High-Yield Congenital Myopathy Pathology

Karra A. Jones, MD, PhD
Associate Professor of Pathology
Division of Neuropathology
Duke University
@BrainIsThePath

AMERICAN ASSOCIATION OF NEUROPATHOLOGISTS

Duke Pathology
Duke University School of Medicine

Disclosures

- I have the following relevant financial relationships to disclose
  - Consultant
    - Astellas Gene Therapies (formerly Audentes Therapeutics, Inc)

Learning Objectives

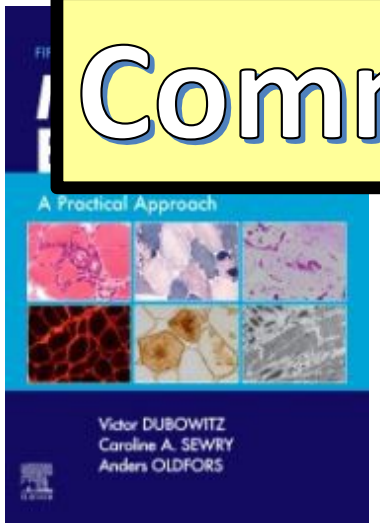
- Summarize frequently encountered congenital myopathy clinical presentations
- Identify congenital myopathy structural abnormalities including rods, cores, and others using multiple histopathologic techniques including electron microscopy
- Compare and contrast common genes involved in congenital myopathies and their associated structural abnormalities

Congenital myopathies

Common

Pitfalls to avoid

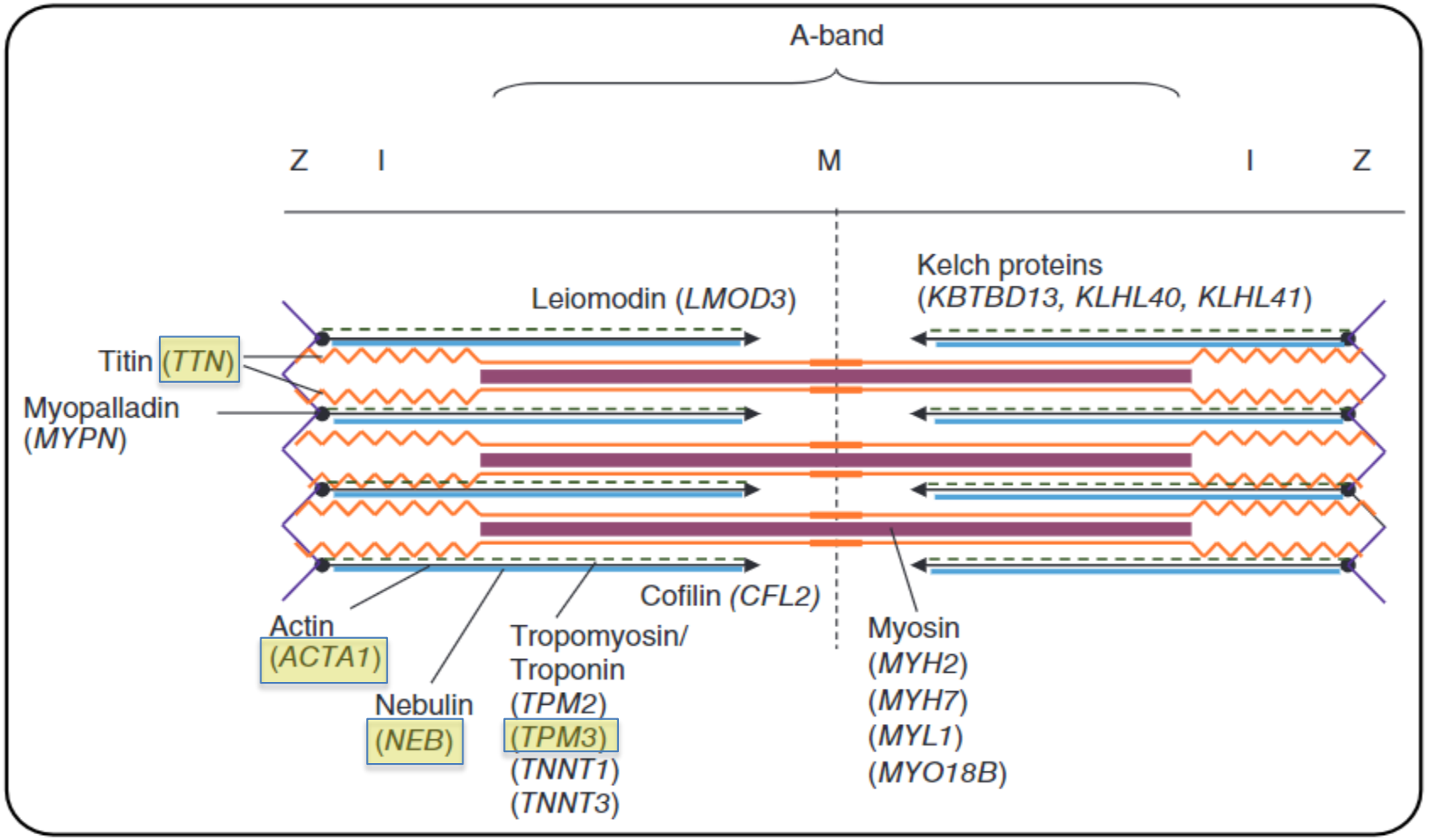
Tips for diagnosis



What are congenital myopathies?

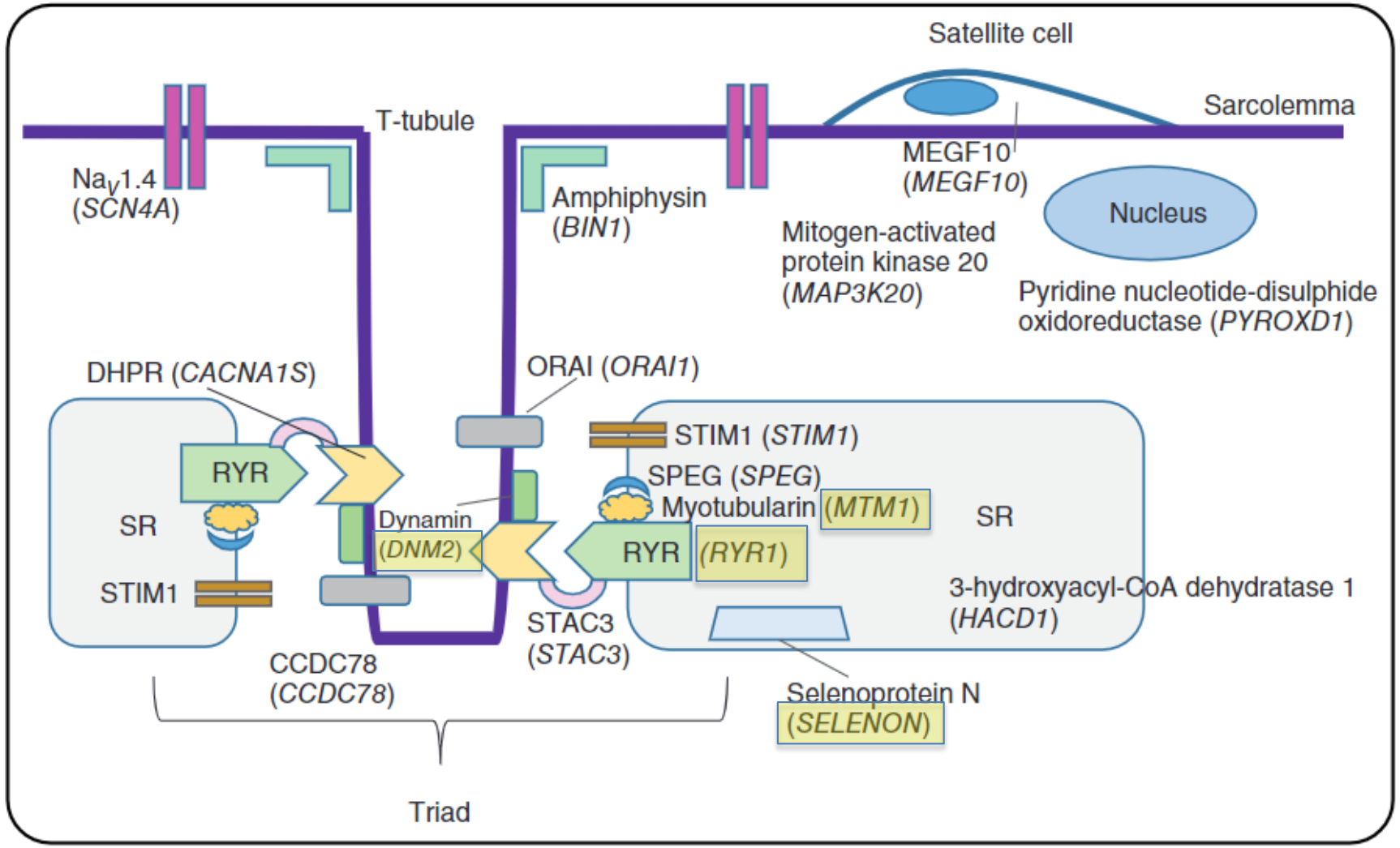
- Myopathies = diseases characterized clinically by muscle weakness
- Congenital myopathy = weakness present at birth or in early childhood*
- Genetic (mostly inherited) muscle disorders
- Gene alterations → protein alterations → muscle disease
- STRUCTURAL ABNORMALITIES
- Genes involved encode proteins related to the sarcomere, sarcoplasmic reticulum, transverse (T-) tubules, triads, myoblast growth/differentiation, or muscle energy metabolism

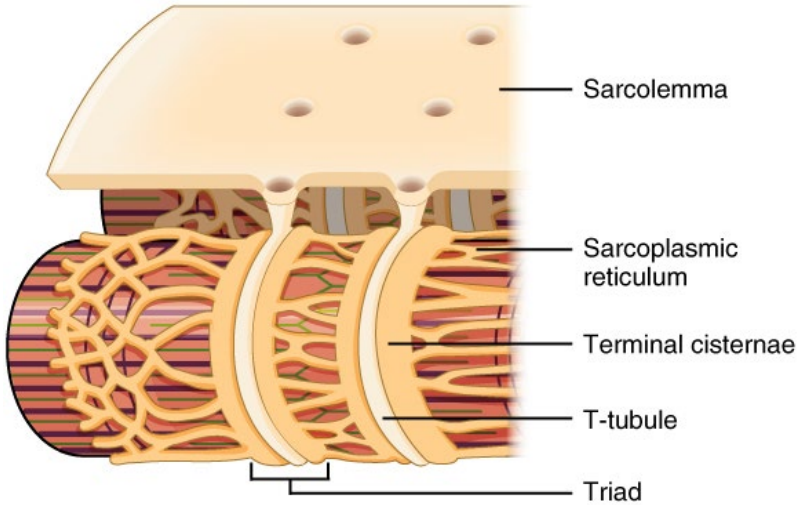
Majority of congenital myopathy genes encode structural or regulatory proteins



Pelin, K.Genetics of the Congenital Myopathies, eLS,Vol2: 1–9, 2021.

Congenital myopathy genes related to the SR/T-tubule/triad





Pelin, K.Genetics of the Congenital Myopathies, eLS,Vol2: 1–9, 2021.

Genetics of congenital myopathies

- Dominant, recessive, or X-linked recessive
  - Some genes can have both dominant and recessive disease (*RYR1*, *ACTA1*)
- *De novo* dominant mutations are actually common
  - Particularly *RYR1* and *ACTA1*
- Complicated because alterations in the same gene can cause more than one pathological feature (rods, cores, etc) and clinical phenotype
- And, the same pathological feature can result from alterations in multiple different genes

Rods – *ACTA1, NEB, TPM2, TPM3, TNNT1, CFL-2, KBTBD13, KLHL40, KLHL41, RYR1, [MYO18]*
Cores – *RYR1, SEPN1, ACTA1, TTN, CFL-2, DNM2, MYH7, MYH2*
[multiminicores are a nonspecific feature of several disorders]
Central nuclei – *MTM1, DNM2, BIN1, RYR1, CCDC78, SPEG, TTN, [MTMR14, DM1]**
Rods and/or cores – *ACTA1, RYR1, NEB, KBTBD13, CFL2*
Rods or caps – *TPM2, TPM3, ACTA1, NEB*
Fibre-type disproportion with no other defect – *ACTA1, TPM2, TPM3, SEPN1, MYH7, RYR1, HACD1*
Distal myopathy with no rods – *NEB, ACTA1*

*DM1 is not a congenital myopathy but congenital cases can show similar pathology to *MTM1* cases and it is often necessary to exclude the DMPK gene. *MTMR14* is associated with central nuclei but thought to be a gene modifier. The variant of *MYO18B* identified is currently listed in OMIM as being of unknown significance.

Sewry CA, Wallgren-Pettersson C. Myopathology in congenital myopathies. Neuropathol Appl Neurobiol. 2017 Feb;43(1):5-23.

Learning objective #1:
Summarize frequently encountered congenital myopathy clinical presentations

- But isn't this a neuropathology teaching rounds?

Clinical features to suggest a possible congenital myopathy

- Hypotonia at birth (floppy baby), sometimes arthrogryposis
- Mild to moderate, slowly progressive or static generalized muscle weakness later in childhood
- Respiratory involvement common and disproportional to limb muscle weakness
- CK usually normal, but can be mildly elevated

Exceptions to the classic clinical presentation

- Presentation in later childhood, adolescence, or even adulthood

Congenital myopathies: not only a paediatric topic

Heinz Jungbluth[a,b,c] *and Nicol C. Voermans*[d]

Curr Opin Neurol 2016, 29:642–650

Congenital myopathies in the adult neuromuscular clinic

Diagnostic challenges and pitfalls

Stefan Nicolau, MD, Teerin Liewluck, MD, Jennifer A. Tracy, MD, Ruple S. Laughlin, MD, and Margherita Milone, MD, PhD

Neurol Genet 2019;5:e341. doi:10.1212/NXG.0000000000000341

- Clinical severity and presentation can vary quite a lot, even within a single genetic cause

Table 1. Clinical and histopathological clues to a specific diagnosis in congenital myopathies in adults

Features	Congenital myopathy	Genes	Differential diagnosis
Clinical feature			
Childhood onset	CCD, MmD, NM and CNM	*RYR1* (AR > AD), *NEB*, *ACTA1*, *MTM1* (milder cases) and *DNM2*	CMS, DM1 and mitochondrial conditions
Adult onset	CCD, CNM and NM	*RYR1* (AD > AR), *DNM2*, *BIN1* (AD) and *KBTD13*	DM1 and mitochondrial conditions
Facial weakness	MmD, CNM and NM	*RYR1* (AR), *DNM2* and *NEB*	DM1, CMS, mitochondrial conditions and FSHD
Ptosis	CNM, MmD and CCD	*DNM2* and *RYR1*	DM1, CMS and mitochondrial conditions
EOM	MmD and CNM	*RYR1* (AR), *DNM2* and *MTM1* (mild cases, manifesting carriers)	CMS and mitochondrial conditions
Scoliosis	MmD, CNM and NM	*SEPN1* and *RYR1* and *NEB*	*COL6*-related myopathies and MFM
Rigid spine	MmD and NM	*SEPN1*, *MYH7*, *TTN* and *NEB*	*COL6*-related myopathies, EDMD and MFM
Distal weakness lower limbs	NM, CNM and MmD	*NEB*, *DNM2* and *MYH7*	Peripheral neuropathy
Pes cavus	CNM	*DNM2*	Peripheral neuropathy
Bulbar weakness	NM and MmD	*NEB* and *RYR1* (AR)	CMS, DM1 and mitochondrial conditions
Respiratory impairment	MmD, NM and CNM	*SEPN1*, *NEB*, *ACTA1* and *DNM2*	Acid maltase deficiency and mitochondrial conditions
Cardiac involvement	MmD and NM	*TTN*, *MYH7*, (*ACTA1*) and (*KBTBD13*)	EDMD, mitochondrial conditions and MFM
Neuropathy	CNM	*DNM2*	Peripheral neuropathy and MFM
Malignant hyperthermia	CCD and MmD	*RYR1*	Other causes of MH

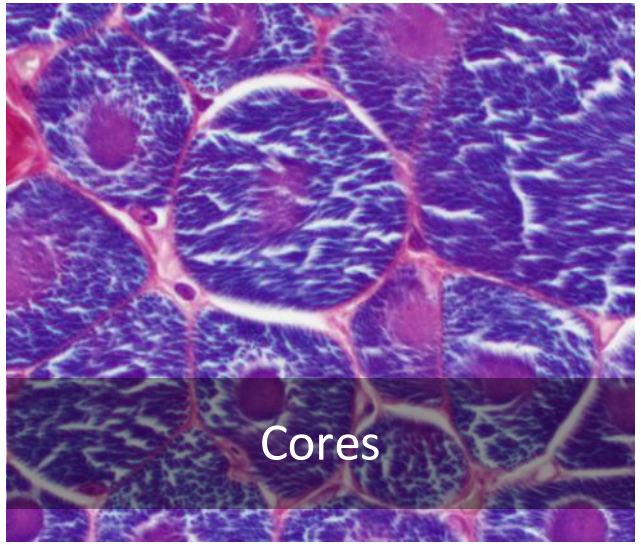
- CCD: central core disease
- MmD: multi-minicore disease
- NM: nemaline myopathy
- CNM: centronuclear myopathy
- CMS: congenital myasthenic syndrome
- DM1: myotonic dystrophy type 1
- FSHD: facioscapulohumeral muscular dystrophy
- MFM: myofibrillar myopathy
- EDMD: Emery-Dreifuss muscular dystrophy
- MH: malignant hyperthermia

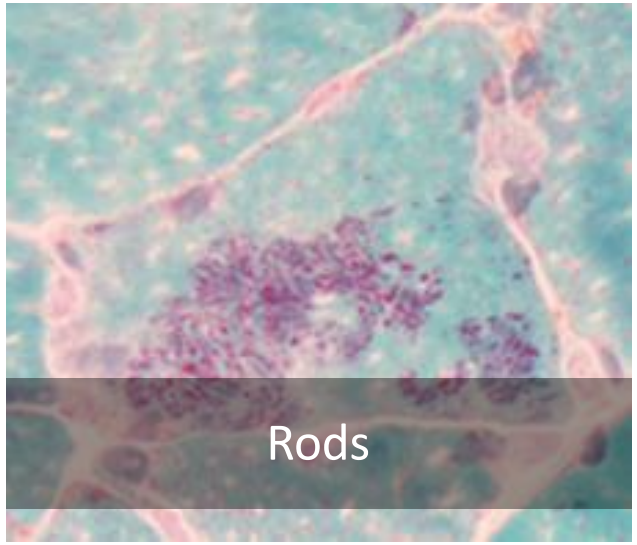
Jungbluth H, Voermans NC. Congenital myopathies: not only a paediatric topic. Curr Opin Neurol. 2016 Oct;29(5):642-50.

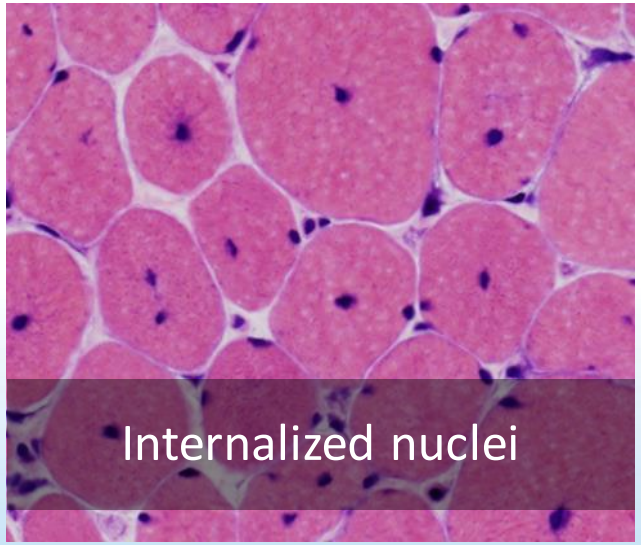
General tips: Initial diagnostic approach

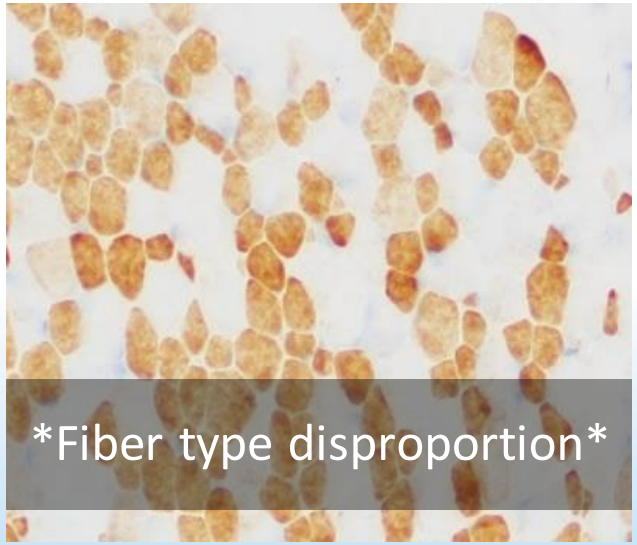
- H&E:
  - Two distinct fiber sizes?
  - Internally placed nuclei?
  - Cores?
  - Caps?
  - Lack of significant myonecrosis, regeneration, endomysial fibrosis?
- Fiber typing
  - Type 1 fiber predominance?
  - Type 1 fiber atrophy?
- Modified Gomori trichrome
  - Rods?
  - Cores?
- NADH, COX, SDH
  - Cores?
  - Abnormal central aggregation of staining?
- AUTOMATICALLY order EM (or at least have a very low threshold to order EM)

Common structural abnormalities in congenital myopathies





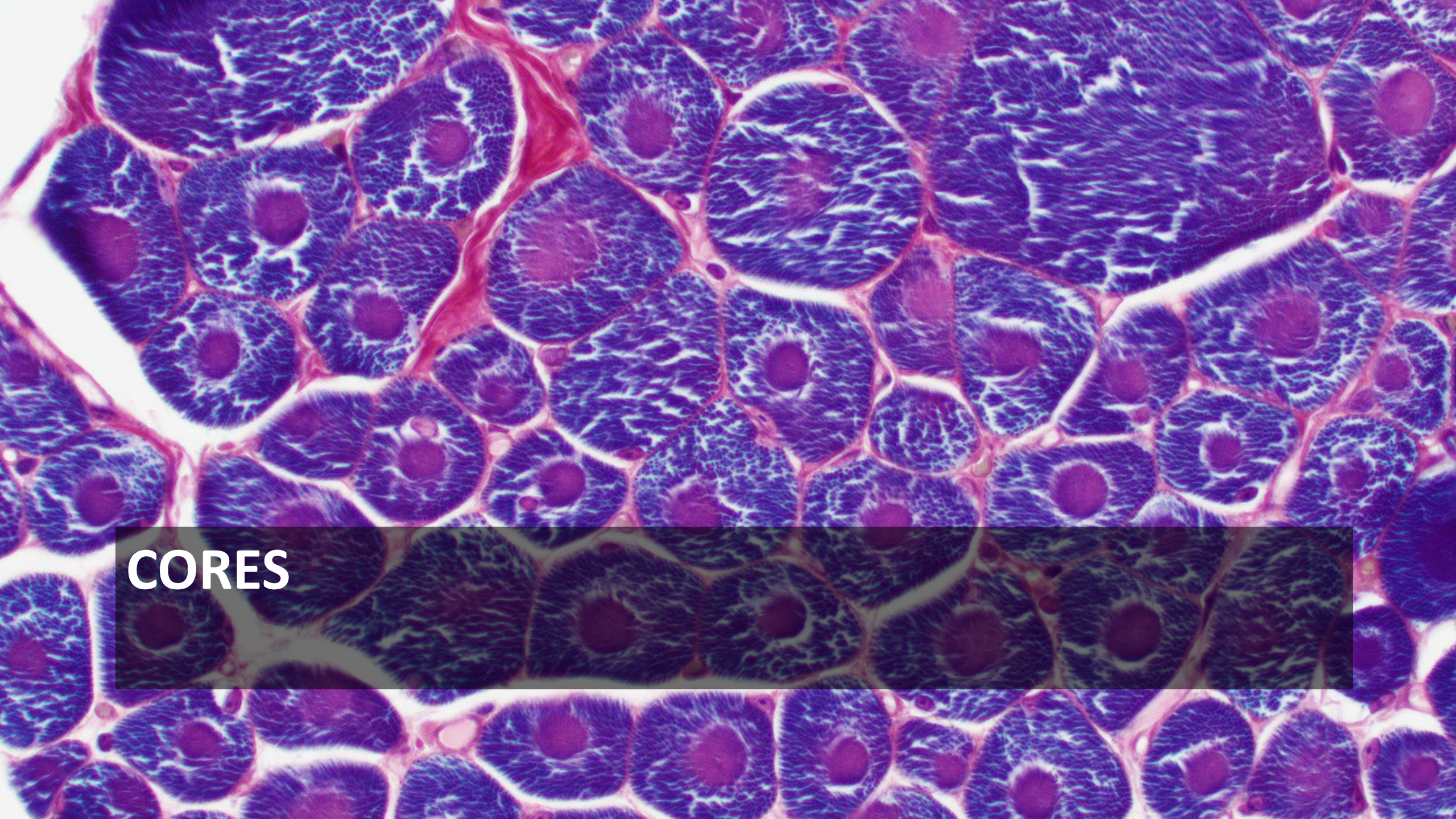




Overall outline of each section:

1. Muscle biopsy histopathologic and/or ultrastructural findings

2. Clinical disease and common genes


CORES

A New Congenital Non-Progressive Myopathy

A NEW CONGENITAL NON-PROGRESSIVE MYOPATHY

BY

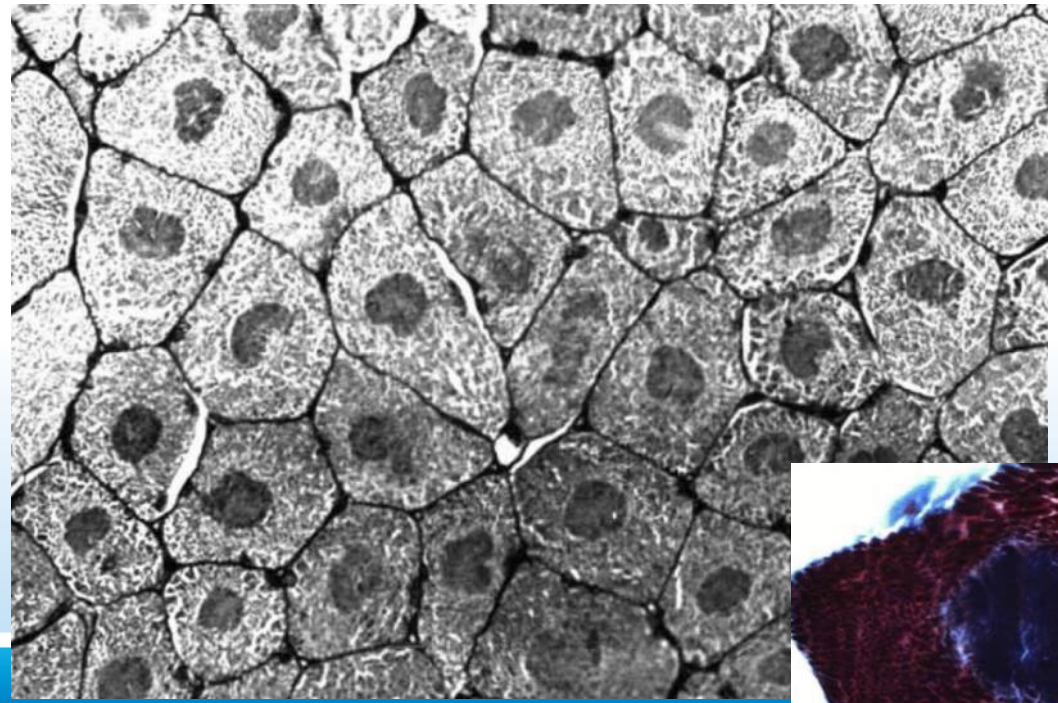
G. MILTON SHY AND KENNETH R. MAGEE

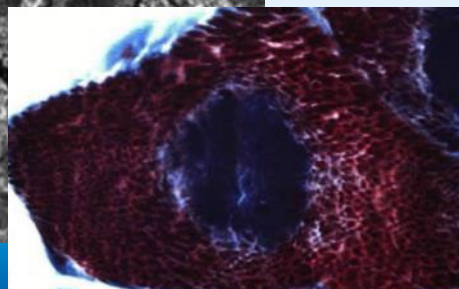
(From the National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare, Bethesda, Maryland)

Brain, Volume 79, Issue 4, December 1956, Pages 610–621,
https://doi.org/10.1093/brain/79.4.610

Published: 01 December 1956

In summary, the principal histological change was in the anatomical arrangement and histochemical characteristics of aberrant fibrillary bundles found internally in the centre of almost every muscle fibre. A reconstruction of such a muscle fibre may be seen in fig. 11. Frequent large fibres and central nuclei were the other characteristics of the disease and were present in all afflicted members of the family. In Cases 1, 4, 5, and 8, almost every fibre was abnormal. In Case 7, however, only a few such fibres could be found. This case showed the least clinical involvement.



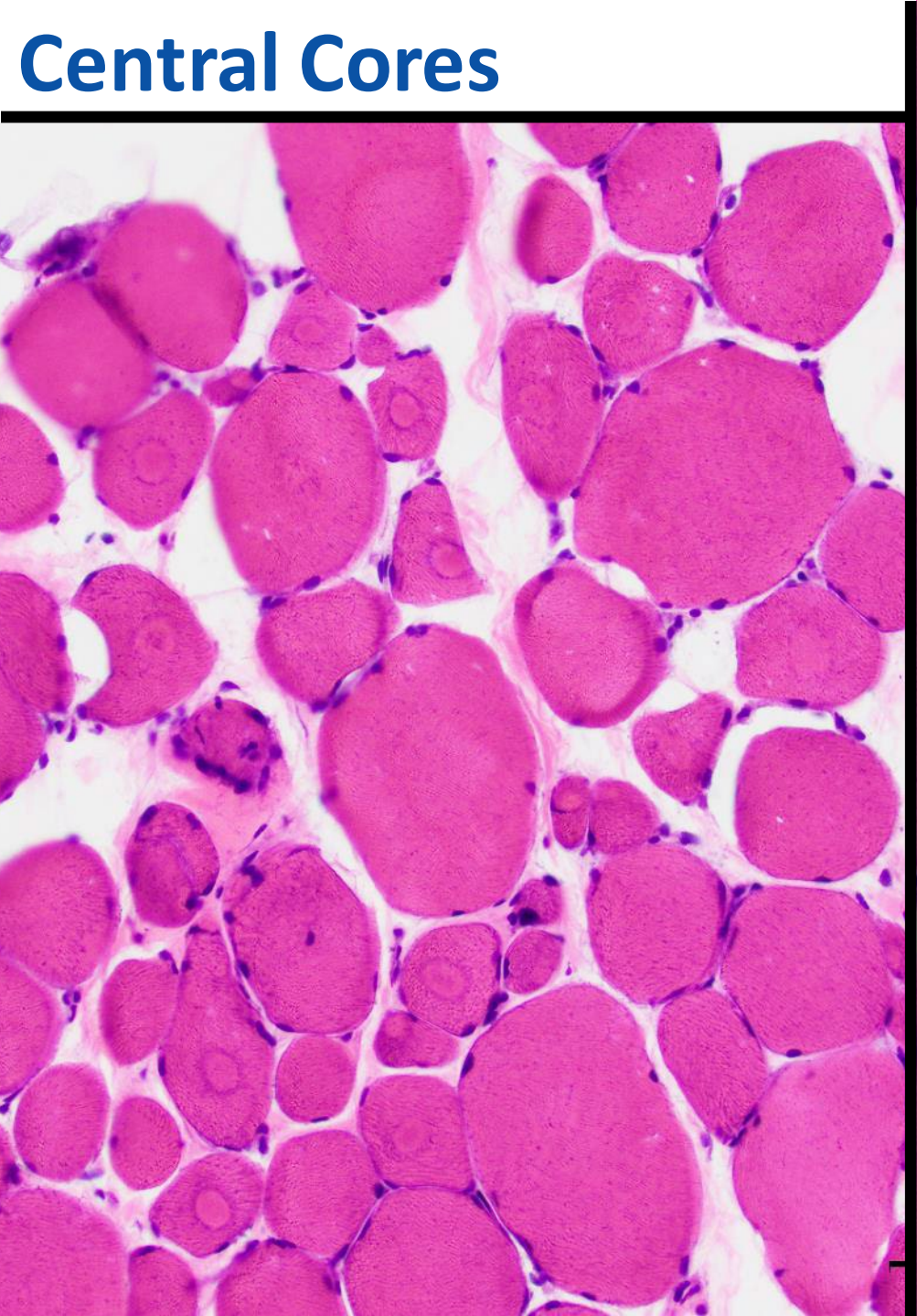


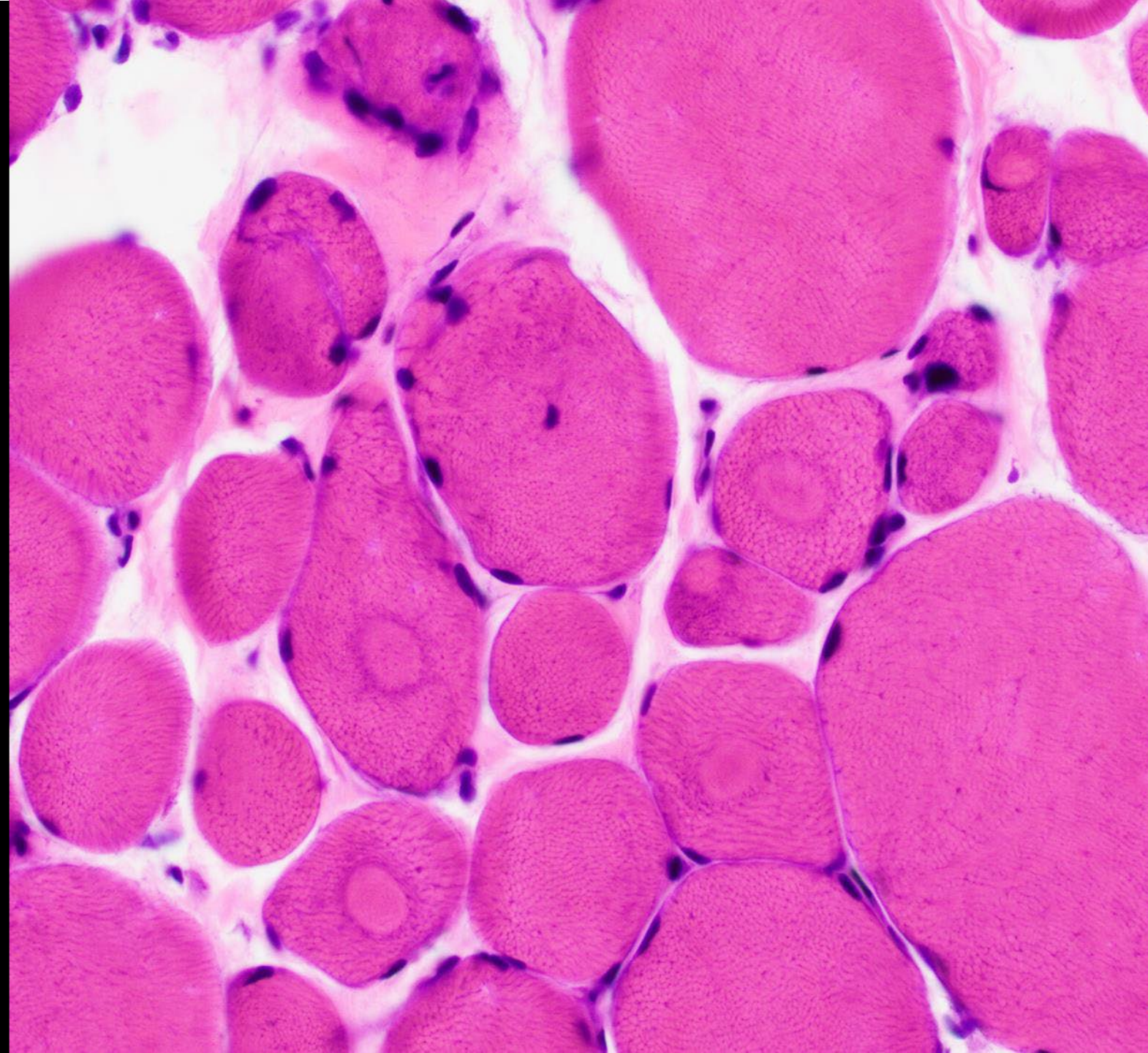
Cores = areas of skeletal muscle that lack oxidative enzyme staining

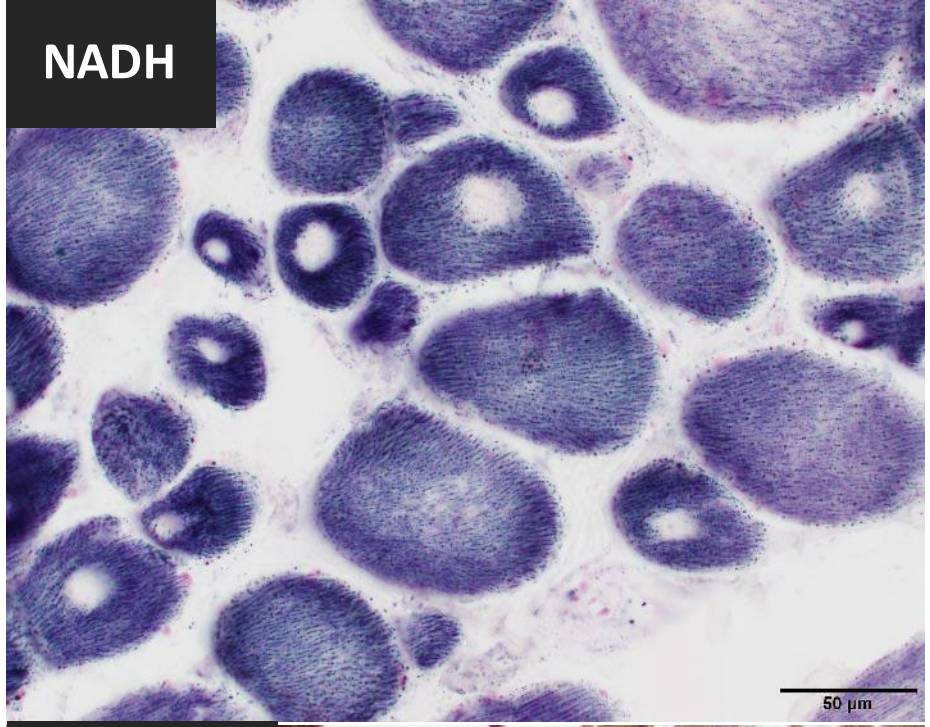
- Mitochondria are excluded from the core → no oxidative enzyme activity within the core
- Also myofibrillar/sarcomeric disruption
- NADH, SDH, COX most helpful for recognition

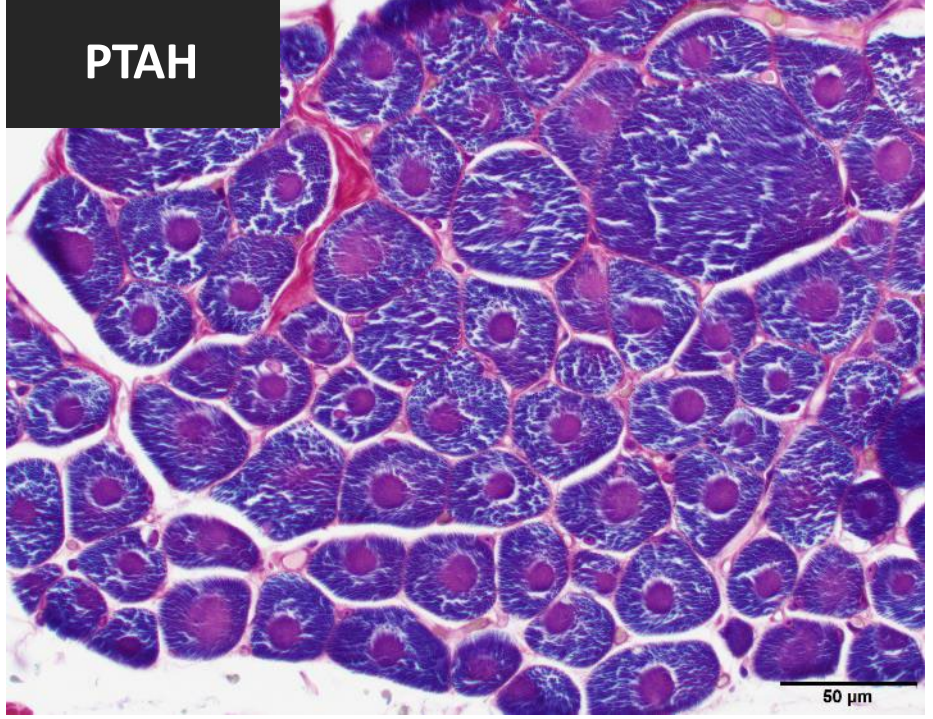
Diagnostic tip! phosphotungstic acid hematoxylin (PTAH) can also be really helpful due to altered myofibrillar architecture

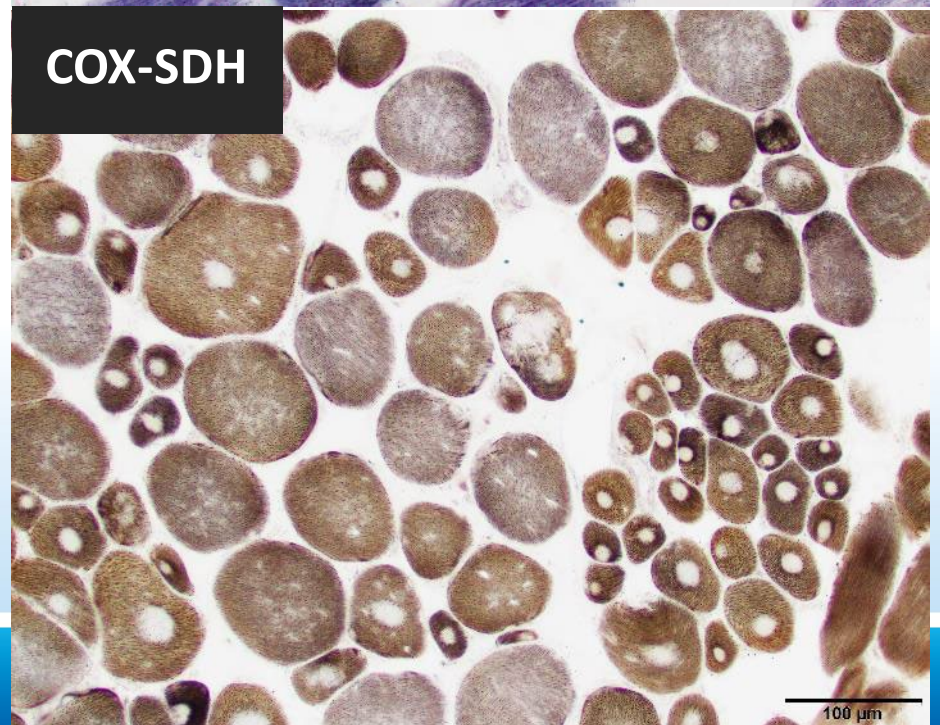
Central Cores

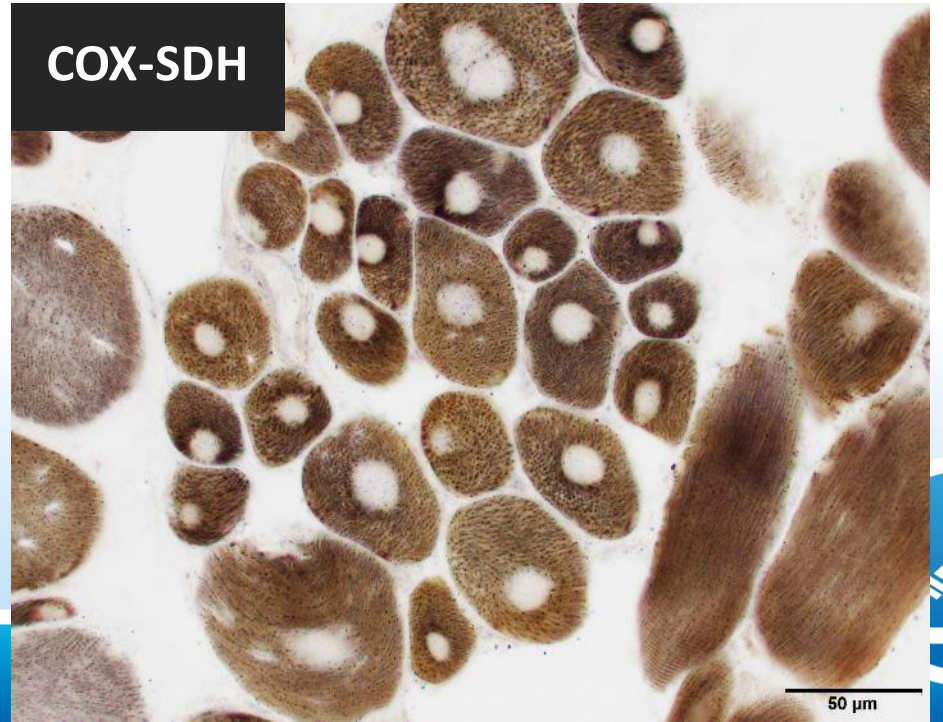





NADH
50 µm

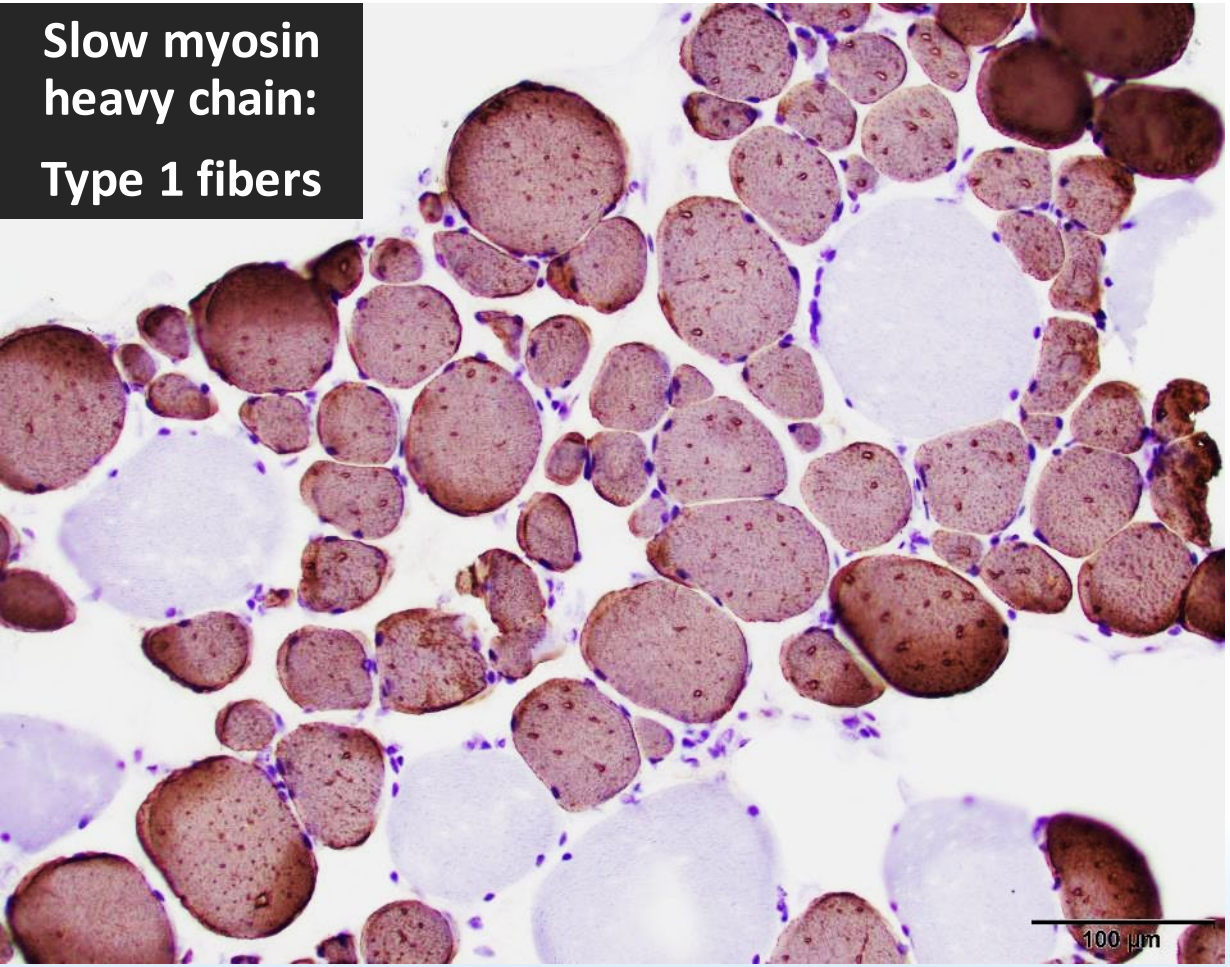

PTAH
50 µm


COX-SDH
100 µm


COX-SDH
50 µm

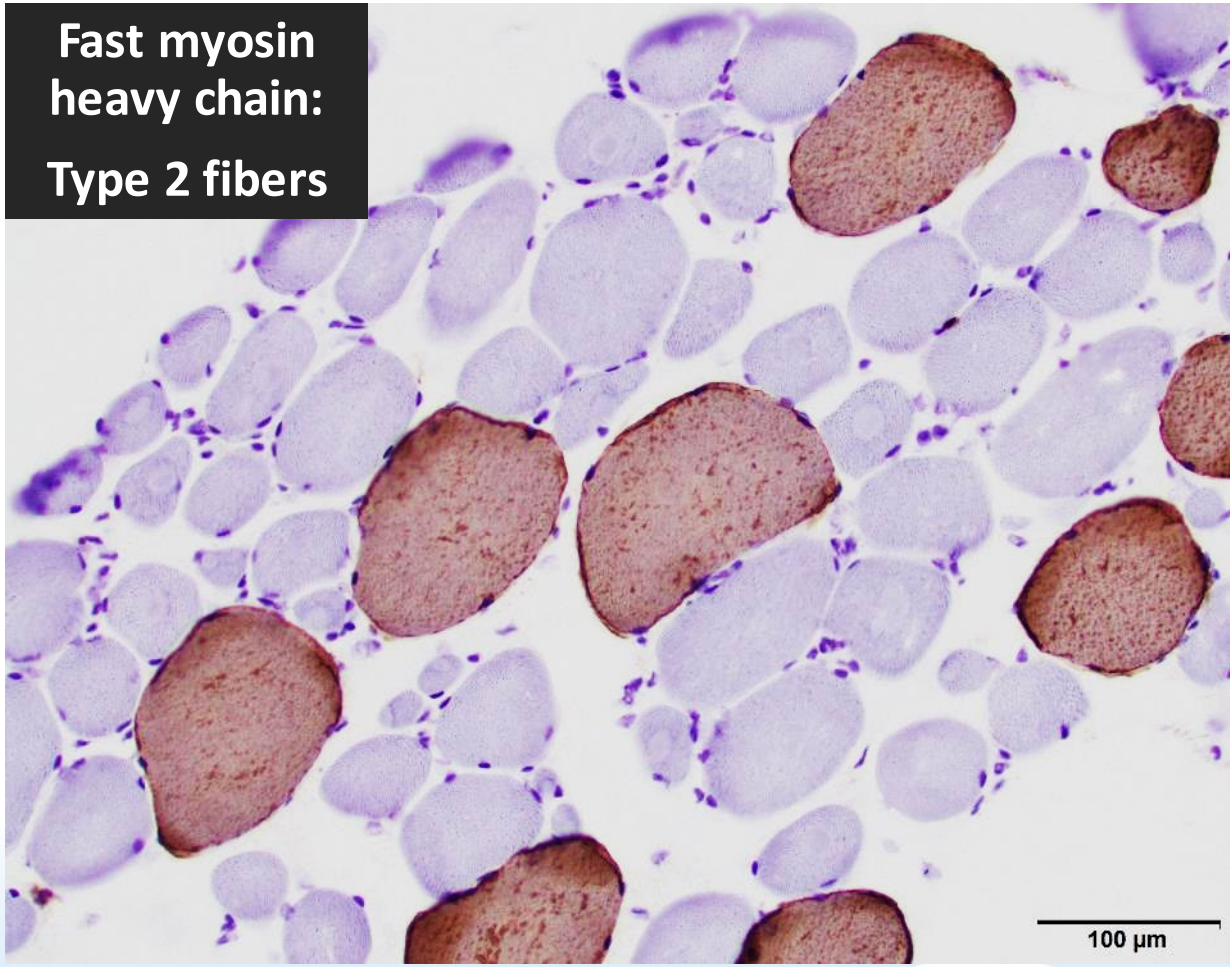
Slow myosin heavy chain:

Type 1 fibers

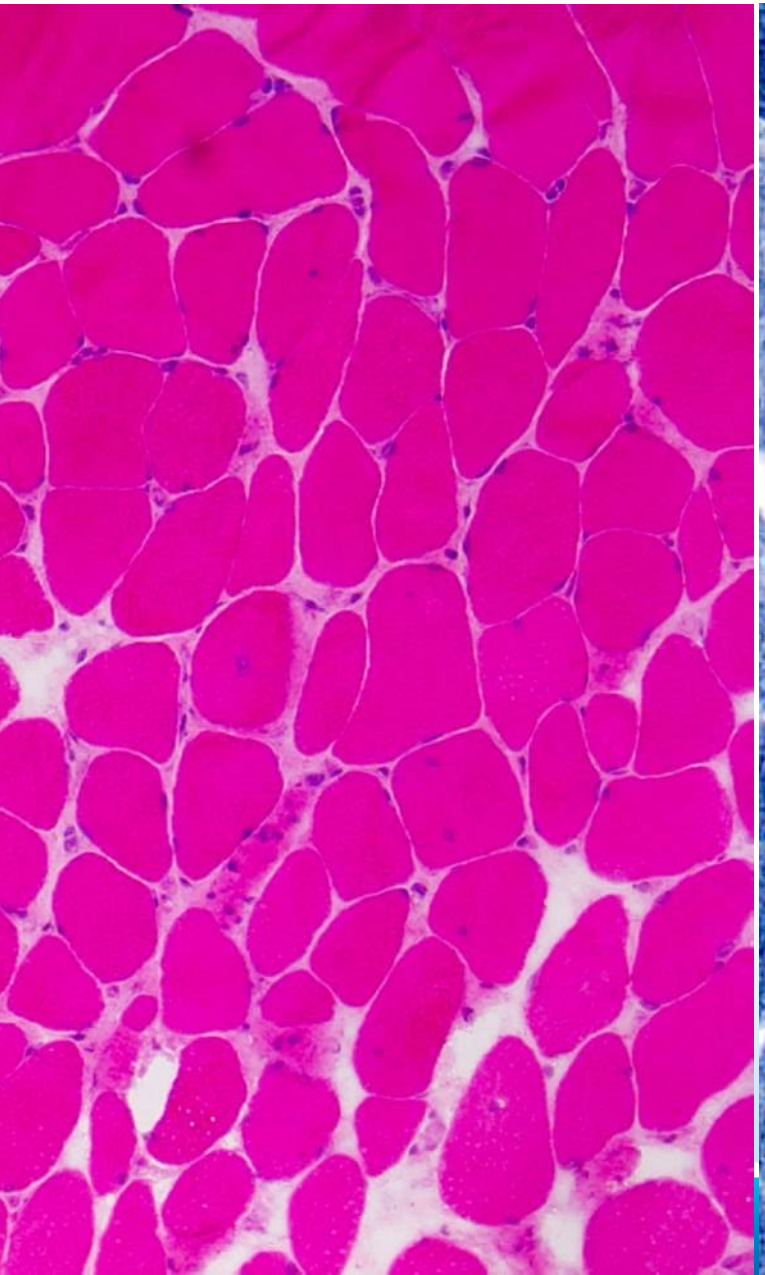


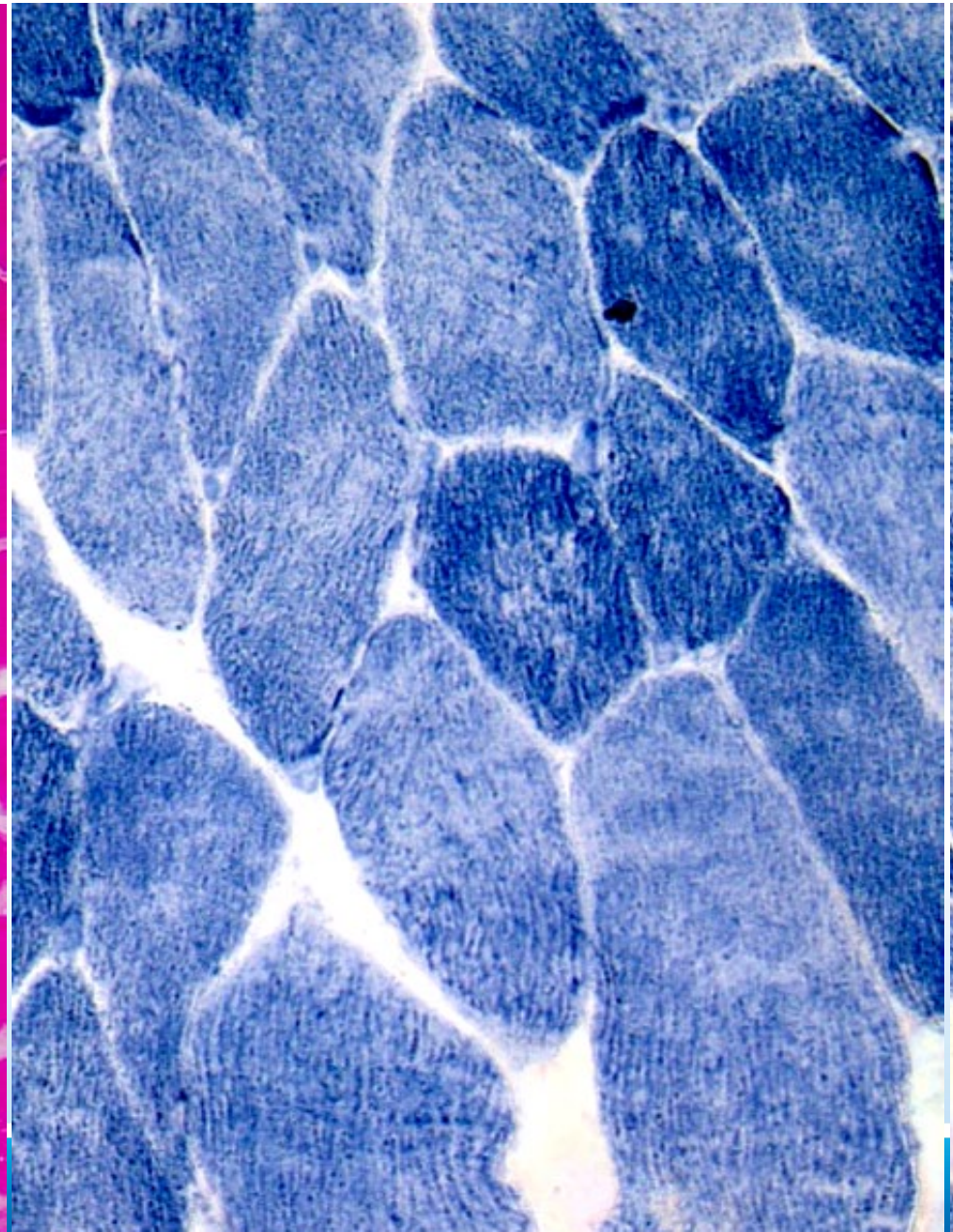
Fast myosin heavy chain:

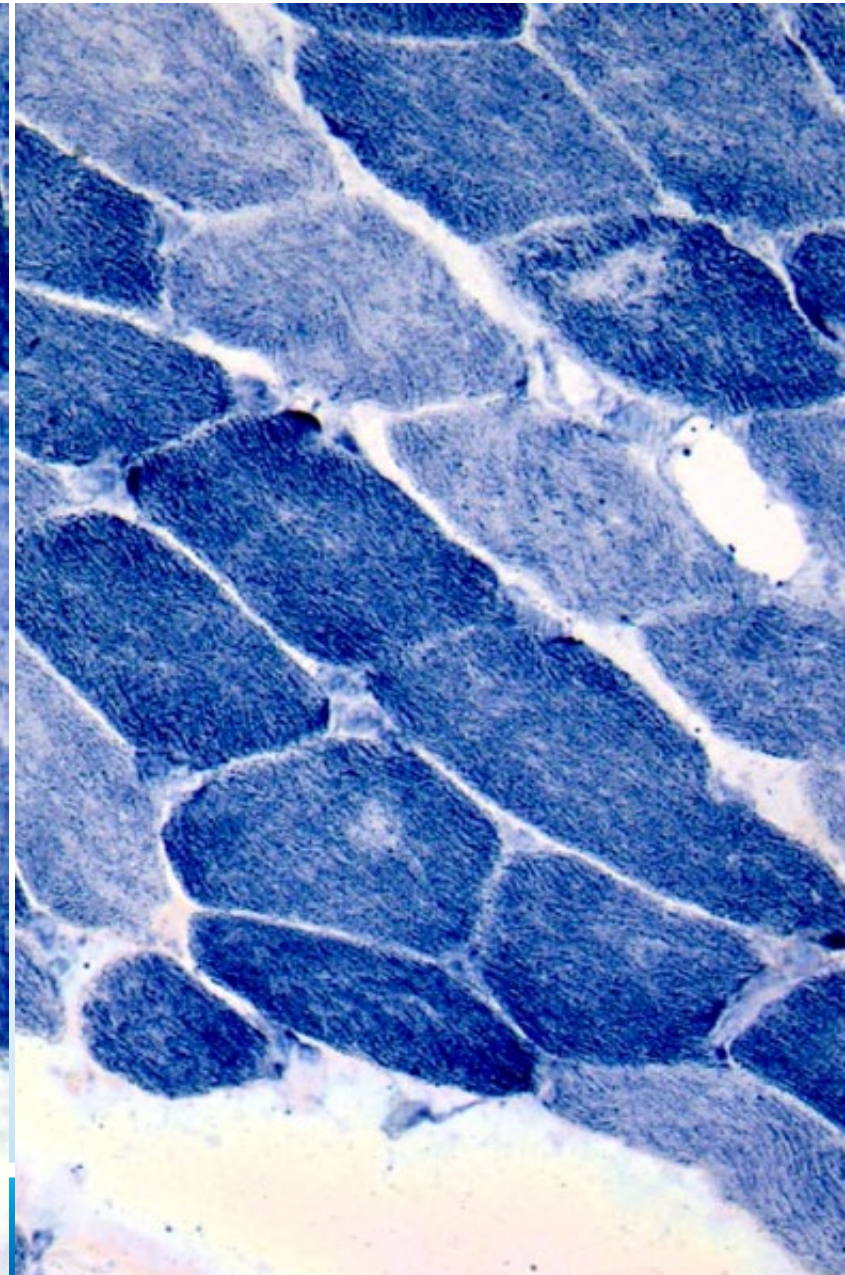
Type 2 fibers



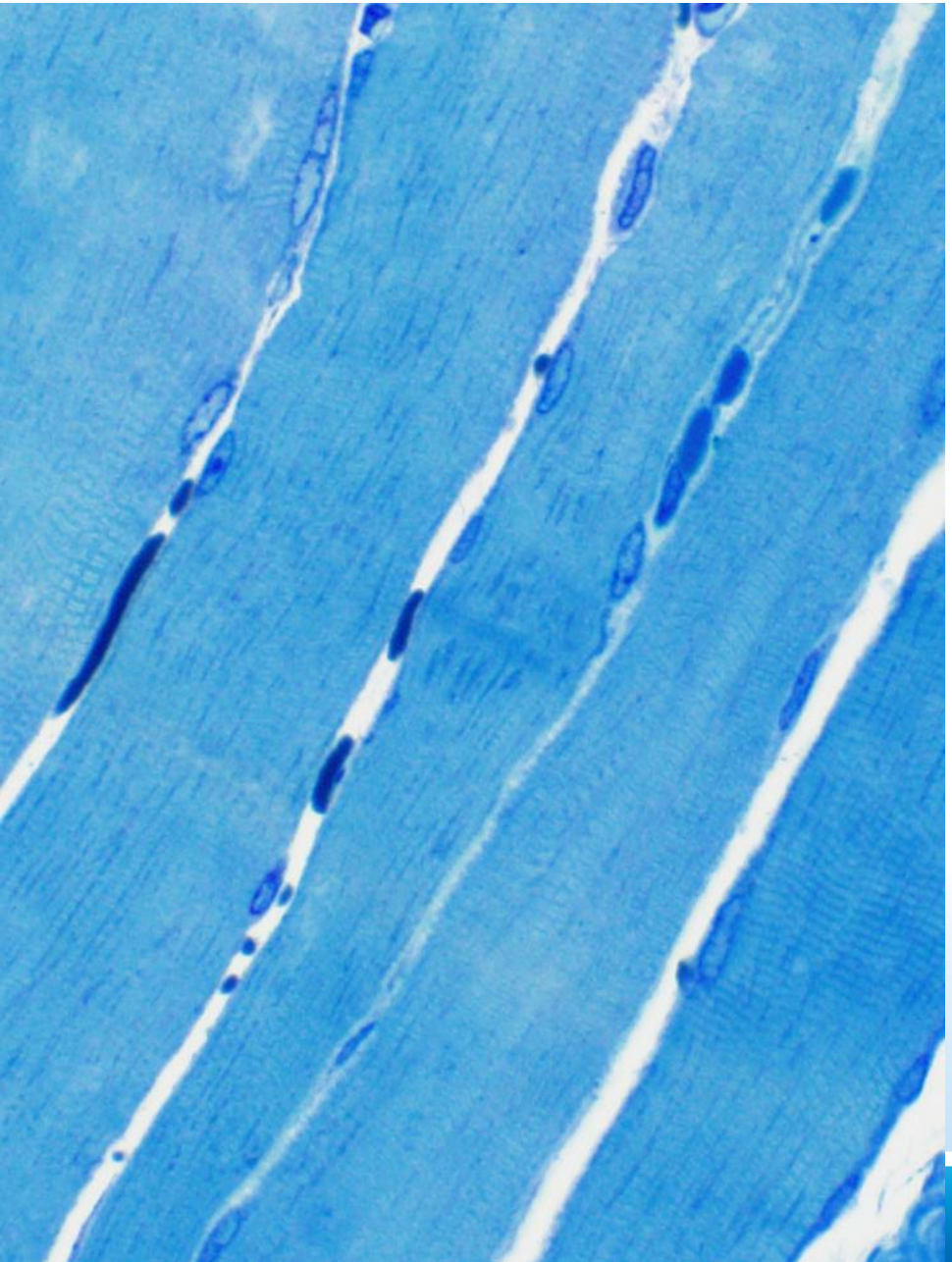
Minicores

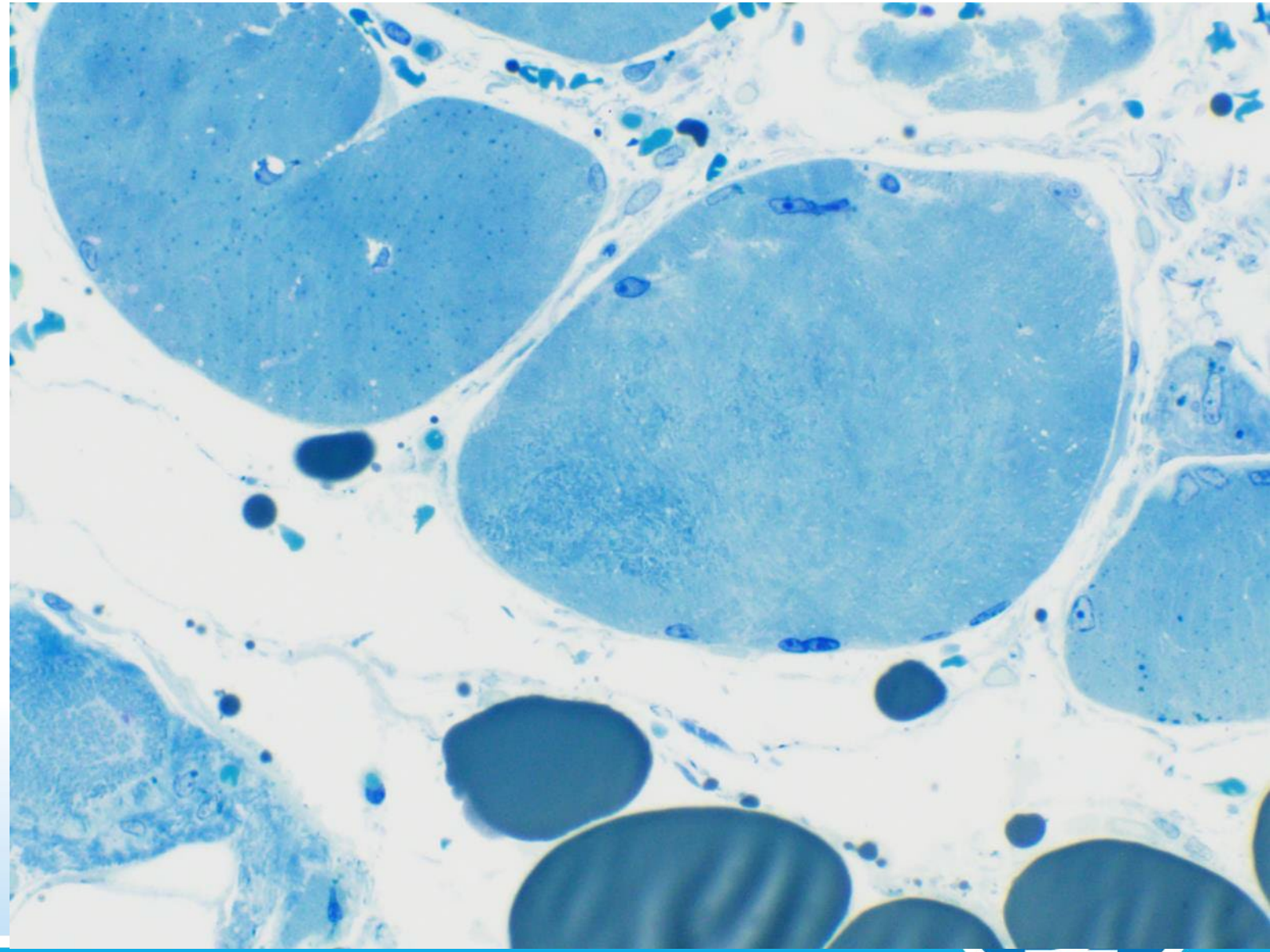




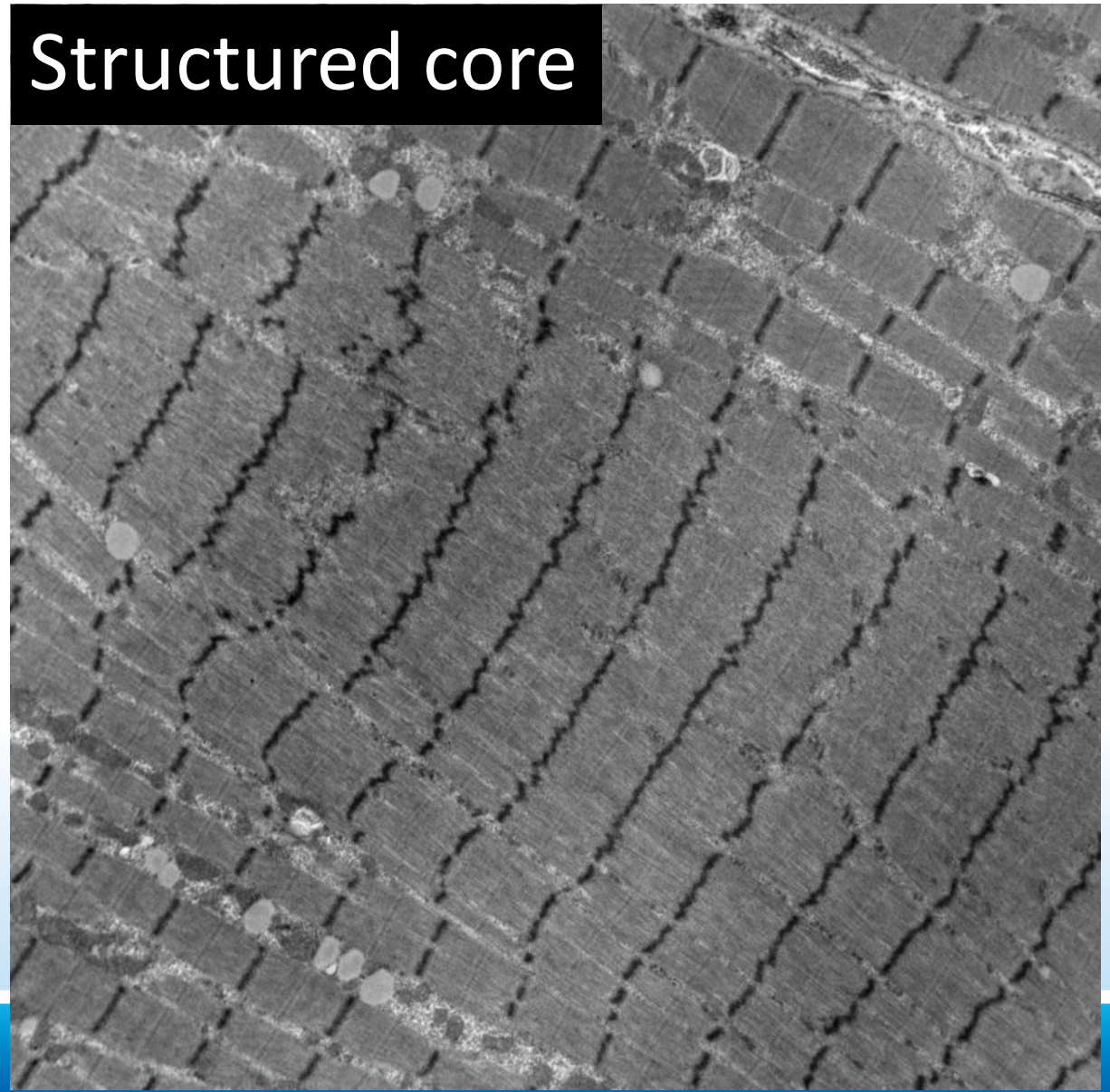


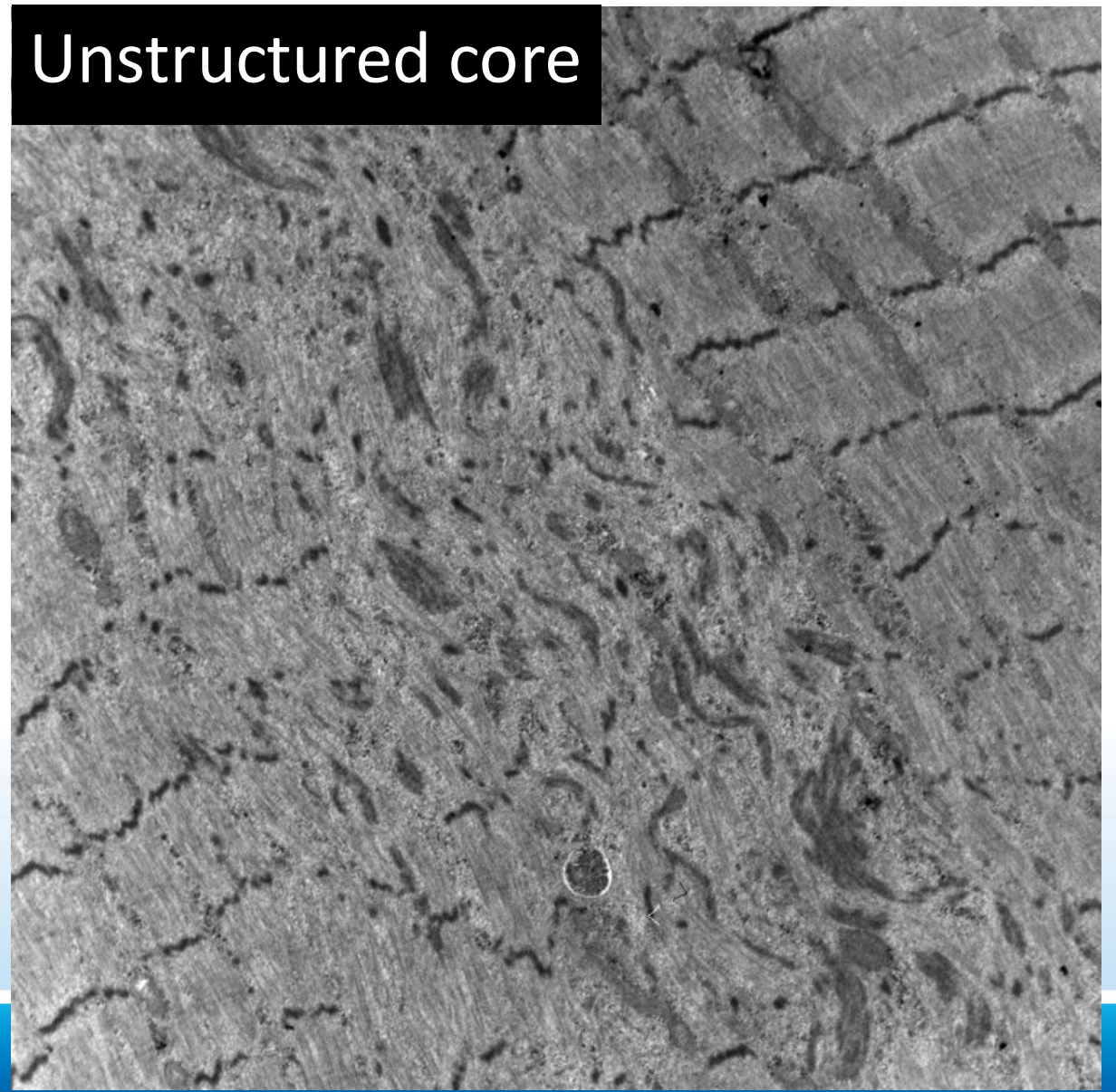
Cores on toluidine blue stained epon sections



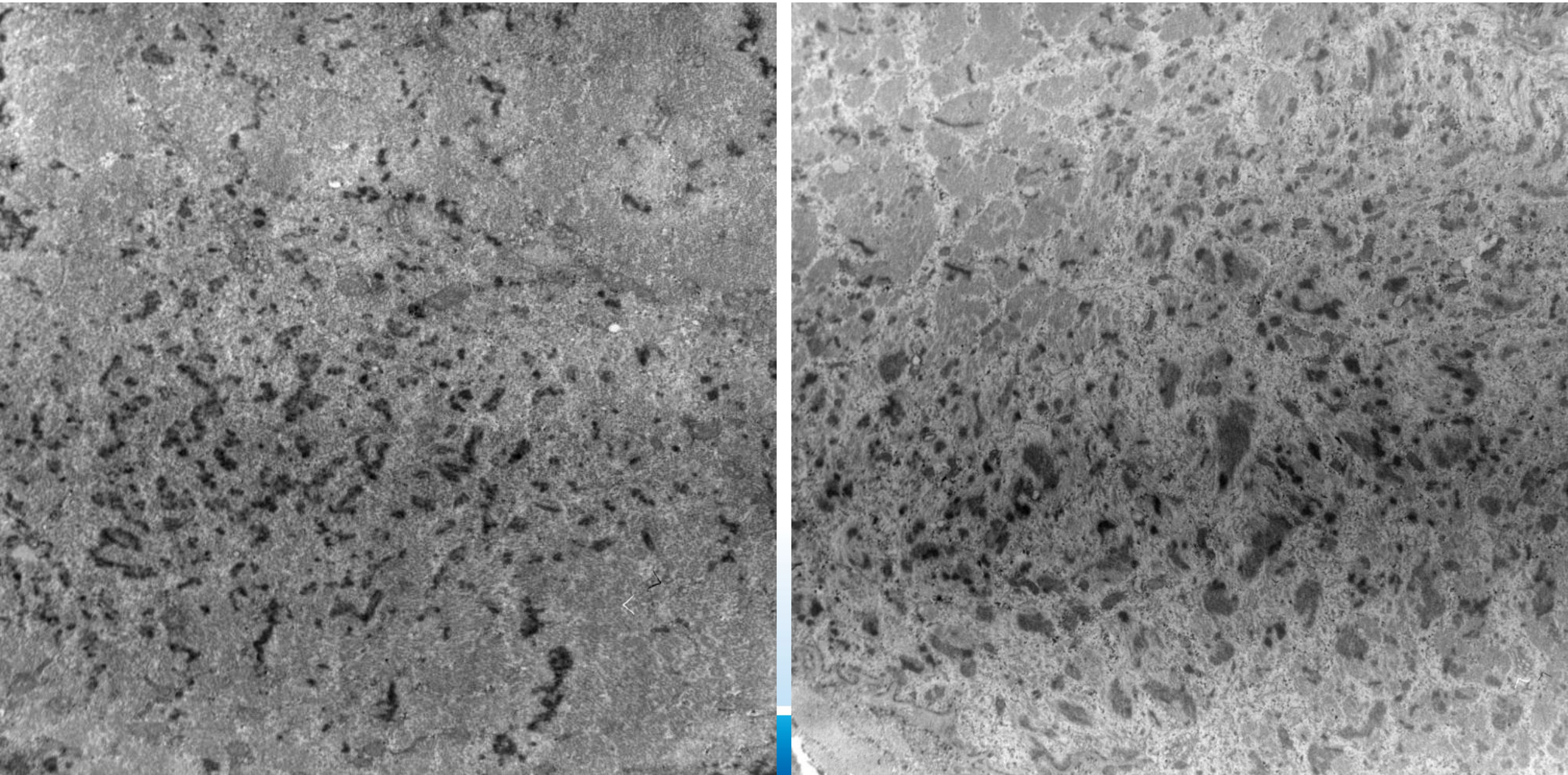


Cores in longitudinal section

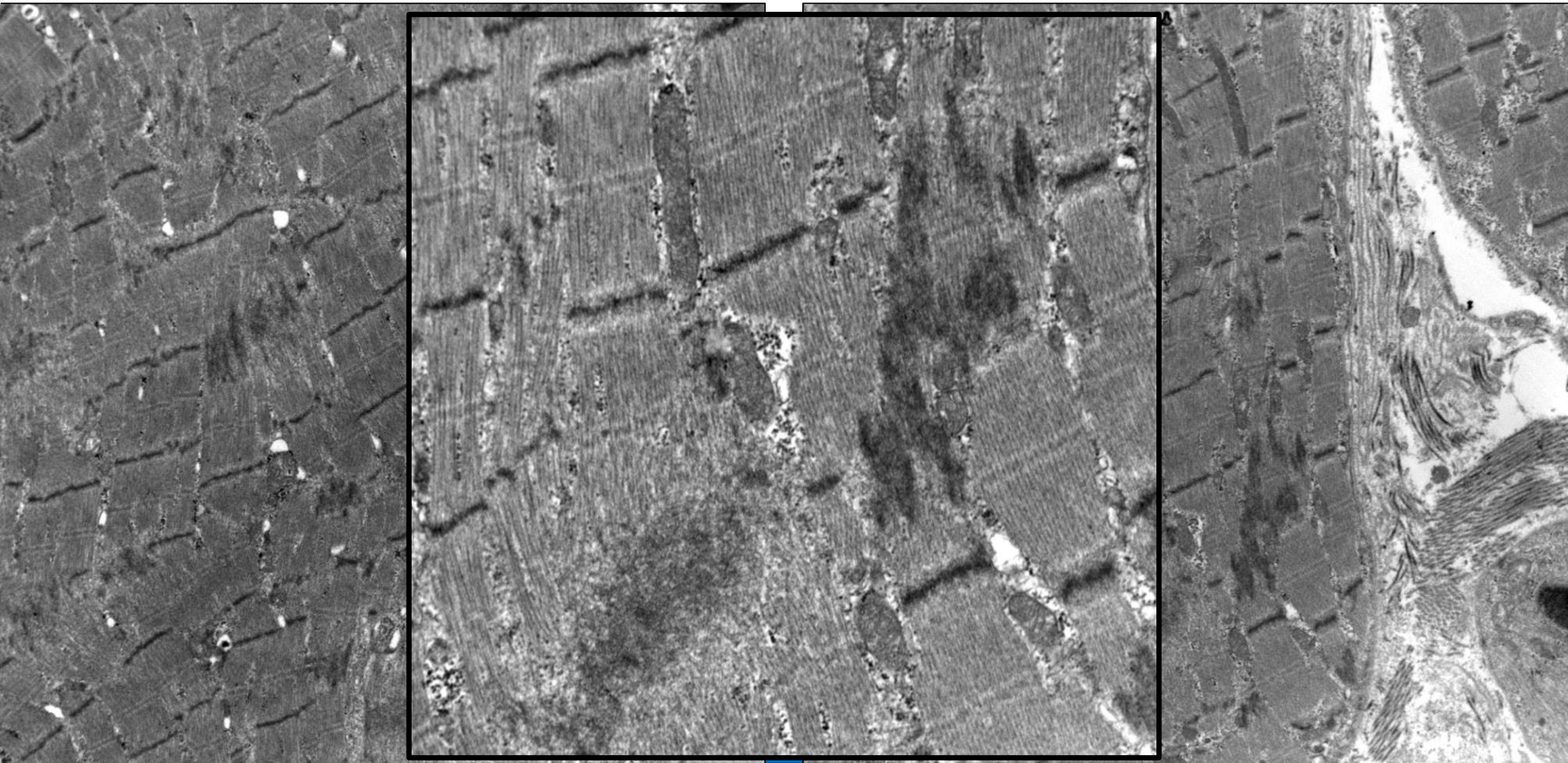




Cores in transverse section

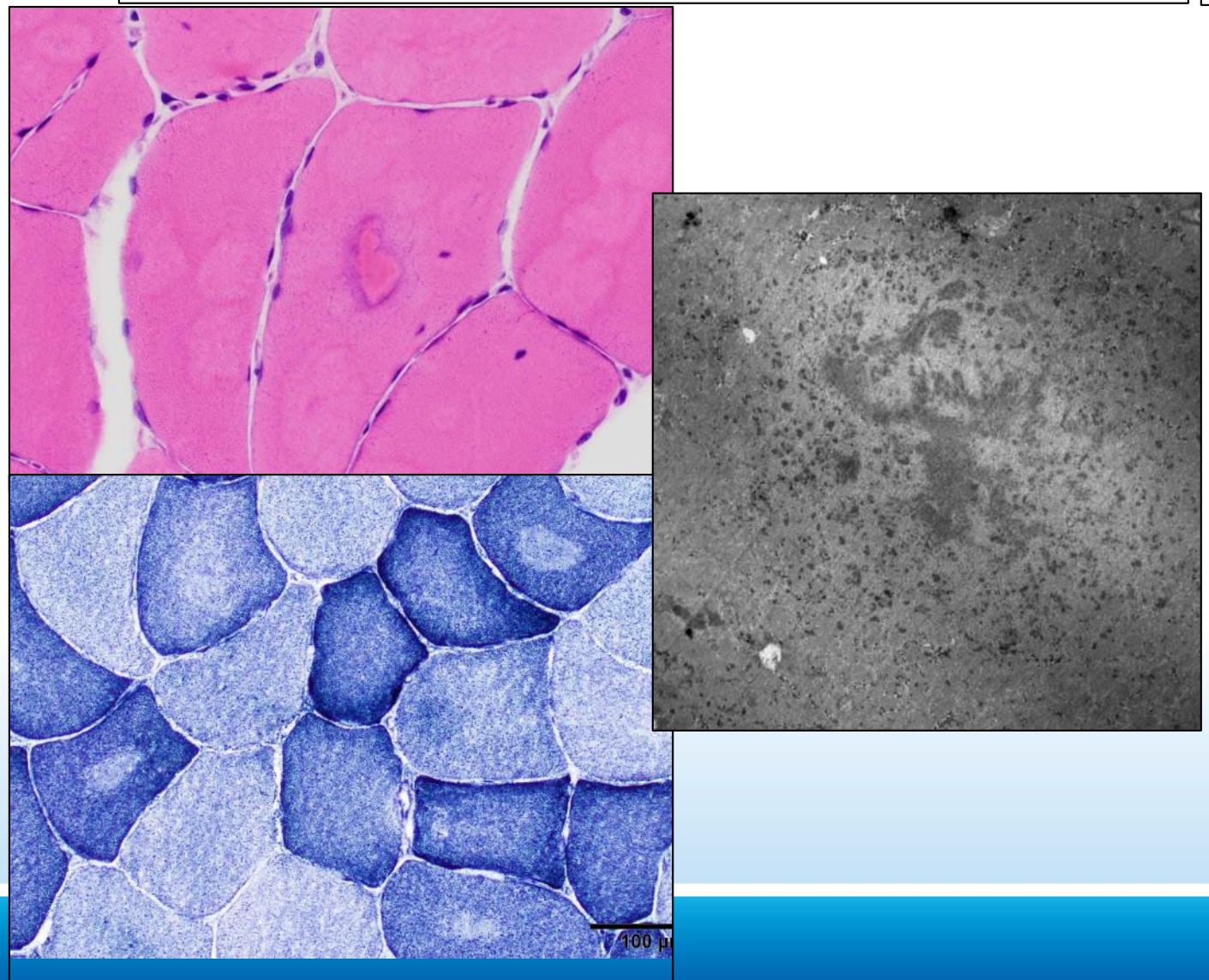


Minicores in longitudinal section

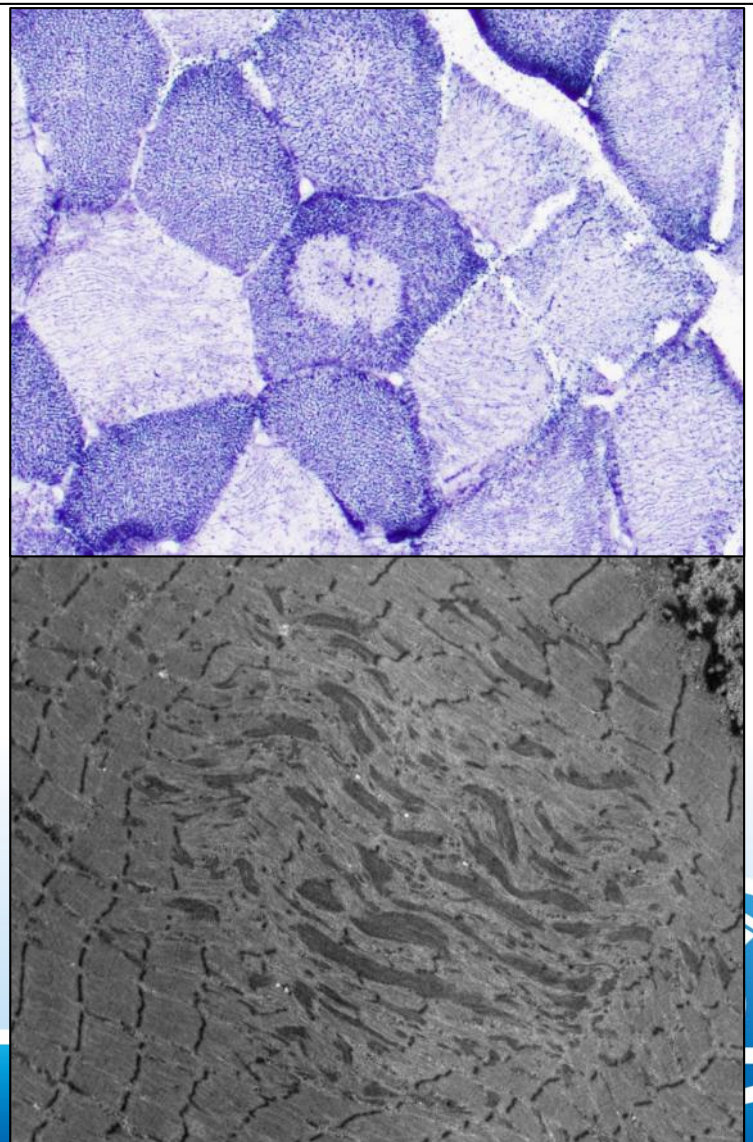


Potential pitfalls! core-like areas can be seen in other entities

Targetoid change in neurogenic atrophy



Core-like areas in dermatomyositis



Core myopathy

- All encompassing term for central core disease, minicore disease, multi-minicore disease, and “dusty” core disease
- Highly clinically, pathologically, and genetically heterogeneous

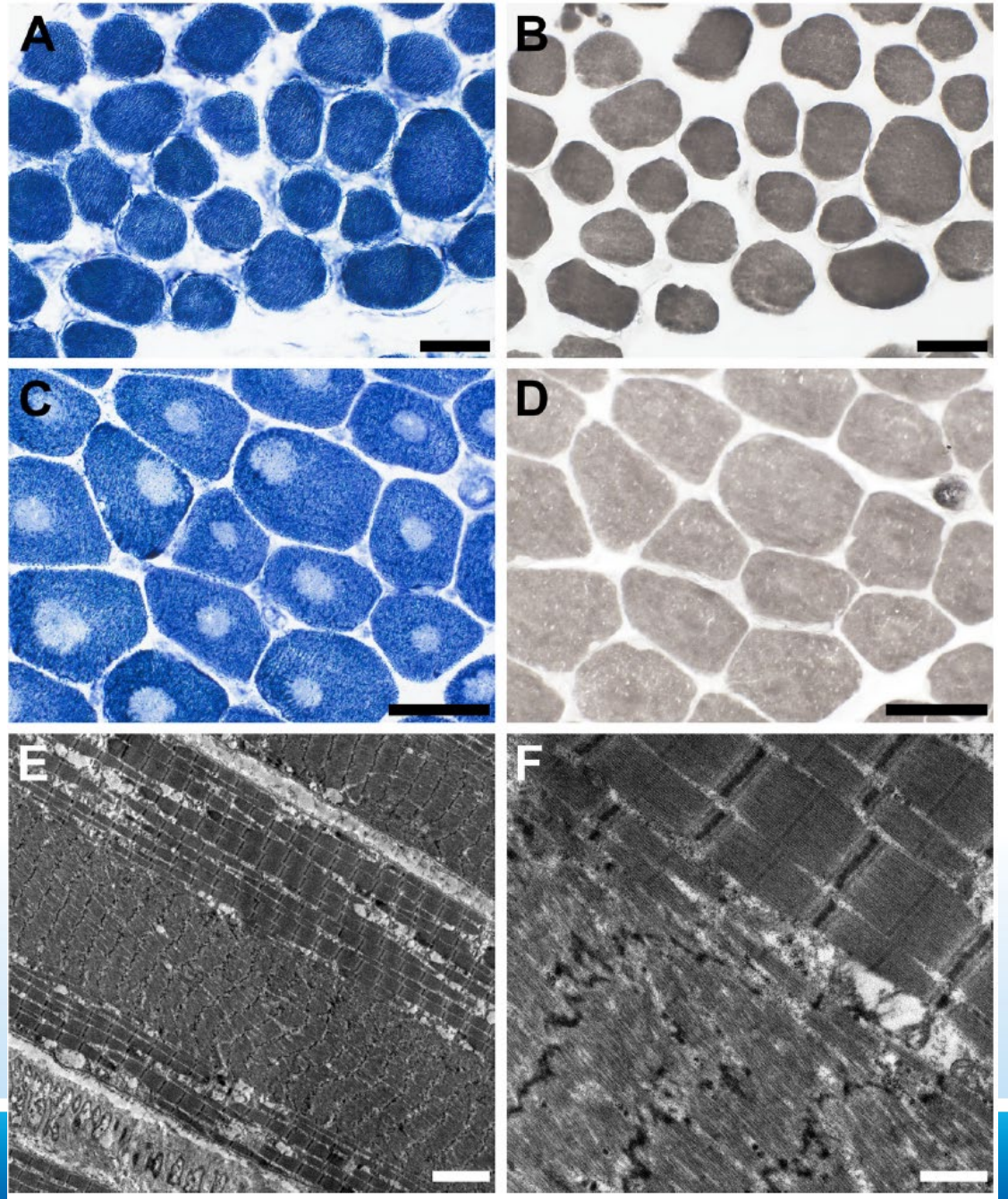
Table 1
Pathological features of core myopathy for each gene.

Gene	CCD	MmD	DuCD	Core-rod myopathy
RYR1	+++	+	+	+
SELENON	–	++	–	–
MYH2	–	+	–	–
MYH7	–	+	–	–
TTN	–	+	–	–
CCDC78	–	+	–	–
UNC45B	–	+	–	–
ACTN2	–	+	–	–
MEGF10	–	+	–	–
NEB	–	–	–	+
ACTA1	–	–	–	+
KBTBD13	–	–	–	+
CFL2	–	–	–	+
TRIP4	–	–	–	+
TNNT1	–	–	–	+

Ogasawara M, Nishino I. A review of core myopathy: central core disease, multiminicore disease, dusty core disease, and core-rod myopathy. Neuromuscul Disord. 2021 Oct;31(10):968-977.

Central core disease

- Pathologic findings:
  - Type 1 fiber predominance
    - Can be extreme – "uniform type 1 fiber"
    - Early on, some patients show "congenital neuromuscular disease with uniform type 1 fiber" (CNMDU1) and familial studies have shown older patients in the same family can have classic central cores
      - Suggests that fiber-type conversion precedes core formation in disease development
  - Cores have a predilection for type 1 fibers
  - Single cores classically, centrally placed
  - Cores extend along the length of a myofiber in longitudinal sections
  - Increased central nuclei (AR>AD)



Ogasawara M, Nishino I. A review of core myopathy: central core disease, multiminicore disease, dusty core disease, and core-rod myopathy. Neuromuscul Disord. 2021 Oct;31(10):968-977.

RYR1-related disease

- Genetics:
  - Most AD; some AR forms have been described
  - AD *RYR1* pathogenic variants within the C-terminus
- Clinical phenotype:
  - AD *RYR1*-related disease classically shows early onset hypotonia and/or motor delay
    - BUT Severity is highly variable and can present up to adulthood
  - Weakness is often axial and pronounced in the hip girdle; can also involve facial weakness
    - Joint laxity can be seen (cause some confusion with collagen VI disease) as well as orthopedic problems
  - Ophthalmoplegia and bulbar involvement is common with AR *RYR1*-related disease
  - Typically stable clinical presentation or very slowly progressive (less common)

Table 2
Clinicopathological features of core myopathies for each genetic mutation.

Gene/ Reference	Inheritance	Onset	Clinical features	Pathological features	Muscle imaging
RYR1 [7,9,42,87]	AD/AR	Neonatal to adult	External ophthalmoplegia, bulbar involvement, scoliosis, dislocation of the hips, malignant hyperthermia	Central and peripheral core, multiminicores, T1FP / uniform type 1, rods and cores, fiber-type disproportion, dusty core	Involvement; Sa, AM, Vasti Sparing; RF, Gra, AL

Congenital neuromuscular disease with uniform type 1 fiber and *RYR1* mutation

I. Sato, MD
S. Wu, MD
C.A. Ibarra M., MD, PhD
Y.K. Hayashi, MD, PhD
H. Fujita, MD
M. Tojo, MD
S.J. Oh, MD
I. Nonaka, MD, PhD
S. Noguchi, PhD
I. Nishino, MD, PhD

Address correspondence and reprint requests to Dr. I. Nishino, Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP), 4-1-1 Ogawahigashi-cho, Kodaira, Tokyo 187-8502, Japan
nishino@ncnp.go.jp

ABSTRACT

Background: Congenital neuromuscular disease with uniform type 1 fiber (CNMDU1) is a rare form of congenital myopathy, which is pathologically diagnosed by the presence of more than 99% of type 1 fiber, with no specific structural changes. Its pathogenic mechanism is still unknown. We recently reported that almost all patients with central core disease (CCD) with ryanodine receptor 1 gene (*RYR1*) mutations in the C-terminal domain had type 1 fibers, nearly exclusively, in addition to typical central cores.

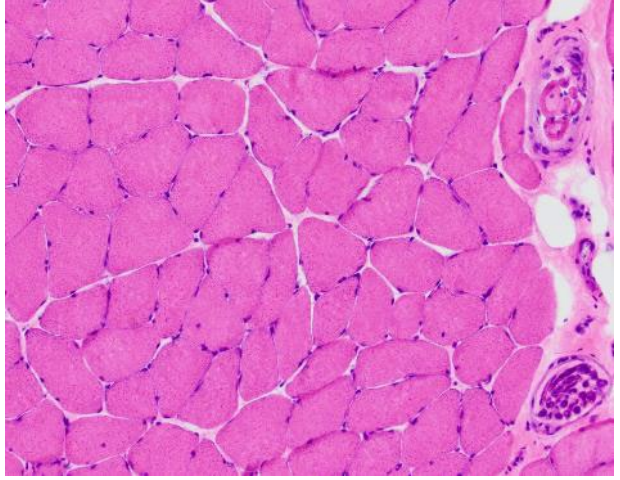
Objective: To investigate whether CNMDU1 is associated with *RYR1* mutation.

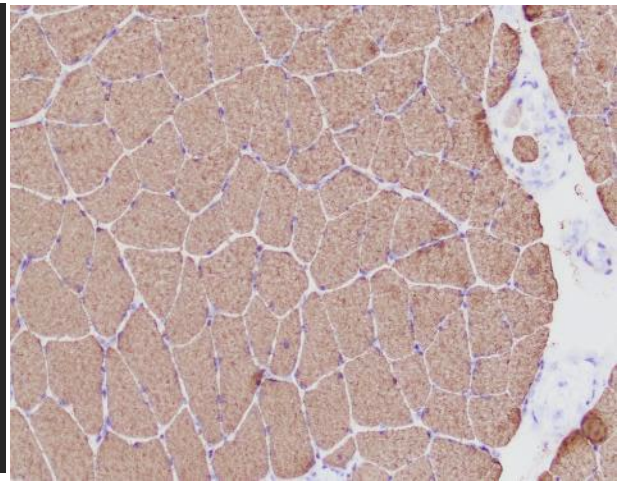
Methods: We studied 10 unrelated Japanese patients who were diagnosed to have CNMDU1 based on clinical features and muscle pathology showing more than 99% type 1 muscle fibers. We extracted genomic DNA from frozen muscles and directly sequenced all 106 exons and their flanking intron–exon boundaries of *RYR1*.

Results: Four of 10 patients had a heterozygous mutation, three missense and one deletion, all in the C-terminal domain of *RYR1*. Two missense mutations were previously reported in CCD patients. Clinically, patients with mutations in *RYR1* showed milder phenotype compared with those without mutations.

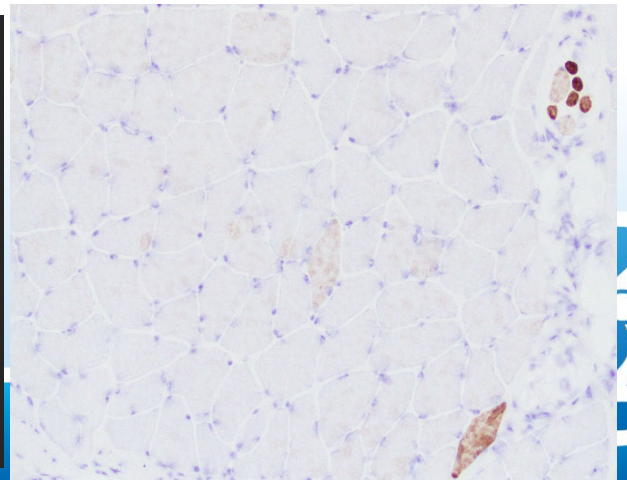
Conclusion: Congenital neuromuscular disease with uniform type 1 fiber (CNMDU1) in 40% of patients is associated with mutations in the C-terminal domain of *RYR1*, suggesting that CNMDU1 is allelic to central core disease at least in some patients.

Neurology® 2008;70:114-122





slow myosin heavy chain



fast myosin heavy chain

Phenotype-Gene Relationships https://www.omim.org/entry/117000

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
19q13.2	Neuromuscular disease, congenital, with uniform type 1 fiber	117000	AD, AR	3	RYR1	180901
19q13.2	Central core disease	117000	AD, AR	3	RYR1	180901

Malignant hyperthermia

- Pathogenic variants in *RYR1* can also lead to malignant hyperthermia susceptibility trait
- Muscle rigidity and increased body temperature after exposure to anesthetics via inhalation

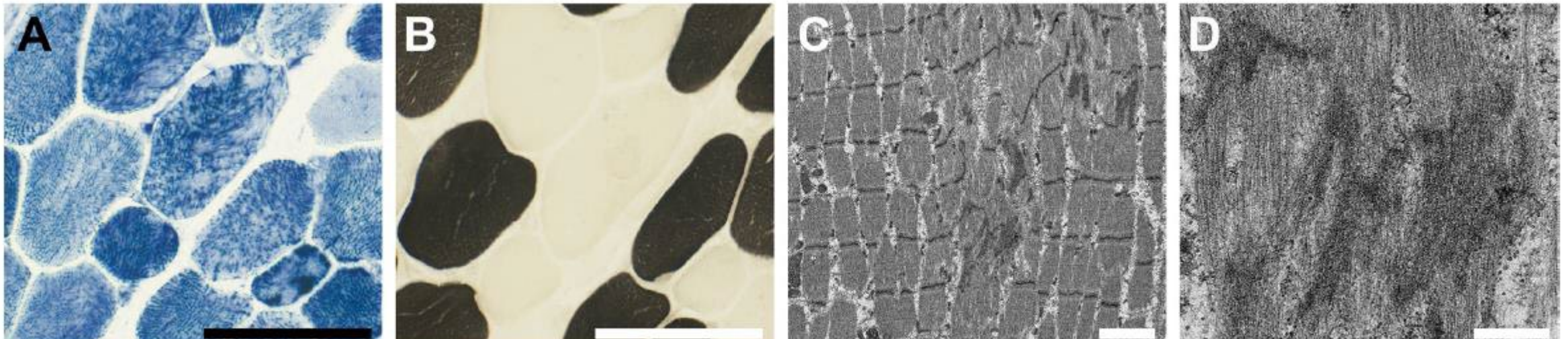
Clinical communication tip! *Best diagnosed with fresh tissue sent to a lab that performs caffeine-halothane contracture testing*

Multiminicore disease

- Pathologic findings:
  - Multiple small areas devoid of oxidative enzyme staining
  - Named “multicore disease” by Engel in 1971
  - Can be easily overlooked or show overlap with “moth-eaten” fibers
  - Cores can be in either type 1 or type 2 fibers
  - Disruption of Z-lines/myofibrils involves only a few sarcomeres

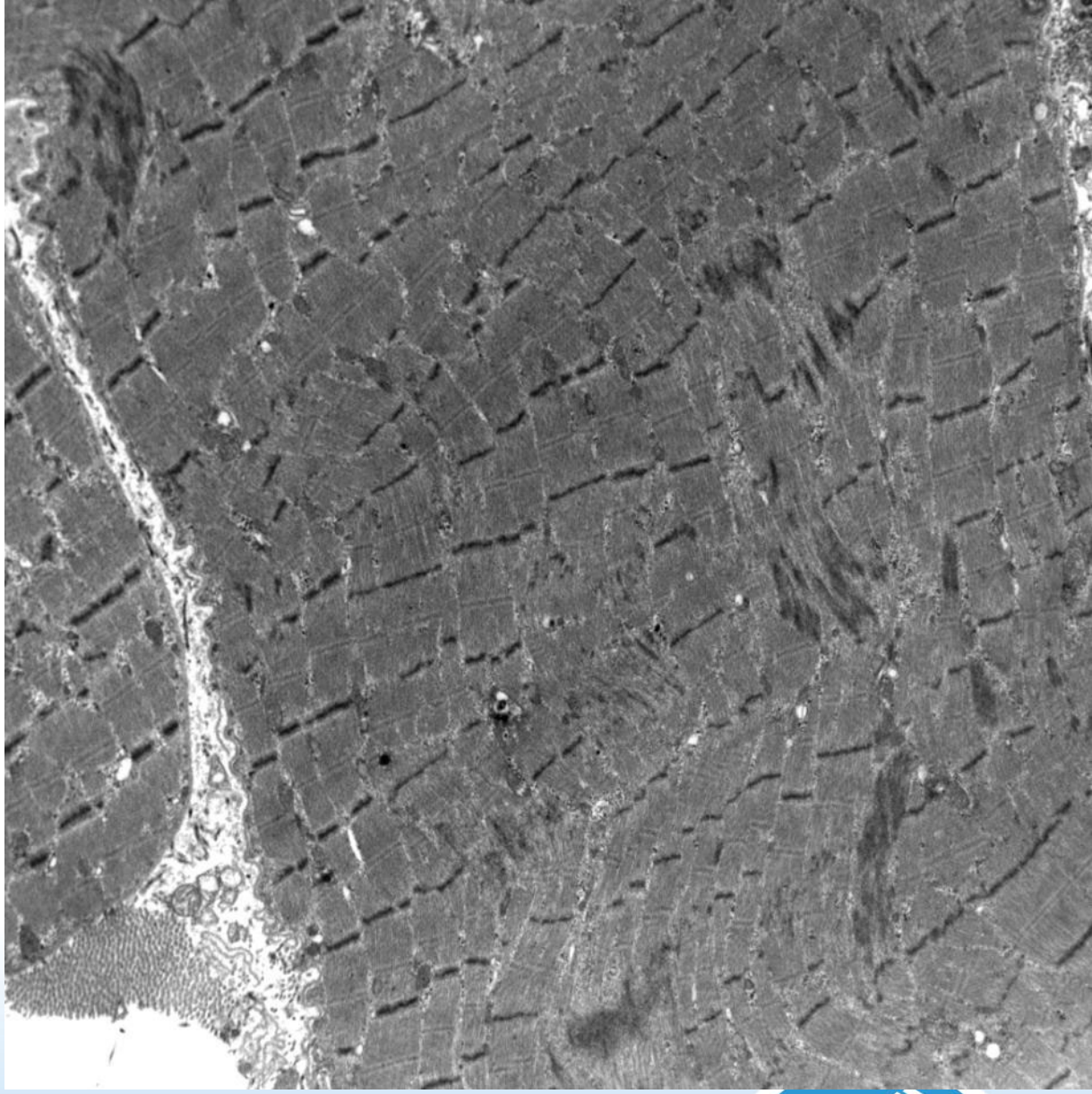
Ogasawara M, Nishino I. A review of core myopathy: central core disease, multiminicore disease, dusty core disease, and core-rod myopathy. Neuromuscul Disord. 2021 Oct;31(10):968-977.

Gene	CCD	MmD
RYR1	+++	+
SELENON	–	++
MYH2	–	+
MYH7	–	+
TTN	–	+
CCDC78	–	+
UNC45B	–	+
ACTN2	–	+
MEGF10	–	+
NEB	–	–
ACTA1	–	–
KBTBD13	–	–
CFL2	–	–
TRIP4	–	–

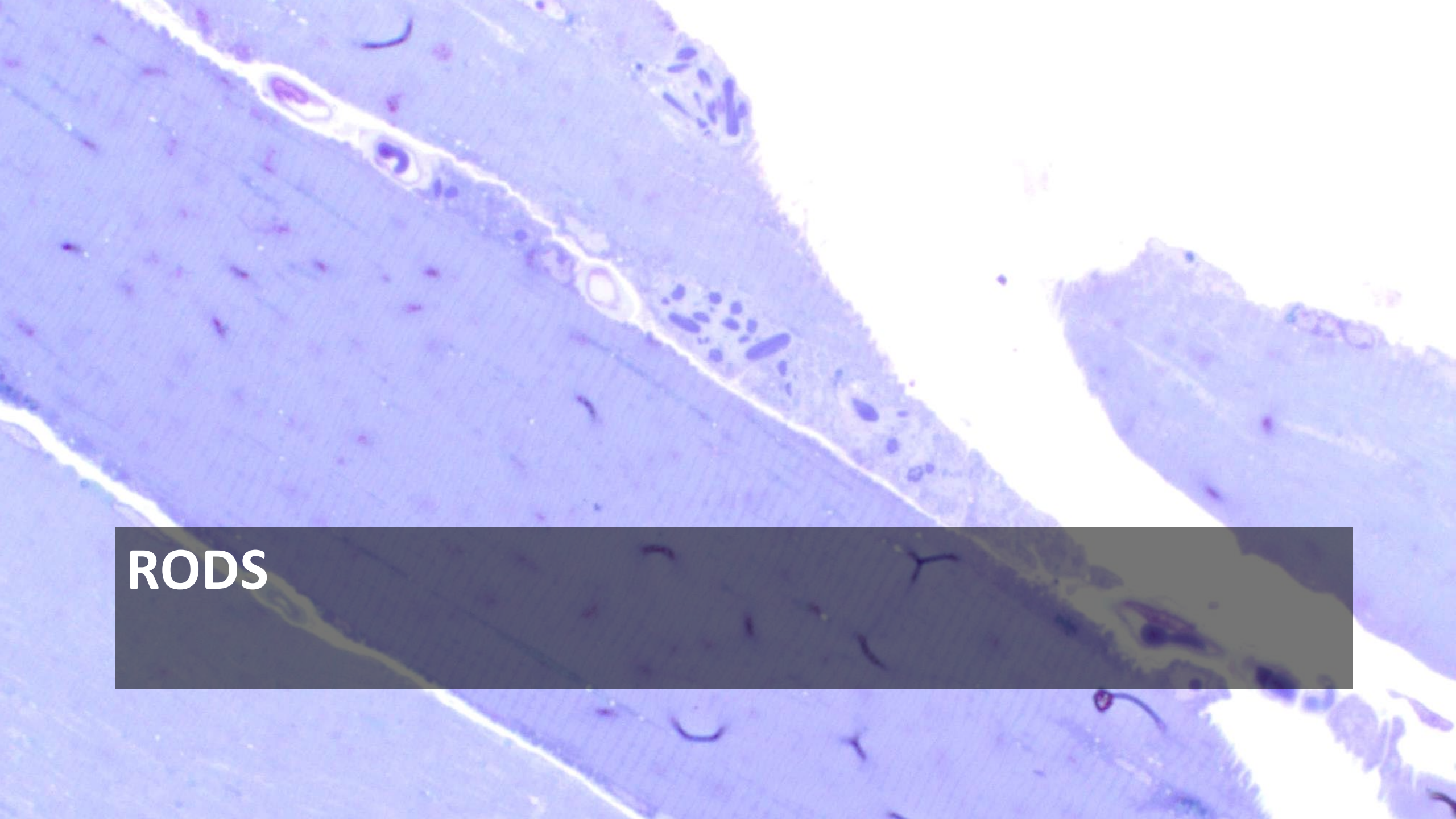


SELENON-related myopathy

- *SELENON* (previously *SEPN1*) encodes selenoprotein (AR most commonly)
- Clinical:
  - Typical early onset in neonatal period or early childhood
  - Axial myopathy with scoliosis and/or torticollis and respiratory failure
  - Muscle MRI shows selective high-level sartorius muscle involvement

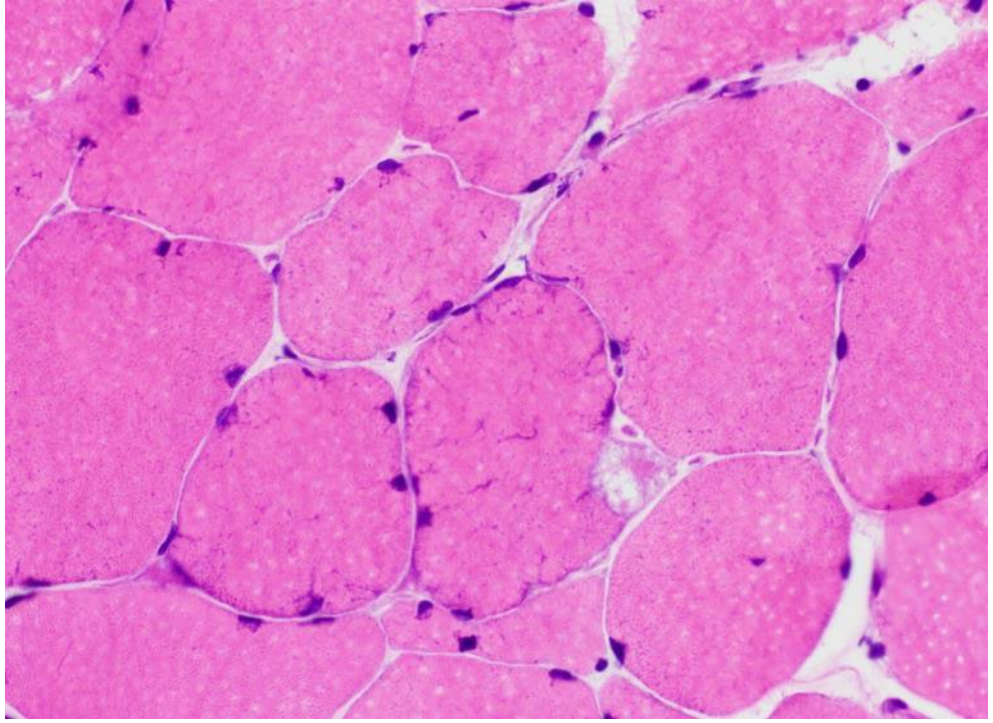


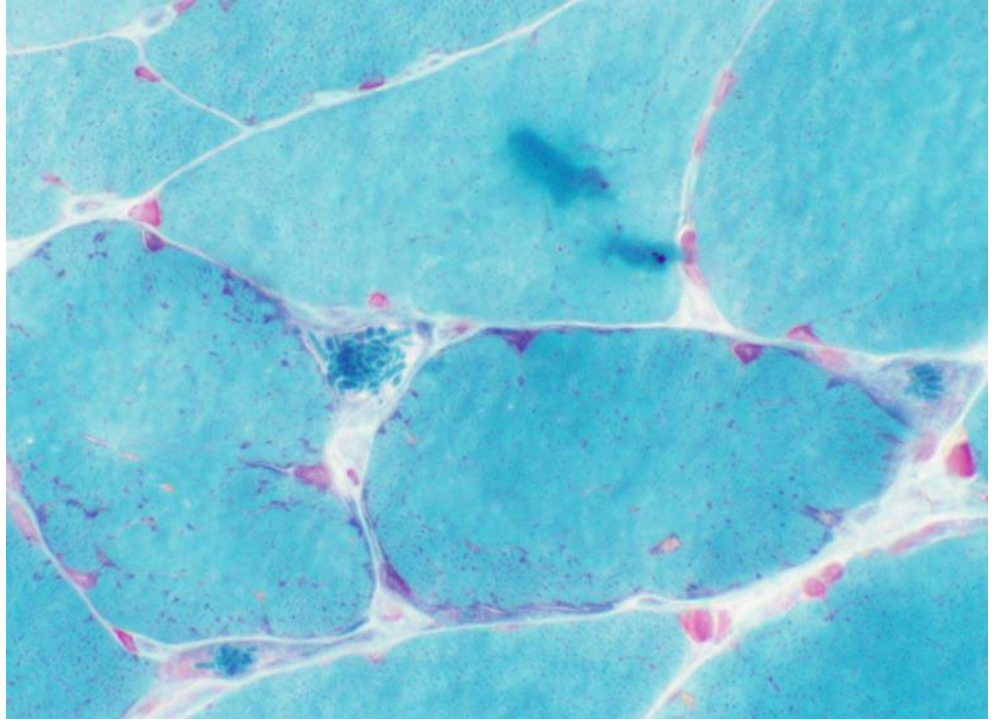
SELENON [11,51]	AR	Neonatal to late adult	Axial myopathy with scoliosis, respiratory failure, spinal rigidity	Multiminicores in both fiber types, T1FP	Involvement; Sa

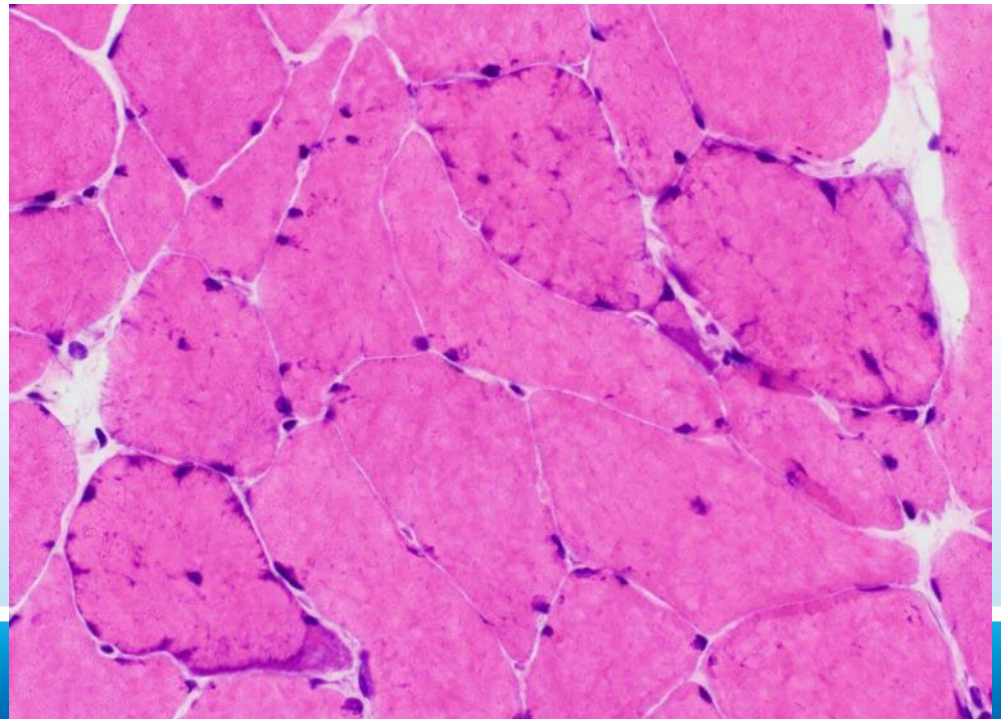

RODS

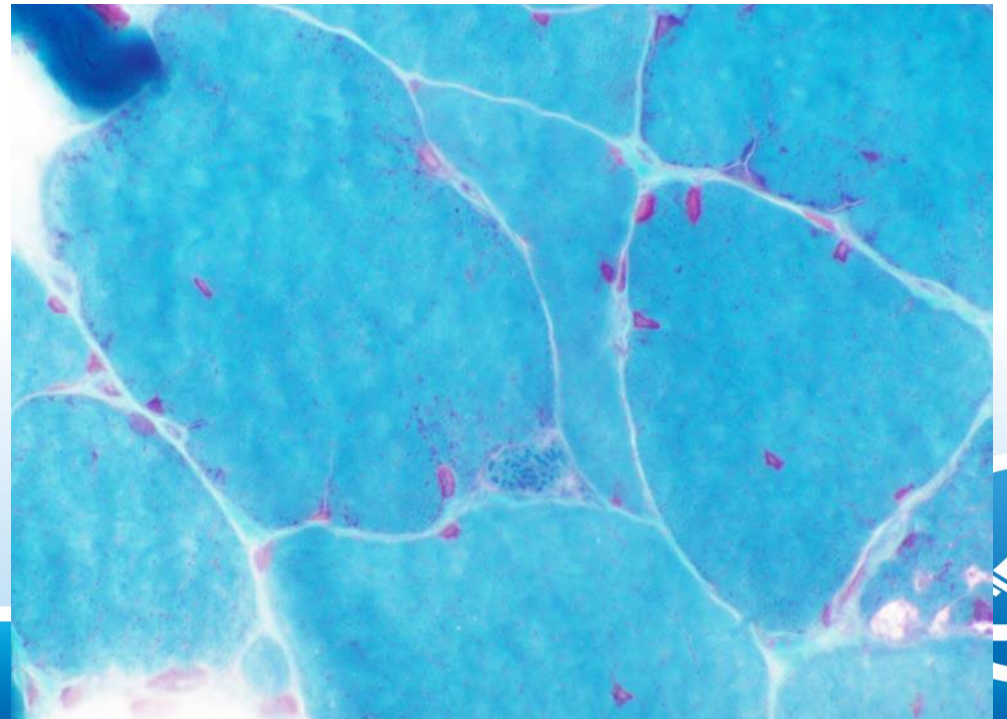
Rods = elongated electron dense inclusions (nemaline rods)

- Nemaline rods are derived from Z-lines
- Maintain the lattice-like structure found in normal Z-lines
- On H&E they may be impossible to see, but sometimes you have clues (cap-like areas)
- Trichrome is the most helpful histochemical stain for identification
- Epon sections and EM for definitive identification
- Can also be stained with alpha-actinin, myotilin, nebulin, and phalloidin



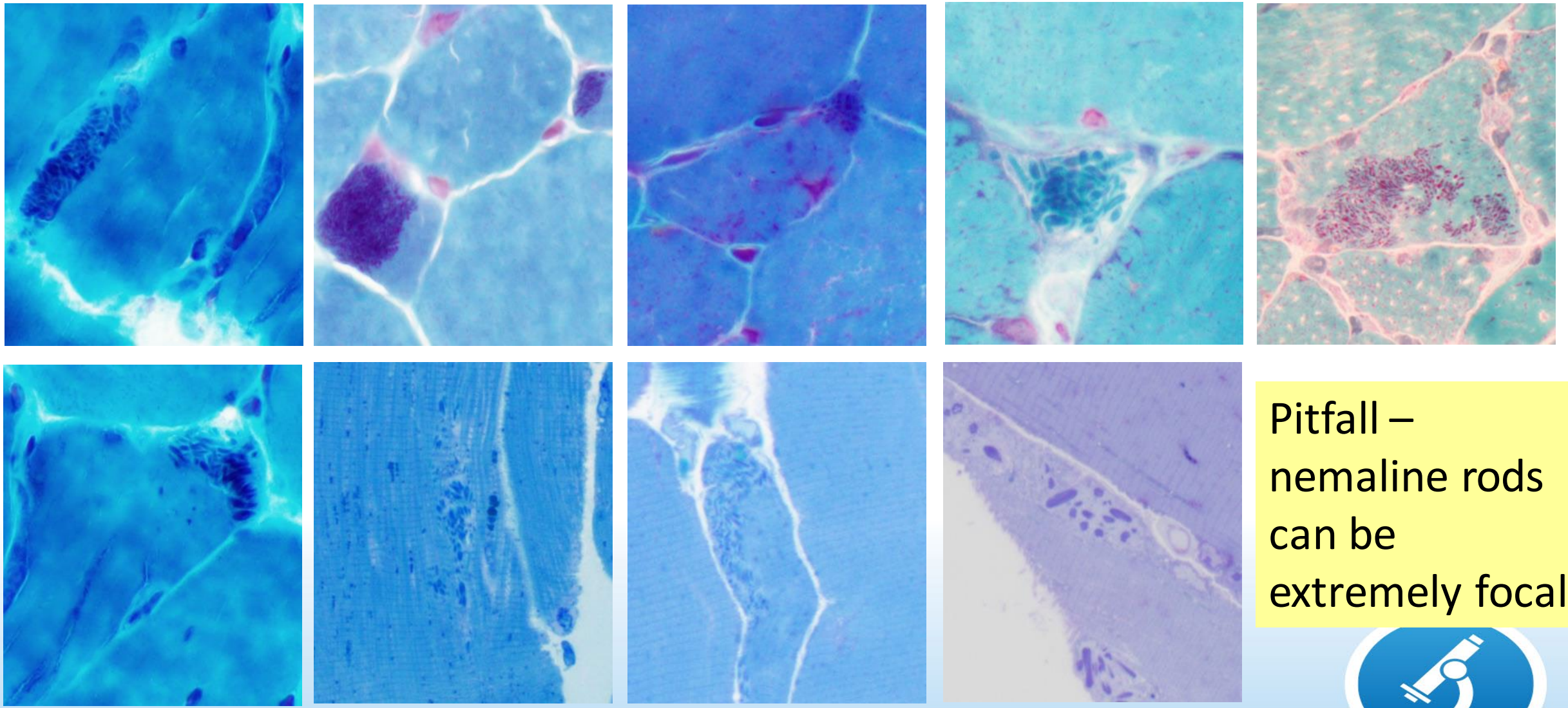






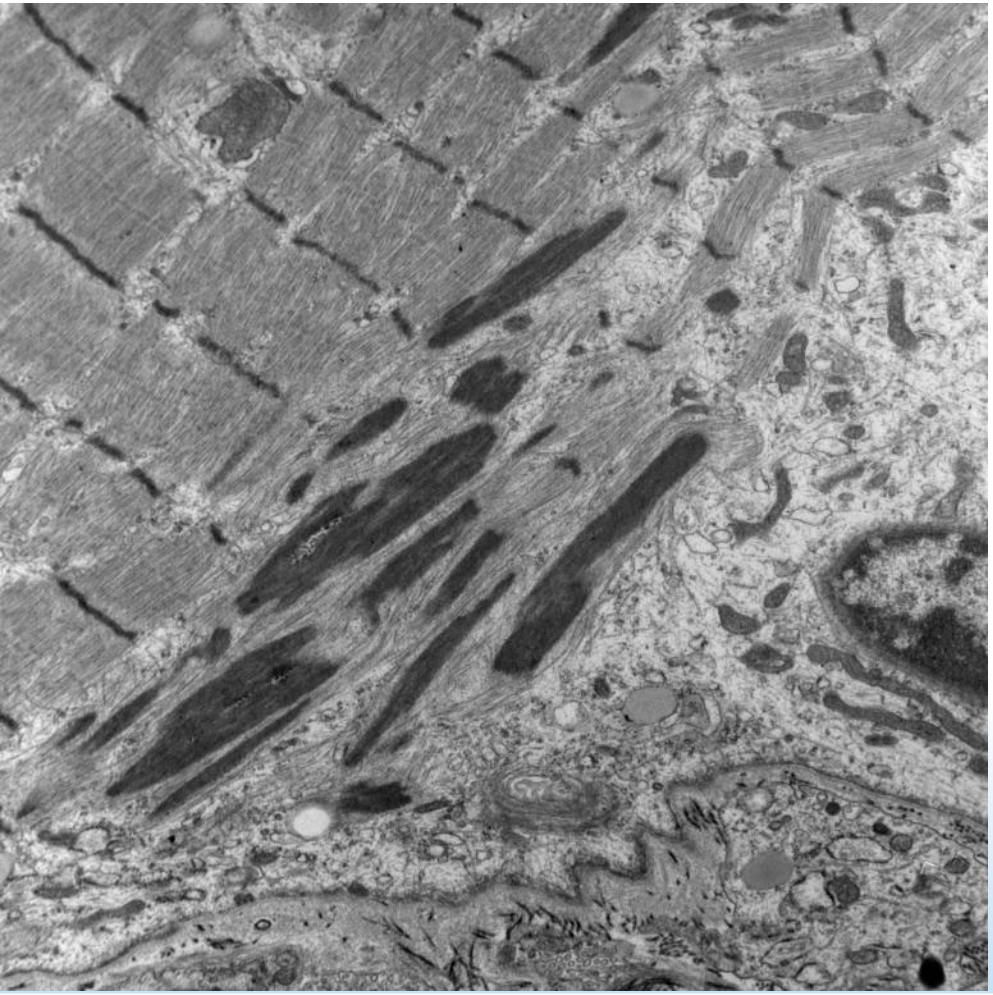
Many-Faced Rods

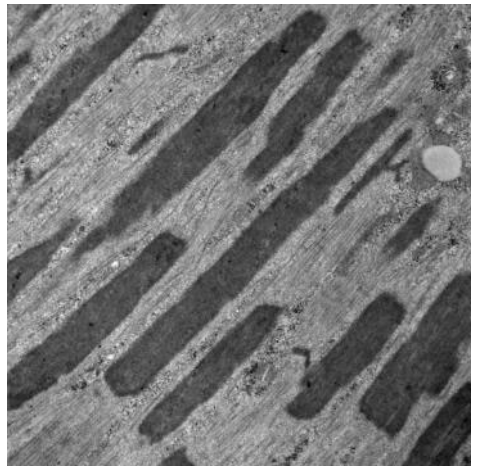
Frozen sections stained with trichrome (MGT) and epon sections stained with toluidine blue

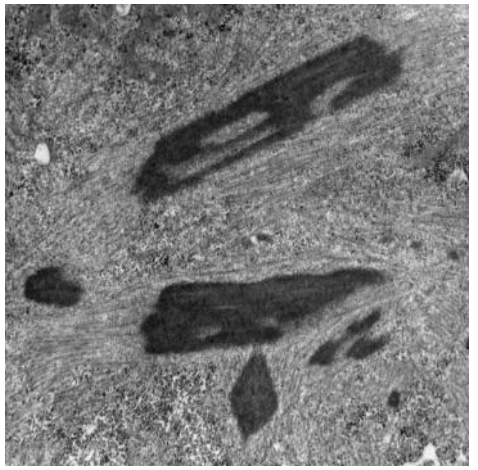


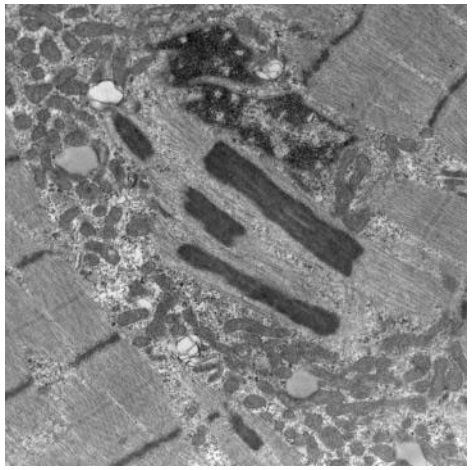
Pitfall – nemaline rods can be extremely focal

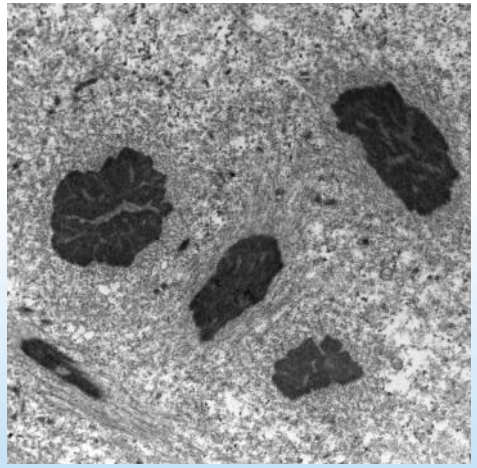
Rods (and bodies?) under EM

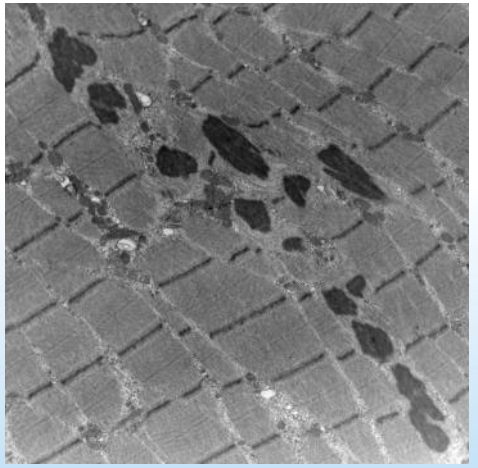


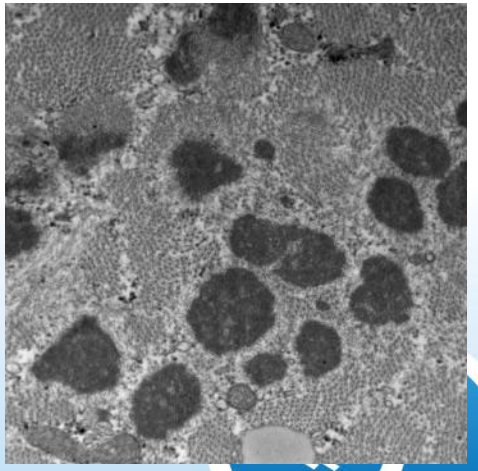






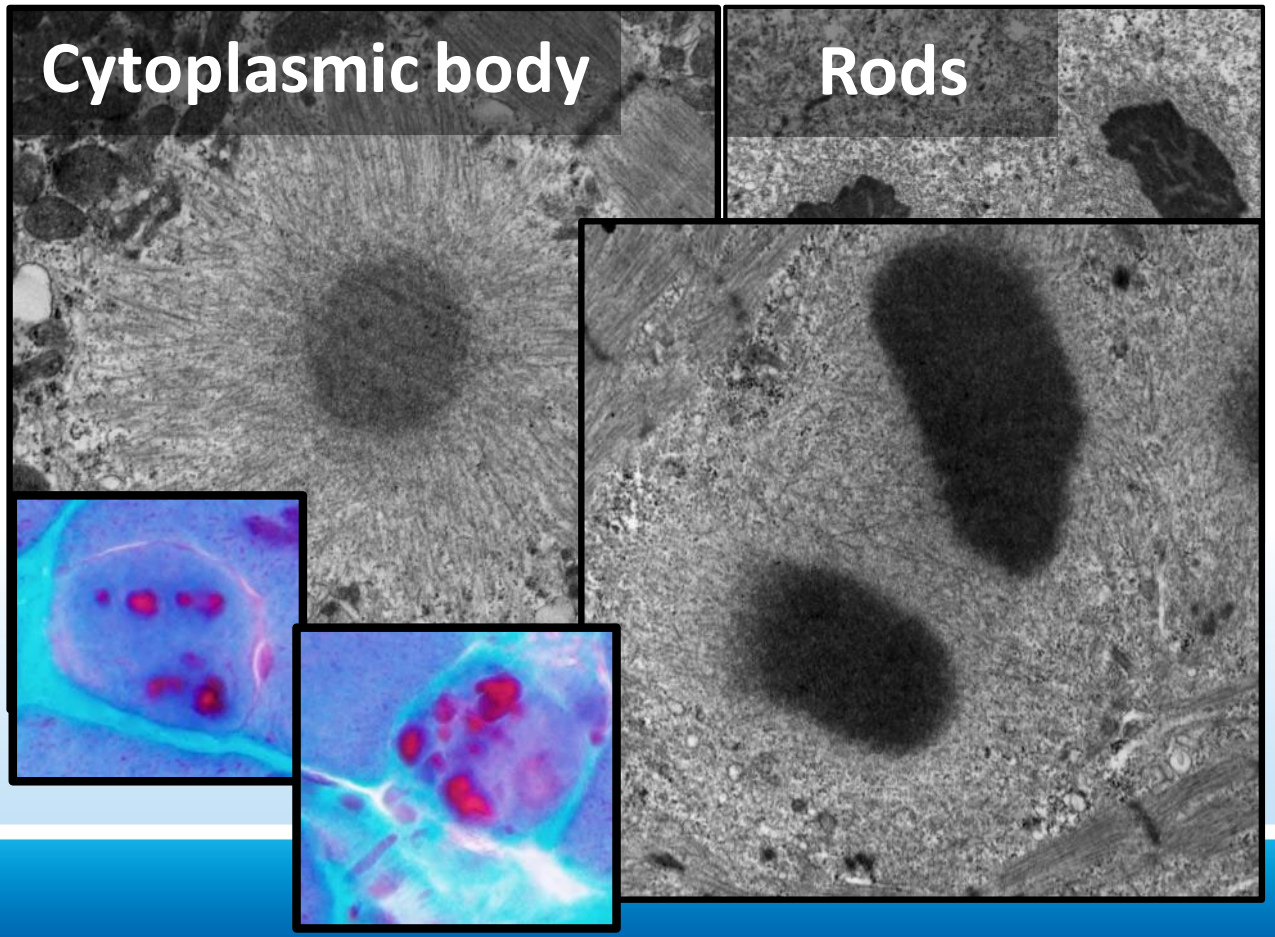


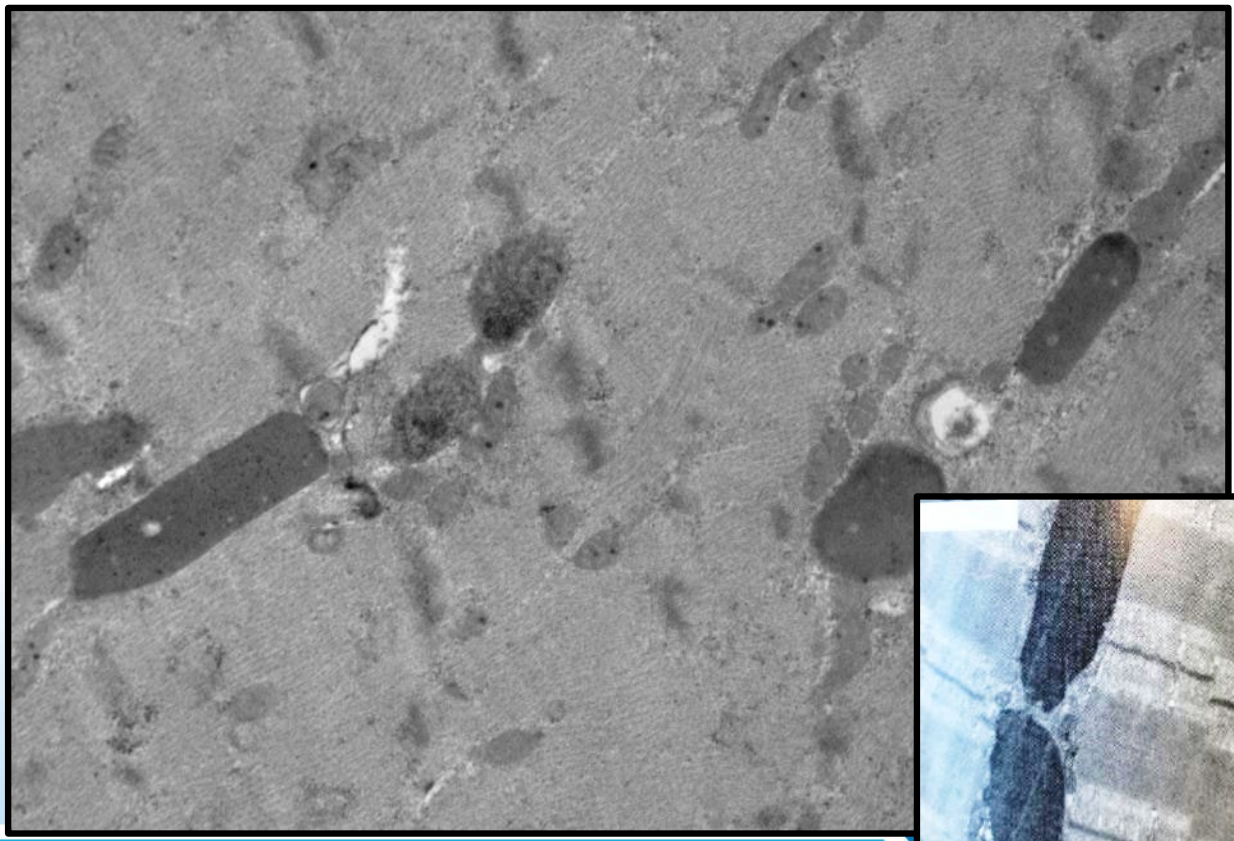




Potential pitfalls! – nemaline rod look-alikes on EM

- Rod vs cytoplasmic body
  - Dense filamentous core with surrounding lighter halo
- Rod vs giant abnormal lysosomes
  - Dense filamentous core and are membrane bound

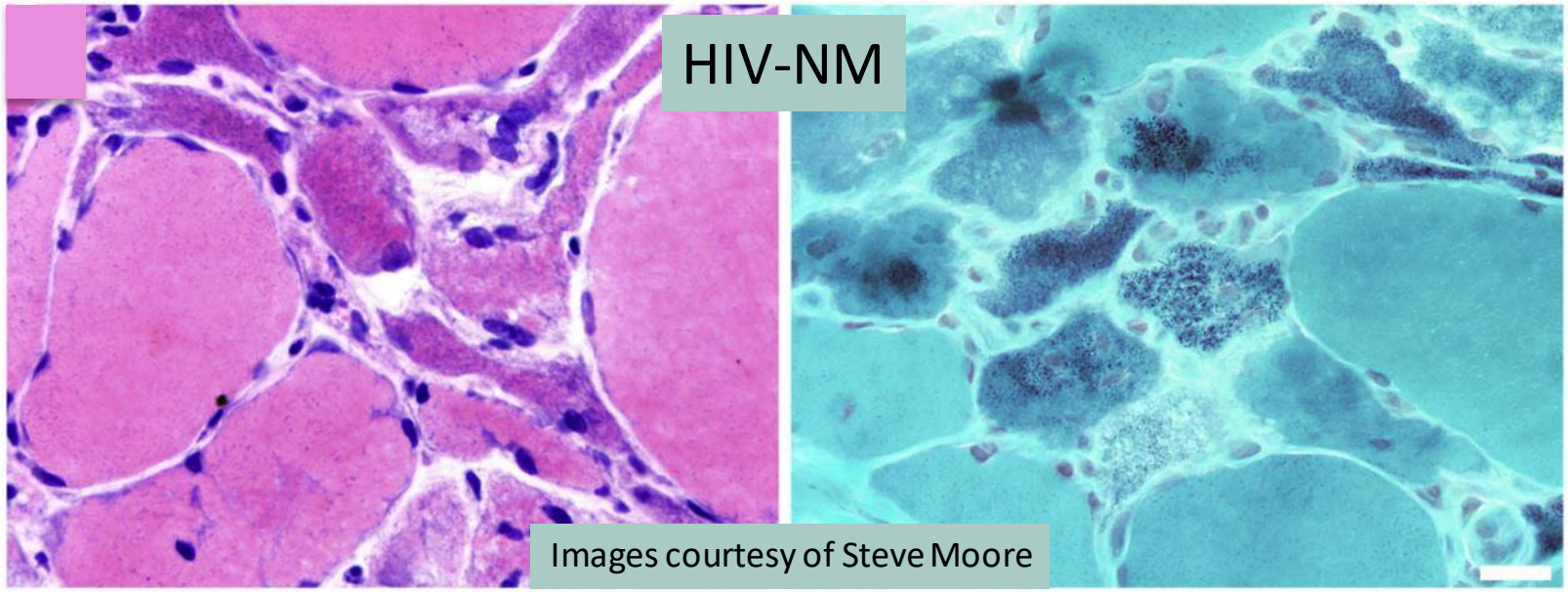




From Myology; Engel and Franzini-Armstrong

Rods do not always = congenital myopathy

- Rods can be present in other situations not related to congenital myopathy:
  - Normal myotendinous junction
  - Normal extraocular muscles
  - **HIV associated nemaline myopathy**
  - **Sporadic late-onset nemaline myopathy** (MGUS)



Nemaline myopathy

Gene	Protein	Chromosome locus	Inheritance	Pathological features in addition to numerous rods that may occur
ACTA1	Slow skeletal alpha-actin	1q42.1	AD, often *de novo* a few AR	Actin accumulation Nuclear rods Zebra bodies Type 1 hypotrophy FTD only Cores Rods in cap-like areas Cytoplasmic bodies
NEB	Nebulin	2q23.3	AR	Type 1 hypotrophy Type 2 predominance (in contrast to the common type 1 predominance) Rods in cap-like areas
CFL-2	Cofilin-2	14q13.1	AR	Cores Actin accumulation
TPM2	Beta- tropomyosin	9p13.3	AD	Caps FTD only
TPM3	Slow alpha- tropomyosin	1q21.3	AD, AR	Caps FTD only
TNNT1	Slow troponin T	19q13.4	AR	Fibrosis
KBTDB13	Kelch repeat and BTB containing 13	15q22.3	AD	Cores
KLHL40	Kelch-like family member 40	3p33.1	AR	Fibres with numerous small rectangular rods, some with a 'fringe' and sometimes very few 'myofibrils'
KLHL41	Kelch-like family member 41	2q31.1	AR	Variation in fibre size Reduced KLHL41 protein No cores, no nuclear rods
LMOD3	Leiomodin3	3p14.1	AR	Rectangular rods with a 'fringe' Cytoplasmic bodies
*MYO18B**	Myosin 18B	22q12.1	AR	Occasional central nuclei Absent C-terminal MYO18 B protein in reported case

*MYO18B is listed in OMIM as a variant of unknown significance.
AD, autosomal dominant; AR, autosomal recessive; FTD, fibre-type disproportion.

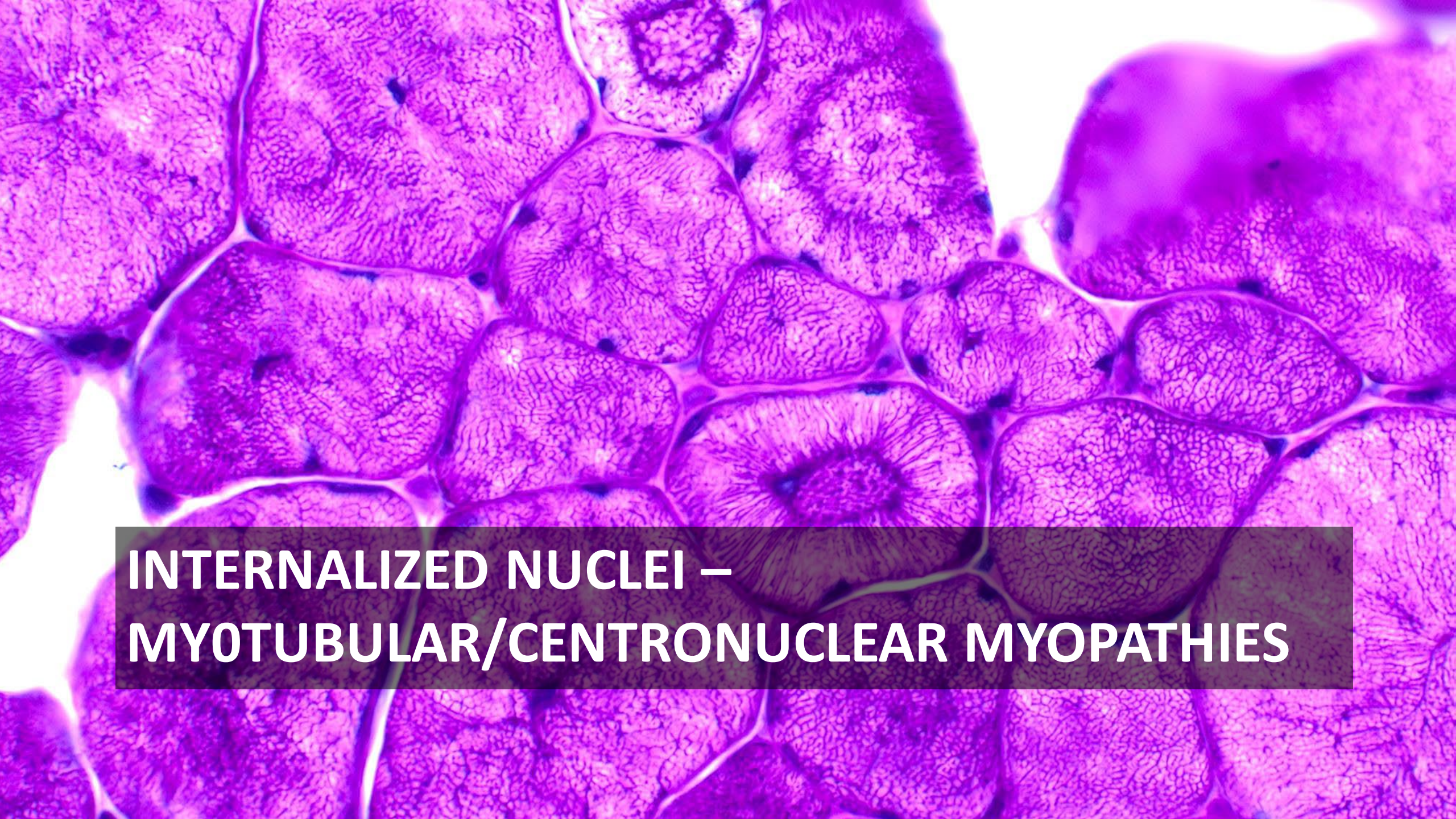
- At least 12 genes that encode structural or regulatory proteins of the thin filament can cause nemaline myopathy
- Wide variation in clinical and histologic pictures
- Respiratory involvement is common and can lead to mortality

Sewry CA, Wallgren-Pettersson C. Myopathology in congenital myopathies. Neuropathol Appl Neurobiol. 2017 Feb;43(1):5-23.

Novel classification of genetically caused nemaline myopathy (NM) and the genes known to cause these forms of the disorder

Category of nemaline myopathy	Clinical features	Causative genes	
Severe NM	Intrauterine onset Neonatal features include at least one of the following - major contractures of large joints - fractures - absence of respiratory effort - absence of movements	*ACTA1, NEB, LMOD3, KLHL40, KLHL41, RYR1, TNNT3, TPM2, TPM3*	
Typical NM	Perinatal onset Motor milestones delayed but reached	***NEB, ACTA1,*** *CFL2, TPM2* *LMOD3*	
Mild NM	Childhood or juvenile onset	*ACTA1, NEB, TPM2, TPM3, KBTBD13, MYPN,* dominant, or sometimes recessive mutations in *TNNT1* *LMOD3?*	
Distal NM	Presentation with distal weakness only (or mainly) Presentation with distal arthrogryposis also possible	*NEB, ACTA1, TNNT3, TPM2, FLNC?*	
Childhood onset NM with slowness	Characteristic slowness of movements Core-rod histology	*KBTBD13*	
Recessive *TNNT1* (former Amish) NM	Progressive course Thoracic immobility Restrictive lung disease Early endomysial fibrosis	Recessive mutations in *TNNT1*	Subtype of severe nemaline myopathy
Other (unusual) forms	Unusual distribution of muscle weakness Hypertrophic cardiomyopathy Unusual histological features (e.g. core-rod combination, caps, actin aggregates, intranuclear rods, lipid droplets)	*ACTA1, NEB, RYR1, TPM2, TPM3, MYPN, CFL2, RYR1, MYO18B?, ADSSL?*	

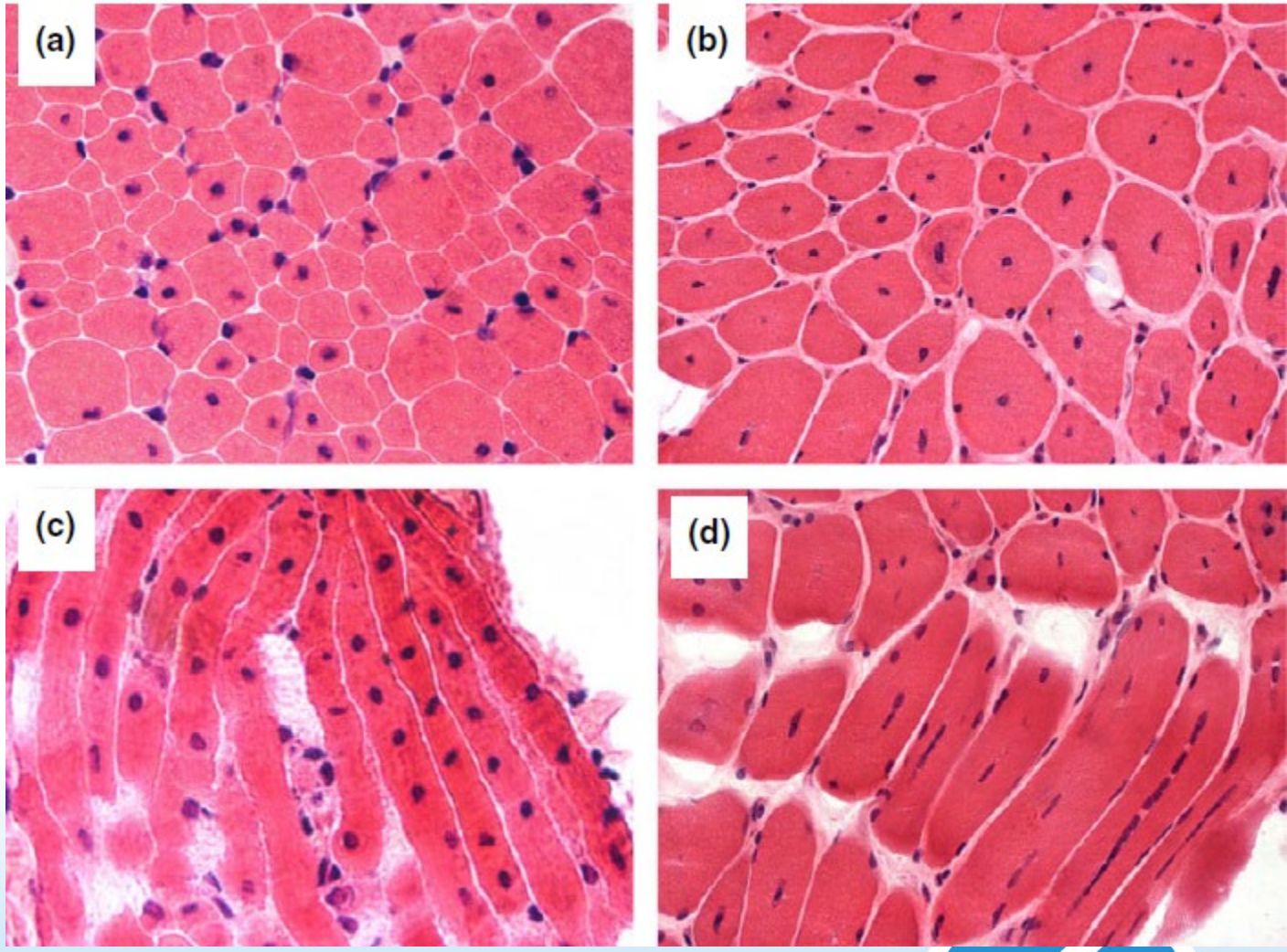
Laitila J, Wallgren-Pettersson C. Recent advances in nemaline myopathy. Neuromuscul Disord. 2021 Oct;31(10):955-967.



INTERNALIZED NUCLEI – MYOTUBULAR/CENTRONUCLEAR MYOPATHIES

Internalized or centrally placed nuclei

- Normal muscle can have up to ~3% of the fibers showing internal nuclei in transverse section
- Increased internalized nuclei is a nonspecific myopathic change, but it can also be a sign of a congenital myopathy (centronuclear or myotubular myopathy)
- When internal nuclei are centrally placed, there is even greater concern for a congenital myopathy

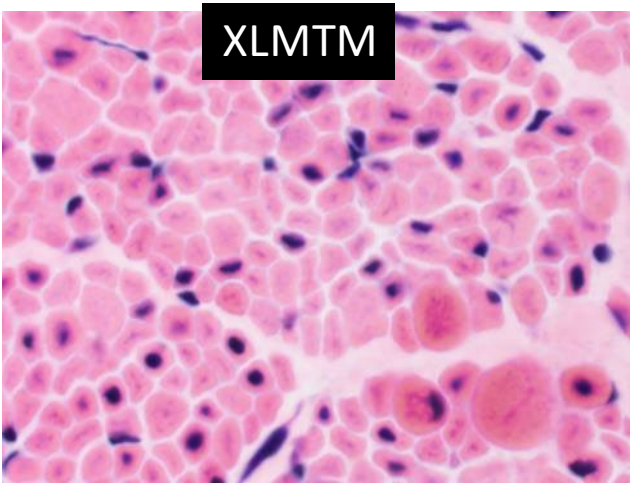


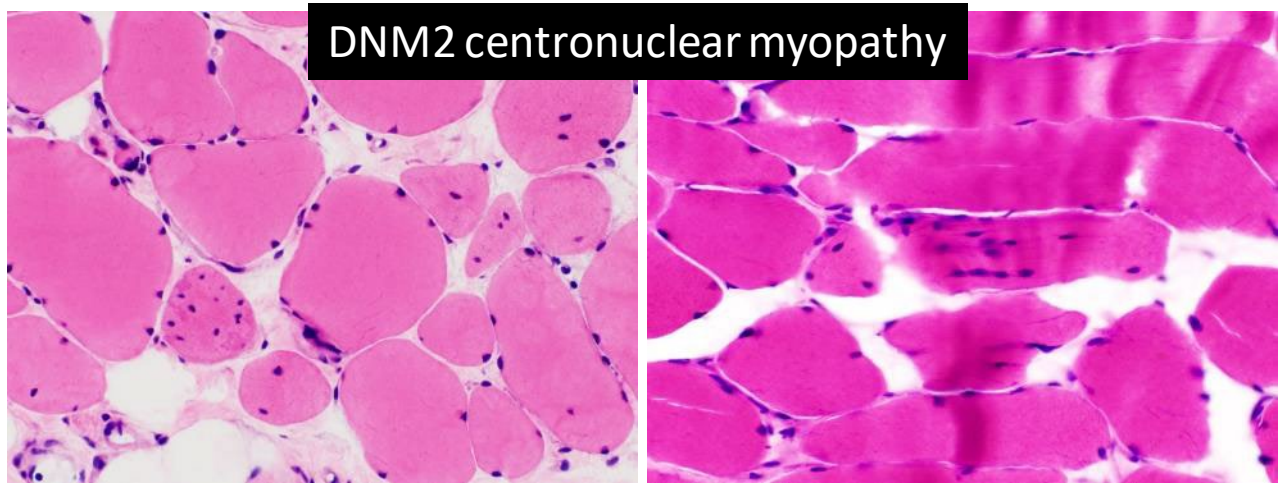
Sewry CA, Wallgren-Pettersson C. Myopathology in congenital myopathies. Neuropathol Appl Neurobiol. 2017 Feb;43(1):5-23.

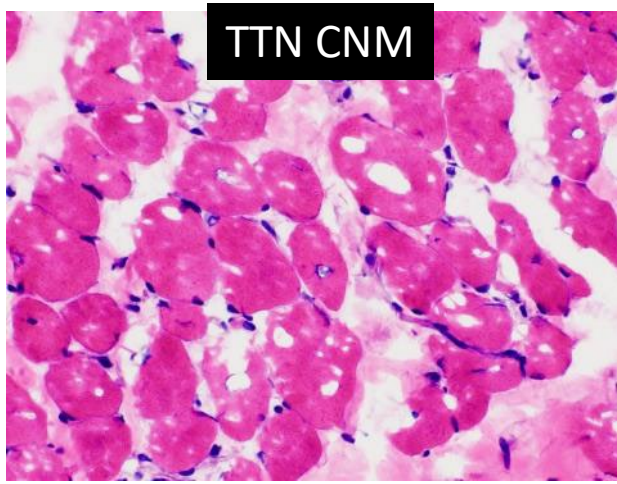
Internalized nuclei variations

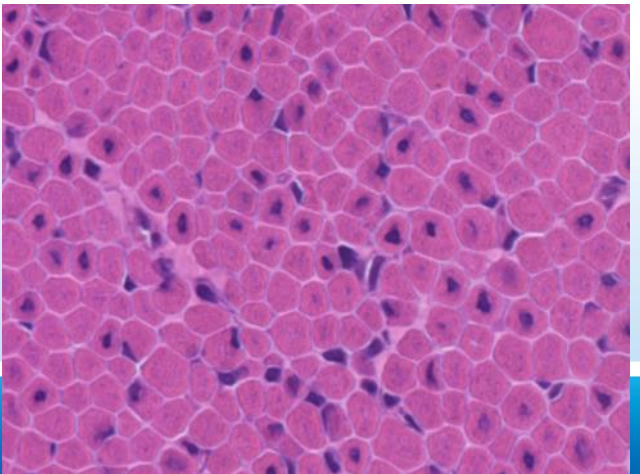
- Single, centrally placed vs multiple internalized nuclei

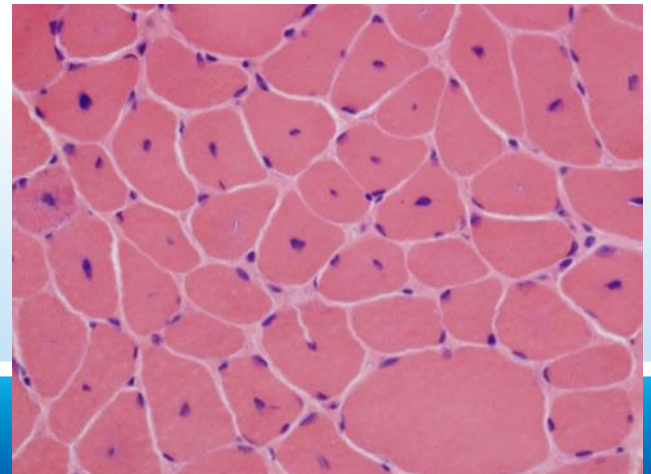
Pitfall **hole or vacuole surrounding or adjacent to the nucleus

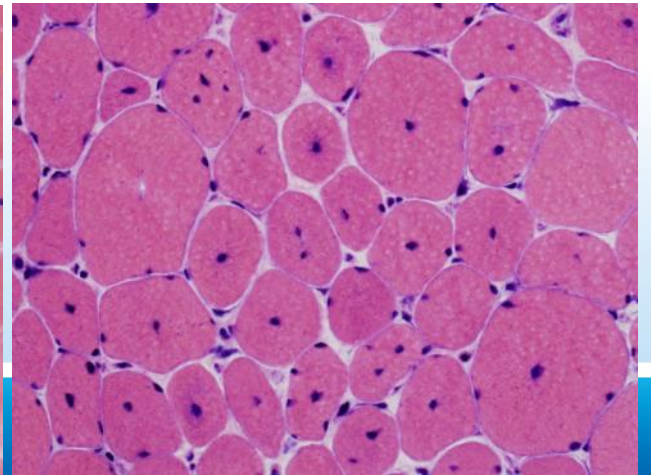


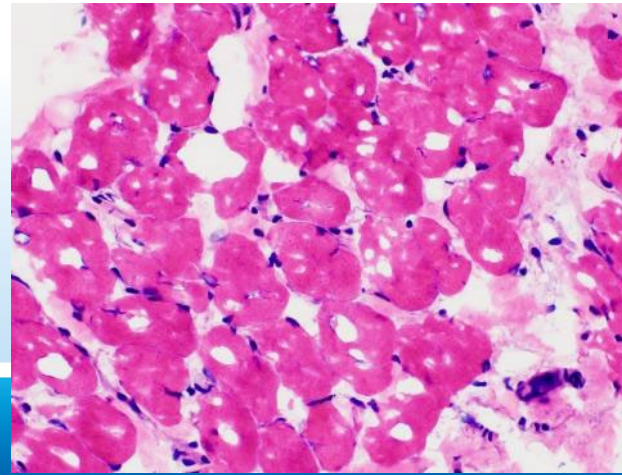












Genetics of congenital myopathies with internalized nuclei

Disease name	Gene	Inheritance pattern	Protein name
Myotubular myopathy	*MTM1*	XLR	Myotubularin
Centronuclear myopathy	*DNM2*	AD	Dynamin-2
	BIN1	AR	Amphiphysin-2
	RYR1	AD	Ryanodine receptor 1
	MTMR14	AD	Myotubularin-related protein (hJUMPY)
Centronuclear myopathy with cores	*CCDC78*	AD	Coiled-coil domain-containing protein 78
Congenital myopathy and fatal cardiomyopathy	*TTN*	AR	Titin

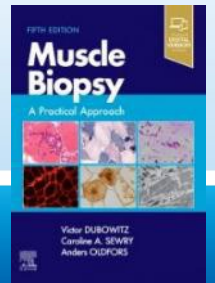
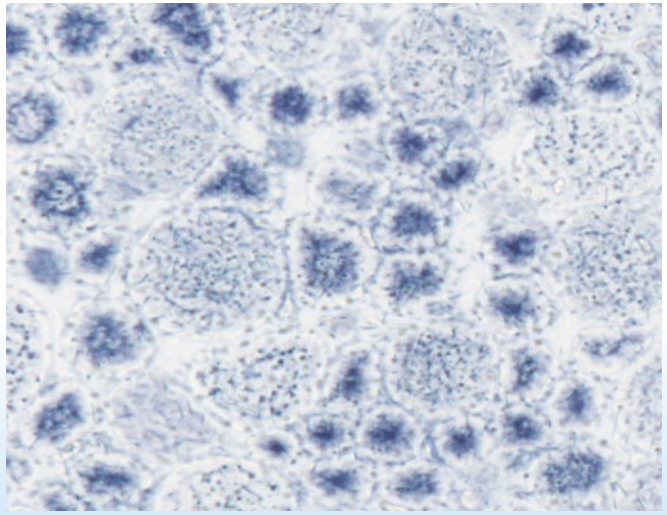


Table modified from Muscle Biopsy: A Practical Approach. Dubowitz, Sewry, Oldfors

Most common genetic forms of centronuclear myopathy

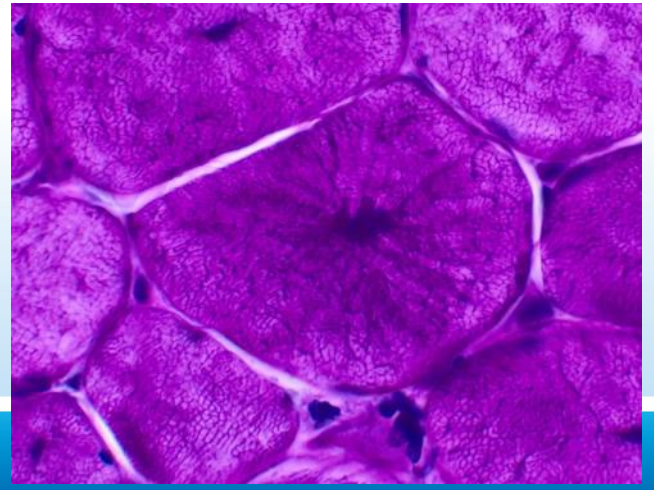
Myotubular myopathy – *MTM1*

- X-linked recessive
- Central nuclei regularly spaced down the length of fibers in both fiber types
- Abnormal central aggregation of organelles
  - Pale halo with oxidative enzyme stains
- Necklace fibers in mild patients or female carriers



Centronuclear myopathy – *DNM2*

- Autosomal dominant
- Central nuclei, sometimes in chains, and subsarcolemmal nuclei
- Version of necklace fiber without the nucleus
- Radiating strands



Tip for diagnosis

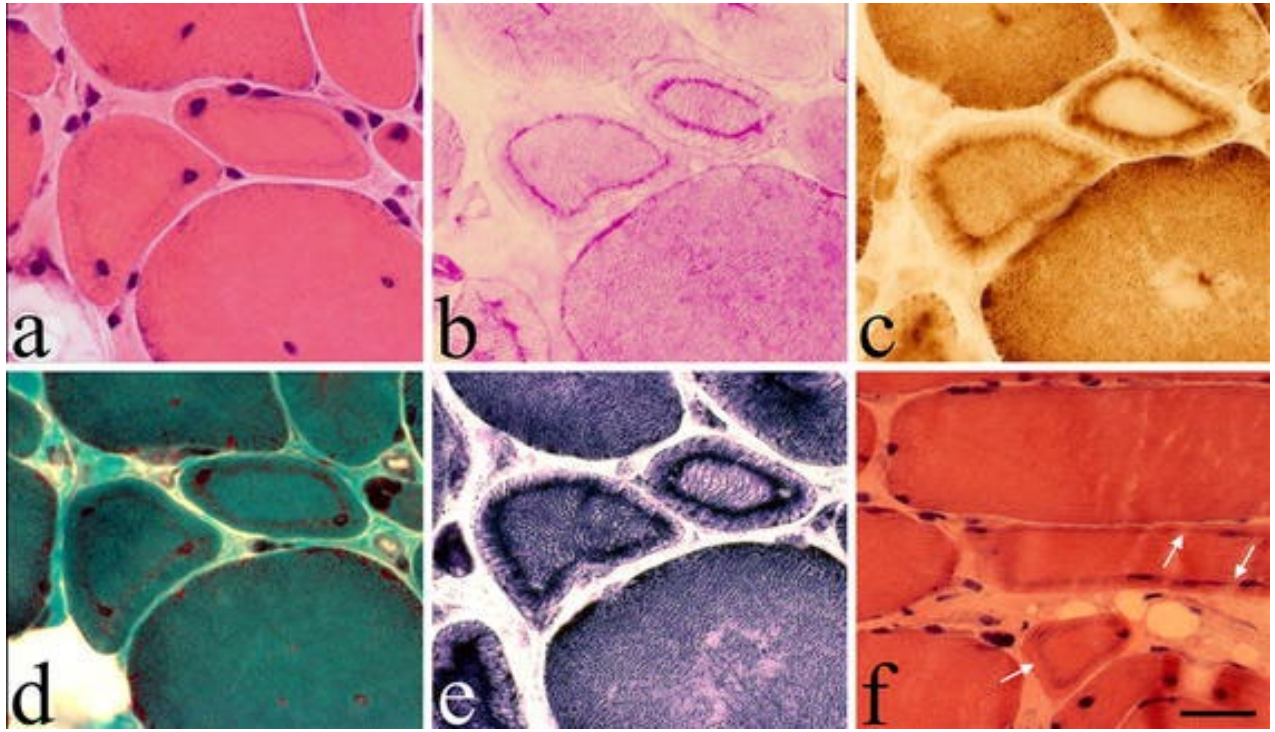
Necklace Fibers

Acta Neuropathologica
March 2009, 117:283 | Cite as

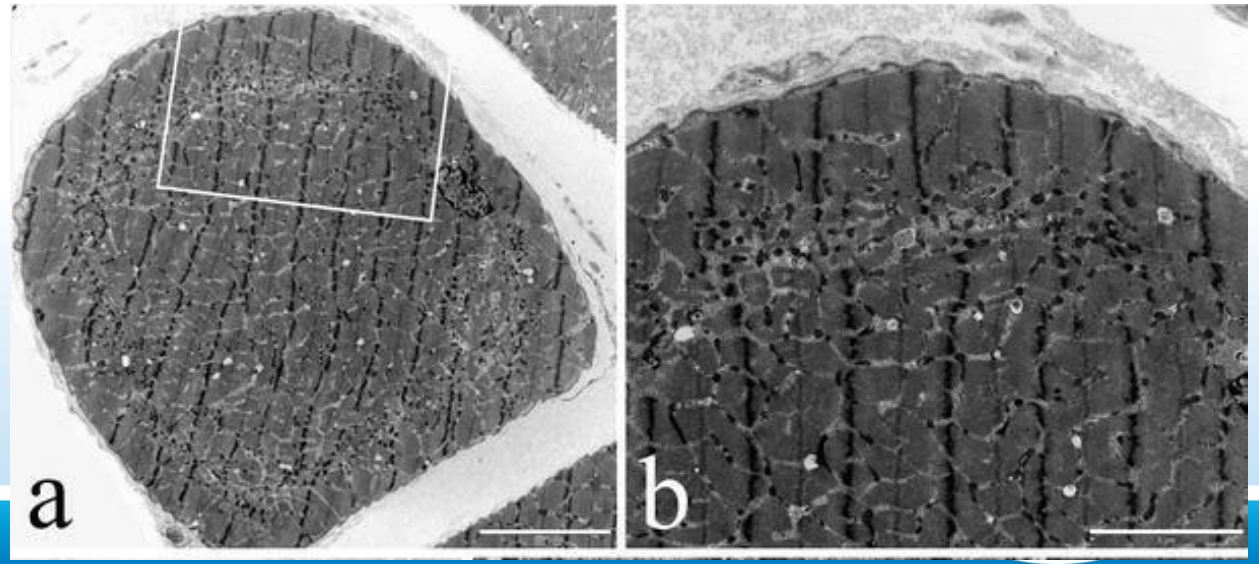
"Necklace" fibers, a new histological marker of late-onset *MTM1*-related centronuclear myopathy

Authors | Authors and affiliations

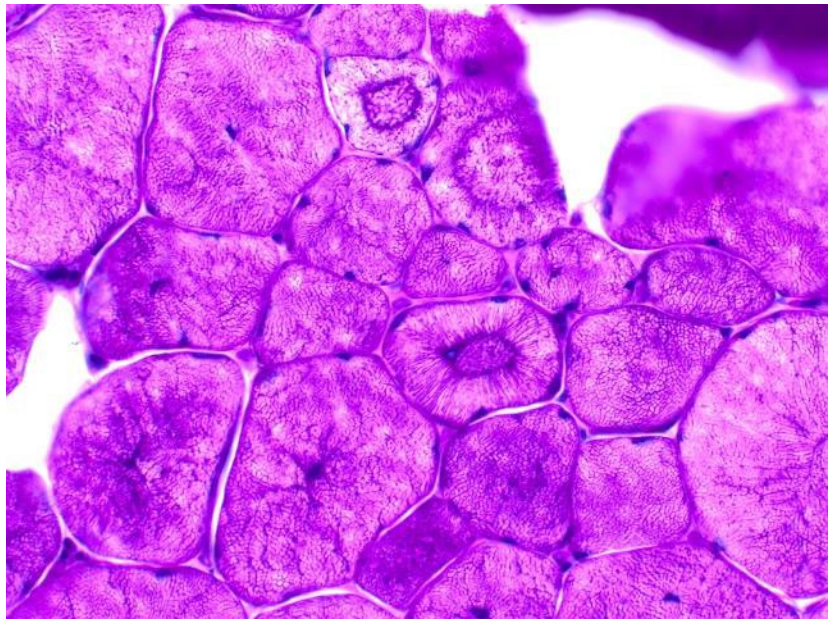
Jorge A. Bevilacqua, Marc Bitoun, Valérie Biancalana, Anders Oldfors, Gisela Stoltenburg, Kristl G. Claeys, Emmanuelle Lacène, Guy Brochier, Linda Manéré, Pascal Laforêt, Bruno Eymard, Pascale Guicheney, Michel Fardeau, Norma Beatriz Romero

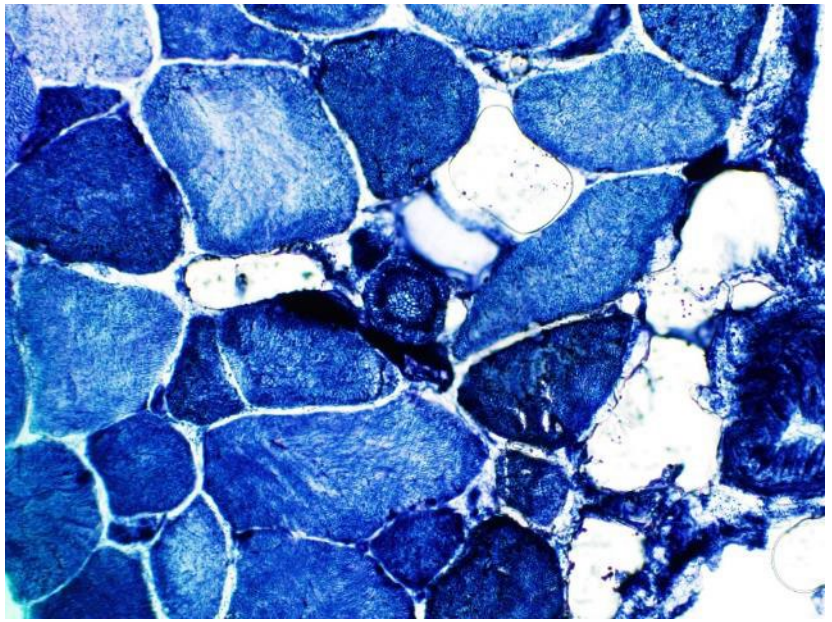


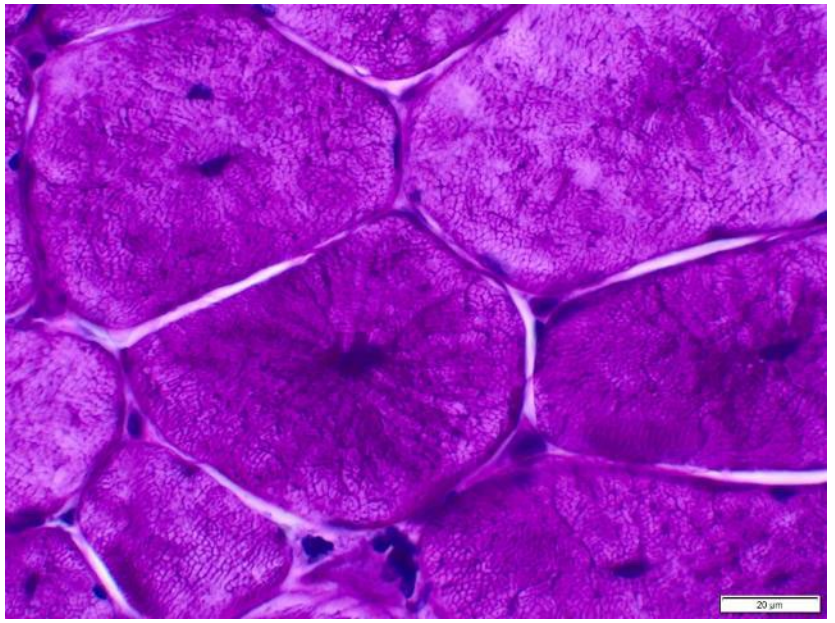
- Found in patients with mild *MTM1* (including carriers) and *DNM2* mutations (without nucleus)
- Positive for SERCA1 and -2, alphaB-crystallin, and desmin
- Increased mitochondria, sarcoplasmic reticulum, and glycogen granules by EM

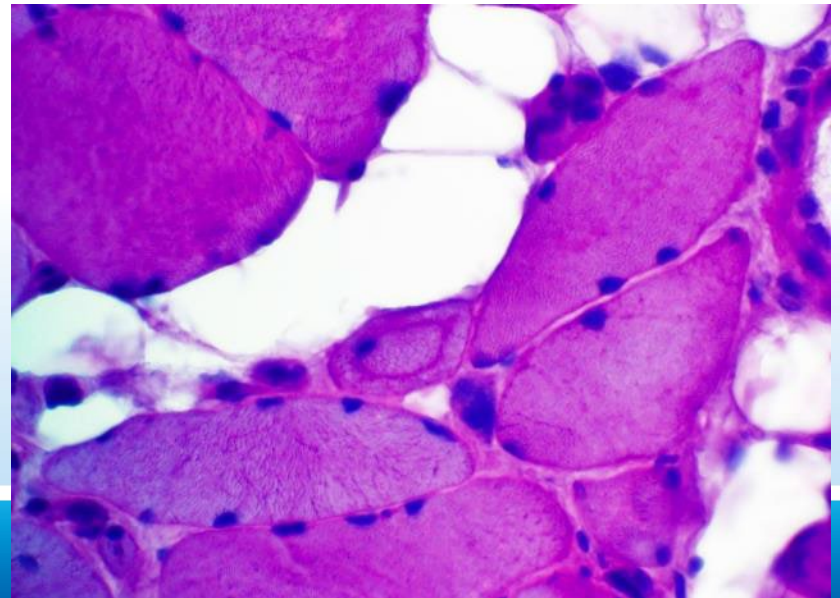


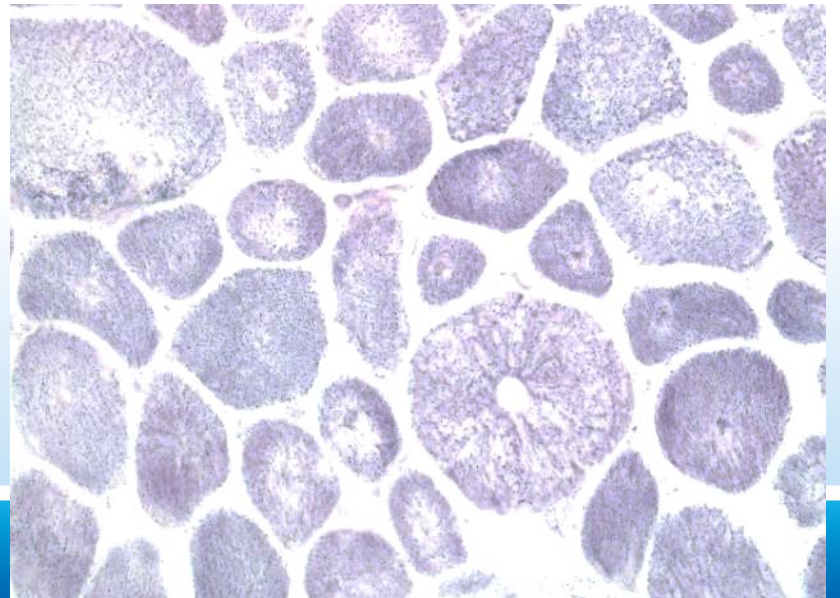
Necklace fibers and spokes on a wheel/radiating strands

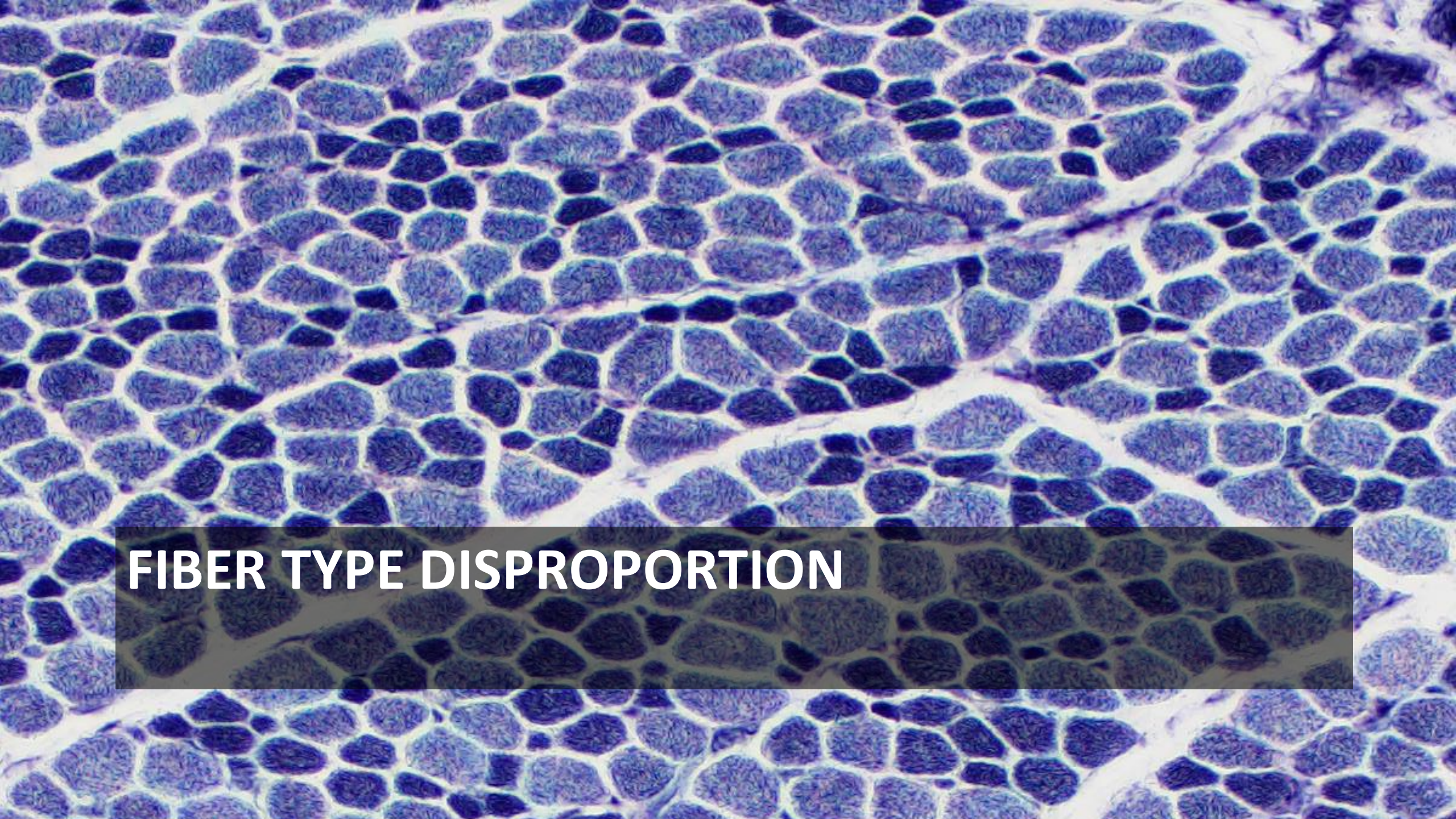












FIBER TYPE DISPROPORTION

Fiber type disproportion = uniform smallness of type 1 fibers

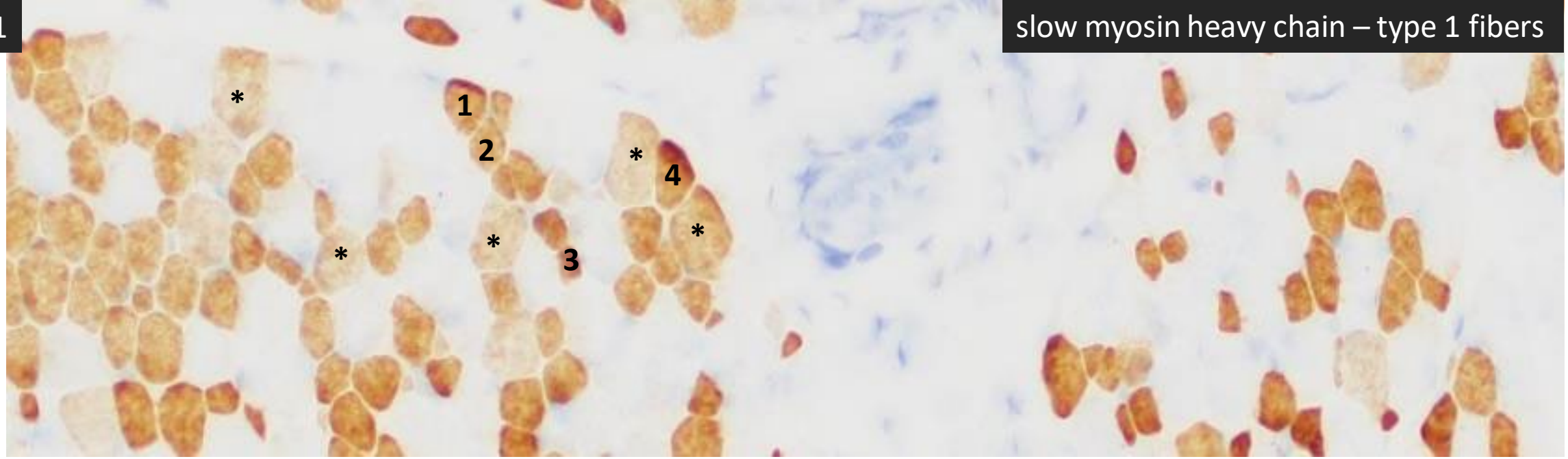
- Can be seen in isolation (as its own entity): congenital fiber type disproportion
- Can be seen in conjunction with cores, rods, central nuclei, caps
- Fiber-type disproportion with no other defect – *ACTA1*, *TPM2*, *TPM3*, *SELENON*, *MYH7*, *RYR1*
- Atrophy versus hypotrophy: EM in atrophy shows ruffled/redundant basal lamina

Pitfall sometimes there is dual expression of slow and fast myosin heavy chains making it difficult to identify CFTD

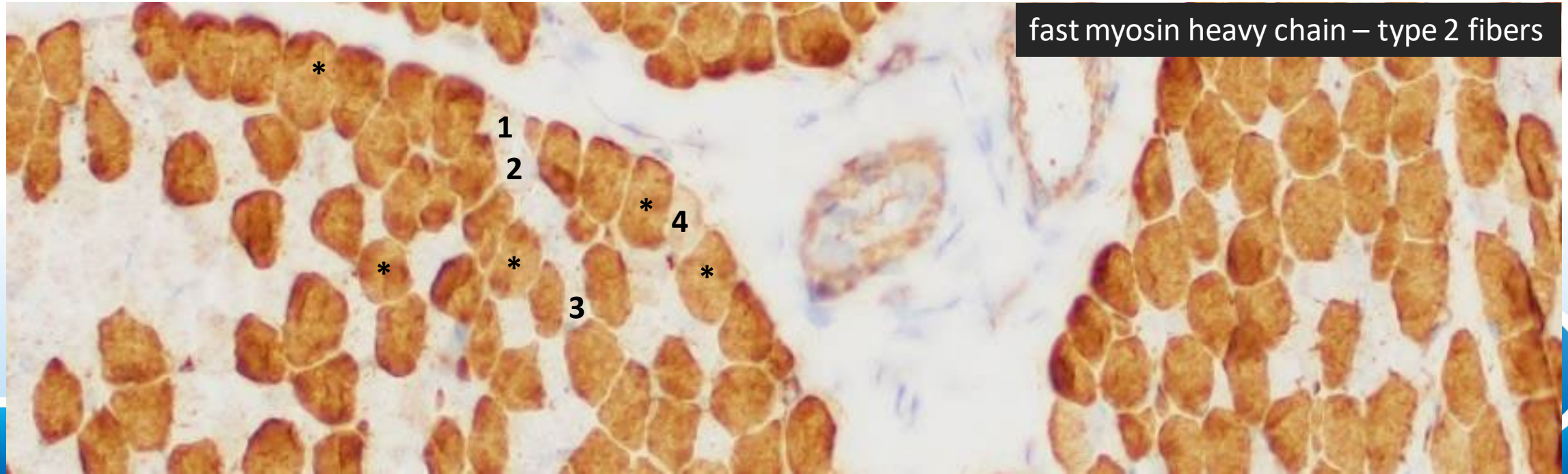
Tip for diagnosis photograph stains side by side

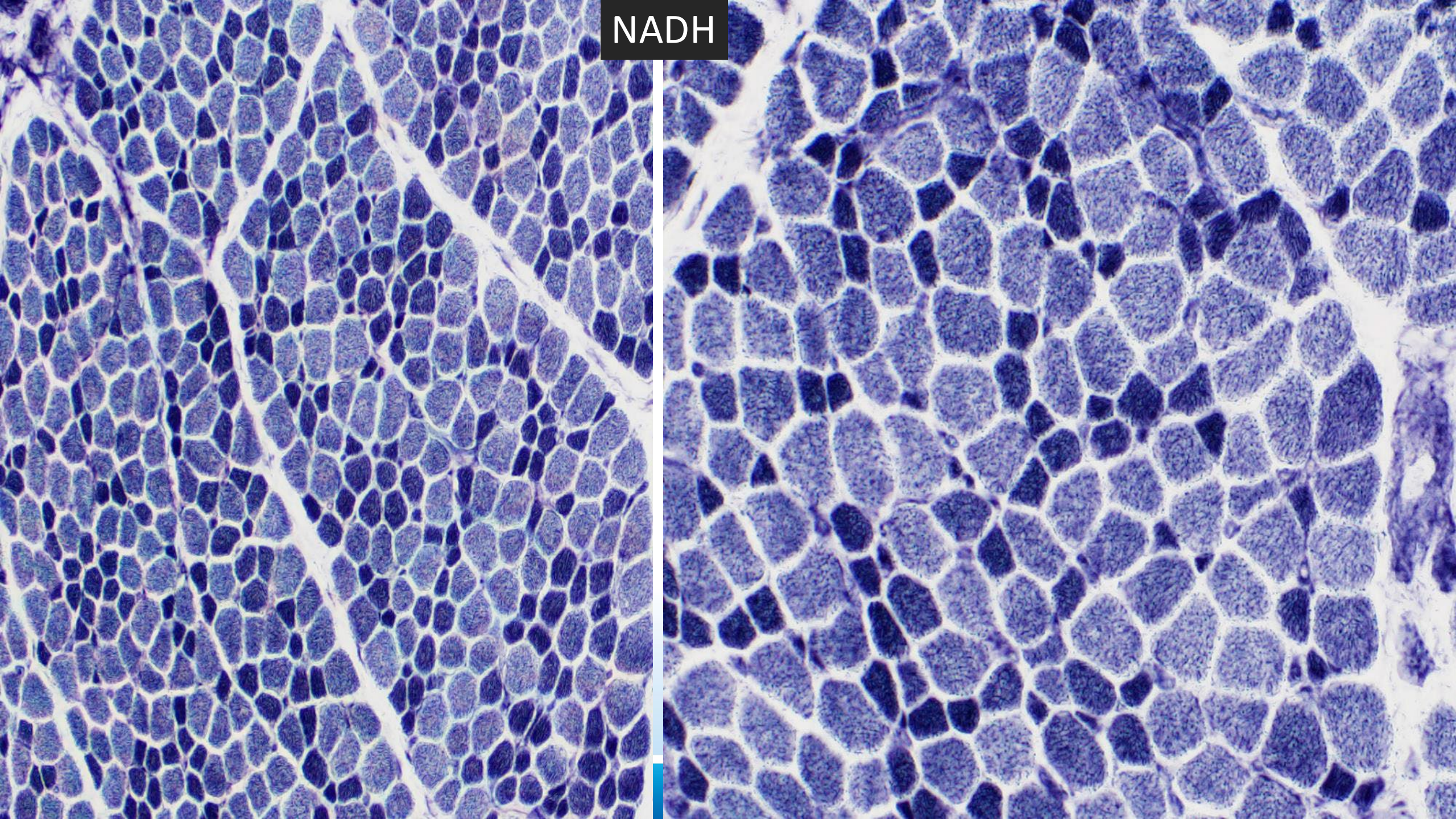
ACTA1

slow myosin heavy chain – type 1 fibers



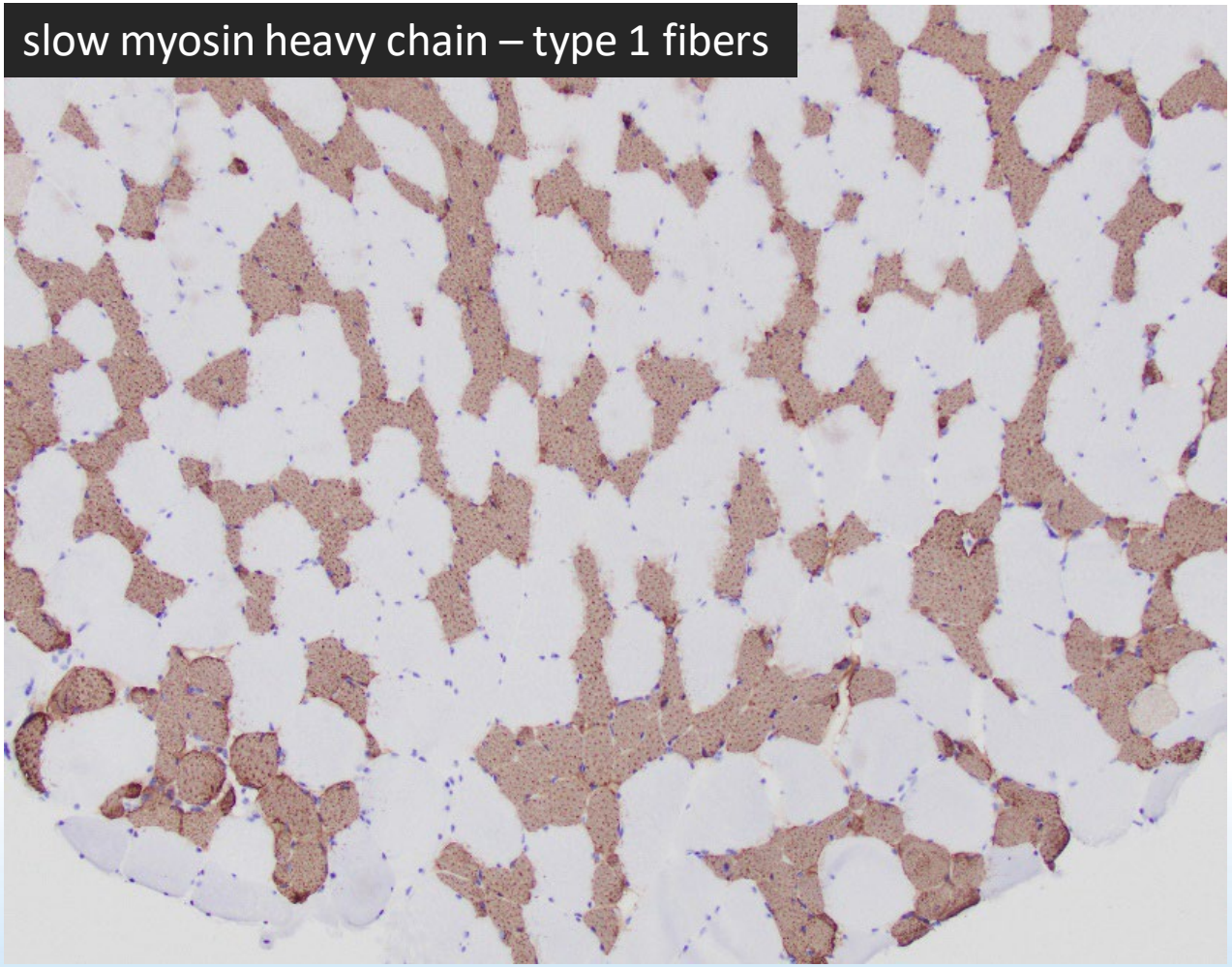
fast myosin heavy chain – type 2 fibers



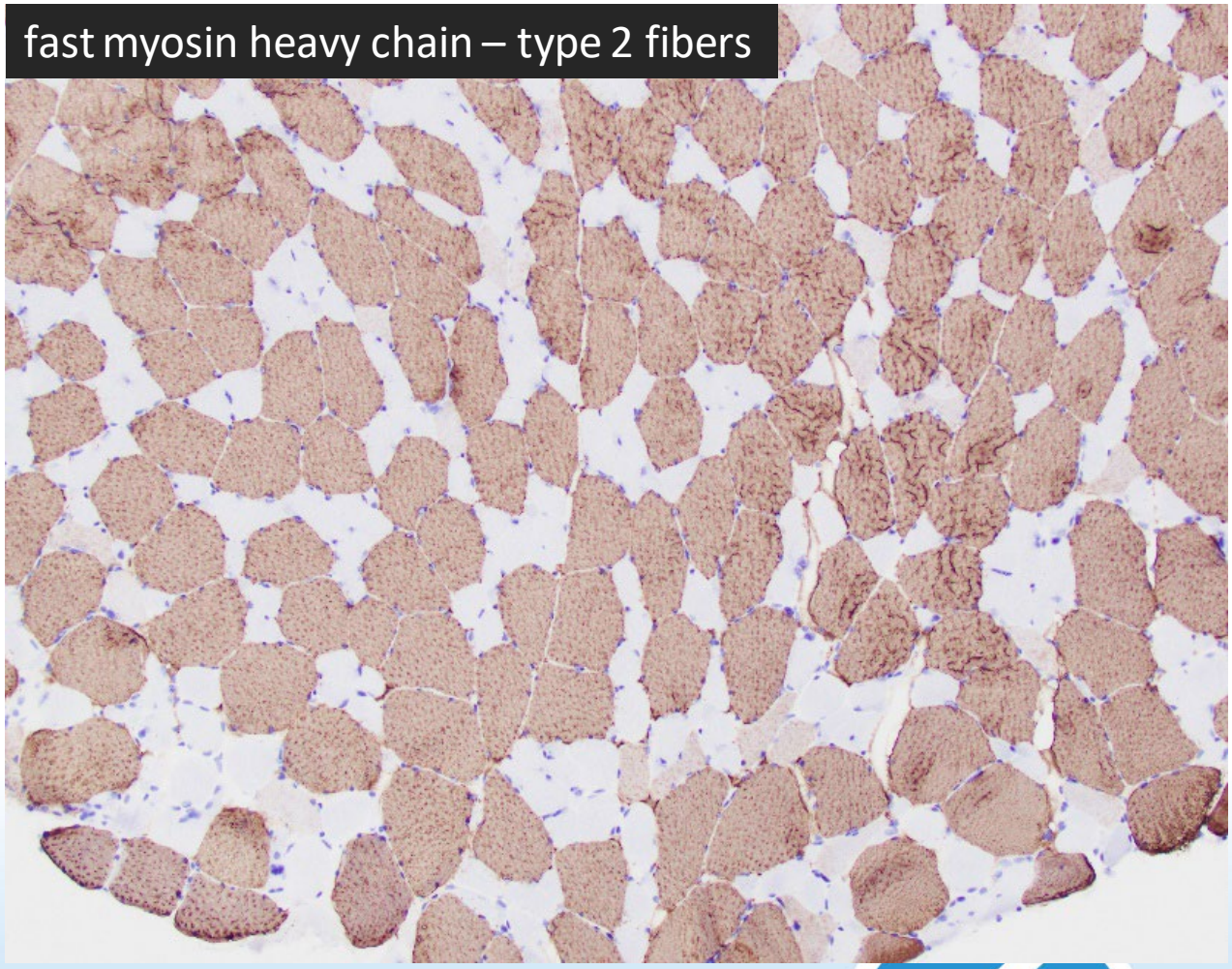

NADH

Type 1 fiber smallness in *TPM3*-related nemaline myopathy

slow myosin heavy chain – type 1 fibers



fast myosin heavy chain – type 2 fibers



Remember - overlapping pathologic features can occur

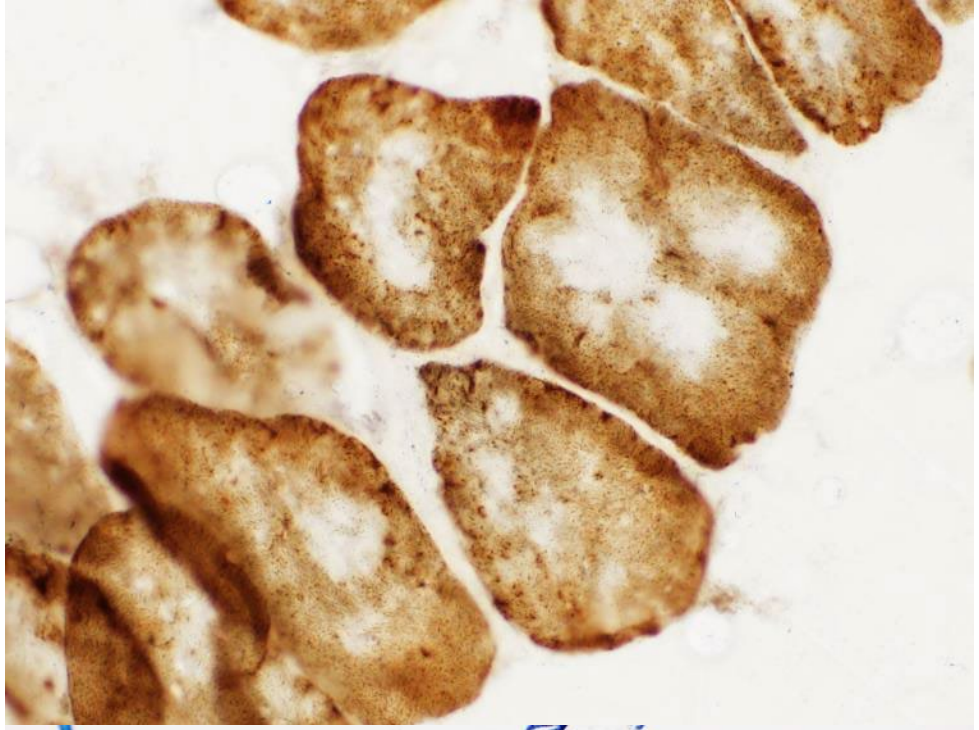
- Core-rod
- Rods-caps
- FTD with rods
- FTD with caps
- FTD with centronuclear myopathy
- Centronuclear myopathy with cores

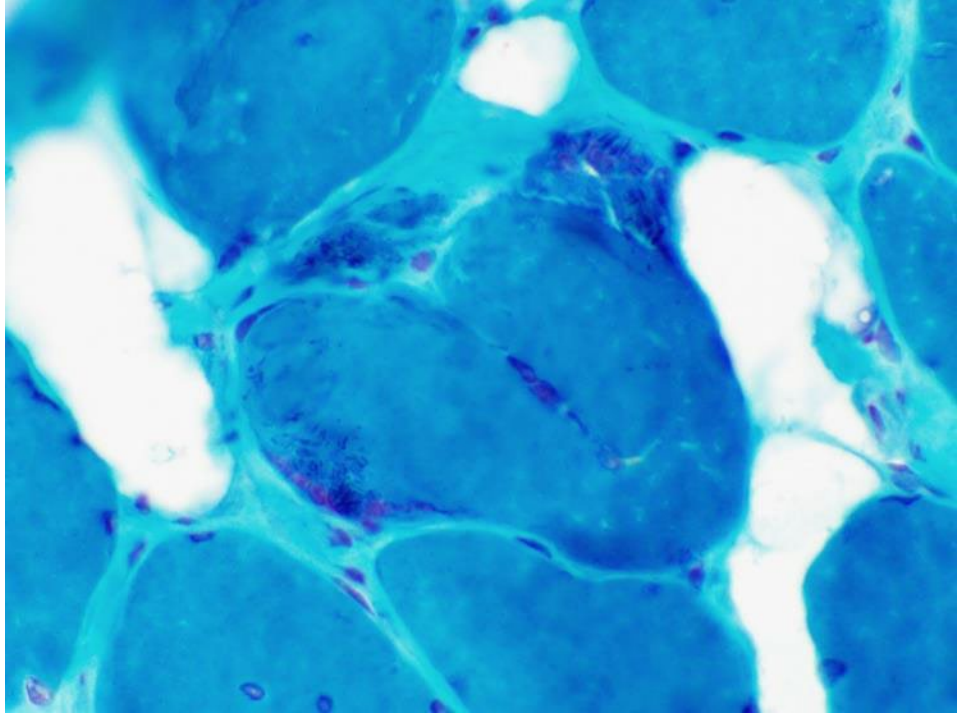
PathPresenter

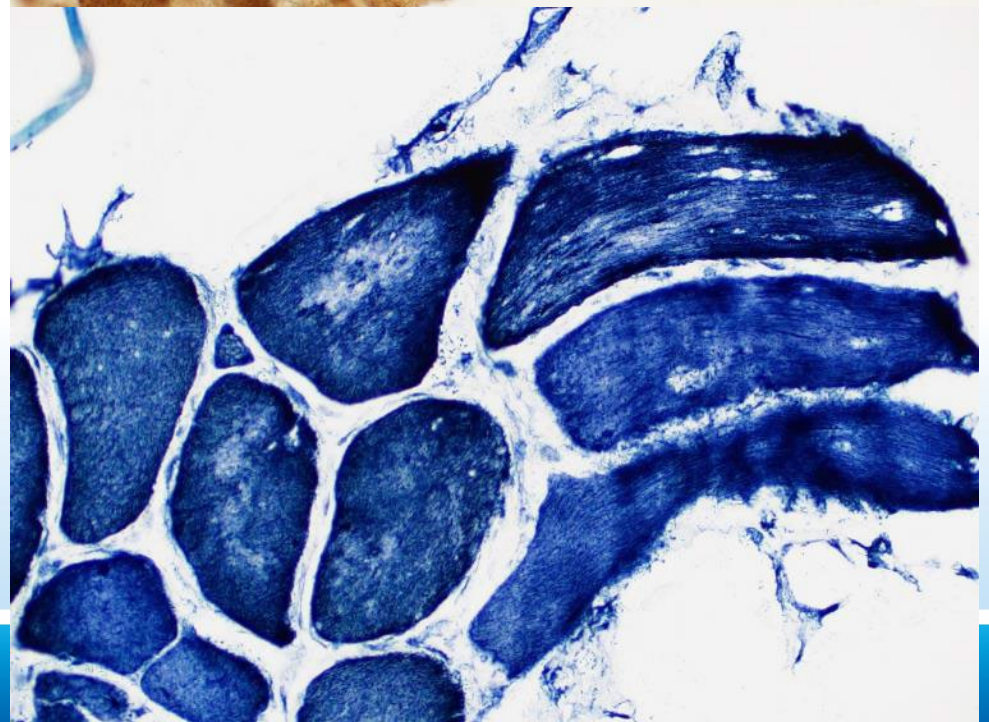
https://pathpresenter.net/#/public/display?token=1f62ac95

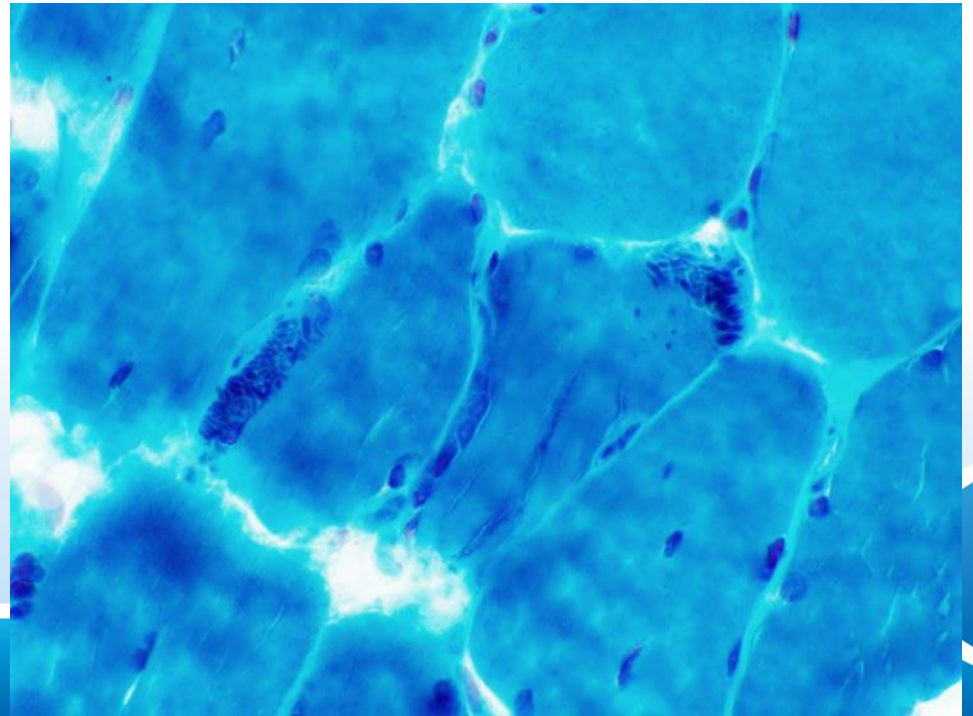
Unknown case:

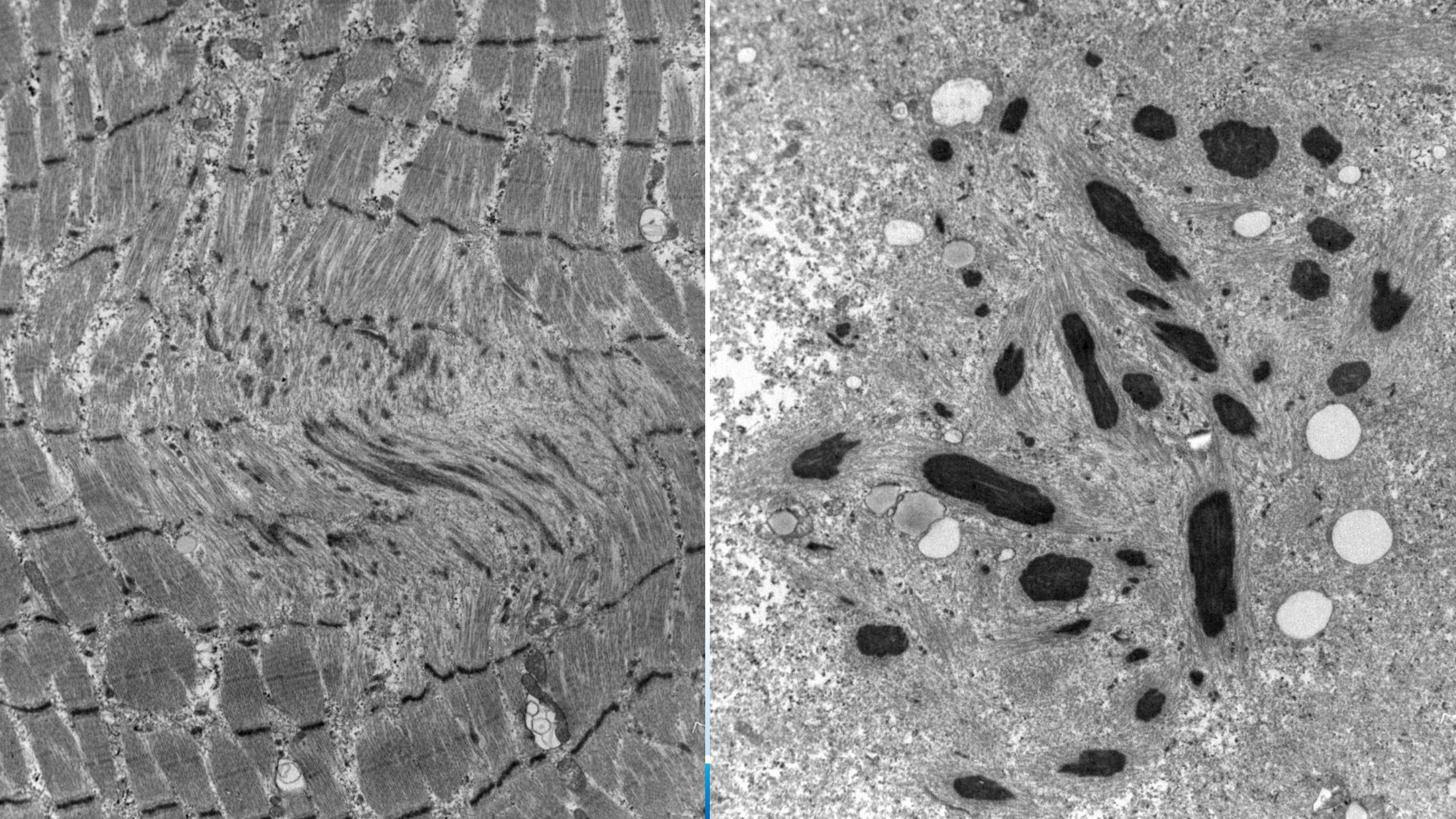
- 48-year-old woman
- Muscle weakness began around 5 years of age
- It progressed slowly and she was wheelchair bound in her 30s
- Exam showed proximal and distal muscle weakness
- CK level has always been normal











Lornage *et al. Acta Neuropathologica Communications* (2019) 7:138
https://doi.org/10.1186/s40478-019-0781-8

Acta Neuropathologica Communications

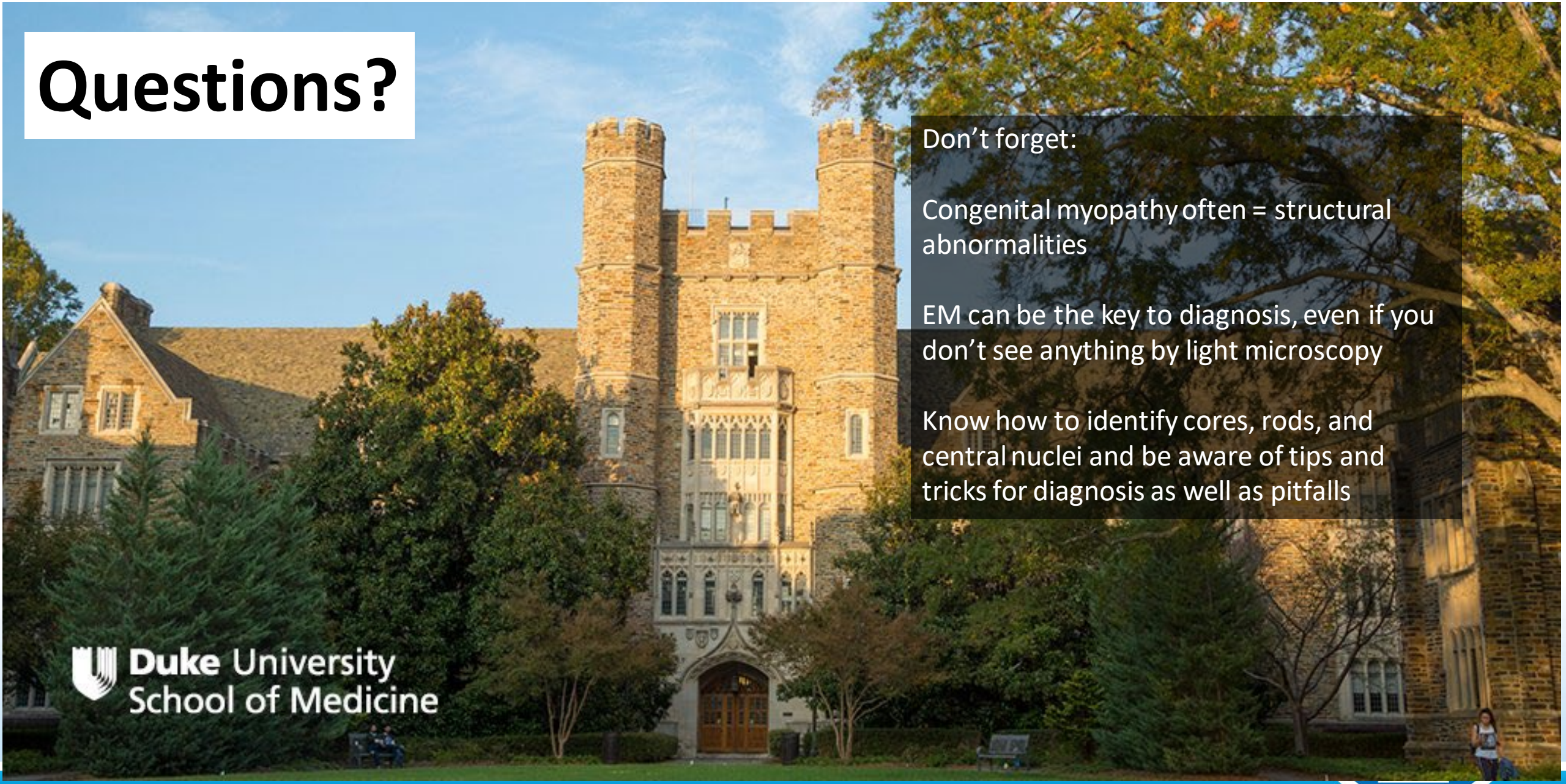
RESEARCH Open Access

Clinical, histological, and genetic characterization of *PYROXD1*-related myopathy

Xavière Lornage[1,2,3,4], Vanessa Schartner[1,2,3,4], Inès Balbueno[1,2,3,4], Valérie Biancalana[1,2,3,4,5], Tracey Willis[6], Andoni Echaniz-Laguna[7,8,9], Sophie Scheidecker[10], Ros Quinlivan[11], Michel Fardeau[12,13,14], Edoardo Malfatti[15], Béatrice Lannes[16], Caroline Sewry[6,17], Norma B. Romero[12,13,14], Jocelyn Laporte[1,2,3,4*] and Johann Böhm[1,2,3,4*]

- Our patient was found to have homozygous pathogenic variants in *PYROXD1* gene
- Relatively newly described congenital myopathy gene
- Pathologic findings include: fiber size variability, endomysial fibrosis, grouped fibers with multiple internalized nuclei, cores, rods, and “myofibrillar disorganization”/myofibrillar inclusions?

Questions?



Don’t forget:

Congenital myopathy often = structural abnormalities

EM can be the key to diagnosis, even if you don’t see anything by light microscopy

Know how to identify cores, rods, and central nuclei and be aware of tips and tricks for diagnosis as well as pitfalls

Useful references

1. Dowling JJ, Weihl CC, Spencer MJ. Molecular and cellular basis of genetically inherited skeletal muscle disorders. Nat Rev Mol Cell Biol. 2021 Jul 13. PMID: 34257452.
2. Jungbluth H, Voermans NC. Congenital myopathies: not only a paediatric topic. Curr Opin Neurol. 2016 Oct;29(5):642-50. PMID: 27538056.
3. Laitila J, Wallgren-Pettersson C. Recent advances in nemaline myopathy. Neuromuscul Disord. 2021 Oct;31(10):955-967. PMID: 34561123.
4. Lawal TA, Todd JJ, Witherspoon JW, Bönnemann CG, Dowling JJ, Hamilton SL, Meilleur KG, Dirksen RT. Ryanodine receptor 1-related disorders: an historical perspective and proposal for a unified nomenclature. Skelet Muscle. 2020 Nov 16;10(1):32. PMID: 33190635; PMCID: PMC7667763.
5. Nix JS, Moore SA. What Every Neuropathologist Needs to Know: The Muscle Biopsy. J Neuropathol Exp Neurol. 2020 Jul 1;79(7):719-733. PMID: 32529201; PMCID: PMC7304986.
6. Sewry CA, Wallgren-Pettersson C. Myopathology in congenital myopathies. Neuropathol Appl Neurobiol. 2017 Feb;43(1):5-23. PMID: 27976420.