Myopathy

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Introduction

Objectives

- Understanding normal muscle histology and physiology
- Understanding Myopathy definition
- Understanding Approach to myopathy
- Knowing the most common hereditary myopathies
- Knowing the most common acquired myopathies

Normal Muscle

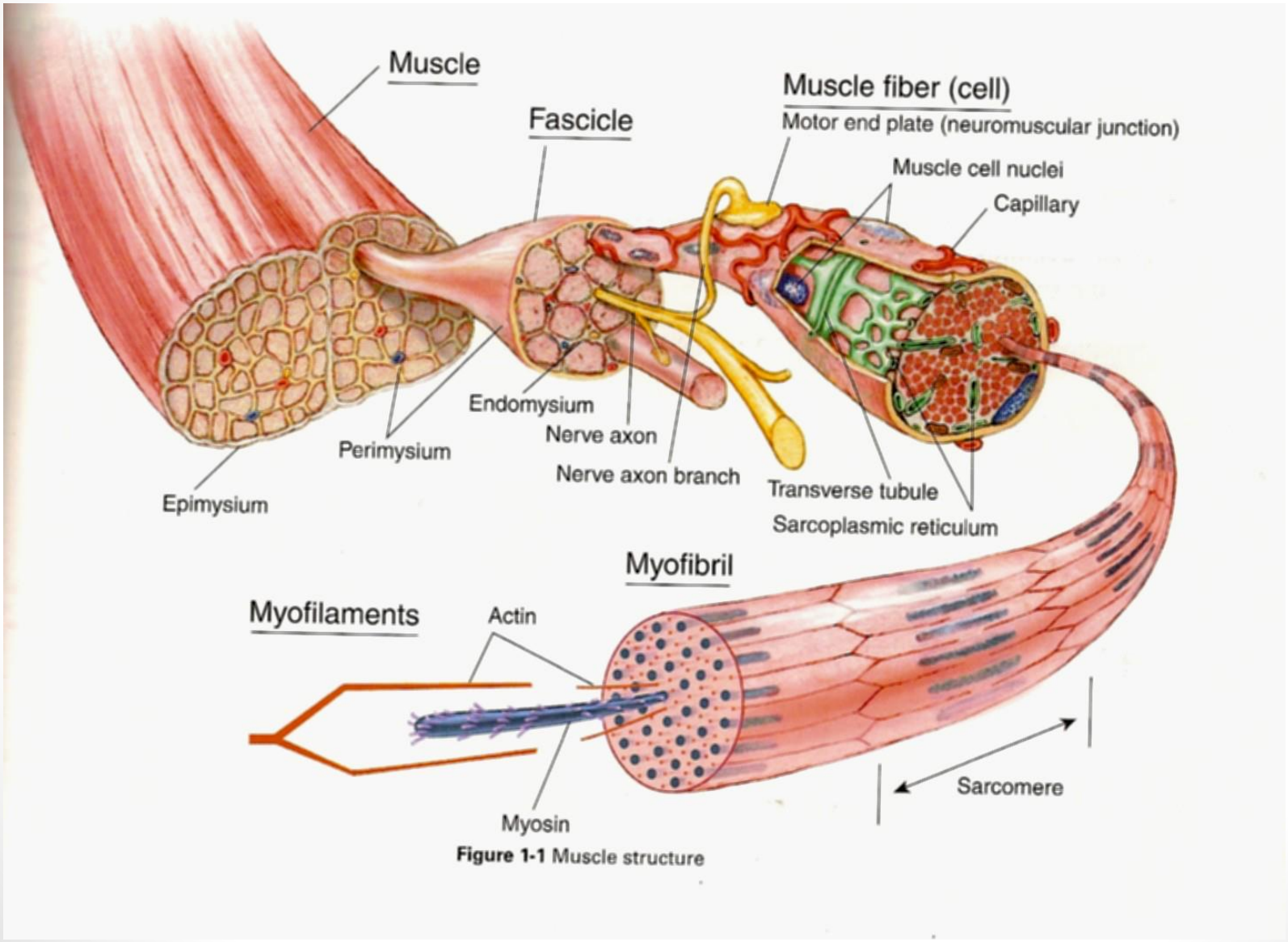
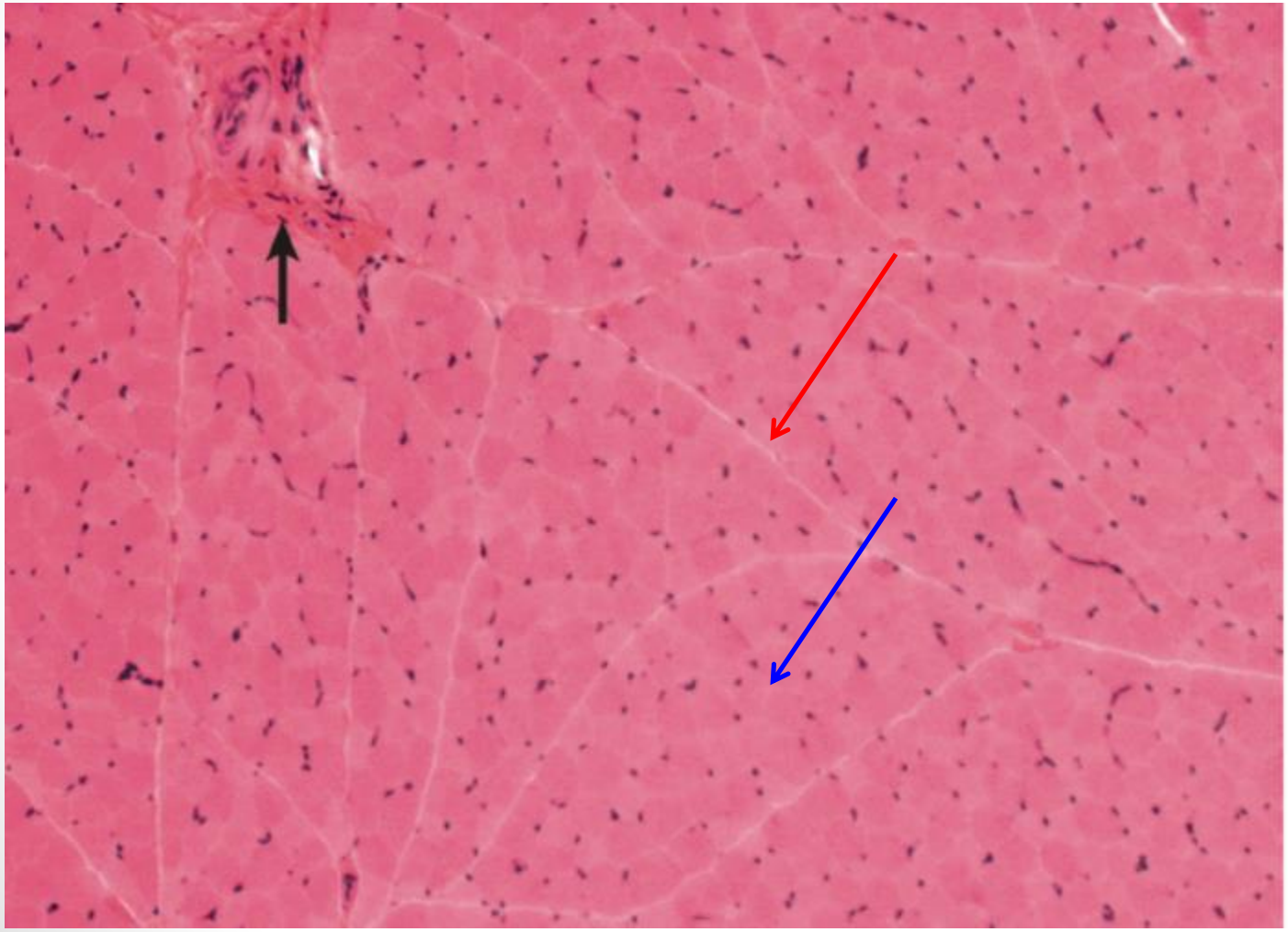
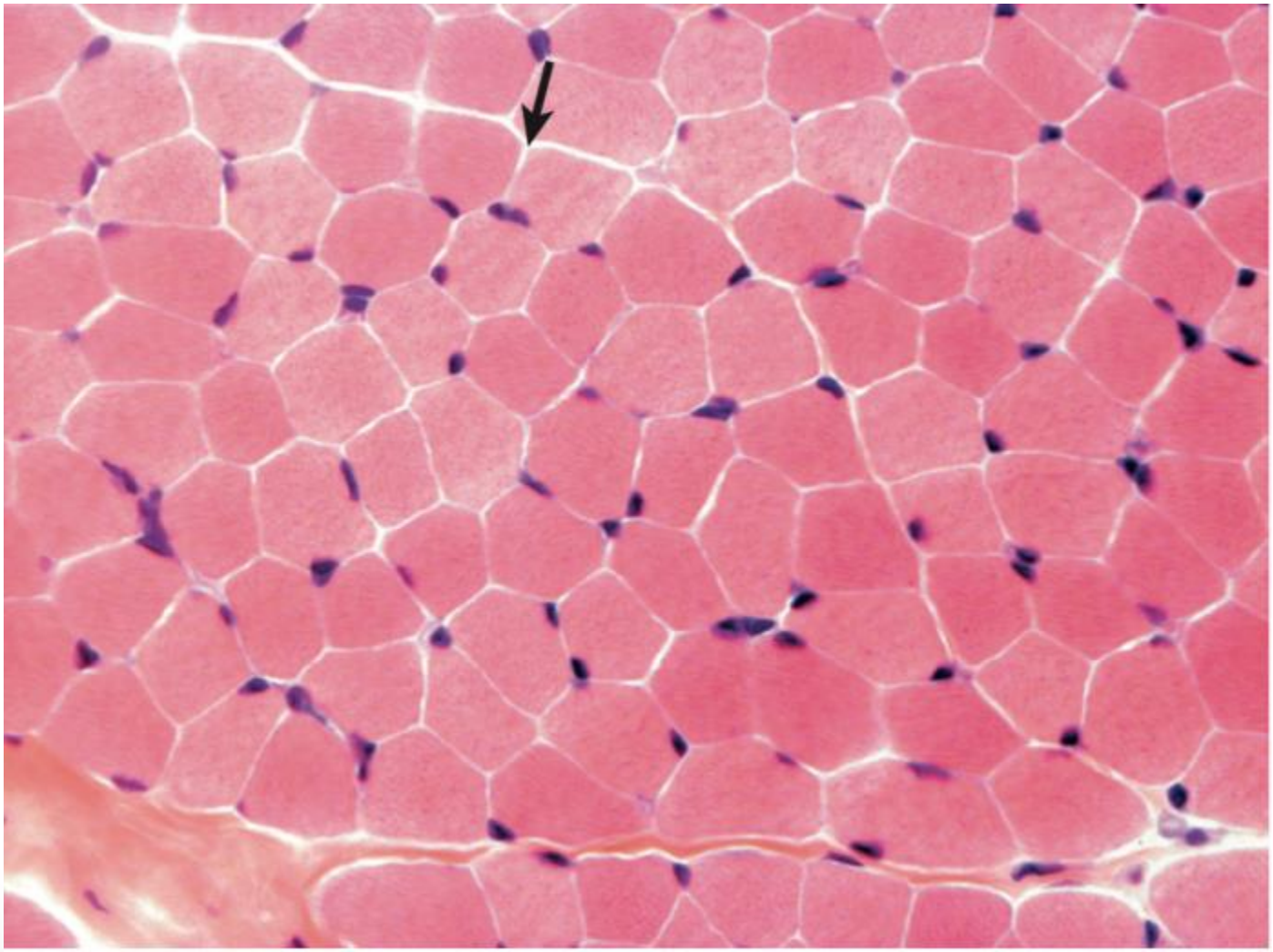


Figure 1-1 Muscle structure

Normal Muscle



Normal Muscle



Normal Muscle

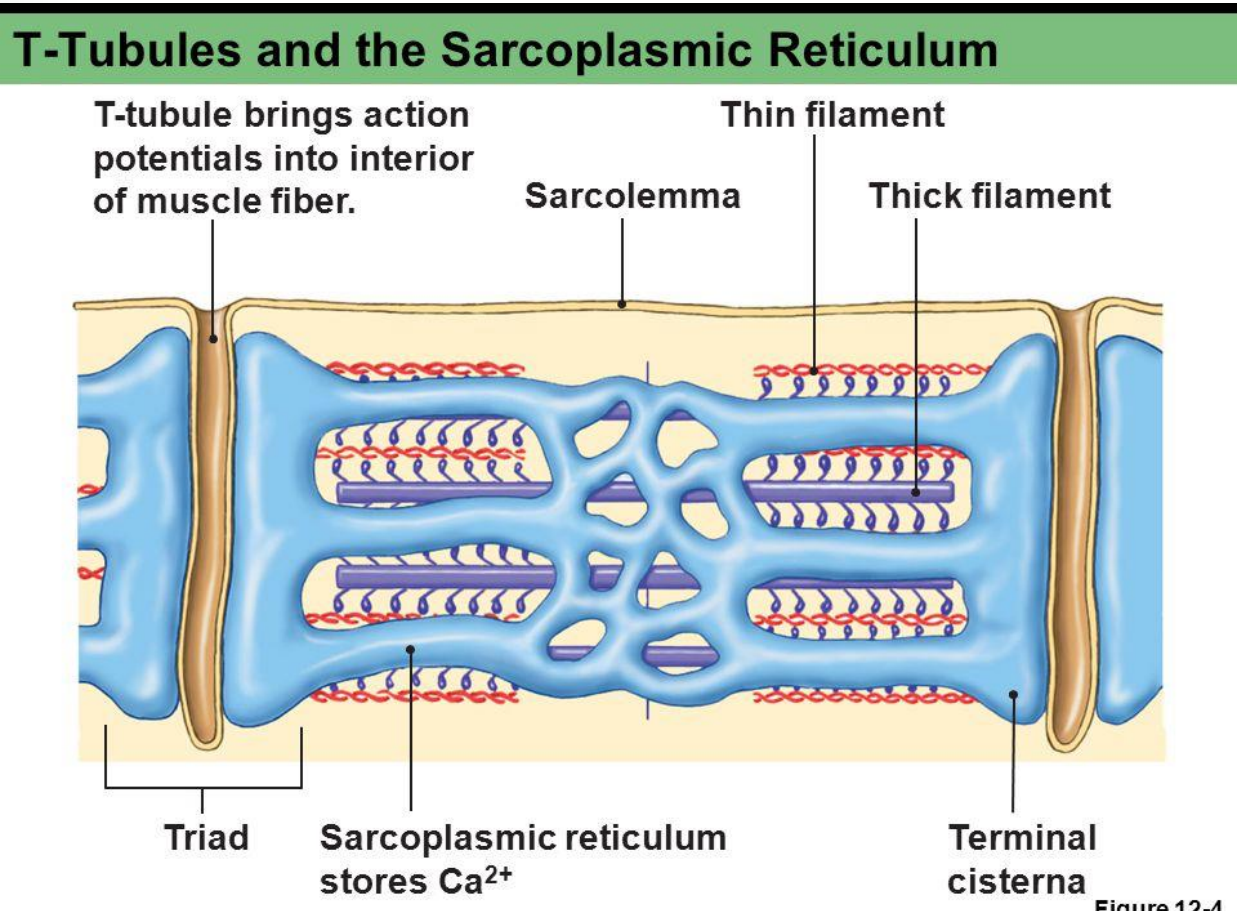


Figure 12-4

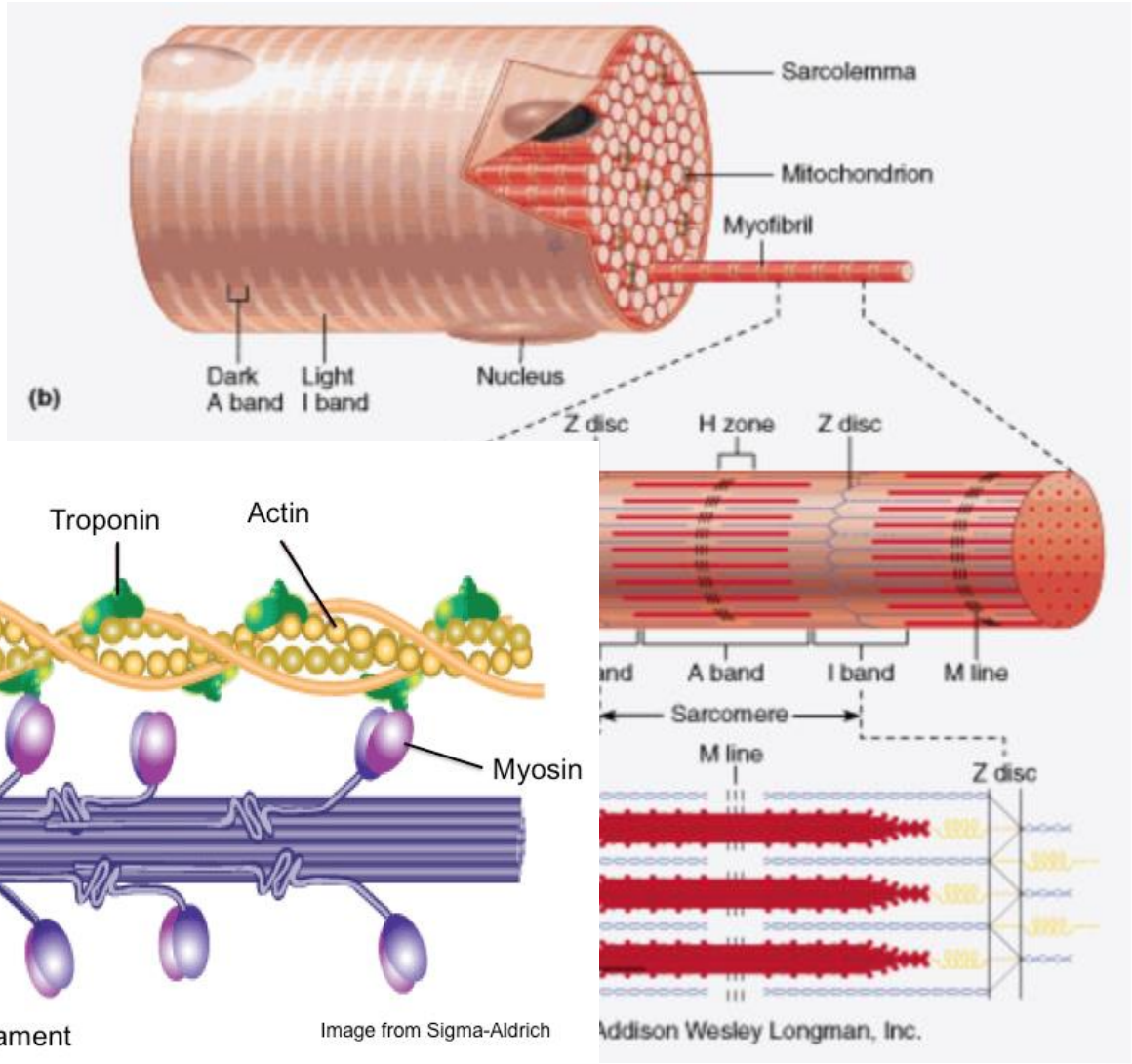
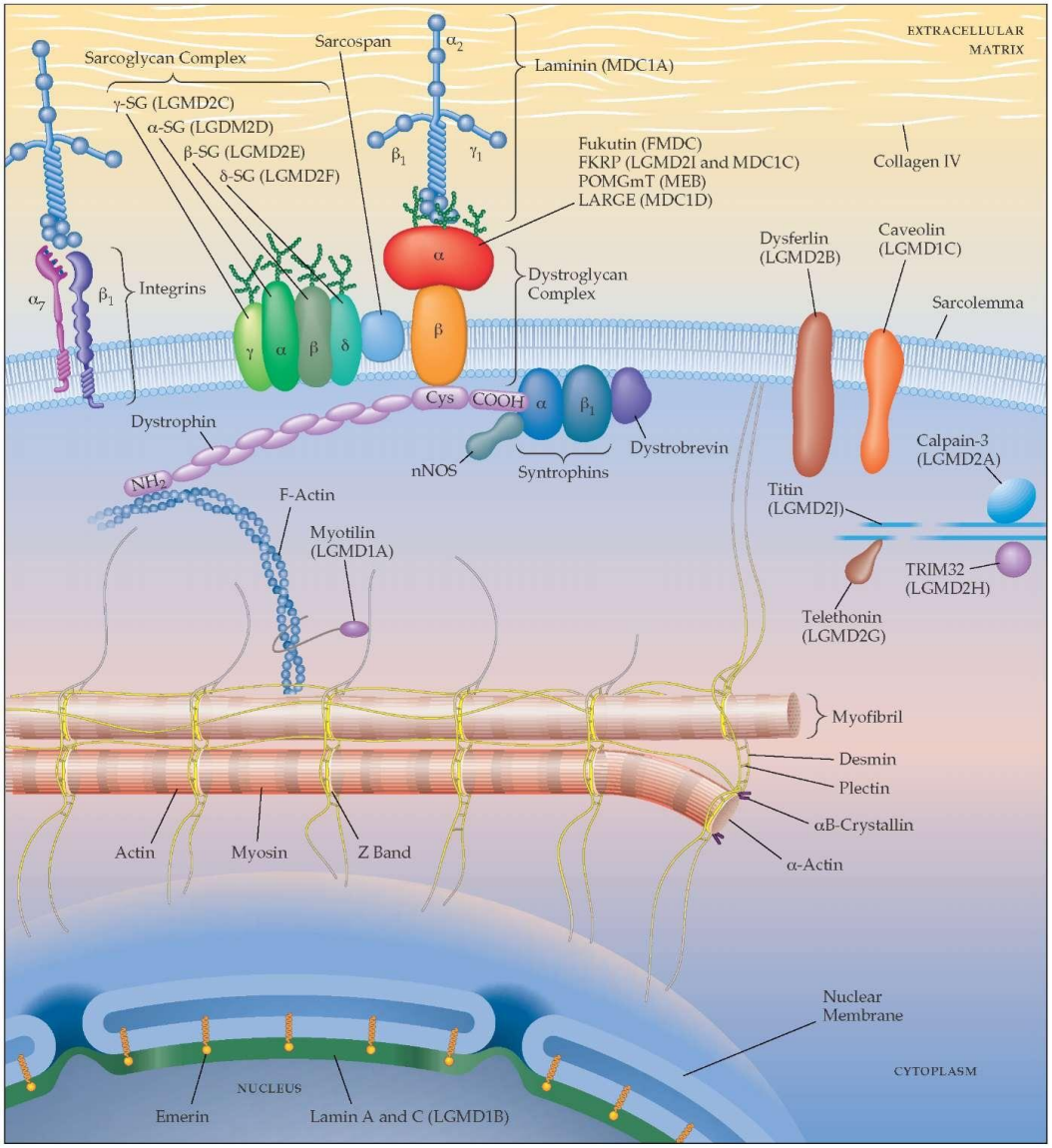


Image from Sigma-Aldrich

Normal Muscle

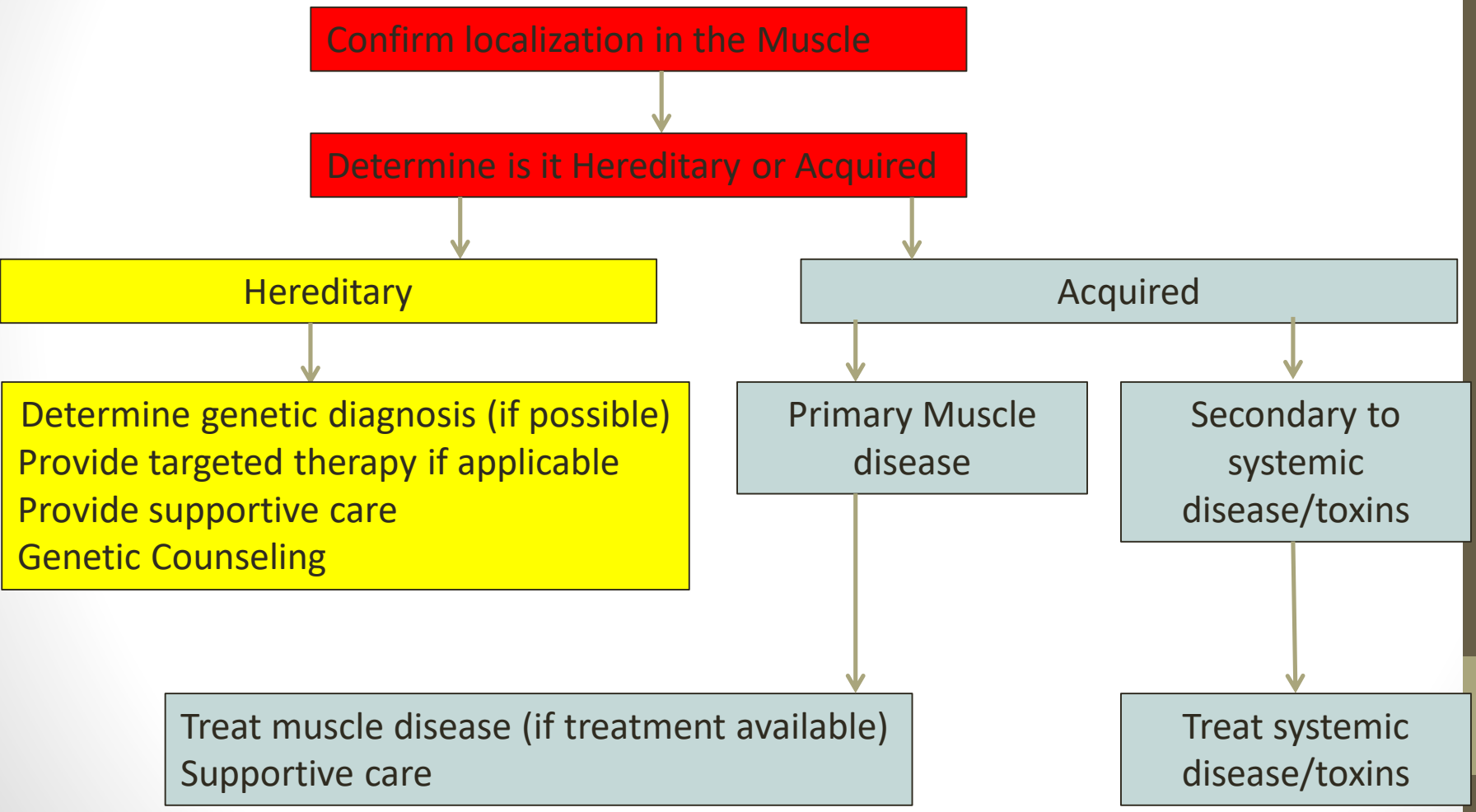


Myopathy definition

Myopathies are disorders affecting the channel, structure, or metabolism of skeletal muscle

The Big Picture

The Big Picture



Skyscraper view of the Disease !

History in Myopathy

What do we want to know ?

1- Does the patient have weakness? **(discussed later)**

2- Positive and Negative symptoms of Myopathy? **(discussed later)**

3- Age of the patient when first developed symptoms? (some myopathies unlikely to develop after a certain age limit- e.g. Duchene muscular dystrophy does not start after childhood- certain myopathies unlikely to develop before a certain age – sIBM before 40 years of age)

4- What was the onset of the myopathy? (chronic –likely inherited, acute/subacute – likely acquired)

5- distribution of weakness ? Certain myopathies have unique distribution; e.g. sIBM- usually starts in quadriceps and then to deep flexors hand + foot dorsiflexors in asymmetric fashion.

Be carful sometime patient come to you late when the weakness is diffuse try to establish where the disease started

6- Cardiac or Respiratory involvement?

7- Pharyngeal Muscle involvement?

8- Systemic symptoms?

9- Is patient coping with disease or not ? E.g. depression, anxiety..

10- what is his limitations in terms of activities of daily living? E.g. Can he feed himself, can he dress by himself…etc

8- Is patient coping with disease or not ? E.g. depression, anxiety..

9- what is his limitations in terms of activities of daily living? E.g. Can he feed himself, can he dress by himself…etc

10- Detailed family history

11- detailed medications/toxin history

History in Myopathy

TABLE 8-2 Symptoms Associated With Myopathies[a]

- **Negative**
  - Exercise intolerance
  - Fatigue
  - Muscle atrophy
  - Weakness
- **Positive**
  - Cramps
  - Contractures
  - Muscle hypertrophy
  - Myalgia
  - Myoglobinuria
  - Stiffness

History in Myopathy

Weakness:

What is the first thing you want to know when the patient say they are weak ?

1- Are they really describing weakness (people describe many things as weakness; fatigue, pain, numbness…etc)

TRUST YOUR PATIENT **BUT VERIFY**

History in Myopathy

To verify weakness by hx:

Ask about how the weakness affecting their ACTIVITIES OF DAILY LIVING

Difficulty with using arms to wash hair/difficulty w combing hair/reaching above head ----- PROXIMAL UPPER LIMB WEAKNESS

Difficulty with going up and down the stairs/ standing from sitting position----- PROXIMAL LOWER LIMB WEAKNESS

History in Myopathy

To verify weakness by hx:

Difficulty with opening door knops, opening jars-----

DISTAL UPPER LIMB WEAKNESS

Difficulty with walking due to tripping over toes , lifting their lower limb high and slapping it----

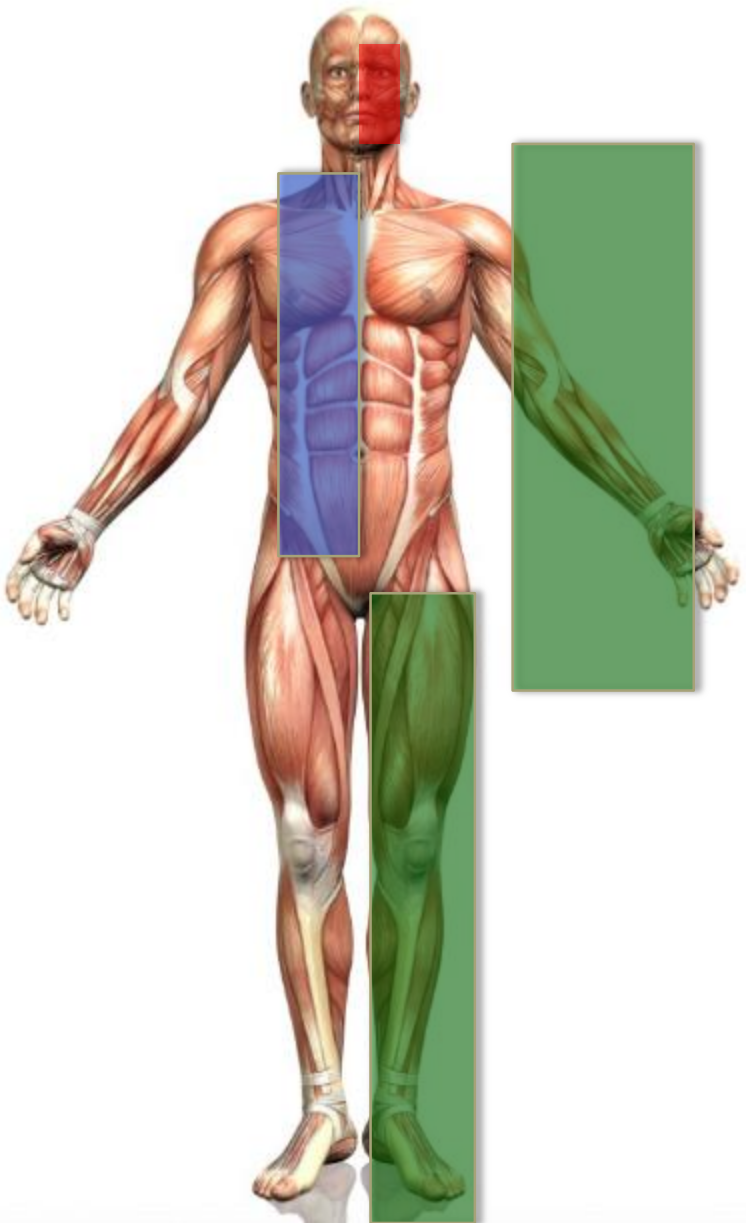
DISTAL LOWER LIMB WEAKNESS

History in Myopathy

?

Motor system is not upper and lower limbs only !

- **Occulo-facial-bulbar axis**
- **Axial (neck/diaphragm/spine/abdominal/scapular) axis**
- **Appendicular axis (upper and lower limbs)**



History in Myopathy

2- Distribution of weakness ?

Proximal > distal weakness : Acquired/inherited

Distal>proximal weakness: Acquired (e.g. Inclusion Body Myositis) Inherited (e.g. myotonic dystrophy type1)

Facial-Scapular-peroneal : inherited (FSHD)

Oculopharyngeal weakness : inherited (OPMD)

History in Myopathy

True or False:

Myopathy is always proximal more than distal weakness F

History in Myopathy

- **3- symmetrical weakness or asymmetrical ?**

True or false:

Inherited myopathies are always symmetrical F

FSHD inherited asymmetrical
IBM acquired asymmetrical

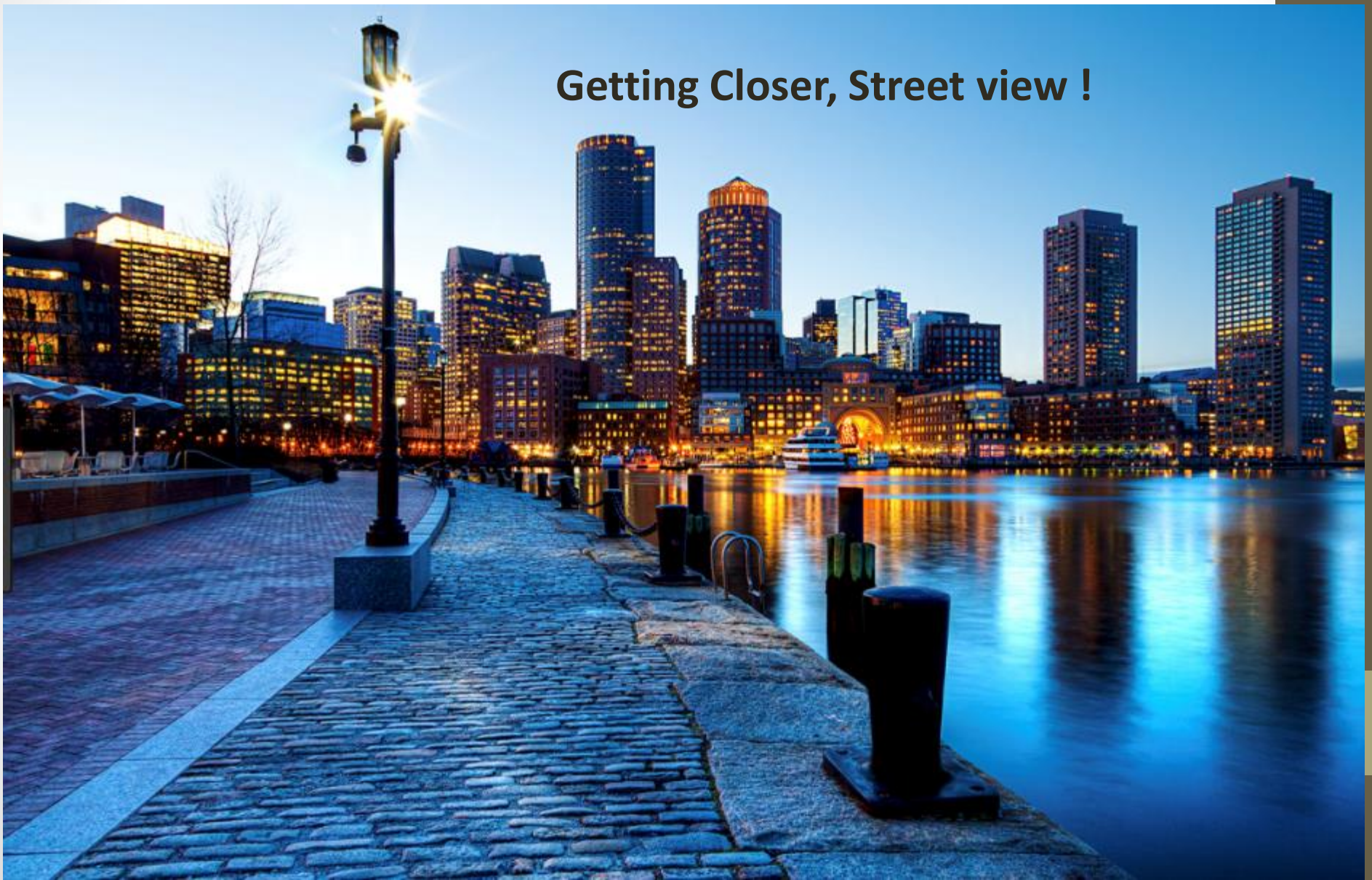
History in Myopathy

- **Temporal profile ?**

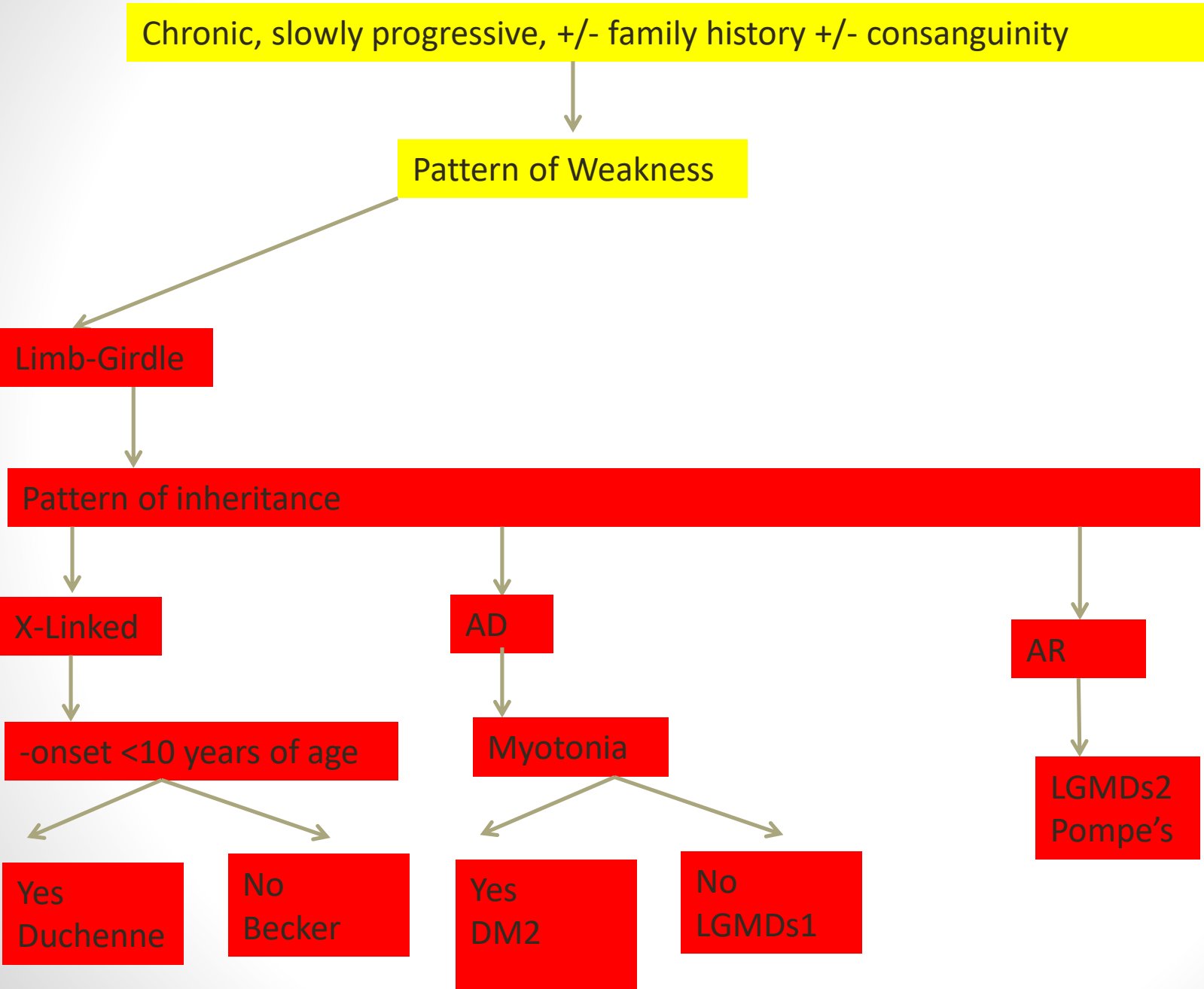
Chronic slowly progressive myopathy **+**/- family hx **+**/- consanguinity---- INHERITED MYOPATHY

Subacute onset in previously healthy person with fast progression ACQUIRED MYOPATHY

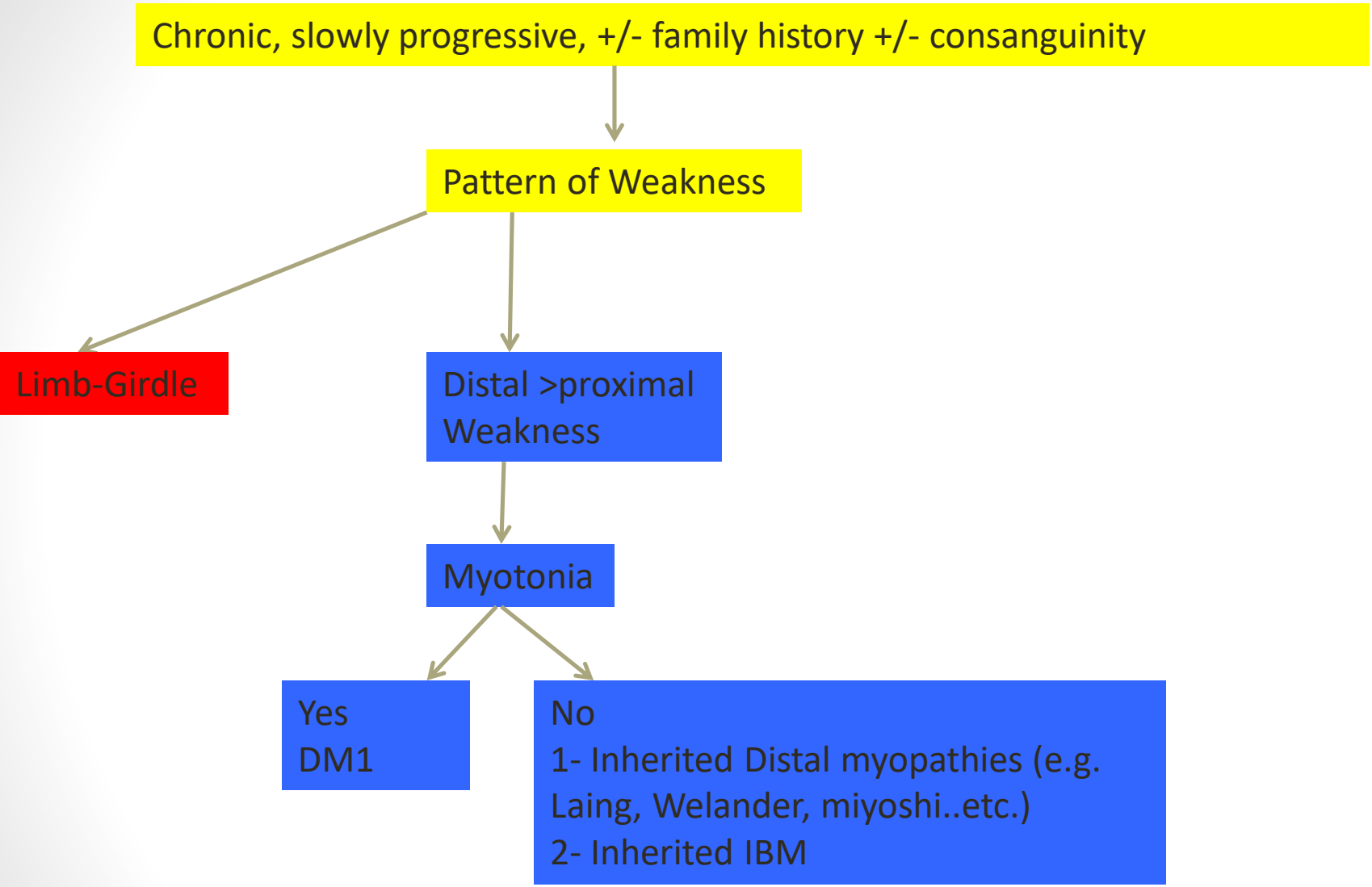
EXCEPTIONS EXIST !


Getting Closer, Street view !

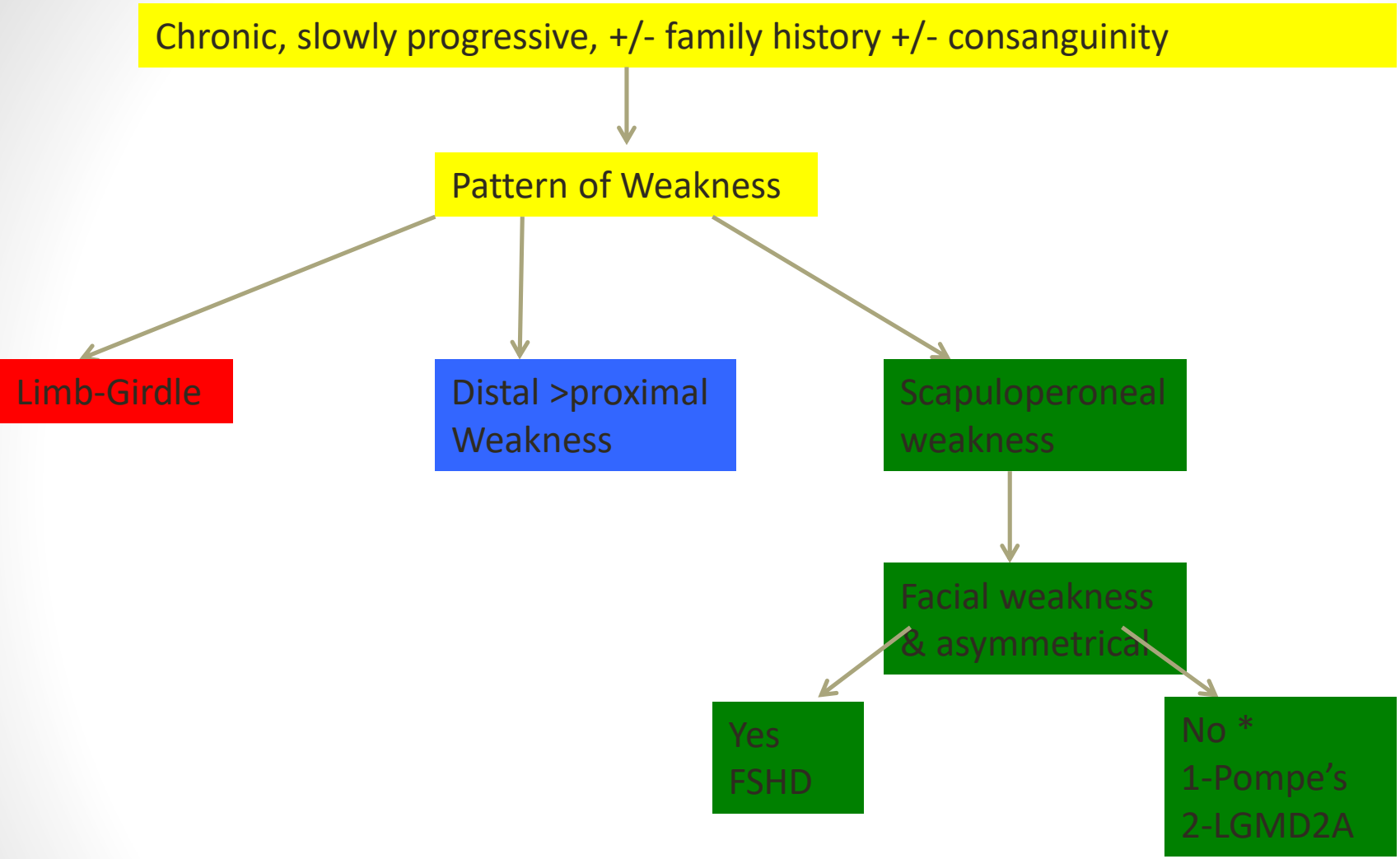
Inherited Myopathy



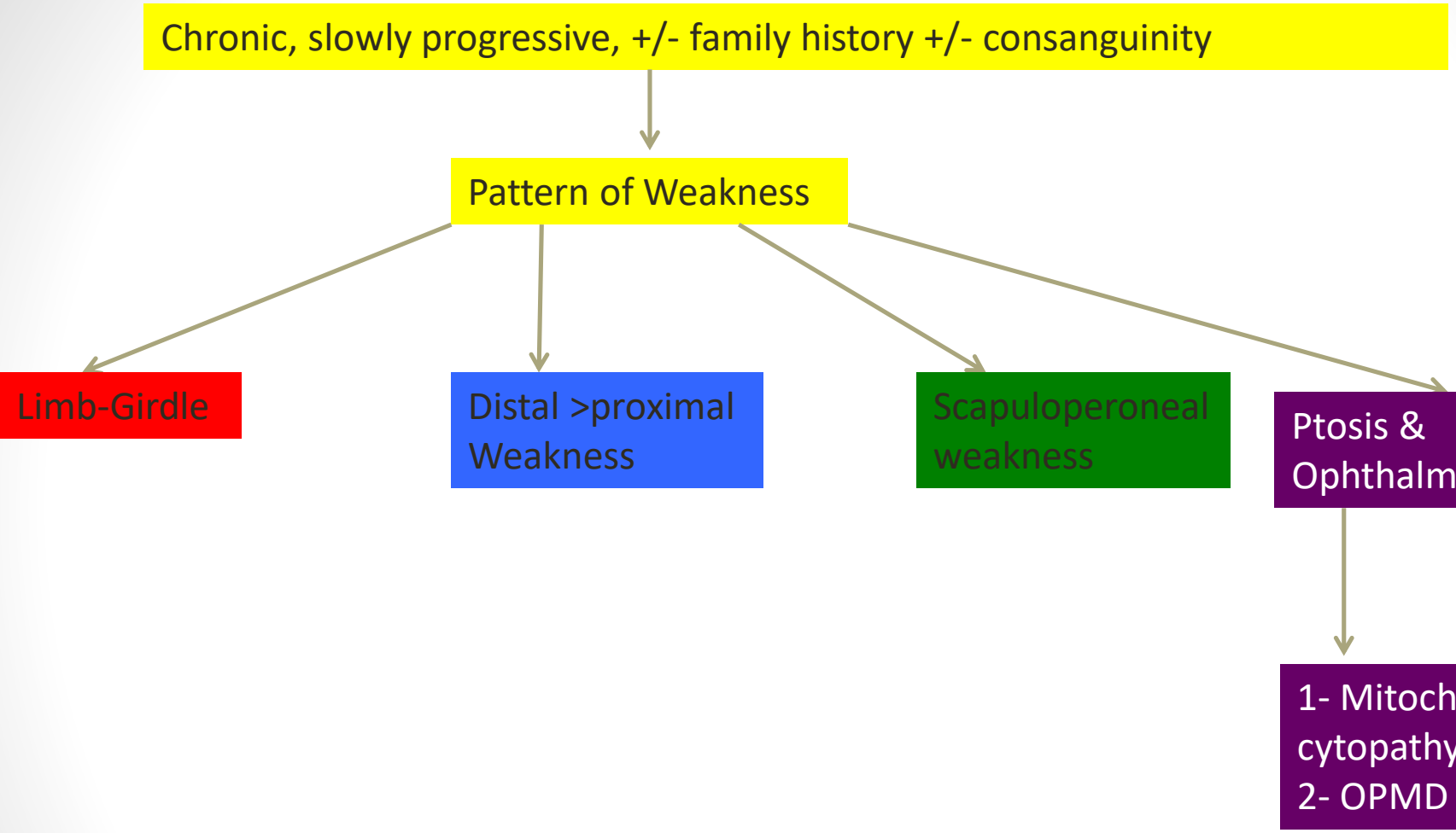
Inherited Myopathy

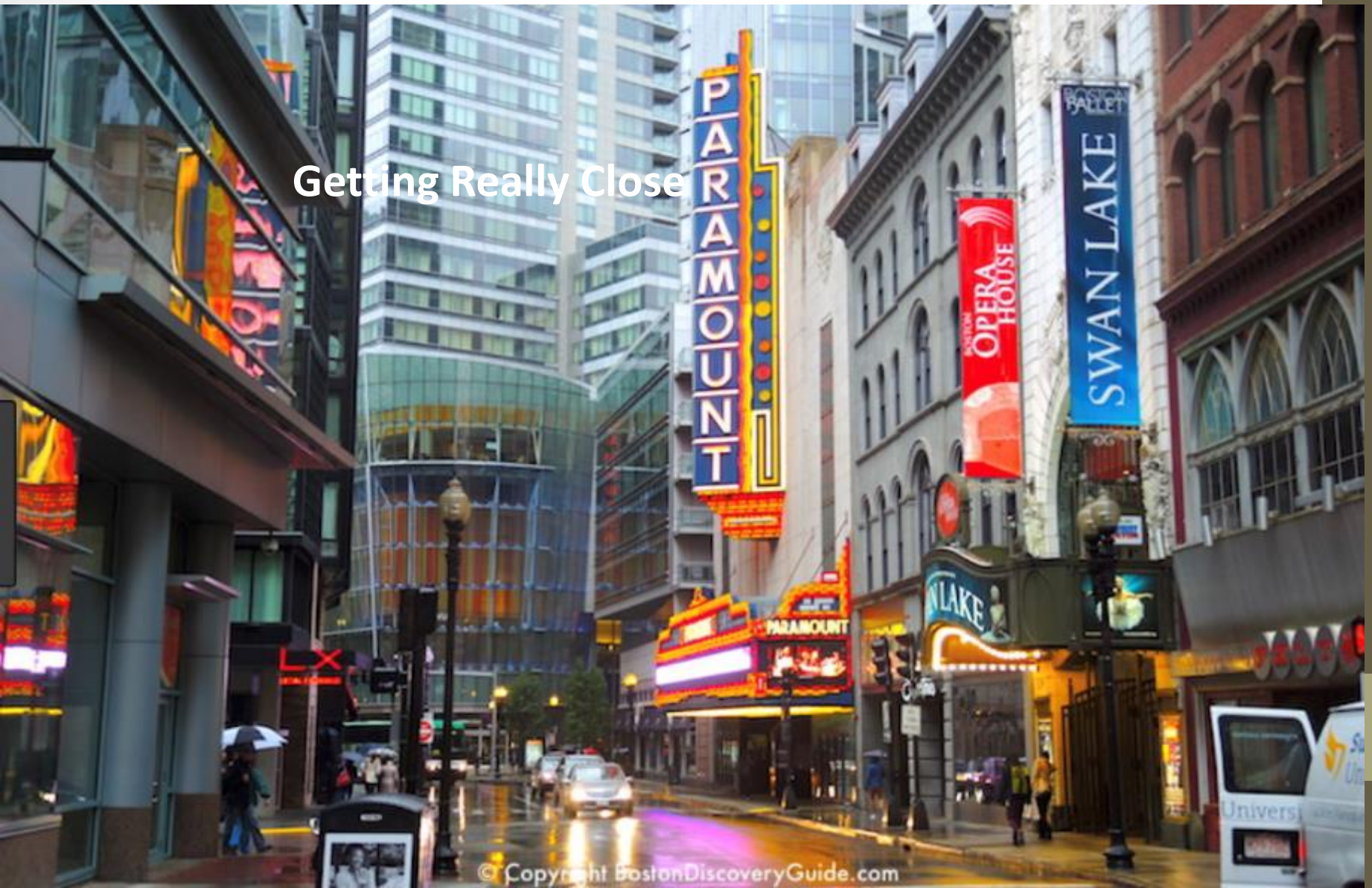


Inherited Myopathy



Inherited Myopathy




Getting Really Close
PARAMOUNT
SWAN LAKE
OPERA HOUSE
PARAMOUNT
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Inherited Myopathy

1- Abnormality in structural proteins (Dystrophinopathies, LGMD)

2- Abnormality in Mitochondria (Mitochondrial Cytopathies)

3-Abnormality in Glycogen/fat metabolism (Fat/glycogen storage diseases)

4-Abnormality in mRNA splicing (Myotonic dystrophy)

5- Abnormality resulting in toxic protein (FSHD)

Inherited Myopathy

1- Abnormality in structural proteins:

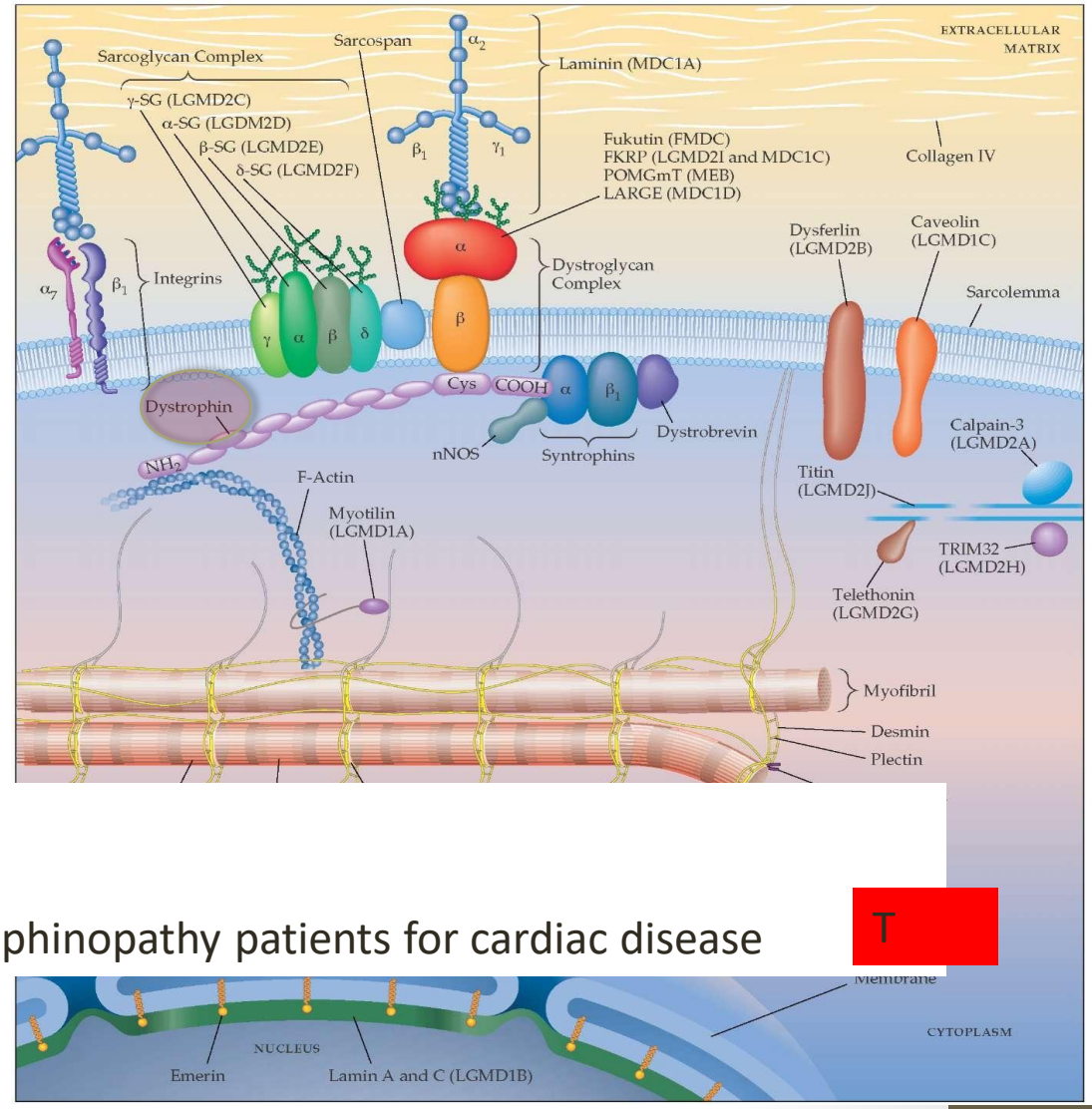
Dystrophin:

cytoplasmic protein that stabilize the cell during contraction.

Mutation in Dystrophin gene, usually X-inked, cause 2 muscular dystrophies:

1- Duchenne: severe, childhood onset (<10 y/o), calf pseudohypertrophy, contractures, initially Limb-girdle pattern, later diffuse weakness, +/-respiratory system and cardiac muscle involvement with very high CK (50-100xnormal

2- Becker's: Less severe, onset in teens or adulthood (>10 y/o),limb girdle, calf pseudohypertrophy, +/-cardiac involvement +/- respiratory, very high ck



True or false

We need to screen asymptomatic Dystrophinopathy patients for cardiac disease

T

Inherited Myopathy

1- Abnormality in structural proteins:

Limb Girdle Muscular Dystrophies(LGMD):

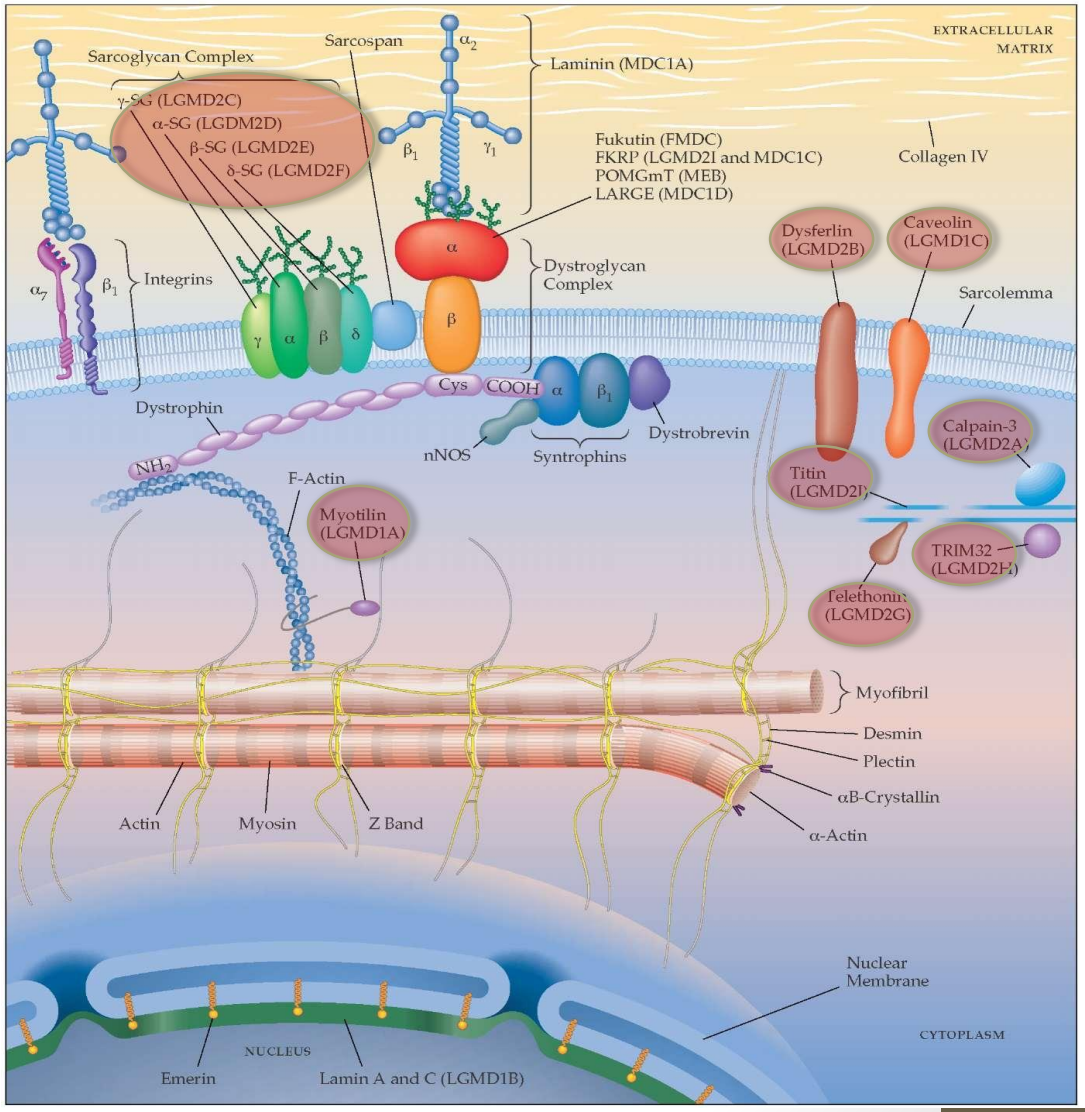
Inherited group of muscular dystrophy that share Limb-girdle pattern of weakness but have variable involvement of other muscle groups.

Divided to 2 groups based on inheritance:

1- LGMD1 (AD) group
2- LGMD2 (AR) group

LGMD2 is more common than LGMD1

The most common LGMD2 in western world is LGMD2A (Calpainopathy)



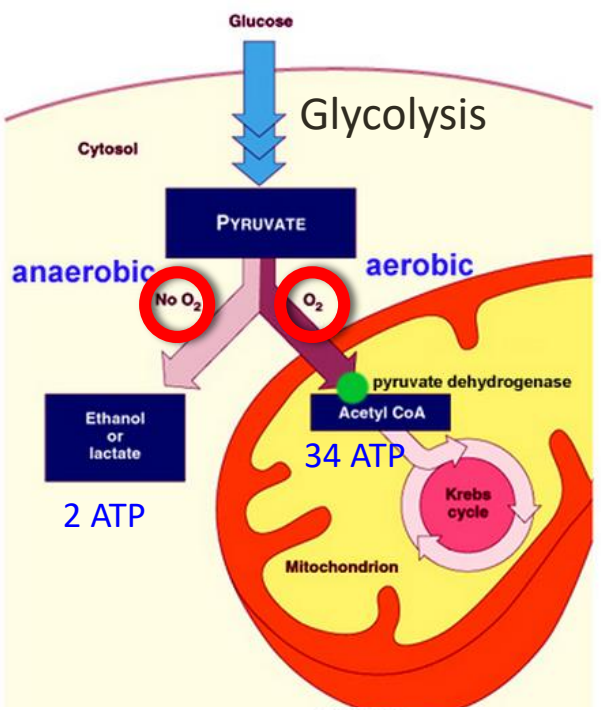
Inherited Myopathy

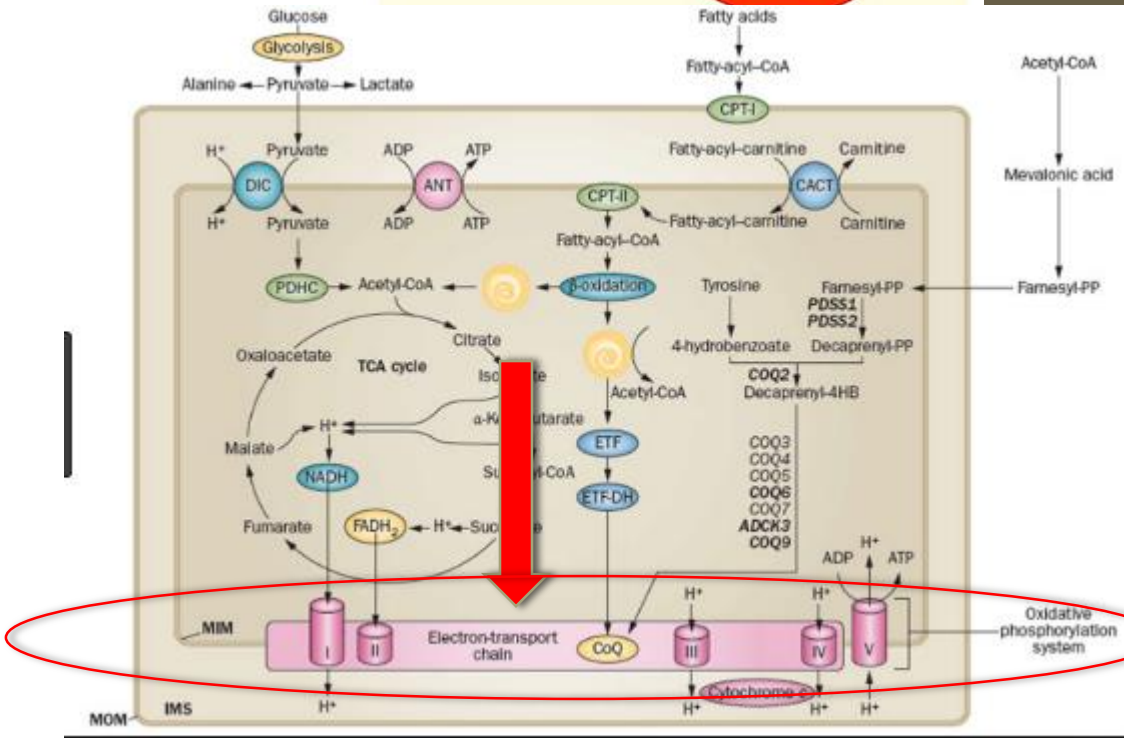
2- Abnormality in Mitochondria
(Mitochondrial Cytopathies):

Mitochondria are intracellular organelles responsible for aerobic energy production (present in all mammalian cells).

Mitochondrial cytopathies result from primary dysfunction of the mitochondrial respiratory chain.

Some components in the respiratory chain encoded by nuclear DNA and some encoded by mitochondrial DNA





Inherited Myopathy

2- Abnormality in Mitochondria (Mitochondrial Cytopathies):

Mitochondria cytopathies may result from either nuclear DNA or mitochondrial DNA mutation.

Mitochondrial cytopathies affect systems with high energy need:

1-CNS (seizures, encephalopathy, stroke like, optic neuropathy, Depression, fatigue)

2-PNS (myopathy, neuropathy), 3-cardiac (cardiomyopathy, conduction defects)

4-Endocrine (Hypo-T/ParaT/Growth hormone, DM, Gonadal failure)

5-GI (Dysmotility, hepatic failure)

There is a lot of distinct complex syndromes with combination of the above.

Inherited Myopathy

3-Abnormality in Glycogen/fat metabolism (Fat/glycogen storage diseases)

Hereditary myopathies caused by specific enzymatic defect in carbohydrate or fat metabolism.

Divided to 2 groups :

1- Episodic weakness group

2- Static Weakness group

Inherited Myopathy

3-Abnormality in Glycogen/fat metabolism (Fat/glycogen storage diseases)

1- Episodic weakness group

Episodes of exercise intolerance with muscle contractures/stiffness and pain. In severe cases may result in Rhabdomyolysis. 2 diseases :

A- Mcardle (glycogen metabolism defect)

B-CPT II deficiency (Fat metabolism defect)

Inherited Myopathy

3-Abnormality in Glycogen/fat metabolism (Fat/glycogen storage diseases)

1- Episodic weakness group

A- Mcardle: (AR)

- Enzyme defect- **muscle glycogen phosphorylase** which normally breaks glycogen (Glycogenolysis)
- Attacks happen in **short term high intensity exercise**
- In the 1st minutes of exercise Mcardle patients have energy crisis due to blocked muscle glycogenolysis and low availability of extramuscular fuels.(cause muscle symptoms and tachycardia)
- In 6-8 minutes extramuscular fuels supplies become available and the patient feels less exertion and heart rate normalize (**2nd wind phenomena**)
- CK high between attacks
- They have cramps

Inherited Myopathy

3-Abnormality in Glycogen/fat metabolism (Fat/glycogen storage diseases)

1- Episodic weakness group

B- Carnitine Palmitoyltransferase II (CPTII) deficiency (AR)

- Enzyme defect- **CPTII** which normally transport long chain FA to mitochondrial matrix

- Attacks happen with prolonged exercise and fasting
- No cramps
- CK between attacks normal.

Inherited Myopathy

3-Abnormality in Glycogen/fat metabolism (Fat/glycogen storage diseases)

2- Static Weakness group

Pompe disease (AR):

- Enzyme defect- **Acid maltase** which lead to accumulation of glycogen in lysosomes of skeletal, cardiac and smooth muscles.
- Adult onset phenotype: Weakness (onset 3rd or 4th decade) in truncal and proximal muscles (can present initially with respiratory insufficiency)
- CK elevated
- Can measure Acid maltase enzymatic activity
- Muscle biopsy
- Treatment enzyme replacement Therapy

Inherited Myopathy

4-Abnormality in mRNA splicing (Myotonic dystrophy)

Myotonic Dystrophy 1

- AD from expantion of triplet repeat (CTG) on the myotonic dystrophy protein kinase (DMPK) gene.

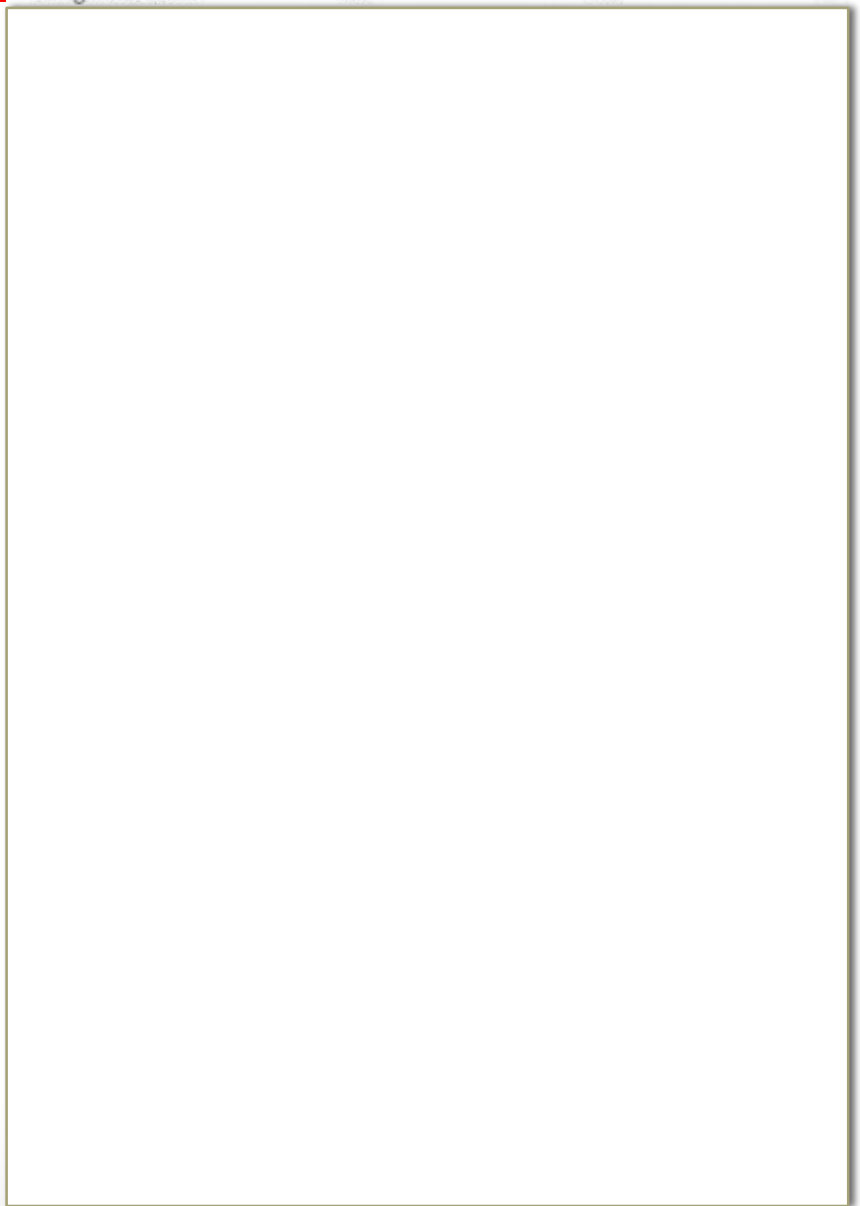
Myotonic Dystrophy 2

- AD from expantion of triplet repeat (CCTG) on the Zinc Finger protein 9 (ZNF9) gene.

Inh

4-Abnorma strophy)

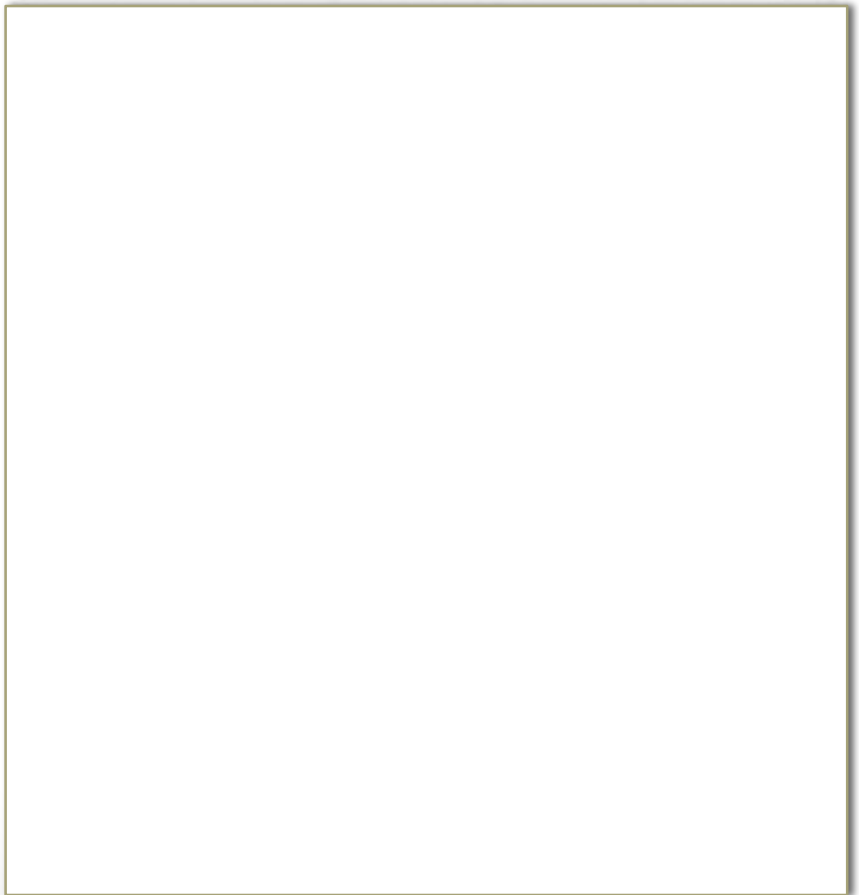
Feature	DM1	DM2
Epidemiology	Widespread	Regionally selective
Age of onset	Any	Adulthood
Anticipation	Yes	No/mild
Congenital form	Yes	No



Inh

4-Abnorma strophy)

Feature	DM1	DM2
Epidemiology	Widespread	Regionally selective
Age of onset	Any	Adulthood
Anticipation	Yes	No/mild
Congenital form	Yes	No
Muscle		
Weak face/neck/swallow	Common	Uncommon
Weak limbs—proximal	Late	Early
Weak limbs—distal	Early	Late
Myotonia	Mild to moderate	Mild to moderate
Myalgia	Mild to moderate	Mild to severe



Inh

4-Abnorma ystrophy)

Feature	DM1	DM2
Epidemiology	Widespread	Regionally selective
Age of onset	Any	Adulthood
Anticipation	Yes	No/mild
Congenital form	Yes	No
Muscle		
Weak face/neck/swallow	Common	Uncommon
Weak limbs—proximal	Late	Early
Weak limbs—distal	Early	Late
Myotonia	Mild to moderate	Mild to moderate
Myalgia	Mild to moderate	Mild to severe
Systemic		
Cataracts	Very common/early	Common
Frontal balding	Very common	Uncommon
Cardiac arrhythmias	Very common/early	Common/late
Respiratory failure	Very common/late	Uncommon/late
Cognitive disorder	Common/mild to severe	Uncommon/mild
Gonadal failure	Common	Uncommon
Excessive daytime sleepiness	Very common and early	Common and late
Hyperhidrosis	Mild	Mild to severe

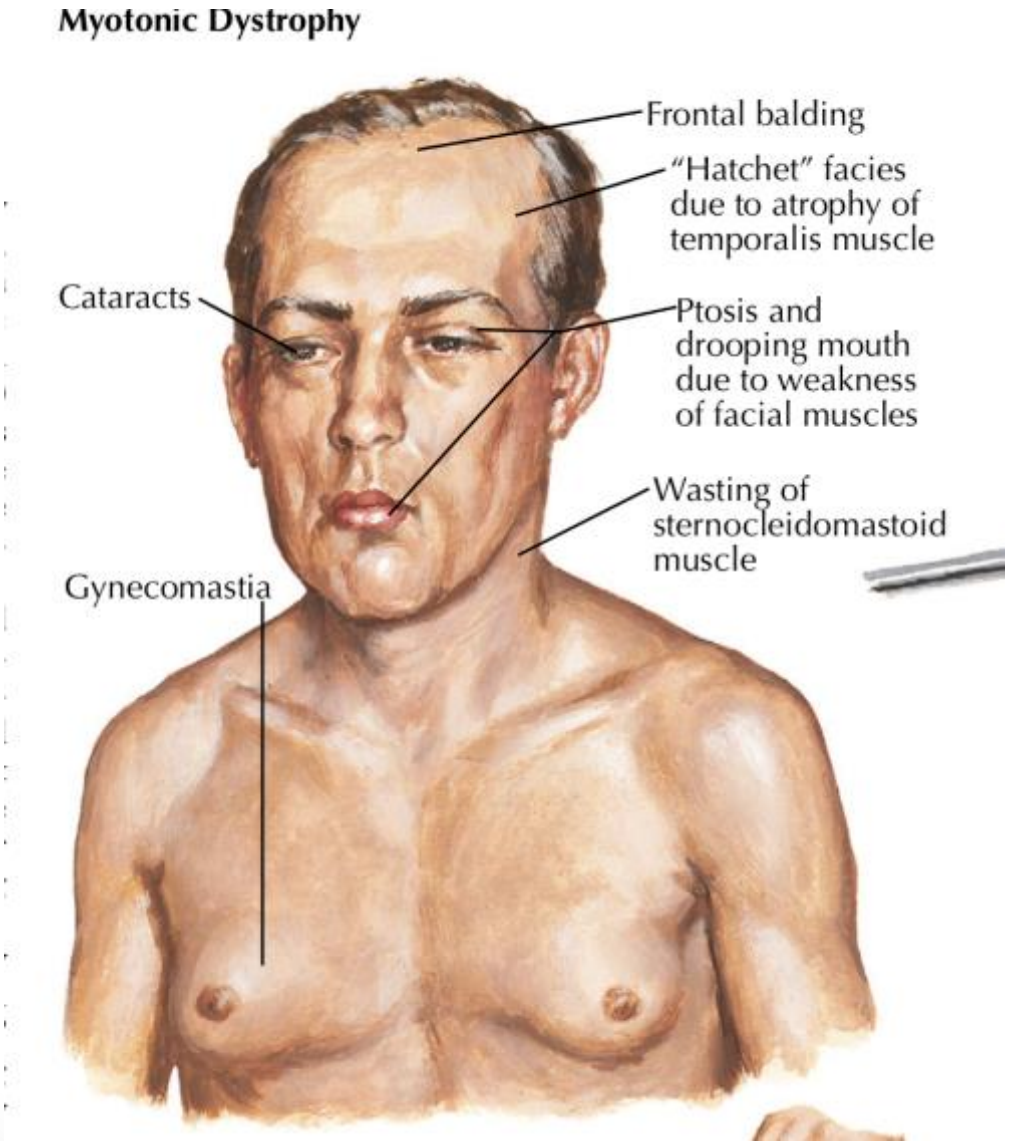
Inh

4-Abnorma strophy)

Feature	DM1	DM2
Epidemiology	Widespread	Regionally selective
Age of onset	Any	Adulthood
Anticipation	Yes	No/mild
Congenital form	Yes	No
Muscle		
Weak face/neck/swallow	Common	Uncommon
Weak limbs—proximal	Late	Early
Weak limbs—distal	Early	Late
Myotonia	Mild to moderate	Mild to moderate
Myalgia	Mild to moderate	Mild to severe
Systemic		
Cataracts	Very common/early	Common
Frontal balding	Very common	Uncommon
Cardiac arrhythmias	Very common/early	Common/late
Respiratory failure	Very common/late	Uncommon/late
Cognitive disorder	Common/mild to severe	Uncommon/mild
Gonadal failure	Common	Uncommon
Excessive daytime sleepiness	Very common and early	Common and late
Hyperhidrosis	Mild	Mild to severe
Laboratory		
Hyperinsulinaemia	Common/mild	Common/moderate
Electromyography: myotonia	Very common	Common
Chromosome	19q13.3	3q.21
Gene	*DMPK*	*ZNF9*
Mutation type	CTG repeat	CCTG repeat
Repeat size	50–4000	Mean in 1000s

Inherited Myopathy

4-Abnormality in mRNA splicing (Myotonic dystrophy)



Inherited Myopathy

4-Abnormality in mRNA splicing (Myotonic dystrophy)

True or false

We need to screen asymptomatic Myotonic dystrophy patients for cardiac disease T

Inherited Myopathy

4-Abnormality in mRNA splicing (Myotonic dystrophy)

Inherited Myopathy

4-Abnormality in mRNA splicing (Myotonic dystrophy)

True or False:
Myotonia on EMG only happen in Myotonic Dystrophy

F

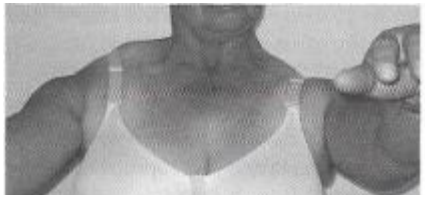
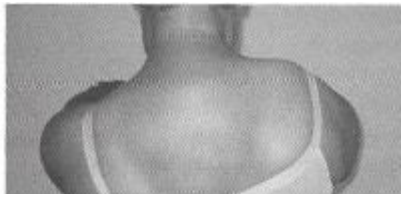
Inherited Myopathy

5- Abnormality resulting in toxic protein (FSHD)

Autosomal dominant.

ASYMMETRICAL facial-scapulo-peroneal weakness.



True or false

We need to screen asymptomatic FSHD patients for cardiac disease

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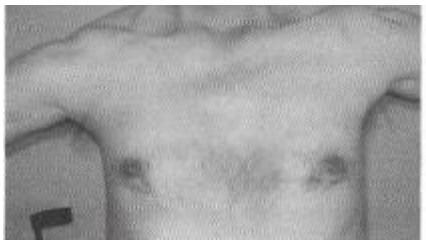
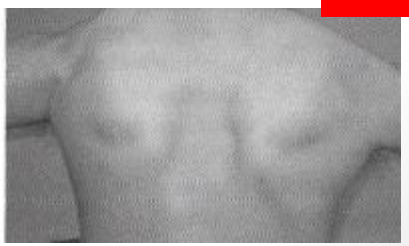



Acquired Myopathy

Inflammatory Myopathy:

1- Polymyositis

2-Dermatomyositis

3- Sporadic IBM

Polymyositis

- **Diagnostic Criteria:**

1- Subacute (weeks to months) symmetrical limb girdle, neck flexors weakness.

2- elevated serum CK

3- EMG finding of irritable myopathy

4- Muscle biopsy consistent with polymyositis

5- Order Myositis antibody panel

Treatment : Immunosuppression, screen for malignancy (3-5 years)& monitor for ILD

Dermatomyositis

- **Diagnostic Criteria:**

1- Subacute (weeks to months) symmetrical limb girdle, neck flexors weakness.

2- Skin changes consistent with dermatomyositis

3- elevated serum CK

4- EMG finding of irritable myopathy

5- Muscle biopsy consistent with Dermatomyositis

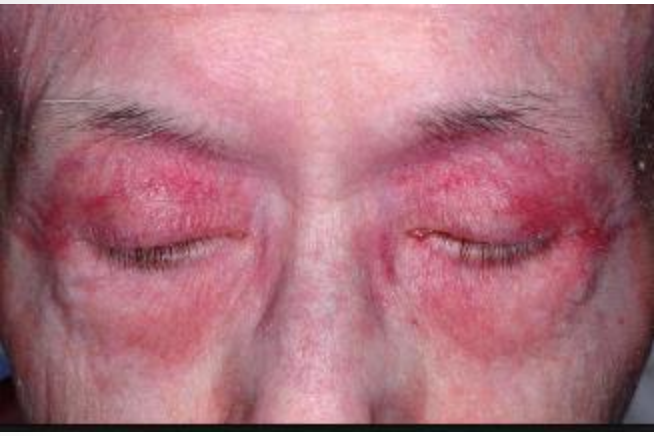
6- Increased risk of malignancy

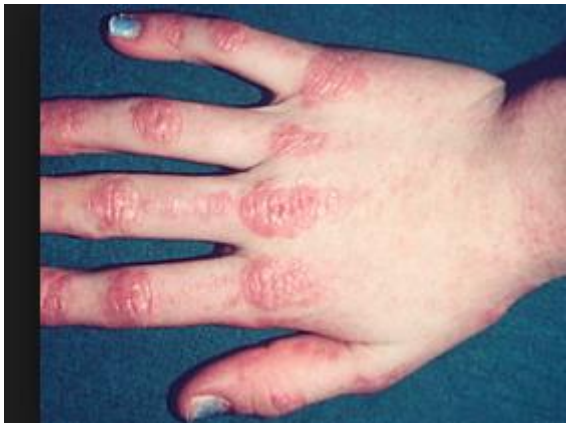
7- increased risk of interstitial lung disease(ILD)

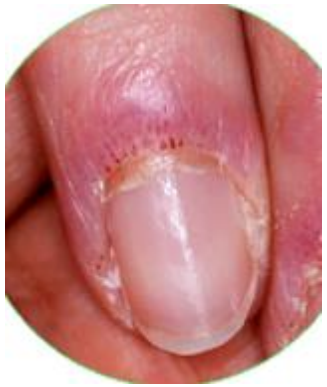
8-Order Myositis panel

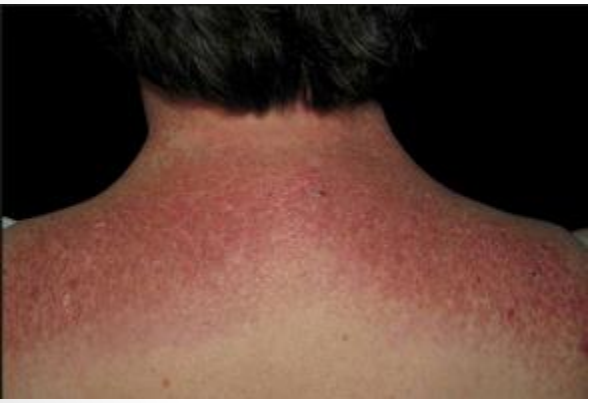
Treatment : Immunosuppression, screen for malignancy & ILD

Dermatomyositis









Inclusion Body Myositis

Diagnosis:

Insidious onset of proximal and distal asymmetrical weakness (wrist and finger flexors, quadriceps and ankle dorsiflexion), Severe dysphagia develops

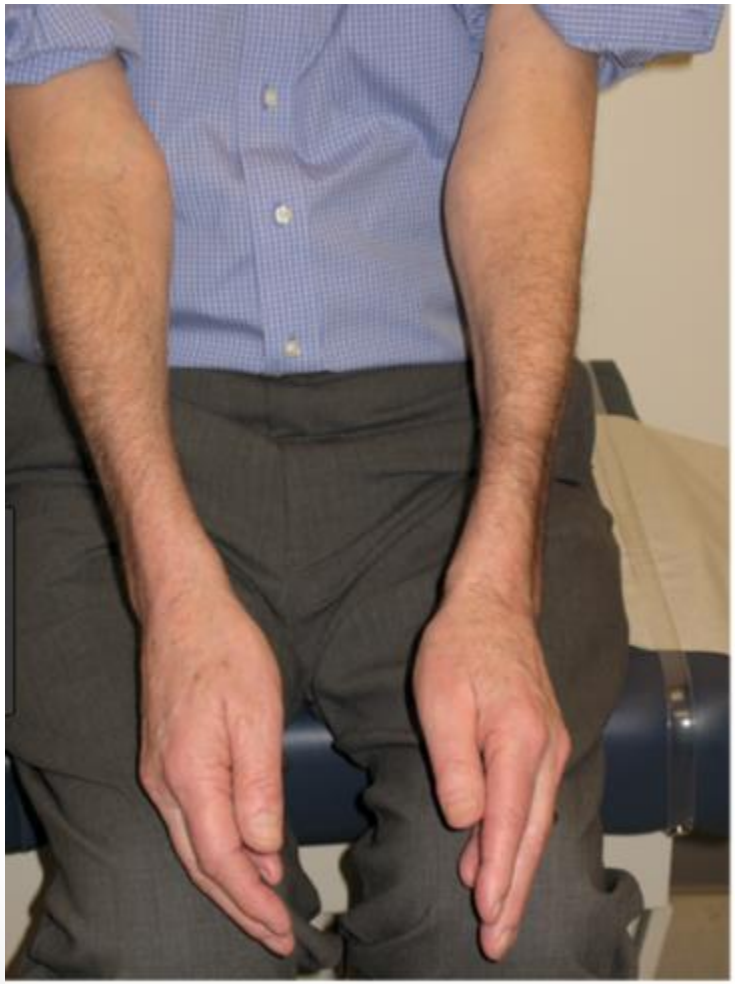
EMG: irritable myopathy

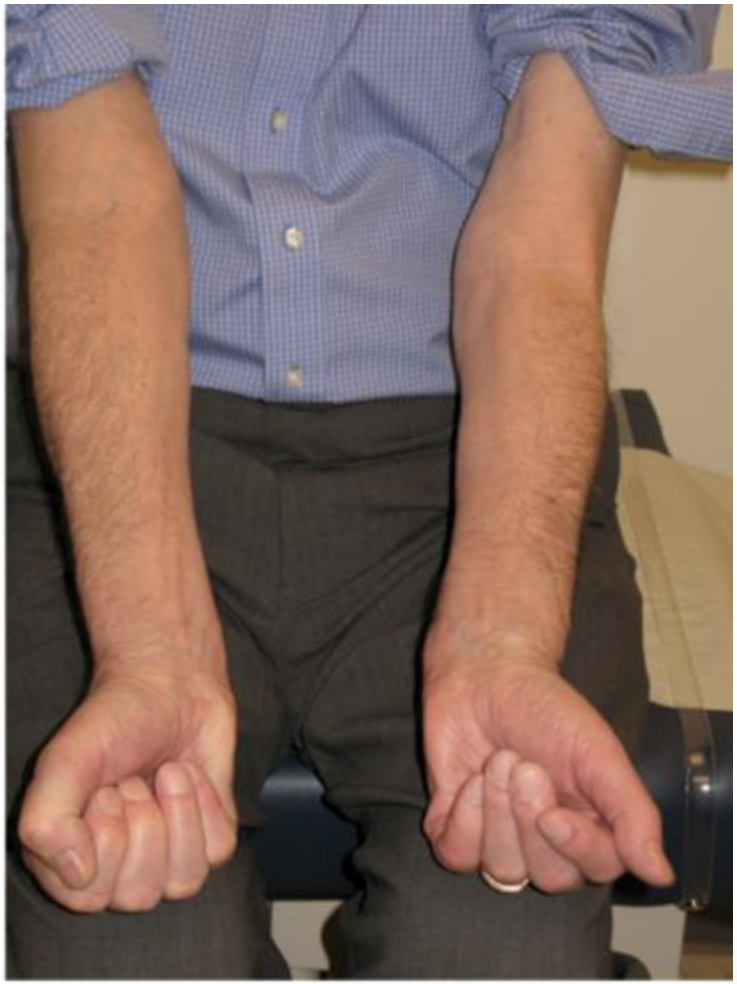
Biopsy suggestive of IBM

Severe dysphagia develops

Treatment: supportive

Inclusion Body Myositis






Thank
you!