Overview of Myopathic Disorders

SYED AHMED

Weakness and Pattern Recognition

	Prox	Dis	Asymm	Symm	Sensory Symptoms	Severe Proprioceptive Loss	UMN Signs	Autonomic Symps/Signs	Diagnosis
Pattern 1 - Symmetric prox & Distal weakness w/sensory loss	+	+		+	+				GBS/CIDP
Pattern 2 - Distal sensory loss with/without weakness		+		+	+				CSPN, metabolic, drugs, hereditary
Pattern 3 - Distal weakness with sensory loss		+	+		+				Multiple – Vasculitis, HNPP, MADSAM, infection Single – Mononeuropathy, radiculopathy
Pattern 4 - Asymmetric prox & distal weakness w/sensory loss	+	+	+		+				Polyradiculopathy, plexopathy
Pattern 5 - Asymmetric distal weakness w/out sensory loss		+	+				+/−		+ UMN – ALS Pure UMN - PLS - UMN – MMN, PMA, MAMA, BAD, LAD
Pattern 6 - Symmetric sensory loss & upper motor neuron signs		+		+	+	+	+		B12 defic; Copper deficiency, Friedreich's, adrenomyeloneuropathy
Pattern 7* Symmetric weakness without sensory loss	+/−	+		+					Prox & Distal SMA Distal Hereditary motor neuropathy
Pattern 8* Focal midline proximal symmetric	+ Neck/extensor + Bulbar			+ +			+ +		ALS
Pattern 9 - Asymmetric proprioceptive loss w/out weakness			+		+	+			Sensory neuronopathy (ganglionopathy)
Pattern 10 - Autonomic dysfunction								+	HSAN, diabetes, GBS, amyloid, porphyria, Fabry's

Neuromuscular Classification

Muscular dystrophies
1 Congenital muscular dystrophy
2 Duchenne muscular dystrophy
3 Becker muscular dystrophy
4 Dystrophinopathy
5 Facioscapulohumeral dystrophy
6 Limb girdle muscular dystrophy
7 Emery-Dreifuss muscular dystrophy
8 Distal myopathy
9 Oculopharyngeal muscular dystrophy
10 Myotonic dystrophy type 1
11 Myotonic dystrophy type 2
12 Other muscular dystrophies

Myotonic and relaxation disorders
13 Thomsen type myotonia congenita
14 Becker type myotonia congenita
15 Paramyotonia congenita
16 Familial periodic paralysis
17 Other myotonic disorders

Myopathies
Congenital myopathies
18 Central core disease
19 Multiminicore disease
20 Nemaline myopathy
21 Myotubular myopathy
22 Centronuclear myopathy
23 Fibre type disproportion myopathy

Metabolic myopathies
24 Muscle glycogenosis
25 Disorders of fatty acid metabolism
26 Mitochondrial myopathy

Inflammatory myopathies
27 Polymyositis
28 Dermatomyositis
29 Inclusion body myositis

Other myopathies
30 Other myopathies

Disorder of the neuromuscular transmission
31 Myasthenia gravis
32 Congenital myasthenia
33 Lambert-Eaton syndrome
34 Other disorders of neuromuscular transmission

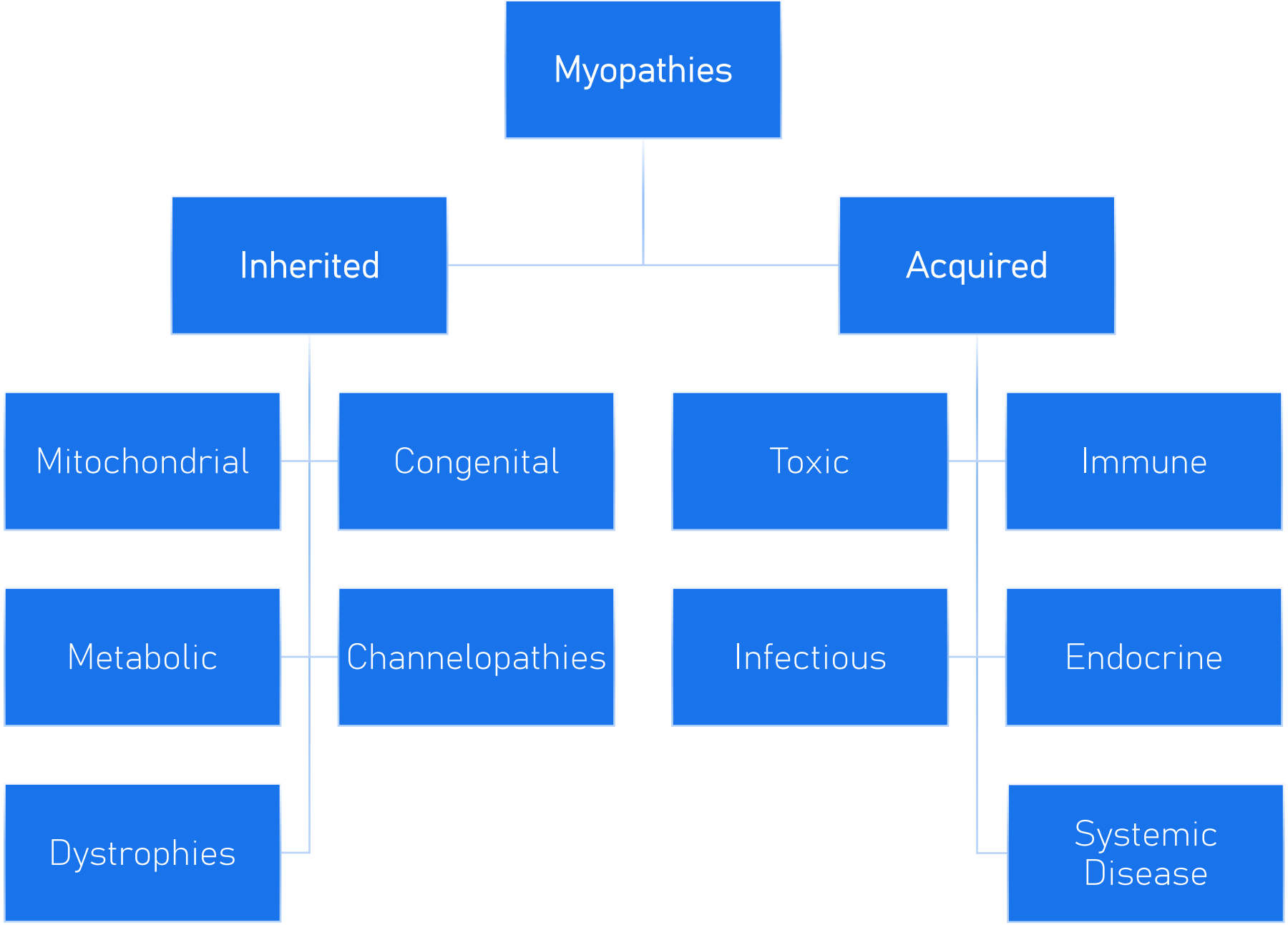
Disorder of the motor neurons
35 Amyotrophic lateral sclerosis
36 Primary muscular atrophy
37 Postpolio syndrome
38 Primary lateral sclerosis
39 Werdnig-Hoffman spinal muscular atrophy
40 Intermediate spinal muscular atrophy
41 Kugelberg–Welander spinal muscular atrophy
42 Adult spinal muscular atrophy
43 X-linked Bulbo-spinal muscular atrophy or Kennedy's disease
44 Distal spinal muscular atrophy
45 Hereditary spastic paraplegia
46 Other disorders of motor neurons

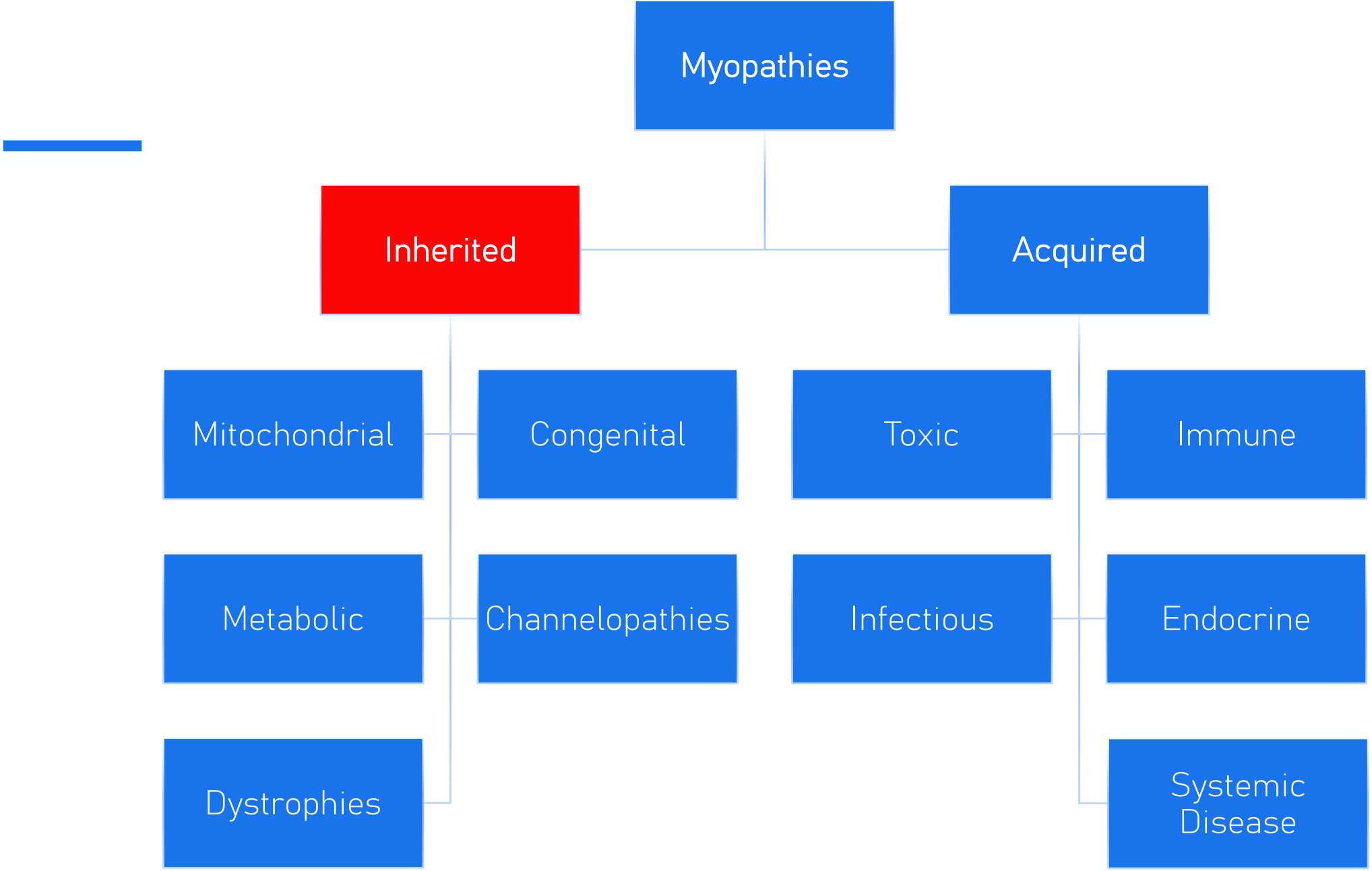
Neuropathies
Hereditary
47 Hereditary motor and sensory neuropathy
48 Hereditary neuropathy with liability to pressure palsies
49 Hereditary sensory and autonomous neuropathy

Inflammatory
50 Guillain-Barré syndrome
51 Chronic inflammatory demyelinating polyneuropathy
52 Multifocal motor neuropathy
53 Vasculitis
54 Neuropathy associated with paraproteinemia
55 Neuropathy associated with plasma cell dyscrasia
56 Amyloidosis
57 Neuropathy in systemic disease
58 Other neuropathies

Hereditary ataxias
59 Friedreich ataxia
60 Spinocerebellar ataxias
61 Other Hereditary ataxias

Various
62 Arthrogryposis multiplex congenita


Myopathies
Inherited
Acquired
Mitochondrial
Congenital
Toxic
Immune
Metabolic
Channelopathies
Infectious
Endocrine
Dystrophies
Systemic Disease


Myopathies
Inherited
Acquired
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Congenital
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Infectious
Endocrine
Dystrophies
Systemic Disease

Inherited Myopathies

- Group of disorders that are inherited and generally grouped by
  - Pattern of Weakness
    - Previously the primary method of diagnosis
    - Same phenotype by different genes
  - Defective gene/protein
  - Histopathological findings

Inherited Myopathies

- Mitochondrial
- Congenital
- Metabolic
- Channelopathies
- Muscular Dystrophy

Inherited Myopathies

- Mitochondrial
  - MELAS
  - Kearns-Sayre syndrome
  - CPEO
  - Leber hereditary optic neuropathy
- Congenital
- Metabolic
- Channelopathies
- Muscular Dystrophy

Nagy H, Veerapaneni KD. Myopathy. [Updated 2023 Aug 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562290/

Inherited Myopathies

- Mitochondrial
- Congenital
  - Nemaline
  - Core myopathy
  - Centronuclear
- Metabolic
- Channelopathies
- Muscular Dystrophy

Nagy H, Veerapaneni KD. Myopathy. [Updated 2023 Aug 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562290/

Inherited Myopathies

- Mitochondrial
- Congenital

- Metabolic
  - Lipid Myopathy
    - CPT II Deficiency
  - Glycogen storage disease
    - Pompe
    - McArdle's Disease

- Channelopathies
- Muscular Dystrophy

Inherited Myopathies

- Mitochondrial
- Congenital
- Metabolic

- Channelopathies
  - Periodic Paralysis
  - Nondystrophic Myotonias

- Muscular Dystrophy

Inherited Myopathies

- Mitochondrial
- Congenital
- Metabolic
- Channelopathies

- Muscular Dystrophy
  - Dystrophinopathies
  - Myotonic Dystrophies
  - FSHD
  - LGMD
  - OPMD

Inherited Myopathies

- Mitochondrial
- Congenital
- Metabolic
- Channelopathies
- Muscular Dystrophy

Congenital Myopathies

- Inherited disorders of inherited skeletal muscle disease
- Prevalence: 1 in 25,000 individuals
- Early infantile or childhood onset
  - Adult variants
- Weakness, hypotonia, developmental delay
- Slowly progressive
- Classic pathological features
  - Myofibrillar disorganization, central nuclei, protein aggregation
- Three groups: core, centronuclear, nemaline

► **Nemaline Myopathy**

TPM3 (autosomal dominant, autosomal recessive)

NEB (autosomal recessive)

ACTA1 (autosomal dominant, autosomal recessive)

TPM2 (autosomal dominant)

TNNT1 (autosomal recessive)

KBTBD13 (autosomal recessive)

CFL2 (autosomal recessive)

KLHL40 (autosomal recessive)

KLHL41 (autosomal recessive)

LMOD3 (autosomal recessive)

► **Central Core Myopathy**

RYR1 (autosomal dominant, autosomal recessive)

SEPN1 (autosomal recessive)

ACTA1 (autosomal dominant)

TTN (autosomal recessive)

► **Multiminicore Myopathy**

SEPN1 (autosomal recessive)

RYR1 (autosomal dominant, autosomal recessive)

MYH7 (autosomal dominant)

TTN (autosomal recessive)

► **Core-rod Myopathy**

RYR1 (autosomal dominant, autosomal recessive)

NEB (autosomal recessive)

KBTBD13 (autosomal dominant)

CFL2 (autosomal recessive)

► **Centronuclear Myopathy**

MTM1 (X-linked)

DNM2 (autosomal dominant)

BIN1 (autosomal recessive)

RYR1 (autosomal recessive)

TTN (autosomal recessive)

MTMR14 (autosomal recessive)

CCDC78 (autosomal dominant)

SPEG (autosomal recessive)

► **Congenital Fiber-type Disproportion**

ACTA1 (autosomal dominant)

SEPN1 (autosomal recessive)

TPM3 (autosomal dominant)

TPM2 (autosomal dominant)

RYR1 (autosomal recessive)

MYH7 (autosomal dominant)

► **Myosin Storage Myopathy**

MYH7 (autosomal dominant)

► **Cap Myopathy**

TPM2 (autosomal dominant)

TPM3 (autosomal dominant)

ACTA1 (autosomal dominant)

► **Zebra Body Myopathy**

ACTA1 (autosomal dominant)

► **Distal Myopathy With No Rods**

NEB (autosomal recessive)

Congenital Myopathies-Diagnosis

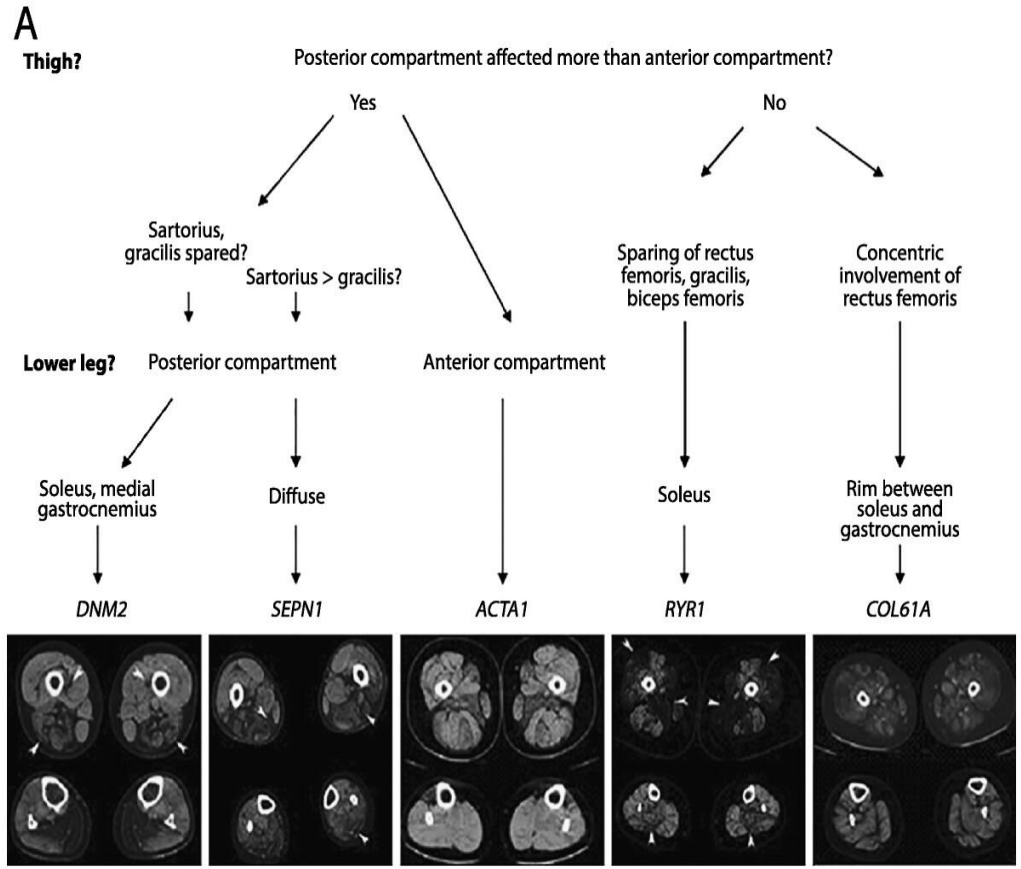
- History and Examination: Pregnancy, development, examination of parents
- Static vs progressive, symptom onset
  - Prenatal onset with reduced fetal movement and polyhydramnios
- Exam:
  - Weakness and hypotonia
  - myopathic facies, high arched palate, ophthalmoplegia, bulbar involvement, atrophy, hyporeflexia,
  - Contractures, facial dysmorphism, hip dysplasia, atrophy,
- Systemic
  - Orthopedic: spinal deformities, clubfoot
  - Cardiomyopathy
  - Malignant hyperthermia
  - Respiratory insufficiency





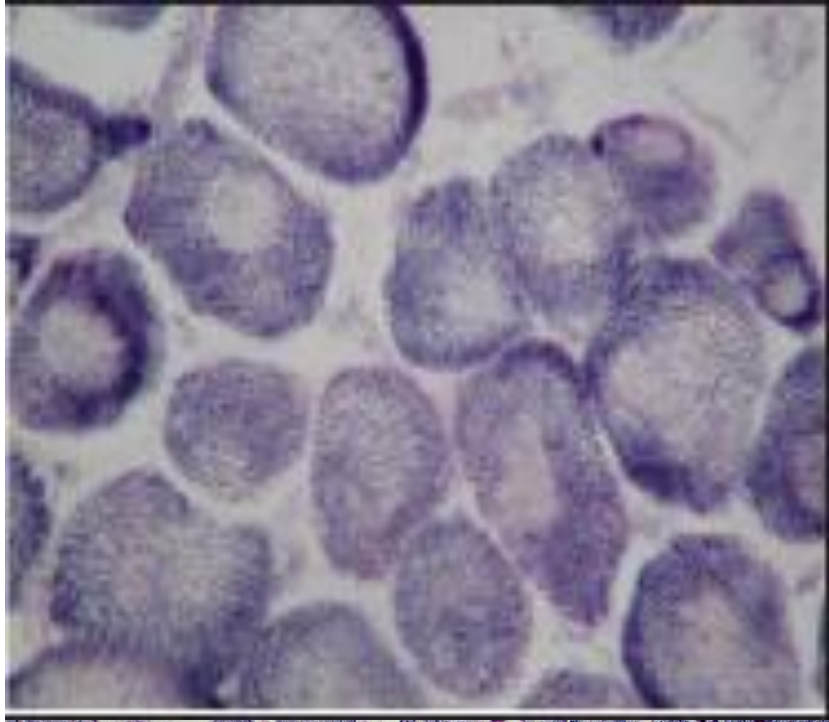
Congenital Myopathies-Diagnosis

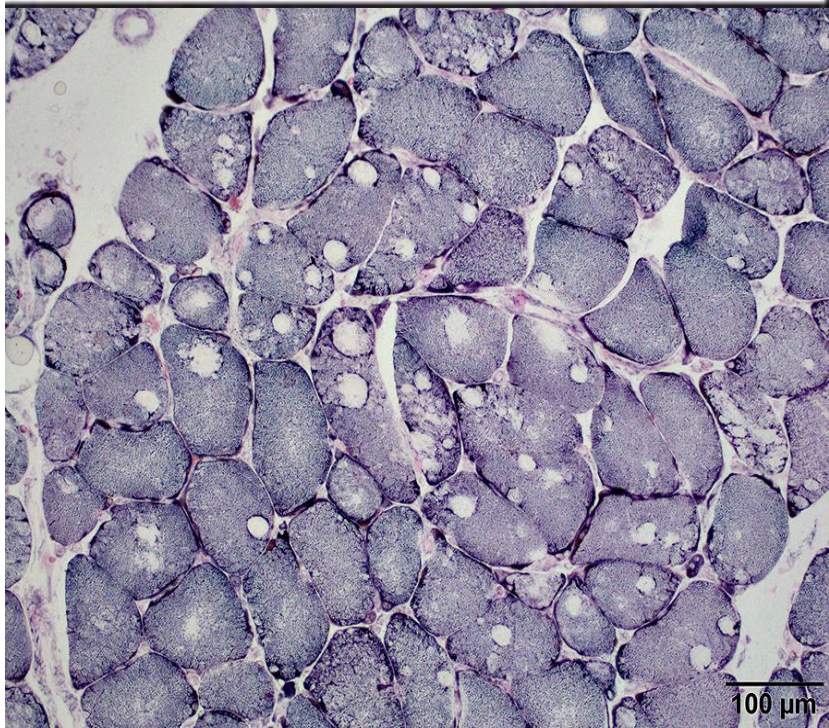
- CK
  - Normal or mildly elevated
- Electrodiagnostic studies
  - Generally normal NCS
  - EMG: Myopathic (can have neurogenic findings)
- Muscle imaging
  - Pattern of muscle involvement
    - Anterior vs posterior
    - Sparing of muscles
- Muscle biopsy
- Genetic testing



Congenital Myopathies- Core Myopathies

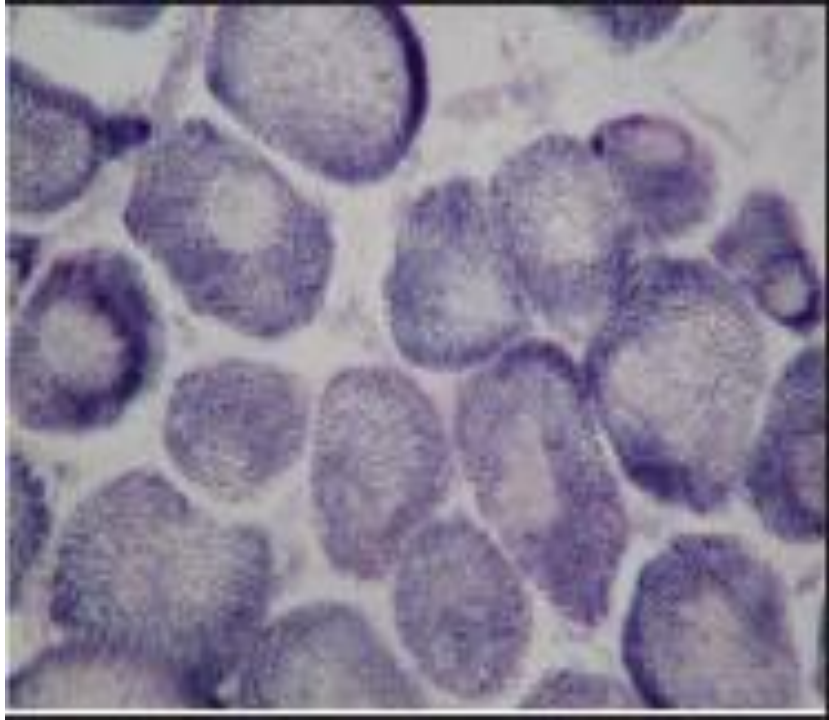
- Most common form of congenital myopathy
- Pathologically: Loss of central mitochondrial activity
- Central and multiminicore myopathies
- Mutations
  - AD/AR RYR1 Mutation
  - AR SEPN1

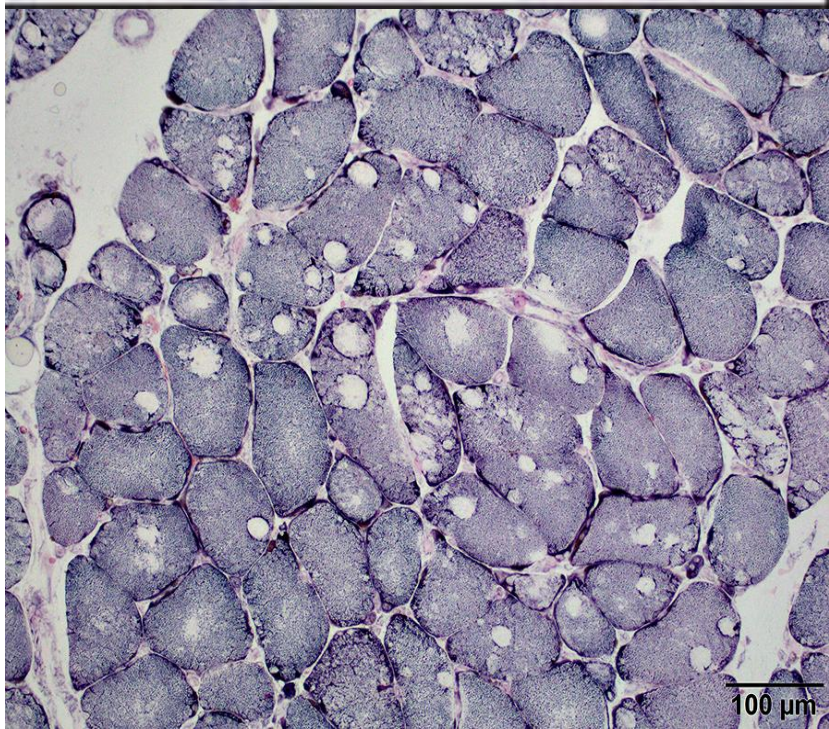




Congenital Myopathies- Core Myopathies

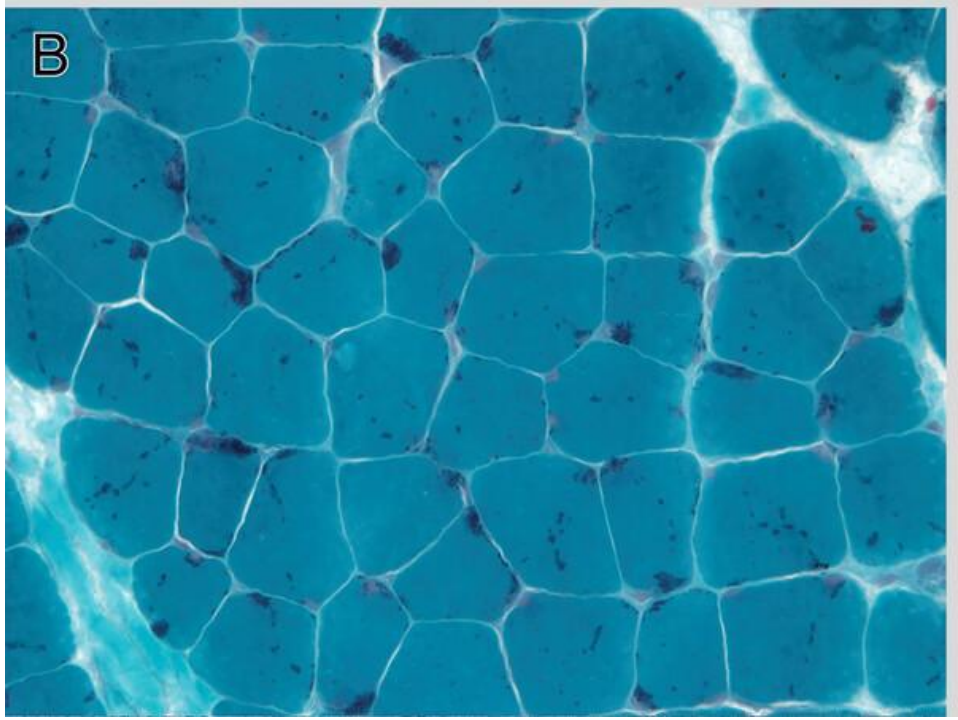
- Variable phenotypes
  - Milder phenotype: Hypotonia, joint laxity, motor developmental delays, weakness
  - Muscle stiffness, exertional myalgia, rhabdomyolysis
  - Static or slowly progressive
  - Worsens in pregnancy
- Orthopedic complications: Dislocations, hip dysplasia
- Spares posterior muscles: Selectively affected anterior/medial compartment
  - Quadriceps with sparing of rectus/gracilis
- Malignant hyperthermia: Avoid volatile anesthetics and succinylcholine

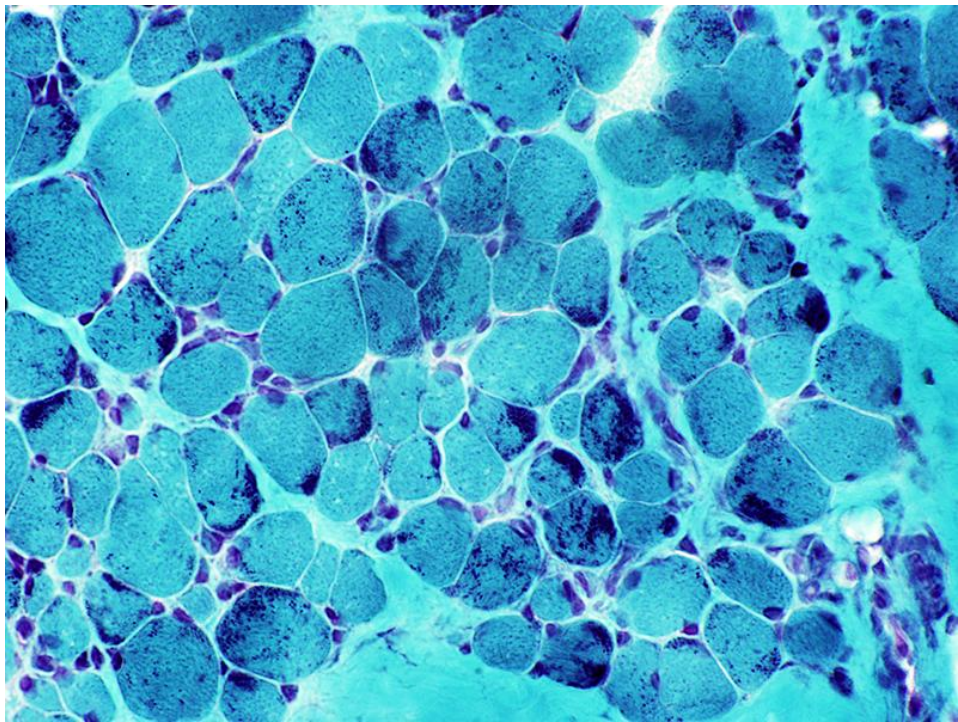




Congenital Nemaline Myopathies

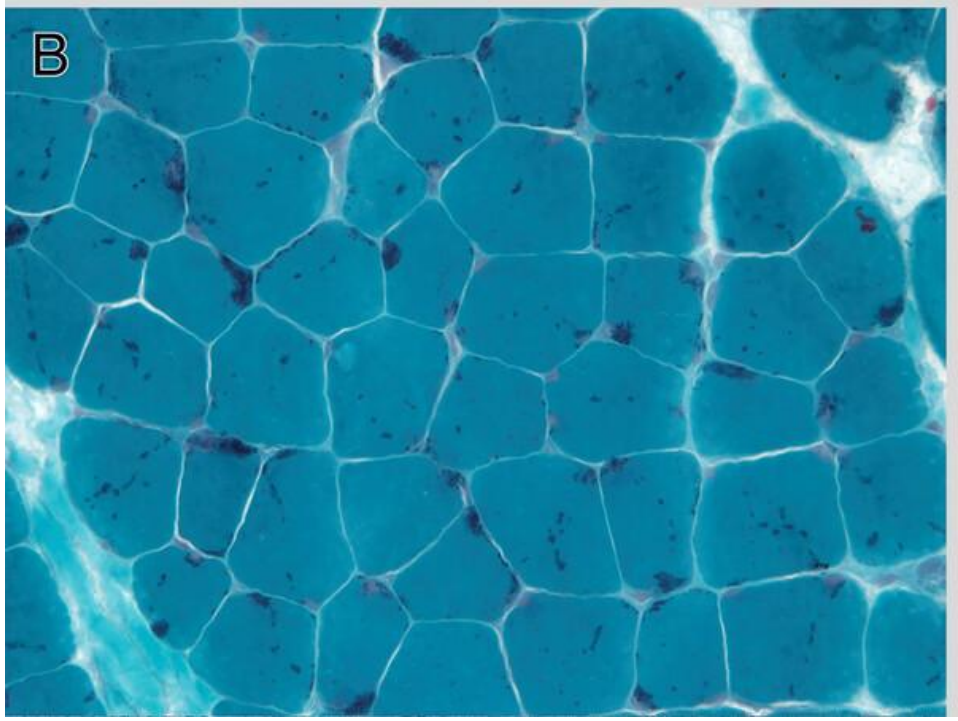
- Thread or rod like structures on biopsy
- Wide spectrum
  - Mild adult onset
    - Axial and hip girdle weakness that spread distally
    - Atypical distal forms
  - Severe congenital
    - Classic: Facial, respiratory, axial, and generalized weakness
- ACTA1 (AD), NEB (AR)1

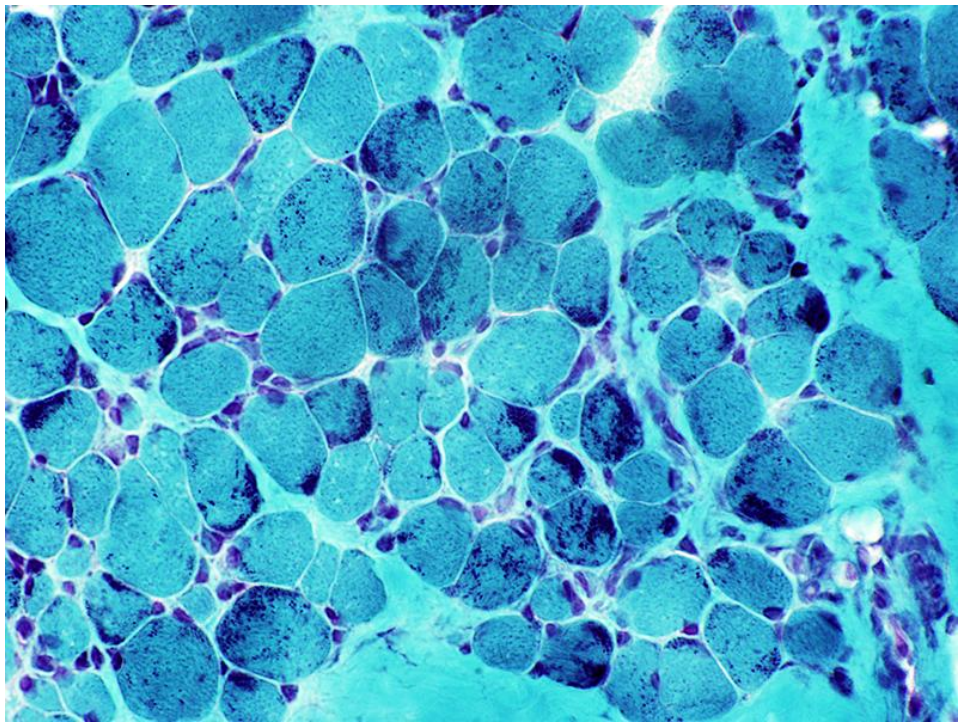




SLONM

- Sporadic Late-Onset Nemaline Myopathy
- 3rd to 9th decade of life: Mean onset 52-54 years
- Associations: HIV/Monoclonal gammopathy
- Sx
  - Limb and axial weakness
  - Proximal>Distal
  - Axial-neck weakness, camptocormia
  - Facial weakness with dysarthria, dysphagia
  - Respiratory involvement-common cause of death
  - Uncommon cardiomyopathy
- High mortality with 5-40% dying within one year
- Treatment: IVIG, prednisone





Inherited Myopathies

- Mitochondrial
- Congenital
- Metabolic
- Channelopathies
- Muscular Dystrophy

Mitochondrial Myopathies



- Diverse group of diseases that can affect skeletal muscle
- Mutation in mitochondrial or nuclear encoded proteins related to oxidative metabolism
- Can affect muscle, heart, nervous, kidneys, endocrine organs
- Skeletal muscle can be severely affected due to high oxidative demand
- Weakness, episodic symptoms (exercise intolerance, cramps, and fatigue)
- CK levels mildly elevated or normal
  - Can presents with rhabdomyolysis

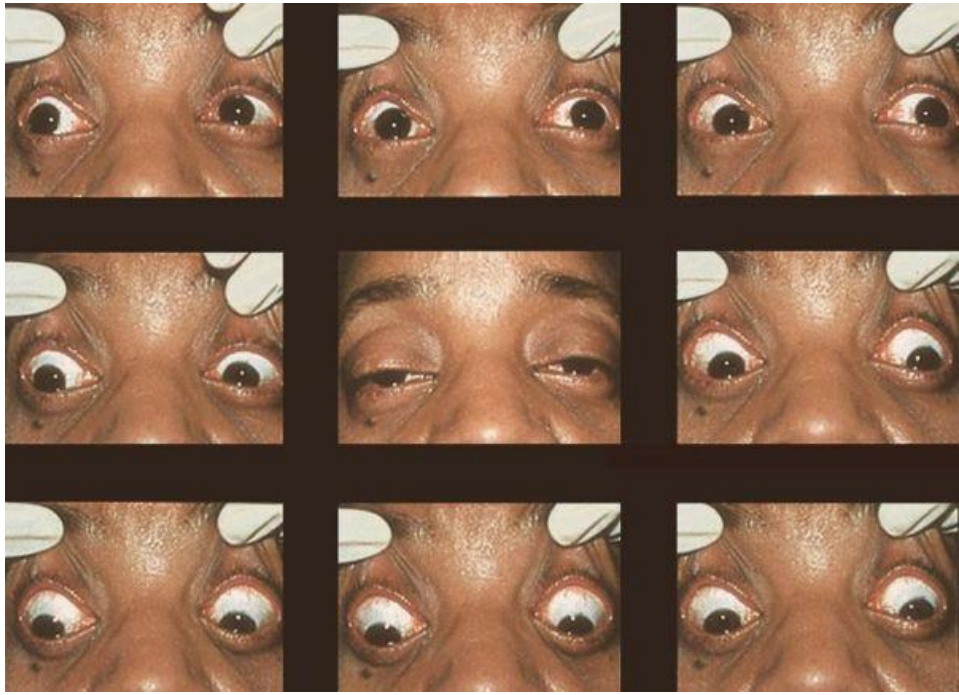
Mitochondrial Myopathies



- Prevalence: 1/5000
- Genetics: Maternal or Mendelian
- Mitochondrial heteroplasmy contributes to variable phenotypic disease presentation even within family members
  - Variable presentation but childhood onset MM have more significant weakness and systemic involvement

CPEO

- Most common presentation in adults
- Defined as:
  - Progressive ptosis and impaired mobility of the eye
  - Bilateral
  - Affected muscles are innervated by more than one nerve
  - Pupil spared
  - Gradual progression over months or year
  - No remissions/exacerbations
- No evidence of specific disorder



Mitochondrial Myopathies Syndromes

- CPEO
- MELAS
- Kearn-Sayre Syndrome
- Myoclonic Epilepsy with Ragged Red Fibers
- TK2 Deficiency

Mitochondrial Myopathies Syndromes

- CPEO
  - POLG and MT-TL1 mutation
  - AD,AR,mitochondrial
  - 20-40's
  - Ptosis, opthalmoplegia, hearing loss, weakness, dysphagia, cataracts
- MELAS
- Kearn-Sayre Syndrome
- Myoclonic Epilepsy with Ragged Red Fibers
- TK2 Deficiency

Mitochondrial Myopathies Syndromes

- CPEO
- MELAS-**mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes.**
  - MT-TL1
  - Mitochondrial inheritance
  - Stroke like episodes, seizures, hearing loss, weakness, vision changes
  - Renal impairment, diabetes
- Kearn-Sayre Syndrome
- Myoclonic Epilepsy with Ragged Red Fibers
- TK2 Deficiency

Mitochondrial Myopathies Syndromes

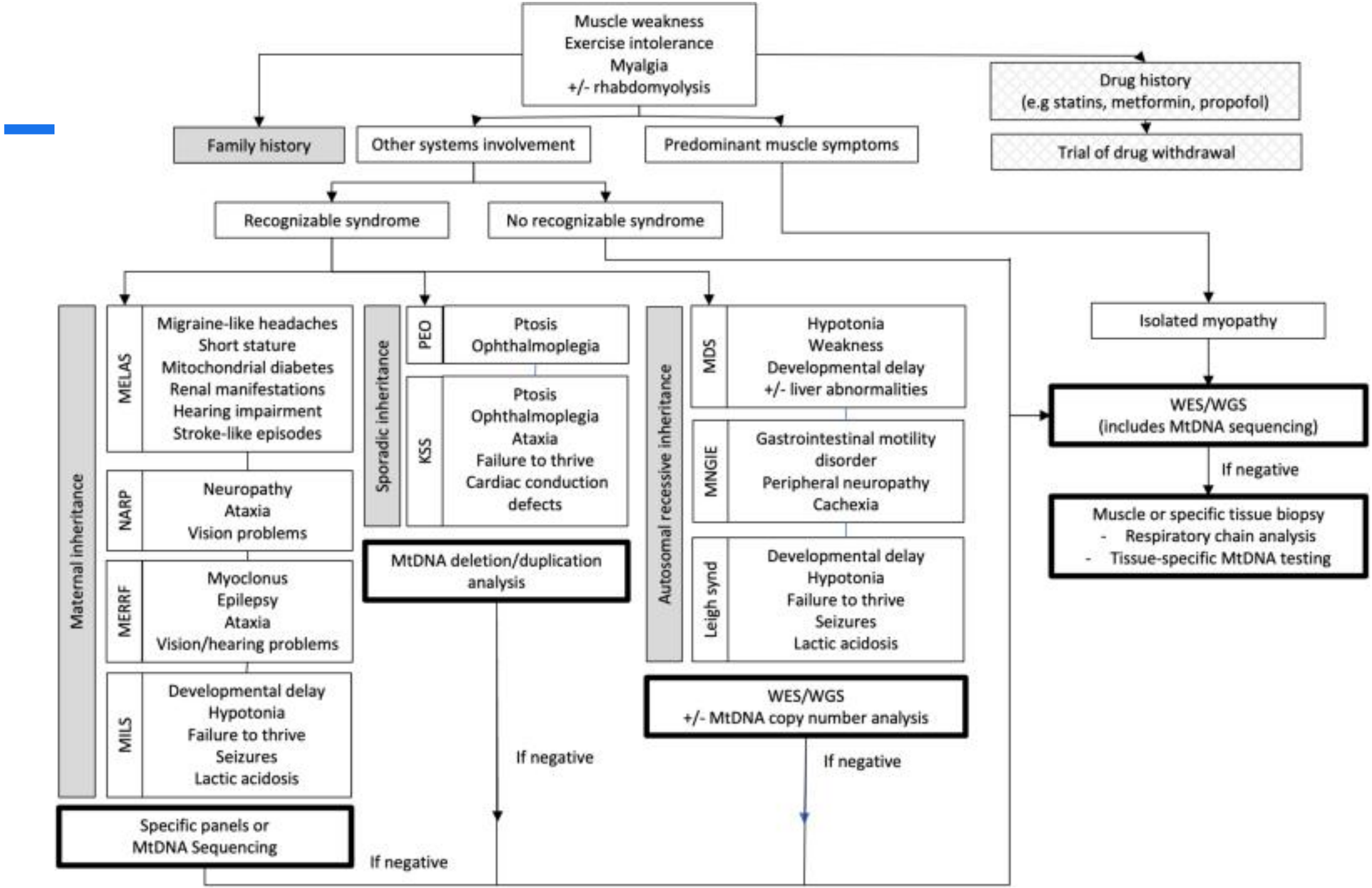
- CPEO
- MELAS
- Kearn-Sayre Syndrome
  - Large scale deletions of mitochondrial DNA
  - Sporadic
  - Onset <20 years
  - CPEO
  - Pigmentary retinopathy, cardiac conduction block, cerebellar ataxia, deafness, short stature
  - CSF protein elevated (>100mg/dL)
- Myoclonic Epilepsy with Ragged Red Fibers
- TK2 Deficiency

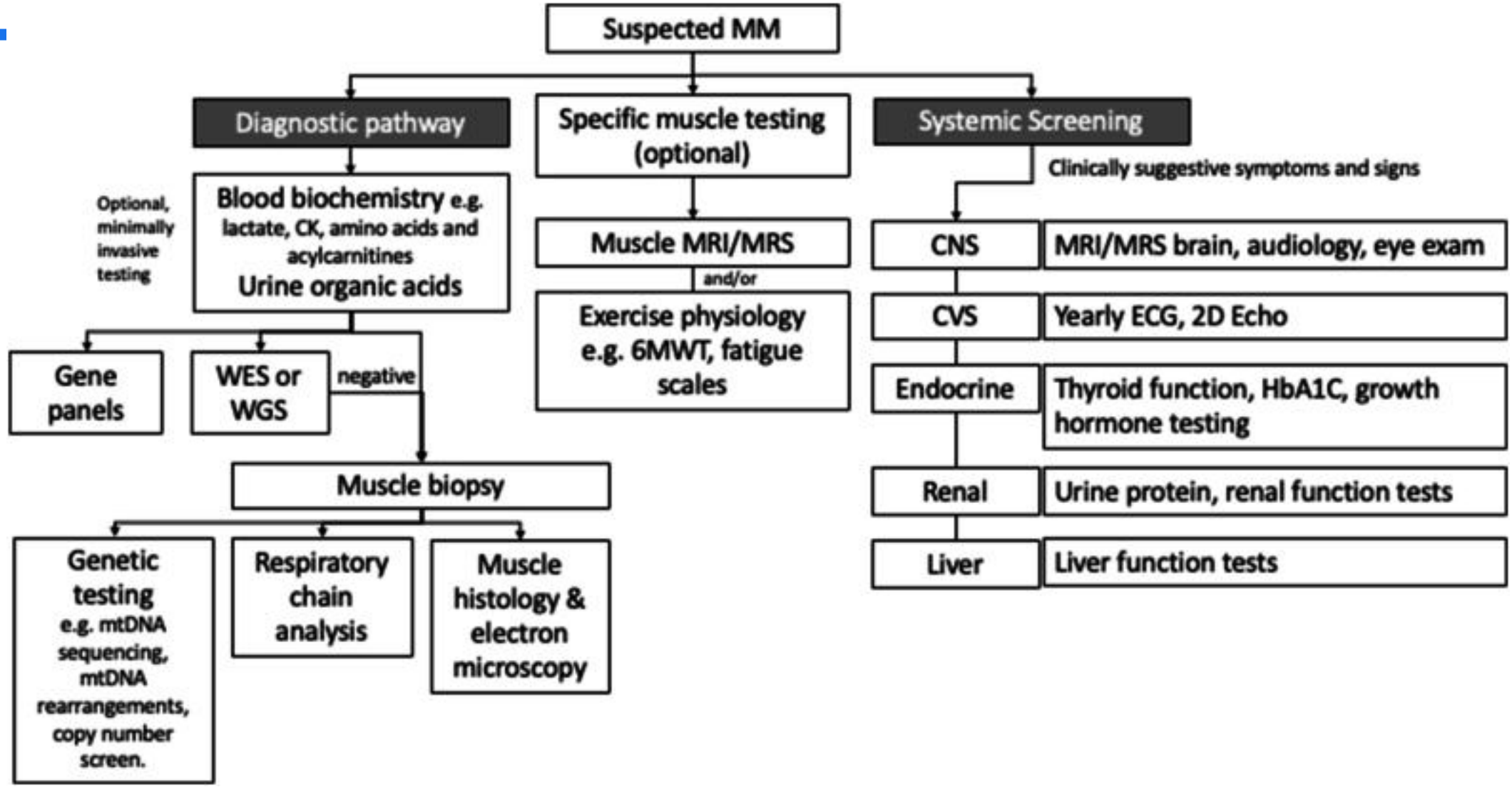
Mitochondrial Myopathies Syndromes

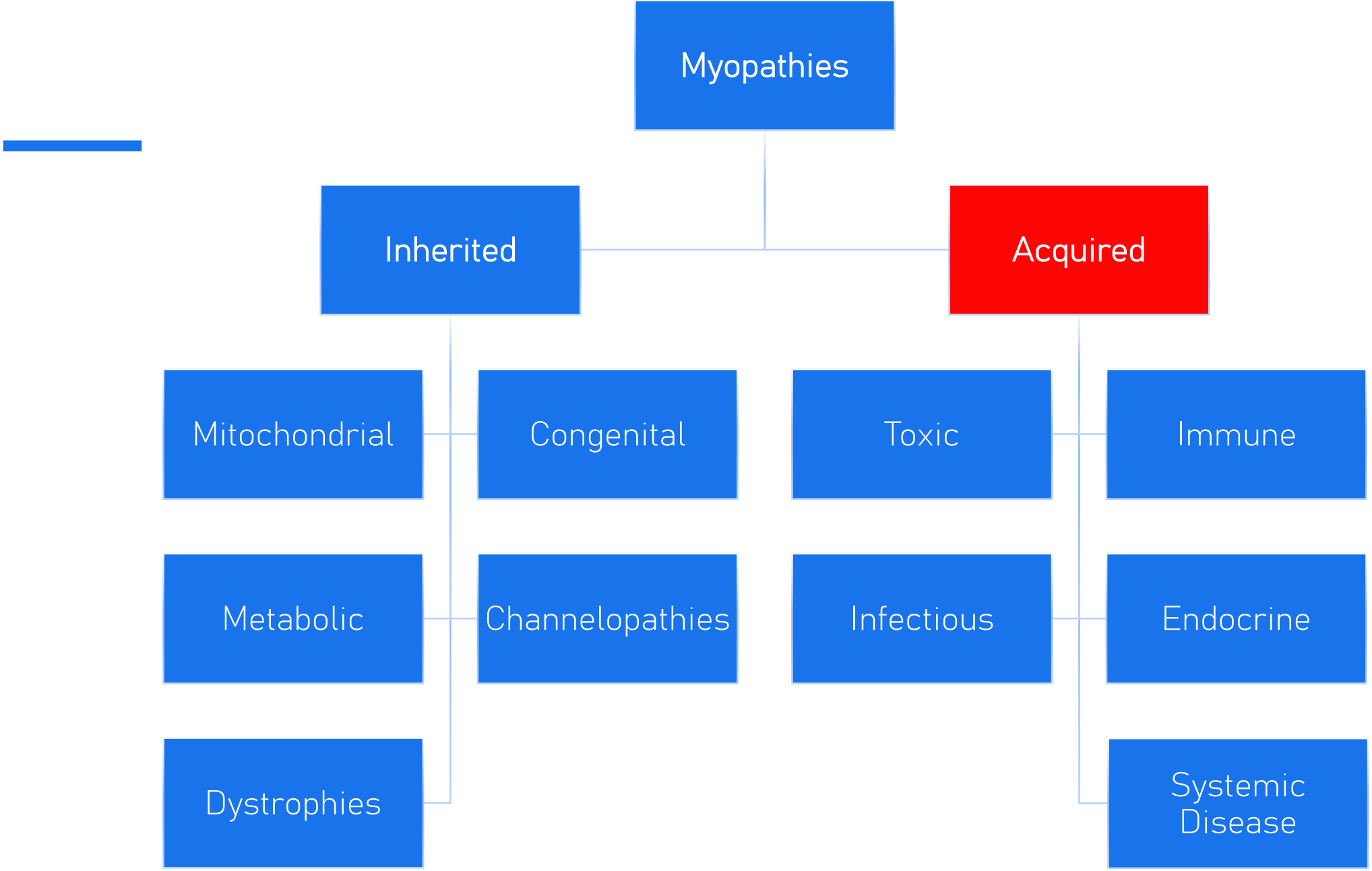
- CPEO
- MELAS
- Kearn-Sayre Syndrome
- Myoclonic Epilepsy with Ragged Red Fibers
  - MT-TK mutation
  - Sporadic or mito inheritance
  - Myoclonic epilepsy, ataxia, myopathy, optic atrophy, deafness, neuropathy, cardiomyopathy, WPW syndrome
- TK2 Deficiency

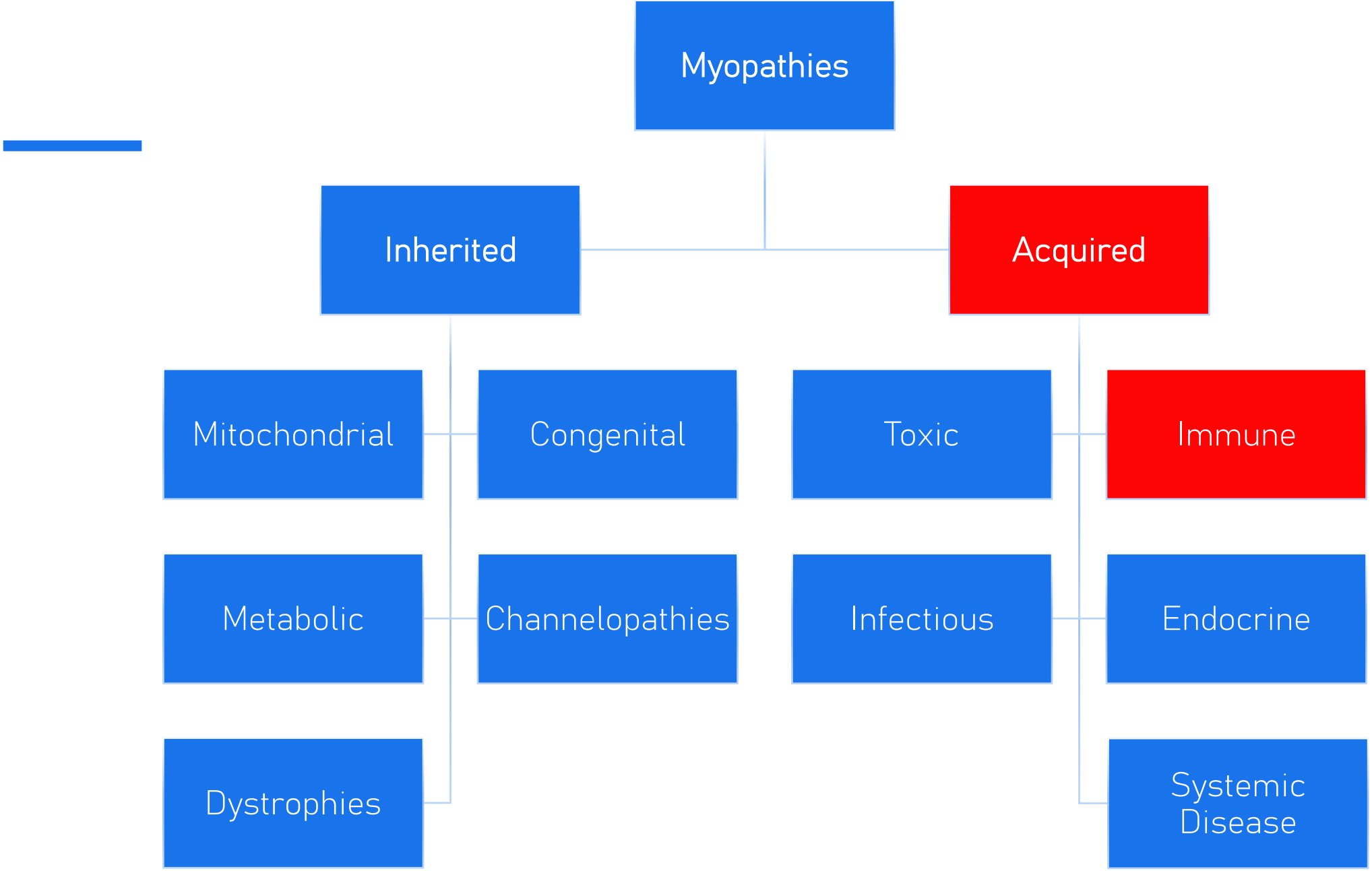
Mitochondrial Myopathies Syndromes

- CPEO
- MELAS
- Kearn-Sayre Syndrome
- Myoclonus Epilepsy with Ragged Red Fibers
- TK2 Deficiency
  - TK2 mutation
  - AR
  - Infantile and childhood onset
  - Muscle weakness, hypotonia, bulbar weakness with dysarthria/dysphagia


Muscle weakness
Exercise intolerance
Myalgia
+/- rhabdomyolysis
Drug history
(e.g statins, metformin, propofol)
Trial of drug withdrawal
Family history
Other systems involvement
Predominant muscle symptoms
Recognizable syndrome
No recognizable syndrome
Maternal inheritance
MELAS
Migraine-like headaches
Short stature
Mitochondrial diabetes
Renal manifestations
Hearing impairment
Stroke-like episodes
NARP
Neuropathy
Ataxia
Vision problems
MERRF
Myoclonus
Epilepsy
Ataxia
Vision/hearing problems
MILS
Developmental delay
Hypotonia
Failure to thrive
Seizures
Lactic acidosis
Specific panels or
MtDNA Sequencing
Sporadic inheritance
PEO
Ptosis
Ophthalmoplegia
KSS
Ptosis
Ophthalmoplegia
Ataxia
Failure to thrive
Cardiac conduction defects
MtDNA deletion/duplication analysis
If negative
Autosomal recessive inheritance
MDS
Hypotonia
Weakness
Developmental delay
+/- liver abnormalities
MNGIE
Gastrointestinal motility disorder
Peripheral neuropathy
Cachexia
Leigh synd
Developmental delay
Hypotonia
Failure to thrive
Seizures
Lactic acidosis
WES/WGS
+/- MtDNA copy number analysis
If negative
Isolated myopathy
WES/WGS
(includes MtDNA sequencing)
If negative
Muscle or specific tissue biopsy
- Respiratory chain analysis
- Tissue-specific MtDNA testing
If negative


Suspected MM
Diagnostic pathway
Specific muscle testing (optional)
Systemic Screening
Clinically suggestive symptoms and signs
Optional, minimally invasive testing
Blood biochemistry e.g. lactate, CK, amino acids and acylcarnitines
Urine organic acids
Muscle MRI/MRS
and/or
Exercise physiology e.g. 6MWT, fatigue scales
CNS
MRI/MRS brain, audiology, eye exam
CVS
Yearly ECG, 2D Echo
Endocrine
Thyroid function, HbA1C, growth hormone testing
Renal
Urine protein, renal function tests
Liver
Liver function tests
Gene panels
WES or WGS
negative
Muscle biopsy
Genetic testing e.g. mtDNA sequencing, mtDNA rearrangements, copy number screen.
Respiratory chain analysis
Muscle histology & electron microscopy


Myopathies
Inherited
Acquired
Mitochondrial
Congenital
Toxic
Immune
Metabolic
Channelopathies
Infectious
Endocrine
Dystrophies
Systemic Disease


Myopathies
Inherited
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Endocrine
Dystrophies
Systemic Disease

Immune Mediated Myopathies

- Inflammatory myopathies are a large group of disorders associated with Inflammatory response targeting skeletal muscle.
- Incidence of IIM: 0.2 to 2 per 100,000 person-years
- Prevalence from 2 to 25 per 100,000 people.
- May have systemic manifestations: Heart, lung, joint, skin
- Associated infections and cancer
- Subtypes
  - Immune mediated necrotizing myopathy
  - Dermatomyositis
  - Anti-synthetase Syndrome
  - Inclusion Body Myositis
  - Polymyositis

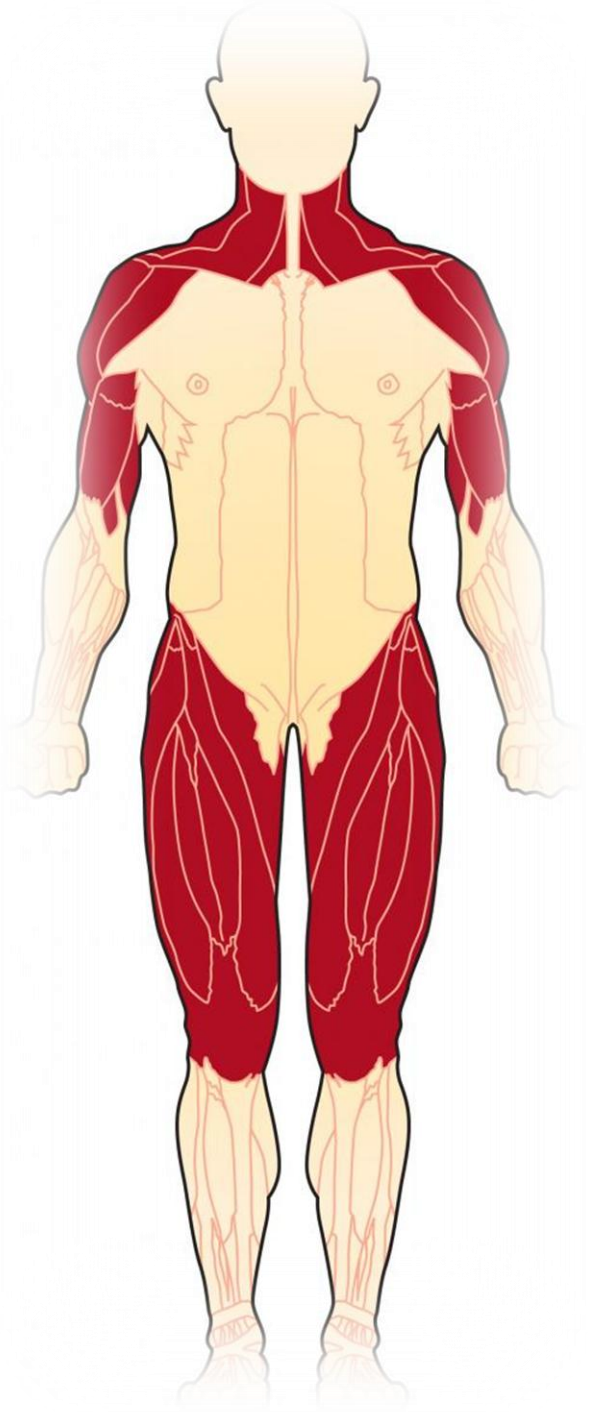


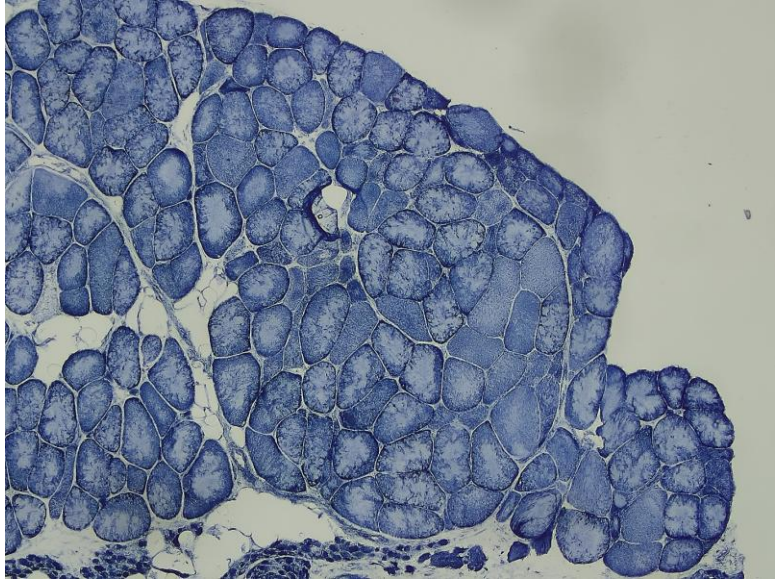
Table 1. Bohan and Peter classification criteria for polymyositis and dermatomyositis

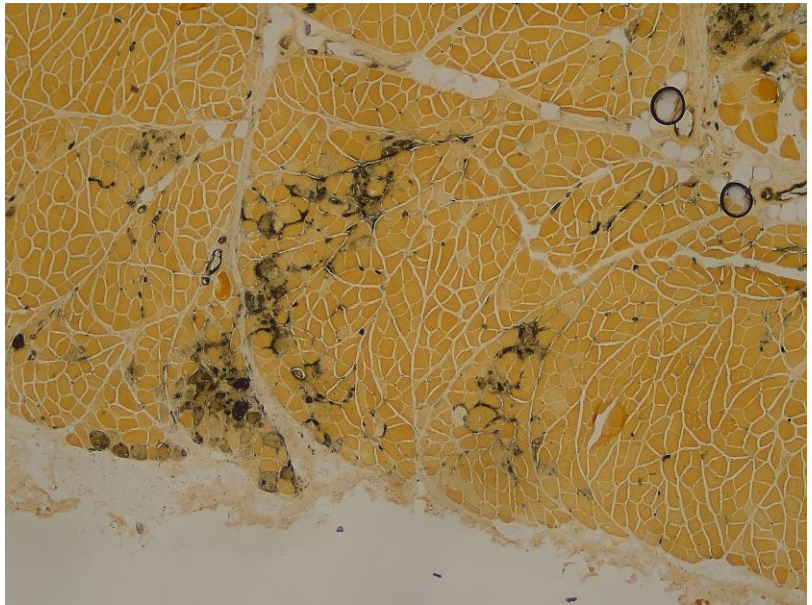
Criteria	Description
A	Proximal and symmetrical muscle weakness of the pelvic and scapular girdle, anterior flexors of the neck, progressing for weeks to months, with or without dysphagia or involvement of respiratory muscles
B	Elevation of the serum levels of skeletal muscle enzymes: creatine kinase, aspartate aminotransferase, lactate dehydrogenase and aldolase
C	Electromyography characteristic of myopathy (short and small motor units, fibrillation, positive pointy waves, insertional irritability and repetitive high-frequency firing)
D	Muscle biopsy showing necrosis, phagocytosis, regeneration, perifascicular atrophy, perivascular inflammatory exudate
E	Typical cutaneous changes: (1) Heliotrope rash with periorbital oedema and violaceous erythema (2) Gottron's sign: vasculitis in the elbow, metacarpophalangeal and proximal interphalangeal joints
Polymyositis	(1) Definite – all of A–D (2) Probable – any three of A–D (3) Possible – any two of A–D
Dermatomyositis	(1) Definite – E plus and three of A–D (2) Probable – E plus and two of A–D (3) Possible – E plus and one of A–D

Exclusion criteria: congenital muscular dystrophies, central or peripheral neurological disease, infectious myositis, metabolic/endocrine myopathies and myasthenia gravis.
Adapted with permission [2].

IMM: Clinical Pathogenesis

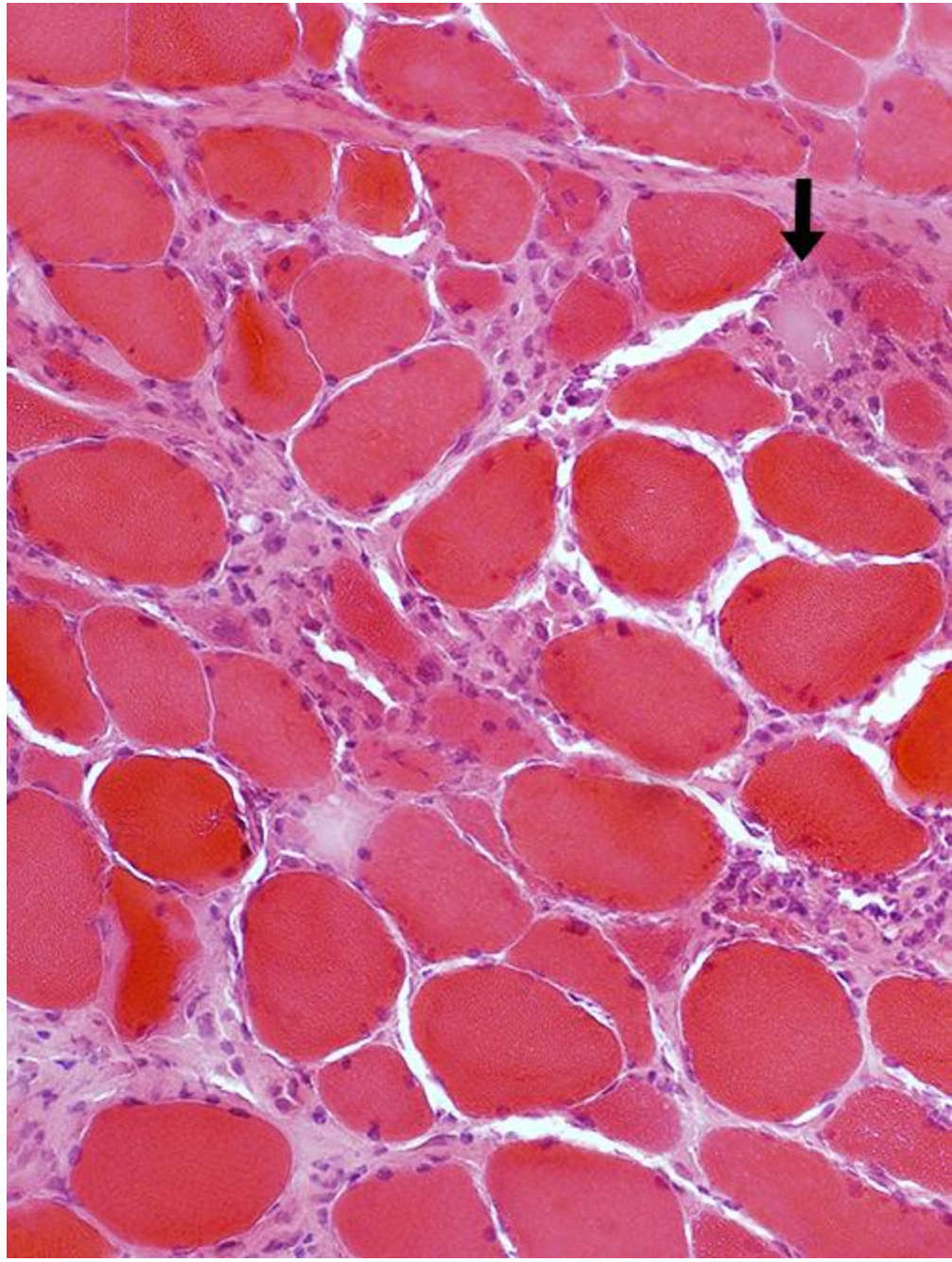
- Subacute progressive weakness affecting the proximal muscles
  - Neck flexors
  - Shoulder and hip girdle
  - Patients complain about being unable to set up from seated position, use stairs, holding arms above head
  - Dysphagia
  - Respiratory involvement
  - Ocular spared
- IBM is the exception





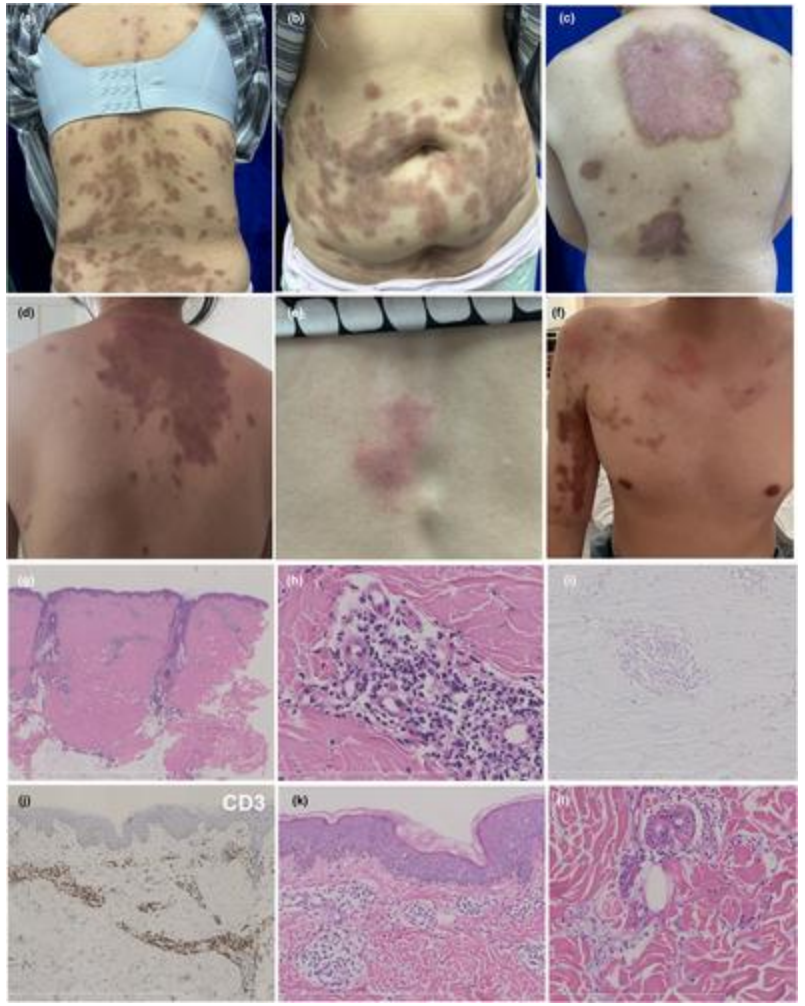
Immune Mediated Necrotizing Myopathy

- Inflammatory myopathies associated with insidious of acute/subacute weakness
- Necrosis on pathology
- Associated with HMGCR or SRP antibodies
  - HMGCR antibody noted in 70%, SRP in 10%. Otherwise antibody negative
- Incidence/Prevalence unknown:
  - Incidence likely 1.16-19/million and prevalence 2.4 to 33.8/million
- Females more involved, Mean onset: 40-65
- Risks
  - Poorly defined: Statin exposure not always noted
  - Ask about natural HMGCR inhibitors



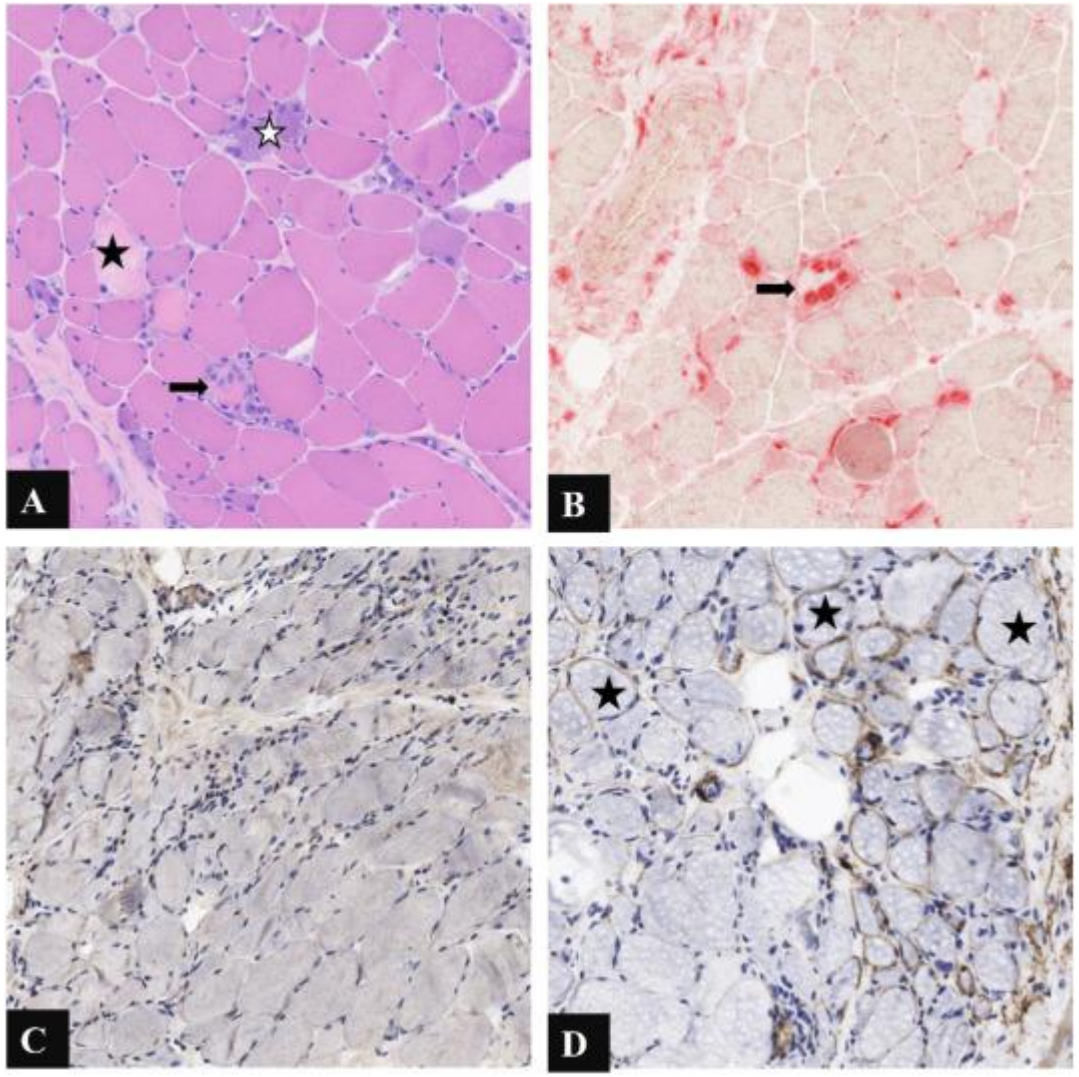
IMNM: Presentation

- Muscle
  - 2/3 acute, 1/3 chronic muscle weakness with or without exposure to statin
  - Proximal (LE>UE), 16% laterality
  - Neck weakness, dysphagia, facial involvement
- Extramuscular
  - ILD- SRP with higher incidence
  - Cardiac-Becoming more and more recognized among all 3 subtypes
  - Cutaneous- Higher in HMGCR, exanthema and violaceous plaques
  - DVT
- Malignancy
  - Suspected to be higher in seronegative and HMGCR patients compared to SRP



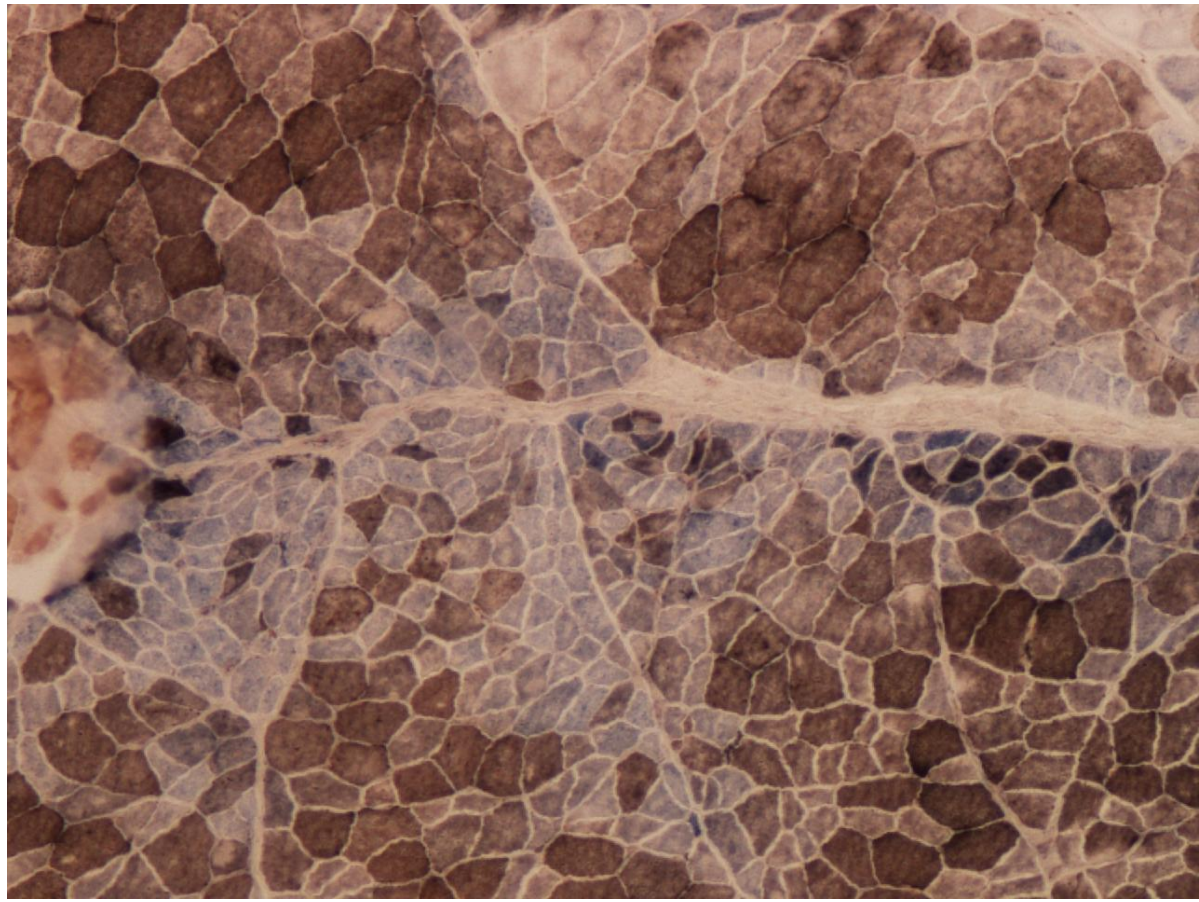
IMNM: Workup

- Antibodies
  - ELISA with 95% sensitivity, 100% specificity
- CK: 10-30X ULN
- Muscle biopsy
  - Necrotic scattered fibers
  - Different stages of necrosis
  - Paucilymphocytic infiltrates composed of predominantly macrophages
- MRI
  - Biopsy selection
  - Monitoring activity, severity, treatment response



Dermatomyositis

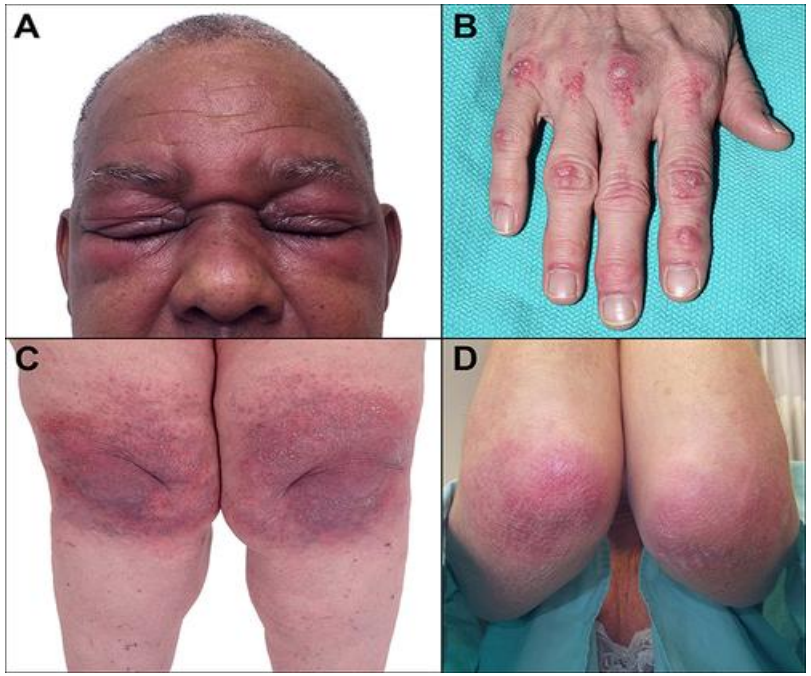
- Inflammatory myopathy that presents with weakness developing subacutely over days to weeks or insidiously over months
  - Affects proximal more than distal muscles
- Incidence: 1-15/million
- Prevalence: 1.2 to 21 per 100000
- Associated with non-muscular manifestations and malignancy



Dermatomyositis: Skin changes

- May not be present: Adermatopathic dermatomyositis, dermatomyositis sine dermatitis
- Purplish erythematous/discoloration or papules over
  - Heliotrope rash: eyelids with periorbital edema
  - Malar rash: Face
  - V sign: Neck and anterior chest
  - Shawl: Shoulder and upper back
  - Holster: hip
  - Gottron: Extensor surfaces (elbow, knuckles, knees, malleoli)





Dermatomyositis: Other Systemic Manifestations

- Cardiac symptoms: Rare
  - Cardiac arrhythmias, congestive heart failure, pericarditis, myocarditis
- Respiratory involvement
  - Interstitial lung disease
    - 20–40%
  - Aspiration pneumonia
- Gastrointestinal
  - Reduced gastric motility and vasculopathy
  - Juvenile dermatomyositis
- Arthralgia
  - With or without arthritis

Table 1 *Myositis-specific antibodies and associated clinical phenotypes*

Antigen	Antibody prevalence among patients with DM (%)	Clinical features
Transcription intermediary factor 1γ (TIF-1γ)	8–41 (USA, Europe), 7–14 (Japan)	Malignancy, severe rash, "red on white" poikiloderma, ovoid palatal patch
Melanoma differentiation-associated gene 5 (MDA-5)	0–13 (USA, Europe), 11–37 (Asia)	ILD, clinically amyopathic, arthritis, cutaneous ulcers, alopecia, hyperferritinemia, calcinosis
Nuclear matrix protein (NXP-2)	3–30 (USA, Europe), 2–4 (Japan)	Calcinosis, malignancy severe dysphagia, myalgia, distal weakness, intestinal vasculopathy
Small ubiquitin-like modifier activating enzyme (SAE)	5–10 (USA, Europe), 2–3 (Asia)	Dysphagia, "angel wing" rash on back, skin predominant precedes variable myositis
Nucleosome-remodeling deacetylase complex (Mi-2)	10–21 (USA, Europe), 2–30 (Asia), ~8 (Brazil)	Photo-distributed rash, good prognosis with common relapse, high CK with nearly universal muscle involvement

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Antisynthetase Syndrome

Table 1. Comparison of two proposed classification criteria for ASyS.

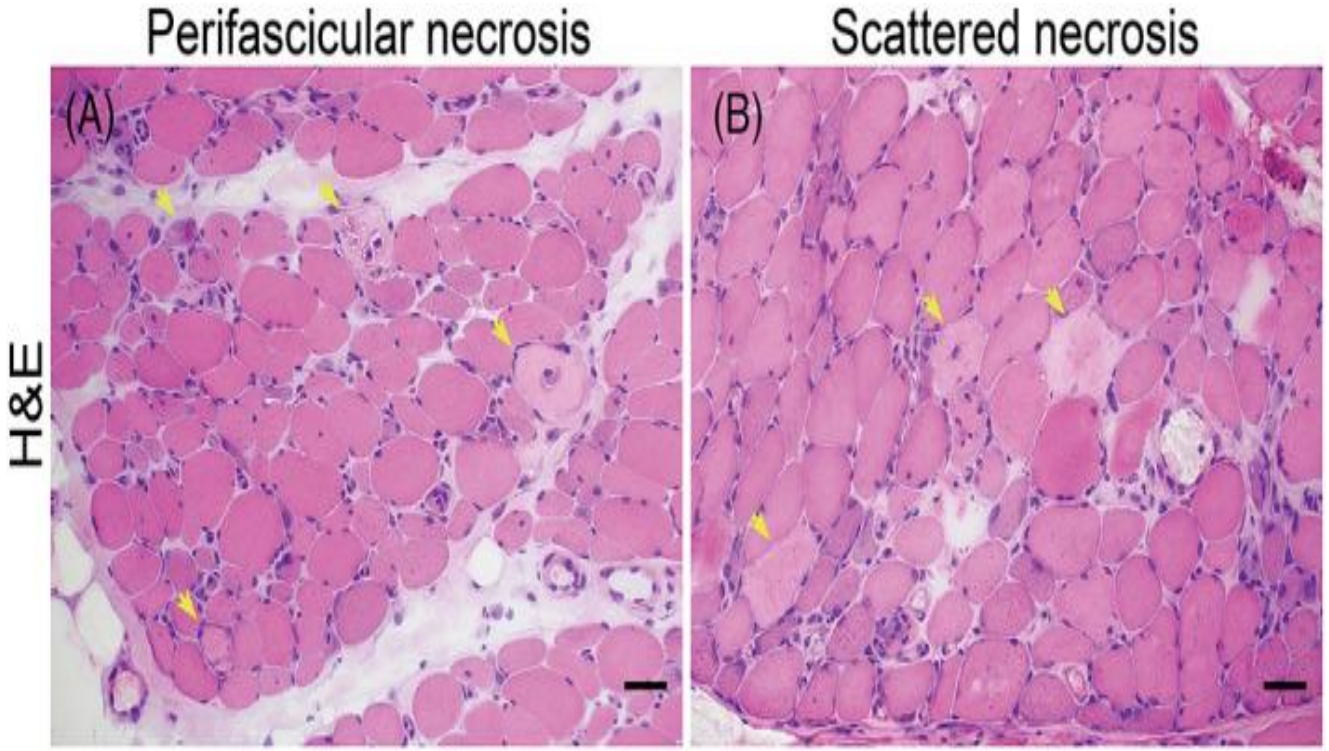
Entry criterion: Presence of an anti-tRNA synthetase antibody	
Connors etal., 2010 [14]	**Solomon etal., 2011** [15]

Antisynthetase antibody plus one or more of the following:
• Myositis by Bohan and Peter criteria [9]
• Interstitial lung disease (ILD) not explained by other causes
• Arthritis
• Unexplained, persistent fever
• Raynaud's phenomenon
• Mechanic's hands
	Antisynthetase antibody plus two major criteria or one major and two minor criteria.
	• Major criteria:
	  • Myositis by Bohan and Peter criteria [9]
	  • ILD not explained by other causes
	• Minor criteria:
	  • Arthritis
	  • Raynaud's phenomenon
	  • Mechanic's hands

Antisynthetase syndrome	
Anti-Jo-1	Most common antisynthetase syndrome antibody, highest muscle involvement, interstitial lung disease, fever, mild rash, Raynaud phenomenon, mechanic's hands, arthritis
Anti-PL-7	Severe interstitial lung disease, moderate muscle involvement, fever, Raynaud phenomenon, arthritis, mechanic's hands, rash
Anti-PL-12	Severe interstitial lung disease, mild muscle involvement, fever, Raynaud phenomenon, possible esophageal involvement, arthritis, mechanic's hands, rash
Anti-EJ	Severe interstitial lung disease, moderate muscle involvement, fever, Raynaud phenomenon, arthritis, mechanic's hands, rash
Anti-OJ	Severe interstitial lung disease, moderate muscle involvement, fever, Raynaud phenomenon, arthritis, mechanic's hands, rash
Anti-KS	Severe interstitial lung disease, mild muscle involvement, fever, Raynaud phenomenon, arthritis, mechanic's hands, mild rash
Anti-Zo	Rare, mild interstitial lung disease, mild muscle involvement, arthritis, Raynaud phenomenon, mechanic's hands, mild rash
Anti-Ha	Rare, mild interstitial lung disease, mild muscle involvement, arthritis, mechanic's hands, mild rash

Anti-Synthetase Syndrome: Anti-Jo-1

- Most common antibody
- Most likely to present with classic triad
- Better prognosis because it is recognized sooner
- Will have more muscle and joint involvement.



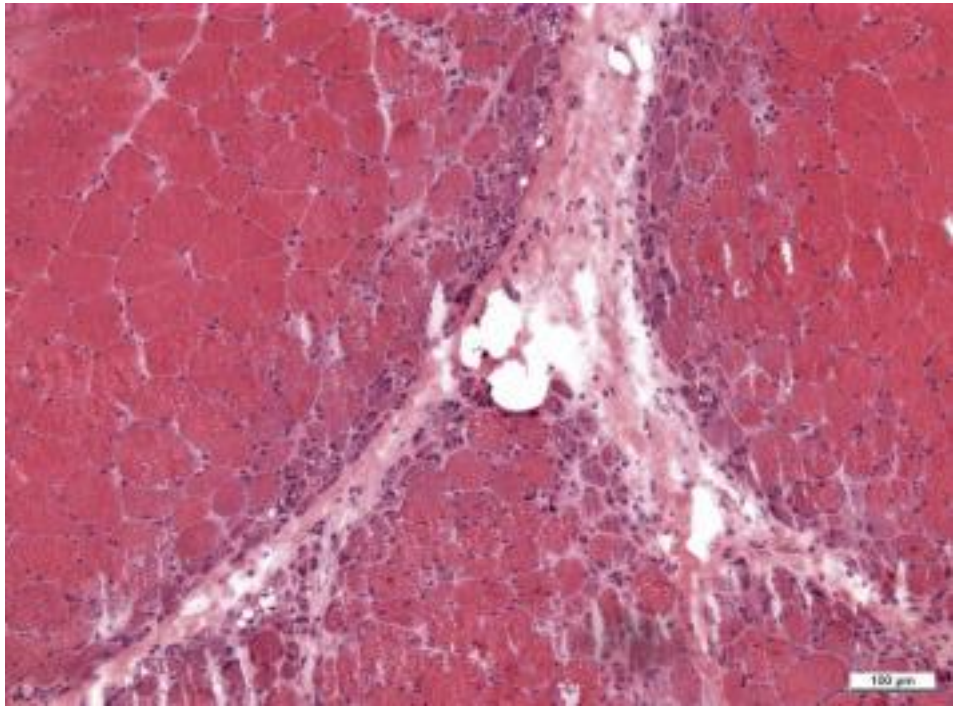
Interstitial Lung Disease

- Hallmark pulmonary findings
  - Pulmonary HTN
- High risk of mortality requiring aggressive treatment
- Presenting symptom in 15-30%
- Prevalence ranges from 70-90%
- Diagnosis: PFT and imaging
  - High resolution CT
  - PFT with restrictive pathology
- 9% have rapidly progressive form



Anti-Synthetase Syndrome: Muscular manifestations

- Generally symptomatic with weakness and myalgias
  - 25% can be hypomyopathic
- CK elevated: 6272 ± 1255 IU/L
- EMG
  - Diagnosis: Irritable myopathy
  - Biopsy selection
- MRI: Muscle edema
- EMG and MRI can be useful to monitor disease activity
  - CK and exam may be challenging to follow
- Biopsy: Not always necessary
  - Perifascicular atrophy and necrosis
  - Diffuse necrosis with perimysial inflammation



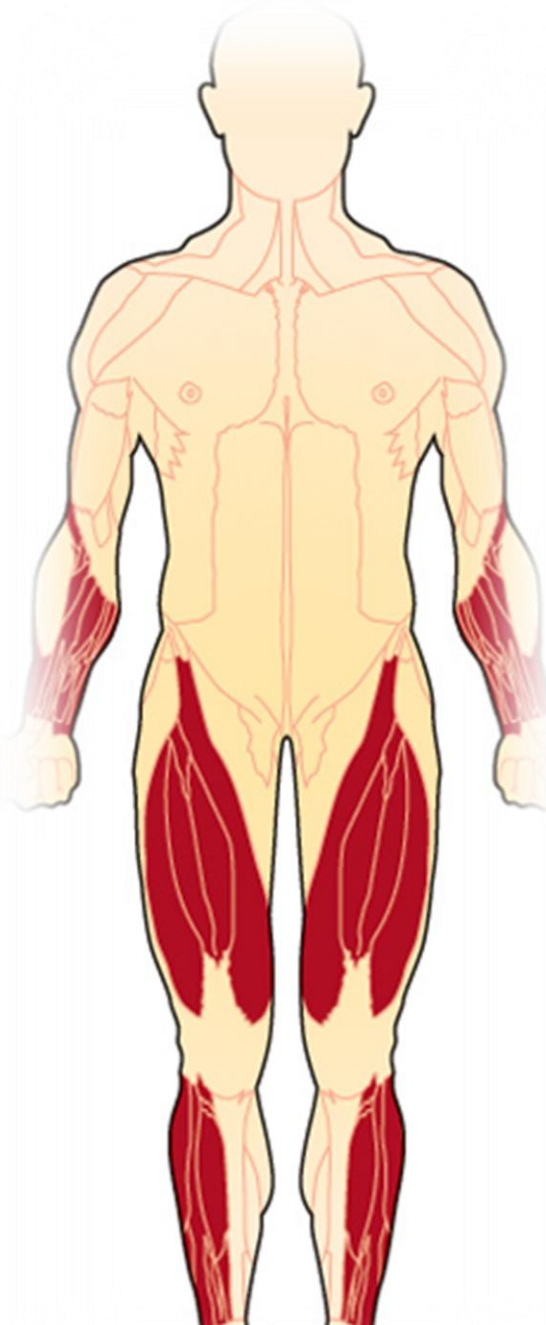
Anti-Synthetase Syndrome: Other findings

- Joint
  - Polyarthalgia and polyarthritis (60% of patients)
  - More common in Anti-Jo1
  - Joint erosions
- Skin
  - Mechanic's hands
  - Hiker's Feet
  - Gottron's papules, gottron's signs, heliotrope rash, shawl and holster sign
- Cardiac
  - Less common (3.4%)-asymptomatic or present with heart failure
  - Myocarditis (with active myositis)
  - Pericardial effusions



Inclusion body myositis

- Sporadic idiopathic myopathy and a part of a group of inflammatory myopathies.
- 1st description of case published in 1967 (Chou)
  - Described histopathological features that later became synonymous with diagnosis
  - Initially considered a chronic form of polymyositis refractory to immunotherapy
  - Become a separate disorder in the 1970s
- Most common idiopathic myopathy after age 50.
  - Male to female ratio 3:1
  - Prevalence ranges from 1 to 182/1,000,000 based on country.
  - Underestimated due to rates of misdiagnosis



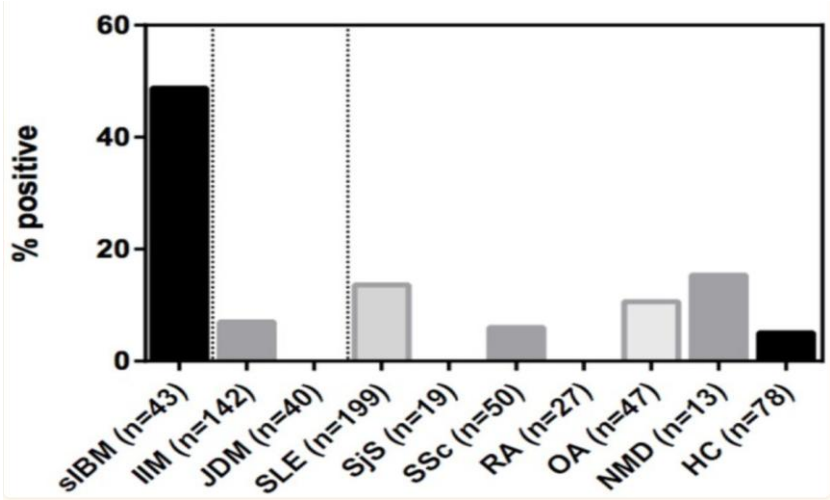
Typical clinical presentation

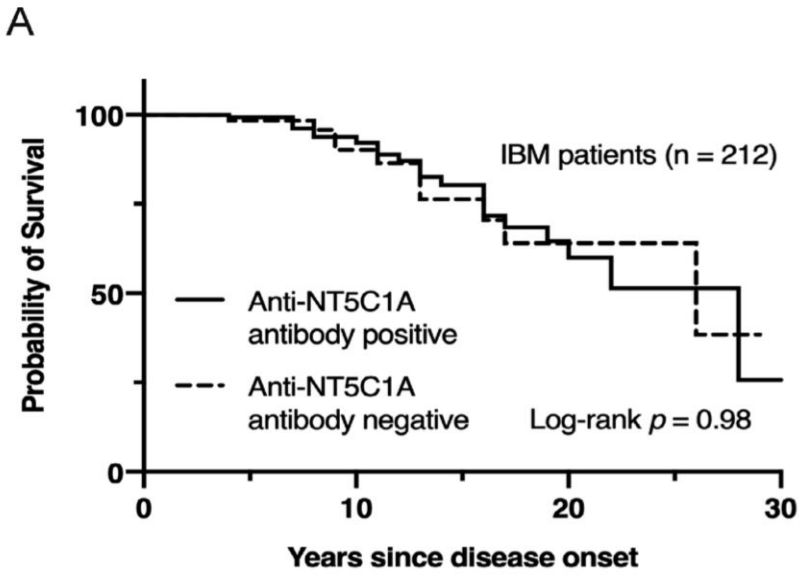
- Distinct clinical presentation
  - Classic presentation is distal upper and proximal lower extremity weakness
    - Involving long finger flexors and quadriceps
  - Manifests early as slowly progressive quadricep weakness with falls
    - Can present with finger flexor weakness, foot drop, dysphagia (70%)
  - Up to 82% have asymmetric presentation with finger flexor weakness in the non-dominant hand
  - Can be differentiated from myotomal disease by assessing for thenar/hypothenar involvement which are spared
  - In lower extremity, knee extension weakness is out of proportion to hip flexor weakness
  - Ankle dorsiflexion weakness



Laboratory Testing

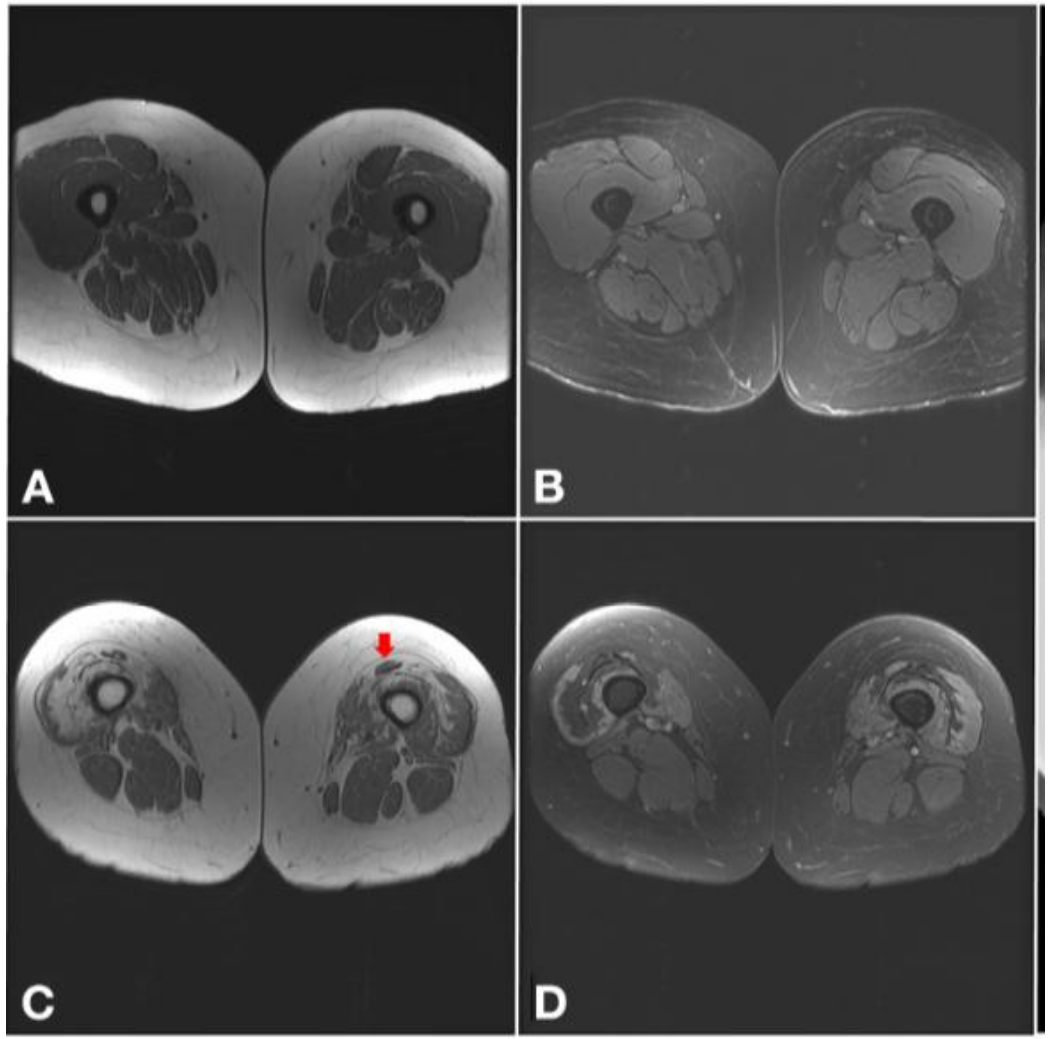
- Creatine kinase(CK): Typically elevated in 75-80%
  - Usually less than 15x ULN
  - Can be normal or mildly elevated
- Autoantibodies to cytosolic 5′-nucleotidase 1A (cN-1A; NT5C1A)
  - In 2011, Salajegheh et al detected an antibody that targeted Mup44 (44 kDA human muscle protein)
  - In 2013, Larman et al./ Pluk et al. independently identified the antibody target to be cytosolic 5’ nucleotidase 1A (NT5c1A)
  - Wide range of sensitivities: 33-80%.
  - Specificity 92-100%. Was challenged and in 2019, specificity established at 91.8%.
  - Reports of seropositivity correlated with dysphagia and more severe phenotype. Not supported in follow up study.





Other testing

- Electrophysiology
  - Determining if weakness is neurogenic vs myopathic
  - Target selection for biopsy
  - NCS normal in most patients but can show concurrent axonal sensory neuropathy in 30%.
  - Irritative myopathy with myotonic/myotonic-like discharges in 1/3 of patients
  - Pseudo-neurogenic changes in 1/3 of patients due to reinnervation of denervated fibers can lead to misdiagnosis.
- Muscle imaging
  - Use limited
  - Changes follow clinical pattern of IBM: Asymmetric involvement of finger flexors, flexor digitorum profundus, quadriceps femoris
  - Fatty infiltration
  - Leg muscle involvement in decreasing frequency: Quadriceps and medial head of gastrocnemius followed by soleus
  - Melted appearance of distal anterior thigh muscles



2024 ENMC Criteria for the Diagnosis of Inclusion Body Myositis.

Diagnosing IBM should involve consultation of a neuromuscular specialist. These criteria should be applied where clinicians suspect a diagnosis of IBM and where there is no better explanation for the clinical presentation.

STEP 1: Presentation Type		
Common Presentation	**Uncommon Presentation** *Patient may have IBM, but search for alternative diagnosis is mandatory.*	**Considerations for alternative diagnoses** *Where present, alternative diagnosis is likely. Alternative diagnosis should be stringently evaluated.*

All three of:
• Age ≥ 45 years at symptom onset, *AND*
• ≥ 12-month history of progressive weakness, *AND*
• CK ≤ 15x ULN
 	
With common IBM muscle involvement pattern *at presentation* (often asymmetric and accompanied by dysphagia):
• Deep finger flexor (FF) weakness *AND/OR*
• Knee extensor (KE) weakness
	Patient with suspected IBM, but with any of:
	• Age <45 years at symptom onset, *OR*
	• <12 months of progressive weakness, *OR*
	• CK > 15x ULN, *OR*
	• Uncommon muscle involvement pattern and the absence of FF *AND/OR* KE weakness *at presentation*:
	  • Axial weakness,
	  • Isolated dysphagia,
	  • Foot drop,
	  • Facial diplegia,
	  • Proximal limb weakness
		Presence of any of the following suggests that an alternative diagnosis is more likely than IBM:
		• Positive family history of neuromuscular disease,
		• EMG not consistent with IBM (e.g., signs of severe axonal loss or fasciculations),
		• Myositis *specific* autoantibody positive (e.g., Jo-1)

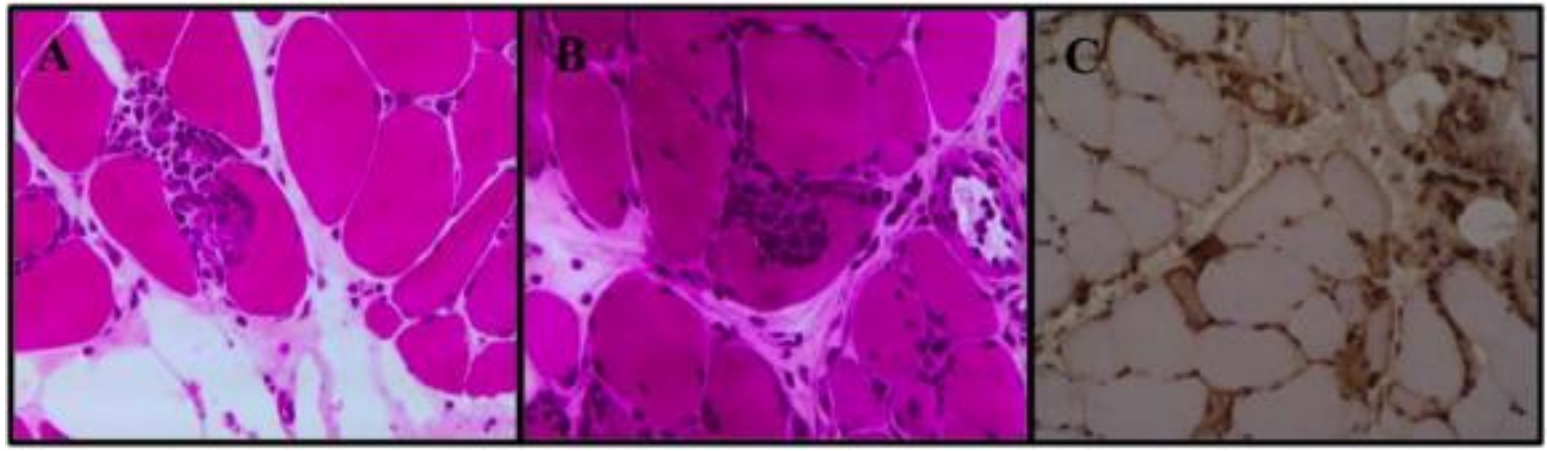
STEP 2: Investigations	
Mandatory	**Supportive**
Myopathology*: • Inflammation consisting of endomysial lymphocytes surrounding non-necrotic muscle fibers (with or without invasion) *see pathology section in main text for additional details	**Myopathology*:** 1. Rimmed vacuoles *and/or* cytoplasmic protein aggregates 2. Mitochondrial abnormalities (COX- SDH+ fibers > age-related) *see pathology section in main text for additional details **Lab tests:** 3. Anti-cN1a autoantibody positive **Imaging:** 4. Typical muscle MRI appearance *and/or* typical muscle ultrasound pattern

Diagnosis of IBM is confirmed when there is:

1. **Common** presentation with FF **and** KE weakness, **and** mandatory investigation finding, OR
2. **Common** presentation with FF **or** KE weakness, **and** mandatory investigation, **and** at least one supportive investigation finding(s) (1–4), OR
3. **Uncommon** presentation **and** mandatory investigation, **and** at least two supportive investigation findings (1–4)

CK = serum total creatine kinase; cN1a = cytosolic nucleotidase 1A; COX = cytochrome oxidase; EMG = electromyogram; FF = deep finger flexor; IBM = inclusion body myositis; KE = knee extensor; MRI = magnetic resonance imaging; SDH = succinate dehydrogenase; ULN = upper limit of normal.

Polymyositis



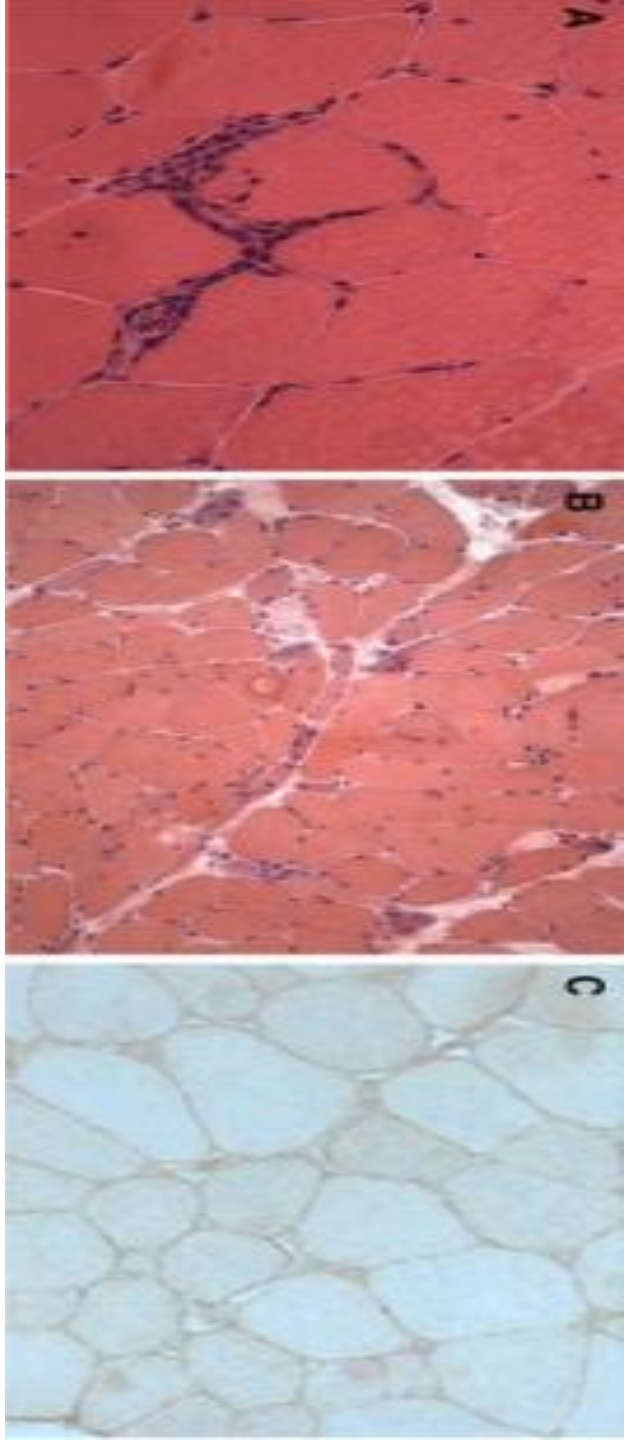
- Shares many features with other inflammatory myopathies
- CD8/Macrophage mediated damage to muscular antigens
- Affects patients affected by:
  - Viruses: HIV, HepC, Coxsackievirus
  - Malignancy-Lung carcinoma, lymphoma
  - Autoimmune conditions: Celiac
  - Medications: Hydralazine, ACE-I
- Epidemiology
  - Patients older than 20
  - 0.5-8.4/100,000 individuals

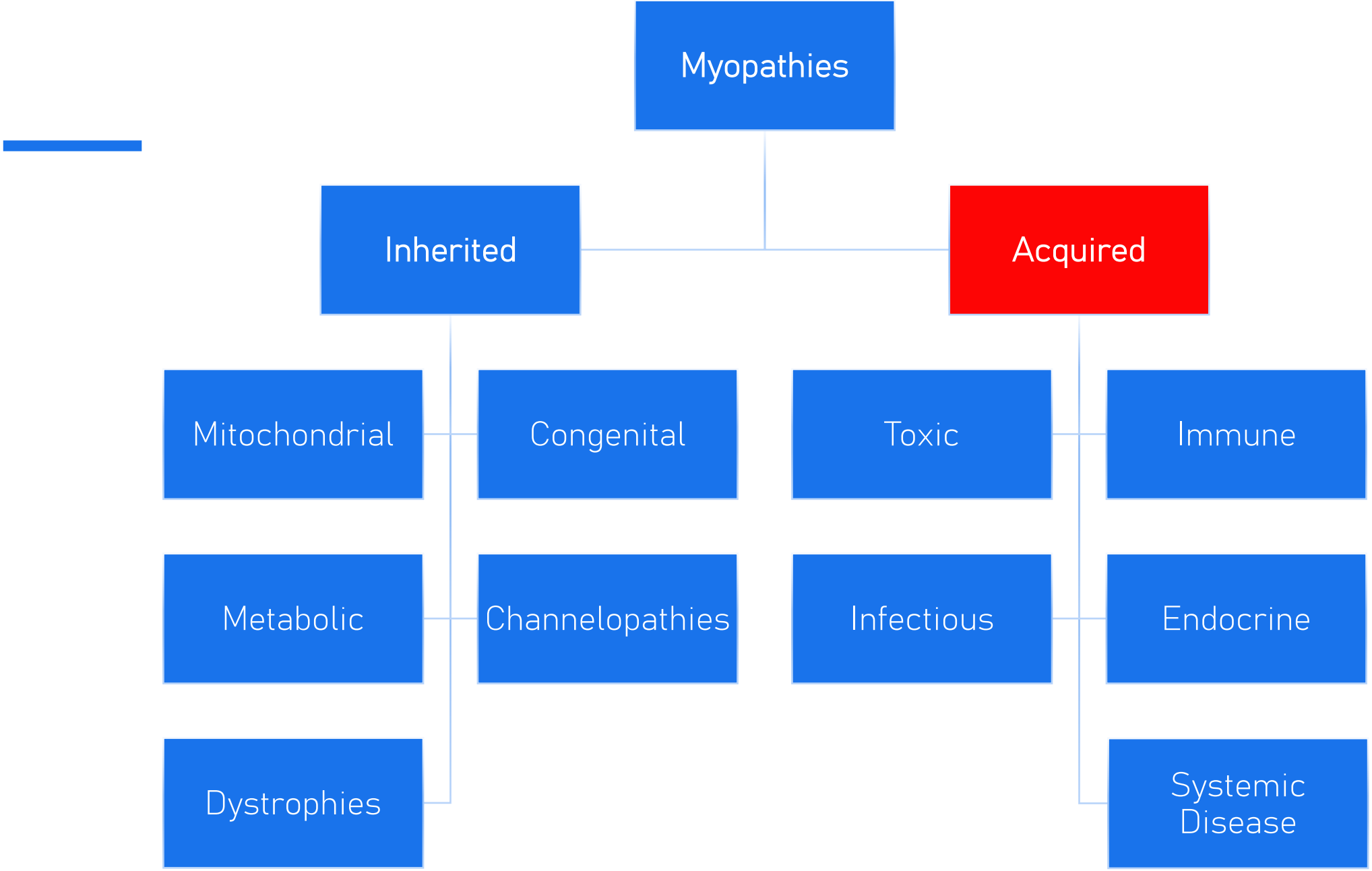
Polymyositis-History and Physical

- Progressive symmetric proximal muscle weakness
  - Truncal weakness-camptocormia
  - Speech changes
  - Distal weakness
- Constitutional symptoms
- Systemic symptoms
  - ILD
  - GI involvement
  - Raynauds

Polymyositis: Evaluation

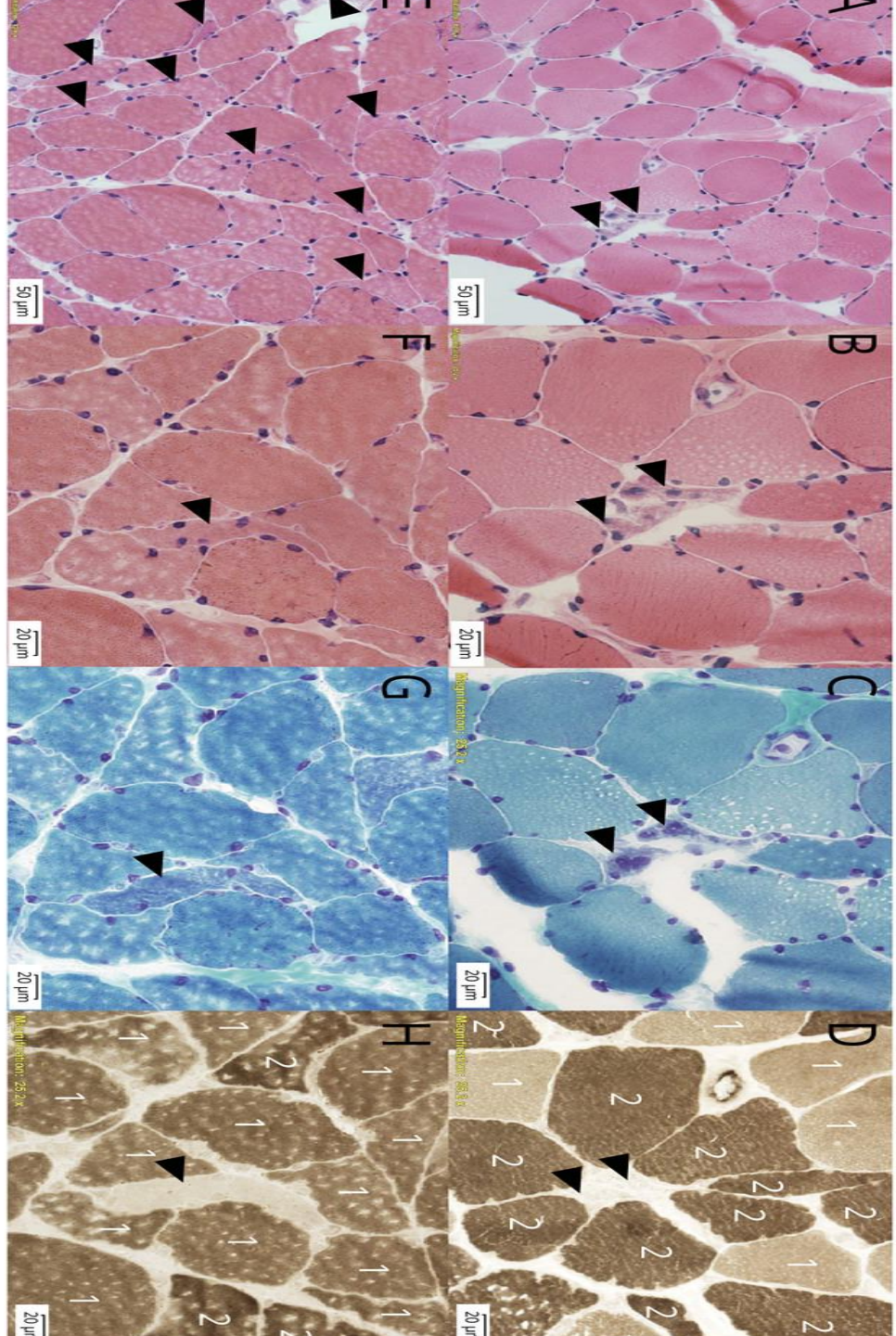
- Labs
  - CBC- Elevated lymphocyte count, thrombocytosis
  - ESR elevation
  - CK- Elevated (50x ULN)
  - Antibodies: Jo-1, SRP, HMGCR
- EMG-irritable myopathy
- Muscle biopsy
  - Myopathic changes
  - Endomysial inflammation




Myopathies
Inherited
Acquired
Mitochondrial
Congenital
Toxic
Immune
Metabolic
Channelopathies
Infectious
Endocrine
Dystrophies
Systemic Disease

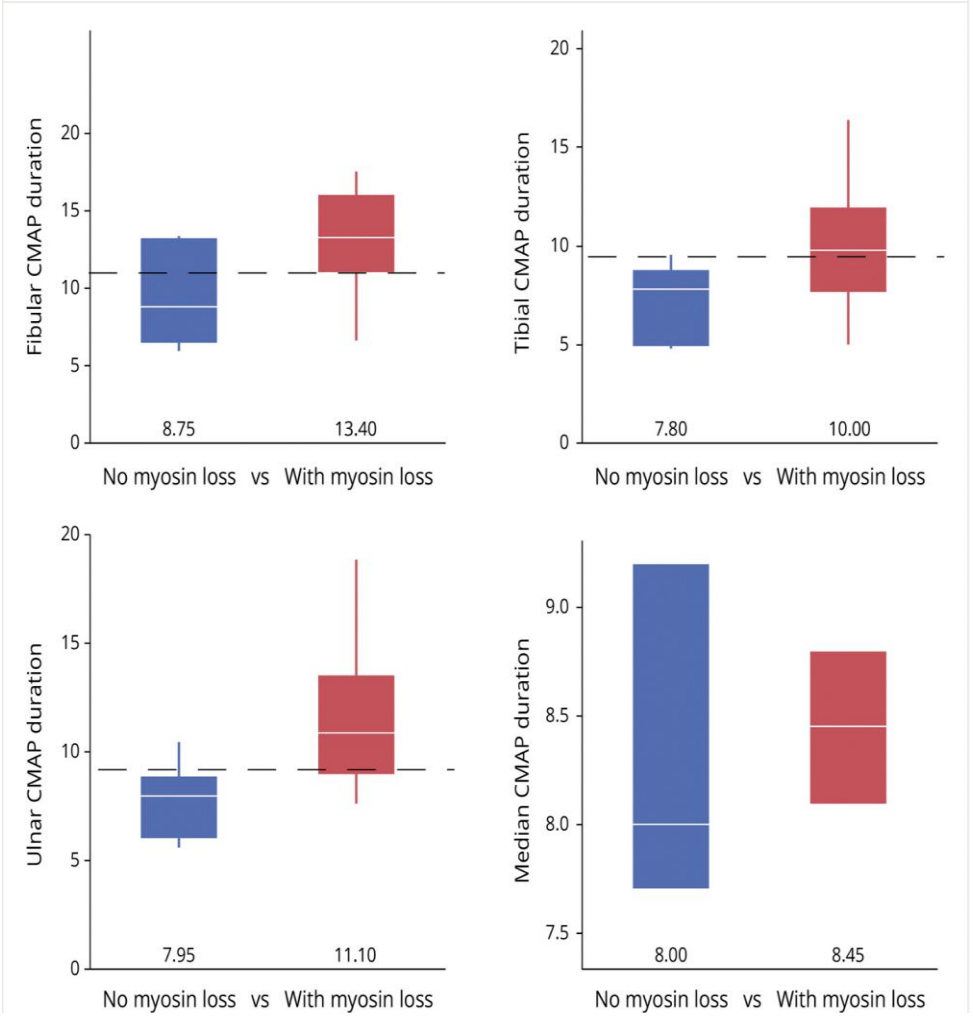
Critical Illness Myopathy

- Primary myopathy in critically ill patients
- Flaccid paralysis
- Preferential loss of myosin/thick filaments
- Wide incidence 9-86%
- 15-25% increase in mortality
- Risk factors
  - Uncontrolled BG
  - Multiorgan Failure
  - Corticosteroid use, neuromuscular blockage, sedation?



Critical Illness Myopathy: Presentation/Workup

- Subacute phase of critical illness
- Revealed once patient stabilized from acute illness and sedation reduced
- Clinical
  - Positive history of critical illness
  - Limb weakness
    - Flaccid muscle paralysis
    - Craniofacial spared
    - Respiratory involved
- Electrophysiological
  - Nerve conduction studies
    - Reduced CMAP amplitudes
    - Prolonged distal CMAP durations (>15 msec in fibular motor TA studies and >8msec in other nerves)
    - EMG: Myopathic units, spontaneous activity. Normal recruitment
- Exclude other disorders
- Muscle biopsy: Myosin:Actin ratio



Myopathy of Systemic Disorders

- Endocrine
- Inflammatory Myopathies
- Paraneoplastic
- Infectious Diseases
- Critical Illness
- Drug/Toxins

Endocrine Myopathies

- Hypothyroidism
  - Frequent muscle complaints
  - 1/3 have muscle weakness, cramps, pain, stiffness
  - Stretch reflex is prolonged (ankle/biceps) 25%
  - CK elevated (up to 10x ULN) even in the setting of minimal muscle disease
  - Hoffman syndrome: Prominent muscle enlargement, weakness, and muscle stiffness
- Hyperthyroidism
  - Thyrotoxic-Proximal weakness and atrophy
  - Will rarely complain of deficit
  - Preserved/Brisk reflexes
  - Dysphagia, dysphonia, aspiration
  - Associated neuromuscular disorders: Hypokalemic PP, MG, progressive ocular myopathy
  - Serum CK often not elevated

Endocrine Myopathies

- Hypoparathyroidism
  - Rare myopathy in the setting of hypocalcemia
  - Sx due to localized sustained tetany resulting in muscle damage (elevated CK)
  - Hyporeflexia
- Hyperparathyroidism
  - Proximal muscle, wasting.
  - Brisk reflexes
  - Normal or slightly elevated CK
  - No correlation to calcium/phosphorus levels

Endocrine Myopathies

- Pituitary
  - Acromegaly-Mild proximal weakness without atrophy
  - Muscles appear enlarged
  - Duration correlates with degree of myopathy
- Adrenal
  - Excess- Glucocorticoid excess=various degrees of proximal limb weakness and wasting
  - Deficiency-Fatigue with mild weakness,
  - Hyperaldosteronism (Conn's Syndrome)-Weakness due to potassium depletion, elevated CK, vacuoles on bx
- Diabetes
  - Muscle ischemic infarction: Poorly controlled DM
  - Abrupt onset pain, tenderness, and edema of one thigh
  - Hard and indurated area of infarction
  - Vastus lateralis, thigh adductors, biceps femoris
  - CT/MRI demonstrate focal abnormalities (Imaging>Bx)

Myopathy-Drug Use

- Glucocorticoid Myopathy
  - Most common drug induced myopathy
  - Prednisone equivalent >30mg/day
  - Higher risk in fluorinated glucocorticoids
  - Symmetric proximal muscle weakness, hip girdle>shoulder
  - EMG normal
  - Bx: Type 2 muscle atrophy
  - Almost always reversible
    - Improvement within 3-4 weeks of tapering steroids
    - Recovery can take months to a year

RHABDOMYOLYSIS AND MYOGLOBINURIA

Cholesterol-lowering drugs

Alcohol

Amphetamine

Heroin

Cocaine

e-Aminocaproic acid

Pentazocine

Phencyclidine

Toluene

INFLAMMATORY

D-Penicillamine

Procainamide

L-Tryptophan

Cimetidine

Levodopa

NON-INFLAMMATORY

Cholesterol-lowering agents

Steroids (associated with myosin loss)

Non-depolarizing neuromuscular blocking agents (

Chloroquine

Colchicine

Emetine

e-Aminocaproic acid

Labetalol

Cyclosporine

Isoretinoic acid

Vincristine

Alcohol

	Male CK			
	N	90th percentile	95th percentile	97.5th percentile
White	532	237 (201,273)	312 (268,356)	382 (295,469)
Black	391	544 (443,645)	712 (530,894)	1001 (718,1284)
Hispanic	304	274 (234,314)	394 (258,530)	572 (338,806)
Asian	214	267 (188,346)	378 (185,571)	520 (222,818)
	Female CK			
	N	90th percentile	95th percentile	97.5th percentile
White	655	142 (130,154)	188 (122,254)	295 (216,374)
Black	485	254 (205,303)	323 (218,428)	487 (310,664)
Hispanic	359	145 (124,166)	207 (176,238)	279 (88,470)
Asian	216	135 (120,150)	162 (139,185)	194 (163,225)

CK = creatine kinase, NHANES = National Health and Nutrition Examination Survey.

Citation

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