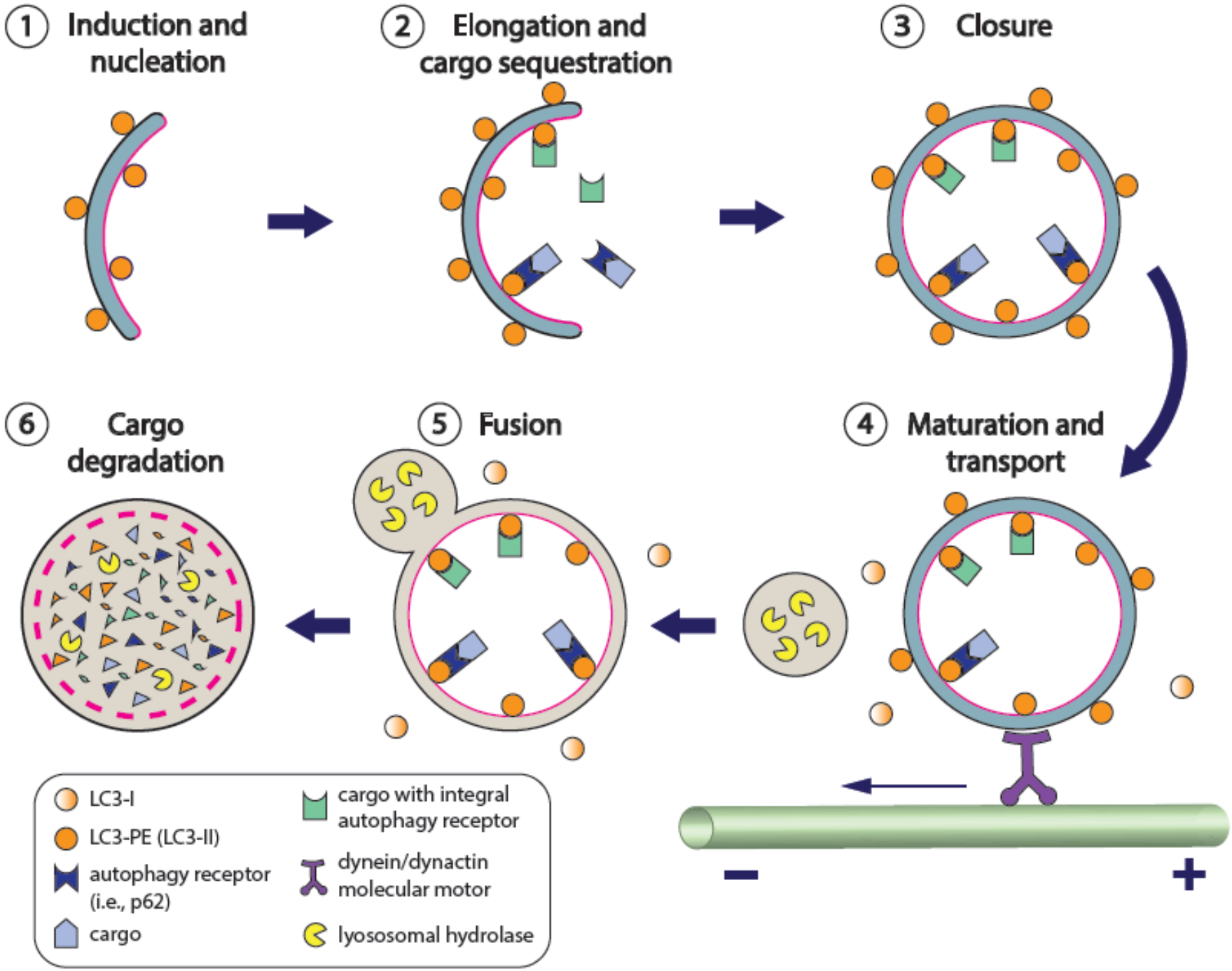
Autophagy

Autophagy (macroautophagy) is a catabolic process in which the cytoplasm and organelles in a cell are sequestered within double membrane vacuoles (autophagosomes), and then delivered to the lysosome for degradation.

AuTophagy Genes (ATGs), which regulate autophagy in yeast, are conserved in mammals.

Two ubiquitin-like conjugation systems are required for early autophagosome formation.

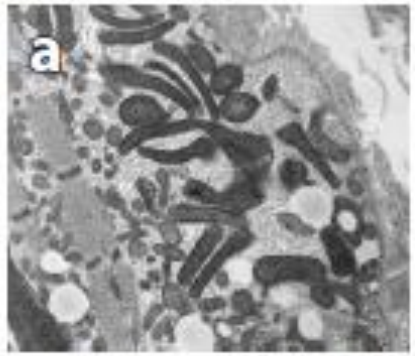
Macroautophagy steps



From: Margeta M. Autophagy Defects in Skeletal Myopathies. Annu Rev Pathol 2020;15:261-285.

(Step 1)

Induction defect



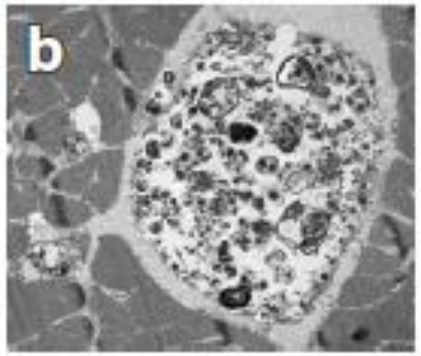
Accumulation of damaged organelles

Fiber atrophy
Fiber apoptosis

Muscular dystrophies
Centronuclear myopathies
Other myopathies?

(Steps 4-6)

Flux defect



Accumulation of undigested cargo

Reduction in force generation
Failure of satellite cell activation

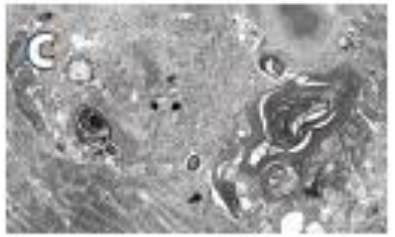
Autophagic vacuolar myopathies

(Step 2)

Cargo recognition defect

Granulophagy defect

Accumulation of stress granules

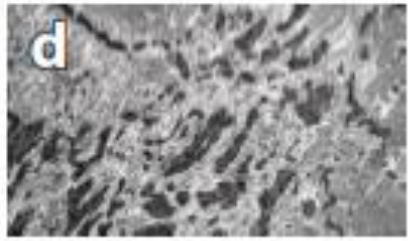


Rimmed vacuole formation
Fiber degeneration

MSP-associated myopathies
Inclusion body myositis?

CASA defect

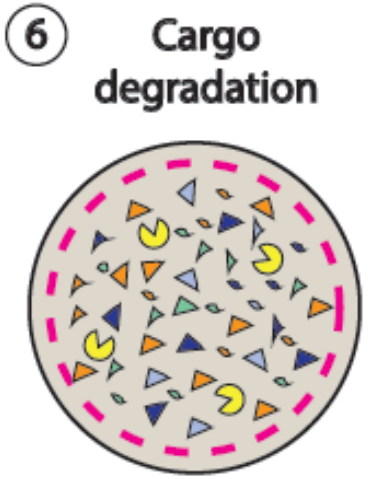
Z-disc instability



Myofibrillar disorganization

Myofibrillar myopathies

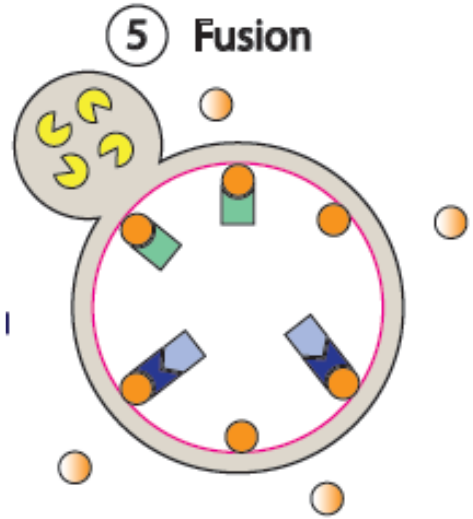
Defect of Cargo Degradation (Step 6)



- X-linked myopathy with excessive autophagy (XMEA)
  - mutations in VMA21, a chaperone that is critical for the proper assembly of the vacuolar ATPase
- Chloroquine / hydroxychloroquine myopathy
- Neuronal ceroid lipofuscinosis type 3 (CLN3 disease; other NCLs?)
- Pompe disease (acid α-glucosidase deficiency)

- Shared mechanism: Impairment of lysosome acidification

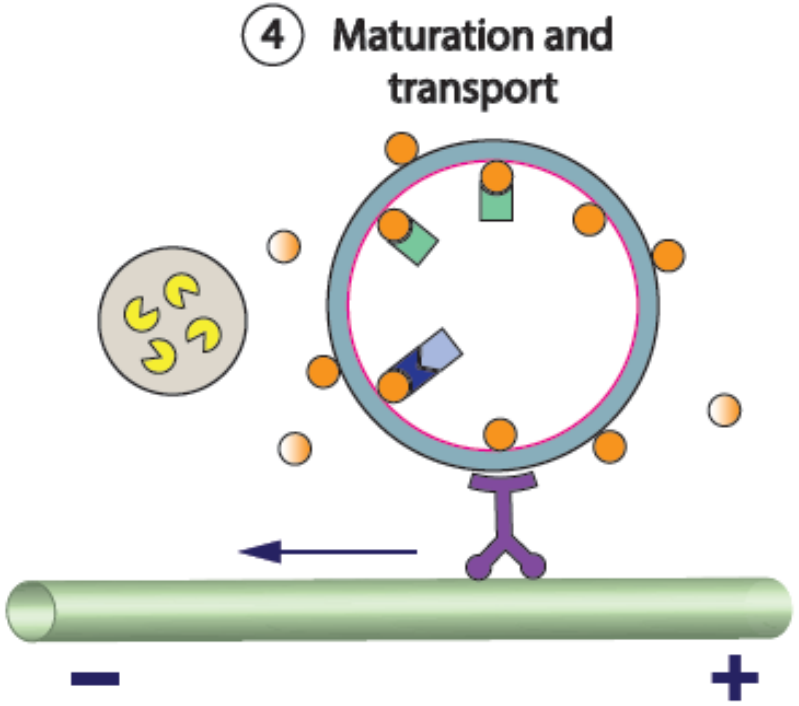
Defect of Autophagosome-Lysosome Fusion (Step 5)



Danon disease

- X-linked disease (female carriers are also affected, but the phenotype is milder)
- Initially classified as "lysosomal glycogen storage disease with normal acid maltase"
- Loss-of-function mutations in LAMP2 gene, resulting in deficiency of LAMP2B protein (which is required for autophagosome / lysosome fusion)
  - Lack of LAMP2 staining is a key diagnostic feature
- Cardiac phenotype is more severe than skeletal muscle phenotype

Defect of Autophagosome Maturation (Step 4)

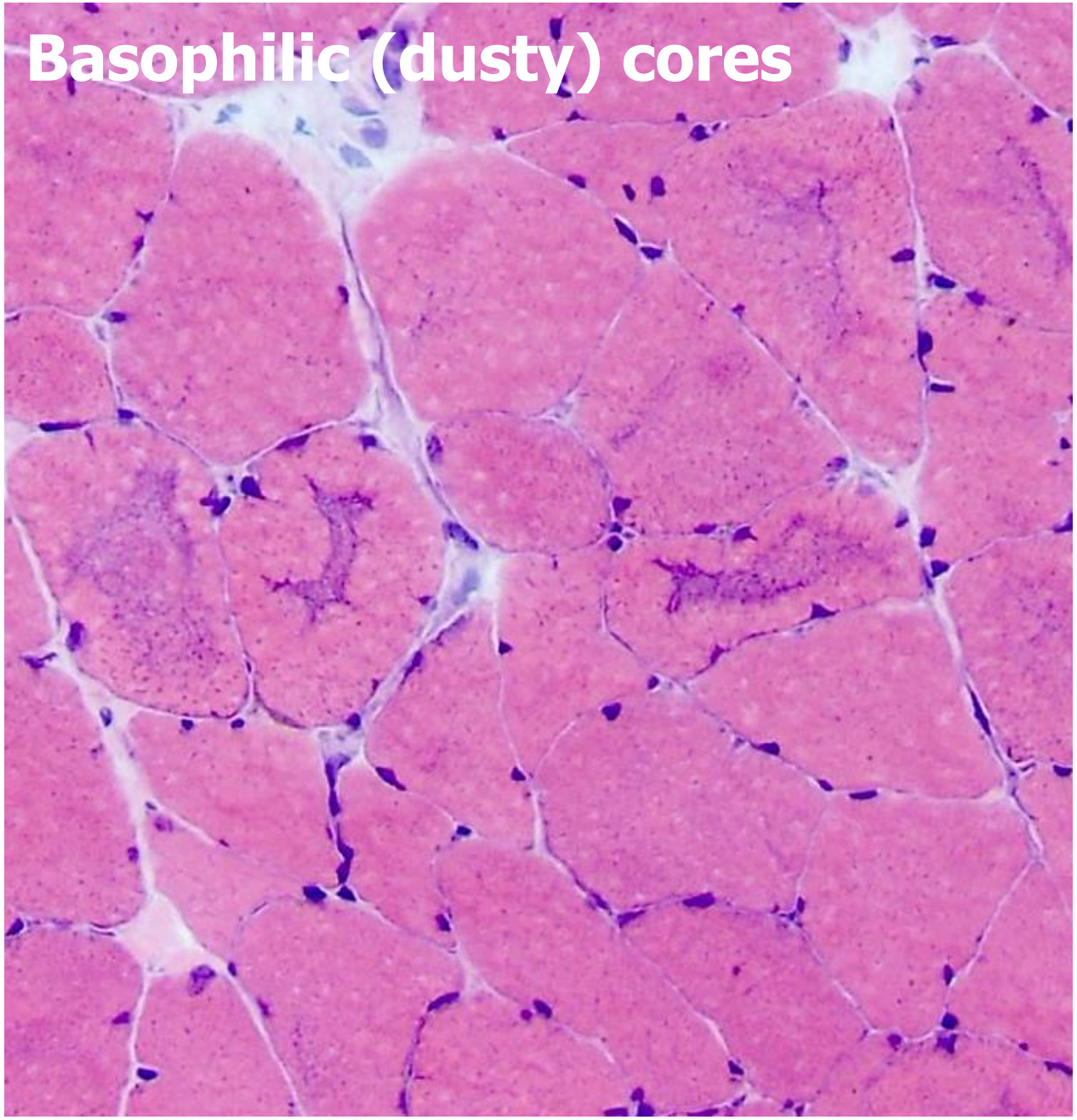


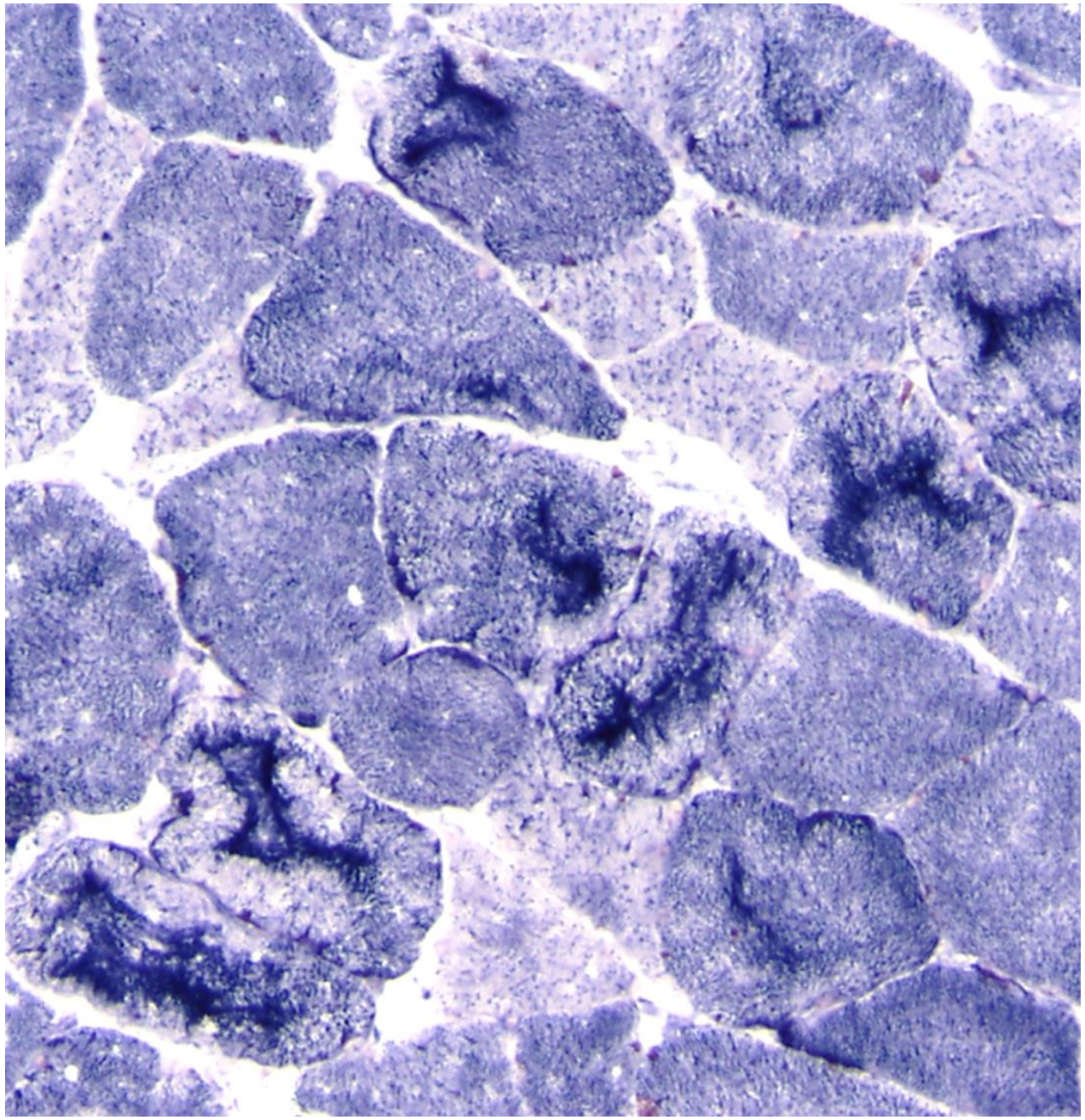
Colchicine myopathy

- Colchicine prevents microtubule polymerization; this blocks autophagosome maturation by interfering with autophagosome transport
- Vincristine and other microtubule blocking agents have the same effect
- Typical AVM features + patchy myofibrillar disorganization on EM

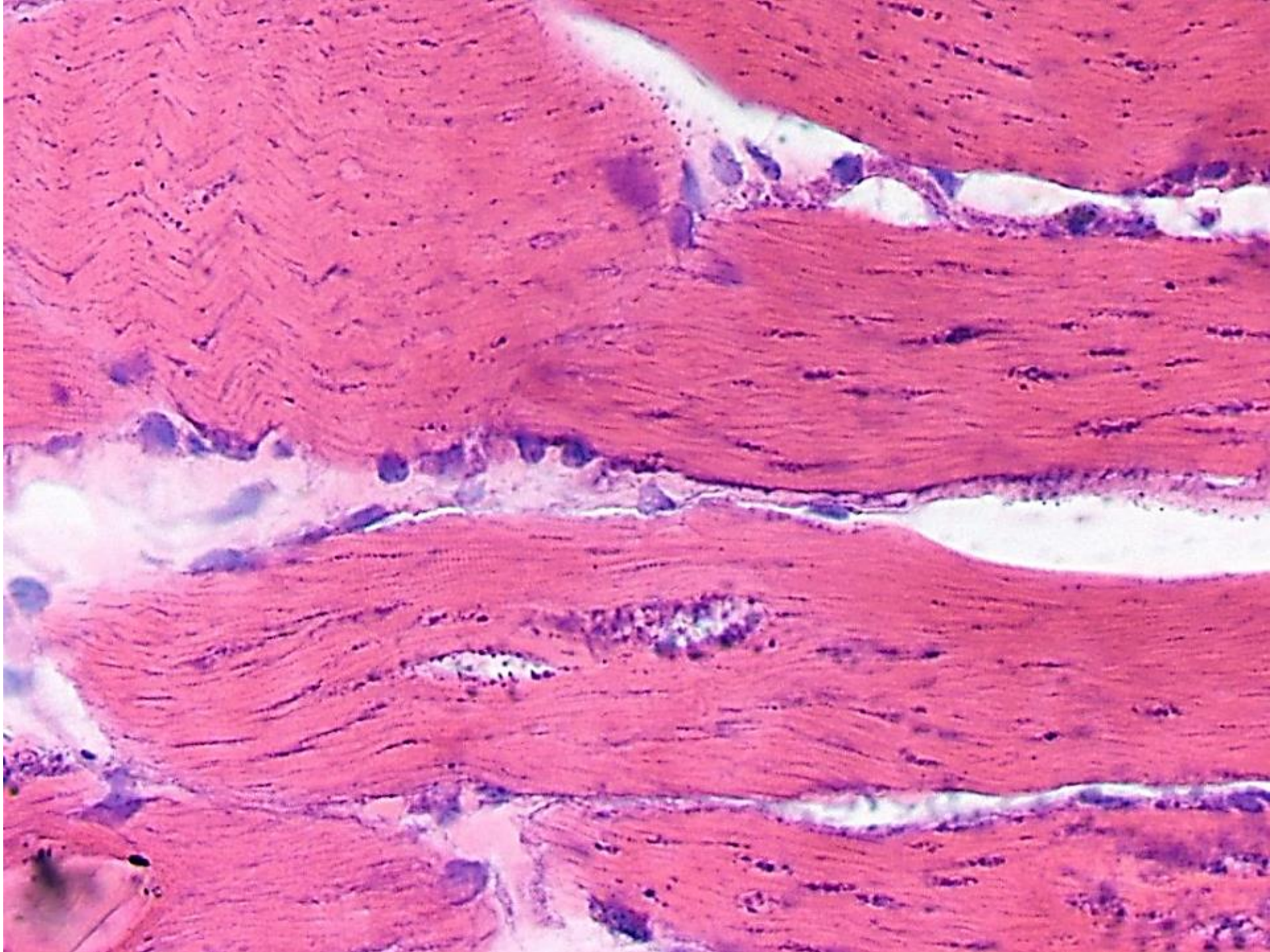
General AVM Histologic Features

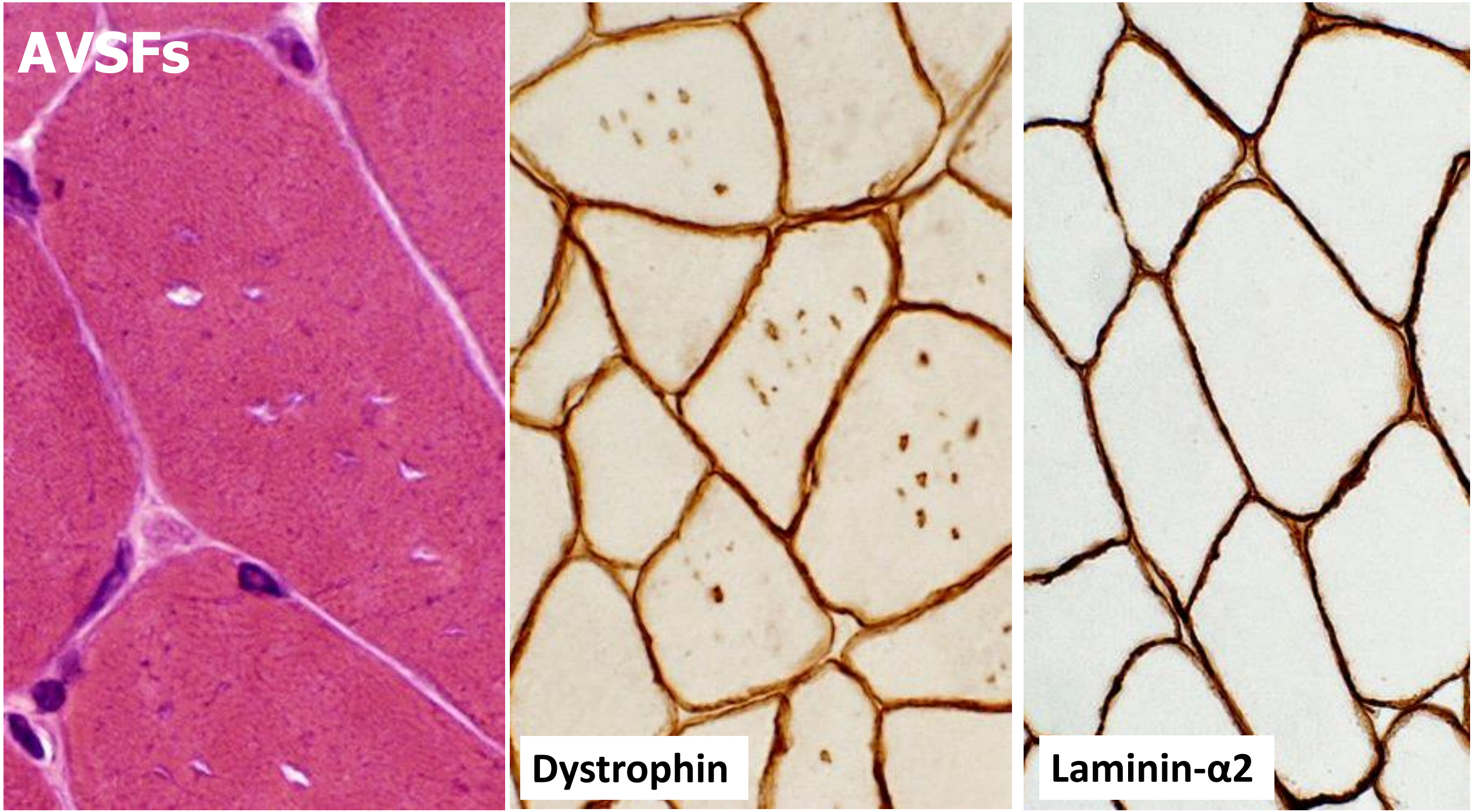
- Vacuolization: basophilic (dusty) cores // rimmed vacuoles // autophagic vacuoles with sarcolemmal features (AVSFs) // ill-defined vacuoles that can be mistaken for artifactual changes
- Basophilic stippling and increased acid phosphatase staining
- Coarse LC3+ and p62+ puncta, often clustered in the vacuolated central core
- EM:
  - autophagic vacuoles
  - curvilinear bodies (CQ/HCQ myopathy; CLN3 myopathy)
  - glycogen accumulation (Pompe disease, Danon disease)
- MHC-1 and complement can be positive in sarcolemma, but there is no lymphocytic inflammation
- Can be necrotizing (if severe)

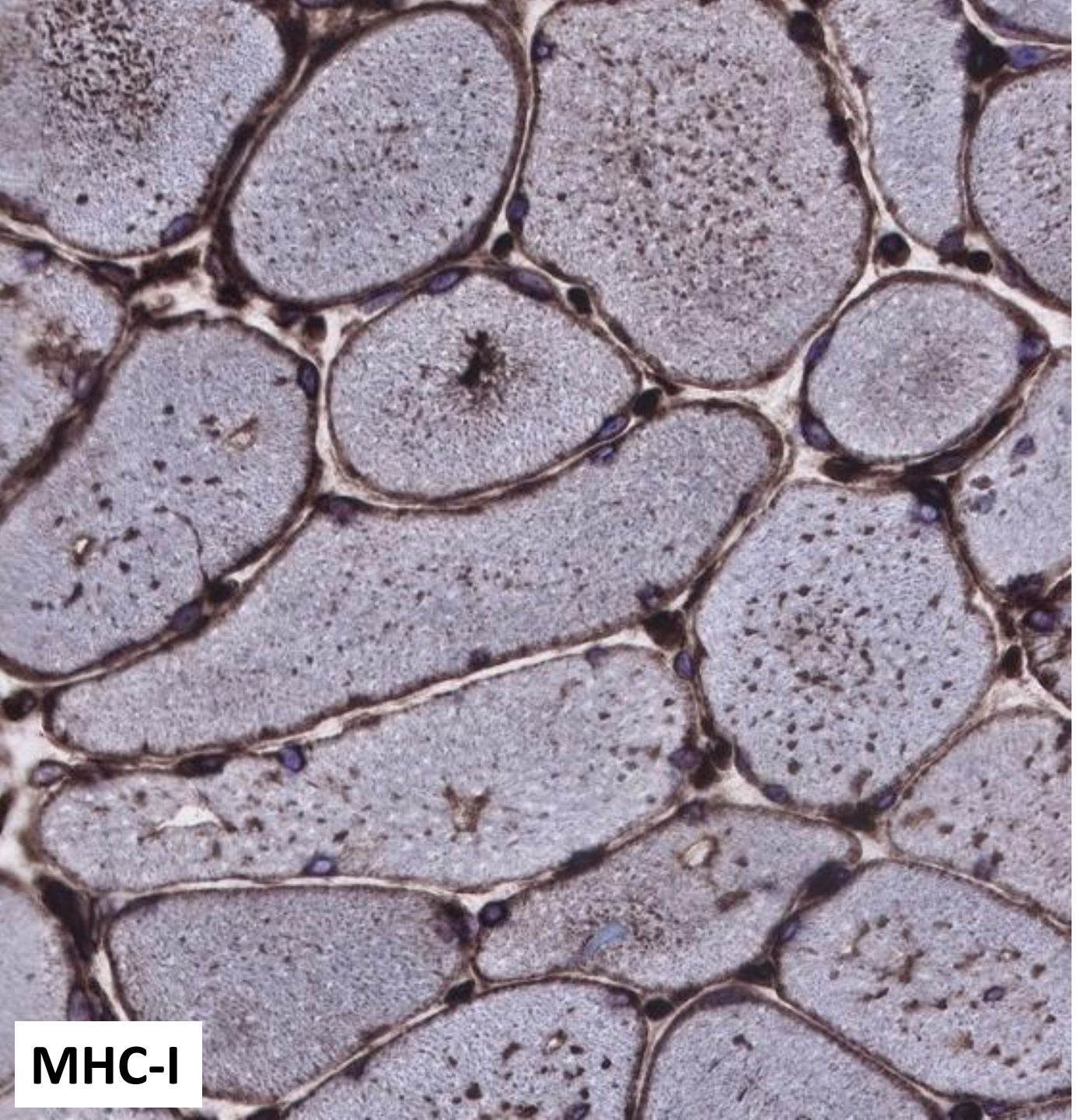

Basophilic (dusty) cores

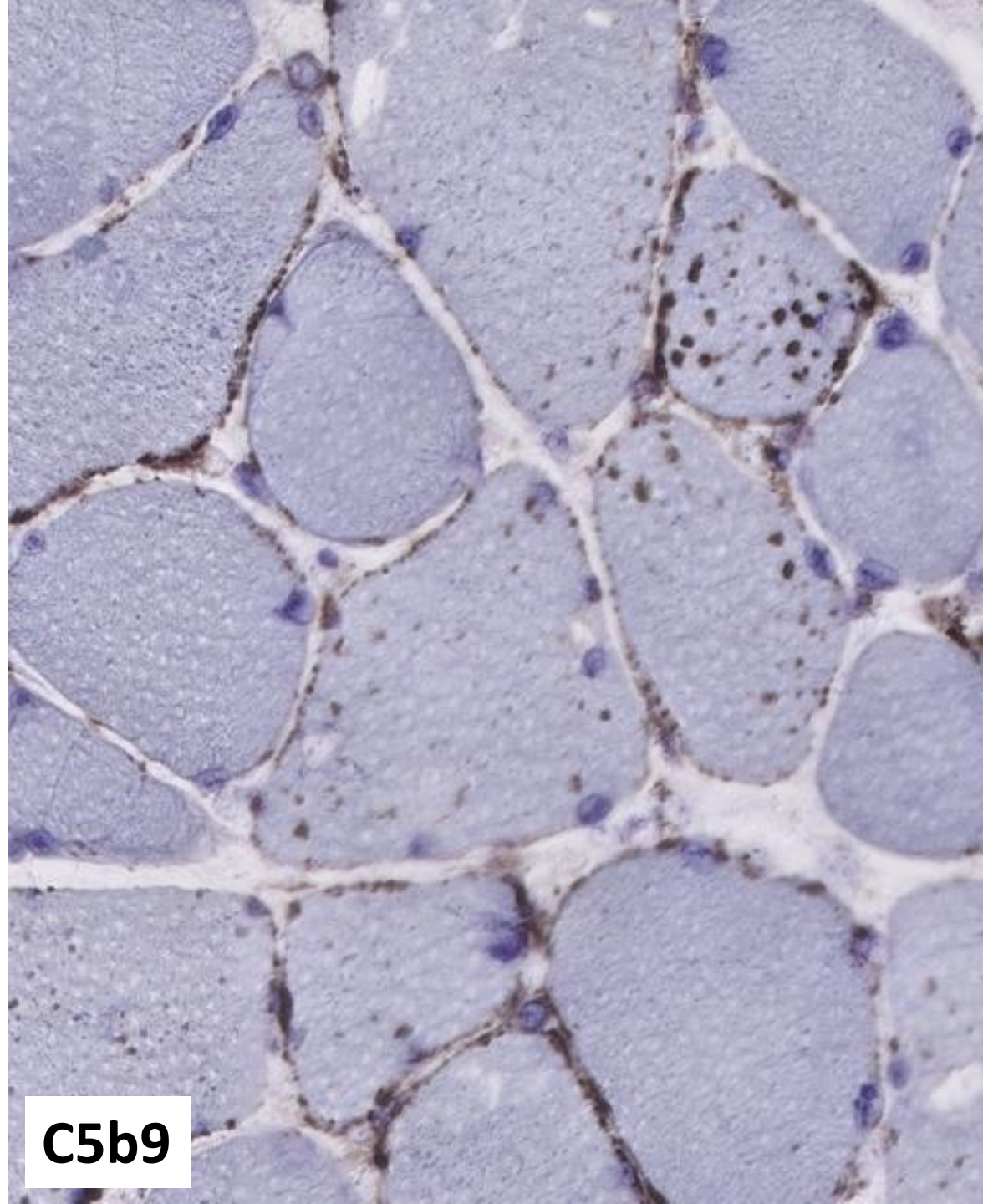


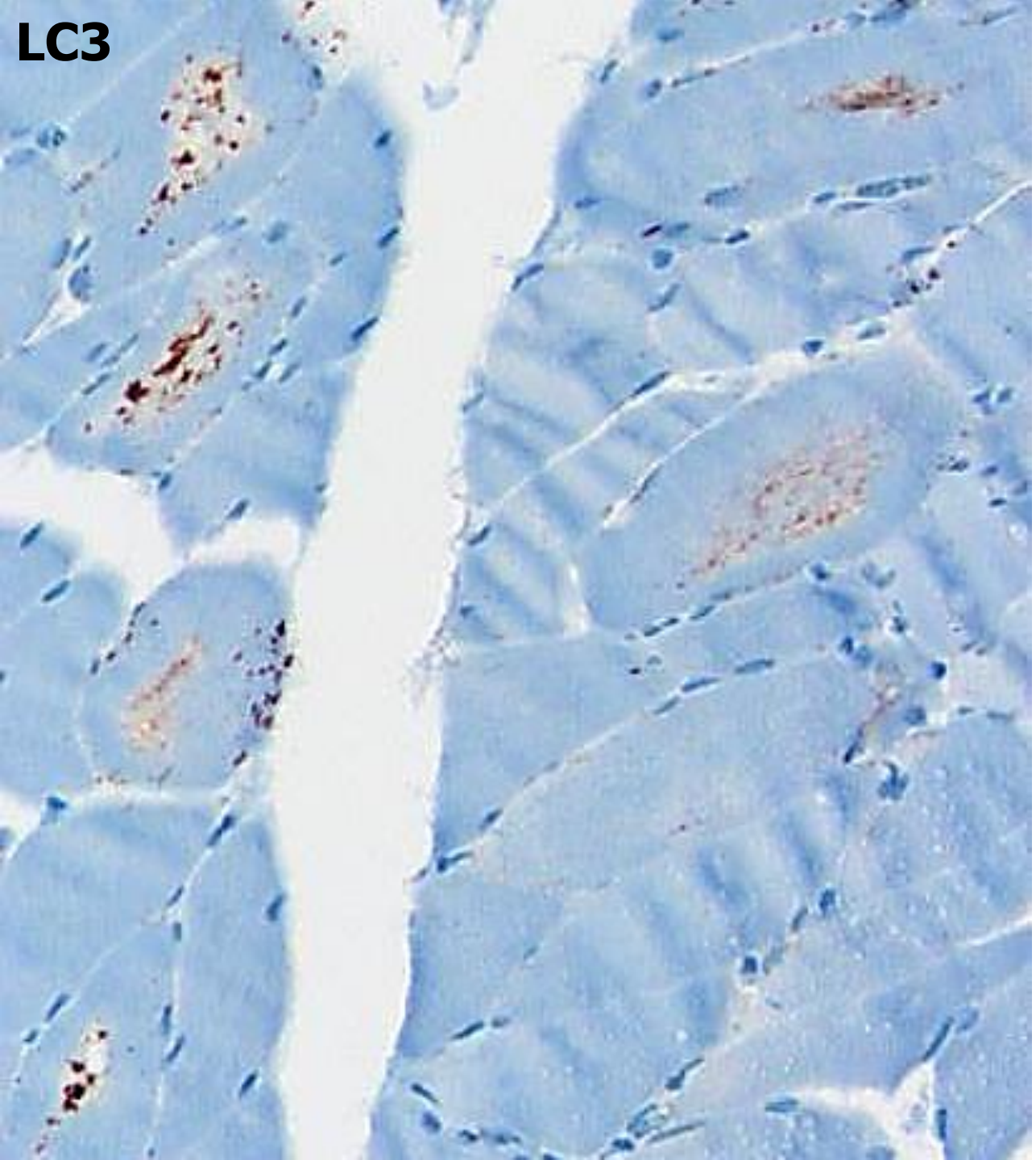
Rimmed vacuoles and basophilic stippling

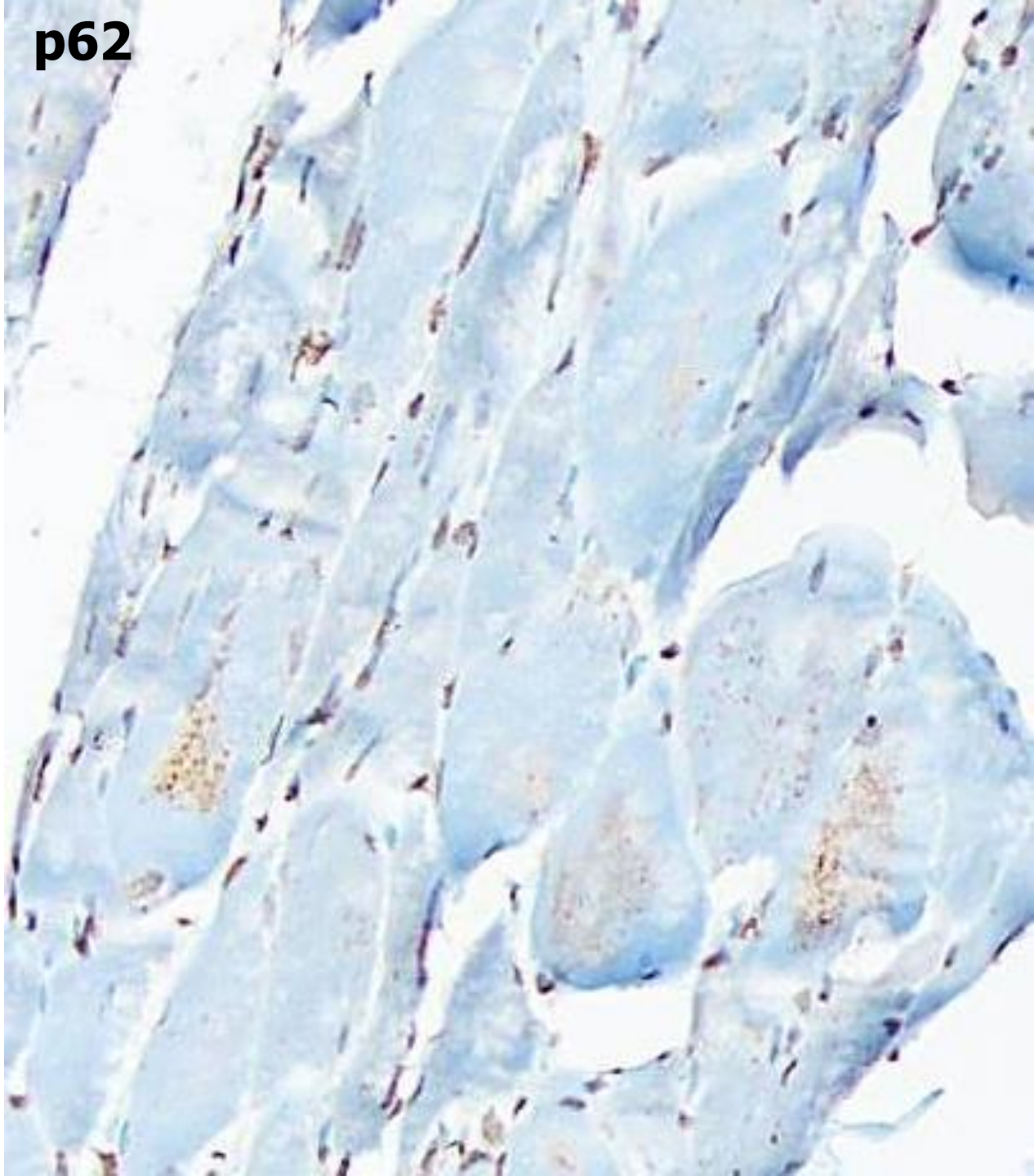


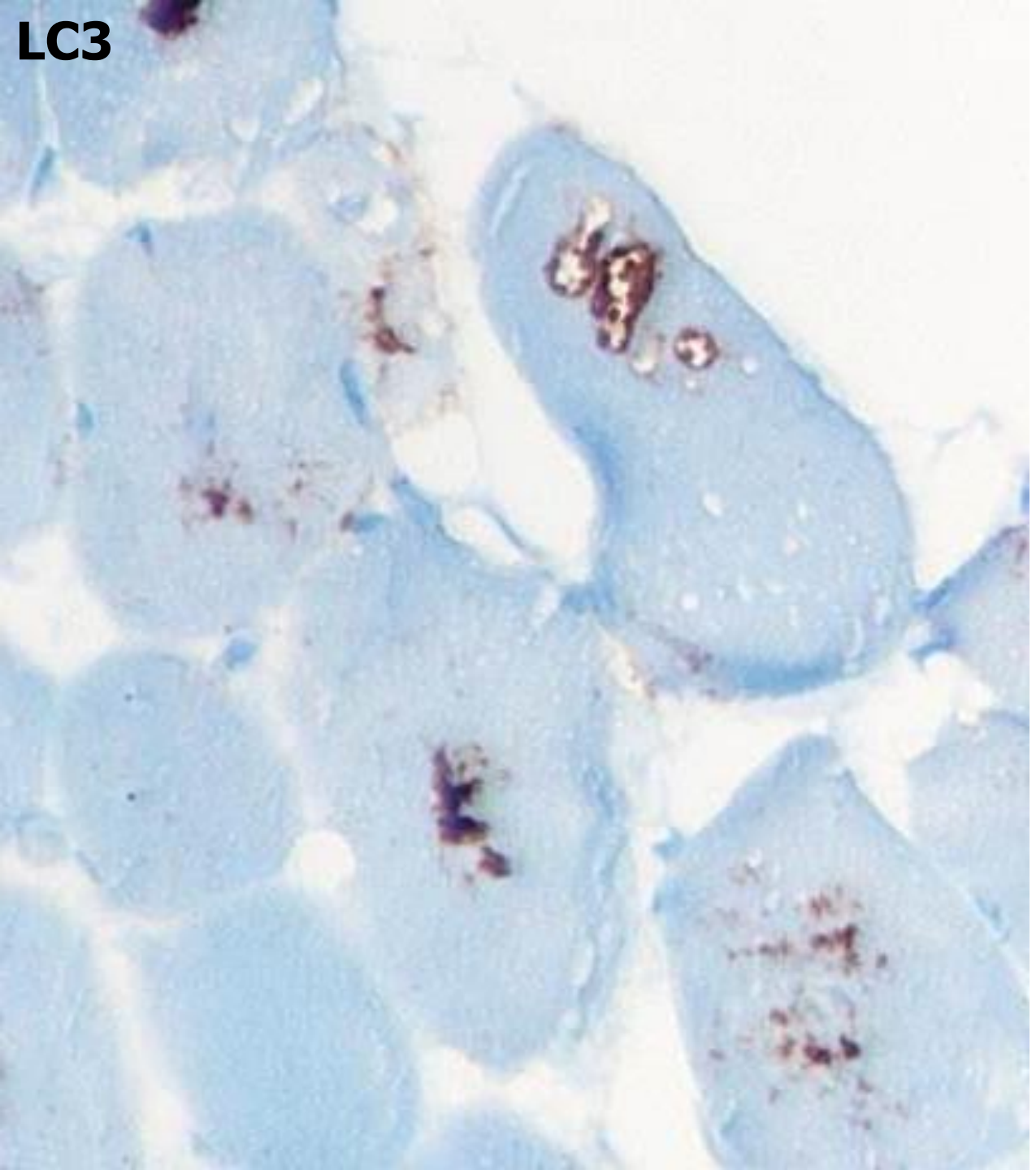

AVSFs
Dystrophin
Laminin-α2

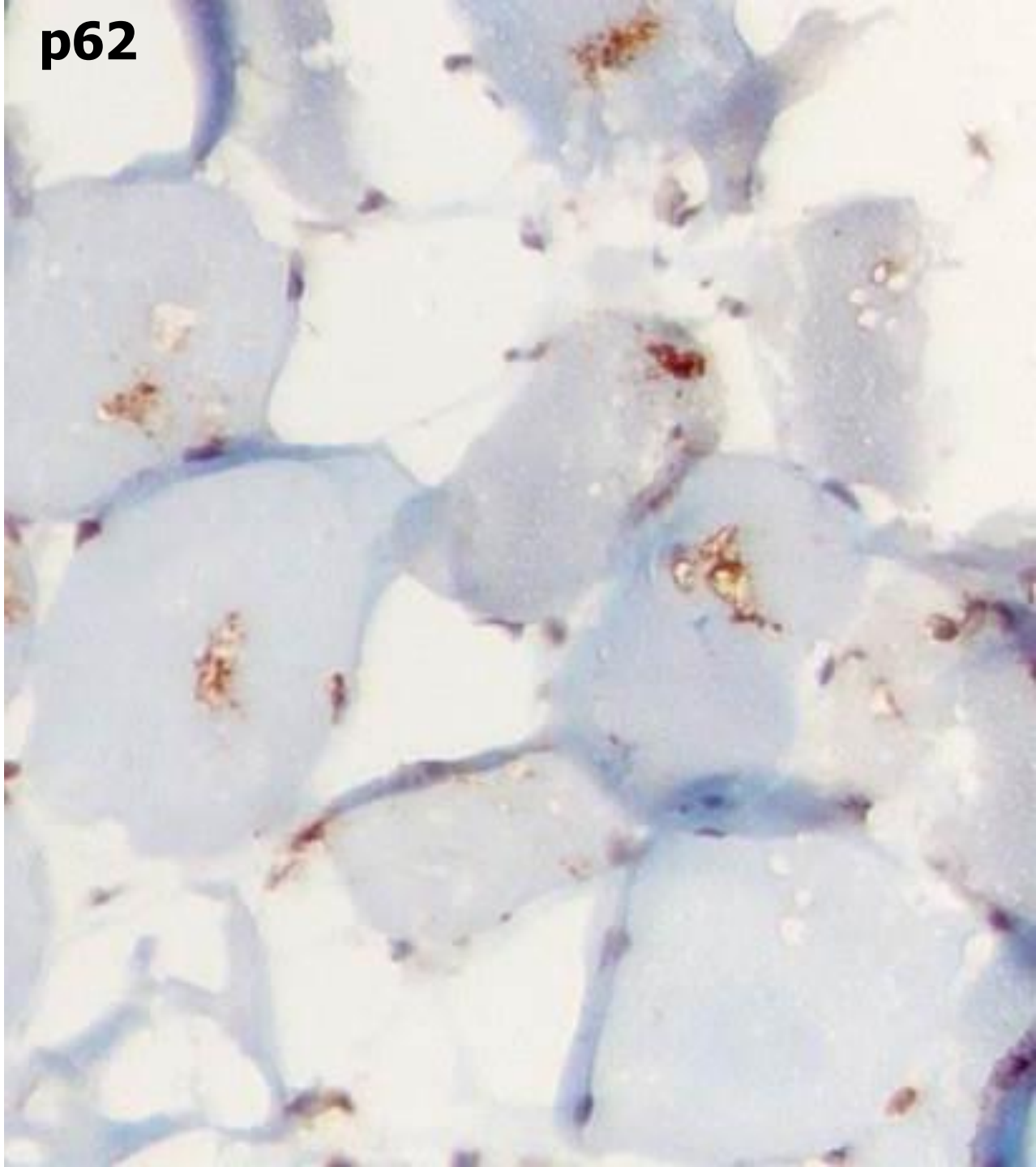

MHC-I


C5b9


LC3


p62


LC3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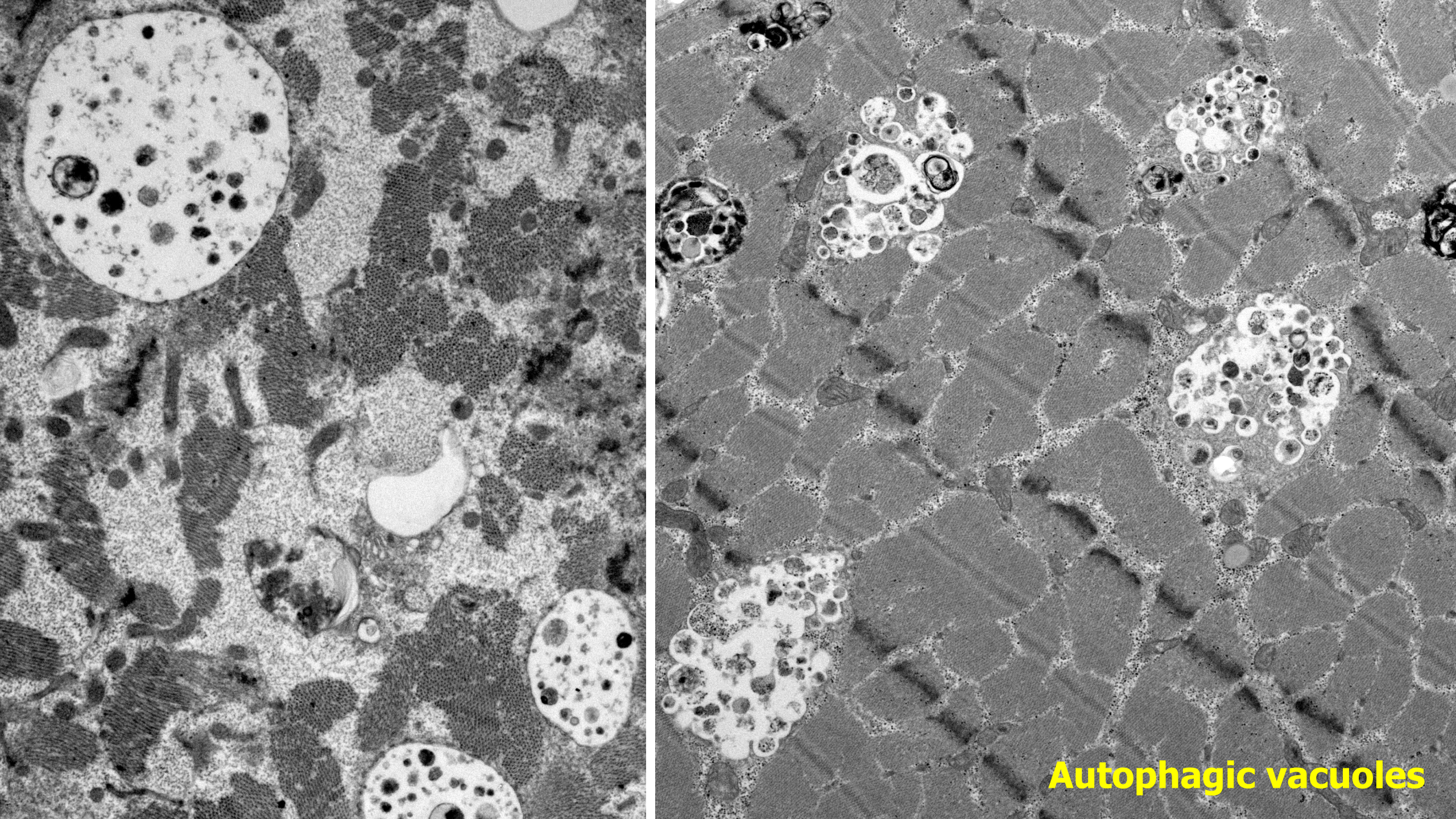
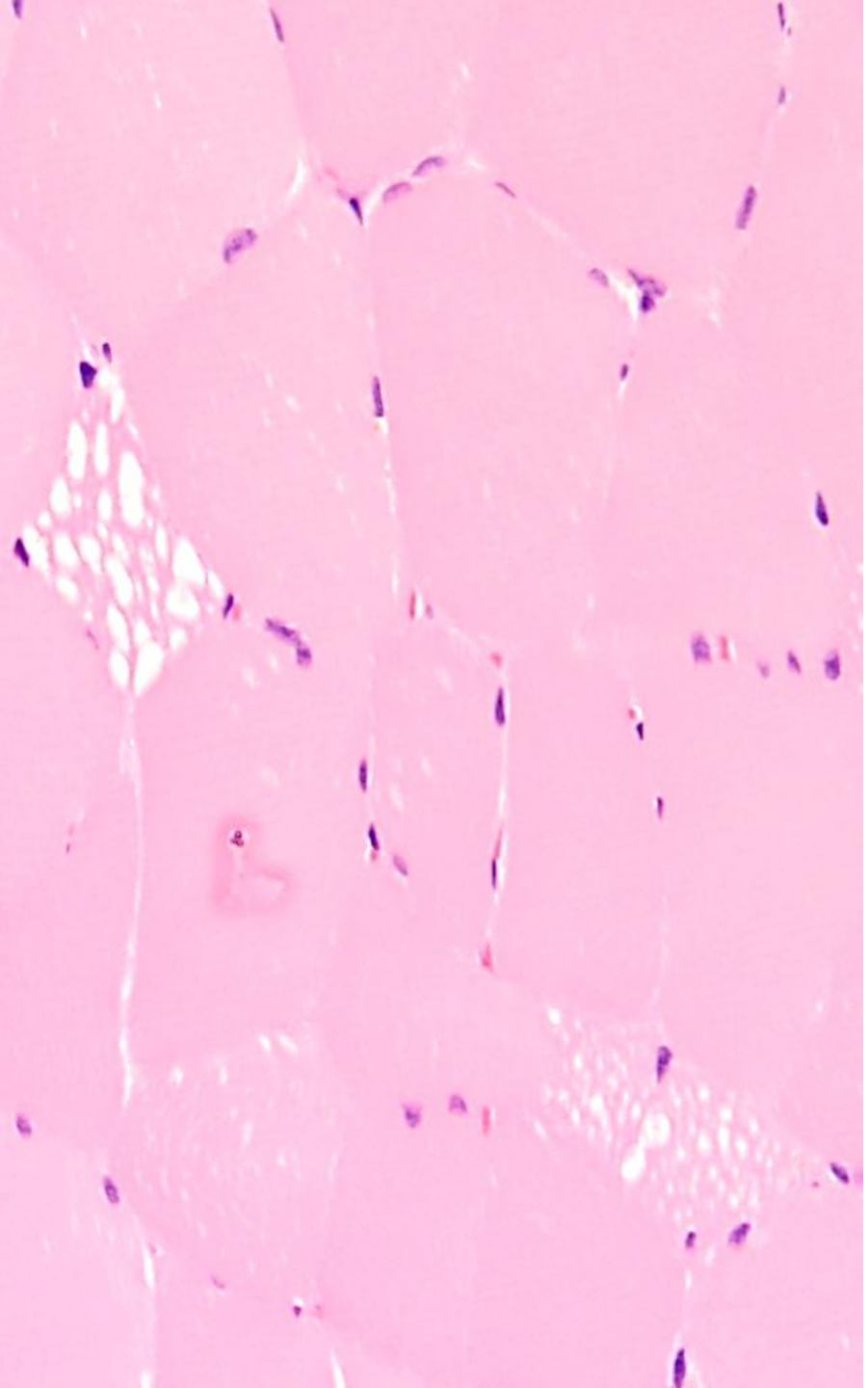
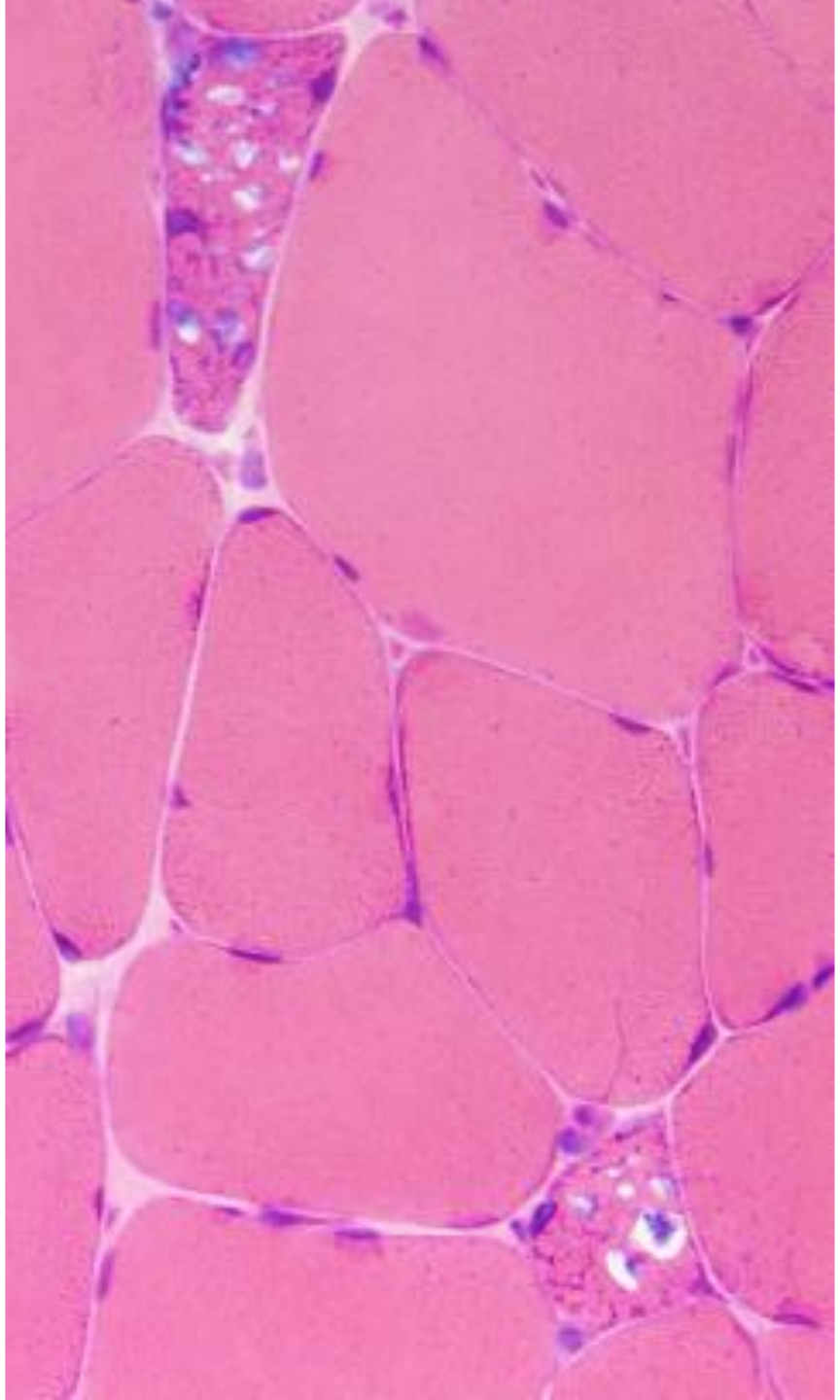
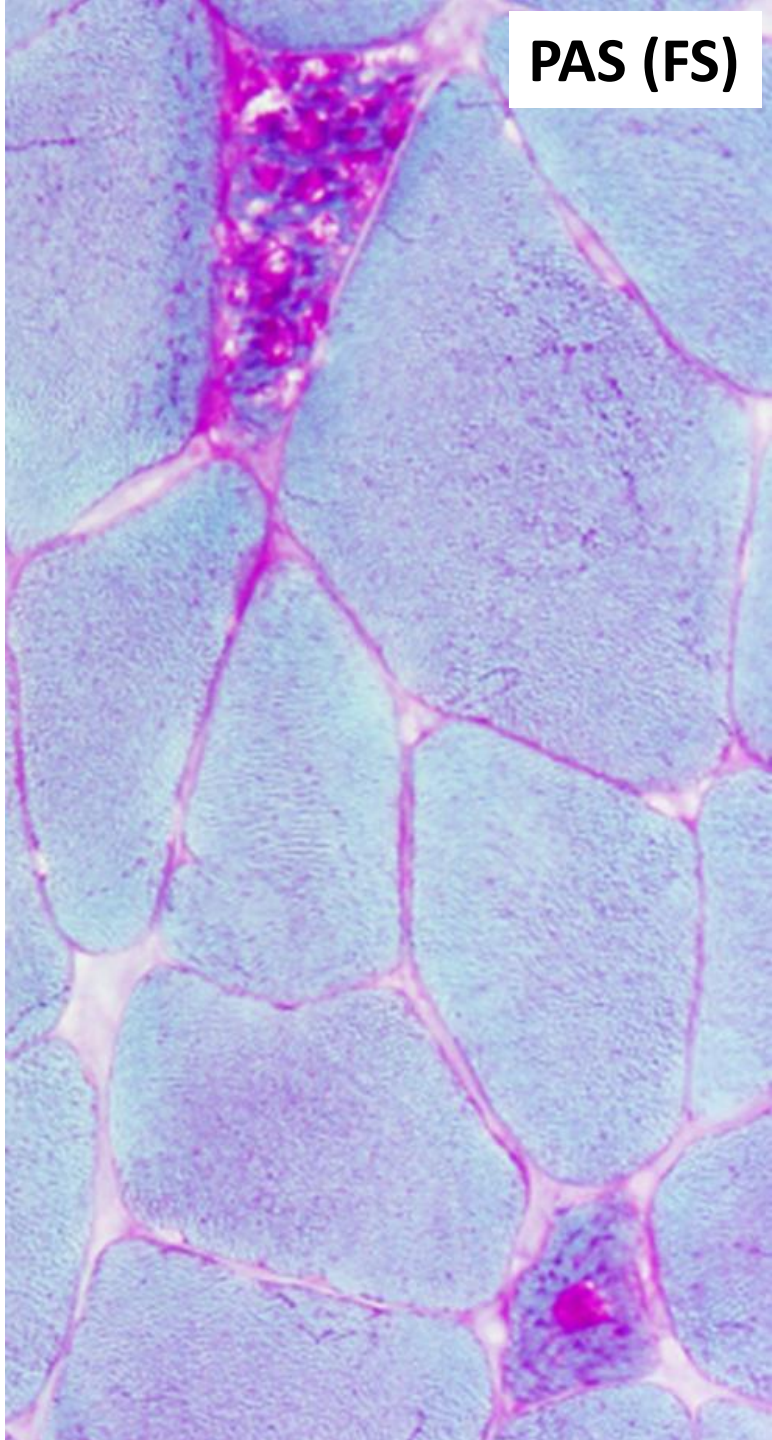

Autophagic vacuoles

Late-Onset Pompe Disease



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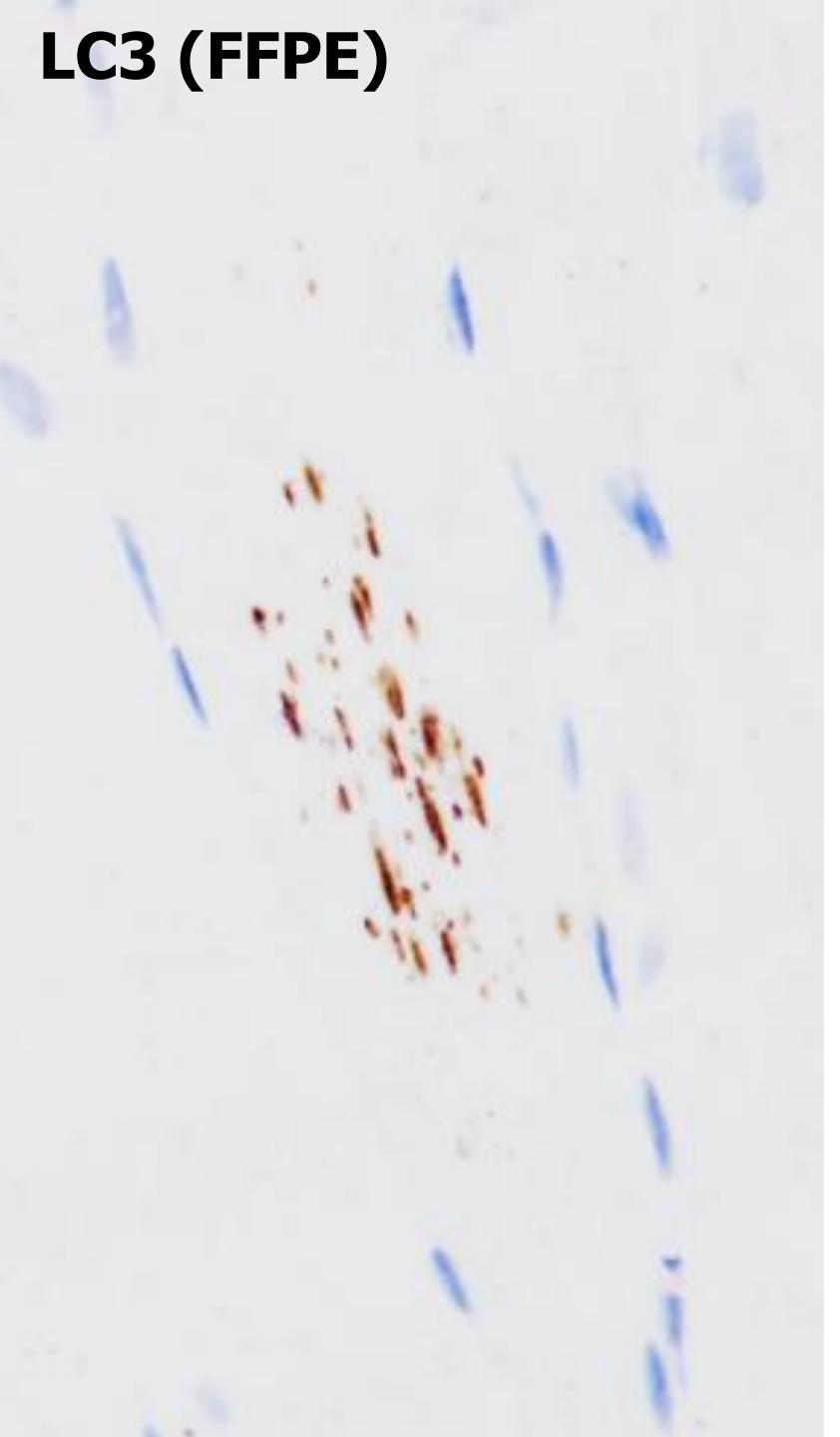
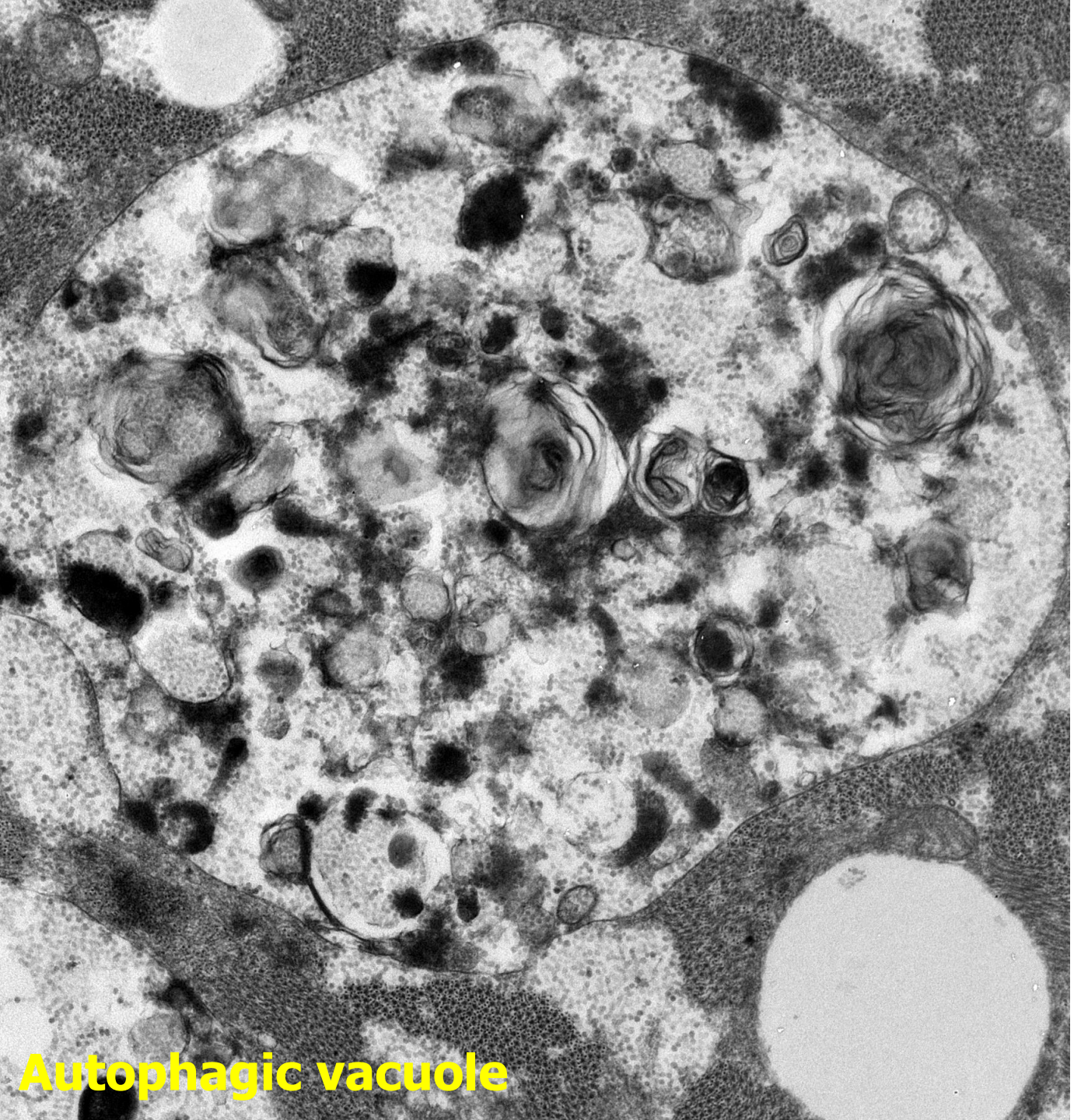
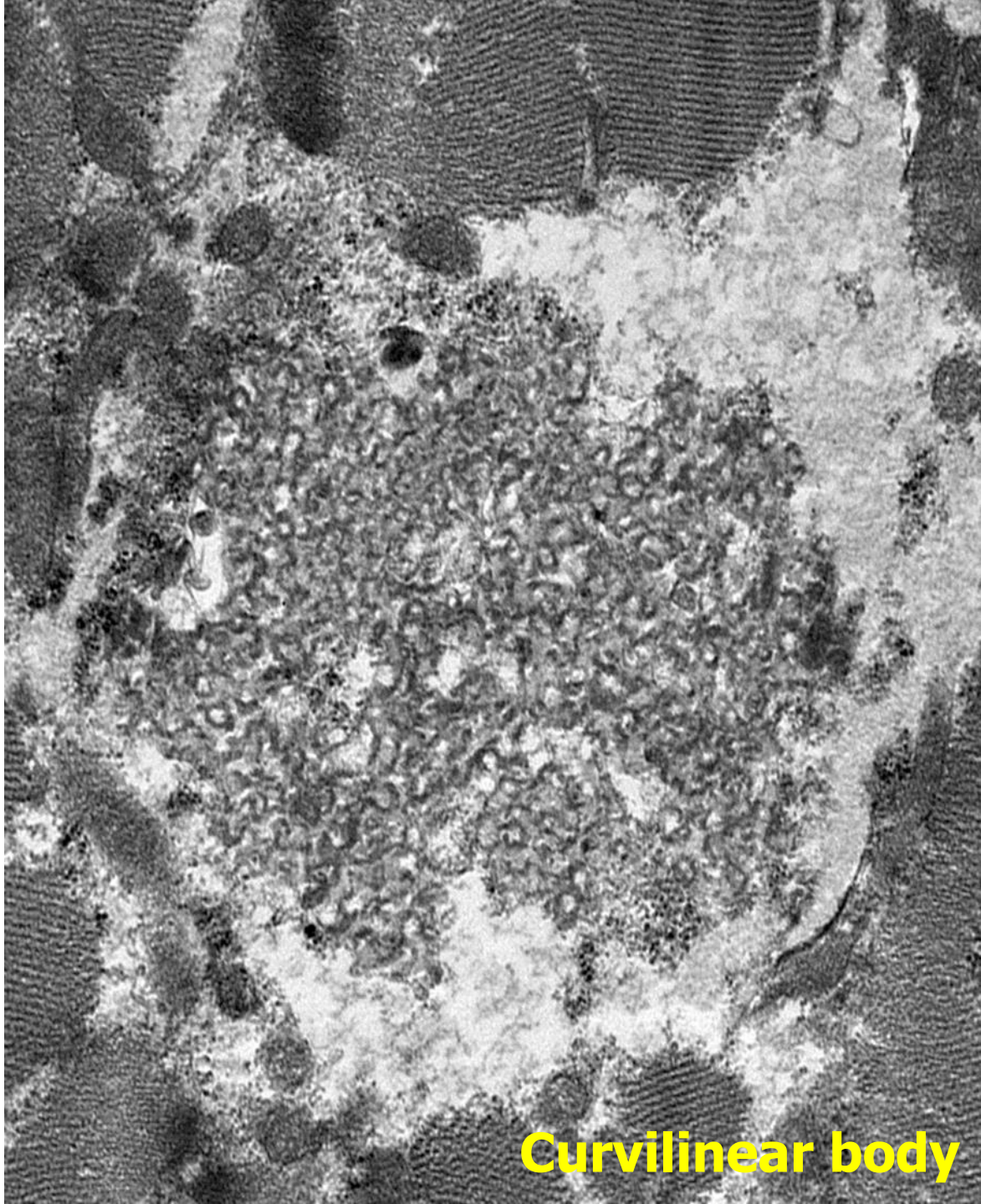

LC3 (FFPE)

Chloroquine / hydroxychloroquine toxic myopathy

Key Features

- CQ and HCQ were developed to treat malaria, but are now most frequently used to treat autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis)
- 4-aminoquinoline cationic (positively charged) compounds that accumulate in lysosomes and raise lysosomal pH
- Very long drug half-life (years) due to accumulation in adipose tissue
- Clinical presentation: skeletal myopathy, restrictive cardiomyopathy, retinopathy
  - cardiomyopathy can be fatal
- Unique EM feature: curvilinear bodies (also seen in NCLs, but not in other AVMs)

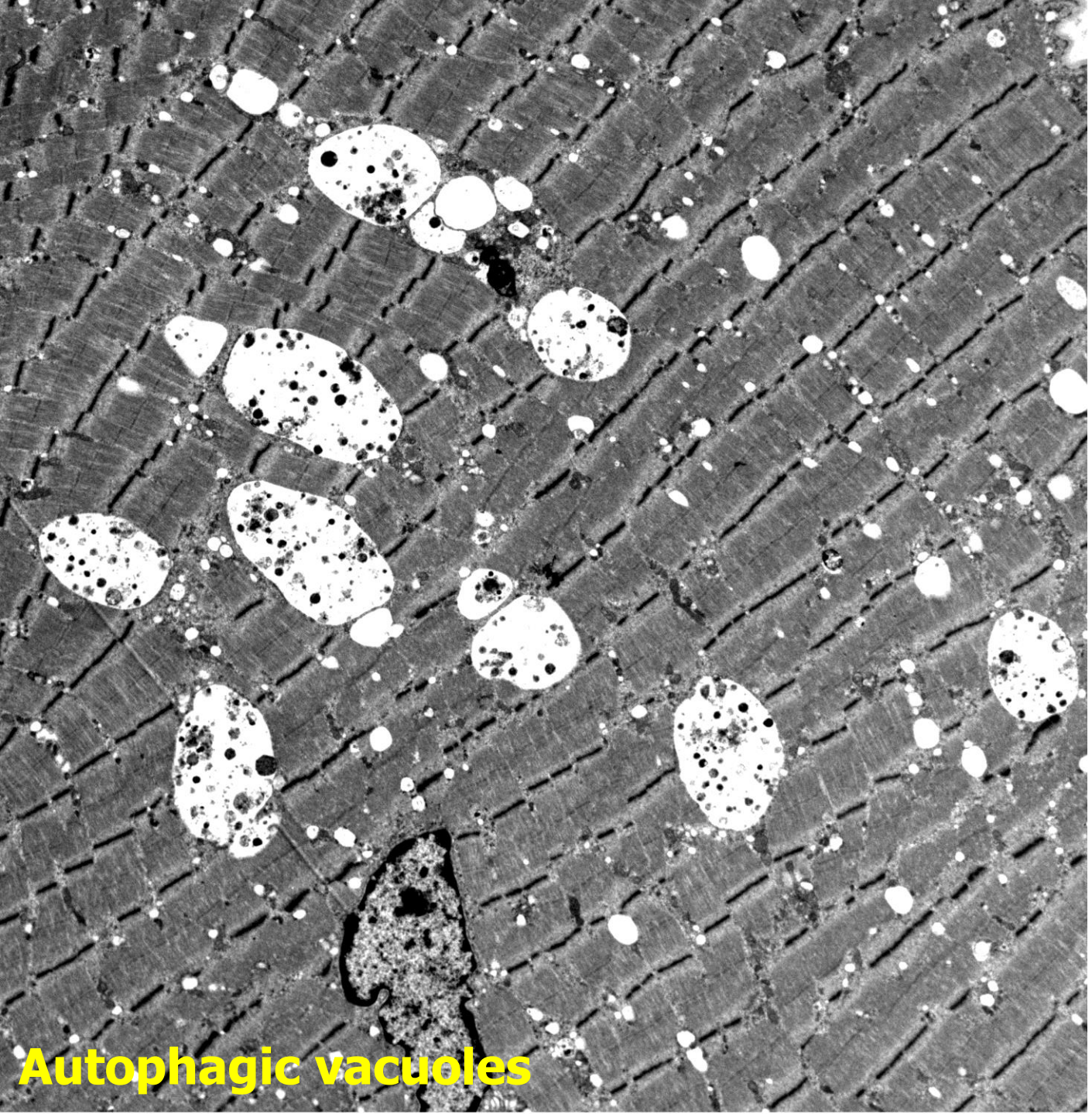

Autophagic vacuole

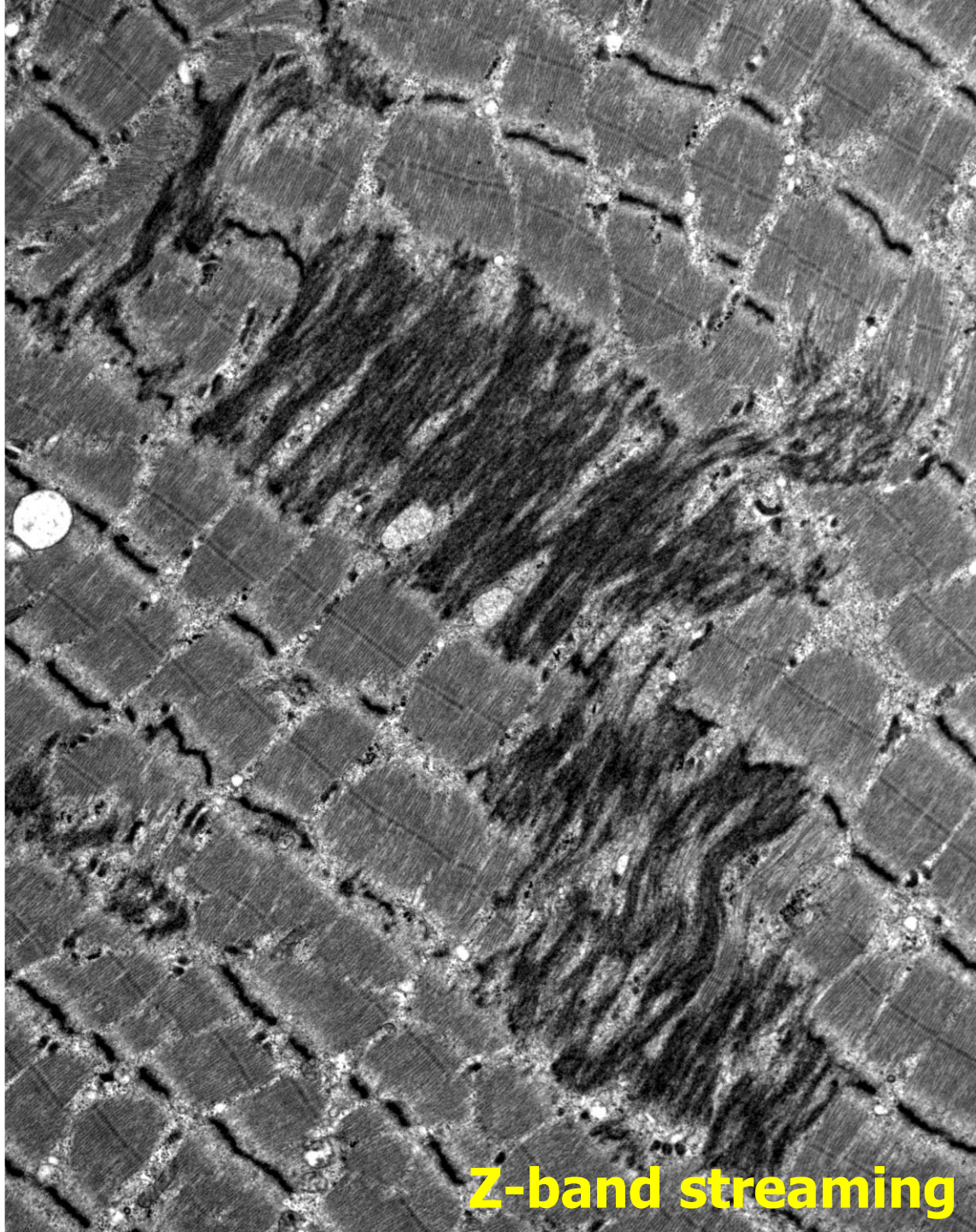

Curvilinear body

Colchicine toxic myopathy

Key Features

- Colchicine is plant-derived alkaloid used to treat and prevent gout and to treat familial Mediterranean fever
- Narrow therapeutic index:
  - Acute toxicity: multisystem organ failure and death
  - Chronic toxicity: peripheral neuropathy, skeletal myopathy
  - Increased risk: concurrent chronic kidney or liver disease, higher dose of colchicine, or concomitant use of a drug that inhibits the CYP3A4 isoform of cytochrome p450
- Binds to tubulin, preventing microtubule polymerization
- Chemotherapeutic drug vincristine has similar mechanism of action and similar side effects
- Unique EM feature: Myofibrillar disorganization (Z-band streaming, granulofilamentous material)


Autophagic vacuoles


Z-band streaming

Virtual slides

https://pathpresenter.net/#/public/presentation/display?token=29cf893e

Useful References

1. Lucas CG, Margeta M. Educational Case: Mitochondrial Myopathy. Acad Pathol. 2019 Nov 29;6:2374289519888732.
2. Vincent AE et al. The Spectrum of Mitochondrial Ultrastructural Defects in Mitochondrial Myopathy. Sci Rep. 2016 Aug 10;6:30610.
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4. Kulessa M et al. An integrative correlation of myopathology, phenotype and genotype in late onset Pompe disease. Neuropathol Appl Neurobiol. 2020 Jun;46(4):359-374.
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