Mystery Myopathy: Lessons in Genetic Testing

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Patient Overview

27 year old Northern Indian software engineer presents with weakness.

- Childhood onset weakness
- Presented in early 20s with proximal muscle weakness with progressive worsening through the years.
- Muscle biopsy in India with “chronic myopathy”
- Multiple evaluations in the US in late 20s with EMG showing irritative myopathy, muscle biopsy with lymphocytic infiltrates.
- Prednisone trial with minimal improvement.

PMH

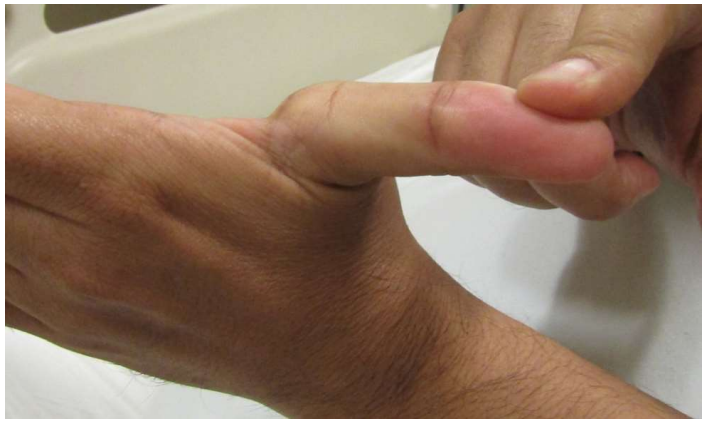
- Has been told his “heart sometimes beats too fast”

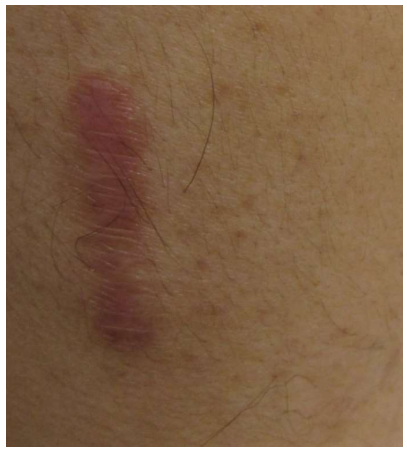
Family History

- No muscle or cardiac disease

Exam

HR 121, Normal BP



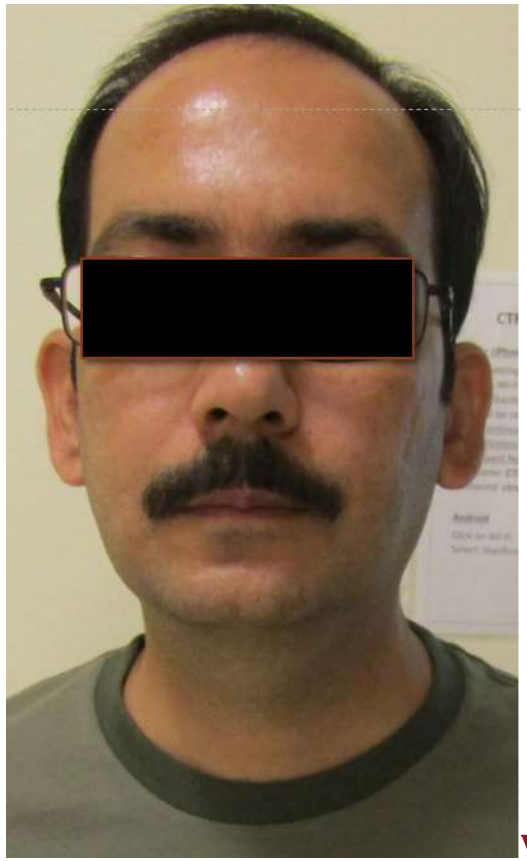


Musculoskeletal

- Joint hyperextensibility, atrophic scarring

Bulbar

- Mild temporal wasting
- Mild frontal balding
- Weakness of eye closure and tongue protrusion



versity

Exam

Motor

- No atrophy, no fasciculations, no myotonia
- Neck flexion weakness
- Increased effort with 10 deep knee bends
- Symmetric 4/5 weakness in all tested muscles except 3/5 in elbow extension and 5/5 hip extension and knee extension
- Difficult heel walking

Normal sensation, coordination, reflexes

Over the years, develops a **overlying distal pattern of weakness** in addition to his proximal weakness

- Hand intrinsics, ankle dorsiflexion
- Deep finger flexors preserved.

Labs, Echo, PFT, EMGs

Labs

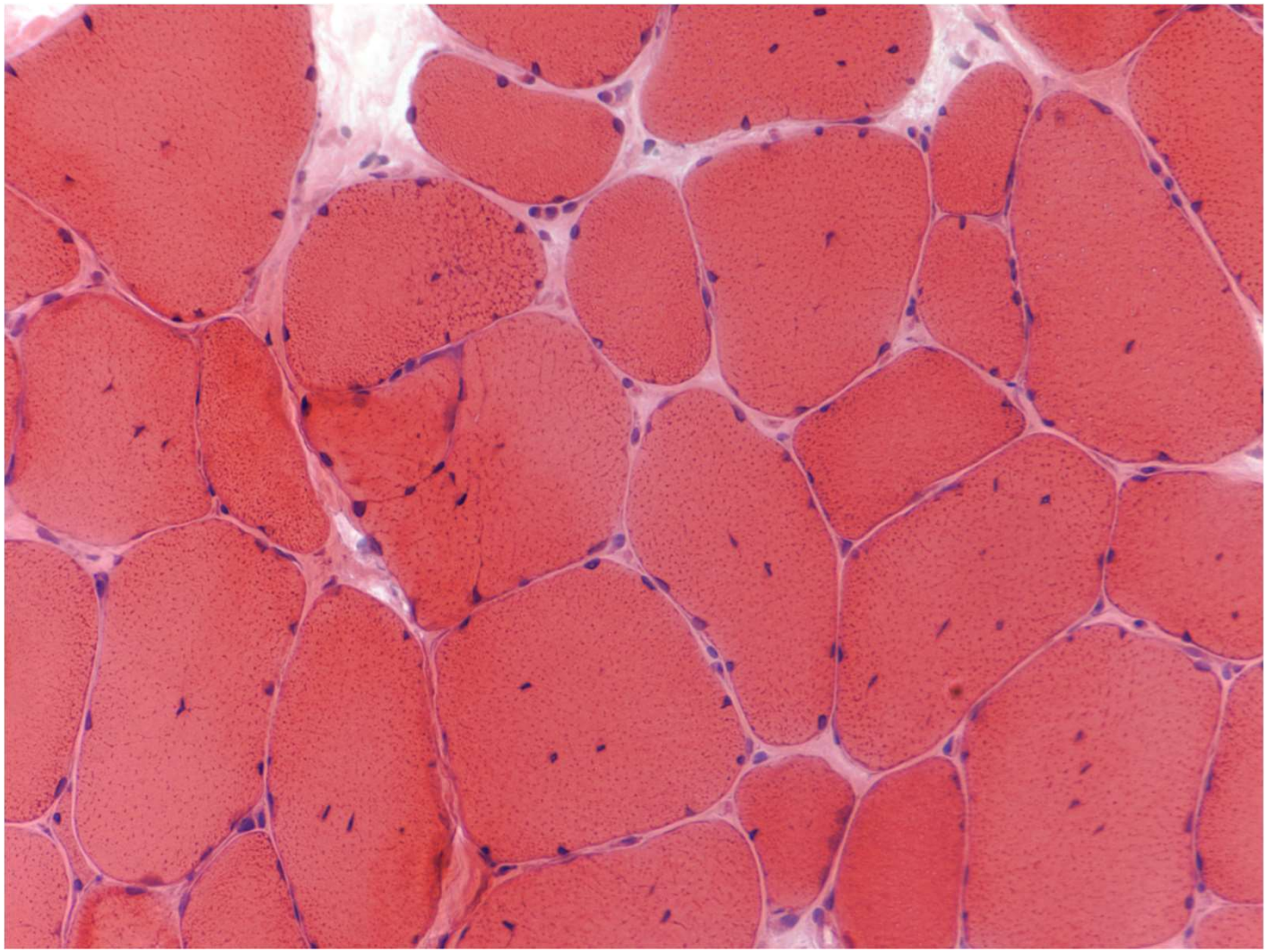
- CK 738-1350 (<300 U/L)
- Aldolase 8.0 (<7.7 U/L)
- AST 45-66 (<40 U/L), ALT 69-86 (<60 U/L), AP 110-150 (<130 U/L)
- Unremarkable ESR, CRP, BUN/Cr, ANA, RF, SPEP
- AChR antibodies negative
- Mayo myomarker panel negative

Echocardiogram – EF 44%, mild global hypokinesis, mild RV dilation

PFTs – Restrictive FVC 46% and NIF -49

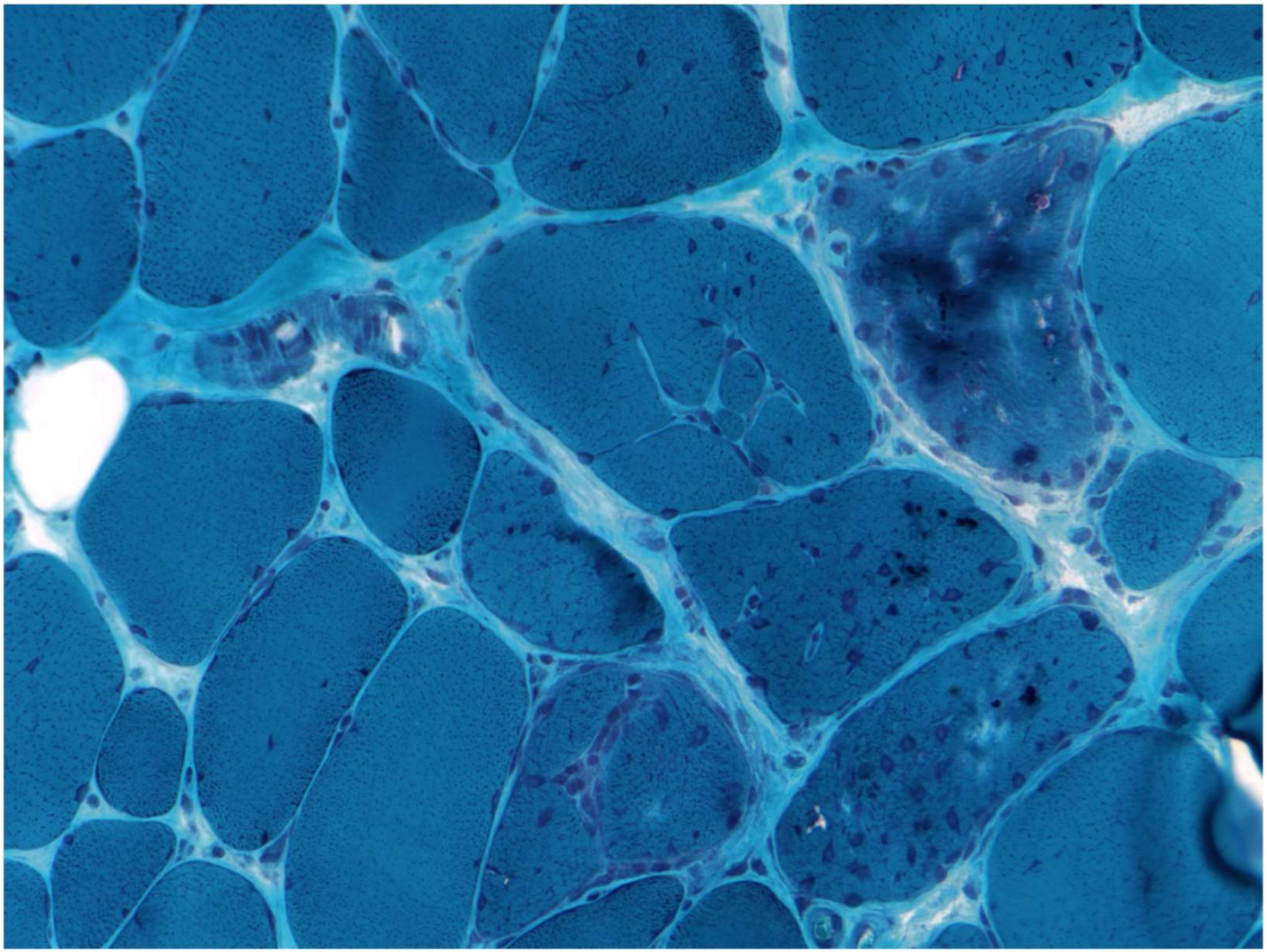
EMG - Irritative myopathy with most significant changes in proximal muscles (triceps, vastus medialis, vastus lateralis). No myotonia

H&E – Fiber size variability, internally placed nuclei, fiber splitting

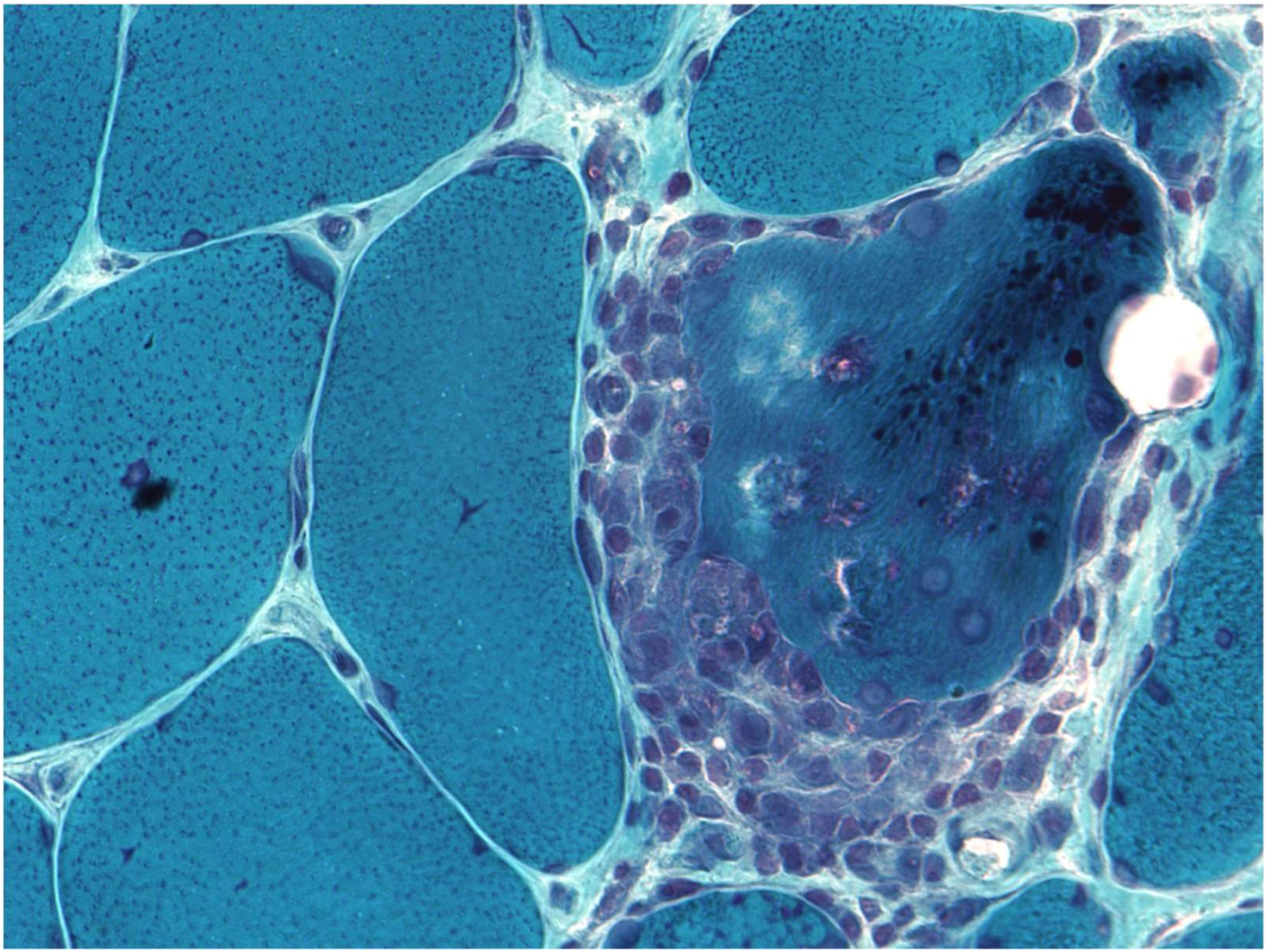


ATPase pH 9.4 – Type 2 Predominance

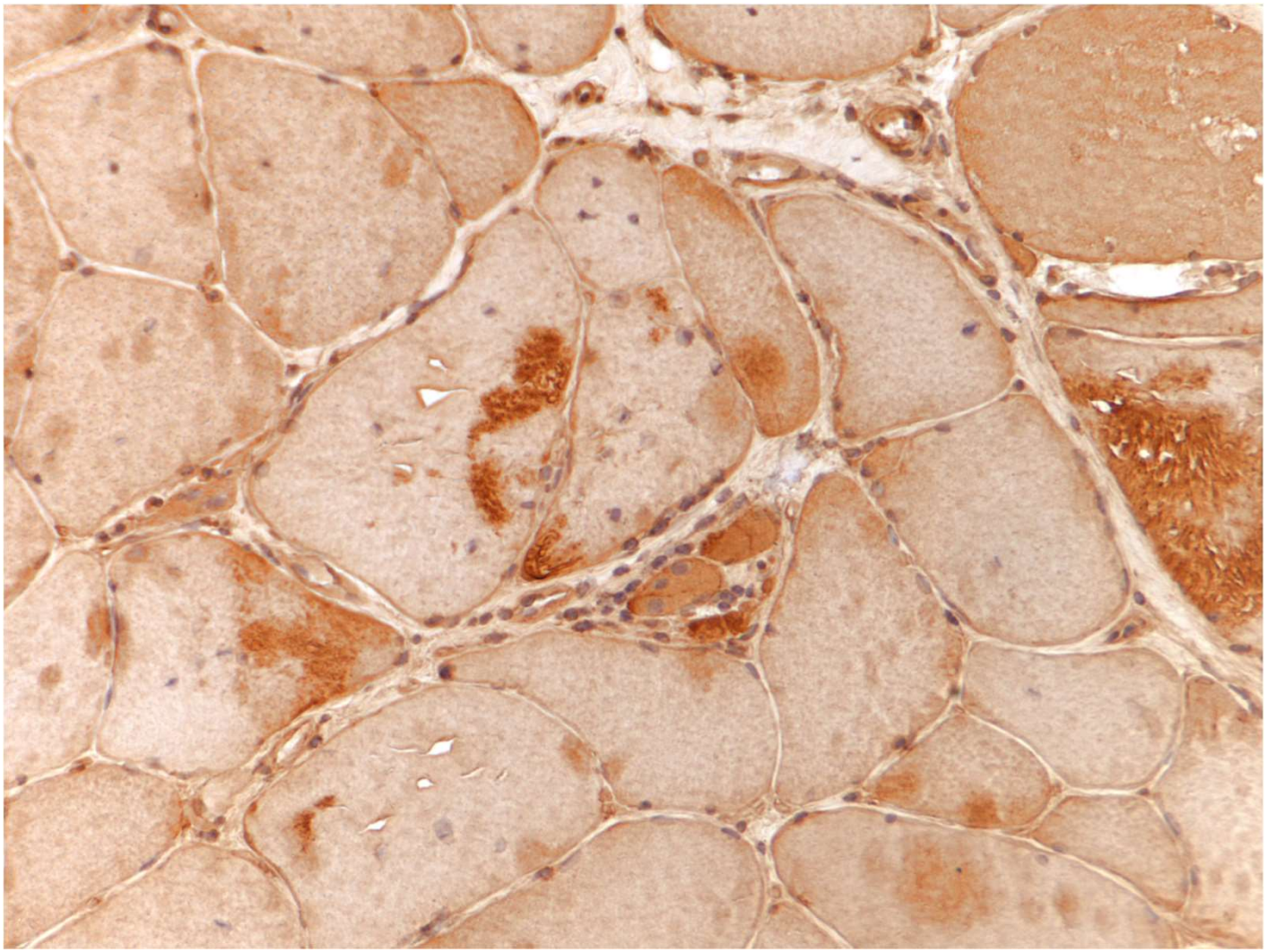
Fiber splitting, Rimmed vacuoles



Inflammatory foci, Sarcolemmal bodies/dark blue structures



IHC – Myotilin



Muscle Biopsy Special Staining

Immunofluorescence – normal sarcolemmal staining for dystrophin-glycoprotein complex, caveolin 3, merosin, collagen 6/perlecan, and spectrin.

MRI Thighs at 30 years old

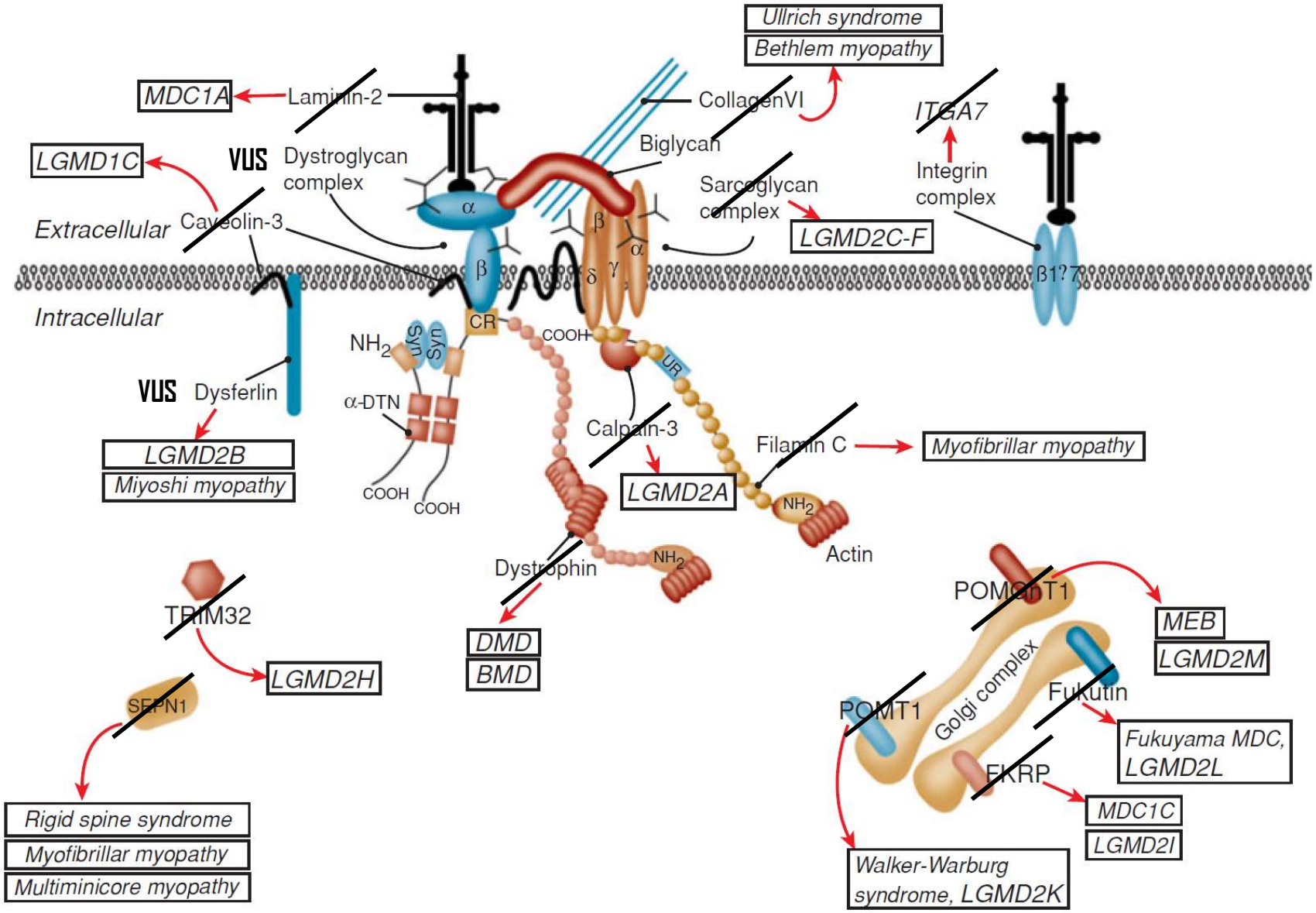
Nonspecific atrophy of the left gluteus maximus, sartorius, vastus intermedius, adductor minimus, and posterior compartment thigh muscles.

Thoughts prior to Genetic Testing?

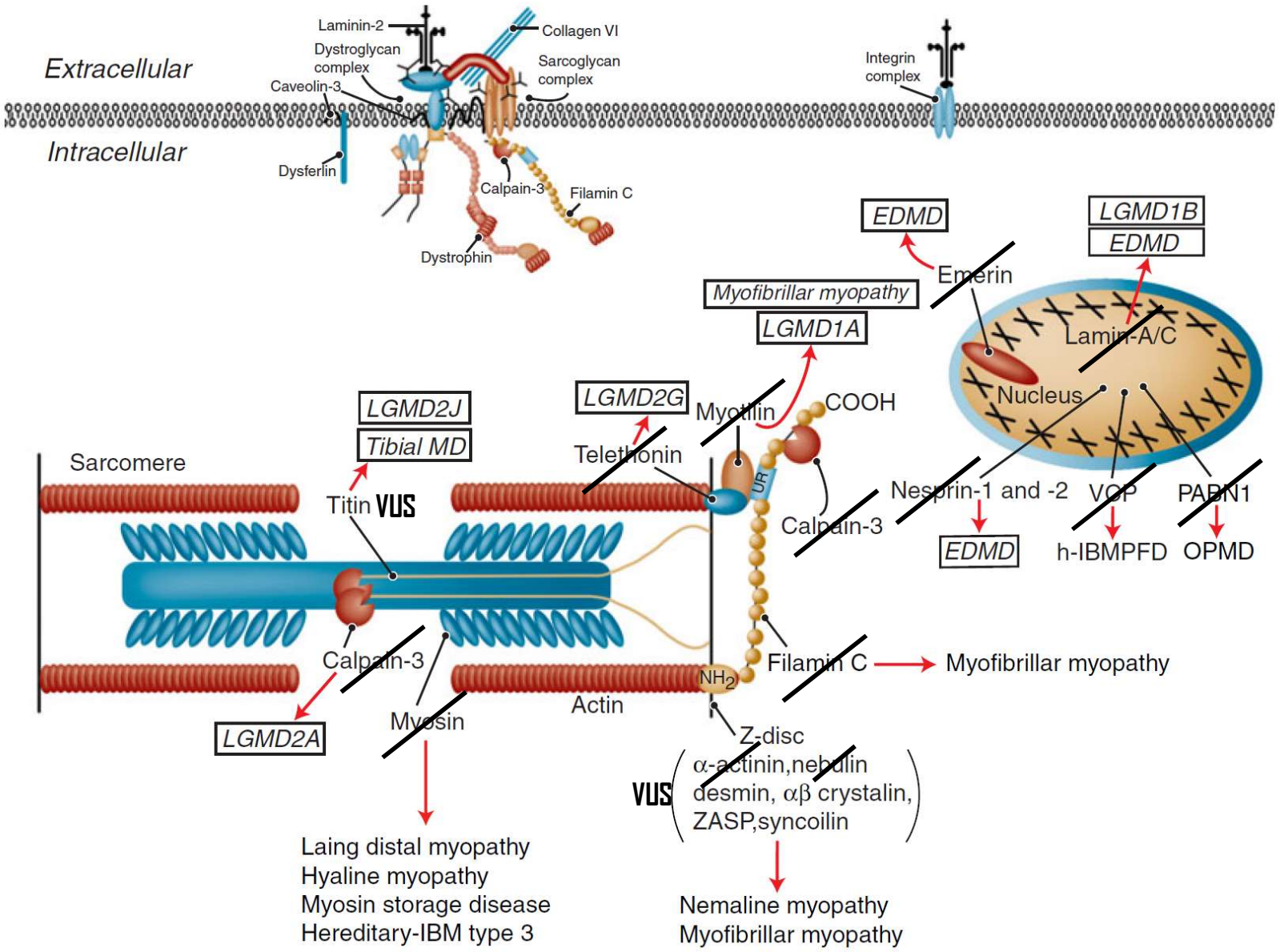
27 year old Northern Indian software engineer presents with progressive proximal and distal weakness with childhood onset weakness presenting to clinical attention at age 23. Mild bulbar weakness on exam. CK~1000. EMG with irritative myopathy more prominent in proximal muscles. Muscle biopsy with signs of chronic myopathy, foci of chronic inflammation, rimmed vacuoles, type 2 predominance.

Genetic Testing Unrevealing

- MYOT – Myofibrillar myopathy
- DMD – Duchenne Muscular Dystrophy
- DMPK and CNBP – Myotonic dystrophy types 1 and 2
- TCAP – LGMD7
- EMD – Emery Dreifuss
- MATR3 – Distal Myopathy 2
- VCP – Inclusion body myopathy
- OPMD – Oculopharyngeal muscular dystrophy
- FSHD – Facioscapulohumeral dystrophy
- Proband only whole exome sequencing
  - VUS in ACADS x2, AMPD1
- Congenital Muscular Dystrophy Panel + mtDNA
  - VUS in ACADS, EARS2, MTFMT, HSPG2, TTN x5, DES
- Muscular dystrophy panel (29 genes)
  - VUS in TTN x2, DAG1, DYSF



Dalkilic I, Kunkel LM. Muscular dystrophies: Genes to pathogenesis. Curr Opin Genet Dev 2003;13(3):231–238.)



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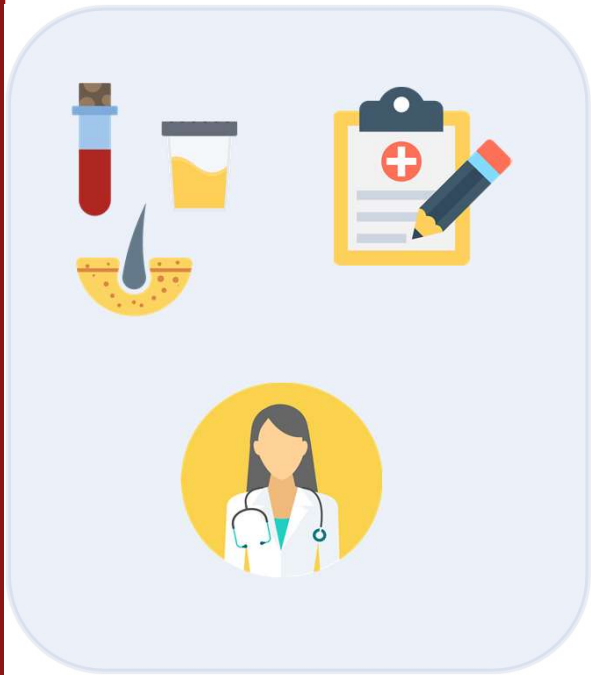
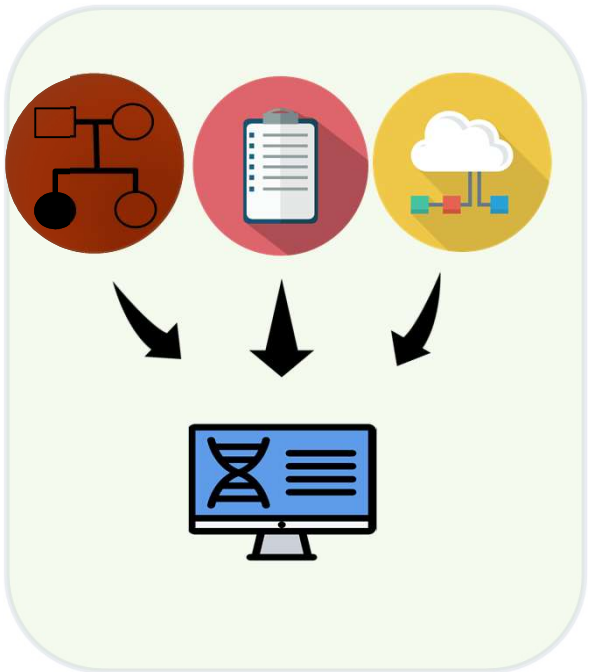
Undiagnosed Disease Network Evaluation

https://undiagnosed.hms.harvard.edu/

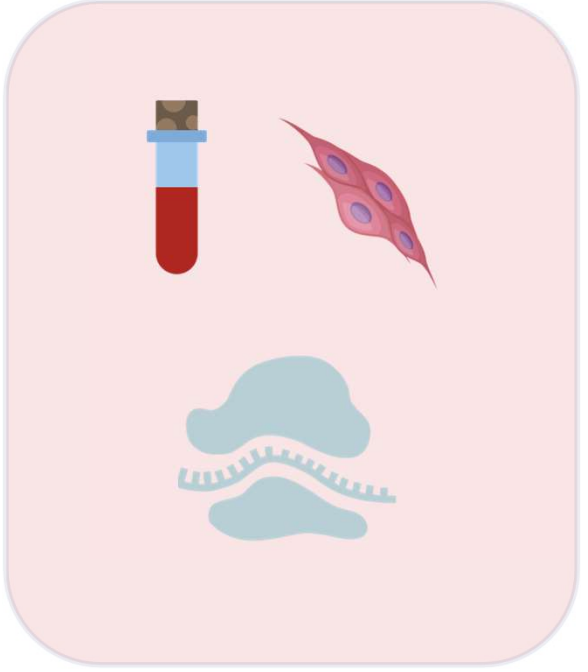
Clinical



Genetics



Research



Criteria
1.) Rare
2.) Undiagnosed
3.) All clinical and diagnostic options exhausted

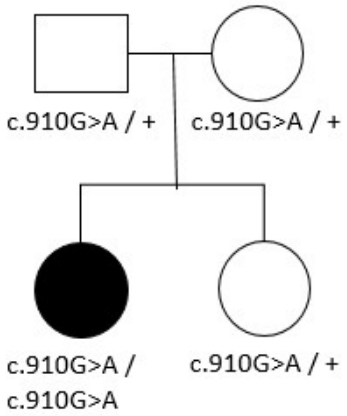
Undiagnosed Diseases Network

Stanford | Center for Undiagnosed Diseases

Whole Exome Sequencing Report

Homozygous: *ADSSL1*

- c.910G>A (p.Asp304Asn)



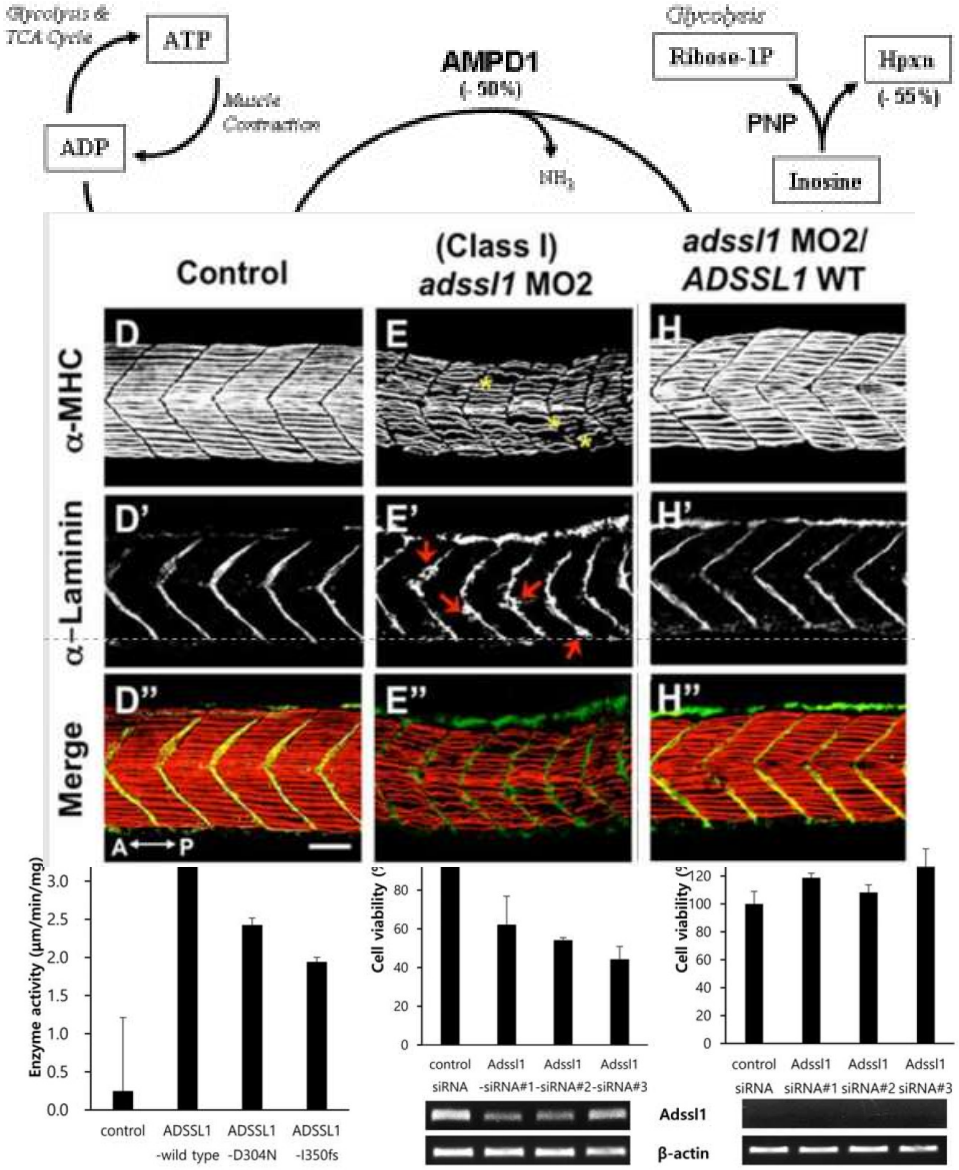
- Homozygous Missense variant in ADSSL1
- Autosomal Recessive Distal Myopathy
- Described in 2016 in Korea

ADSSL-1 Adenylsuccinate Synthase-like 1

Park, Hyung Jun, et al. "*ADSSL1* Mutation Relevant to Autosomal Recessive Adolescent Onset Distal Myopathy." *Annals of Neurology*, vol. 79, no. 2, 2016 Feb, pp. 231–243.

- 4 patients from 2 families with compound heterozygous variants – one frameshift c.1048delA (p.I350fs) and one missense c.910G>A (p.D304N)

- Proof of concept using
  - Patient muscle sample
  - Cellular model
  - Zebrafish model



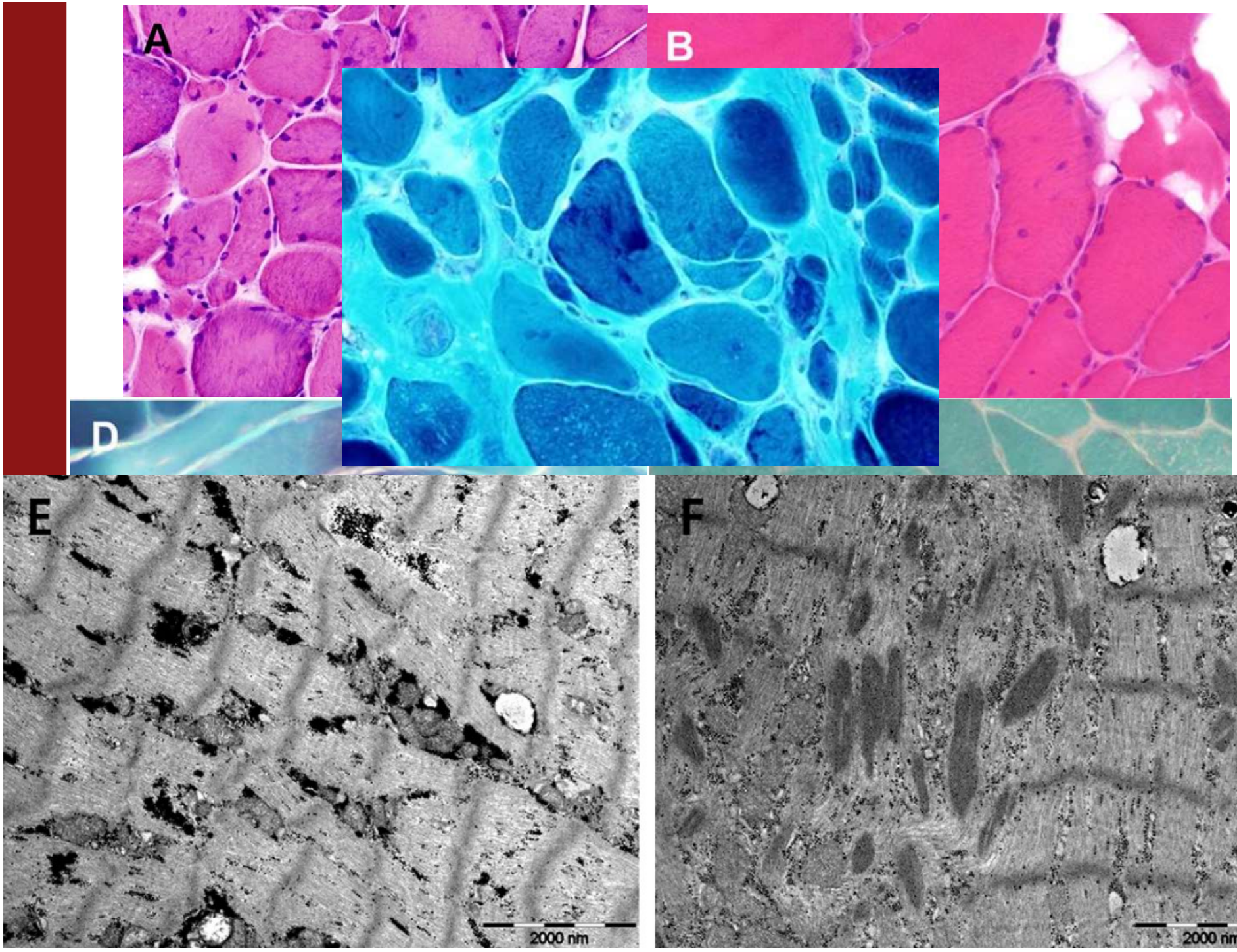
ADSSL1 Myopathy Phenotype

Hyung Jun Park, et al, Distal myopathy with ADSSL1 mutations in Korean patients, Neuromuscular Disorders, Volume 27, Issue 5, 2017, Pages 465-472.

- Age of onset 5-7yo diffuse weakness
- Foot drop 13-17yo
- Quadriceps weakness in early 30s
- Mild facial weakness
- No sensory abnormalities, joint contractures, craniofacial dysmorphisms
- CK 108-493
- Normal EKG and echocardiogram

Imaging

- MRI with fatty infiltration of gastrocnemius>other calf muscles>quadricep (vastus lateralis)> adductors> biceps femoris
- Fatty infiltration of tongue at early stage


A
B
D
E
2000 nm
F
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Takeaway points

ADSSL1 AR Distal Myopathy with generalized weakness in childhood, distal weakness in adolescence, mild facial weakness, normal to mildly elevated CK with chronic myopathic features, rimmed vacuoles, fiber splitting, whorled fibers, type 1 predominance, nemaline bodies. MRI possibly with early tongue involvement.

Unique Case Features

- Patients can present with more proximal weakness
- Mild dilated cardiomyopathy
- Type 2 predominance
- Mild restrictive PFTs

Lesson in Genetic Testing

- Reanalysis of whole exome sequencing
- UDN referral via https://undiagnosed.hms.harvard.edu/

Thank you for your attention!

Special thanks to:

Undiagnosed Disease Network

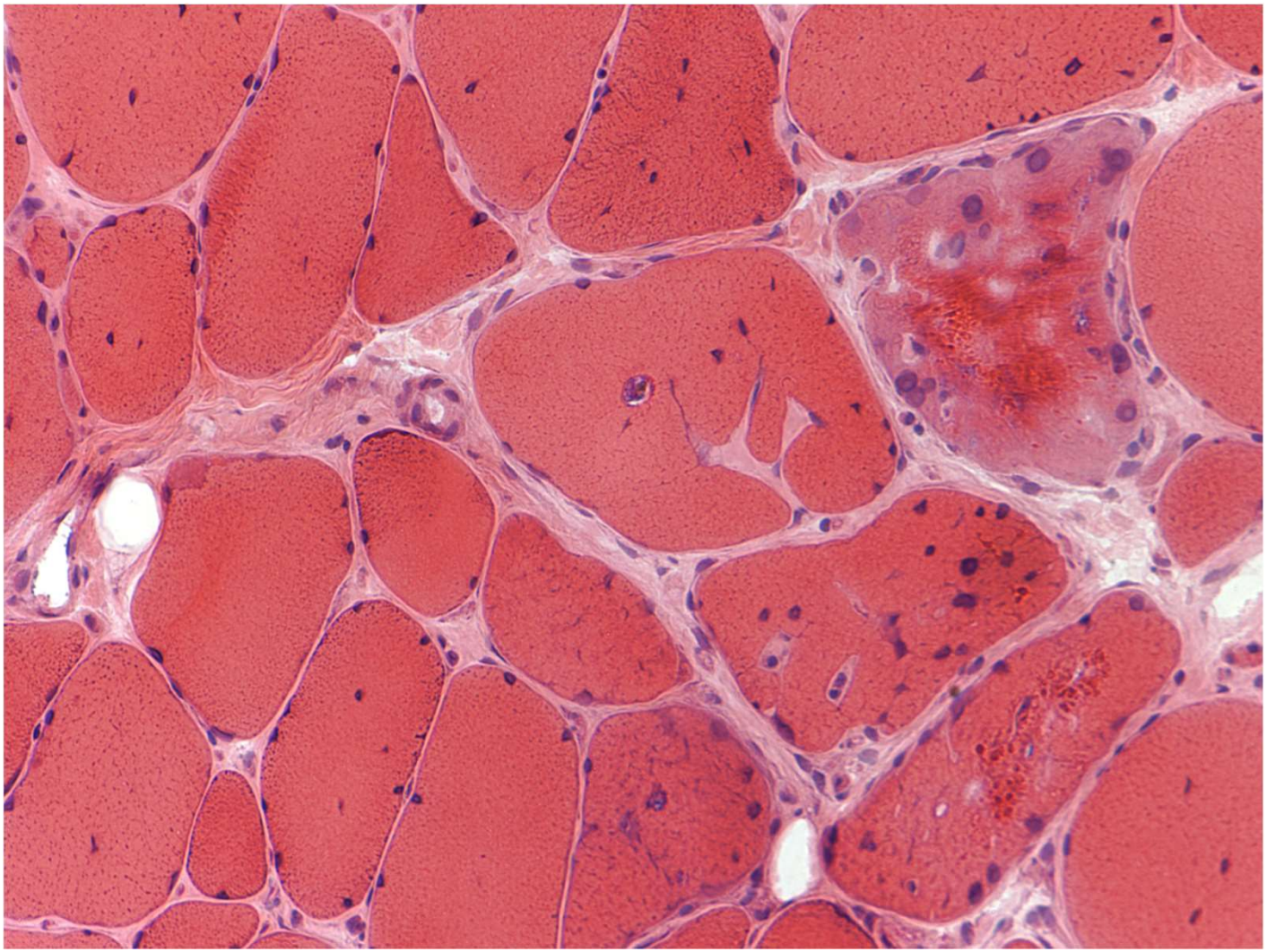
Stanford UDN Team:

- Devon Bonner
- Marta Majcherska
- Liz Worthey
- Matthew Wheeler
- Jacinda Sampson

John Day

Sarada Sakamuri

Fiber splitting



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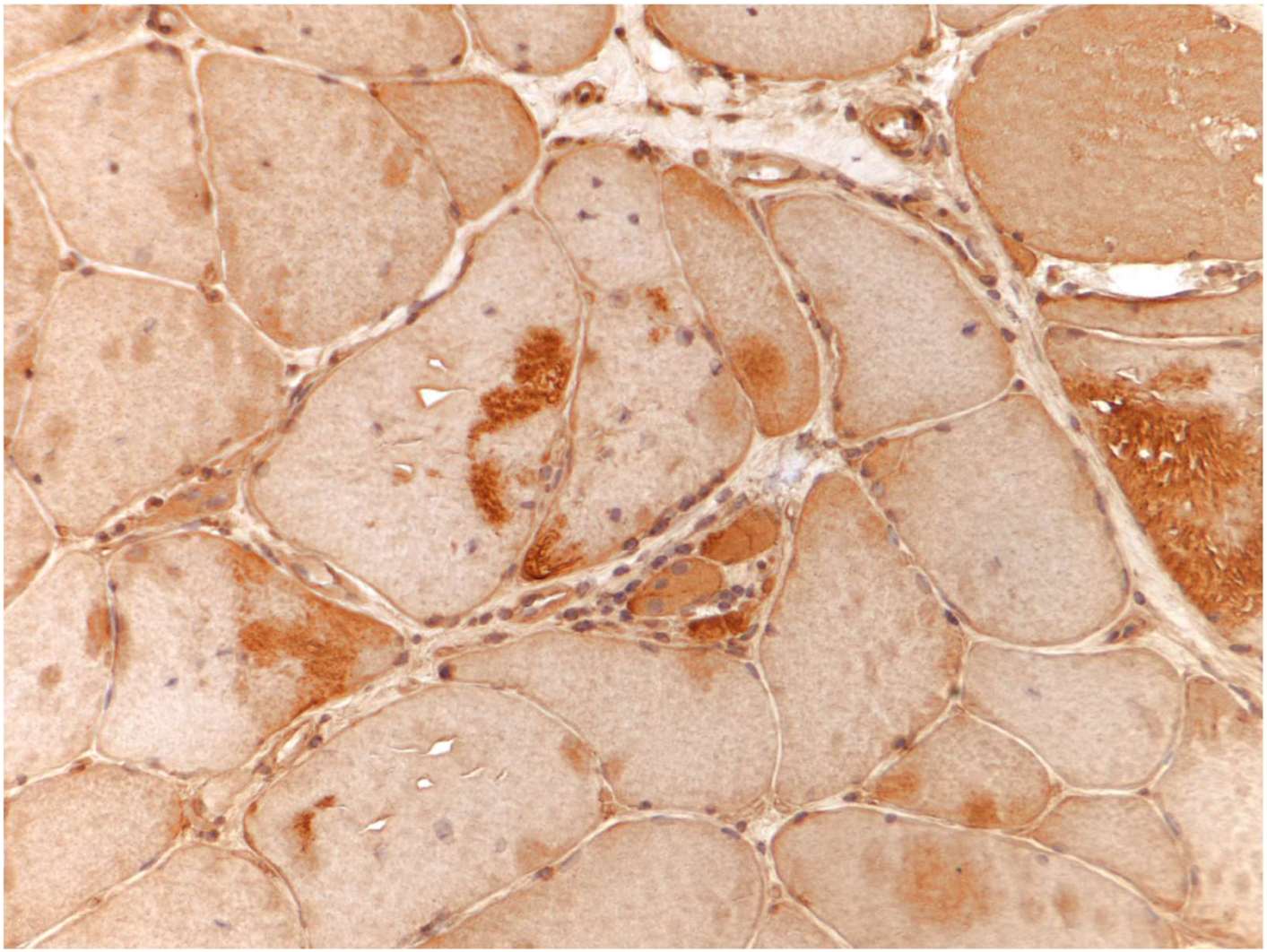

EMGs

2011	Insertional	Spontaneous Activity			Volitional MUAPs			
Muscle	Activity	Fibs and PSW	CRD	Fascic	Amplitude	Duration	Poly	Recruitment
R Deltoid	Normal	1+	0	0	Decr	Decr	None	Normal
R Biceps Brachii	Normal	1+	0	0	Decr	Decr	None	Full, Early
R Triceps	Normal	2+	0	0	Decr	Decr	None	Full, Early
R Vastus Lateralis	Normal	0	0	0	Decr	Decr	None	Full, Early

2013	Insertional	Spontaneous Activity			Volitional MUAPs			
Muscle	Activity	Fibs and PSW	CRD	Fascic	Amplitude	Duration	Poly	Recruitment
R Deltoid	Increased	1+	None	None	None	Decr	None	Early
R Biceps Brachii	Increased	1+	None	None	Decr	Decr	None	Early
R Triceps	Increased	2+	None	None	Decr	Decr	None	Early
R FDI	Normal	None	None	None	Decr	Decr	None	Early
R Vastus lateralis	Increased	2+	None	None	Decr	Decr	None	Early
R Tibialis anterior	Normal	1+	None	None	Normal	Decr	Few	Early

2017	Insertional	Spontaneous Activity			Volitional MUAPs			
Muscle	Activity	Fibs and PSW	CRD	Fascic	Amplitude	Duration	Poly	Recruitment
L Brachialis	Increased	1+	None	None	Decr	Decr	Few	Full, Early
L Flexor carpi radialis	Reduced	1+	None	None	Decr	Decr	Few	Full, Early
L FDI	Increased	1+	None	None	Mildly Decr	Mildly Decr	None	Mildly Early
L L1 paraspinal	Increased	1+	None	None	Decr	Decr	Rare	Mildly Early
L Vastus medialis	Increased	3+	None	None	Decr	Mildly Decr	Few	Full, Early
L Tibialis Anterior	Reduced	1+	None	None	Mixed	Normal	None	Mod Early
L Med Gastrocnemius	Reduced	1+	None	None	Mixed	Normal	None	Mod Early