AANP 2023 Diagnostic Slide Session: Case 7

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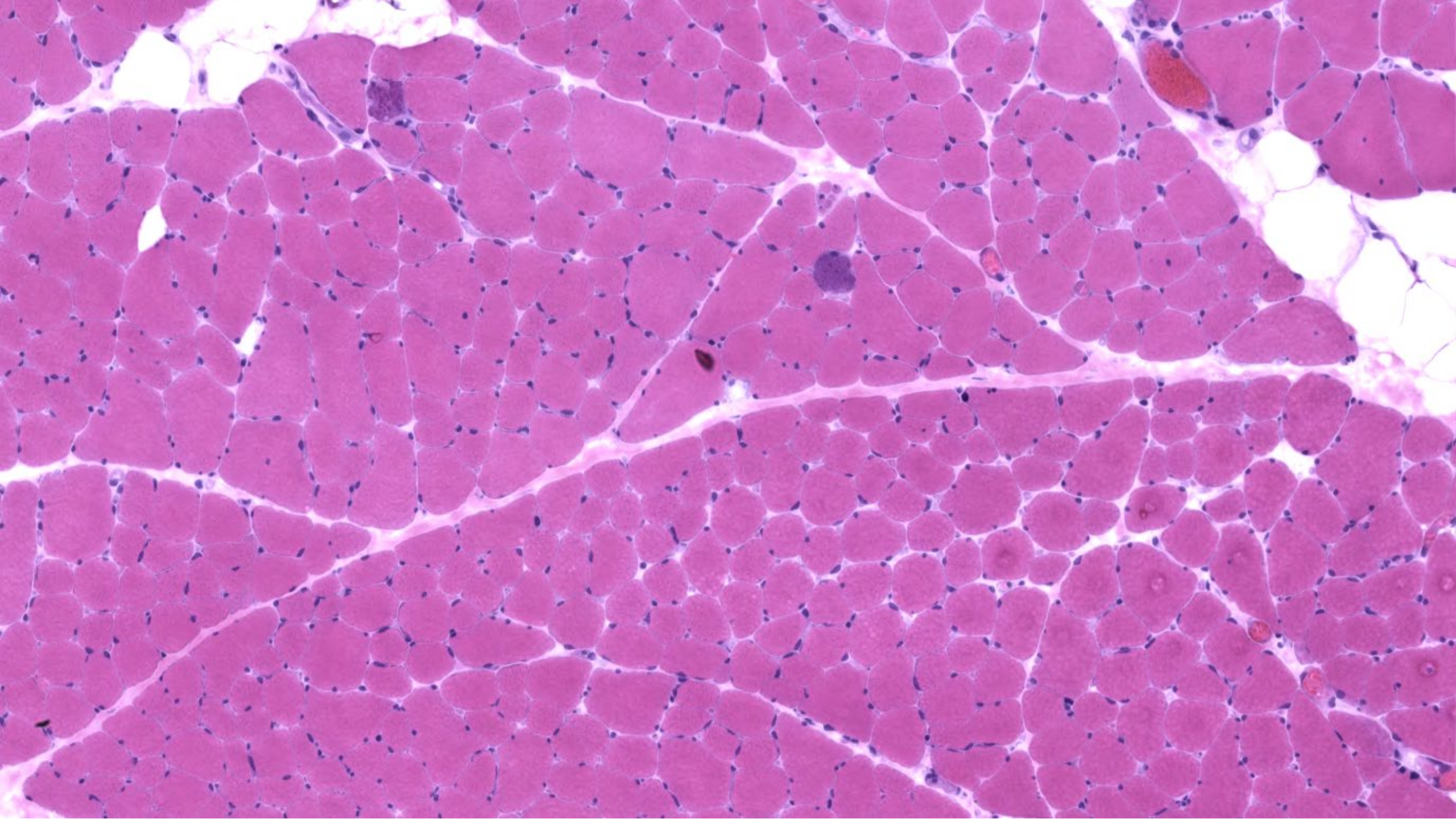
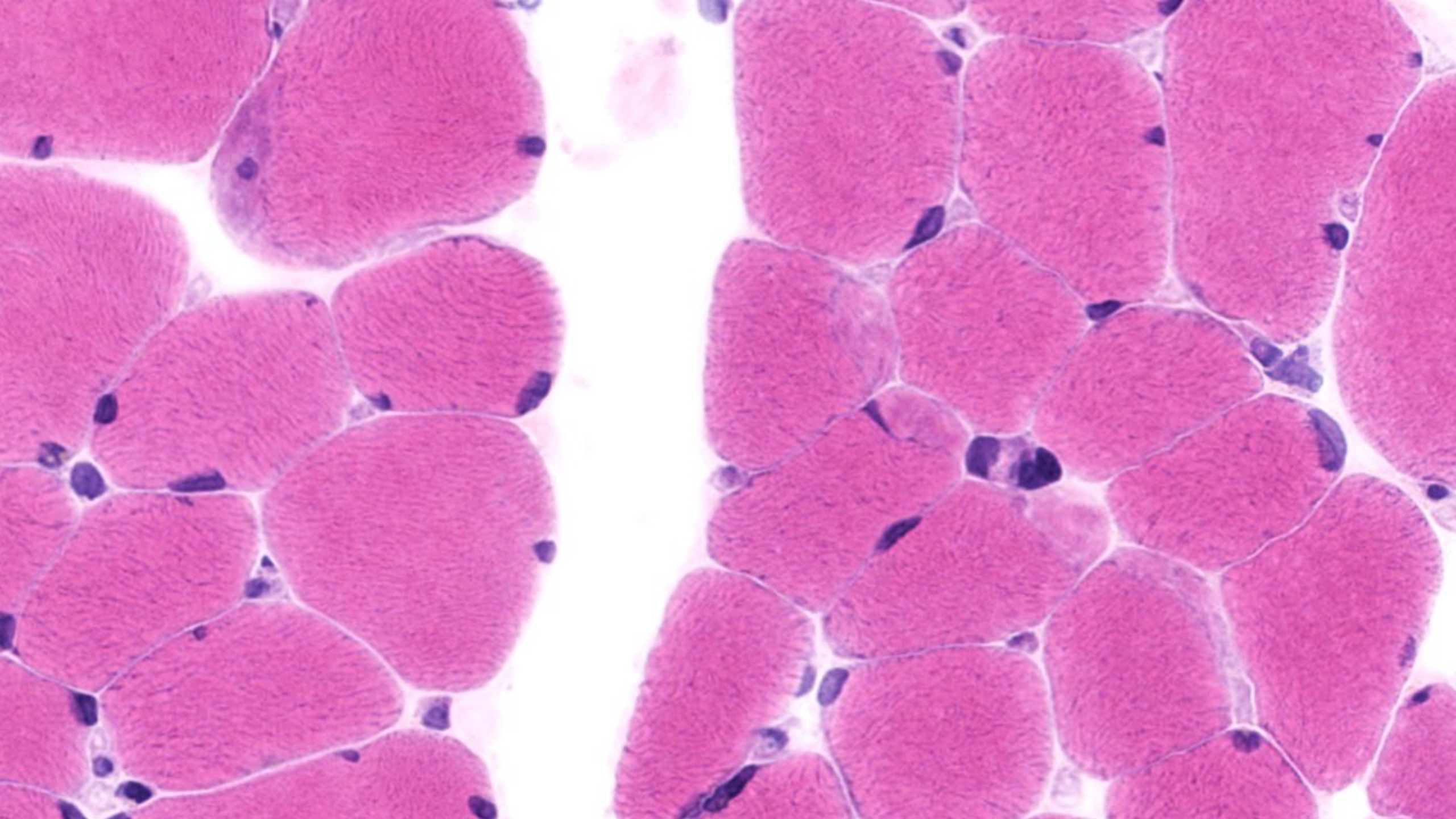
Clinical presentation

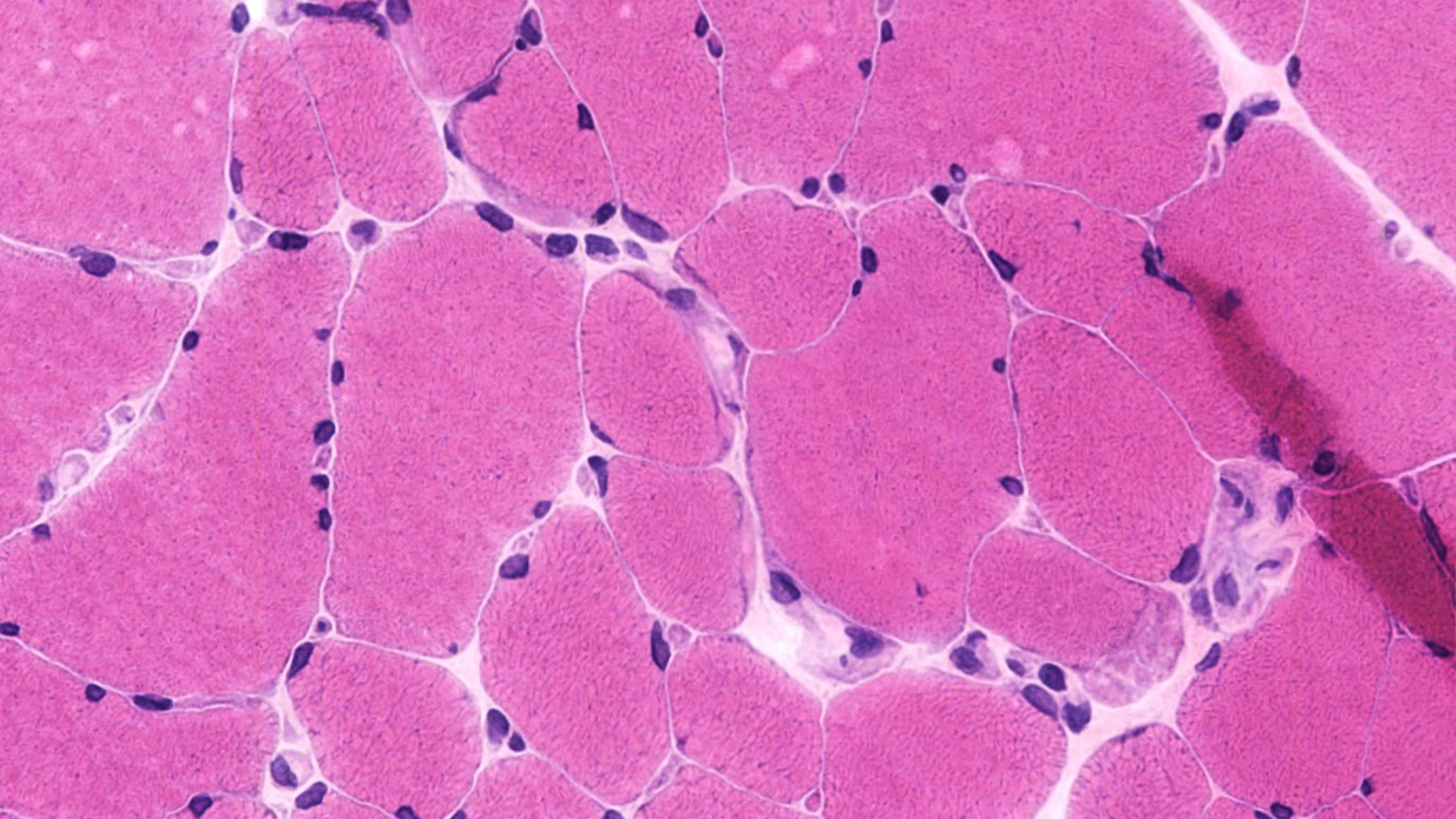
- 48-year-old man presenting with right heart failure and mixed hypoxic/hypercapnic respiratory failure several months following an asymptomatic COVID infection
- Physical exam:
  - “Marfanoid” body habitus (tall, with long arms and pectus carinatum) and a thin sharp face
  - Weak facial muscles
  - Mild bilateral tongue weakness
  - Bilateral scapular winging
  - Reduced muscle bulk in legs, pectoralis, deltoid, triceps, and biceps
  - High steppage gait
  - Inability to heel walk

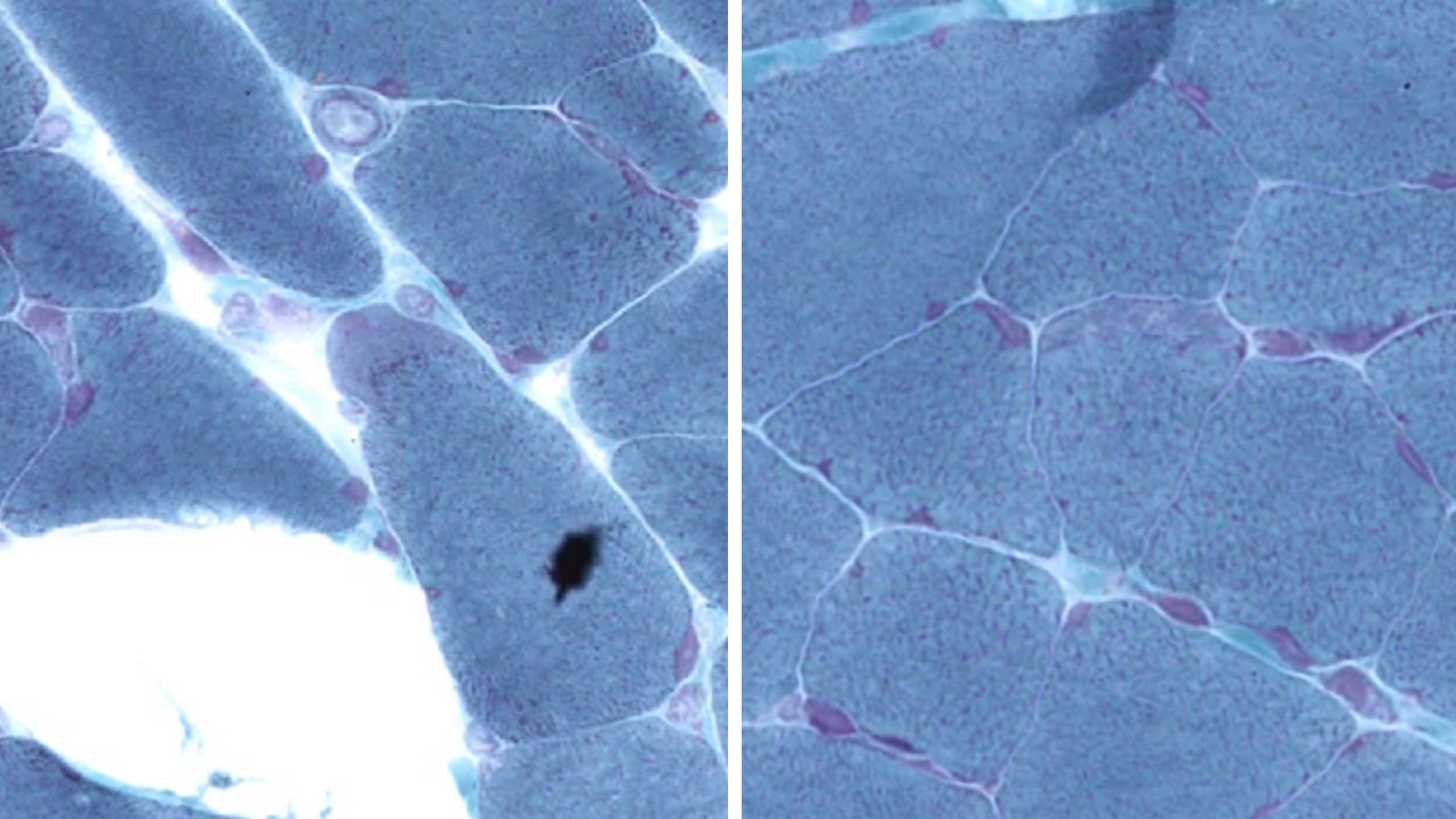
Additional findings

- Longstanding difficulty reaching things overhead and jumping
- No known family history of neuromuscular disorders
- Evaluated for Marfan syndrome at age 14, testing results unrevealing
- Electrodiagnostic studies: Evidence of a myopathic process affecting both upper and lower extremities
- CK levels: within normal limits
- **Based on the geneticist's recommendation, the neurology team ordered a deltoid muscle biopsy to guide the work-up**



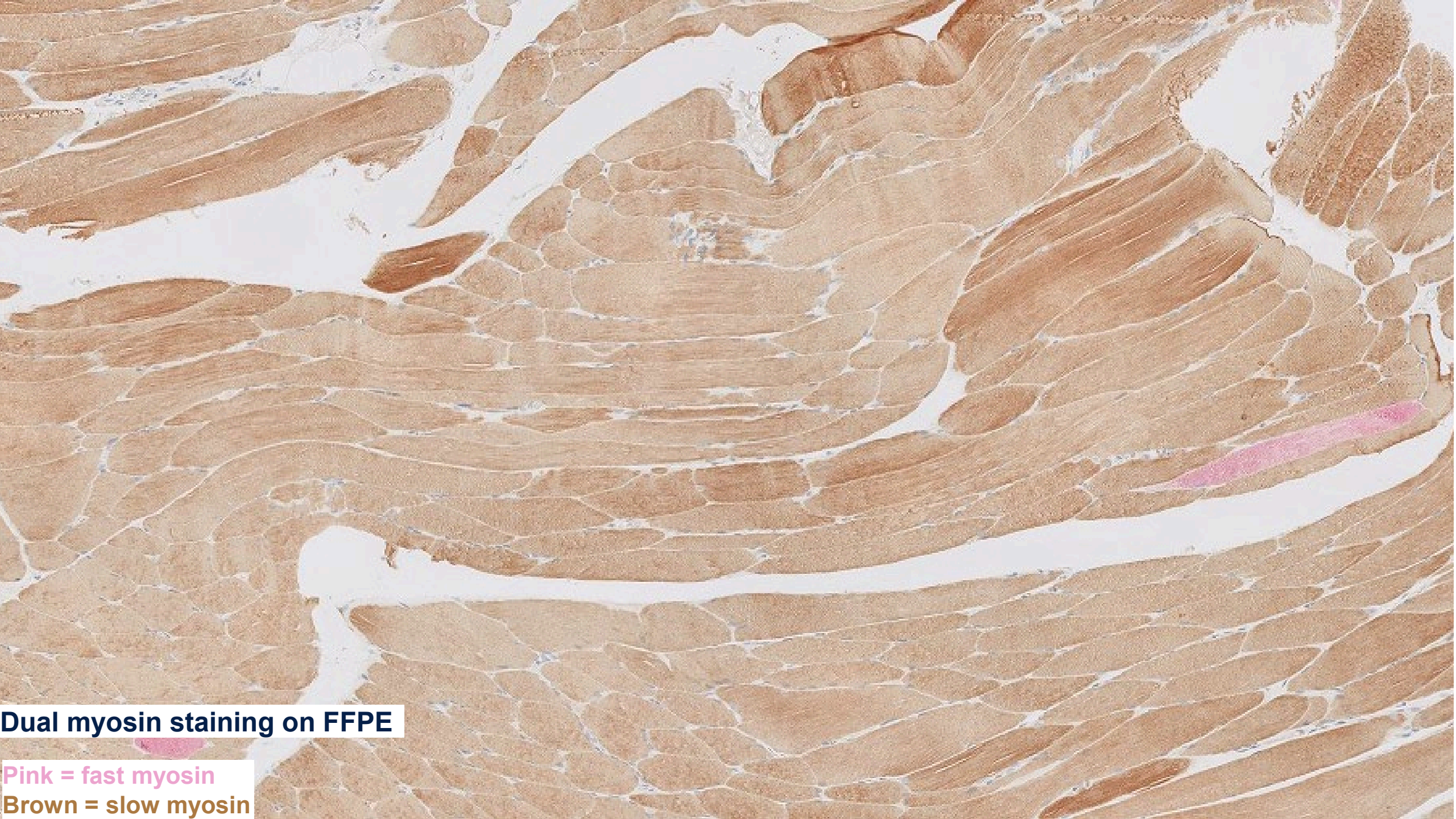


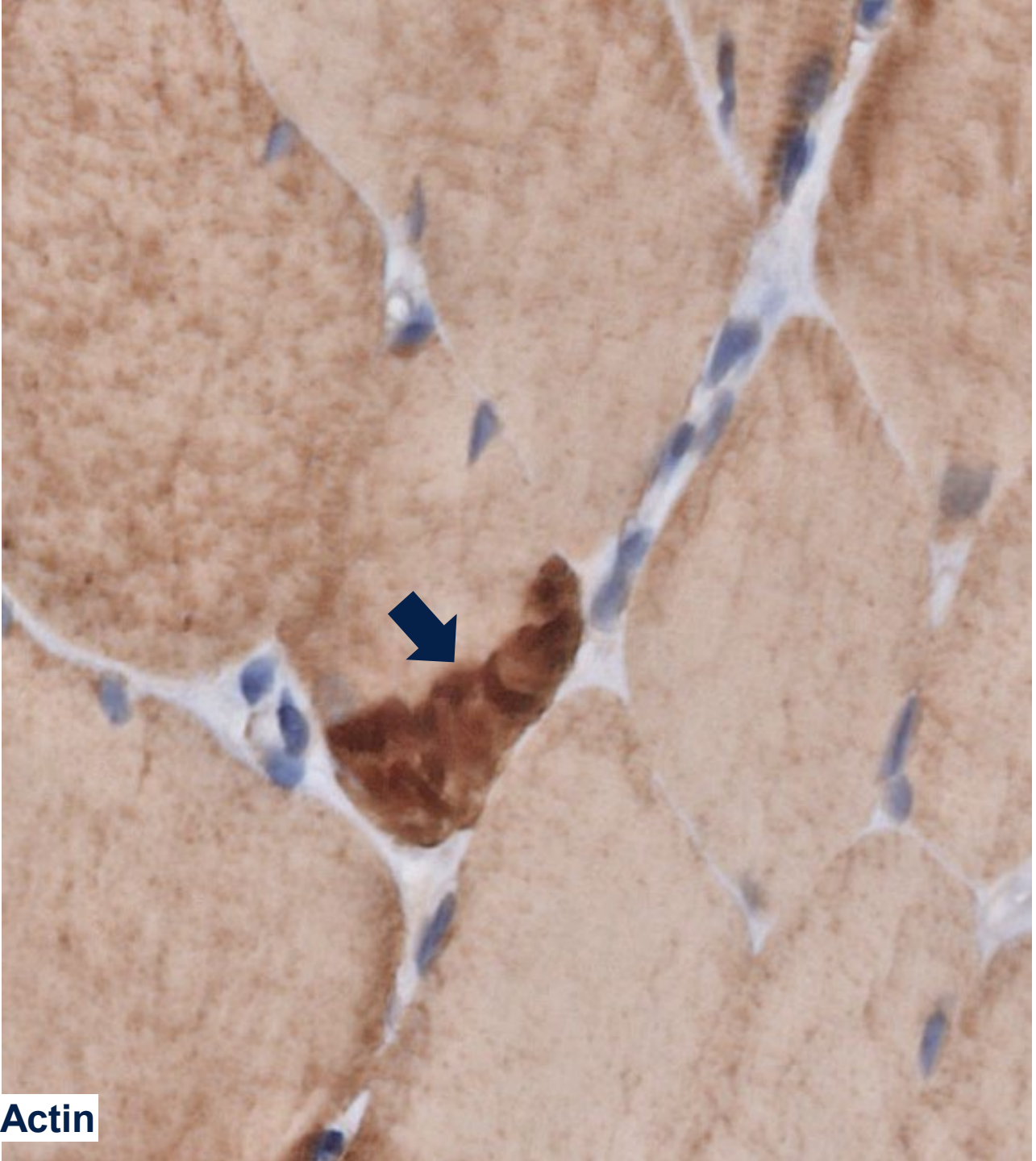




Differential diagnosis?

Additional testing?


Dual myosin staining on FFPE
Pink = fast myosin
Brown = slow myosin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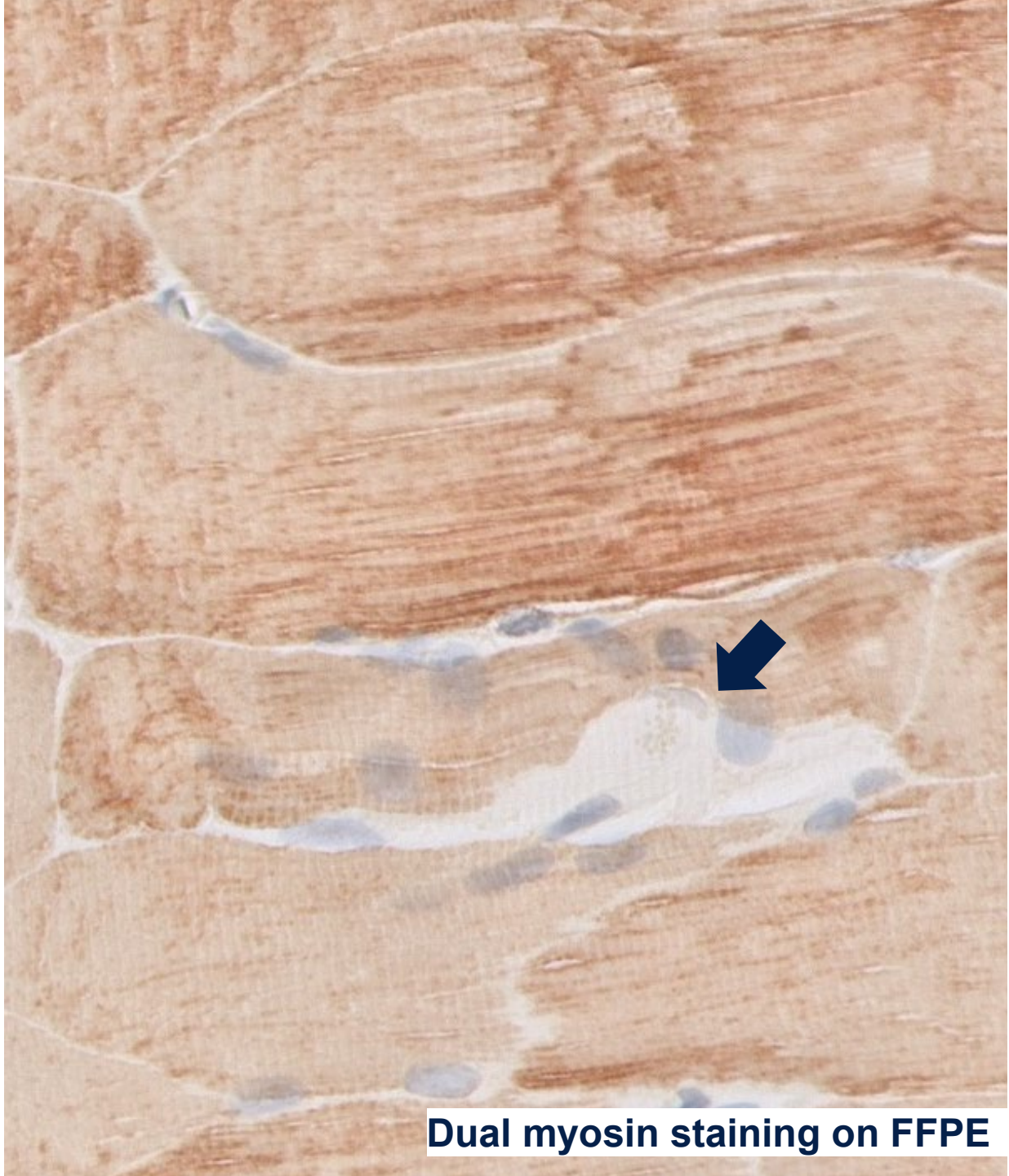
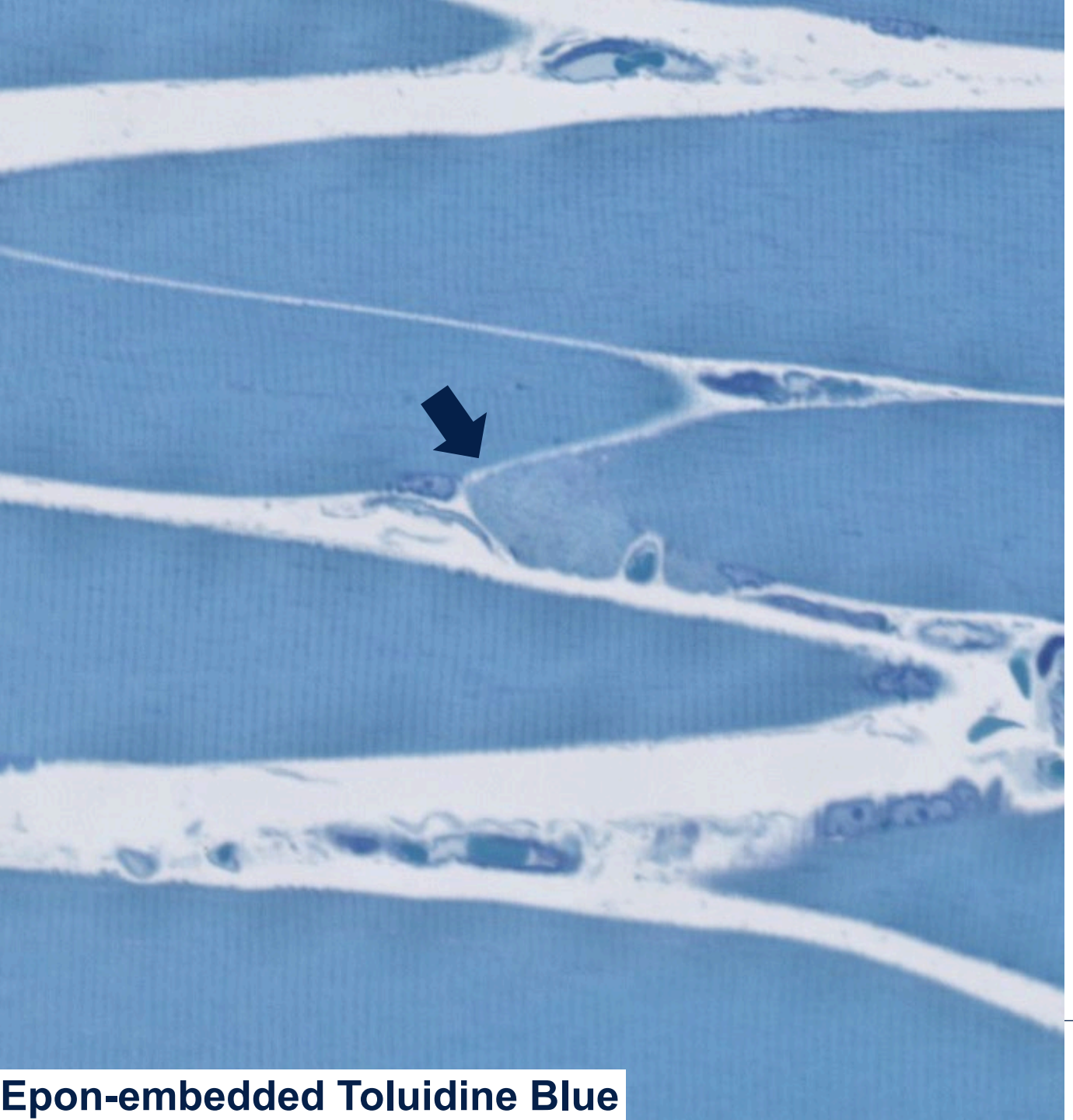
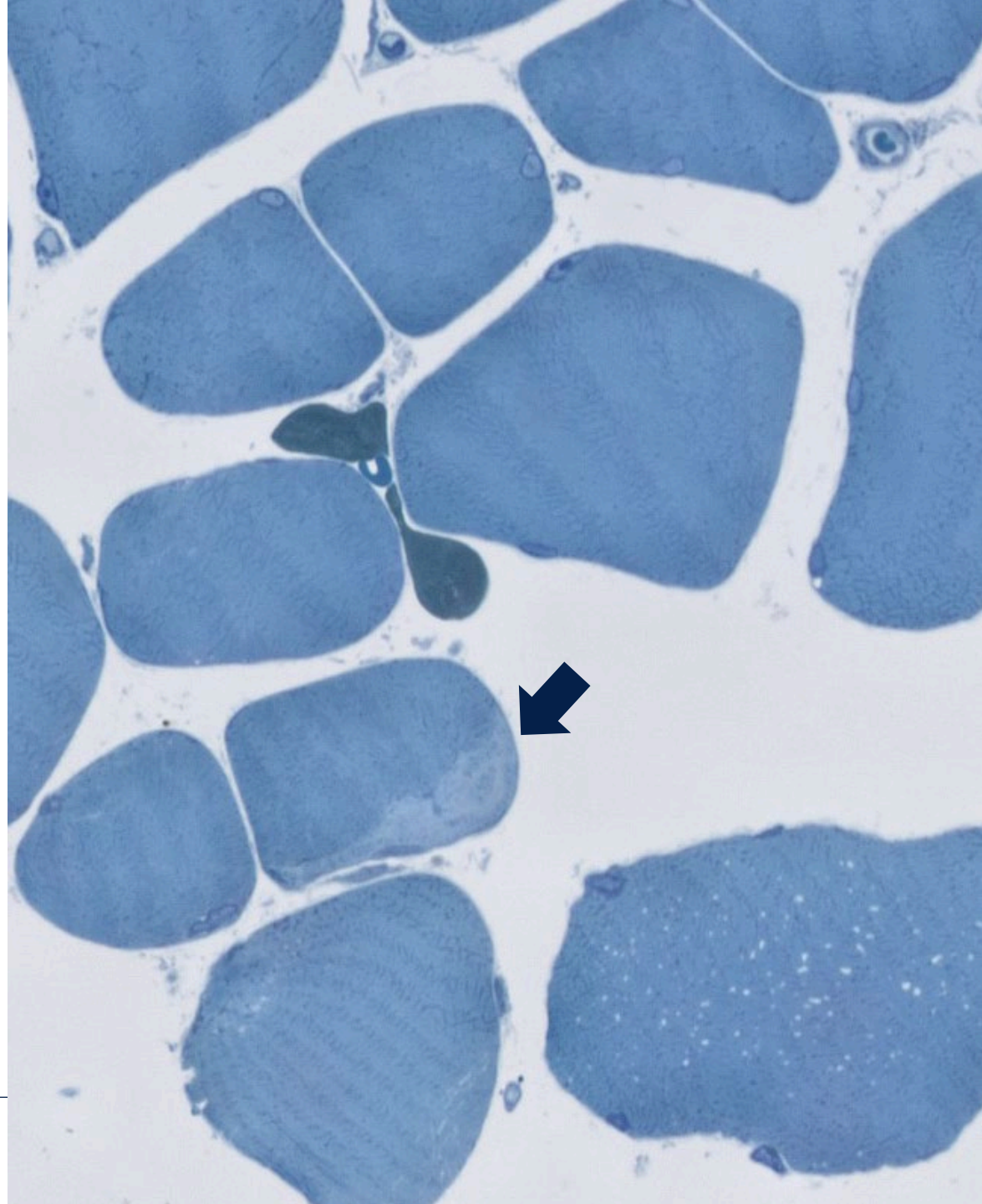
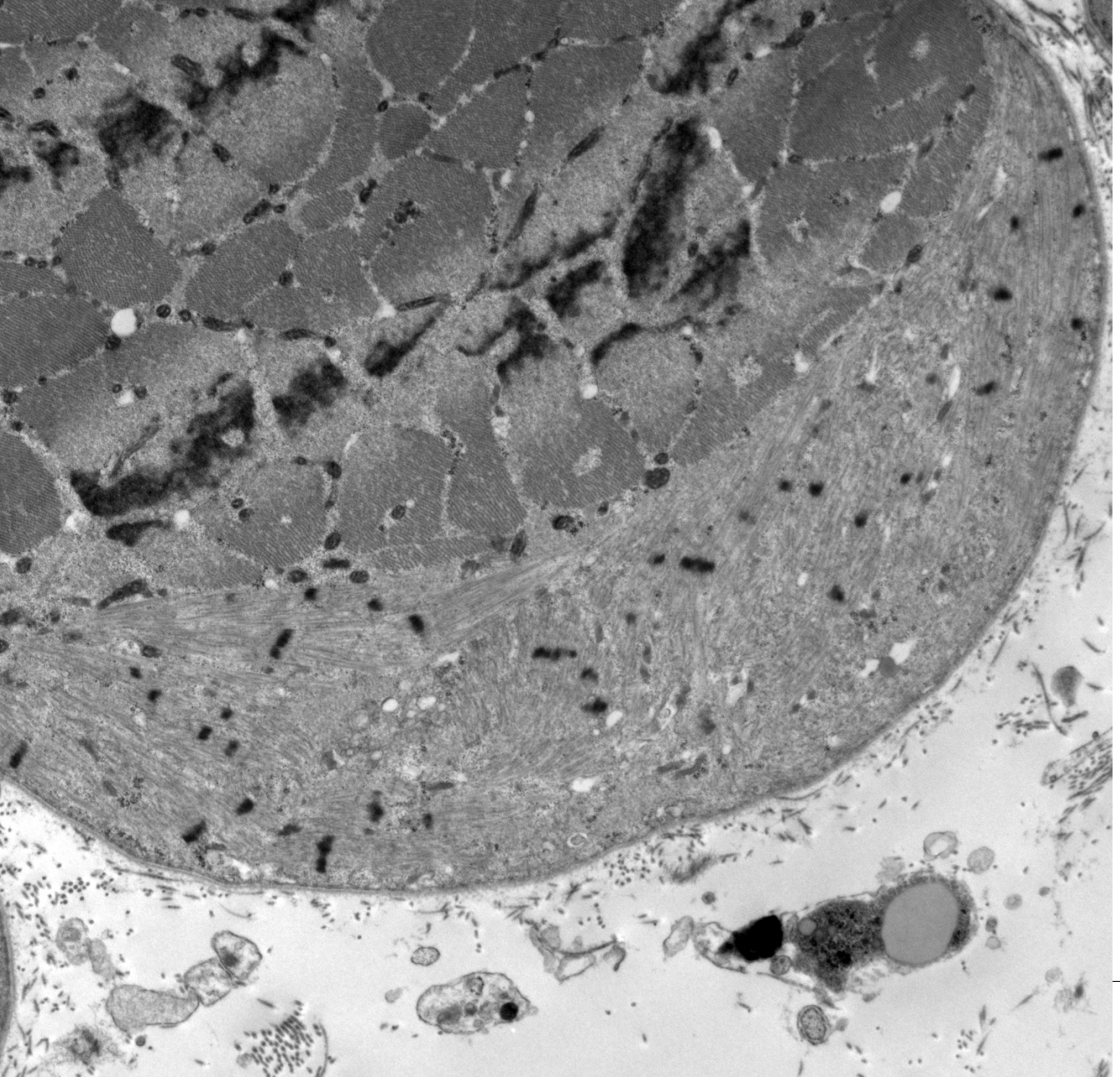
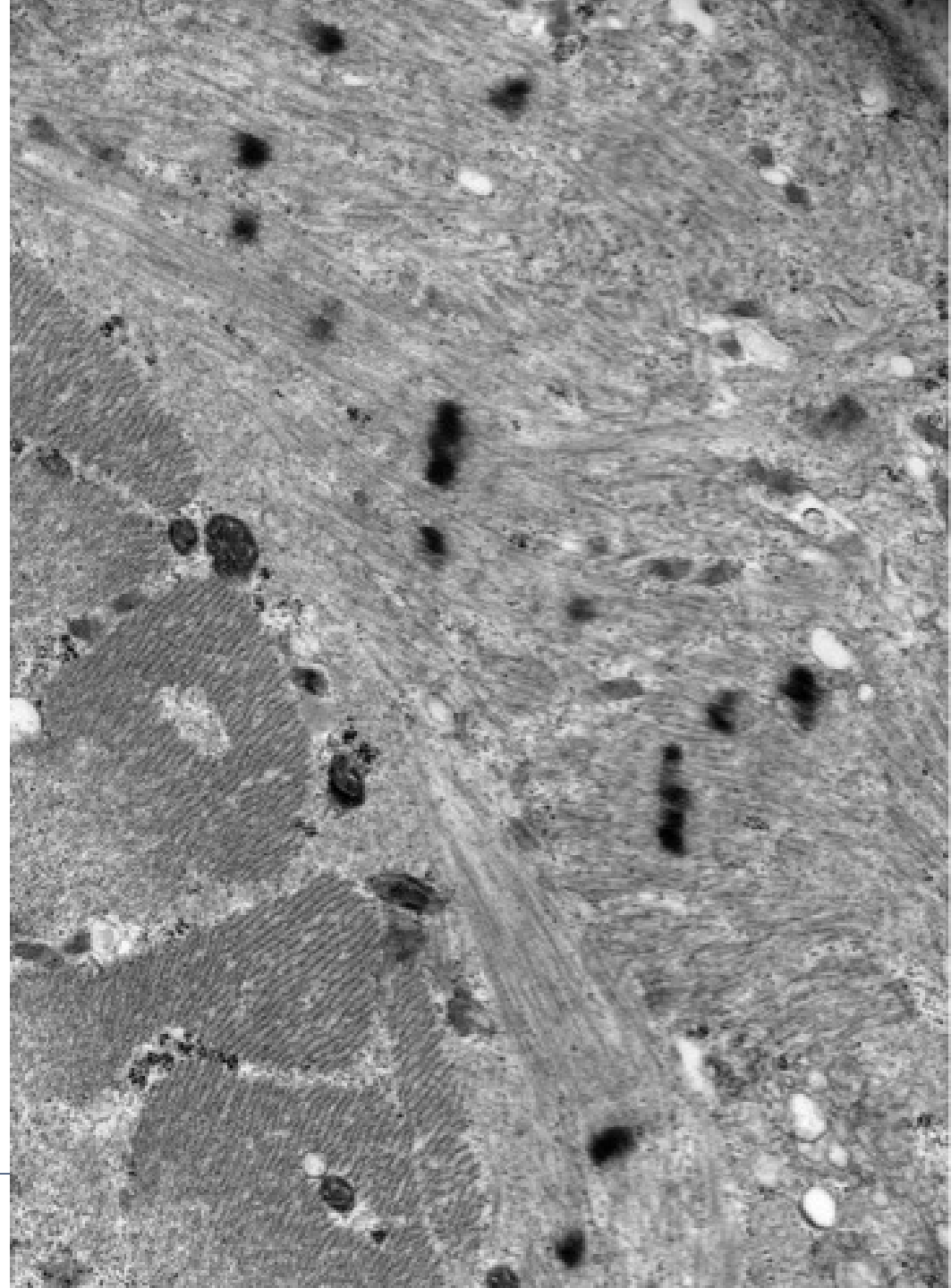

Dual myosin staining on FFPE



Epon-embedded Toluidine Blue







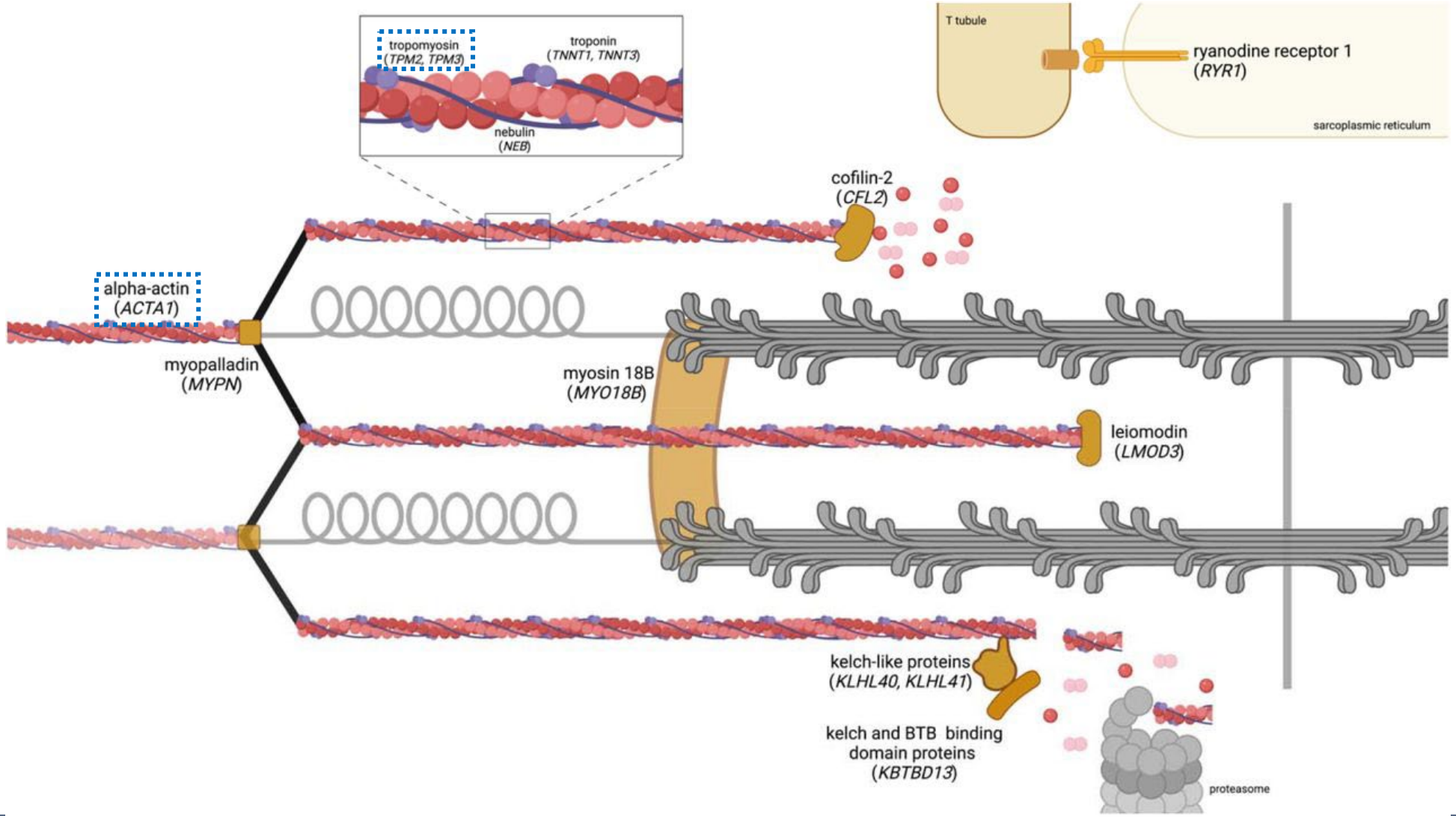
Histopathologic diagnosis:

Cap myopathy

Cap myopathy

- Congenital myopathy first described in 1981 in a 7-year-old boy
- Characterized by multiple peripherally located accumulation of disorganized myofibrils, which form the cap-like structures
- Genetics:
  - First reported genetic alteration: heterozygous single amino acid deletion in beta-tropomyosin gene (TPM2)
  - Subsequently, mutations in TPM3 and ACTA1 have been reported in rare cases of cap myopathy
  - Mutations in these genes can also cause nemaline myopathy, suggesting closely related pathogenesis

Genes involved in cap myopathy



Christophers B, Lopez MA, Gupta VA, Vogel H, Baylies M. Pediatric Nemaline Myopathy: A Systematic Review Using Individual Patient Data. Journal of Child Neurology. 2022;37(7):652-663. doi:10.1177/08830738221096316

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Genetic testing

- Novel, likely pathogenic [c.479G>T (p.Arg150Leu) heterozygous] variant in **tropomyosin 2 (TPM2)**
- Two variants of uncertain significance:
  1. Ryanodine receptor 1 (RYR1): c9101A>C (p.Lys3034Thr) heterozygous
  2. Titin (TTN): c102329G>A (p.Arg34110Gln) heterozygous

Integrated diagnosis:

Cap myopathy caused by de novo TPM2 mutation*

* The TPM2 variant was not detected in either parent

Clinical presentation of cap myopathy

Gene	Mutation	Age at onset	Age at diagnosis	Weakness pattern	Cardiac involvement	Respiratory weakness	Family history	Reference
TPM2	R150L	Child	48	Diffuse and bulbar	Right heart failure	VC reduced	None	This case
	E41K	Infant	35, 66	Diffuse and bulbar	Normal	VC reduced	Mother and daughter	Tajsharghi
	K49del	Infant	42	Proximal upper and lower limbs	Normal	Normal	Not reported	Ohlsson
	G52dup	Infant	6	Diffuse and facial	Normal	Normal	Not reported	Ohlsson
	E138del	Child	~14	Proximal upper and distal lower limbs	NA	VC reduced	Brother	Tasca
	E139del	Infant	14	Diffuse and bulbar	Valve insufficiency EF reduced	VC reduced	None	Clarke
	E139del	Birth	36	Diffuse and bulbar, dysphagia	Normal	Require NIV	None	Lehtokari
	N202K	Prenatal	8	Diffuse and facial, EOM restriction	Normal	VC reduced	Not reported	Ohlsson
TPM3	L149I	Child	~20	Diffuse sparing face	Reduced RV function, VI, LV hypertrophy	VC reduced	Mother and son	Schreckenbach
	R168C	**Child**	**19**	**Diffuse**	**Normal**	**Ventilated**	**None**	**Zheng**
	R168C	Infant	20	Diffuse	Aortic dilation	Reduced VC	None	Waddell
	R168C	Child	38	Proximal	Normal	Ventilated	Not reported	Ohlsson
	R168H	4	42	Leg weakness	Normal	Reduced VC	None	De Paula
ACTA1	M49N	Prenatal	5	Diffuse, dysphagia	Hypertension	Ventilated	None	Hung

Histopathologic findings in cap myopathy

Gene	Mutation	Nemaline rods?	% of fibers with caps	Reference
TPM2	R150L	No	5-10	This case
	E41K	One of two cases	N/A	Tajsharghi
	K49del	N/A	15	Ohlsson
	G52dup	N/A	N/A	Ohlsson
	E138del	One case	N/A	Tasca
	E139del	No	4	Clarke
	E139del	No	N/A	Lehtokari
	N202K	N/A	N/A	Ohlsson
TPM3	L149I	No	6-10	Schreckenbach
	R168C	**No**	**15**	**Zheng**
	R168C	No	25	Waddell
	R168C	No	20-25	Ohlsson
	R168H	No	10-15	De Paula
ACTA1	M49N	No	N/A	Hung

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Clinical follow-up and summary

- The patient recovered fully and is doing fine
- Clinical manifestations of cap myopathy are highly variable, with a wide range of symptoms and age of onset/presentation
- Histologically, fibers with peripherally located accumulations of disorganized myofibrils (caps) are characteristic of the entity
- The number of affected fibers varies widely and loosely correlates with the degree of weakness
- In genetic myopathies with a broad differential diagnosis, muscle biopsy can help guide the subsequent molecular studies

References

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