

Muscular Dystrophies

Mechanisms • tissue injury • clinicopathologic patterns

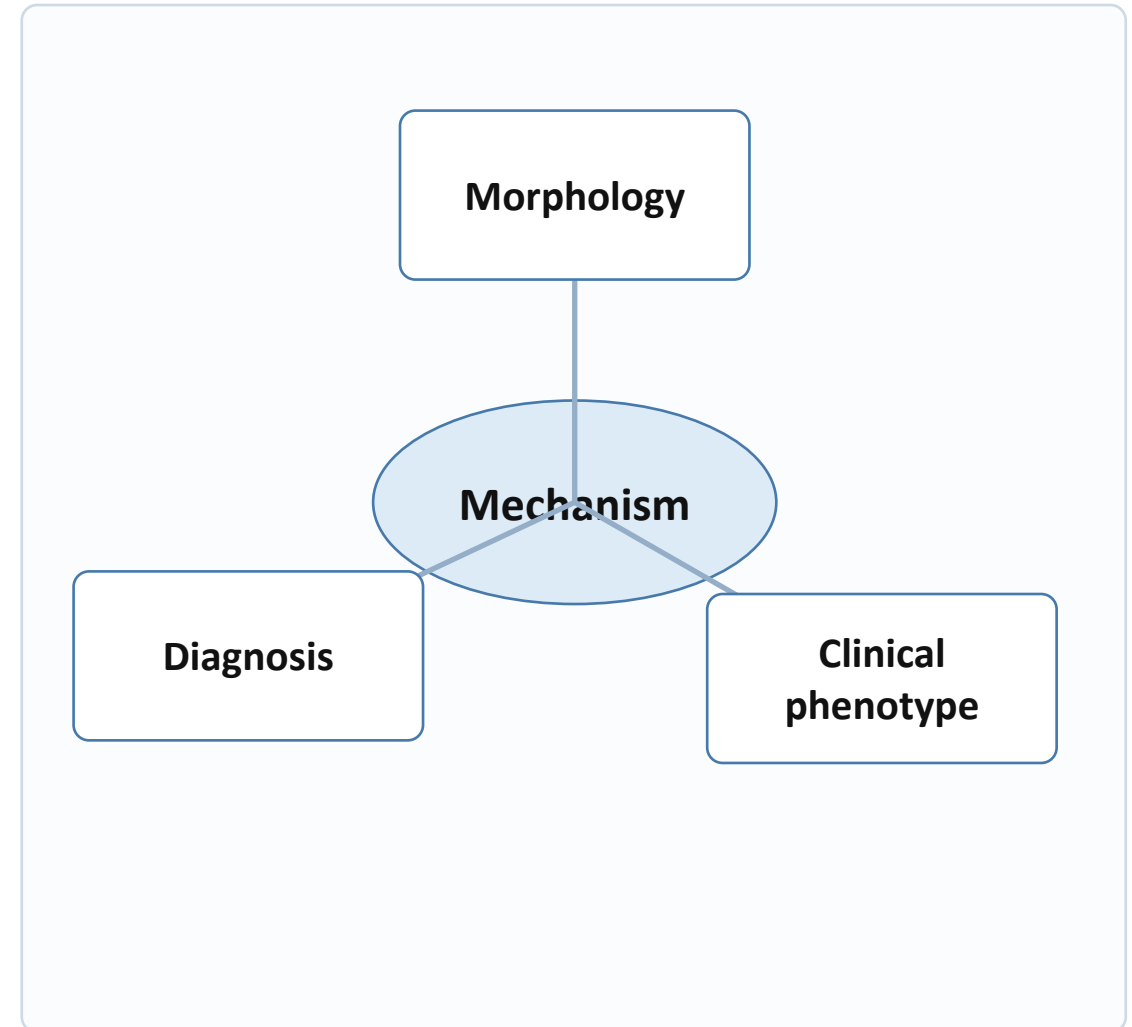
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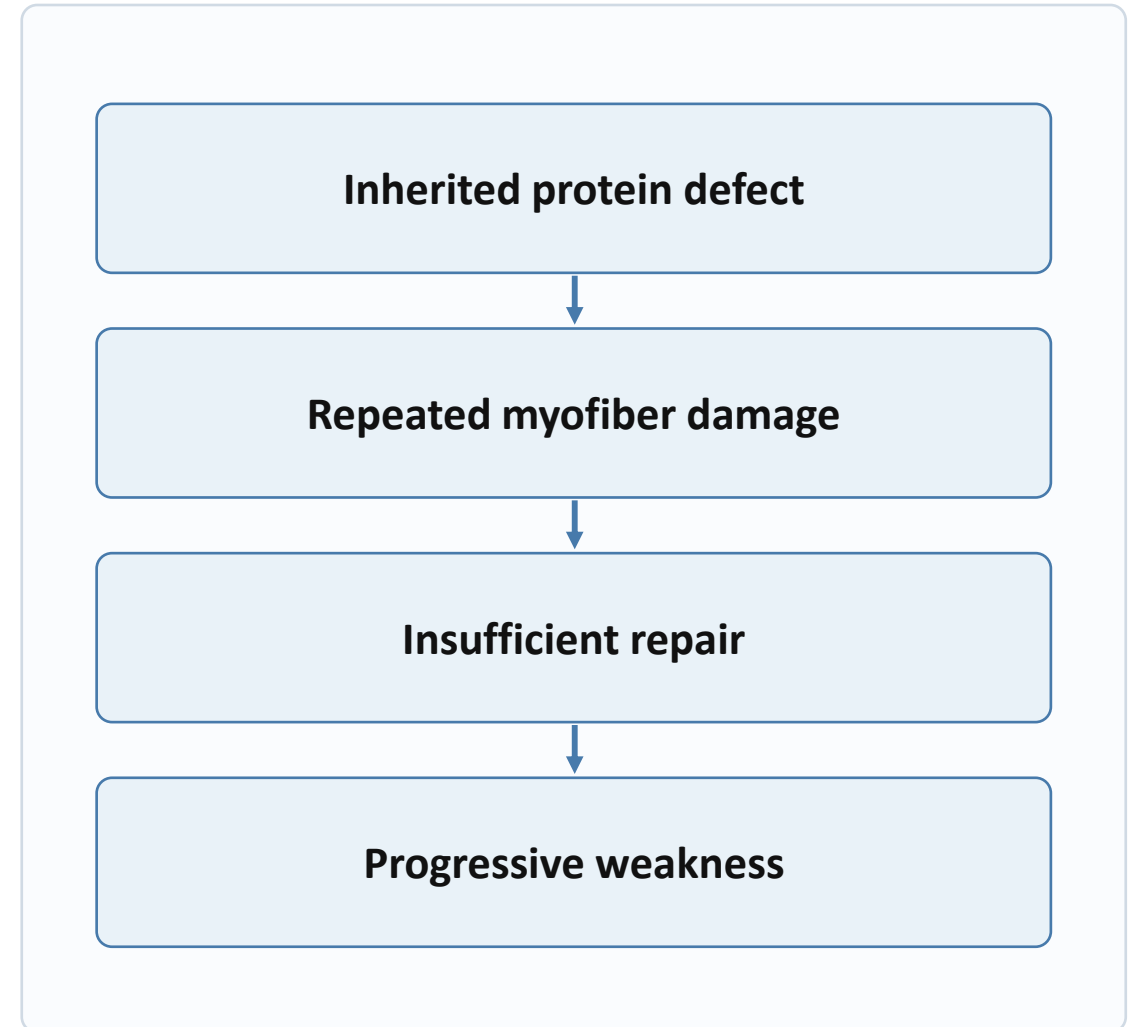
Learning objectives

- Explain the structural and molecular basis of progressive muscle injury.
- Relate dystrophin deficiency to histomorphology and Duchenne/Becker phenotypes.
- Distinguish limb-girdle, Emery–Dreifuss and facioscapulohumeral dystrophies.
- Integrate clinical patterns, CK, genetics and selected muscle biopsy findings.



Progressive damage defines muscular dystrophy

- Inherited disorders characterized by chronic, progressive skeletal muscle injury.
- Most noncongenital forms become clinically evident from childhood to adulthood.
- Loss of functional myofibers eventually exceeds regenerative capacity.

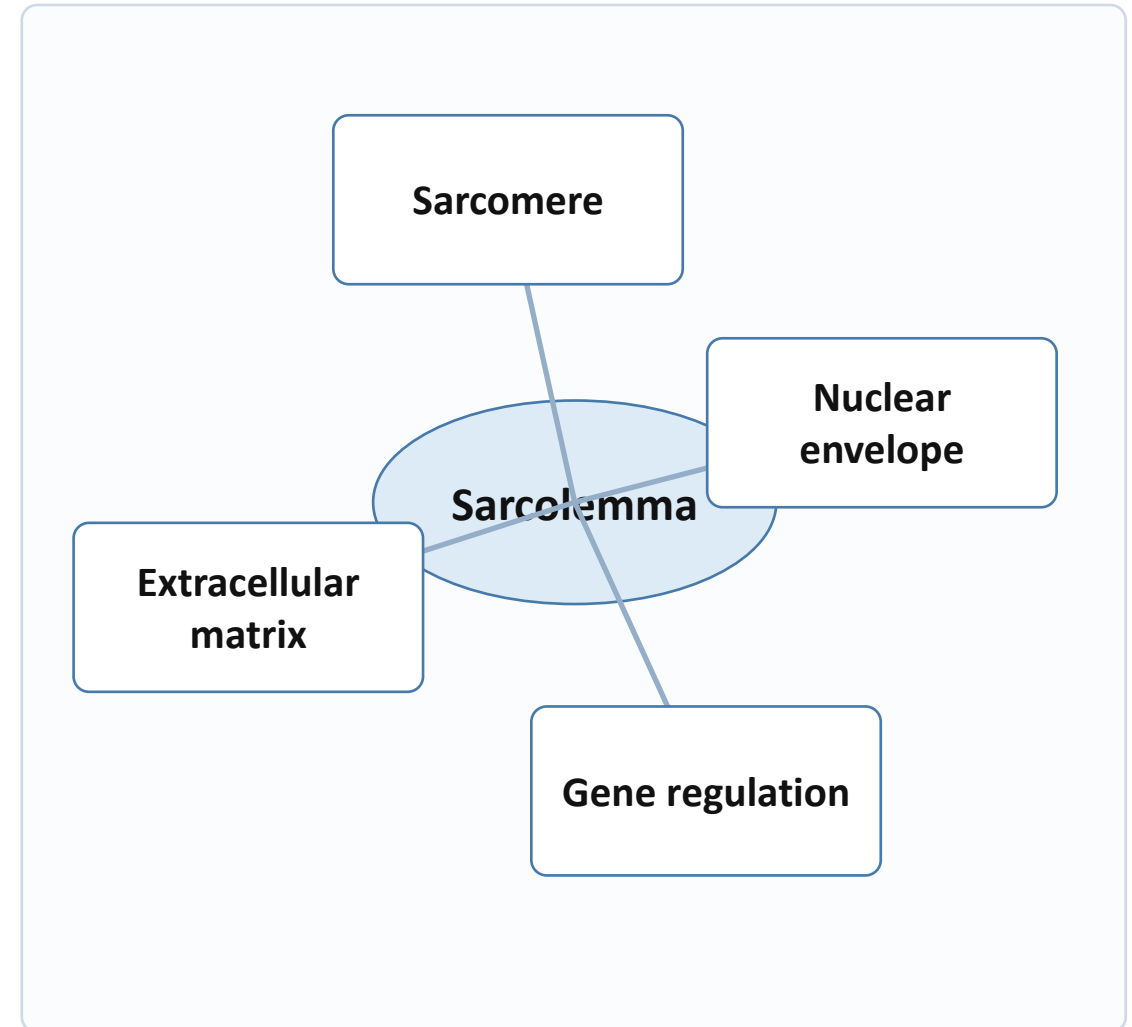


Age at presentation defines important boundaries

Group	Typical presentation	Key distinction
Congenital myopathy	Infancy	Structural muscle abnormalities; course may be static
Congenital dystrophy	Infancy	Progressive dystrophic damage $\pm$ CNS abnormalities
Other dystrophies	Childhood–adulthood	Progressive skeletal muscle injury

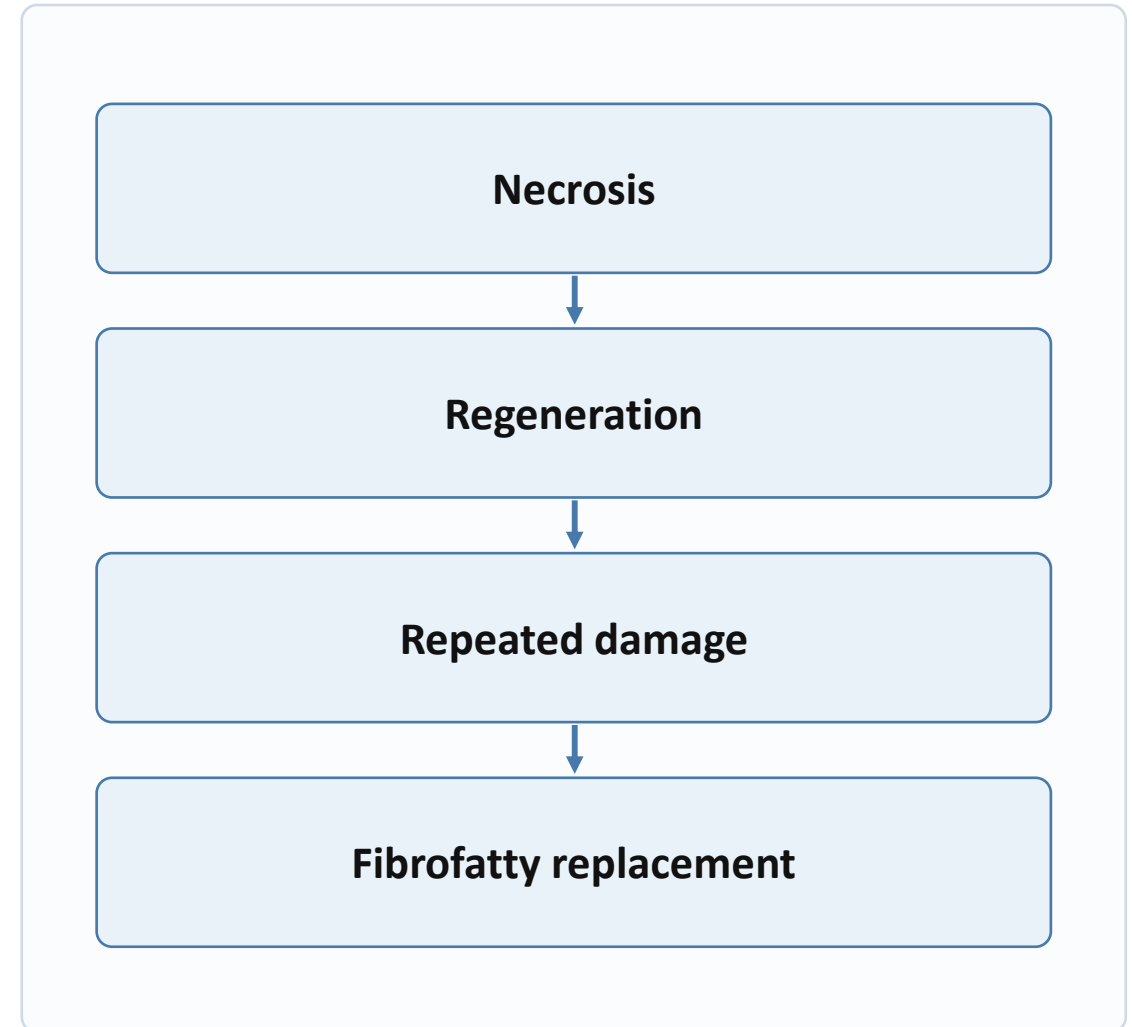
Different molecular defects converge on myopathy

- The molecular lesion predicts the affected cell compartment.
- The clinical pattern can guide the differential before molecular confirmation.
- Cardiac or neurologic involvement is not uniform across categories.



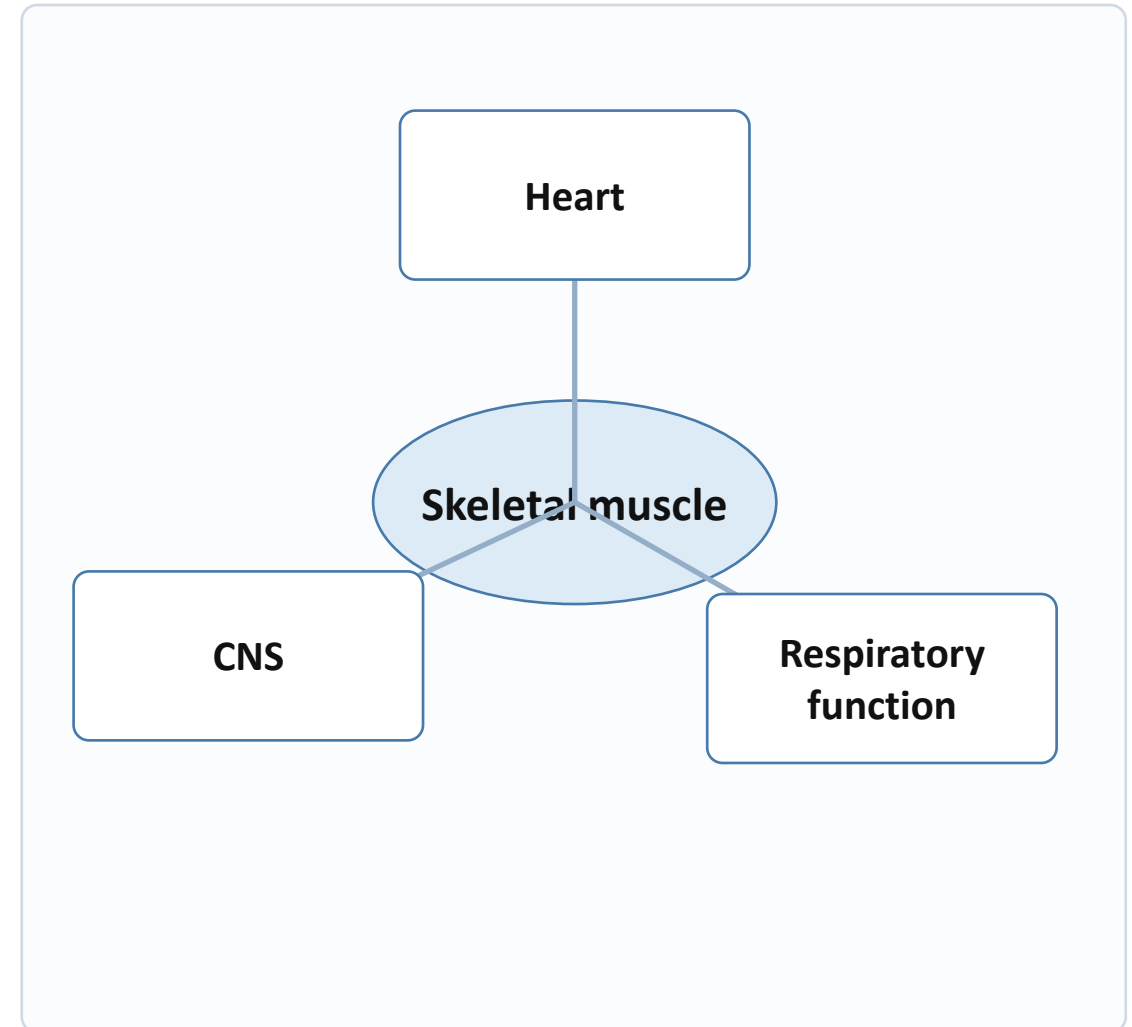
Repeated injury creates a cumulative tissue deficit

- Necrotic fibers can initially be replaced by regenerating myofibers.
- Persistent injury progressively impairs normal tissue organization.
- Fibrous tissue and adipocytes increasingly occupy lost muscle volume.



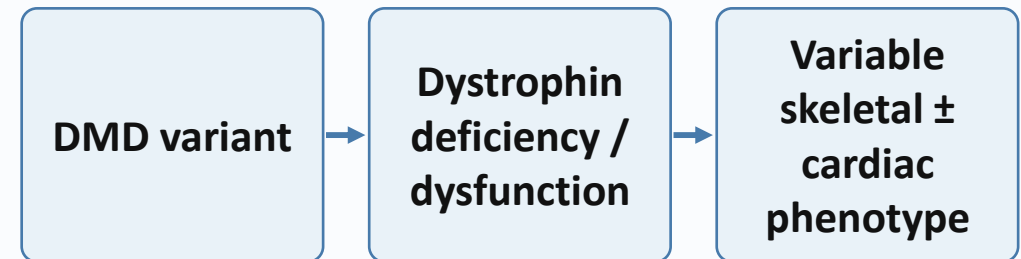
Extramuscular disease changes prognosis

- Several inherited muscular disorders also involve cardiac muscle.
- Dystrophin is expressed in the CNS as well as skeletal and cardiac muscle.
- Respiratory insufficiency and cardiac disease may become life limiting.



Dystrophinopathies are X-linked conditions

- Duchenne and Becker muscular dystrophies result from pathogenic DMD variants.
- The DMD gene is on the X chromosome.
- Dystrophinopathies include phenotypes milder than classic limb-girdle weakness.



Duchenne and Becker differ chiefly in severity

- Duchenne muscular dystrophy is the severe, earlier-onset phenotype.
- Becker muscular dystrophy generally begins later and progresses more slowly.
- The presence of partially functional dystrophin helps explain the contrast.

Duchenne

Usually absent
dystrophin

Earlier onset

Severe progression

Becker

Partially functional
dystrophin

Later onset

Slower progression

DMD is an exceptionally large human gene

- The DMD gene spans approximately 2.3 million base pairs.
- It contains 79 exons.
- Dystrophin is a key intracellular constituent of the dystrophin glycoprotein complex.

X chromosome

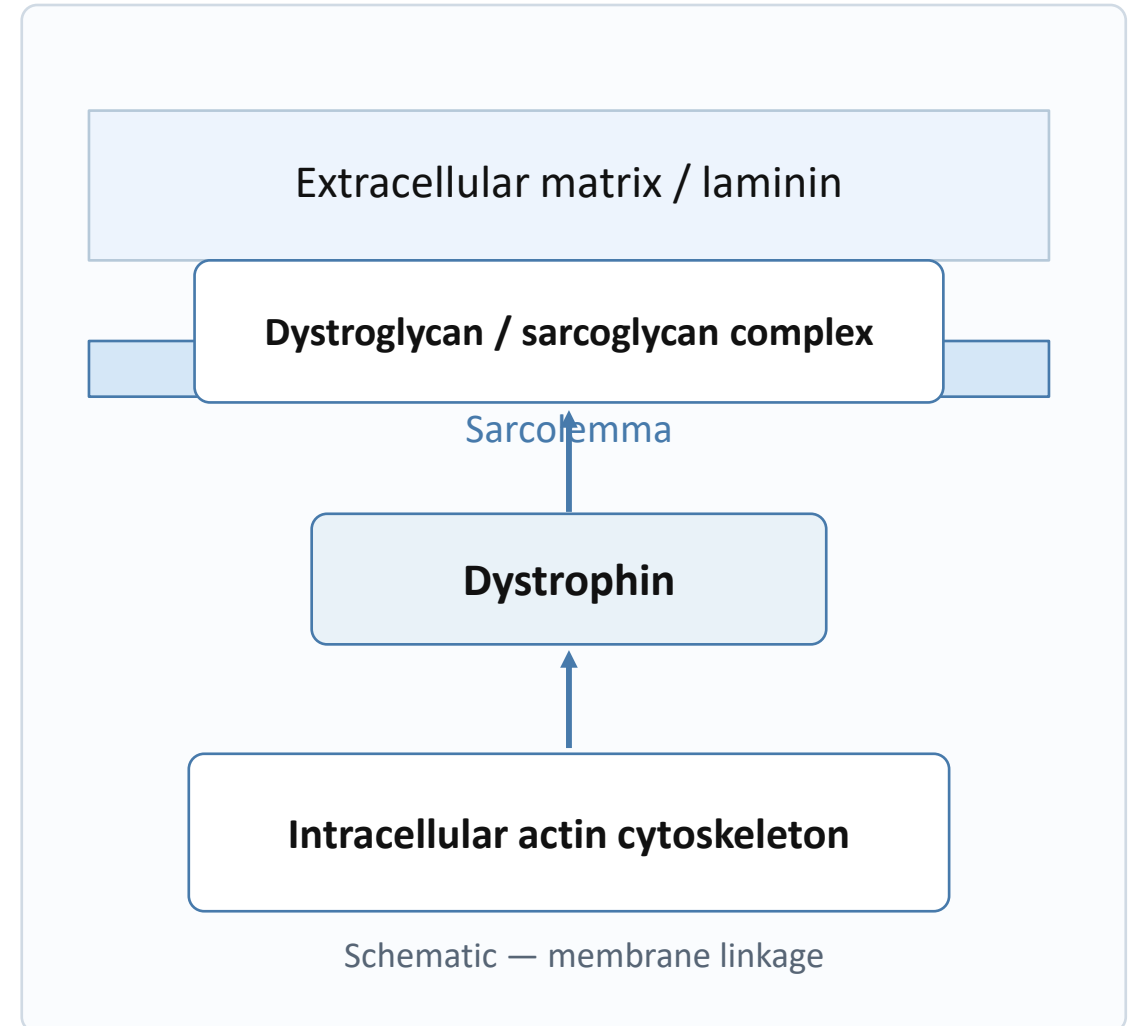
DMD gene: 2.3 Mb

79 exons

Dystrophin protein

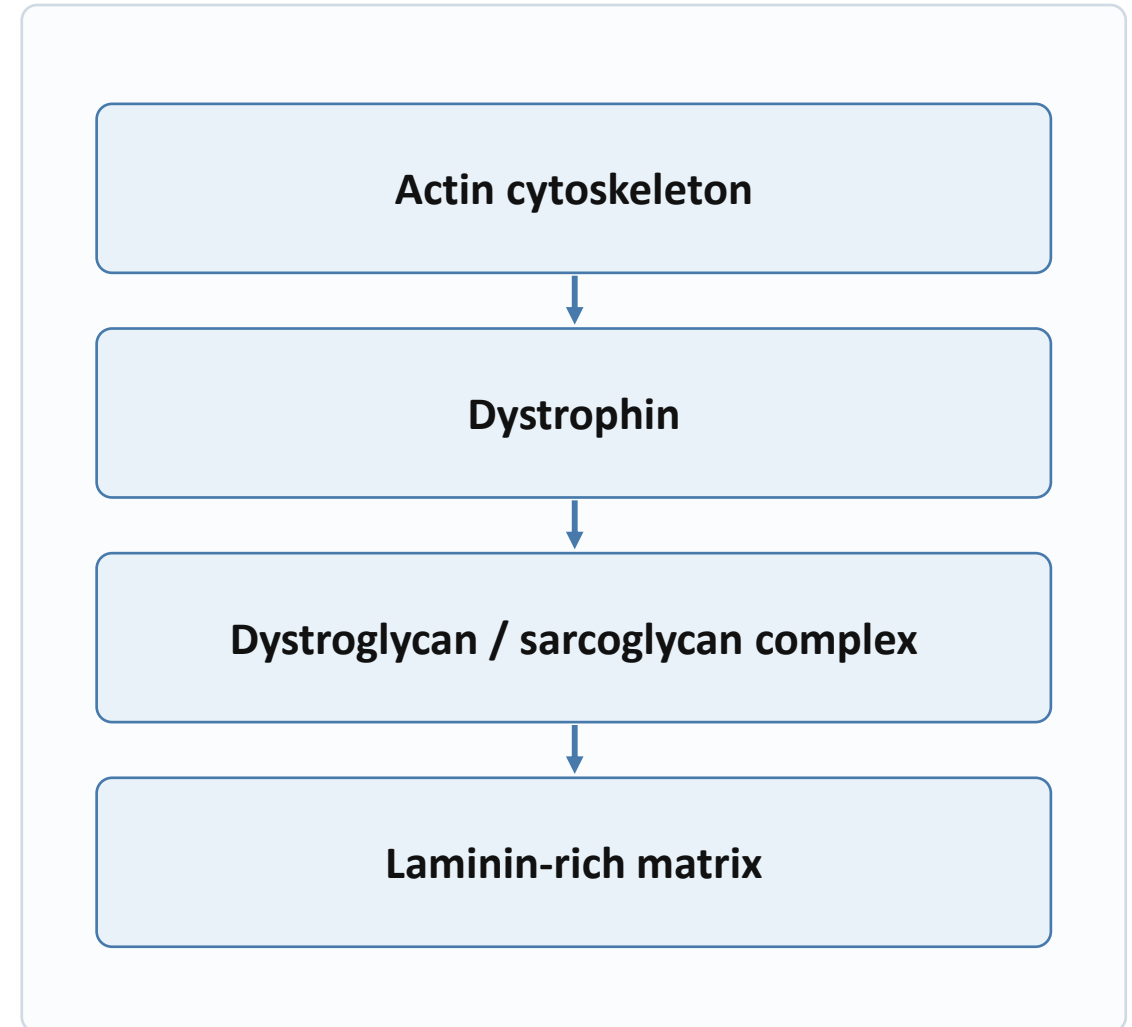
Dystrophin bridges cytoskeleton and matrix

- Dystrophin lies beneath the sarcolemma.
- It links intracellular cytoskeletal proteins to transmembrane complex components.
- The complex connects to extracellular laminin-containing basement membrane.



The glycoprotein complex spans the sarcolemma

- Dystroglycans and sarcoglycans form a transmembrane interface.
- Their extracellular connections help couple a myofiber to the matrix.
- Disturbances at different points can give rise to different dystrophy groups.



The dystrophin complex stabilizes a contracting fiber

- Muscle contraction exposes the sarcolemma to repeated mechanical stress.
- Dystrophin-associated connections are thought to stabilize the membrane.
- Loss of this mechanical support increases susceptibility to injury.

Intact linkage

Cytoskeleton coupled
to matrix

Membrane support
during contraction

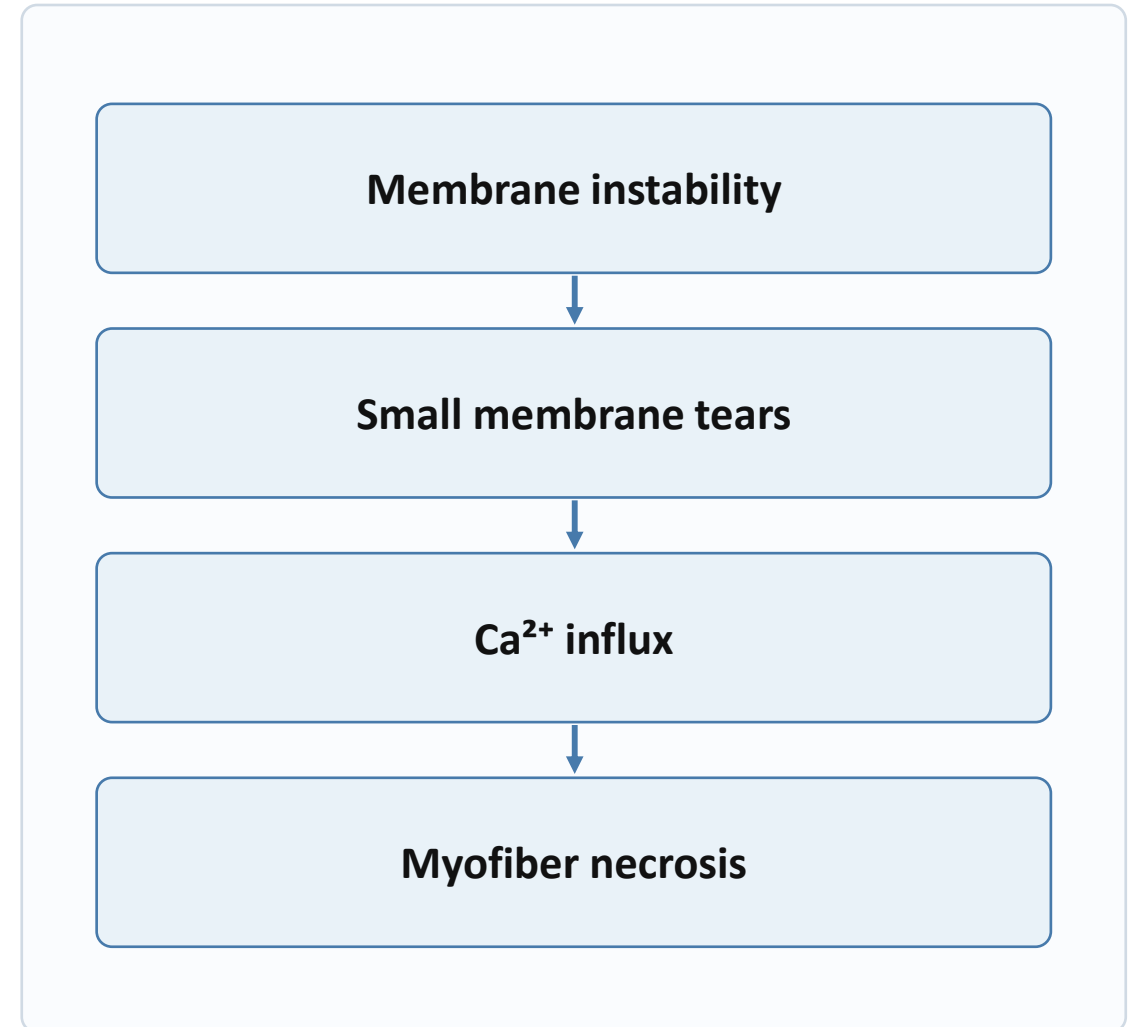
Disrupted linkage

Less stable
sarcolemma

Greater susceptibility
to damage

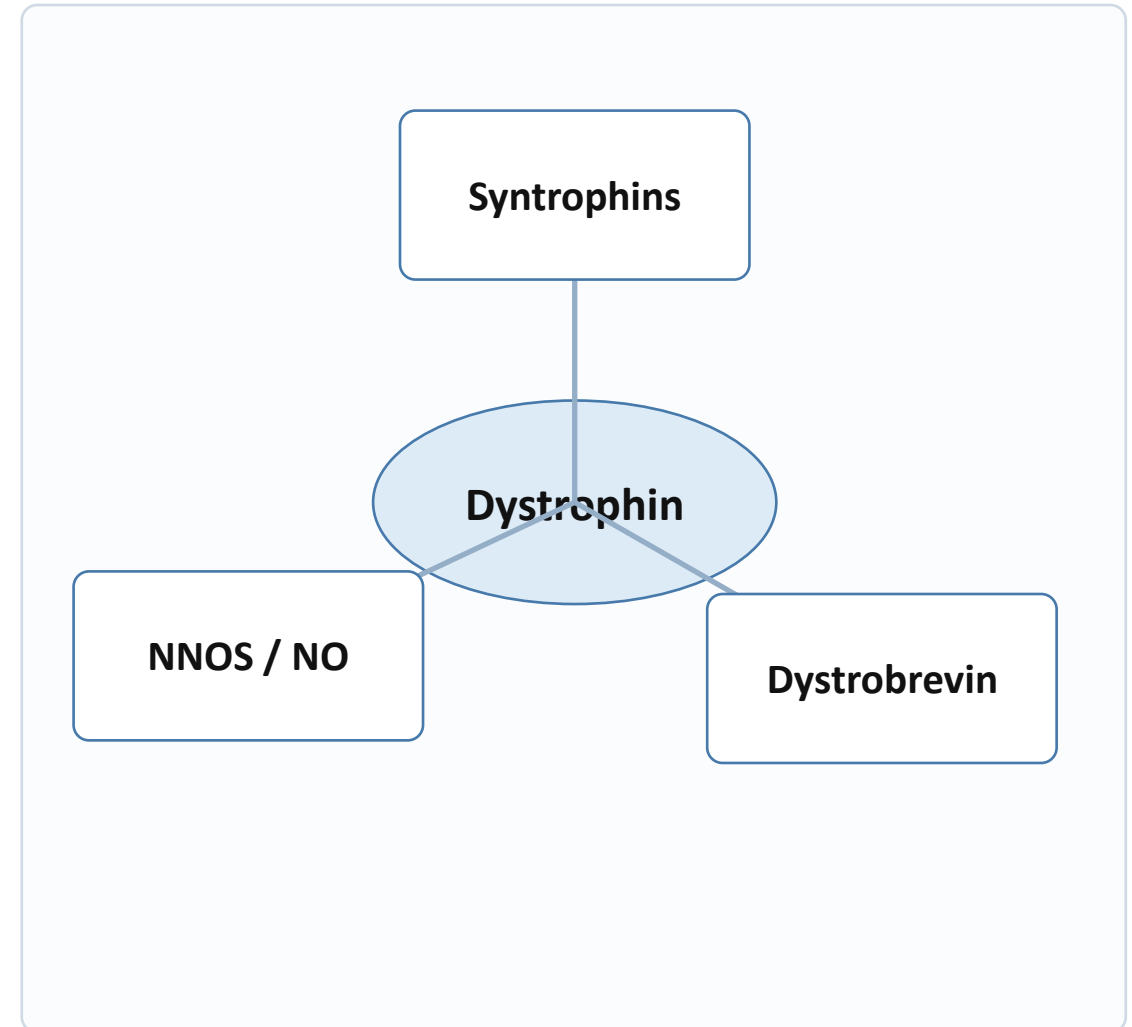
Membrane injury permits calcium influx

- Defective membrane stabilization may create microscopic sarcolemmal tears.
- Calcium entering damaged fibers triggers downstream injurious events.
- Myofiber necrosis produces the characteristic destructive process.



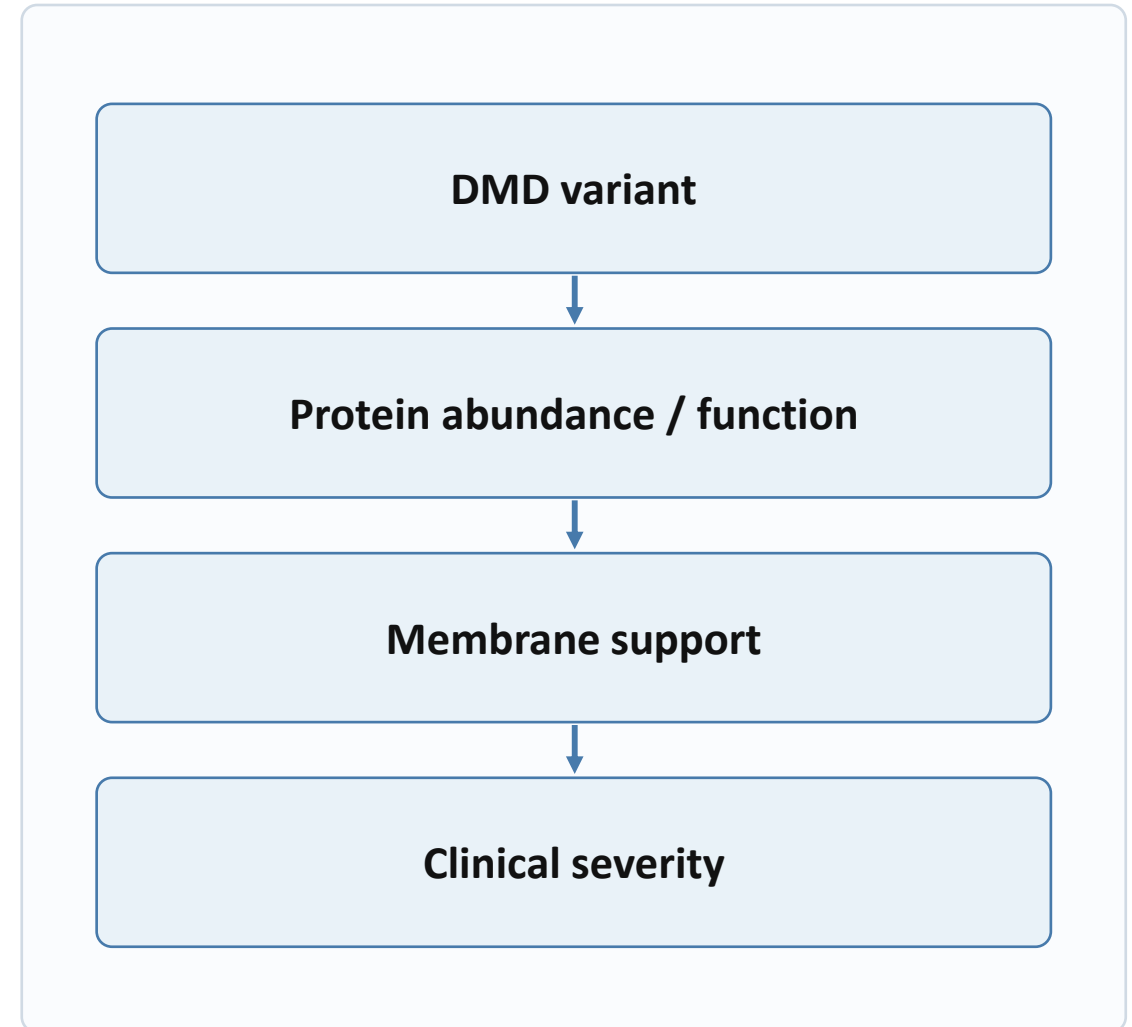
Dystrophin also participates in signaling

- The dystrophin complex is not exclusively a mechanical scaffold.
- Dystrophin associates with syntrophins and dystrobrevin.
- Its signaling interactions include neuronal-type nitric oxide synthase (nNOS).



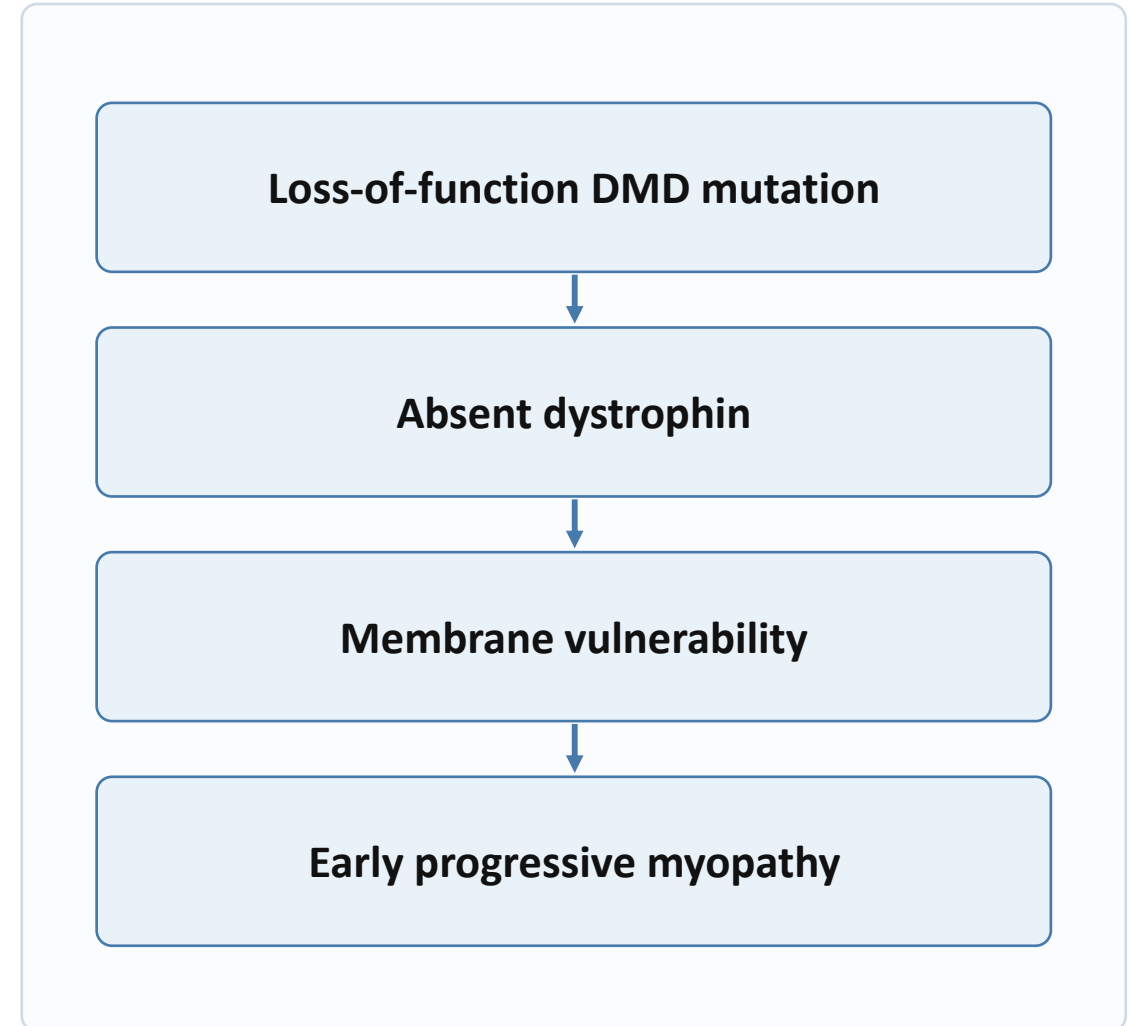
Genotype helps explain the phenotypic spectrum

- Duchenne commonly results from alterations producing essentially no dystrophin.
- Becker variants may permit a shortened protein with residual function.
- Genotype–phenotype relationships explain many—but not all—differences.



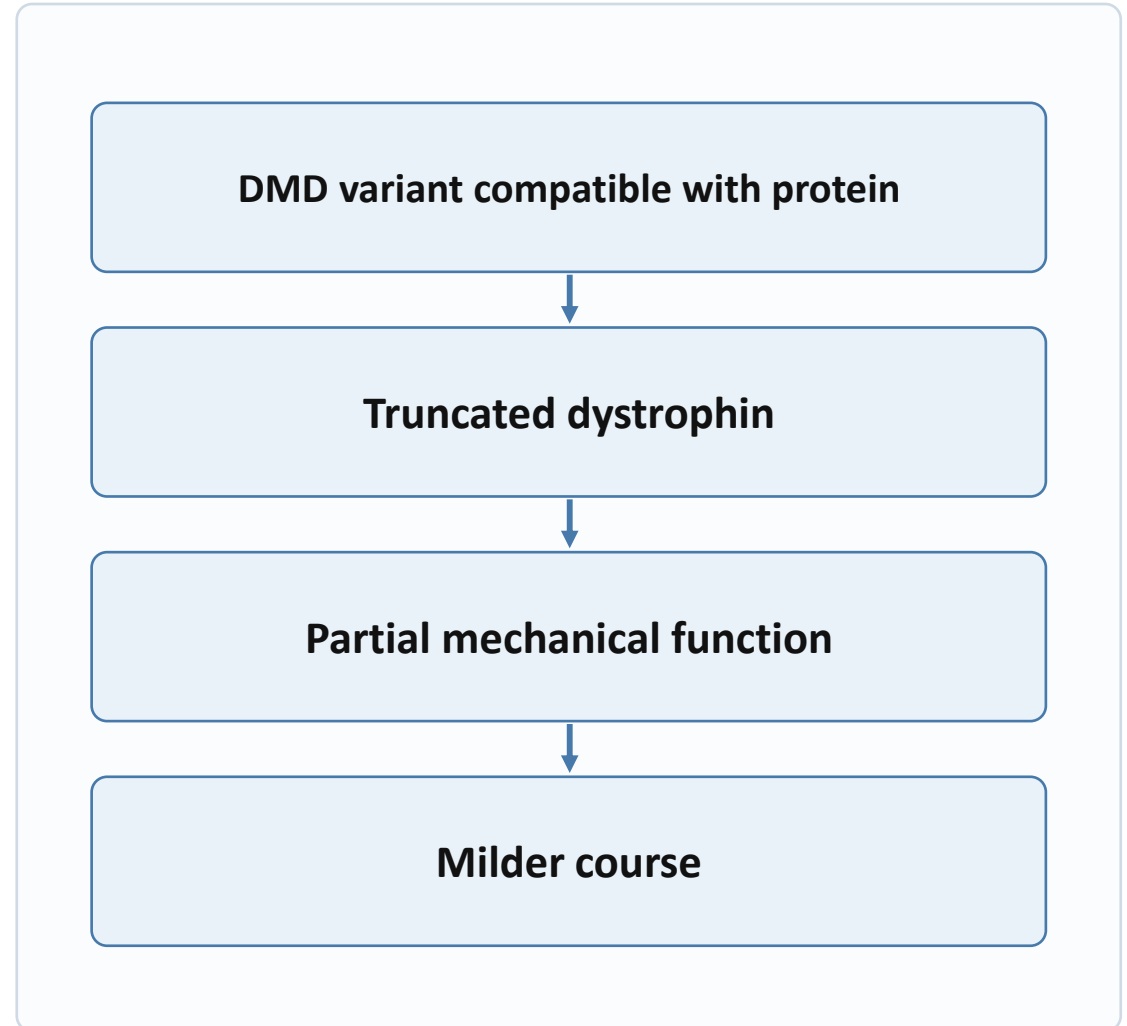
Duchenne mutations usually abolish protein expression

- Deletions and frameshifting variants commonly produce a severe null phenotype.
- Loss of dystrophin destabilizes the sarcolemmal linkage.
- Ongoing muscle damage begins well before advanced fibrofatty change.



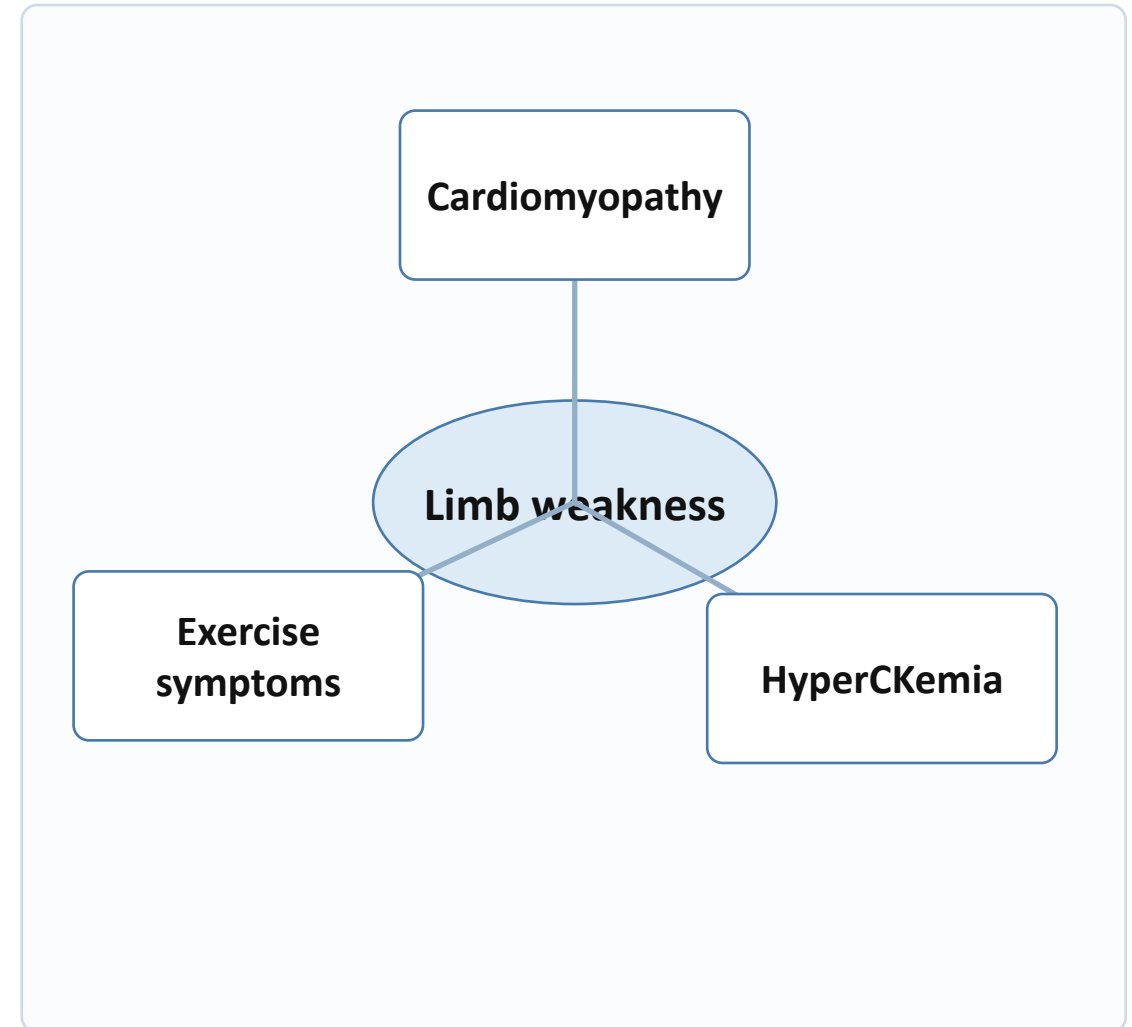
Becker variants preserve some protein function

- Certain deletions or altered splicing permit synthesis of shorter dystrophin.
- The residual protein retains at least partial function.
- Residual function is associated with later onset and slower disease progression.



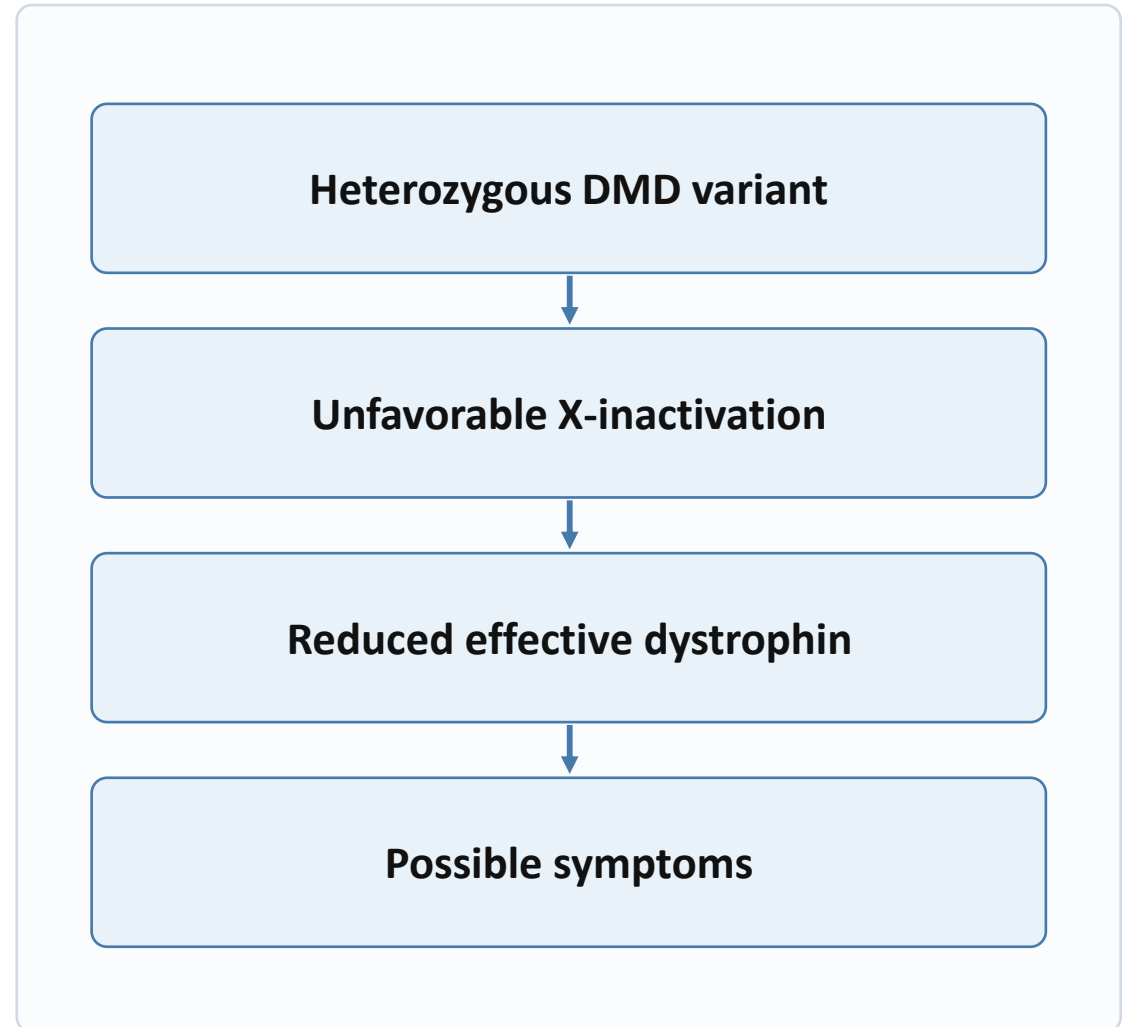
Dystrophin deficiency has a broader phenotype

- Some individuals develop predominant cardiomyopathy.
- Others are identified through asymptomatic CK elevation.
- Exercise intolerance, cramps and myalgias can also occur.



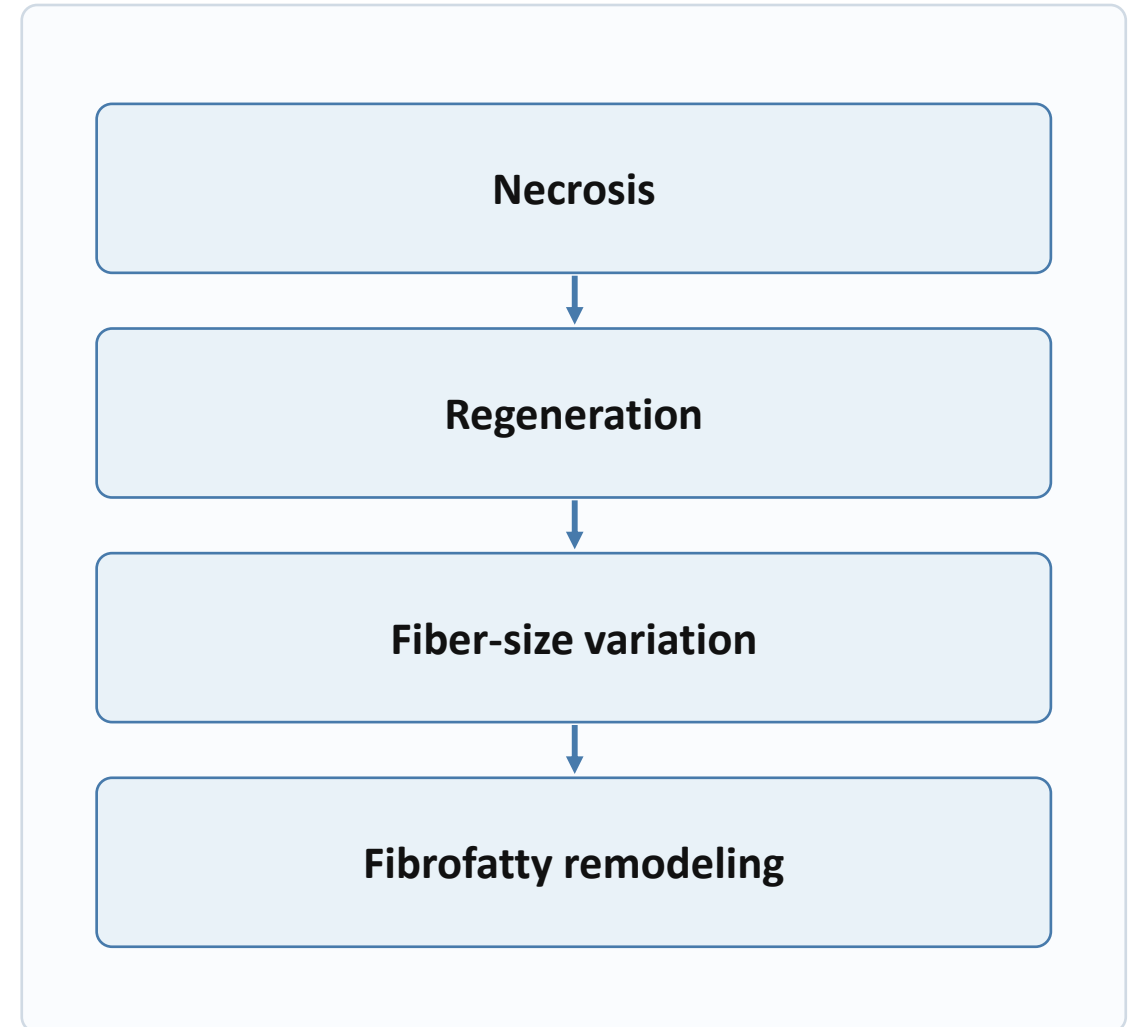
Female DMD carriers may be symptomatic

- Female carriers are not invariably free of manifestations.
- Skewed X-chromosome inactivation can increase the effect of a pathogenic allele.
- A symptomatic carrier may show relatively mild muscular manifestations.



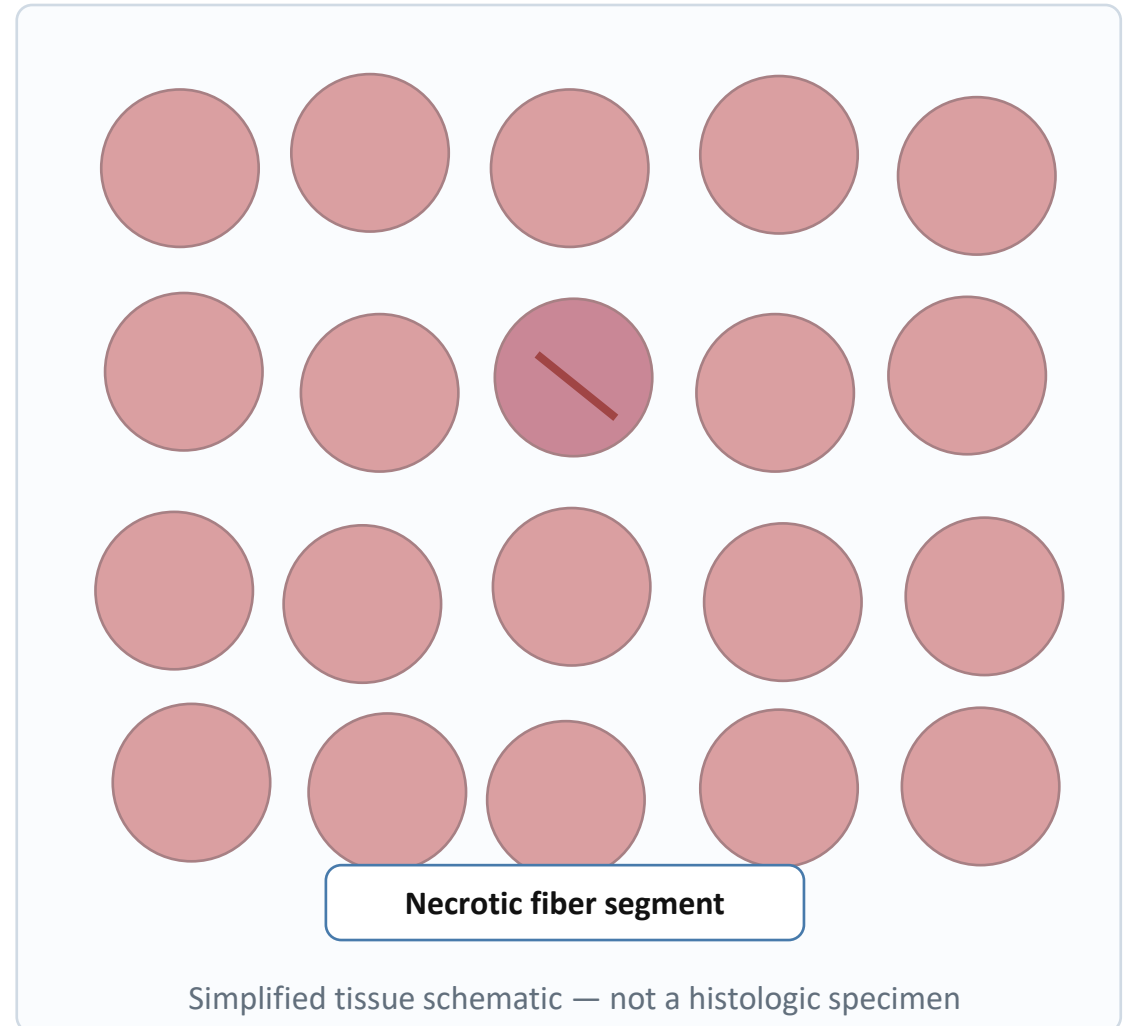
Dystrophic pathology reflects chronic destruction and repair

- Segmental myofiber necrosis coexists with attempts at regeneration.
- Atrophic and hypertrophied fibers can occur in the same specimen.
- Progressive injury eventually leads to connective tissue and fatty replacement.



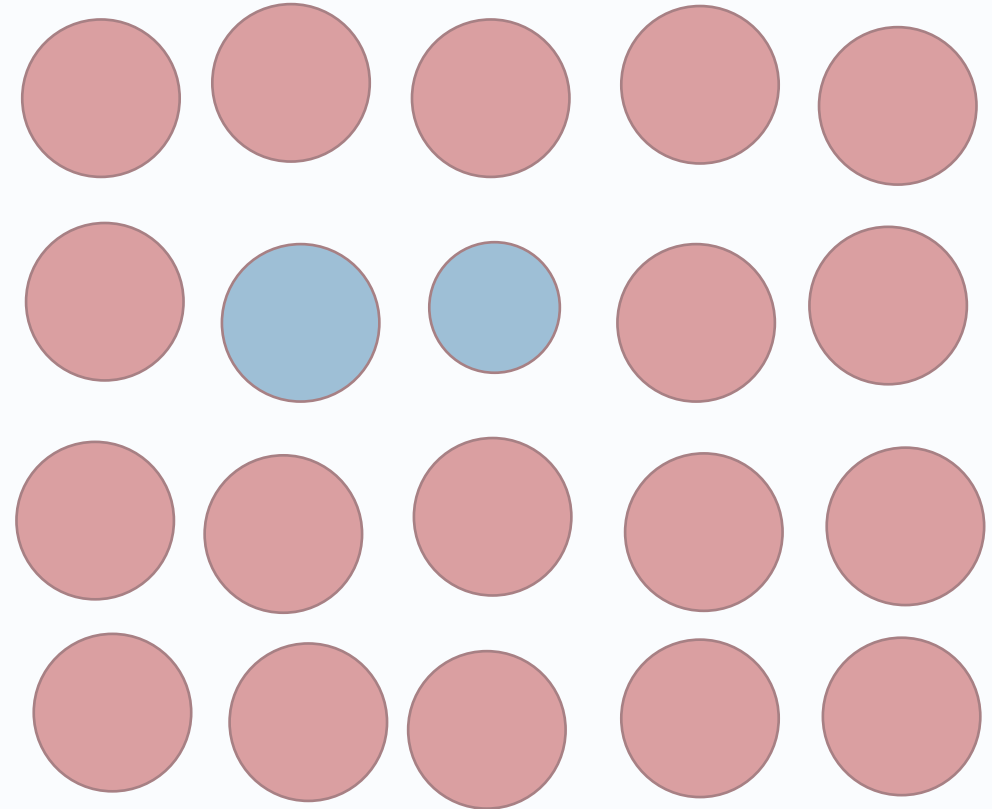
Segmental necrosis is an active injury pattern

- Only portions of individual muscle fibers may undergo necrosis.
- Necrotic fiber segments are removed by phagocytic cells.
- This process indicates active myofiber injury rather than denervation alone.



Regeneration accompanies ongoing necrosis

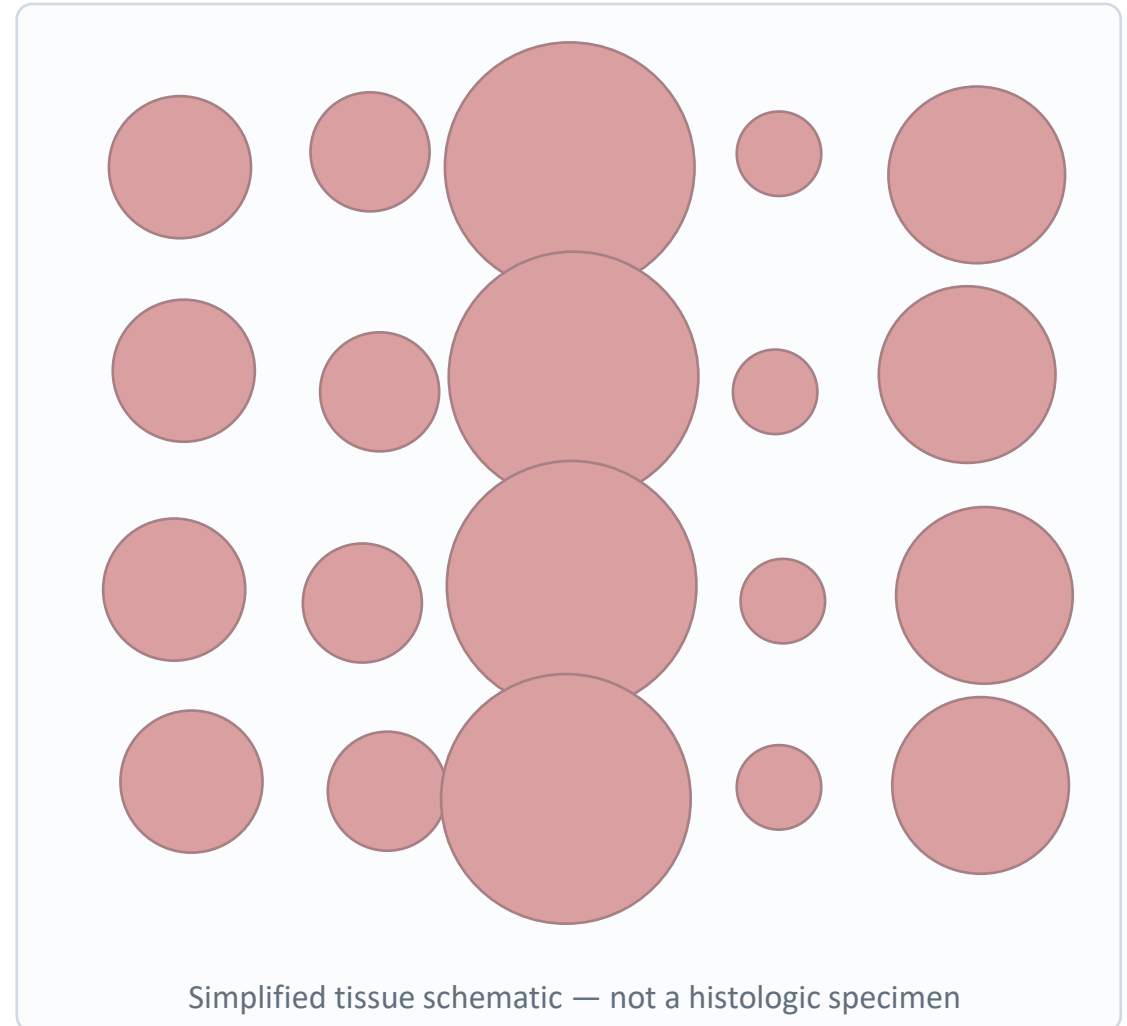
- Regenerating fibers appear among injured and atrophic myofibers.
- Basophilic regenerating fibers in an early Duchenne biopsy.
- Regeneration does not necessarily keep pace with repeated injury.



Simplified tissue schematic — not a histologic specimen

Fiber-size variation marks the dystrophic process

- Small atrophic fibers coexist with enlarged surviving fibers.
- Differences in caliber become increasingly striking as disease progresses.
- Size heterogeneity is important but not by itself disease specific.



Early fascicular architecture can be preserved

- An early Duchenne biopsy can retain recognizable fascicles.
- Fiber necrosis and regeneration may still be evident within the fascicle.
- A deceptively preserved overall pattern does not exclude active dystrophy.

Early stage

Recognizable fascicles

Focal degeneration
and regeneration

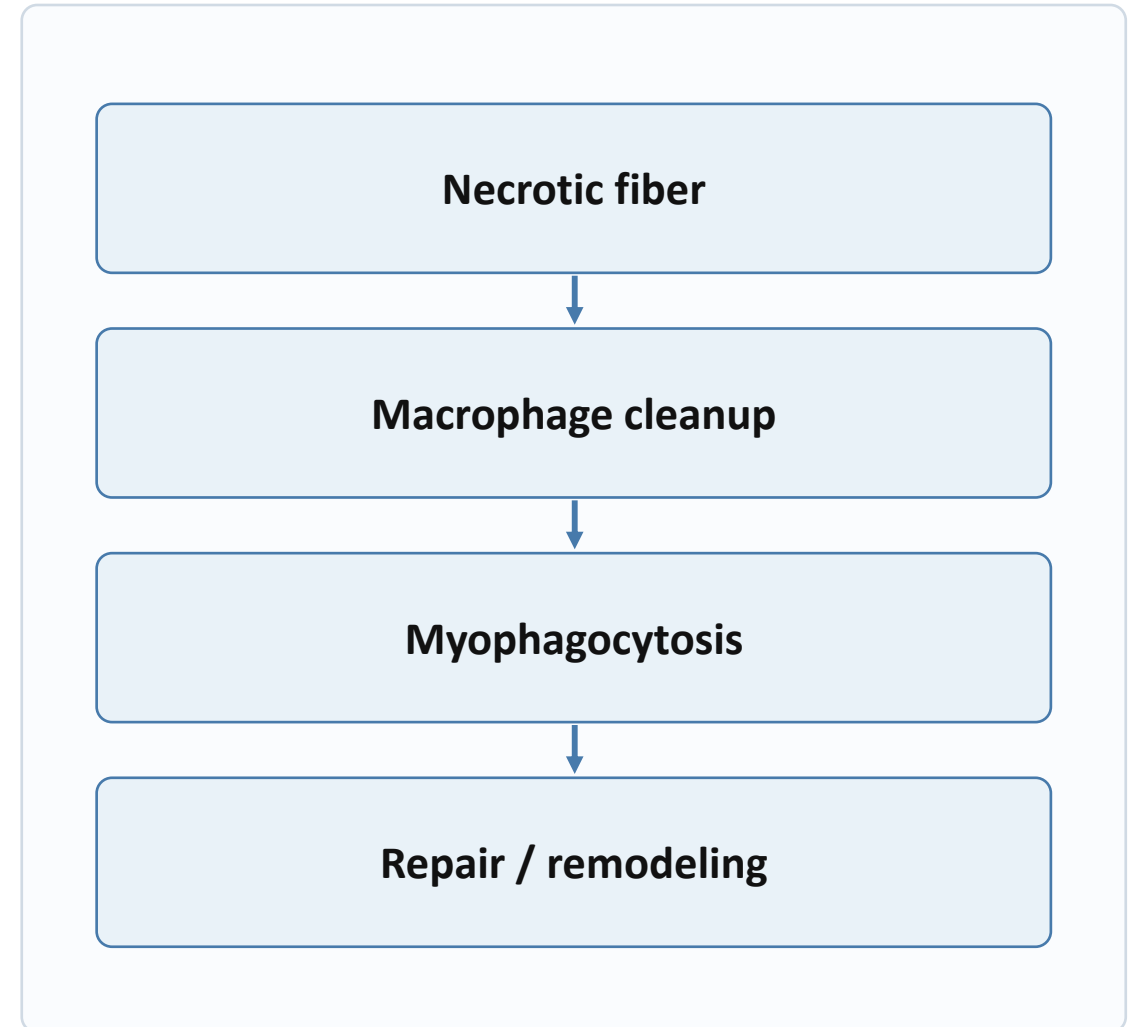
Later stage

Architectural
disruption

Prominent fibrosis and
fat

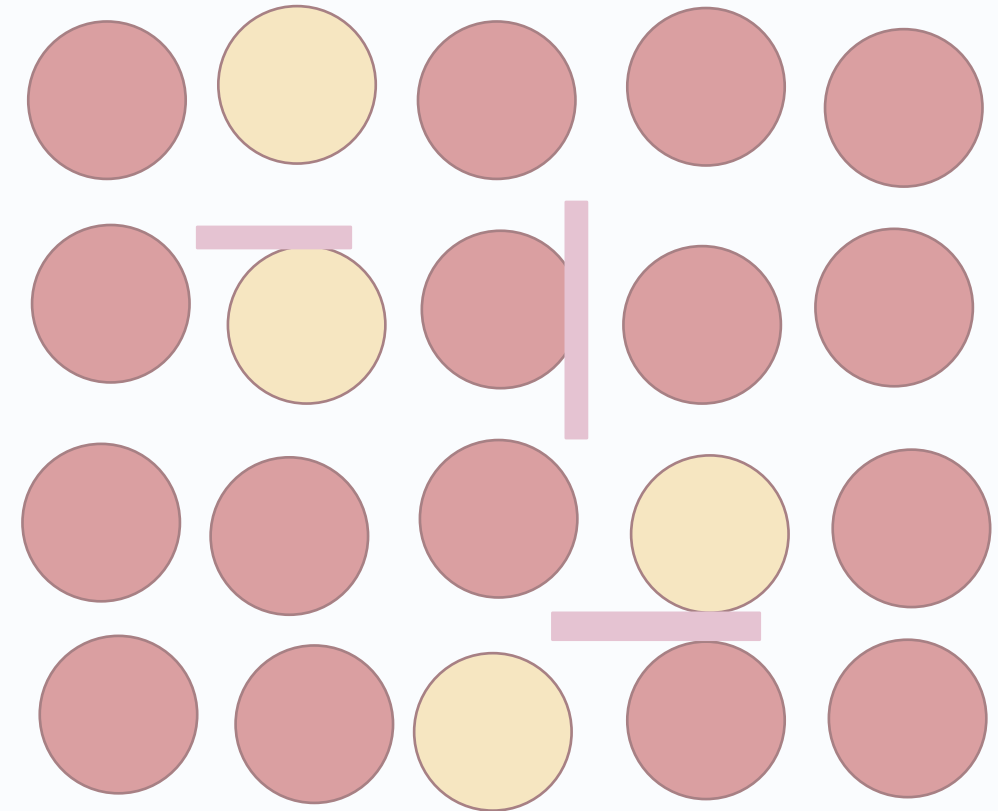
Myophagocytosis is not diffuse inflammatory myositis

- Macrophage removal of necrotic fiber material is expected after injury.
- Little inflammation beyond myophagocytosis in typical early Duchenne biopsies.
- Inflammatory cells must be interpreted alongside the overall pattern.



Fibrosis and fatty replacement are progressive

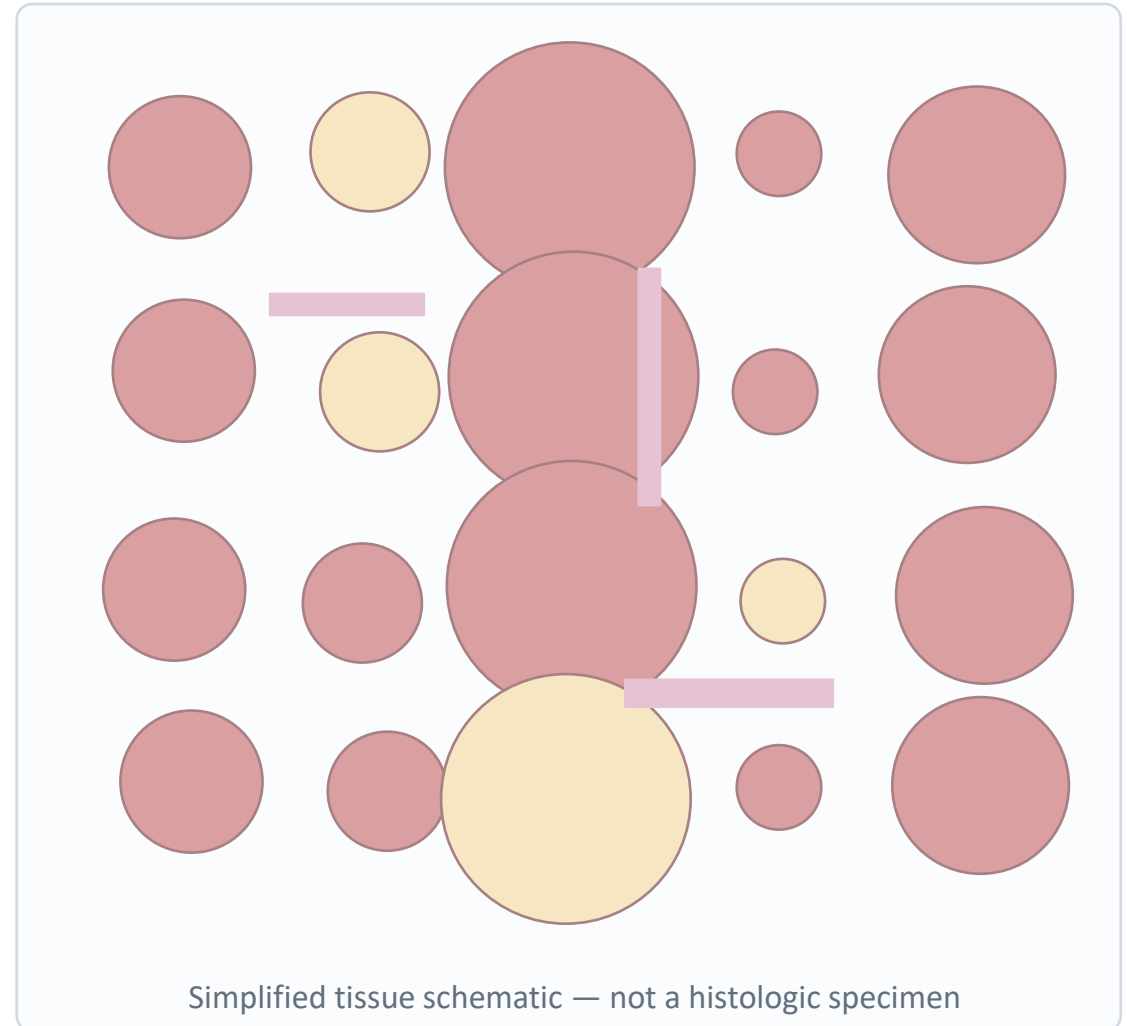
- Collagen and adipose tissue replace lost functional muscle.
- Endomysial expansion increasingly separates surviving myofibers.
- Replacement drives irreversible architectural distortion.



Simplified tissue schematic — not a histologic specimen

Advanced disease disorganizes fascicular architecture

- Myofibers are unevenly distributed among collagen and adipocytes.
- Normal muscle organization becomes markedly abnormal.
- Remaining fibers range from small and atrophic to enlarged and hypertrophic.



Muscle biopsy findings depend on disease stage

- Early biopsy: Necrosis and regeneration with fairly preserved organization.
- Intermediate biopsy: Increasing fiber-size variation and connective tissue.
- Late biopsy: Extensive fibrofatty replacement may dominate the field.

Early: Active injury



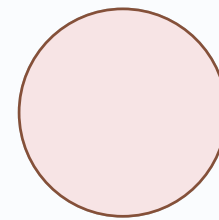
Intermediate: Remodeling



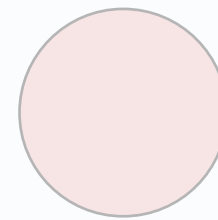
Late: Replacement

Dystrophin immunostaining assesses membrane expression

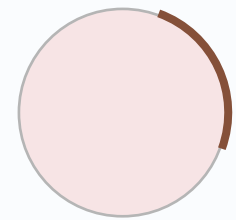
- Dystrophin is normally demonstrable at the myofiber membrane.
- Complete loss is characteristic of many Duchenne biopsies.
- Reduced or altered expression can support a Becker phenotype.



Normal



Duchenne

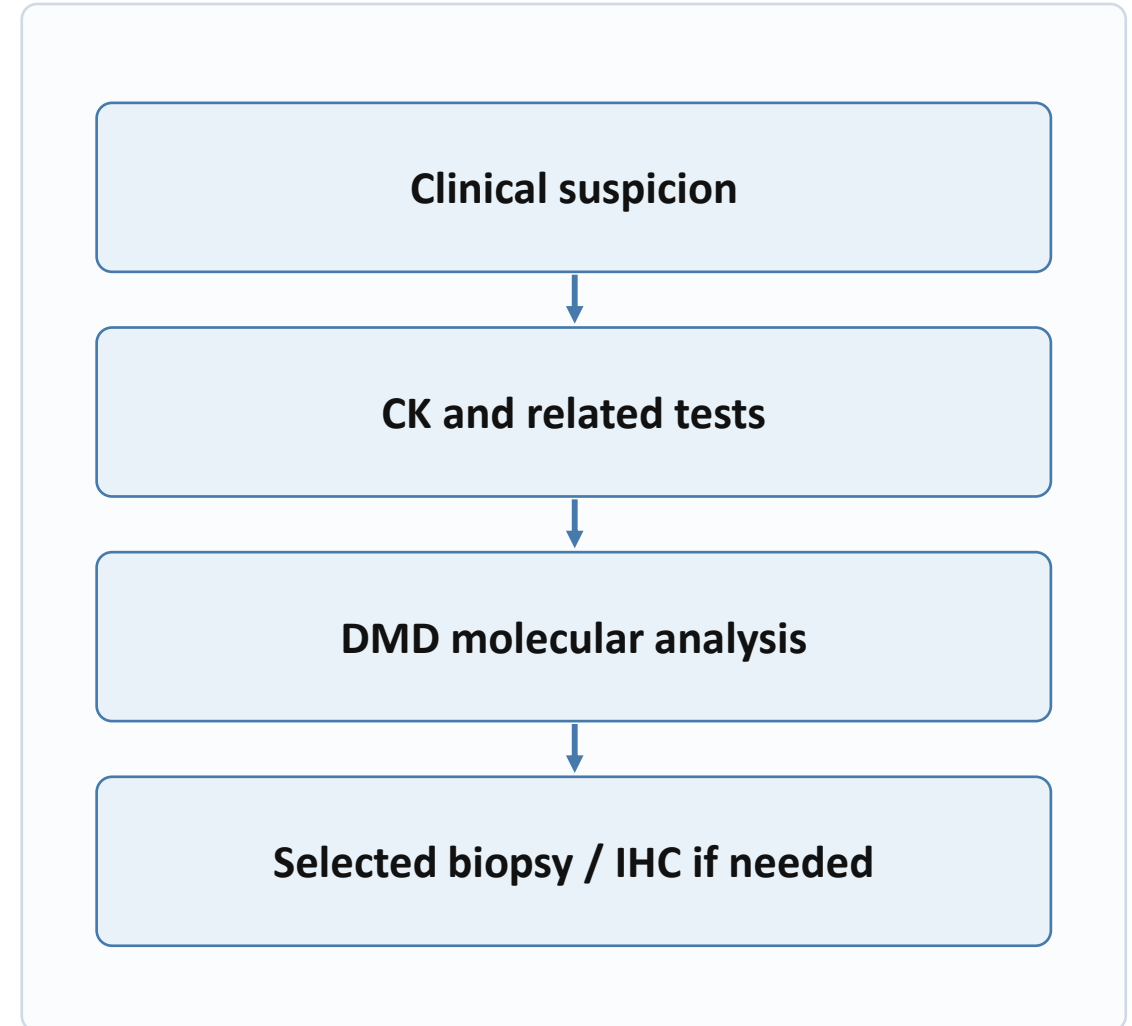


Becker

Idealized schematic membrane staining patterns

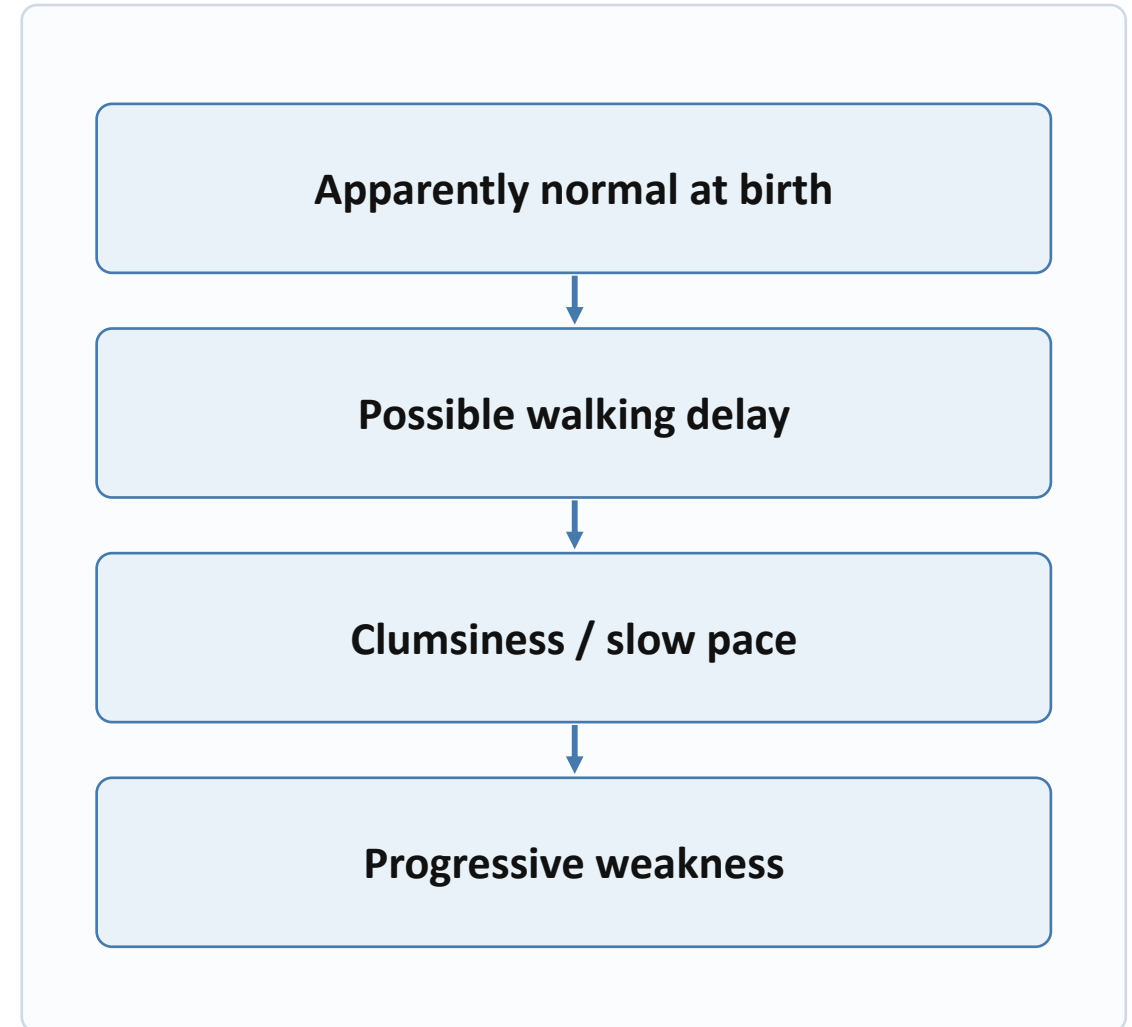
Immunostaining must be interpreted with genetics

- Protein expression varies with underlying pathogenic variants.
- Abnormal dystrophin labeling supports the molecular diagnosis.
- Genetic testing remains the definitive confirmatory investigation.



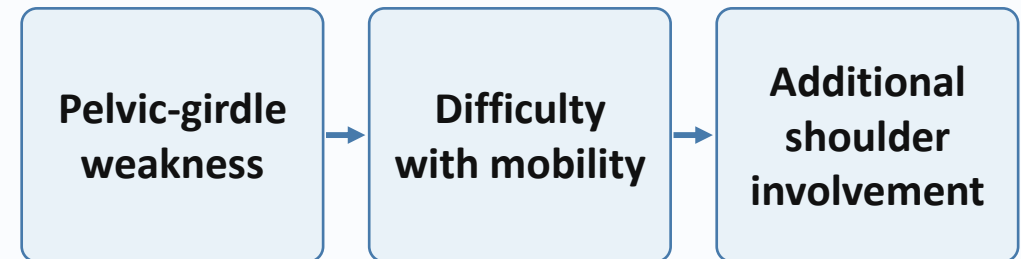
Duchenne disease begins after a normal neonatal appearance

- Affected boys usually appear normal at birth.
- Earliest motor milestones may be attained despite underlying disease.
- Delayed walking and later weakness may be the first recognizable indications.



Early functional symptoms reflect proximal weakness

- Clumsiness and difficulty keeping up with peers are common early complaints.
- Weakness initially involves pelvic-girdle muscles.
- Shoulder-girdle muscle weakness appears as the disease progresses.



Pelvic-girdle muscles are affected before the shoulder

- The distribution is initially proximal rather than purely distal.
- Anatomic pattern is an important clinical clue.
- Pattern recognition alone does not establish a molecular genotype.

Pelvic girdle: Early weakness

Shoulder girdle: Later involvement

Generalized functional decline

Calf pseudohypertrophy masks tissue loss

- Enlarged lower-leg muscles may coexist with marked weakness.
- Progressive replacement by fat and connective tissue increases bulk.
- Apparent muscle size is therefore not a measure of contractile strength.

Apparent enlargement

Increased calf volume

May seem well developed

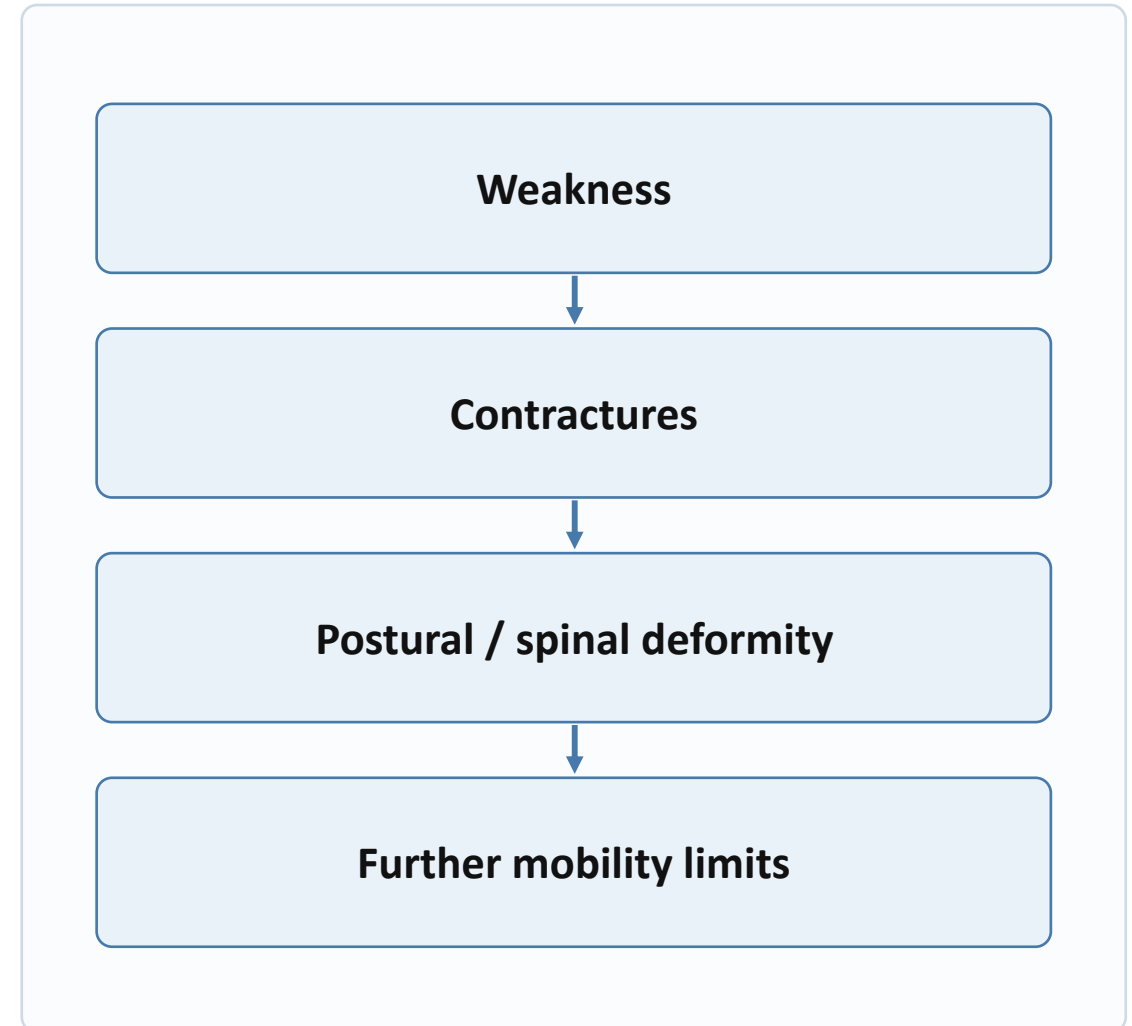
Functional pathology

Lost contractile myofibers

Fibrofatty replacement

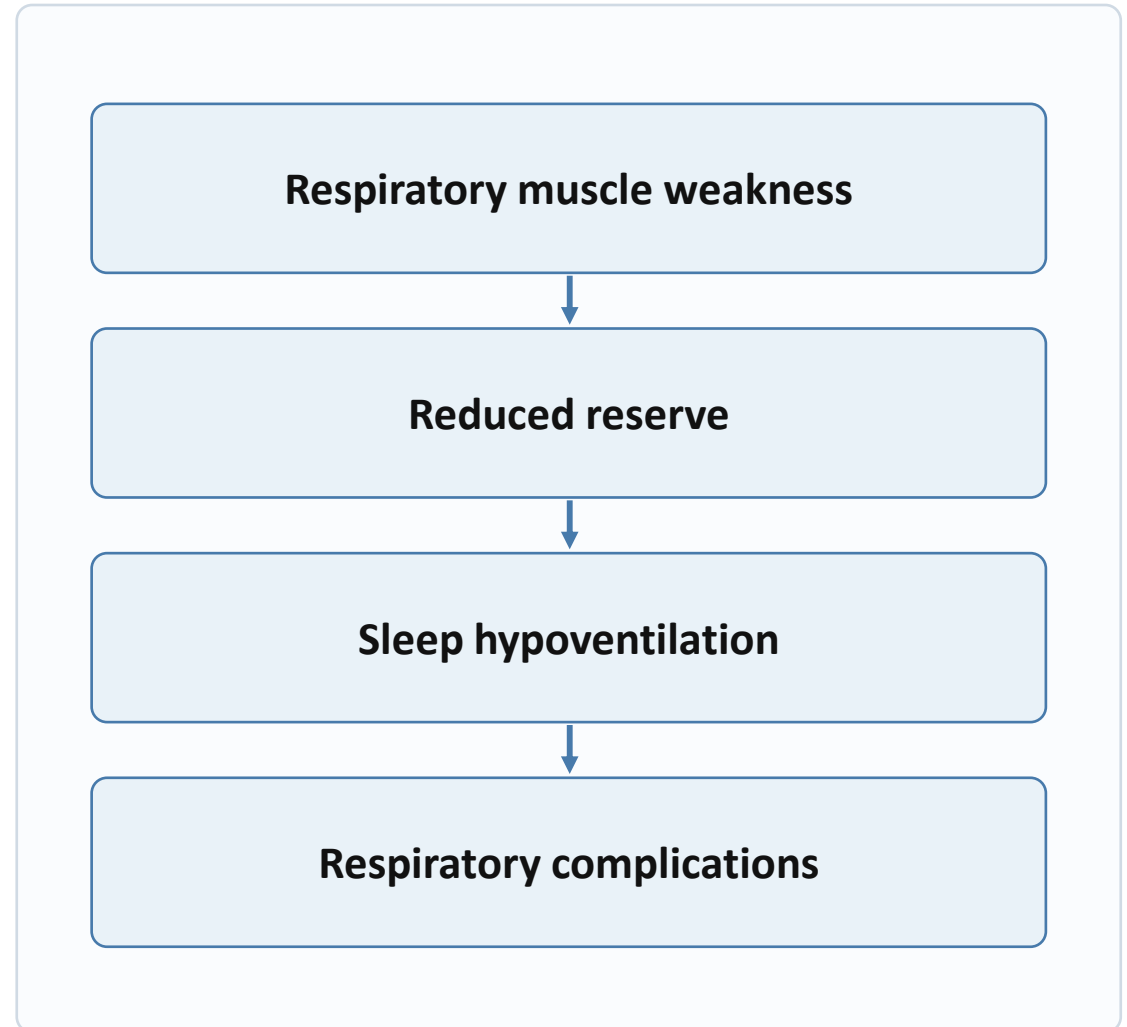
Contractures and scoliosis reflect advancing disease

- Progressive weakness contributes to reduced joint mobility and deformity.
- Joint contractures can develop with increasing muscle involvement.
- Spinal deformity and scoliosis compound functional disability.



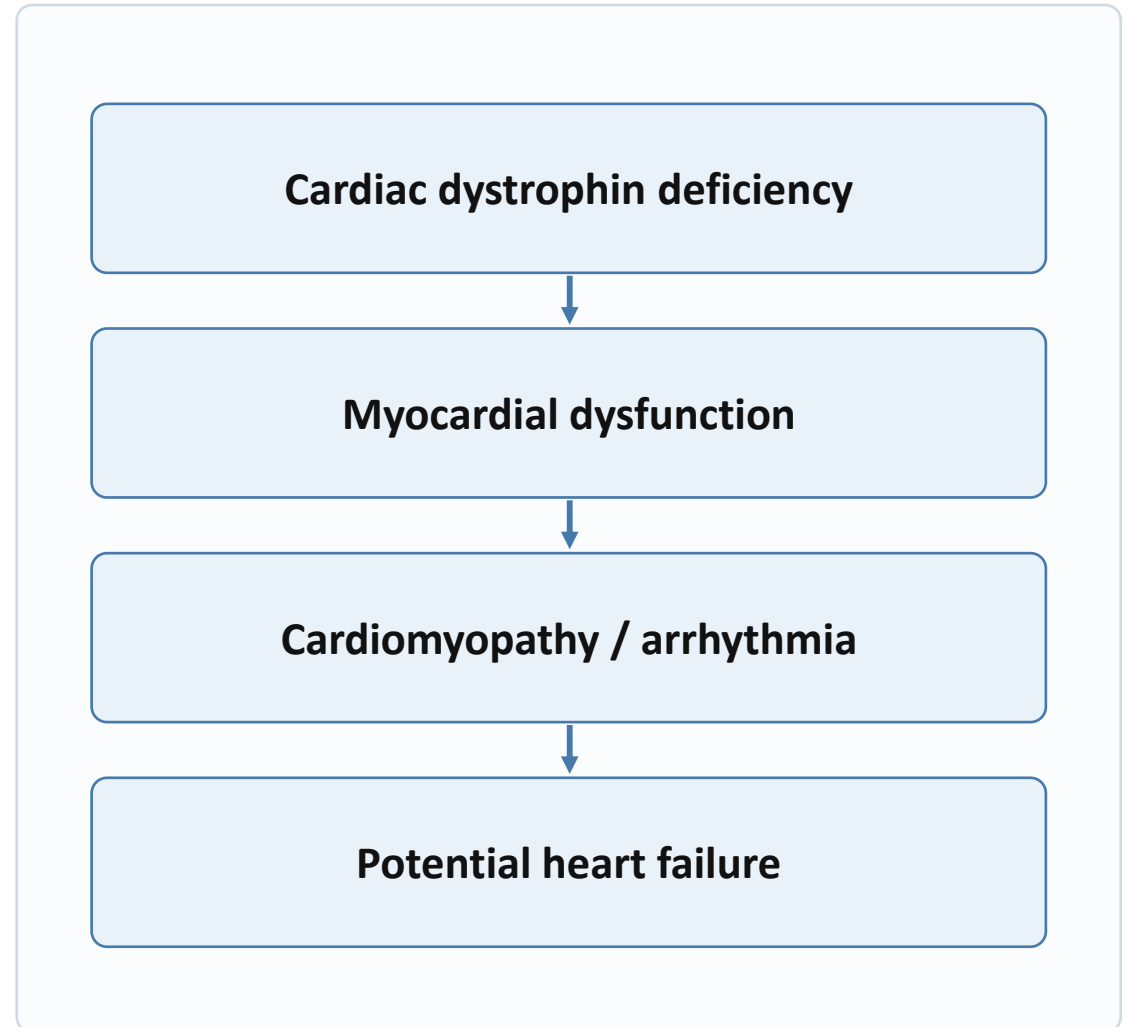
Respiratory complications become consequential

- Respiratory muscle involvement progressively reduces reserve.
- Sleep-related hypoventilation can occur in advanced disease.
- Respiratory insufficiency and pulmonary infections contribute to mortality.



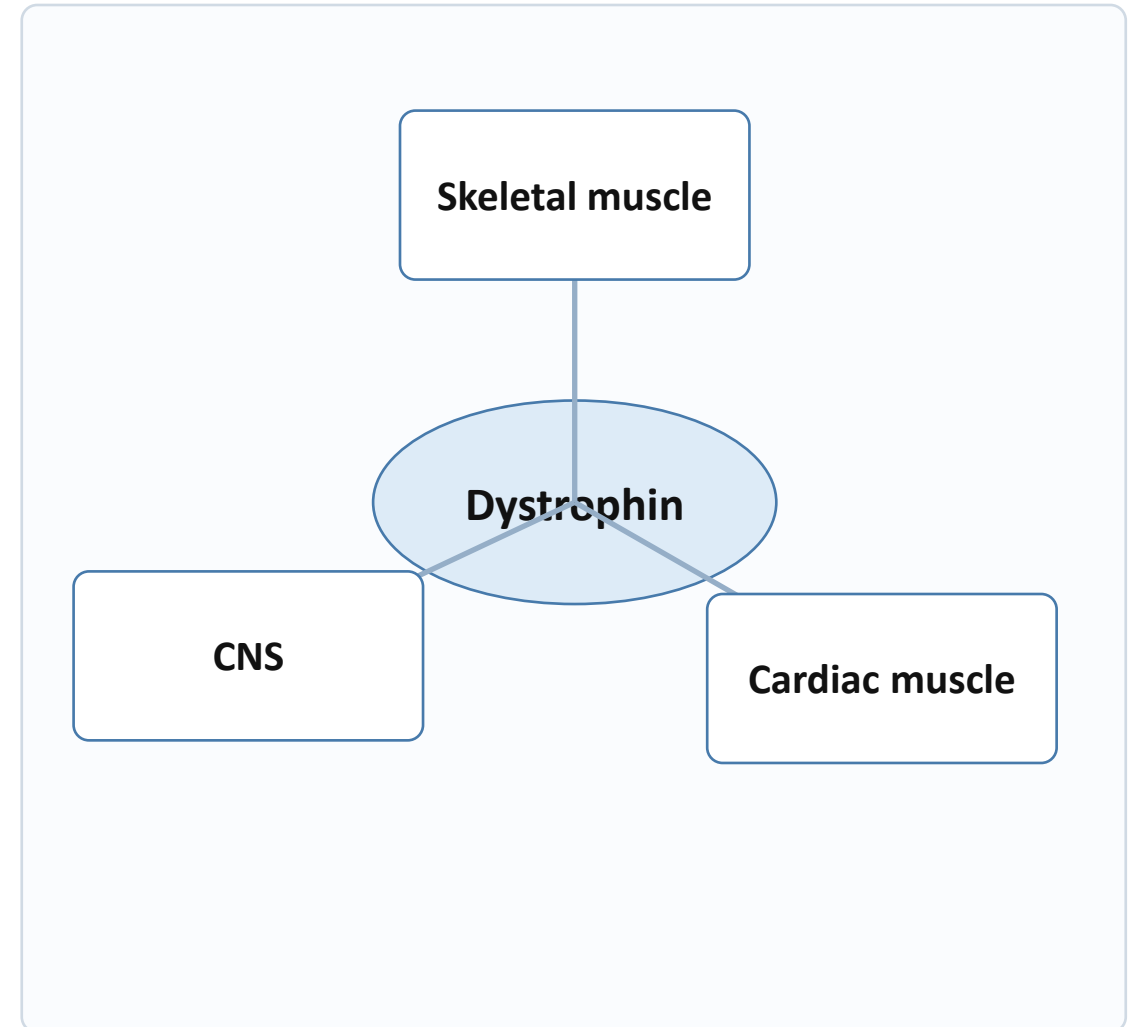
Cardiomyopathy is a major dystrophinopathy manifestation

- Dystrophin is normally expressed in cardiac muscle.
- Deficiency can produce cardiomyopathy and arrhythmias.
- Cardiac involvement may dominate survival even in milder skeletal phenotypes.



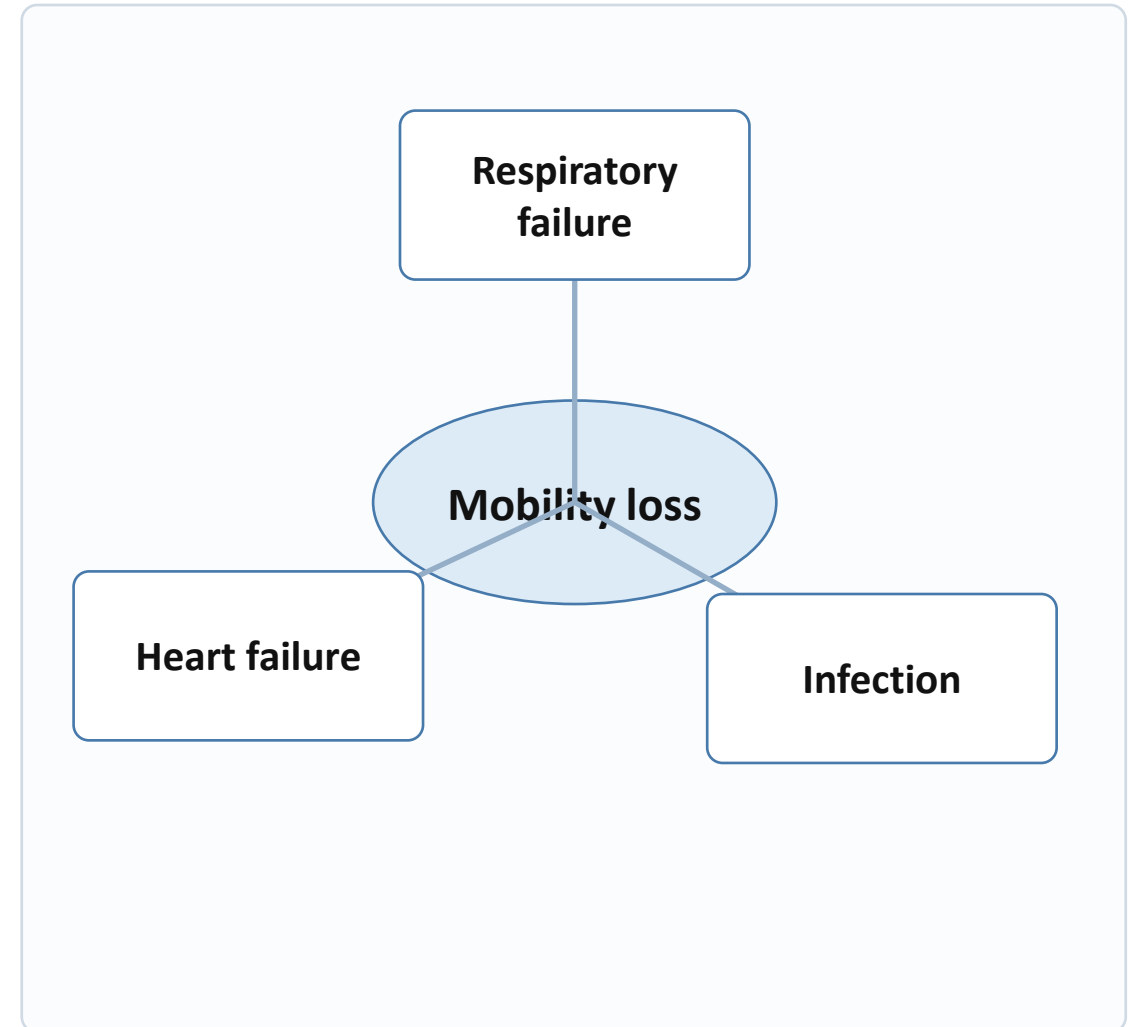
Dystrophin expression in the CNS has clinical correlates

- Dystrophin is expressed beyond muscle, including the brain.
- Learning disability and cognitive impairment may accompany Duchenne disease.
- These findings vary and should not be presumed in every patient.



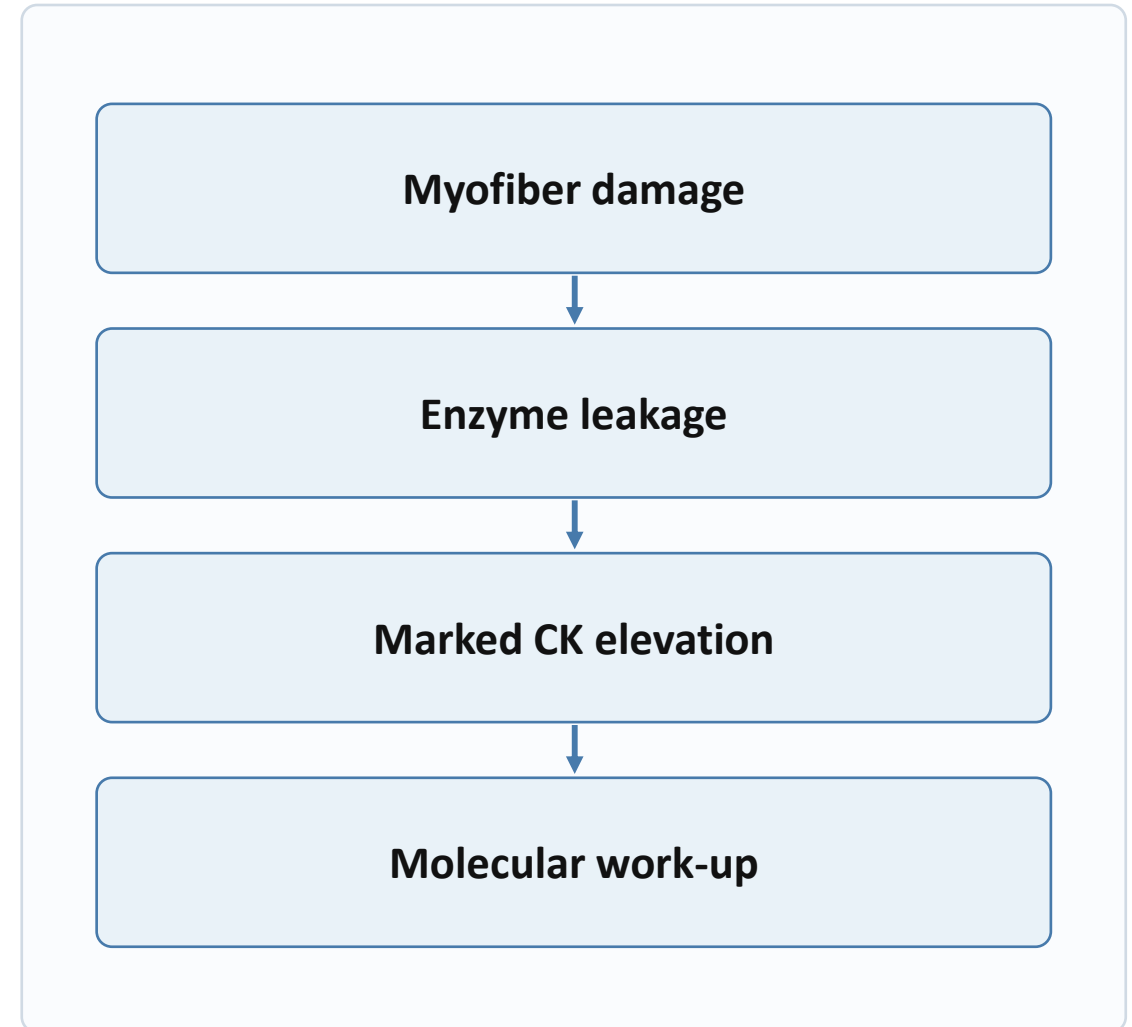
Duchenne prognosis involves multiple organ systems

- Progressive weakness eventually limits ambulation and independence.
- Pulmonary infection, respiratory insufficiency and heart failure are important threats.
- Major mortality in young adulthood despite support; Individual outcomes vary.



Serum CK reflects active muscle membrane injury

- Creatine kinase becomes markedly elevated during active early injury.
- Leakage of muscle enzymes accompanies necrosis.
- A high CK supports a muscle injury process but is not dystrophinopathy-specific.



CK can decline as muscle mass is lost

- CK often peaks during the first decade, when active destruction is prominent.
- Levels can fall later despite clinically worsening disease.
- Serial CK must be interpreted with stage and remaining muscle mass.

Earlier disease

More intact muscle
undergoing injury

Marked CK elevation

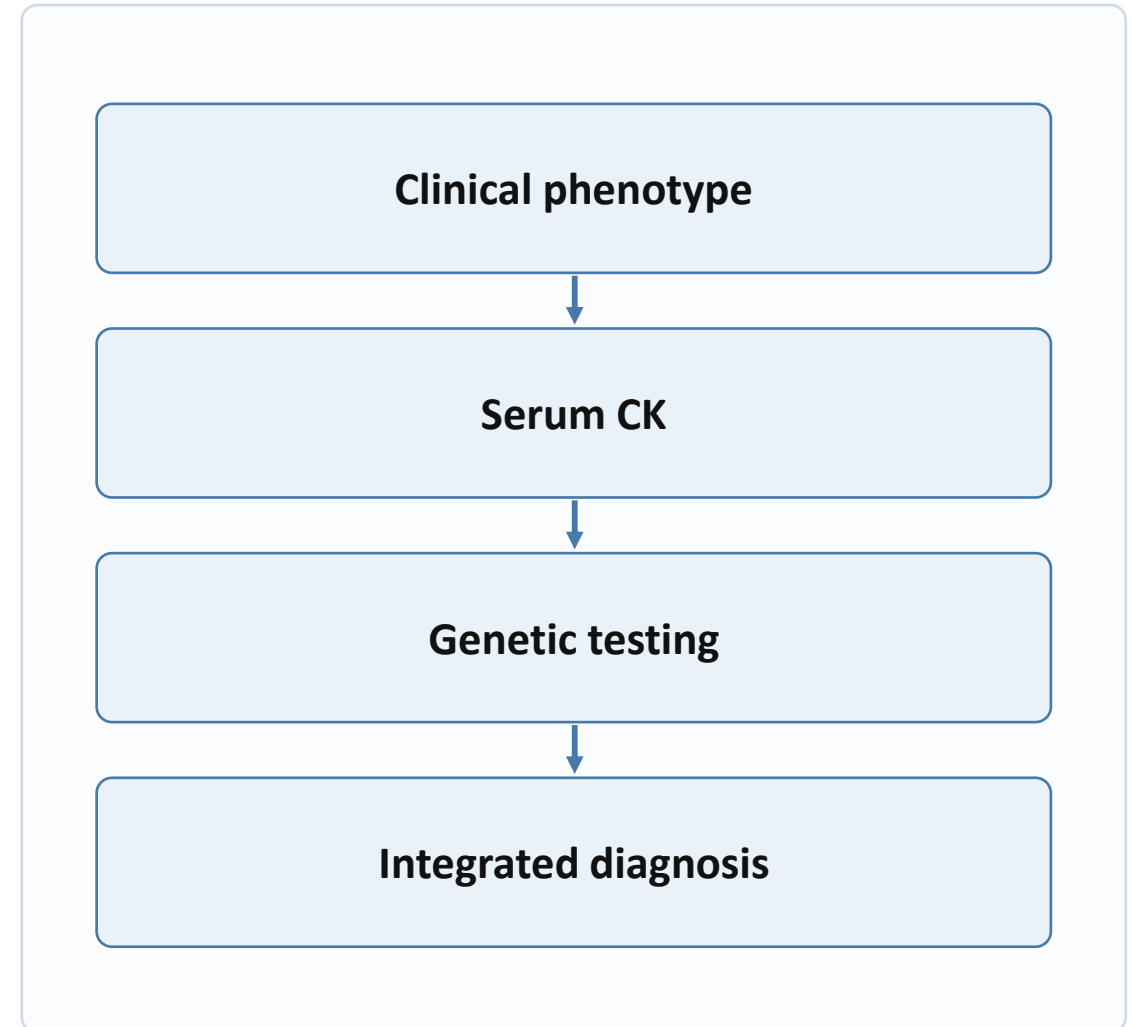
Advanced disease

Less remaining muscle
mass

CK may decrease

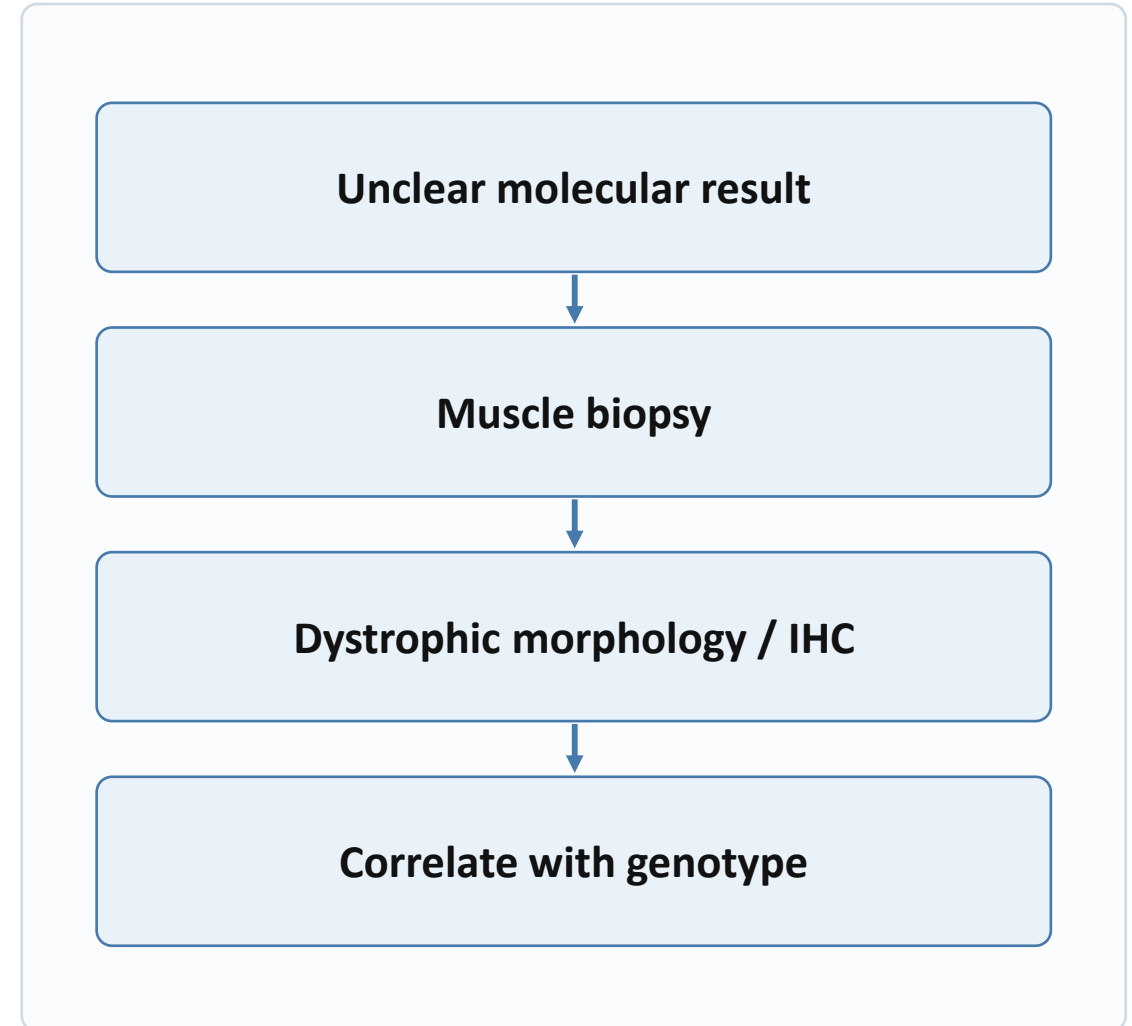
Clinical pattern and testing are complementary

- History and examination establish the pattern of weakness and progression.
- Serum CK indicates active muscle damage.
- Molecular testing confirms a pathogenic dystrophin alteration.



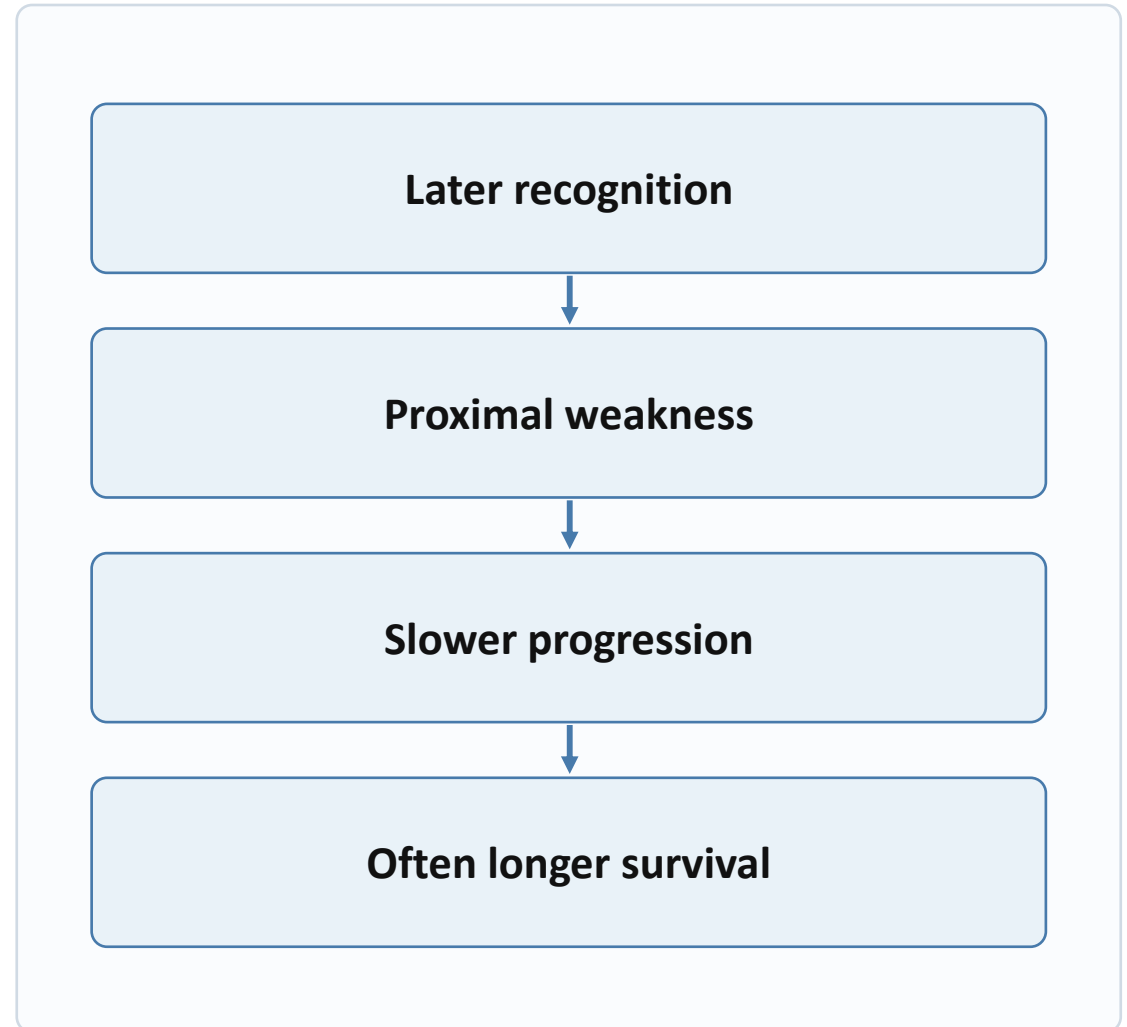
Biopsy is most valuable when genetics is unresolved

- Genetic testing as the ultimate confirmation.
- Muscle biopsy can be informative for difficult-to-identify alterations.
- Morphology and dystrophin staining provide additional protein-level evidence.



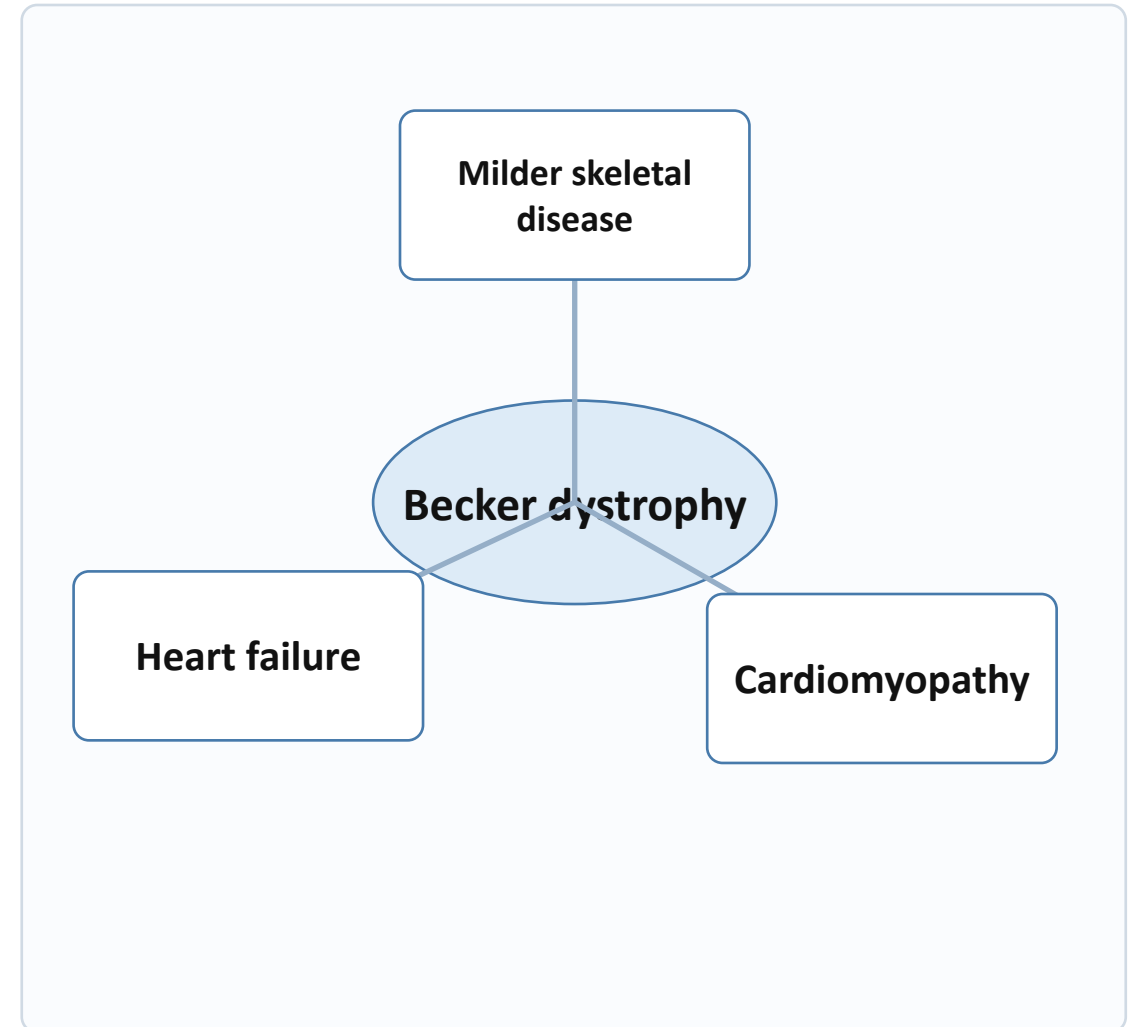
Becker dystrophy typically progresses more slowly

- Symptoms may appear in later childhood, adolescence or adulthood.
- Some affected individuals maintain function for much longer than in classic Duchenne.
- Residual dystrophin function is a major molecular explanation.



Cardiac disease may dominate Becker outcome

- Less severe skeletal muscle weakness does not eliminate cardiac risk.
- Heart failure remains a common life-limiting complication in Becker disease.
- Clinical comparisons must consider cardiac as well as skeletal phenotype.

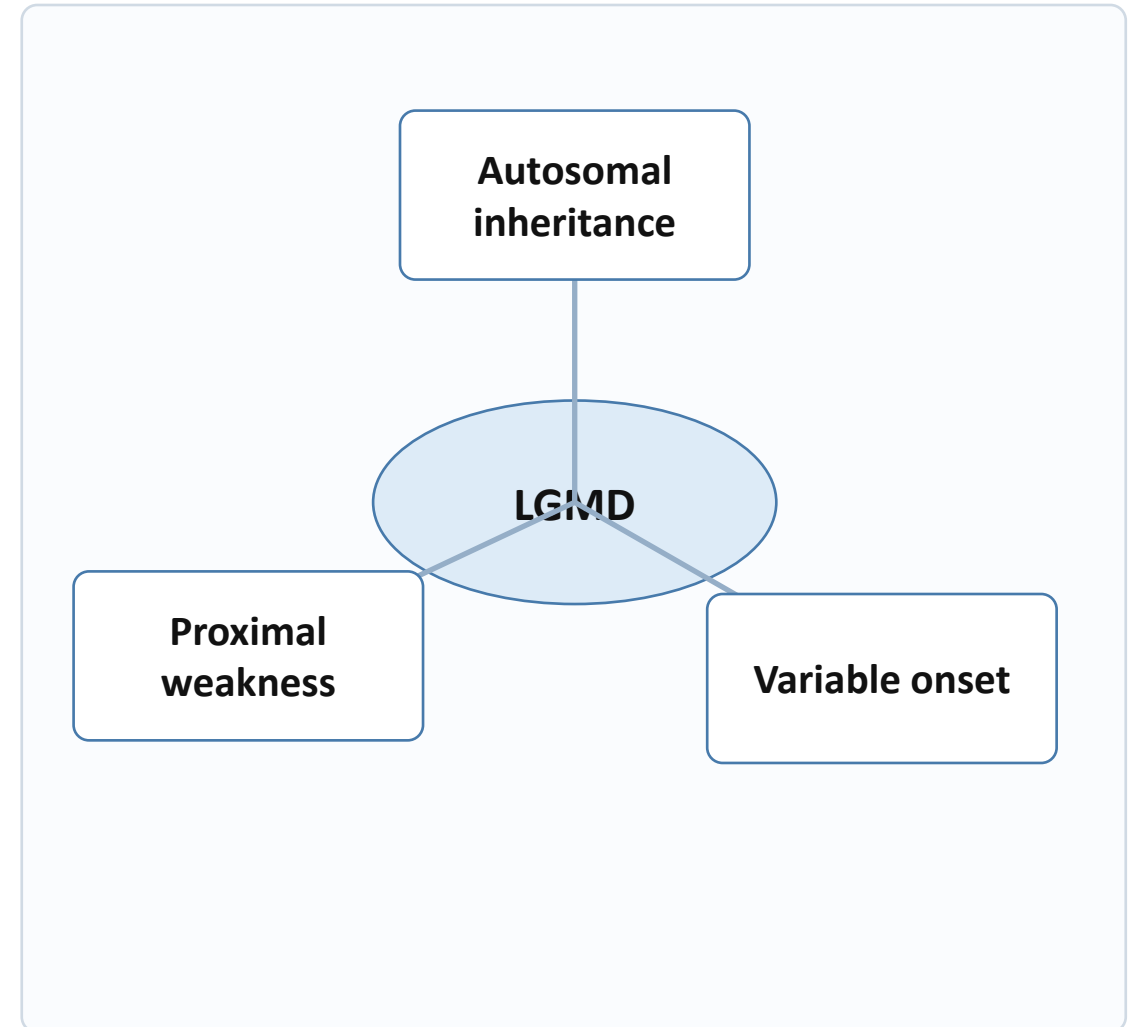


Duchenne versus Becker: Integrated comparison

Dimension	Duchenne	Becker
Dystrophin	Usually absent	Usually shortened / partly functional
Onset	Typically early childhood	Later childhood to adult life
Clinical course	Severe; rapid progression	Typically milder; slower progression
Cardiac disease	Common and serious	Can be major life-limiting feature
Molecular diagnosis	DMD pathogenic variant	DMD pathogenic variant

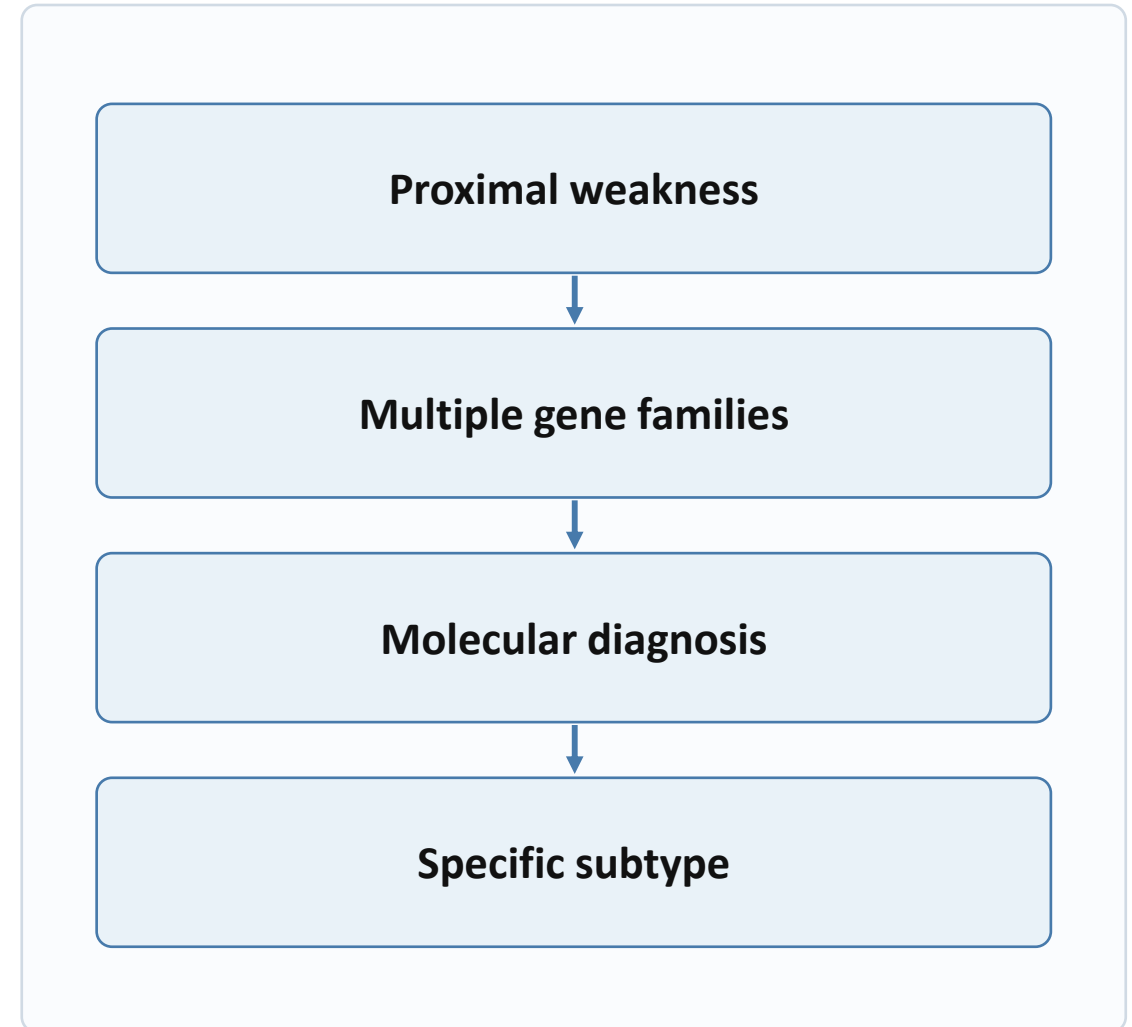
Limb-girdle muscular dystrophy is heterogeneous

- A broad collection of autosomal dominant and recessive disorders.
- Age of onset and clinical severity differ widely.
- The shared clinical pattern is preferential proximal muscle weakness.



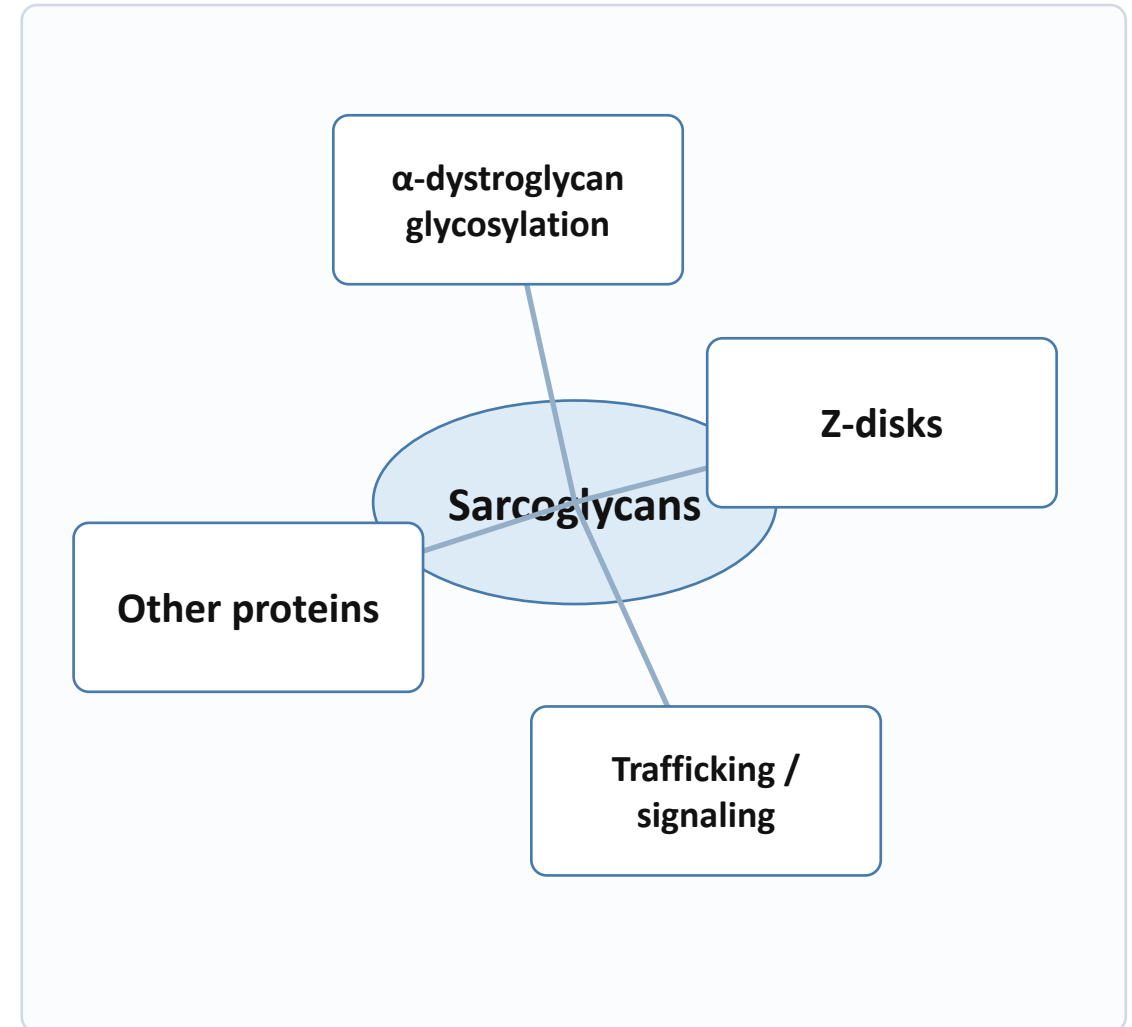
Limb-girdle weakness is a phenotype, not a genotype

- Many molecular lesions can produce similar proximal weakness.
- Clinical distribution alone cannot identify the causative gene.
- Protein compartment and molecular analysis organize the differential.



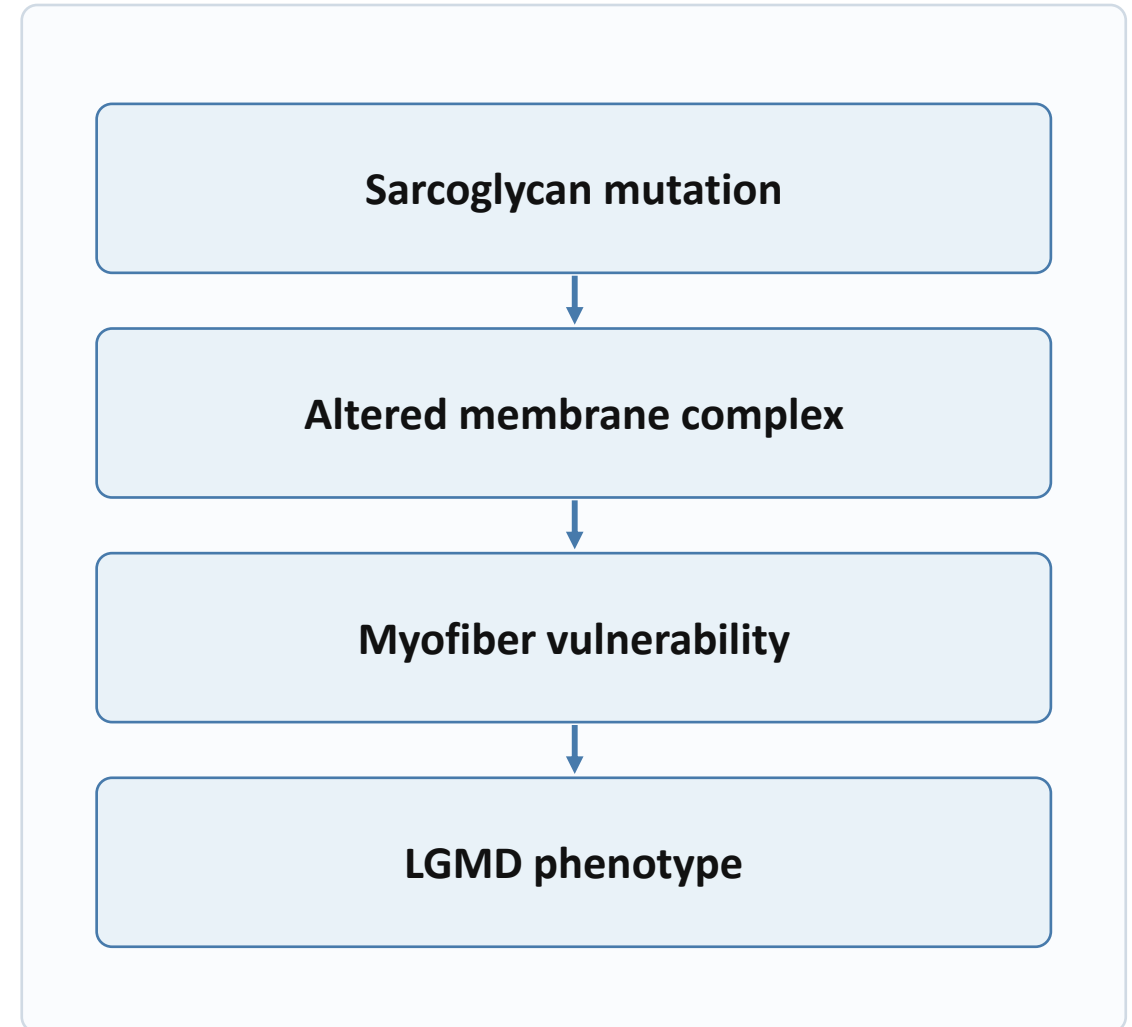
LGMD genes affect several cellular compartments

- Sarcoglycans: Dystrophin-associated membrane complex.
- Glycosylation enzymes: α -dystroglycan processing.
- Z-disk, trafficking and signaling proteins:
Other mechanisms.



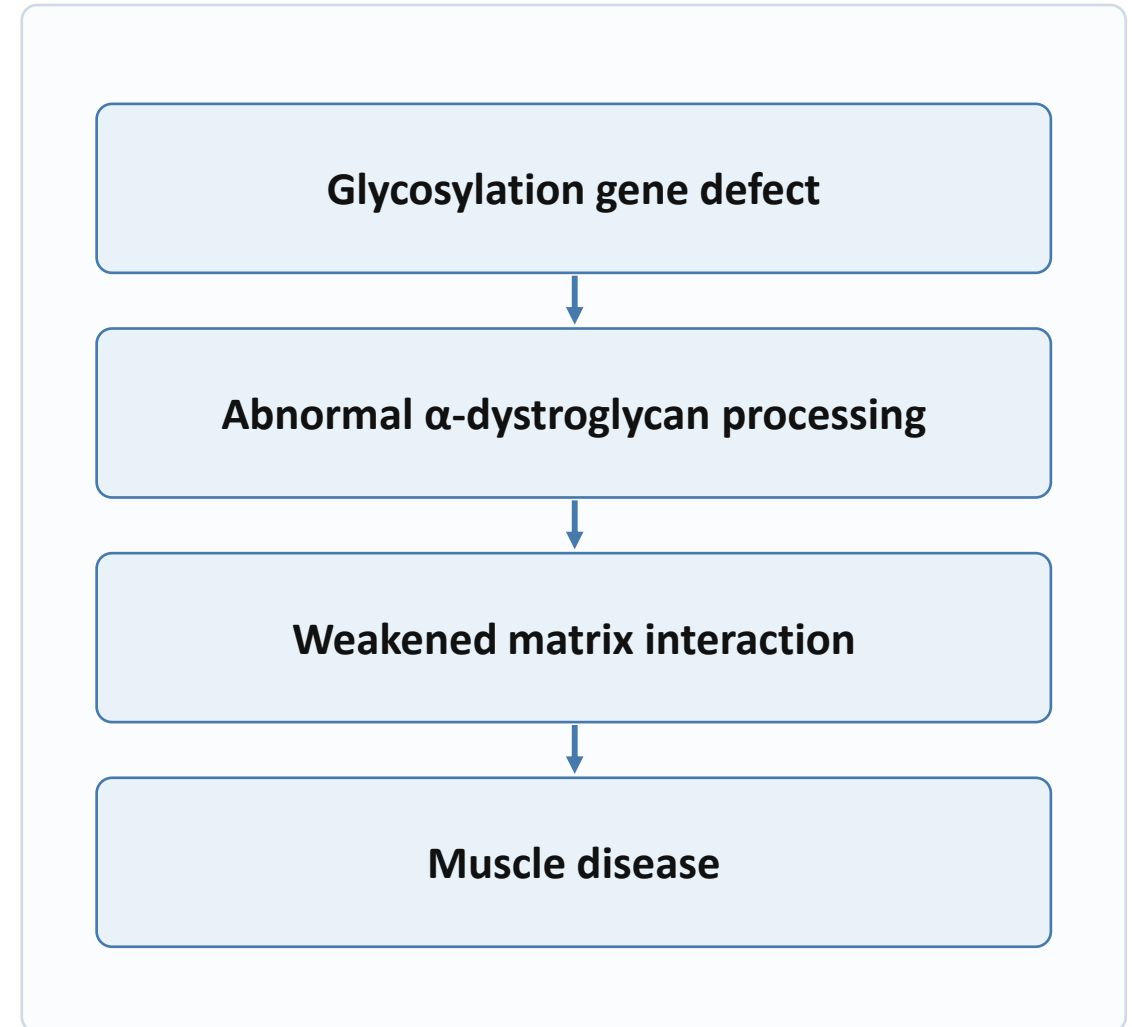
Sarcoglycan defects disturb structural linkage

- Sarcoglycans participate in the sarcolemmal protein complex.
- Pathogenic variants provide a structural route to proximal dystrophy.
- The affected protein is not necessarily dystrophin itself.



Dystroglycan glycosylation modifies matrix binding

- α -Dystroglycan requires post-translational glycosylation.
- Genes affecting this processing can cause limb-girdle dystrophy.
- Some related defects cause congenital muscular dystrophy with broader involvement.



Other LGMD pathways broaden the differential

- Associated genes encode Z-disk proteins and vesicle-traffic machinery.
- Additional examples include calpain-3 and lamin A/C.
- A single unifying pathogenesis is not established across all LGMDs.

Sarcomere-associated proteins

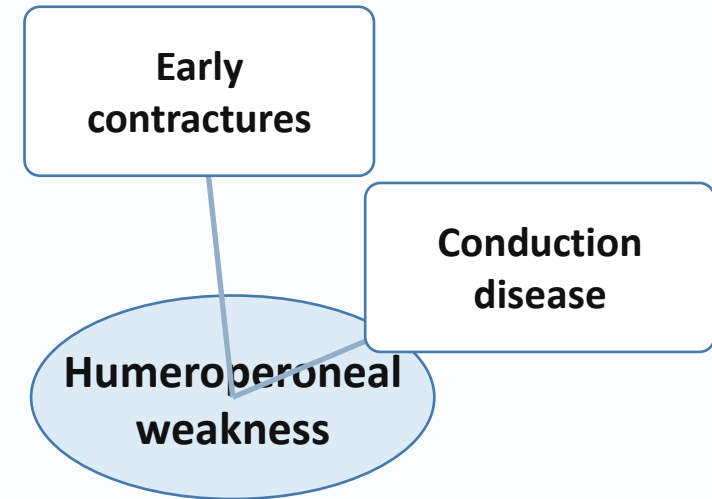
Trafficking / cell signaling

Calpain-3

Lamin A/C

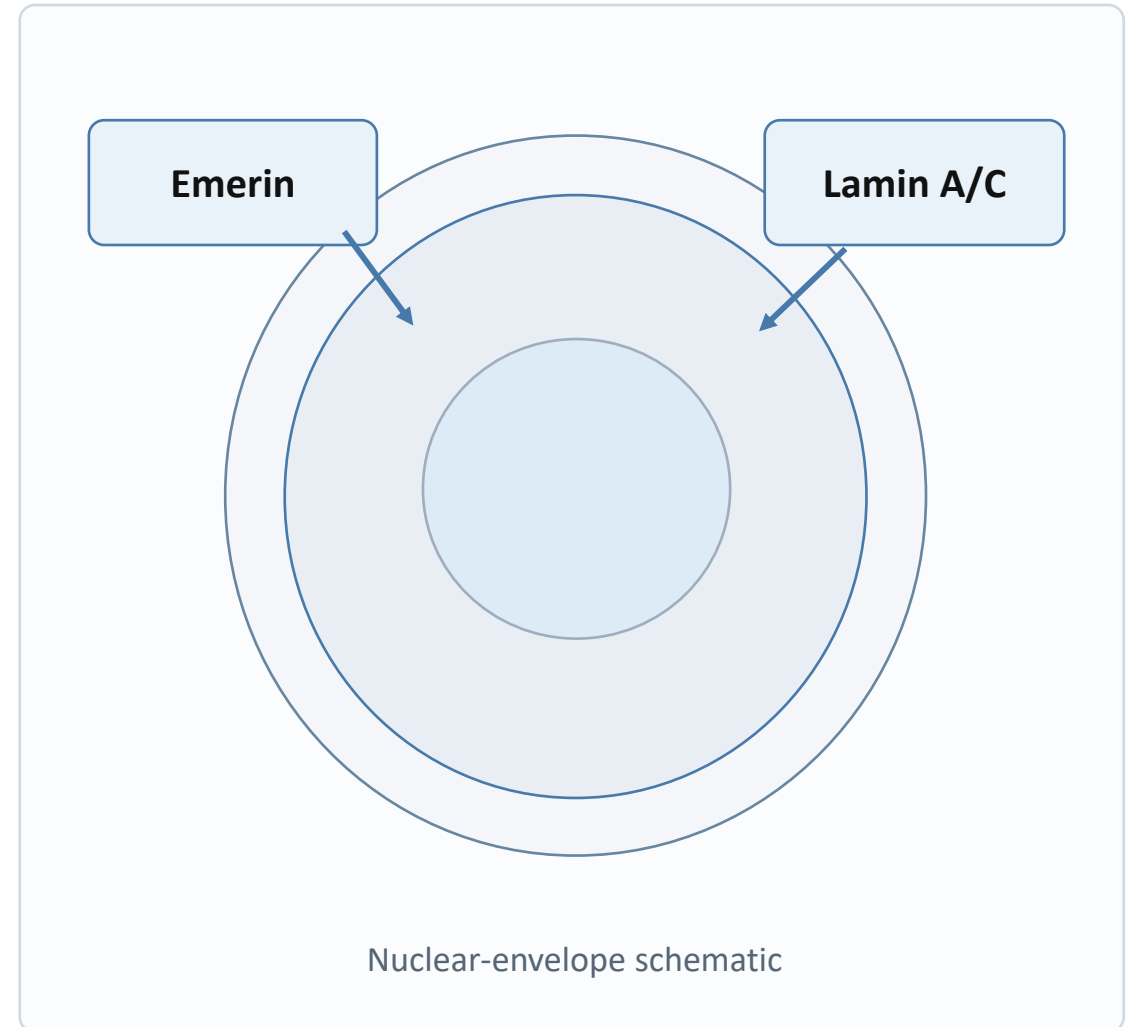
Emery–Dreifuss dystrophy has a clinical triad

- Slowly progressive humeroperoneal weakness.
- Early contractures of the Achilles tendon, spine and elbows.
- Cardiomyopathy associated with conduction abnormalities.



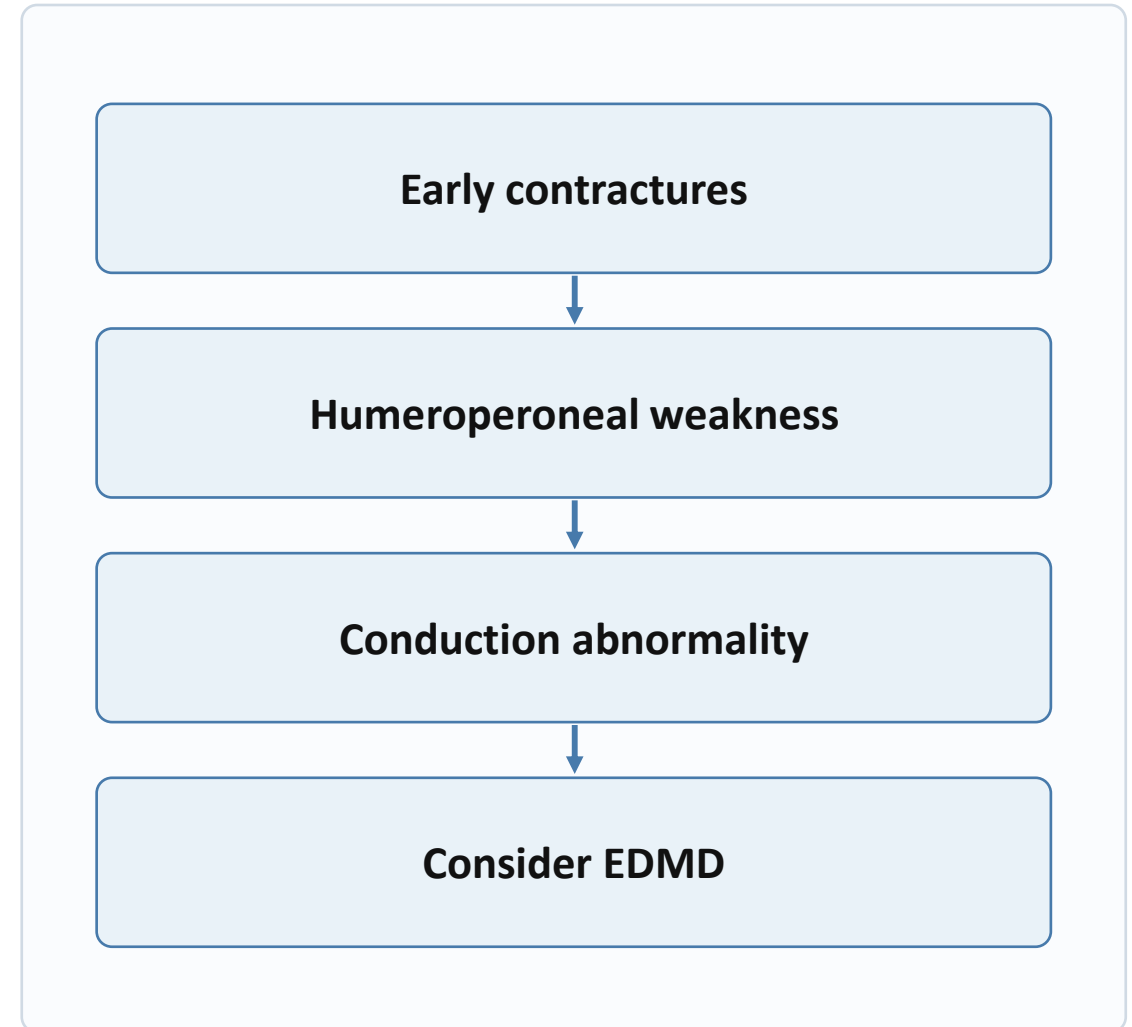
EDMD targets the nuclear-envelope apparatus

- The X-linked form is associated with emerin variants.
- An autosomal form is associated with lamin A/C variants.
- Both proteins are associated with the inner nuclear membrane.



Cardiac conduction defects are diagnostic clues

- The combination of contractures and conduction disease is particularly suggestive.
- Cardiomyopathy can coexist with muscular weakness.
- Muscular severity alone does not describe the cardiologic phenotype.



How nuclear-envelope defects cause EDMD remains unclear

- Nuclear shape and mechanical stability during contraction may be affected.
- Altered chromatin organization and gene expression are plausible mechanisms.
- Robbins explicitly characterizes the full disease mechanism as unknown.

Proposed mechanical model

Fragile nuclear envelope

Stress during contraction

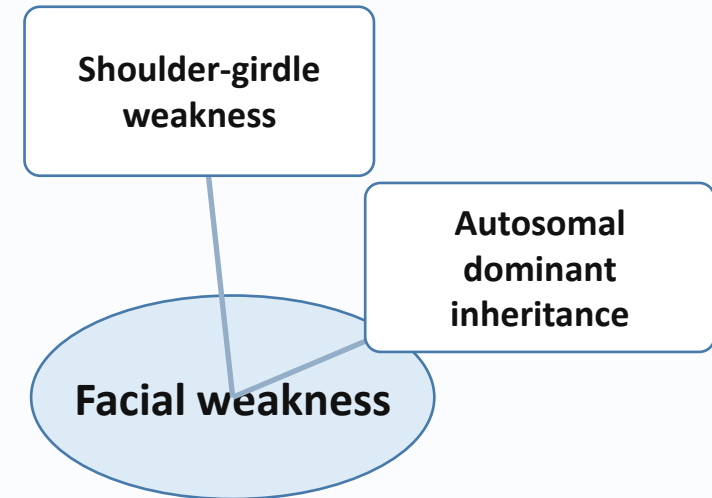
Proposed regulatory model

Changed chromatin organization

Altered expression

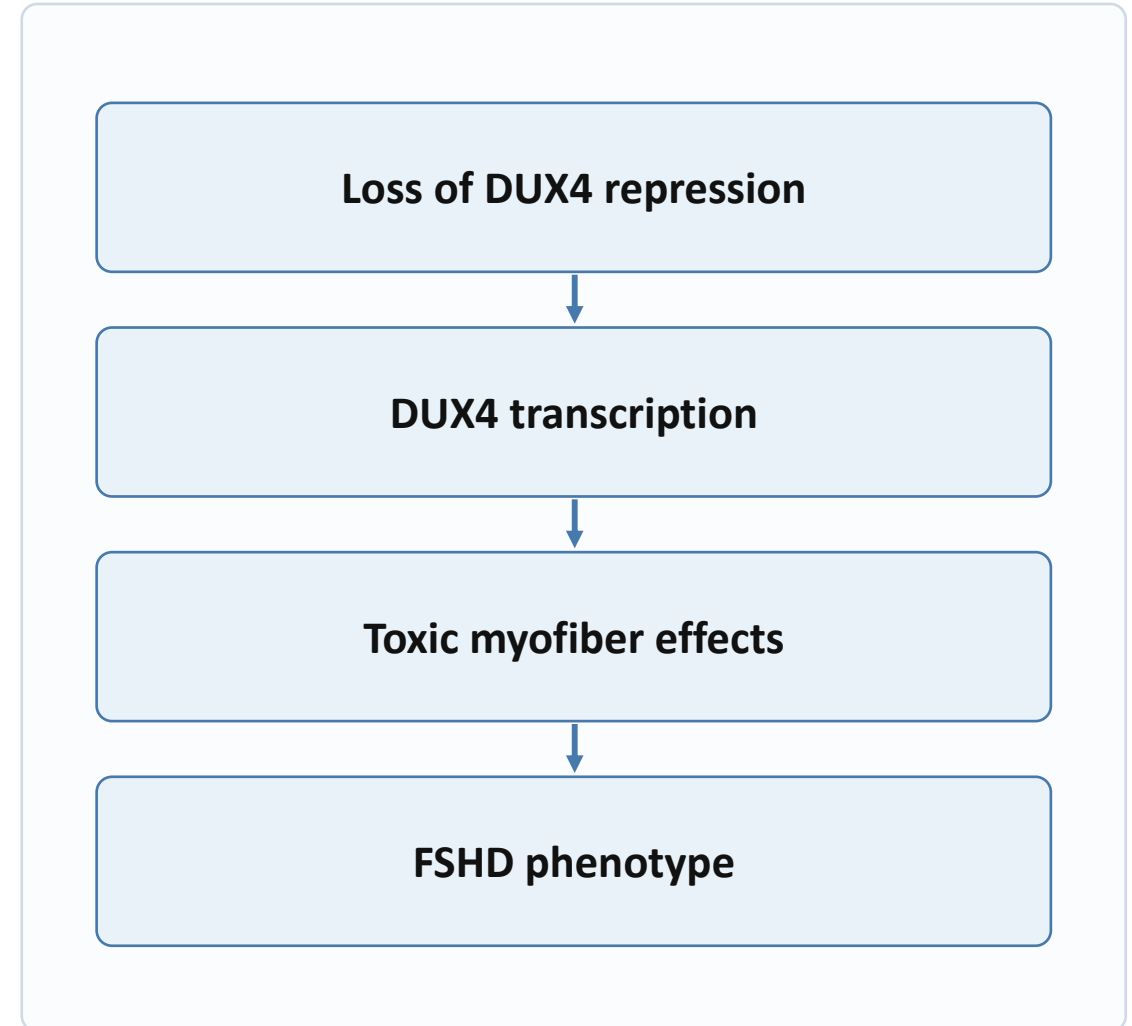
FSHD has a characteristic distribution of weakness

- Facial muscles and the shoulder girdle are prominently involved.
- FSHD is described as an autosomal dominant muscular dystrophy.
- The pattern differs from the more general limb-girdle phenotype.



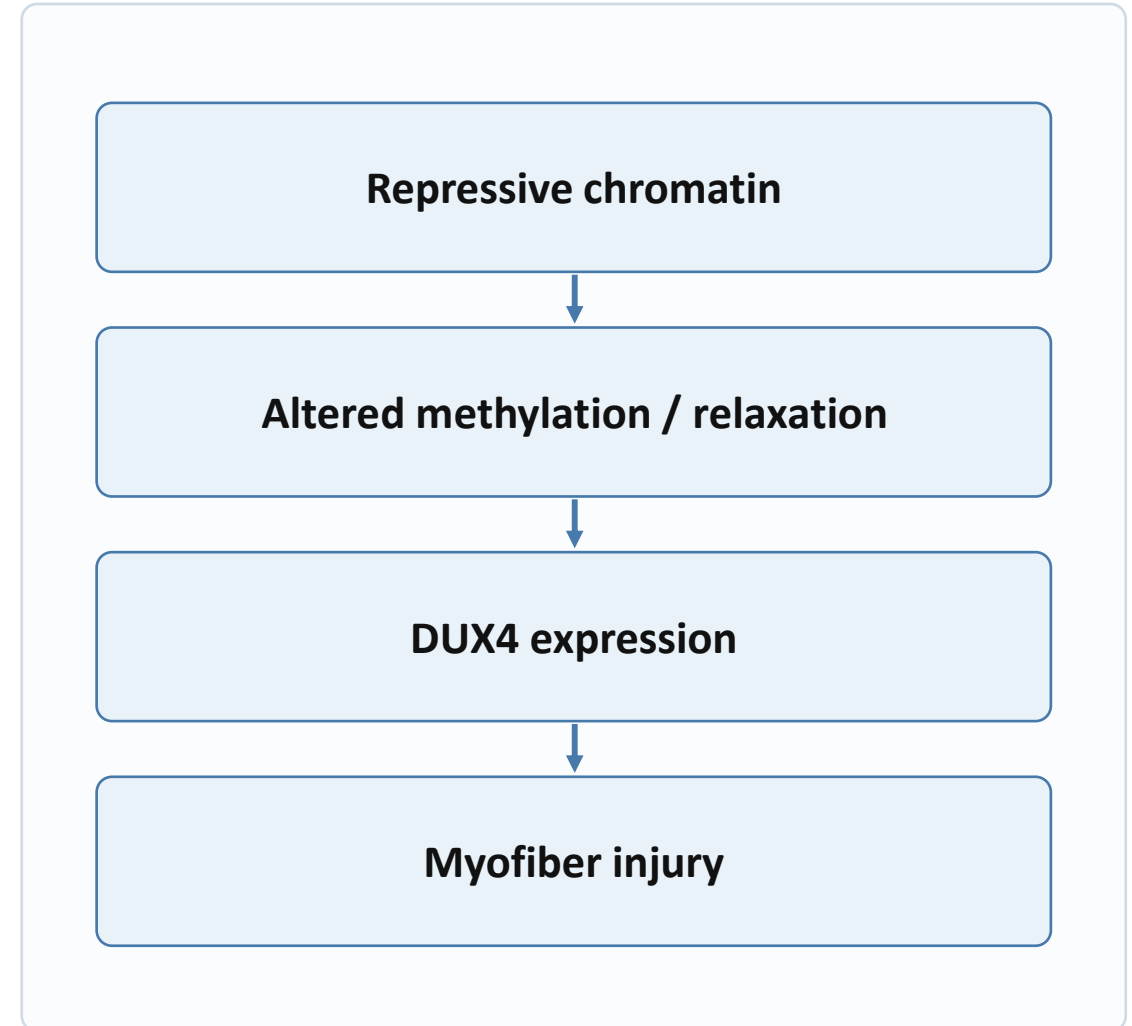
Facioscapulohumeral dystrophy involves DUX4

- DUX4 encodes a transcription factor normally silenced in most somatic tissues.
- Abnormal expression in skeletal muscle is associated with toxicity.
- The fundamental defect is epigenetic derepression rather than sarcolemmal protein loss.



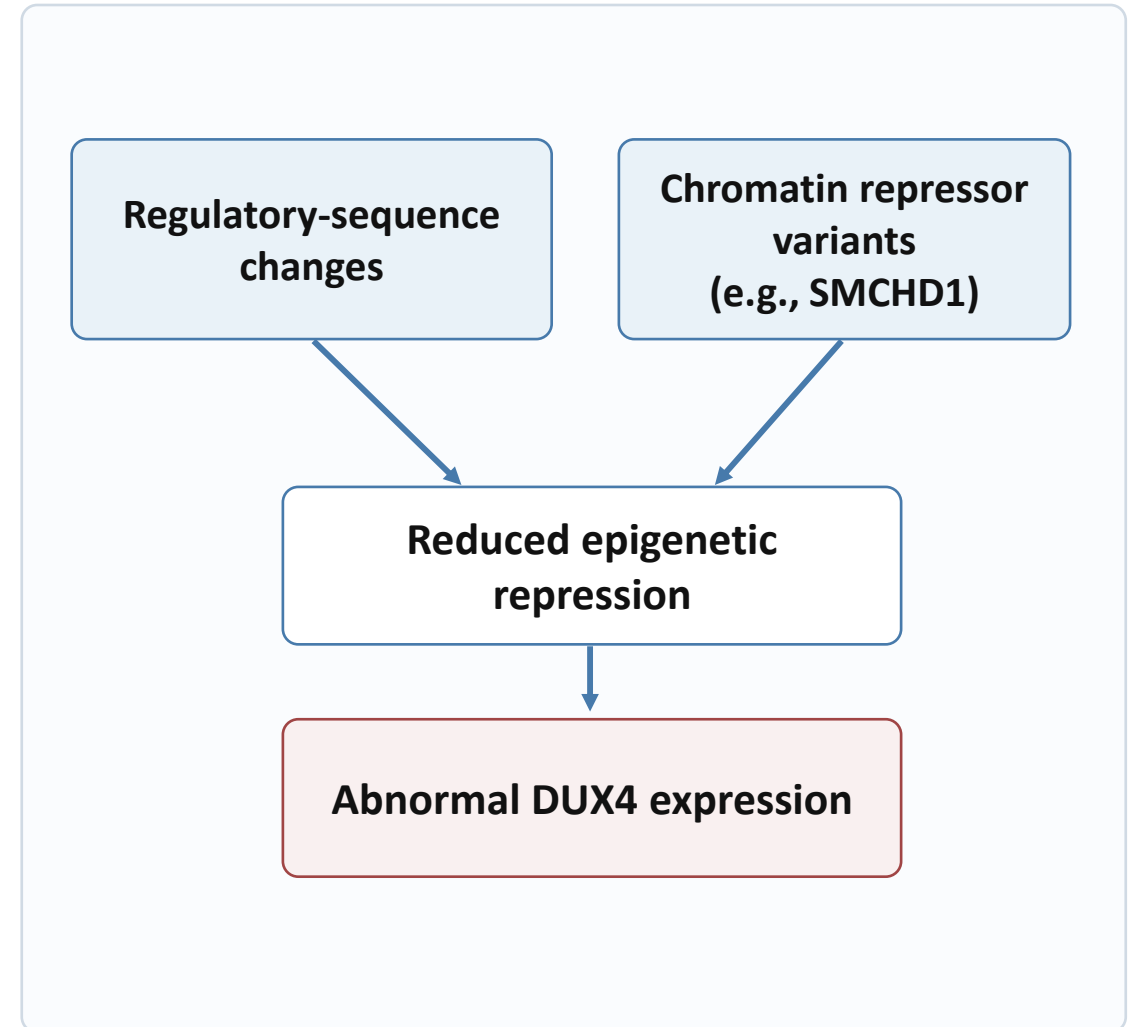
Chromatin relaxation permits DUX4 expression

- Normal somatic DUX4 silencing depends on repressive chromatin state.
- Altered regulatory sequences can reduce DNA methylation and relax chromatin.
- The resulting DUX4 derepression drives muscle pathology.



Different regulatory routes converge on DUX4

- Most cases involve changes in regulatory sequences affecting repression.
- A smaller fraction involve mutations in chromatin repressors such as SMCHD1.
- The common mechanistic endpoint is inappropriate DUX4 transcription.



The clinical pattern helps rank dystrophy diagnoses

Entity	Characteristic clues	Key molecular mechanism
Duchenne	Early progressive proximal weakness; pseudohypertrophy	DMD; dystrophin usually absent
Becker	Later onset; slower skeletal course	DMD; residual dystrophin
LGMD	Preferential proximal weakness; variable course	Multiple structural / enzymatic pathways
Emery–Dreifuss	Early contractures; cardiac conduction disease	Emerin / lamin A/C
FSHD	Facial and scapular weakness	DUX4 derepression

Congenital dystrophy is a related—but distinct—category

- Unlike the major noncongenital dystrophies, onset is during infancy.
- The parent Robbins section includes extracellular matrix and α -dystroglycan defects.
- Some congenital entities also feature eye or CNS developmental abnormalities.

Congenital onset

Progressive muscle damage

Matrix / receptor defects

Variable extra-muscular disease

Congenital matrix disorders include collagen VI and merosin

- Ullrich congenital muscular dystrophy is linked to collagen VI genes.
- Merosin deficiency is linked to LAMA2.
- These defects involve extracellular matrix components surrounding muscle fibers.

Collagen VI defects

Ullrich congenital muscular dystrophy

Hypotonia;
Contractures; Distal hyperextensibility

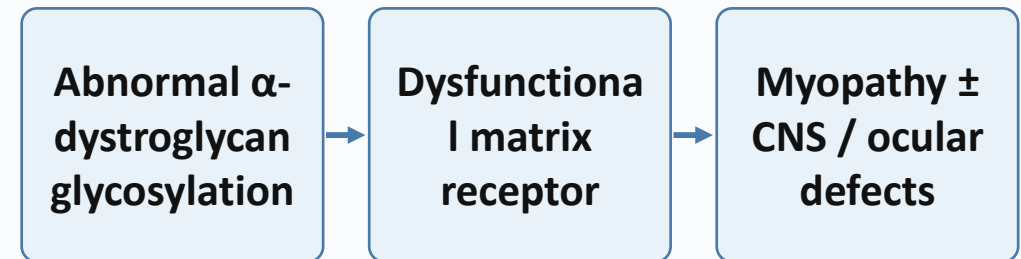
LAMA2 defects

Merosin-deficient dystrophy

Extracellular matrix linkage abnormality

α -Dystroglycan defects can affect muscle, brain and eye

- Glycosylation of α -dystroglycan supports its extracellular interactions.
- Severe dysfunction can cause congenital muscle disease with CNS and eye defects.
- Milder defects may be predominantly skeletal-muscle disease.



Case A: Early pelvic weakness and calf enlargement

- Illustrative scenario: A boy has delayed walking, poor pace with peers and enlarging calves.
- Clinical examination suggests progressive proximal weakness.
- Marked serum CK elevation strengthens suspicion of dystrophinopathy.

CLINICAL CLUES

Delayed walking

Pelvic-girdle weakness

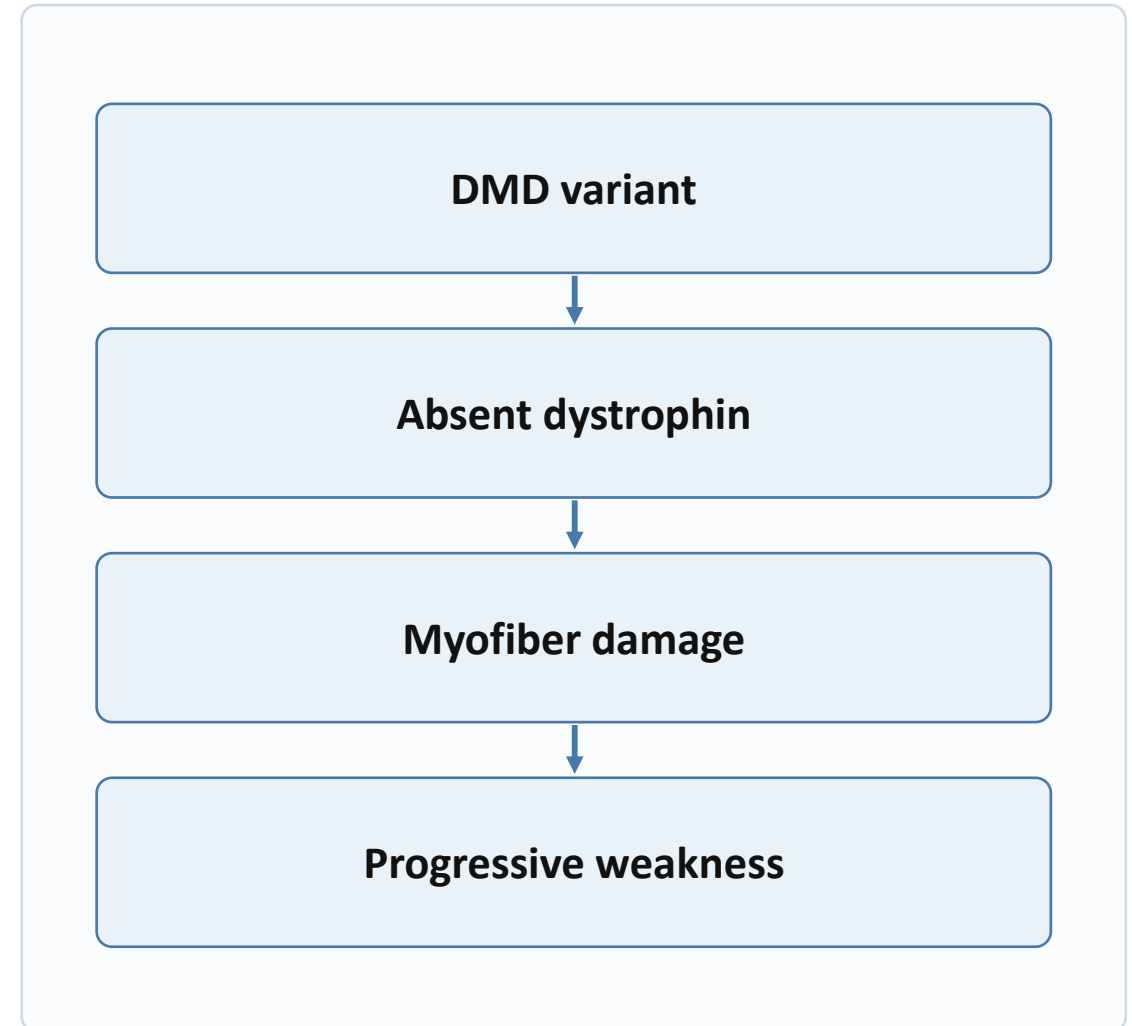
Calf pseudohypertrophy

Marked CK

Which disorder should lead the genetic differential?

Case A: Connect genotype to pathologic consequences

- A severe Duchenne phenotype is the leading clinical consideration.
- DMD molecular testing is needed for diagnostic confirmation.
- The predicted mechanism is loss of dystrophin-mediated membrane stability.



Case B: Weakness plus early elbow contractures

- Illustrative scenario: Slowly progressive weakness accompanies early elbow and Achilles contractures.
- Cardiac assessment shows conduction abnormality.
- The combination is characteristic of Emery–Dreifuss dystrophy.

CLINICAL CLUES

Humeroperoneal weakness

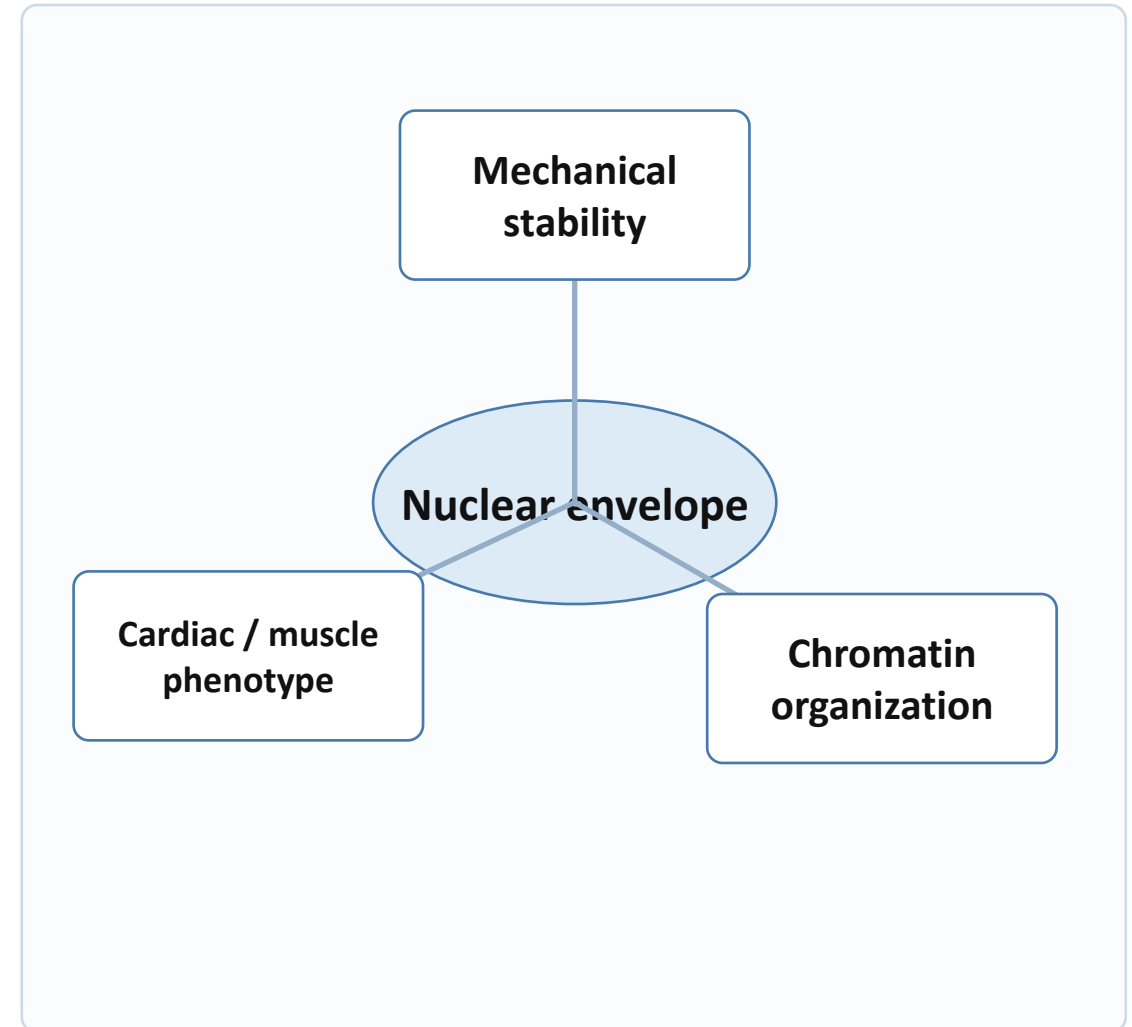
Early joint contractures

Conduction abnormality

Which nuclear-envelope proteins are implicated?

Case B: Recognize nuclear-envelope pathogenesis

- Emerin and lamin A/C are principal proteins in the source description.
- Mechanical and transcriptional consequences are both proposed.
- The detailed causal link from mutation to phenotype remains unresolved.



Case C: Prominent facial and scapular weakness

- Illustrative scenario: Weakness mainly affects facial and shoulder-girdle muscles.
- The phenotype raises consideration of FSHD.
- The distinctive mechanism involves inappropriate DUX4 expression.

CLINICAL CLUES

Facial muscle weakness

Shoulder-girdle weakness

Autosomal dominant pattern

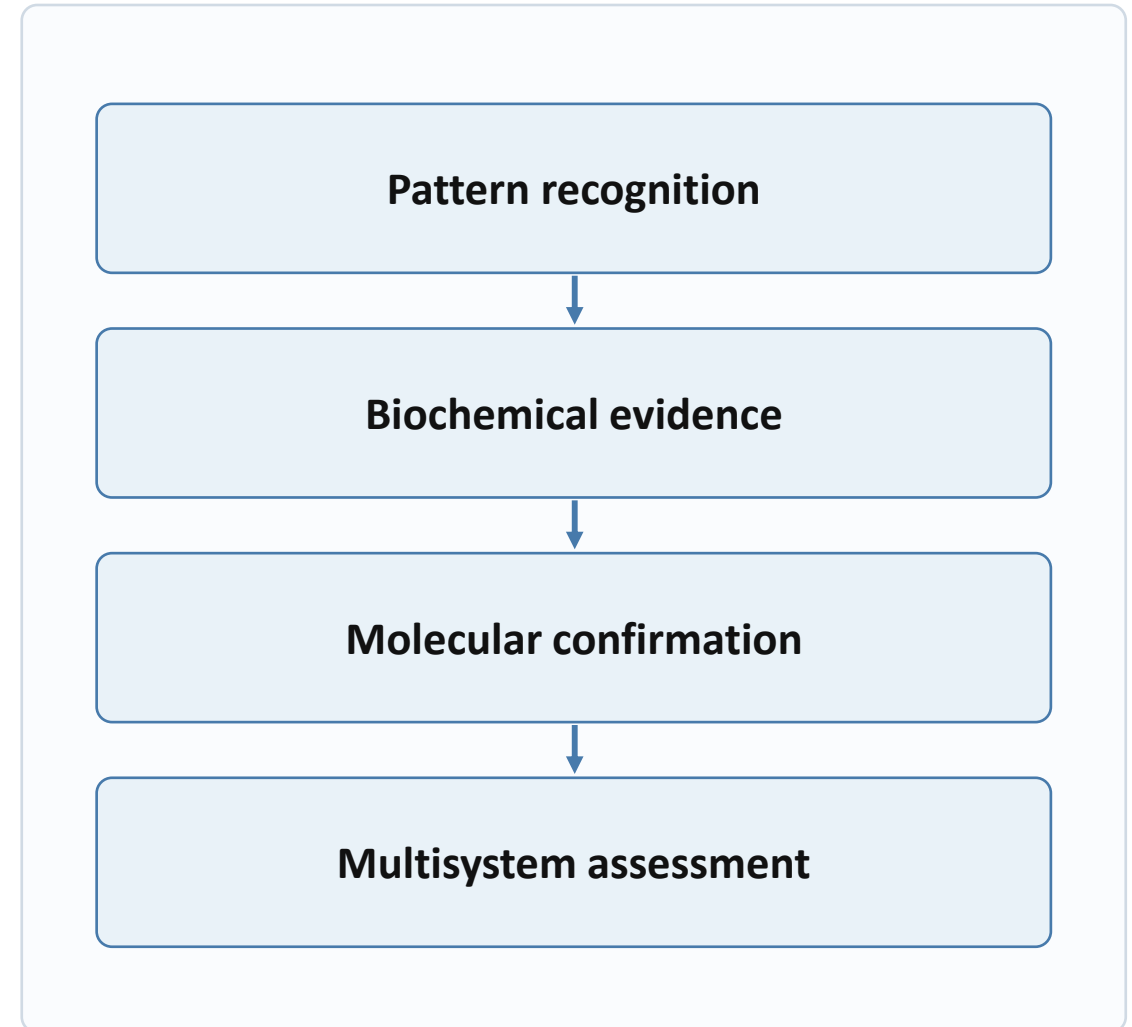
What is the molecular endpoint?

Five mechanistic anchors

Disease group	Mechanistic anchor
Duchenne / Becker	Quantity and residual function of dystrophin
LGMD	Diverse structural, metabolic and signaling protein defects
Emery–Dreifuss	Emerin / lamin A/C; nuclear-envelope dysfunction
Facioscapulohumeral	Epigenetic derepression of DUX4
Congenital dystrophy	Matrix or α -dystroglycan linkage defects

Diagnostic synthesis: Phenotype, tissue and gene

- Distribution and age of onset guide the initial clinical differential.
- Serum CK supports active muscle injury but is not gene specific.
- Molecular analysis generally confirms dystrophinopathies; Biopsy adds value selectively.
- Never ignore cardiac or respiratory involvement when assessing severity.



Primary source and evidentiary limits

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026).
- Chapter 27, Peripheral Nerves and Skeletal Muscles, pp. 1120–1123.
- Conceptual diagrams and muscle schematics are original editable teaching illustrations.
- No authentic biopsy photograph was embedded; original textbook plates were not available for direct verification.