

Proximal Myopathy, Rhabdomyolysis and Ataxia

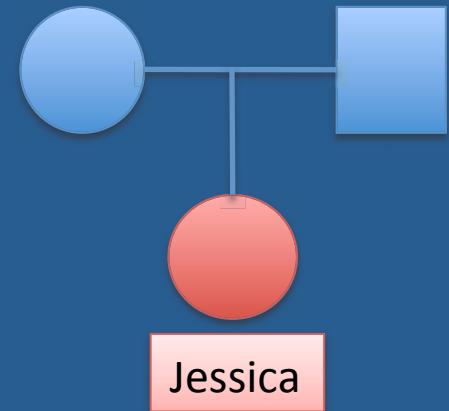
Is this a case of mitochondrial myopathy?

Dr. Roula Ghaoui

Prof. Carolyn Sue

Jessica

- A floppy infant (non-consanguineous) with delayed milestones
 - walked at the age of four wide based gait
 - delayed speech
 - cognitively delayed
 - Microcephaly
 - Closely set eyes with angular mouth
- First reviewed at the age of six months after a blood test revealed an elevated creatine kinase level
- An EEG revealed epileptiform discharges and although Jessica has not suffered a seizure, she was commenced on Tegretol.



Age 7 years

- Recurrent episodes of rhabdomyolysis precipitated by exercise
 - Muscle cramps
 - Elevated CK up to about 10,000

Examination

- Wide-based gait and appeared to be complicated by the presence of multiple dyskinesias, which at the time were interpreted as being choreiform.

Investigations

- A number of metabolic studies were performed-**ALL NORMAL**
 - fatty acid oxidation defects
 - carnitine defects and amino and organic acid defects
 - myotonic dystrophy

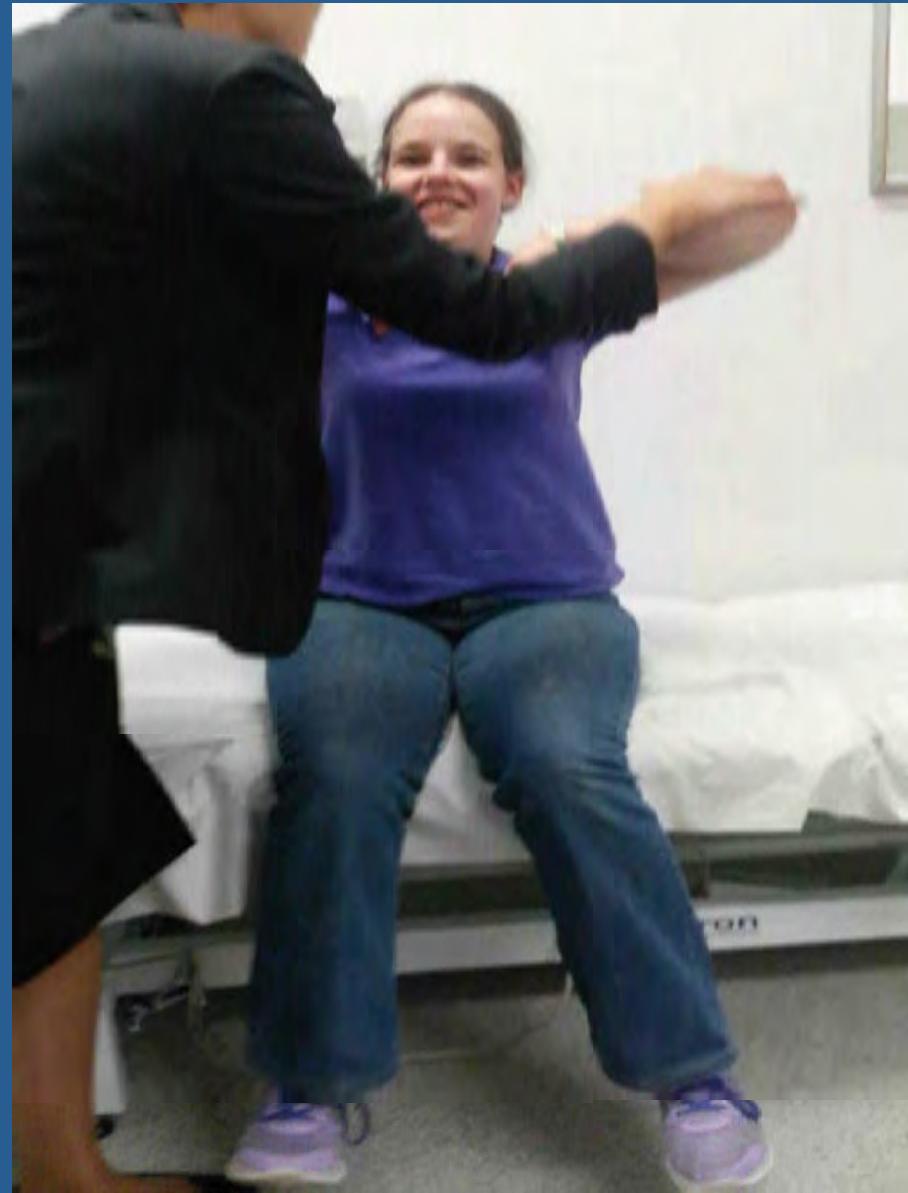
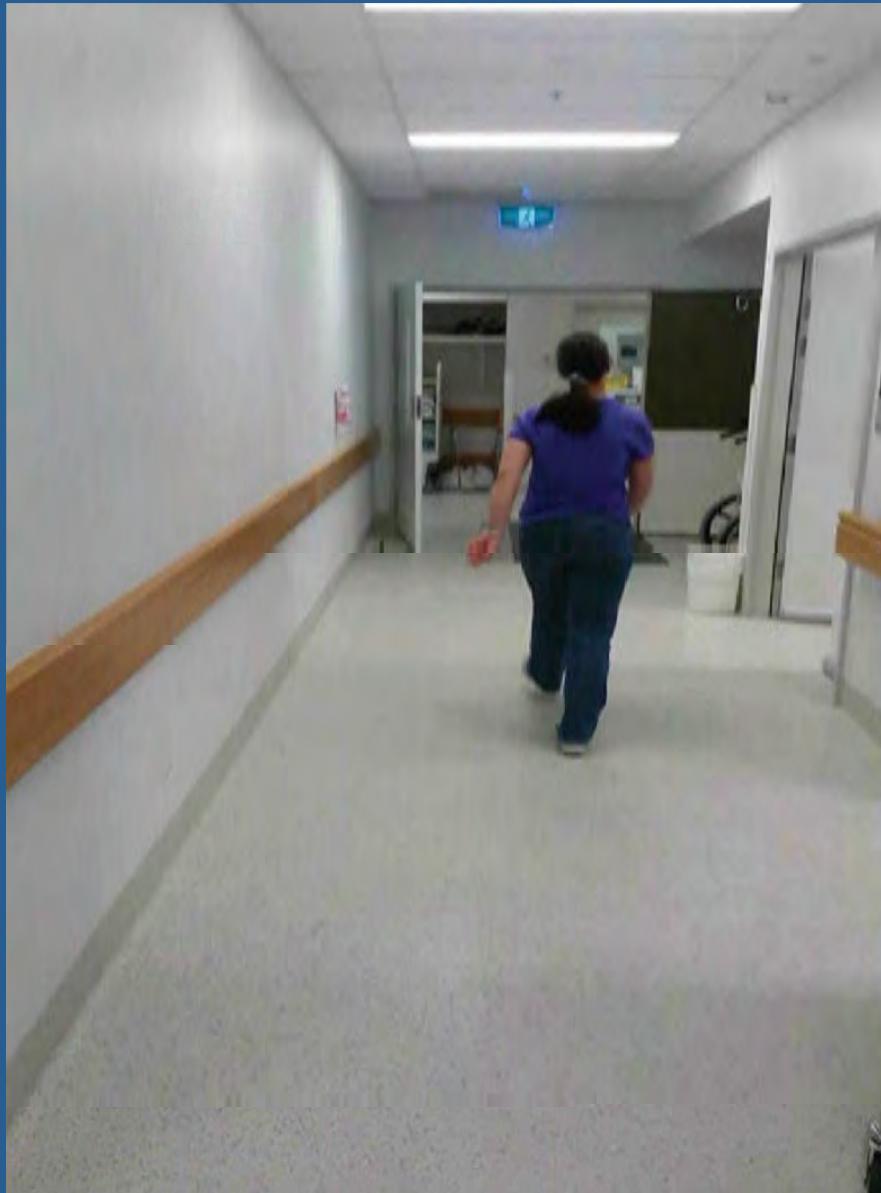
Age 16 years

- Myalgias mainly occur on her sports days
- Examination
- No evidence of the choreiform movements which she had as a younger child. Myoclonic jerks involving trunk and proximal upper limbs.
- Cranial nerves-Saccadic intrusions to smooth pursuit eye movements
- Normal Tone. Mild distal weakness in the upper extremities, MRC grade 4+/5, along with mild proximal lower limb weakness
- Normal reflexes and sensation
- Difficulty with tandem gait, Romberg test was negative

Age 22 years

- Working in a sheltered employment area sorting mail
- Sleeps 11-12 hours a night
- Complaints of fatigue
- Examination
 - Myoclonic jerks
 - Mild proximal myopathy
 - Mild ataxia

Examination



Summary

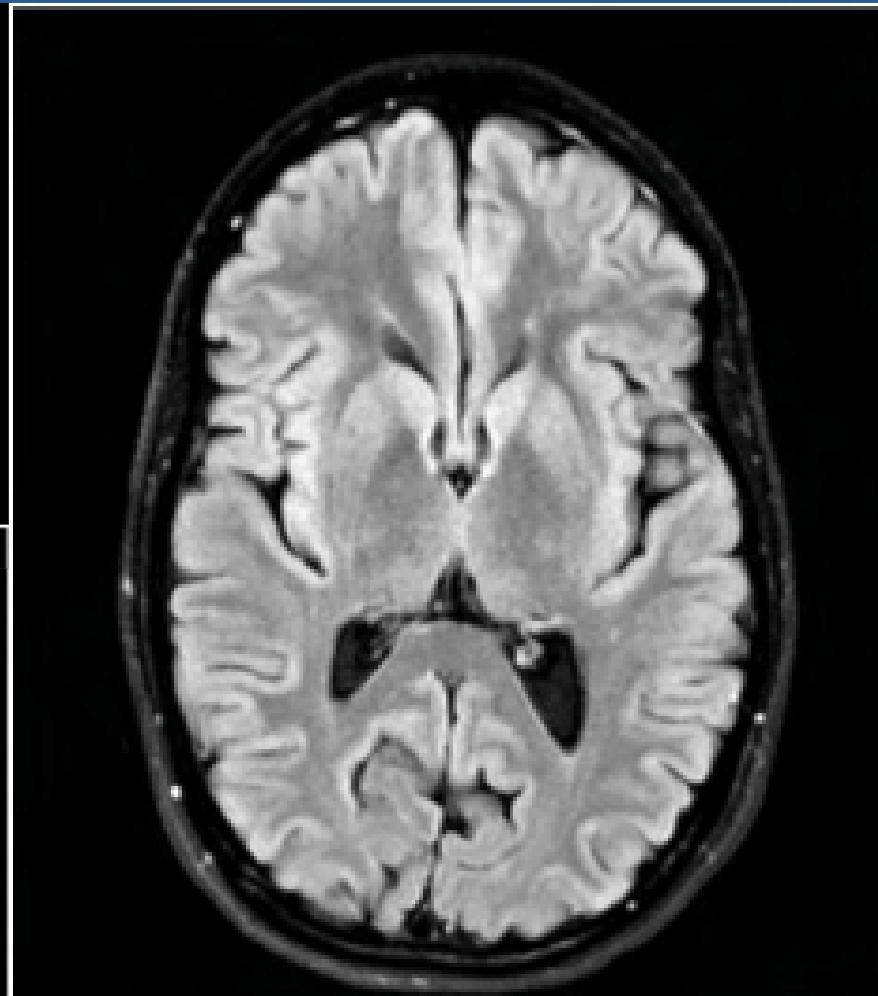
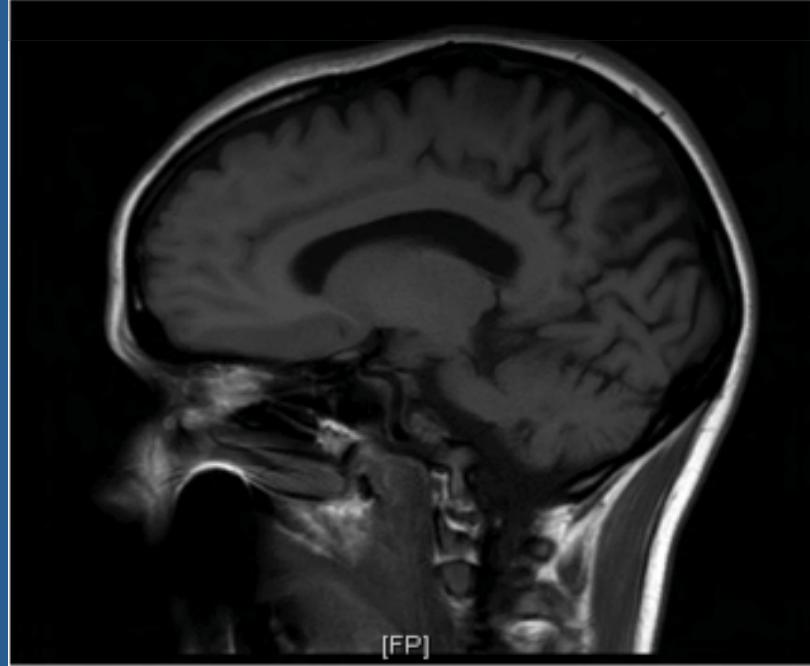
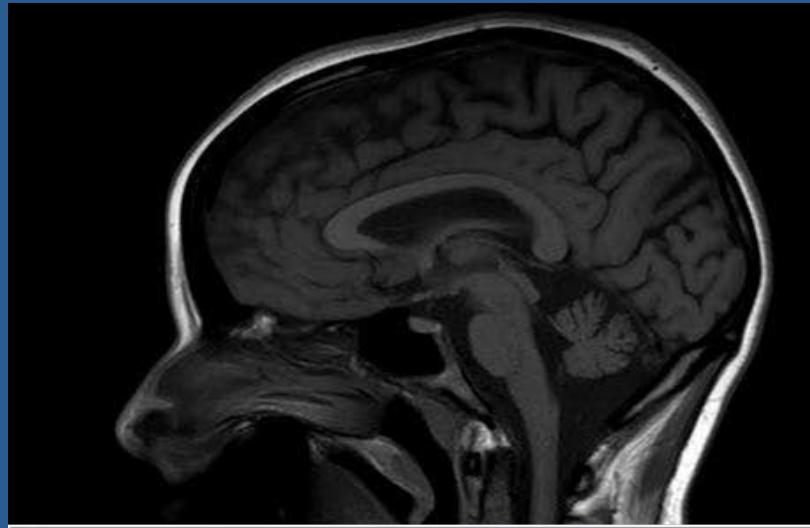
- 22 year old female with congenital onset disorder characterised by
 - Dysmorphic features
 - Myopathy
 - Rhabdomyolysis
 - Myoclonus
 - Mild cerebellar ataxia
 - Intellectual impairment

?Investigations

Investigations

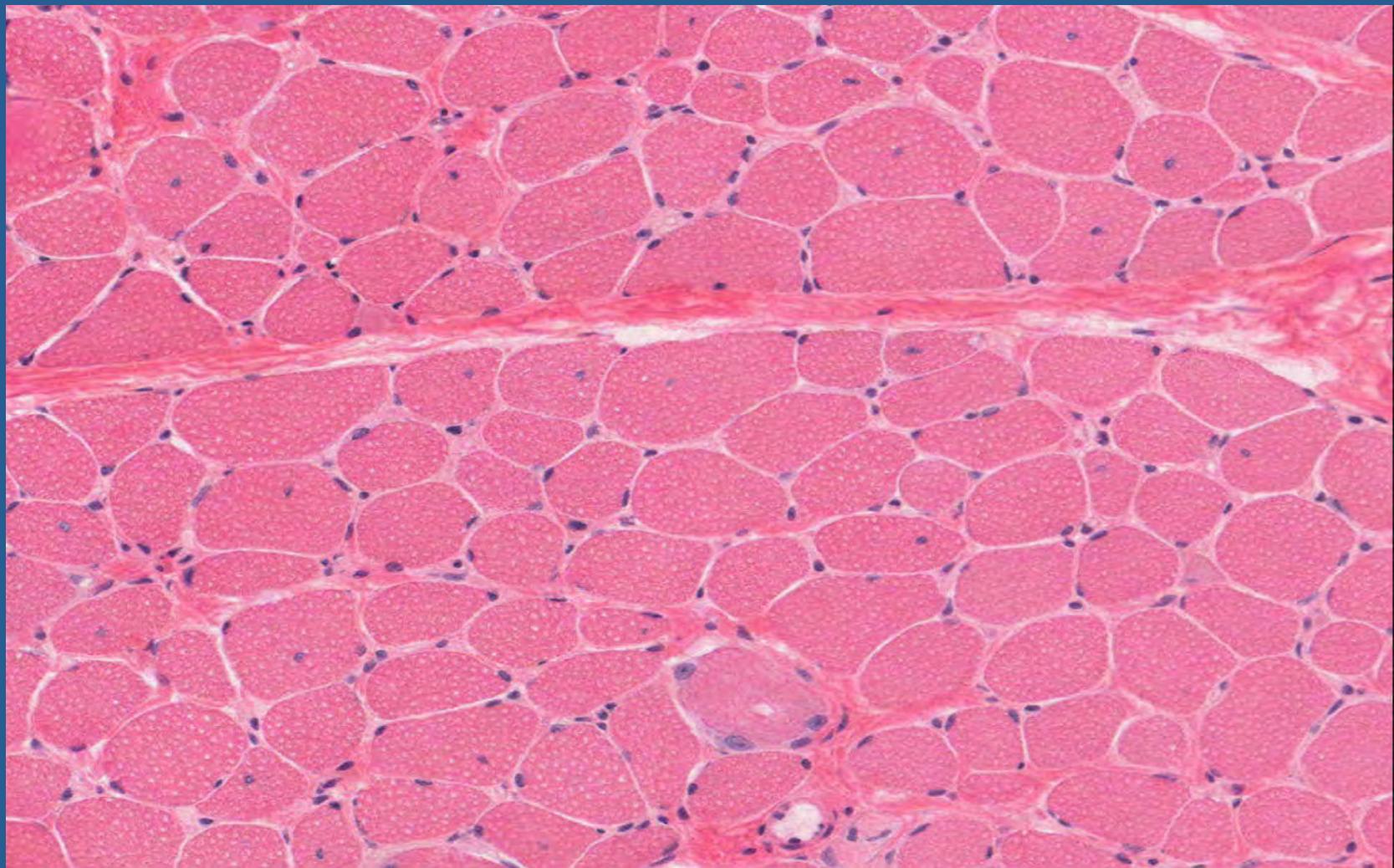
- Bloods-lactate 1.10, pyruvate 0.06, CK 800-3000
- Nerve conduction studies and EMG-normal.
- Cardiac and respiratory function-normal
- MERRF genetic testing-m.8344A>G mutation negative
- POLG whole genome sequencing-negative

MRI Brain



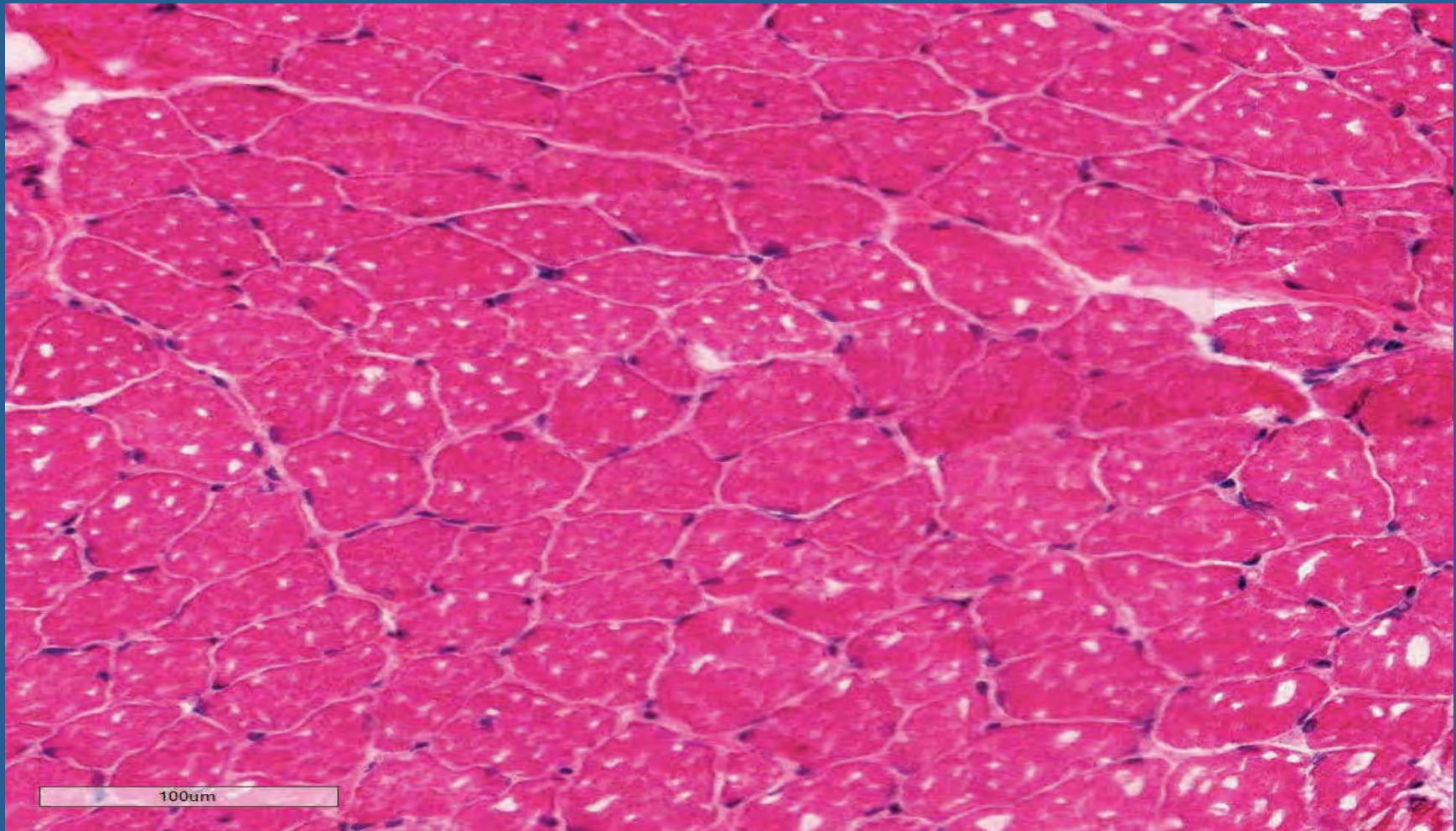
Mild cerebellar atrophy
MR spectroscopy normal

H&E – Jessica (2yrs Biopsy)



Jessica (M) - 2yrs 3months 20days

H&E – Jessica (9yrs Biopsy)



Jessica (BX) - 9yrs 6months 21days

Differential Diagnosis

- Mitochondrial myopathy
 - 1. Complex 1 deficiency
 - ranges from lethal neonatal disease to neurodegenerative disorder
 - MERRF
 - 2. Coenzyme Q10 deficiency
 - Leigh syndrome with growth retardation
 - Isolated myopathic form
- Spinocerebellar ataxia
- Congenital disorder of glycosylation

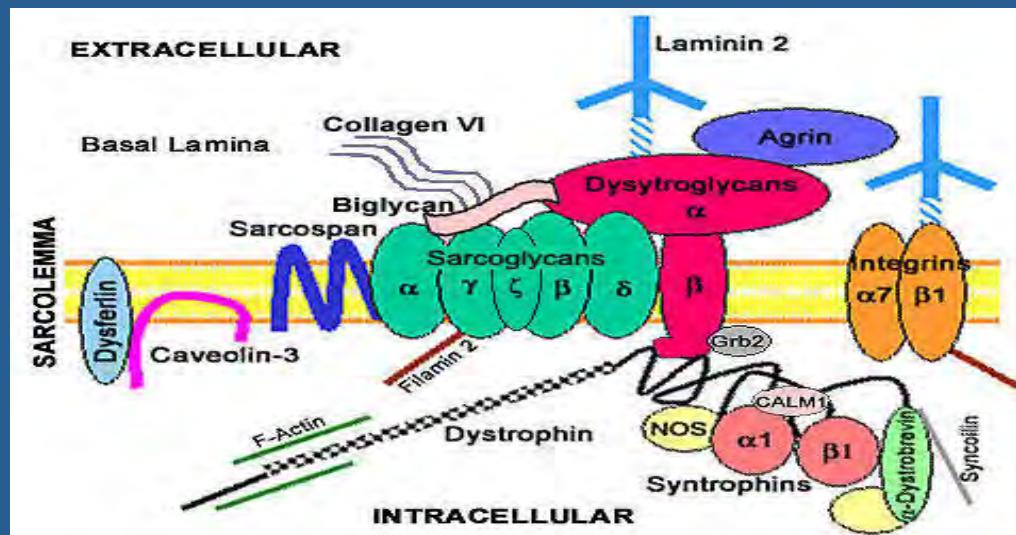
NEUROMUSCULAR PANEL GENE SEQUENCING

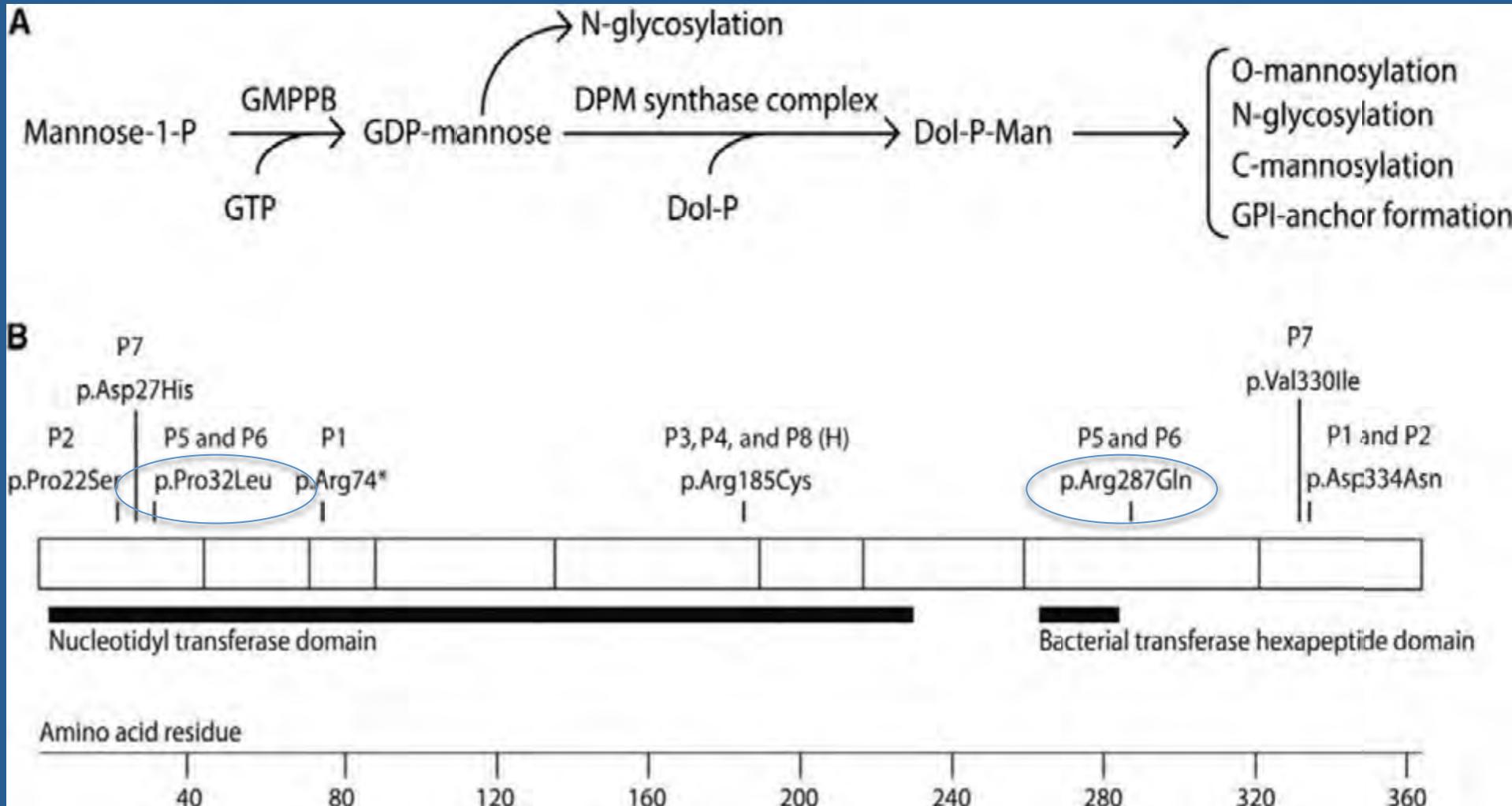
GMPPB

- Heterozygous mutations in the *GMPPB* gene
- Exon 1 c. 95C>T, p. Pro32Leu
- Exon 8 c. 860 G>A, p. Arg287Gln

Mutations in GDP-Mannose Pyrophosphorylase B Cause Congenital and Limb-Girdle Muscular Dystrophies Associated with Hypoglycosylation of α -Dystroglycan

Keren J. Cars, ^{1,30} Elizabeth Stevens, ^{2,30} A. Reghan Foley, ² Sebahattin Cirak, ^{2,3} Moniek Riemersma, ^{4,5,6} Silvia Torelli, ² Alexander Hoischen, ⁶ Tobias Willer, ⁷ Monique van Scherpenzeel, ⁵ Steven A. Moore, ⁸ Sonia Messina, ⁹ Enrico Bertini, ¹⁰ Carsten G. Bönnemann, ¹¹ Jose E. Abdenur, ^{12,13} Carla M. Grosmann, ¹⁴ Akanchha Kesari, ³ Jaya Punetha, ^{3,15} Ros Quinlivan, ^{2,16} Leigh B. Waddell, ¹⁷ Helen K. Young, ^{18,19} Elizabeth Wraige, ²⁰ Shu Yau, ²¹ Lina Brodd, ²¹ Lucy Feng, ² Caroline Sewry, ^{2,22} Daniel G. MacArthur, ^{23,24} Kathryn N. North, ^{17,25,26} Eric Hoffman, ^{3,15} Derek L. Stemple, ¹ Matthew E. Hurles, ¹ Hans van Bokhoven, ^{27,28} Kevin P. Campbell, ⁷ Dirk J. Lefeber, ^{4,5} UK10K Consortium, Yung-Yao Lin, ^{1,29} and Francesco Muntoni^{2,*}





- Figure 2. GMPPB Function, Structure, and Identified Substitutions
- (A) The function of GMPPB in glycosylation pathways.
- (B) GMPPB has 360 amino acids and two functional domains: a nucleotidyl transferase domain and a bacterial transferase hexapeptide domain

GMPPB

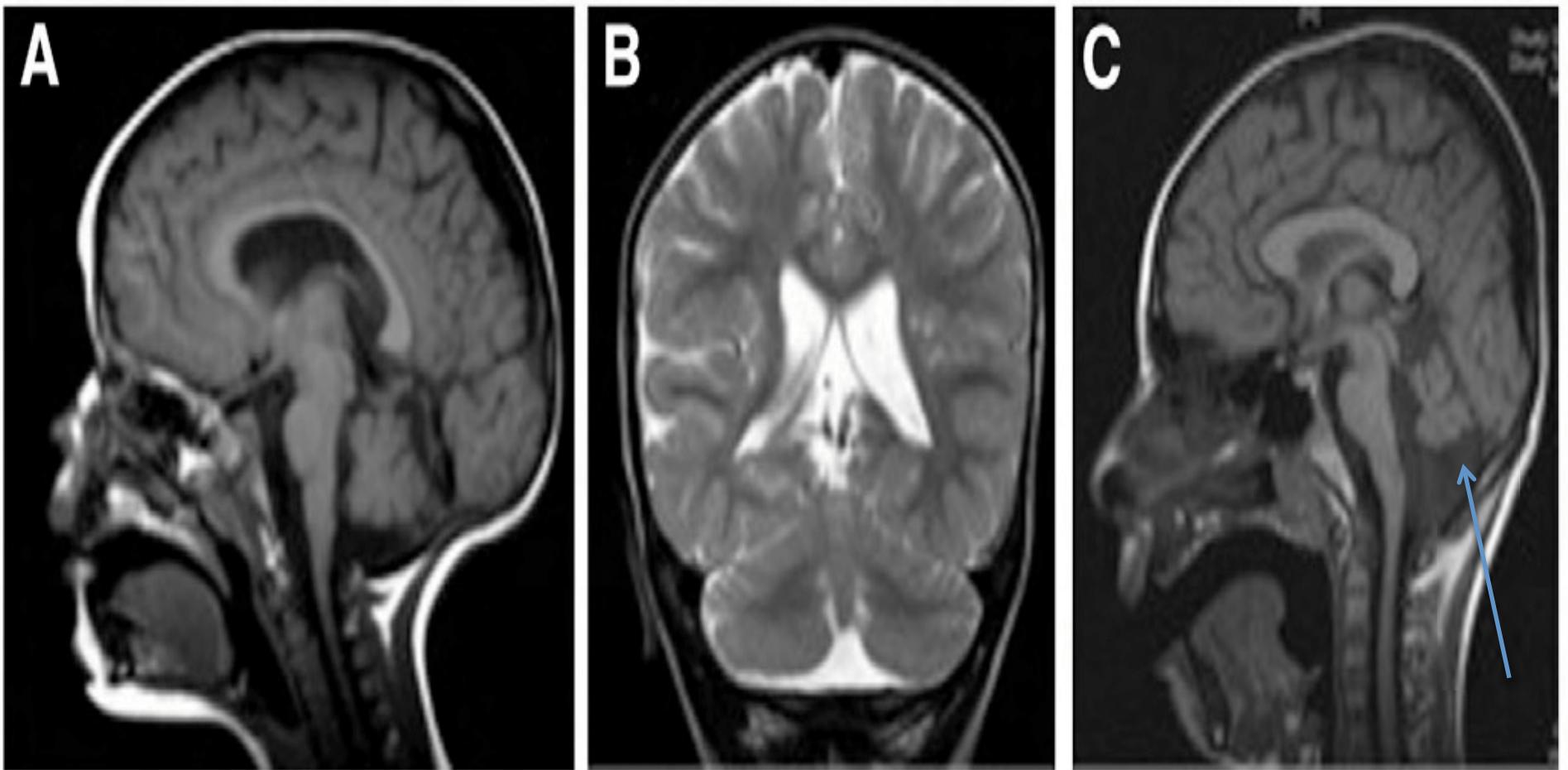
Clinical Presentations

- The main clinical features of the eight unrelated cases (P1–P8) were reported
- Range from a child with a classical CMD presentation to children presenting in the first few months of life with hypotonia, muscle weakness.
- P1-hypotonia and motor and cognitive developmental delays including ataxia, absent speech development, and inability to walk unsupported.
- P2 and P8- children presenting in the first few years of life with mild limb-girdle weakness and mild intellectual disability
- P7-child with normal cognitive function following a LGMD disease course

GMPPB

Other organ involvement

- Evidence of combined cardio-respiratory compromise was evident by the age of 10 years in one patient (P8).
- Features of cardiac involvement, including a long QT interval and left ventricular dilation, were documented in P3 and P4, respectively.
- Other associated features included
 - Epilepsy
 - Microcephaly
 - Cataracts
 - Strabismus and nystagmus

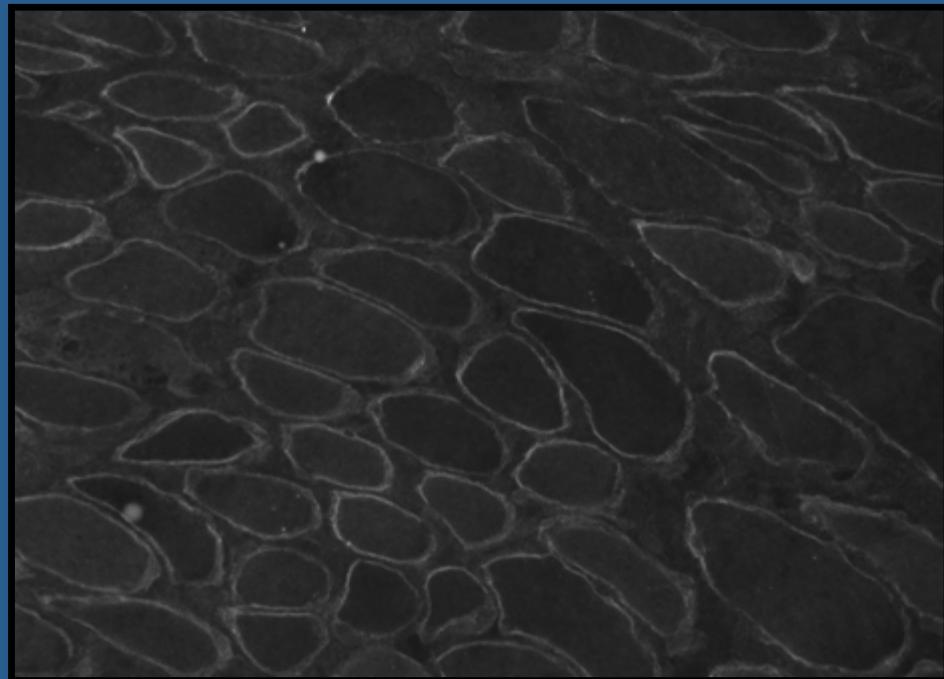


- Brain MRI showed a range of abnormalities
 - structural defects such as cerebellar and pontine hypoplasia,
 - was normal in P2, P3, P4, and P8, who were all affected by a milder variant.

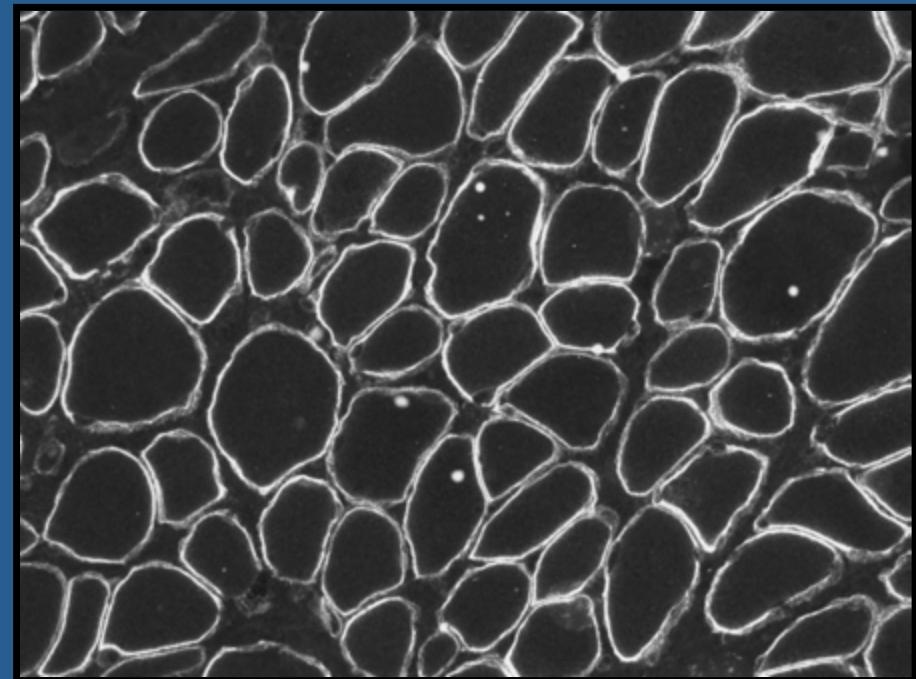
GMPPB

Is this the right diagnosis?

Alpha DG –2yrs Biopsy



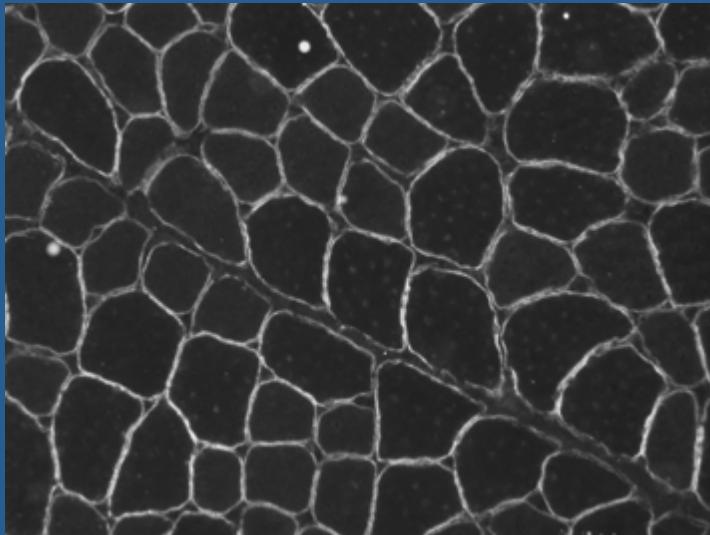
DMD CONTROL (1yr8m) – 6sec



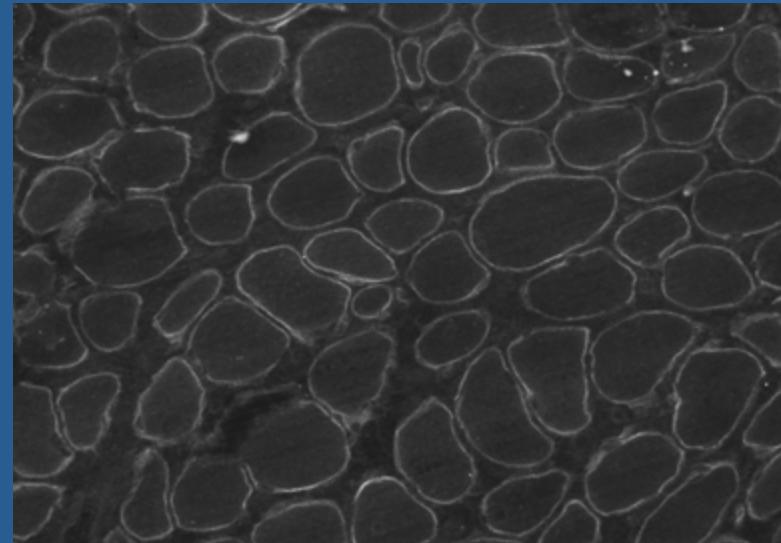
PATIENT(~2yrs3months20days) - 6sec

20x

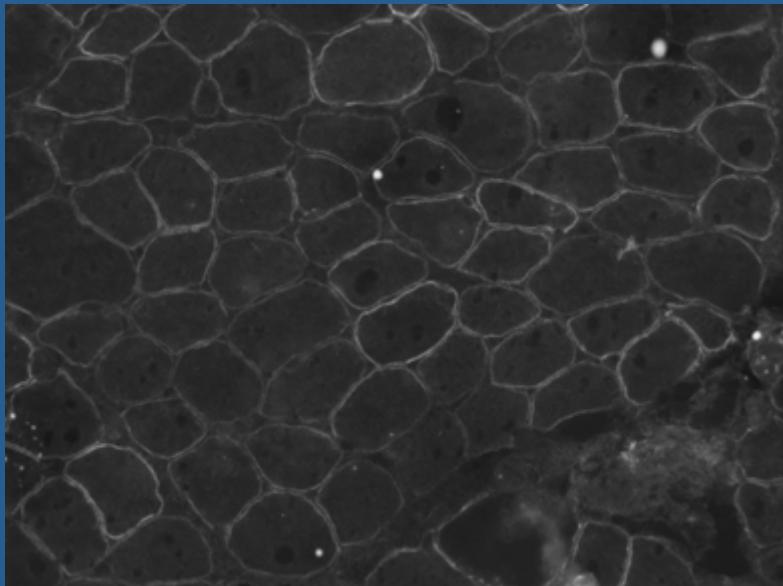
Alpha DG-9yrs Biopsy



CONTROL WATTS (9yr7m) - 6sec



DMD CONTROL (5yr1m) – 6sec



PATIENT(9yrs6months) - 6sec

20x

WB – alpha DG Patients & Controls

Control - 2yrs 3months

Control 1819 - 30yrs 9m

Control 2182 - 26yrs

Control Watts - 9yrs

GMPPB patient - 32yrs

GMPPB Patient - 18yrs

GMPPB Patient - 2yrs 6months

Jessica -(M) - 2yrs 3months

Jessica -(BX) - 9yrs 6months

5 min
exposure

10 min
exposure

Investigations Supportive of *GMPPB* Diagnosis



α-DG (156kDa)



Merosin (80kDa)

Take Home Message

α -dystroglycanopathy with
brain and eye abnormalities

WWS, MEB, FCMD

α -dystroglycanopathy
without brain and eye
abnormalities

Intellectual impairment > normal

LGMD

POMT1

POMT2

FKRP

FKTN

FKRP

POMGNT1

LARGE

ISPD

GTDC2

GMPPB

FKRP

FKTN

POMGNT1

ISPD

GMPPB

FKRP

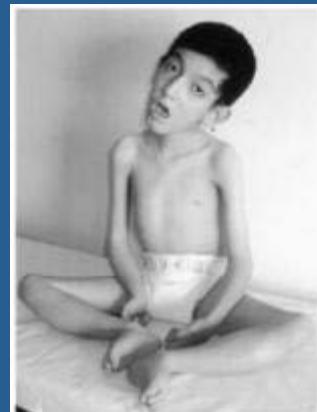
ISPD

FKTN

POMT1

POMT2?

GMPPB



ACKNOWLEDGEMENTS

Supervisors

A. Prof Nigel Clarke and Prof Carolyn Sue

Research Collaborators

Dr. C. Liang-Royal North Shore Hospital, NSW

Dr. Kate Ahmad-Royal North Shore Hospital, NSW

Dr. Nigel Laing-Centre for Medical Research, University of Western Australia, Harry
Perkins Institute of Medical Research, Perth, WA

Dr. Mark Davis-Centre for Medical Research, University of Western Australia, Harry
Perkins Institute of Medical Research, Perth, WA

Dr. Macarena Cabrera-Centre for Medical Research, University of Western Australia,
Harry Perkins Institute of Medical Research, Perth, WA

Funding



NEXT SPEAKER

Case Presentation

Mr C.M

Background

- 39 year geophysicist
- Background
 - Chromosome 7-13 translocation
 - Infertility
- 1 son via IVF and donor
- 2 half siblings
- No known family history of NMD's or anaesthetic problems

Presentation

- Presented age 32yrs with pain RUQ
 - Occurred about 1/12 after starting Crestor
 - Resolved spontaneously after 4/52
- 2 further episodes throughout 2007
- Found to have AN LFT's
- CK 7,000
 - Pain in calves after exercise but riding 3-4 X per week for an hour
 - No rhabdo

Examination

- Mild erythematous rash over knuckles and nail fold changes
- Malar rash
- Mild weakness shoulder abduction, elbow extension and hip flexion
- Otherwise normal

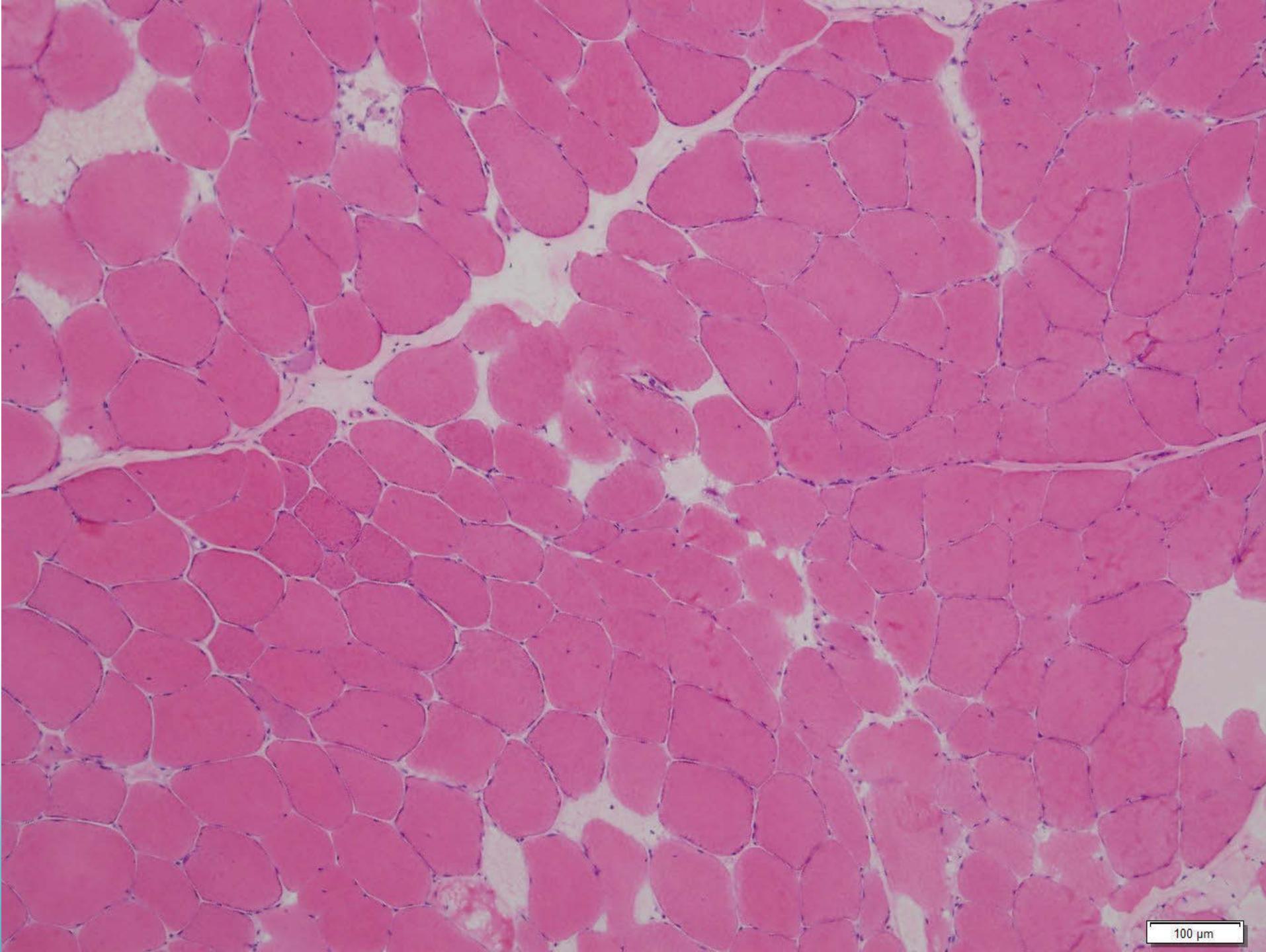
Investigations

- LFT's
 - GGT 58-78
 - ALT 121-181
- ESR 17
- Normal ANA/TFT's
- CK 7,046

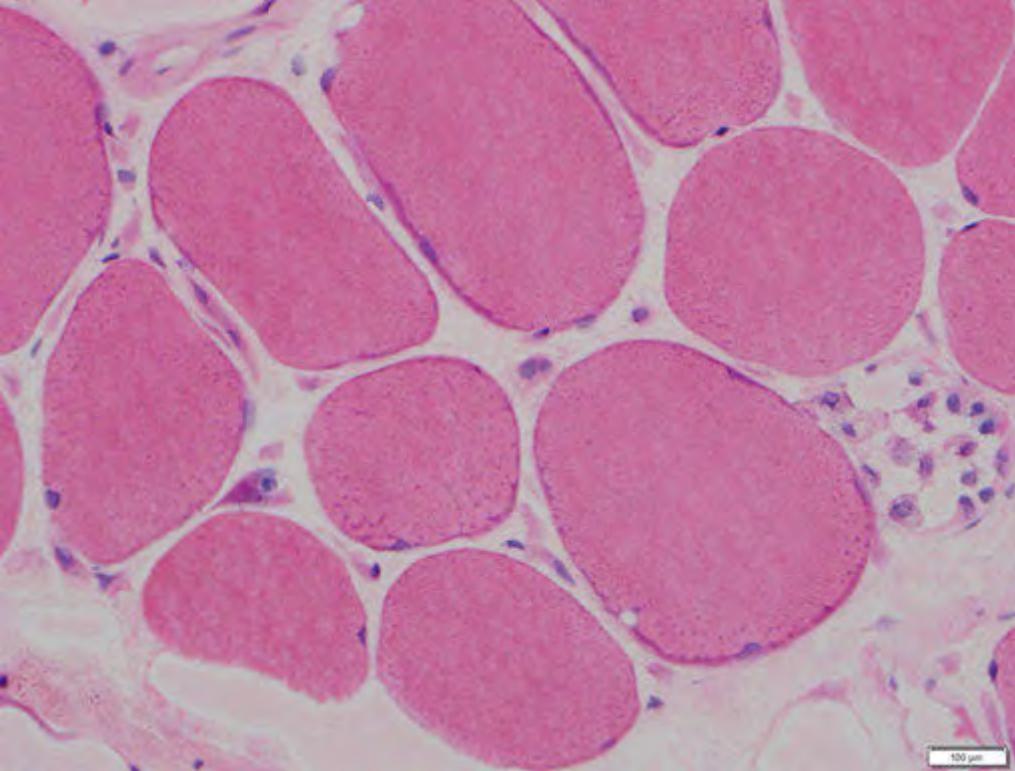
? Thoughts and further Ix

Thought by consulting physician

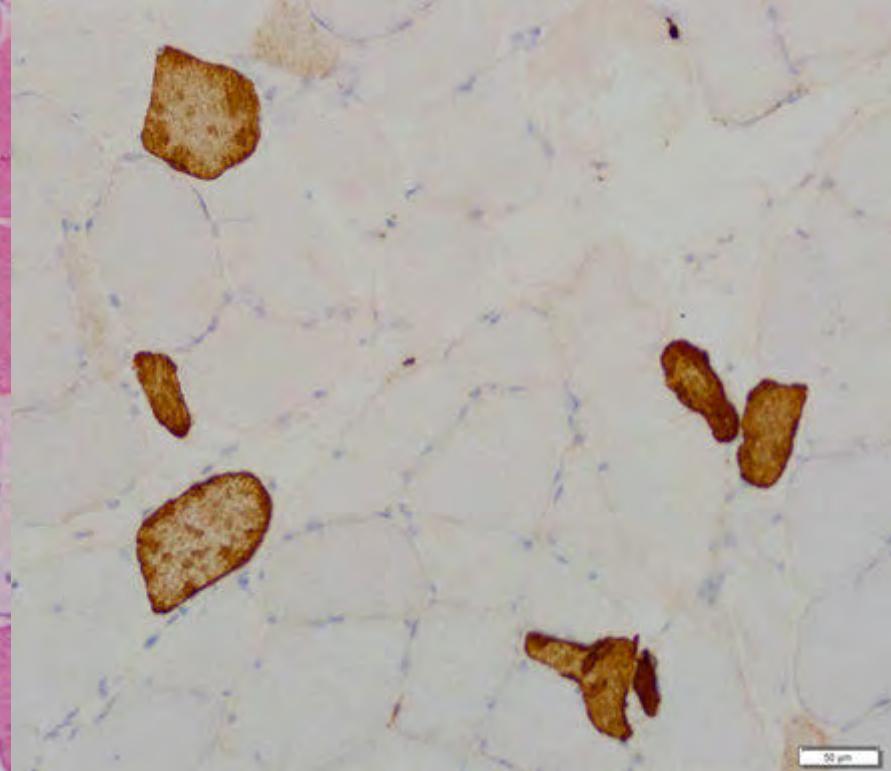
- Persistant HyperCKaemia, mild proximal weakness and DM-like rash suggestive of DM



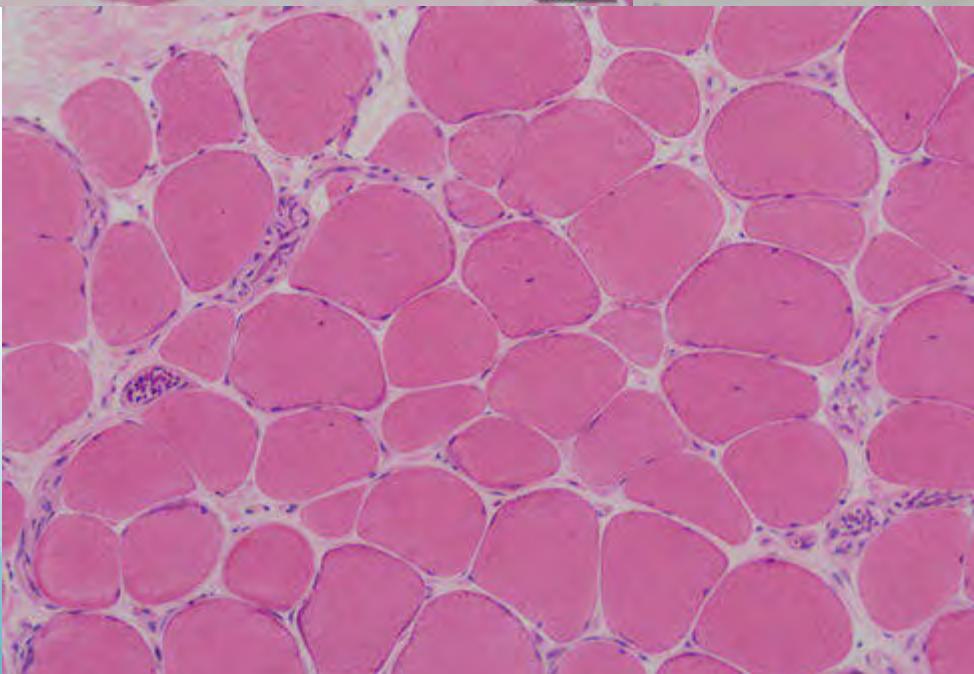
100 µm

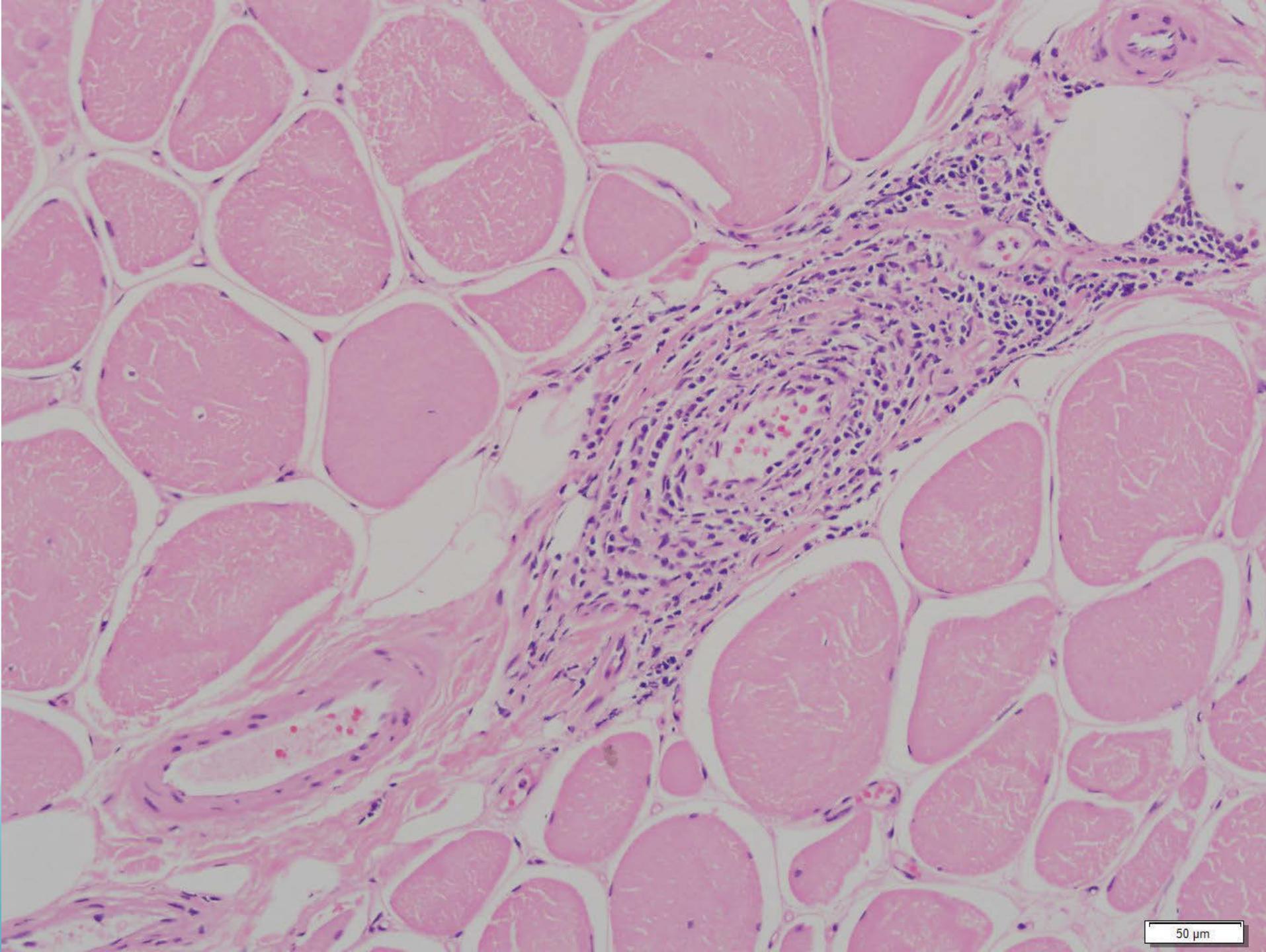


Necrotic
fibres and
variation
Fibre Size

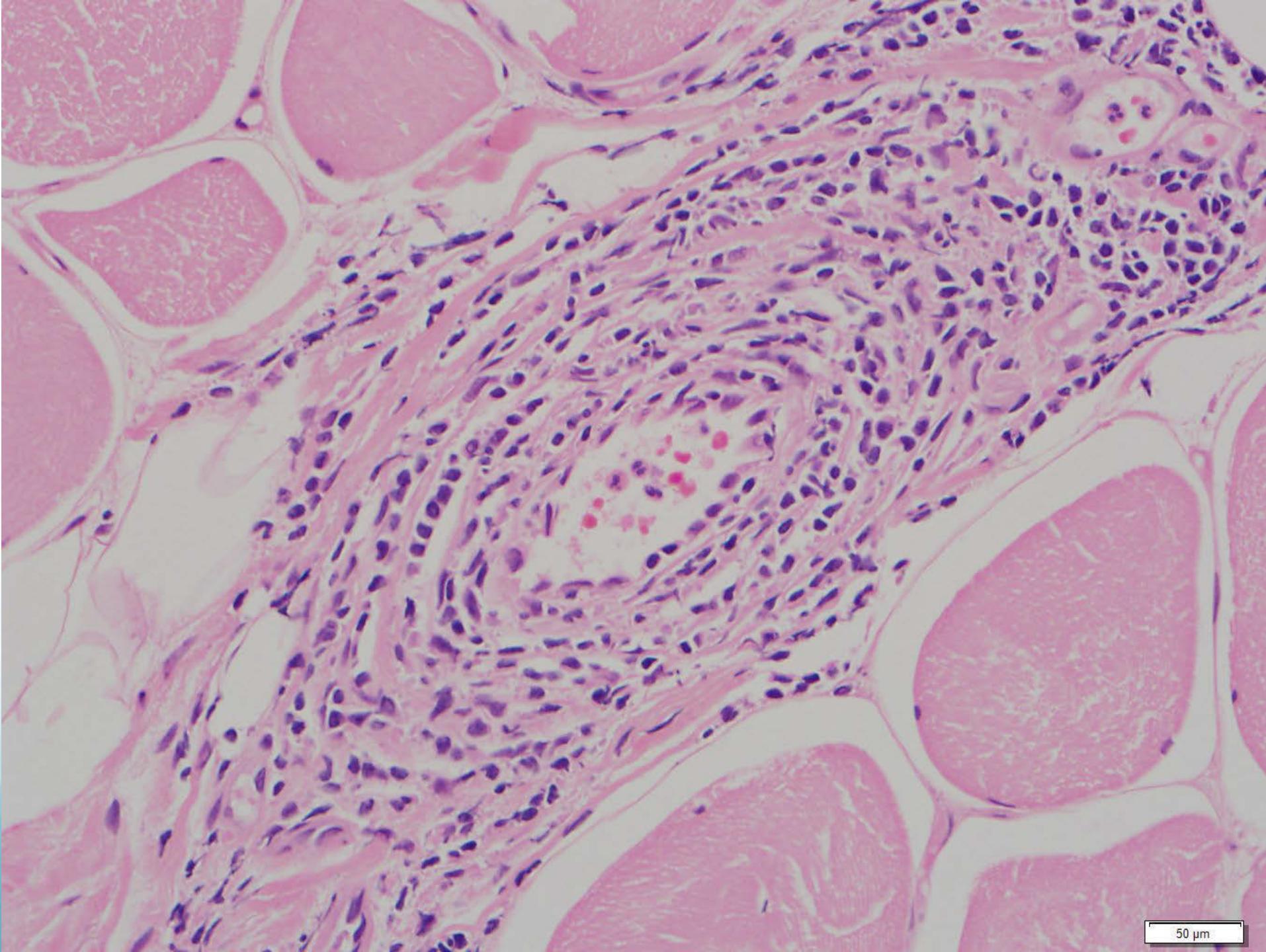


Developmental
Myosin





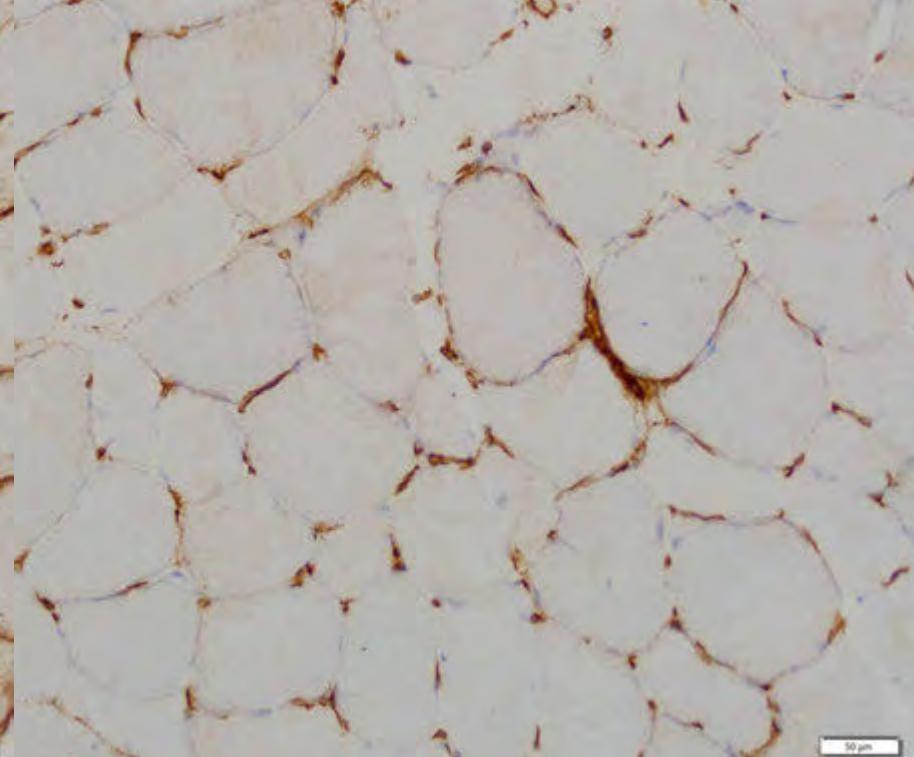
50 μ m



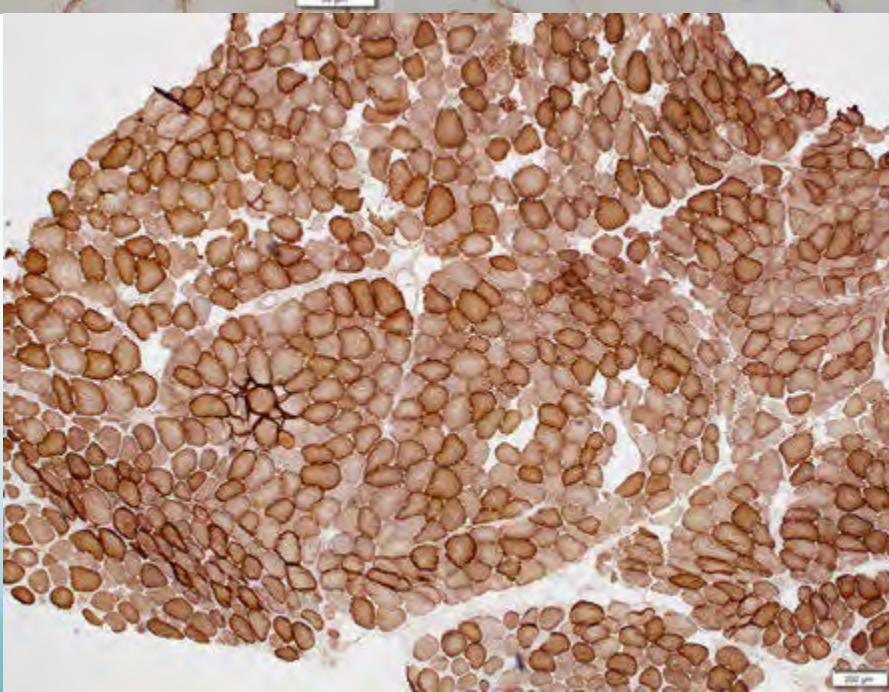
50 μ m



MHC-I



MHC-II



COX-SDH

Biopsy report

- Chronic active inflammatory myopathy
 - Lymphocytic vasculitis (T-cells)
- Type 2 fibre atrophy
 - No Perifascicular atrophy
- Variation fibre size with some hypertrophic fibres
- Frequent vacuolated fibres
 - 1/3 internal nuclei
- Endomysial fibrosis
- MHC I diffusely positive
- MHC II negative
- MAC positive in numerous fibres – mainly perifascicular
- Normal dystrophin, sarcoglycans, beta-dystroglycan, dysferlin, merosin, emerin, caveolin 3

Diagnosis and treatment

- Diagnosed with DM
- Started on Prednisolone/MTX
- CK dropped 6800-2800 over weeks
- Increased again to 5000 when Pred 25mg
- Clinical examination normal

Progress

- Treatment increased
- Pred back to 50mg
- MTX up to 20mg
- Clinically stable but CK remained 5,548
- MMF added

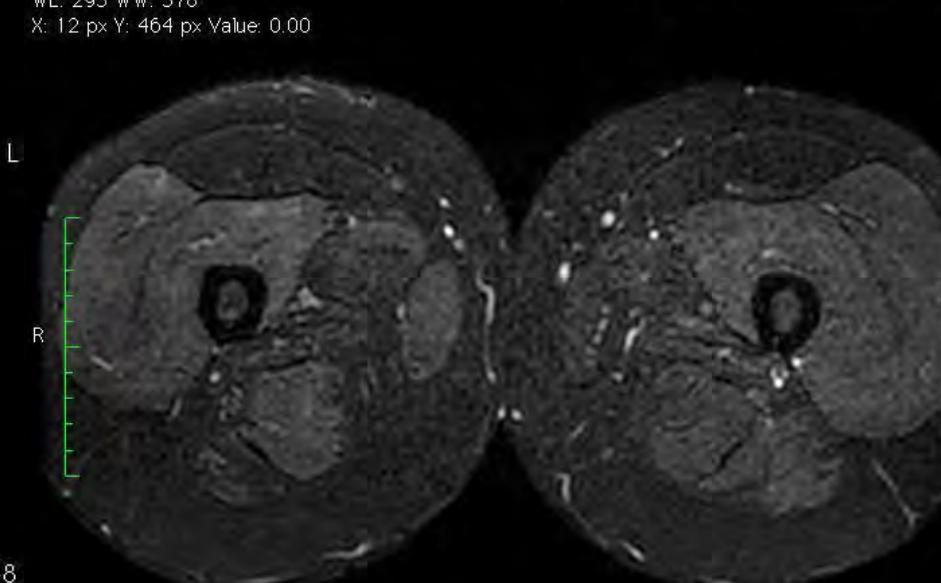
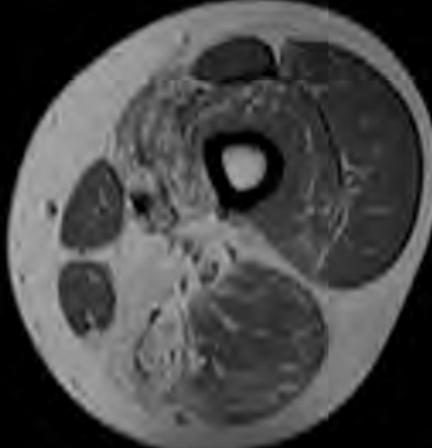
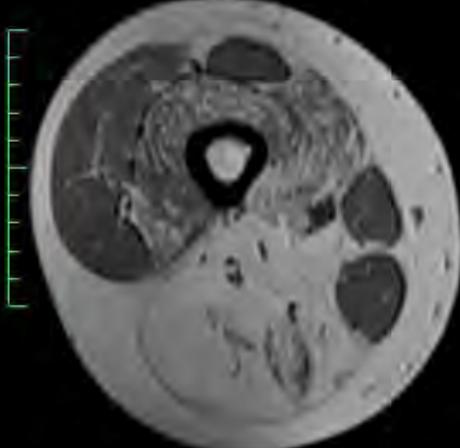
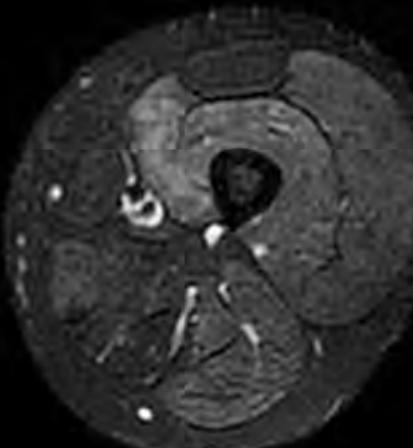
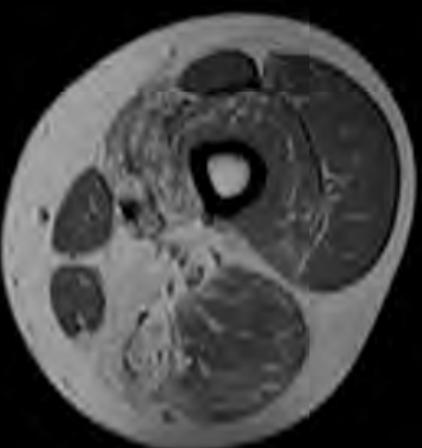
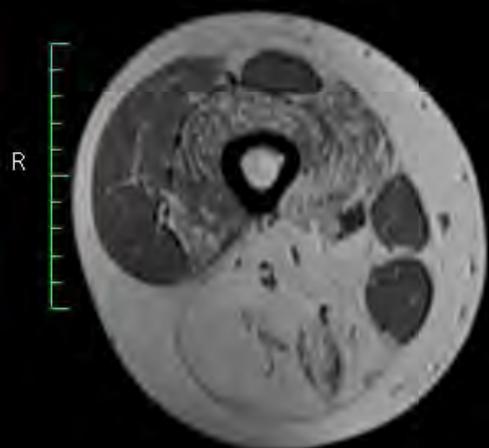
Progress

- CK rose 12,000 after some increase in exercise
- Pred gradually weaned and remained on MTX 20mg and MMF 2g/daily
- Continued exercising daily
- Muscle power remained normal
- CK around 5,000

Progress

- MMF and MTX continued
- Developed mild weakness
 - HF
 - right gastrocnemius (wasted medial gastroc)
- More severe weakness/Wasting
 - Hip extension
 - knee flexion (wasted hamstrings)

MRI Thigh 2011



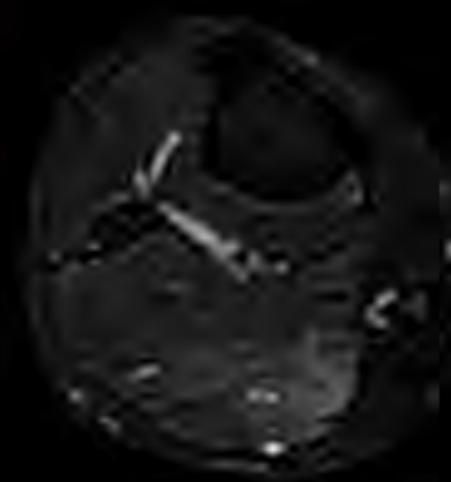
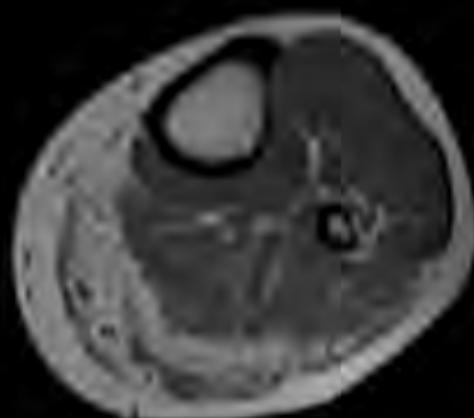
Zoom: 120% Angle: 0
Im: 6/46 I (S > I)
compressed

TE: 9.4 TR: 748

FS: 1.5

21/02/11 9:19:24 AM

R L MRI Calf 2011



Zoom: 122% Angle: 0
Im: 39/46 I(S > I)

TE: 115.6 TR: 3010
FS: 1.5

? Further thoughts/Next Ix/
Rx

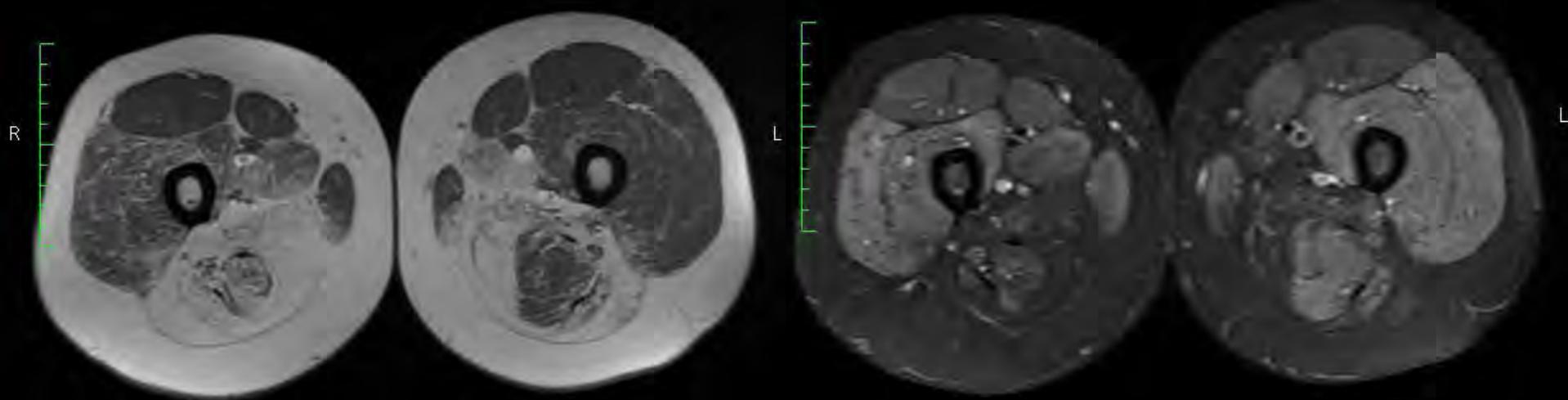
Muscle biopsy reviewed

- Still lymphocytic vasculitis seen
- Minimal dystrophic features
- Normal Dystrophic IH stains

Progress

- Immunosuppression weaned and ceased mid 2013 without adverse effects

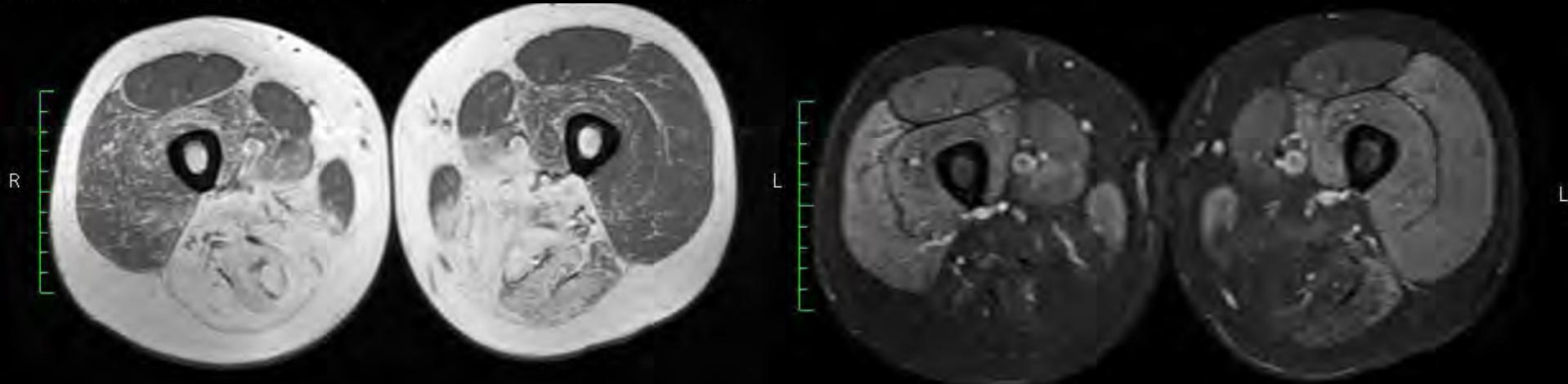
MRI 2013



Zoom: 120% Angle: 0
Im: 45/46 I (S → I)
Uncompressed
Thickness: 5.00 mm Location: -139.74 mm P

TE: 9 TR: 432 Zoom: 120% Angle: 0
FS: 1.5 I: 45/46 I (S → I)
15/01/14 8:06:59 AM Uncompressed
Made In OsiriX thickness: 5.00 mm Location: -139.74 mm P

TE: 60.6 TR: 9526
FS: 1.5
15/01/14 8:17:22 AM
Made In OsiriX

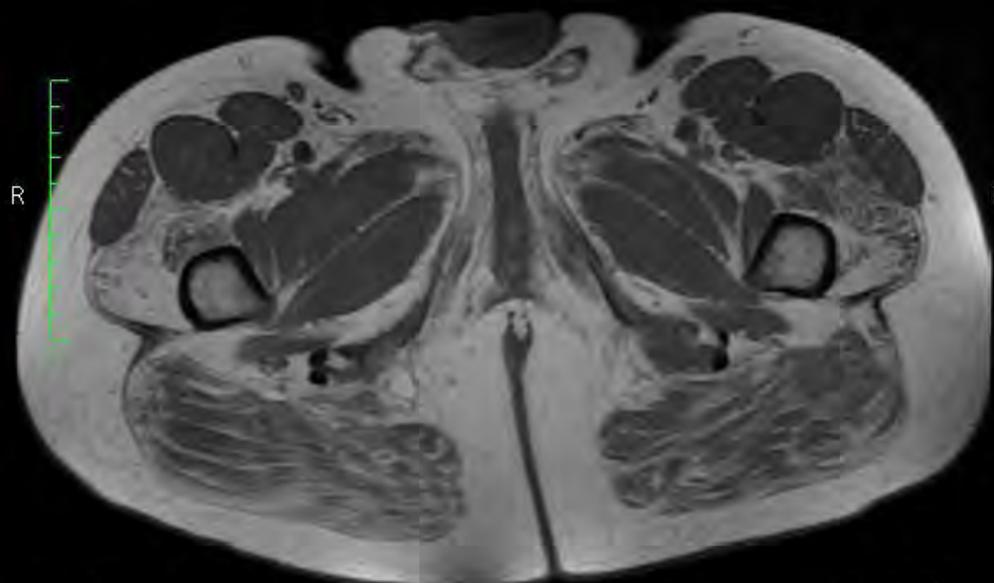


WL: 1042 WW: 2084

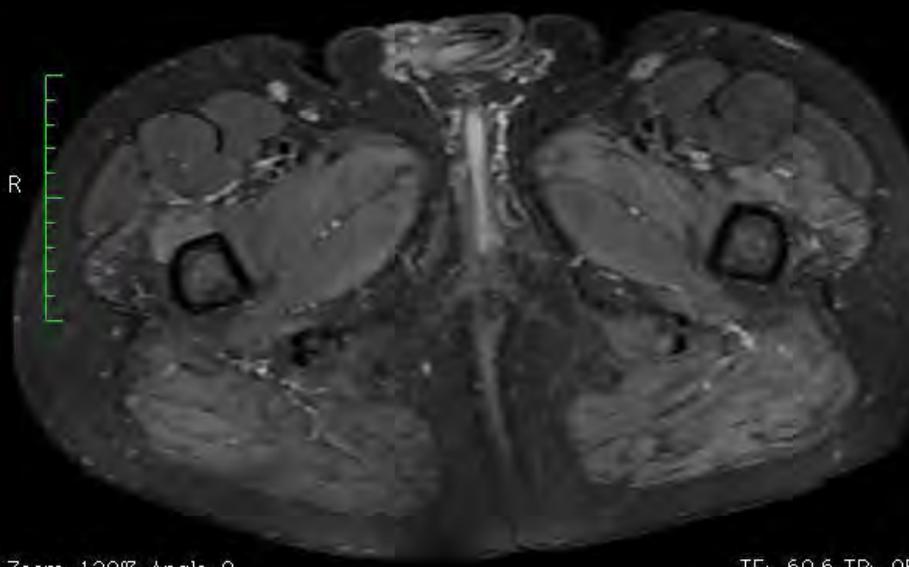
9136 Image size: 512 x 512
View size: 615 x 615
W: 499 WW: 999

A ICJ498Z (39 y , 38
7E ROUTINE PELVIS - WATER AX T2 ID
9

MRI 2013

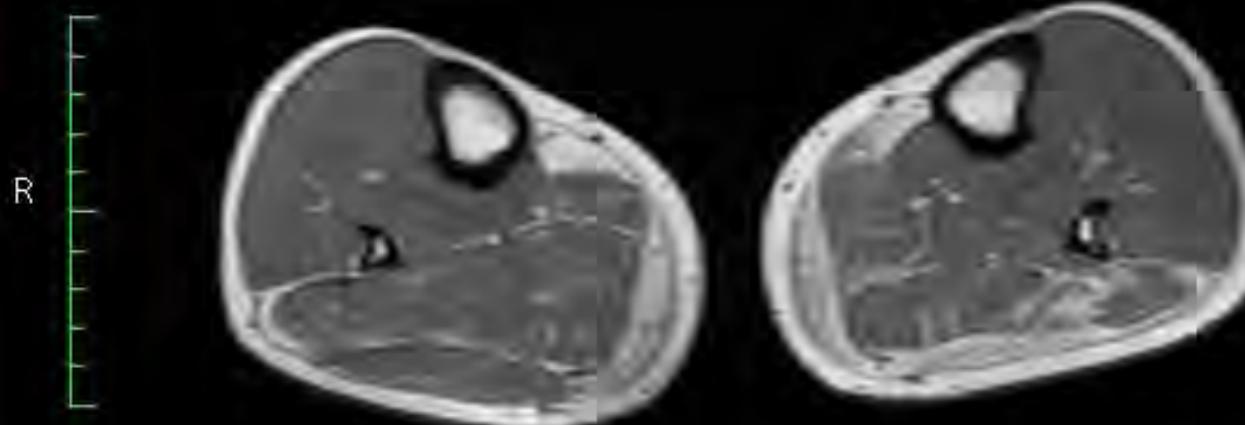


Zoom: 120% Angle: 0
Im: 31/46 I(S > I)
Uncompressed
Thickness: 5.00 mm Loc:



TE: 9 TR: 432 Zoom: 120% Angle: 0

TE: 60.6 TR: 95
FS:
5/01/14 8:17:22
Made In O



Genetic testing (Prof Laing/Dr Davis)

- Apparent Homozygous c.191dupA (p.Asn64fs) mutation in ANO5 gene

ANO5/LGMD2L

- Asymptomatic hyperCKaemia
- Exercise-induced myalgia
- LGMD (onset 30's-40's)
- Distal myopathy (Miyoshi-like) (onset 20-25yrs)
- Complete penetrance
- Females more mild than males

Clinically

- No Bulbar or respiratory complications
- Dilated Cardiomyopathy has been reported
- Slowly progressive
- CK often 10-50X ULN
- Ambulation preserved until late

Treatment

- No Specific therapy
 - Exercise
 - Stretching
 - Splinting
 - Mobility aids
- Avoid:
 - Eccentric muscle contractions
 - Statins If possible

NEXT SPEAKER

Sydney Neurophysiology Workshop

Case Presentation

History of Presenting Complaint - 2010

- 69 year old male
- 2 year history of muscle aches and pains associated with a raised CK (800-1200U/L)
 - Predominantly in arms and legs bilaterally
 - Constant
 - Waking him at night
 - No complaints of weakness
 - No sensory symptoms
 - No symptomatic relief with paracetamol/codeine, amitriptyline, sodium valproate
 - Partial relief with NSAIDs

Medical Background

- Past Medical History
 - Asthma
- Medications
 - Mobic

Background

- Social History
 - Living with wife
 - Railway guard
 - Prior alcohol dependence – abstinent for 40 years
 - Ex-smoker – 15-pack-yr history (quit in 1972)
- Family History
 - No family history of neuromuscular disease

Examination

- Normal neurological and systemic examination

??? THOUGHTS ?

Investigations

- CK 800-1200U/L
- FBC/EUC normal
- LFT
 - AST 58U/L
 - ALT 66U/L
 - LDH 291U/L
- TSH normal
- CRP 0.6mg/L
- ESR 5mm/hr
- Connective tissue screen normal

Neurophysiology

Nerve Conduction Studies

Nerve / Sites	Amplitude mV	Latency ms	Distance cm	Velocity m/s
R MEDIAN - APB				
Wrist	9.2	4.20		
Elbow	8.9	9.35	26	50.5
R ULNAR - ADM				
Wrist	8.3	3.85		
B.Elbow	6.4	8.10	25	58.8
A.Elbow	6.4	9.50	9	64.3
R COMM PERONEAL - EDB				
Ankle	4.7	5.65		
Fib Head	4.3	13.90	33	40.0
R TIBIAL - FHB				
Ankle	6.9	5.50		
Knee	2.9	17.65	45	37.0

Nerve	Min F Lat ms	Max F Lat ms	% F %
R ULNAR - ADM	32.75	34.75	100
R TIBIAL - FHB	66.70	70.70	100

Nerve Conduction Studies

Nerve / Sites	Rec. Site	Amplitude µV	Latency ms	Distance cm	Velocity m/s
R MEDIAN - Ortho Palm					
Palm	Wrist	16.1	2.15	8	37.2
R MEDIAN - Ortho Dig II					
Digit II	Wrist	6.3	3.05	14	45.9
R ULNAR - Ortho Dig V					
Digit V	Wrist	5.1	2.20	11	50.0
R ULNAR - Ortho Palm					
Palm	Wrist	12.8	1.35	8	59.3
R SURAL - Ortho					
Ankle	Calf	4.3	2.40	10	41.7

EMG

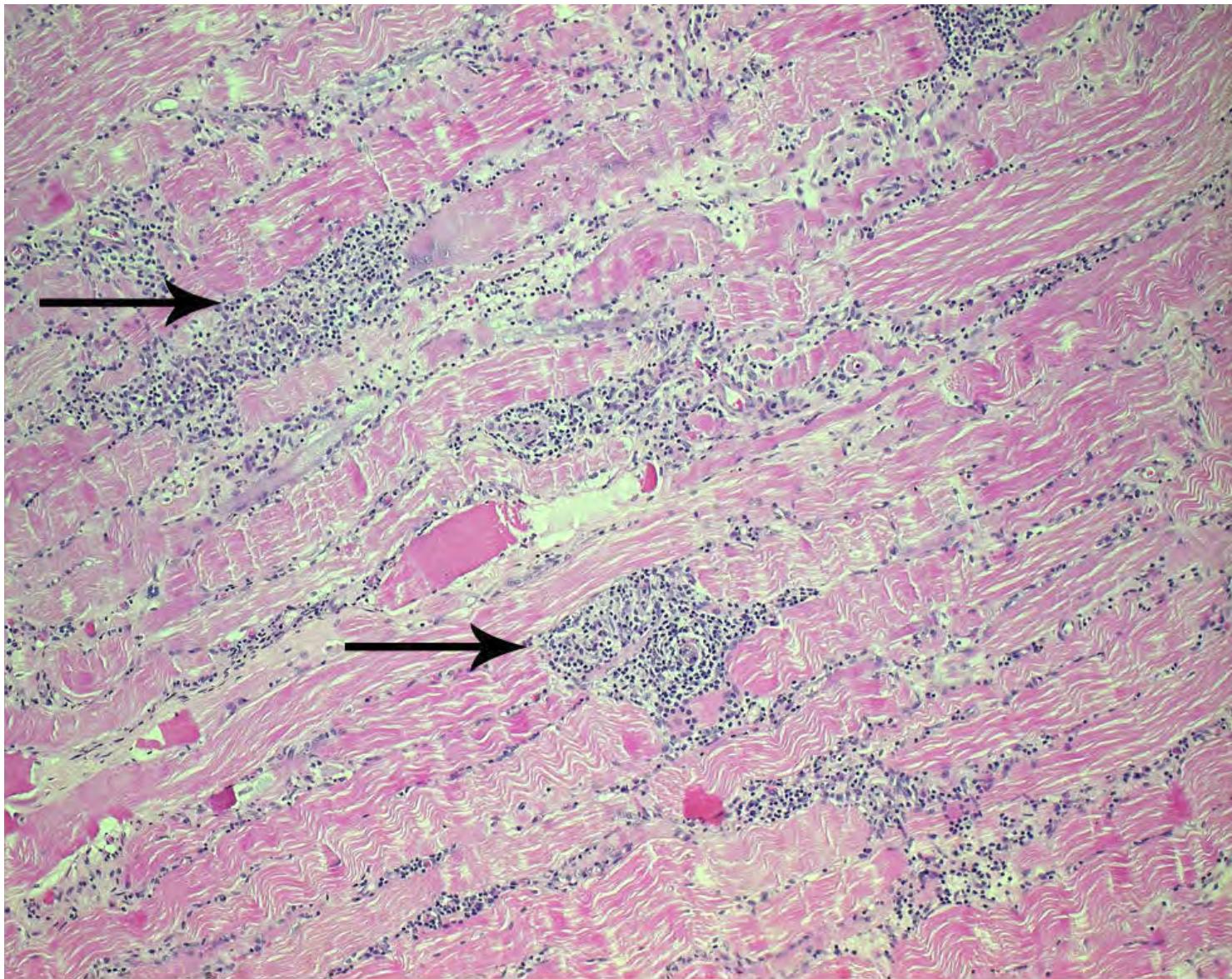
EMG Summary Table											
	Spontaneous			MUAP						MaxIP	Remark
	Fib	Fasc	Misc	Amp	Dur.	Poly	Satellite	Unstable	Rate	Pattern	--
R. DELTOID	0	0	None	N	N	N	,	.	.	Mixed	Normal
R. TRICEPS	0	0	None	N	N	N	,	.	.	Mixed	Normal
R. VAST LATERALIS	0	0	None	Low	Brief	Incr	,	.	.	Mixed	Normal
R. TIB ANTERIOR	0	0	None	Low	Brief	Incr	,	.	.	Mixed	Normal
L. DELTOID	0	0	None	N	N	N	,	.	.	Mixed	Normal

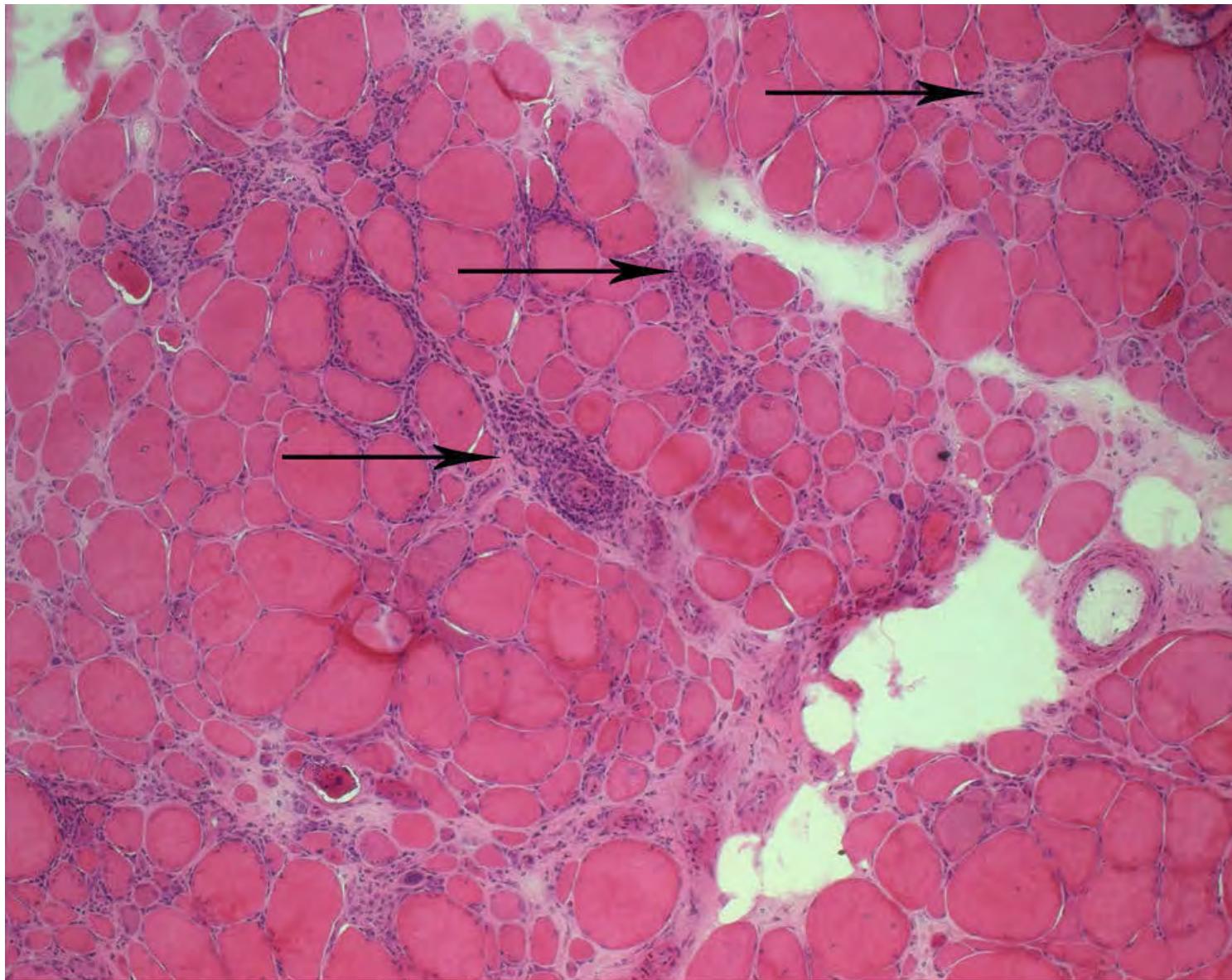
??? Thoughts

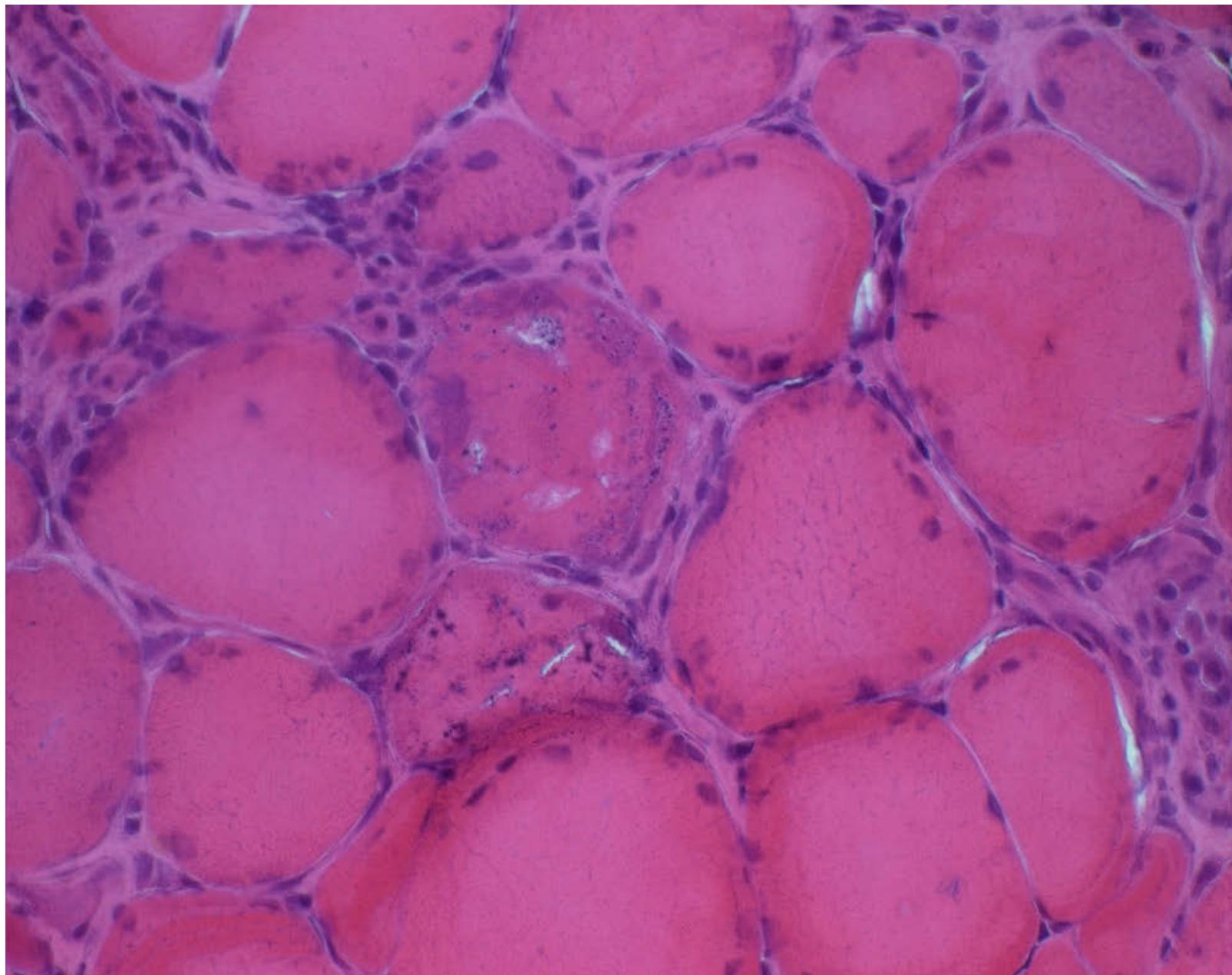
What next?

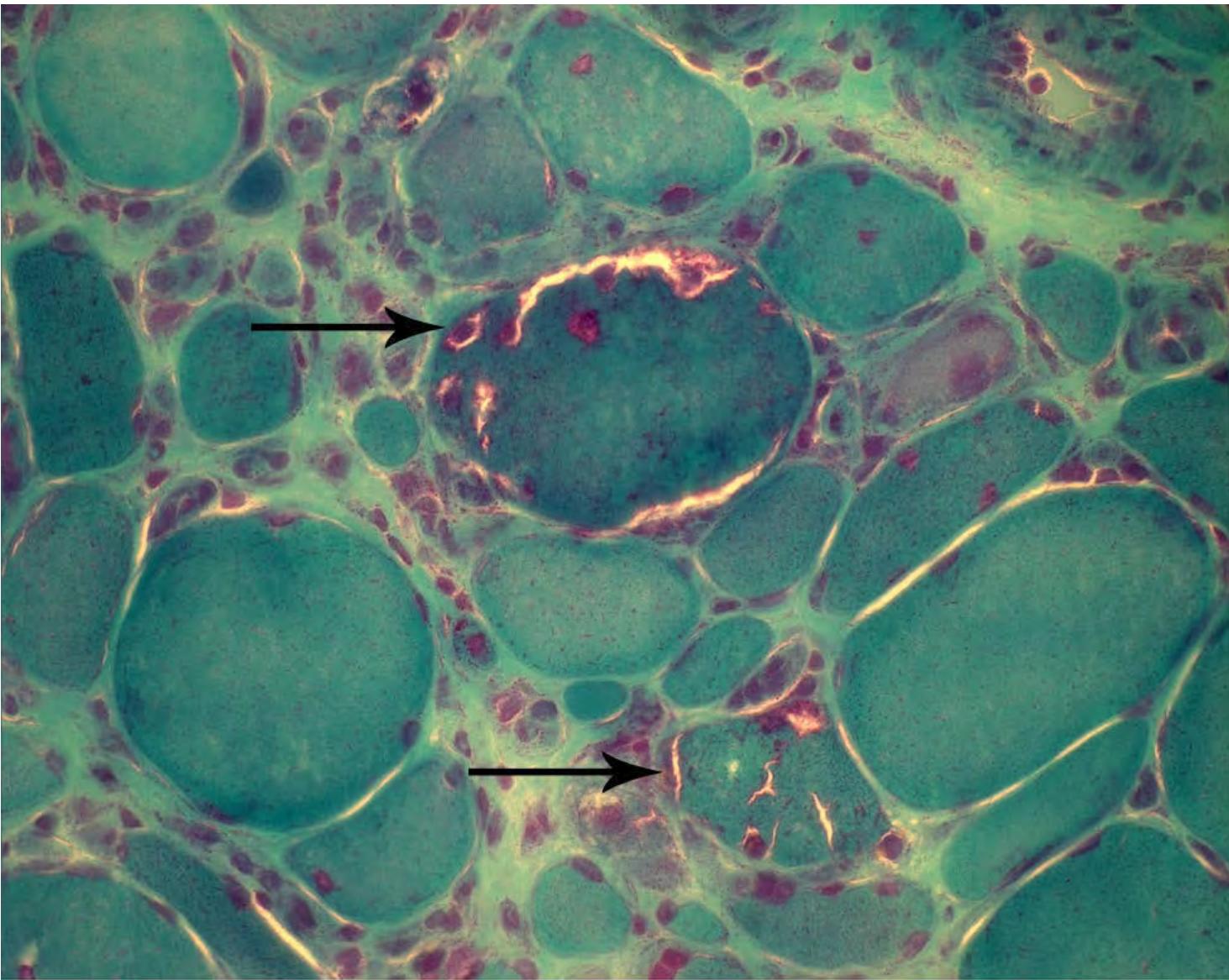
Muscle Biopsy

Vastus Lateralis



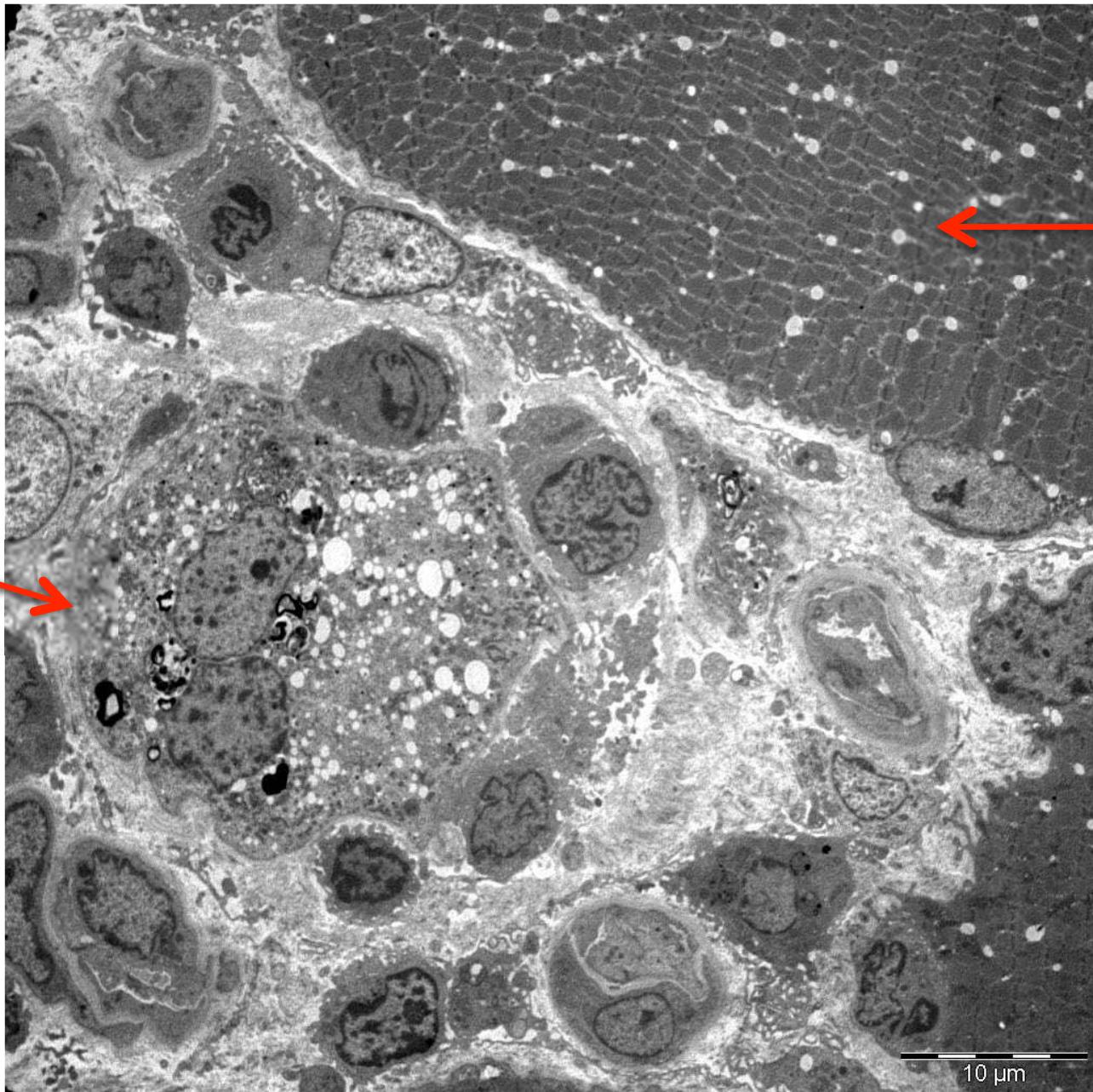






Rimmed vacuoles.

Electron Microscopy

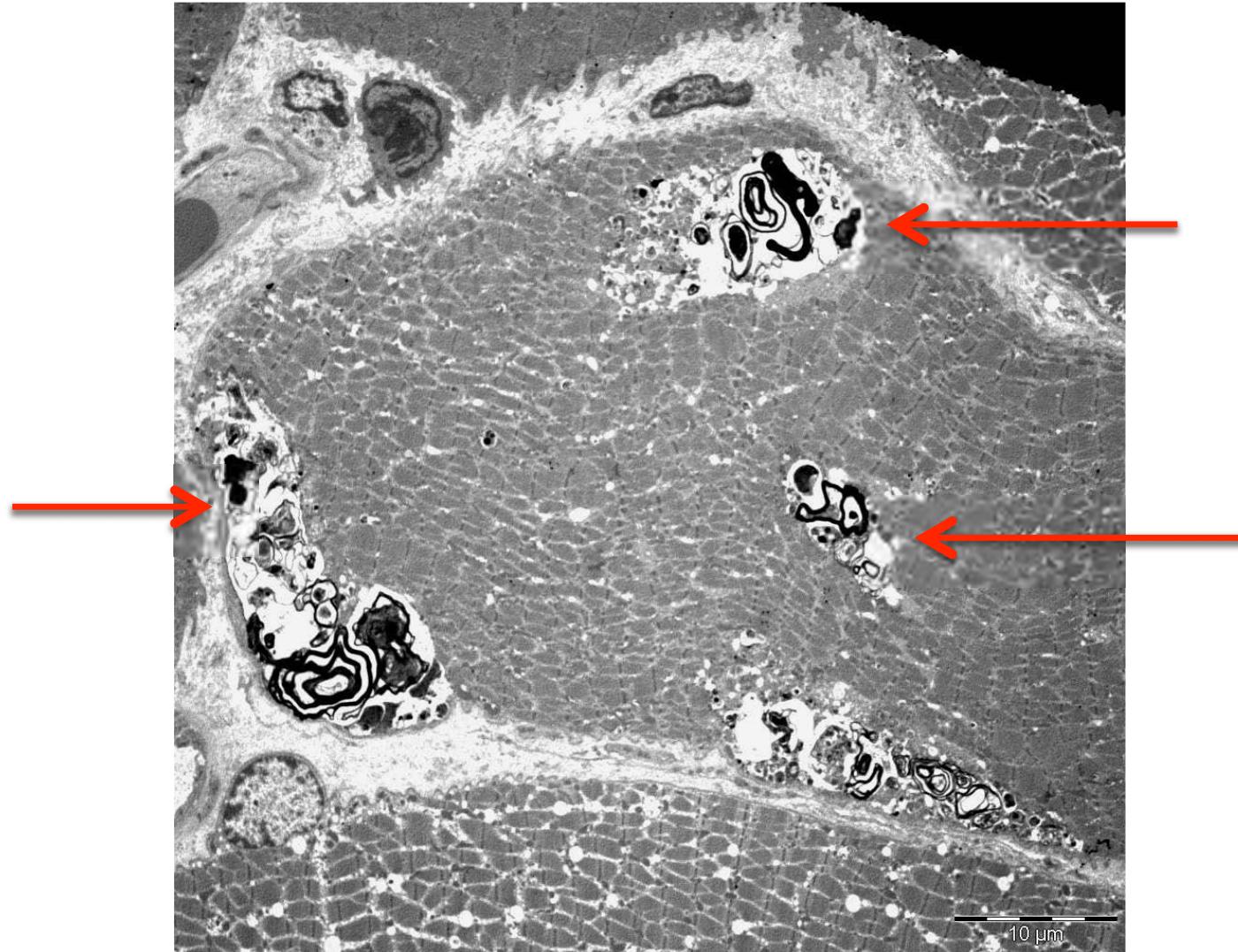


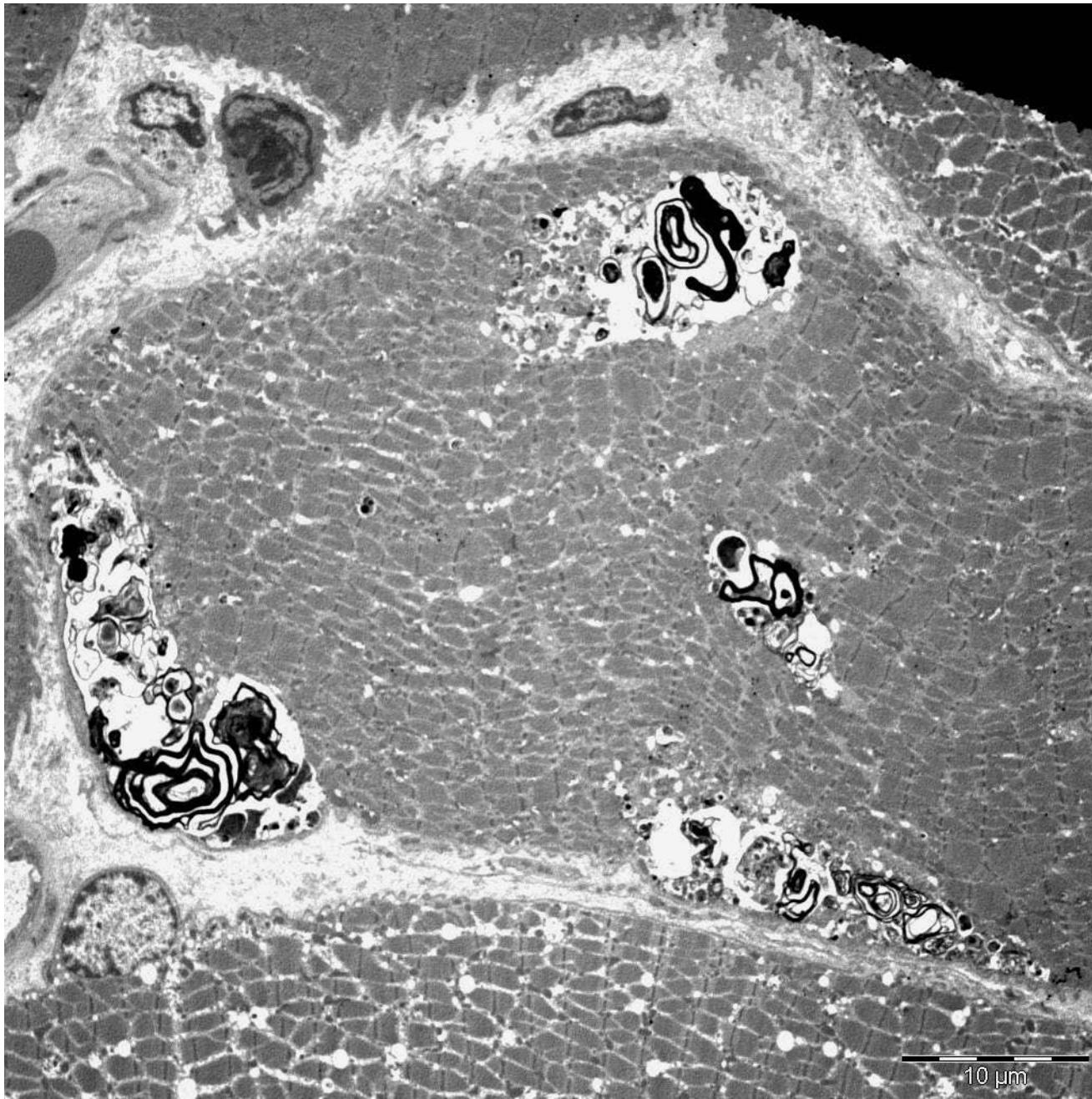
Degenerative
muscle fiber

Normal
muscle
fiber

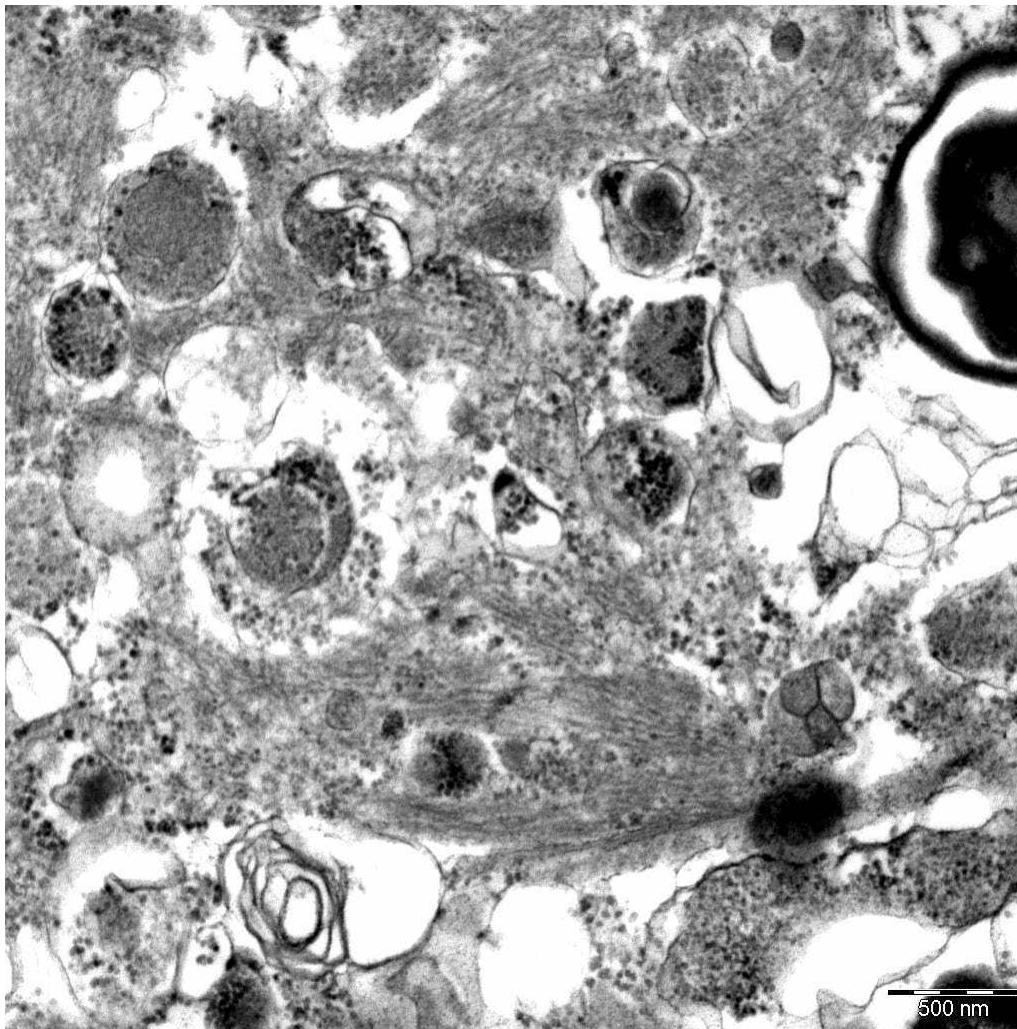
10 μm

Vacuoles

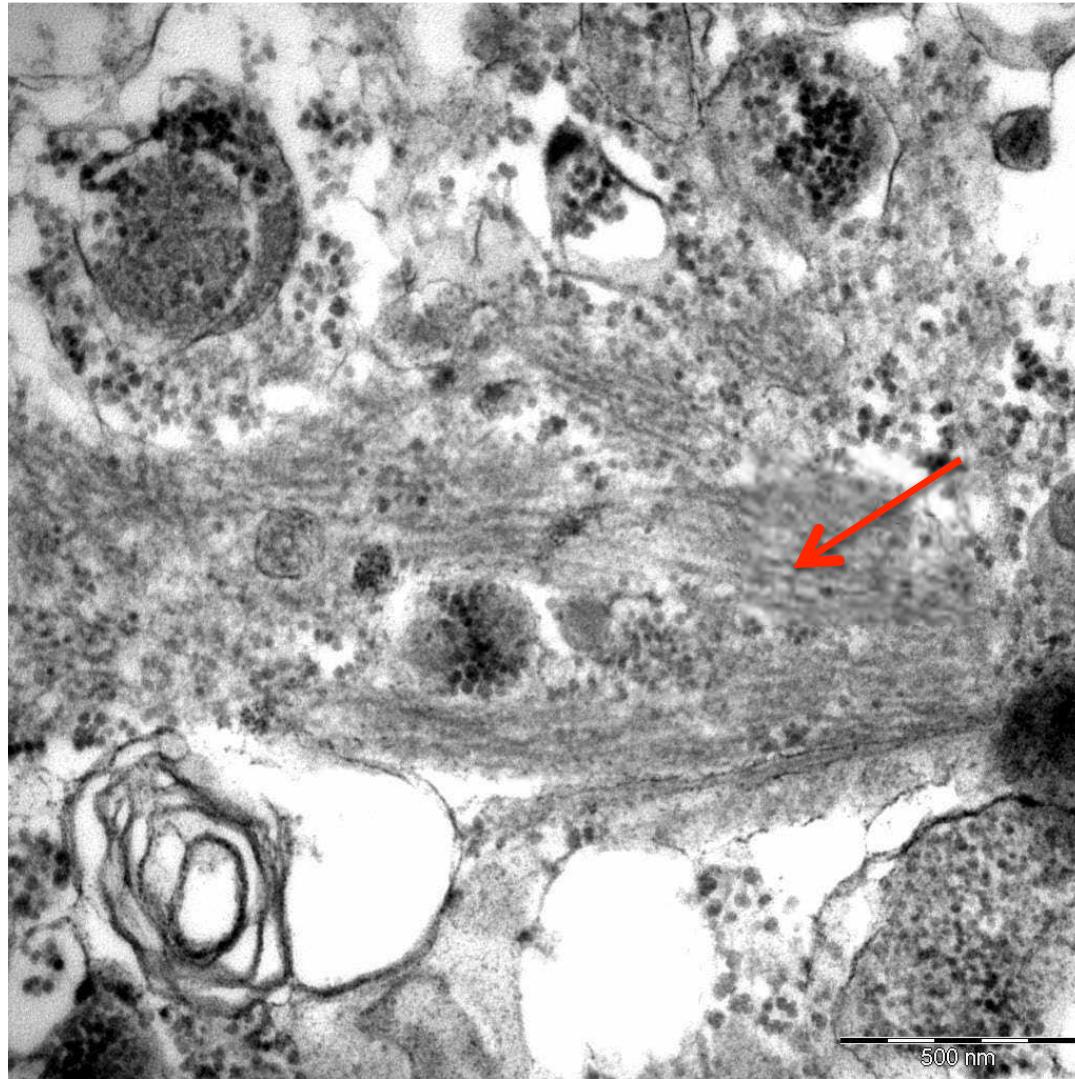




15-18nm thick tubulofilaments



15-18nm thick filaments



Muscle biopsy - VL

- Hypertrophic myofibers and round atrophic/necrotic myofibers present
- Endomysial, perimysial and perivascular chronic inflammatory cell infiltration
- Rimmed vacuoles within fibers
 - contain membrane whorls and sarcoplasmic organelle debris
- Small patches of 18nm filaments typical of IBM filaments
- Collection of smaller (12-14nm), randomly arranged filaments, represent β -amyloid filaments
- “Features consistent with an acute-on-chronic inclusion body myositis with marked inflammation”

Progress

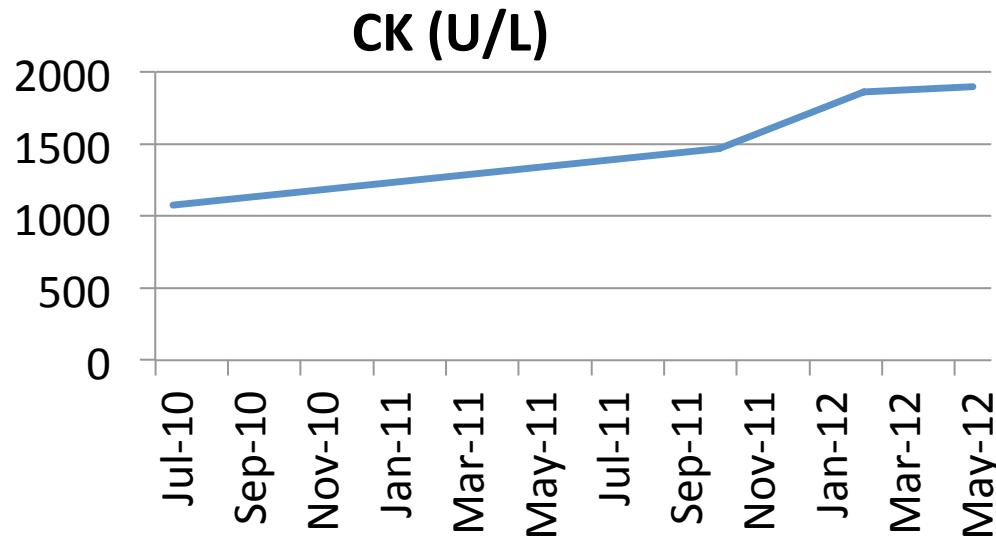
- December 2010
 - Mild proximal weakness
 - Commenced on prednisone 50mg daily
 - Intravenous immunoglobulin 0.4g/kg (Intragam)
- February 2011
 - Significant improvement in pain
 - Weakness unchanged
 - Prednisone reduced to 37.5mg

Progress

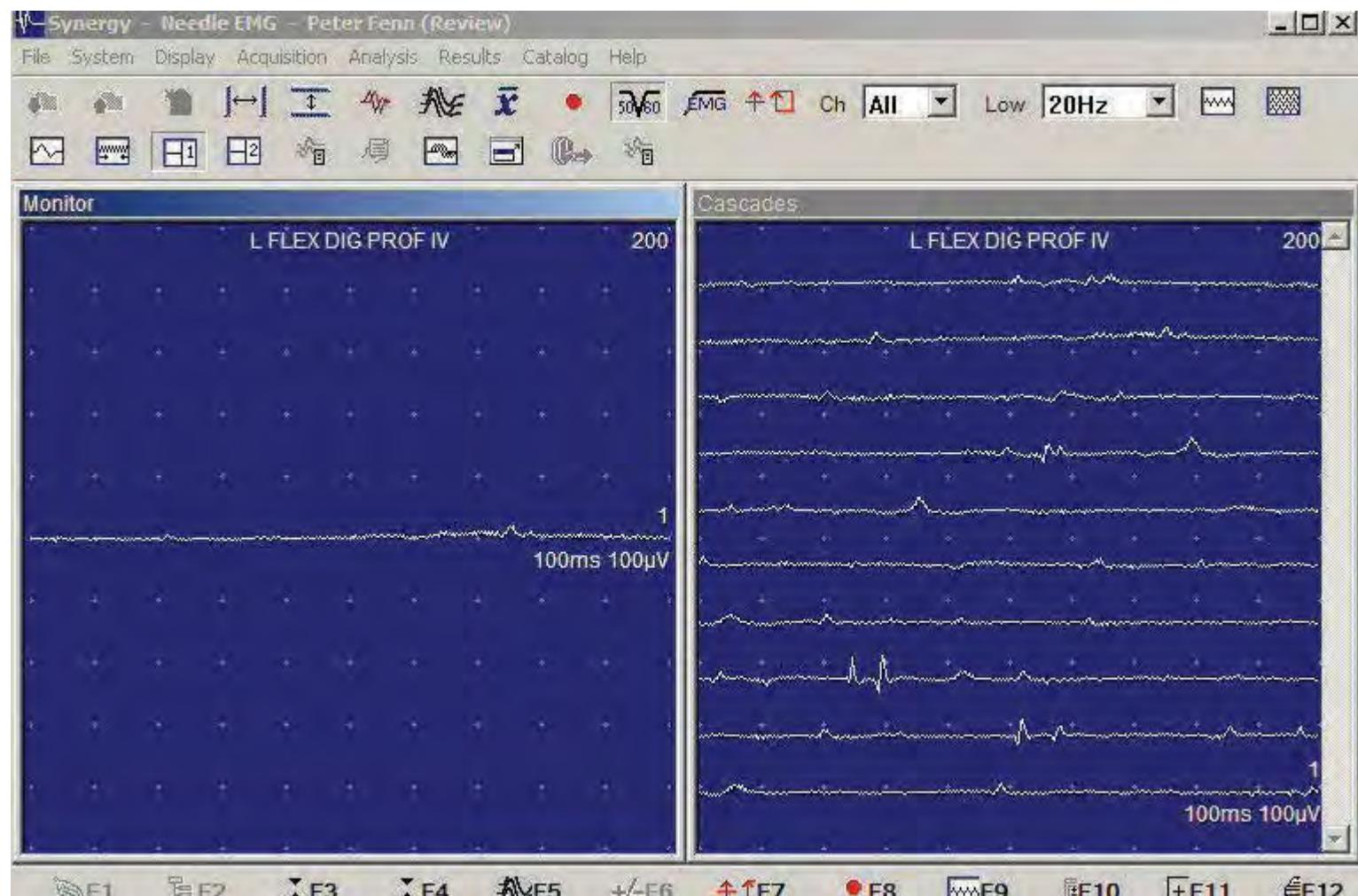
- May 2011
 - Power normal
 - DVT + PE
 - Anticoagulated
 - Homozygous for factor V Leiden mutation
 - IVIg ceased
 - Prednisone increased to 50mg
- August 2011
 - Increased cramping and pain
 - Mild weakness of hip flexion
 - IVIg recommenced

Progress

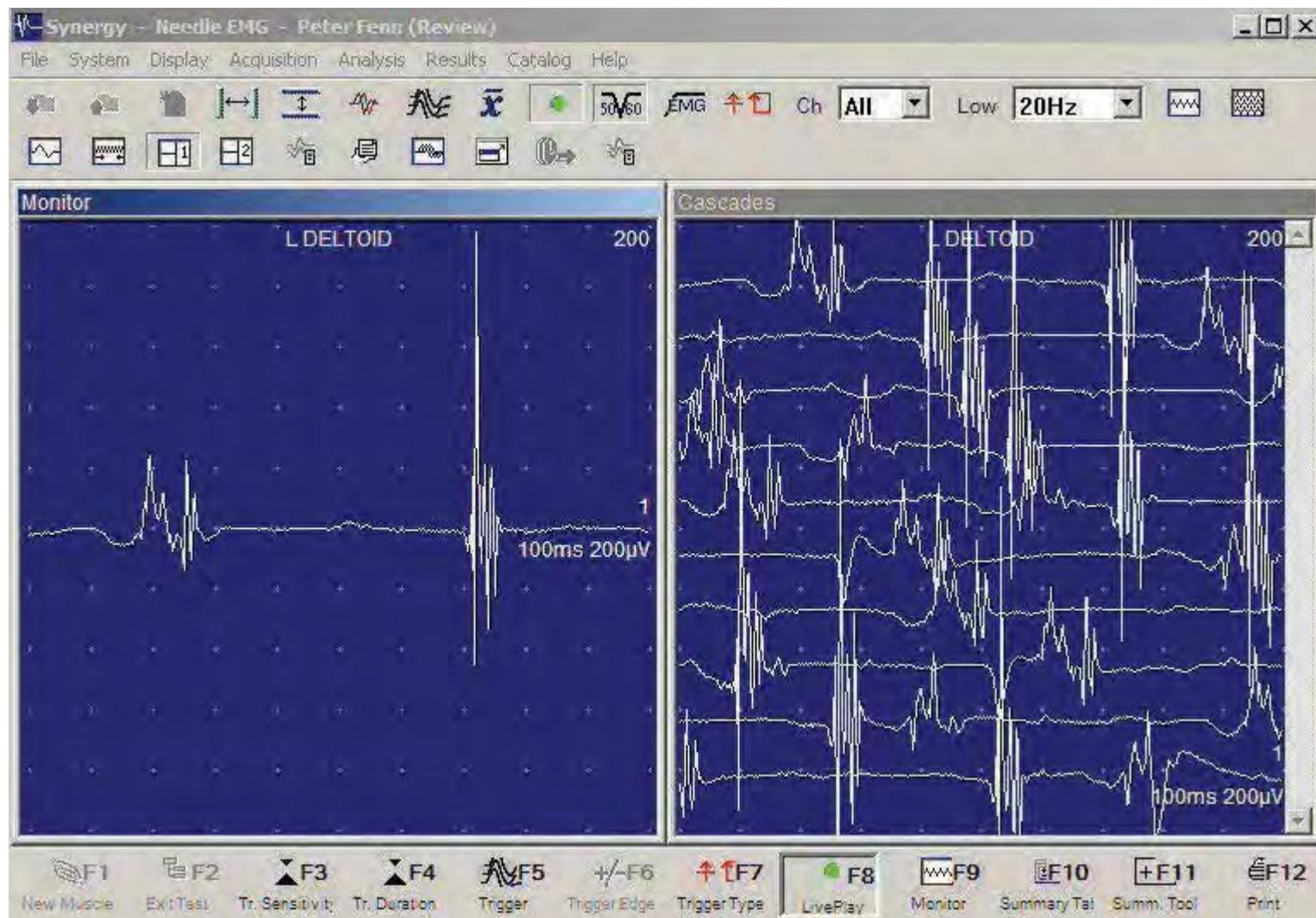
- November 2011
 - Pain markedly improved
 - CK 1000-1400U/L
 - Prednisone 7.5mg/day
- Feb 2012
 - Increasing weakness
 - prox power 4-/5
 - Prednisone ceased by LMO
 - CK 1866U/L

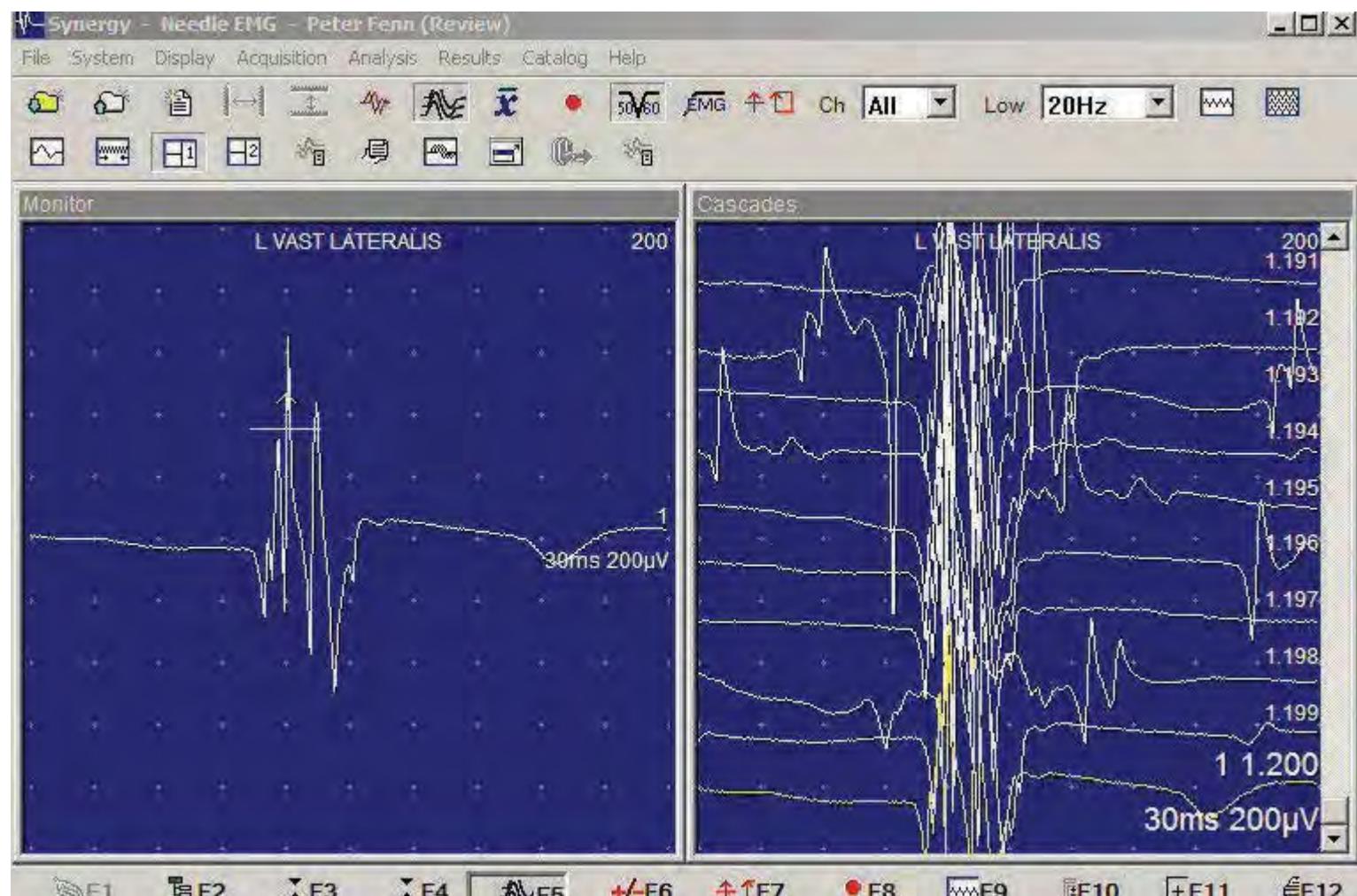


EMG



Vastus Lateralis



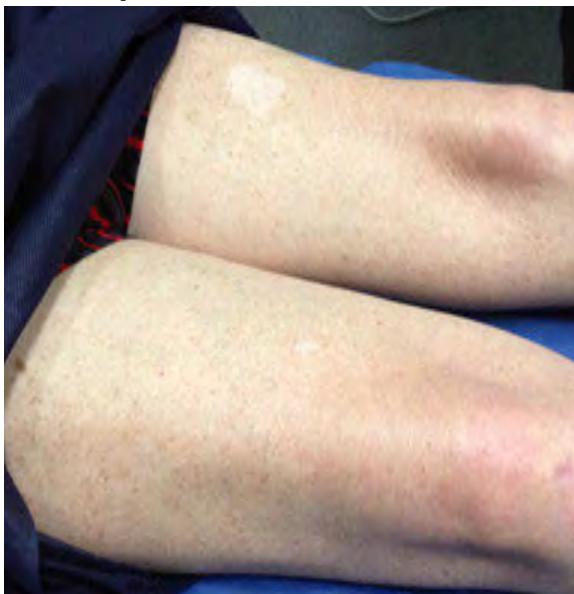


Progress

- Feb 2012
 - IVIg dose increased (60g 4/52)
- May 2012
 - Increasing pain
 - CK 1898
 - IVIg increased 99g
- August 2012
 - Symptomatically much better
 - Normal strength

Progress

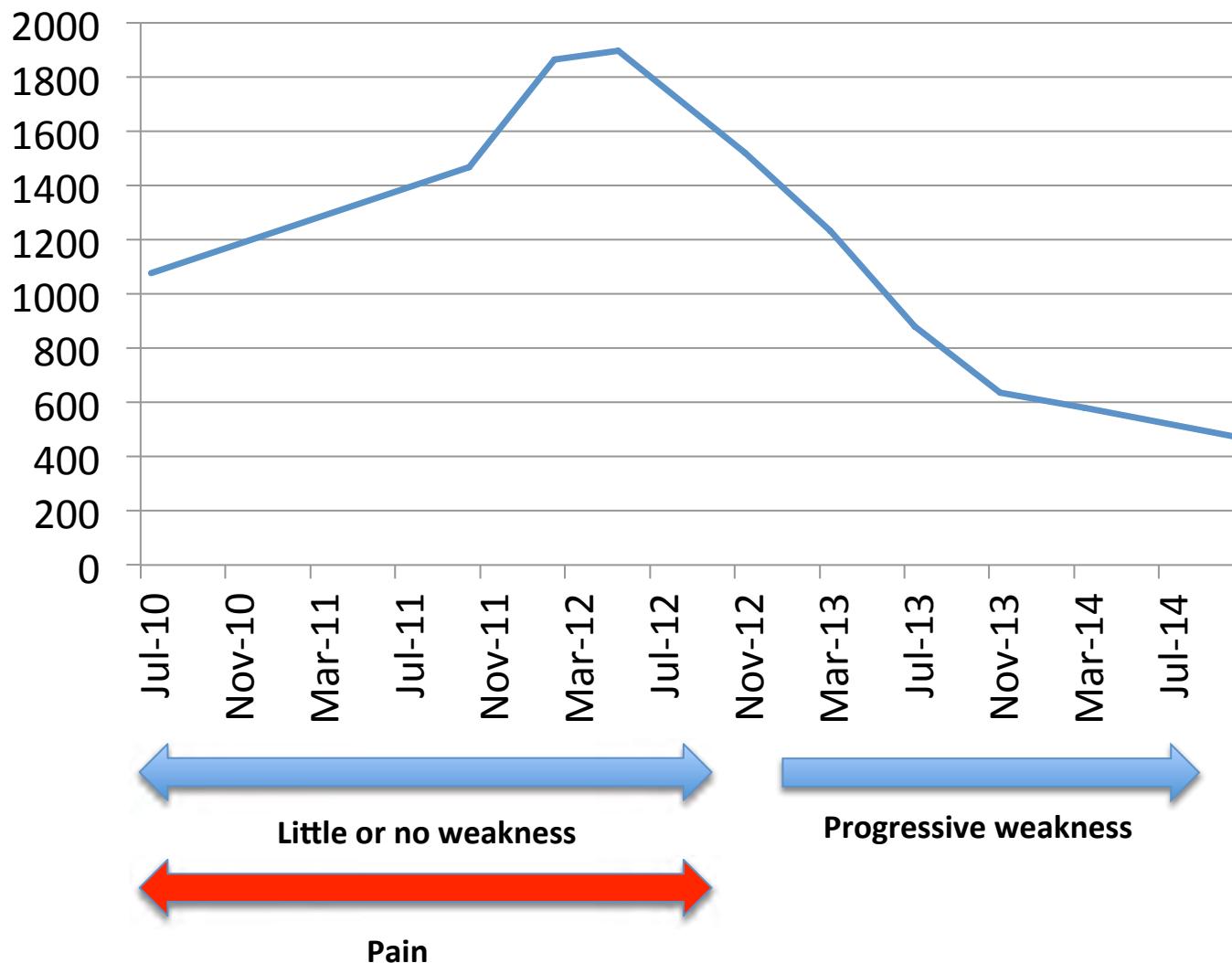
- April 2014
 - Increasing weakness; dysphagia
 - Particular involvement of the forearm flexors and extensors
 - Wasting and weakness of quadriceps



Progress

- Nov 2014
 - Weakness of shoulder abduction, triceps, finger extensors as well as finger flexors and brachioradialis bilaterally
 - Weakness of hip flexion/knee extension bilaterally + wasting of thighs
 - Several falls - requiring a frame
 - CK 400-600U/L

Creatine Kinase (U/L)



Comments

Inclusion Body Myositis

Inclusion Body Myositis

- Classified as a idiopathic inflammatory myopathy
- Distinguished by
 - A characteristic pattern of weakness
 - Asymmetric involvement of forearm flexors and quadriceps muscles
 - Resistance to immunosuppressive therapy
 - Characteristic findings on muscle biopsy

Diagnostic Criteria

Table 1. 1995 Griggs diagnostic criteria

Criteria type	Features
Clinical features	<ol style="list-style-type: none">1. Duration of illness >6 months2. Age of onset >30 years old3. Muscle weakness affecting proximal and distal muscles of arms and legs and patient must exhibit at least one of the following features:<ol style="list-style-type: none">a. Finger flexion weaknessb. Wrist flexion weakness > wrist extension weaknessc. Quadriceps muscle weakness (\leqgrade 4 MRC)
Laboratory features	<ol style="list-style-type: none">4. Serum creatine kinase <12 times normal5. Muscle biopsy<ol style="list-style-type: none">a. Inflammatory myopathy characterized by mononuclear cell invasion of nonnecrotic muscle fibresb. Vacuolated muscle fibresc. Either<ol style="list-style-type: none">i. Intracellular amyloid orii. 15–18 nm tubulofilaments6. Electromyography must be consistent with features of an inflammatory myopathy
Definite IBM	Patients must exhibit all muscle biopsy features, including invasion of nonnecrotic fibres by mononuclear cells, vacuolated muscle fibres and intracellular (within muscle fibres) amyloid deposits or 15–18 nm tubulofilaments
Possible IBM ^a	If the muscle biopsy shows only inflammation (invasion of nonnecrotic muscle fibres by mononuclear cells) without other pathological features of IBM, then a diagnosis of possible IBM can be given if the patient exhibits the characteristic clinical (1–3) and laboratory (4,6) features

Diagnostic Criteria

Table 3. 2011 European Neuromuscular Centre diagnostic criteria [9,47]

Clinical features	Classification	Pathological features
Duration of weakness >12 months	Clinicopathologically defined IBM	All of the following:
Creatine kinase $\leq 15 \times$ ULN		Endomysial inflammatory infiltrate
Age at onset >45 years		Rimmed vacuoles
Finger flexion weakness > shoulder abduction weakness		Protein accumulation ^a or 15–18 nm filaments
AND/OR		
Knee extension weakness \geq hip flexor weakness		
Duration of weakness >12 months	Clinically defined IBM	One or more, but not all, of:
Creatine kinase $\leq 15 \times$ ULN		Endomysial inflammatory infiltrate
Age at onset >45 years		Upregulation of MHC Class I
Finger flexion weakness > shoulder abduction weakness		Rimmed vacuoles
AND		Protein accumulation ^a or 15–18 nm filaments
Knee extension weakness \geq hip flexor weakness		
Duration of weakness >12 months	Probable IBM	One or more, but not all, of:
Creatine kinase $\leq 15 \times$ ULN		Endomysial inflammatory infiltrate
Age at onset >45 years		Upregulation of MHC Class I
Finger flexion weakness > shoulder abduction weakness		Rimmed vacuoles
OR		Protein accumulation ^a or 15–18 nm filaments
Knee extension weakness \geq hip flexor weakness		

^aDemonstration of amyloid or other protein accumulation by established methods (e.g. for amyloid Congo red, crystal violet, thioflavin T/S, for other proteins p62, SMI-31, TDP-43). Current evidence favours p62 in terms of sensitivity and specificity, but the literature is limited and further work is required. MHC Class I, Major histocompatibility complex class I; ULN, Upper limit of normal.

Pathogenesis

- Many theories...
 - Viral infection
 - Accumulation of toxic proteins
 - B-amyloid
 - Autoimmune attack
 - Myonuclear degeneration
 - Impairment of autophagy and proteasomal proteolysis

Pathogenesis

- Autoimmune muscle disease
 - Abundant lymphocytic infiltrate
 - Occurrence with other autoimmune diseases
 - Strong immunogenetic association
 - Individuals with certain HLA genes may have higher likelihood of developing IBM
 - Presence of antibodies against cytosolic 5'-nucleotidase 1A
- Degeneration
 - Some myofibers appear abnormal e.g., congophilic material, rimmed vacuoles without visible immune cells
 - Accumulation of β -amyloid and other proteins seen in neurodegenerative diseases
 - Progression of disease despite reduction in inflammatory components by immunosuppressive agents

Histopathological Findings

- Endomysial inflammation
 - Inflammatory cells surrounding and invading nonnecrotic muscle fibers
 - Myofiber necrosis, regeneration and variation in muscle fiber size
- Presence of rimmed vacuoles and tubulofilaments on EM are hallmark features but may be absent in 20-30%
- Other findings
 - Mitochondrial changes (e.g., cytochrome c oxidase negative fibers, succinic dehydrogenase +ve fibers)
 - Expression MHC-I on surface of myofibers
 - Congophilic inclusions in vacuolated fibers

Treatment

- Disease seems to be resistant to immunosuppressive drugs
- IVIg has not been shown to be effective in clinical trials
 - May have a role in dysphagia
- Case reports of response to immunotherapy
- Often IBM diagnosed years after the onset of symptoms
 - May already be significant muscle damage by this time ? Degenerative phase

? Is there a role for early
immunosuppression in IBM

- NEED TO INSERT CY'S VIDEO OF EXAMINATION!!!!!!!

THE END

β -amyloid

- β -amyloid-mediated myofiber injury has been a widely held theory
- Overproduction of β -amyloid precursor protein (β APP) transcript by myofibers → overproduction of β -amyloid- precursor protein → cleavage to produce β -amyloid → myofiber injury and death
- Not clear whether this is specific to IBM
 - β APP transcript also overproduced in other muscle disease PM/DM/DMD ?related to regenerating myofibers

Autoantibodies to Cytosolic 5'-Nucleotidase 1A

- Cytosolic 5'-nucleotidase 1A – enzyme speculated to be involved in nucleic acid metabolism
 - Specificity 89-98%
 - Sensitivity 33-70% (depending on antibody titer threshold)

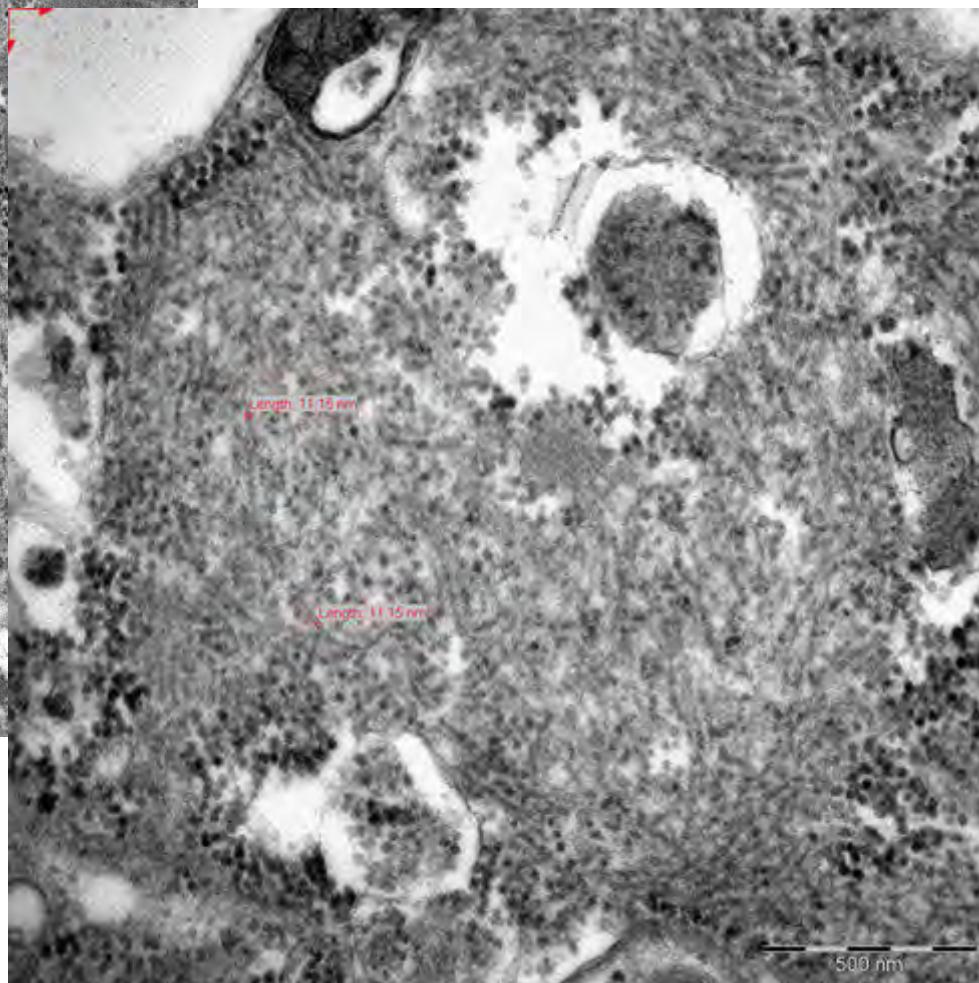
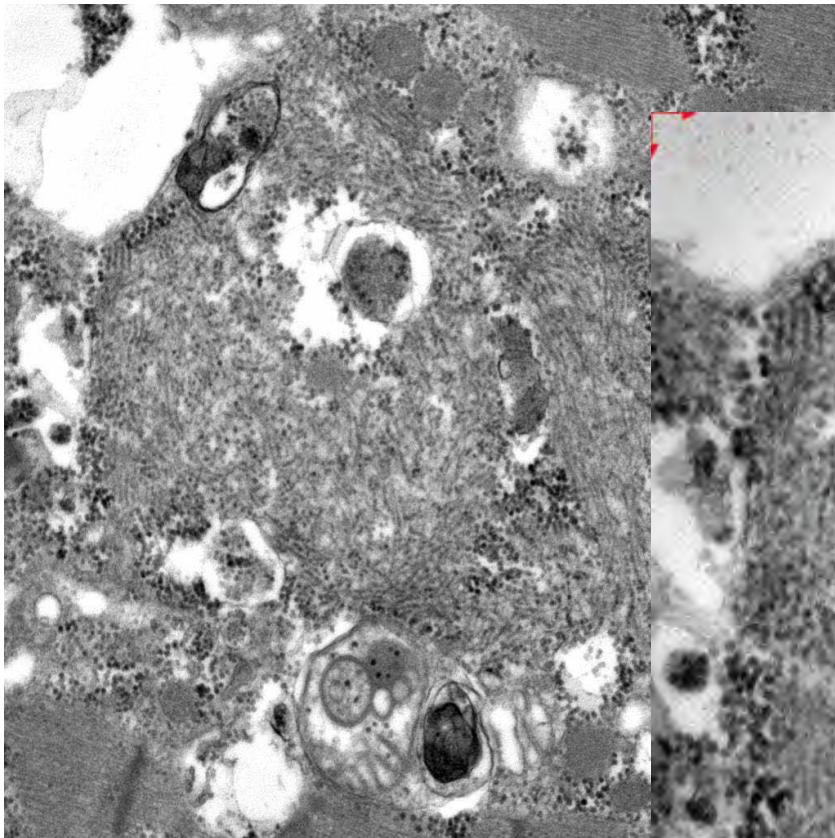
Table I. Clinical characteristics at diagnosis and features on muscle biopsy.

Patient N°.	1	2	3
Age, gender	49, F	62, F	73, F
Duration of symptoms (months)	9	24	39
Previous therapy for myopathy	none	none	IVIg, high-dose steroids, azathioprine, rituximab
Co-morbidities	chronic autoimmune thyroiditis (12 years duration)	none	chronic autoimmune thyroiditis (20 years duration); surgery for thymoma (3 years previously) [§] ; arterial hypertension; type I diabetes
Site of muscle weakness at clinical presentation	proximal muscles of the lower limbs; bilateral involvement of the supraspinate, infraspinatus, deltoid gluteal and ileopsoas; mild involvement of right and left hamstrings	proximal upper and lower limb muscles; bilateral involvement of external shoulder rotators, hip abductors, diaphragm and intercostals	abductors, adductors and external rotators of the shoulder (bilateral), hip abductors and flexors (bilateral), neck extensors and paraspinals; mild involvement of right and left hamstrings
Anti-Jo-1	negative	negative	negative
Other auto-antibodies*	absent	absent	anti-acetylcholine receptor [#]
Electromyography	active myopathic process	active myopathic process	active myopathic process
Morphological diagnosis:			
- % atrophic fibres	s-IBM 5	s-IBM 6	s-IBM 3
- % internalized nuclei	none	3	3
- endomysial non-necrotic fibres penetrated by lymphocytes	present	present	present
- rimmed vacuoles	absent	absent	absent
- non membrane bound, membranous whorls with associated tubo-filamentous inclusions	present	present	present
- immunohistochemical lymphocyte typing	CD3 +, CD20-	CD3 +, CD20-	CD3 +, CD20-

Treatment of inclusion body myositis with cyclosporin-A or tacrolimus: successful long-term management in patients with earlier active disease and concomitant autoimmune features

Clinical and Experimental Rheumatology 2007; **25**: 246-251.

β -amyloid filaments



NEXT SPEAKER

Neuromuscular meeting

Dr Roula Ghaoui

Prof. Bjarne Udd

Professor Carolyn Sue

54 year old female

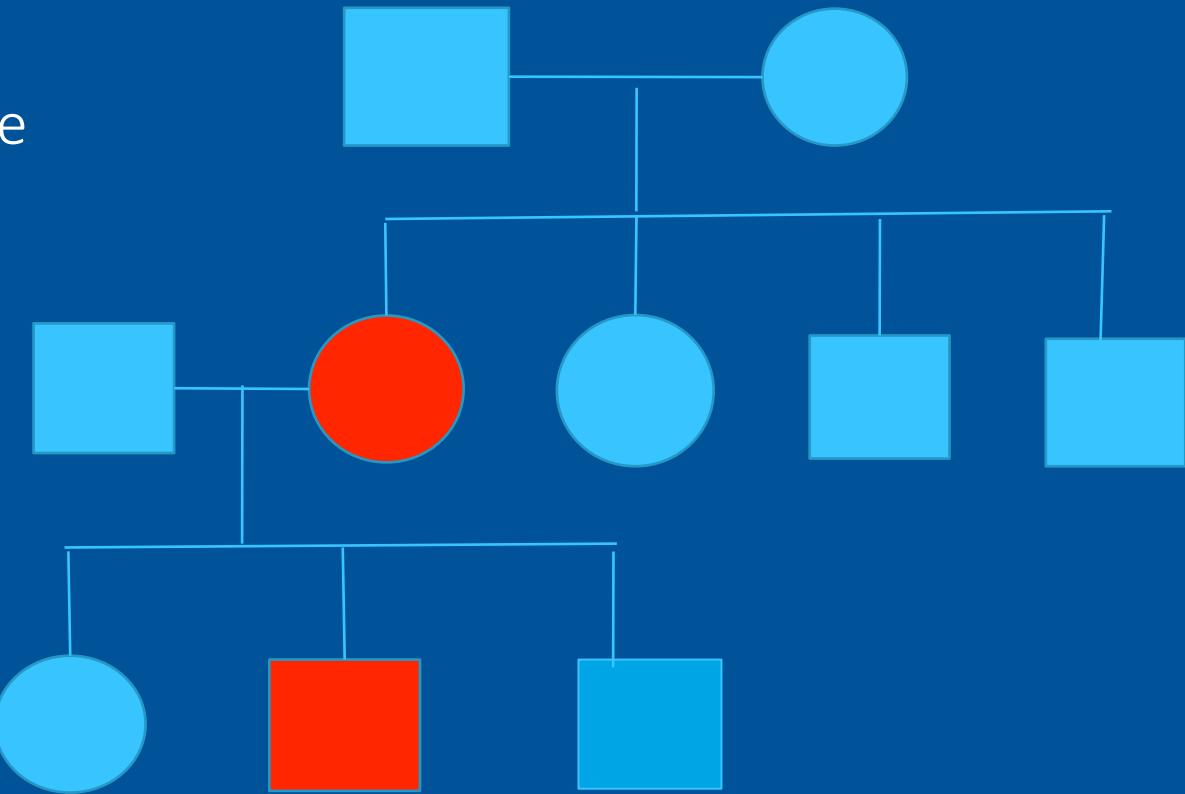
- Eldest of 4 children
- Normal developmental milestones
- Symptoms began in childhood with pain in ankles playing netball at primary school requiring cortisone injections
- Severe cramps in calves-reported falling a lot
- First obvious signs of weakness in 20s
 - weak ankles, associated with pain
 - ankles said to be hypermobile
 - weakness/wasting exacerbated by orthopaedic procedure (ankle fusion)

History of weakness

- Wasting started in calf muscles and progressed to involve quadriceps
- Since 2000 (early 40s), patient has required a walking stick
- Since 2012, a walker was required because of frequent falls and tripping over feet
- Upper limbs relatively spared, but difficulty opening jars
- Intermittent dysphagia to solids

Family history

- Parents unaffected by neuromuscular disease
 - Father had Crohn's disease
- 3 siblings aged 53, 51 and 50
- 3 children
 - Aged 31, 29 and 26
 - 31 year old daughter has Crohn's disease
 - 29 year old son affected with distal weakness



Autosomal dominant pattern of inheritance with a likely
de novo event in the mother

29 year old male

- 4 weeks premature, required oxygen in humidicrib for 10 days
- Normal early milestones, normal childhood sport participation
- Symptoms of muscle weakness since early 20s
 - Falls when trying to change direction
 - Unable to stand on toes
 - Progressive wasting of calves and thighs



Examination





Examination

Mother

- Waddling gait with foot drop
- Mobilises with a walker
- Upper limb-Normal
- Mild finger flexor weakness

Lower Limb

1. Power
 - Hip flexion 1-2/5
 - Distally power 0/5
2. Reflexes
 - Absent R ankle
3. Sensation
 - Impaired vibration to ankles

Son

- Unable to stand on heels/toes & unable to squat
- High arched feet, hammer toes
- Wasting of EDB, gastrocnemius, tib ant, soleus and hamstrings
- Upper Limb-Normal
- Lower limb
 1. Power
 - Proximal 5/5
 - Dorsiflexion 2/5
 - Plantarflexion 4/5
 2. Reflexes
 - Absent at ankles
 3. Sensation
 - Normal all modalities

Investigations

Mother

CK 269

Echo/PFTs: Normal

Barium swallow: Normal

Son

CK 850-2000

Echo/PFTs: Normal

NCS:

Normal sensory nerve SNAPs.

R. common peroneal absent and
reduced CMAP of right tibial (0.4mV).

Normal upper limb CMAPs

EMG chronic neurogenic changes in the
lower limb and some myopathic
changes in the upper limb (deltoid
& triceps).

Right Tibialis anterior

Motor Unit Record

#14



12:33:46

100 uV

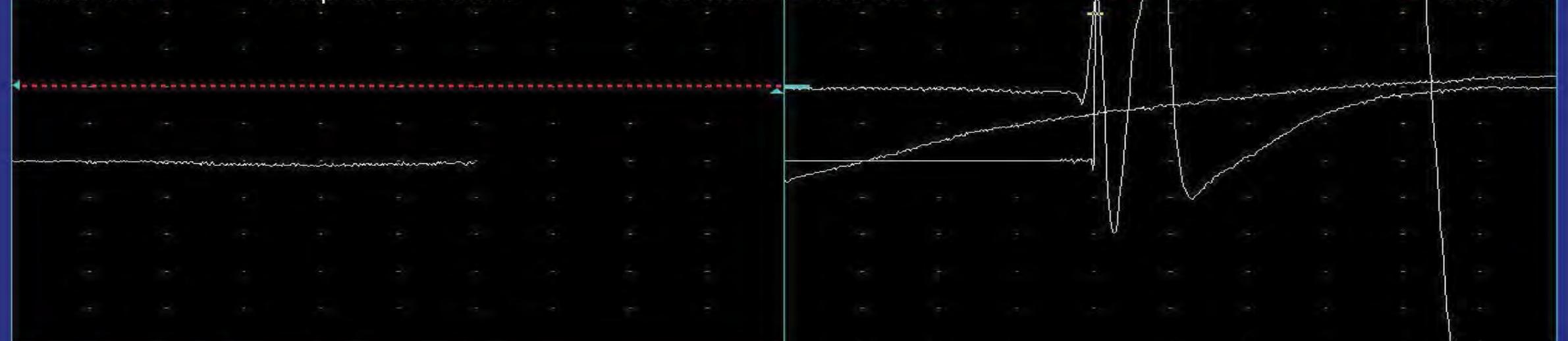
Amp 1: 20-10kHz

10 ms

100 uV

1.-

5 ms



Trig: ↑ -200uV Rate: 1.9Hz

II 18/49s ▲ 1 ▼

Polyphasic: 0 (0.0%) Total MUPs: 1

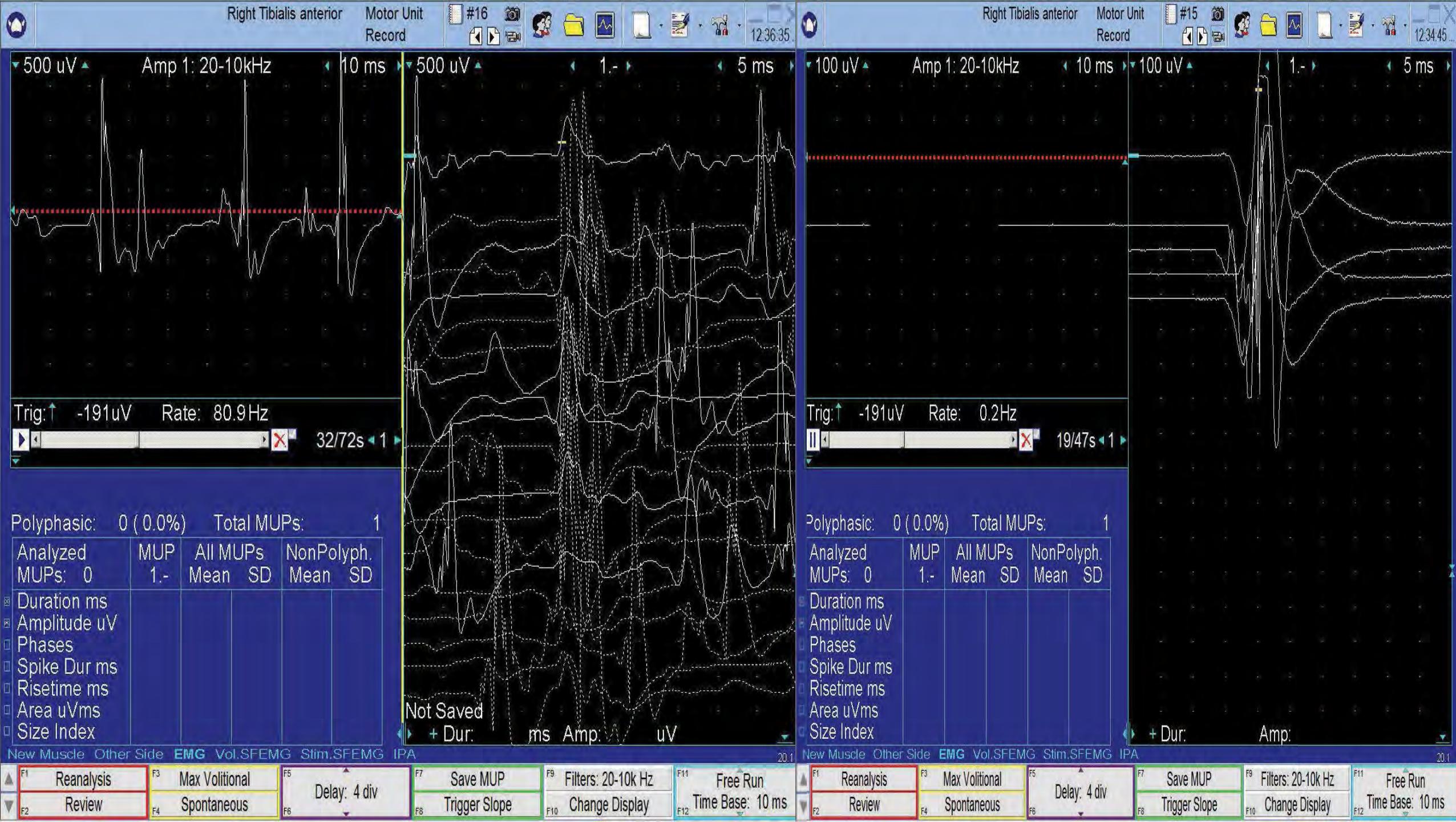
Analyzed MUPs:	MUP 1.-	All MUPs Mean	All MUPs SD	NonPolyph. Mean	NonPolyph. SD
1	1.-	27.3	0.0	27.3	0.0
Duration ms	27.7	27.3	0.0	27.3	0.0
Amplitude uV	518	517	0	517	0
Phases	3	3.0	0.0	3.0	0.0
Spike Dur ms	6.4	6.4	0.0	6.4	0.0
Risetime ms	2.4	2.4	0.0	2.4	0.0
Area uVms	1670	1672	0	1672	0
Size Index	2.66	2.66	0.00	2.66	0.00

Dur: 27.7 ms Amp: 518 uV

New Muscle Other Side EMG Vol.SFEMG Stim.SFEMG IPA

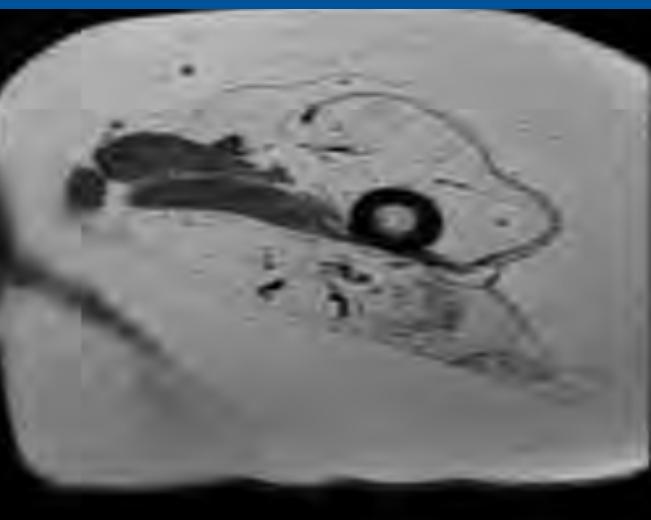
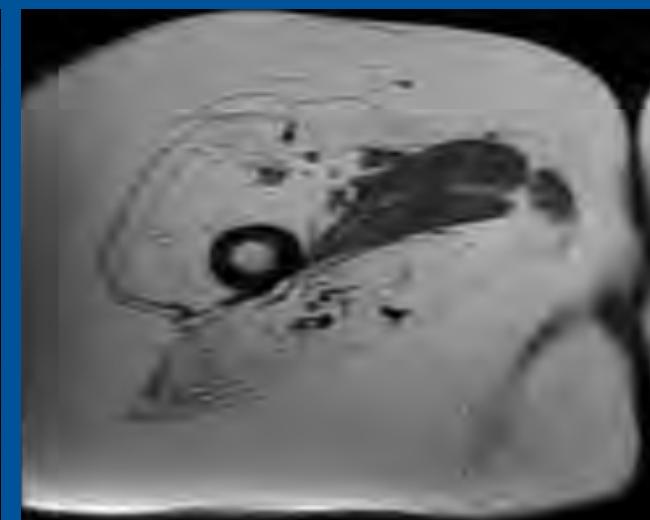
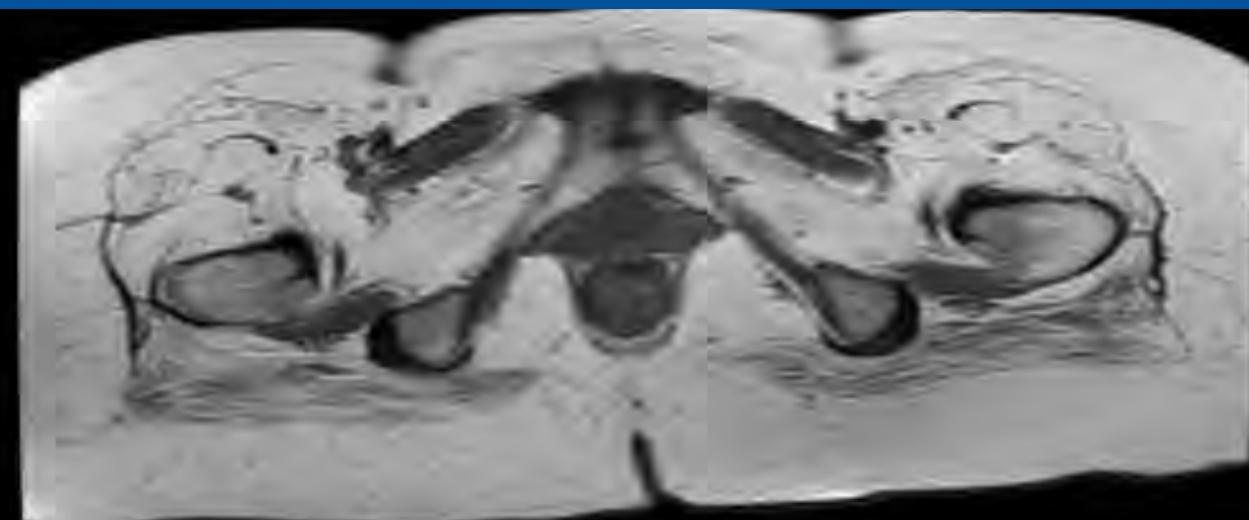
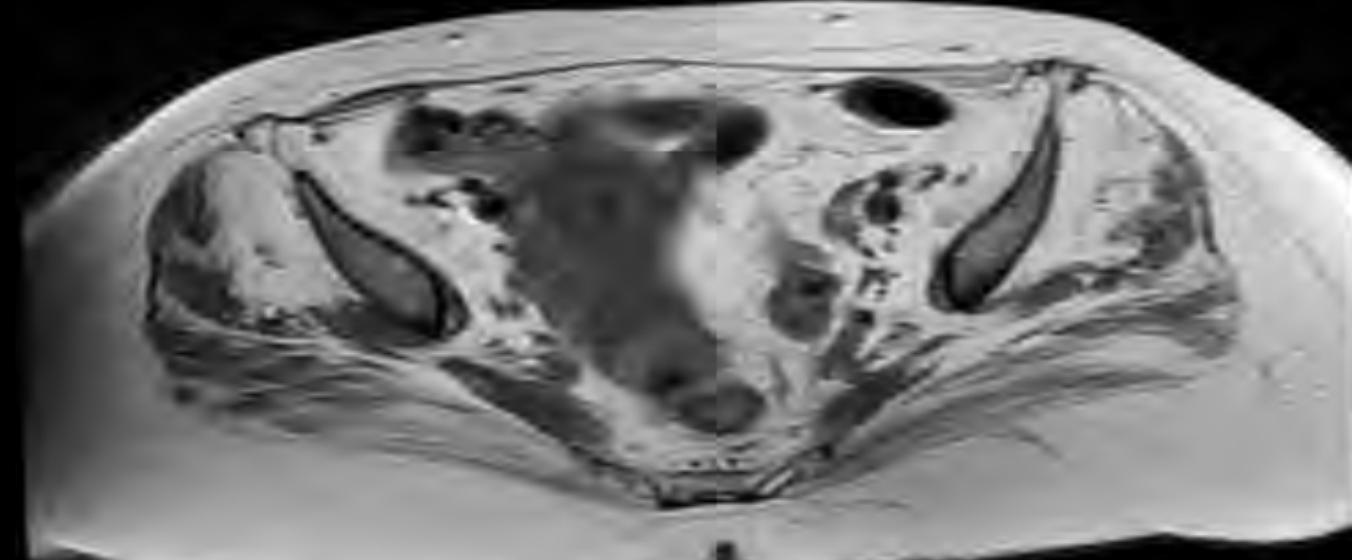
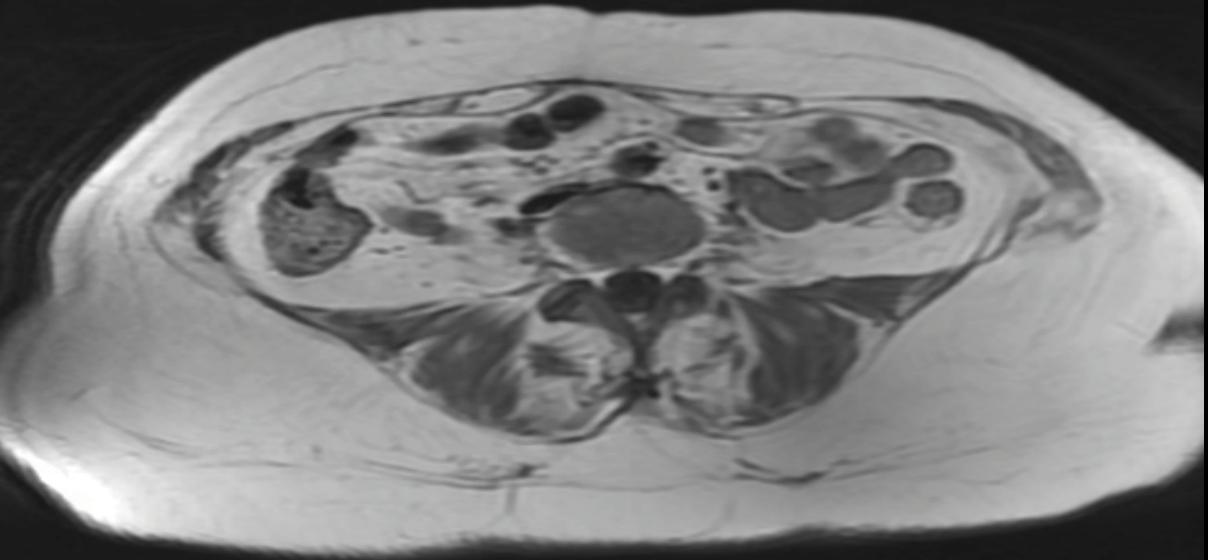
20.1

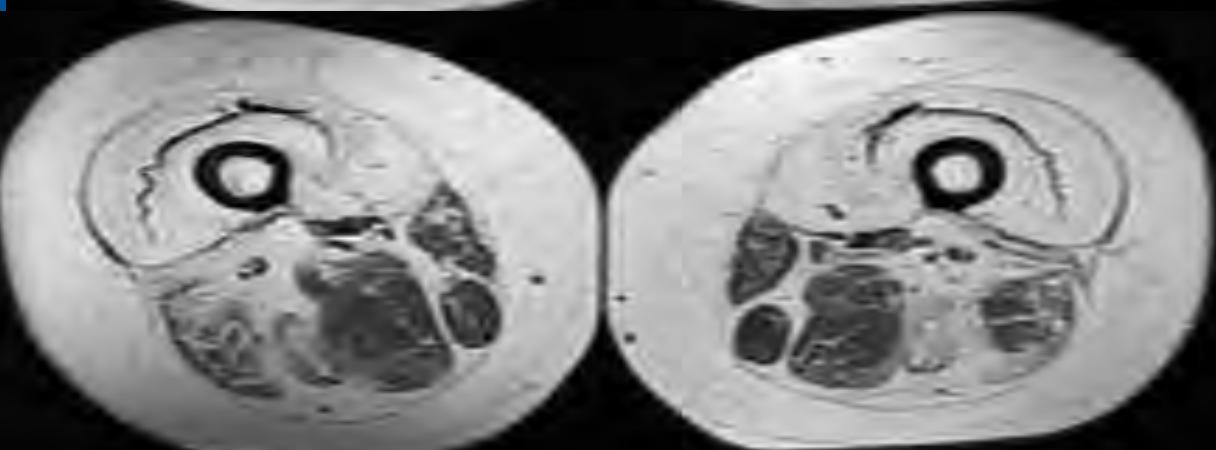
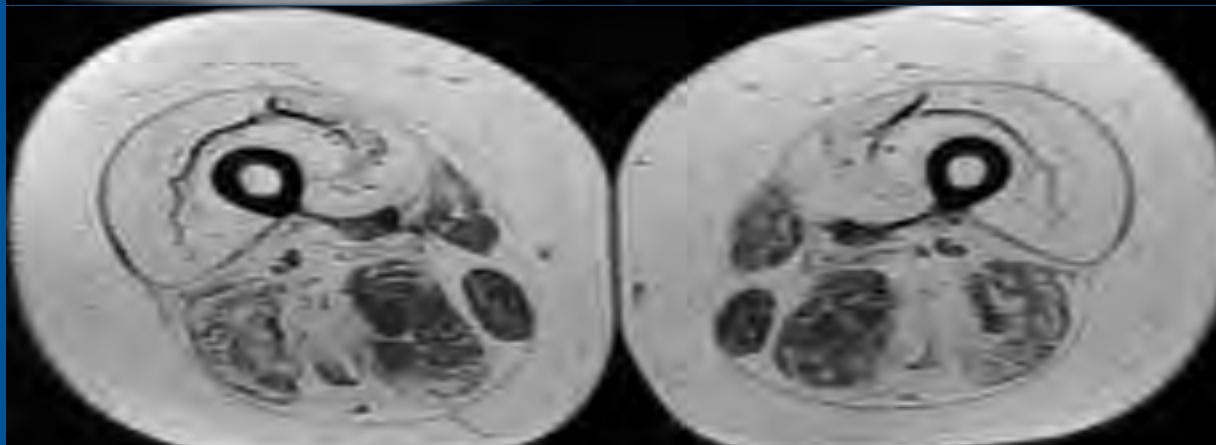
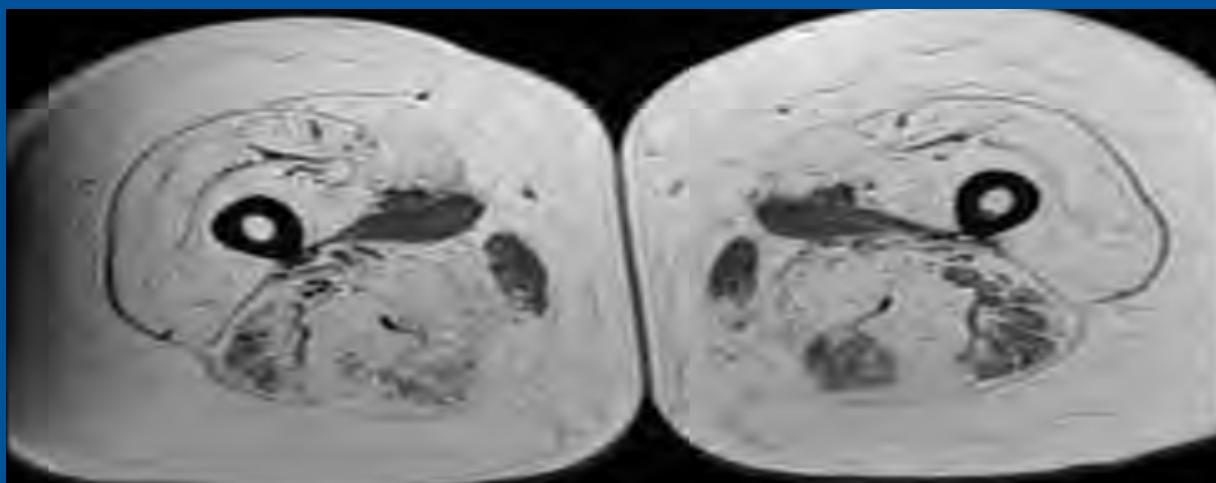
▲ F1 Reanalysis	F3 Max Volitional	F5 Delay: 4 div	F7 Save MUP	F9 Filters: 20-10k Hz	F11 Free Run
▼ F2 Review	F4 Spontaneous	F6	F8 Trigger Slope	F10 Change Display	F12 Time Base: 10 ms



MRI Lower Limbs

MRI Mother





HSPB8 : diff all but AL spared > RF, Gr, St

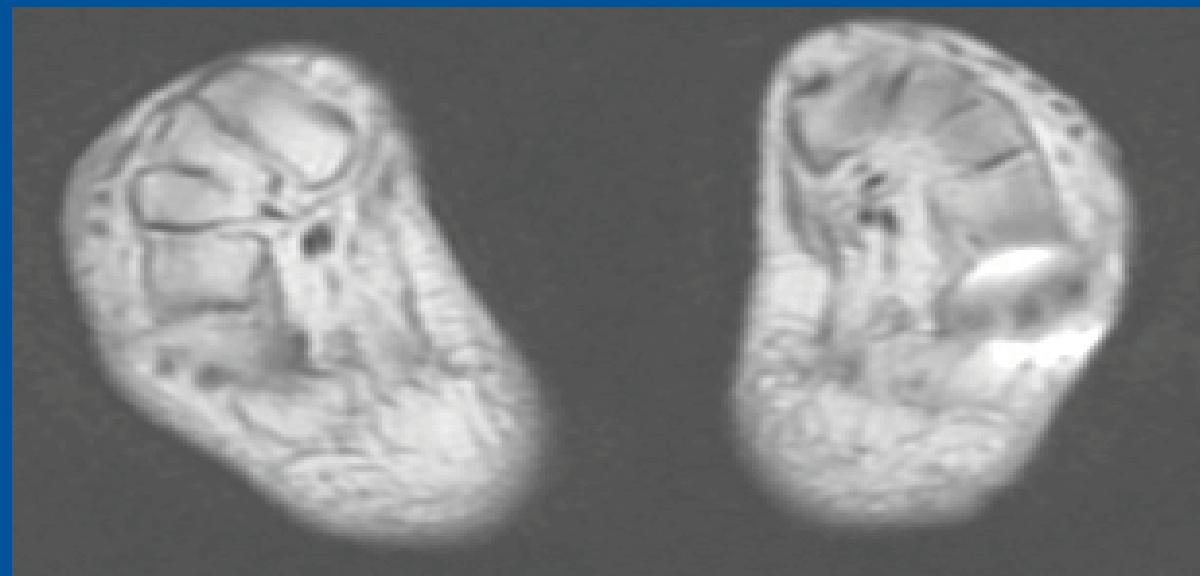
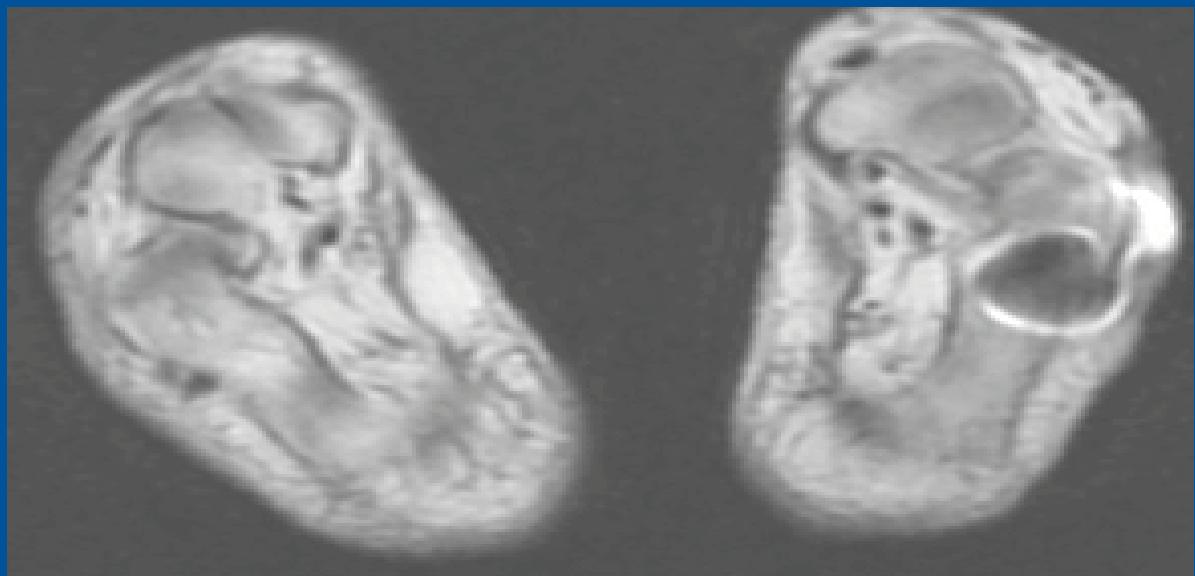


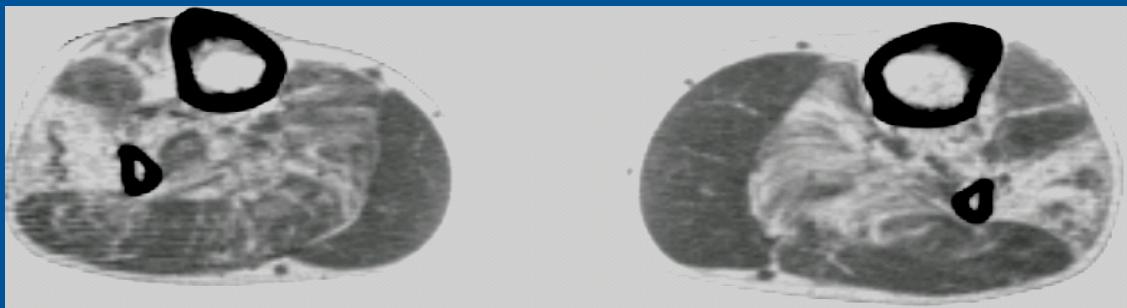
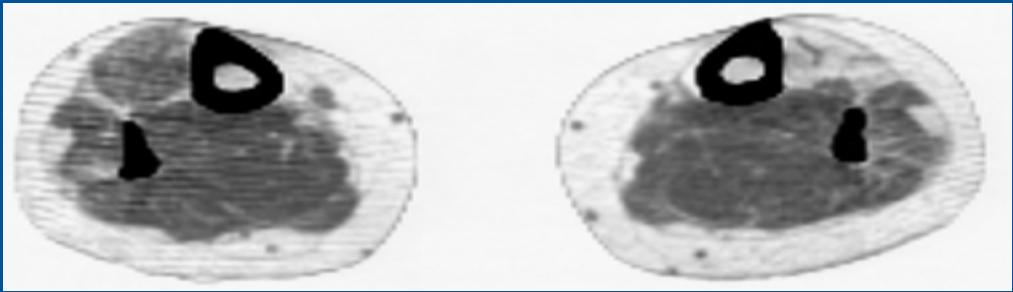
previous



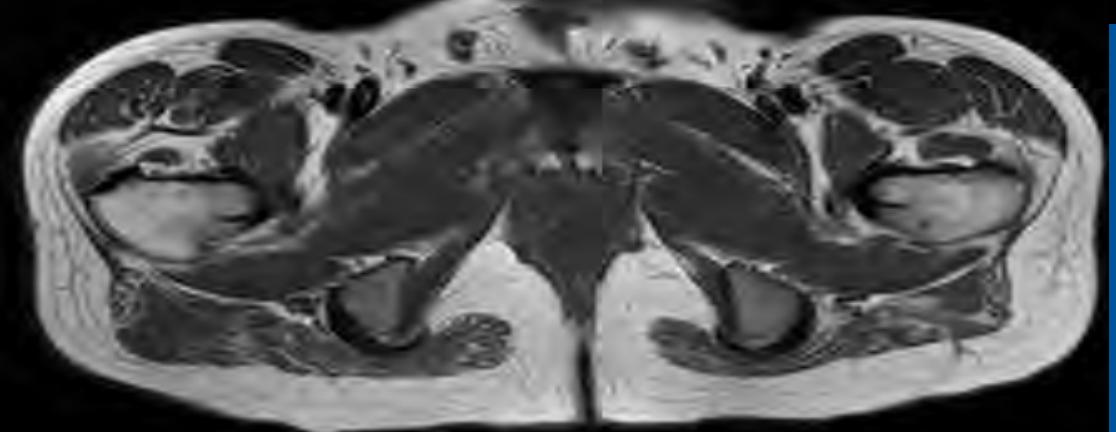
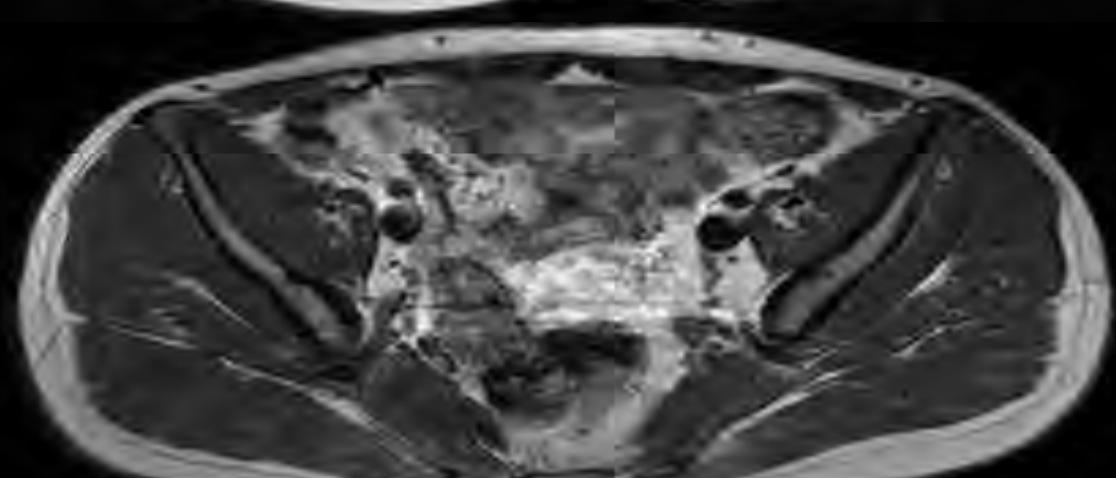
2010



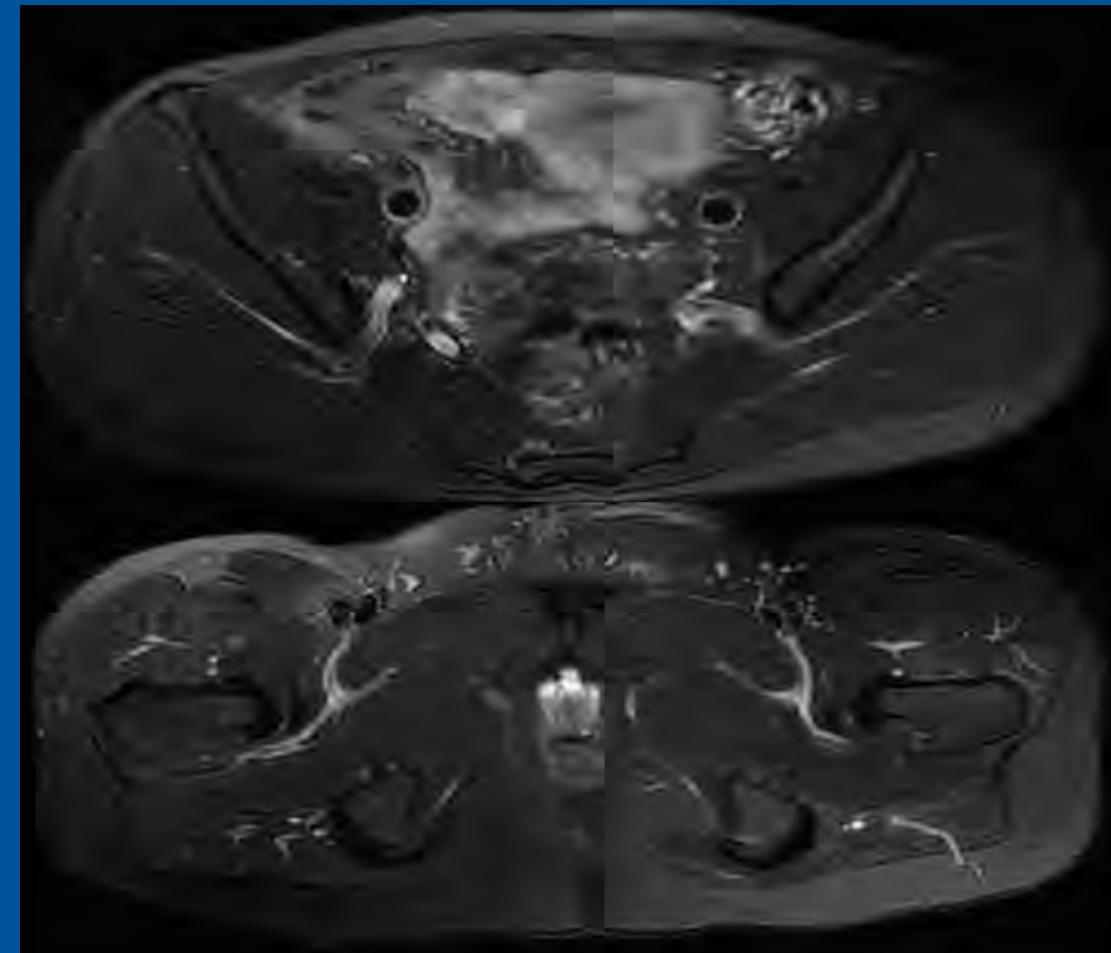


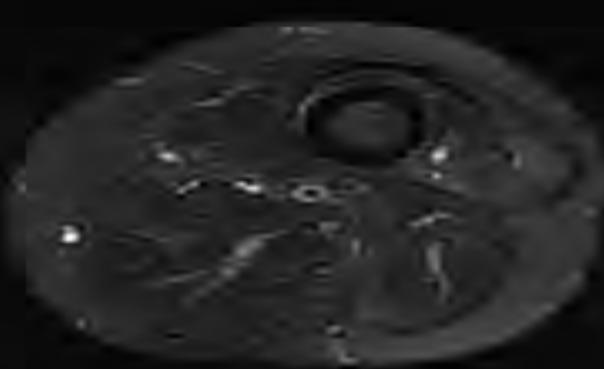
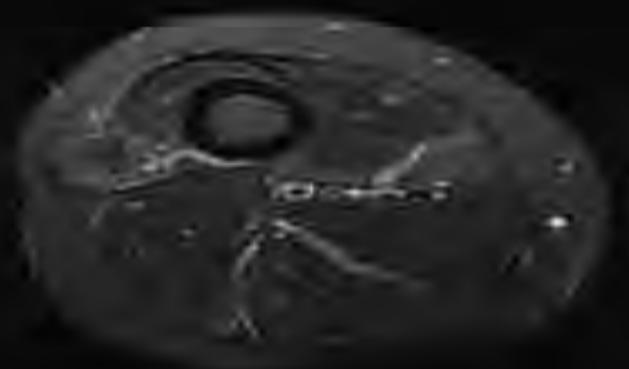
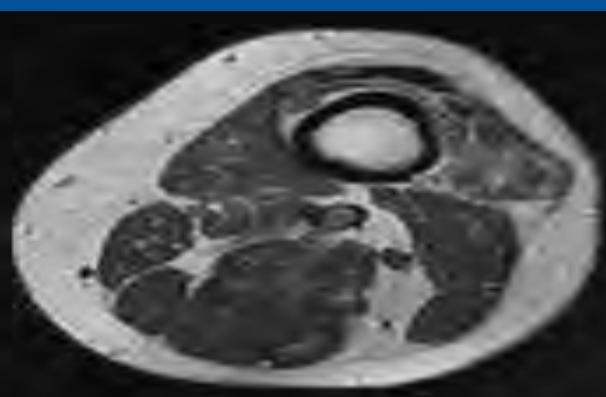
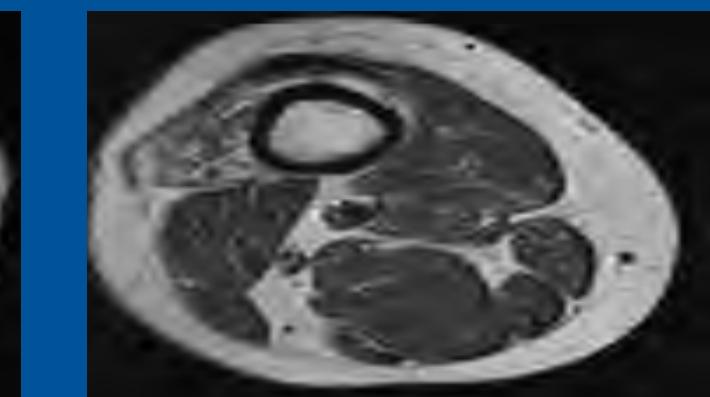
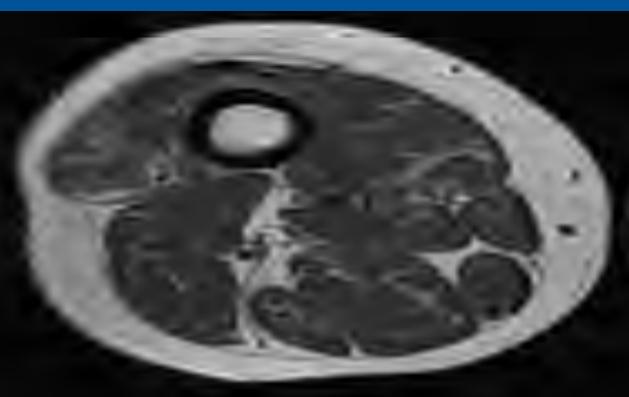
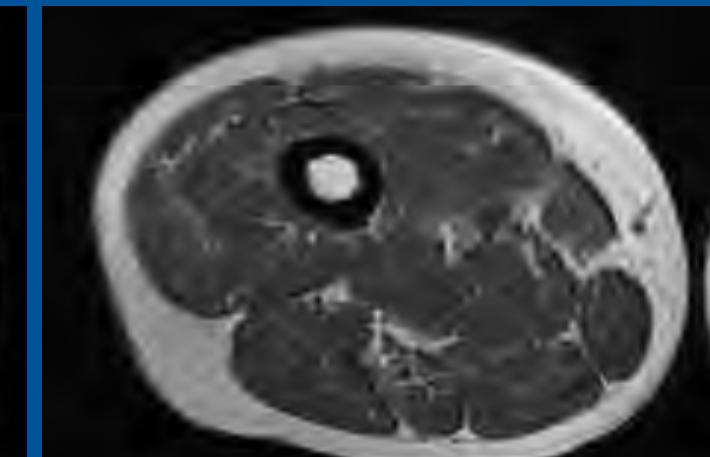
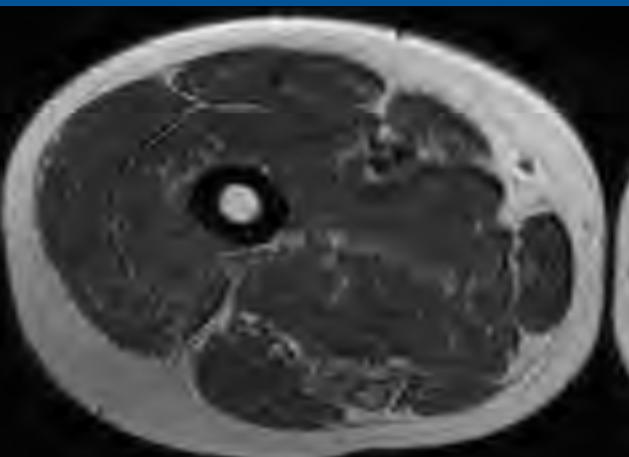


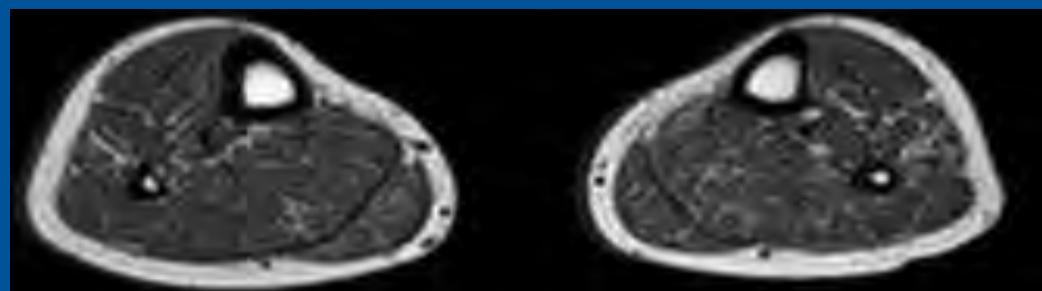
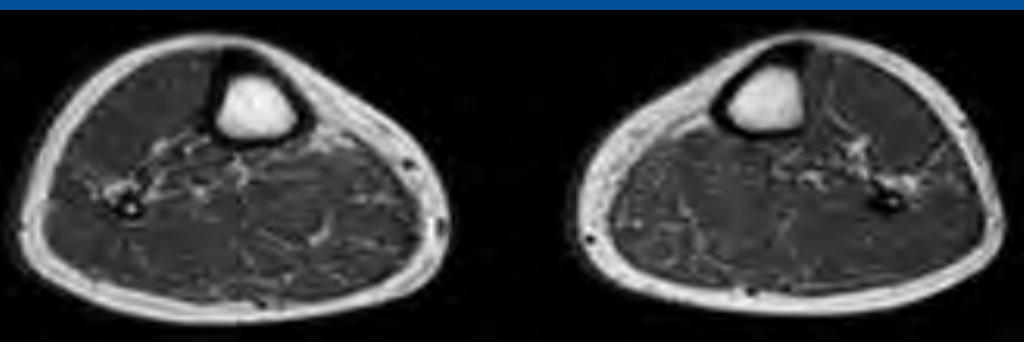
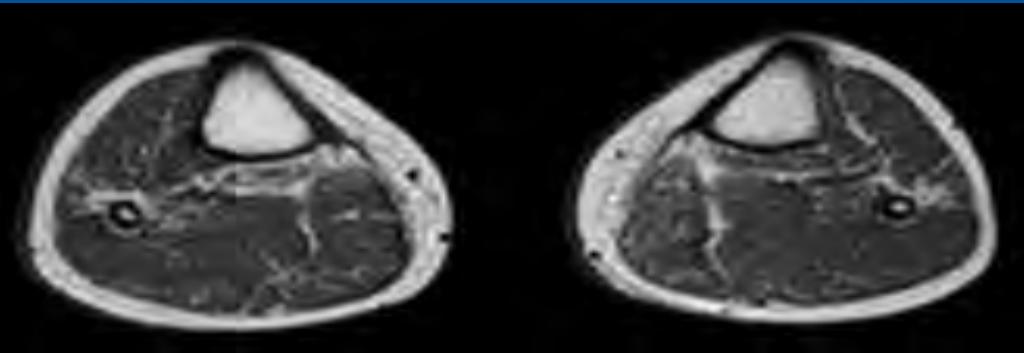
Other distal myopathies gene unknown



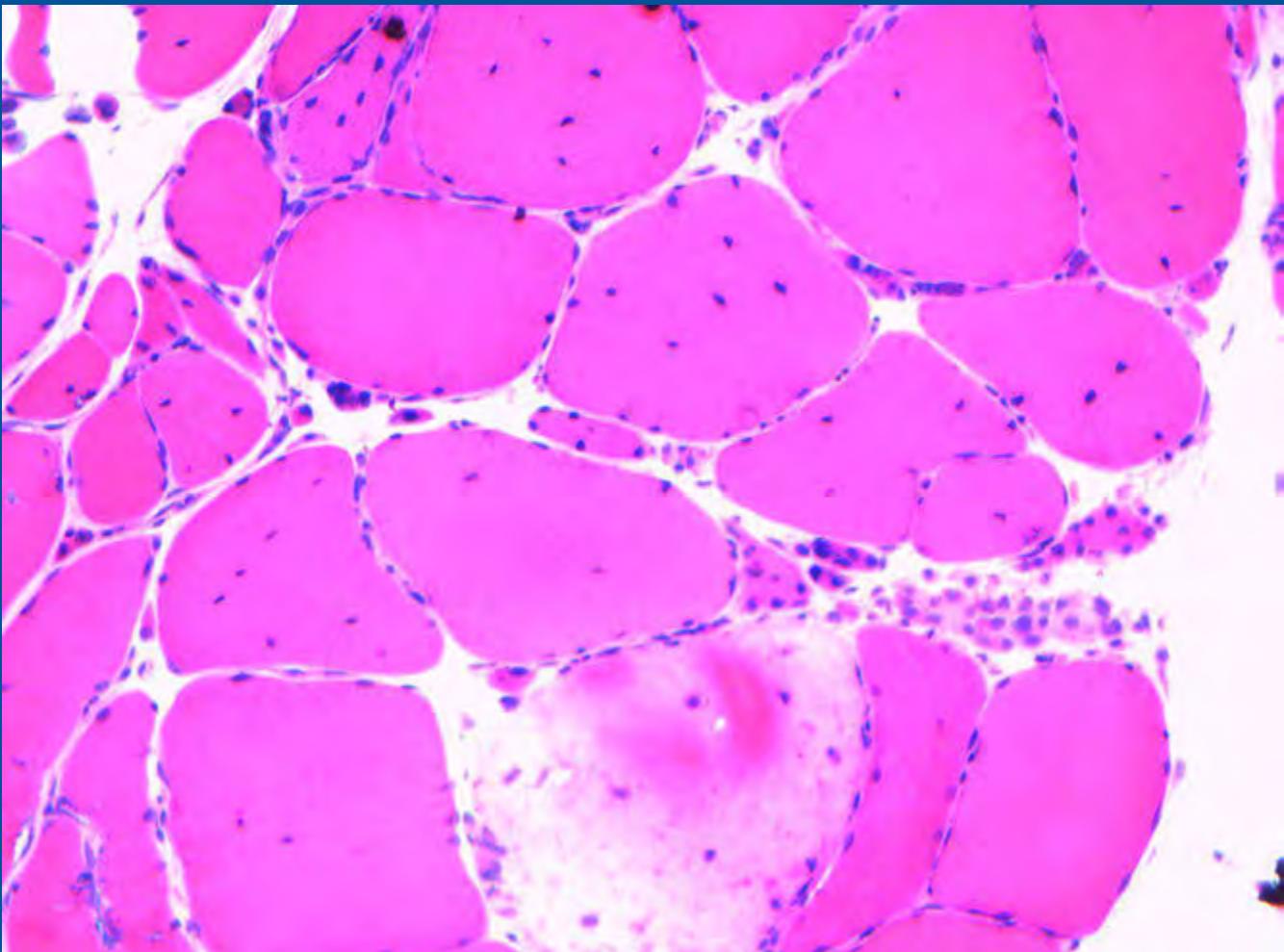
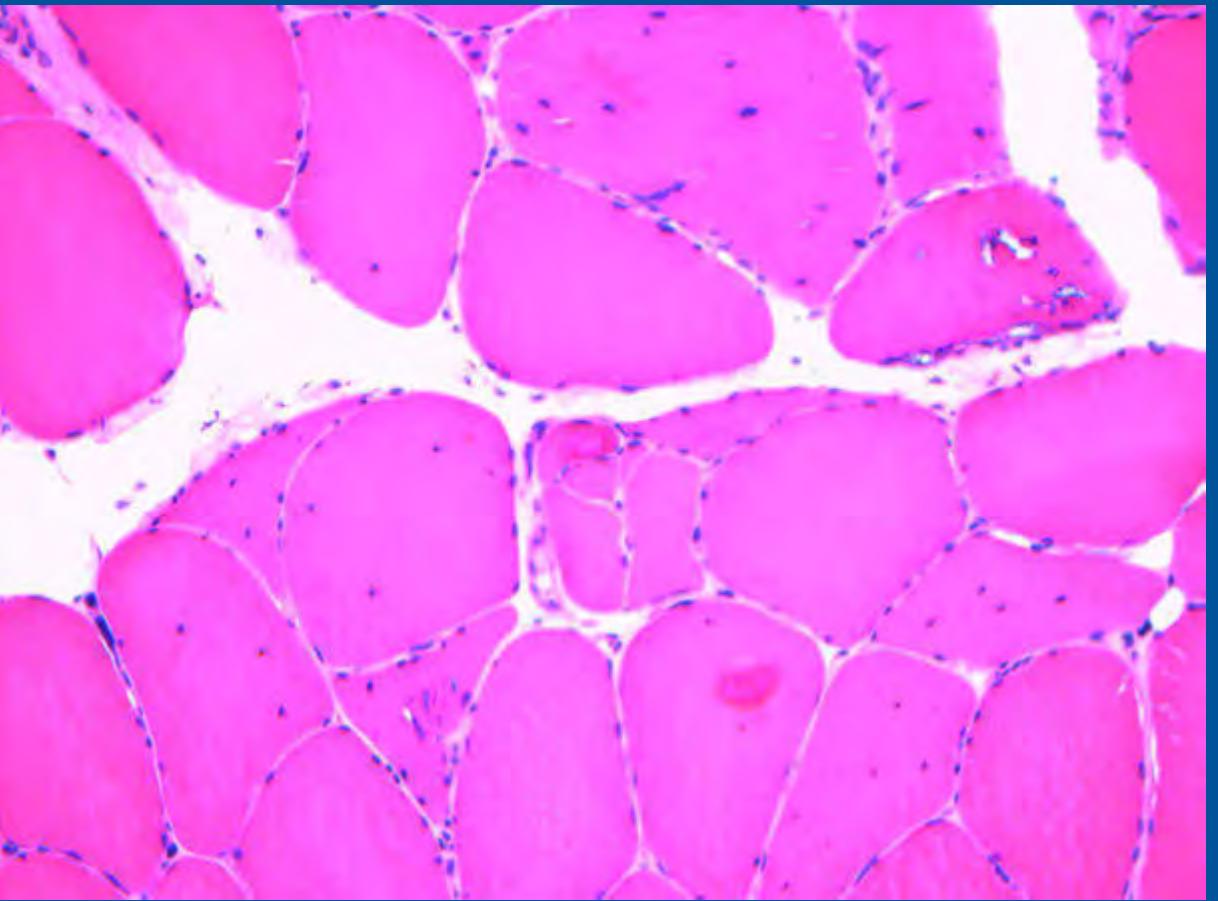
MRI Son







Muscle Biopsy



Vastus Lateralis

Both patients had similar findings

- Fibre size variation with atrophy and hypertrophy
- Fibre splitting, small angulated fibres
- Many central nuclei and rimmed vacuoles

?Myofibrillar Myopathy

Positive inclusions staining with desmin and myotilin

(No abnormality on staining for dystrophins, lamin, dysferlin, emerin, dystroglycan, adhalin, caveolin, beta sarcoglycan, gamma sarcoglycan and spectrin)

Myofibrillar myopathies

- Genetically heterogenous, some AD with adult onset
- Desmin, ZASP, γ -filamin, $\alpha\beta$ -crystalline and myotilin are associated genes
- Distal myopathy pattern can be seen, but limb-girdle patterns seen more often
- Cardiac involvement common
- Respiratory failure also can be life-limiting
- Other organ system involvement – cataracts, neuropathy

Isolated lower limb distal myopathy uncommon phenotype

Prof Bjarne Udd

‘This muscle disease does not easily fit into any of the described categories’

- Autosomal dominant rimmed vacuolar pathology
- Disease onset is age 15 in legs, but evolves in 10 years time to proximal lower limb muscles, so it is not a pure distal myopathy
- Unique pattern of muscle involvement in the legs
 - Muscle wasting distally appears neurogenic but a more characteristic myopathic pattern changes in thighs
- The evolution is like the recessive GNE mutated Nonaka/hIBM disease but there is no sparing of the quadriceps.

Next Generation Sequencing



Ability to rapidly sequence greater number of genes
Whole exome or targeted to neuromuscular disease genes
Good approach for neuromuscular disease
Overlapping phenotypes
Genetic heterogeneity
Large genes



Results

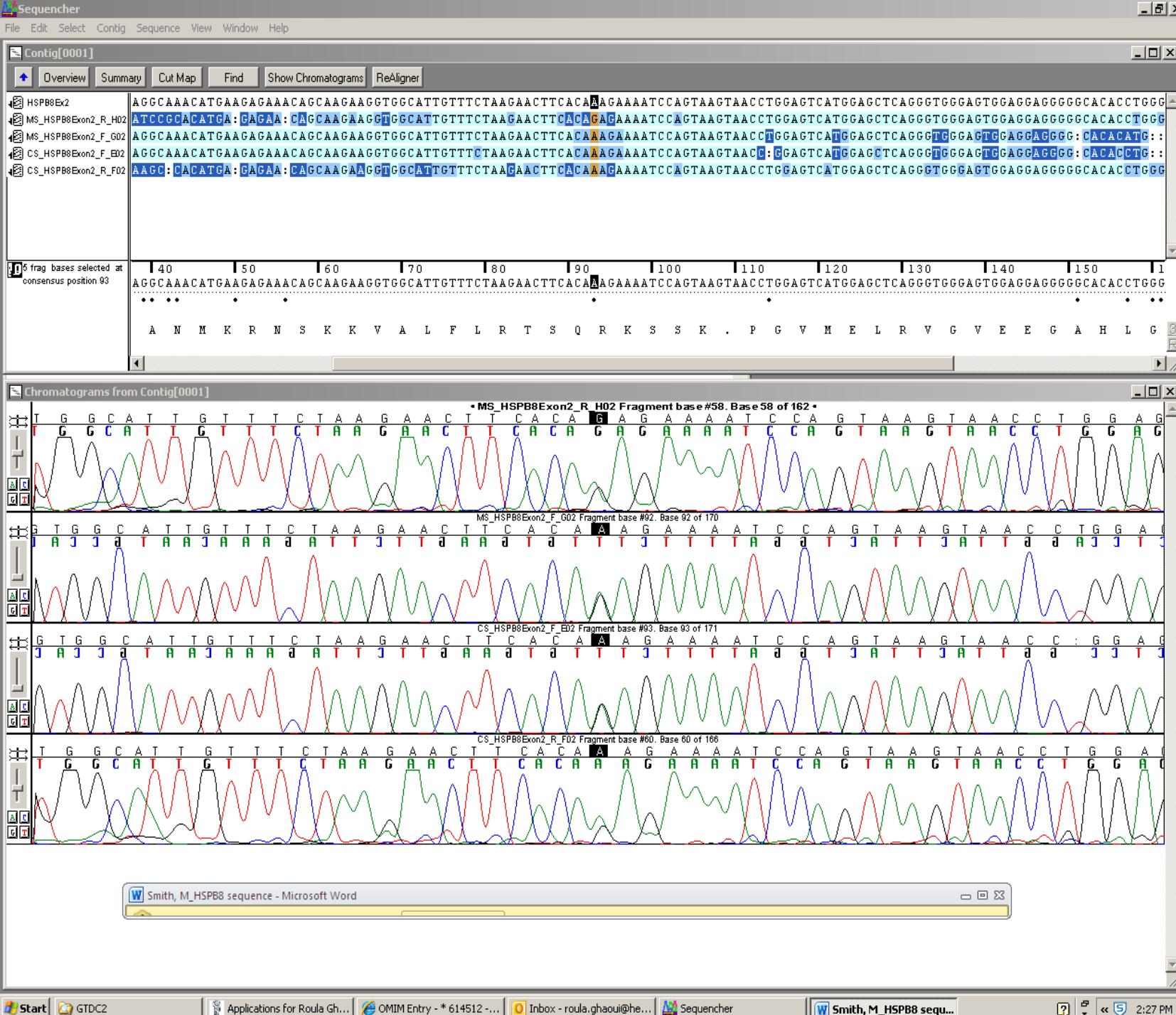
HSPB (heat shock protein B8)

Chromosome 12
(dominant het)

Exon 2

c. 421A>G, p.K141E

Polyphen score
0.999
(probably damaging)



HSPB8

Distal hereditary motor neuropathy type II/CMT2L

HMN 2A, Heat shock 22 kD protein, chromosome 12q 24.23

HSPB8 protein

Heat shock protein

High expression in motor & sensory neurons of spinal cord

Mutated protein (K141E) promotes formation of intracellular aggregates within peripheral nerves

Onset

14 to 35 years

Weakness of toe extension

Weakness

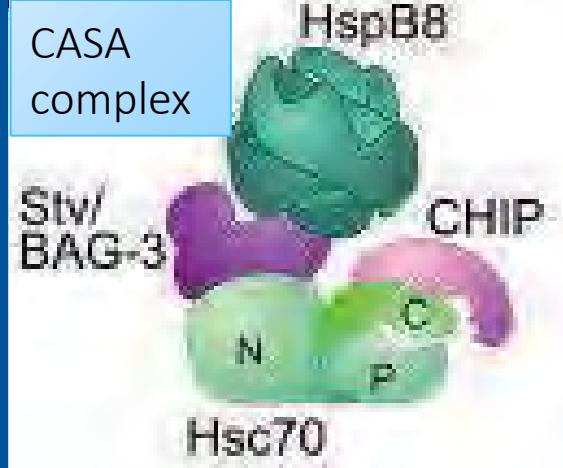
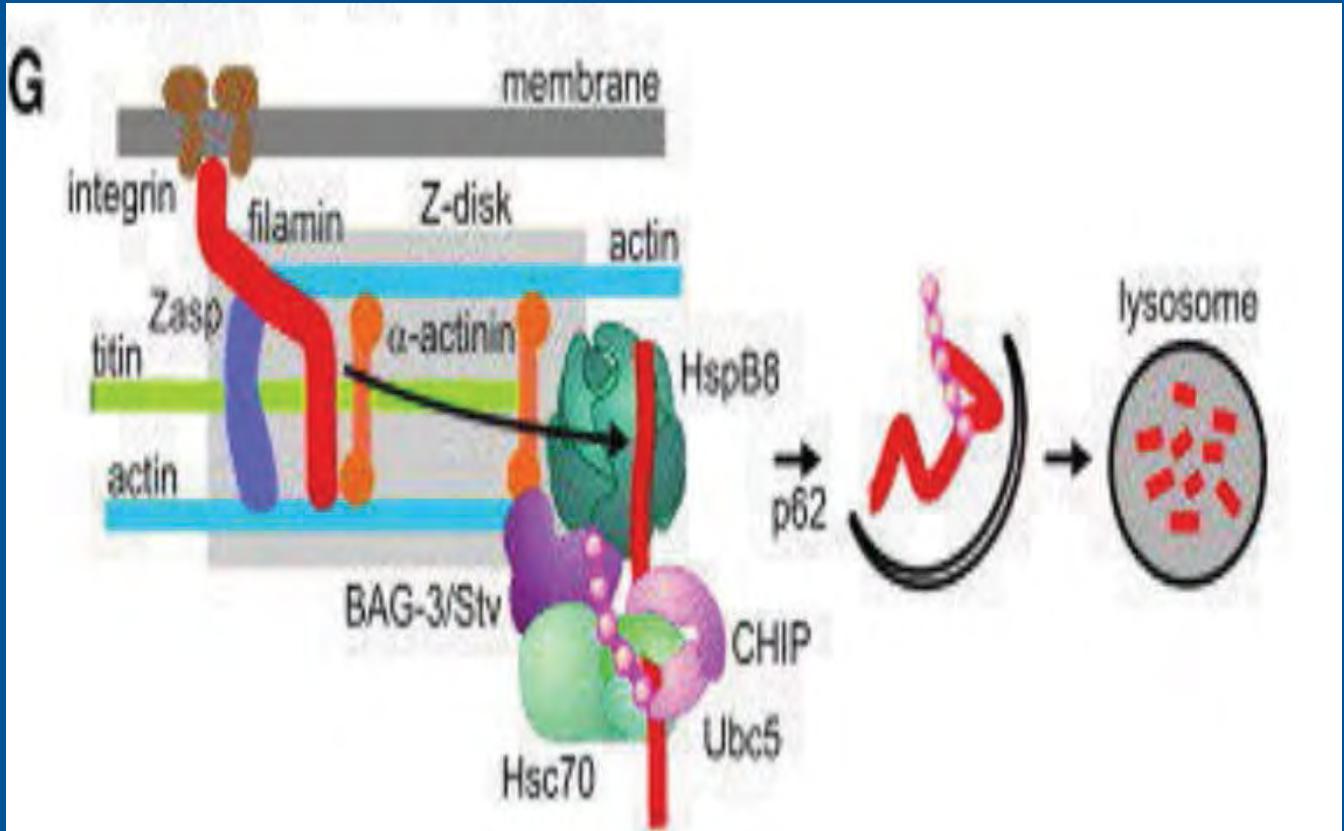
Extensor muscles of feet

Progression over 5 years to complete paralysis of all distal muscles of legs

Legs > Arms

? Diagnosis of Myofibrillar myopathy on
biopsy and IHC

Chaperone-Assisted Selective Autophagy (CASA) Is Essential for Muscle Maintenance



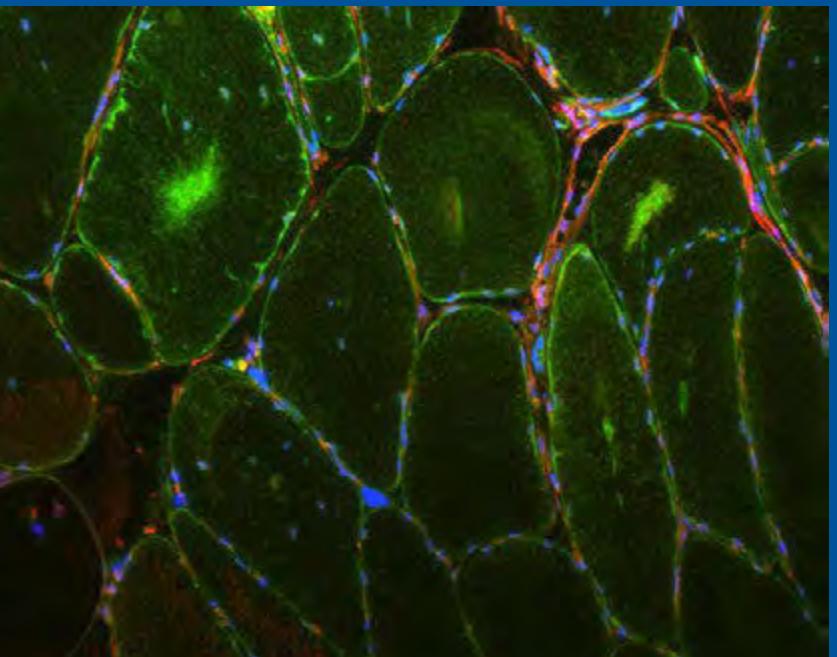
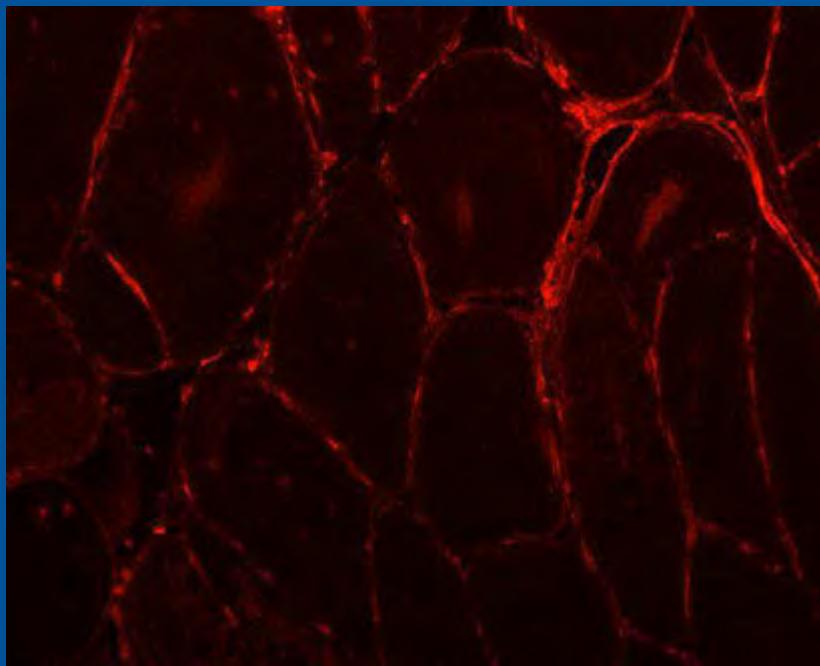
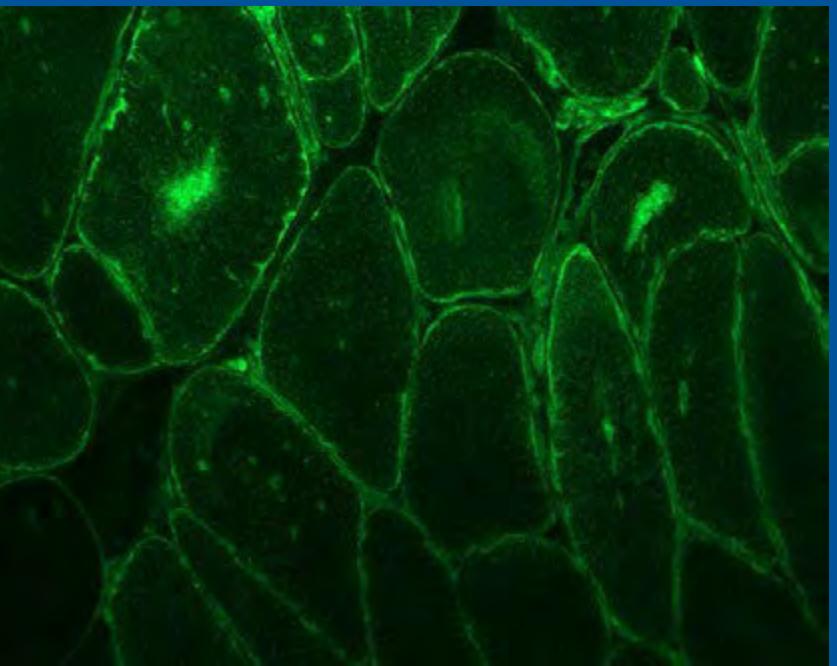
Hypothesis

- CASA interacts with DNAJB6 which causes LGMD1D
- DNAJB6 is a known co-chaperone of HSPA88.
- Both DNAJB6 and the CASA complex localize to the Z-disk.
- Finally, mutations in DNAJB6 cause a myofibrillar myopathy with protein accumulations and autophagic pathology
- ?HSPB8 mutations causes a myopathy in later stages

FURTHER MUSCLE STUDIES REQUIRED TO PROVE
THIS HYPOTHESIS

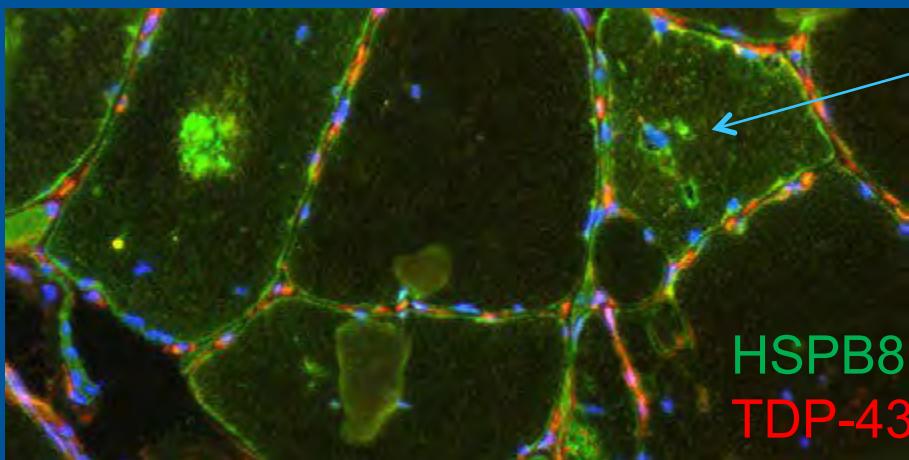
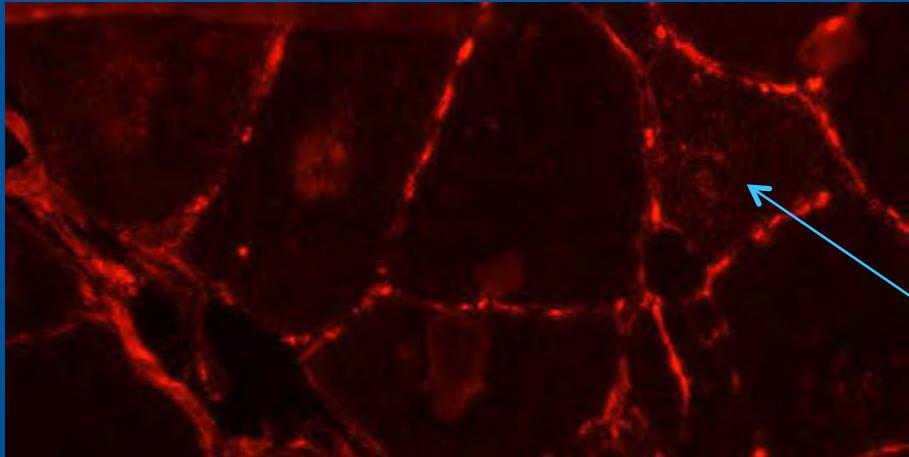
MaSm IF analysis

HSPB8 c.A421G: p.K141E

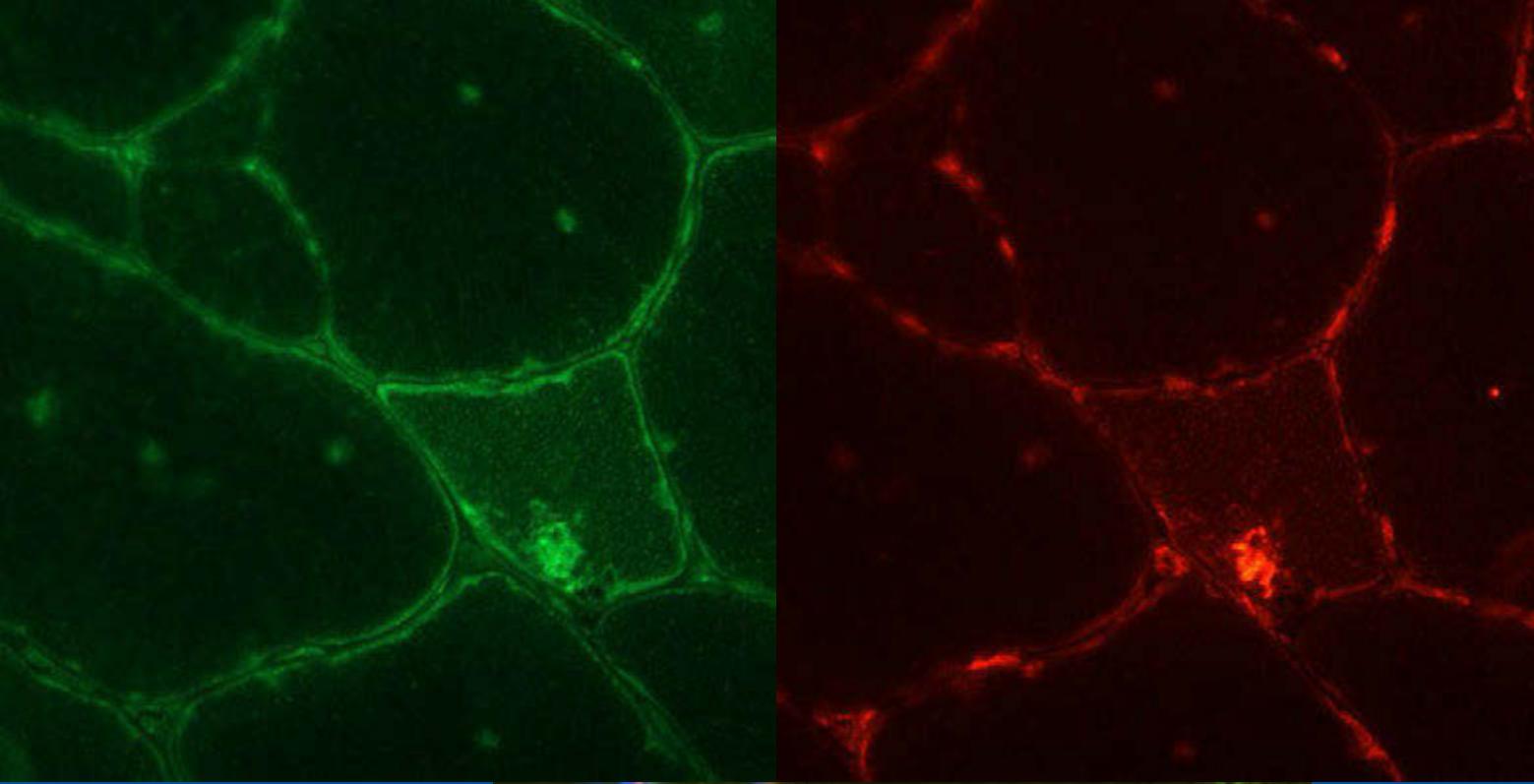


HSPB8
TDP-43

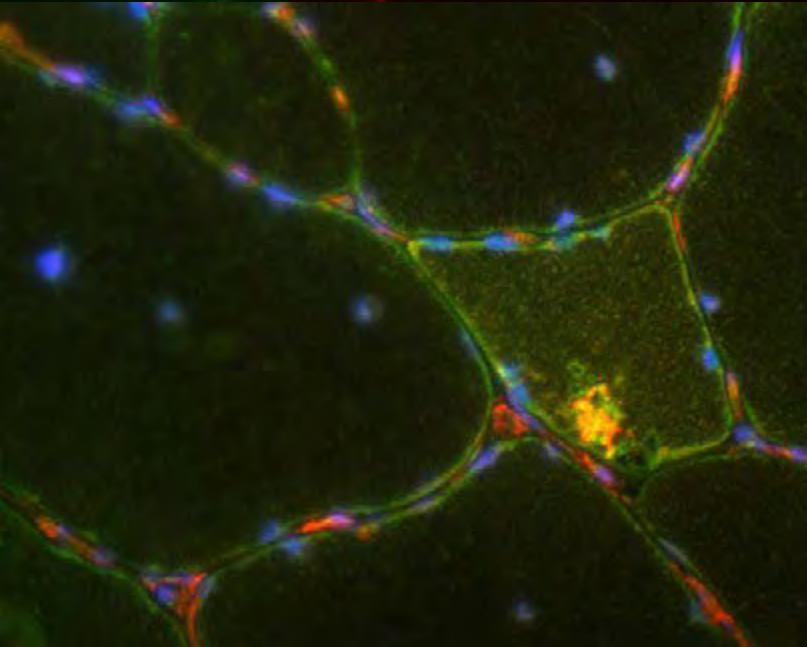
Strong **HSPB8** accumulation in myofibrillar aggregates.
Diffuse increase in atrophic fibers.
Central myonuclei are often positive.
TDP-43 shows moderate to good co-localization in aggregates.



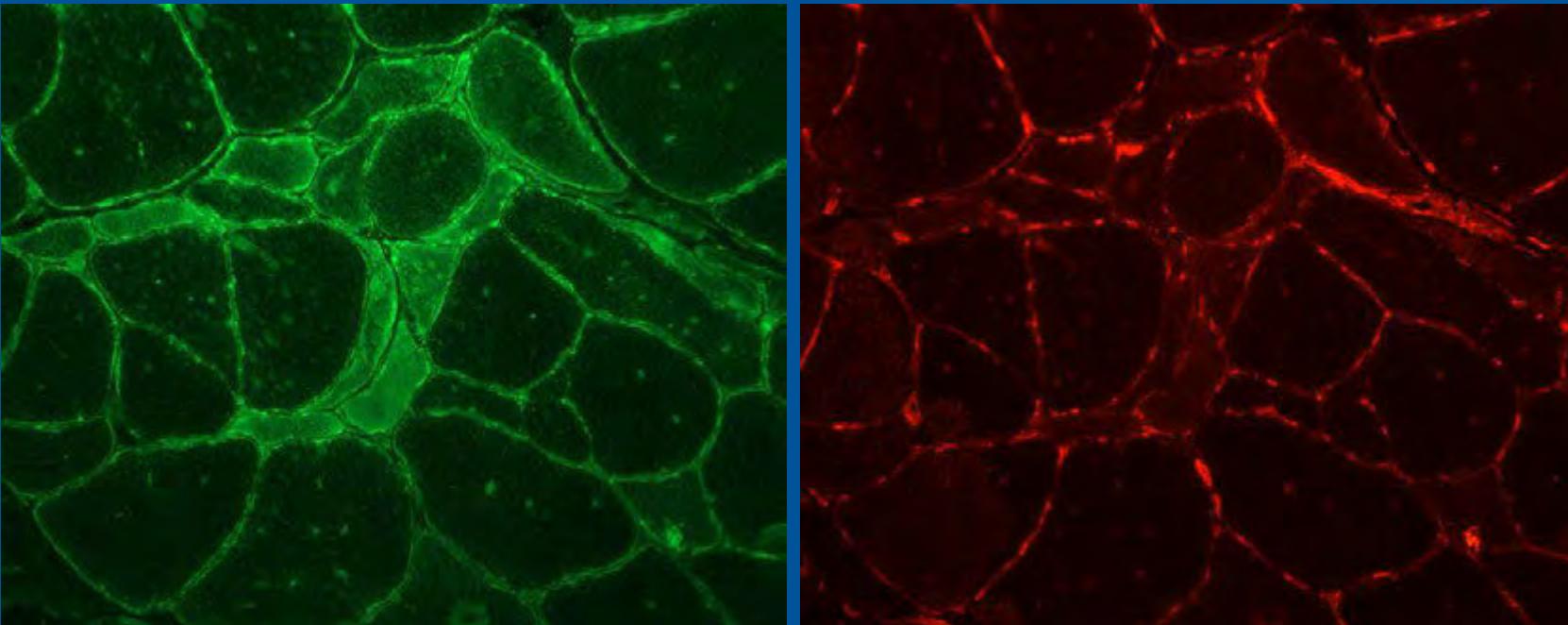
Rimmed Vacuoles
HSPB8 positive;
TDP-43 moderately positive
(where dense bodies absent;
see later)



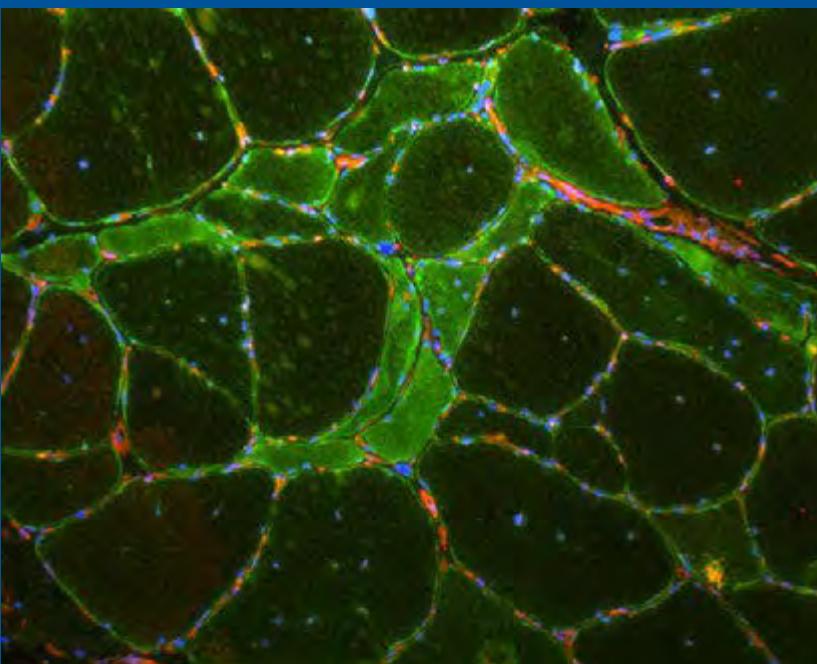
HSPB8
TDP-43
Co-localize
In dense bodies
In rimmed
vacuole



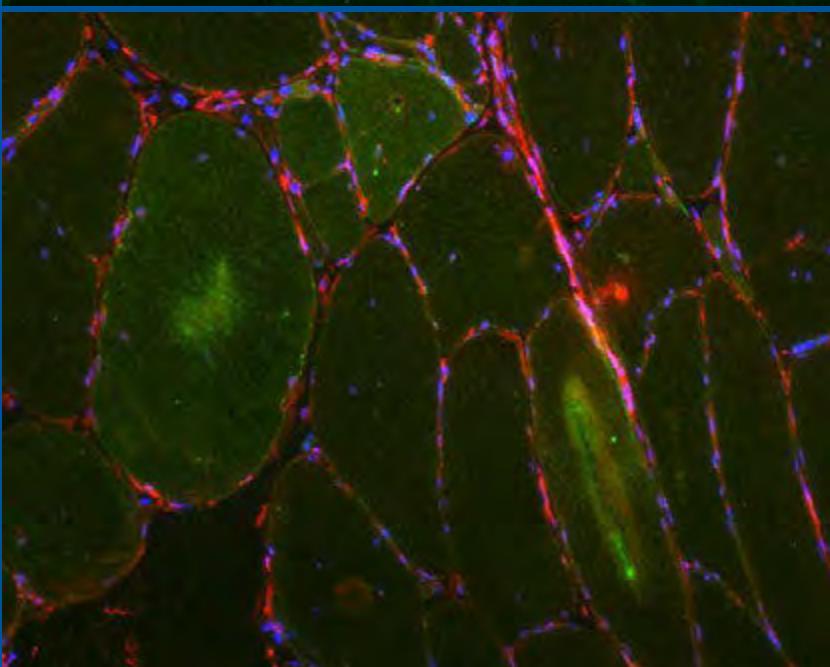
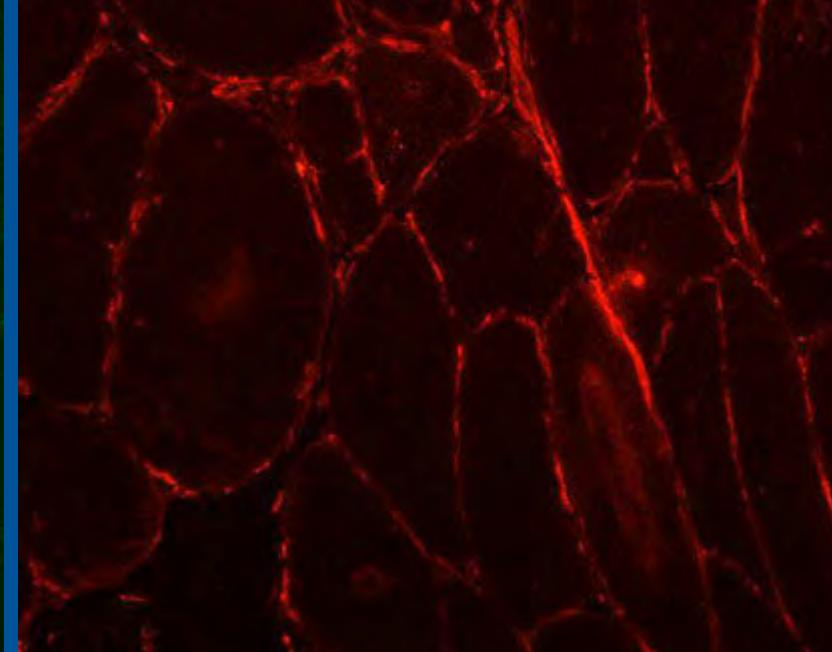
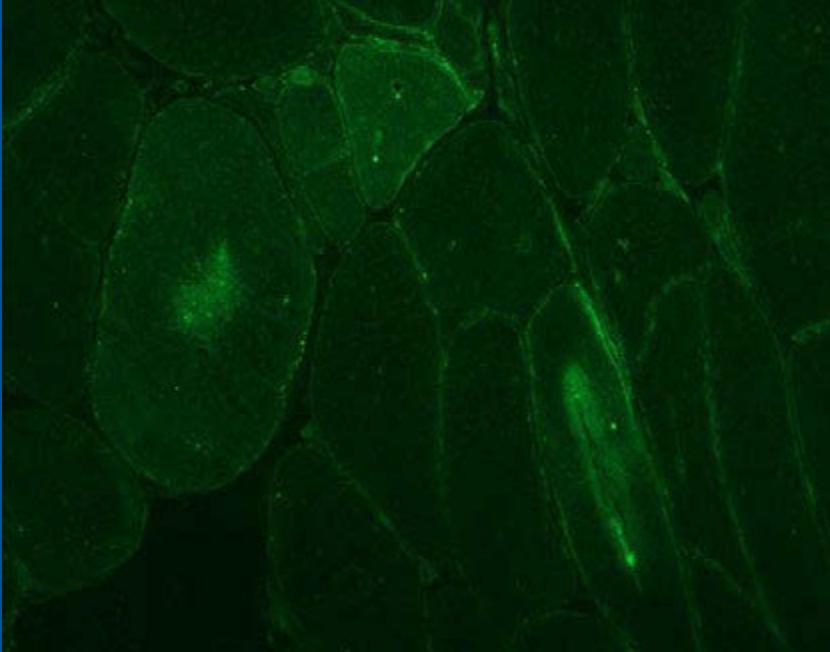
Internal nuclei often
moderately
HSPB8/TDP-43 positive



HSPB8
TDP-43



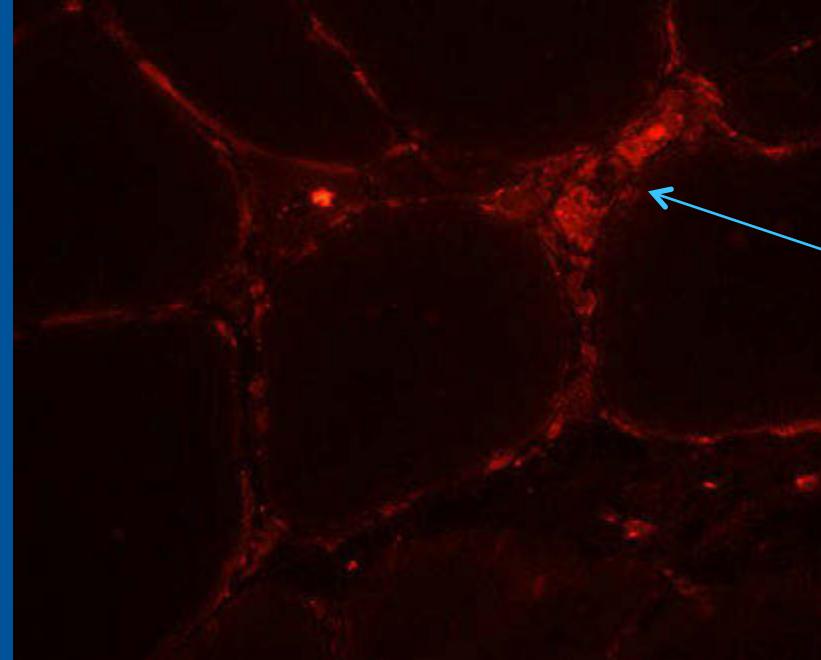
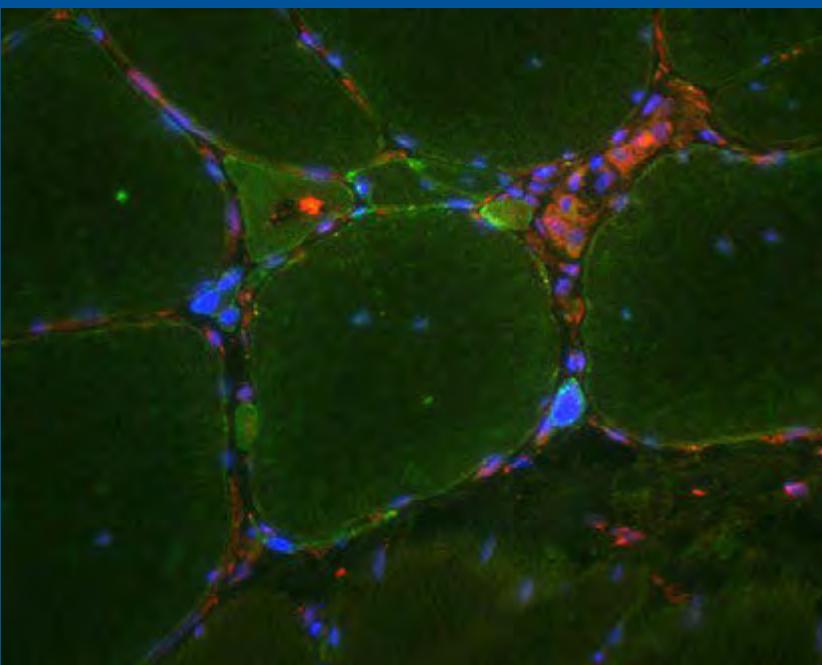
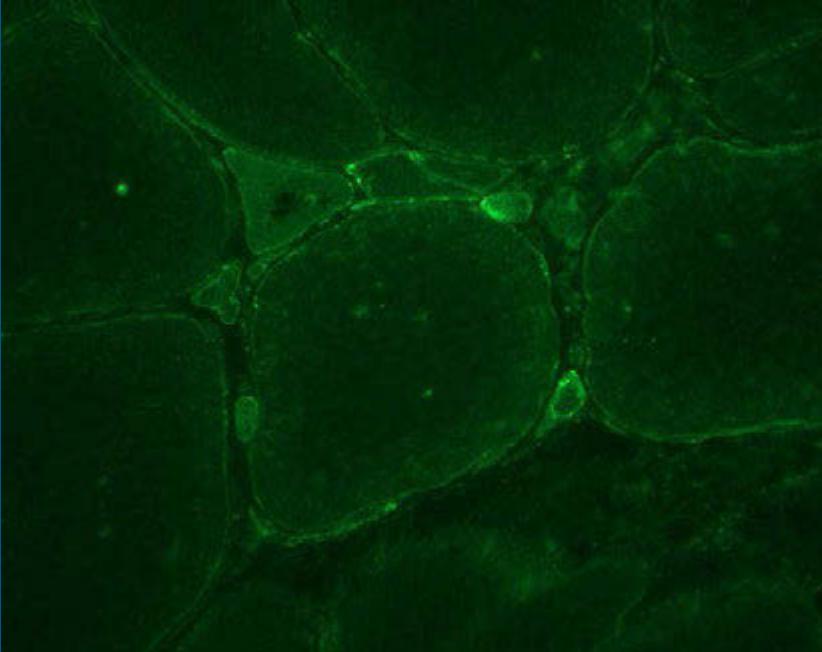
In atrophic fibers diffusely increased expression



DNAJB6
TDP-43

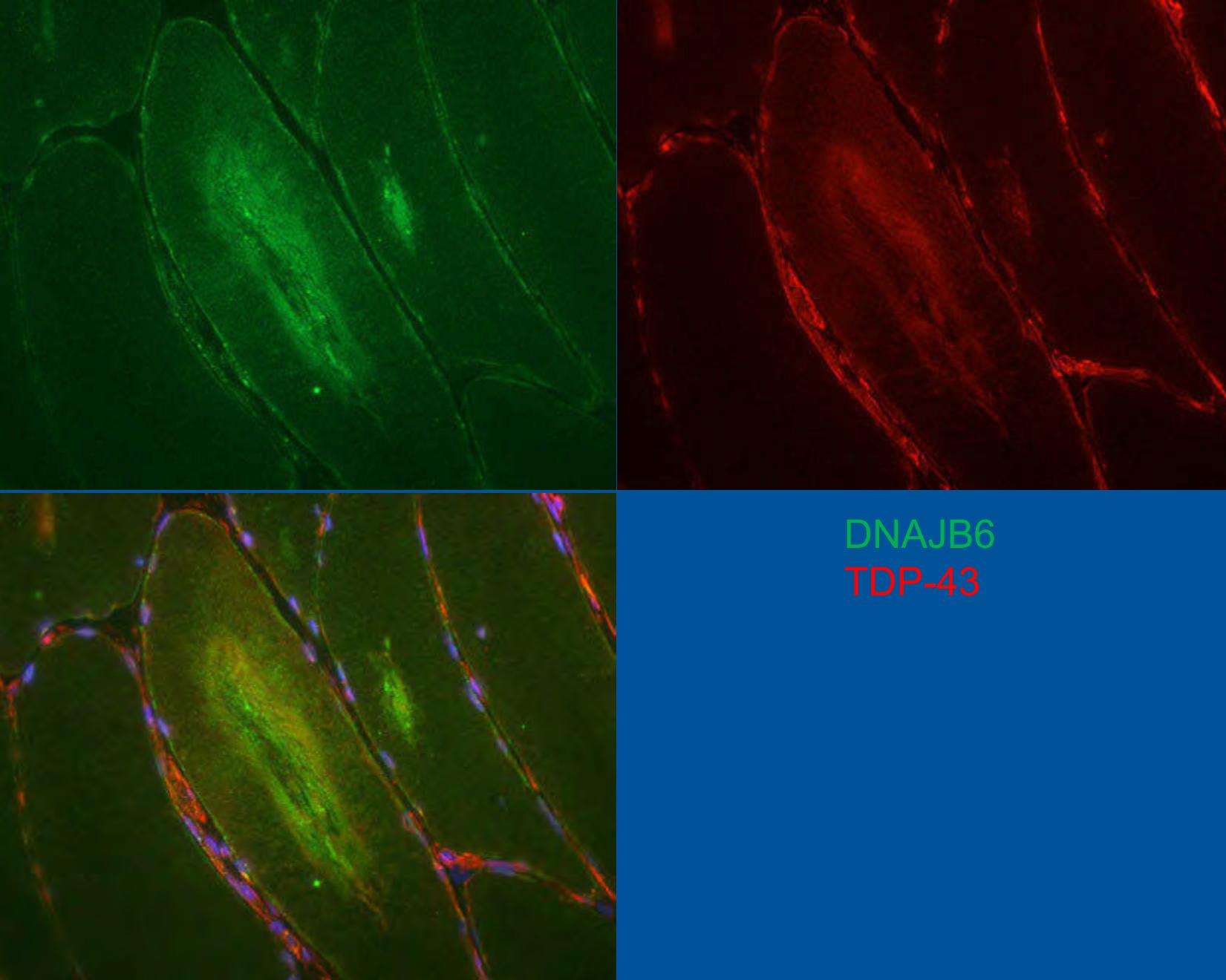
Myofibrillar aggregates and the rim
Of the Rimmed Vacuoles DNAJB6
Positive.
TDP-43 faintly

AV



DNAJB6
TDP-43

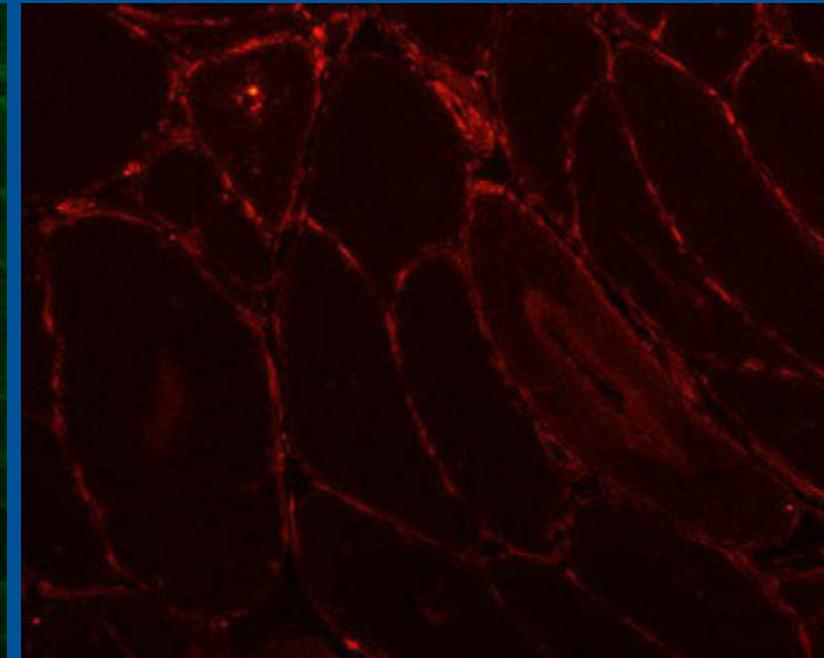
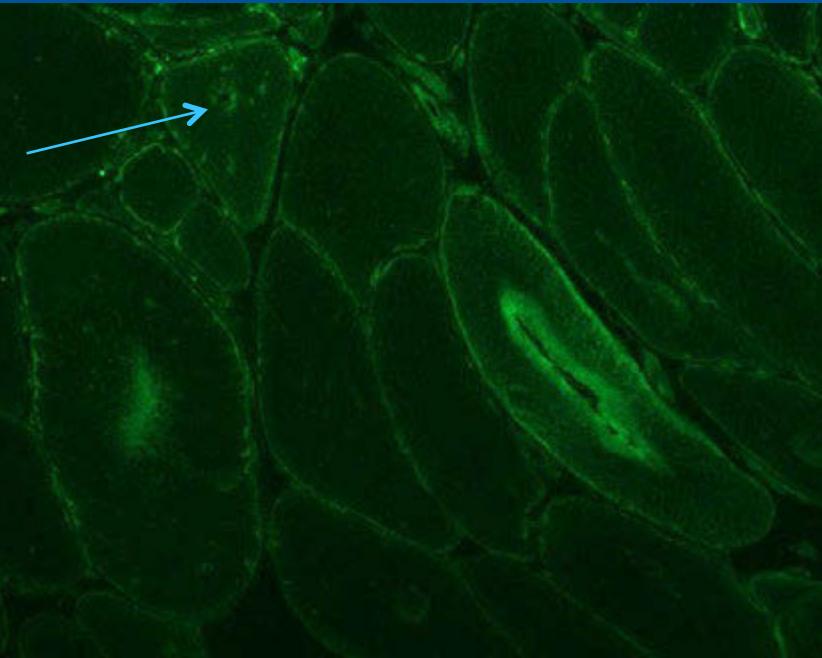
Internal nuclei show
moderate DNAJB6 positivity



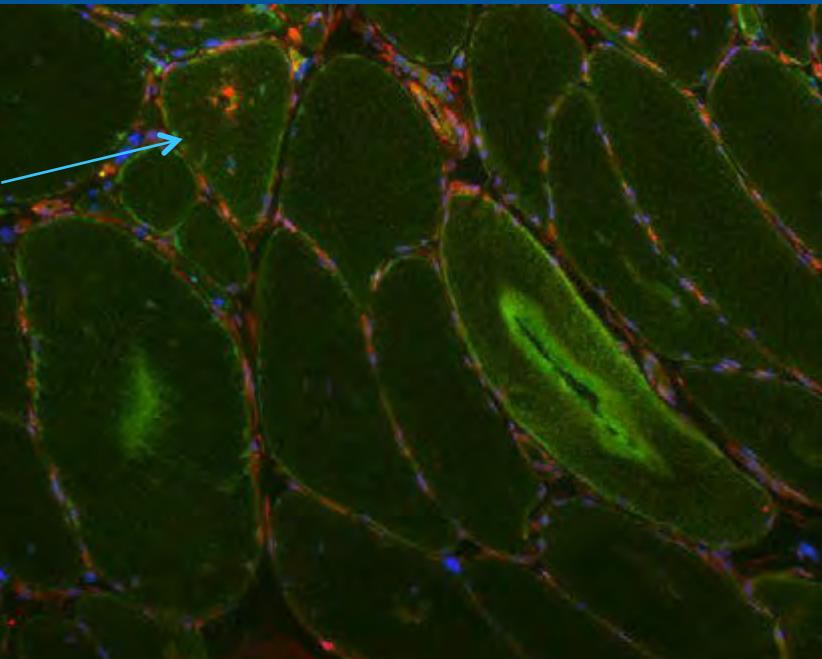
DNAJB6
TDP-43

AV

RV

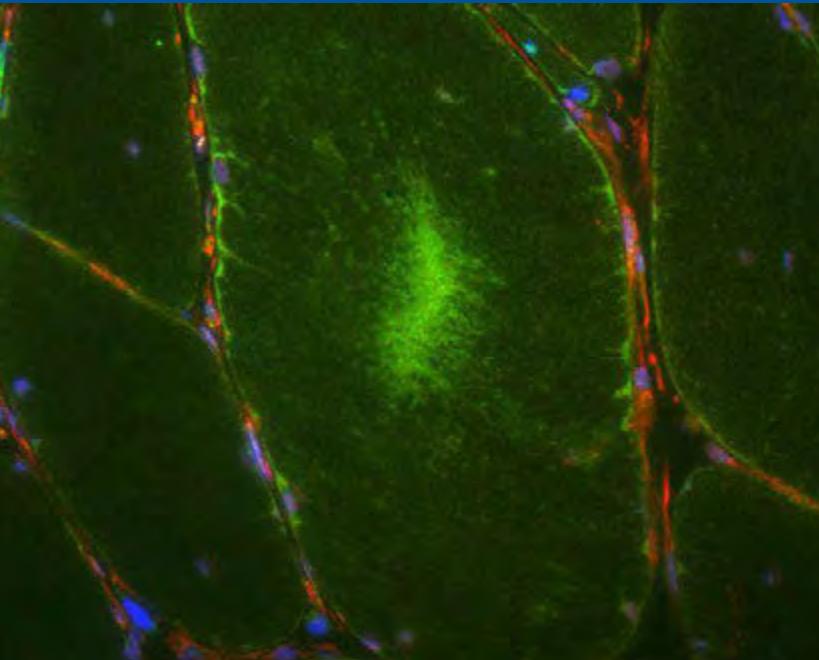
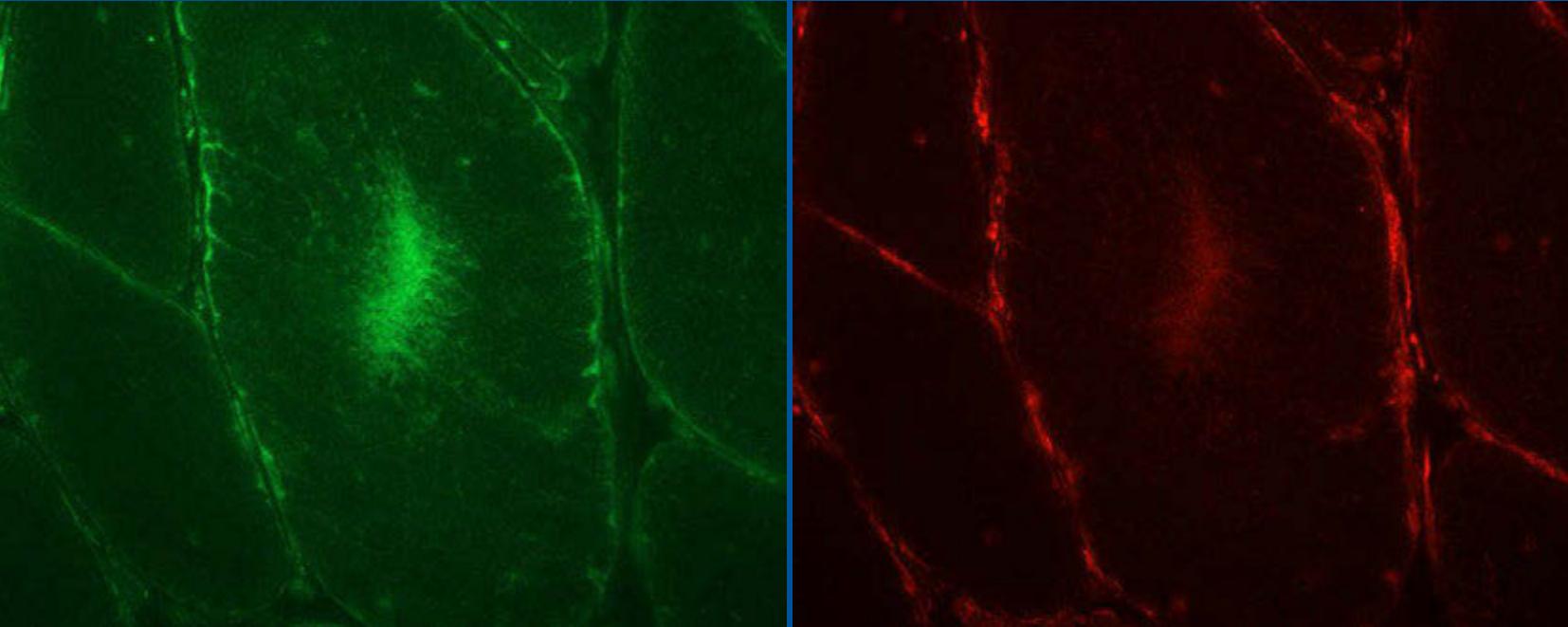


RV

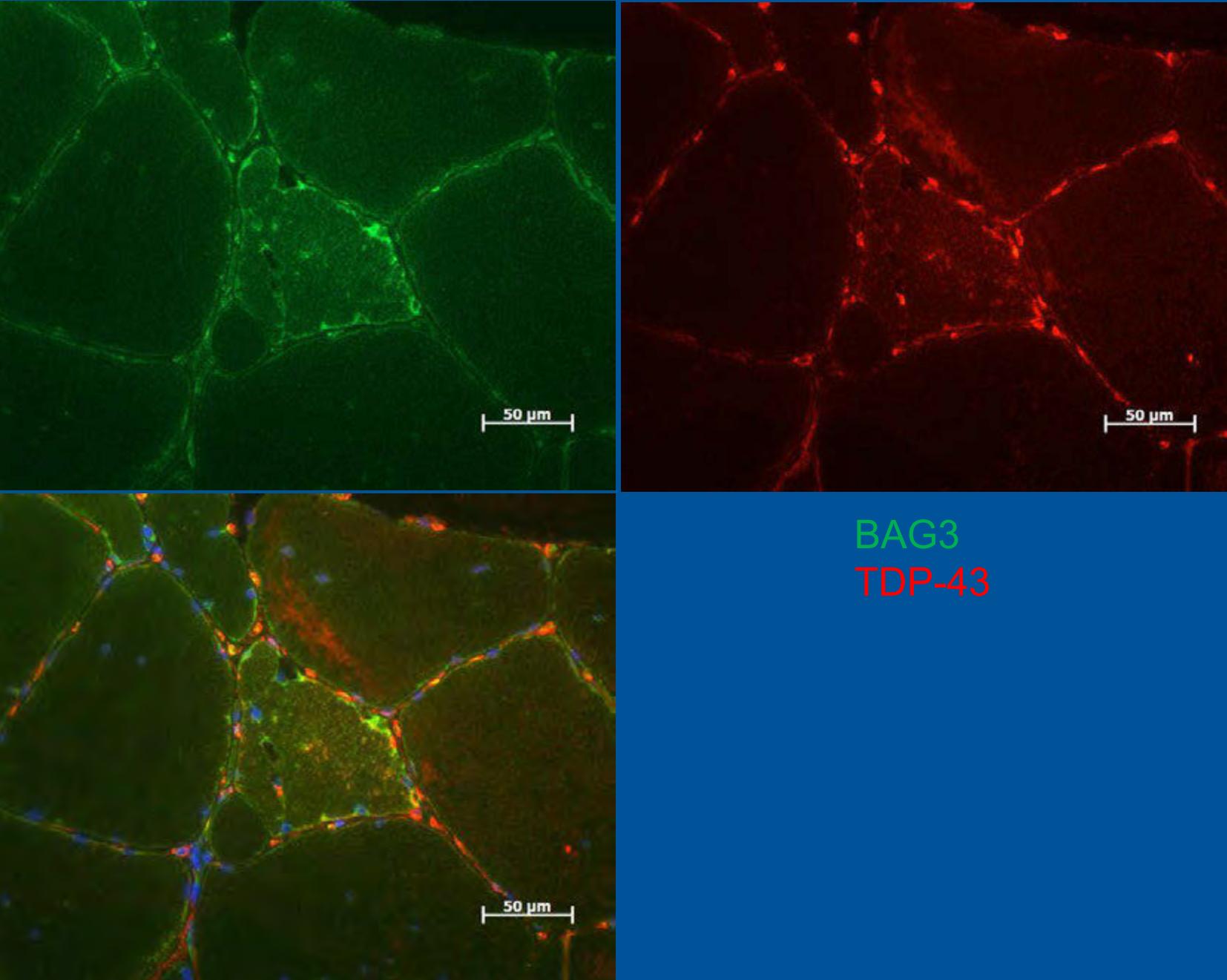


BAG3
TDP-43

BAG3: MFM aggregates positive. RV rim Positive.
In RVs, TDP-43 usually shows its typical "dense body" accumulation (instead of rim positivity).



BAG3
TDP-43



BAG3
TDP-43