2018 AANP DSS Case #3

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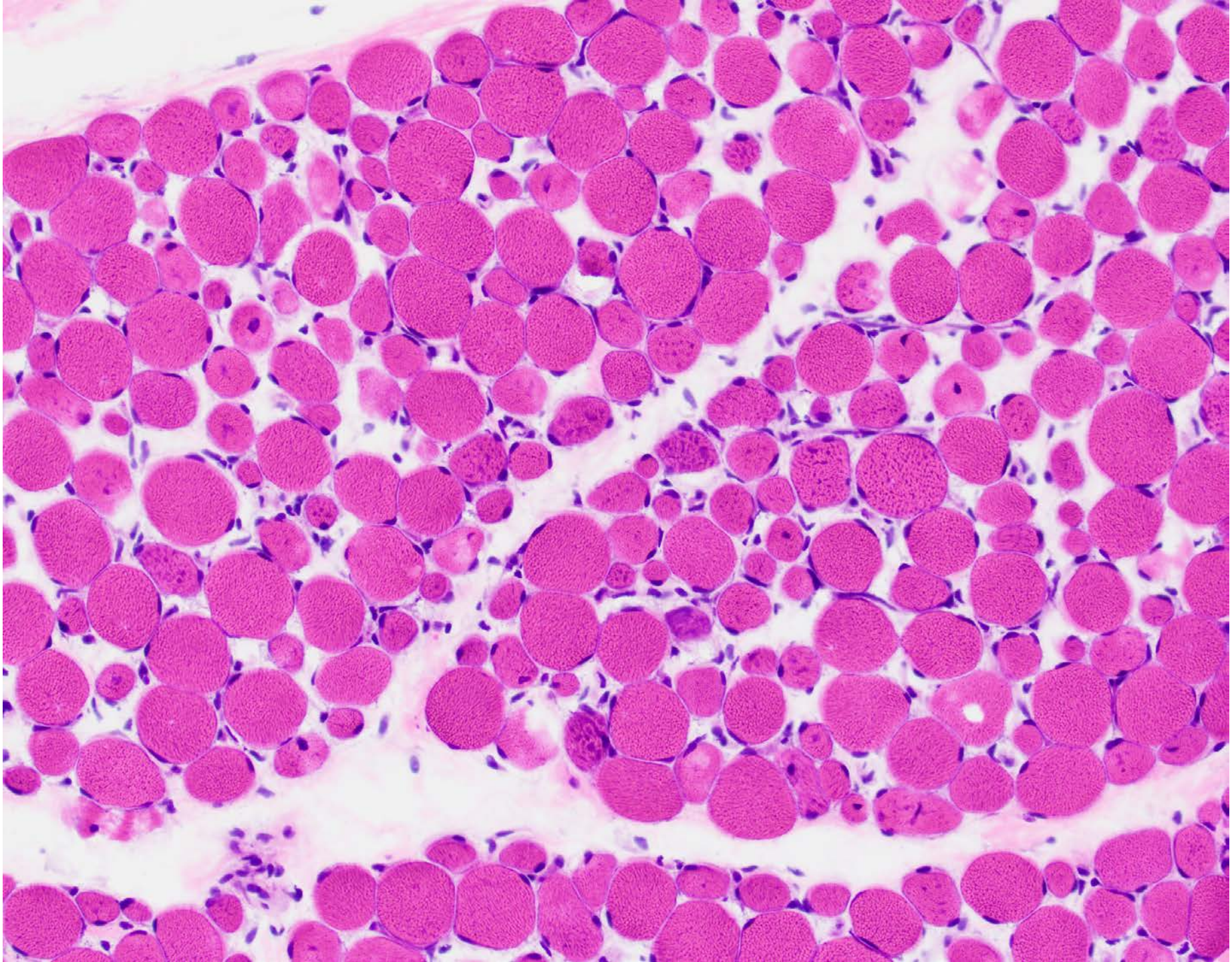
There are no financial relationships to disclose.

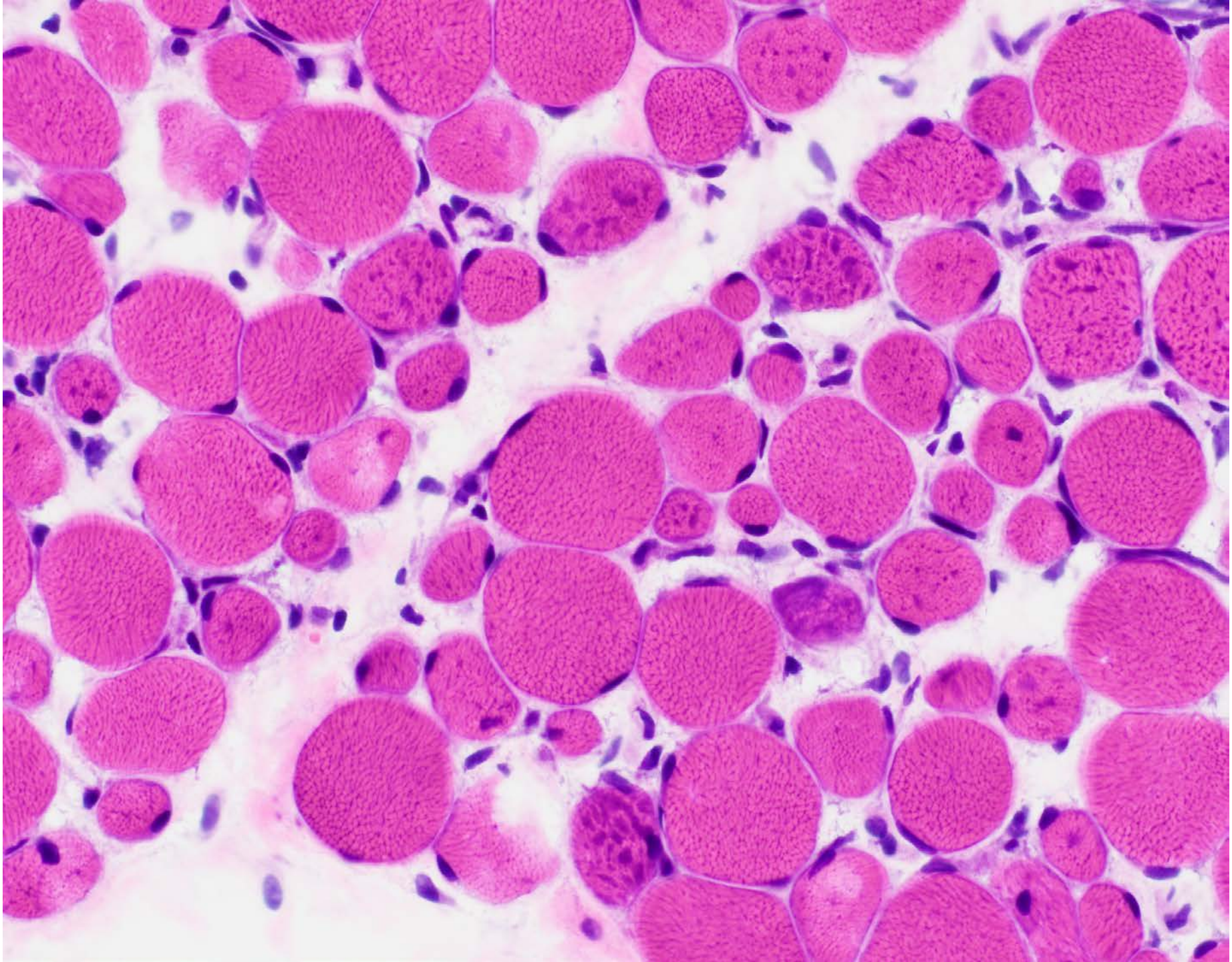
Clinical history

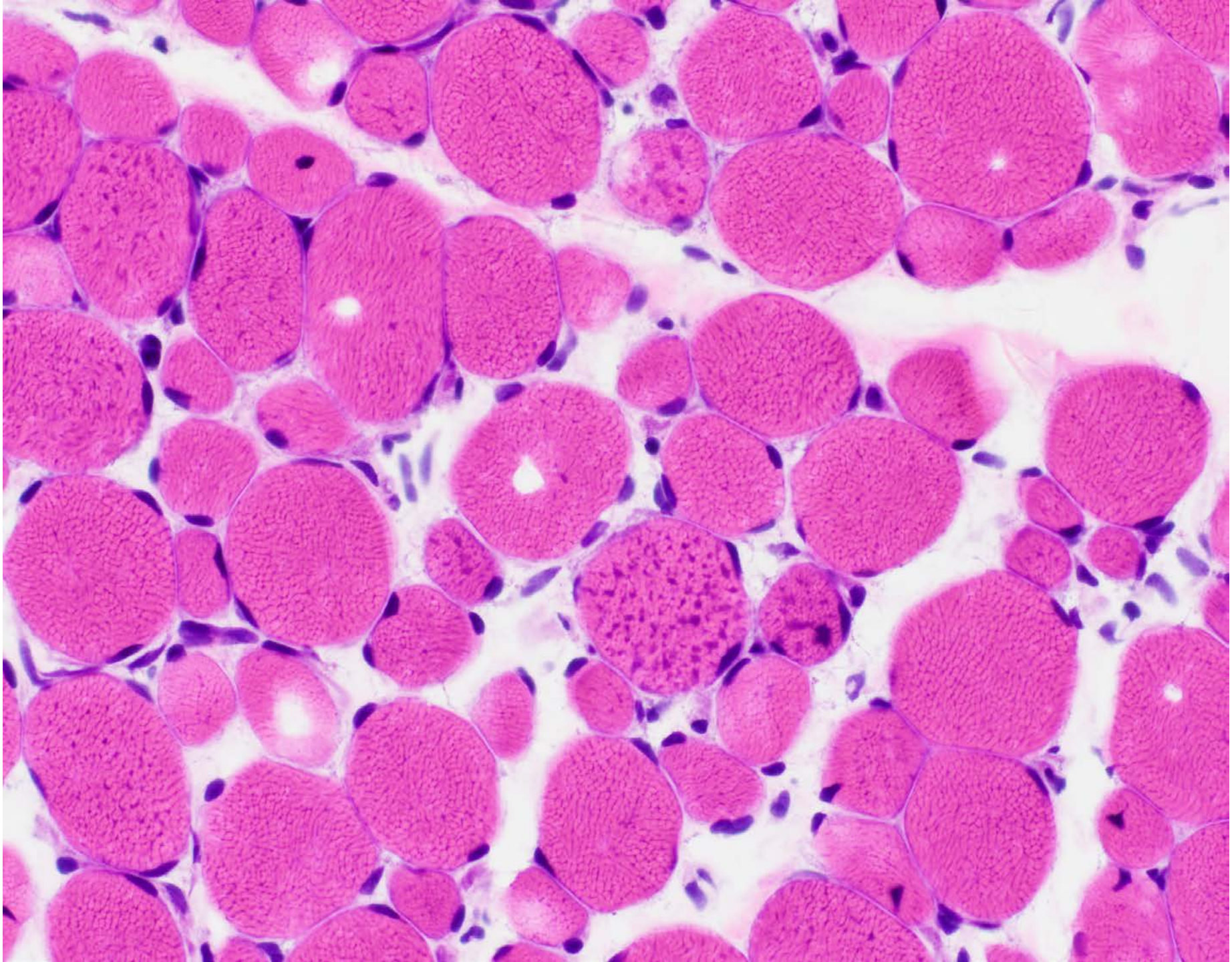
- 2 year old boy with mild global developmental delay, frequent falls, and oropharyngeal dysphagia
- Neurologic exam:
  - Positive Gower's sign
  - Abnormal gait; compensated Trendelenburg
- Family history:
  - Maternal uncle with unknown neuromuscular disease requiring use of a wheelchair since age 12
- CK elevated to 1300-1400 U/L (normal <192 U/L)

Clinical history

- Genetic testing prior to muscle biopsy all normal/negative including:
  - Chromosomal microarray
  - *DMD* deletion/duplication testing
  - *DMD* complete sequencing
  - GAA enzymatic activity
  - Congenital hypotonia NGS panel







Points for discussion

- Differential diagnosis
- Approach to diagnostic testing

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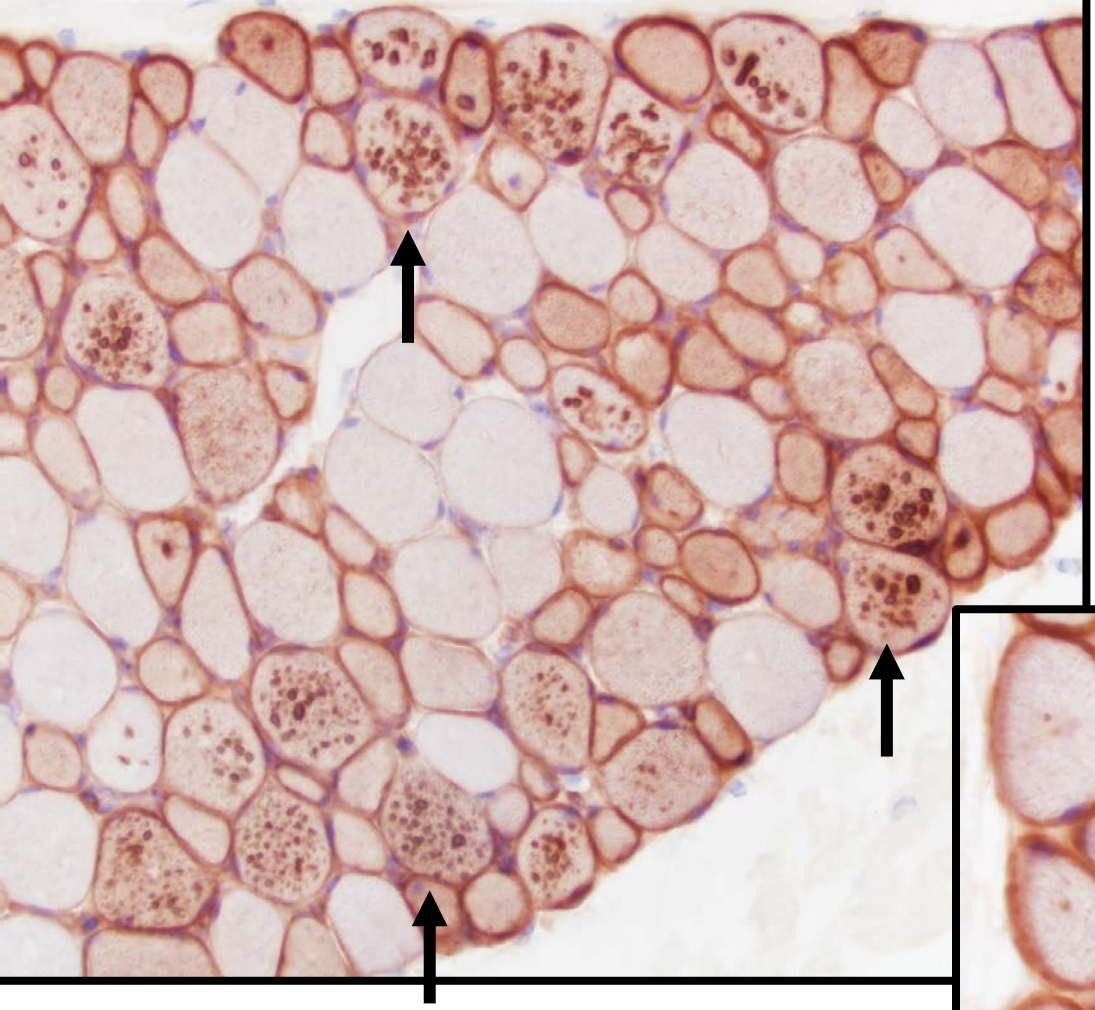
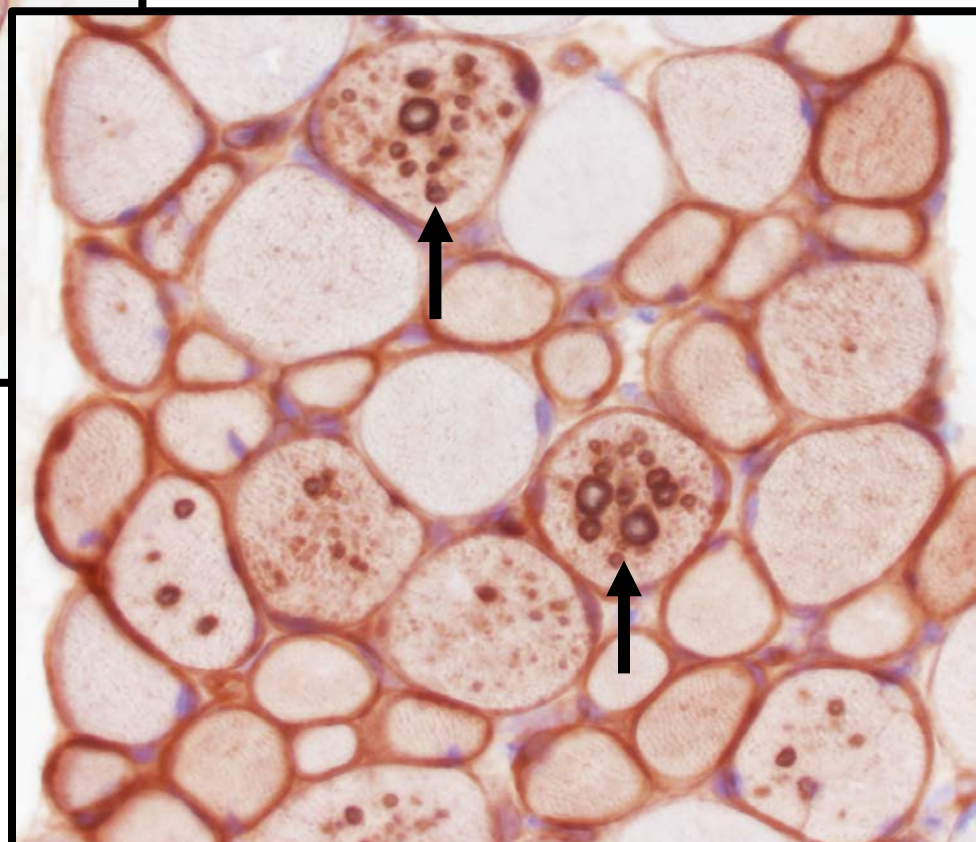
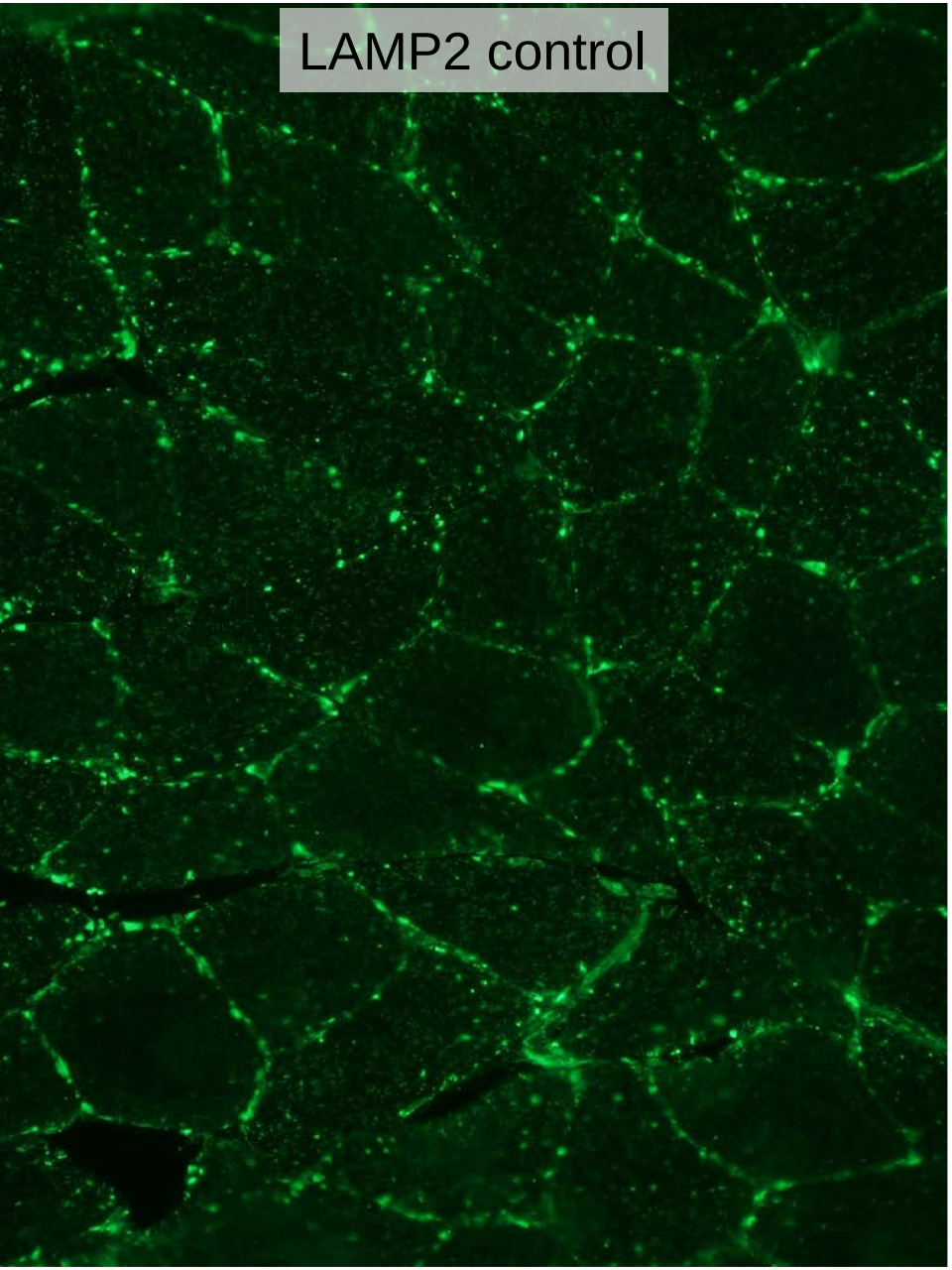
- Differential diagnosis:
  - Autophagic vacuolar myopathy
  - Myopathy or dystrophy with vacuoles
  - Mitochondrial myopathy/mitochondrial alterations

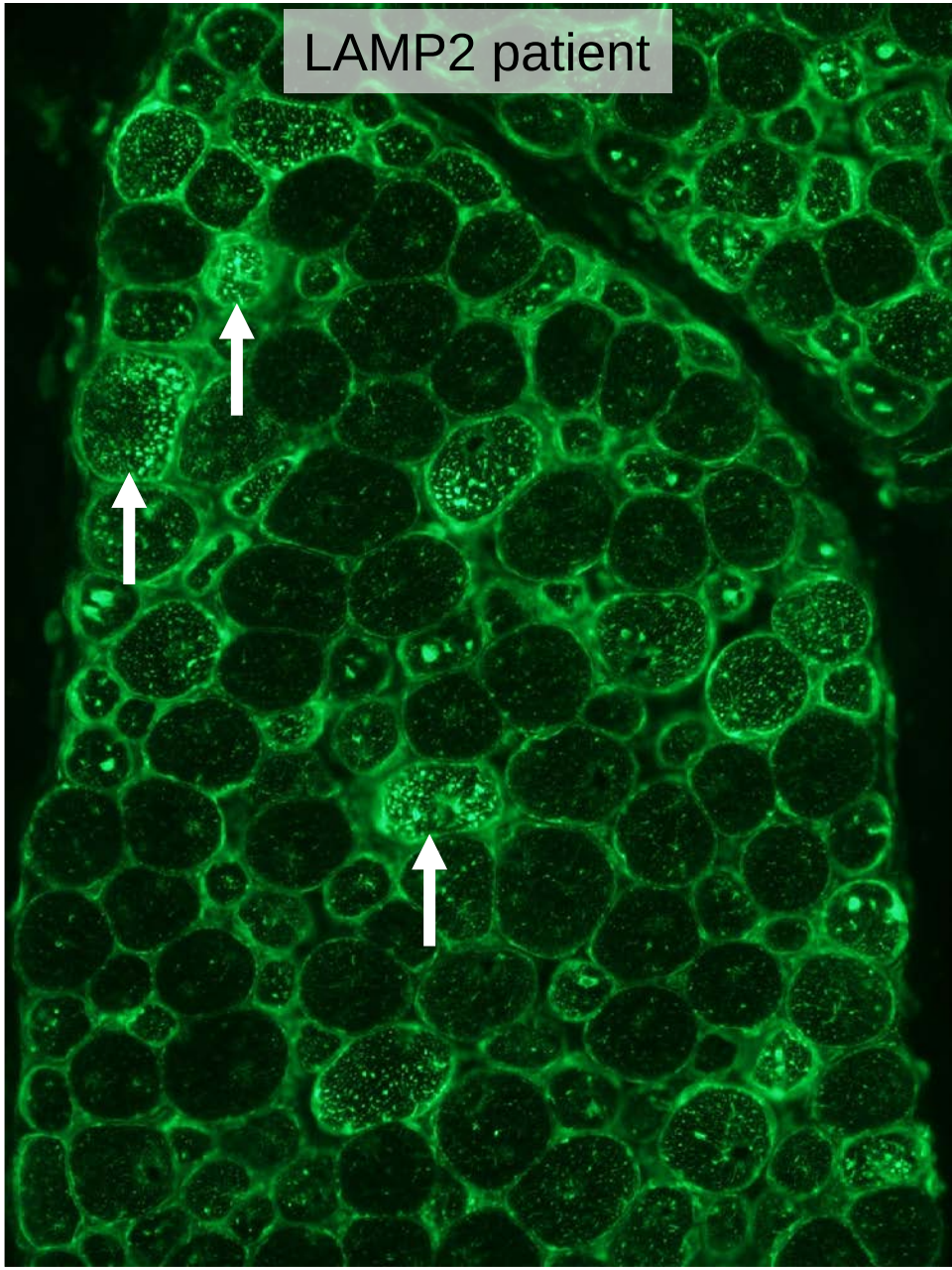
- Approach to diagnostic testing
  - Acetylcholinesterase staining
  - Immunostaining for LAMP2, complement C5b-9, and if needed dystrophin, merosin, alpha-dystroglycan, and spectrin
  - Electron microscopy, as needed
  - Genetic testing, as needed

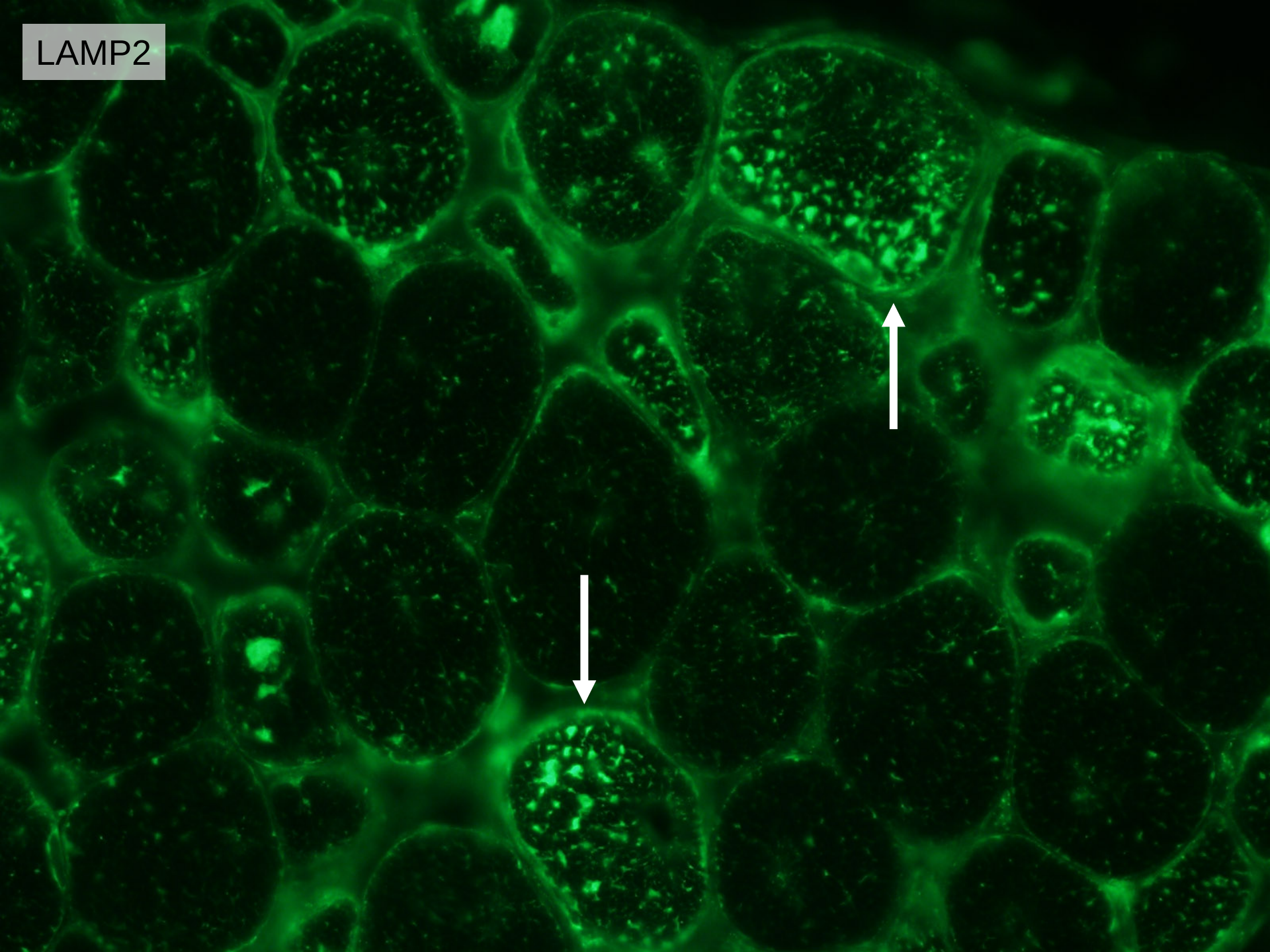
Acetylcholinesterase

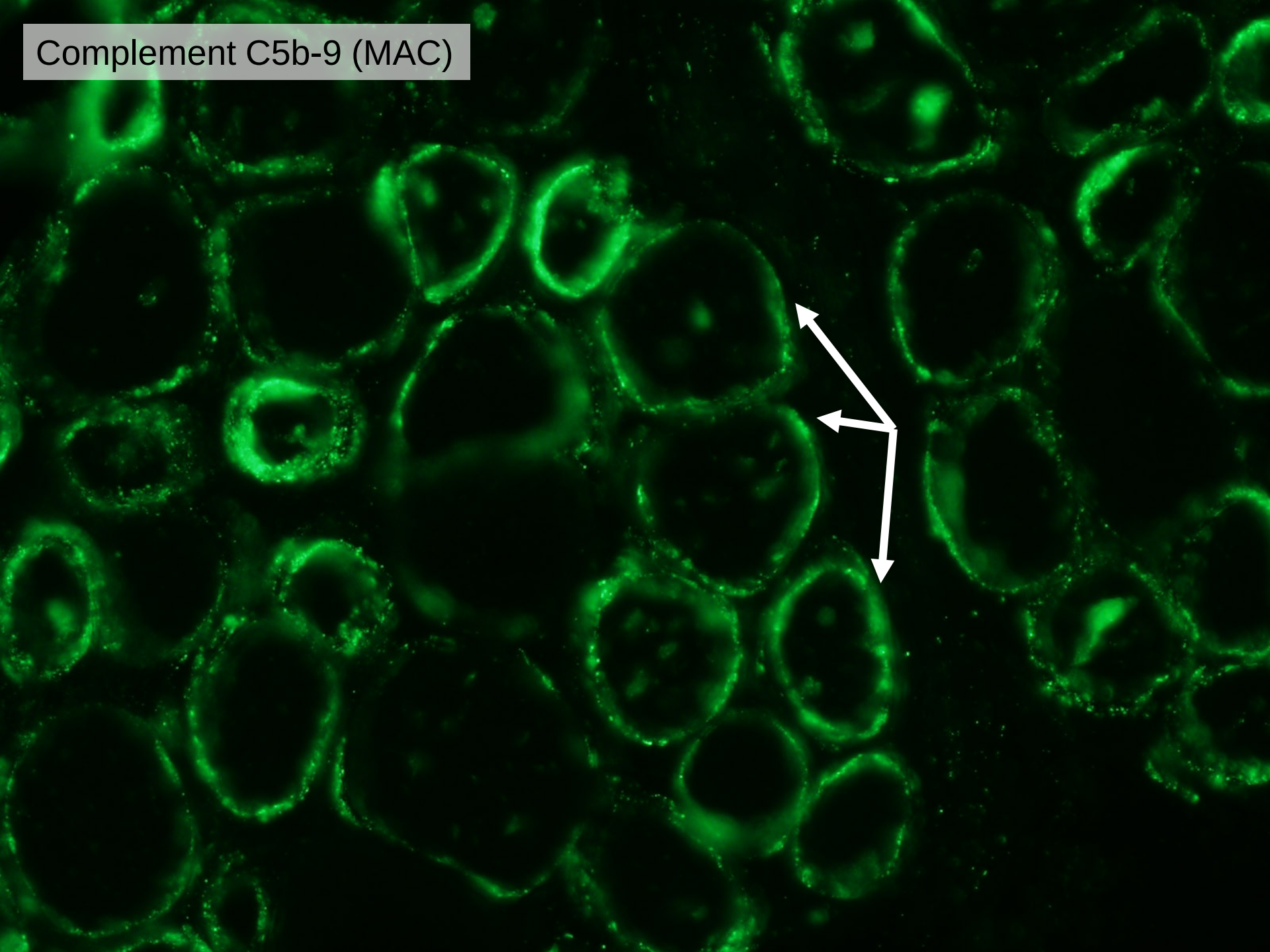


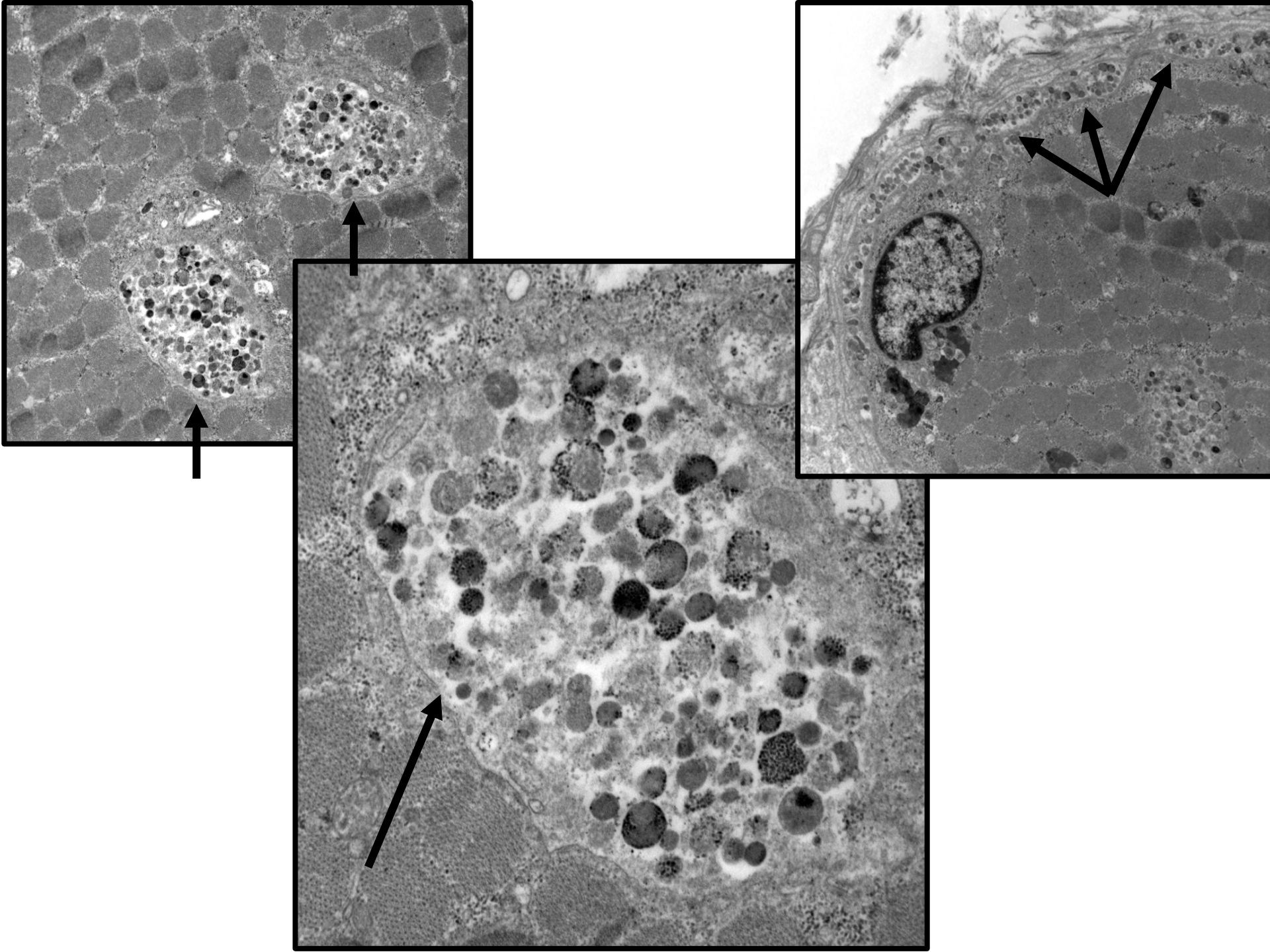



LAMP2 control


LAMP2 patient


LAMP2


Complement C5b-9 (MAC)



Diagnosis

- Muscle biopsy diagnosis:
  - Autophagic vacuolar myopathy with LAMP2 positivity
- Additional testing:
  - Directed sequencing of the *VMA21* gene revealed a novel splice site mutation: c.164G>T; p.Gly55Val → loss of splice acceptor
- Final diagnosis:
  - X-linked myopathy with excessive autophagy (XMEA)

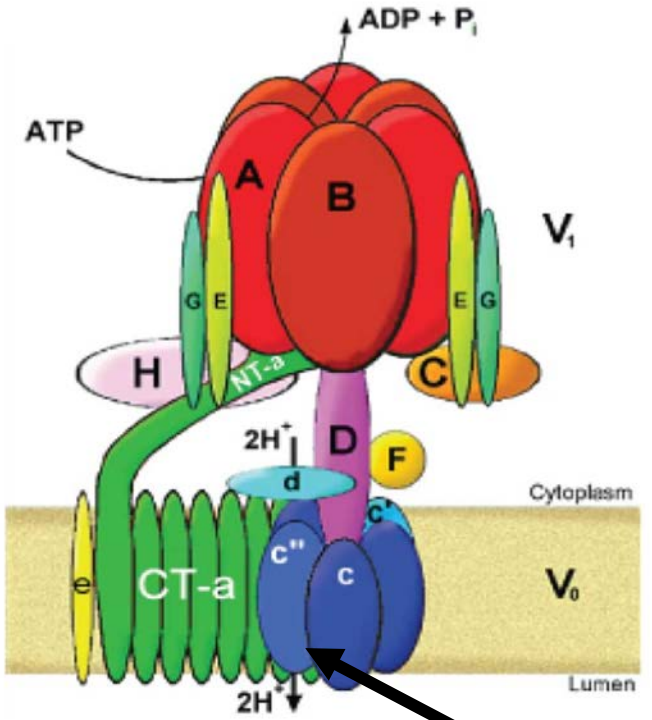
Autophagic vacuolar myopathies

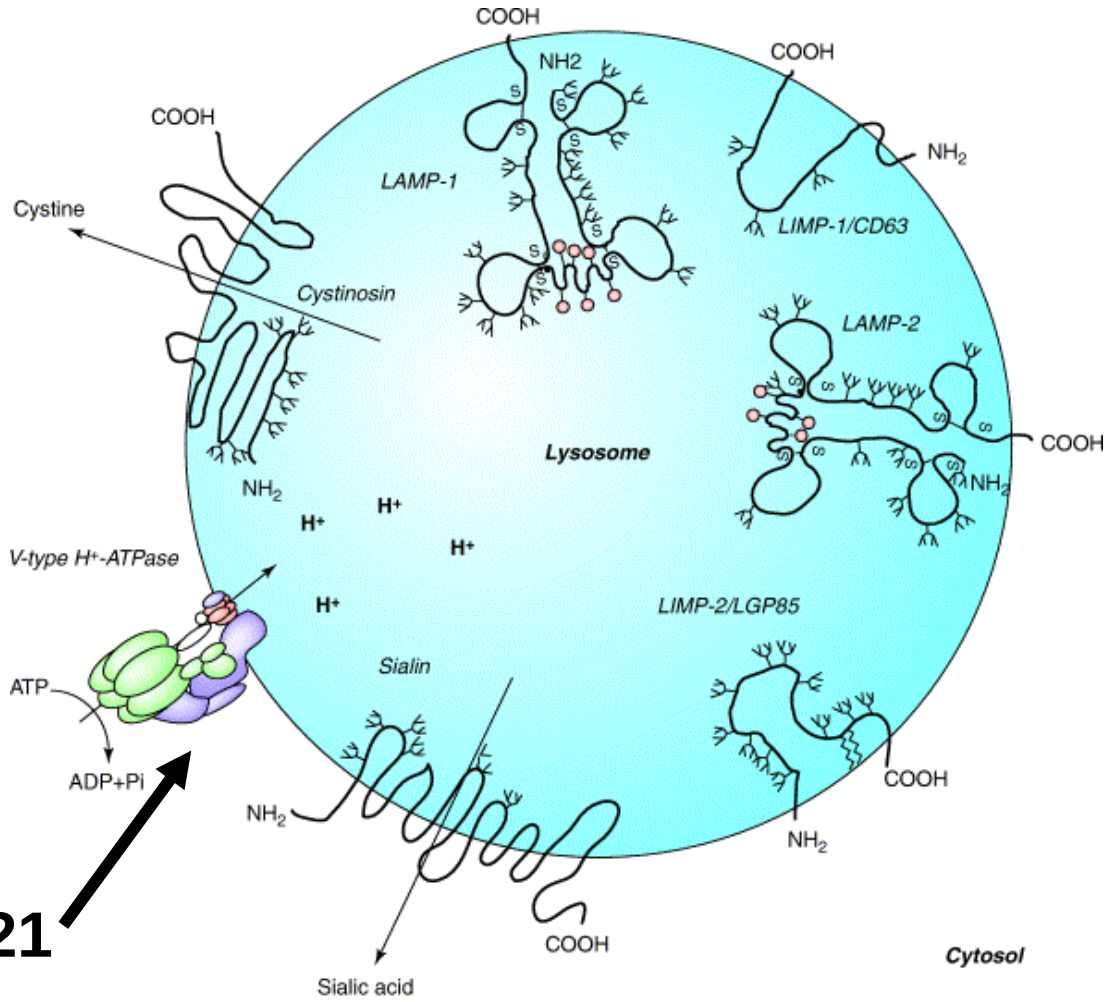
- **X-linked myopathy with excessive autophagy (XMEA)**
- Danon disease
  - X-linked autosomal dominant mutations in *LAMP2*
  - Cognitive impairment and cardiomyopathy
  - *Loss of LAMP2 expression that can be detected by immunostaining*
- Pompe disease
  - Recessive mutations in *GAA*
  - Acid maltase deficiency
  - Variable clinical presentation, but can involve heart and brain

XMEA

- Mutations in *VMA21*
- X-linked recessive
- Present anytime between birth and adulthood
- Slowly progressive weakness, proximal > distal
- No cardiac or cognitive involvement
- CK usually 2-3x normal, but highly variable
- EMG shows electrical myotonia
- Biopsies characterized by cytoplasmic vacuoles with sarcolemmal features, deposition of complement C5b-9, and positivity for LAMP2
- EM shows intracellular membrane bound autophagic vacuoles and extrusion of vacuoles with redundant basal lamina

V-ATPases acidify lysosomes





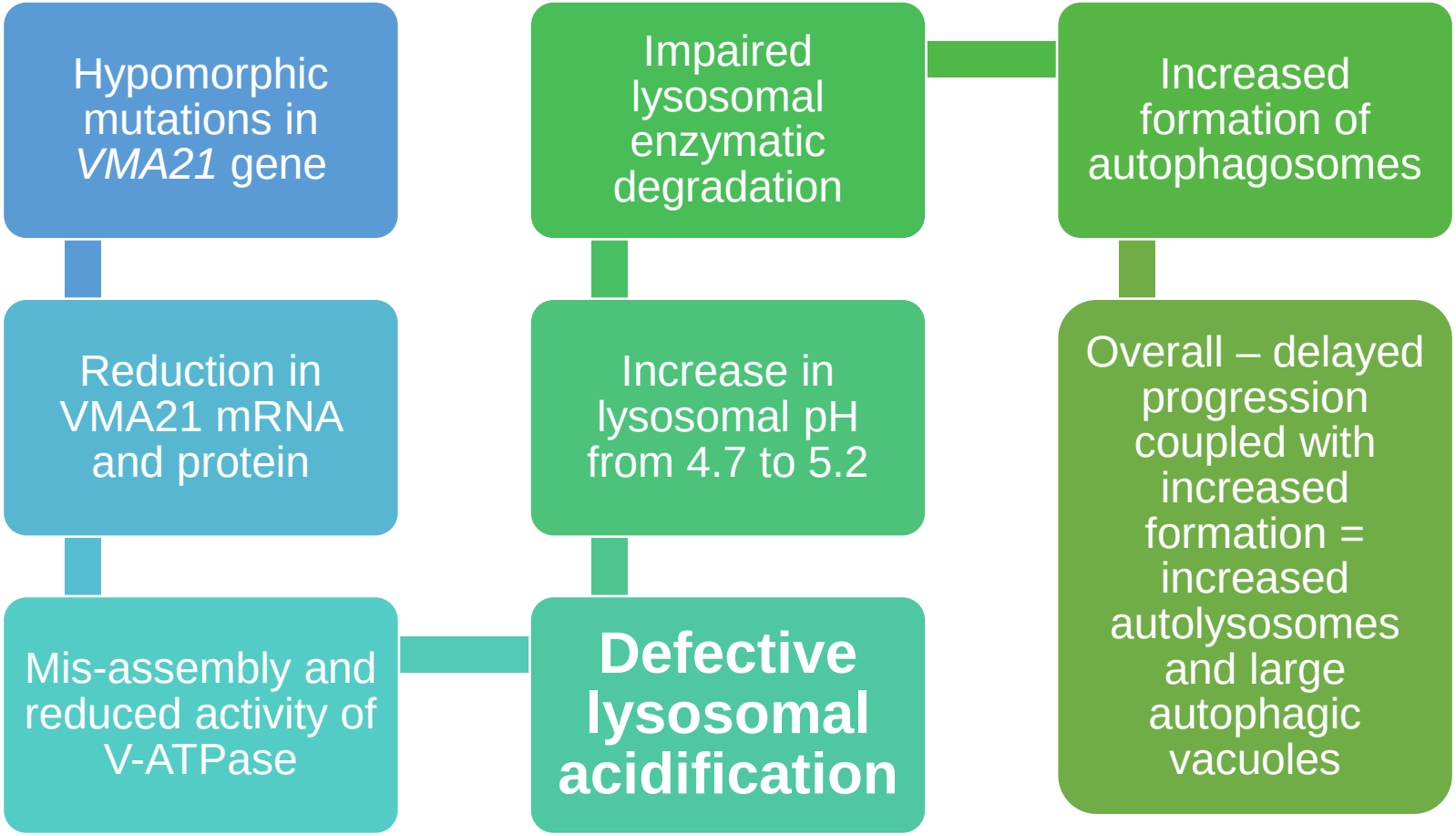
VMA21

Ramachandran et al. Neurology 2009;72:A104

Eskelinen et al. Trends Cell Biol 2003;13:137

TRENDS in Cell Biology

Pathogenesis of XMEA



THANK YOU!