Pompe disease and its differential diagnosis

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  - Sanofi
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  - Horizon Therapeutics
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  - Ministry of Health, Labor and Welfare
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Pompe disease (GSD II)

- **Acid α-glucosidase (acid maltase) deficiency**
- ***GAA* gene mutations**
  - Autosomal recessive
  - 17q25.3
  - 754 disease-causing mutations (HGMD 2023.3)
- **Enzyme replacement therapy**
  - **Alglucosidase alfa**
    recombinant human GAA
  - **Avalglucosidase alfa**
    M6P-conjugated rhGAA
  - Cipaglucosidase alfa + miglustat
    M6P-conjugated rhGAA + chaperone

Joannes C. Pompe
1901-1945

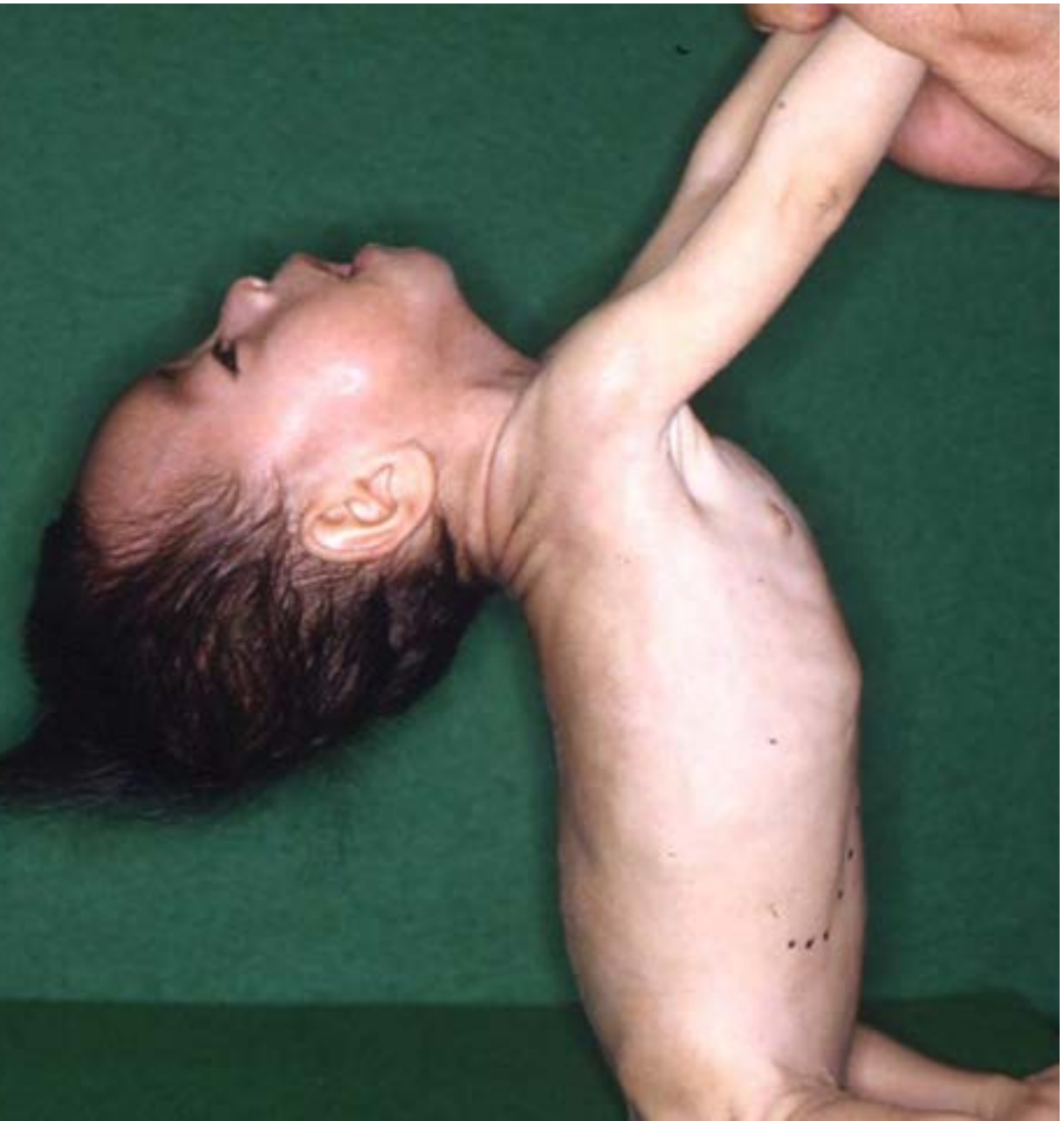
Picture from
Muscle Nerve. 2012 Jul;46(1):134-8

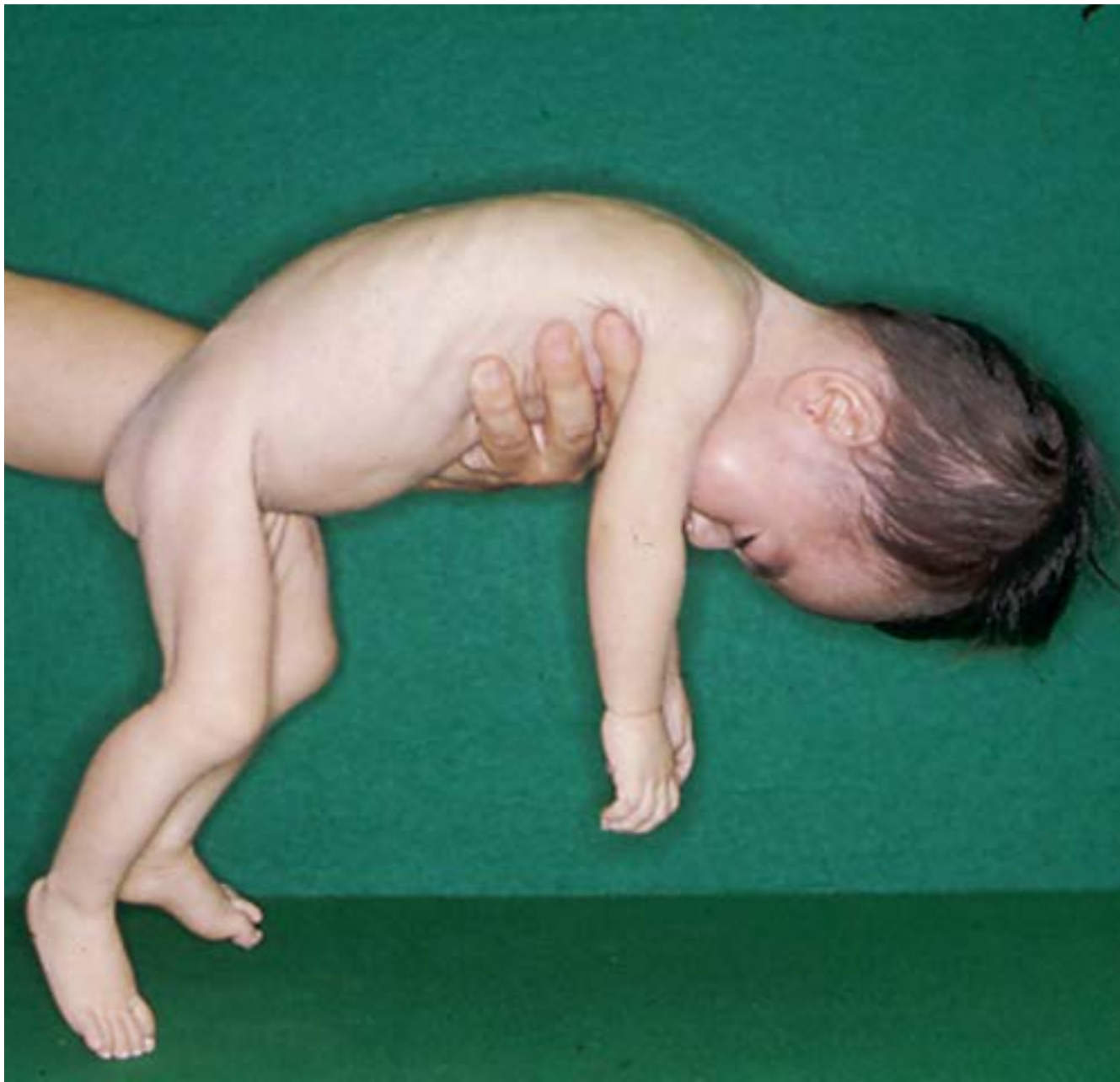
Clinical features of Pompe disease

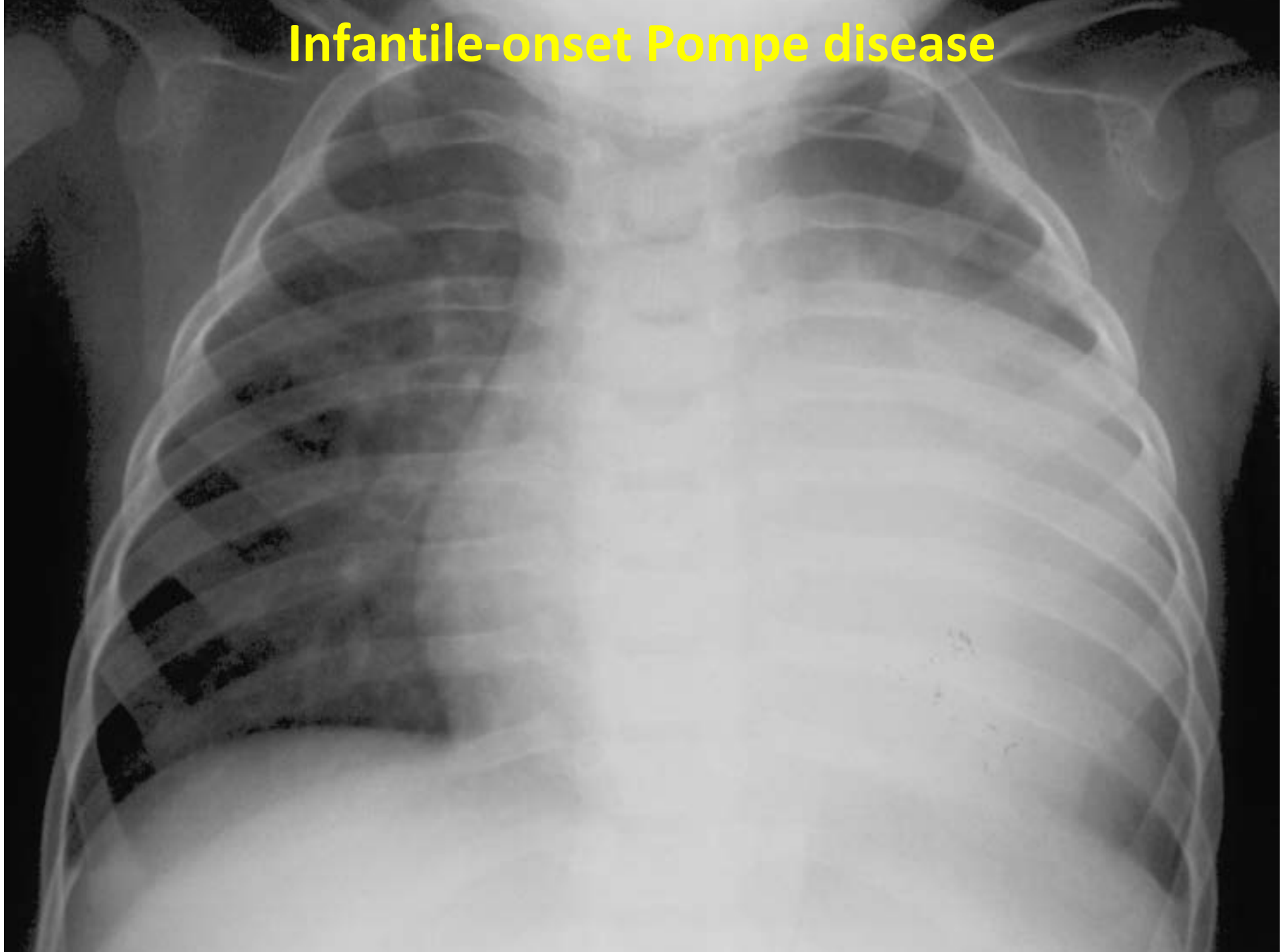
	Onset	Symptoms	Major cause of death
Infantile-onset (IOPD)	- 6m	Hypertrophic CM Hypotonia	Cardiac failure Respiratory failure
Late-onset (LOPD)	6m - Childhood	Proximal m. weakness	Respiratory failure
	Adulthood	Proximal m. weakness	Respiratory failure

Modified from Tsujino S. Glycogenosis II. Pediatric Medicine (小児内科) 2003

Infantile-onset Pompe disease






Infantile-onset Pompe disease

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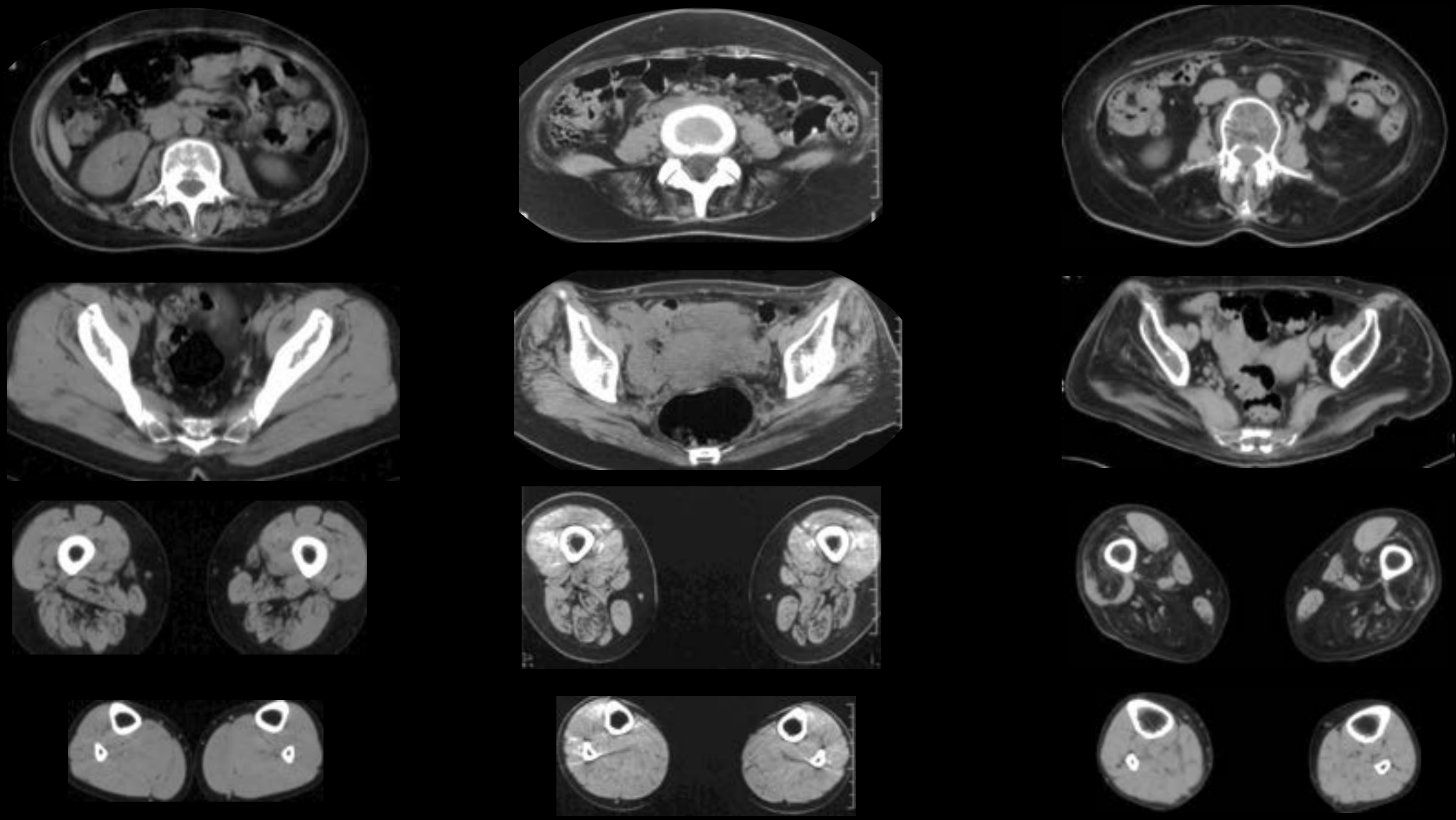
Modified from Tsujino S. Glycogenosis II. Pediatric Medicine (小児内科) 2003

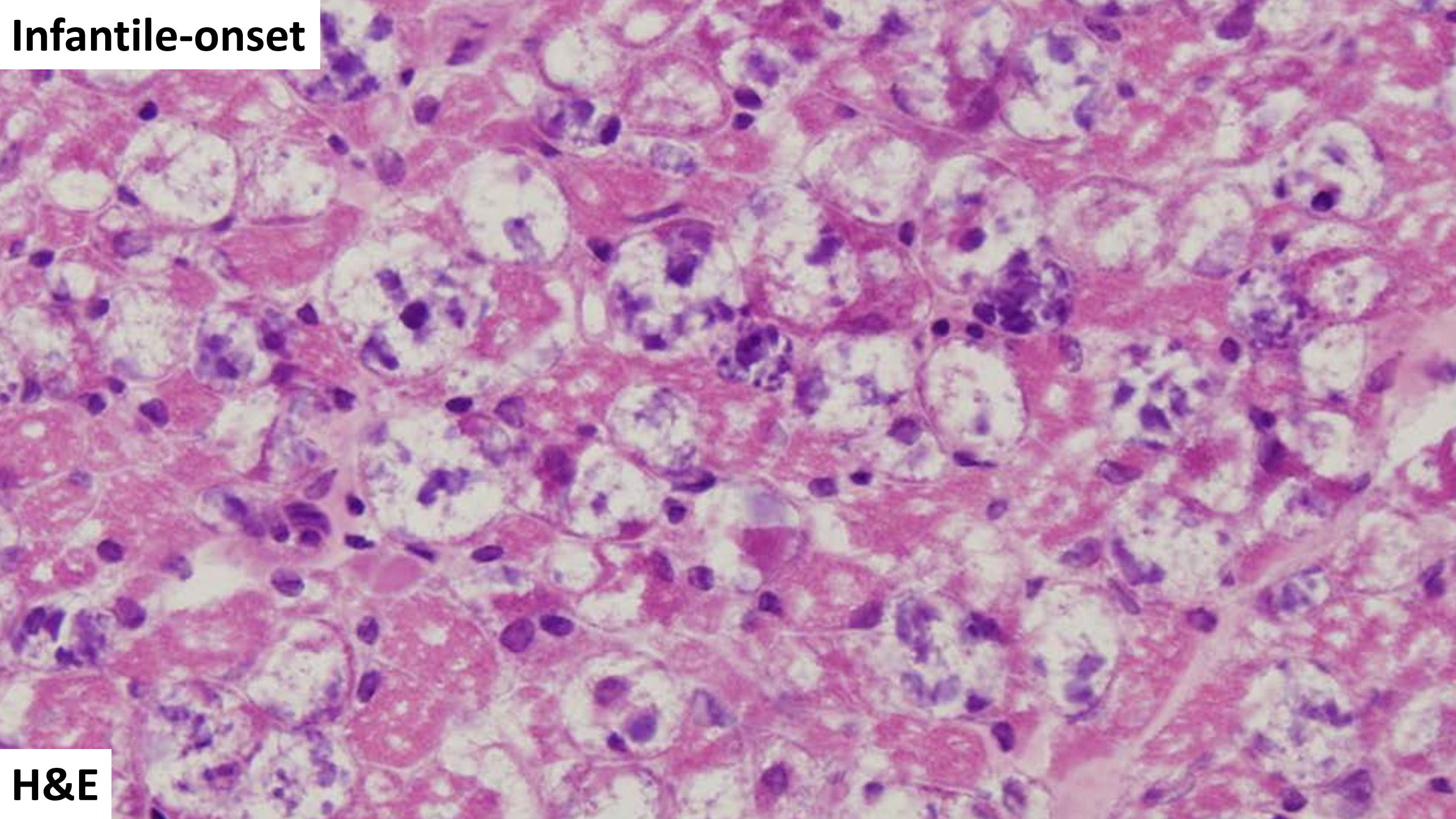
Progressive proximal muscle loss in LOPD

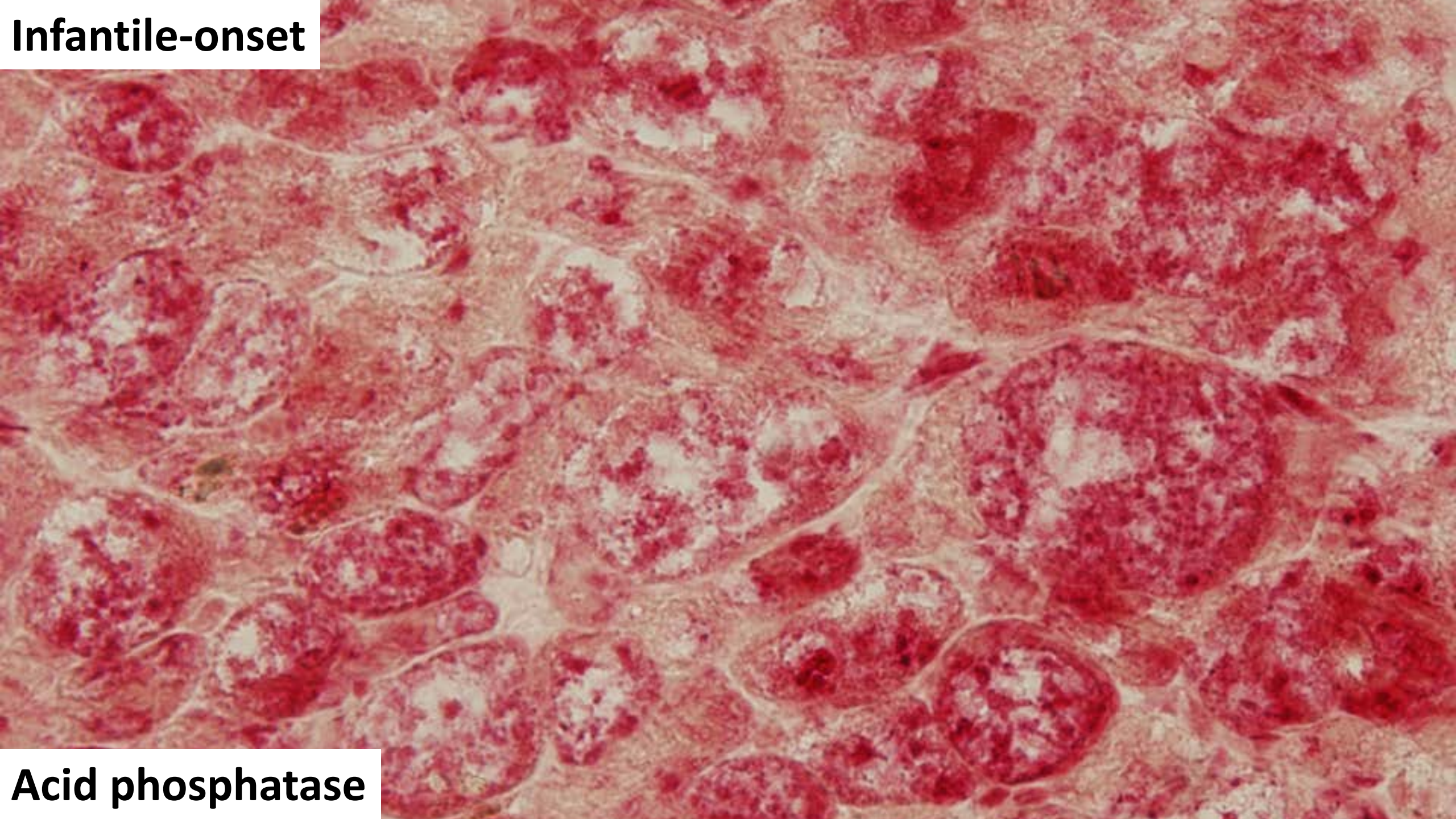


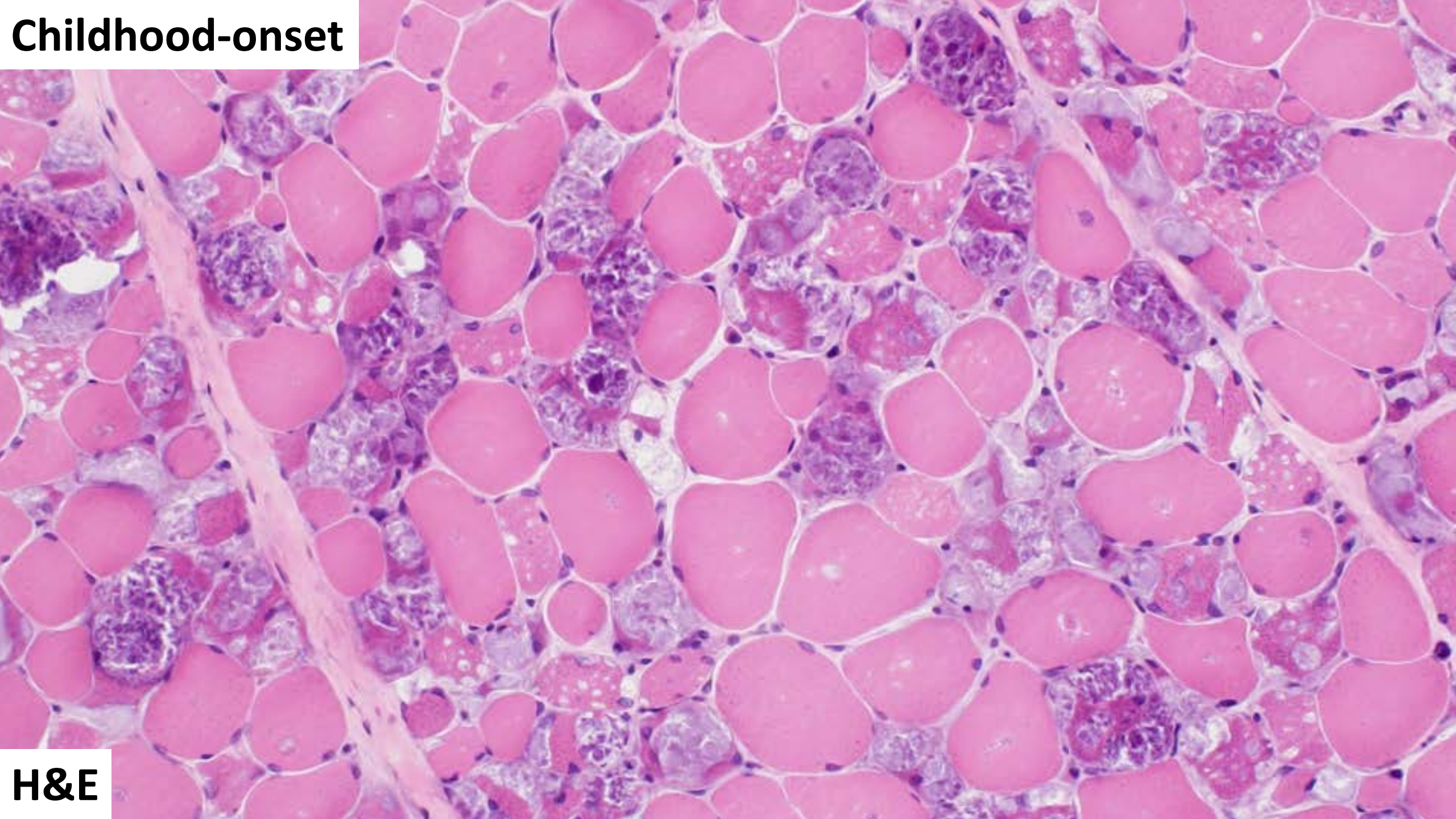
CT

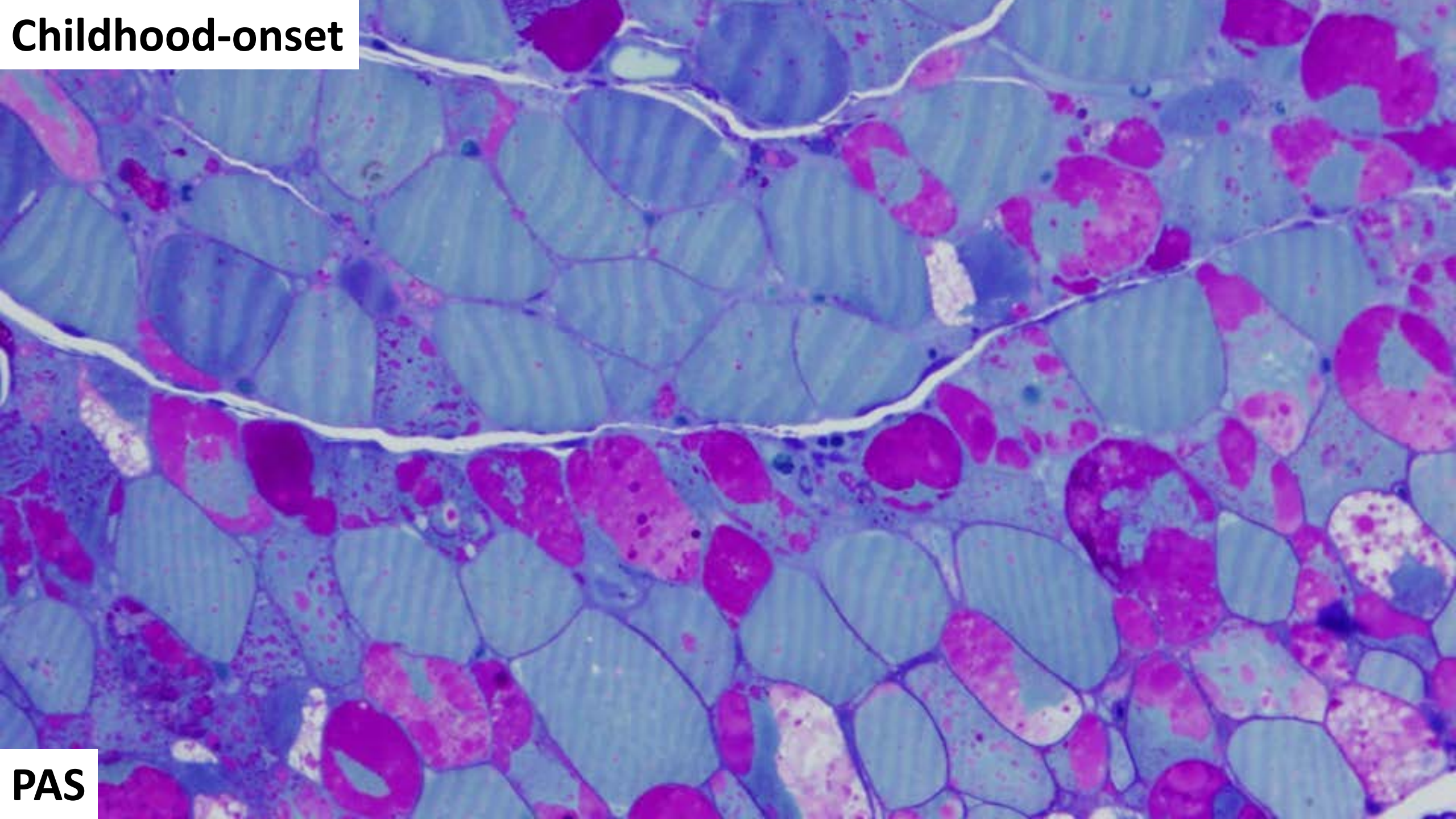
Courtesy
Dr. Madoka Mori, NCNP Hospital

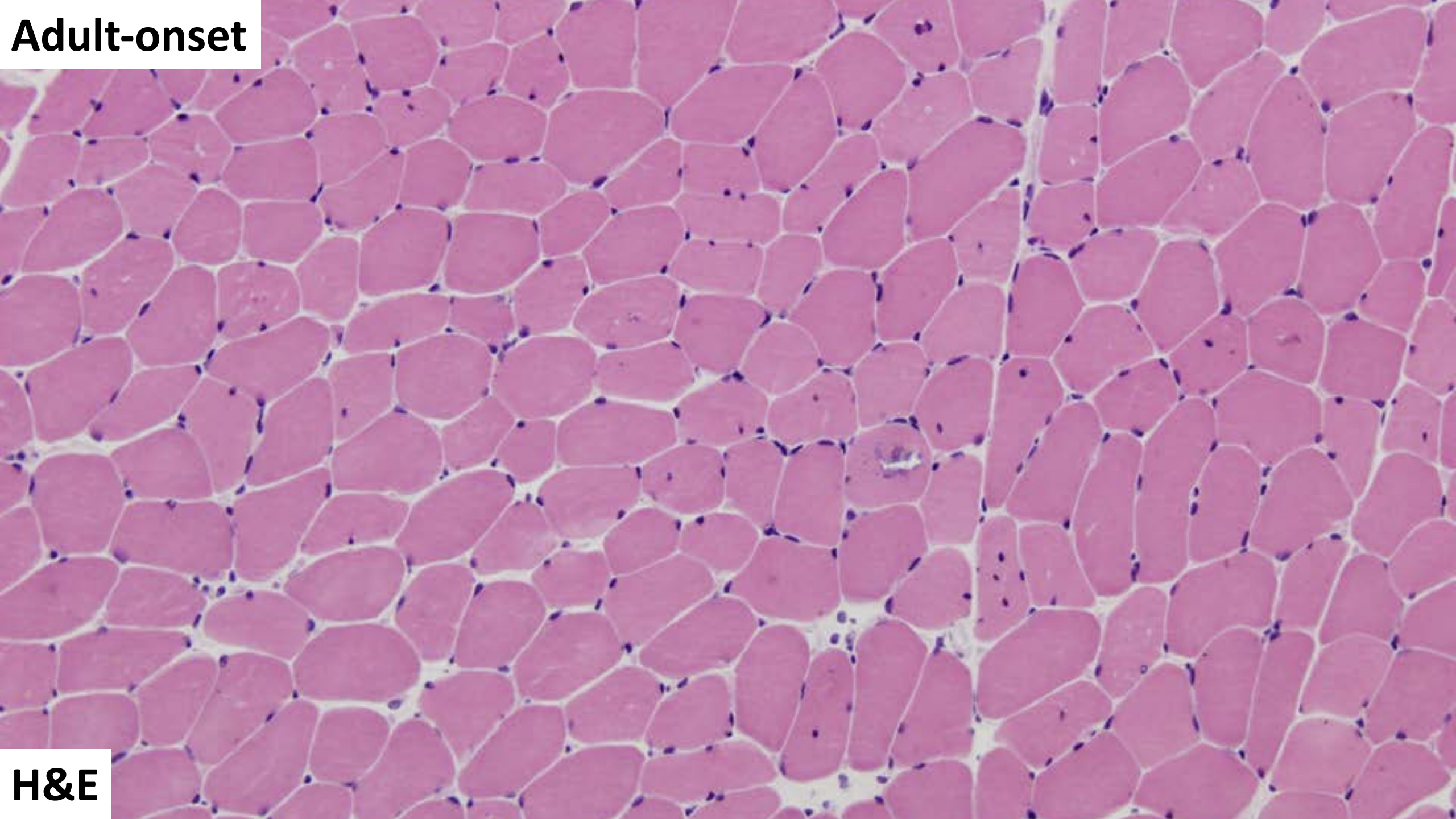
Muscle pathology


Infantile-onset
H&E


Infantile-onset
Acid phosphatase


Childhood-onset
H&E


Childhood-onset
PAS


Adult-onset
H&E

Enzyme replacement therapy

Early diagnosis!

Screening for Pompe disease

- Proximal weakness
- High CK
- Nonspecific MBx

→ **Dried blood spot test**

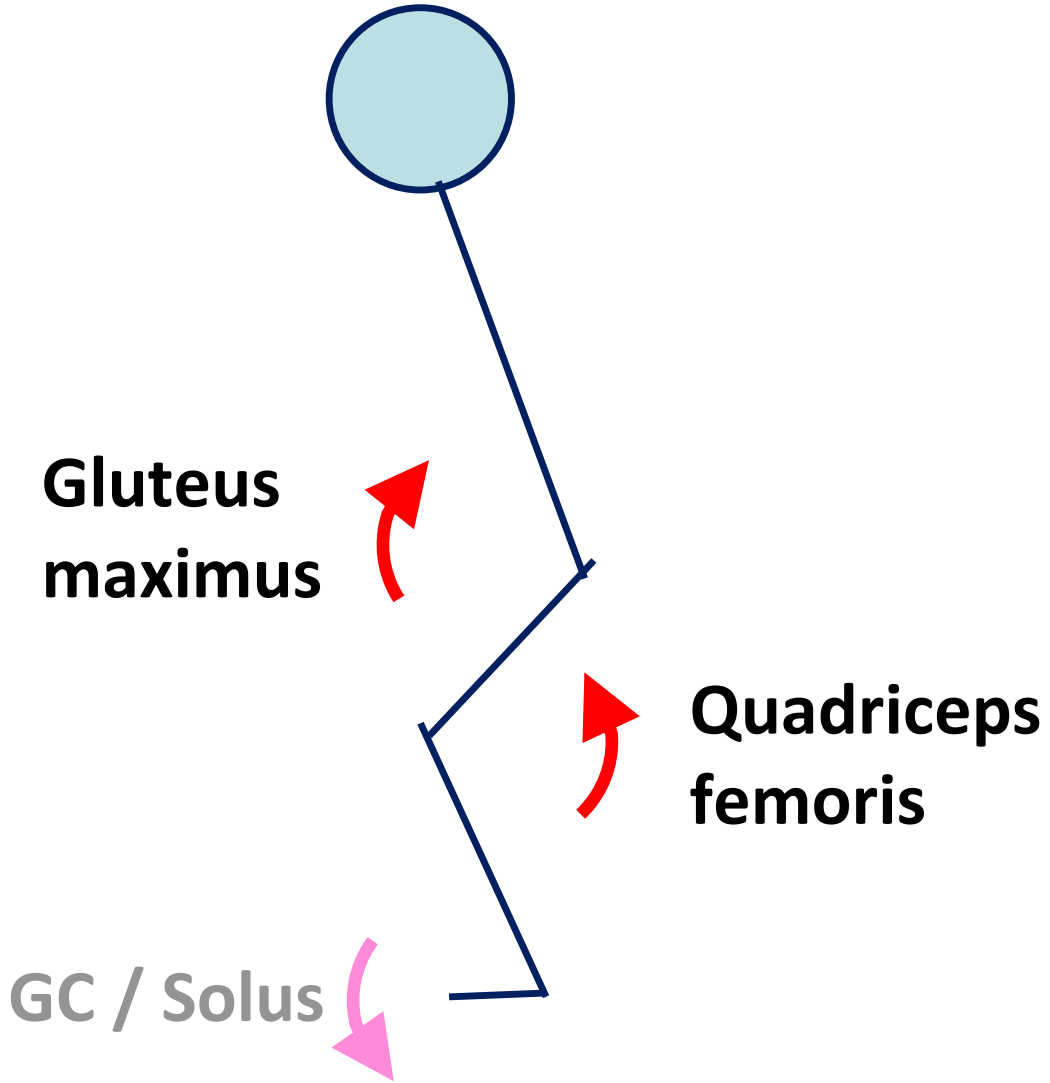
Clinicopathological findings of LOPD

Truly nonspecific?

Proximal weakness

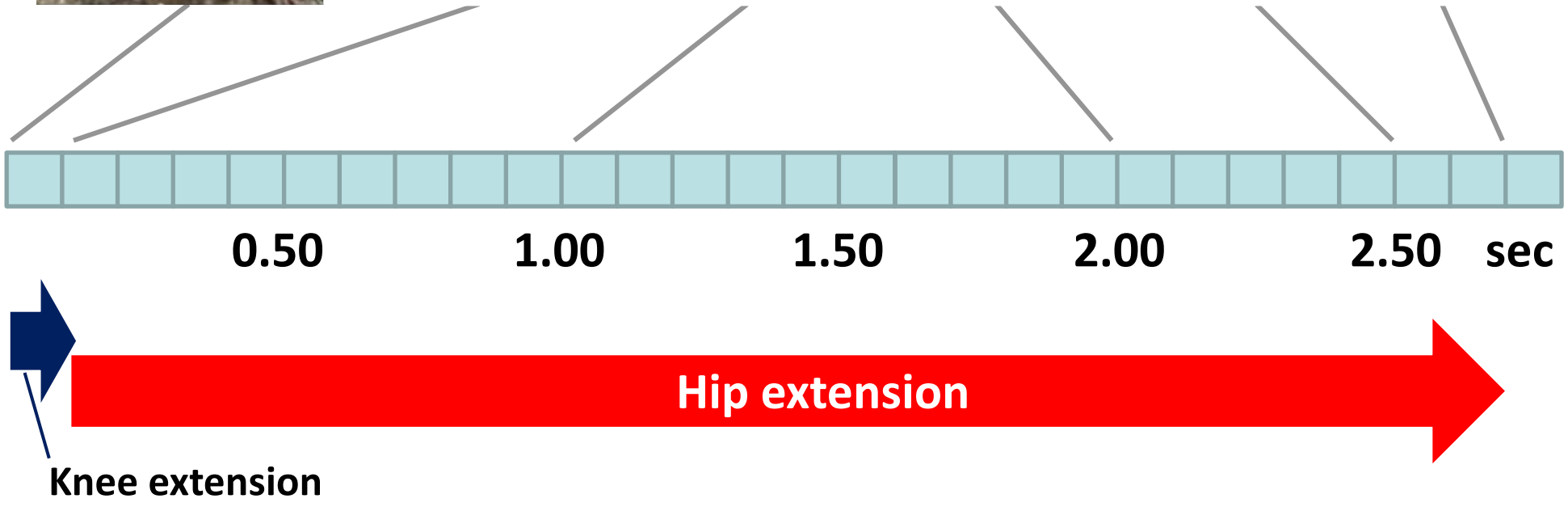

Which muscle is most severely affected?
Consent given for video presentation
2y4m M, DMD

Muscles used for standing up



Gowers sign in early DMD

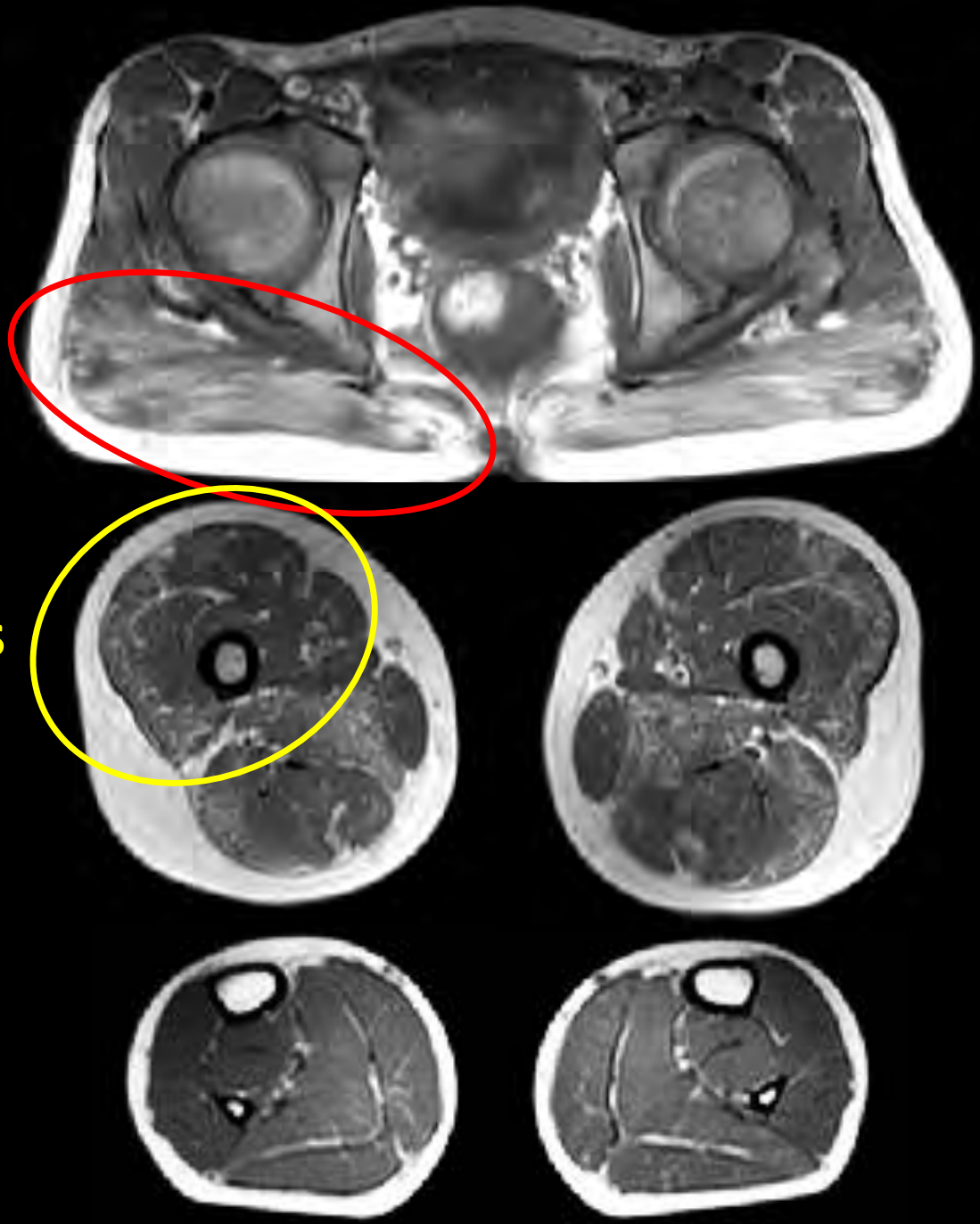
= Difficulty extending hip joint



Consent given for video presentation

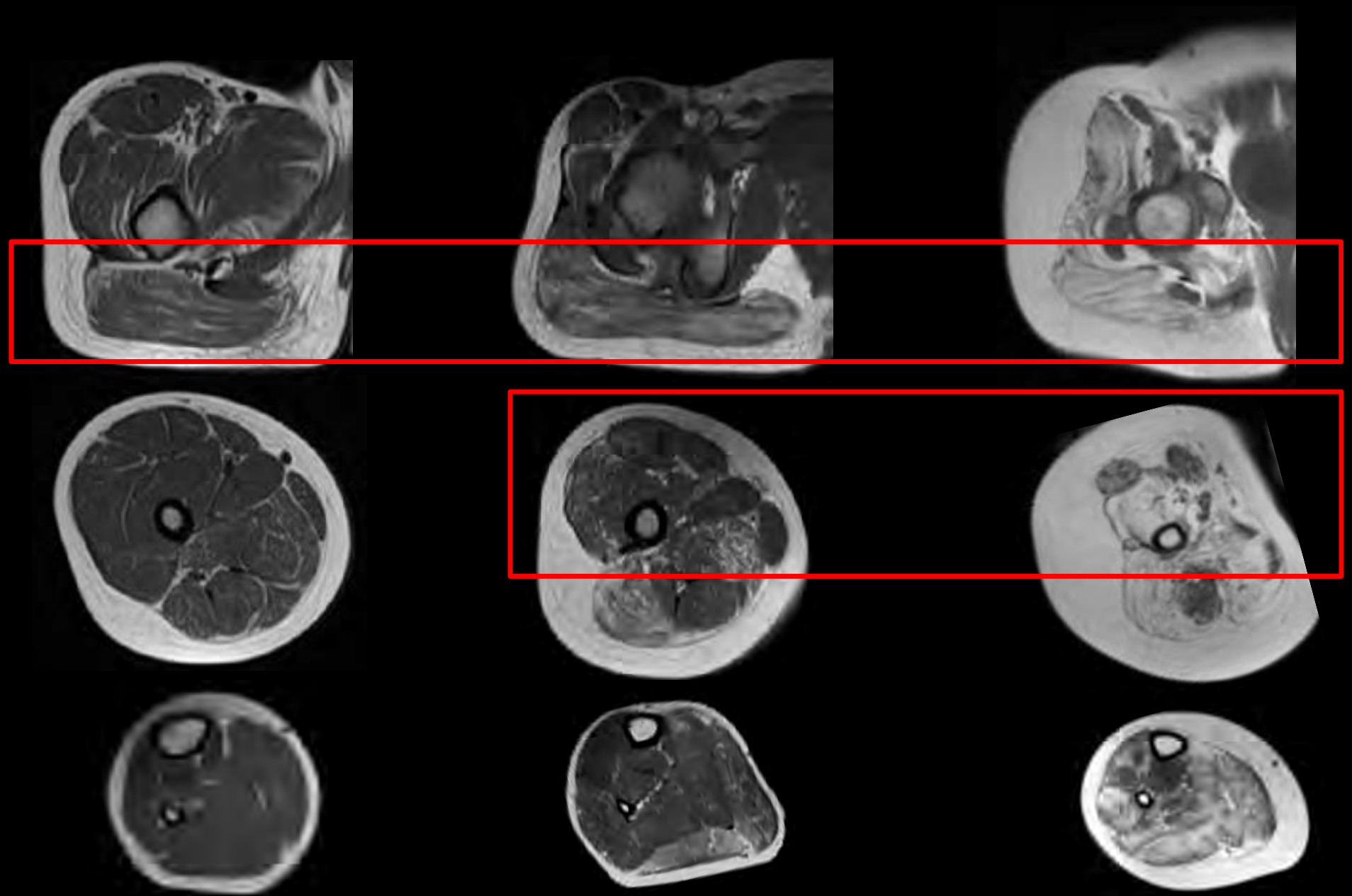
2y4m M, DMD

7y M
DMD



T1WI

DMD



5y2m

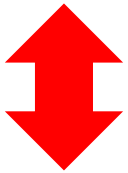
9y7m

Nonambulant

T1WI

Courtesy of Dr. Akihiko Ishiyama, NCNP Hospital

Imaging data



Motor function

LGMD2A/R1

Which is weaker?

hip extension

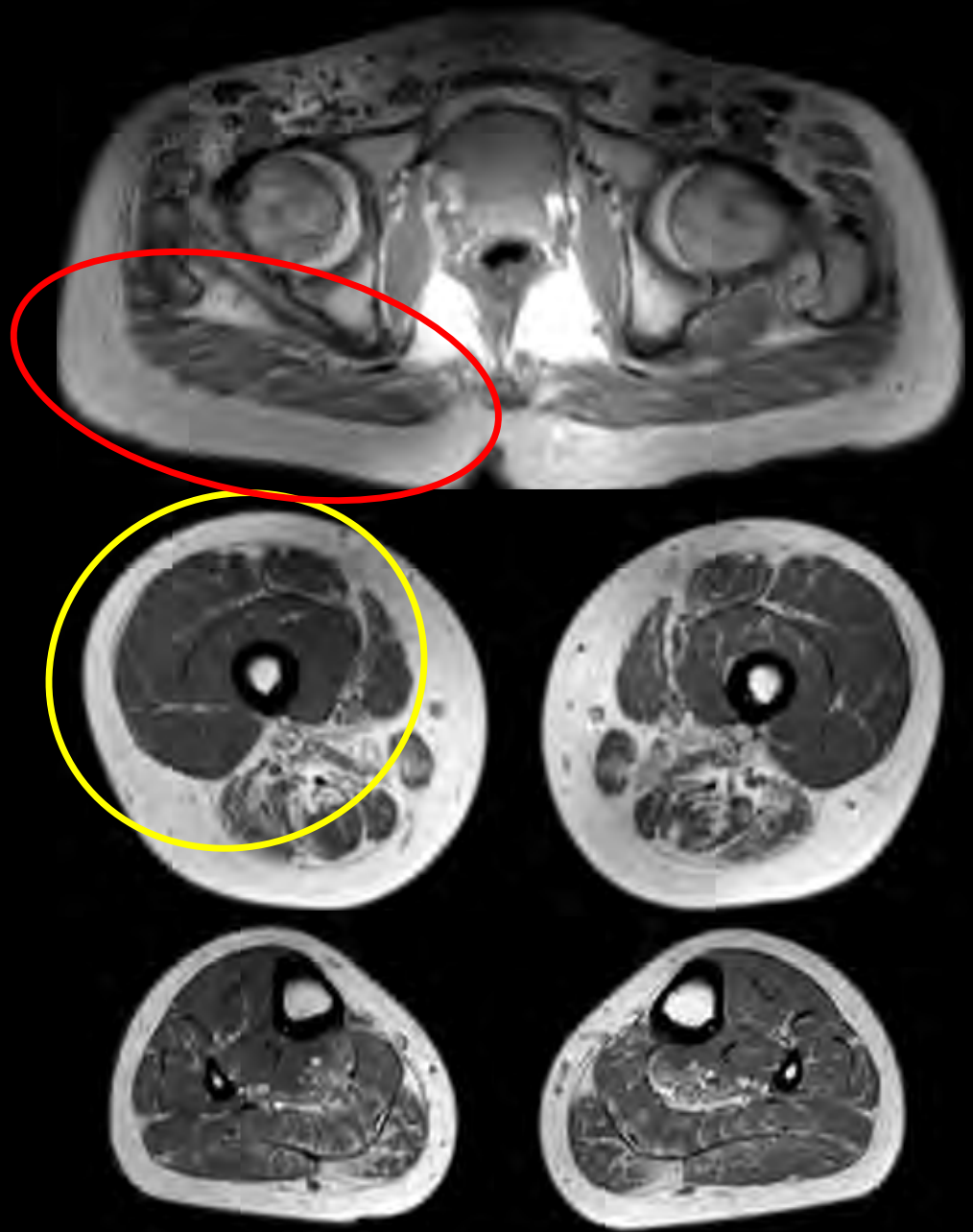
or

knee extension

Consent given for video presentation

12y M

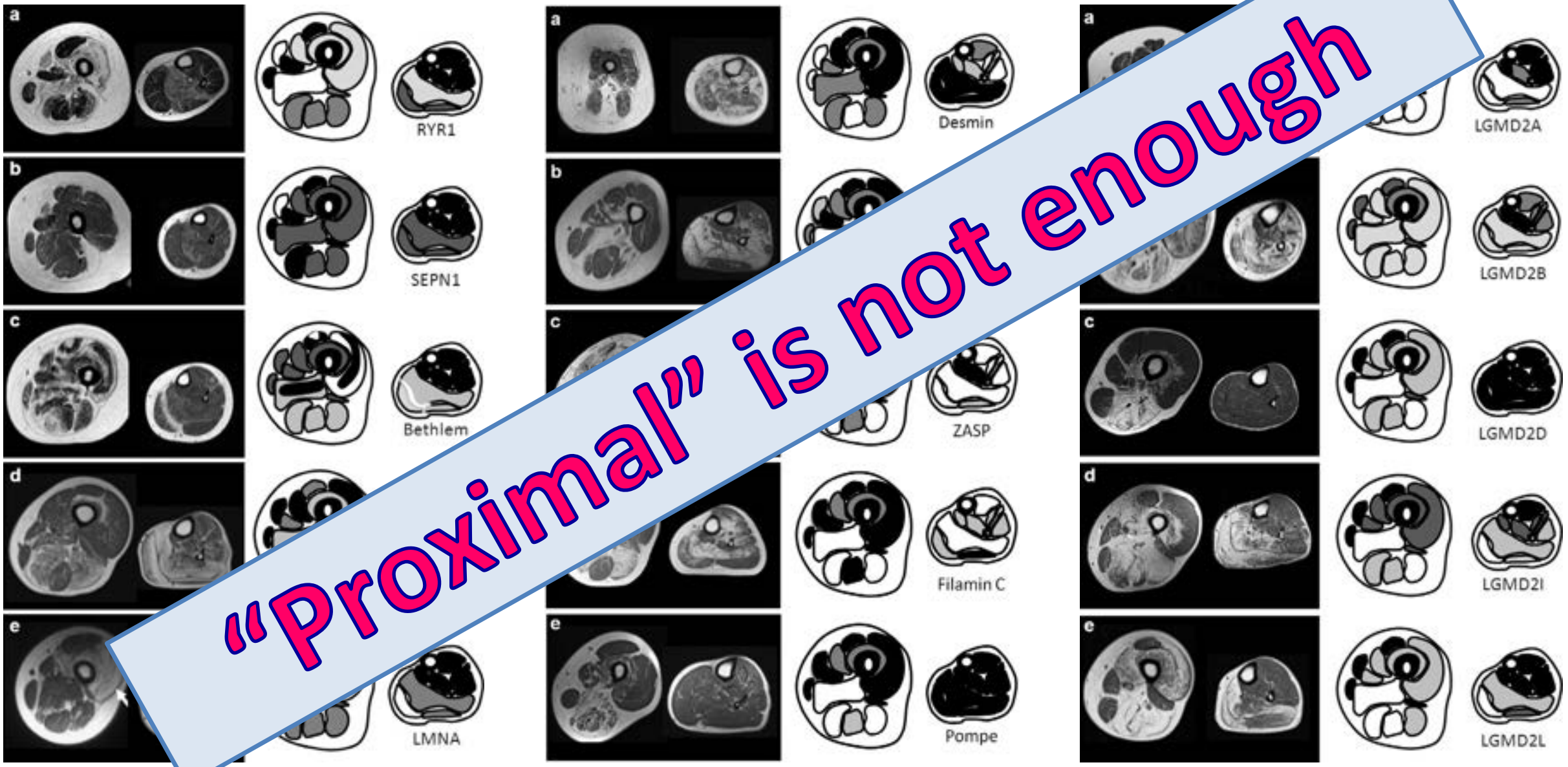
LGMD2A/R1



T1WI

Courtesy of Dr. Akihiko Ishiyama, NCNP Hospital

Selective muscle involvement
in hereditary muscle disease



"Proximal" is not enough

Straub V, et al. Neuromuscul Disord. 2012

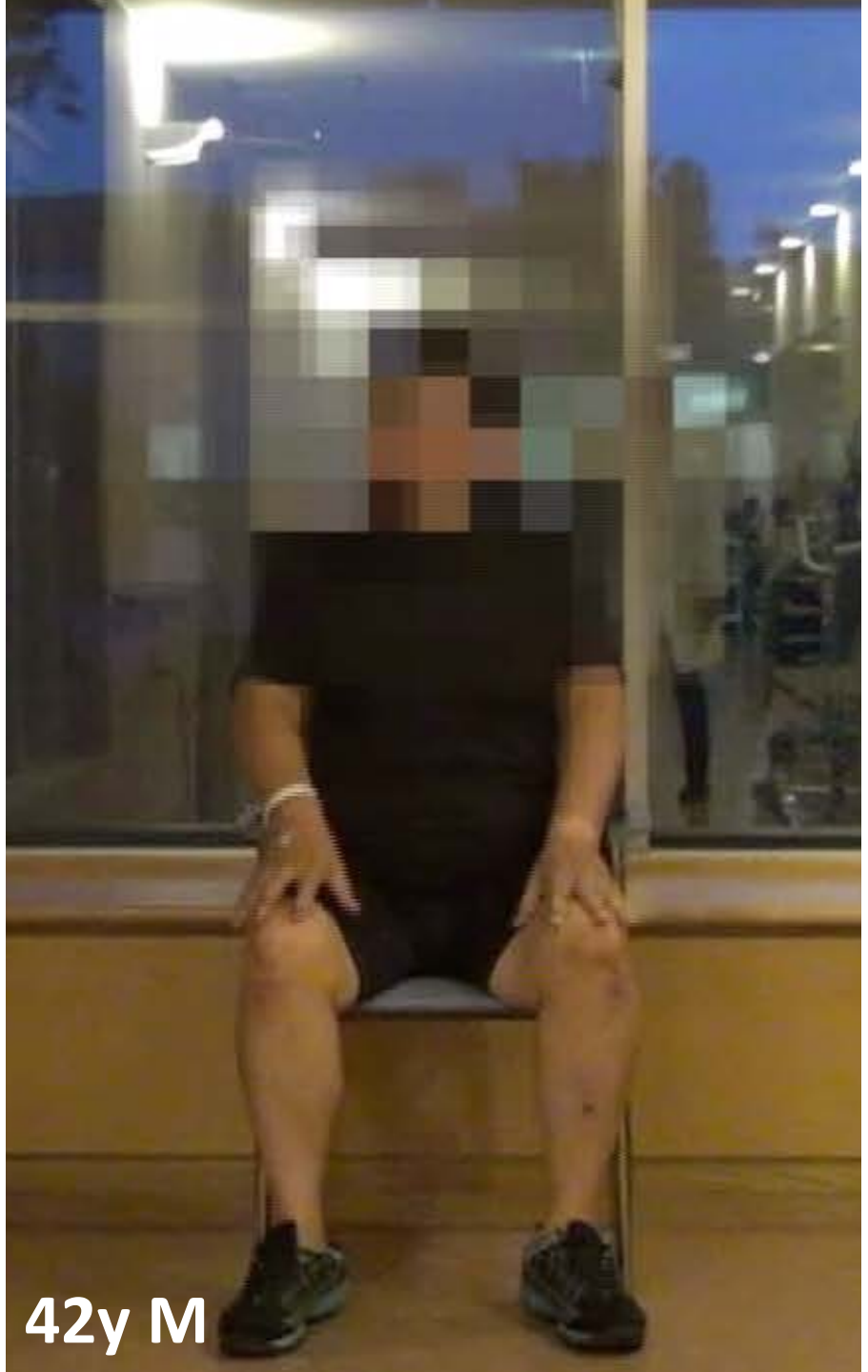
LOPD

Which is weaker?

hip extension

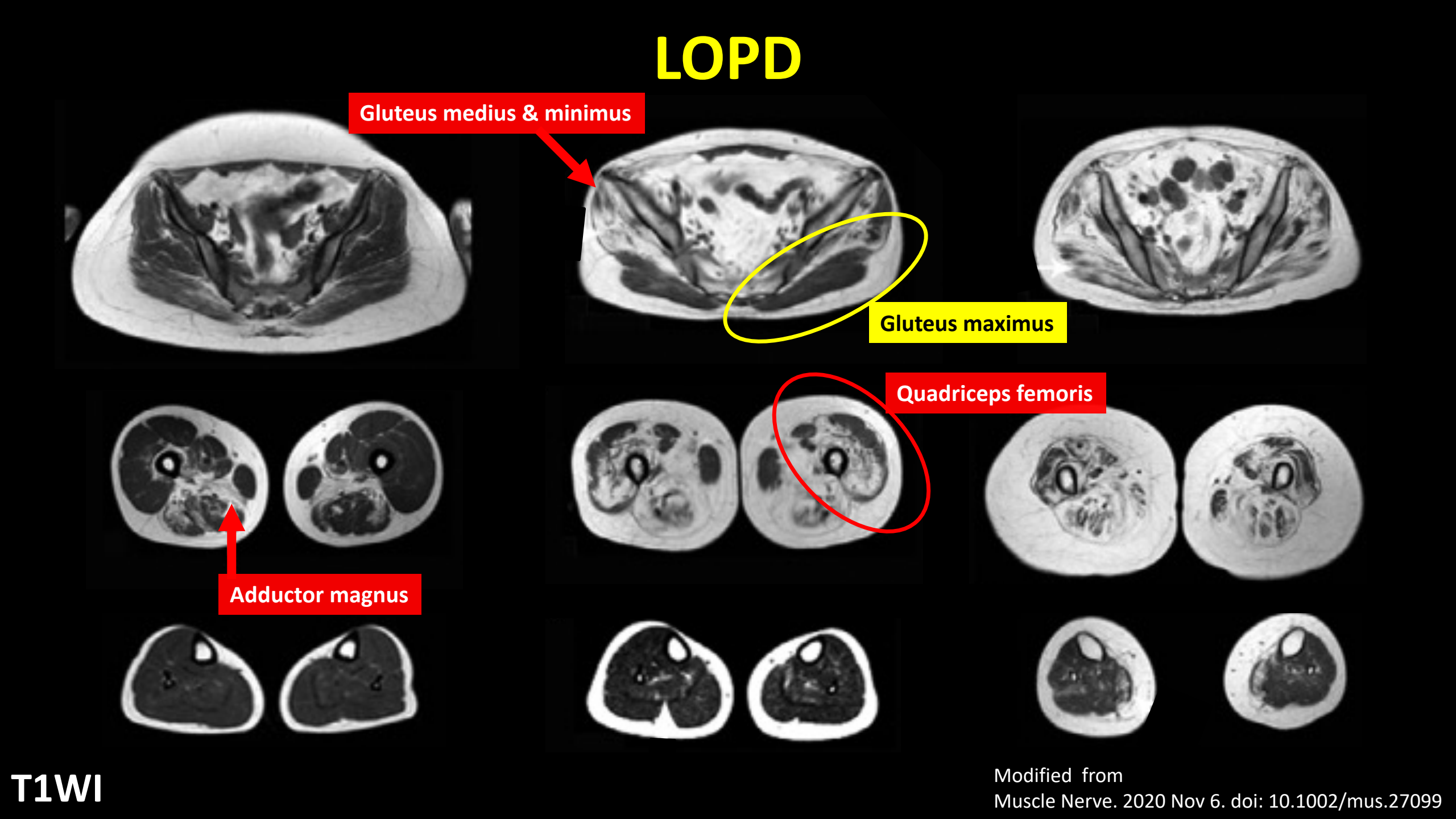
or

knee extension



Courtesy
Dr. Madoka Mori, NCNP Hospital

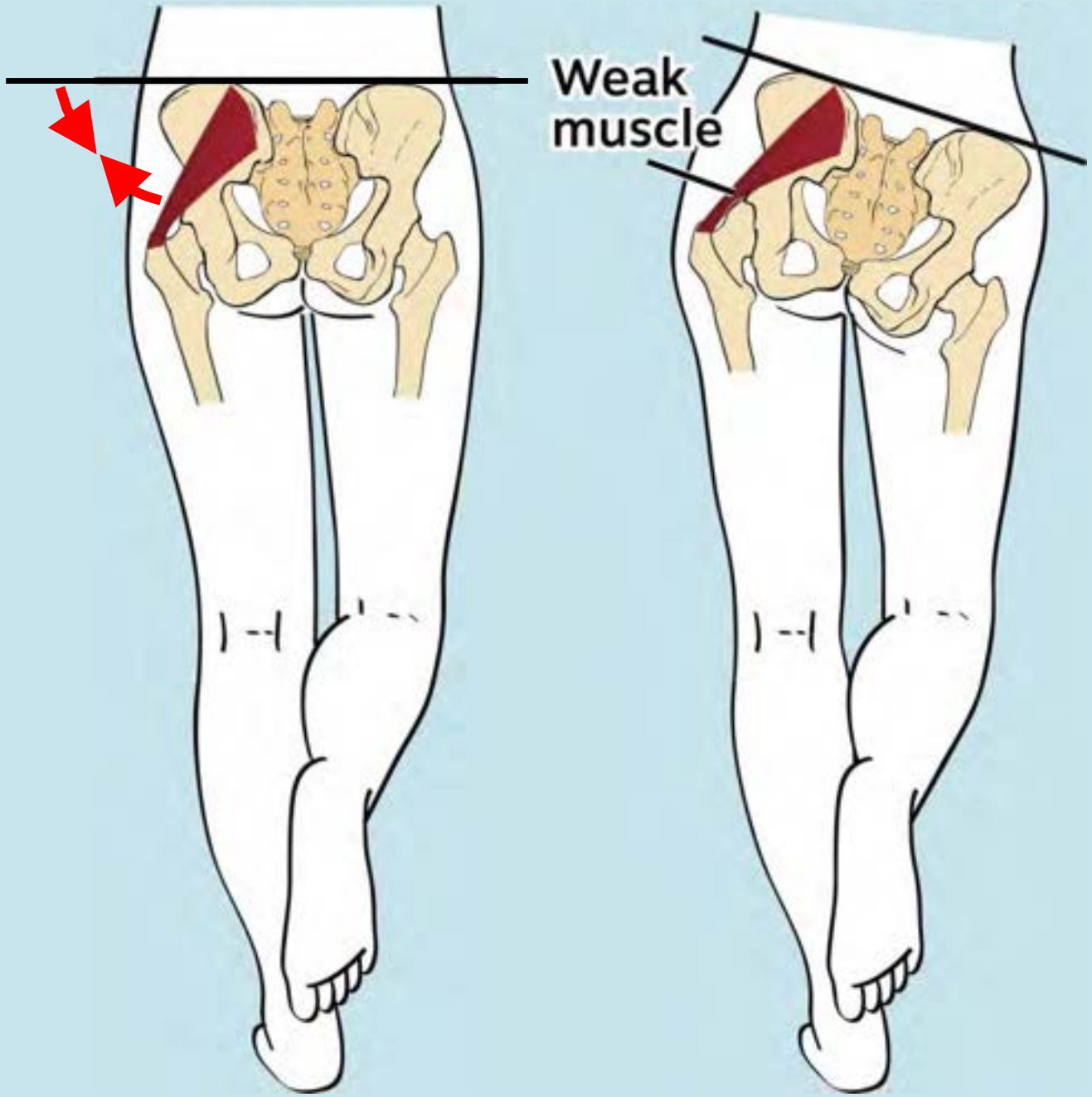
LOPD



T1WI

Modified from
Muscle Nerve. 2020 Nov 6. doi: 10.1002/mus.27099

Weak gluteus medius results in waddling gait



Hamdy, R., Saran, N. (eds) Pediatric Pelvic and Proximal Femoral Osteotomies. Springer, Cham. doi.org/10.1007/978-3-319-78033-7_1

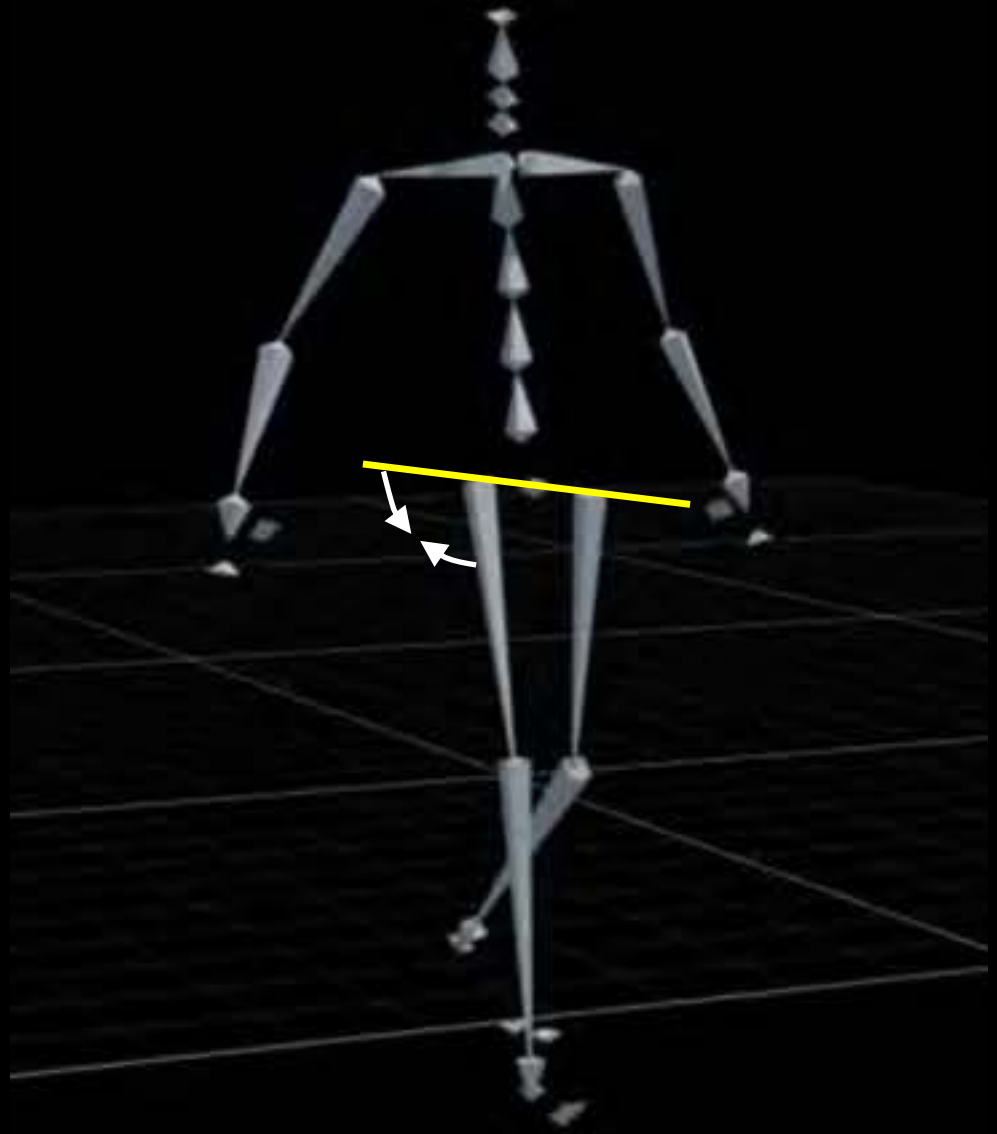
LOPD

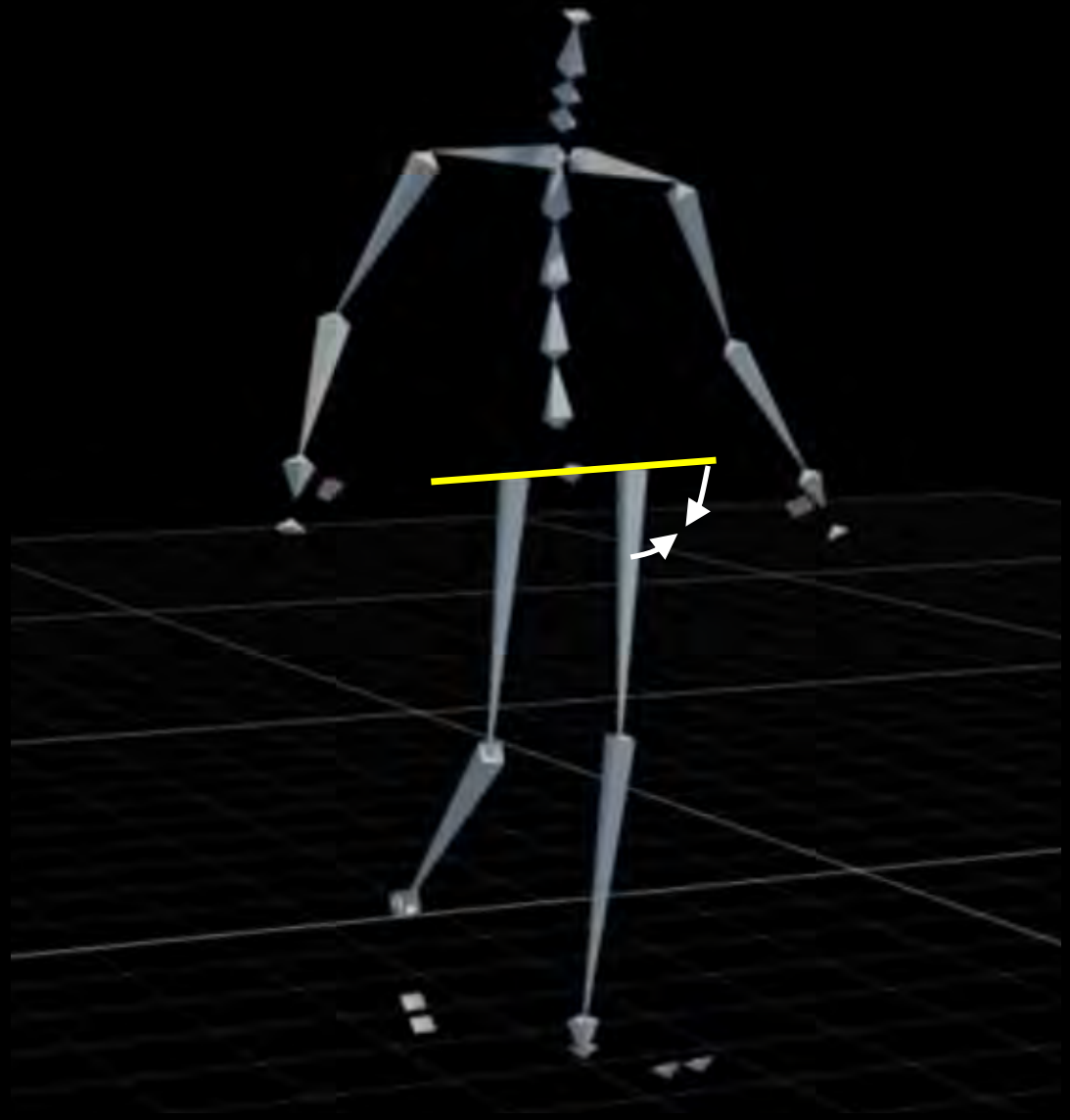
10y M

Courtesy of
Dr. Keiko Ishigaki
Tokyo Women's Medical University

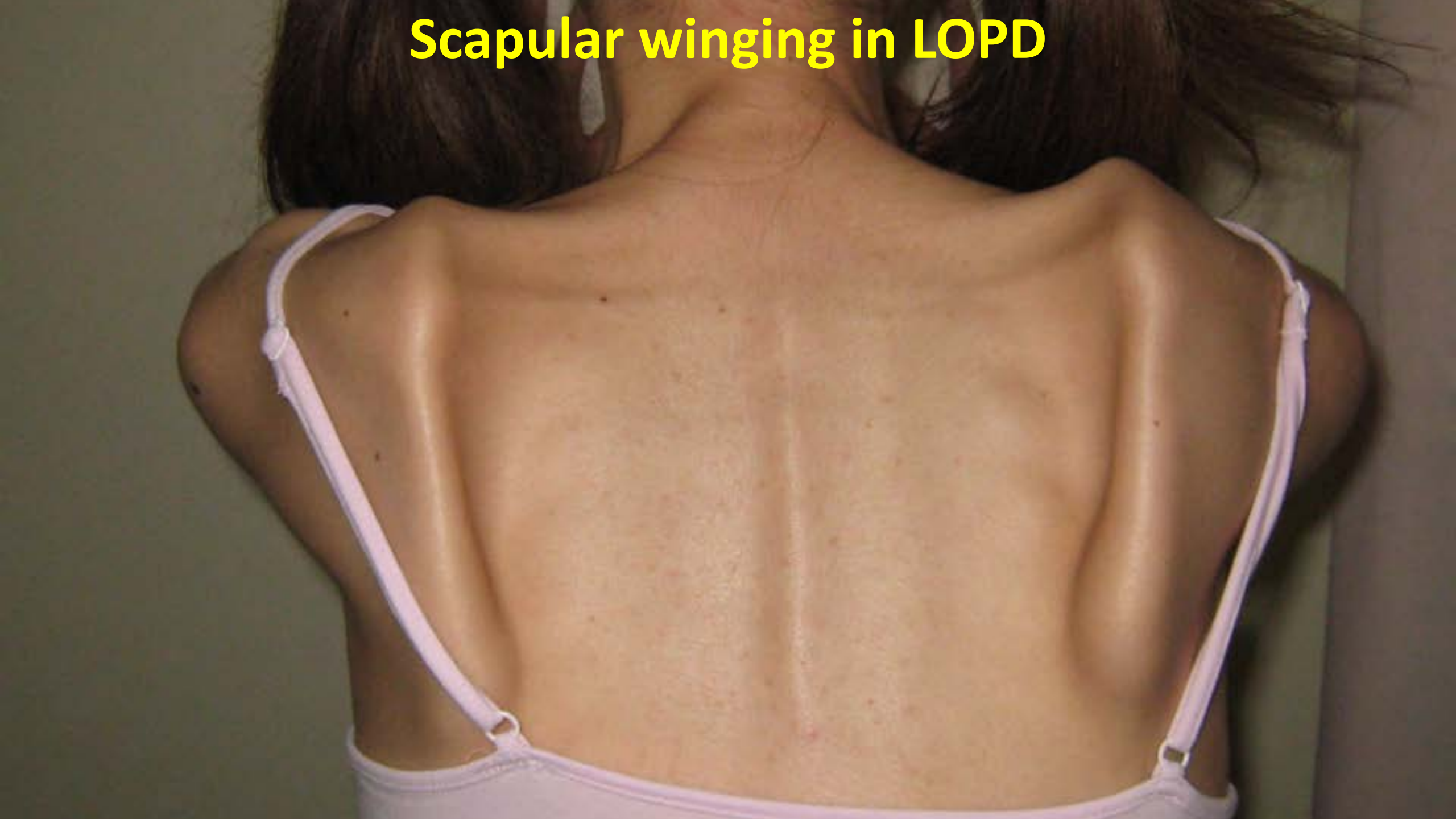

遅発性ポンペ病（LOPD）は

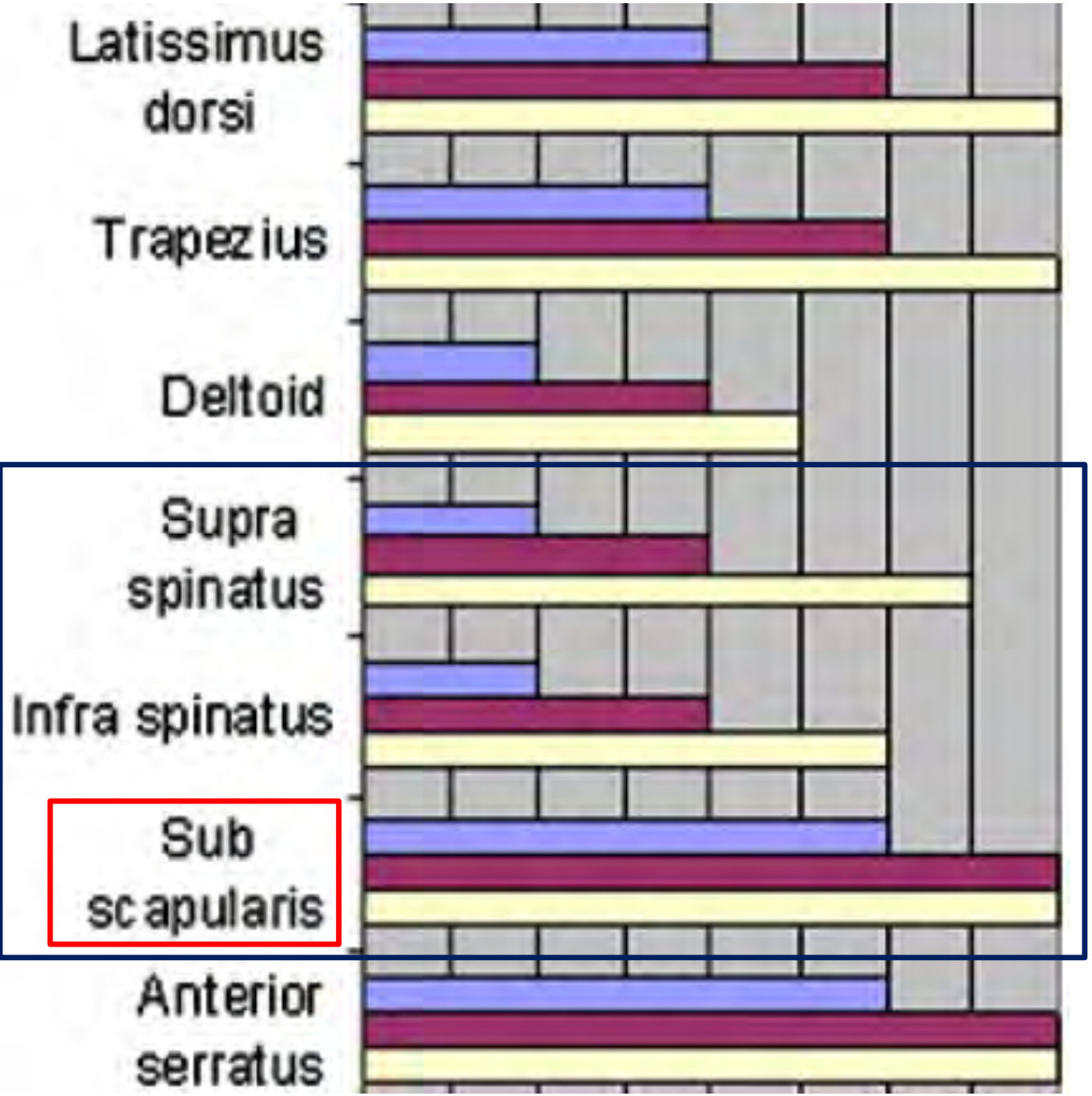
Trendelenburg gait in LOPD





Scapular winging in LOPD





LOPD

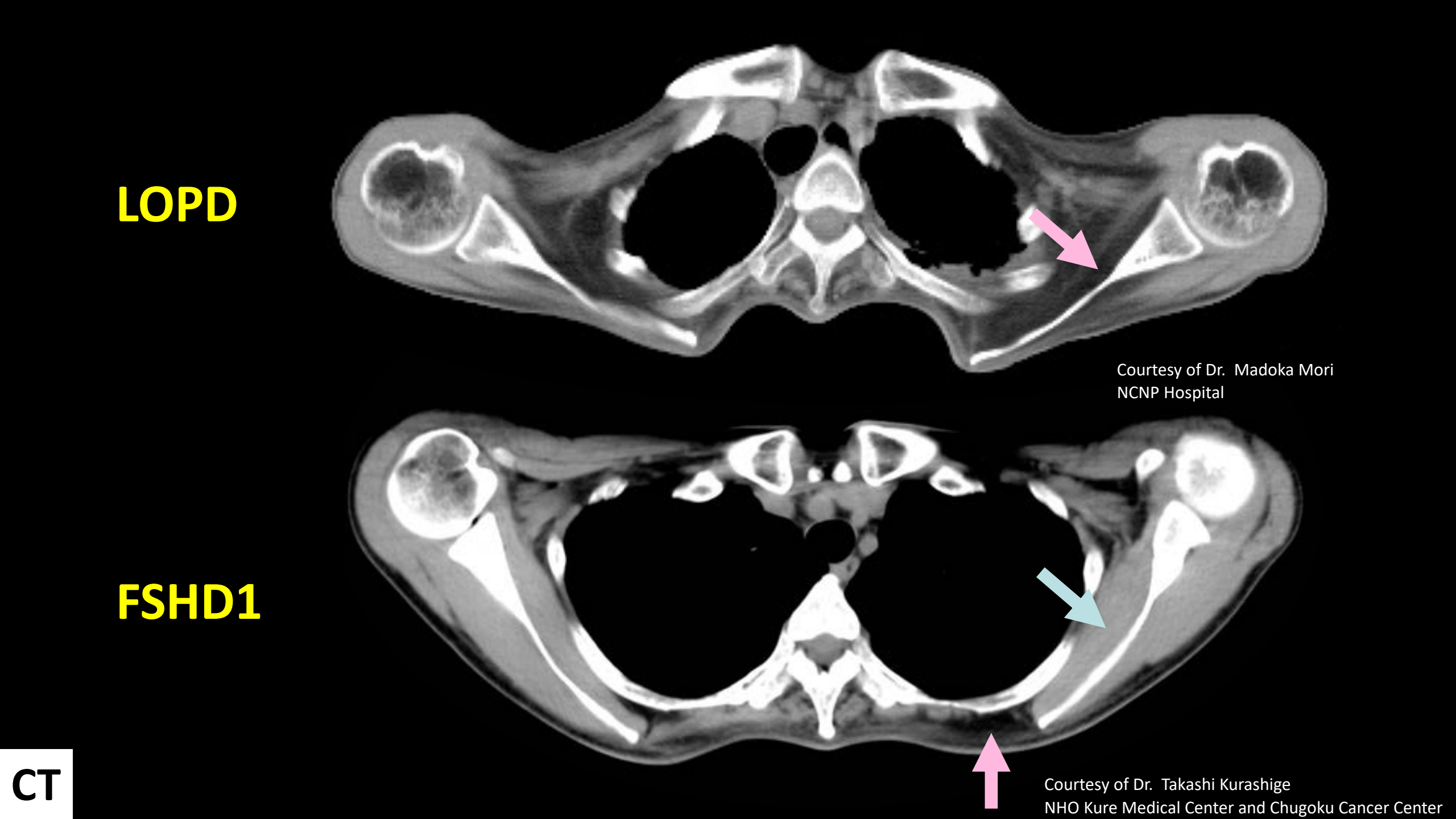
Atrophy in all periscapular muscles especially, subscapularis

Mild — Able to walk without assistance and not requiring ventilatory support

Moderate — Able to walk without assistance and requiring ventilatory support

Severe — Unable to walk or only 10 meters or less if assisted and requiring ventilatory support

Neuromuscul Disord. 2011 Nov;21(11):791-9


LOPD
FSHD1
Courtesy of Dr. Madoka Mori
NCNP Hospital
Courtesy of Dr. Takashi Kurashige
NHO Kure Medical Center and Chugoku Cancer Center
CT

Diagnostic finding of FSHD on MRI

Trapezius involvement

Bil. **Subscapularis** sparing

MRI from 295 patients
- 187 FSHD
- 108 non-FSHD

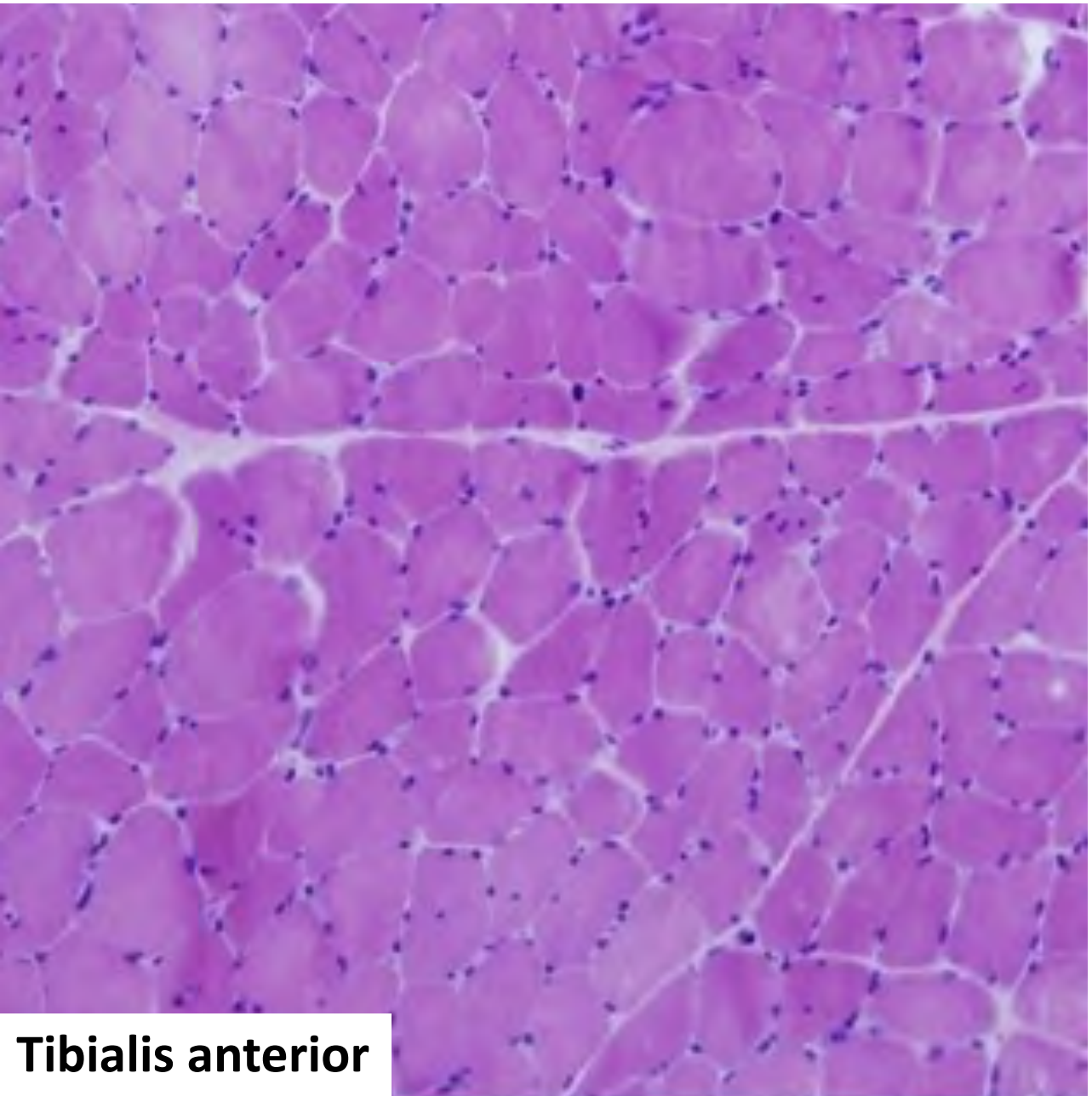
Diagnostic accuracy 0.89
Sensitivity 0.90
Specificity 0.88

J Neurol. 2022 Apr;269(4):2055-2063

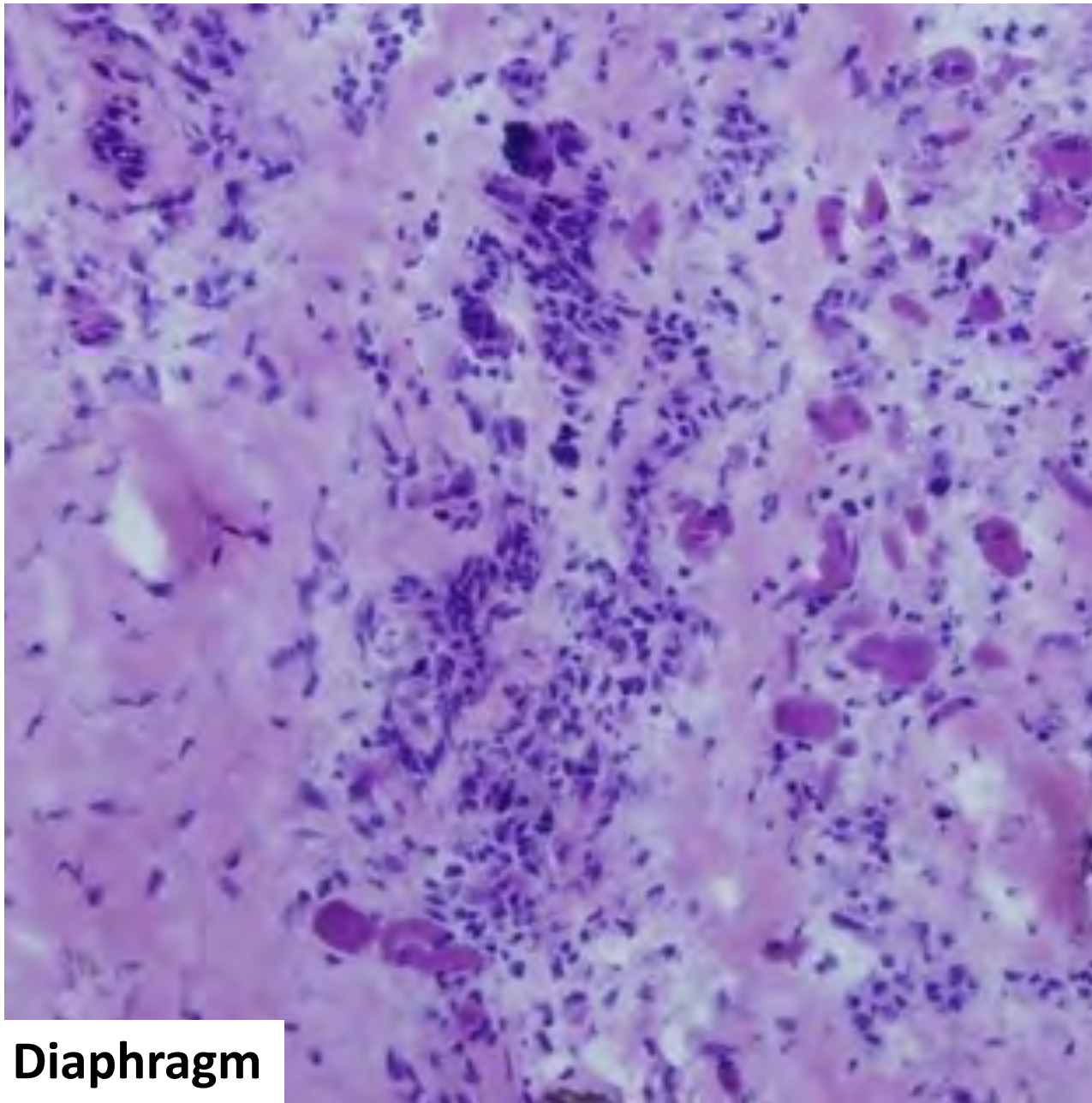
Respiratory failure

Marked diaphragm involvement in Pompe disease

43y F, autopsy



Tibialis anterior



Diaphragm

Respiratory failure before loss of ambulation in half of LOPD patients

Patient No.	1	2	3	4	5
Sex	M	M	F	F	F
Age at inclusion	66	55	44	38	32
Age at onset	35	35	20	8	7
Genotype	c.1585-1586TC>GT (p.S529V) homo	c.546G>T (p.T182T) homo	c.307T>C (p.C103R)/ c.546G>A (p.T182T)	NT	c.546G>T (p.T182T)/ c.1798C>T (p.R600C)
Observation period (week)	78	104	104	104	104
Symptom at onset	weakness of lower extremities	weakness of lower extremities	weakness of lower extremities	weakness of neck	weakness of lower extremities
Ventilator since (age)	**58**	**49**	**36**	**32**	**21**
Duration of ventilator use (year)	8	7	8	6	11
Ventilator use (hours /day)	24	10 (at night)	24	22	10 (at night)
Tracheotomy (age)	N	48	36	N	N
Wheelchair since (age)	**51**	**48**	**36**	**36**	**29**
Enzyme activity (M): muscle (nmols 4 MU/mg/30 min) (normal: 7.3±2.2) (F): fibroblast (mmol/pg protein) (normal:161±32.4)	0.6 (M)	0.3 (M)	0.94 (M)	0.46 (F)	0 (M)
Complications	diabetes mellitus	atrial fibrillation	interstitial pneumonia pneumothorax	Pneumothorax, subcutaneous/mediastinal emphysema	—
Muscle pathology	PAS-positive vacuoles	Vacuoles stained with acid phosphatase	Vacuoles stained with acid phosphatase	Vacuoles stained with acid phosphatase	Vacuoles stained with acid phosphatase

Furusawa et al. J Inherit Metab Dis 2012

Muscle disease with early respiratory failure

Hereditary

- **Late-onset Pompe disease**
  - ***GAA* (AR)**
- **Nemaline myopathy**
  - *NEB*, etc (12 genes)
- **Hereditary myopathy with early resp failure (HMERF)**
  - *TTN* (exon 343) (AD)
- Rigid spine muscular dystrophy (RSMD)
  - *SELENON* (AR)
- Early-onset myopathy, areflexia, respiratory distress, and dysphagia (EMARDD)
  - *MEGF10* (AR)

Acquired

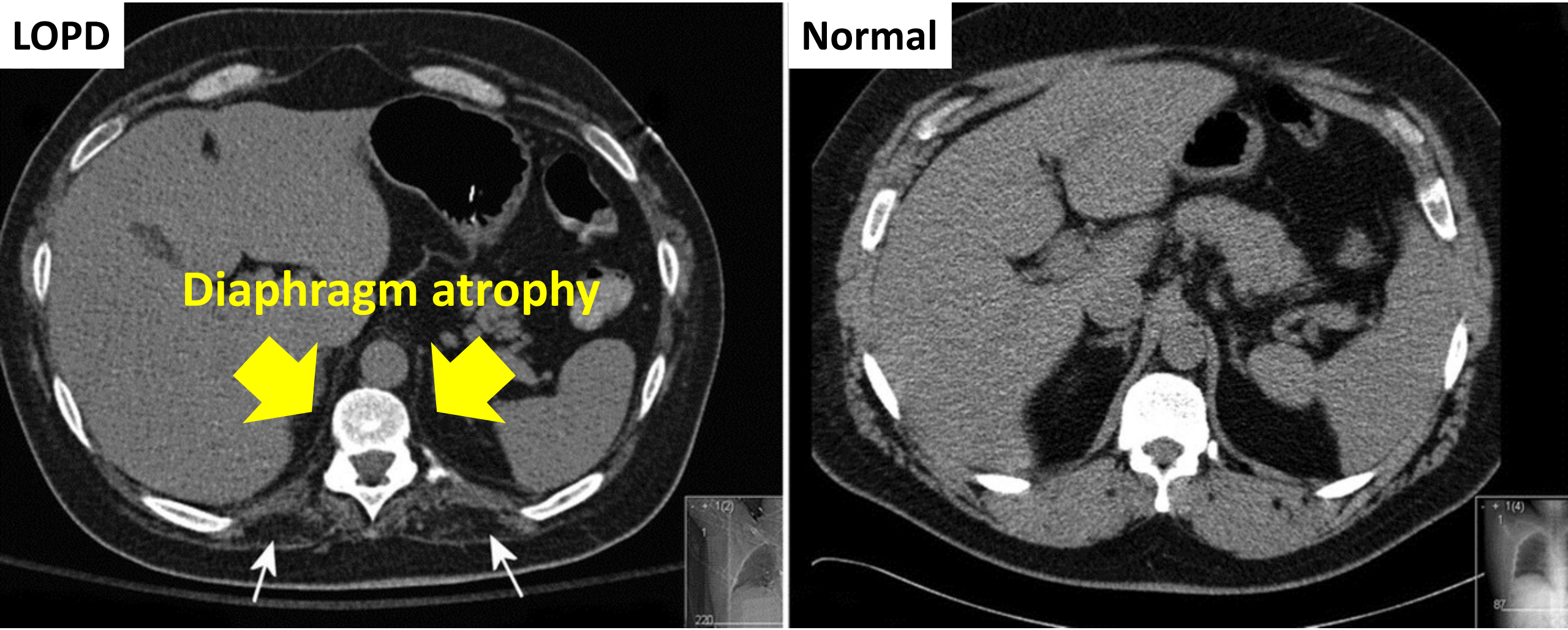
- **Sporadic late-onset nemaline myopathy (SLONM)**
- Anti-mitochondrial M2 myositis

Clinical manifestations associated with respiratory failure

- Respiratory
  - Dyspnea, orthopnea
  - Frequent respiratory infections
  - Weak coughing
- Sleep-related
  - Sleep apnea
  - Daytime sleepiness
  - Nightmare
- Others
  - **Morning headache**
  - Loss of appetite
  - Poor concentration
  - Anxiety and depression

Teaching Neuro*Image*: Axial muscle atrophy in adult-onset Pompe disease

Neurology. 2008 Mar 4;70(10):e36

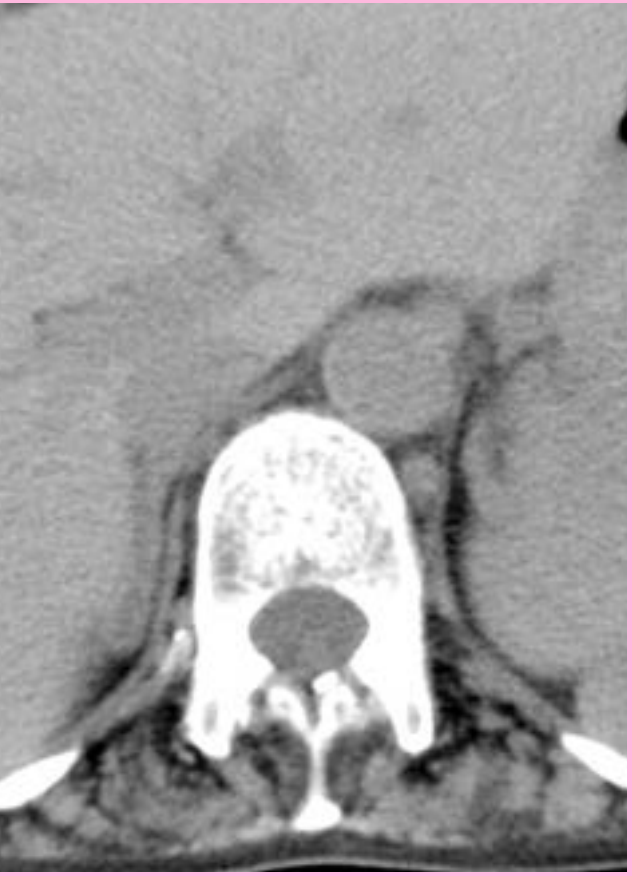


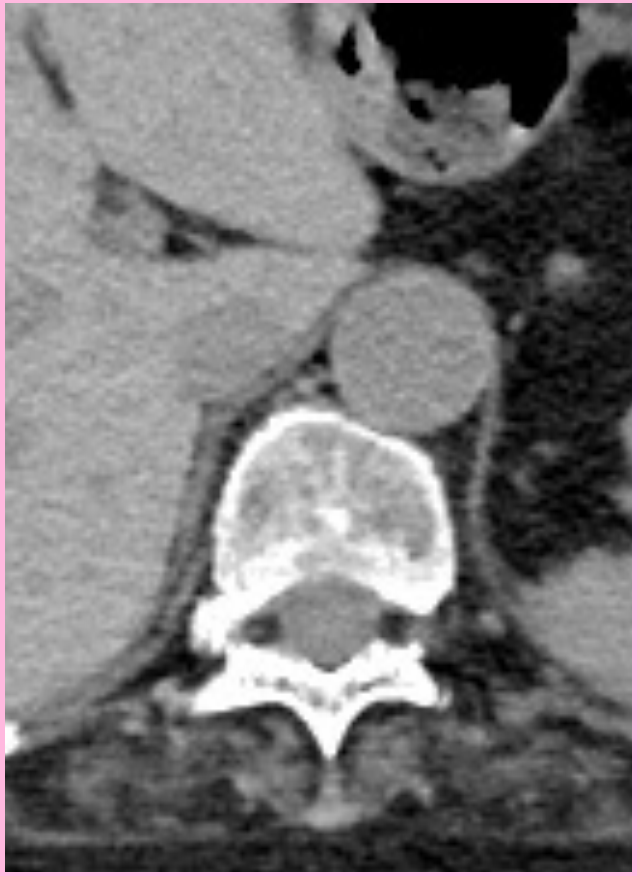
HMERF
TTN

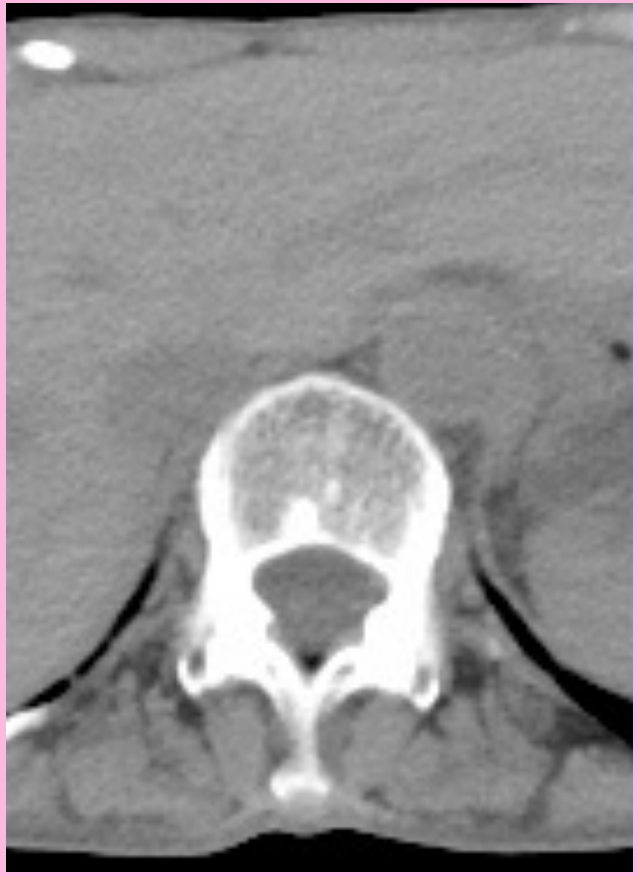
Rigid spine
SELENON

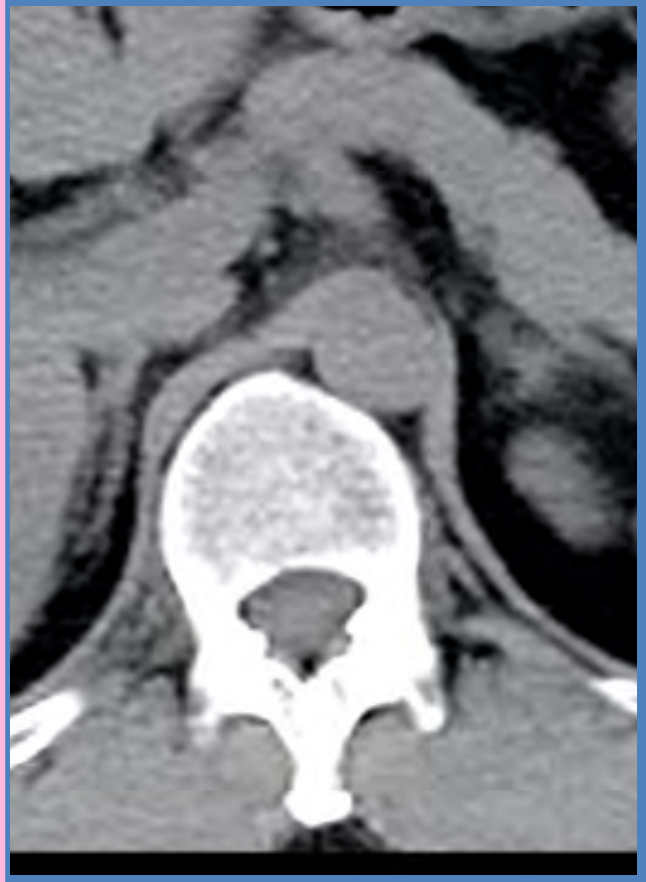
Nemaline MP
NEB

Control





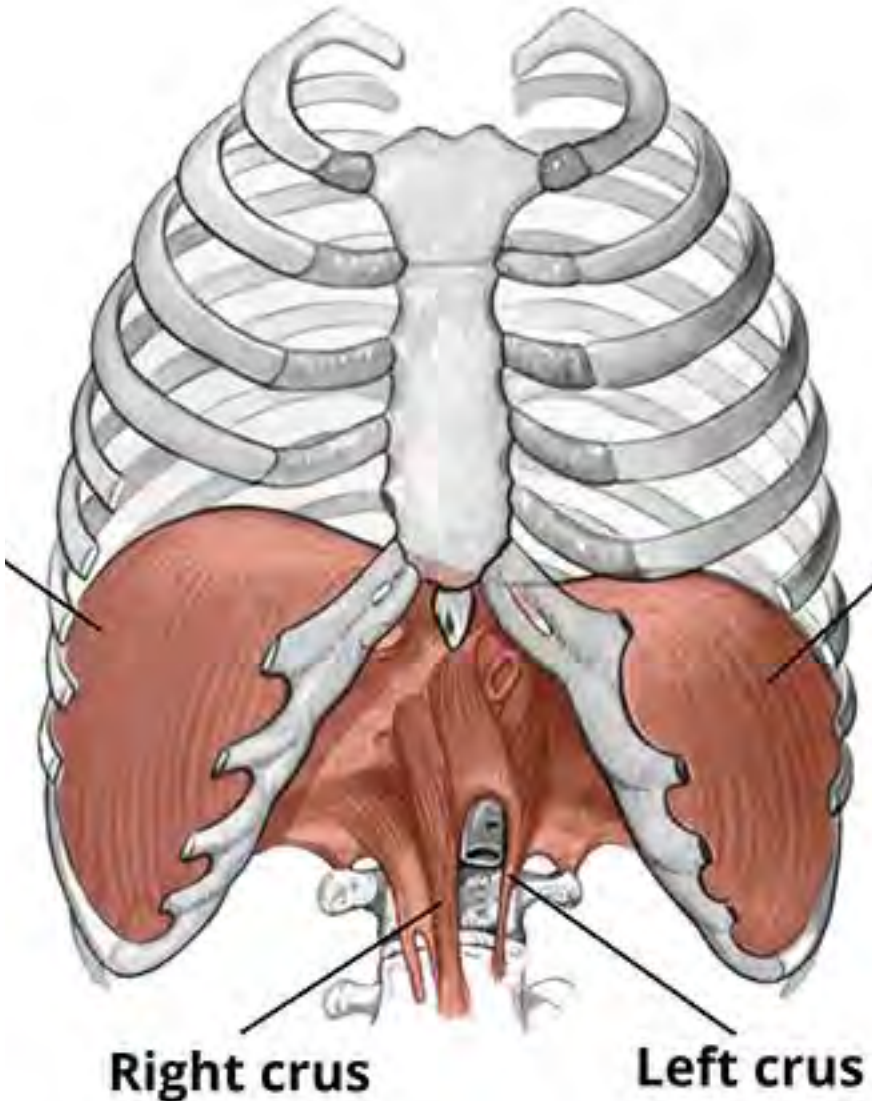




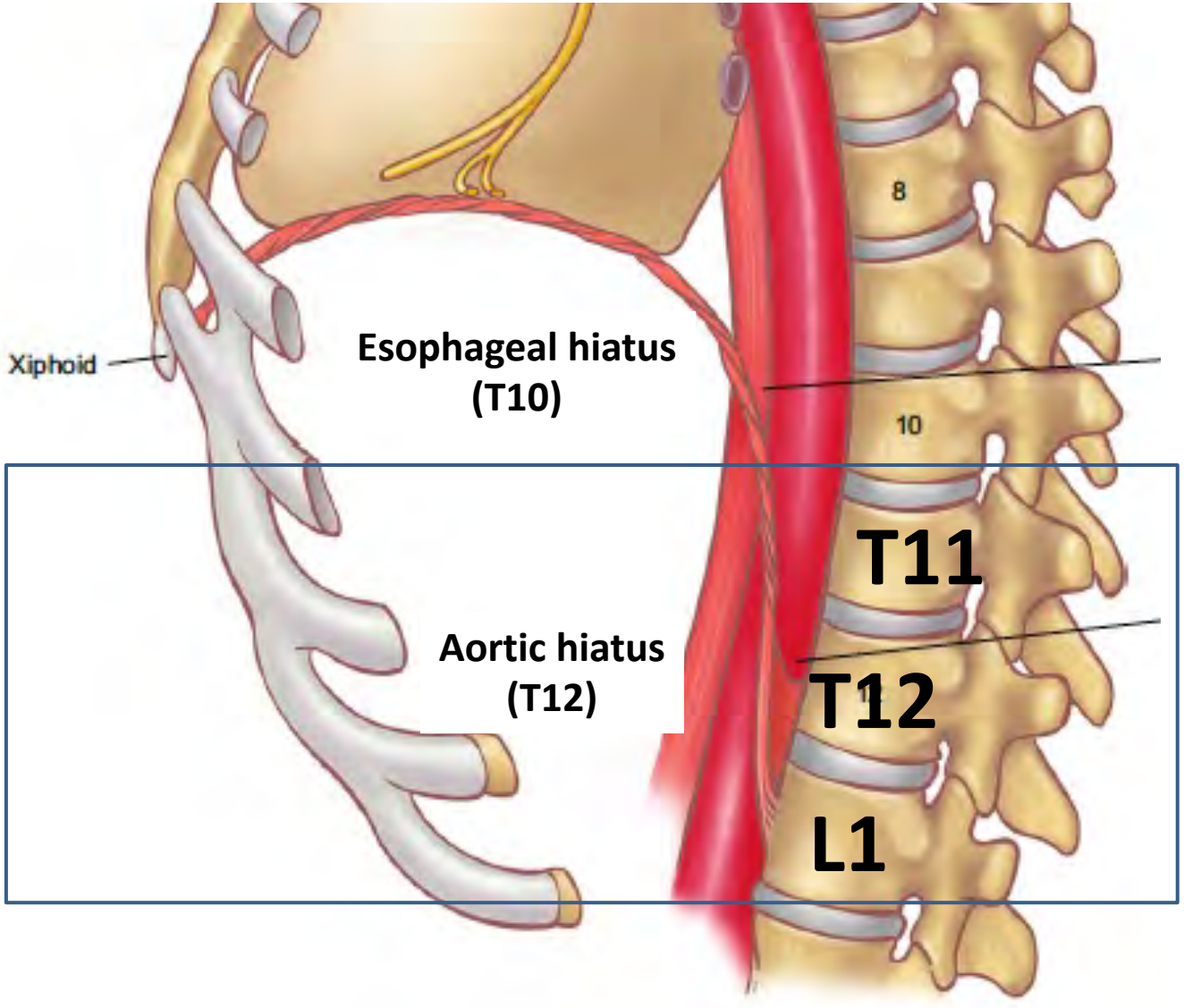
CT

Axial CT at aortic hiatus level

– useful for evaluating diaphragmatic crus



https://teachmeanatomy.info/thorax/muscles/diaphragm/



Thorac Surg Clin. 2007 Nov;17(4):449-61

Differential diagnosis on muscle pathology

Article abstract—Two unrelated 16-year-old boys had mental retardation, cardiomegaly, and proximal myopathy. One also had hepatomegaly. Histochemistry and electronmicroscopy of muscle biopsies showed lysosomal glycogen storage resembling acid maltase deficiency. Biochemical studies of skeletal muscle showed increased content of glycogen of normal structure; acid α-glucosidase activity in both urine and muscle was normal. Other enzymes of glycogen metabolism were also normal. The cause of this apparently generalized glycogenosis with no demonstrable enzyme defect is unknown.

NEUROLOGY (Ny) 31: 51-57, **January 1981**

Lysosomal glycogen storage disease with normal acid maltase

Moris J. Danon, M.D., Shin J. Oh, M.D., Salvatore DiMauro, M.D., Jose R. Manaligod, M.D., Ph.D., Abe Eastwood, Ph.D., Sakkubai Naidu, M.D., and Louis H. Schliselfeld, Ph.D.

Danon disease

- X-linked disease

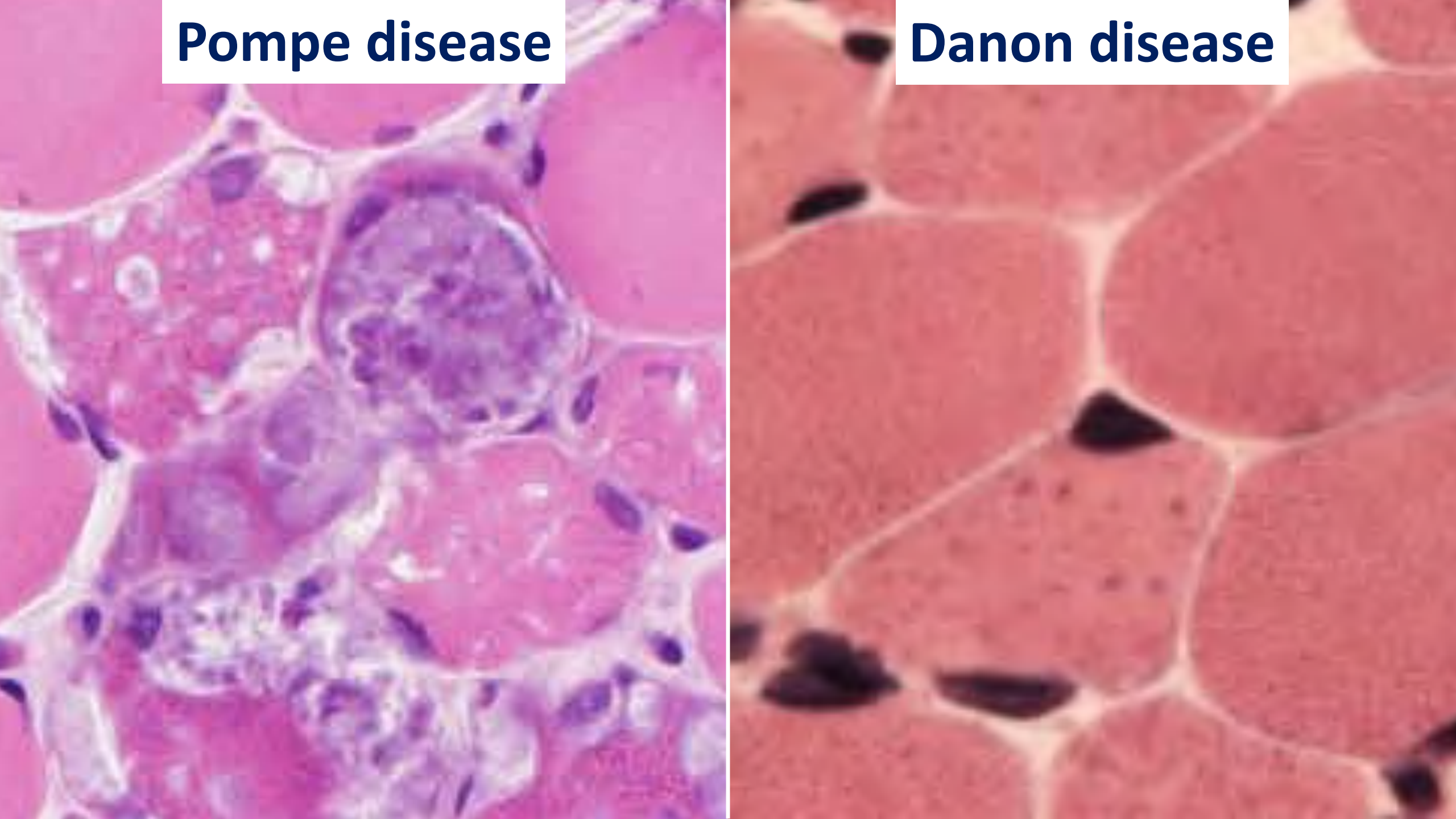
	Male	Female
Onset	10 y ~	30 y ~
Diagnosis	17 ± 7 y	38 ± 12 y
Death	19 ± 6 y	40 ± 7 y

Age range – LOPD

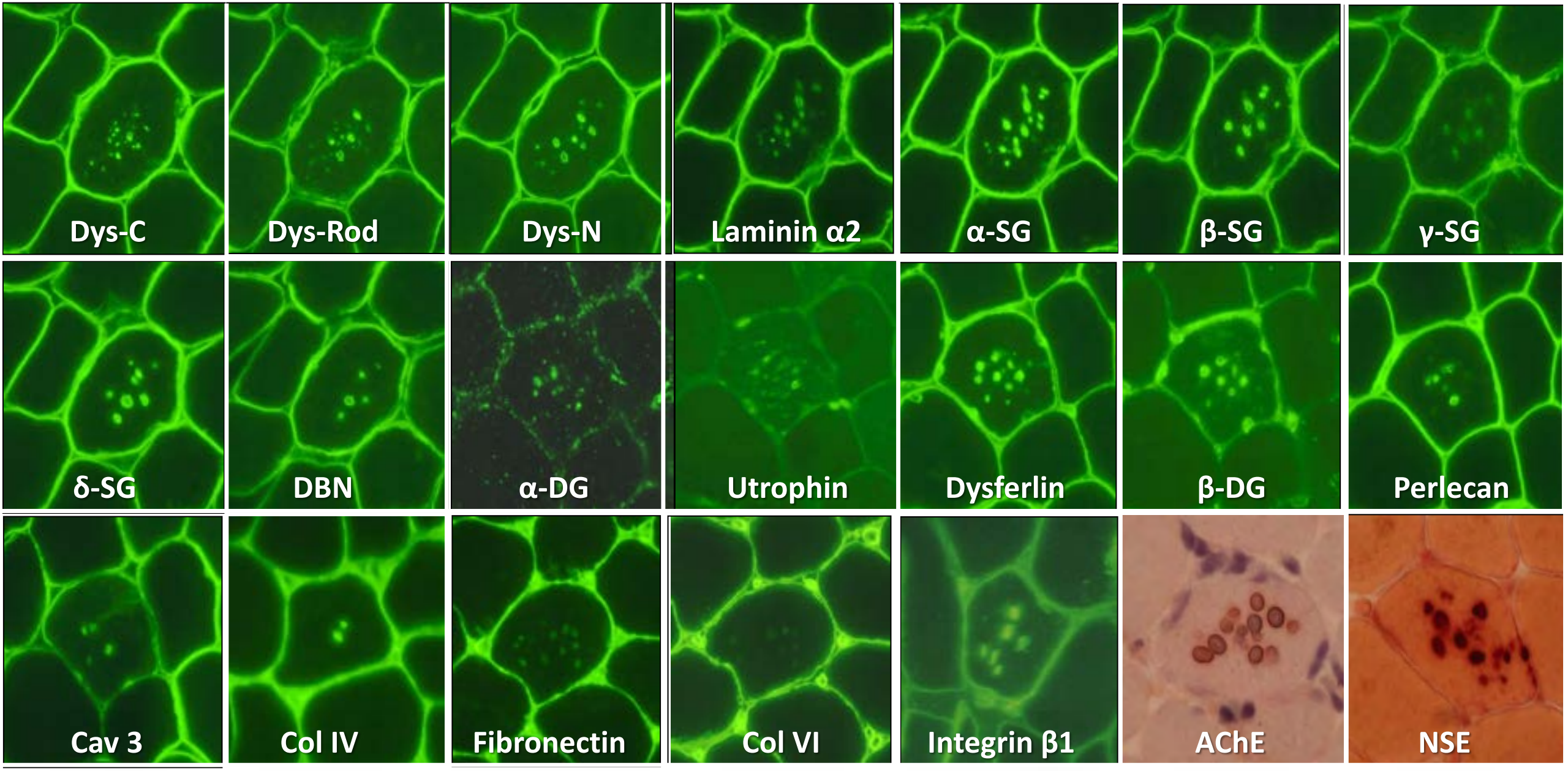
Clinical features – different!

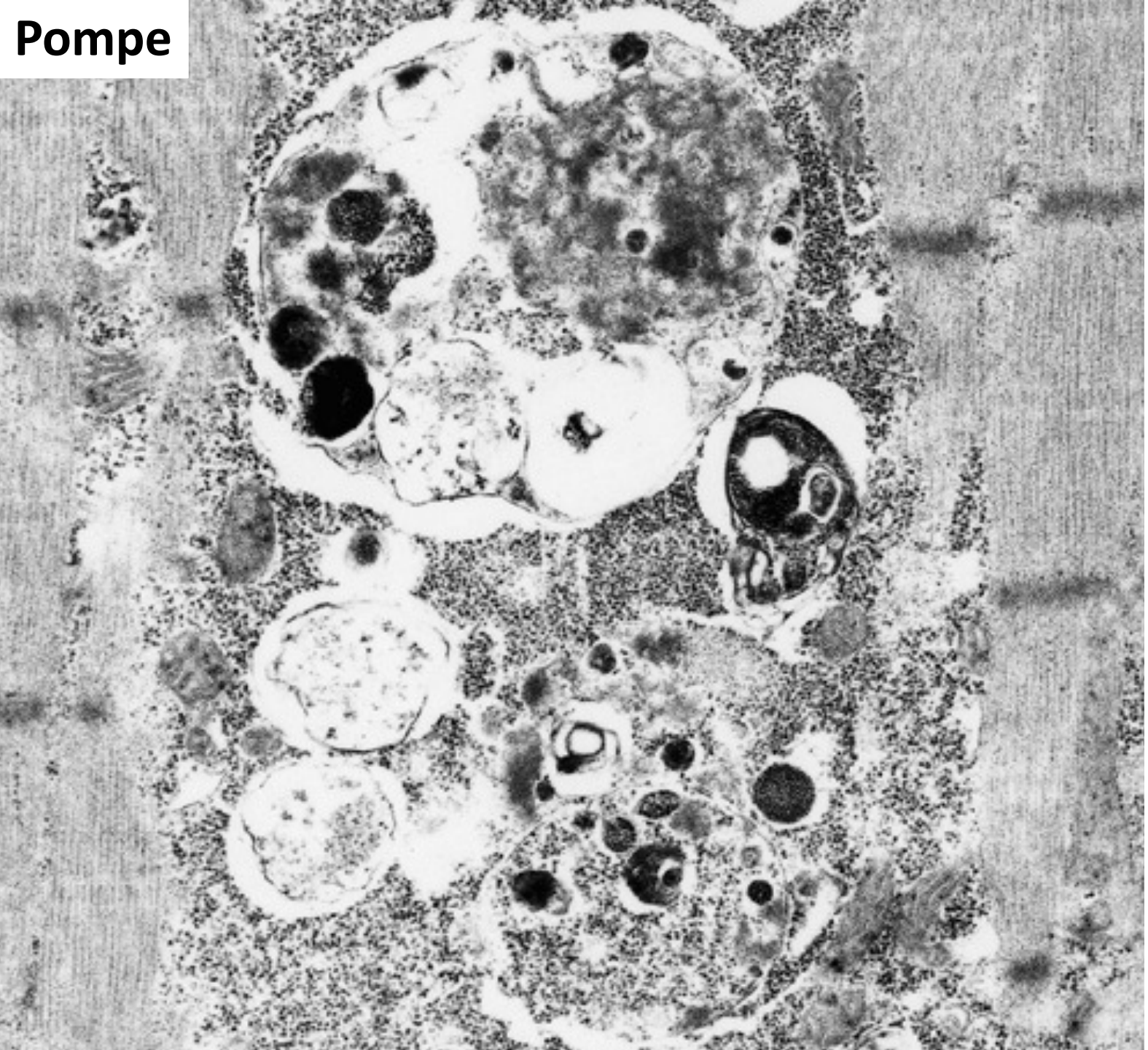
- Clinical features
  - **Cardiomyopathy** 100%
  - **Myopathy**
    - Weakness / Fatigability 80%
    - CK elevation 100%
  - **Mental retardation** 70%
  - Retinopathy

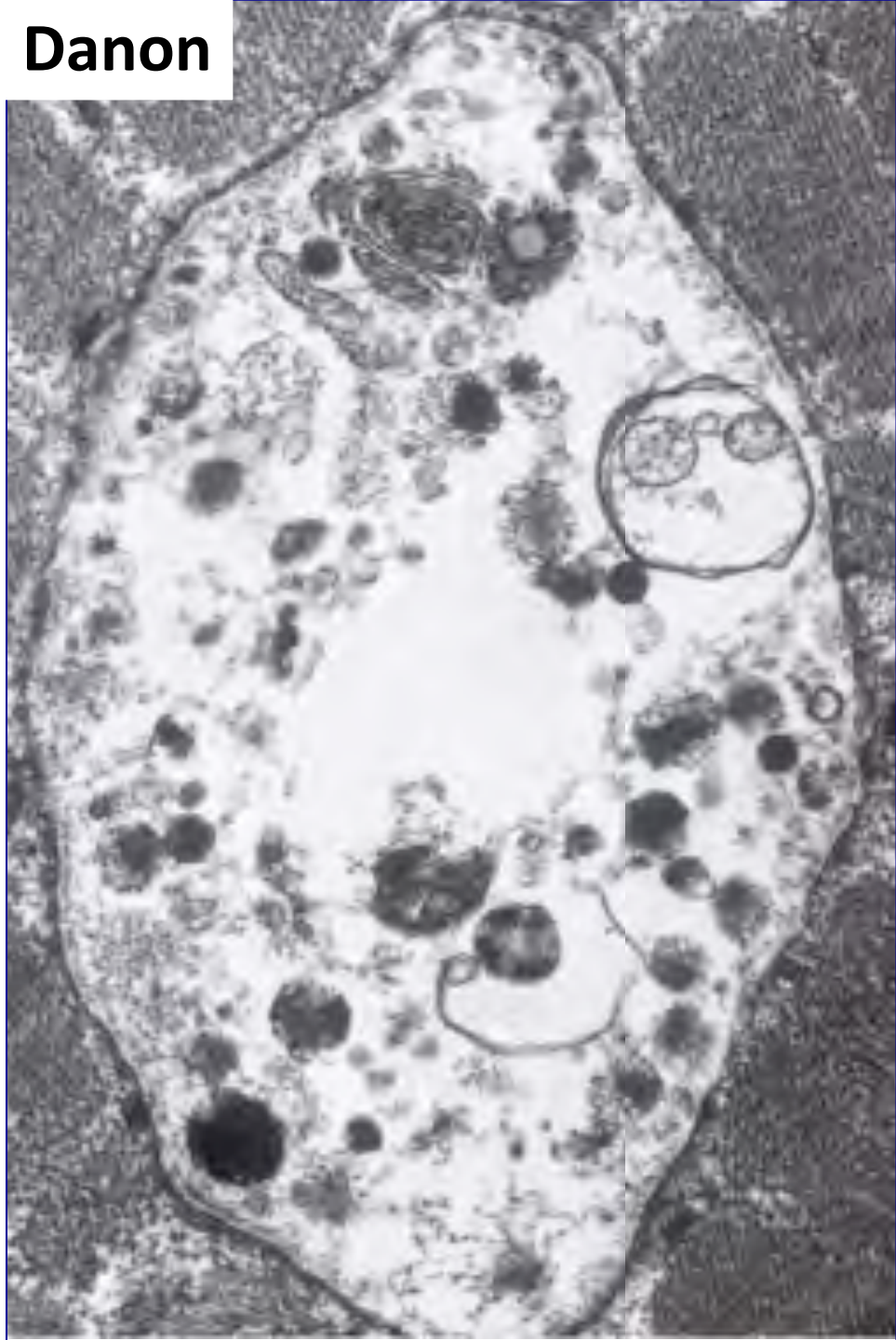
Neurology. 2002 Jun 25;58(12):1773-8


Pompe disease
Danon disease

Autophagic vacuoles with unique sarcolemmal features (AVSF)




Pompe

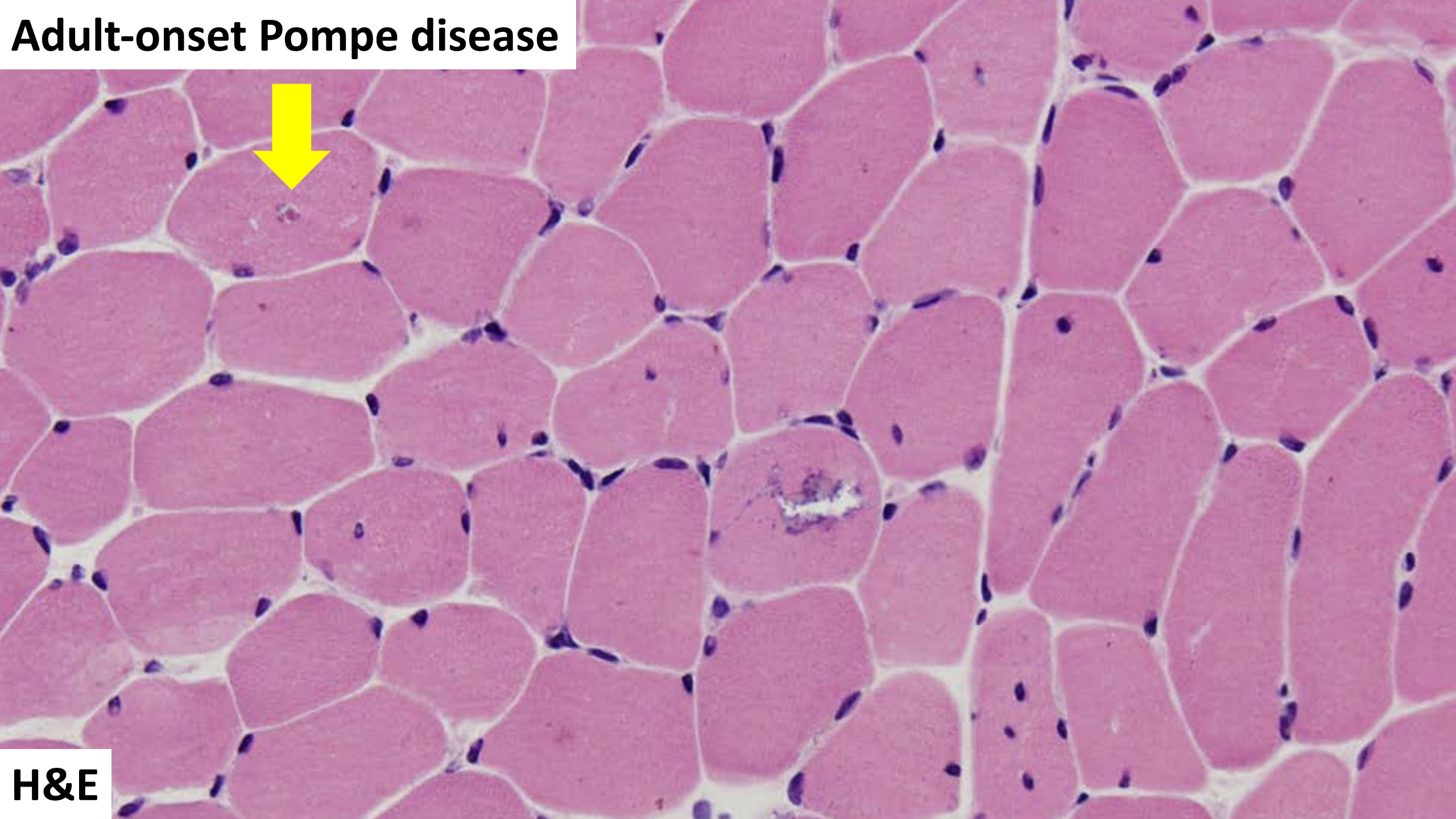

Danon

Danon disease

different from Pompe disease

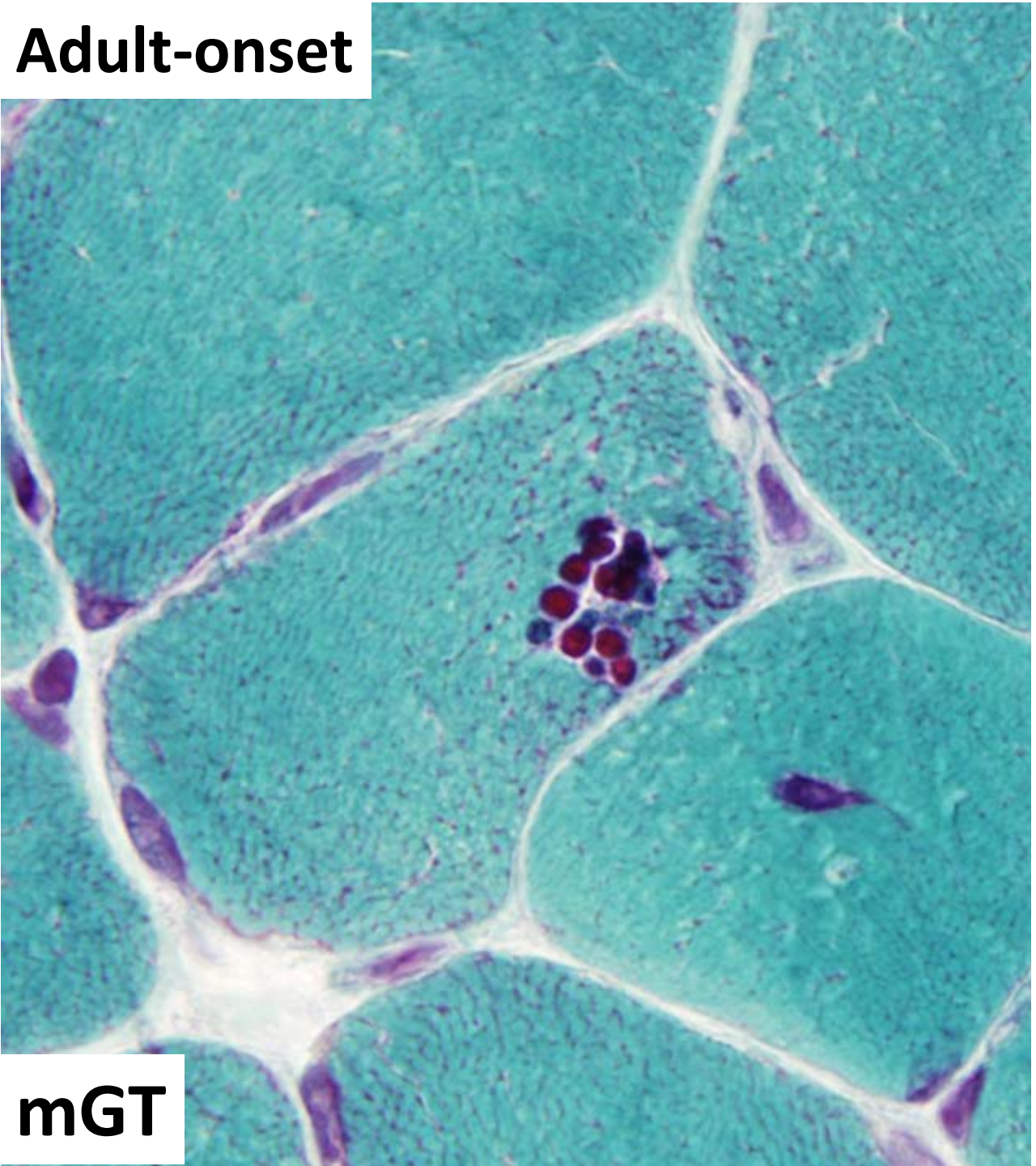
- Clinical – LOPD age but with cardiomyopathy
- Pathological – Different autophagic vacuoles

Adult-onset Pompe disease



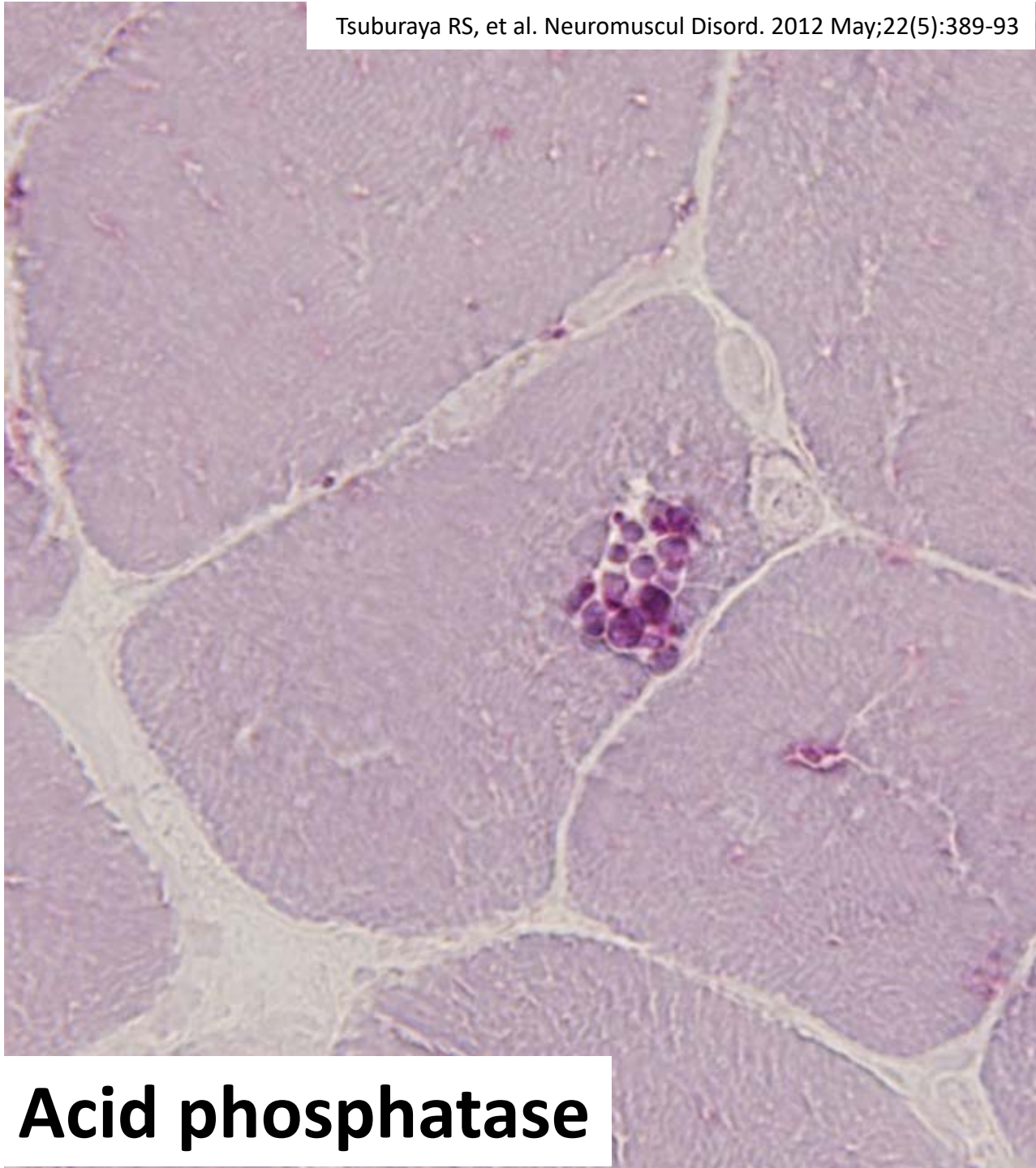
H&E

Adult-onset

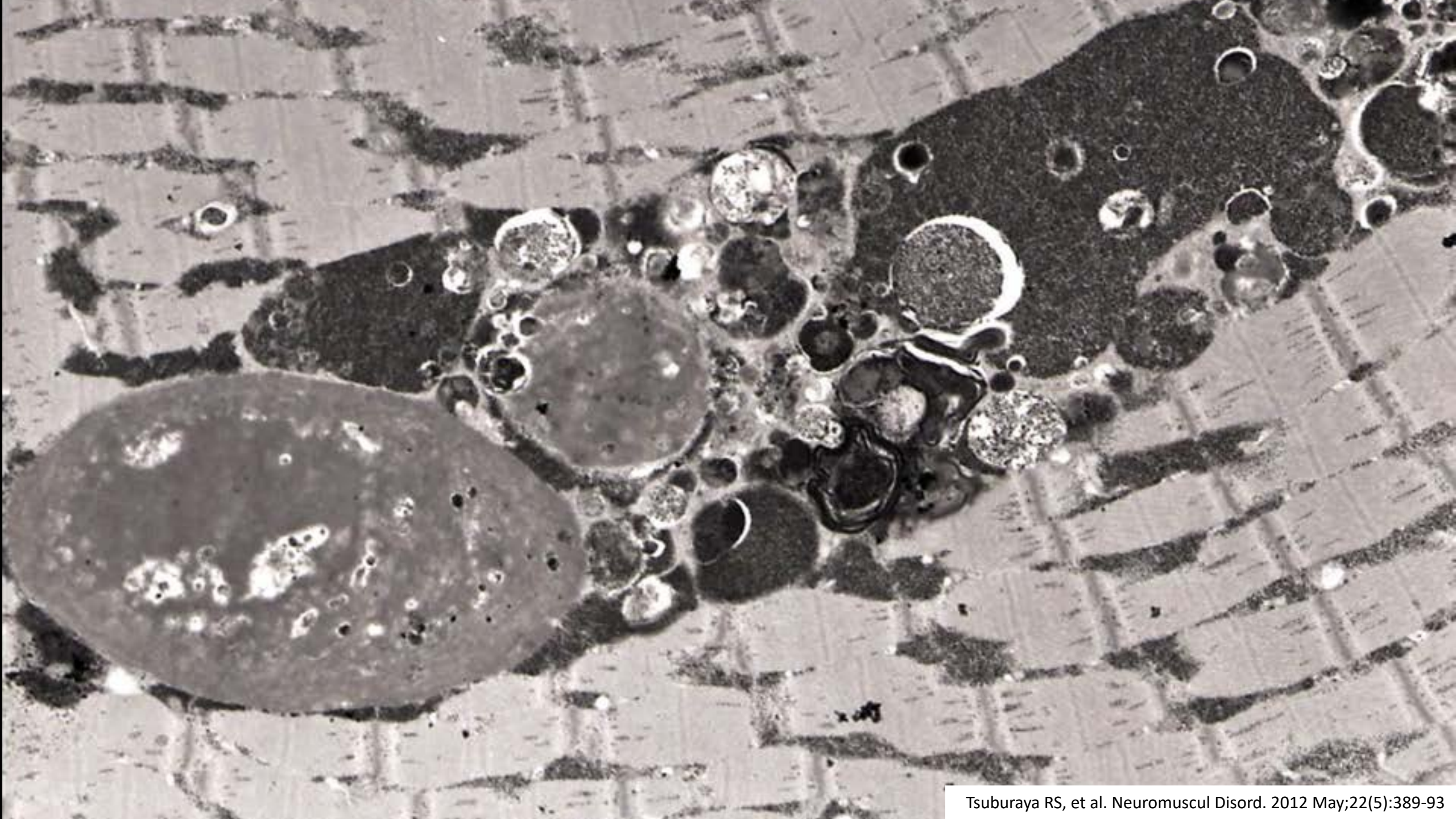


mGT

Tsuburaya RS, et al. Neuromuscul Disord. 2012 May;22(5):389-93



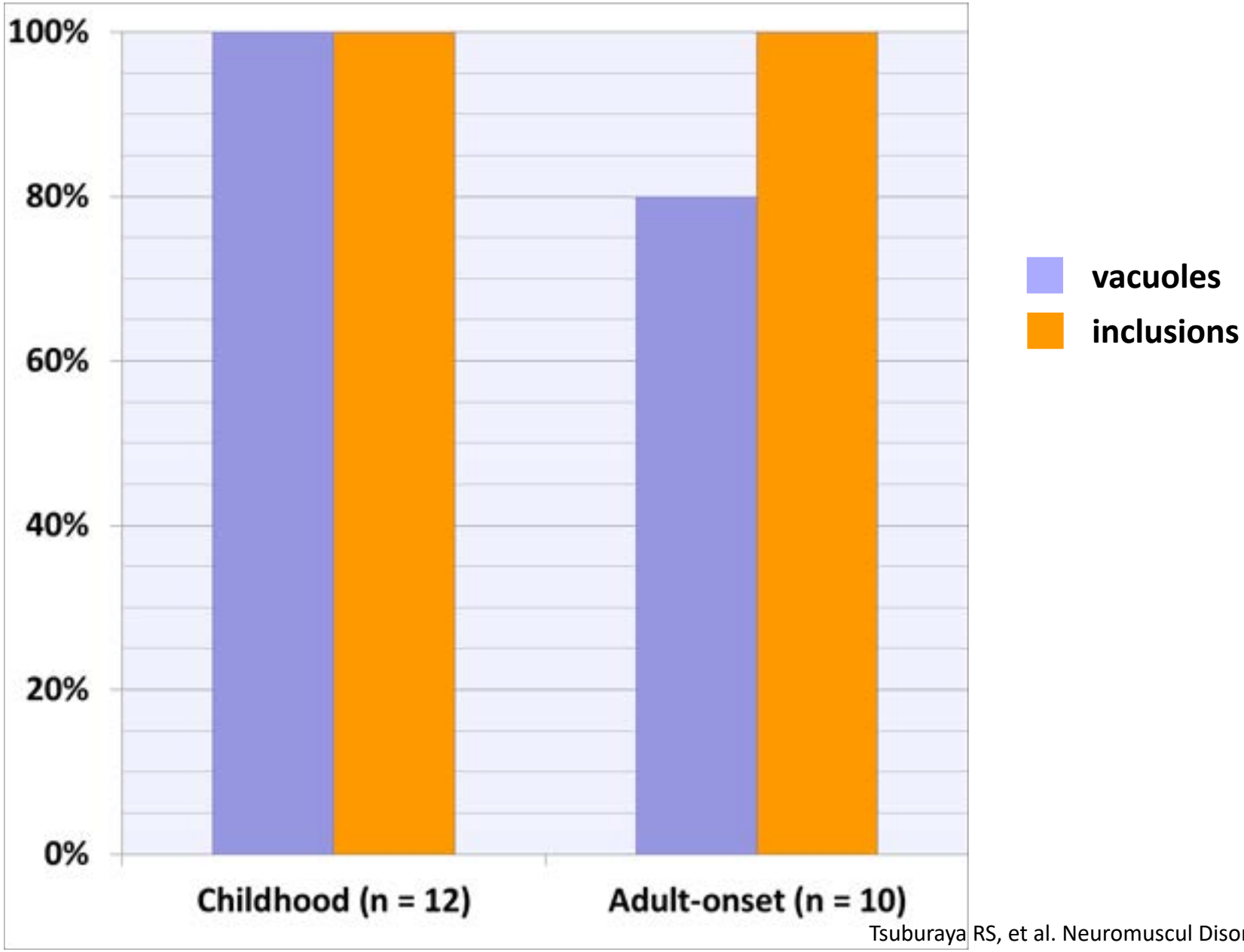
Acid phosphatase



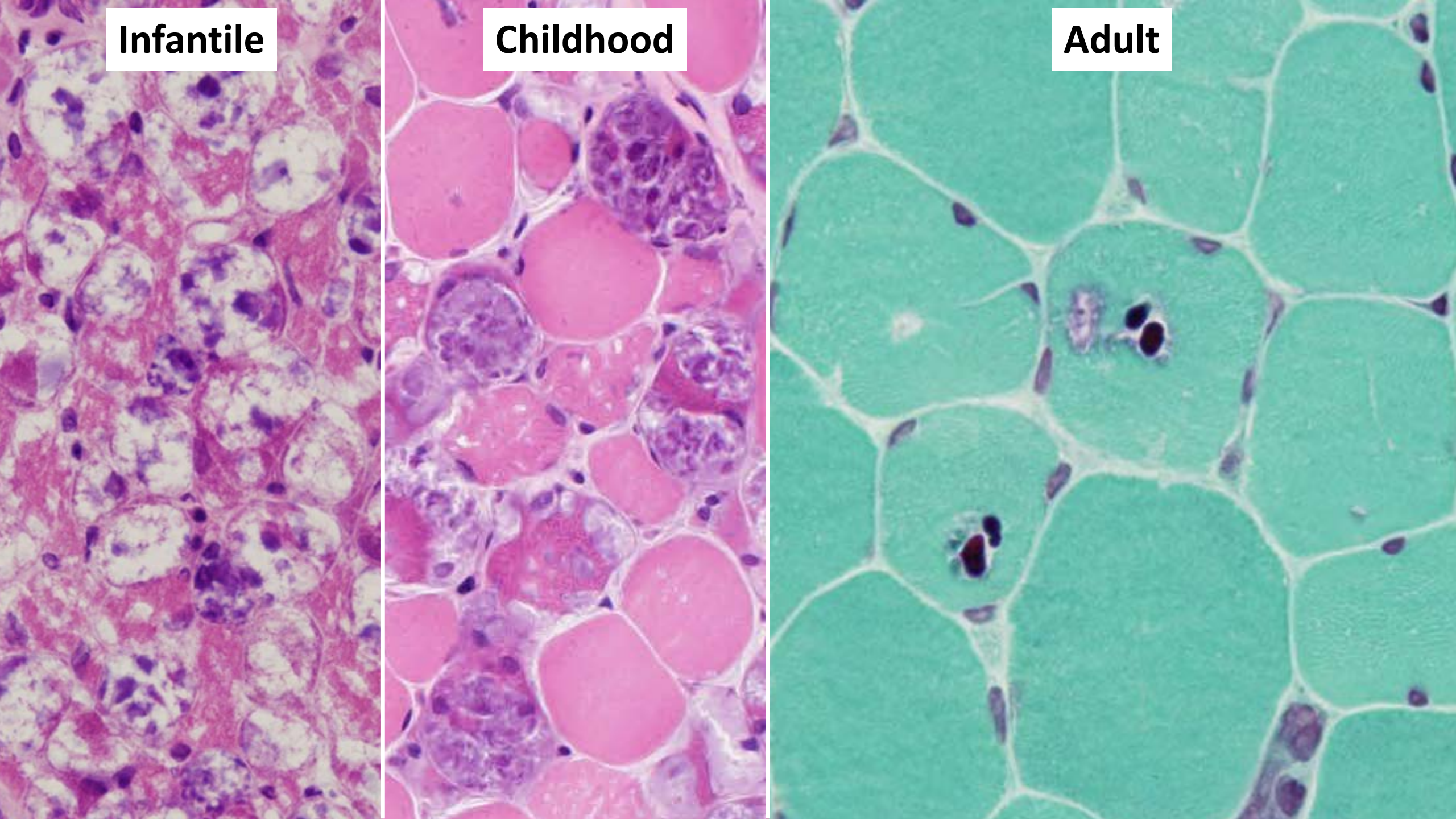
Tsuburaya RS, et al. Neuromuscul Disord. 2012 May;22(5):389-93

ACP-positive global cytoplasmic inclusions

Occurrence



Tsuburaya RS, et al. Neuromuscul Disord. 2012 May;22(5):389-93


Infantile
Childhood
Adult

Patients on ERT

October 2023

	Japan	Taiwan
Infantile	15	66
Late-onset	78	27
Childhood	50	
Adult-onset	28	
	93	**93**

Courtesy of Sanofi Japan /Taiwan

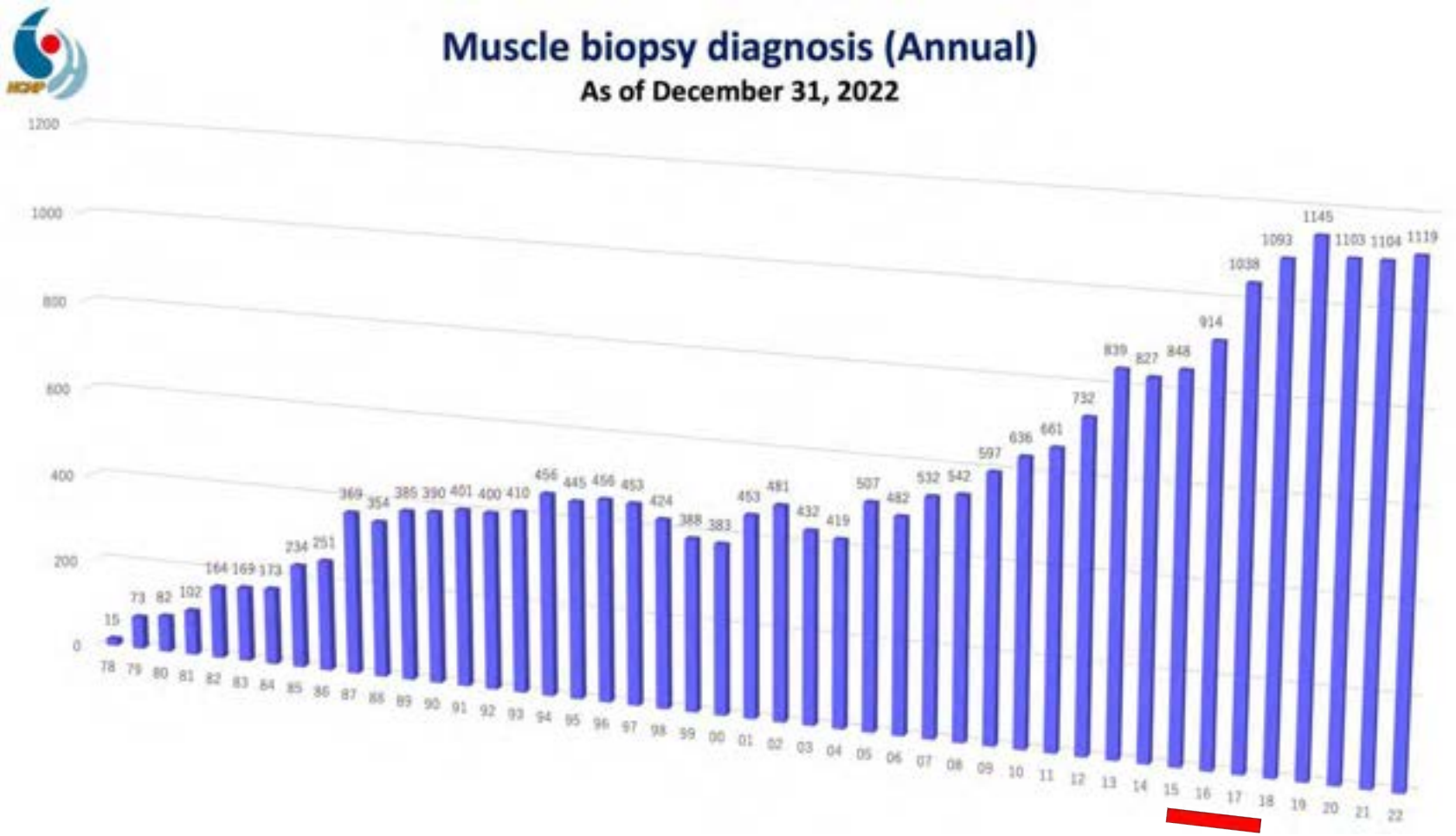
Neuromuscular

Muscle biochemical and pathological diagnosis in Pompe disease

Yoshihiko Saito [1], Kimitoshi Nakamura,[2] Tokiko Fukuda,[3] Hideo Sugie,[4] Shinichiro Hayashi,[1] Satoru Noguchi,[1] Ichizo Nishino [1]

2408 muscle biopsies in 2.5 years
July 2015 – January 2018

J Neurol Neurosurg Psychiatry. *Online ahead of print*



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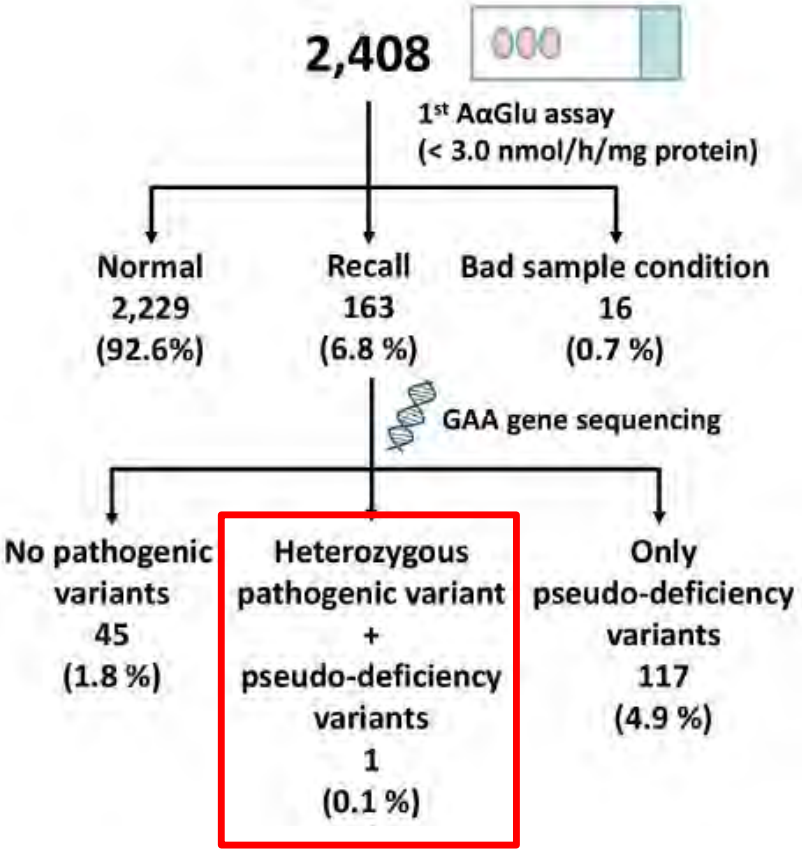
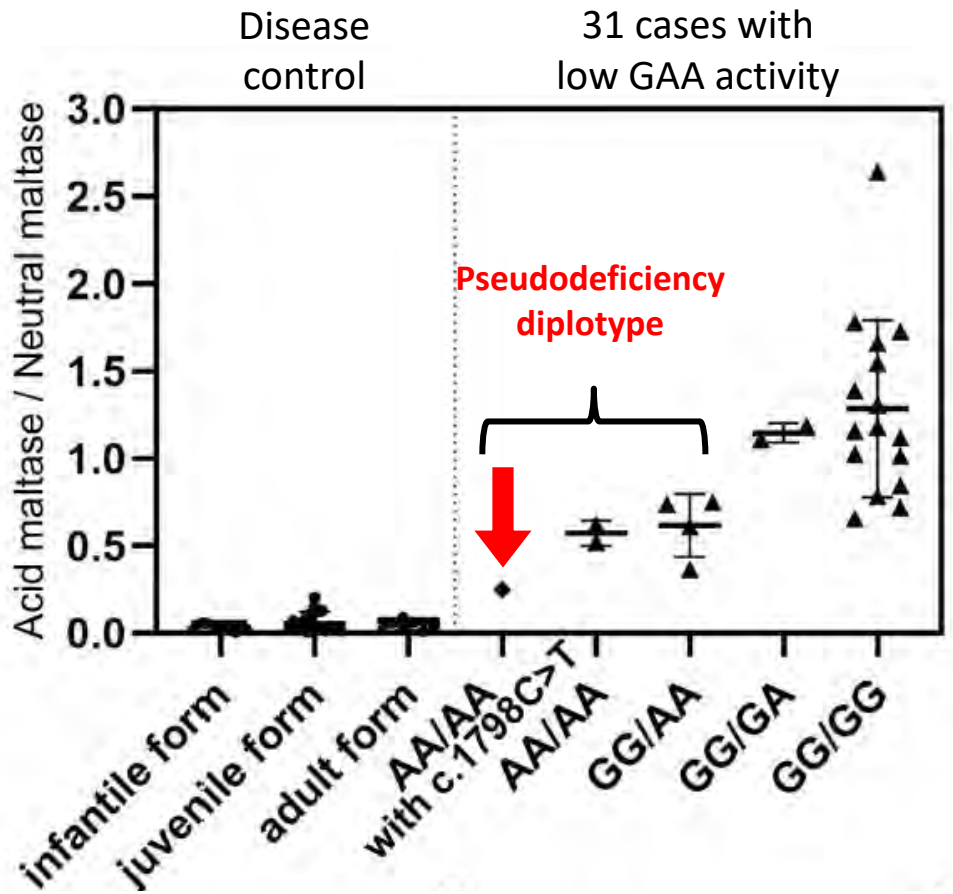
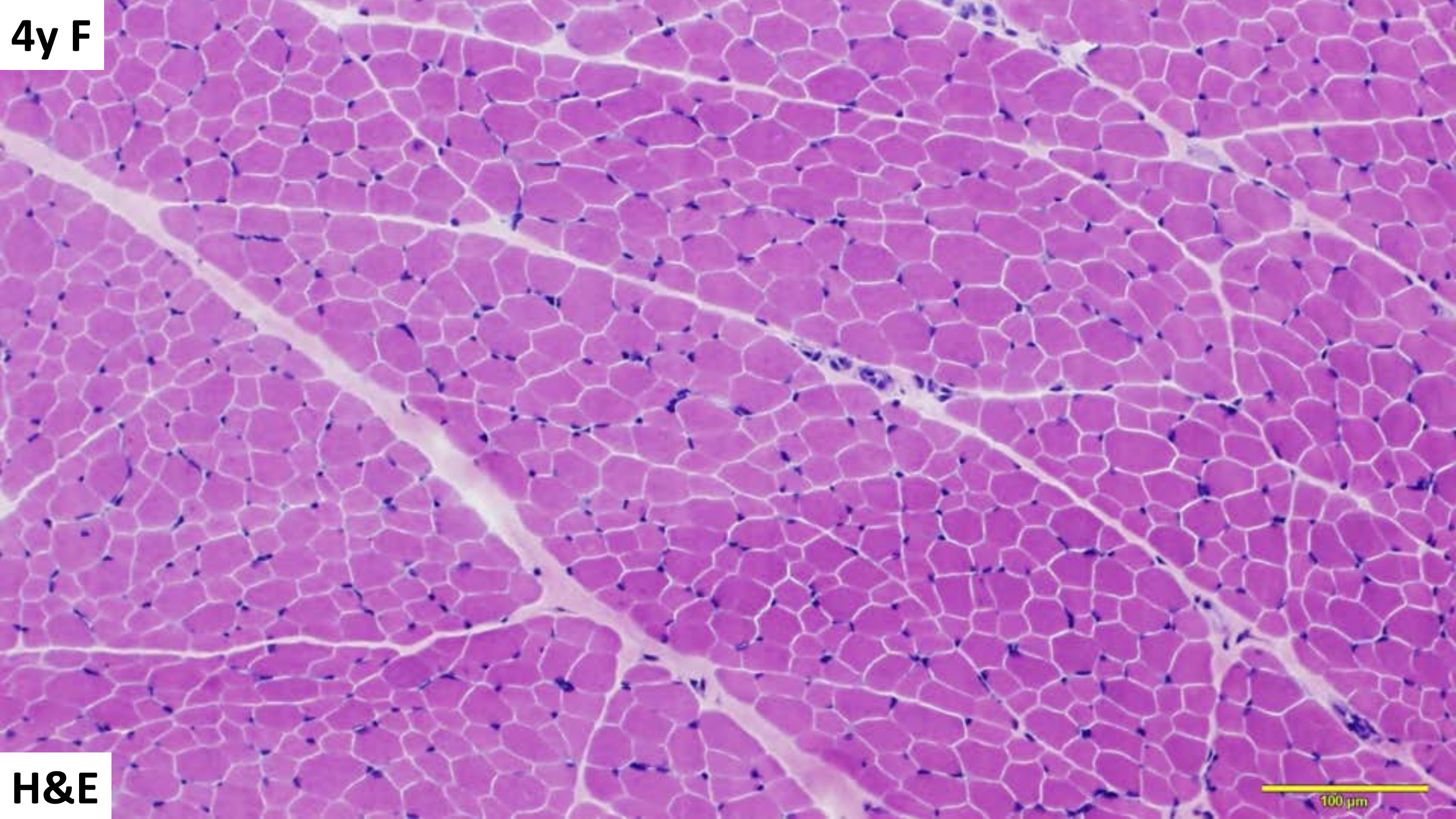
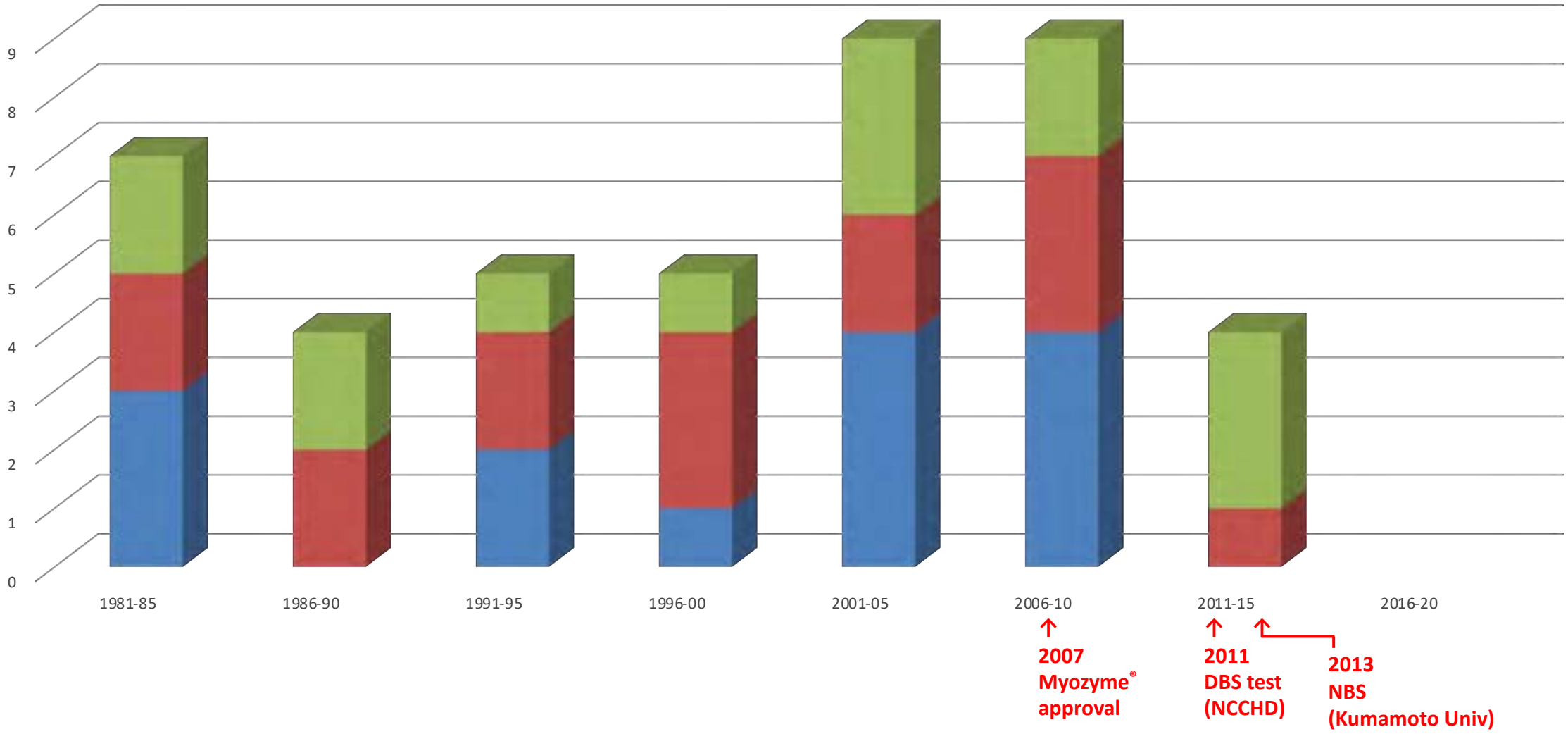




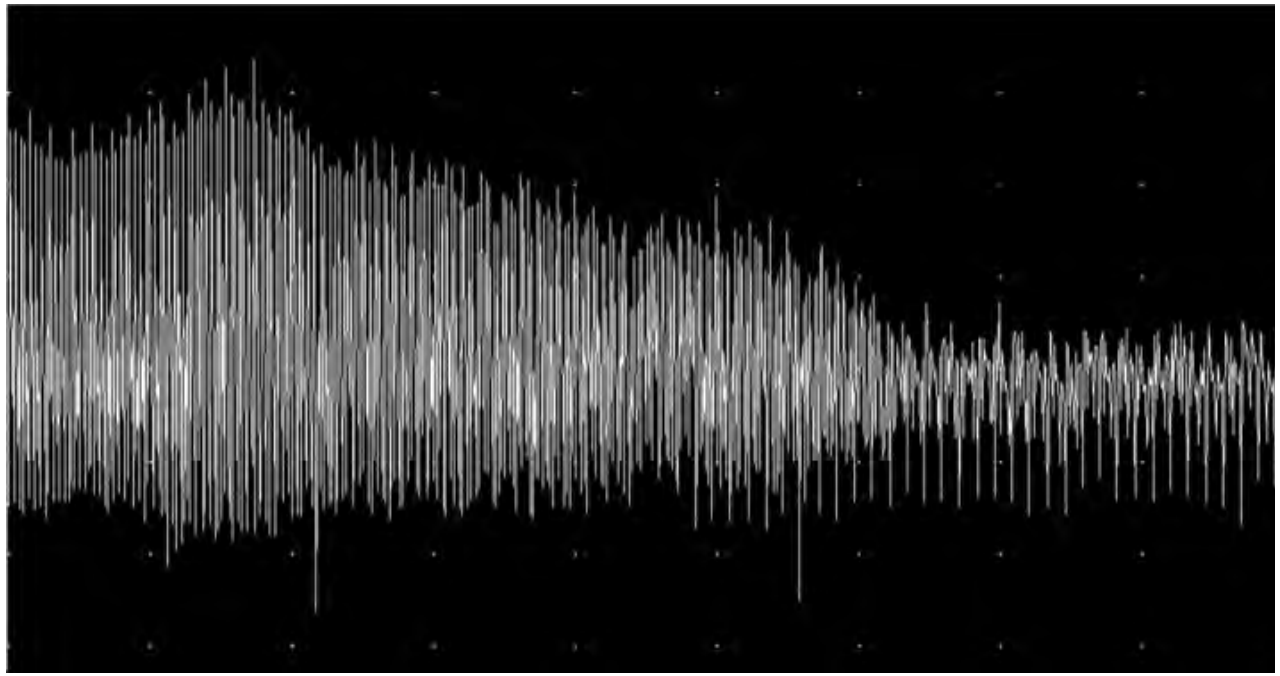

4y F
H&E
100 µm

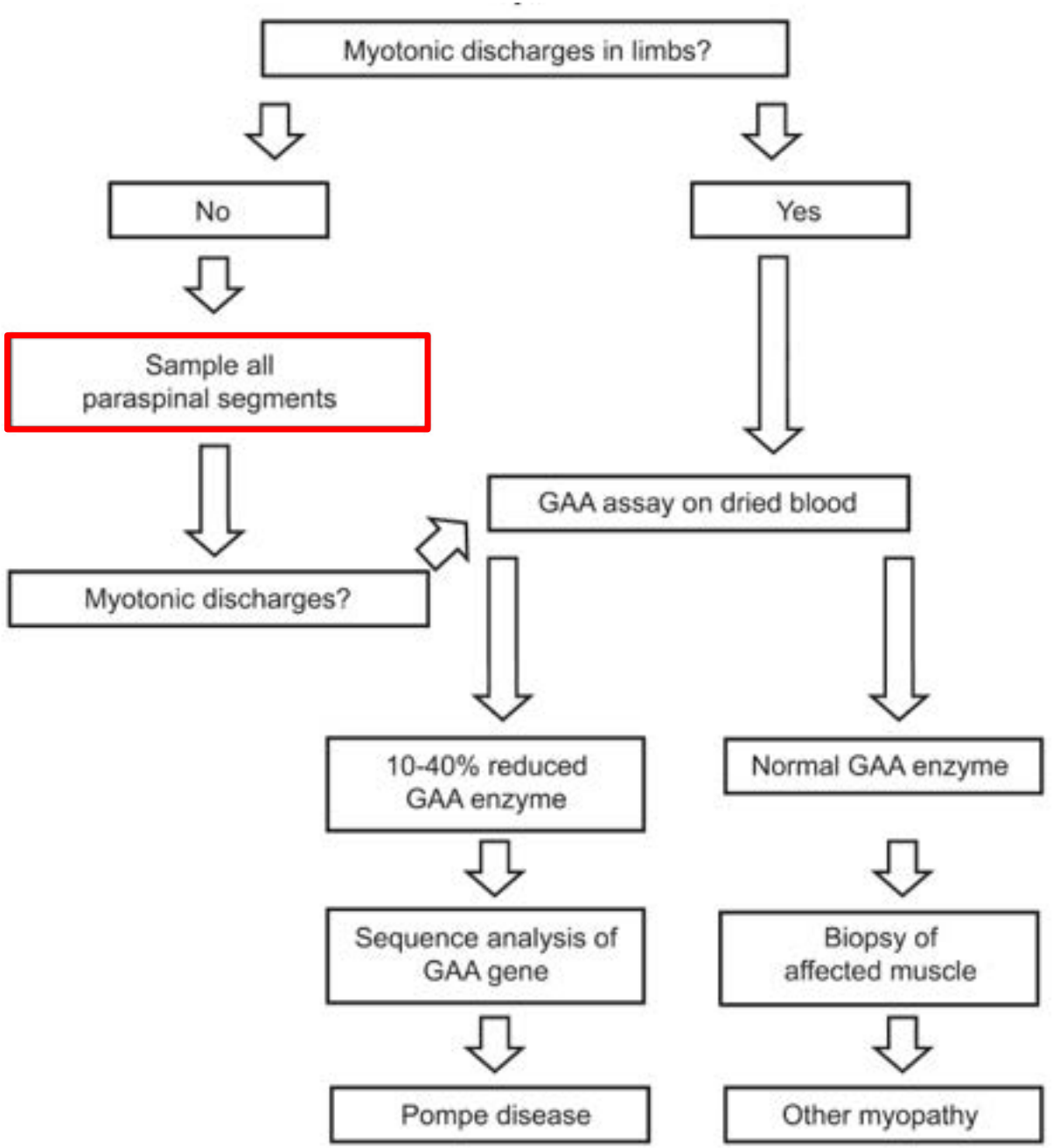
Pathologically diagnosed Pompe disease



Saito Y et al. **J Neurol Neurosurg Psychiatry**. *Online ahead of print*

Myotonic discharge in LOPD





Neurology. 2014 Mar 4;82(9):e73-5

Conclusions

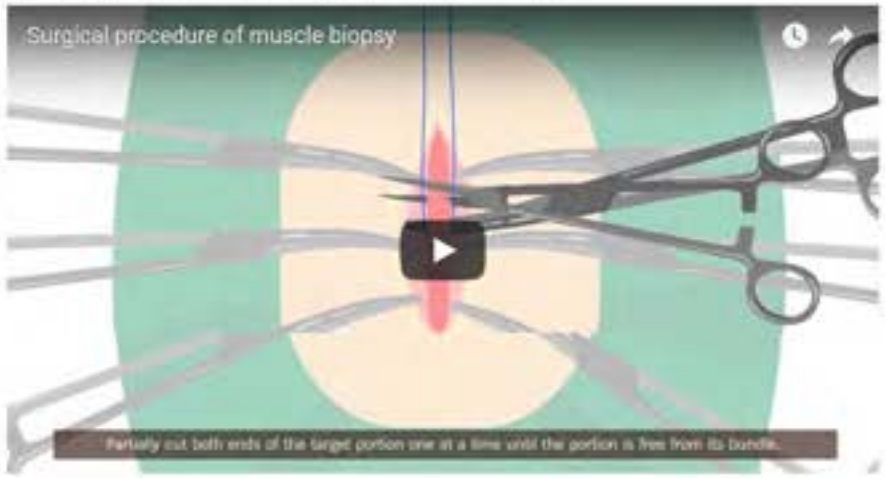
- **LOPD** – Needs to cast a wider net
  - Proximal weakness, respiratory failure, high CK

→ **DBS**

- Helpful findings on laboratory tests
  - **Muscle imaging**
    - Glut med/min, paraspinal, subscapularis, diaphragm
  - **Muscle pathology**
    - ACP-positive global cytoplasmic inclusions
  - **EMG**
    - Myotonic discharge (paraspinal m.)

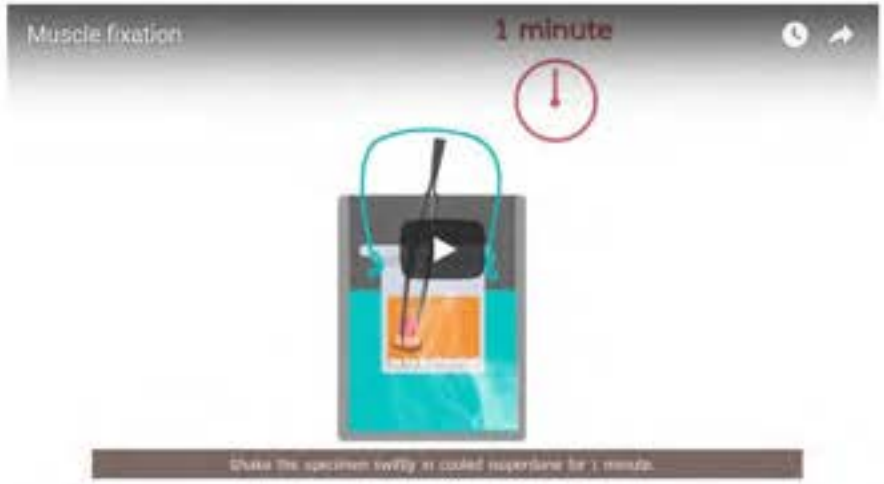
Muscle biopsy

The video shows the recommended surgical technique of muscle biopsy



Fixation of the biopsied muscle

The video shows the recommended techniques of freeze fixation (for histochemistry and immunohistochemistry) and glutaraldehyde fixation (for electron microscopic study) for biopsied muscle. Biopsied muscles should NOT be fixed with formalin unless there is a specific reason. Correct freeze fixation technique must always be used to avoid artifacts which are most frequently caused by inappropriate maneuver during the fixation procedure or mishandling of the frozen sample.



Teaching Videos for Muscle Biopsy and Fixation

https://www.ncnp.go.jp/nin/guide/r1/video_e.html

Acknowledgments

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- Tokiko FUKUDA
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- Masayuuki SASAKI

Department of Neuromuscular Research, National Institute of Neuroscience, NCNP
- Yoshihiko SAITO