

# A 12 year-old-boy with proximal muscle weakness and cardiomyopathy

Samra Vazirian, M.D.\*, Kara Jones, M.D. Ph.D.#, Steven Moore, M.D. Ph.D.#, Perry B. Shieh, M.D. Ph.D.\*

\*University of California, Los Angeles

#University of Iowa Health Care

# Case presentation

12-year-old boy with eight years of progressive leg weakness.

## Birth:

- ⊗ Normal spontaneous vaginal delivery at 41 weeks
- ⊗ Normal prenatal labs and ultrasounds.

## Development:

- ⊗ Cognition is apparently normal. In seventh grade- regular classes.
- ⊗ Language: Bilingual- fluent in Spanish and English.
- ⊗ Normal fine and gross motor development.
- ⊗ Social: apparently normal.

# Initial Presentation and clinical course

- ⊗ At four years of age, he would occasionally fall while playing soccer. He was keeping up with his peers, however, and remained very active.
- ⊗ At four years of age, routine labs revealed elevated transaminases. Subsequent testing revealed consistently elevated CKs ~1500.
- ⊗ He underwent a muscle biopsy, which reportedly showed mild type II fiber hypertrophy.

# Clinical course

- ⊗ Despite this evaluation, he did not develop any obvious progressive weakness or other muscle symptoms over the next several years
- ⊗ At 10 years of age, the patient did recall experienced muscle pain in his legs while playing soccer at school.
- ⊗ He denies having any noticeable symptoms or complain of weakness.
- ⊗ No fatigue or overt exercise intolerance.
- ⊗ No shortness of breath. No swallowing problems.

# Case presentation

## **Past Medical History**

- ⊗ Hypertrophic cardiomyopathy, discovered at age 9 on periodic screening echocardiograms that were being performed because the mother had died of heart failure.

## **Past Surgical History**

- ⊗ Muscle biopsy at four years of age.

## **Social History:**

- ⊗ Lives with his father and two sisters. Currently in seventh grade – regular classes.

# Case presentation

## Family History:

- ⊗ Born to a non-consanguineous parents of Mexican ancestry.
- ⊗ Mother was diagnosed with a heart disease at 31 years of age. She had dilated cardiomyopathy with EF of 15% requiring ICD placement. She passed away at 35 years of age. The mother did not have weakness. She had one miscarriage.
- ⊗ Two sisters – age 8 and 6, both healthy.
- ⊗ Maternal aunt died of hypertrophic cardiomyopathy. Aunt has three children who are apparently healthy

# Neurological Exam

- ⊗ **Mental status:** Age appropriate
- ⊗ **Cranial Nerves:** **Mild nasal sounding speech**, but palate elevation and tongue was normal and the remainder of cranial nerves were normal.
- ⊗ **Sensory:** Intact to all modalities.
- ⊗ **Reflexes:** **Absent throughout.**
- ⊗ **Coordination:** Intact FNF, HTS, RAM.
- ⊗ **Gait:** Slow to rise from the floor, but has apparently normal gait.

# Motor Exam (left/right)

Neck Flexion/Extension 4/5

- ⊗ Shoulder abduction 4/4
- ⊗ Elbow flexion 5/5
- ⊗ Elbow extension 5/5
- ⊗ Wrist flexion 5/5
- ⊗ Wrist extension 5/5
- ⊗ Finger extension 5/5
- ⊗ Finger flexion 5/5
- ⊗ Finger abduction 5/5
- ⊗ Finger adduction 5/5
- ⊗ Thumb abduction 5/5
- Hip flexion 4/4
- Hip Extension 5/5
- Hip abduction 5/5
- Hip adduction 5/5
- Knee extension 5/5
- Knee flexion 5/5
- Foot dorsiflexion 5/5
- Foot plantar flexion 5/5
- Foot inversion 5/5
- Foot eversion 5/5

# Neurological Exam



# Diagnostic work-up

## Labs

- ⊗ AST 491; ALT 465
- ⊗ CK: 1776
- ⊗ CK-MB fraction of 0, CK-MM fraction 100.
- ⊗ LDH 1287
- ⊗ Brain Natriuretic Peptide > 1000

## Hepatic ultrasound:

- ⊗ Mild fatty hepatomegaly.

# Cardiac evaluation

## **EKG:**

- Sinus bradycardia. HR 48 bpm
- LVH with repolarization abnormalities and strain pattern.

## **Holter monitor:**

- Sinus rhythm with junctional rhythm at lower heart rates.
- Rare isolated monomorphic PVCs. Rare isolated PACs.
- No SVT or VT.

## **Stress test:**

- No dysrhythmias or evidence of airway reactivity
- Reduced BP at peak exertion with prompt normalization during recovery

# Echocardiogram

Serial studies until 8 years of age was normal.

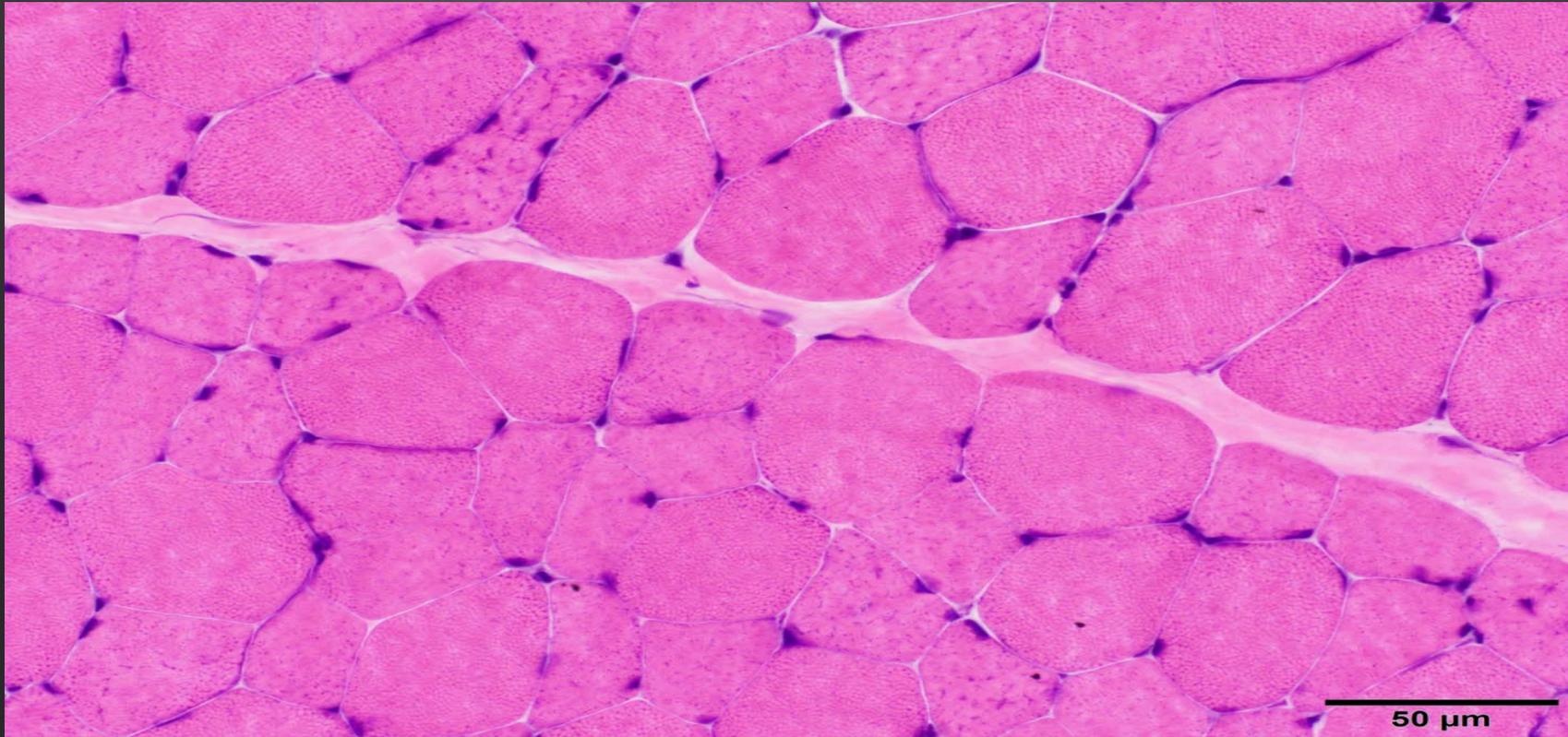
## **Echo May 2016 (at 9 years of age)**

- Hyperdynamic left ventricular systolic function.
- Mild left ventricular intra-cavitary obstruction.
- Severe asymmetric left ventricular hypertrophy.
- Interventricular septum measured 2.9 cm. LV free wall measures 2.2 cm.

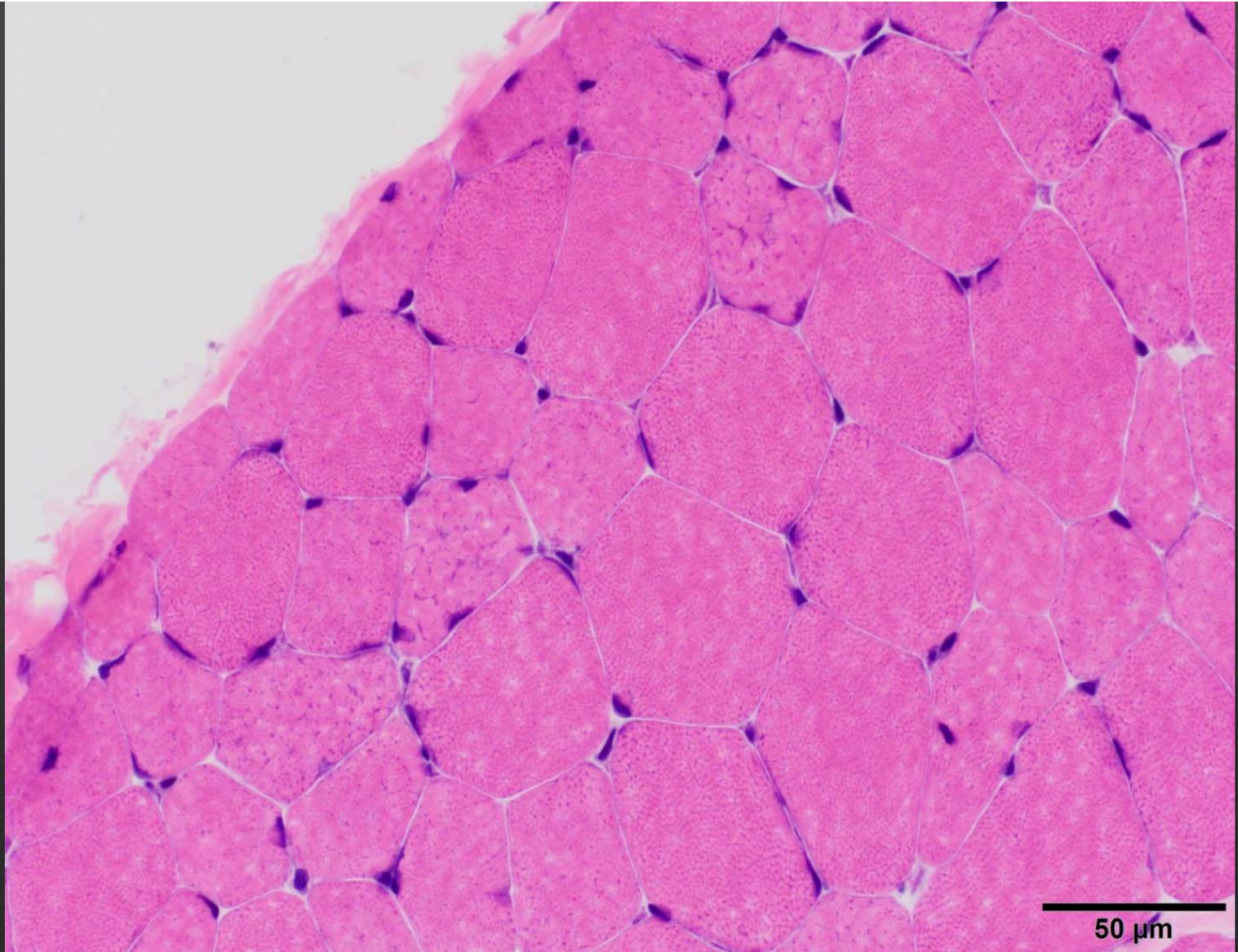
## **Echo – most recent**

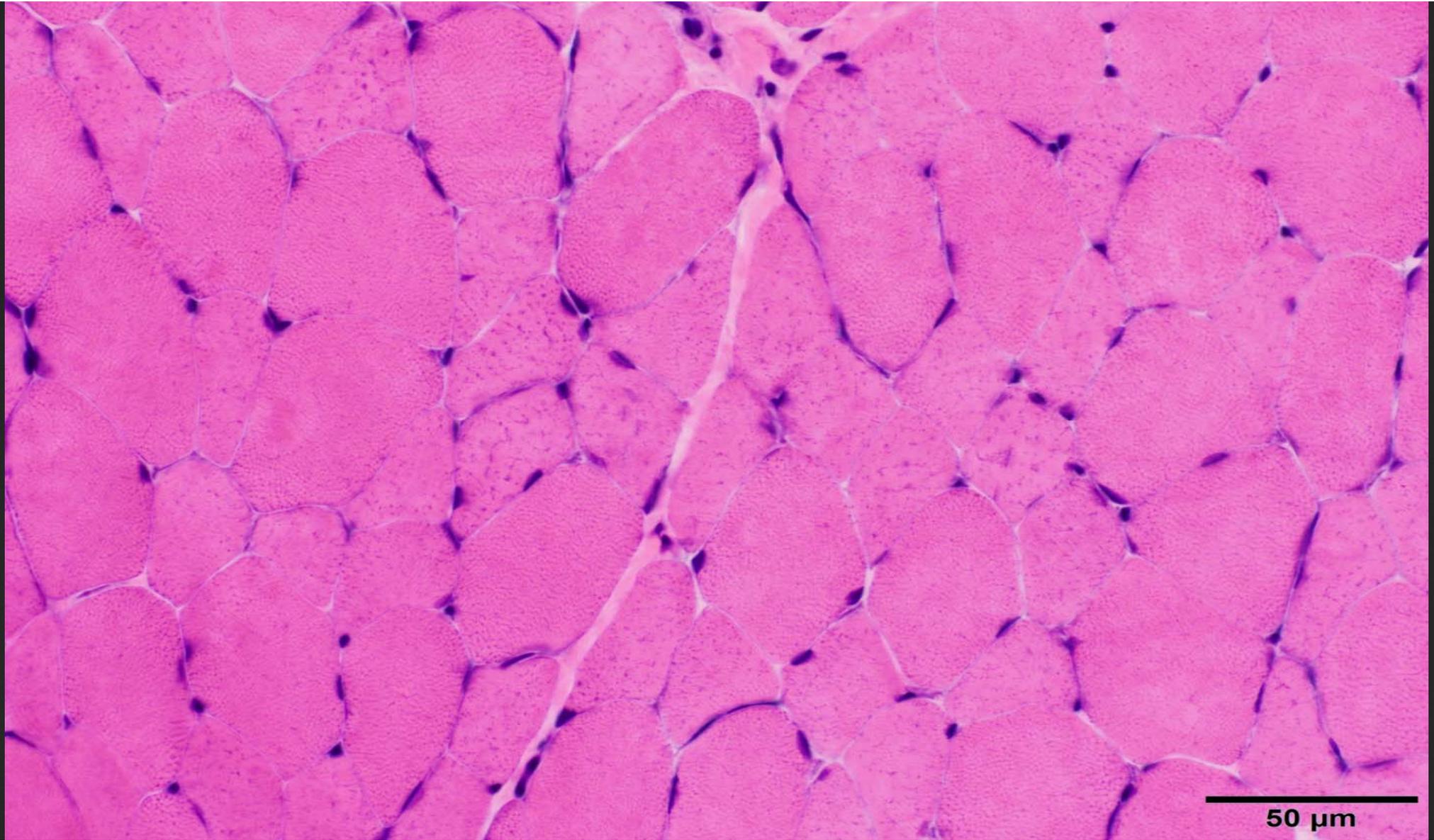
- Hyperdynamic left ventricular systolic shortening.
- Mild dynamic left ventricular outflow tract obstruction
- Severe hypertrophic cardiomyopathy.

# MUSCLE BIOPSY- 2011



Mild type-II fiber hypotrophy; there were no dystrophic changes, evidence of myofiber degeneration, mitochondrial changes, or evidence of storage disease





Thoughts ?



## Next work-up

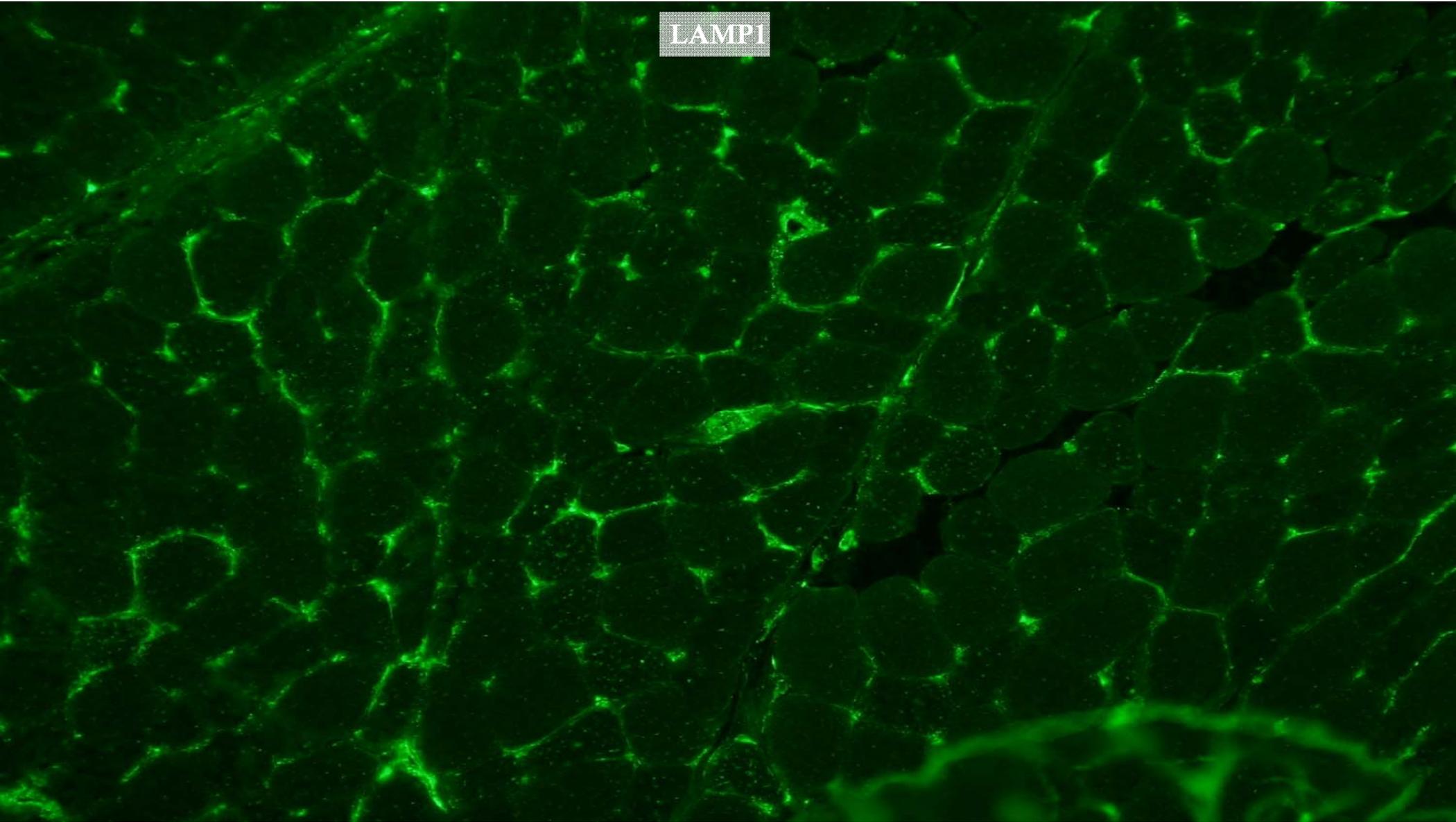
- ⊗ Because of the history of hypertrophic cardiomyopathy and possible muscle disease, we had some concern that he may have **Danon disease** or some other neuromuscular disease associated with hypertrophic cardiomyopathy...

# Genetic testing

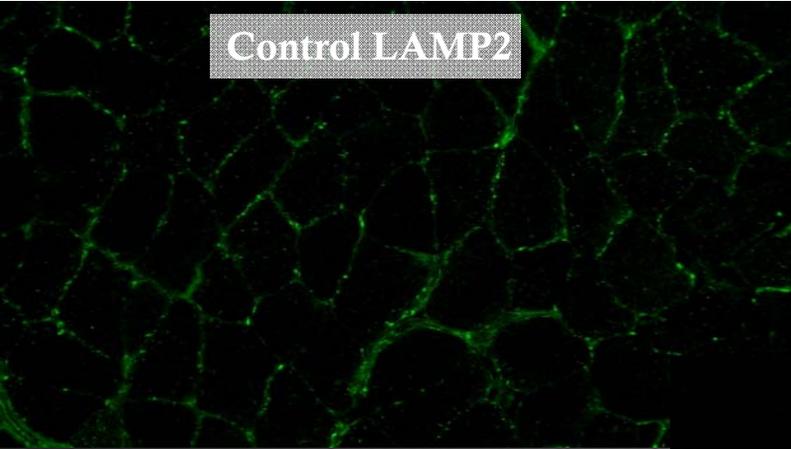
Cardiac Sequencing panel showed hemizygous variant in the **LAMP2 gene**:  
c.815T>C (p.Leu272Pro)

The muscle biopsy specimen was sent for LAMP2 staining.

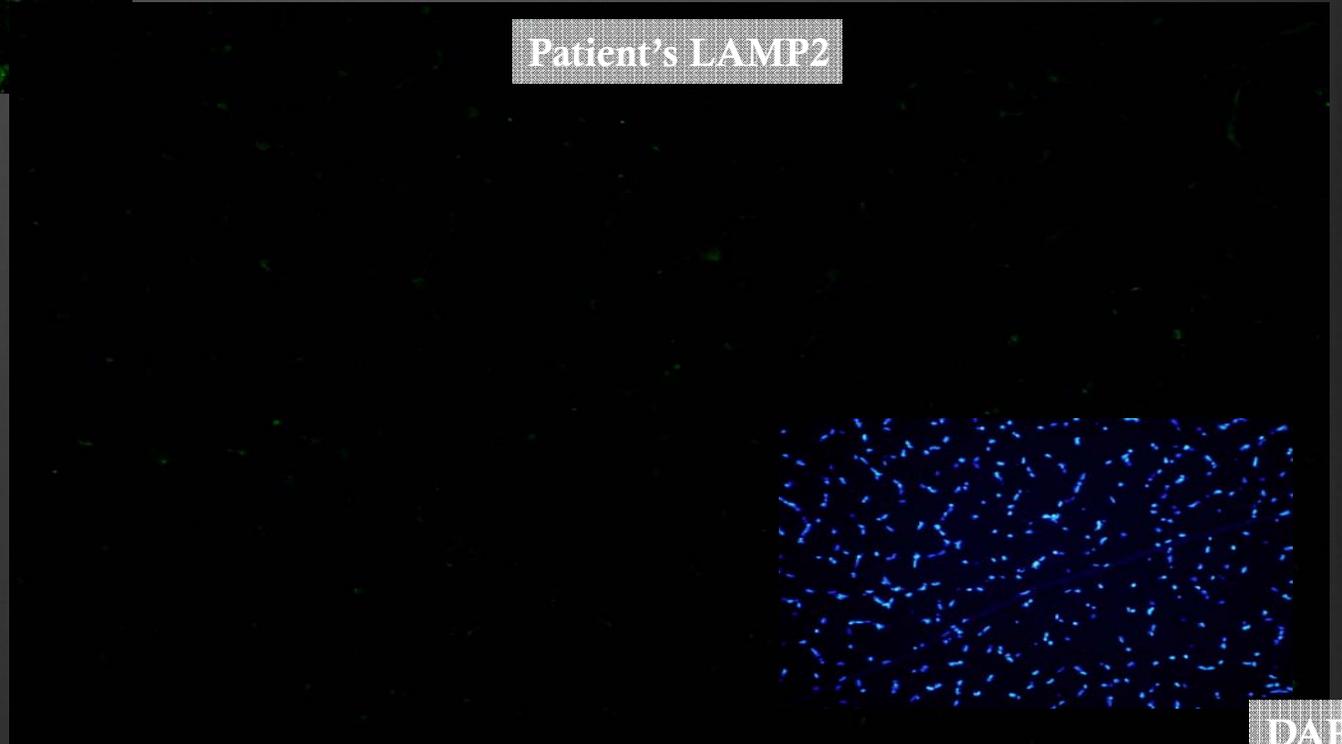
LAMP1



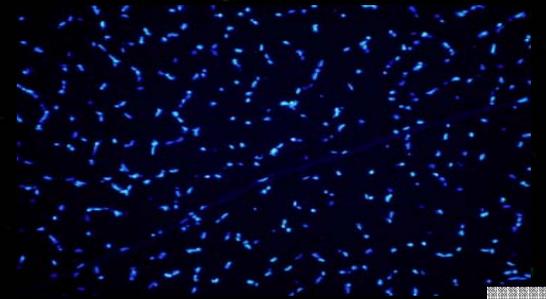
Control LAMP2



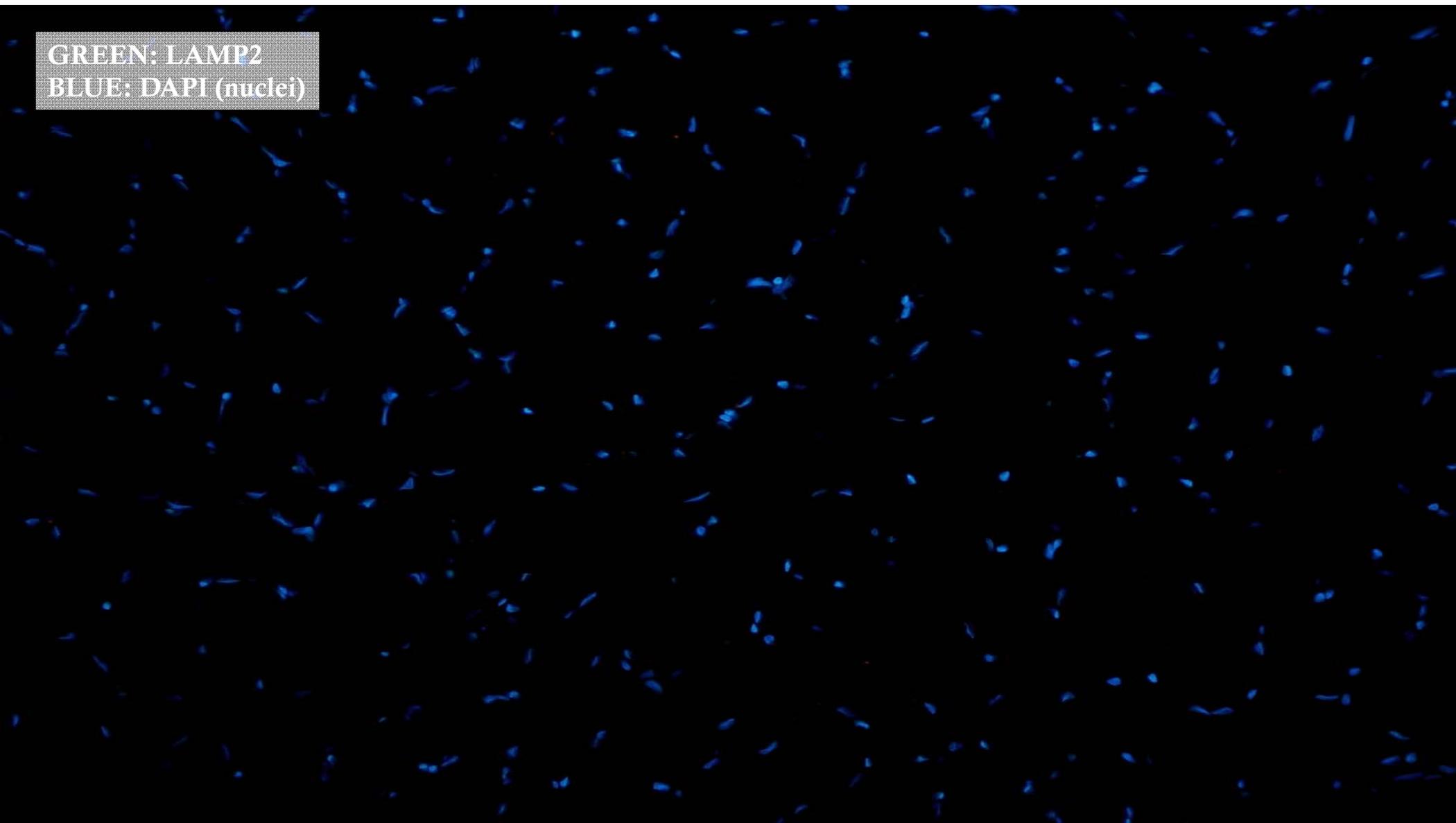
Patient's LAMP2



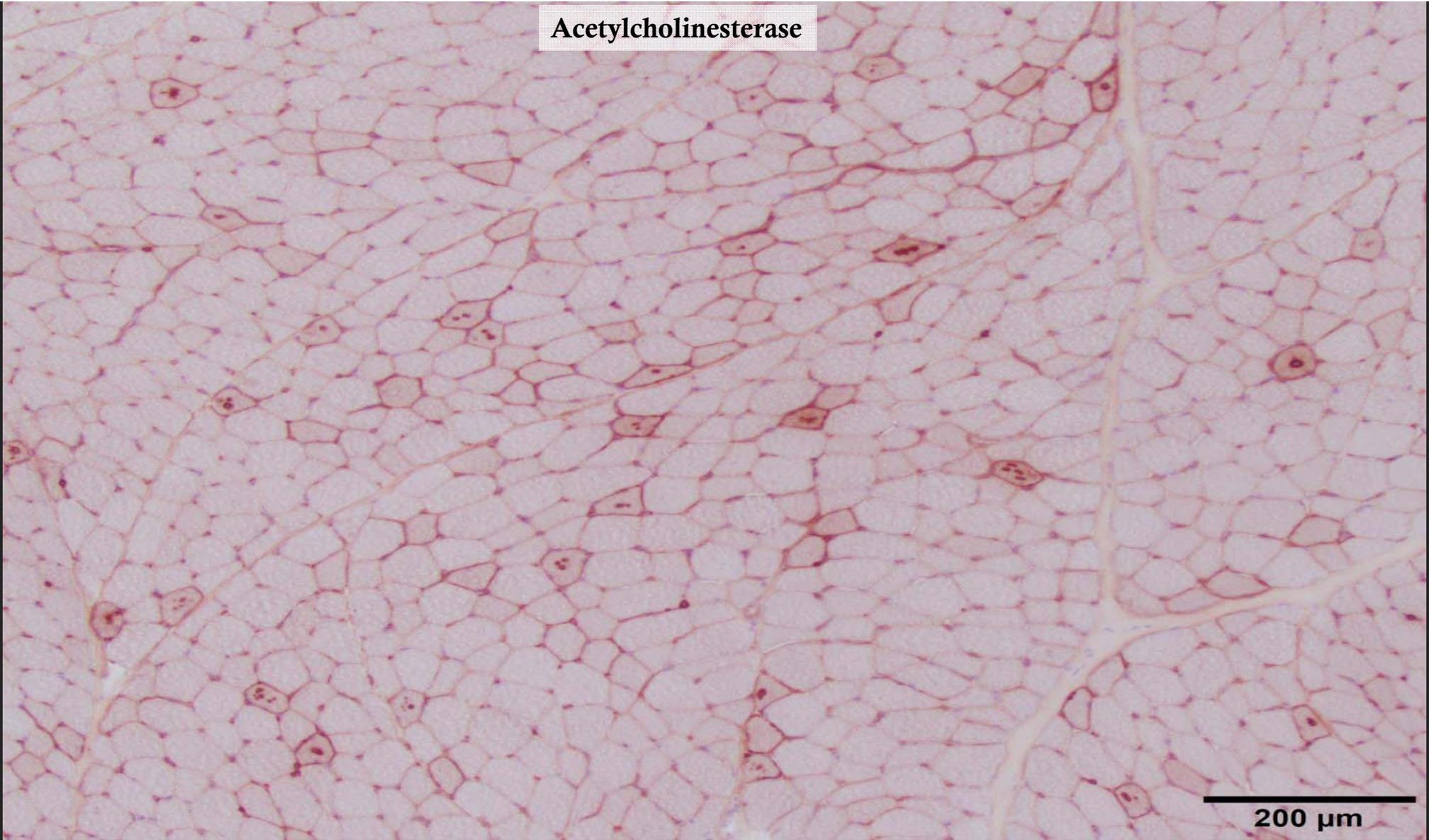
DAPI  
(nuclei)



GREEN: LAMP2  
BLUE: DAPI (nuclei)

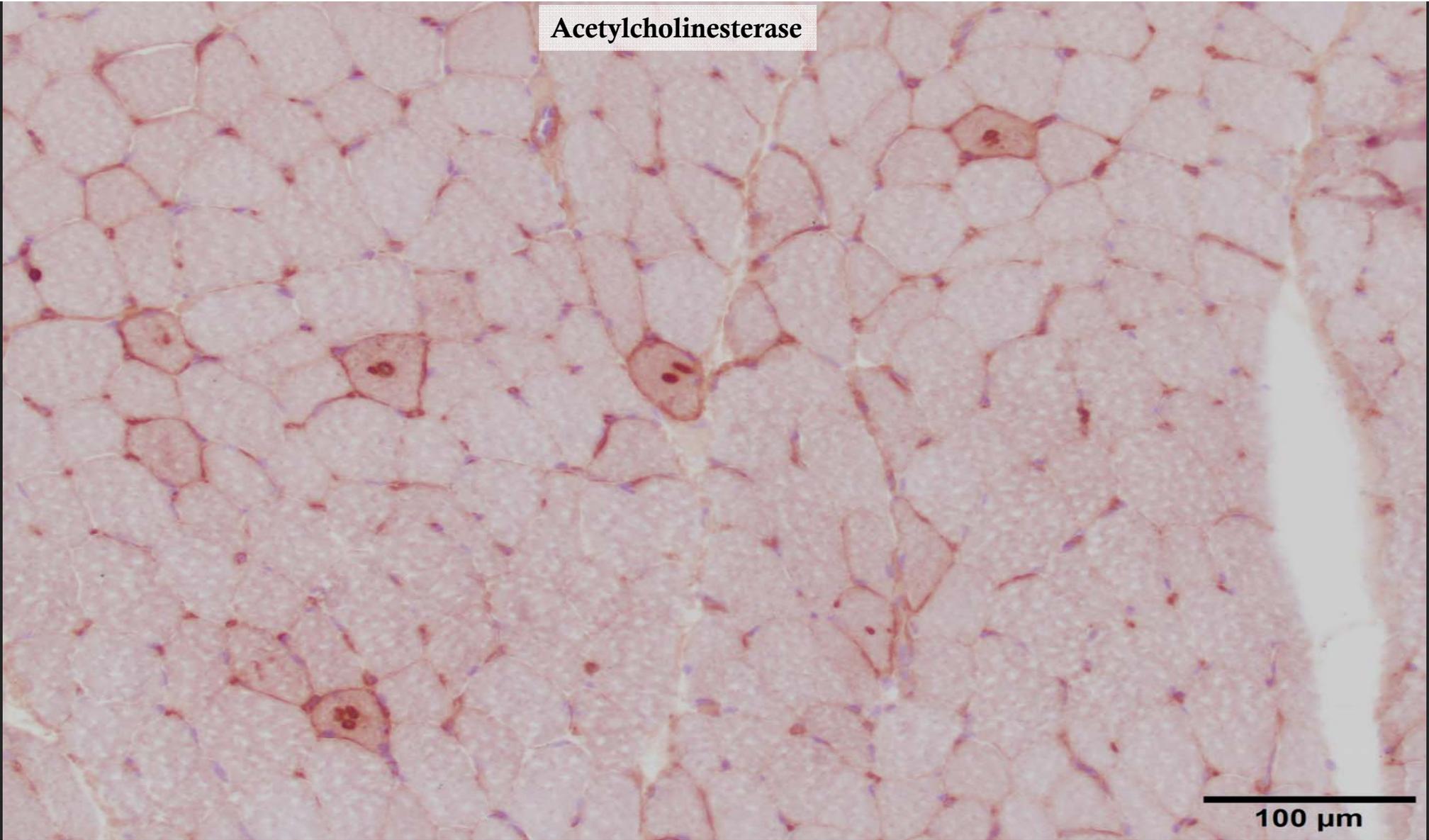


Acetylcholinesterase



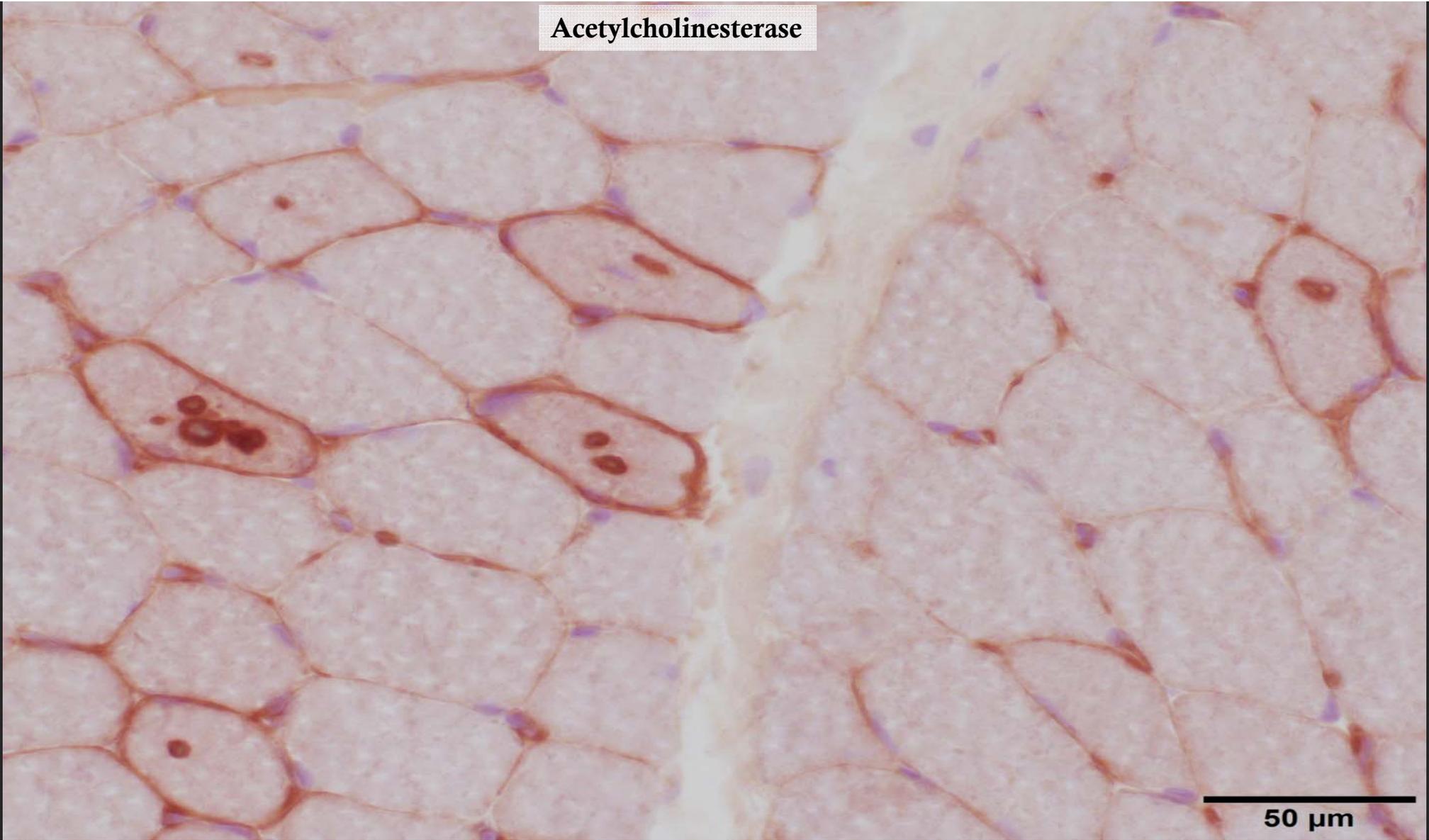
200 μm

Acetylcholinesterase



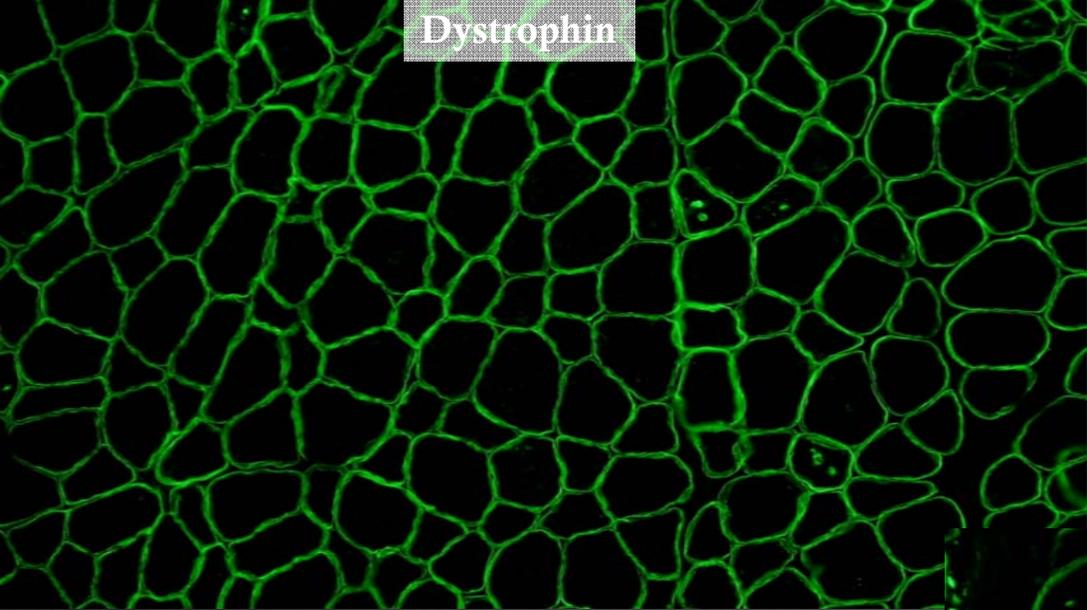
100  $\mu$ m

Acetylcholinesterase

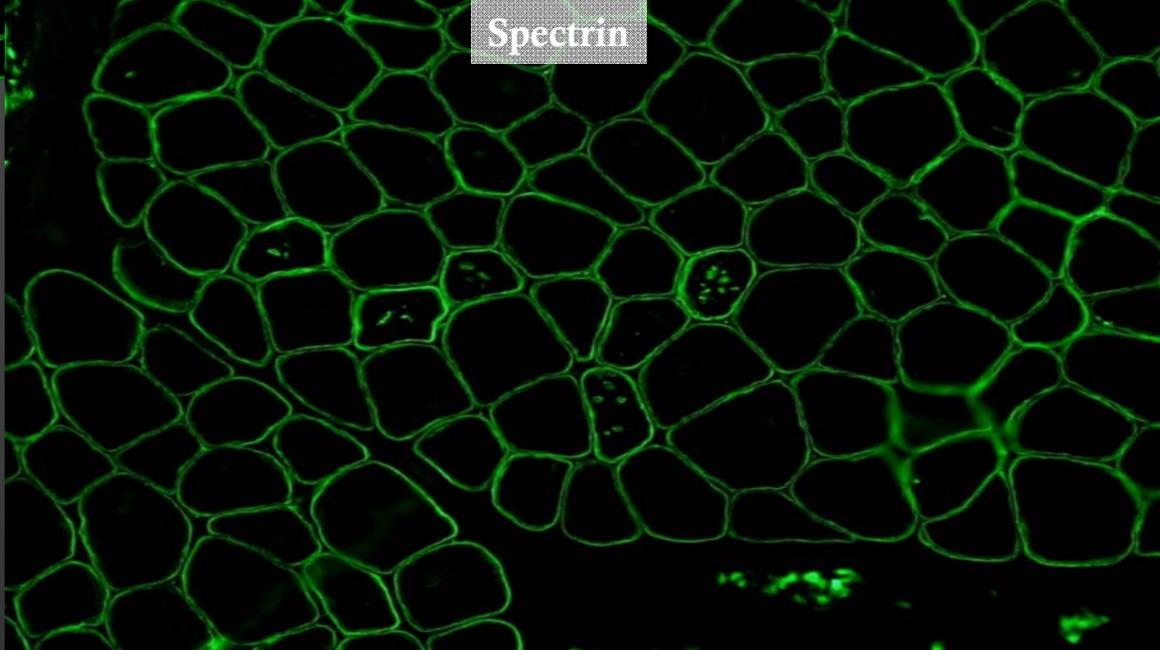


50  $\mu$ m

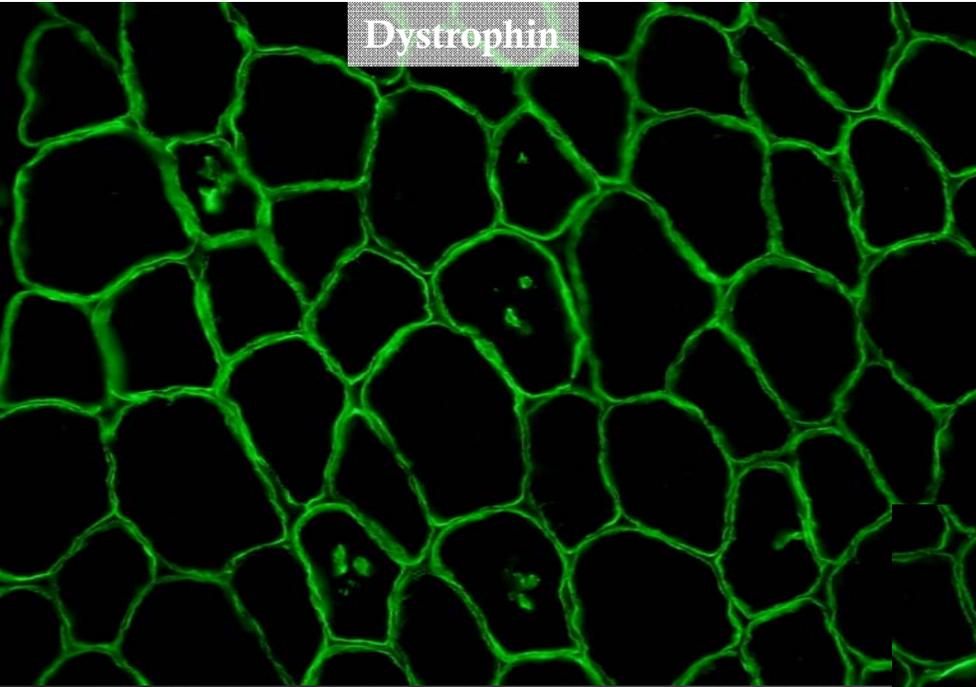
Dystrophin



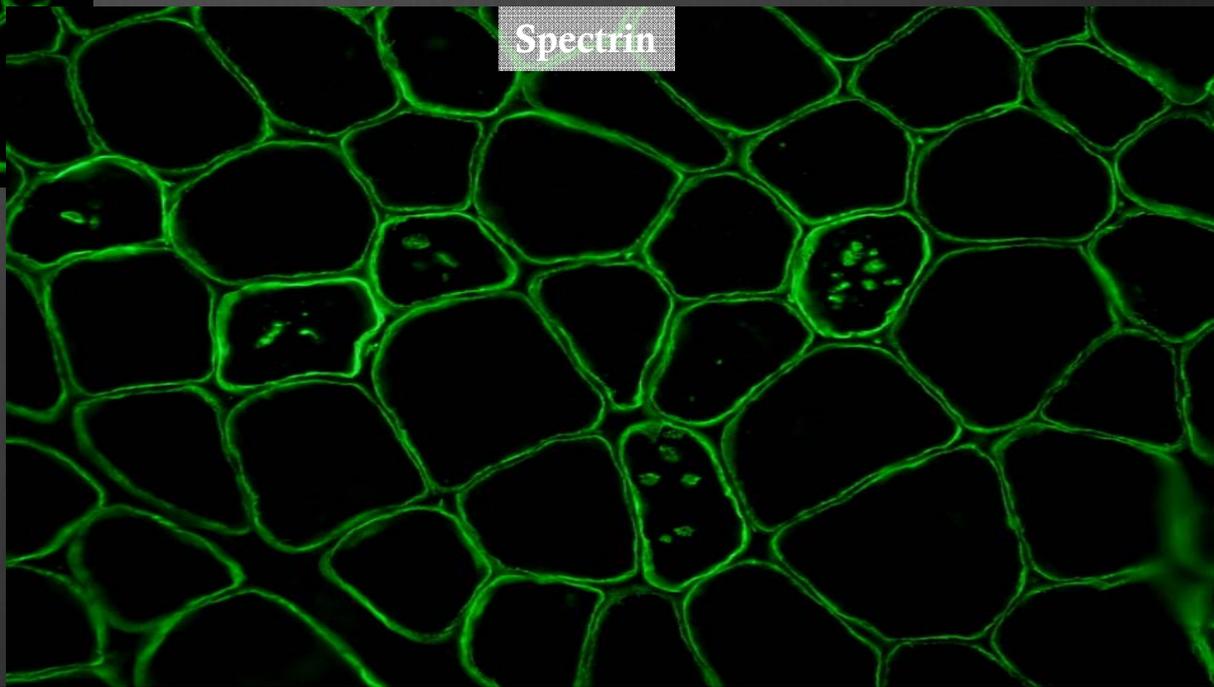
Spectrin



Dystrophin



Spectrin



# Danon disease

- ⊗ Danon disease (DD) is a rare X-linked dominant genetic disorder caused by mutations in the LAMP2 gene (Xq24).
- ⊗ In 1980, Moris Danon first described the disease.
- ⊗ Two frozen muscle specimens, from two patients were reviewed, which were remarkably similar both clinically and pathologically but normal activity of acid malatase.
- ⊗ “Lysosomal glycogen storage disease with normal acid maltase”

# History of Danon disease

- ⊗ **In 1993**, Di Mauro, Servidei, and Tsujino redefined this disorder as “Cardiomyopathy, mental retardation, and autophagic vacuolar myopathy”
- ⊗ **In 2000**, Nishino and coworkers sequenced a candidate gene on chromosome Xq24, *LAMP-2*, in ten unrelated patients with Danon disease, including one of the two boys.
- ⊗ They found pathogenic mutations in all 10 patients and documented lack of *LAMP-2* (lysosome-associated membrane protein 2) both by Western blot analysis and by immunohistochemistry.

# Danon Disease

- ⊗ A classic triad of **cardiomyopathy**, **skeletal myopathy**, and **intellectual disability**.
- ⊗ Males usually manifest at an earlier age of onset (average 12.1 years old) with more severe symptoms than females (average 27.9 years old)
- ⊗ Males invariably require heart transplantation.
- ⊗ The exact prevalence of DD is unknown and the majority of published summary data on Danon disease comes from two major case series.

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# Clinicopathological features of genetically confirmed Danon disease

K. Sugie, MD, PhD; A. Yamamoto, MD; K. Murayama, BS; S.J. Oh, MD; M. Takahashi, MD; M. Mora, MD; J.E. Riggs, MD; J. Colomer, MD; C. Iturriaga, MD; A. Meloni, MD; C. Lamperti, MD; S. Saitoh, MD, PhD; E. Byrne, MD, DSc; S. DiMauro, MD; I. Nonaka, MD, PhD; M. Hirano, MD; and I. Nishino, MD, PhD

Neurology 2002

- ⊗ The features of 20 affected men and 18 affected women in 13 families with genetically confirmed Danon disease were reviewed.
- ⊗ All patients had cardiomyopathy.
- ⊗ 18 of 20 male patients (90%) and 6 of 18 female patients (33%) had skeletal myopathy.
- ⊗ 14 of 20 male patients (70%) and one of 18 female patients (6%) had intellectual disability.
- ⊗ Men were affected before age 20 years whereas most affected women developed cardiomyopathy in adulthood.
- ⊗ Muscle histology revealed basophilic vacuoles that contain acid phosphatase-positive material within membranes that lack lysosome-associated membrane protein-2.

## Natural history of Danon disease

*Dana Boucek, BA, Jean Jirikowic, MS, and Matthew Taylor, MD, PhD*

Genet Med 2011

In 2011- reported 82 patients with Danon disease from 36 families, the largest series to date.

Men are hemizygous:

- ⊗ severely affected with cognitive disabilities (100%),
  - ⊗ hypertrophic cardiomyopathy (88%)
  - ⊗ muscle weakness (80%).
- 
- ⊗ high morbidity and were unlikely to reach the age of 25 years without a cardiac transplantation.

# Clinical Manifestation in Men vs. Women

Women are heterozygous:

- ⊗ Women less severely affected.
- ⊗ Women reported higher than expected levels of cognitive disabilities (47%)
- ⊗ Skeletal muscle complaints in women (50%)
- ⊗ Equal prevalence of dilated cardiomyopathy and hypertrophic cardiomyopathy.

# Age specific manifestation in Men vs. Women

First symptom:

- ⊗ 12.1 years in men
- ⊗ 27.9 years in women.

Cardiac transplantation

- ⊗ 17.9 years in men
- ⊗ 33.7 years in women.

Death

- ⊗ 19.0 years in men,
- ⊗ 34.6 years in women.

# Neurological and ophthalmologic manifestations

## Male

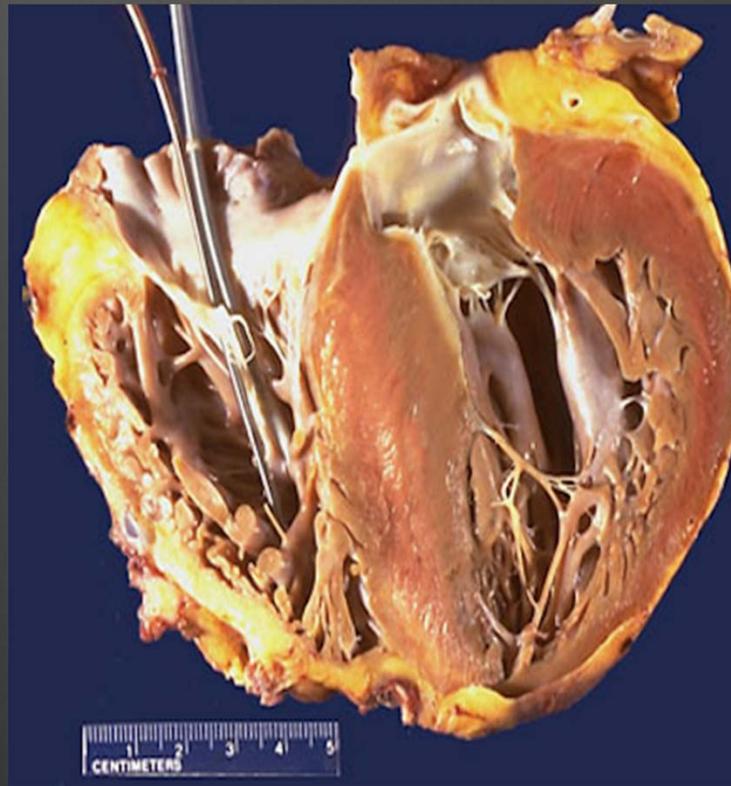
- ⊗ Proximal muscle weakness and neck muscle weakness.
- ⊗ Most have intellectual disability or learning disorder.
- ⊗ Decrease or loss of central and visual acuity.
- ⊗ Peripheral pigmentary retinopathy.

## Female

- ⊗ Mild or no proximal muscle weakness.
- ⊗ Typically no intellectual disability.
- ⊗ Peripheral pigmentary retinopathy.
- ⊗ Lamellar opacities in the lens.

# Cardiac manifestations

- ⊗ Palpitations or documented arrhythmias, syncope, chest pain or cardiac arrest.
- ⊗ Electrical conduction abnormalities are common. WPW pattern is the most common ECG abnormality.
- ⊗ Atrial and ventricular arrhythmias are typically present.



# Labs

- ⊗ Serum CK levels are elevated two-three fold, even if clinical myopathy is mild.
- ⊗ Liver enzymes may be persistently elevated in absence of liver dysfunction.
- ⊗ AST, ALT, LDH, Aldolase tend to be elevated in one half of the patients.

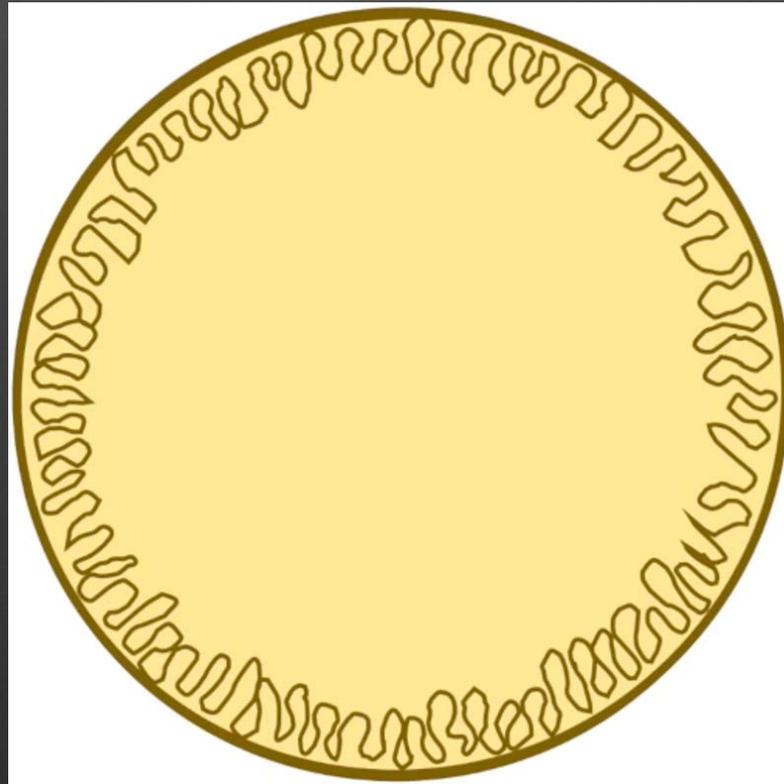
# Imaging

- ⊗ MRI brain: but is often normal.
- ⊗ Echocardiogram and EKGs – signs of hypertrophic cardiomyopathy
- ⊗ Cardiac MRI can be performed to assess hypertrophy

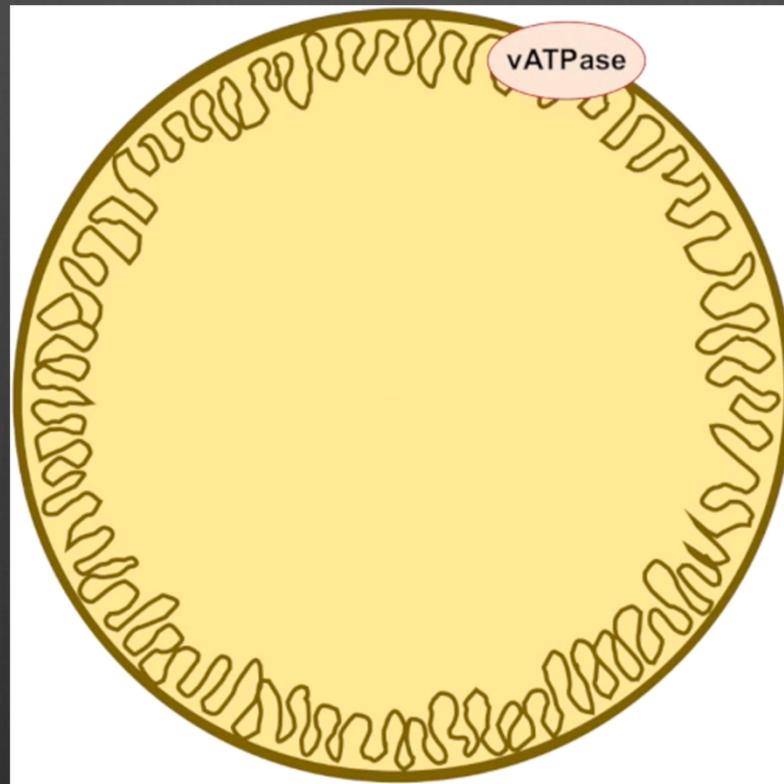
# Genetic Diagnosis

- ⊗ X-linked dominant trait.
- ⊗ pathogenic variants in the *LAMP2* gene (“lysosome-associated membrane protein-2”).
- ⊗ Patients with VUS can be further evaluated based on LAMP2 staining on muscle biopsy

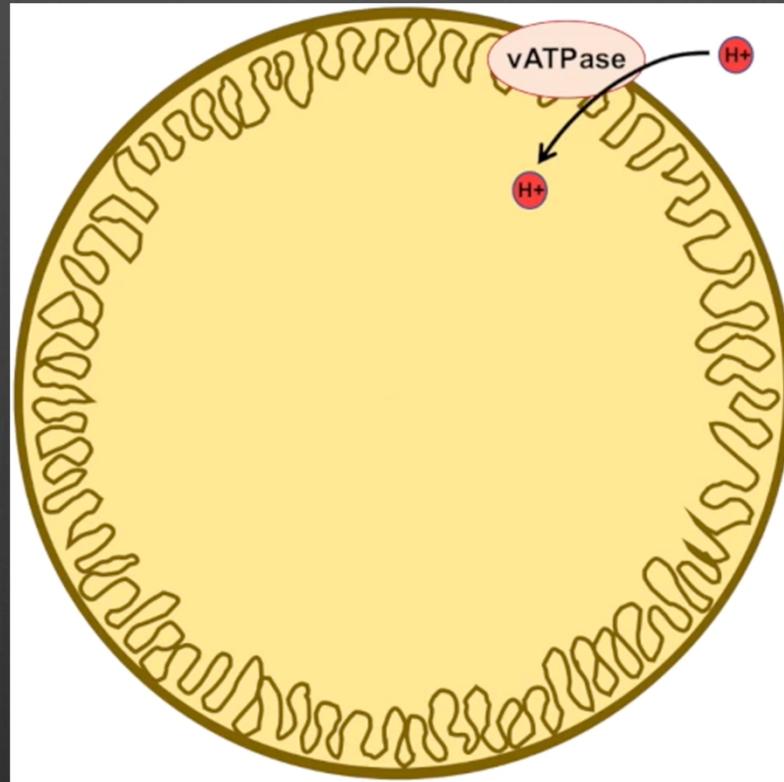
- ⊗ Mutation in LAMP2 gene lead to splicing defects or protein truncation, resulting in a loss of transmembrane protien LAMP-2, impairing the macroatuphagy in the lysosomes.



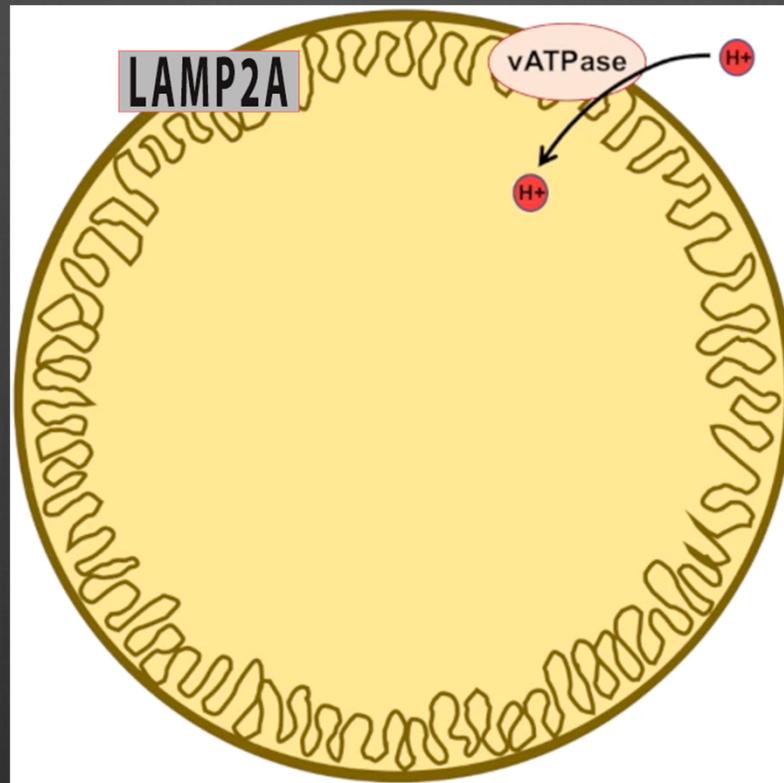
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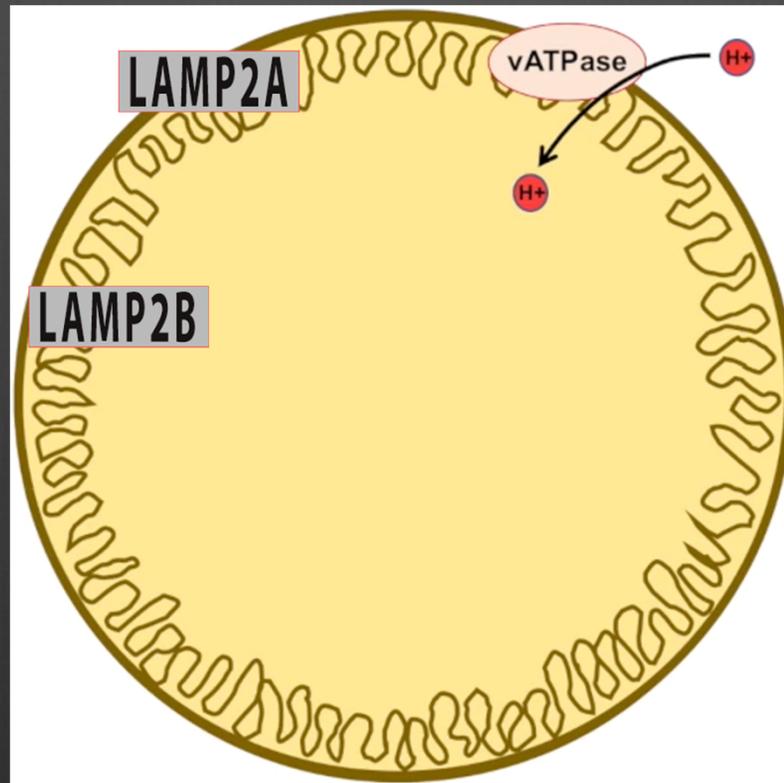
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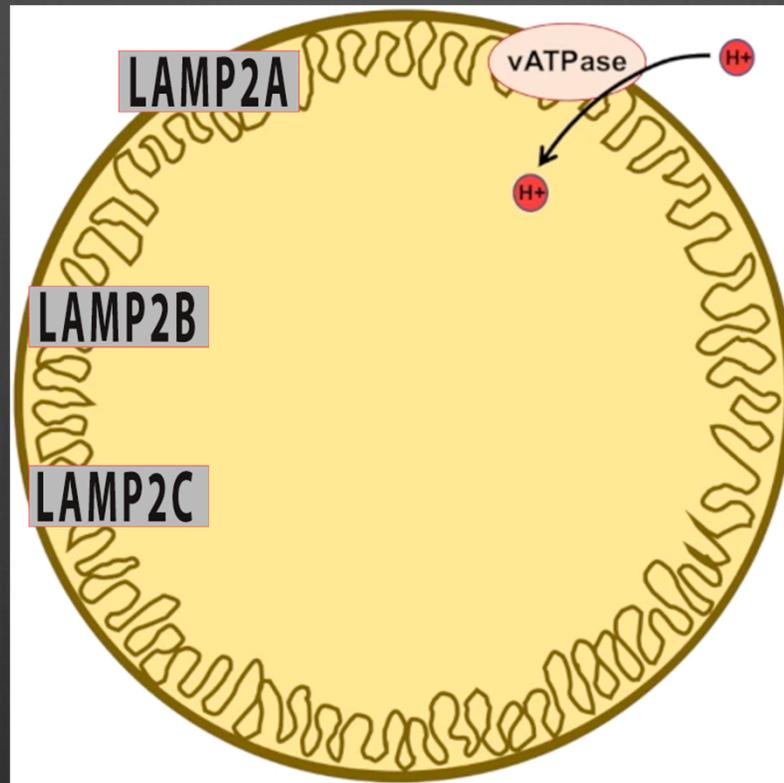
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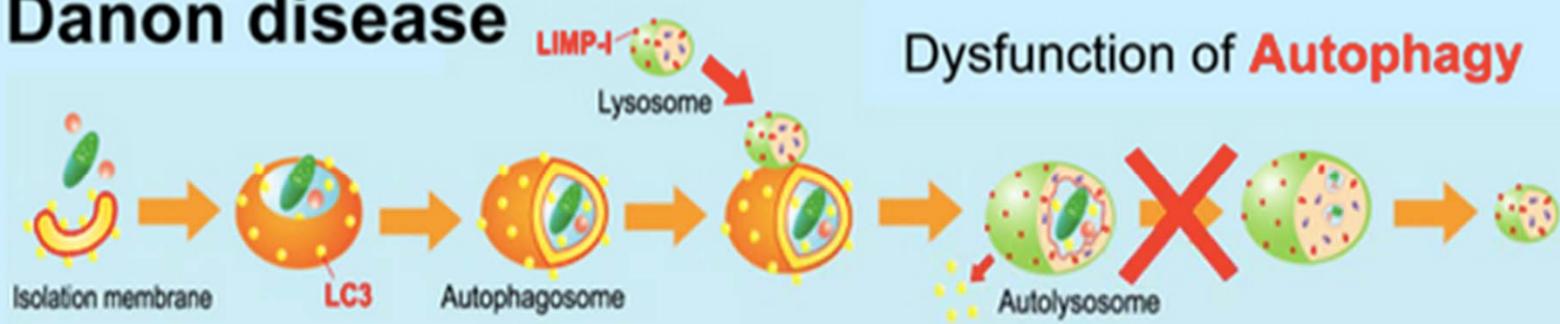
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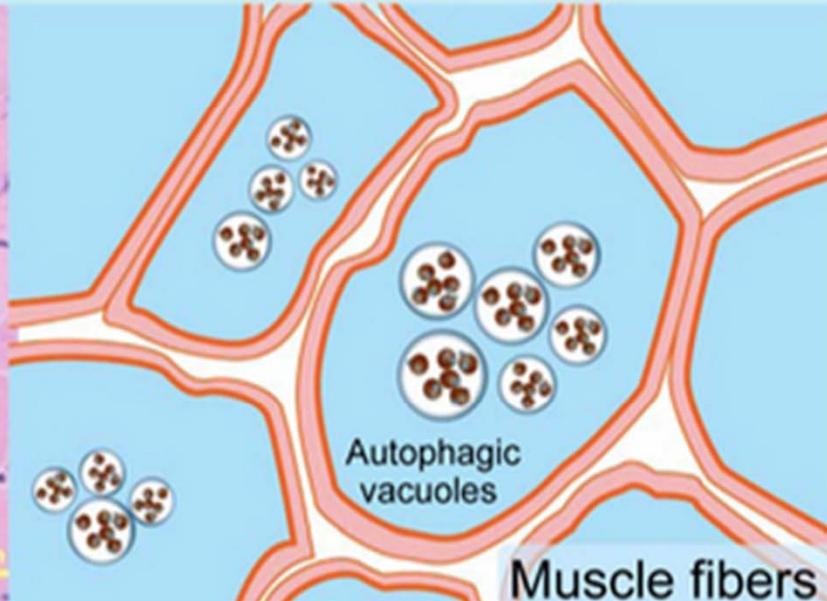
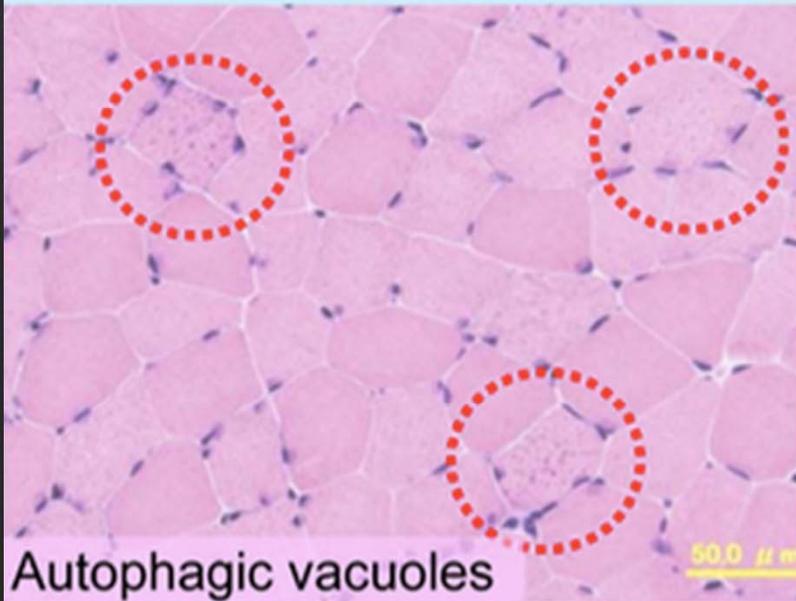
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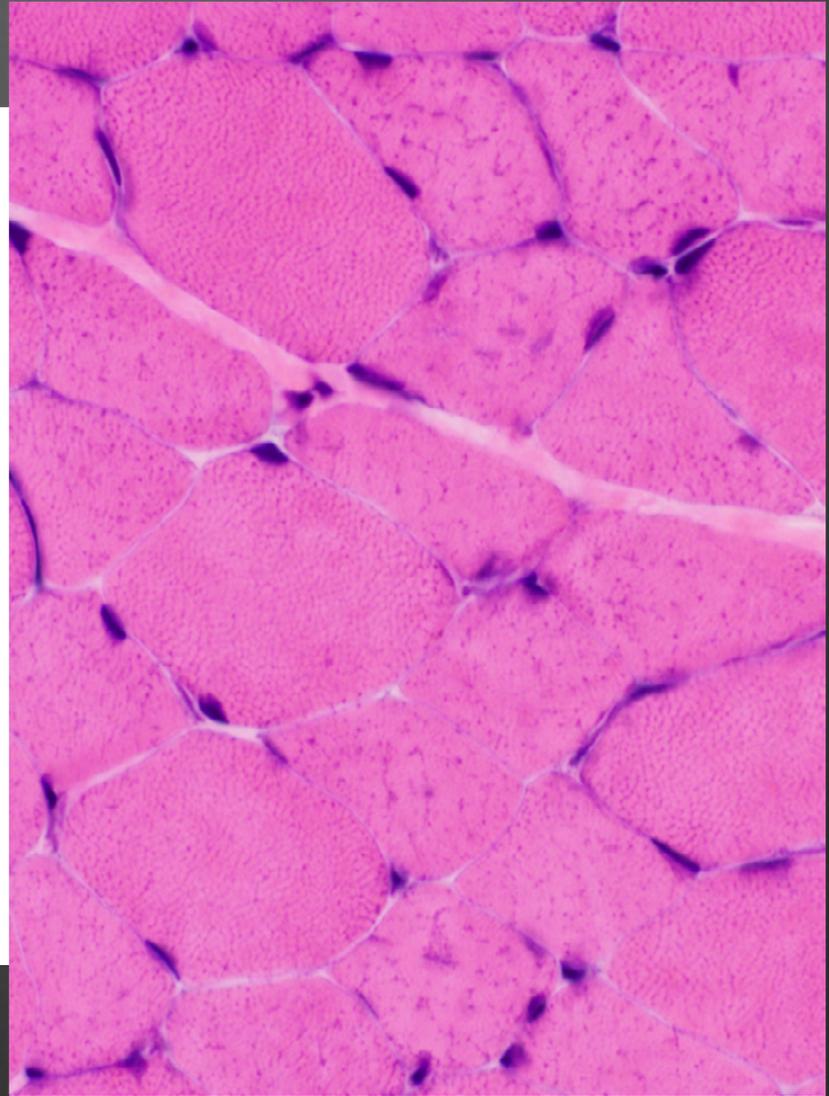
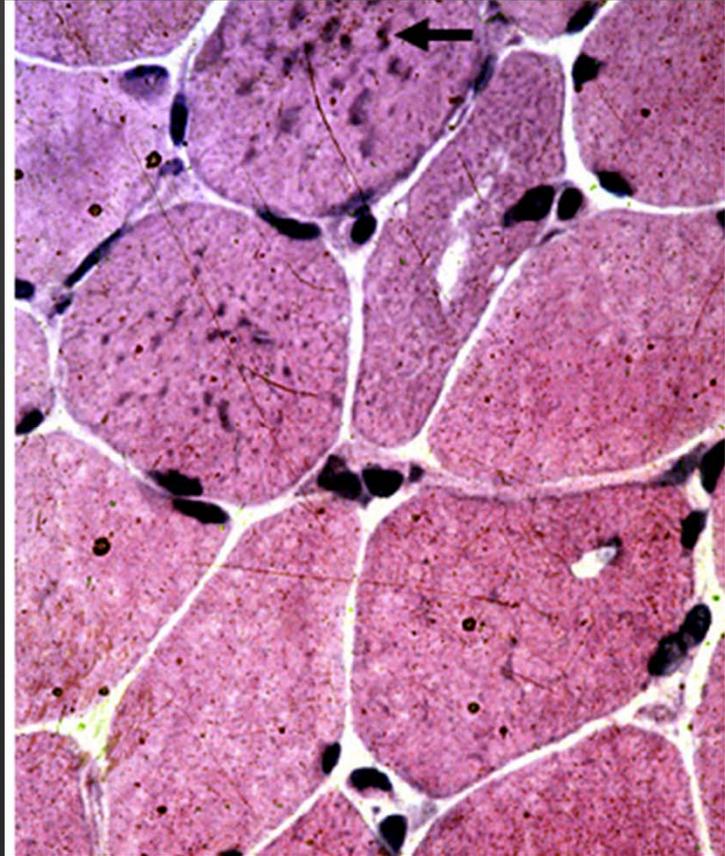


# Danon disease

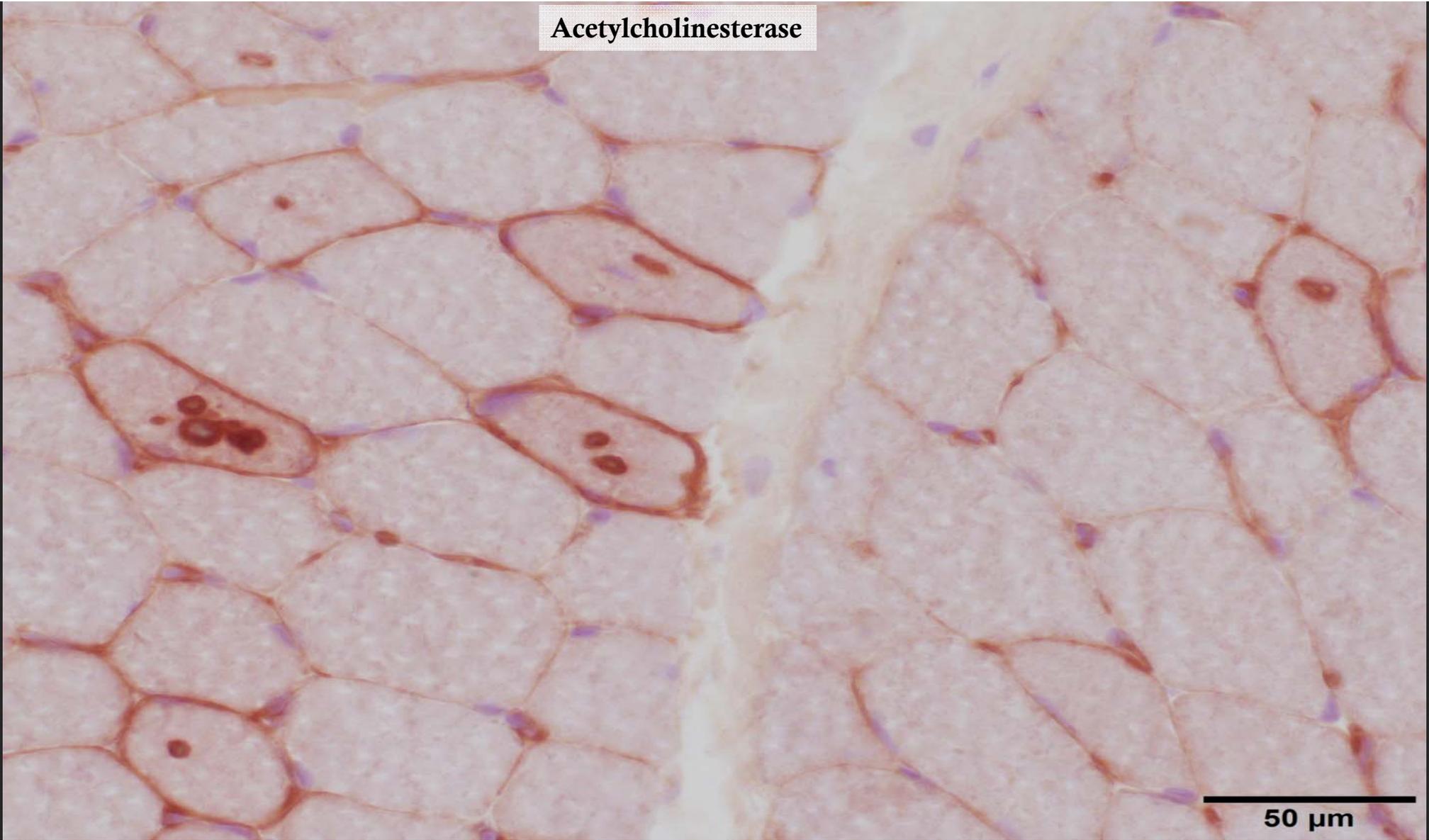


Dysfunction of **Autophagy**



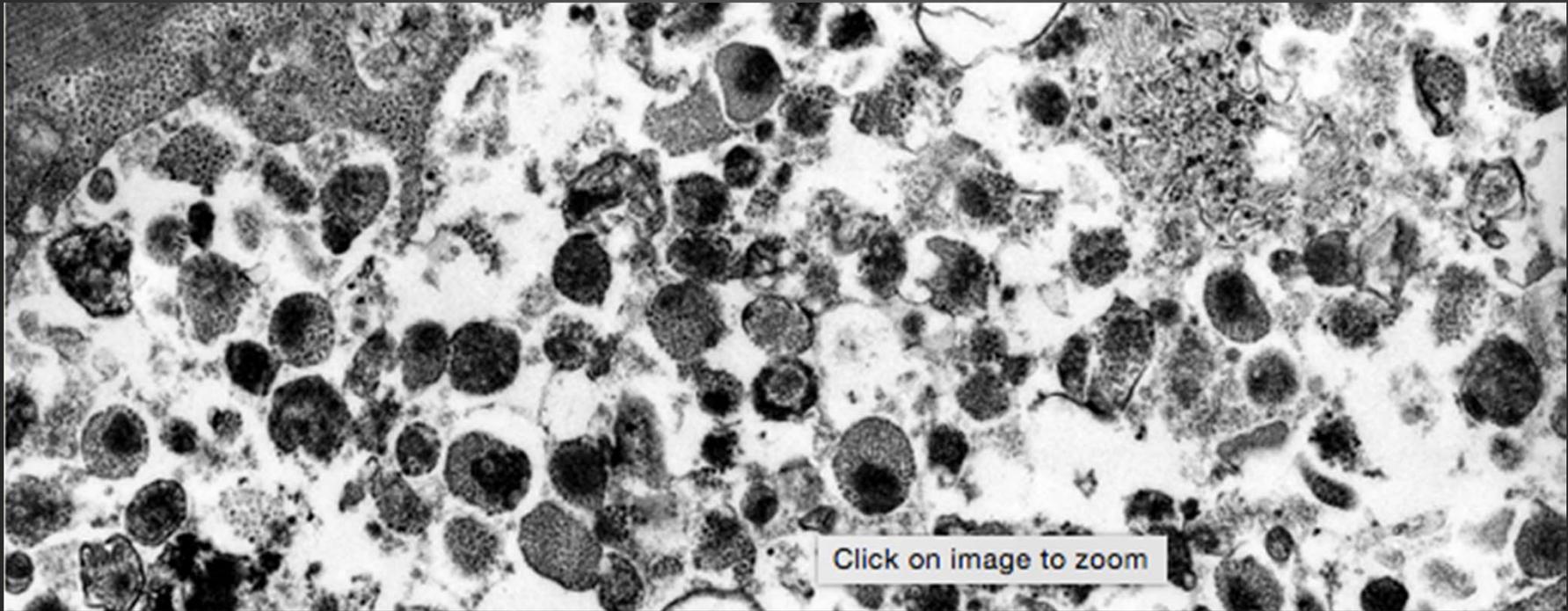


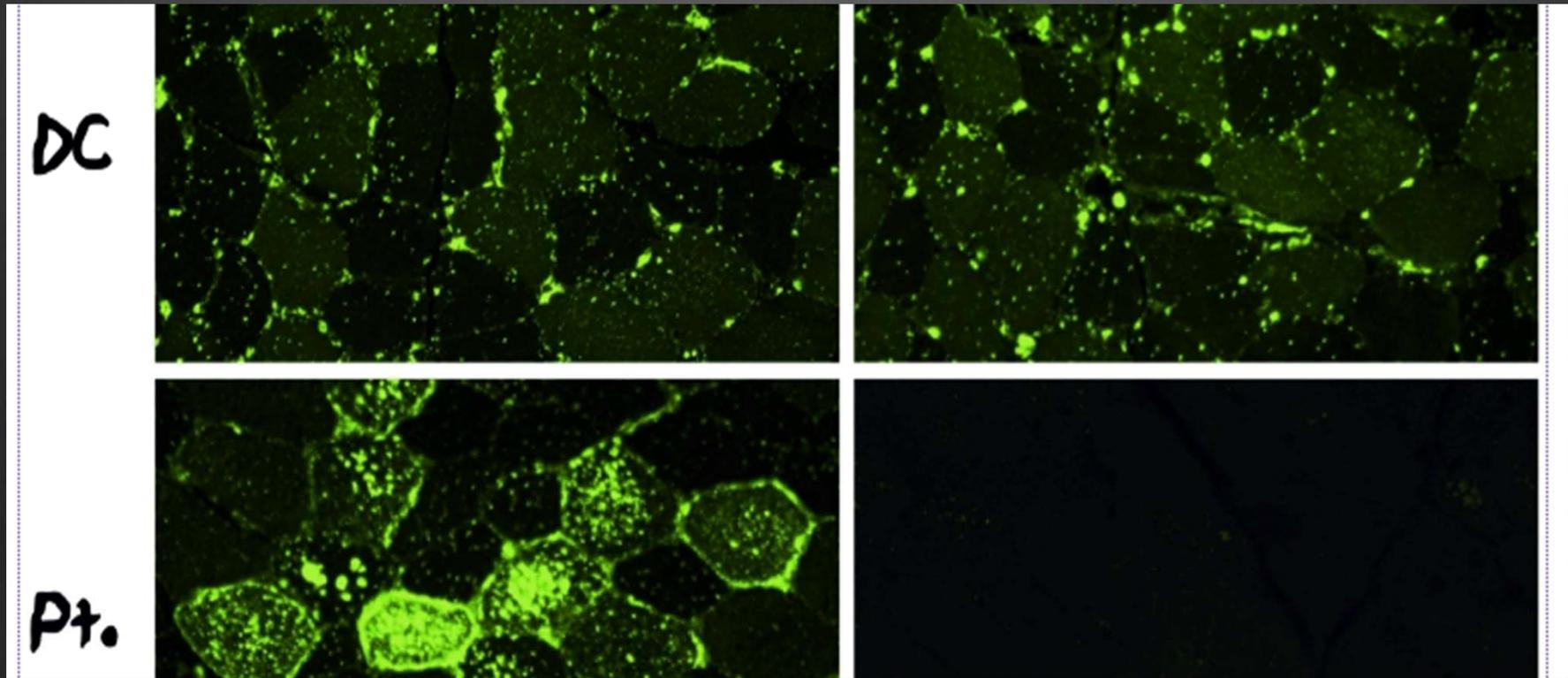
Acetylcholinesterase



50  $\mu$ m

# Electron Microscopy





Immunoreaction with antibodies to LIMP-1 (left panel) immunoreaction with antibodies to *LAMP-2* (right panel) is completely lacking in the patient's muscle.

# Prognosis

- ⊗ The prognosis for male patients is poor. The severity of cardiomyopathy is the major prognostic factor.
- ⊗ Most males require a heart transplant during the second to third decade of life.
- ⊗ In contrast, females may develop either DCM (28%) or HCM (33%) and cardiac transplantation in females typically occurs much later in life.
- ⊗ SCD, likely due to a ventricular arrhythmia, is the major cause of death.

# Management

## Education

- ⊗ Avoid strenuous exercise.
- ⊗ Limit caffeine in case of tachyarrhythmia.
- ⊗ Genetic counseling.
- ⊗ The timely identification of de-novo LAMP2 mutated family members, many of whom are heterozygous females, remains critical for their treatment and family counseling.

# Treatment options

- ⊗ Implantable Cardioverter Defibrillator (ICD)
- ⊗ Heart transplantation.
- ⊗ Medications: Diuretics, beta-blockers, ACE inhibitors

*“Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows tracings of her workings apart from the beaten paths; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by careful investigation of cases of rarer forms of disease”.*

*~ William Harvey, M.D.*

# References

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