DSS-8

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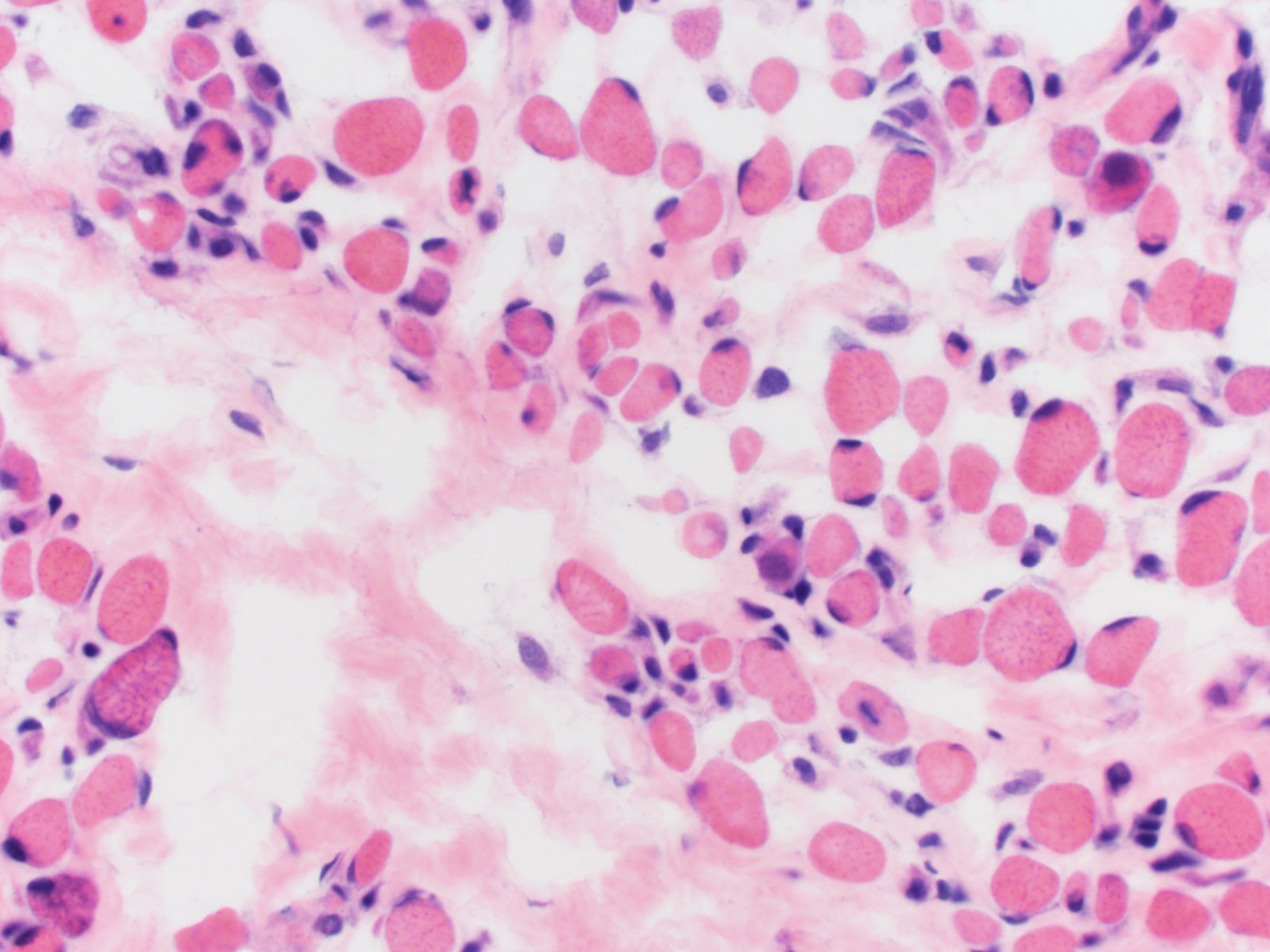
There are no financial relationships to disclose.

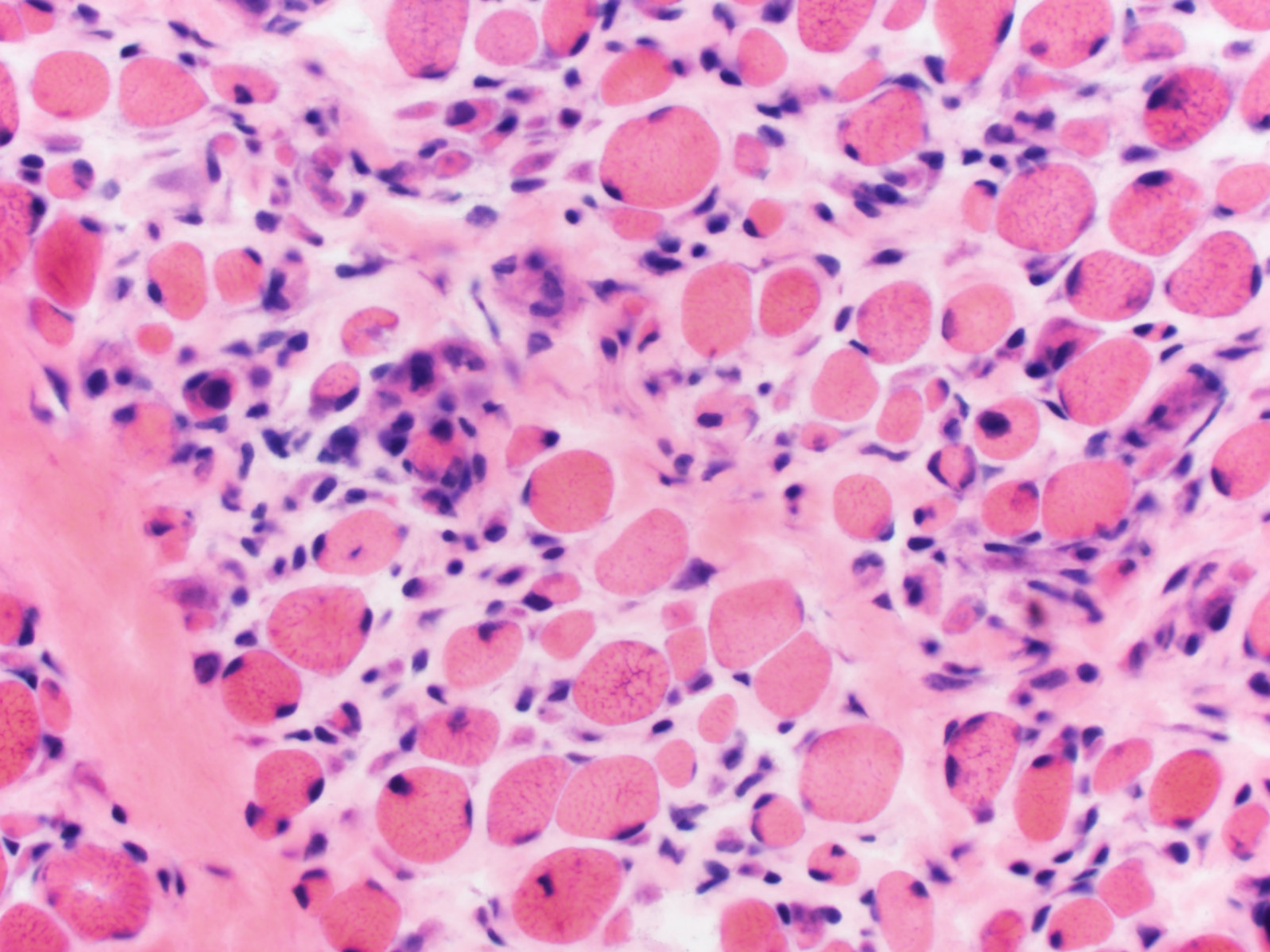
Clinical History

- male infant born by C-section at 41 weeks gestation after a normal pregnancy
- 2 month well-child exam: normal
- At 3 months of age he had significant hypotonia and weakness, proximal > distal.
- EMG: myopathic; NCS: normal; rep. stim: normal
- serum CK: 3170 to 4944 U/L

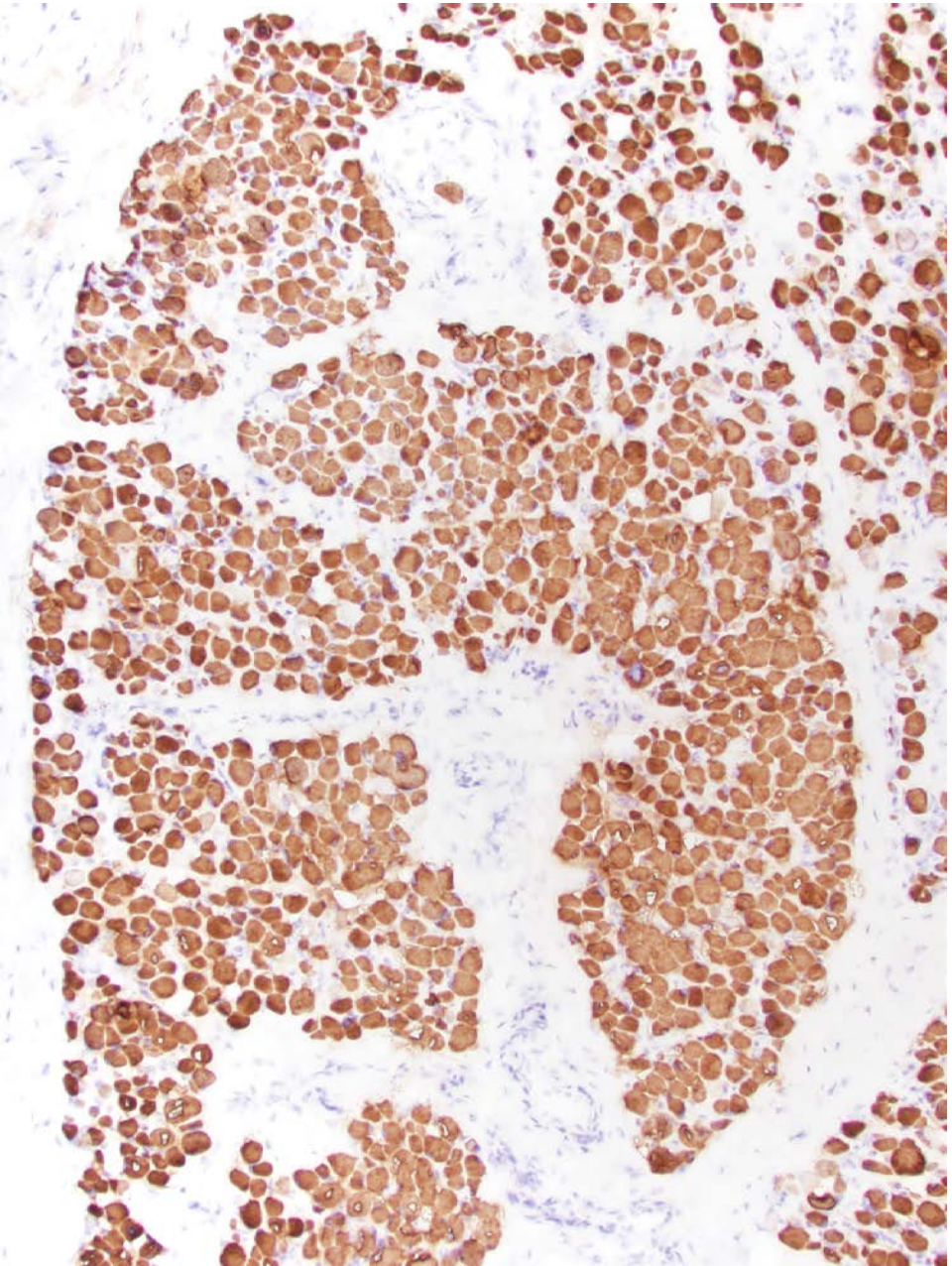
- quadriceps muscle biopsy at 4 months

- clinical course: progressive weakness with repeated hospitalizations for respiratory support; died at 6 months of age

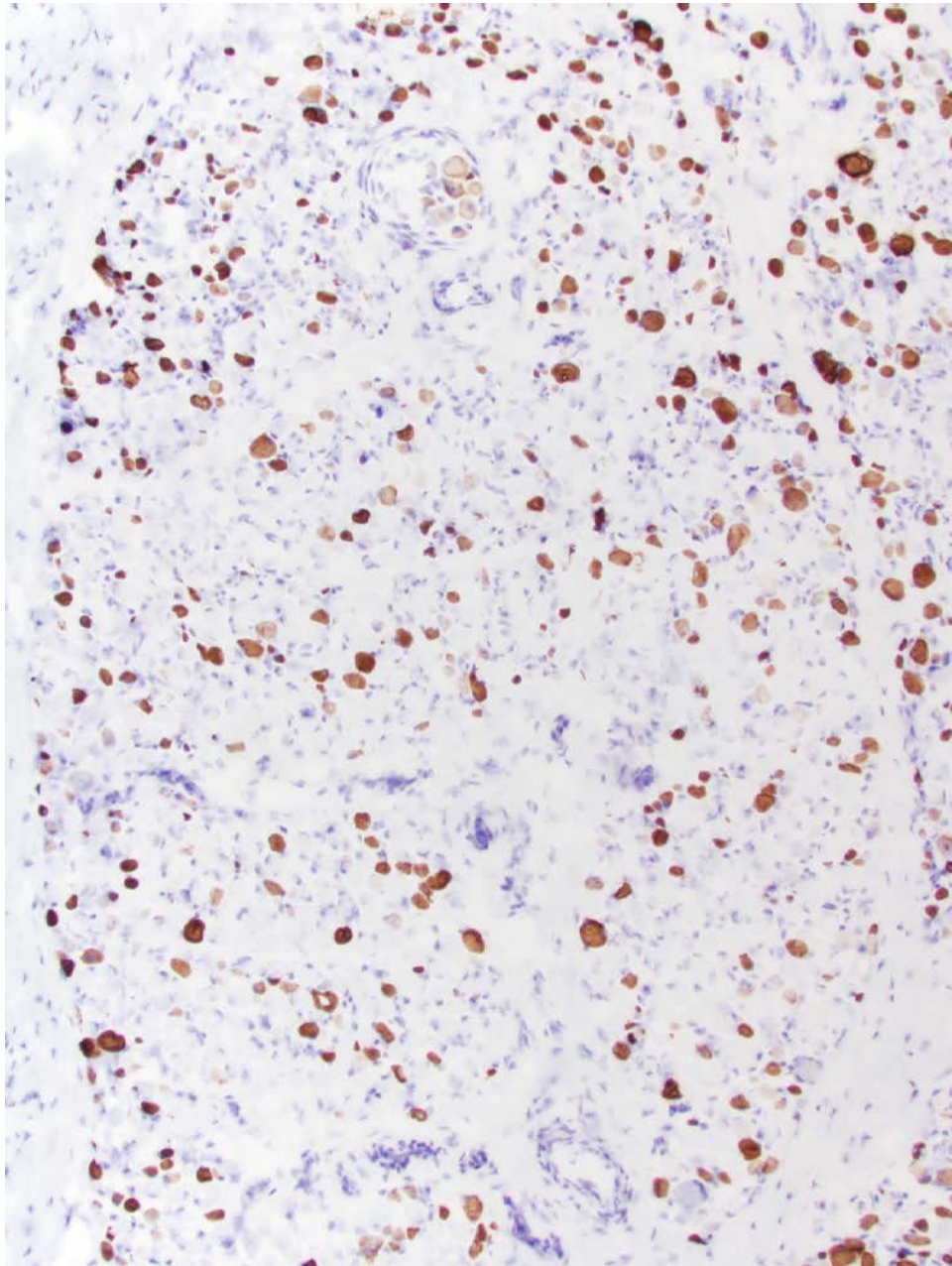


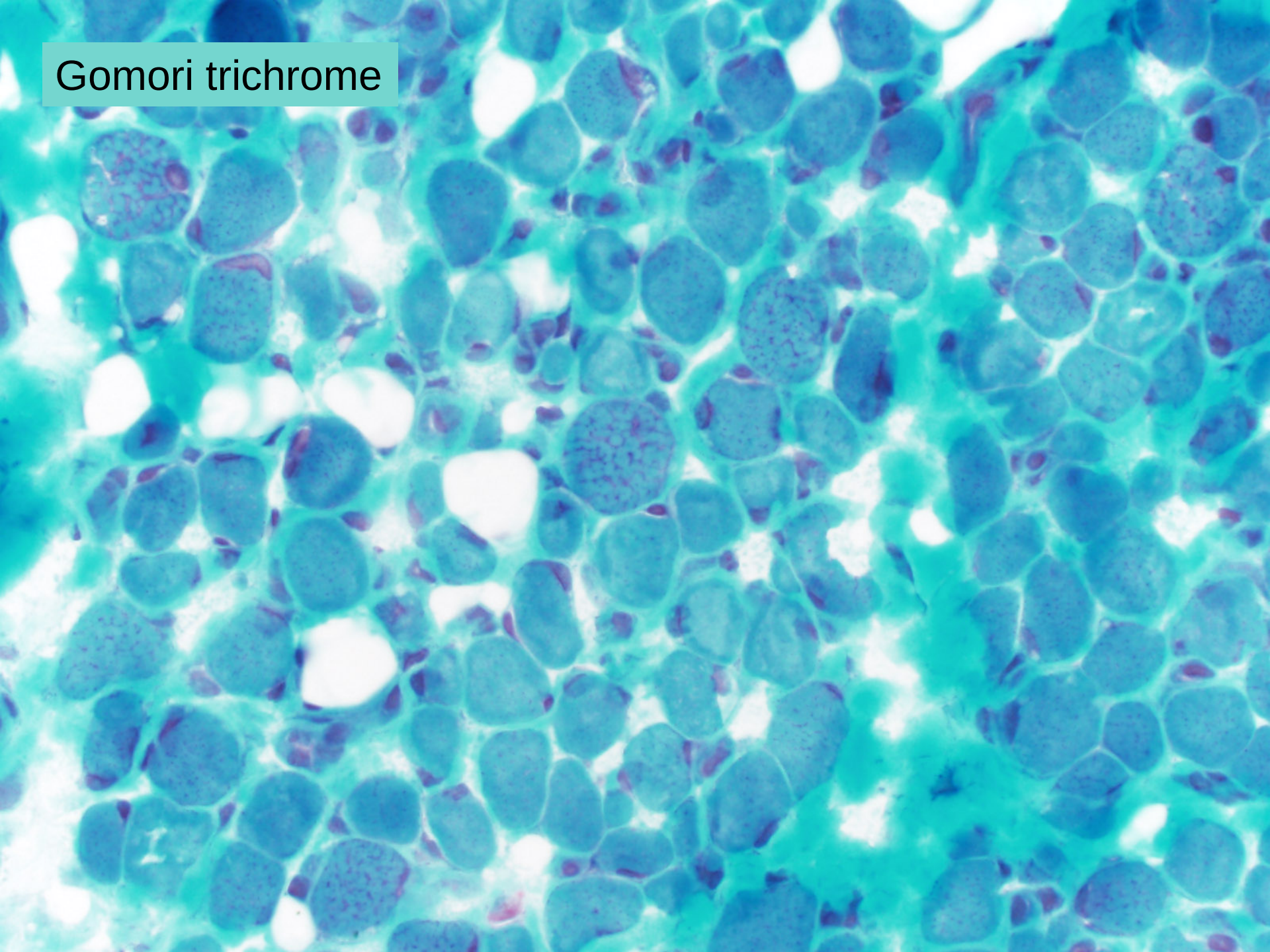


slow myosin (type I fibers)



fast myosin (type II fibers)




Gomori trichrome

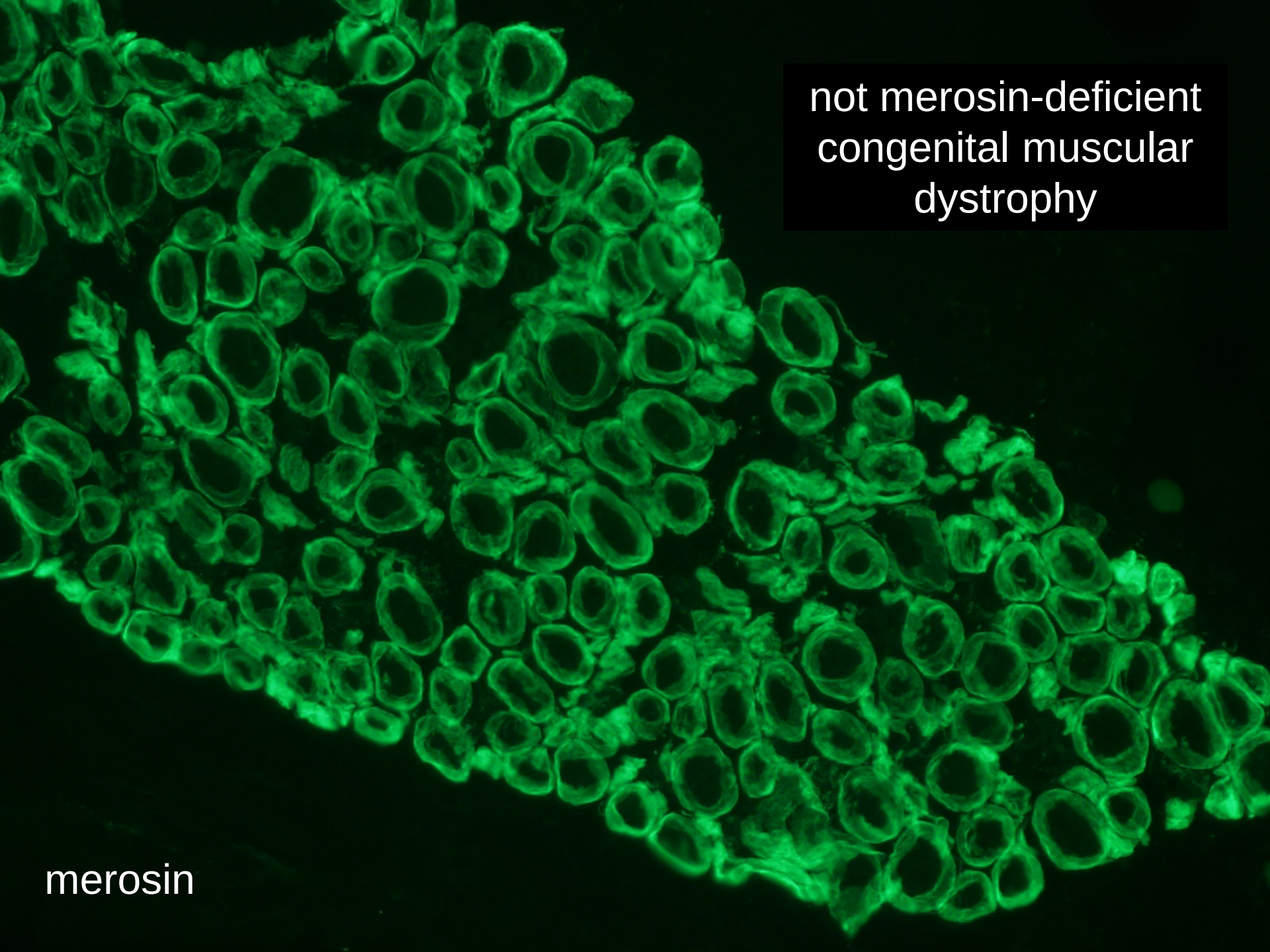
Points for Discussion

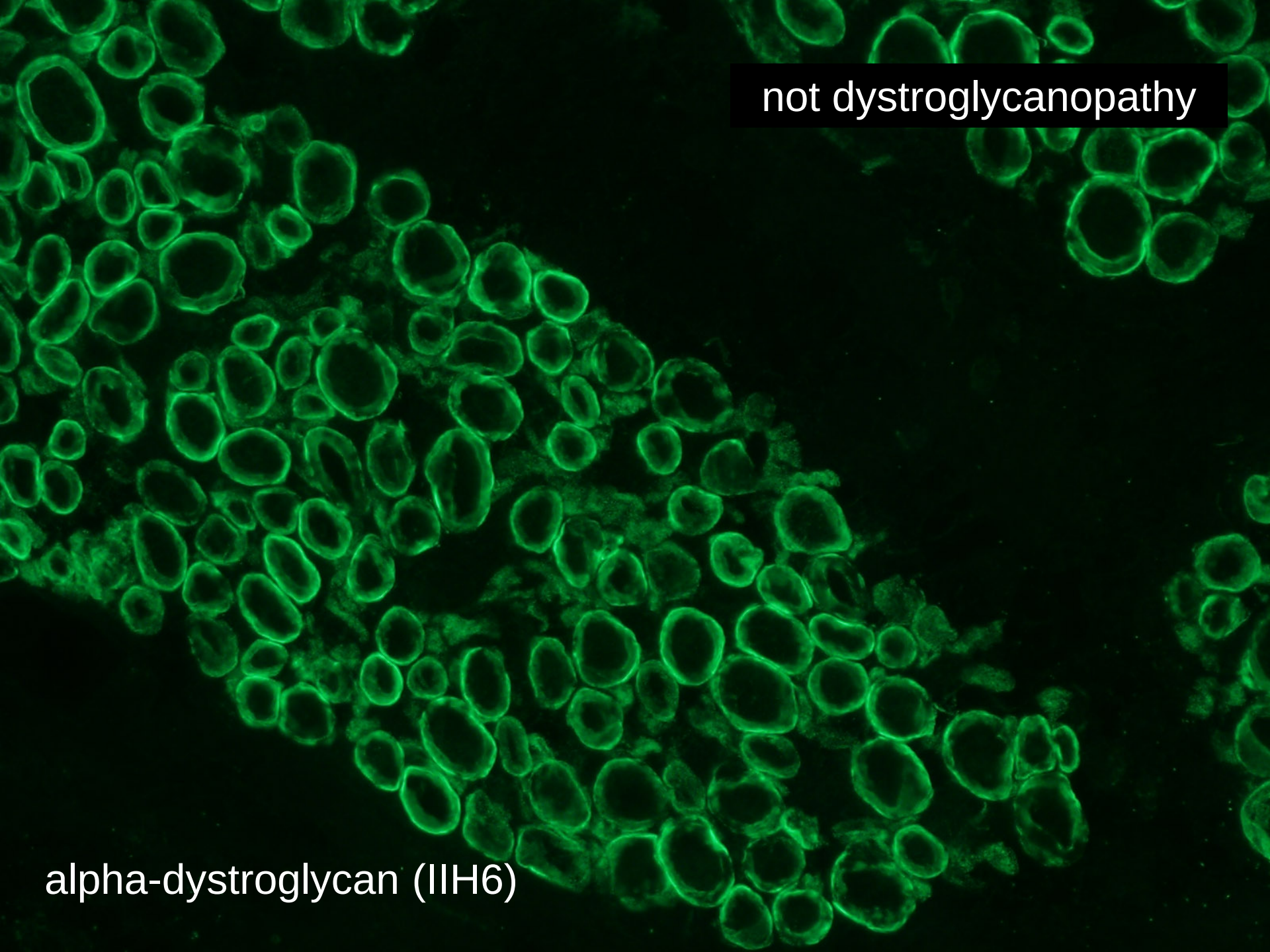
- Differential diagnosis
- Approach to diagnostic testing

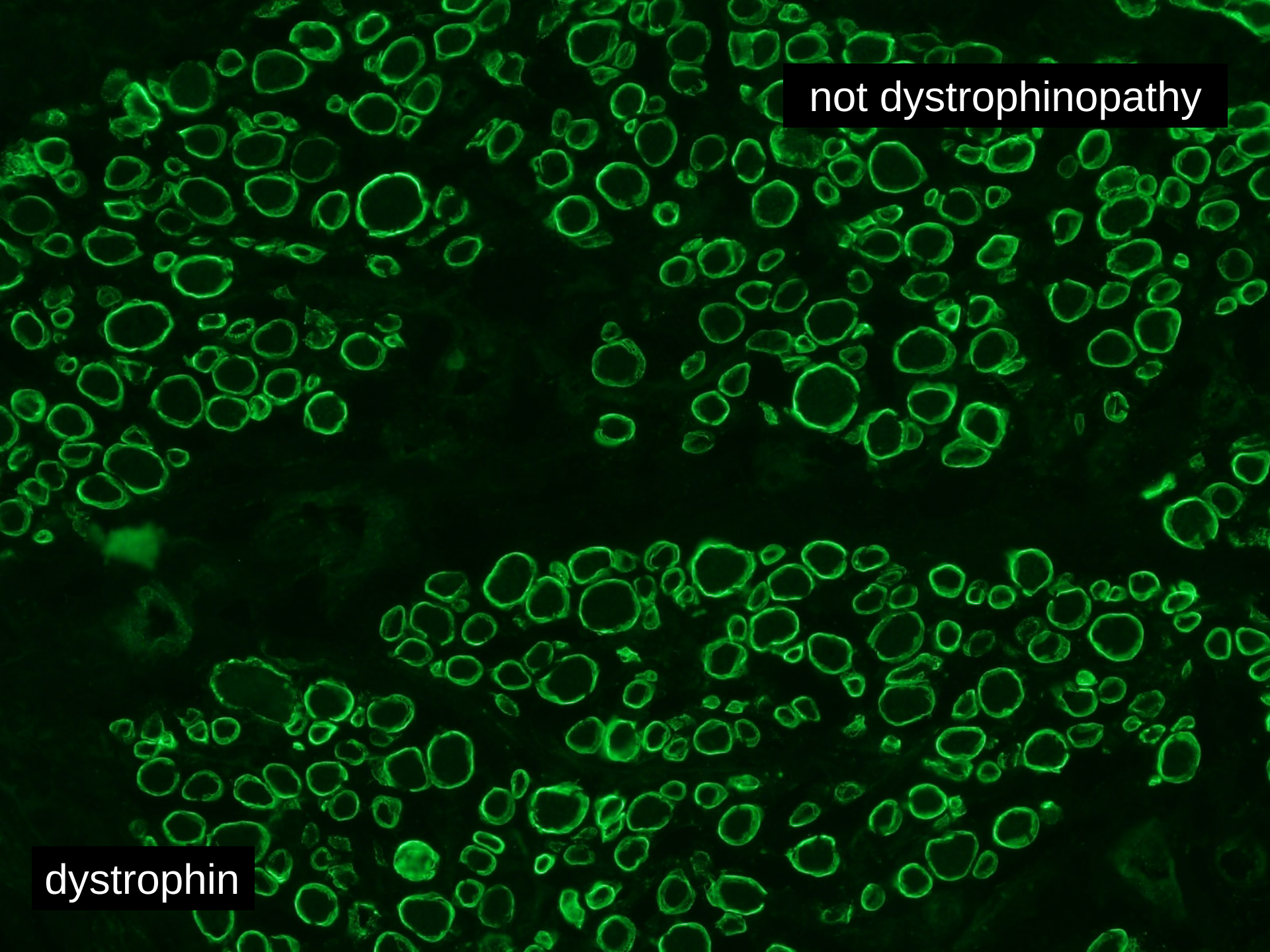
Points for Discussion

- Differential diagnosis
  - congenital muscular dystrophy
  - atypical presentation of Duchenne muscular dystrophy
  - other necrotizing myopathies

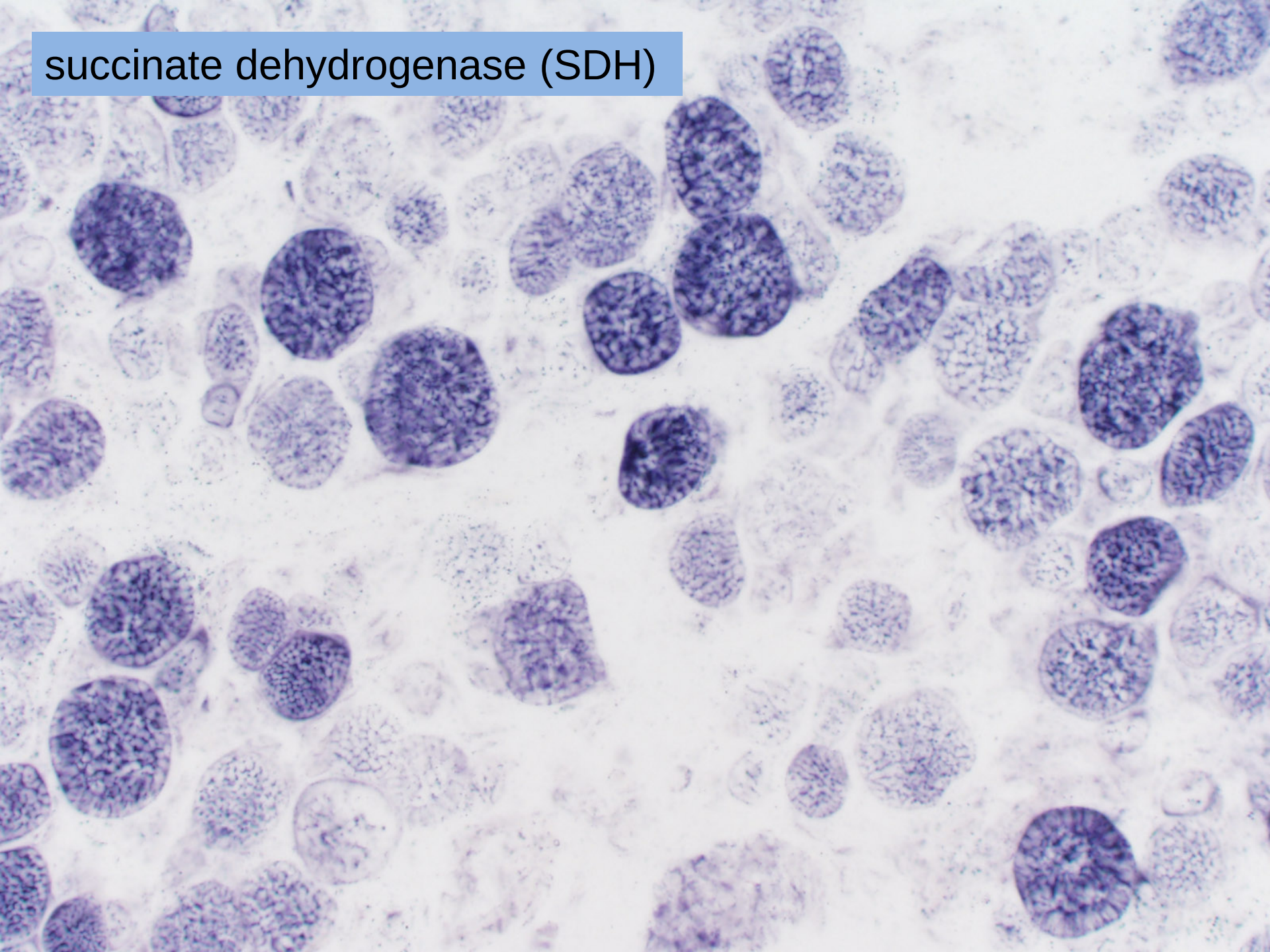
- Approach to diagnostic testing
  - immunostaining for merosin, alpha-dystroglycan, and dystrophin
  - routine enzyme histochemistry
  - electron microscopy, as needed
  - genetic testing, as needed

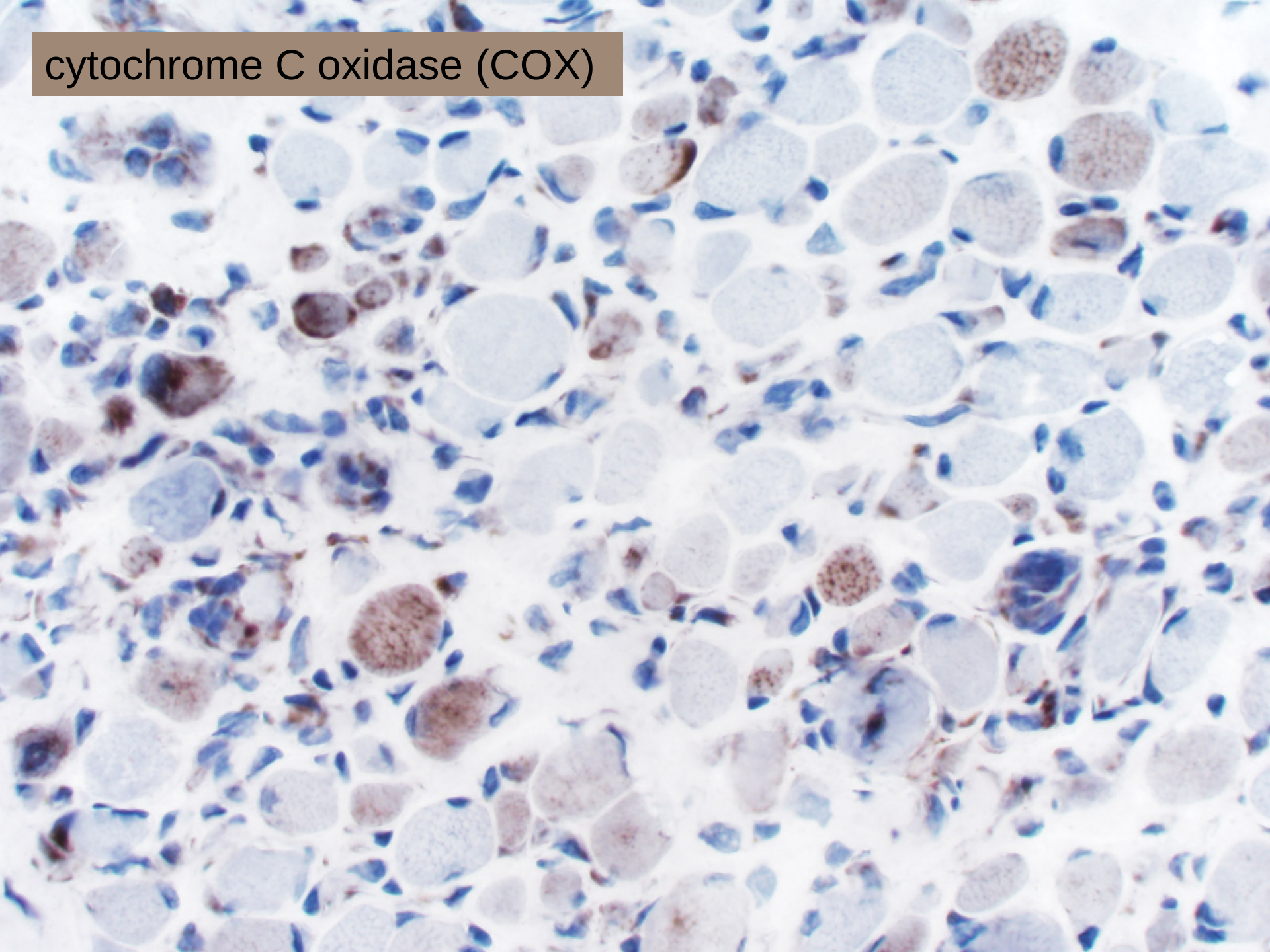

not merosin-deficient congenital muscular dystrophy
merosin

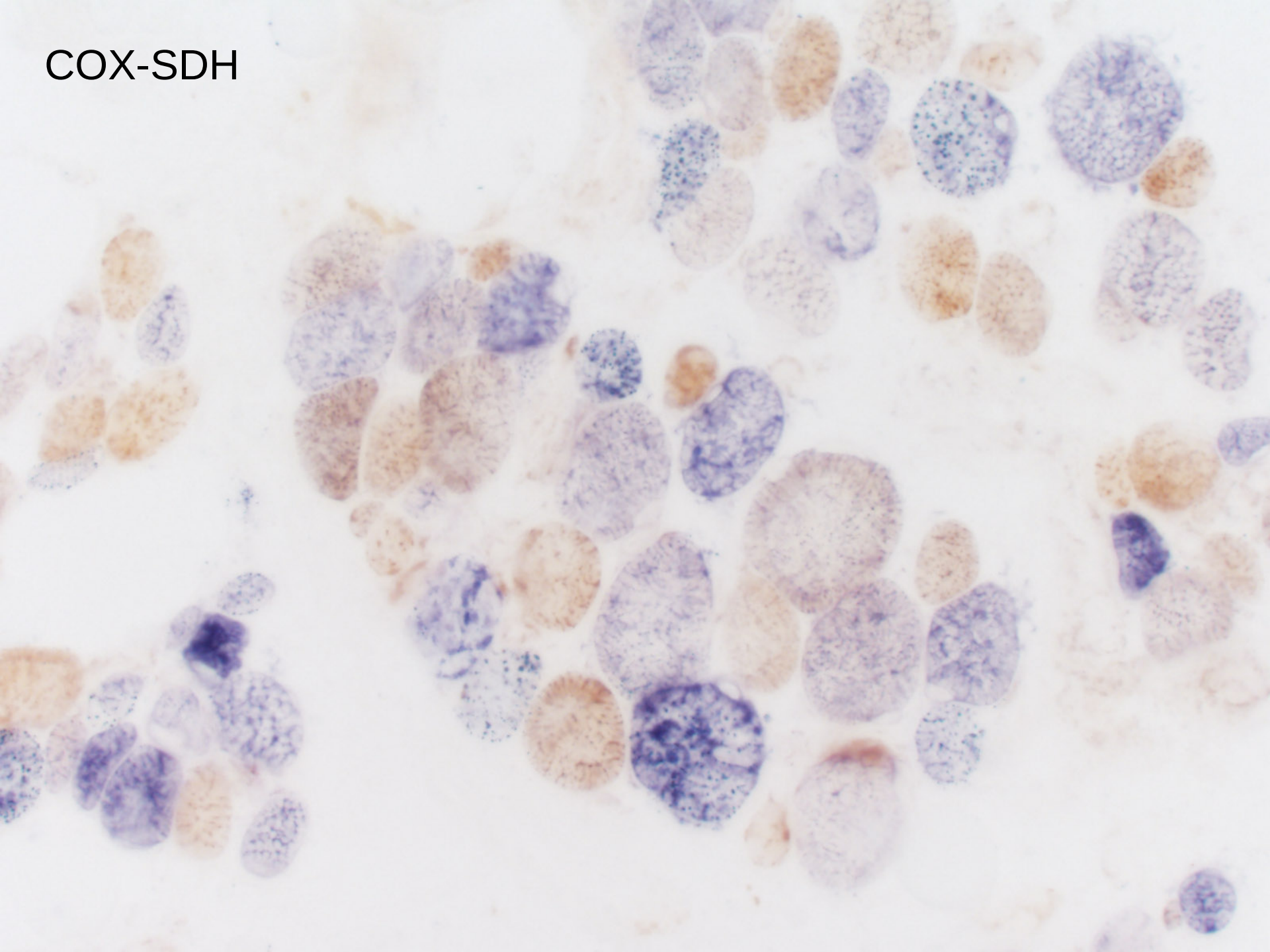

not dystroglycanopathy
alpha-dystroglycan (IIH6)

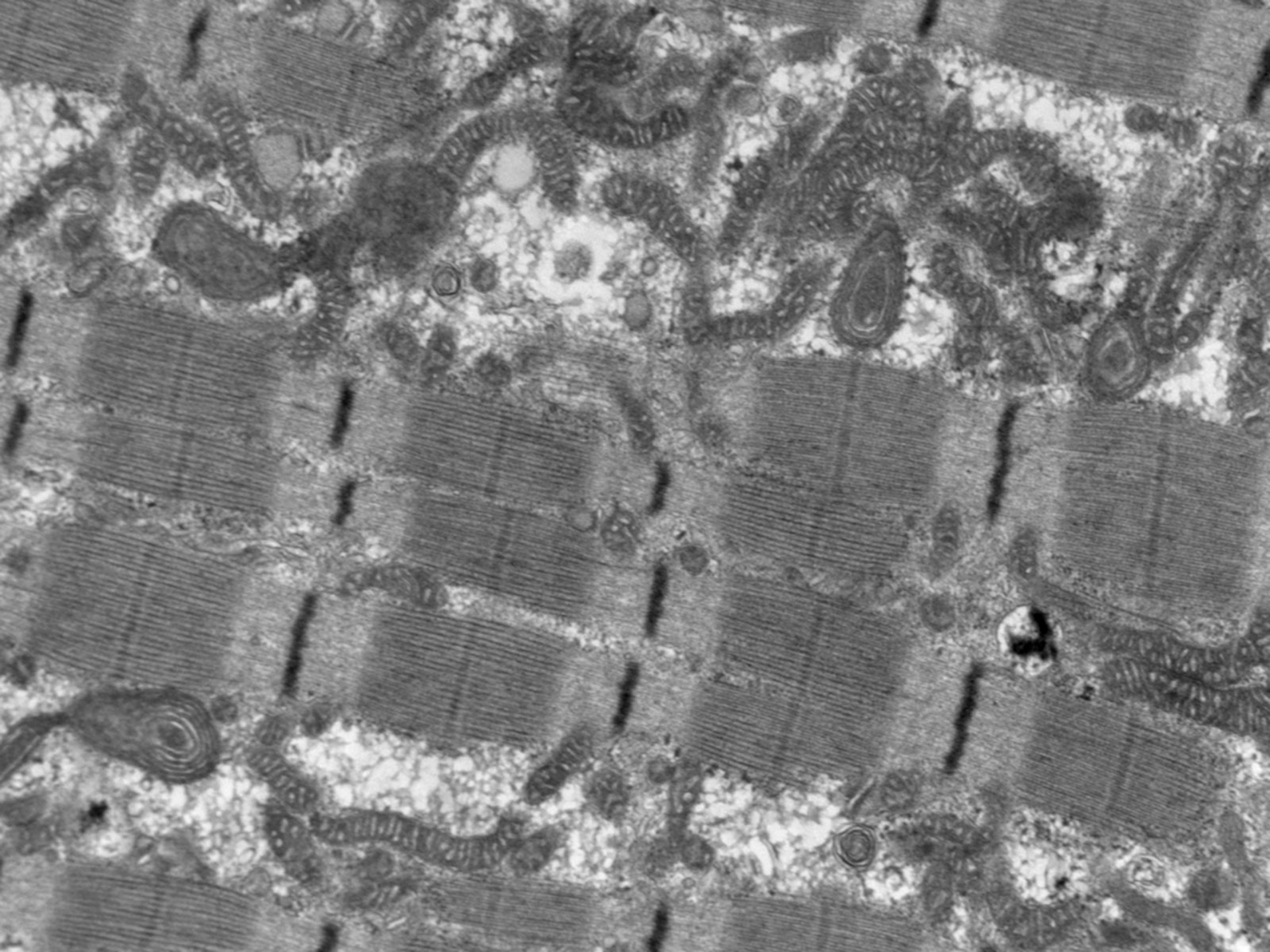

not dystrophinopathy
dystrophin

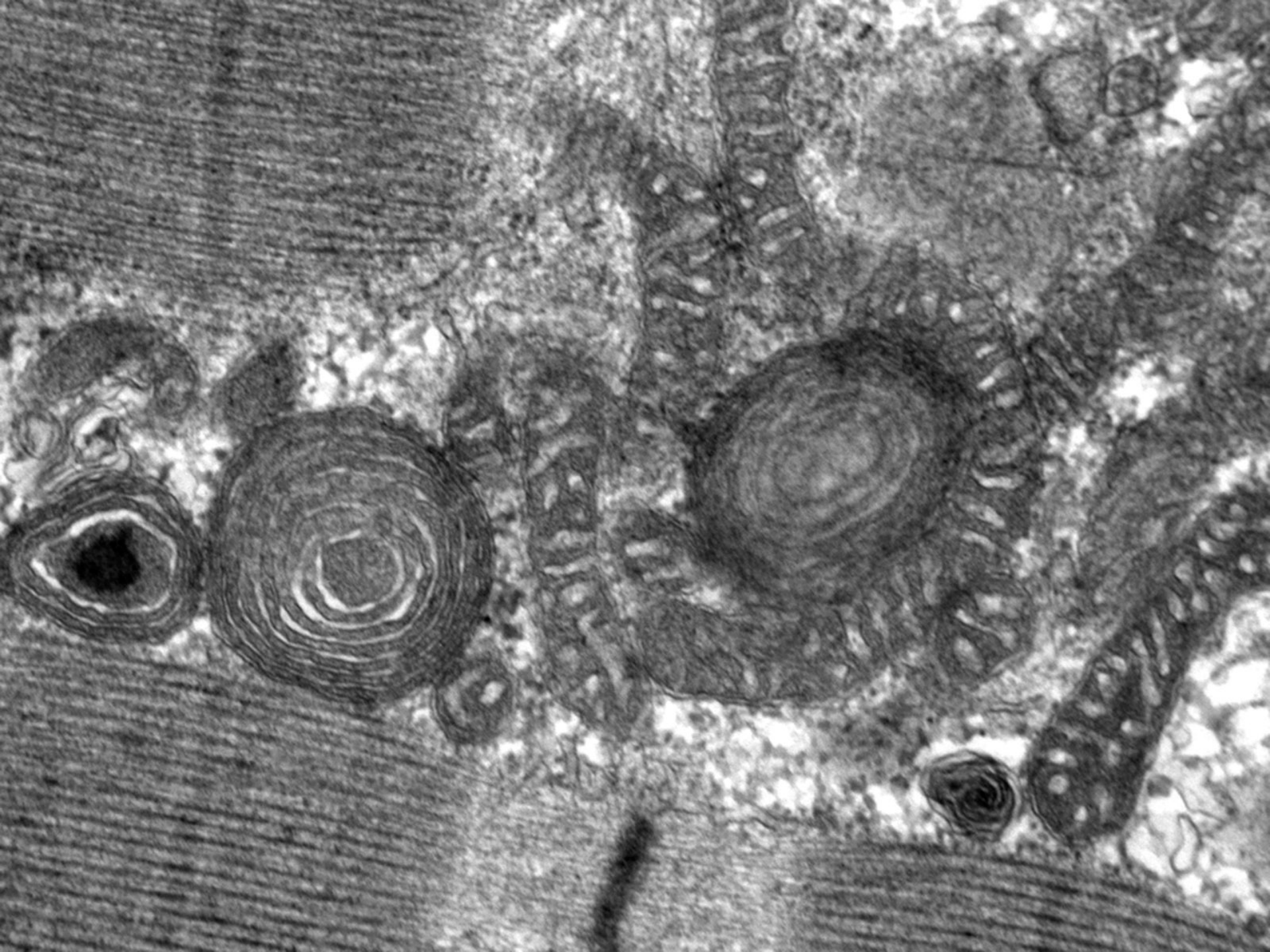
succinate dehydrogenase (SDH)

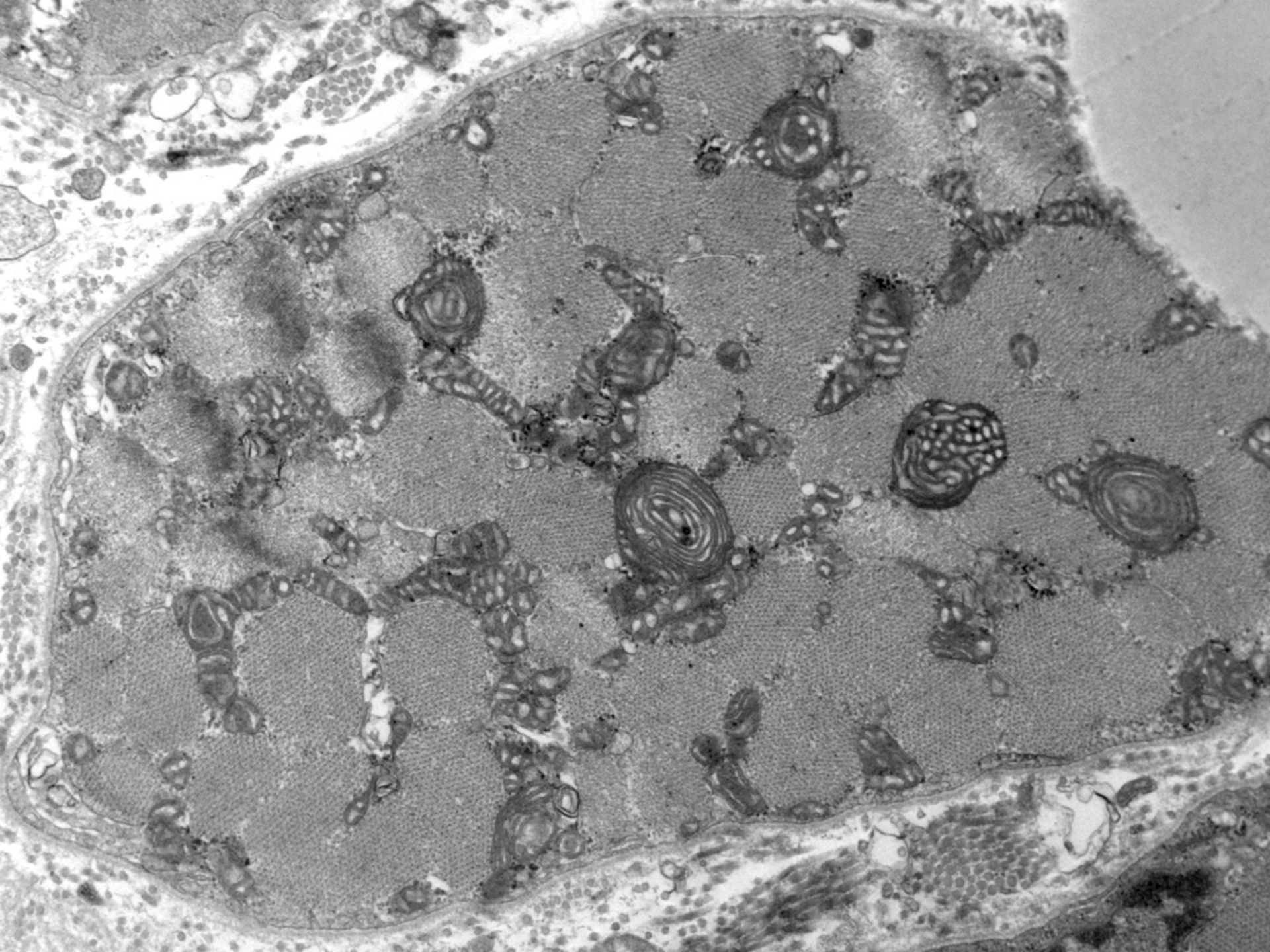


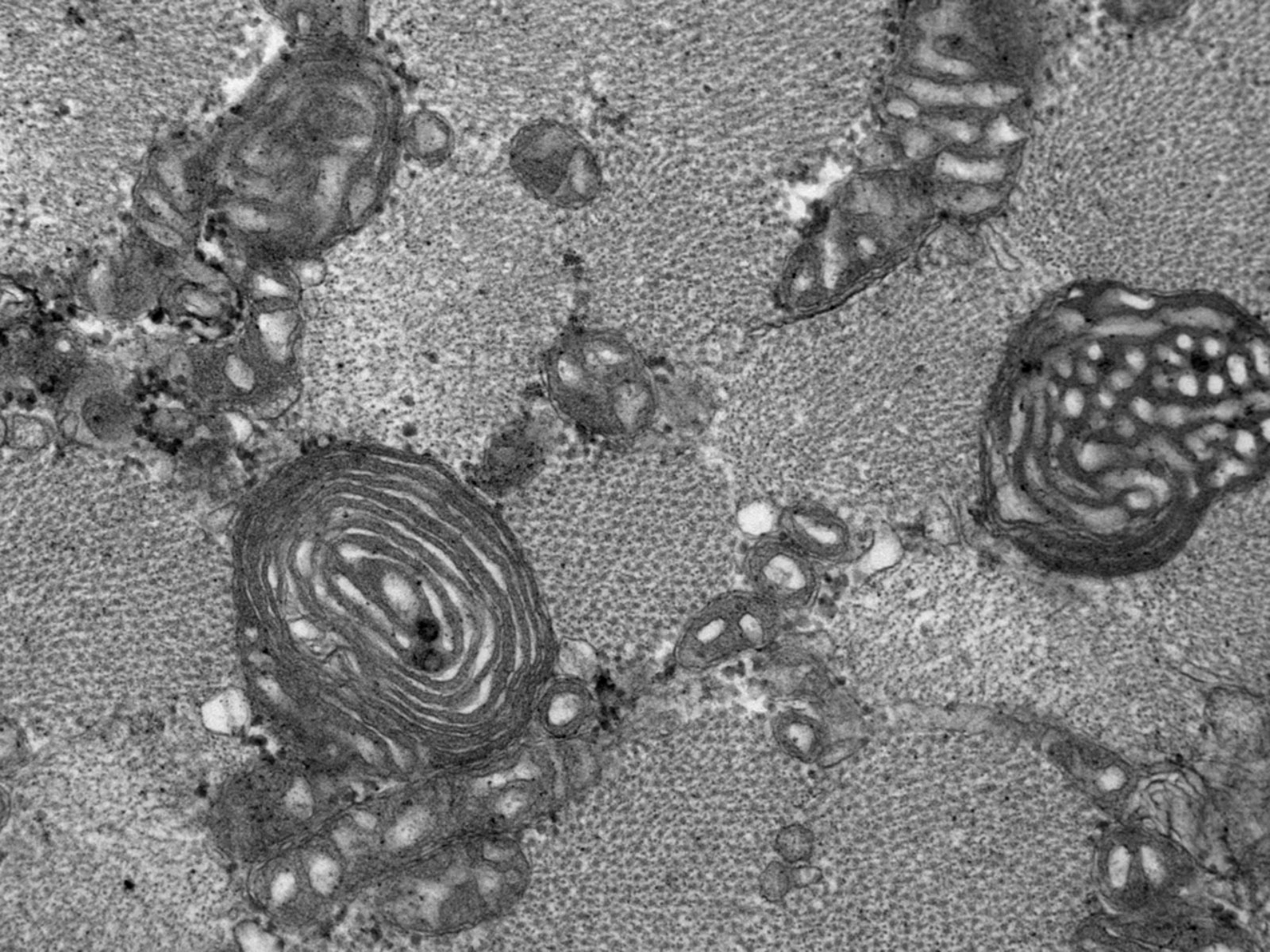

cytochrome C oxidase (COX)


COX-SDH









Muscle Biopsy Diagnosis

- Mitochondrial myopathy

Additional Testing

- Next generation sequencing identified compound heterozygous variants in *thymidine kinase 2 (TK2),* a known cause of mtDNA depletion syndrome.
  - c.329A>G, p.Gln110Arg
  - c.704T>C, p.Ile235Thr
    - Each parent is a carrier of one variant.
    - Each amino acid is highly conserved.
    - *In silico* analysis with SIFT: each variant deleterious.
    - Neither variant was reported in ExAC database.
  - No other pathologic gene variants were detected.

- Mitochondrial DNA depletion was confirmed by qPCR on frozen muscle – only 10% of control.

Final Diagnosis

- *Thymidine Kinase 2 (TK2)* mitochondrial DNA depletion syndrome, myopathic type

Mitochondrial DNA Depletion Syndromes

- At least 18 genes
- Rare: ~100 (or fewer) cases per gene
- Phenotypes: hepatocerebral, encephalomyopathic, cardiomyopathic, neurogastrointestinal, and myopathic
  - Increasing overlap observed among the various phenotypes as more patients are diagnosed
- Frequently fatal in early childhood; milder presentations also occur
- Treatment: supportive care

Basis for Mitochondrial DNA Depletion Syndromes

- Most mitochondrial proteins are encoded by nuclear DNA.
- Mitochondria also carry out their own DNA replication and transcription for protein synthesis.
- In order to support mtDNA synthesis, the mitochondrial nucleoside pool is maintained by two methods.
  - import from the cytosol (S-phase; replicating cells)
  - **salvage pathway within mitochondria** (continuously; non-replicating cells)

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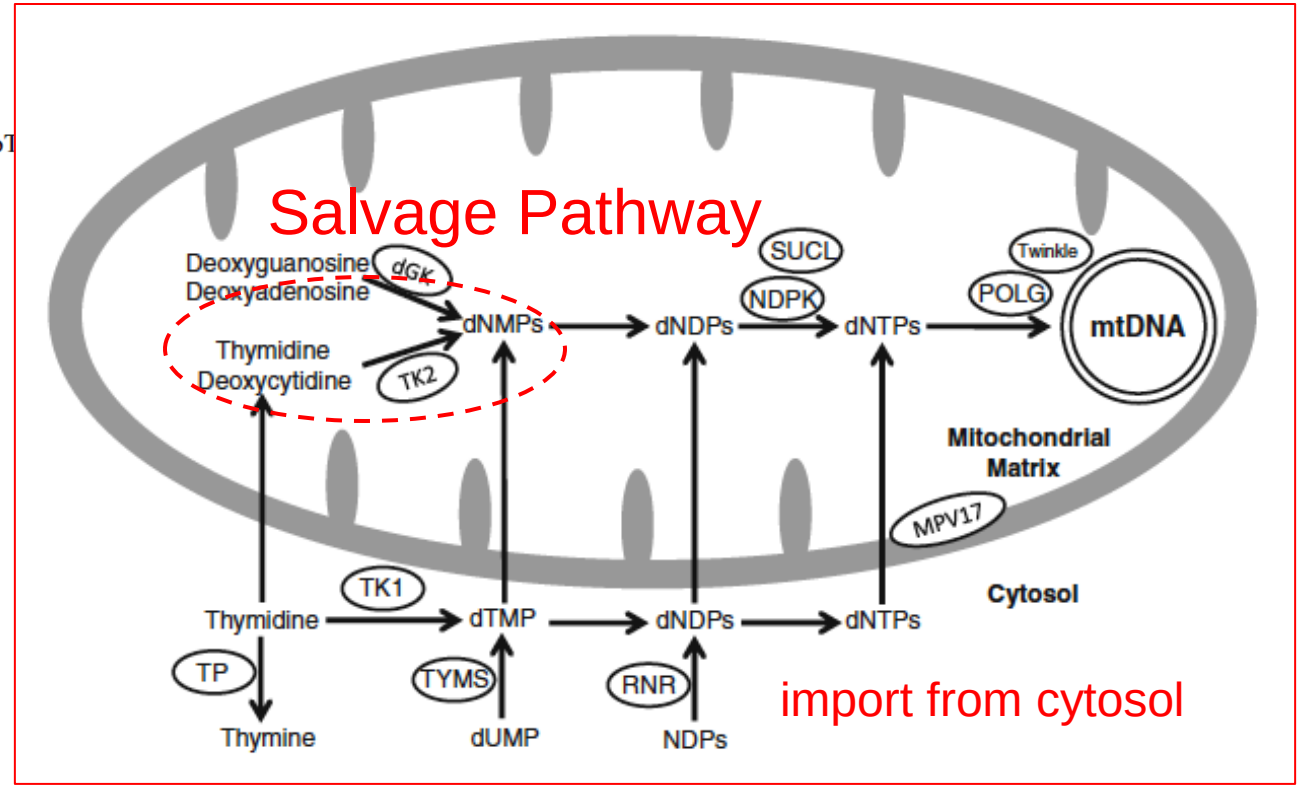
REVIEW

Mitochondrial DNA Depletion Syndromes: Review and Updates of Genetic Basis, Manifestations, and Therapeutic Options

Ayman W. El-Hattab · Fernando Scaglia

Published online: 6 February 2013



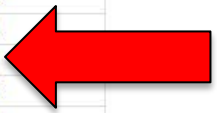
El-Hattab and Scaglia, Neurotherapeutics 10:186-198, 2013

OMIM

Mitochondrial DNA depletion syndrome - PS603041 - 18 Entries

View corresponding clinical synopses as a table

Location	Phenotype	Inheritance	Phenotype mapping key	Phenotype MIM number	Gene/Locus	Gene/Locus MIM number
2p23.3	Mitochondrial DNA depletion syndrome 6 (hepatocerebral type)	AR	3	256810	MPV17	137960
2p13.1	Mitochondrial DNA depletion syndrome 3 (hepatocerebral type)	AR	3	251880	DGUOK	601465
2p11.2	Mitochondrial DNA depletion syndrome 9 (encephalomyopathic type with methylmalonic aciduria)	AR	3	245400	SUCLG1	611224
3q29	?Mitochondrial DNA depletion syndrome 14 (encephalocardiomyopathic type)		3	616896	OPA1	605290
4q35.1	Mitochondrial DNA depletion syndrome 12A (cardiomyopathic type) AD	AD	3	617184	SLC25A4	103220
4q35.1	Mitochondrial DNA depletion syndrome 12B (cardiomyopathic type) AR	AR	3	615418	SLC25A4	103220
6q16.1-q16.2	Mitochondrial DNA depletion syndrome 13 (encephalomyopathic type)	AR	3	615471	FBXL4	605654
7q34	Sengers syndrome	AR	3	212350	AGK	610345
8q22.3	Mitochondrial DNA depletion syndrome 8B (MNGIE type)	AR	3	612075	RRM2B	604712
8q22.3	Mitochondrial DNA depletion syndrome 8A (encephalomyopathic type with renal tubulopathy)	AR	3	612075	RRM2B	604712
10q21.1	?Mitochondrial DNA depletion syndrome 15 (hepatocerebral type)	AR	3	617156	TFAM	600438
10q24.31	Mitochondrial DNA depletion syndrome 7 (hepatocerebral type)	AR	3	271245	TWNK	606075
13q14.2	Mitochondrial DNA depletion syndrome 5 (encephalomyopathic with or without methylmalonic aciduria)	AR	3	612073	SUCLA2	603921
15q26.1	Mitochondrial DNA depletion syndrome 4B (MNGIE type)	AR	3	613662	POLG	174763
15q26.1	Mitochondrial DNA depletion syndrome 4A (Alpers type)	AR	3	203700	POLG	174763
16q21	Mitochondrial DNA depletion syndrome 2 (myopathic type)	AR	3	609560	TK2	188250
20p11.23	Mitochondrial DNA depletion syndrome 11	AR	3	615084	MGME1	615076
22q13.33	Mitochondrial DNA depletion syndrome 1 (MNGIE type)	AR	3	603041	TYMP	131222



http://omim.org/phenotypicSeries/PS603041

INHERITANCE

- Autosomal recessive

HEAD & NECK

Face

- Facial diplegia

RESPIRATORY

- Respiratory insufficiency due to muscle weakness

MUSCLE, SOFT TISSUES

- Hypotonia
- Muscle weakness, proximal
- Gowers sign
- Muscle atrophy, diffuse
- Limb muscle weakness
- Delayed motor skills
- Inability to walk
- Loss of ability to walk in early childhood
- Myopathic changes seen on EMG
- Ragged red fibers seen on muscle biopsy
- Skeletal muscle tissue shows 14 to 45% depletion of mitochondrial DNA (mtDNA)
- Skeletal muscle may show less severe mtDNA deletion
- Decreased activities of mitochondrial-encoded respiratory chain complexes

METABOLIC FEATURES

- Lactic acidosis

LABORATORY ABNORMALITIES

- Increased serum creatine kinase
- Aminoaciduria

MISCELLANEOUS

- Onset usually by age 2 years
- Later onset has been reported
- Variable severity
- Progressive disorder

MOLECULAR BASIS

- Caused by mutation in the nuclear-encoded mitochondrial thymidine kinase gene (TK2, 188250.0001)

TK2, mtDNA depletion syndrome 2, myopathic type; clinical synopsis

http://omim.org/entry/609560

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