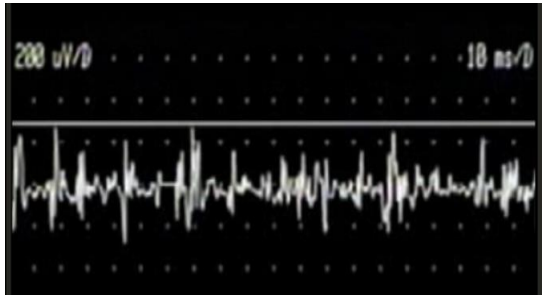
MYOPATHIES IN FOCUS: DECODING CASES TO UNDERSTAND MUSCLE DISEASES

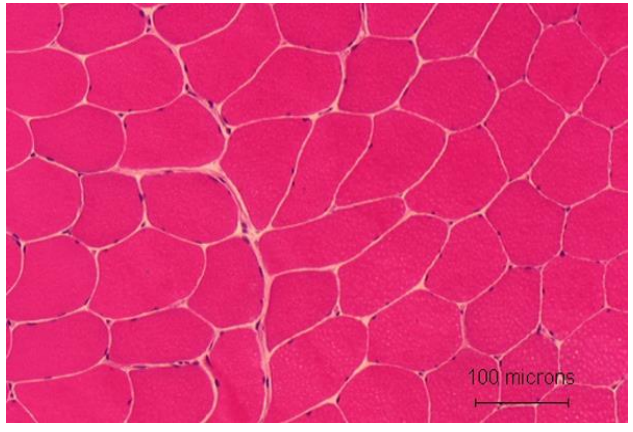
Prof. Dr. Ohnmar
Senior Consultant Neurologist
MBBS, MSc (Int Med), MRCP, FRCP,
Dr.MSc (Neurology), **Fellowship in neuromuscular (NNI)**

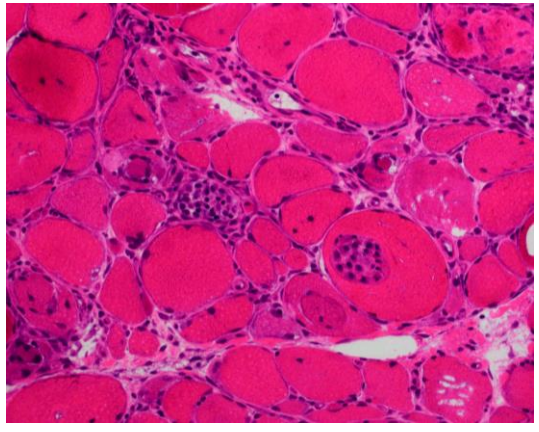
CLINICAL PRESENTATIONS OF MYOPATHY:

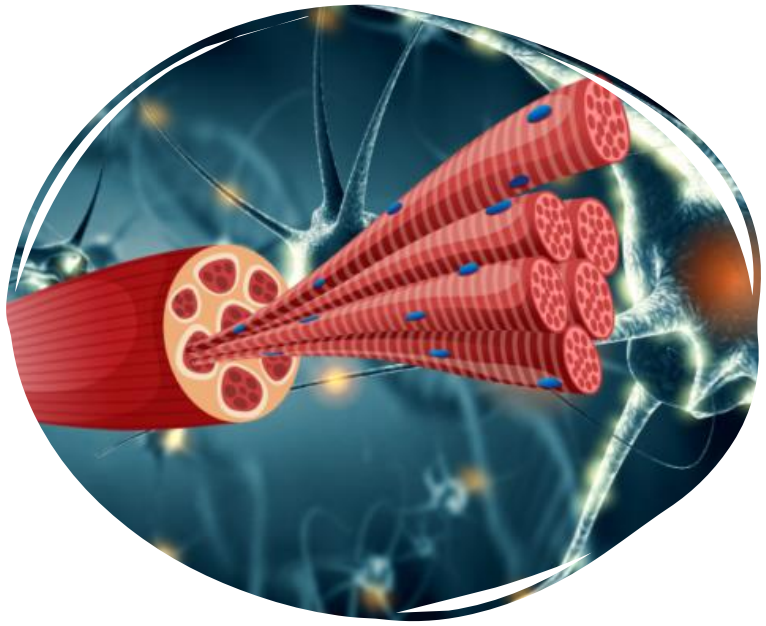
- **Symmetric, proximal-dominant weakness**, sometimes accompanied by fatigue and pain (except distal myopathies which are of genetic)



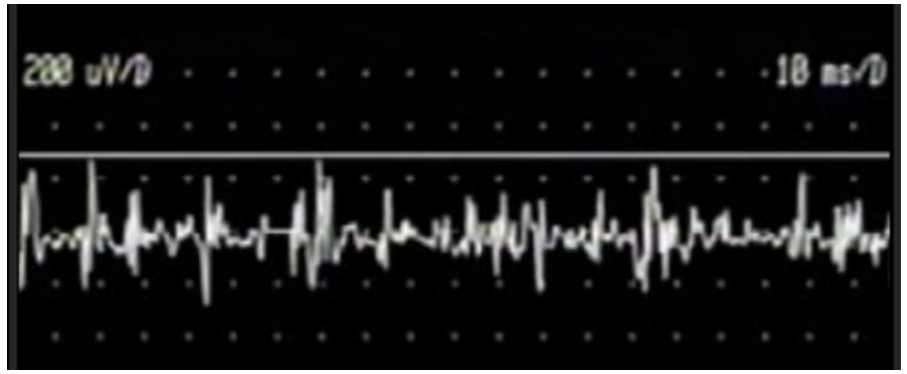
- **High CK >1000U/L** is a good biomarker
- **EMG: myopathic MUP** - brief, low amplitude polyphasic potentials, early recruitment +/- irritative potentials
- **Ultrasound, MRI**
- **Muscle biopsy**







MYOPATHIES

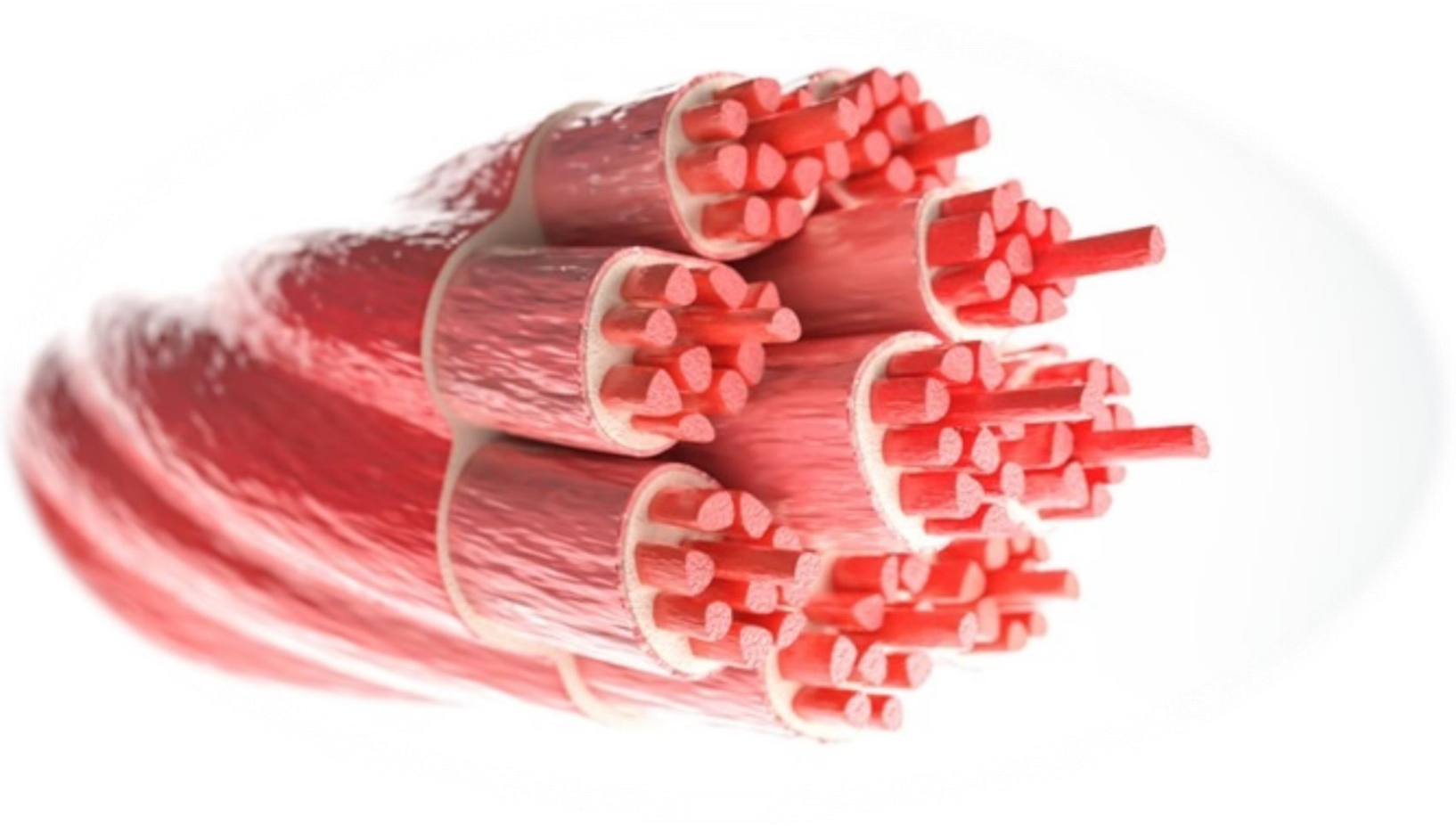


Myopathy Causes	
Inherited	DMD, Myotonic dystrophy, FSHD, LGMD etc
Metabolic/ Endocrine	Hyper/Hypothyroidism, Cushing's syndrome, Vit D defi
Neoplastic/ Paraneoplastic	Dermatomyositis
Inflammatory/ infectious	Dermatomyositis, polymyositis, Immune-mediated
Human activity	**Drugs:** Colchicine, statin, fibrates, telbuvidine, AZT

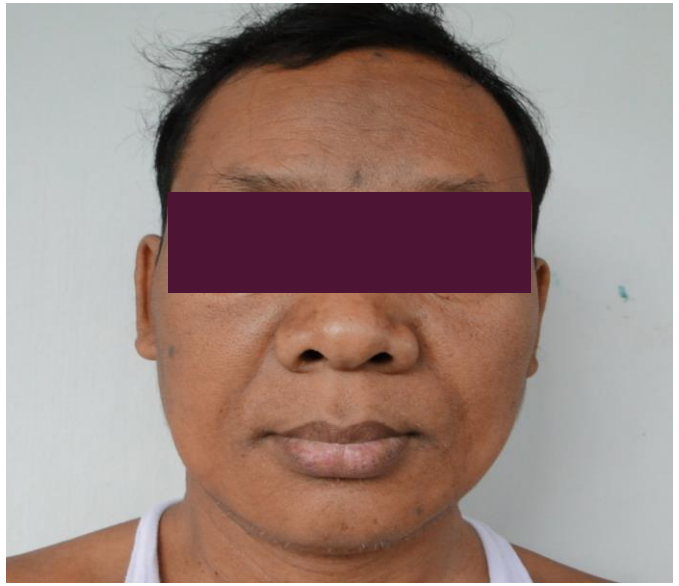
Inherited

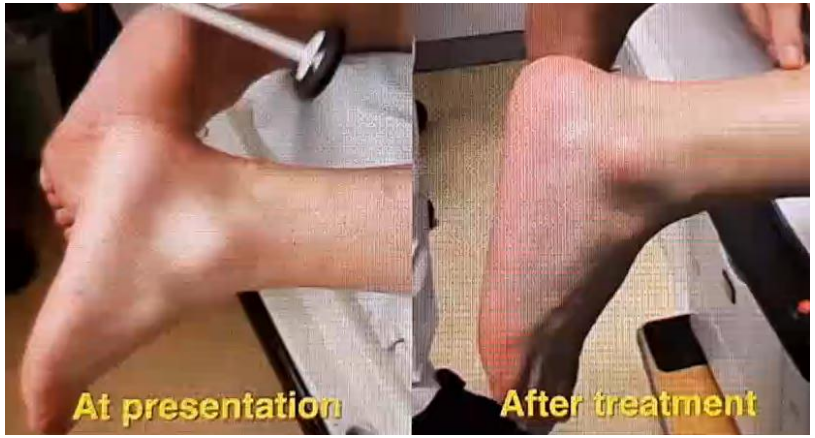
Acquired

ACQUIRED MYOPATHIES



PROXIMAL MYOPATHY

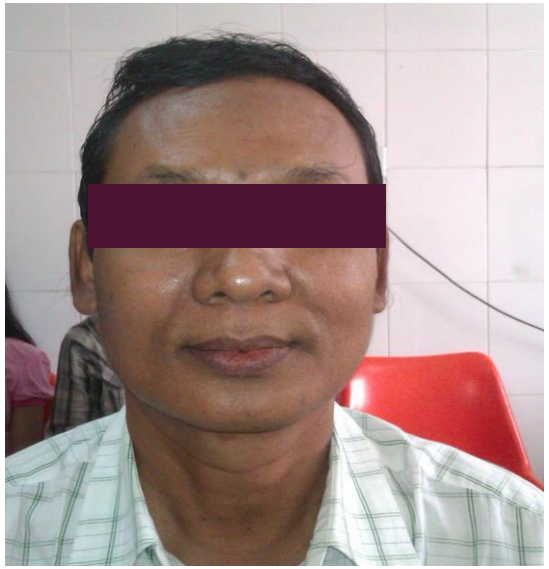


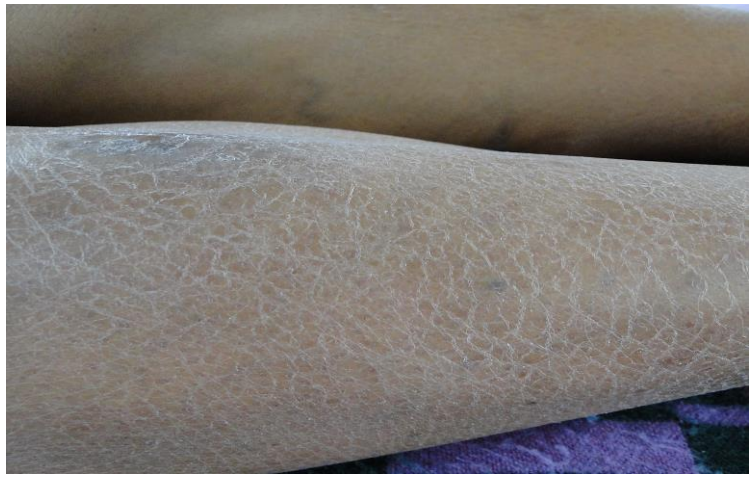


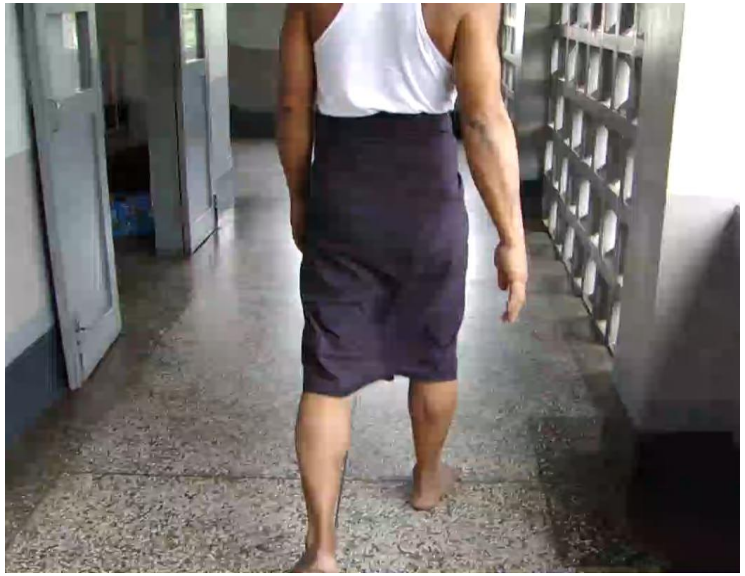
Ankle jerk source: Avraham CooperMD

Hypothyroid Myopathy

After Rx

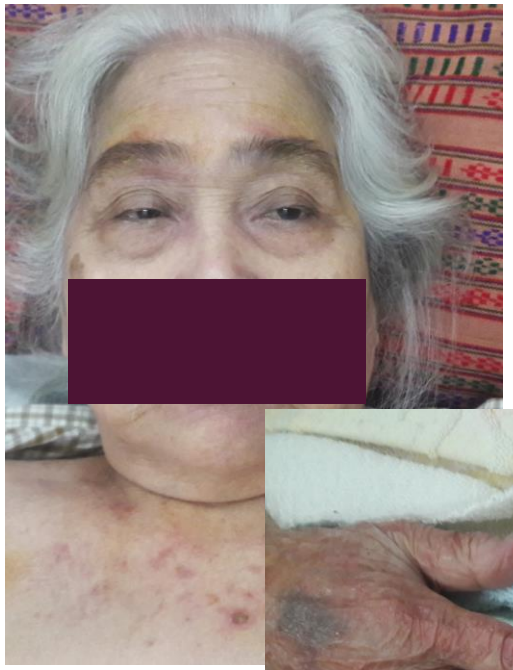


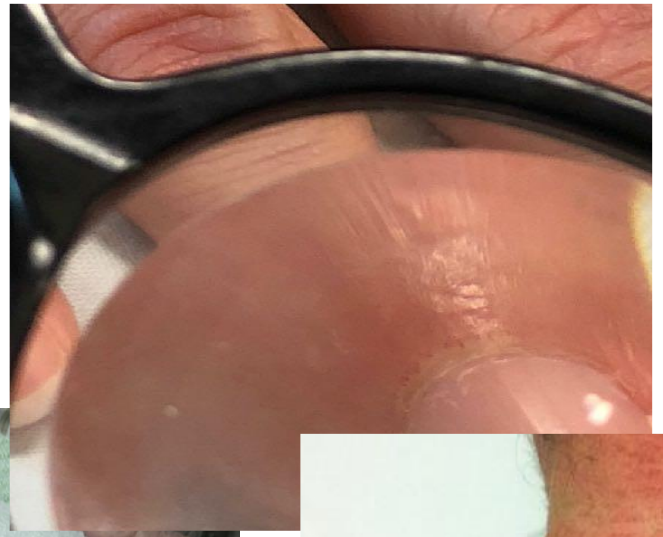


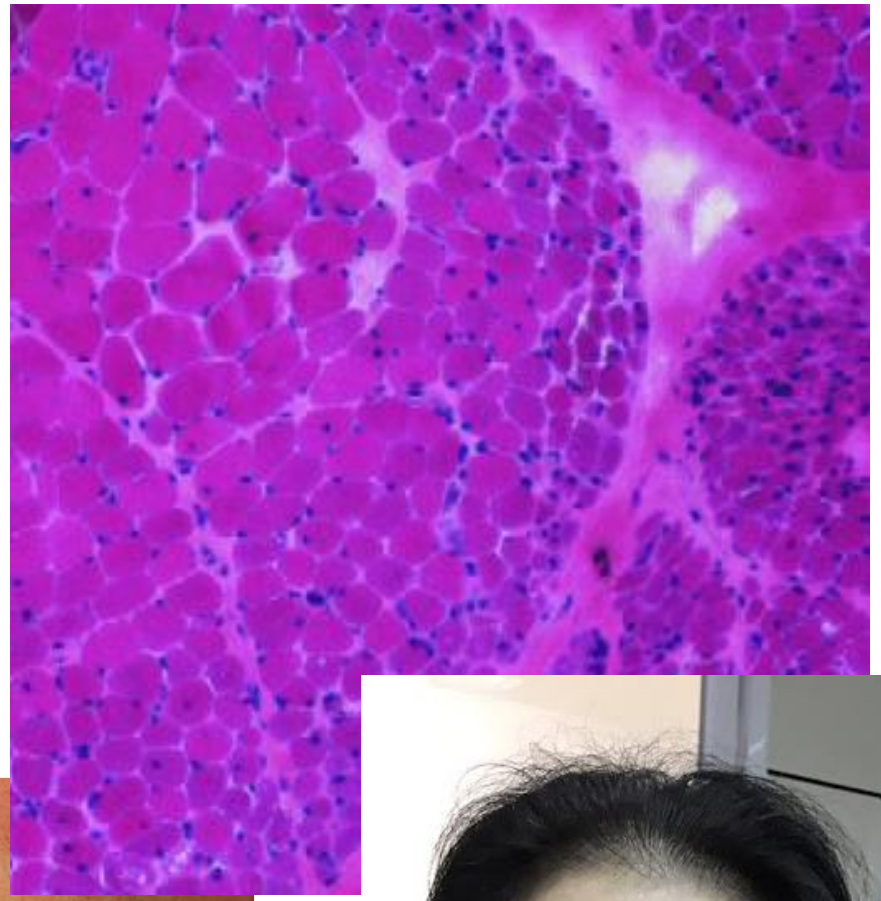


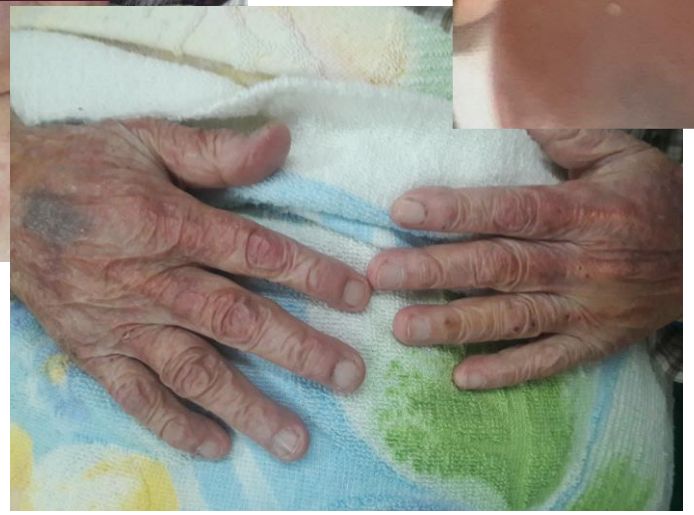
Gait back to normal

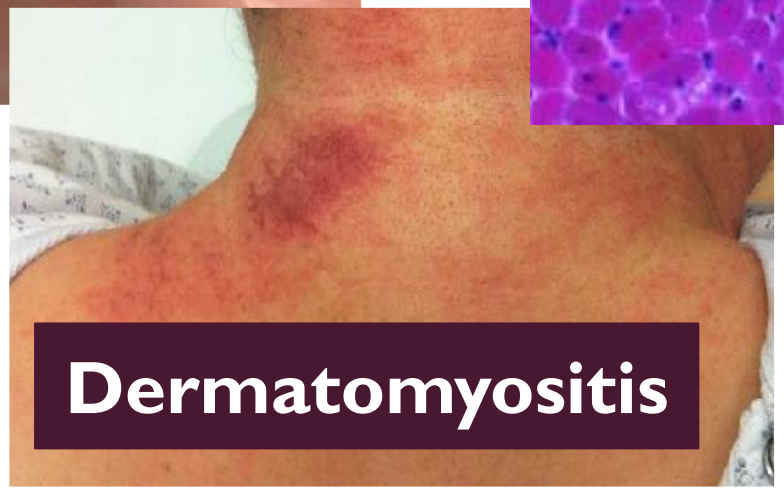
PROXIMAL MYOPATHY







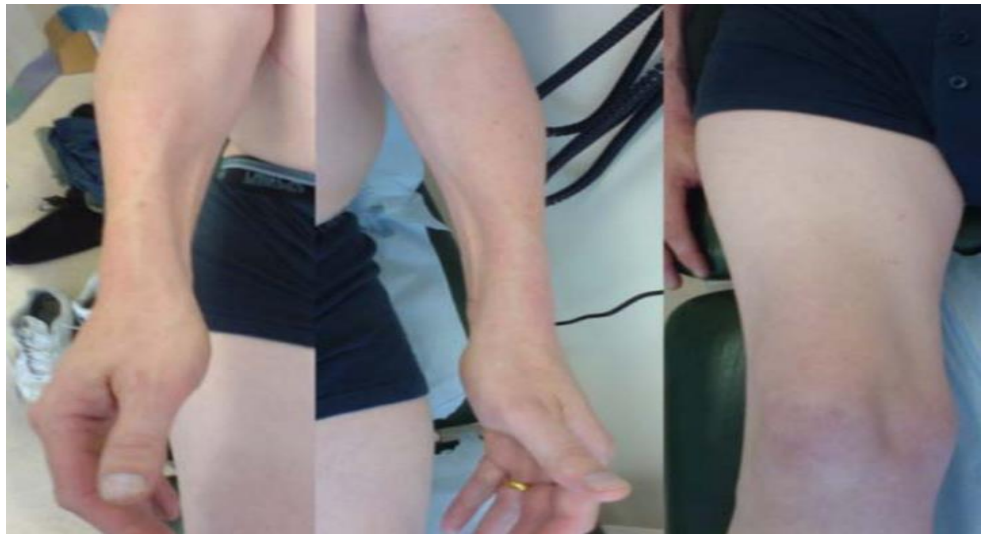


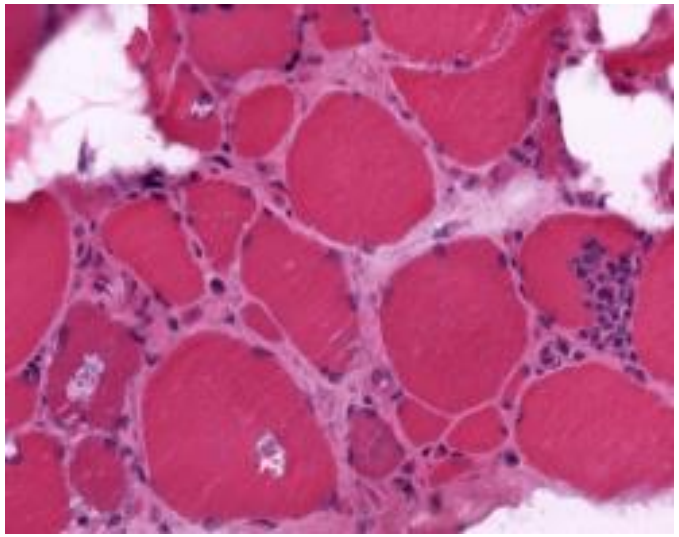


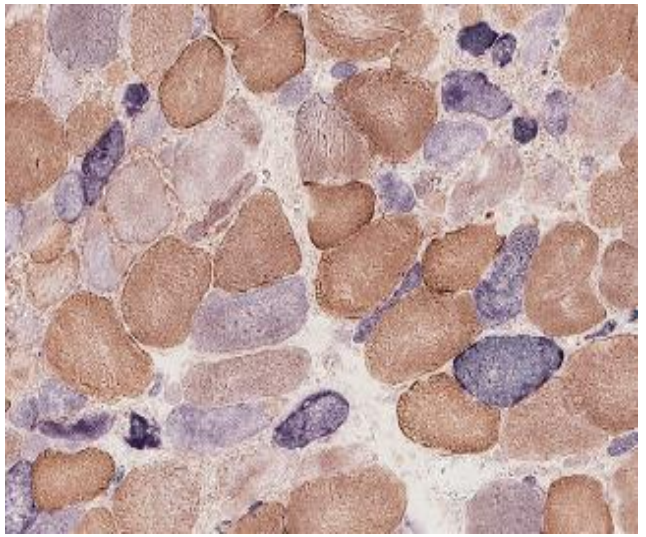
Dermatomyositis

Distal forearm & Proximal thigh weakness

Inclusion Body Myositis







- ✓ Over the age of 45 years
- ✓ Typical pattern: Quadriceps muscle weakness and atrophy, Deep finger flexor weakness
- ✓ *Myositis antibody:* anti-cytosolic 5'–nucleotidase 1A (***anti-cN1A***) antibody
- ✓ *Muscle biopsy:* Inflammation/***lymphocytes surrounding non-necrotic muscle*** fibers, IBM-compatible ***MHC class I***, ***Rimmed vacuoles*** and/or *cytoplasmic protein aggregates*, ***Mitochondrial abnormalities*** with COX negative and SDH positive fibers

Brady S et al. Journal of Neurology, Neurosurgery & Psychiatry 2013;84:1240-1246

BAHAN AND PETER CRITERIA

1. Symmetrical weakness of limb-girdle muscles and anterior neck flexors
2. CK elevation
3. EMG: typical features of myositis
4. Muscle biopsy: typical myositis
5. Typical DM rash: heliotrope and Gottron's papules

Exclusion criteria: Congenital muscular dystrophies, neurological disease, infectious myositis, metabolic/endocrine myopathies, Myasthenia Gravis

For Polymyositis	
Definite:	All 1-4
Probable:	3 of 1-4
Possible:	2 of 1-4

For Dermatomyositis	
Definite:	5 + 3 of 1-4
Probable:	5 + 2 of 1-4
Possible:	5 + 1 of 1-4

Idiopathic inflammatory myopathies (IIMs)

Condition

DM

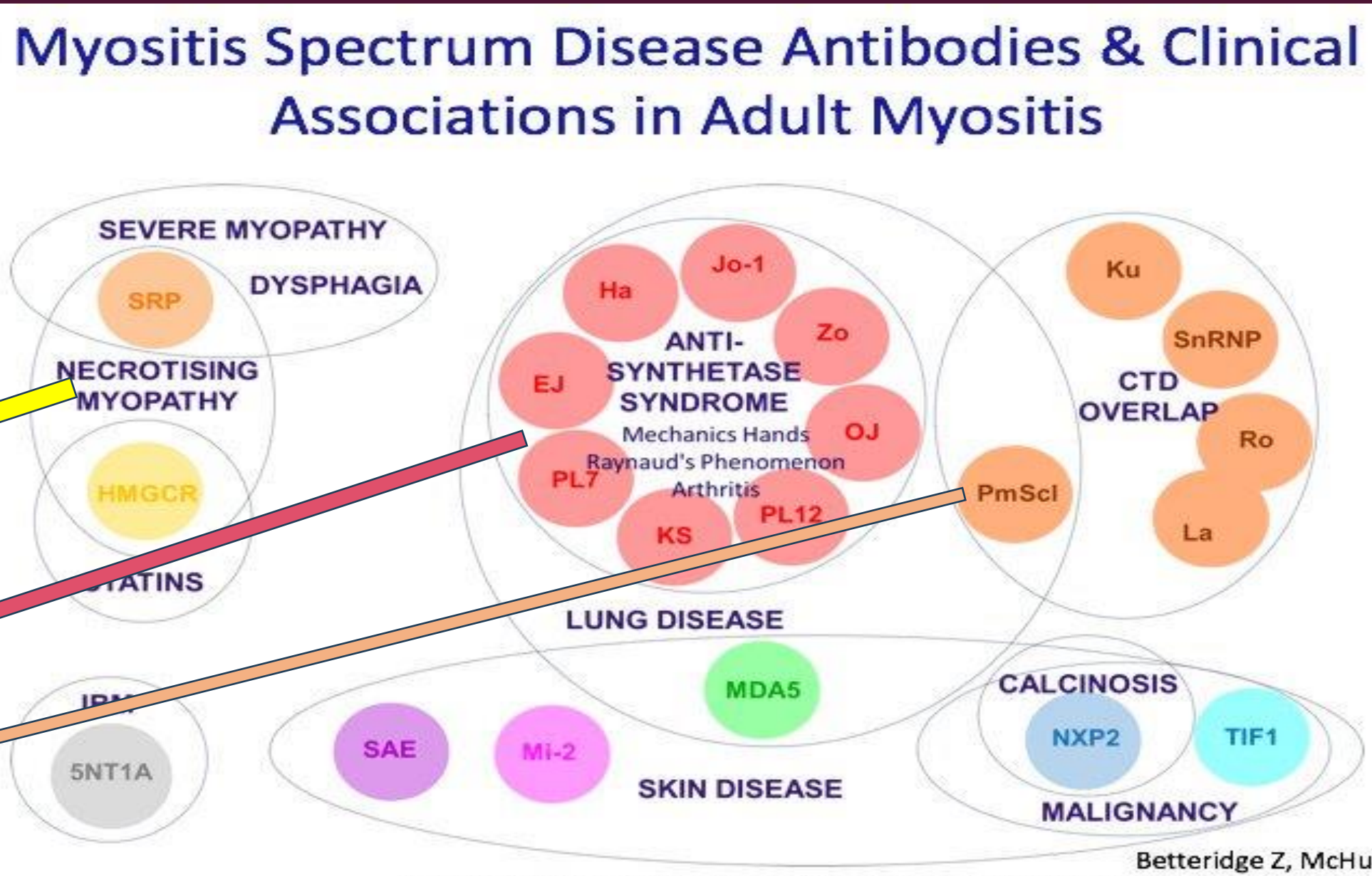
Polymyositis

IBM

IMNM

Antisynthetase syndrome

Overlap myositis



Betteridge Z, McHugh N.
Myositis-specific autoantibodies: an important tool to support diagnosis of myositis.
J Intern Med. 2016 Jul;280(1):8-23

Neurology Asia 2020; 25(3) : 285 – 291

Profile of various idiopathic inflammatory myopathies at two university hospitals in Yangon, Myanmar

[1]Ohnmar *PhD*, [1]Zin Phyu Tun *PhD*, [2]Cho Cho Nyunt *PhD*, [2]Su Lei Htay *MSc*, [2]Soe Lin Oo *MSc*, [3]Cho Mar Lwin *PhD*, [3]Yin Minn Soe *PhD*, [3]Chit Soe *PhD*, [1]Win Min Thit *FRCP*

[1]Department of Neurology, [2]Department of Pathology, Yangon General Hospital/University of Medicine 1, Yangon; [3]Department of Rheumatology, Yangon Specialty Hospital/University of Medicine 1, Yangon, Myanmar.

Abstract

Objective: to determine the distribution of various idiopathic inflammatory myopathies (IIM) and their profile at the largest university hospitals in Yangon, Myanmar. *Method:* It was a hospital based prospective study recruiting IIM patients admitted to Neurology and Rheumatology ward over a 1.5 year period from September 2017 to February 2019. *Results:* Among total 51 IIM patients recruited, 62.7% presented to Neurology ward and 37.3% to Rheumatology ward. Overlap myositis (OM) was the commonest (43%), followed by immune-mediated necrotizing myopathy (IMNM) 27%, dermatomyositis (DM) 24%, polymyositis (PM) 6%. Among OM, anti-synthetase syndrome (ASS) was 23%, and among IMNM, anti-SRP positive was 79%. IMNM and PM patients presented more to neurologists while OM/ASS and DM more to rheumatologists; 82% were females (F:M= 4.6:1). Mean age of onset of myositis was 40.2 ± 17.8 years, and duration of symptoms before presentation was 10-3,600 days (shortest in anti-SRP and longest in anti-HMGCR myopathy). Myositis antibodies were positive in 67%. CK range was 40-25,690 U/l, highest in IMNM and lowest in DM. Associated connective tissue diseases among OM in order of descending frequency were 47% systemic lupus erythematosus, 24% Sjogren syndrome, 41% scleroderma and 12% rheumatoid arthritis. Associated cancer identified were one lung cancer in DM, one breast cancer in OM, one buccal cancer in IMNM cases.

Conclusions: With recent availability of myositis antibody panel and MHC staining in Myanmar, we have applied current updated classification to describe the first Myanmar data on IIM cases.

Keywords: Idiopathic inflammatory myopathies, antibodies, muscle biopsy

Table 1: Distribution of IIM subtypes among study population

	Neurology ward	Rheumatology ward	Total
IMNM	13 (41%)	1 (5%)	14 (27%)
OM	12 (38%)	10 (53%)	22 (43%)
DM	4 (13%)	8 (42%)	12 (24%)
PM	3 (9%)	0 (0%)	3 (6%)
Total	32 (62.7%)	19 (37.3%)	51 (100%)

IIM Idiopathic inflammatory myopathies
IMNM Immune-mediated necrotizing myopathy
OM Overlap myositis
DM Dermatomyositis
PM Polymyositis

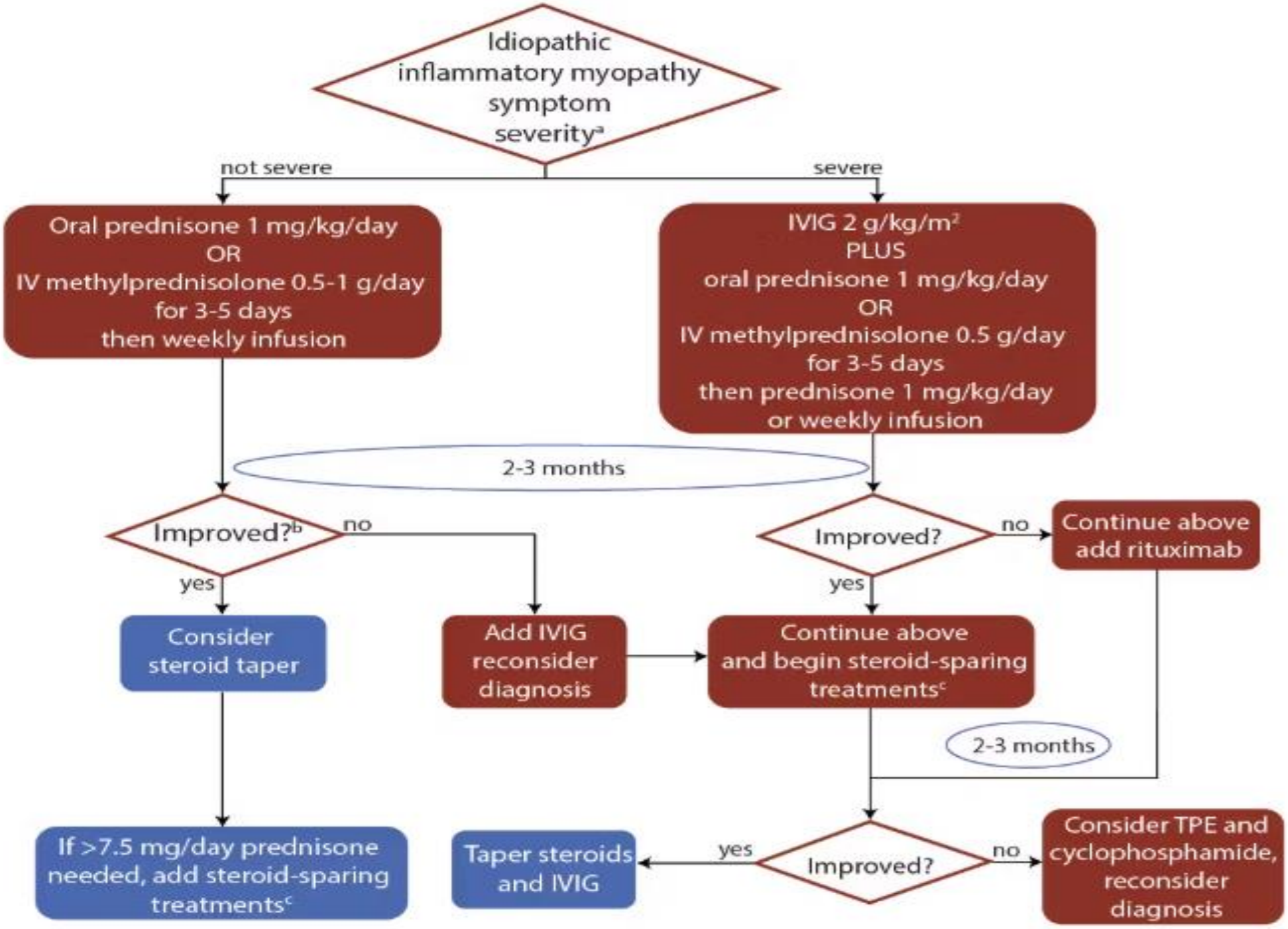
Table 3: Myositis antibody profile and their clinico-pathological presentations

Myositis antibodies	Mi-2	Ku	PM-Scl100	PM-Scl75	Jo-1	SRP	PI-7	Ro-52	HMGCR
No (%)	2 (4)	6 (12)	1 (2)	2 (4)	2 (4)	11 (21)	4 (8)	8 (16)	1 (2)
Type of IIM	DM (100%)	OM(67%) PM(17%) IMNM (17%)	OM (100%)	OM(50%) PM(50%)	ASS (100%)	IMNM (100%)	ASS (100%)	OM/ASS (100%)	IMNM (100%)
Mean age (years)	28	34	56	58	45	41	52	37	16
Gender (F:M)	All F	5:1	All F	All F	All F	4.5:1	All F	3:1	All F
Mean age of onset (years)	28	33	36	58	44	42	52	38	6
Mean duration before admission (days)	135	115	240	128	57	71	237	128	3600
MRC sumscore	50	38	48	49	54	46	42	40	44
Systemic features									
Fever	100%	40%	0	0	50%	18%	0	50%	0
Weight loss	50%	40%	0	0	50%	45%	75%	88%	100%
Bulbar	0	40%	0	0	100%	36%	25%	0	0
Neck weakness	0	0	0	0	0	45%	0	38%	100%
Arthralgia	50%	60%	0	0	100%	9%	75%	38%	0
Arthritis	0	20%	0	0	0	0	25%	13%	0
Skin rash	50%	20%	100%	0	50%	0	25%	13%	0
Raynaud Mechanic hands	0	20%	0	0	50%	0	50%	0	0
ILD	0	0	0	0	50%	0	25%	0	0
Myocarditis	0	0	0	50%	50%	9%	25%	13%	0
Co-morbidities		AIHA, AIH, Hypo-thyroid	Lichen Amyloid of skin	MG, ASD		HBV	HCV	Hyp-othyroid, AIHA, AIH	
Connective tissue diseases									
Sjogren's syndrome	0	0	0	0	0	18%	0	63%	0
Scleroderma	0	60%	100%	50%	0	0	0	13%	0
SLE	0	40%	0	0	0	0	0	38%	0
Mean serum CK level (U/L)	2643	3568	3650	1649	1028	8968	1980	4960	4506
Pathological diagnosis									
DM**	100%	0	0	0	50%	0	80%	0	0
PM*	0	67%	100%	100%	50%	0	20%	71%	0
IMNM***	0	33%	0	0	0	100%	0	29%	100%

CK Creatinine kinase
* Primary endomysial inflammation (endomysial lymphocyte infiltration surrounding non-necrotic muscle fibers, MHC-1 expression
** PFA, Perifascicular structural abnormalities, MHC-1 expression
***Muscle fiber necrosis and regeneration without primary endomysial inflammation, MHC-1 expression

TREATMENT APPROACH

IIMs

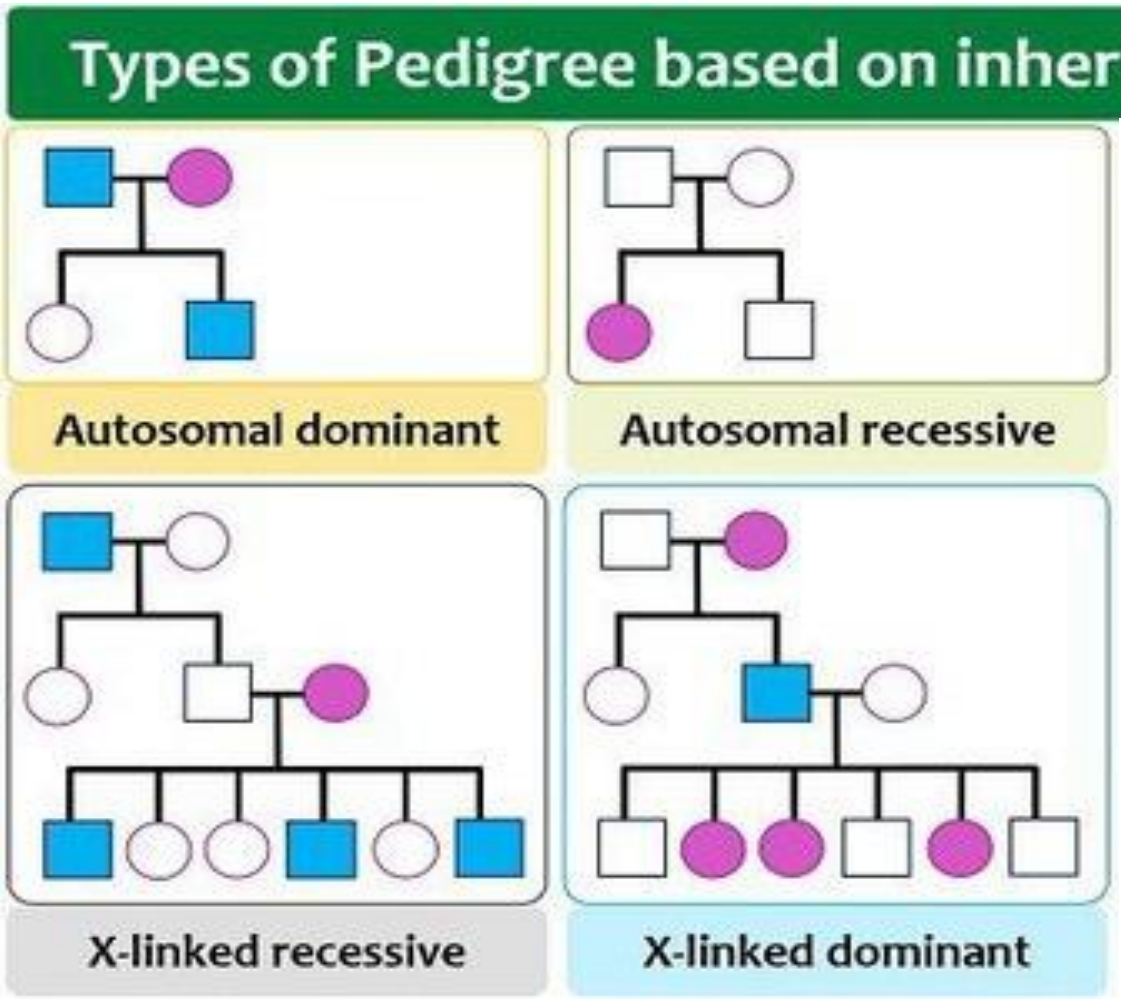


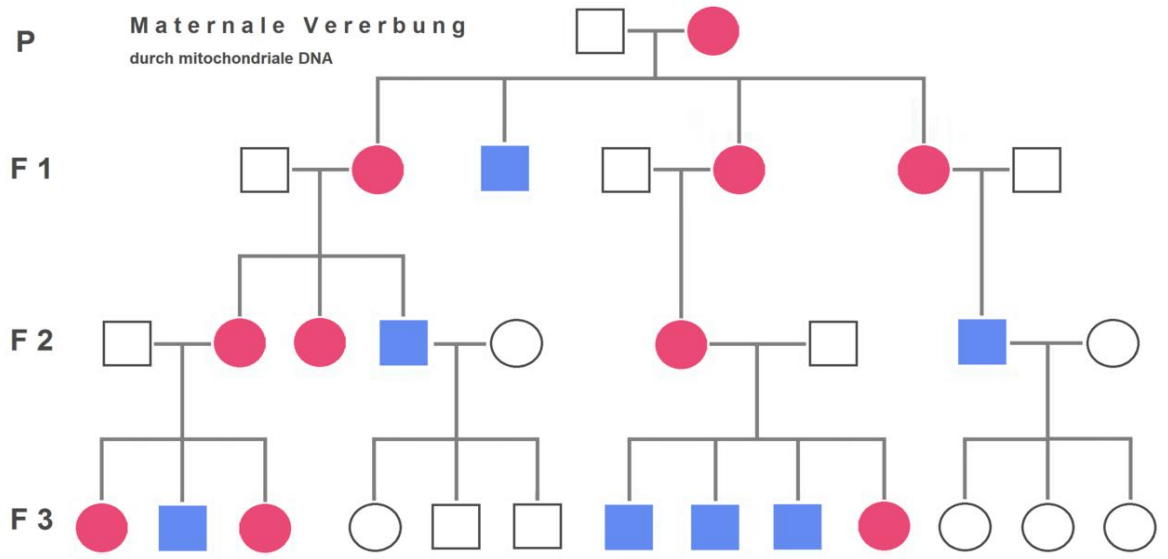
INHERITED MYOPATHIES

PRESENTATIONS LEADING TO SUSPICION OF MUSCULAR DYSTROPHY

- **Family history** (AD, AR, XD, XR, Mitochondrial)
- **Clinical course**
- **Clinical manifestations**
  - Pseudohypertrophy
  - pattern –asymmetric
  - Distal
  - Contracture
  - hyperlaxity
  - extramuscular manifestations- dysmorphism, high arch palate

Family history (AD, AR, XD, XR, Mitochondrial)





Mitochondrial (Maternal inheritance)

PRESENTATIONS LEADING TO SUSPICION OF MUSCULAR DYSTROPHY

- **Family history** (AD, AR, XD, XR, Mitochondrial)
- **Clinical course**
- **Clinical manifestations**
  - Pseudohypertrophy
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  - Contracture
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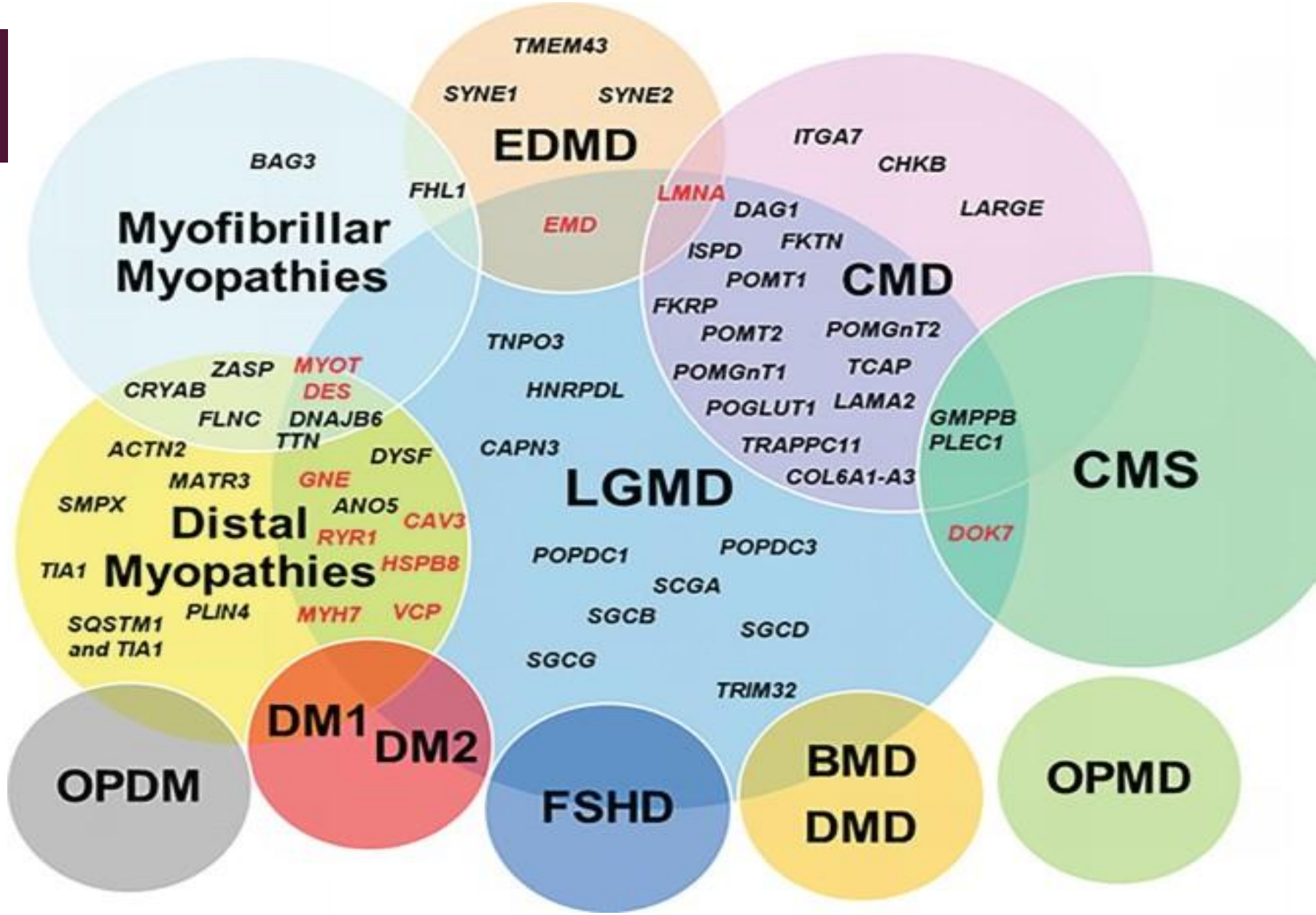
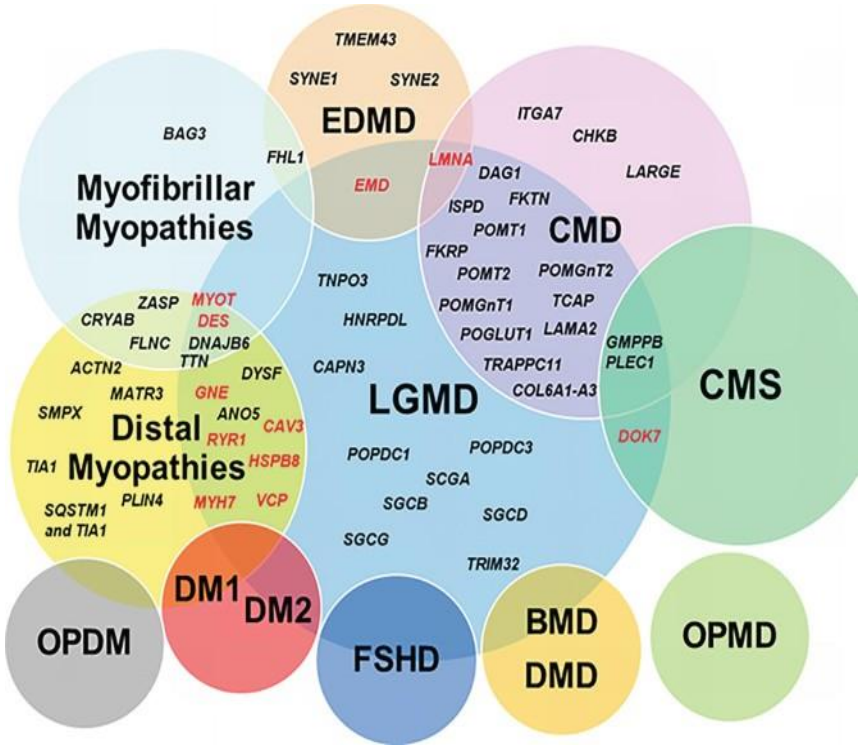
CLINICAL MANIFESTATIONS

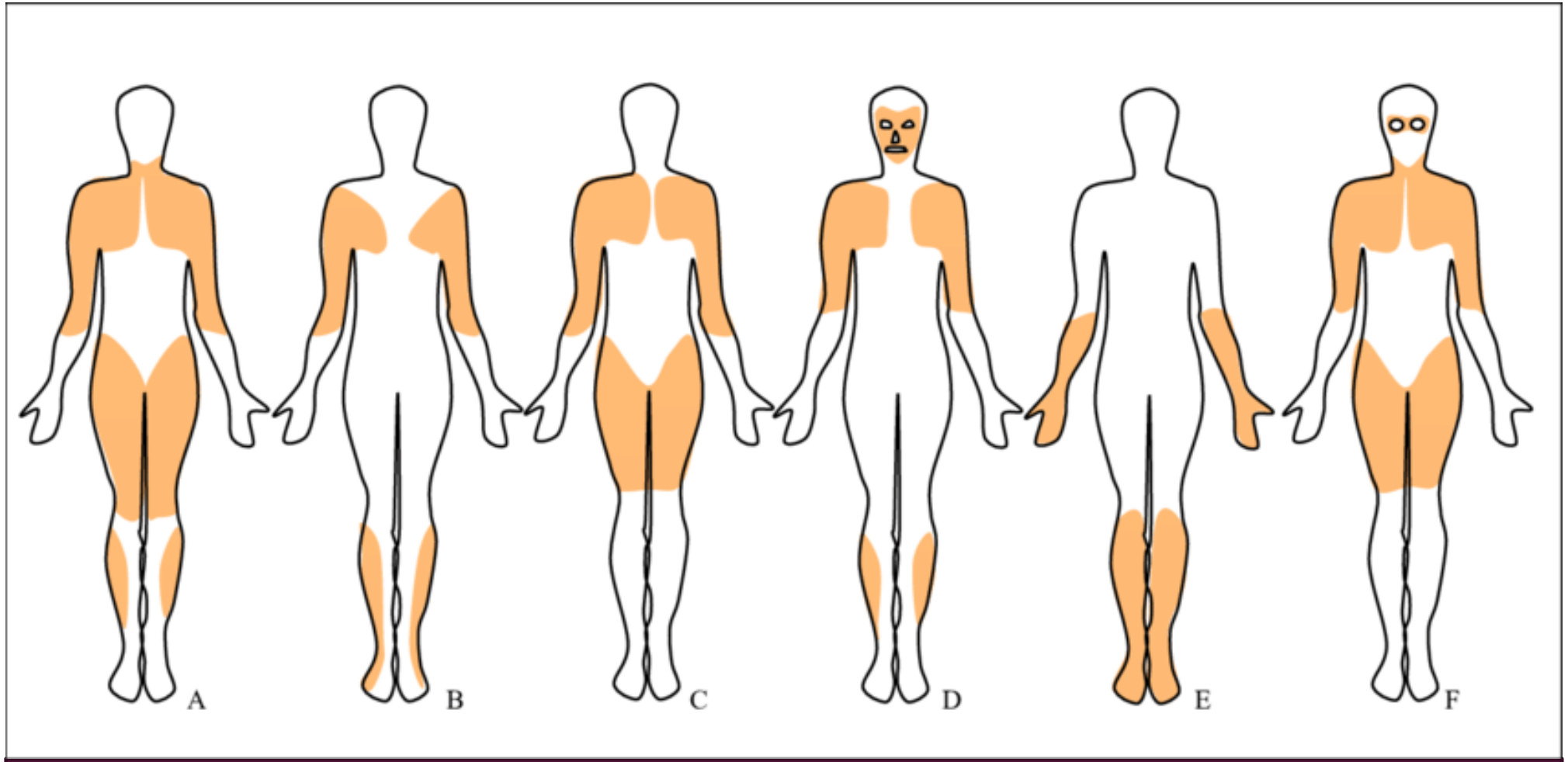
- Pattern –asymmetric
- Distal
- Pseudohypertrophy
- Contractures
- Hyperlaxity
- Dysmorphism
- High arch palate
- Scoliosis
- Rigid spine syndrome
- Dilated CMP
- Cardiac conduction defect
- Hepatosplenomegaly



INHERITED MYOPATHIES

- Muscular dystrophy (DMD/BMD, EDMD, FSHD, LGMD, Congenital MD, Distal myopathy)
- Congenital myopathy
- Metabolic myopathies (disorder of glycogen metabolism, fatty acid metabolism, Mitochondrial myopathies)
- Myotonic disorders and Channelopathies

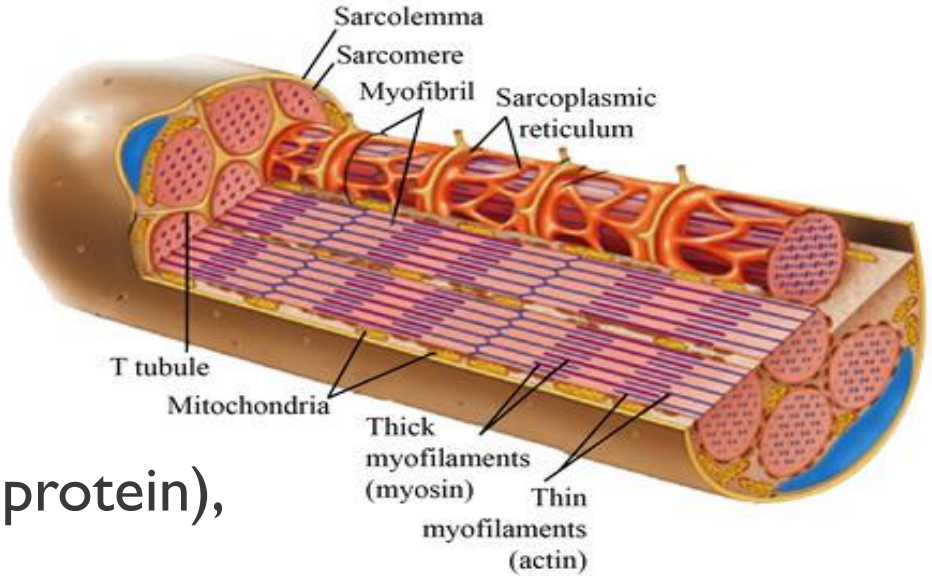


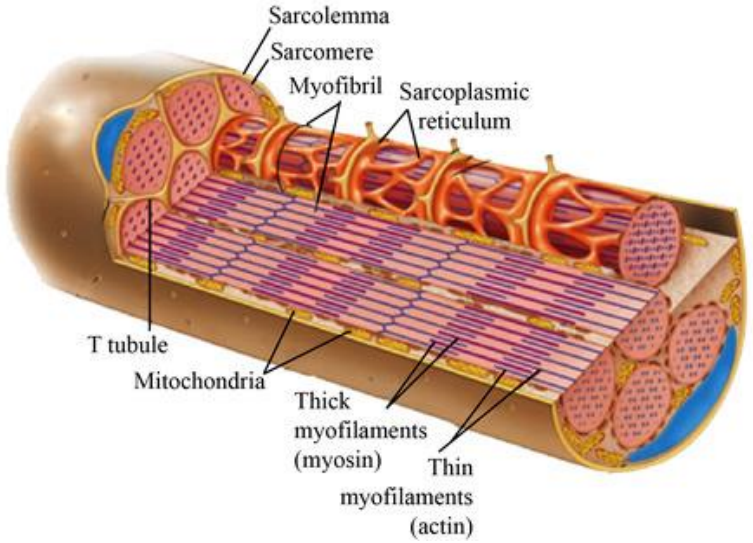


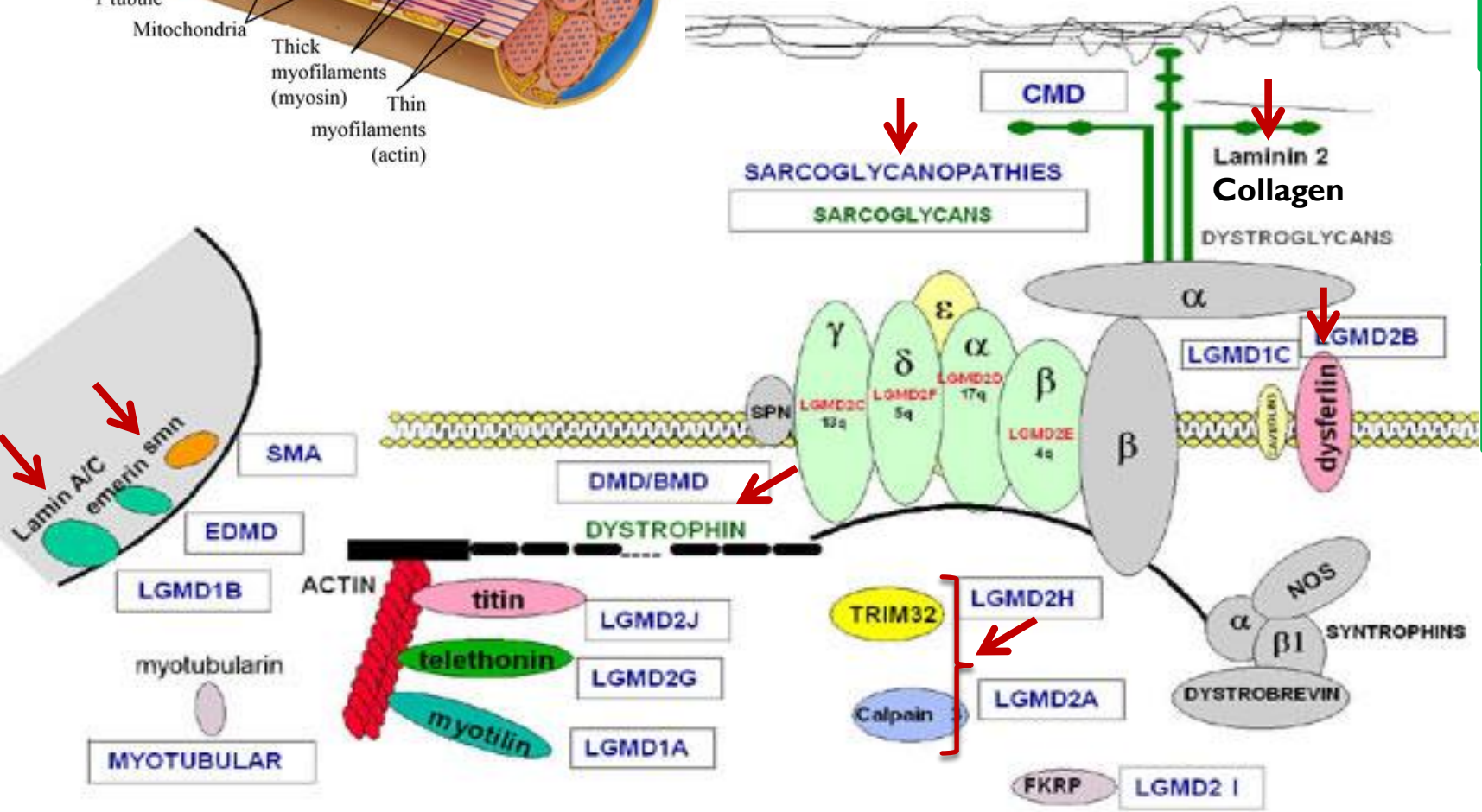
Distribution of Muscular Dystrophy

A. Duchene/Becker-type
B. Emery-Dreifuss
C. Limb-girdle
D. Facioscapulohumeral
E. Distal
F. Oculopharyngeal

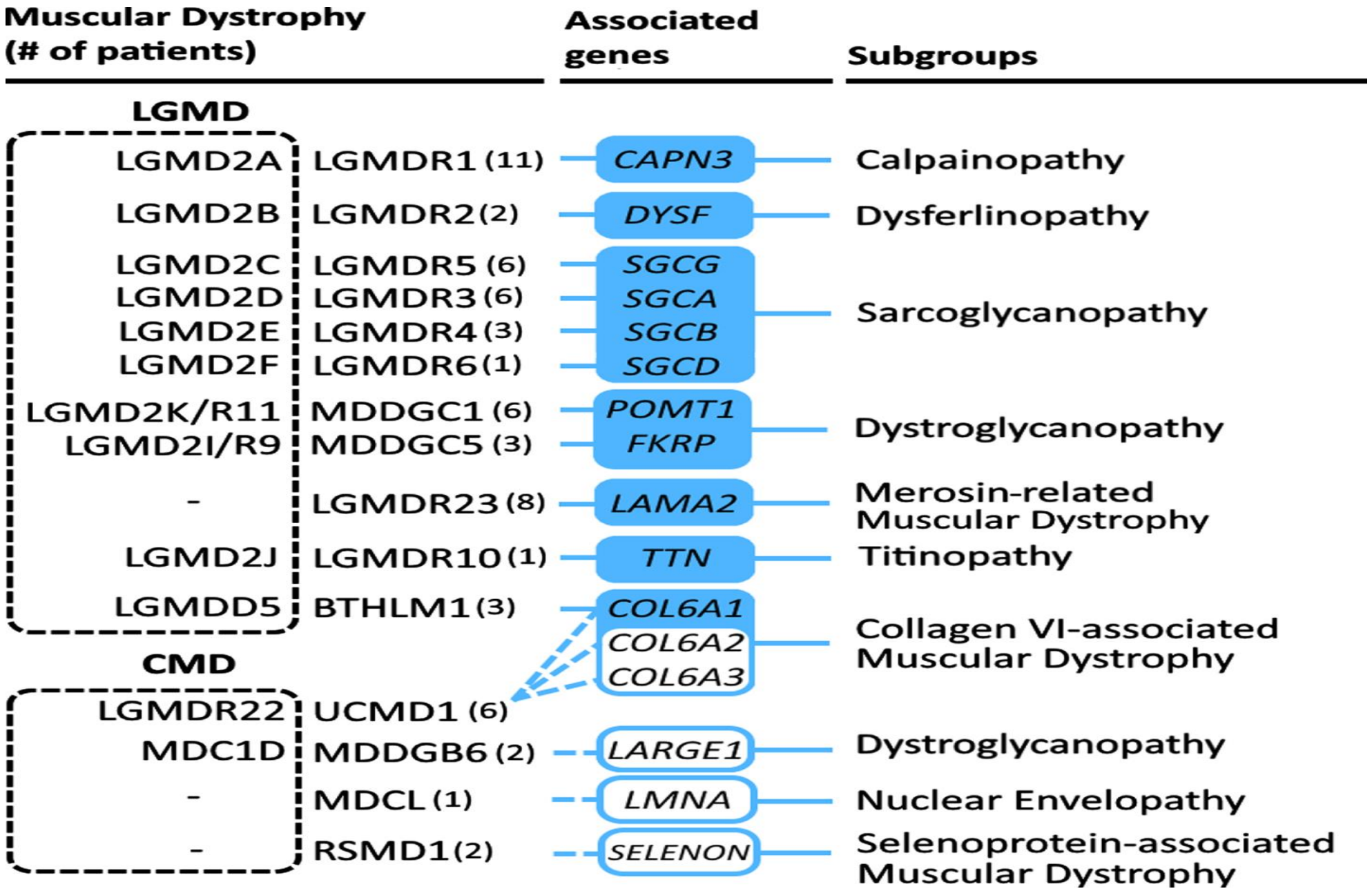
- Sarcolemmal muscle membrane: dystrophin, sarcoglycans, dysferlin, caveolin-3)
- Extracellular matrix (alpha2-laminin, collagen VI)
- Sarcomere (telethonin, myotilin, titin, nebulin)
- Muscle cytosol (calpain 3, TRIM32)
- Nucleus (emerin, lamin A/C, survival motor neuron protein),
- Glycosylation pathway (fukutin, fukutin-related protein)
- Mutations in their respective genes are responsible
- Protein analysis using Western blotting or immunohistochemistry with specific antibodies for diagnosis







Plasma membrane		
Dystrophin	DMD/BMD	XL
α-Sarcoglycan	LGMD2D	AR
ß-Sarcoglycan	LGMD2E	AR
γ-Sarcoglycan	LGMD2C	AR
δ-Sarcoglycan	LGMD2F	AR
Dysferlin	LGMD2B/Miyoshi myopathy	AR
Caveolin-3	LGMD1C	AD
Extracellular matrix		
α2-Laminin	Merosin-deficient CMD	AR
Collagen VI	Ullrich CMD, Bethlem myopathy	AR
Cytosolic		
Calpain 3	LGMD2A	AR
TRIM32	LGMD2H	AR
Sarcomeric proteins		
Titin	LGMD2J	AR
Myotilin	LGMD1A	AD
Telethonin	LGMD2G	AR
Nuclear proteins		
Emerin	Emery-Dreifuss MD	XL
Lamin A/C	LGMD1B	AD
SMN	Spinal muscular atrophy	AR


Muscular Dystrophy (# of patients)
Associated genes
Subgroups
LGMD
LGMD2A
LGMDR1 (11)
CAPN3
Calpainopathy
LGMD2B
LGMDR2 (2)
DYSF
Dysferlinopathy
LGMD2C
LGMDR5 (6)
SGCG
LGMD2D
LGMDR3 (6)
SGCA
LGMD2E
LGMDR4 (3)
SGCB
LGMD2F
LGMDR6 (1)
SGCD
Sarcoglycanopathy
LGMD2K/R11
MDDGC1 (6)
POMT1
LGMD2I/R9
MDDGC5 (3)
FKRP
Dystroglycanopathy
-
LGMDR23 (8)
LAMA2
Merosin-related Muscular Dystrophy
LGMD2J
LGMDR10 (1)
TTN
Titinopathy
LGMDD5
BTHLM1 (3)
COL6A1
COL6A2
COL6A3
Collagen VI-associated Muscular Dystrophy
CMD
LGMDR22
UCMD1 (6)
MDC1D
MDDGB6 (2)
LARGE1
Dystroglycanopathy
-
MDCL (1)
LMNA
Nuclear Envelopathy
-
RSMD1 (2)
SELENON
Selenoprotein-associated Muscular Dystrophy

INHERITED MYOPATHIES

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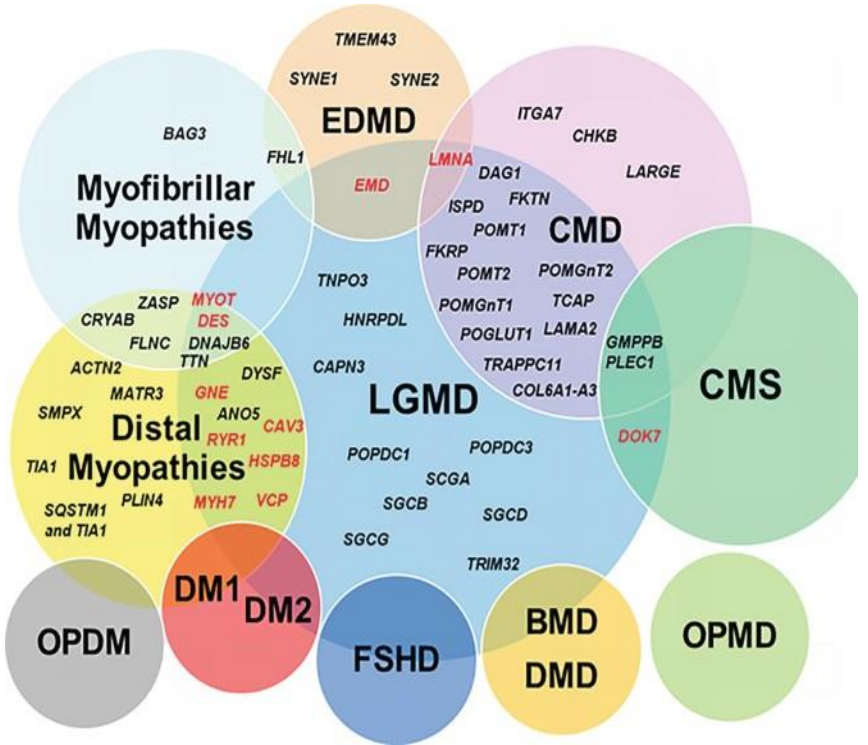
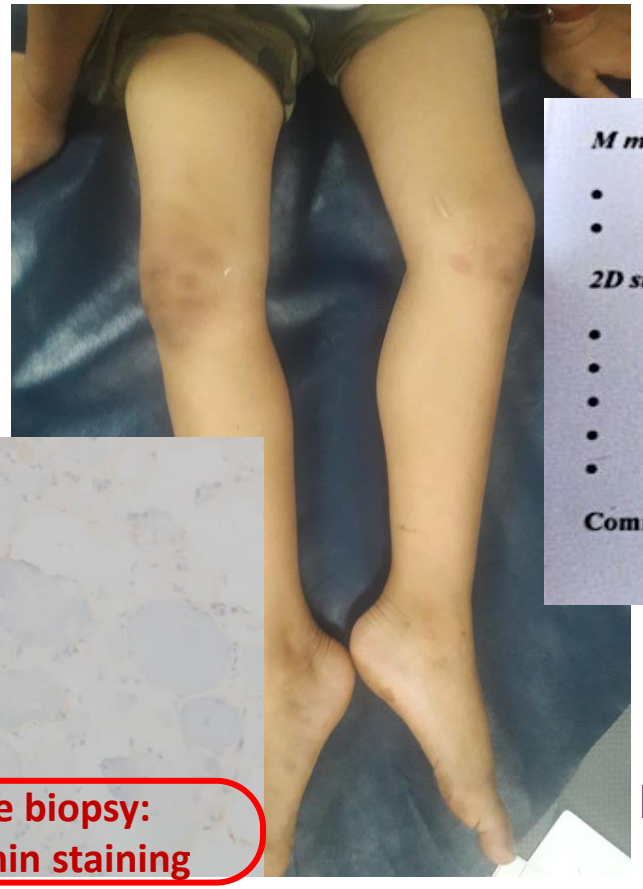
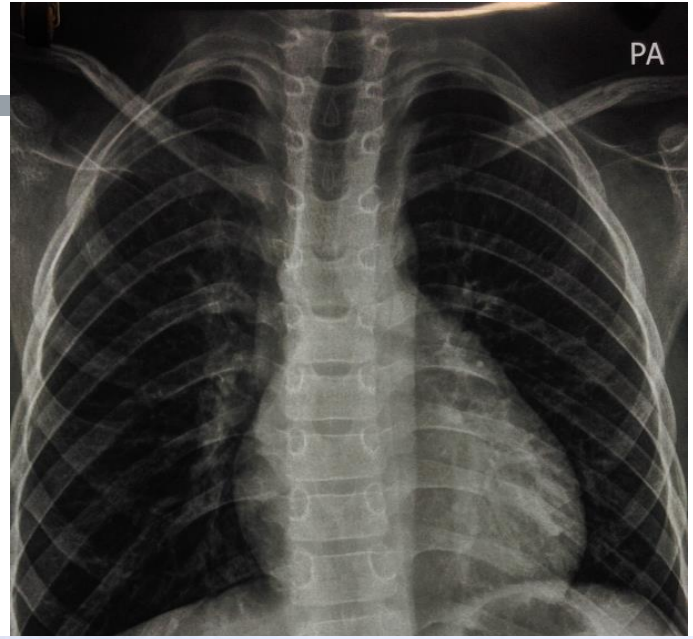


DUCHENNE MUSCULAR DYSTROPHY

A young boy with childhood onset proximal myopathy



Muscle biopsy:
Dystrophin staining



M mode measurements

- LVEDD -51 cm , LVESD – 30cm
- EF- 55 % ,FS - 28 %

2D structural assessment;

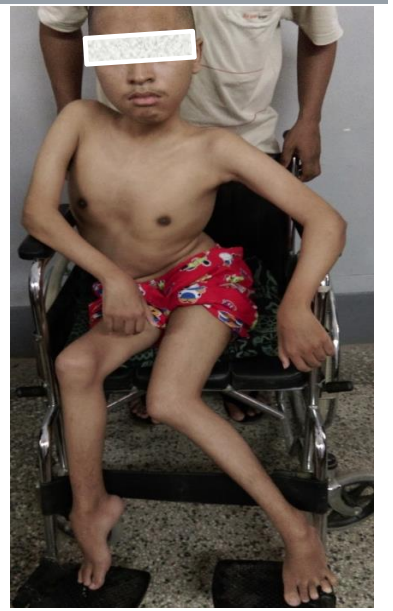
- Situs solitus, AV –VA concordance,
- All four chambers – slightly dilated (LV-3.9cm)
- No significant shunts, All valves- normal
- Aortic arch normal,
- pericardial normal

Comment : Dilated four chambers with reduced LV function

Dilated cardiomyopathy

Deletion of exon 52 DMD gene

A 17-year-old boy

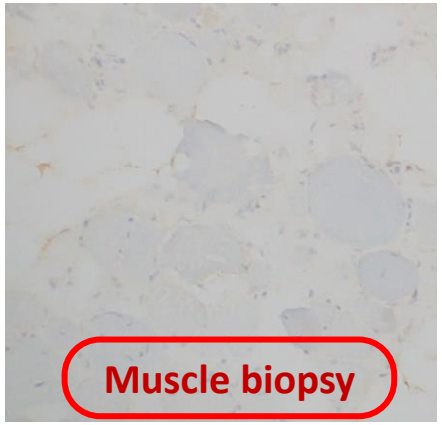


- Prenatal, birth history - unremarkable
- **Delayed developmental milestones** (sit at 6 months, stand at 1 year, walk properly only after 2 years)
- He could not jump since young, he could run, frequent falls on running & he could not press the bicycle pedals since young.

5 years of age	-	Difficulty in standing up, Proximal myopathy, Gower's sign, calves' hypertrophy
7 years of age	-	Calves' hypertrophy, Later proximal arms also weak but he could write well up to 13 years of age
10 years of age	-	Could stand but had to walk with support, contractures
13 years of age	-	Could not stand, wheelchair bound, could not sit well, could not hold head, progressively scoliotic, could not write, could not do his ADL

- Family history – no consanguous marriage, No similar illness in family.
- Cognition – normal, Wheelchair bound, **Mild facial weakness**, Tongue, bulbar, ocular - normal
- Head control – weak 3/5, Trunk control – 3-/5
- **Pigeon chest deformity, severe kyphoscoliosis**, Chest wall expansion – 1 cm, **Scapular winging**
- Wasting all 4 limbs with contractures at both sides of elbows (45°-120°), wrists (extension restricted), knees (Rt 70°-135°, Lt 45°-120°) and ankles (extension restricted with heel cord tightness)

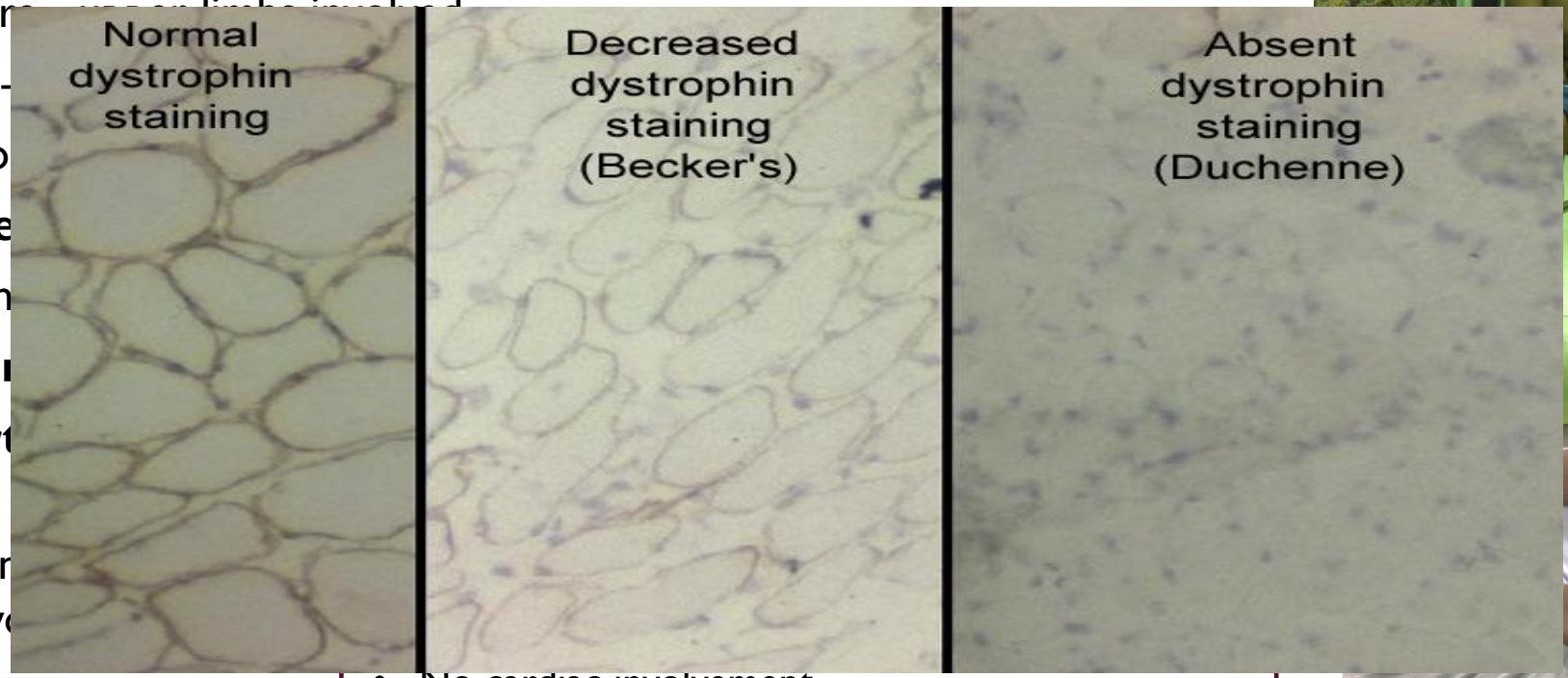
- **CK – 1356** (55-170)
- CXR(PA) – Cardiomegaly, ECG – Q in I, aVL, v5,v6, ST elevation V3,V4, poor R progression
- Echocardiogram –**LVEF 40%, Global hypokinesia and dilated LV**
- **Muscle biopsy: absent dystrophin**
- **Deletion of exons 3 to 17 in dystrophin gene (MLPA analysis)**

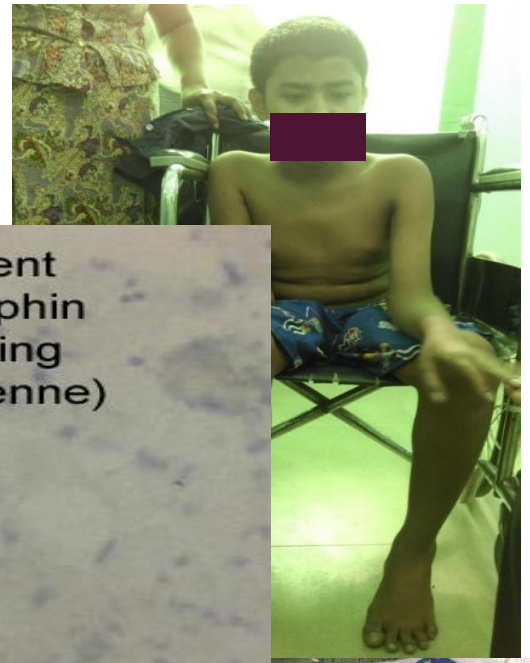


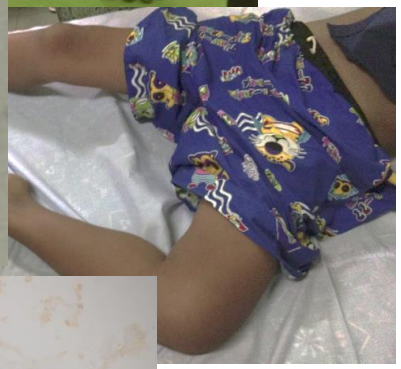
Final Diagnosis: DMD

A 13-year-old boy

- Normal developmental milestones
- 12 years of age - left leg weak **later progressive** and cannot walk well
- 2 months befor
- Family history -
- Cognition – no
- **Mild facial we**
- Scapular wingin
- Wasting **proxi**
- **Calves hyper** (130°-180°)
- Reflexes preser response. Beev

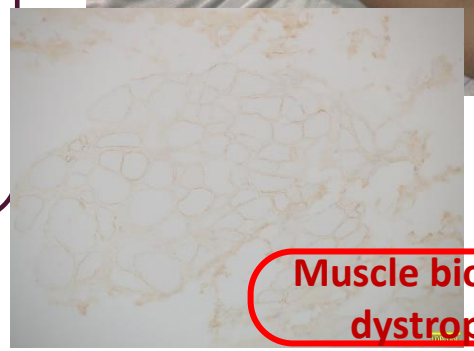






Clinical Diagnosis:
? BMD
? LGMD

- No cardiac involvement
- NCS – normal, EMG – Myopathic
- **CK – 4183**
- CT – Anterior thigh, posterior leg mainly affected



➢ **Becker muscular dystrophy**

Deletion of exon 45 in dystrophin gene

Muscle biopsy: decreased dystrophin staining

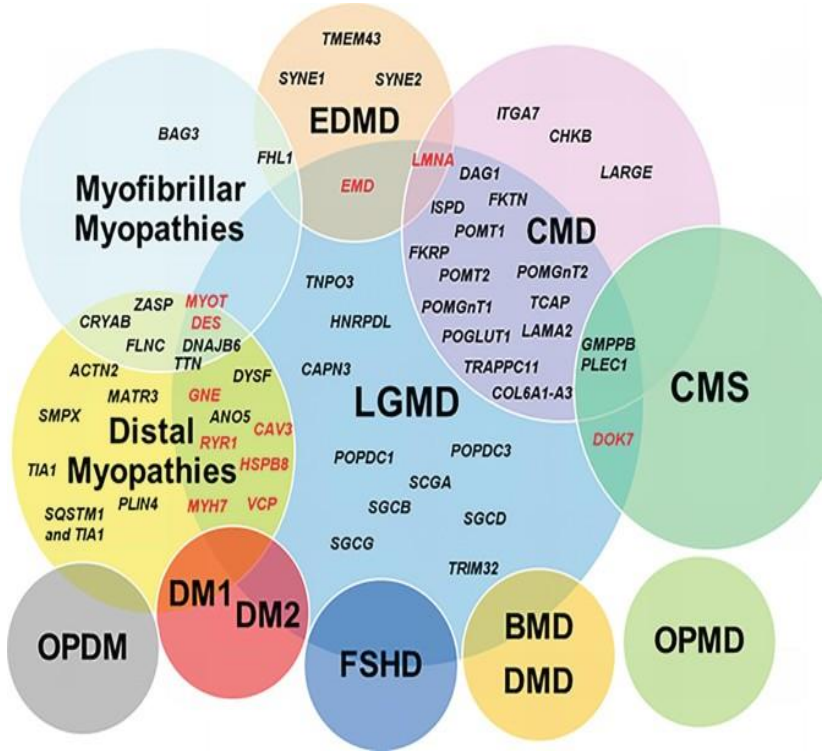
Table. Duchenne Muscular Dystrophy and Becker Muscular Dystrophy		
	DMD	**BMD**
Dystrophin gene	Absent or nonfunctional	Partially functional
Incidence	1/3,600 male births	3 to 6/100,000 male births
Mean age at onset	3-5 years	12 years
Disease progression	Fast	Slow
Mean age at becoming nonambulatory	12 years	27 years
Mean life expectancy	Mid 20s	40s
Onset of cardiomyopathy	Usually follows skeletal progression	May present before skeletal symptoms

INHERITED MYOPATHIES

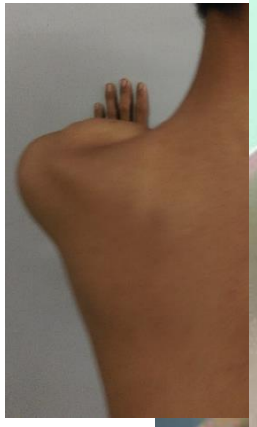
- Muscular dystrophy (DMD/BMD, **FSHD**, LGMD, EDMD, Distal myopathy, Congenital MD, Myofibrillar myopathy)
- Congenital myopathy
- Metabolic myopathies

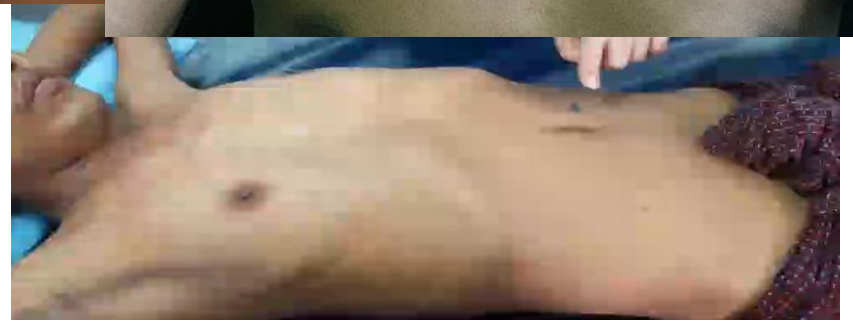
  (disorder of glycogen metabolism, fatty acid metabolism ,

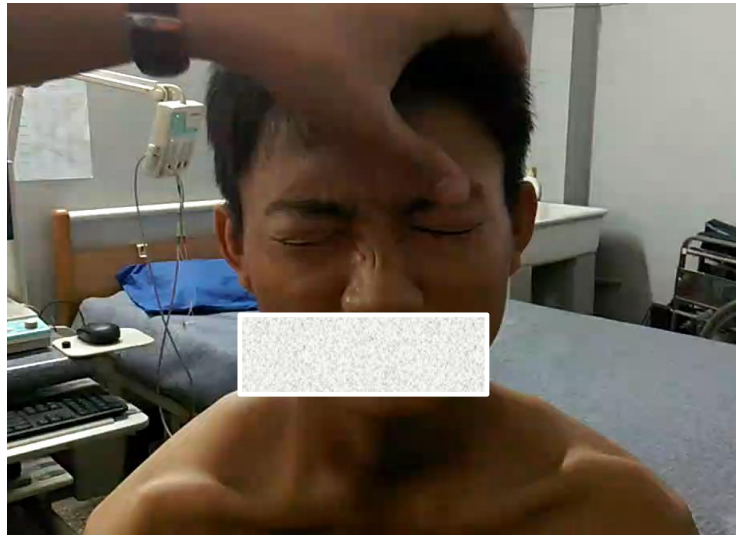
  Mitochondrial myopathies)
- Myotonic disorders and Channelopathies



Tow Siblings with Muscle Weakness







FSHD DNA Analysis Report

Patient Name : 23/M

Clinical Diagnosis : FSHD

NCNP Index : 15-1415

Results and Comments

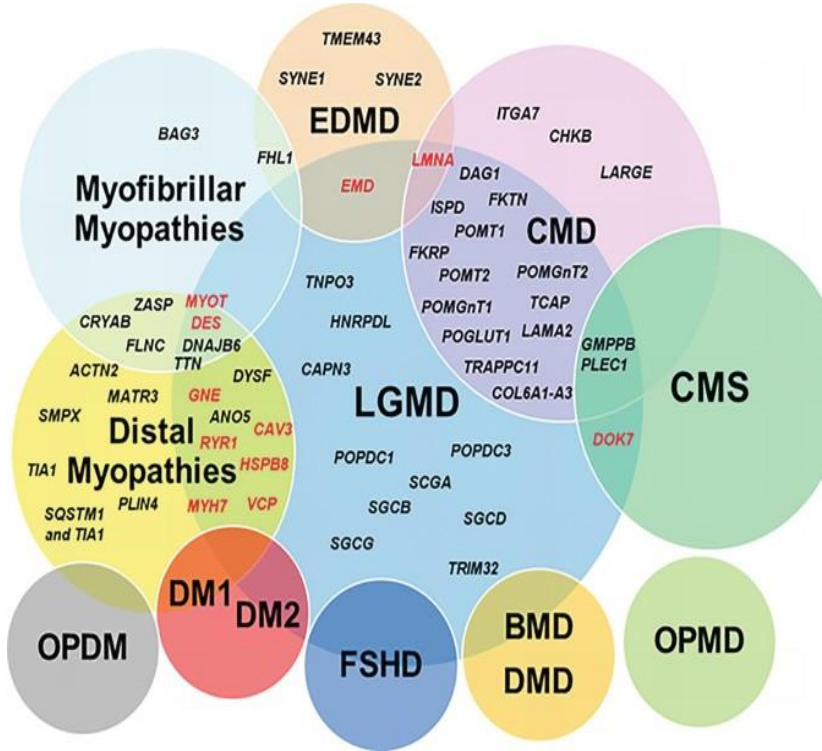
Southern blotting analysis using the probe p13E-11 was performed for FSHD. This patient has a small-size (20-kb) *EcoRI* fragment on Ch. 4q35, and considered to be 4q35-FSHD.

INHERITED MYOPATHIES

- Muscular dystrophy (DMD/BMD, FSHD, **LGMD**, EDMD, Distal myopathy, Congenital MD, Myofibrillar myopathy)
- Congenital myopathy
- Metabolic myopathies

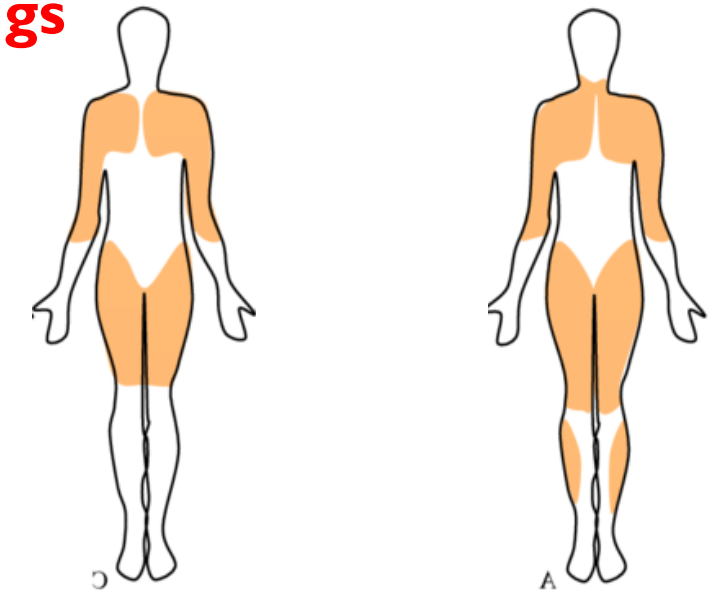
  (disorder of glycogen metabolism, fatty acid metabolism,

  Mitochondrial myopathies)
- Myotonic disorders and Channelopathies



LGMD vs Dystrophinopathies: weaker muscles

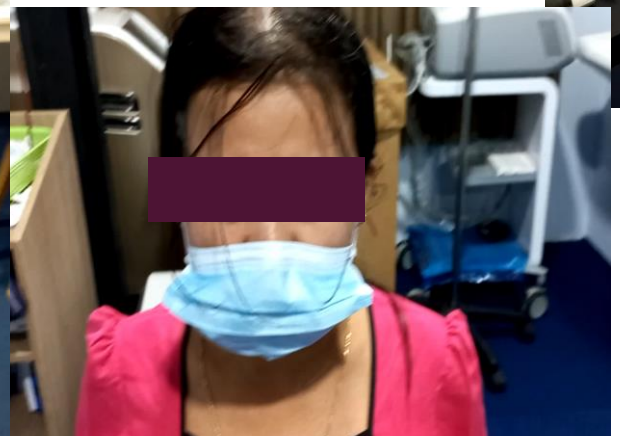
- **Deltoid**
- **Biceps**
- **Iliopsoas**
- **Hip adductors**
- **Hamstrings**



- Progressive
- Predominent proximal muscle weakness
- Family history (AD/AR)
- High CK < DMD/BMD
- Muscle biopsy: dystrophic changes, IHC stain
- Imaging: degenerative changes
- Genetic test

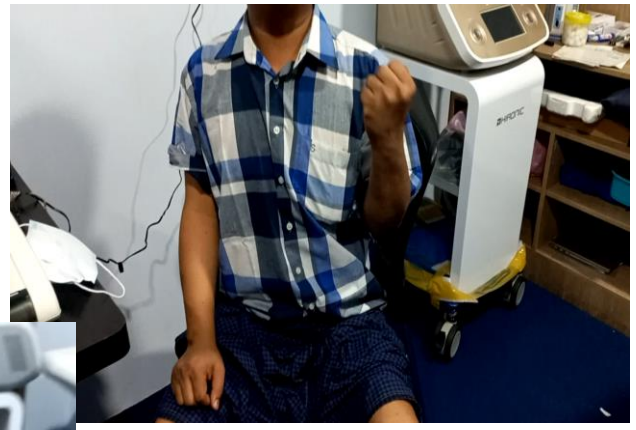
36 years old lady

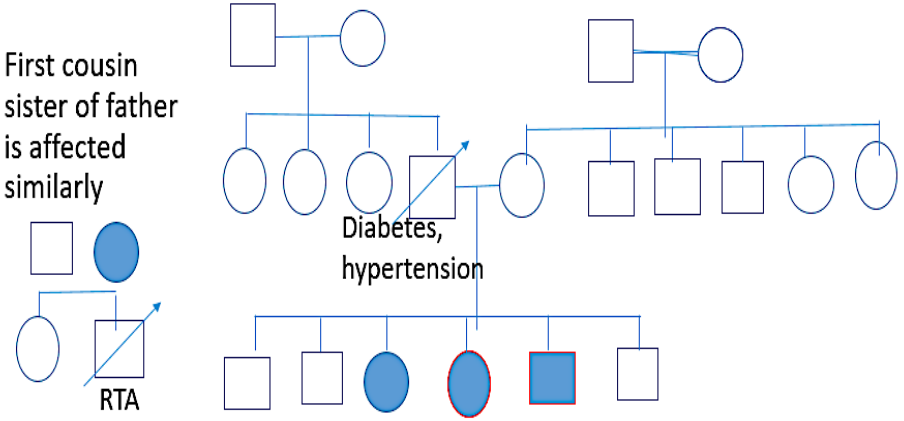
- Onset 30 years of age
- Progressive proximal myopathy
- Normal IQ
- Palate – normal, No dysmorphic features; Ocular, bulbar and cardiac, Respiratory function: normal
- no contracture, no muscle hypertrophy,
- CK 596 (39-308), EMG myopathic



33 years old man

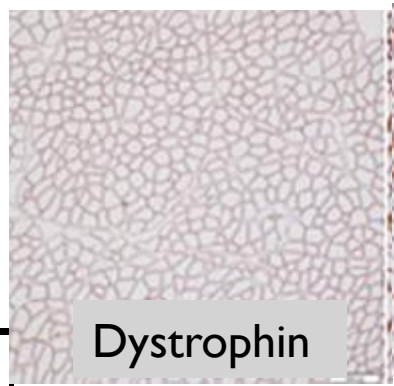
- Onset 22 years of age
- Progressive proximal myopathy
- 35 years: walk
- CK 2498

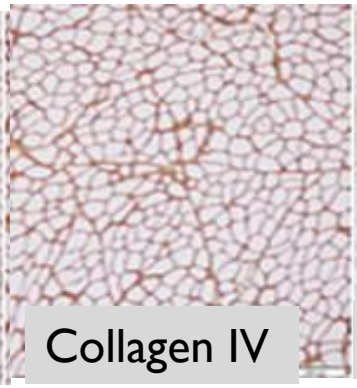


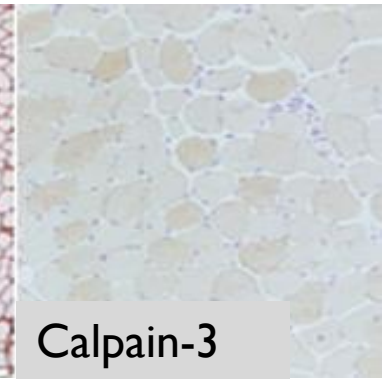


- Past Medical History - Nil
- Family History
  - no parental consanguinity

Gene	Zygosity	RefSeq numbers	Exon /Intron	Variant	HGMD	gnomAD_ EAS	ToMMo	Polyphen2	Mutation taster	Classification*
CAPN3	hetero	NM_000070.3	exon22	c.2303dupT (p.M768Ifs*13)	Unreported	.	.			Pathogenic







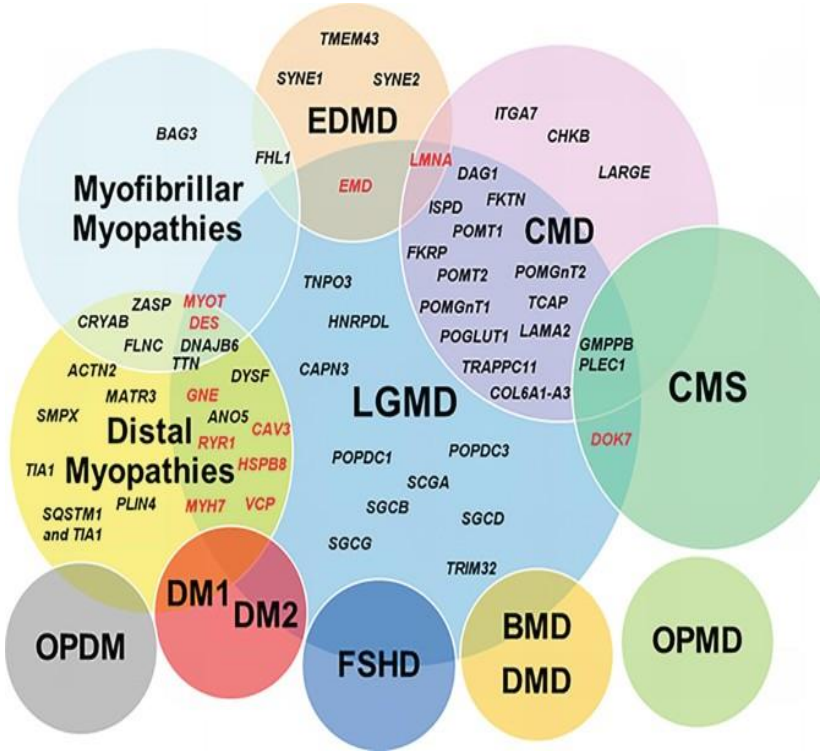
AR LGMD2A/R1 Calpainopathy

INHERITED MYOPATHIES

- Muscular dystrophy (DMD/BMD, FSHD, LGMD, **EDMD**, Distal myopathy, Congenital MD, Myofibrillar myopathy)
- Congenital myopathy
- Metabolic myopathies

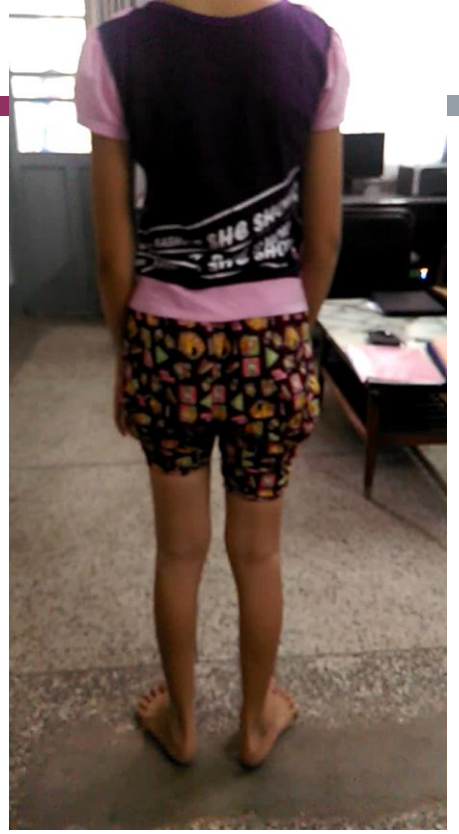
  (disorder of glycogen metabolism, fatty acid metabolism,

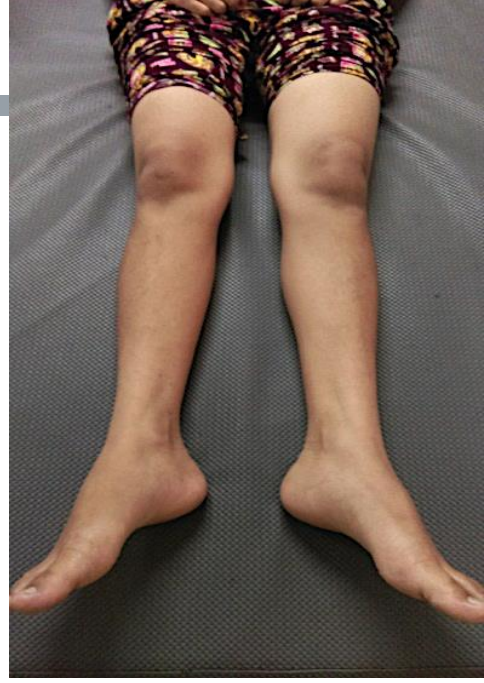
  Mitochondrial myopathies)
- Myotonic disorders and Channelopathies



A 16-year-old girl

- **Onset: 11 years**, slowly progressive difficulty in running, climbing stairs, standing from squatting, No weakness in upper limbs (**proximal LL**)
- Cognition, ocular, bulbar – normal, mild facial weakness
- Mild scapula winging, **ankle joint contracture while ambulant**, cannot heel,
- **Rigid spine syndrome** (neck and back – **rigid spine, cannot bend down**),
- Scoliosis, mild high arch, post thigh, post asymmetric calf atrophy (L>R)
- **can walk on toes but not on heels**
- Family history: Nil



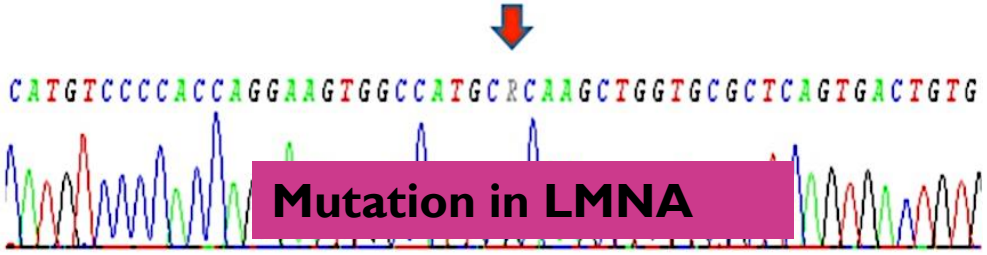


- **CK – 1007 U/l** (30-135)
- Cardiac involve (RBBB, low voltage ECG, **Dilated cardiomyopathy**
-)

Laminopathy/EDMD/LGMD1B

We performed gene analysis using genomic DNA from the above-mentioned patient. We detected a heterozygous mutation in *LMNA*. The mutation was confirmed by Sanger-sequencing.

LMNA:ENST00000368300:NM_170707.3:c.1622G>A:p.Arg541His (het)
Reported (Vytopil (2003) J Med Genet 40, e132)



Mutation in LMNA

Triad of EDMD

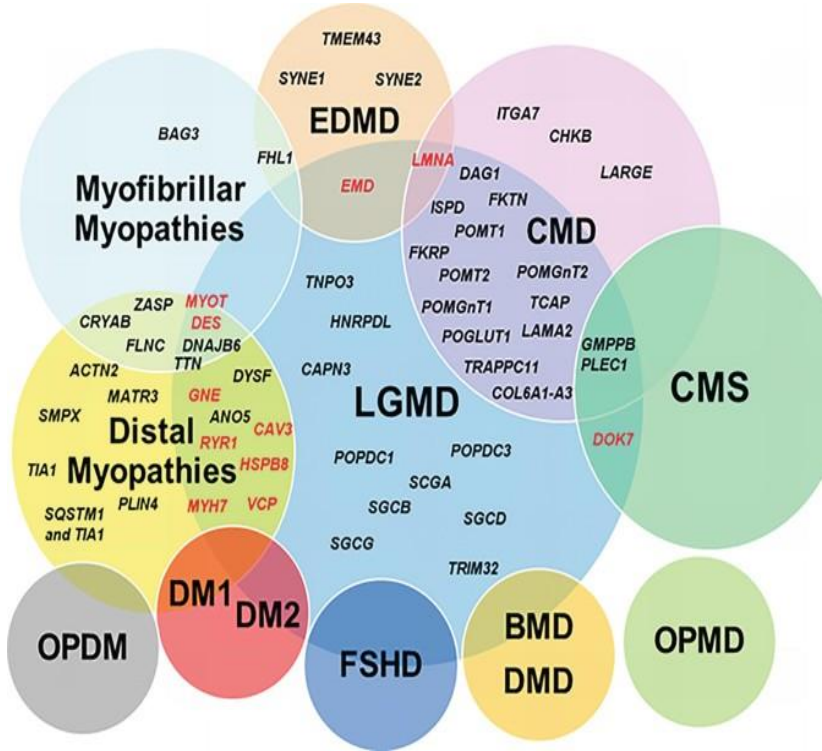
1. Early contractures- difficult movements of arm, neck, ankle, spine (Toe-walking, elbows difficult to bend)
2. Humero-peroneal weakness
3. Cardiac conduction deficits, DCM

INHERITED MYOPATHIES

- Muscular dystrophy (DMD/BMD, FSHD, LGMD, EDMD, **Distal myopathy**, Congenital MD, Myofibrillar myopathy)
- Congenital myopathy
- Metabolic myopathies

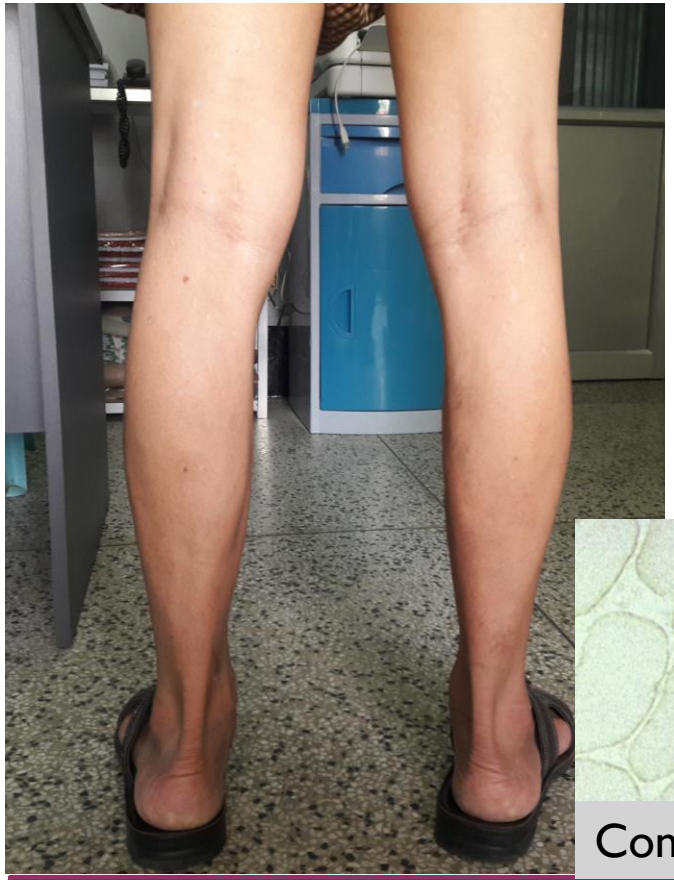
  (disorder of glycogen metabolism, fatty acid metabolism,

  Mitochondrial myopathies)
- Myotonic disorders and Channelopathies

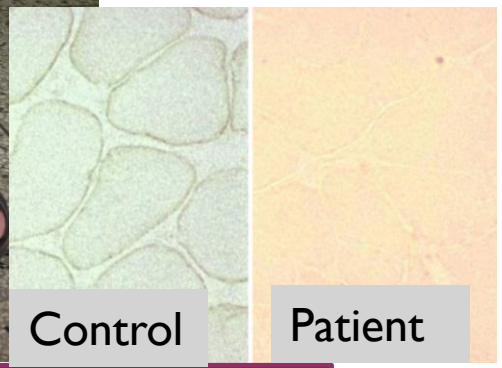


Distal myopathy/weakness onset

Cannot walk tiptoe



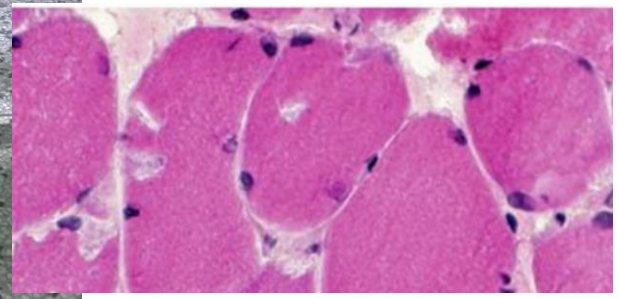
CK: 22194



Miyoshi myopathy/Dysferlinopathy

Cannot walk on heel

CK: 447



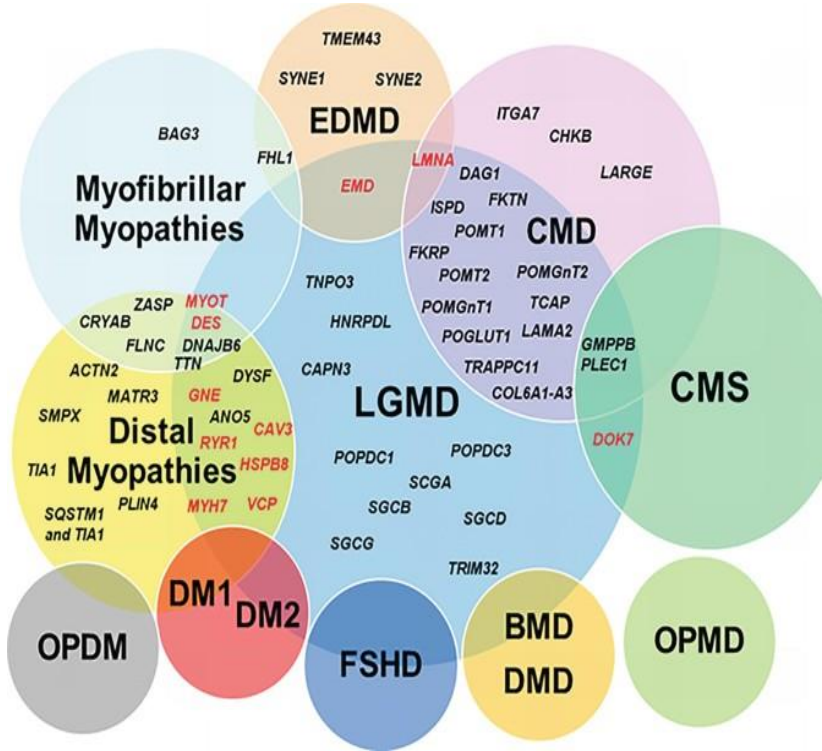
Nonaka (GNE) myopathy/
Hereditary inclusion body myopathy

INHERITED MYOPATHIES

- Muscular dystrophy (DMD/BMD, FSHD, LGMD, EDMD, Distal myopathy, **Congenital MD**, OPMD)
- Congenital myopathy
- Metabolic myopathies

  (disorder of glycogen metabolism, fatty acid metabolism,

  Mitochondrial myopathies)
- Myotonic disorders and Channelopathies



CONGENITAL MUSCULAR DYSTROPHY: ONSET <2 YEARS AGE

- **Laminin-alpha2 deficiency** (40%- most common)
- **Collagen VI–deficient congenital muscular dystrophy** (2nd most common), *COL6A1* and *COL6A2* genes mutation

  Ullrich congenital muscular dystrophy (AR)

  - Facial dysmorphism- micrognathia, a round face with drooping lower lids, prominent ears.
  - distal joint hyperlaxity with a protruding calcaneus
  - Kyphosis and proximal contractures
  - Distal predominant weakness
  - Loss of ambulation after 3-10 years

  Bethlem myopathy (AD)

  - Onset 1st or 2nd decade, as late as 6th decade
  - Flexion contractures of the fingers, wrists, elbows, and ankles are noted. Proximal contractures include at the knees, hips and shoulders
  - Joint laxity
  - slowly progressive, normal life expectancy
  - Normal CK

15 YEARS OLD BOY

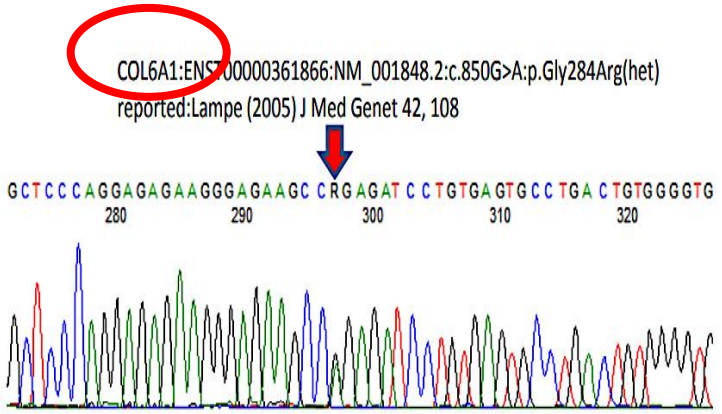
- Unremarkable delivery history, No family history, No parental consanguinity
- **Delayed milestones** (stand only after 2 years, walk only after 3 years of age). In his life, he has never stood up by self. His mom has always to lift him up first before he stood and walked. But he ambulated only short period

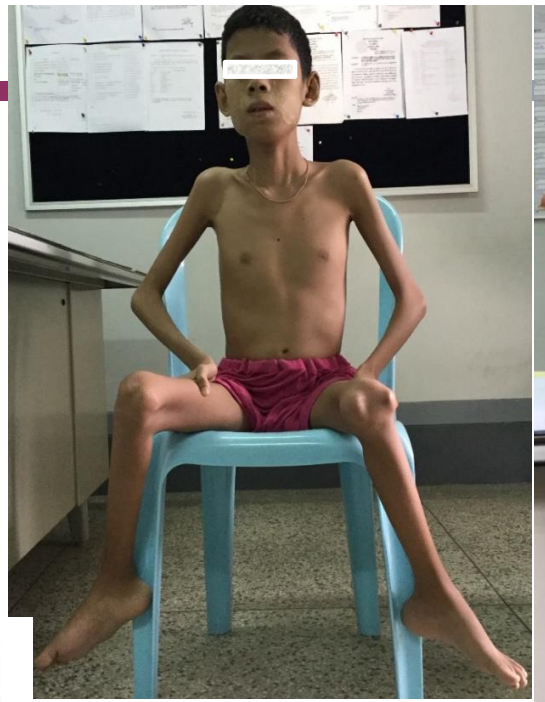
3.5 yr. of age	4 yr. of age	5 yr. of age	5.5 yr. of age
fall on buttock frequently on standing	mostly on wheelchair	Knee contracture started	Elbows contracture started

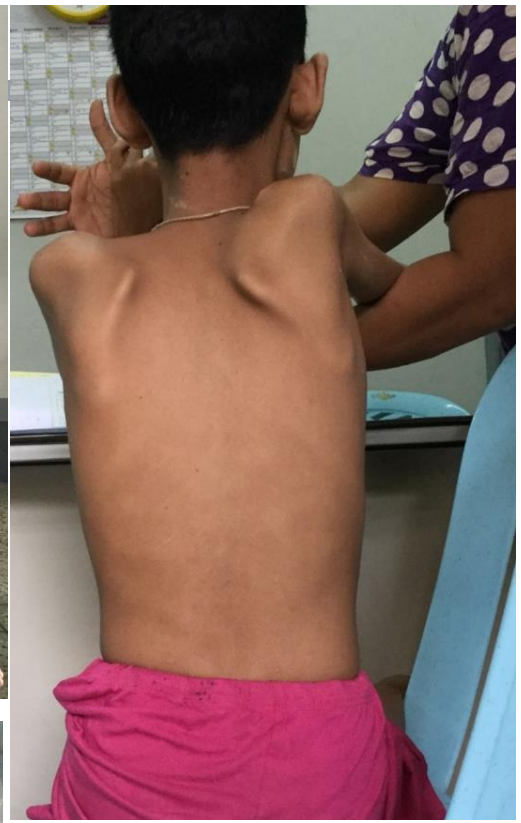
- Generalized muscle atrophy
- **Restricted neck flexion, scoliosis**
- **Early severe proximal contractures, elbows, ankles, knees**
- **Distal joint hyperlaxity**

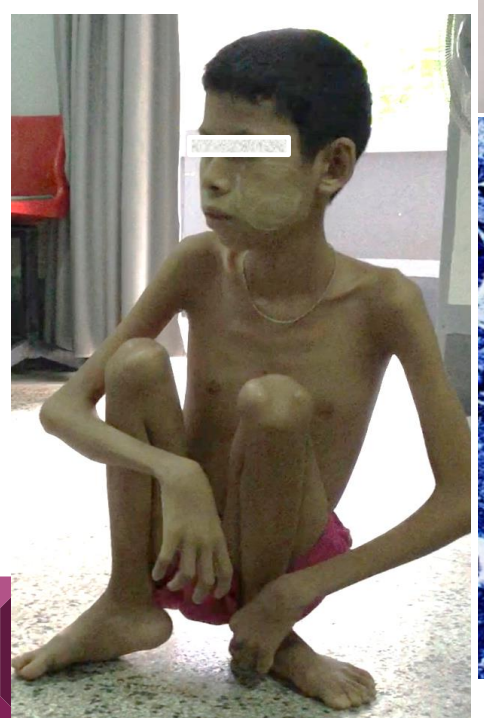
- **CK: 98** (55-170)
- NCS: normal, EMG: myopathic
- **Muscle biopsy: Lobulated fibers**

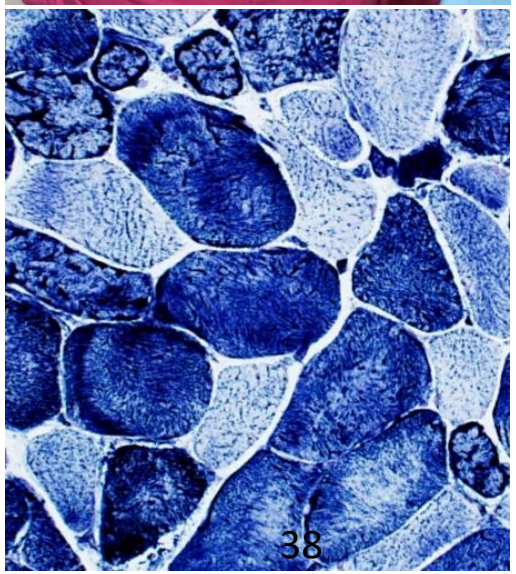
We performed target resequencing analysis to screen for mutations in known muscular dystrophy genes* using next generation sequencer using genomic DNA from the above-mentioned patient. We detected a heterozygous mutation in *COL6A1*. The mutation was confirmed by Sanger-sequencing.











Ullrich congenital muscular dystrophy

INHERITED MYOPATHIES

- Muscular dystrophy (DMD/BMD, FSHD, LGMD, EDMD, Distal myopathy, Congenital MD, **OPMD**)
- Congenital myopathy
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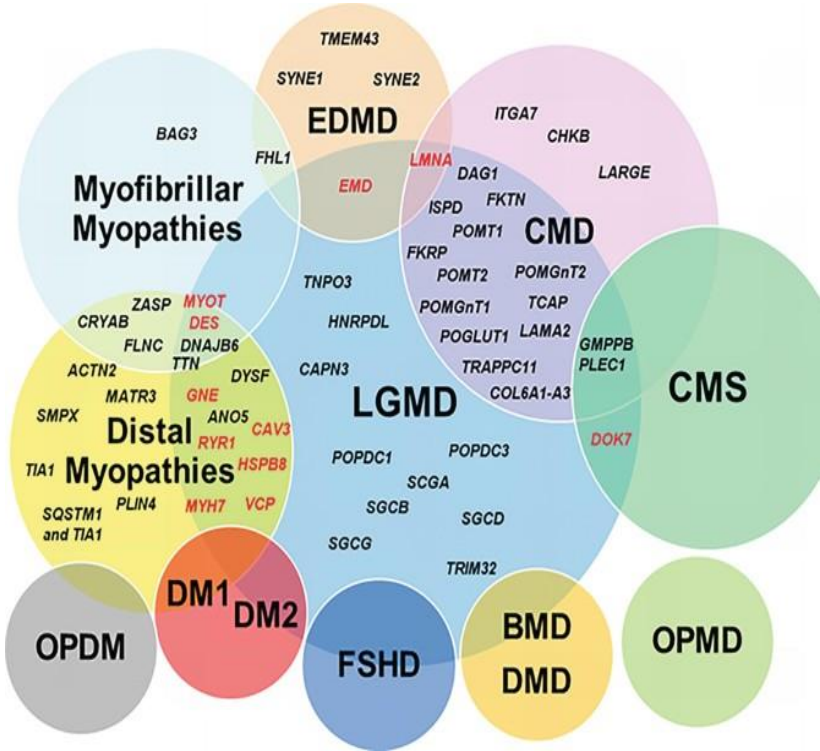
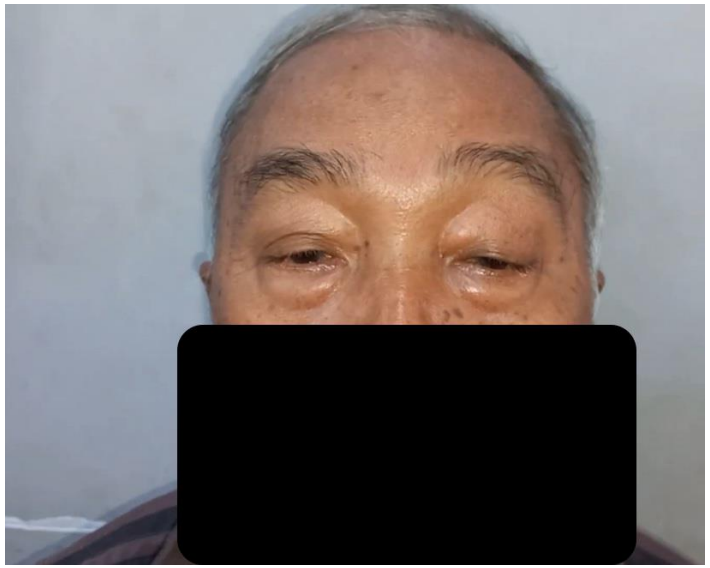
  (disorder of glycogen metabolism, fatty acid metabolism,

  Mitochondrial myopathies)
- Myotonic disorders and Channelopathies



72-YEAR-OLD MAN

- **Onset 60 years - bilateral progressive non-fatiguable ptosis. Ophthalmoparesis but Never diplopia.**
- At 63 years - dysphagia especially solid food
- 68 years of age: difficulty to climb stairs, speech and arms - normal.
- AD family history of bilateral severe ptosis and dysphagia
- CK 104 (55-170)
- DDx Mitochondrial myopathy (CPEO), OPMD, Congenital Myasthenic Syndrome
- Mitochondrial DNA sequencing - Normal
- Genetic test: **GCN trinucleotide expansion in PABPN1**



Mitochondrial DNA sequencing analysis : the attached sheet

Comments

There is no pathogenic variant in mtDNA.

Additional nuclear gene mutation analysis was performed, but no pathological variants were detected.

Genetic test of oculopharyngeal muscular dystrophy (OPMD) was performed as follows.

【Method】 We analyzed the GCN (GCG or GCA) repeat number in exon 1 of poly(A) binding protein nuclear 1 gene (*PABPN1*) by PCR amplification of the repeat region and fragment size analysis. Furthermore, the PCR product was sequenced.

【Results】 The PCR products of the size corresponded to $(GCN)_{10}$ and $(GCN)_{13}$ were detected. The $(GCN)_{13}$ sequence was $(GCG)_9$ $(GCA)_3$ $(GCG)_1$.

【Comment】 The data are cinsistent with OPMD.

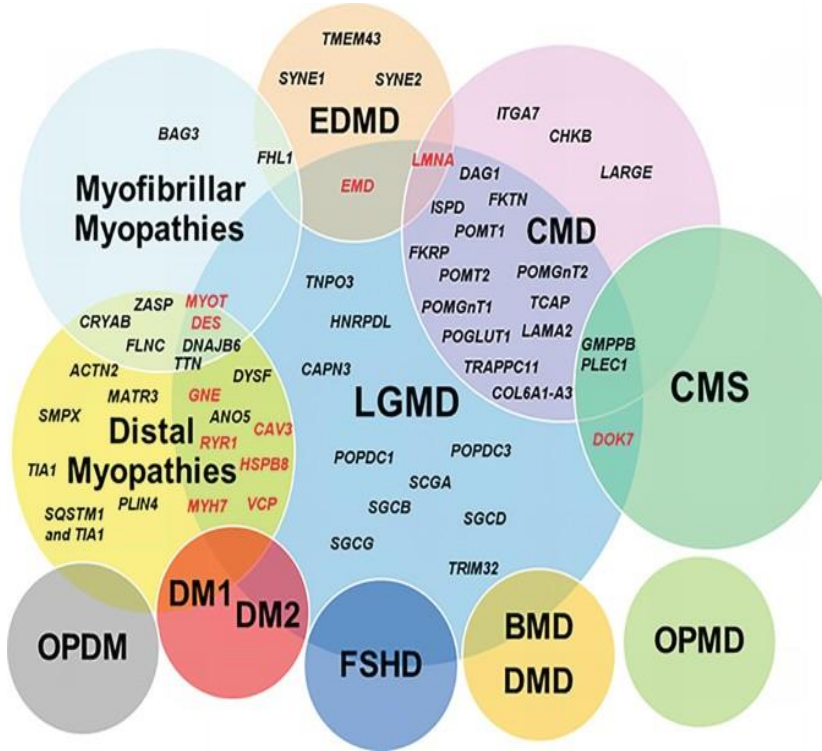
OPMD- Oculopharyngeal Muscular Dystrophy

INHERITED MYOPATHIES

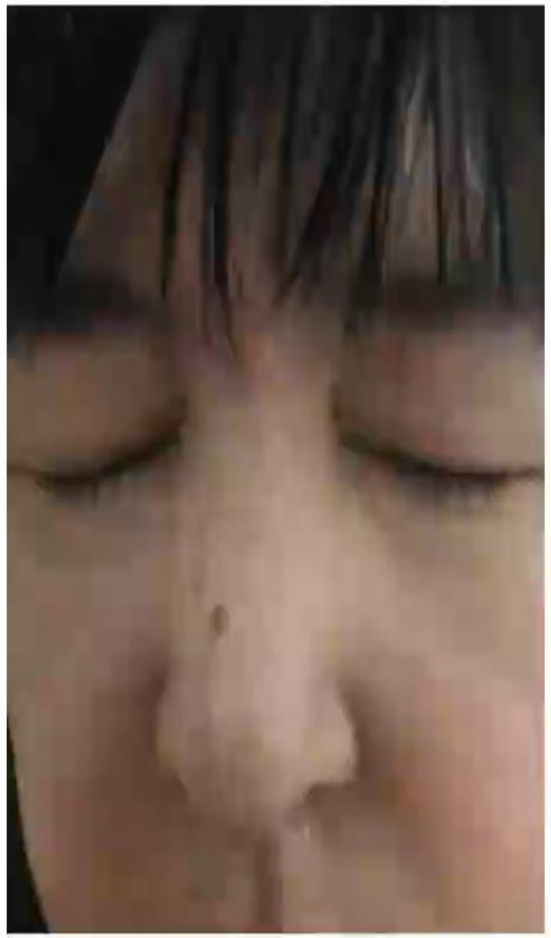
- Muscular dystrophy (DMD/BMD, FSHD, LGMD, EDMD, Distal myopathy, Congenital MD, Myofibrillar myopathy)
- **Congenital myopathy**
- Metabolic myopathies

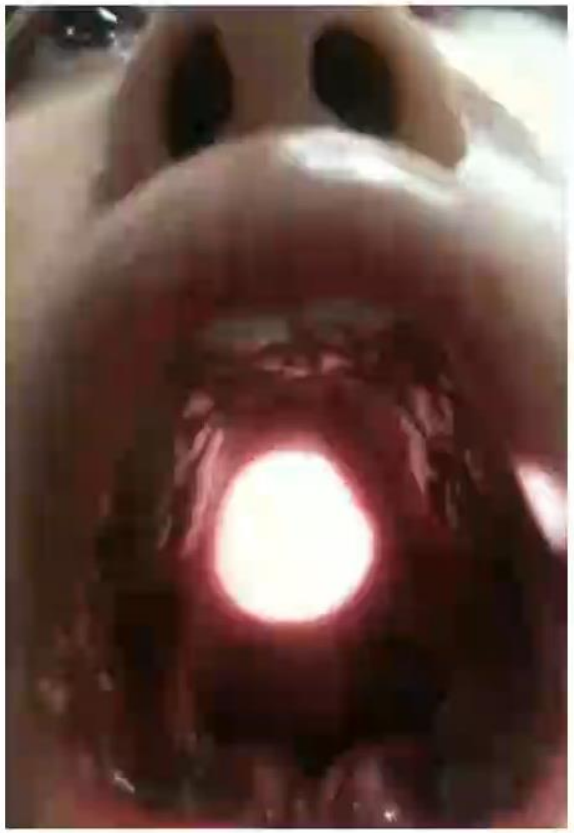
  (disorder of glycogen metabolism, fatty acid metabolism, ,

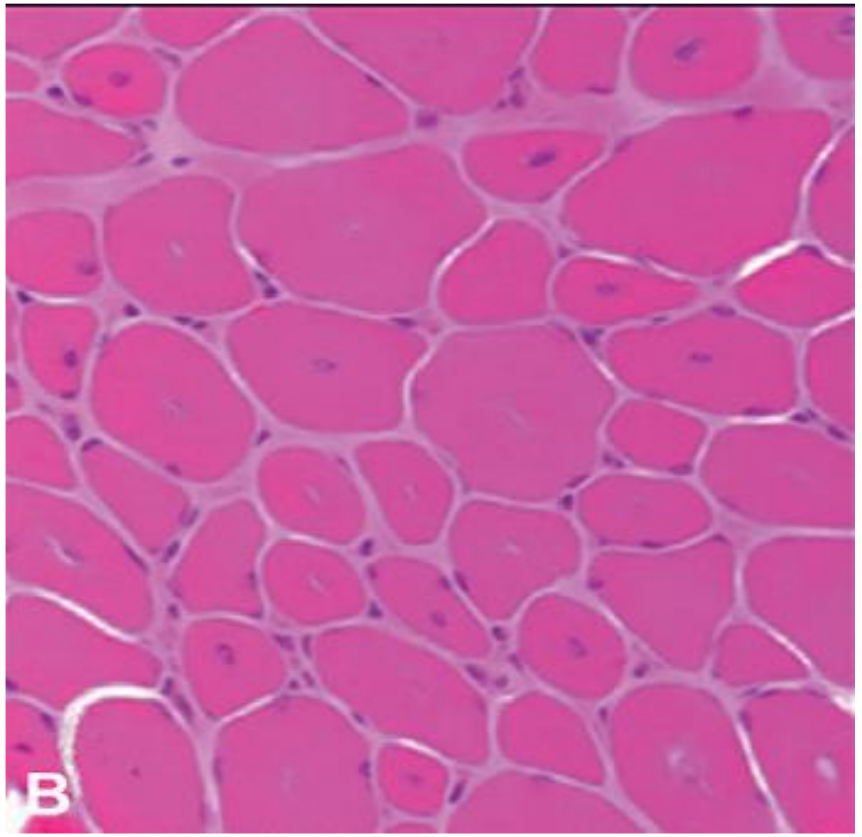
  Mitochondrial myopathies)
- Myotonic disorders and Channelopathies



Myopathy







Congenital myopathy (Centronuclear myopathy)

Courtesy Prof T Umapathi

CONGENITAL MYOPATHIES (CM)

- **Long, narrow face and high arched palate** are common.
- CK: normal to five-fold
- EMG is typically normal or myopathic
- Usually **nonprogressive or slow progression**
- **Specific muscle biopsy features**: cores in central core disease, nemaline rods in nemaline myopathy (usually required)
- Gold standard: **Genetic test** (large number of genes are involved)

Congenital myopathies (CM)

Handbook of Clinical Neurology, Vol. 113 (3rd series)

Congenital fiber type disproportion
TPM3, TPM2, ACTA1, RYR1

Congenital myopathies with protein aggregates

Nemaline myopathy
ACTA1, NEB, TPM2, TPM3, CFL2, TNNT1, KBTBD13

Cap disease
TPM2, TPM3, ACTA1

Actinopathies
ACTA1

Myosin-storage myopathy
MYH7

Congenital myopathies with cores

Central Core Disease
RYR1

Multi-minicore
RYR1, SEPN1

Congenital myopathies with central nuclei

X-linked Myotubular myopathy
MTM1

AD-Centronuclear myopathies
DNM2

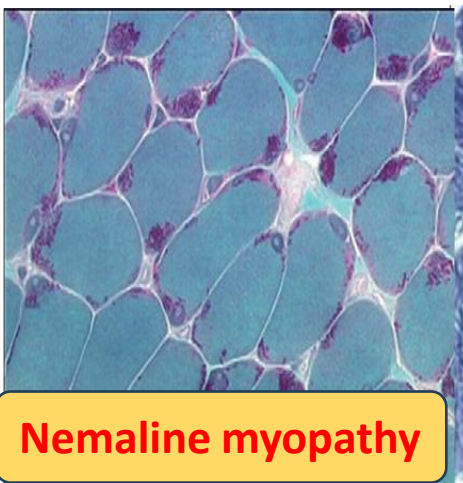
AR-Centronuclear myopathies
BIN1

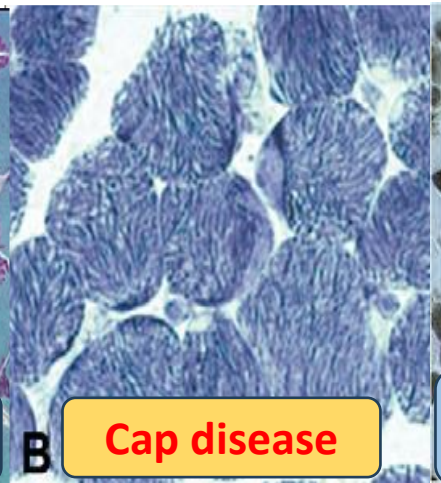
"Necklace" fibers myopathy
MTM1

AR-CM with large areas of myofibrillar disorganization
RYR1

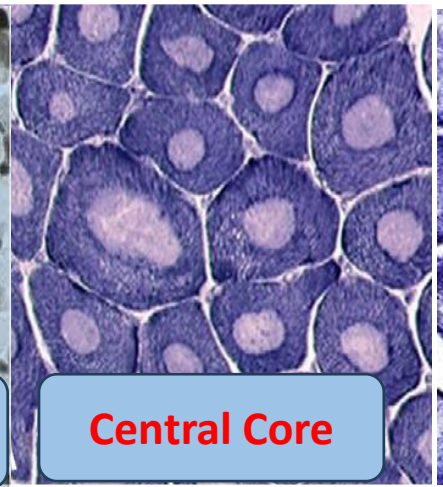
Core-rod myopathy
RYR1, NEB, KBTBD13

CM with nuclear internalization and structure disorganization
RYR1

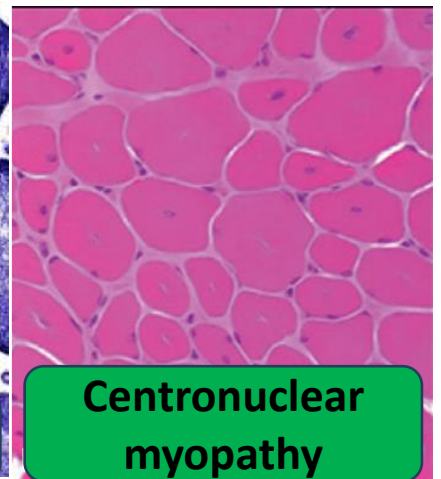

Nemaline myopathy


B Cap disease


Congenital fibre type disproportion


Central Core


Multiminicore

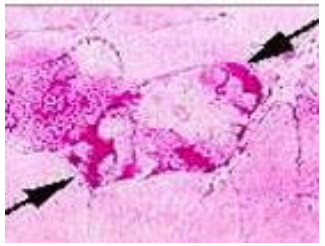

Centronuclear myopathy

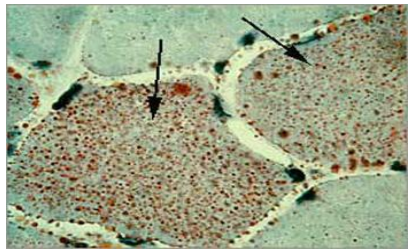
INHERITED MYOPATHIES

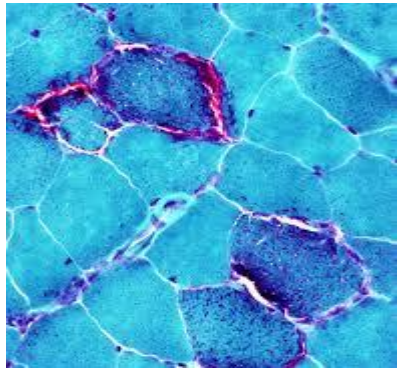
- Muscular dystrophy (DMD/BMD, FSHD, LGMD, EDMD, Distal myopathy, Congenital MD, Myofibrillar myopathy)
- Congenital myopathy
- **Metabolic myopathies (disorder of glycogen metabolism, fatty acid metabolism, Mitochondrial myopathies)**
- Myotonic disorders and Channelopathies

METABOLIC MYOPATHIES

- **Glycogen storage diseases (Pompe, McArdle):** short high-intensity exercise trigger muscle cramps, fatigue and pigmenturia, weakness, hepatosplenomegay, abn ischemic exercise test, measure specific enzyme (myophosphorylase, phosphofructokinase) deficiencies, muscle biopsy-vacuoles containing PAS-positive material, Enzyme replacement therapy: Alglucosidase alfa, Avalglucosidare alfa-ngpt
- **Lipid Storage Disorders:** trigger- prolonged exercise, cardiomyopathy, raised CK, lactate, abnormal lipid deposits in fibres with oil-red-O stain
  - Carnitine Palmitoyltransferase (CPT) Deficiency: (Tx- high dosage L-carnitine)
  - Myoadenylate Deaminase Deficiency (MADD)
  - Neutral Lipid Storage Disease (NLSD-M)
- **Mitochondrial disorders** (Muscle Biopsy: ragged red fibers)
  - Kearns-Sayre Syndrome (KSS)
  - MELAS: Mitochondrial encephalopathy, lactic acidosis, and stroke-like
  - Vitamin supplements: Co-factors and vitamins like thiamine, riboflavin, ubiquinone (Coenzyme Q10), L-creatine, L-Arginine, L-carnitine







A NEAR MISS TO BE TREATABLE: NEURAL LIPID STORAGE DISEASE WITH MYOPATHY IN A MYANMAR LADY

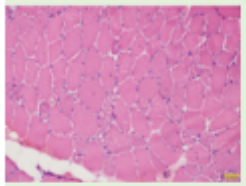
Zin Phyu Tun[1], Htwe Htwe Lin[2], Ohnmar[1], Myo Khaing[2], Moe Moe Zaw[2], Win Min Thit[1]
[1]Department of Neurology, University of Medicine 1/Yangon General Hospital, Yangon, Myanmar
[2]Department of Neurology, University of Medicine Mandalay/Mandalay General Hospital, Mandalay, Myanmar

BACKGROUND

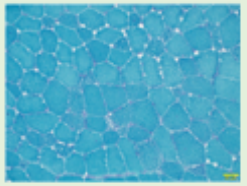
Neutral lipid storage disease with myopathy (NLSDM) is a rare autosomal recessive disorder of neutral lipid metabolism caused by mutations in the PNPLA2 gene which encodes the adipose triglyceride lipase (ATGL), resulting in the accumulation of triglycerides (TG) in various tissues of the body. Clinical manifestations include slowly progressive myopathy, which can be either proximal- or distal-dominant and cardiomyopathy which is exclusively found in almost half of the patients with NLSDM. We describe the clinical and genetic findings in a Myanmar patient with NLSDM caused by PNPLA2 gene mutation.

CASE REPORT

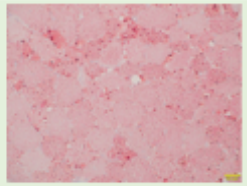
A 32-year old lady presented with right arm weakness at age 27 which was gradually progressive and at age 28, left arm and both lower limbs became weak. She emphasized her weakness worsened about 15-30 minutes after walking. Muscle weakness and atrophy were asymmetrical and proximal dominant. Neck muscles were also involved. No ocular, bulbar, muscle pain or sensory symptoms. She had history of ICD implantation at age 27 because of arrhythmia. Parents were healthy and non-consanguineous. She had normal birth history and milestones. Her elder sister had similar muscle weakness and heart disease. Serum creatinine kinase was 851 U/L. Left rectus femoris muscle biopsy revealed myopathic changes with lipid droplets in almost all fibers predominantly in type 1 fibers indicating lipid storage myopathy..



Hematoxylin and Eosin (HE)



mGT



oil-red O

ATPase

At that point, we were quite happy because our differential diagnoses were (1) primary carnitine deficiency which would show dramatic improvement with high-dose oral L-carnitine supplementation, (2) multiple acyl-coenzyme A dehydrogenase deficiency (MADD) which is riboflavin responsive and (3) neutral lipid storage disease with myopathy (NLSDM) which has no effective treatment up to now, which mean 2/3 would be treatable. So, we performed biochemical assay for fatty acid beta-oxidation pathway and genetic analysis which showed that carnitine palmytoyl transferase II and B oxidative enzymatic activities were normal and there was homozygous mutation in PNPLA2 gene in exon 4, c.478_479insCTCC (p.Q160Pfs) which confirmed neural lipid storage disease with myopathy

DISCUSSION

Lipid storage myopathy (LSM) is pathologically characterized by prominent lipid accumulation in muscle fibers due to lipid dysmetabolism. There are only four types of genetically diagnosable LSMs: primary carnitine deficiency (PCD), multiple acyl-coenzyme A dehydrogenase deficiency (MADD), neutral lipid storage disease with ichthyosis, and neutral lipid storage disease with myopathy. Making an accurate diagnosis, by specific laboratory tests including genetic analyses, is important for treatment of patients because carnitine for PCD and riboflavin for RRMADD have demonstrated excellent efficacy in eliminating the clinical symptoms. Although no specific therapeutic management is available for NLSD so far, accurate diagnosis is necessary to predict disease course, to provide genetic counseling, and to advance further research. To our knowledge, this is the first genetically confirmed NLSDM patient in Myanmar. Moreover, in the literature, forty six NLSDM patients have been clinically and genetically reported.

REFERENCES

1. Wen-Chen Liang & Ichizo Nishino (2011) Lipid Storage Myopathy. Curr Neurol Neurosci Rep. 11: 97–1032.
2. Sara Missaglia, Lorenzo Maggi, Marina Mora, Sara Gibertini, Flavia Blasevich, Piergiuseppe Agostoni, Laura Moro, Denise Cassandrini, Filippo Maria Santorelli, Simonetta Gerevini, Daniela Tavian (2017) Late onset of neutral lipid storage disease due to novel PNPLA2 mutations causing total loss of lipase activity in a patient with myopathy and slight cardiac involvement.

- A 32 year old lady
- Onset: 27 years, gradually progressive right arm weakness
- 28 years: Left arm and both lower limbs weakness
- weakness worsen about 15 minutes after walking
- Muscle weakness and atrophy were asymmetrical and proximally dominant.
- Neck muscle involvement was also noticed
- No ocular, bulbar, muscle pain, sensory signs and symptoms
- Past med history of ICD implantation at age 27 because of arrhythmia due to HOCM.
- Similar muscle weakness was present in her elder sister, normal birth history and milestones, non-consanguineous Myanmar parents.
- CK 851 U/L (normal range 0-170 U/L).
- Left rectus femoris muscle biopsy: myopathic changes with **lipid droplets** in almost all fibers (lipid storage myopathy)
- Carnitine palmytoyl transferase II and B oxidative enzymatic activities were normal.
- Sequencing of PNPLA2 gene revealed a **homozygous mutation in exon 4, c.478_479insCTCC** (p.Q160Pfs).

INHERITED MYOPATHIES

- Muscular dystrophy (DMD/BMD, FSHD, LGMD, EDMD, Distal myopathy, Congenital MD, Myofibrillar myopathy)
- Congenital myopathy
- Metabolic myopathies (disorder of glycogen metabolism, fatty acid metabolism, Mitochondrial myopathies)
- **Myotonic disorders and Channelopathies**

MYOTONIC DISORDERS AND CHANNELOPATHIES

- **Periodic paralysis**
  - Hypokalemic Periodic paralysis
  - Hyperkalemic Periodic paralysis
  - Andersen-Tawil syndrome
- **Dystrophic myotonias**
  - Myotonic dystrophy type I
  - Myotonic dystrophy type II
- **Nondystrophic myotonias**
  - Paramyotonia congenita
  - Myotonia congenita (Thomsen disease, Becker disease)

Myotonic disorders

MYOTONIC DISORDERS AND CHANNELOPATHIES

	HypoKPP	HyperKPP
Age at onset	2nd decade	1st decade
Duration of attack	Hours–days	Min–hours
Severity of attack	Mod–severe	Mild–mod
Triggers	Postexercise, CHO load	Postexercise, fasting, K load
Myotonia	Absent	Present
Serum K^+	Usually low	Normal or high
Progressive weakness	Some patients	Some patients
Treatment for weakness	CAI	CAI
Treatment for myotonia	N/A	Mexiletine

18 years old lady

- **Periodic paralysis** with onset 11 years of age, 1-2/month
- weak at rest after prolonged standing or walking, each attack 3 days but recover after 5-10 days, palpitations +, responding to acetazolamide
- **Short stature, Clinodactyly, micrognathia,** normal IQ, MMSE 30
- **Neck Flexion 4, Hip F and E 4**, rest 5
- K 4.2 after episode
- CK 48, EMG: mildly myopathic MUP
- **Long Exercise test : positive**
- **Holter: arrhythmia, frequent non sustained polymorphic VT**
- Genetic test: KCNJ2 NM_000891.2 Ex2 c.898G>C (p.G300R)
- **Mother has similar anomaly and mutation**

Anderson-Tawil Syndrome

Courtesy Col Prof Nwe Nwe Win

MYOTONIC DISORDERS

- **Myotonic dystrophy type 1 (DM1),** most common, unstable expansion of CTG repeat in DMPK gene, distal wasting
- **Myotonic dystrophy type 2 (DM2)** proximal mytonic myopathy- CCTG tetraplet repeat
- **Myotonia congenita AD (Thomsen's** disease): muscular
- **Becker type** (AR generalized myotonia): muscular

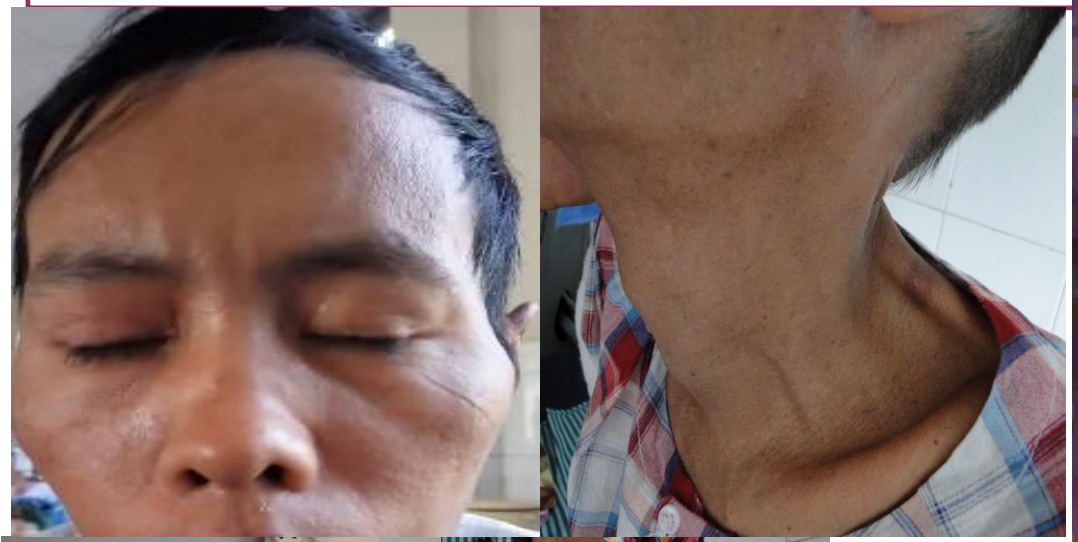
Cl channelopathy

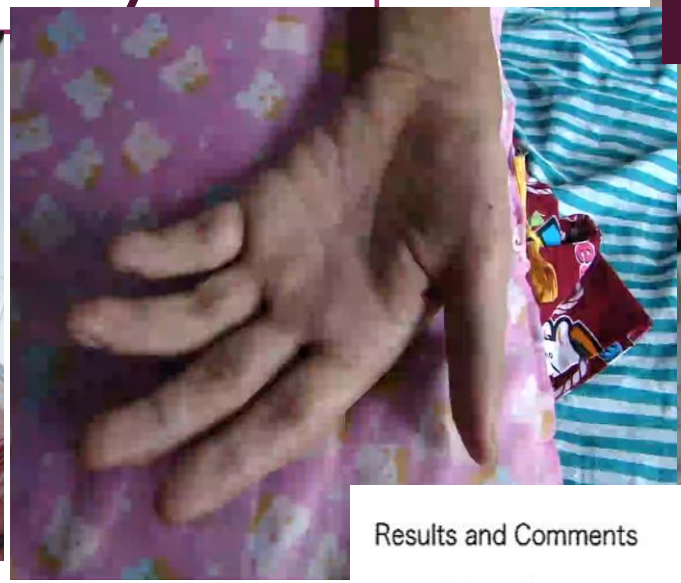
- **Paramyotonia congenita** (Na channelopathy): myotonia in cold climate
- Familial hyperkalemic periodic paralysis
- Treatment: Na channel blockers- mexiletine, phenytoin, carbamazepine

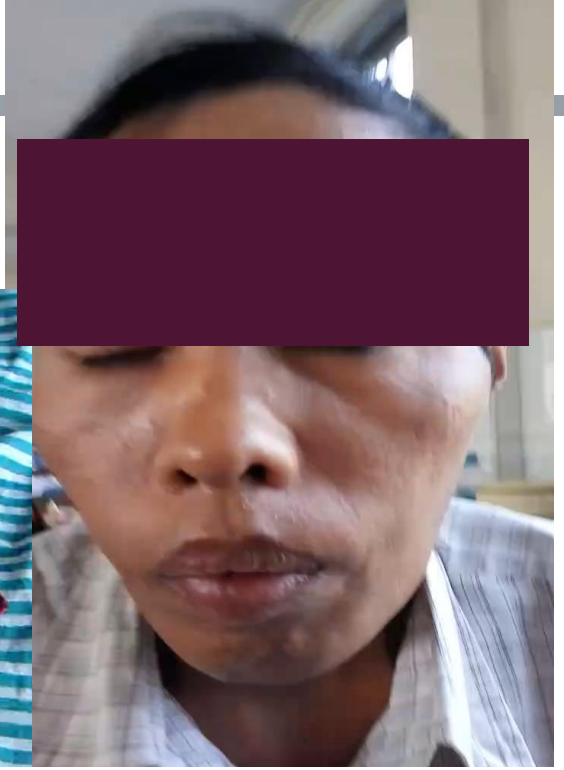
Na channelopathy

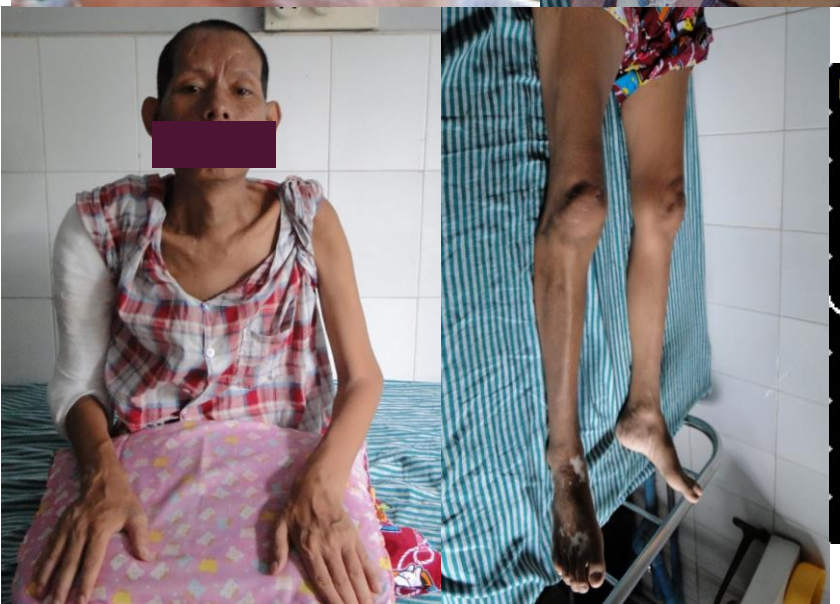
Adult-onset Myotonic dystrophy Type 1 (DM1)

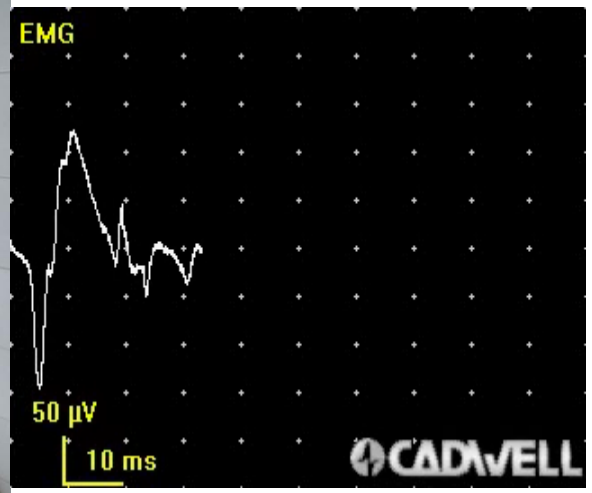
Father & son with distal myopathy











Results and Comments

We performed genetic test for myotonic dystrophy.

<< Myotonic dystrophy type 1 (DM1) >>

[Method]

Analysis of CTG repeats of DMPK gene by TP-PCR (J. Med. Genet. 1996;33:1022-1026).

[Results]

A normal allele $(CTG)_5$ and the other mutated allele $(CTG)_{>100}$ with abnormal repeat expansion were detected. The repeats size is more than 100 at least, though the exact number can not be determined due to a technical restriction of TP-PCR methodology.

[Conclusion]

The patient is suffering from myotonic dystrophy type 1.

Table 1. Clinical, Laboratory, and Genetic Abnormalities of Myotonic Dystrophy Type 1(DM1), and Myotonic Dystrophy Type 2 are Summarized in the Table. To Date, There is No Case Report of DM2 in Japan

	DM1 myotonic dystrophy type 1	DM2 (no case report in Japan) myotonic dystrophy type 2 (proximal myotonic myopathy)
Myotonia	+	+
Cataract	+	+
Muscle weakness	+from distal muscles	+proximal muscles
Muscle pain	–	+
Cardiac arrhythmia	++	+
Muscle enzyme elevation	+	+
Mental disturbance	+	+
Inheritance	autosomal dominant	autosomal dominant
Chromosome locus	19q 13.3	3q 21.3
Genetic abnormality	(CTG)n expansion	(CCTG)n expansion

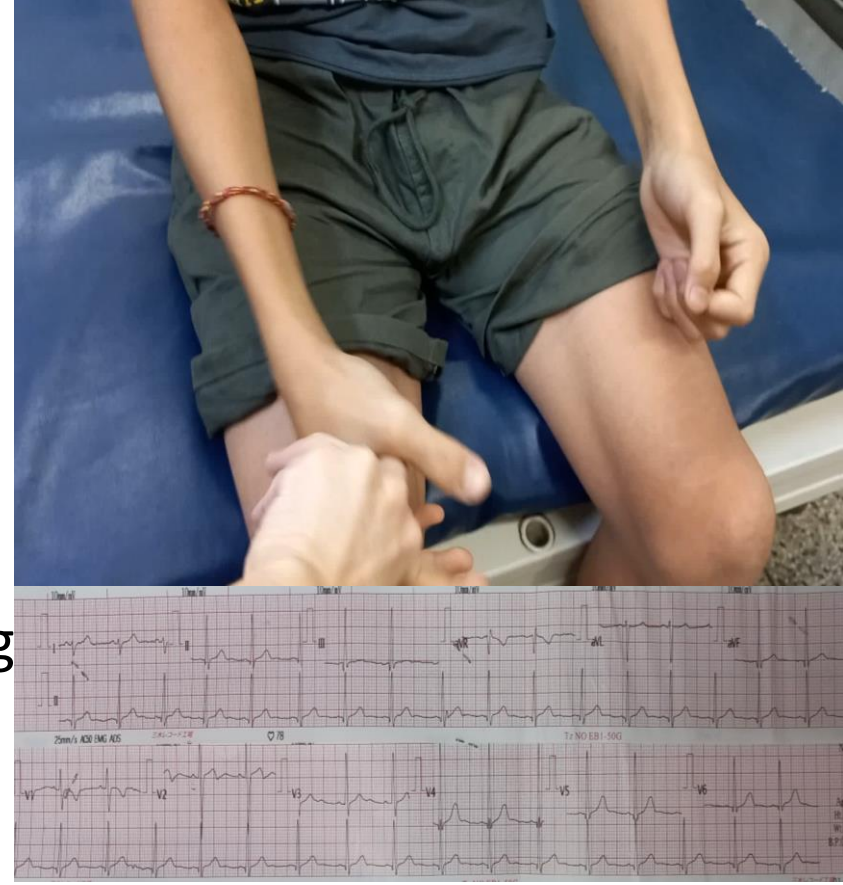
Internal Medicine Vol.44, No. 10 (Oct 2005)

MYOTONIA CONGENITA

- Autosomal recessive (Becker disease) or an autosomal dominant (Thomsen disease)
- Muscle stiffness onset - childhood
- Striated muscle groups including the extrinsic eye muscles, facial muscles, and tongue
- Muscle stiffness (myotonia) or cramps beginning in early childhood
- Alleviation of stiffness by brief exercise (known as the "warm-up" effect)
- Myotonic contraction elicited by percussion of muscles
- Muscles are usually hypertrophic
- CK: ≤3-4x ULN
- Molecular genetic testing: heterozygous CLCN1 or biallelic CLCN1 pathogenic variants
- Treatment: sodium channel blockers- mexiletine, lamotrigine carbamazepine, or phenytoin

A 13-year old boy with muscle stiffness

- Birth history - 3 lb (pre-mature delivery), **Delayed milestones**
- 5 years of age – muscle **stiffness**, difficulty in climbing stairs
- 6-7 yr - dropping of objects
- 11 yr - frequent fell, stiffness improve after repeated exercise
- Speech - difficult to start but improved after prolonged talking
- Exam: **Grip and percussion myotonia**
- No family history, no parental consanguinity
- CK- 375, **EMG: Myotonia, myopathic MUP**
- ECG, CXR: normal



No.	Gene	Zygosity	RefSeq numbers	Exon /Intron	Variant	HGMD	gnomAD_EAS	ToMMo	Polyphen2	Mutation taster	Classification*
1	*CLCN1*	hetero	NM_000083.3	exon15	c.1652G>A (p.G551D)	Myotonia, Thomsen Kumar (2010) MUSC NERVE 41, 412	.	.	Probably damaging	Disease causing	**Pathogenic**

Extracted are the variants within exonic or exon boundary region and with frequency less than 0.01 in the public database (gnomAD, ESP6500, 1000genomes, ToMMo) and in house data. We also refined the data based upon clinicopathological phenotype including inheritance pattern.

※HGMD ：Human Gene Mutation Database 2022.4

CLCN1 gene mutation

*: ACMG guideline [Richards S, et al. Genet Med. 2015;17:405-24.] and ACGS Best Practice Guidelines [https://www.acgs.uk.com/news/acgs-best-practice-guidelines-for-variant-classification-2019/].

The variant was confirmed by Sanger-sequencing.

Interpretation

Previously reported variant was found in heterozygous model in *CLCN1* gene which may be the cause of the disease if phenotype is compatible. Please check whether the clinical, physiological, and radiological manifestations of the patient accord with previously reports in the above gene.

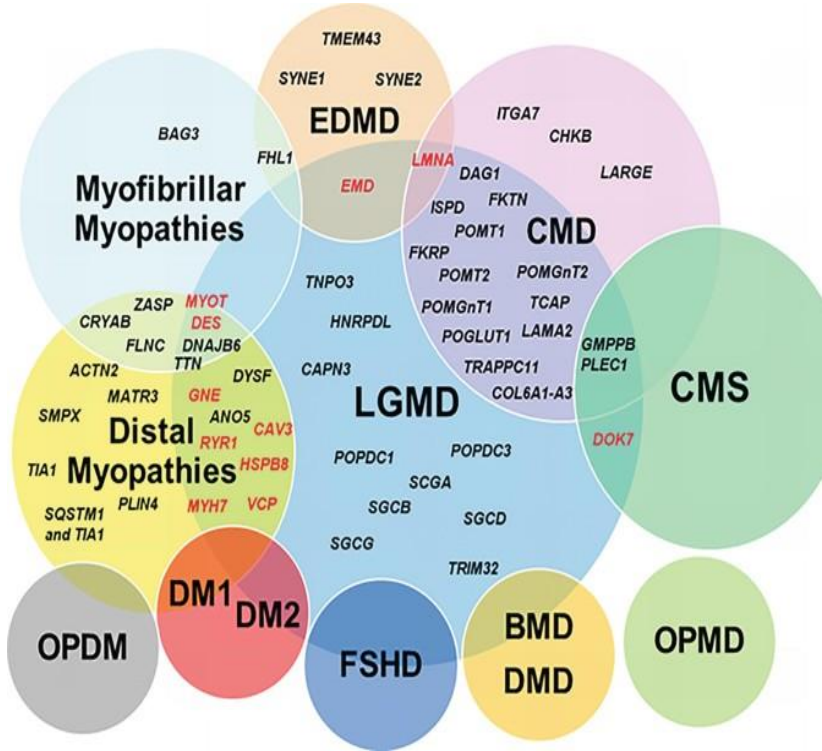
Myotonia congenita AD (Thomsen's disease)

INHERITED MYOPATHIES

- Muscular dystrophy (DMD/BMD, FSHD, LGMD, EDMD, Distal myopathy, Congenital MD, OPMD)
- Congenital myopathy
- Metabolic myopathies

  (disorder of glycogen metabolism, fatty acid metabolism,

  Mitochondrial myopathies)
- Myotonic disorders and Channelopathies



Adult inherited myopathies from Myanmar (2016-2024)

1. DYSTROPHINOPATHY (17)
2. MYOTONIC DYSTROPHY(12)
3. FSHD (10)
4. LGMD AND DISTAL MYOPATHIES
   A. GNE myopathy (6)
   B. Calpainopathy (5)
   C. Dysferlinopathy (5)
   D. LAMA2 myopathy (4)
5. OTHERS (21)

2016 -2024	DMD BMD	DM1	FSHD	Others
2016 (17)	6	3	3	Dysferlinopathy, Calpainopathy Laminopathy, GNE, Ulrich MD
2017 (4)	1	0	1	Myotonia congenita, NLSDM
2018 (20)	7	2	4	2 Dysferlinopathy, GNE, FHL1 myopathy, MYH7-related myopathy OPMD, CMS
2019 (6)	1	1	0	2 Calpainopathy Centronuclear myopathy Andersen-Tawil syndrome
2020-2022 (14)	1	1	0	2 GNE, 4 LAMA2, 2 CAPN3, 1 ANO5, COL6A, CAV3, DES
2023-2024 (19)	1	5	2	2 Dysferlinopathy, 2 GNE, myotonia congenita, OPMD, 4 LAMA2, a-dystroglycanopathy
Total (80)	**17**	**12**	**10**	**41**

SOME TREATABLE GENETIC MYOPATHIES

DMD	Deflazacort/Prednisone, Exon-skipping therapies, gene therapies
Pompe Disease	Enzyme Replacement Therapy (ERT): Alglucosidase alfa (Myozyme,Lumizyme)
Carnitine Palmitoyltransferase II Deficiency	L-carnitine, High-carbohydrate, low-fat diet
Primary Carnitine Deficiency	Oral L-carnitine supplementation (lifelong)
Multiple Acyl-CoA Dehydrogenase Deficiency	High-dose riboflavin (vitamin B2) carnitine and CoQ10
McArdle Disease-Glycogen Storage Disease Type V	High-protein diet, Pre-exercise sucrose
Mitochondrial myopathies	Coenzyme Q10, L-carnitine, riboflavin, creatine

TAKE HOME MESSAGES

- Selective muscle involvement is well known in muscular dystrophies and so we learn to get clinical diagnosis from pattern and signs
- Clinical pattern, muscle biopsy and genetic testing are crucial for diagnosing genetic myopathies.
- Remember that acquired and some genetic myopathies are treatable.

  Advancements in genetic therapies offer hope for better treatments.
- Identifying the causative gene prevents patients from visiting multiple clinics in search of a diagnosis, helps predict prognosis, and guide management.

THANK YOU FOR KIND ATTENTION!