Inherited diseases of skeletal muscles

Dr Tehmina

Learning objectives

- Describe genetic abnormality, morphology and clinical features of Muscular Dystrophies

Introduction

- Inherited mutations are responsible for a diverse collection of disorders marked by defects in skeletal muscle. In some of these disorders, skeletal muscle is the main site of disease, but in others multiple organs are involved.
- Muscular dystrophies and congenital myopathies that result from mutations disrupting the function of proteins are important for various aspects of muscle development, function, and regeneration. Some of these diseases present in infancy, others in adulthood. They may be relentlessly progressive or cause relatively static deficits.

- Muscular dystrophies include several inherited disorders of skeletal muscle that have in common progressive muscle damage that typically manifests itself between childhood and adulthood.

- The prevalence for congenital muscular dystrophy seems to be between 2.6-4.5 in 10,000 according to Reed, 2009

Genetics

- The genetics of congenital muscular dystrophy are autosomal recessive which means two copies of an abnormal gene must be present for the disease or trait to happen. In the case of collagen VI-deficient, it is autosomal dominant, which means a child could inherit the disease from only one copy of a gene present in only one parent.

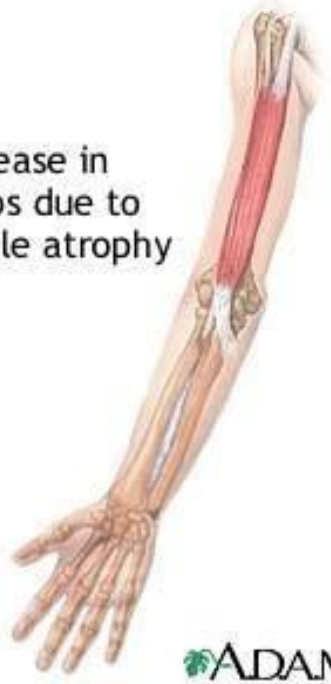
- **Sex-linked:** DMD, BMD, EDMD
- **Autosomal recessive:** LGMD, infantile FSHD
- **Autosomal dominant:** FSHD,

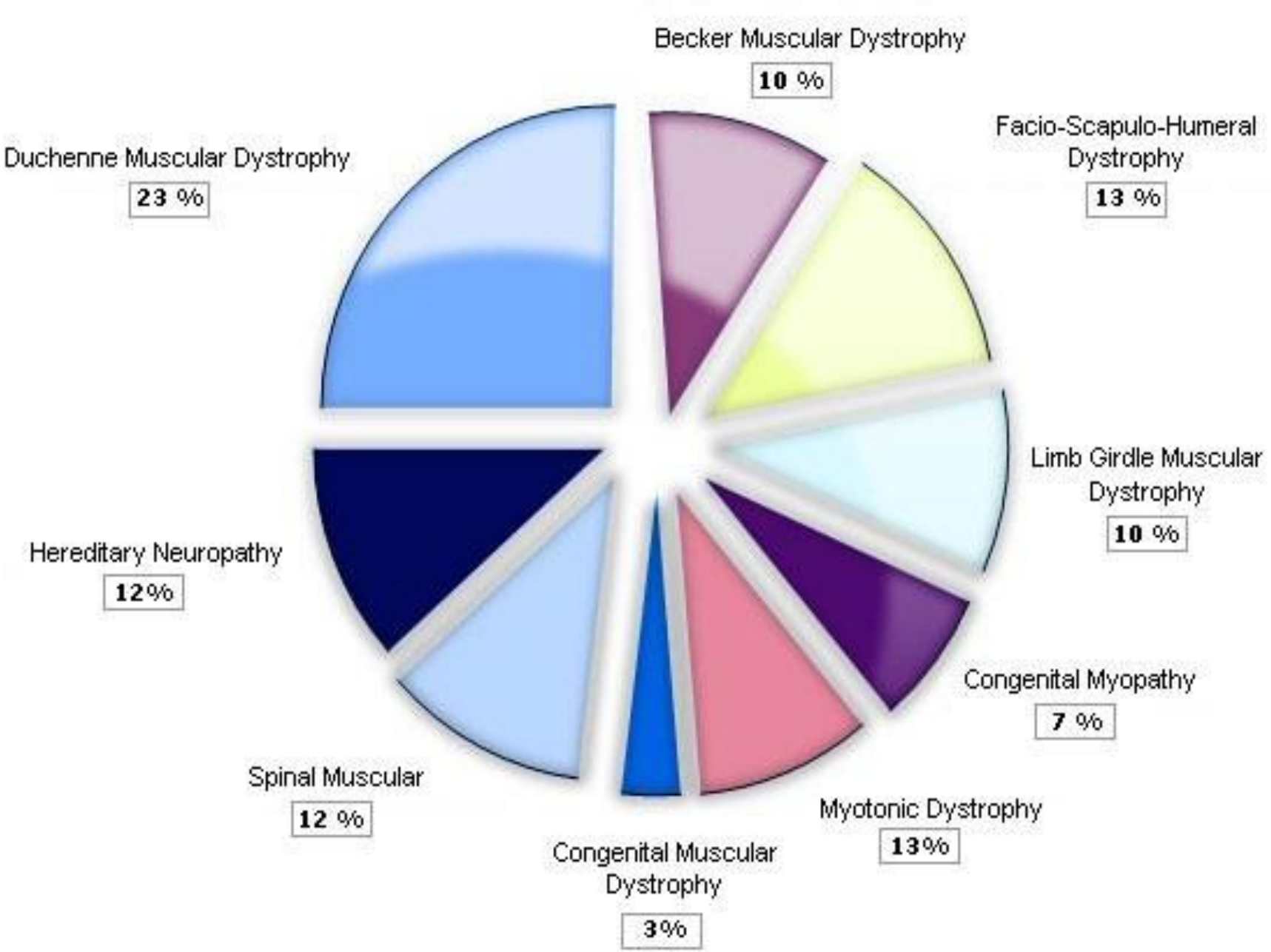
  Distal MD, ocular MD, oculopharyngeal MD.

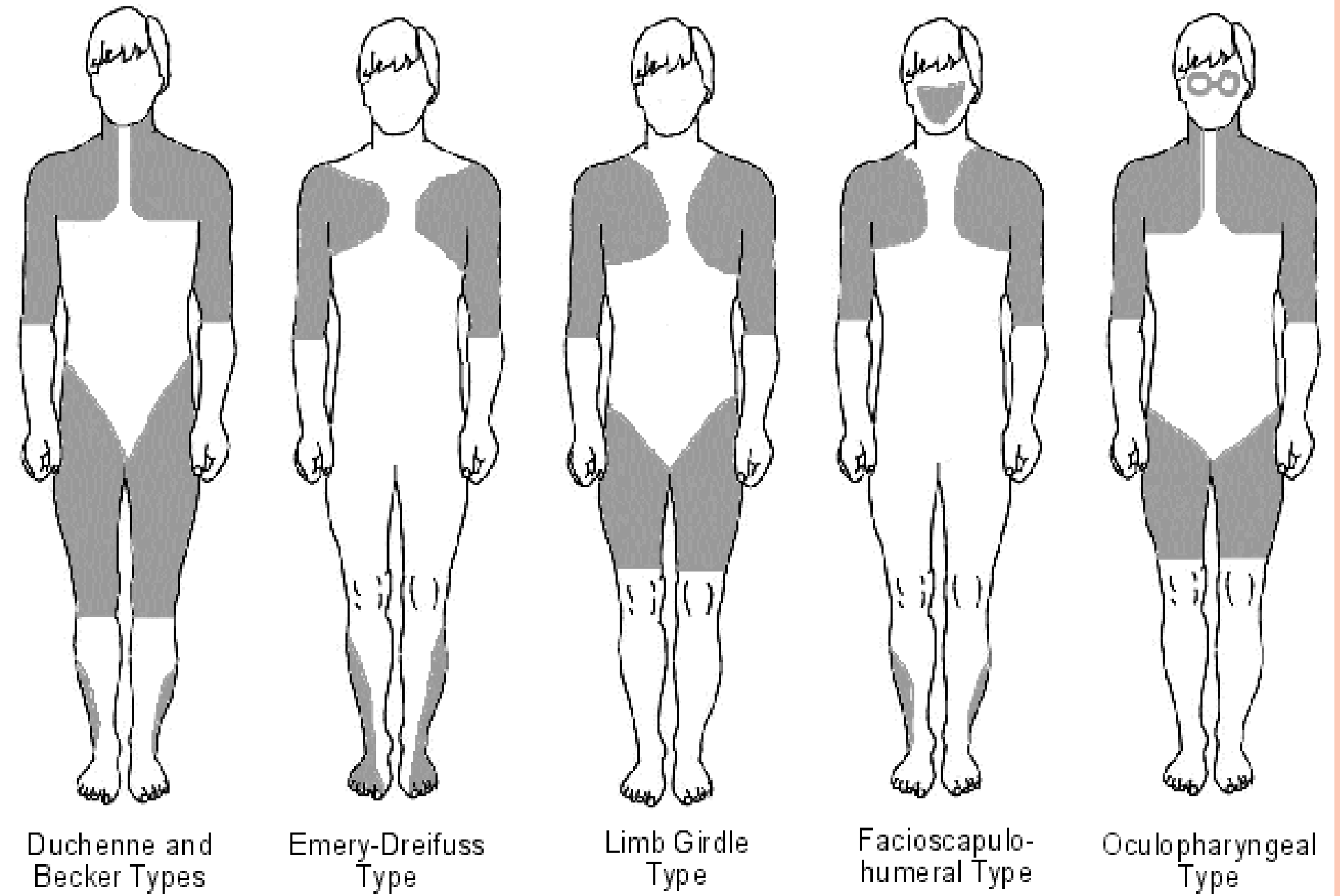
Muscular Dystrophy

Normal biceps

Biceps with MD




Becker Muscular Dystrophy
10 %
Facio-Scapulo-Humeral Dystrophy
13 %
Duchenne Muscular Dystrophy
23 %
Limb Girdle Muscular Dystrophy
10 %
Hereditary Neuropathy
12%
Congenital Myopathy
7 %
Spinal Muscular
12 %
Myotonic Dystrophy
13%
Congenital Muscular Dystrophy
3%



Main areas of muscle weakness in different types of dystrophy

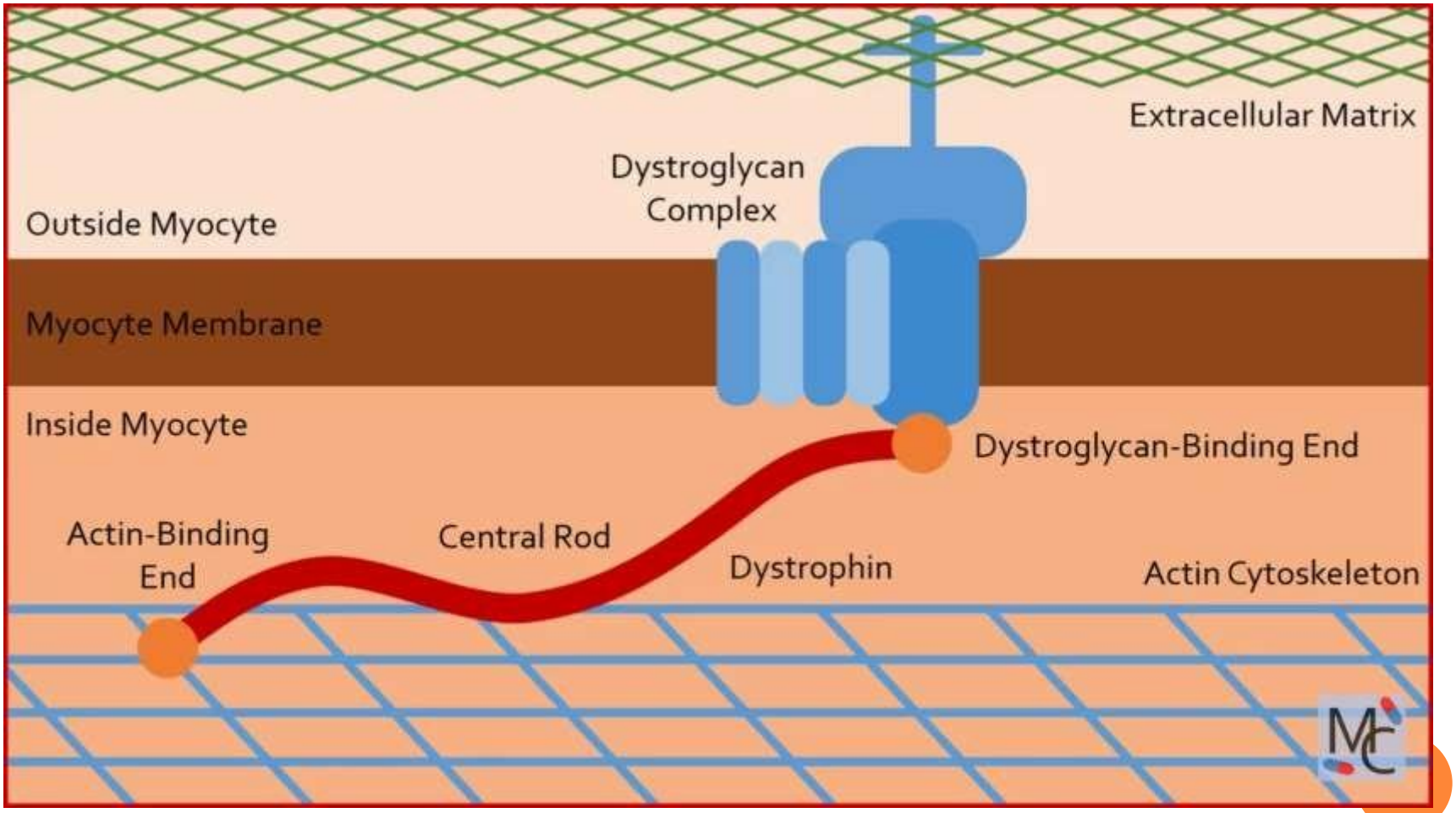
X- Linked: Ducenne, Beker..

- X- linked, recessive transmission
- Affects males
- Females are Carrier
- Onset: 2-5 years in Duchenne, end 1st decade in Becker)
- Proximal muscles: mainly , (early)
- Severe disease (+ other systems: cardiac..)
- death in the 2d decade

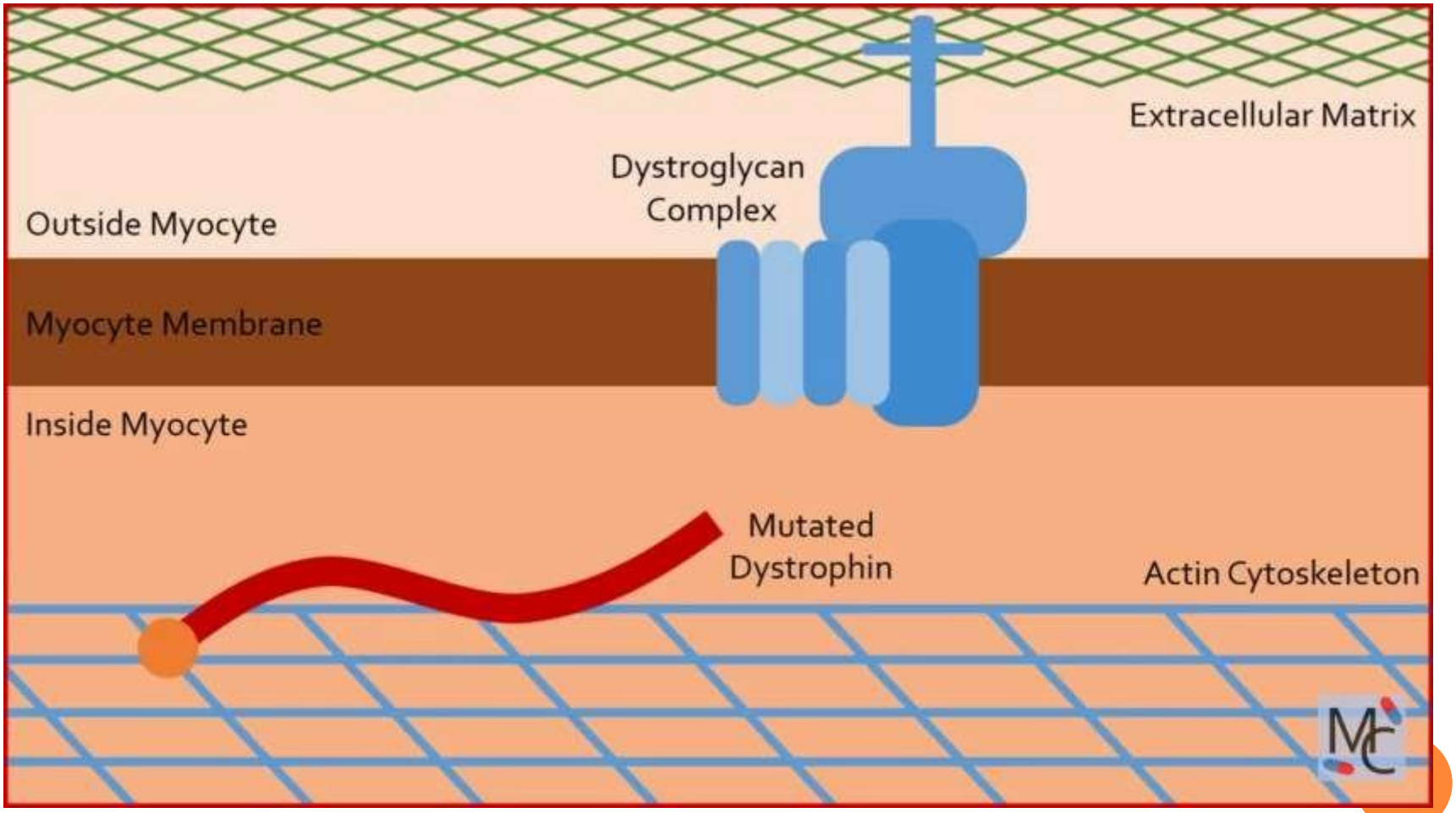
Clinical features

- Typical feature – the child uses his hands to climb up, while getting up from the floor.
- Wheelchair by age 12
- Fatal by age 30
- Progressive muscle weakness, that becomes apparent by age 4-5
- Muscle hypertrophy especially calf & pelvifemoral muscles
- Cardiomegaly
- Enlargement occurs due to gradual degeneration & necrosis of muscle fibers that are replaced by more fibrous & fatty tissue

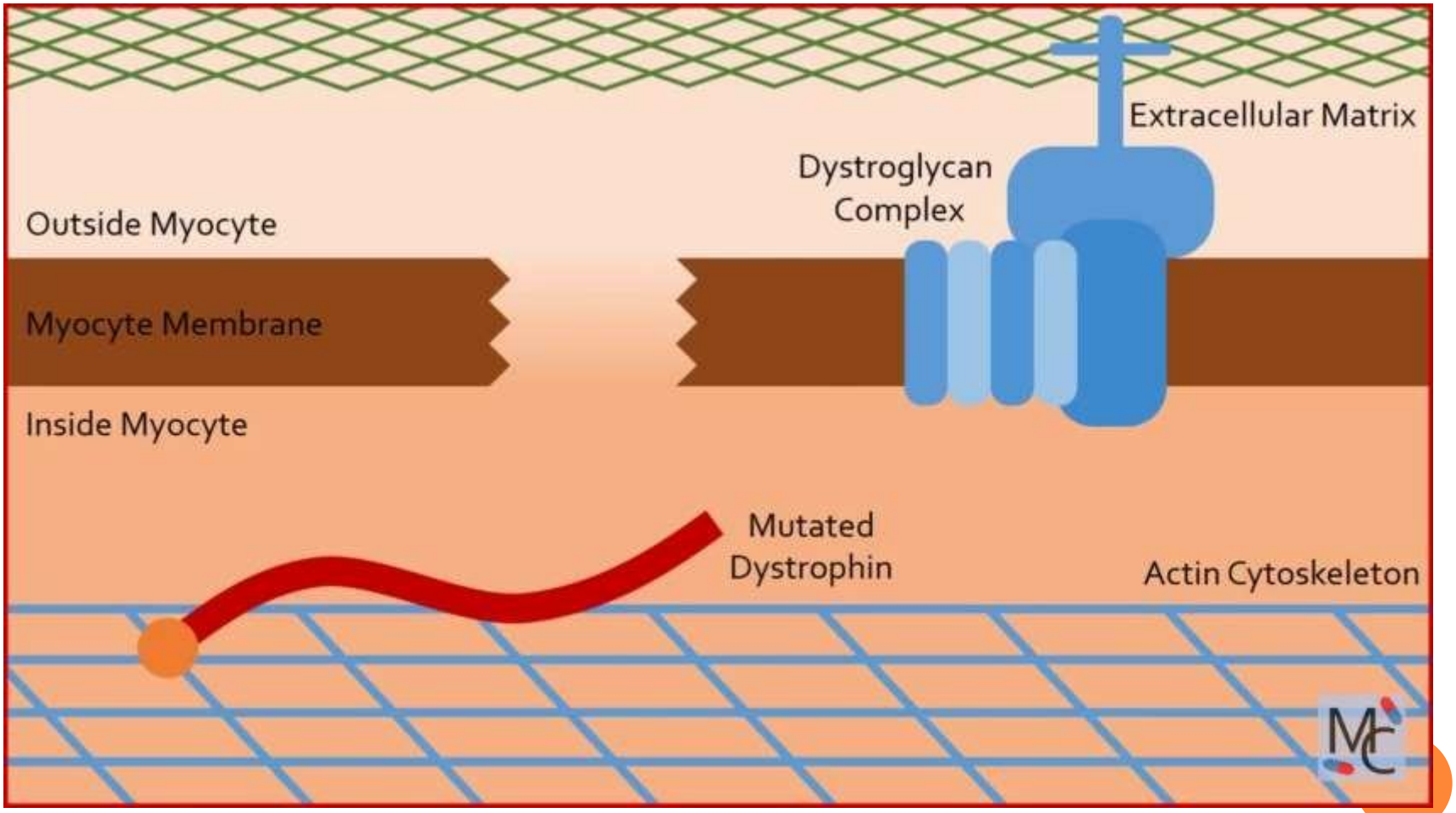
Normal protein



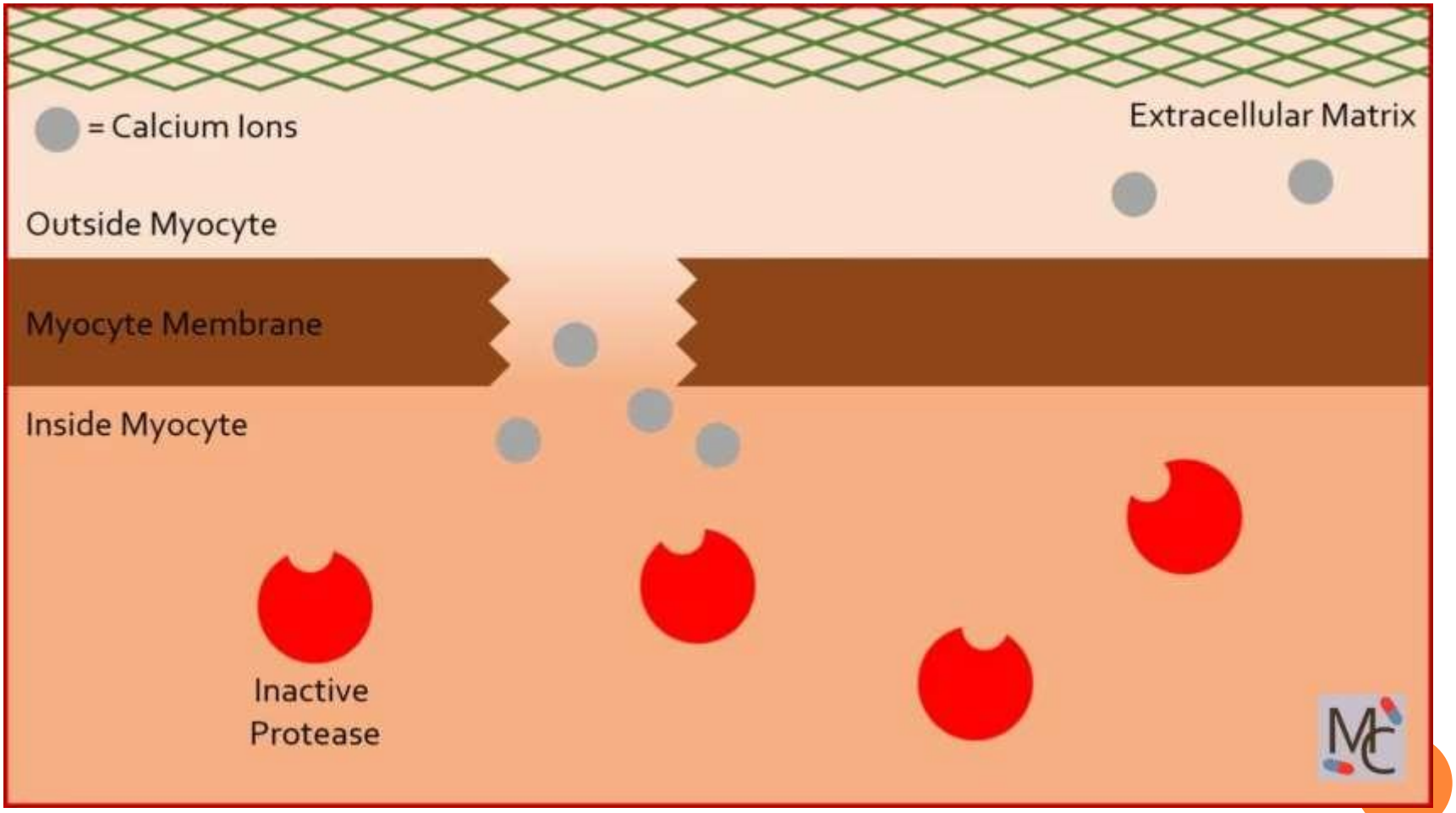
Mutation


Extracellular Matrix
Dystroglycan Complex
Outside Myocyte
Myocyte Membrane
Inside Myocyte
Mutated Dystrophin
Actin Cytoskeleton

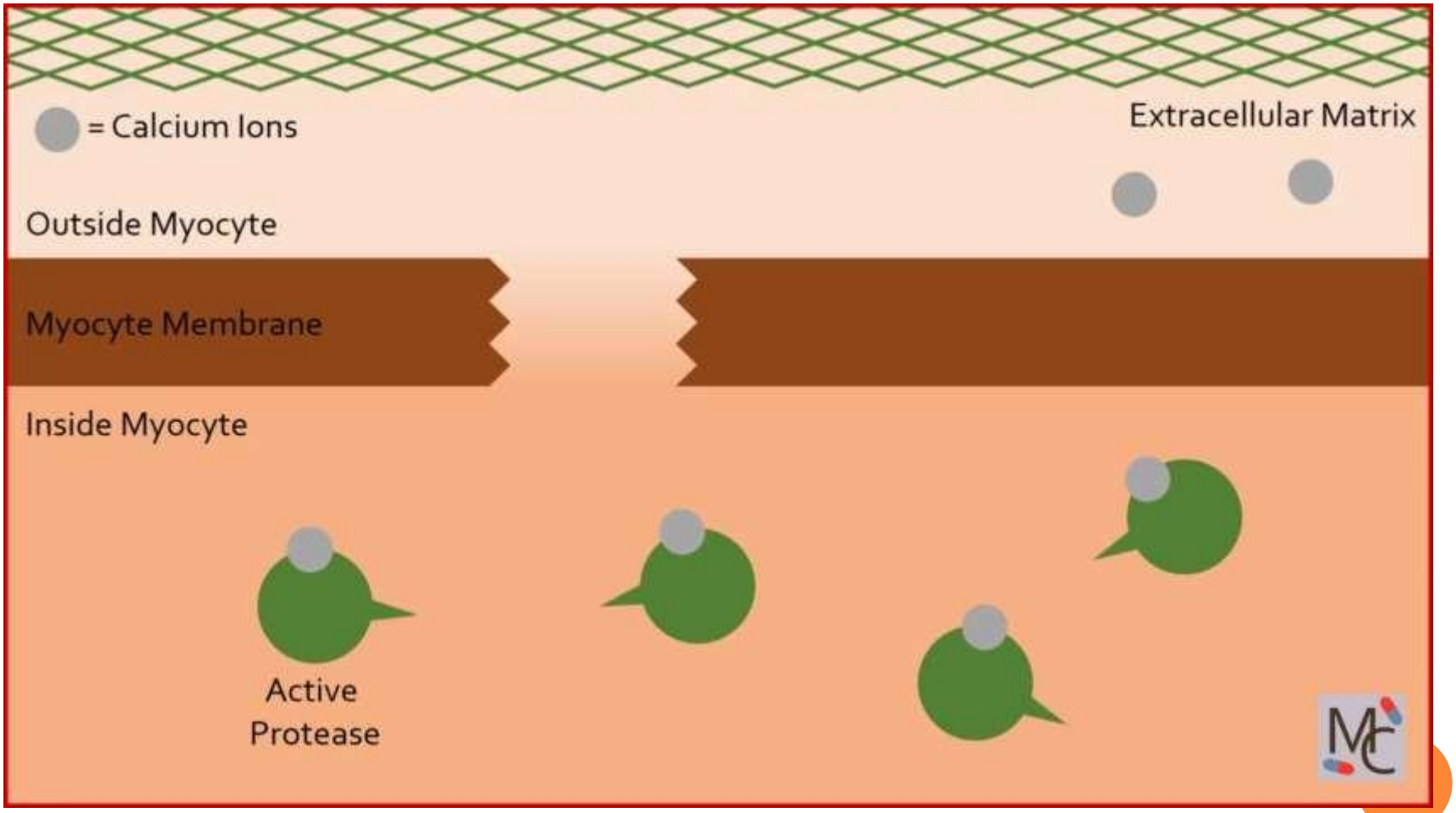
Breakage in cell membrane following muscle contractions



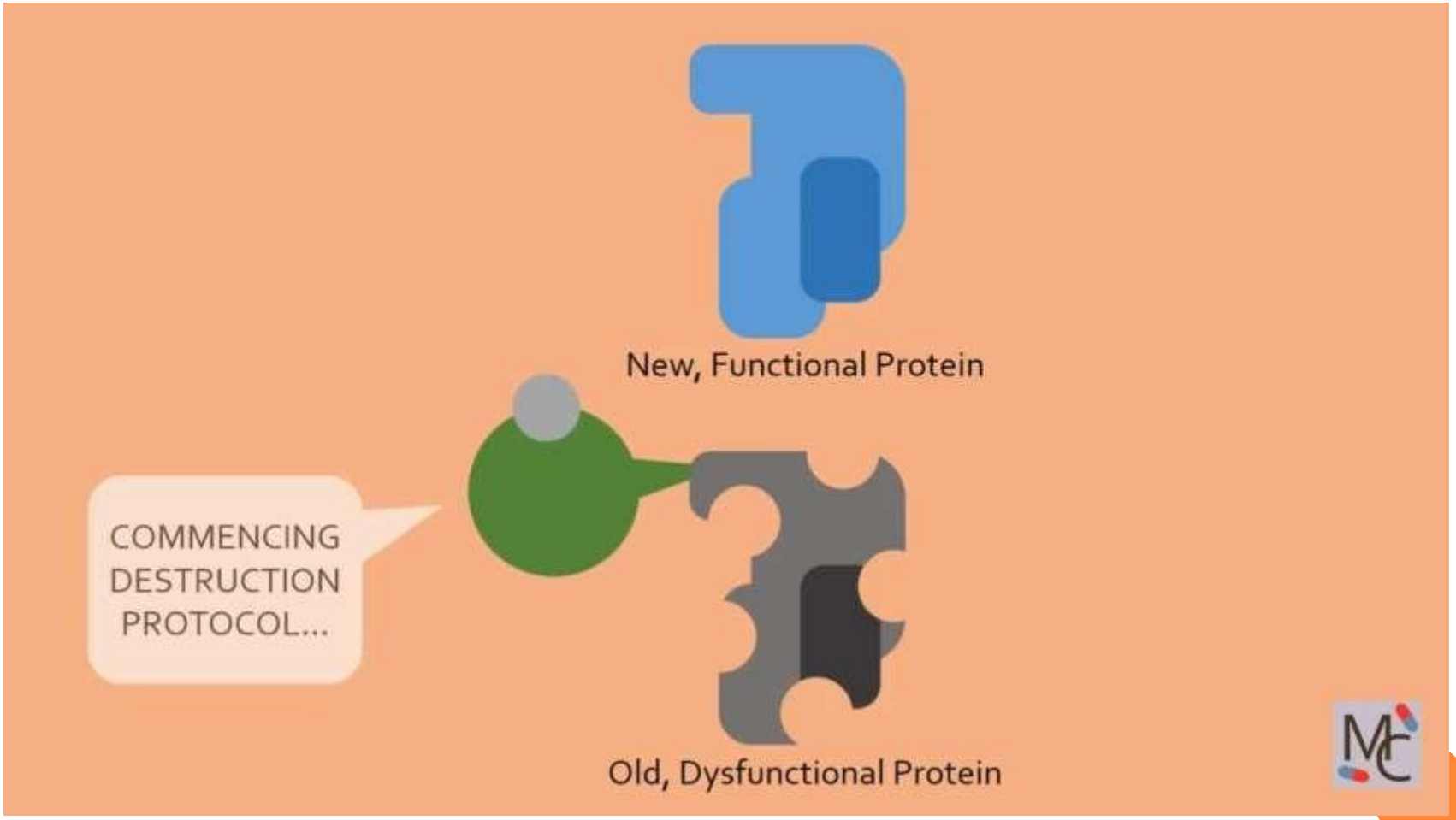
Entry/leakage of calcium from ECF to ICF



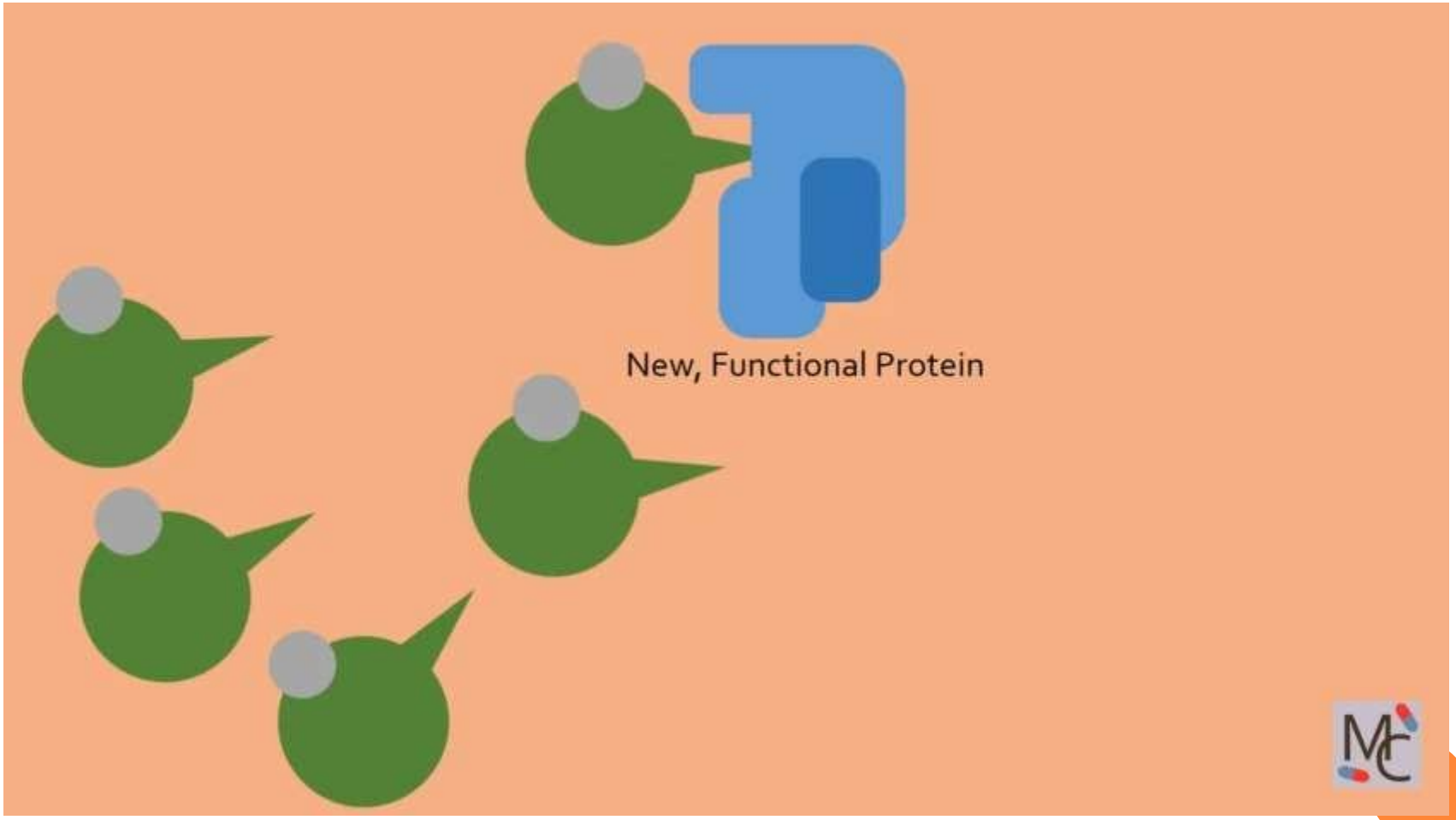
Calcium activates proteases that breakdown proteins in the muscle



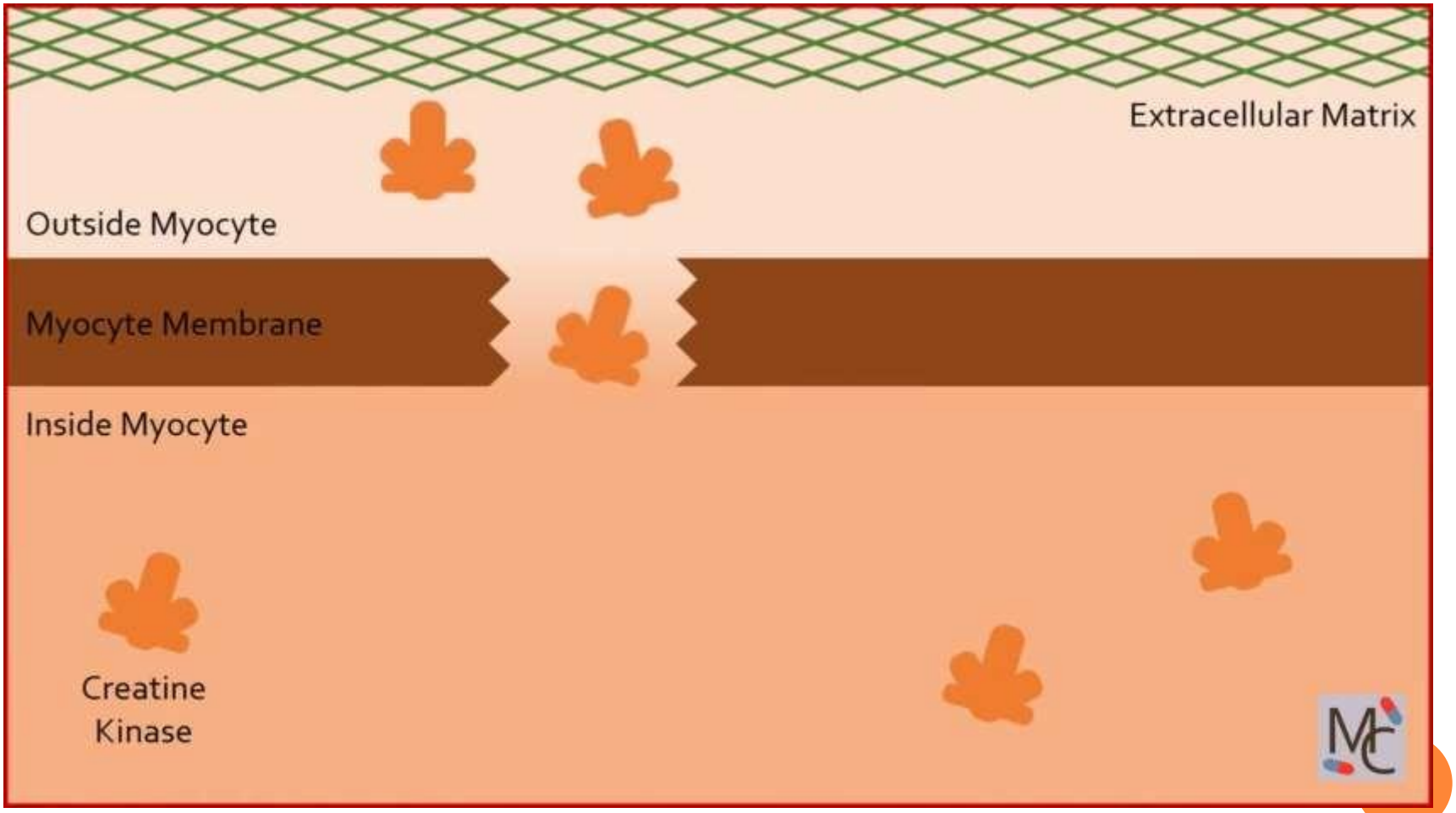
Action of proteases in normal levels

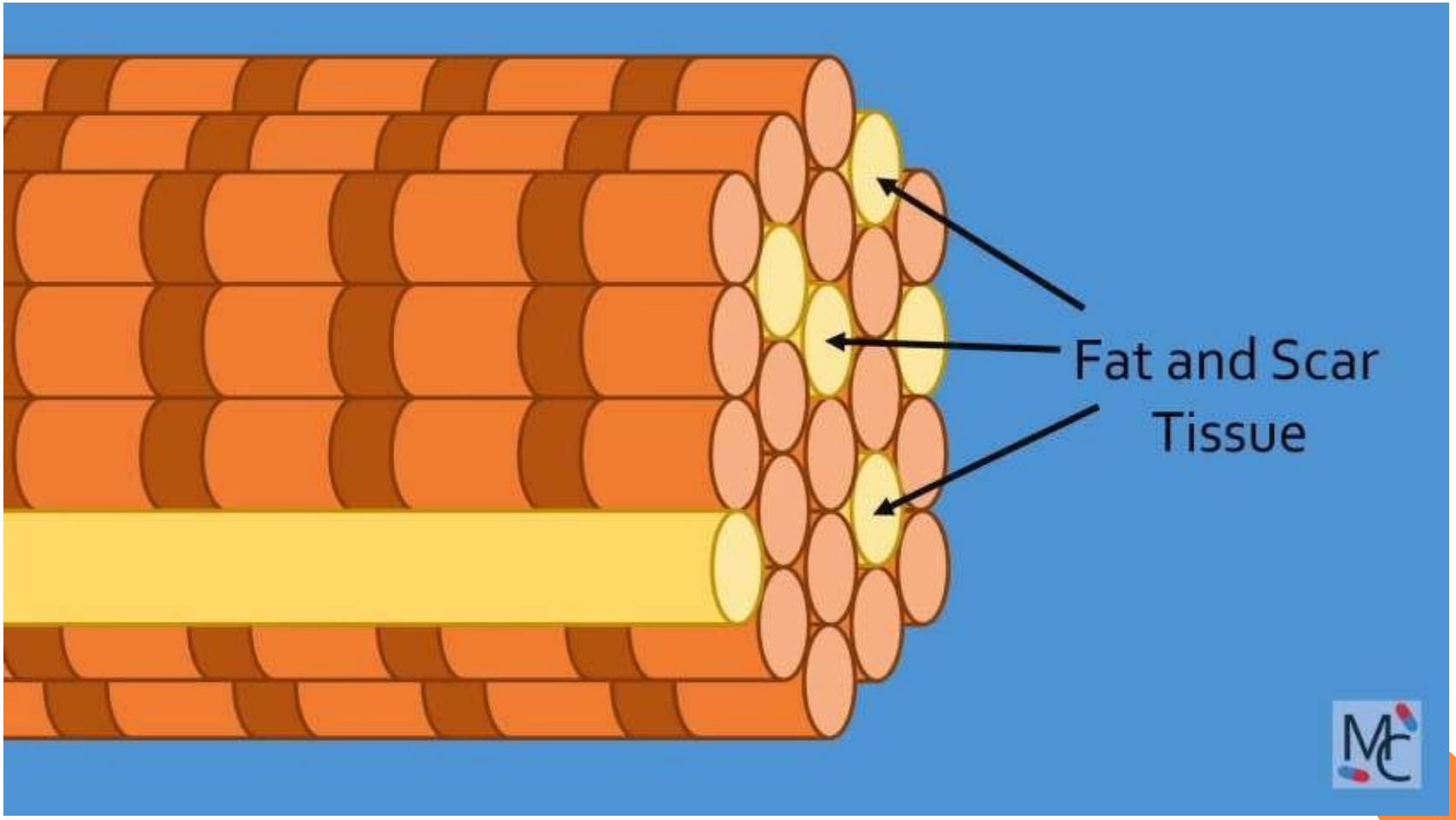


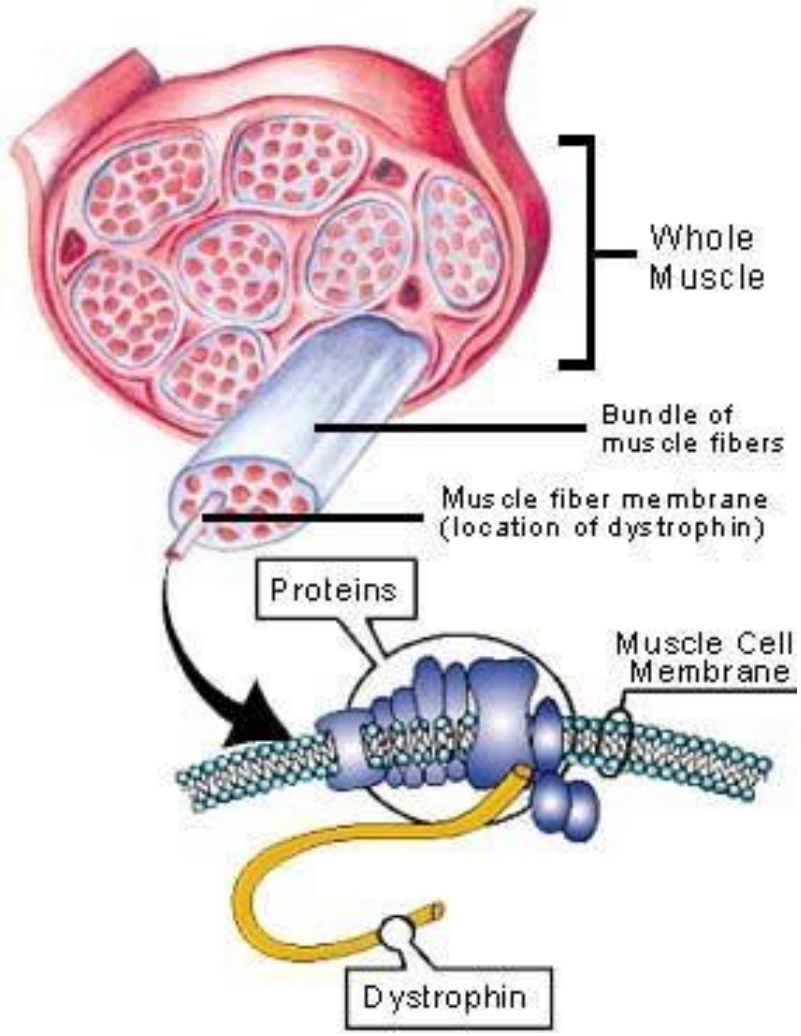
When protease conc inc

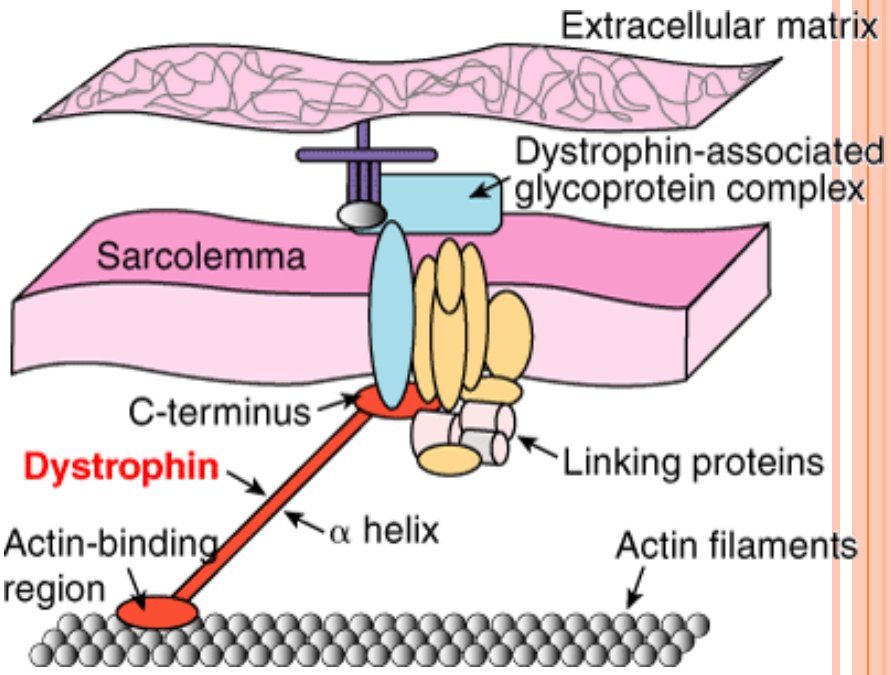


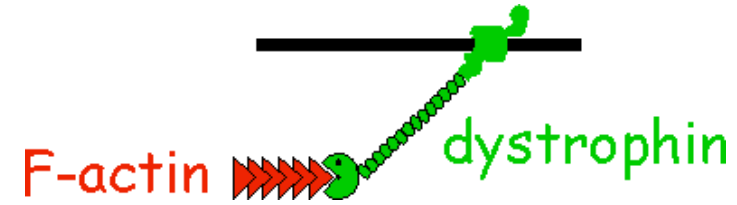
Leakage of CK




Fat and Scar
Tissue





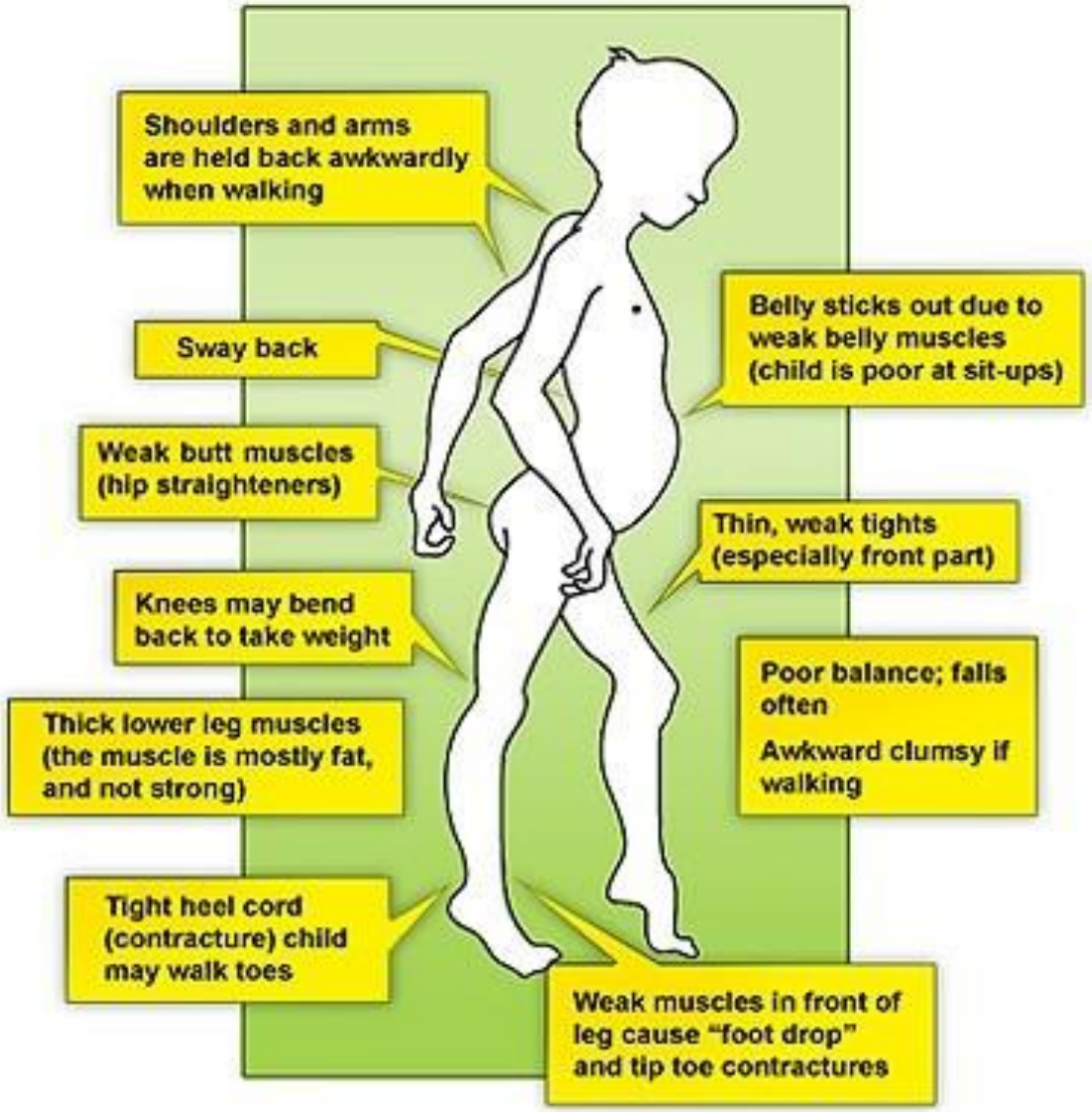


Duchenne

out-of-frame transcript

Dysfunctional and unstable dystrophin

CLINICAL MANIFESTATION



Onset : age 3-6 years

Progressive weakness

Pseudohypertrophy of calf muscles

Spinal deformity

Cardiopulmonary involvement

Mild - moderate MR

Morphology

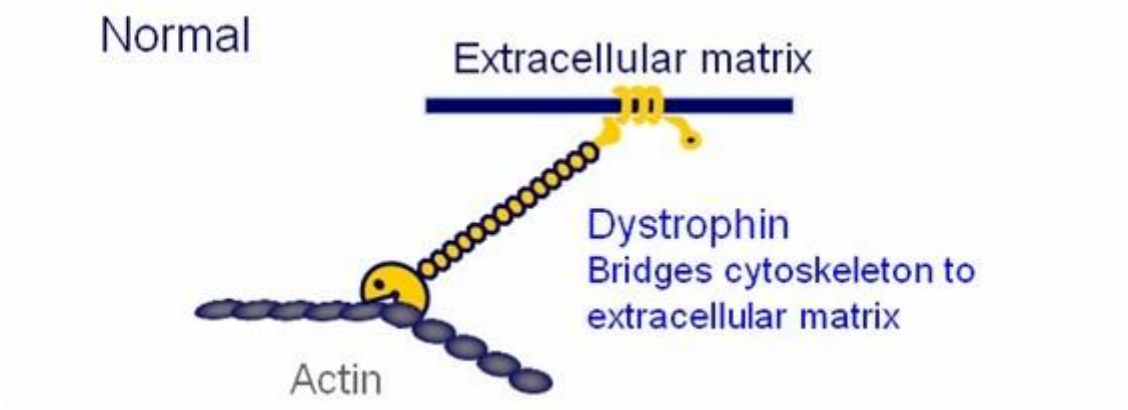
- Muscle biopsies in young boys show ongoing damage in the form of segmental myofiber degeneration and regeneration associated with an admixture of atrophic myofibers, there is usually no inflammation except for the presence of myophagocytosis. As the disease progresses, muscle tissue is replaced by collagen and fat cells ("fatty replacement" or "fatty infiltration"). The remaining myofibers at this point in the course show prominent variation in size, from small atrophic fibers to large hypertrophied fibers.

- This remodeling distorts the fascicular architecture of the muscle, which becomes markedly abnormal over time. Immunohistochemical studies for dystrophin show absence of the normal sarcolemmal staining pattern in Duchenne muscular dystrophin and reduced staining in Becker muscular dystrophy.

Dystrophinopathies: dystrophin staining

Becker muscular dystrophy

- X linked genetic disease
- Mutation in the gene coding for dystrophin-glycoprotein complex
- Milder form of muscular dystrophy; not very fatal
- **Dystrophin protein is present** in the muscle
- **but altered or reduced in amount.**



Becker

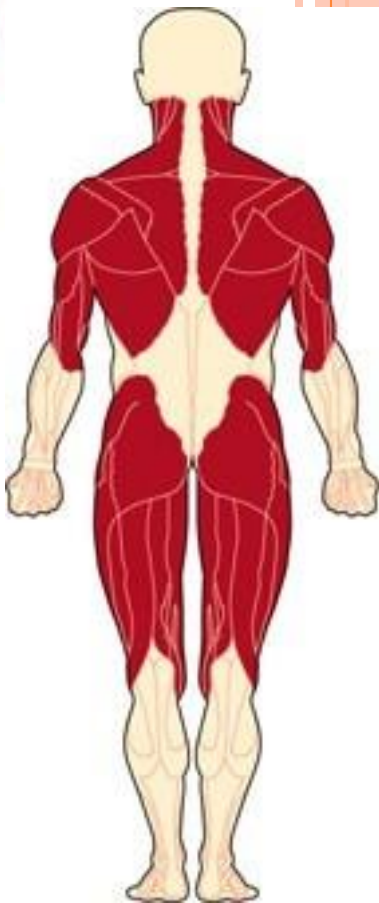
In-frame mutation
Partly functional protein
Bridge function maintained
Milder phenotype

Duchenne

Out-of-frame mutation
Prematurely truncated protein
Bridge function lost
Severe phenotype

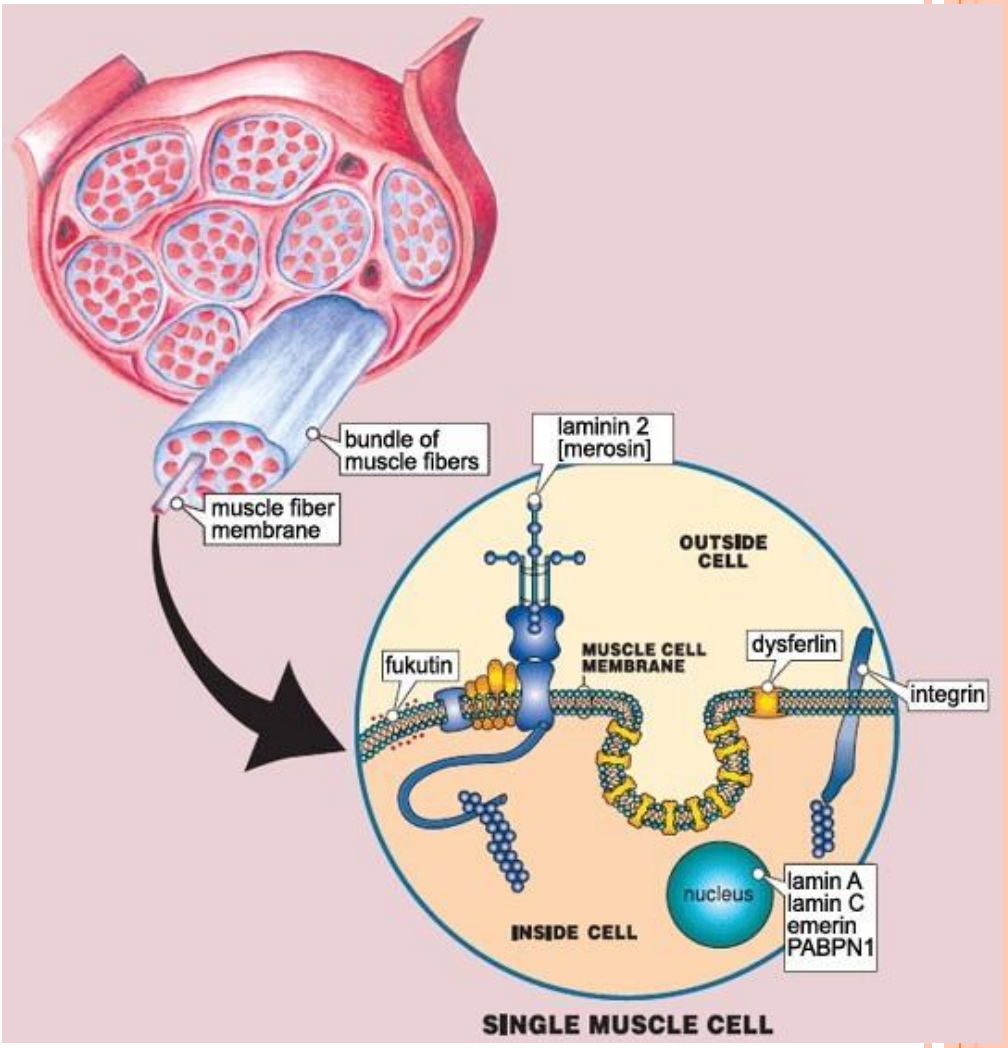
Clinical features

- Less common
  - 1: 30000 live male birth
- Less severe
- Family history: atypical MD
- Similar & less severe than DMD
- Onset: age > 7 years
- Pseudohypertrophy of calf
- Equinous and varus foot
- High rate of scoliosis
- Less frequent cardiac involvement



Emery-Dreifuss Muscular Dystrophy

- **Etiology**
  - X-linked recessive
  - Xq28
  - Emerin protein (in nuclear membrane) the autosomal form EMD2 are caused by mutations in the genes encoding emerin and lamin
- **Epidemiology**
  - Male: typical phenotype
  - Female carrier: partial

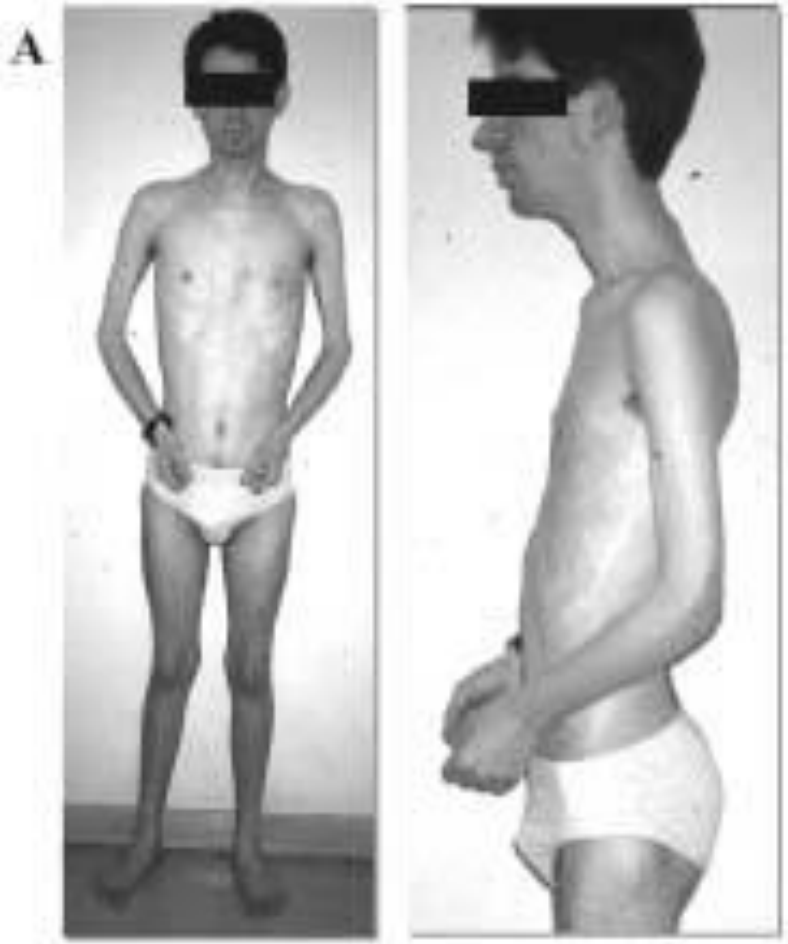


Genetics

- Emerin,
- lamin,
- merosin, etc.

- Clinically, it is marked by a triad consisting of slowly progressive humeroperoneal weakness, cardiomyopathy associated with conduction defects, and early contractures of the Achilles tendon, spine, and elbows.

Scoliosis: common, low incidence of progression
Bradycardia, 1st degree AV block , sudden death



Limb - Girdle Muscular Dystrophy

- **Etiology**

  Autosomal recessive at chromosome 15q

  - Autosomal dominant at 5q

    LGMD are a heterogeneous group of at least six autosomal dominant and 15 autosomal recessive entities

- **Epidemiology**

  - Common
  - More benign

Genetics

- Calpain-3,
- Dysferlin,
- Caveolin-3,
- αβδγ- sargoglycans, etc.

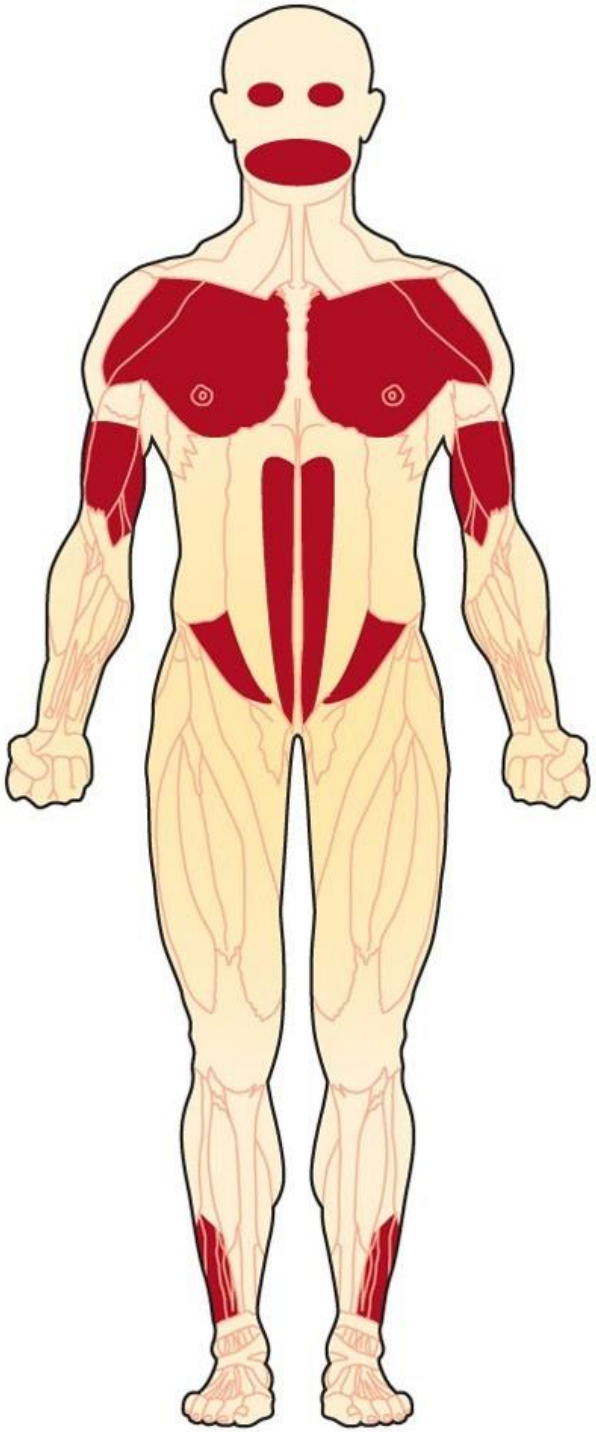
Common features

- Expression in either male or female sex
- Onset usually in the late first or second decade of life (but also middle age)
- Usually autosomal recessive and less frequently autosomal dominant
- Involvement of shoulder or pelvic-girdle muscles with variable rates of progression
- Severe disability within 20-30 years
- Muscular pseudohypertrophy and/or contractures uncommon

- **Classification**
  - Pelvic girdle type
    common
  - Scapulohumeral
    type
    rare

Fascioscapulohumeral Muscular Dystrophy

- **Etiology**
  - Autosomal dominant
  - Gene defect (*FRG1*)
  - DUX4 gene
- **Epidemiology**
  - Female > male
- **Clinical manifestation**
  - Age of onset: late childhood/ early adult
  - No cardiac, CNS involvement
  - Winging scapula
  - Markedly decreased shoulder,flexion abduction
  - Horizontal clavicles
  - Rare scoliosis



- **Muscle weakness**
  - face, shoulder, upper arm
- **Sparing**
  - Deltoid
  - Distal pectoralis major
  - Erector spinae

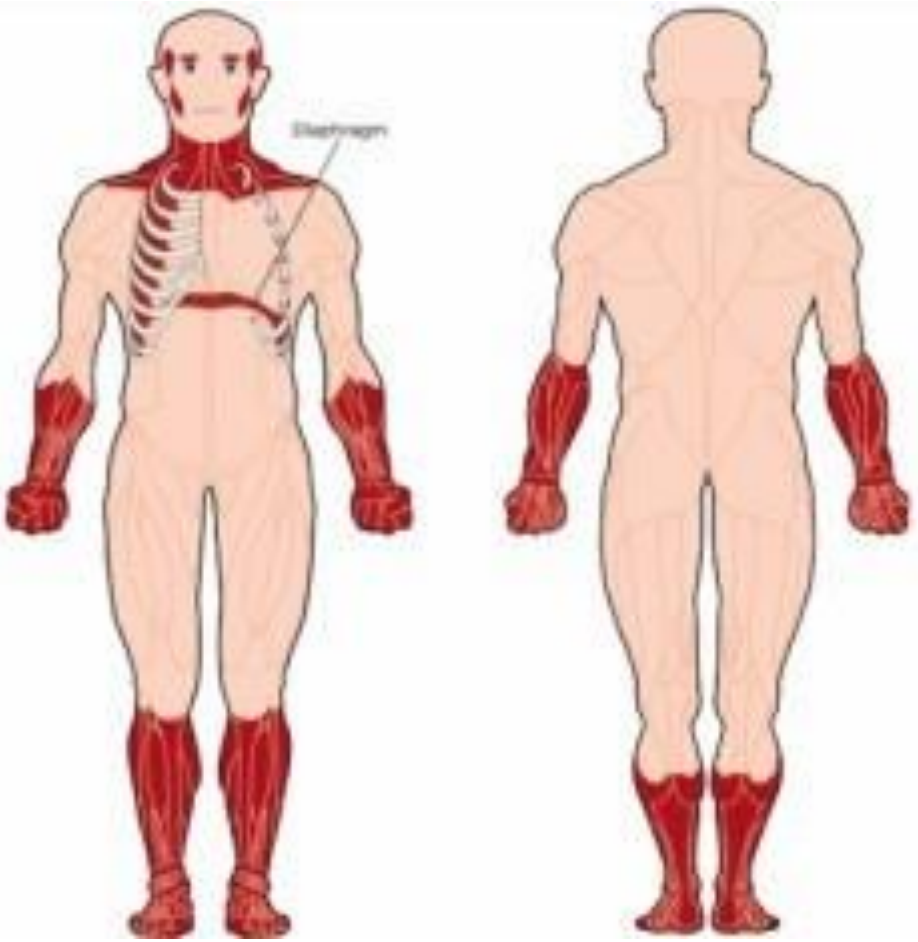
Myotonic dystrophy

- Myotonic dystrophy is an autosomal dominant multisystem disorder associated with skeletal muscle weakness cataracts, endocrinopathy, and cardiomyopathy.
- It affects about 1 in 10,000 individuals. Myotonia, a sustained involuntary contraction of muscles, is a key feature of the disease. Some patients present with *"congenital myotonia,“* marked by severe manifestations in infancy.

Pathogenesis

- The disease is caused by expansions of CTG triplet repeats in the 3'-noncoding region of the myotonic dystrophy protein kinase *(DMPK) gene,*

Myotonic Muscular Dystrophy



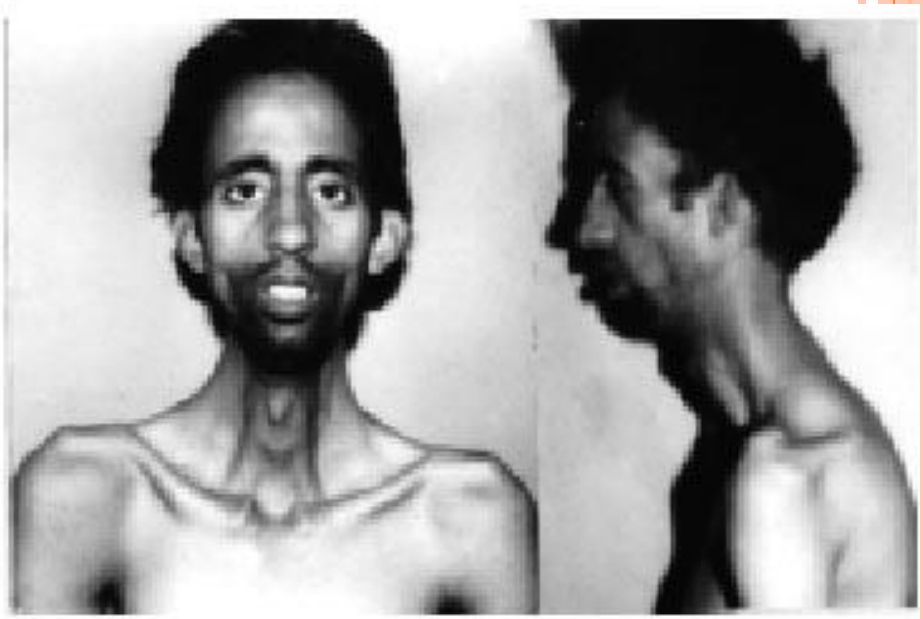
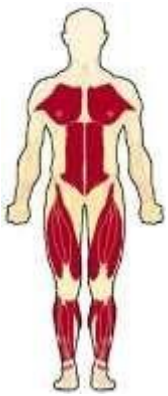
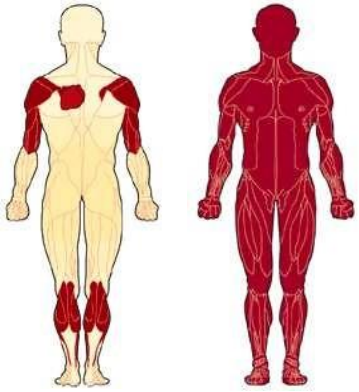
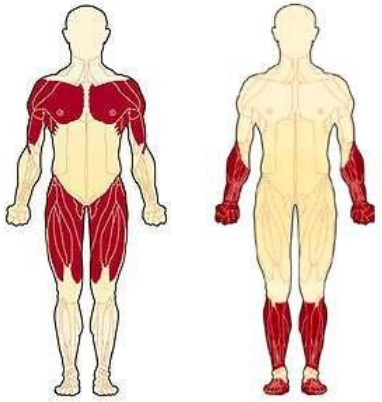


Fig. 1 : Showing frontal baldness, swan neck and low set ears.

HATCHET FACIES

Muscular Dystrophy

	Duchenne/ Becker	Emery-Dreifuss, Congenital	Limb-Girdle, Distal Myopathy
Onset	2-6 years	Childhood to early teens, infancy	Late childhood-middle age
Muscle groups affected			
Life expectancy	Rarely beyond 20's	varies	Middle age +
Inheritance	X-linked recessive	X-linked recessive, autosomal dom & rec.	Autosomal dominant & recessive
Genetic linkage	Dystrophin	Emerin, lamin, merosin, etc.	Calpain-3, **Dysferlin**, Caveolin-3, αβδγ-sargoglycans, etc.

THANKS