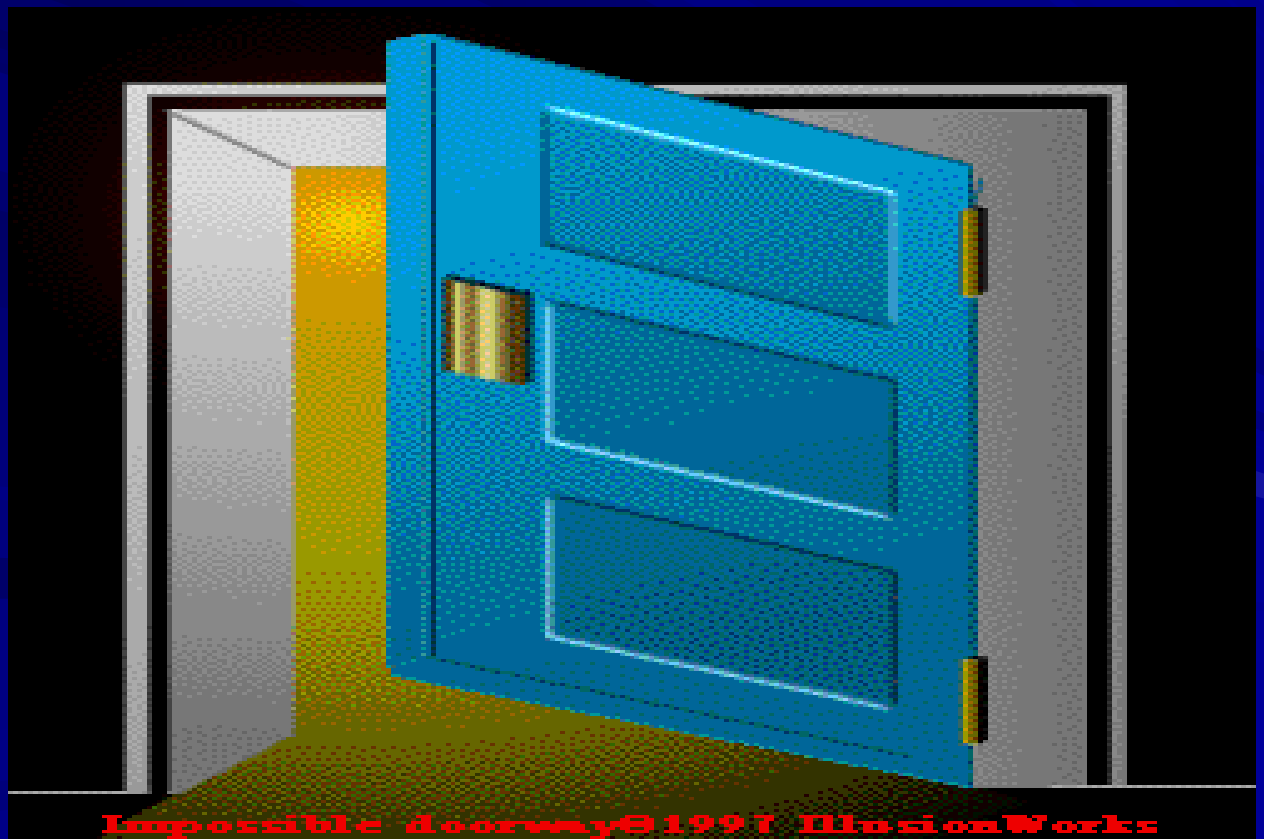
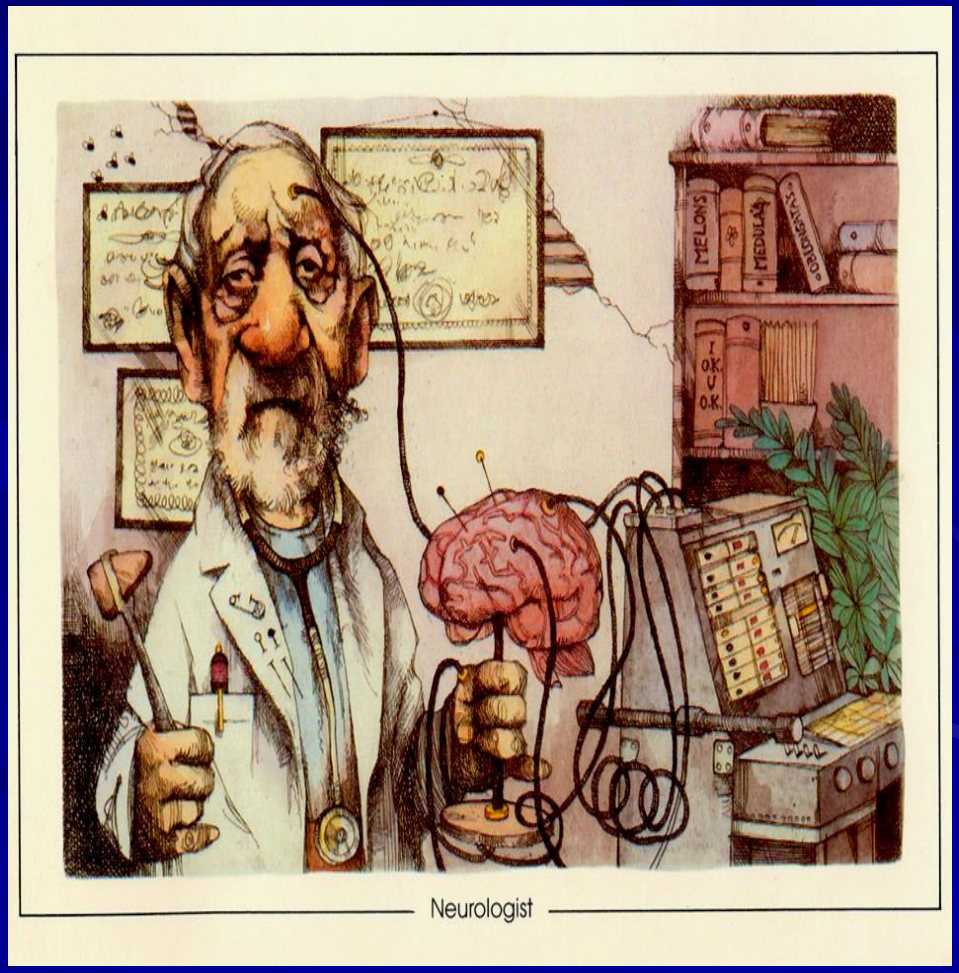
Pediatric Muscle Disorders: Approach and Diseases.

ד"ר שי מנשקו- היחידה לנוירולוגית ילדים



Objectives

- Overview
- Clinical Examples
- Diagnosis
- Management: role of the pediatrician



Myopathy Patients Present with Muscle Symptoms:

- Negative symptoms (commonly)
  - Weakness
  - Fatigue and exercise intolerance
- Positive symptoms (rarely)
  - Myalgia, contractures, muscle swelling, myoglobinuria (usually exercise-induced)
  - Myotonia

What Else Can Present as a Pure Motor Syndrome?

- Motor neuron disorders
  - Fasciculations, cramping, weakness of muscle groups that would be unusual for most or any myopathy
- Myoneural junction disorders
  - Ocular muscle involvement, striking fatiguability
  - Proximal weakness in LEMS and rare cases of limb-girdle MG
- Some neuropathies
  - Especially CIDP
  - Reflex loss, cramps, fasciculations, unusual patterns of weakness

Symptoms of Weakness

- Proximal lower extremities
  - Difficulty climbing stairs, using arms to pull self up using railings
  - Difficulty rising from toilet or chair, or getting out of a car
- Proximal upper extremities
  - Lifting or reaching for objects over head, combing hair
- Distal extremities (atypical for most myopathies, but can occur)
  - Foot drop, loss of grip strength, loss of fine hand movements

Fatigue

- Always present, but so non-specific as to be essentially useless in diagnosis

- Fatigable focal muscle weakness causing specific deficits is much more useful
  - Usually suggests myoneural junction disease
  - Much less often, a muscle disease
    - Periodic paralyses
    - Myotonic disorders
    - Bioenergetic defects

Myalgia

- Uncommon in most muscle diseases. Principle exception is dermatomyositis, where pain is common (due to muscle ischemia)
- Non-specific, particularly in cases where examination and investigations are normal (most patients with myalgias and no weakness do not have an identifiable myopathy)
- Episodic myalgia can be seen in metabolic myopathies

Myoglobinuria

- Due to rhabdomyolysis with release of myoglobin into blood
- Recurrent myoglobinuria suggests metabolic myopathies
- Renal failure can occur
- “Coke-coloured” urine
  - Patients routinely endorse this symptom, however, and it ends up being quite unhelpful to elicit this history in nearly all patients

Family history

- Detailed family tree to look for evidence of inherited disease and mode of inheritance
  - Use of canes or wheelchairs
  - Skeletal deformities
  - Other functional limitations

Precipitating Factors

- Illicit drug use
- Medications
- Exercise
- Fever, fasting
- Carbohydrate meal
- Cold exposure

Systemic Symptoms and Signs

- Systemic involvement is common in muscle disorders, much more so than in nerve or anterior horn cell disorders

- A brief list…not all-inclusive

- Cardiac (most important)
  - Myotonic dystrophy, Duchenne/Becker, Emery-Dreifuss
  - Amyloid myopathy
  - Desminopathies
  - Nemaline myopathy
  - Mitochondrial disease (e.g. Kearn-Sayre syndrome)

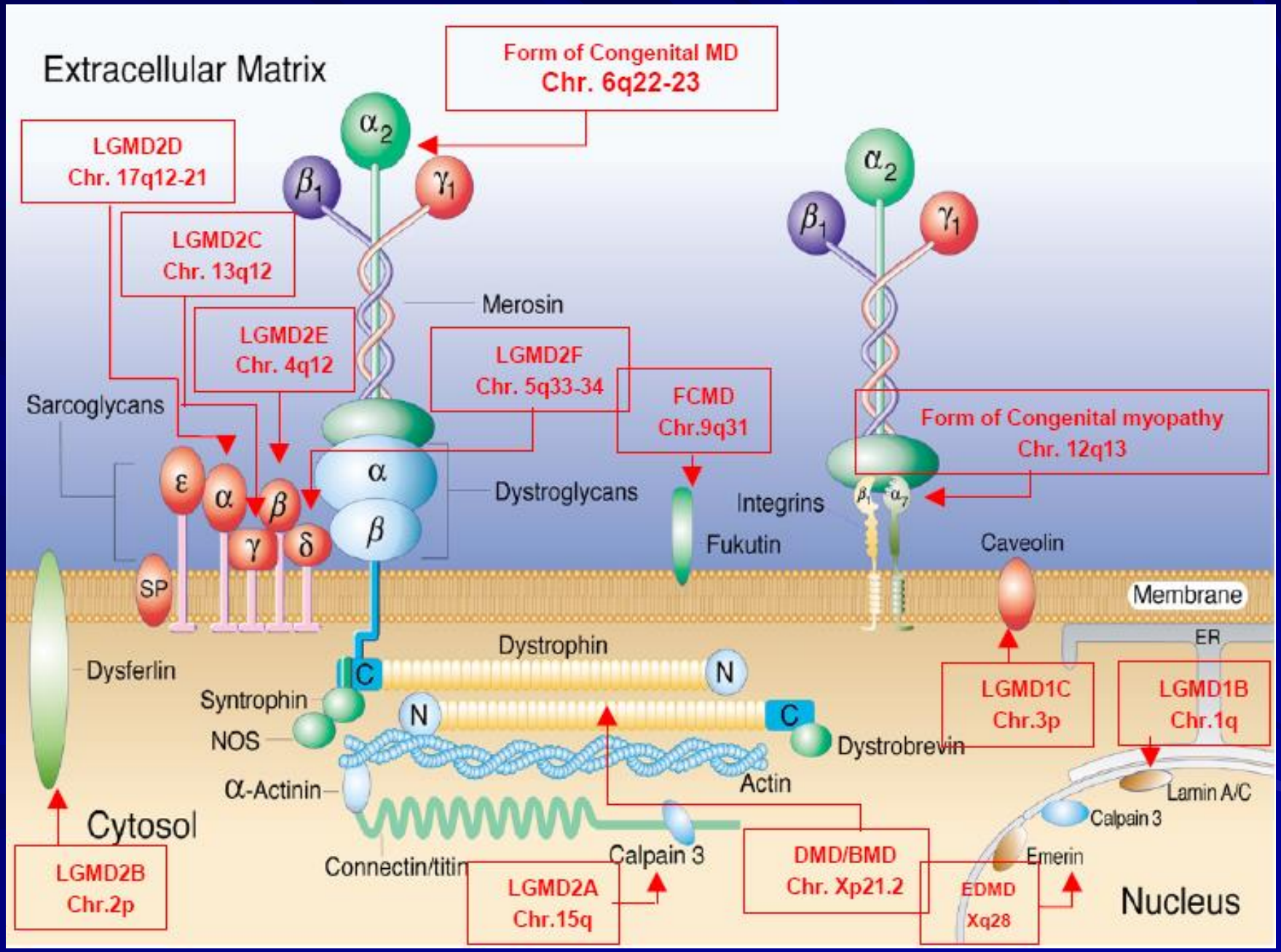
- Respiratory
  - Dermatomyositis, polymyositis (interstitial pneumonitis)
  - Myotonic dystrophy, Duchenne/Becker
  - Centronuclear myopathy, nemaline myopathy
  - Acid maltase deficiency

Systemic Symptoms and Signs

- Ophthalmologic (cataracts)
  - Myotonic dystrophy
- Endocrine
  - Myotonic dystrophy
  - Mitochondrial disease
- Renal
  - Amyloid
  - Any disorders causing myoglobinuria
- GI motility
  - Myotonic dystrophy
  - Mitochondrial disease
- Cognitive involvement
  - Myotonic dystrophy (severe cases)
  - Mitochondrial disease
  - FSHD (large deletions)

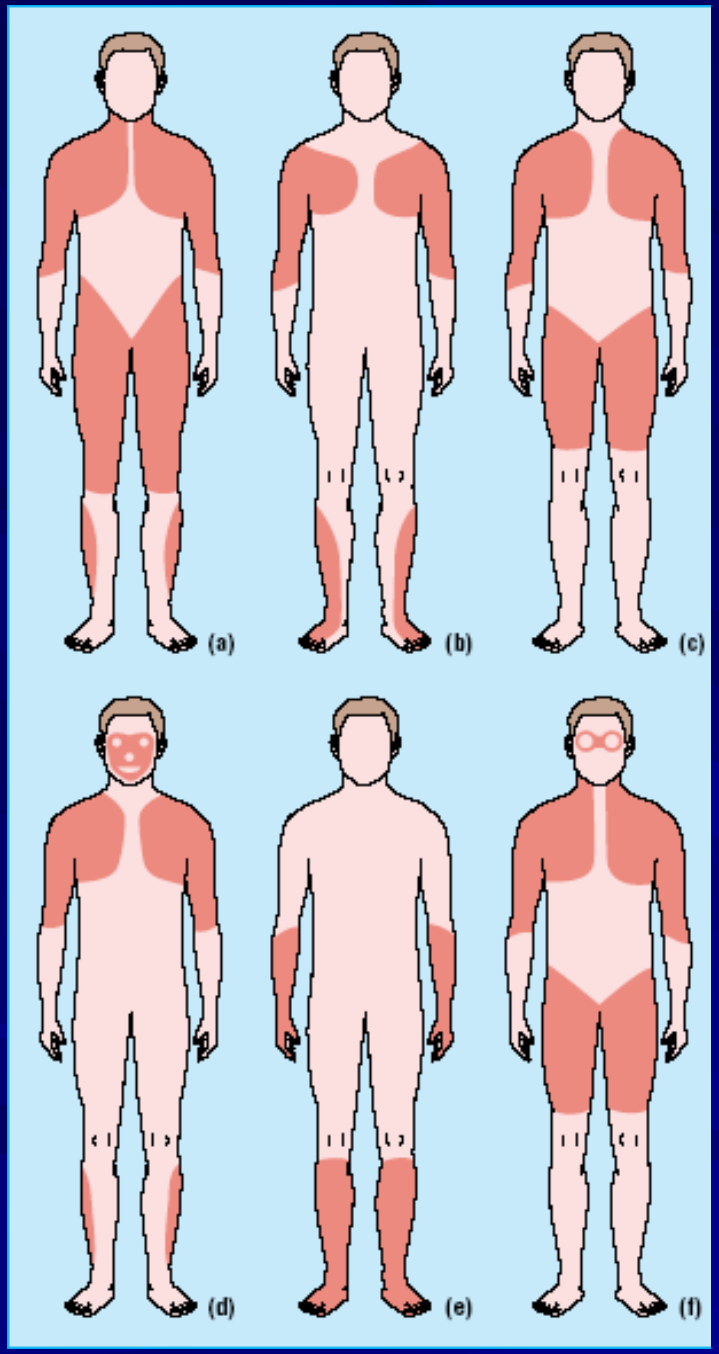
Muscular diseases

- Congenital muscular dystrophy
- Congenital myotonic dystrophy
- Infantil FSHD
- Congenital myopathies
- Metabolic myopathies
- Mitochondrial myopathies


Extracellular Matrix
Form of Congenital MD
Chr. 6q22-23
LGMD2D
Chr. 17q12-21
LGMD2C
Chr. 13q12
LGMD2E
Chr. 4q12
LGMD2F
Chr. 5q33-34
FCMD
Chr.9q31
Merosin
Sarcoglycans
Dystroglycans
Integrins
Fukutin
Form of Congenital myopathy
Chr. 12q13
Caveolin
Membrane
ER
SP
Dysferlin
Dystrophin
Syntrophin
NOS
α-Actinin
Actin
Dystrobrevin
Connectin/titin
Calpain 3
Lamin A/C
Emerin
Cytosol
Nucleus
LGMD2B
Chr.2p
LGMD2A
Chr.15q
DMD/BMD
Chr. Xp21.2
EDMD
Xq28
LGMD1C
Chr.3p
LGMD1B
Chr.1q

INCIDENCE

- Duchene Muscular Dystrophy 1/3300
- Becker Muscular Dystrophy 1/18,000-1/31,000
- Female dystrophinopathy carriers 40/100,000
- Manifesting female dystrophinopathy carriers 1/100,000
- Emery-Dreifuss Muscular Dystrophy 1/100,000
- Myotonic Dystrophy 1/8000
- Oculopharyngeal Muscular Dystrophy 1/200,000
- Fascioscapulohumeral Muscular Dystrophy 1/20,000
- Muscle-Eye-Brain Disease 1/50,000 Finland, isolated cases elsewhere
- Fukuyama Congenital Muscular Dystrophy 7-12/100,000 (Japan)



Patterns of Weakness in Muscular Dystrophies

(a) Duchenne/Becker
(b) Emery-Dreifuss
(c) Limb-girdle
(d) Facioscapulohumeral
(e) Distal
(f) Oculopharyngeal

X-LINKED DYSTROPHIES

Duchene dystrophy dystrophin	Xp21.2
Becker dystrophy	Xp21.2 (dystrophin)
Emery-Dreifuss	Xq28 (emerin)
XMEA	Xq28
LAMP2	Xq24

AUTOSOMAL DOMINANT DYSTROPHIES

Disease	Locus	Gene product
LGMD 1A	5q22-q34	myotilin
LGMD 1B	1q11-21	lamin A/C
LGMD 1C	3p25	caveolin
LGMD 1D	6q23	
LGMD 1E	7q	
FSH	4q35	
FSH type 2		
Myotonic dystrophy	19q13	myotonin protein kinase
DM2	3q21	zinc finger 9
OMD	14q11.2-q13	poly(A) binding protein 2
Bethlem myop.	21q22.3	collagen type VI a1 or a2 subunit
Bethlem myop.	2q37	collagen type VI a3 or a3 subunit
EDMD-dominant	1q11-23	lamin A/C
Myofibrillar myop.	11q22, 2q35	αB-crystallin desmin
Tibial musc. dys.	2q	titin
Distal myopathy	14	
Welander's dist. myop.		
FDC	6q23	

Autosomal Recessive Dystrophies

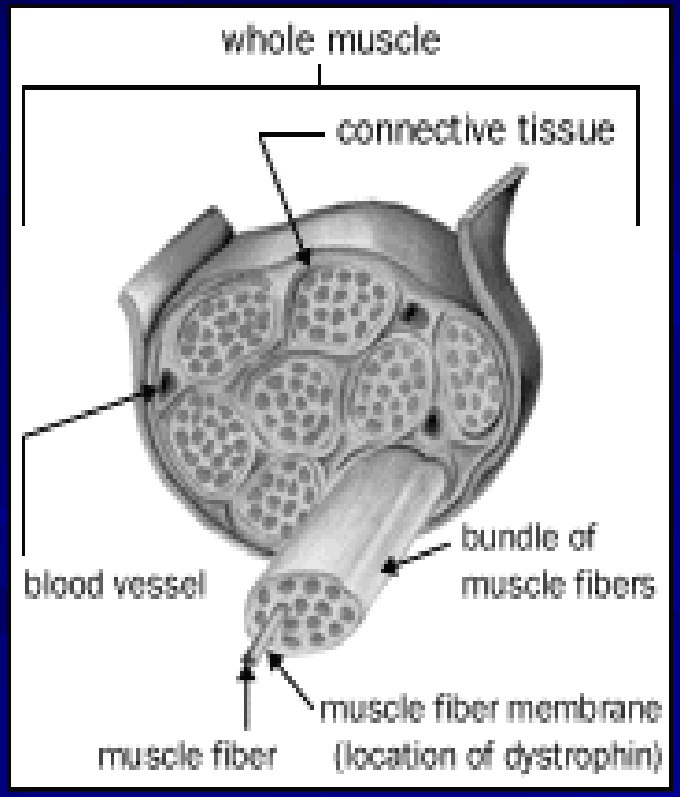
Disease	Locus	Gene Product
LGMD 2A	15q15	calpain 3
LGMD 2B	2p13	dysferlin
LGMD 2C	13q12	gamma sarcoglycan
LGMD 2D	17q12-21.3	alpha sarcoglycan
LGMD 2E	4q12	beta sarcoglycan
LGMD 2F	5q33-q34	delta sarcoglycan
LGMD 2G	17q11-12	telethonin
LGMD 2H	9q31-34.1	
LGMD 2I	19q13.3	fukutin-related protein
LGMD 2J	2q31	titan
EBS-MD	8q24	plectin
Distal Myop.	9p1-q1	
Miyoshi	2q12-14	dysferlin
Distal myop.	9p1-q1	

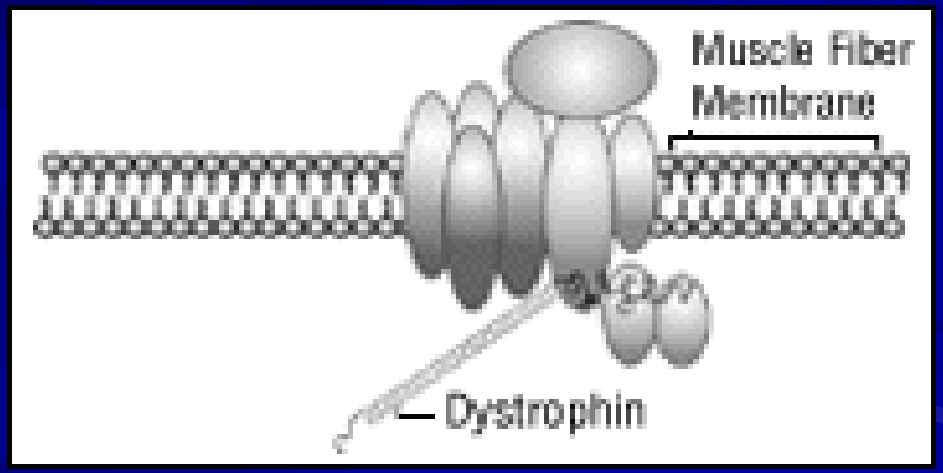
CONGENITAL DYSTROPHIES

Disease	Locus	Gene Product
CMD with merosin deficiency	6q2	laminin alpha 2 chain
CMD without merosin deficiency		
Congenital musc. dys. 1C	19q1	fukutin-related protein
CMD with integrin deficiency	12q13	integrin alpha 7
CMD with rigid spine	1p35-36	selenoprotein N
Fukuyama CMD	9q31-33	fukutin
Muscle-Eye-Brain disease	1p32-p34	POMGnT1
Walker Warburg		
Ullrich syndrome	21q2	collagen VI

Dystrophinopathy

Dystrophin


whole muscle
connective tissue
blood vessel
bundle of
muscle fibers
muscle fiber membrane
(location of dystrophin)
muscle fiber


Muscle Fiber
Membrane
Dystrophin

Dystrophin

- 427 kDa protein
- Gene located on Xp21.2
- Predominantly expressed in skeletal and cardiac muscles (small amounts in brain also)
- Absent in DMD (frame-shift mutations) and reduced in BMD (in-frame mutations)
- Interacts with membrane proteins of the dystrophin-glycoprotein complex (DGC)
  - DGC stabilizes the sarcolemma and protects muscle fibres from contraction-induced damage and necrosis

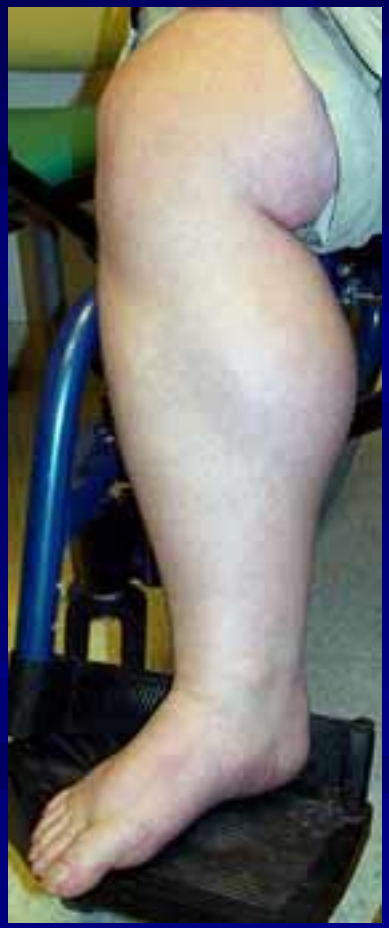
DMD

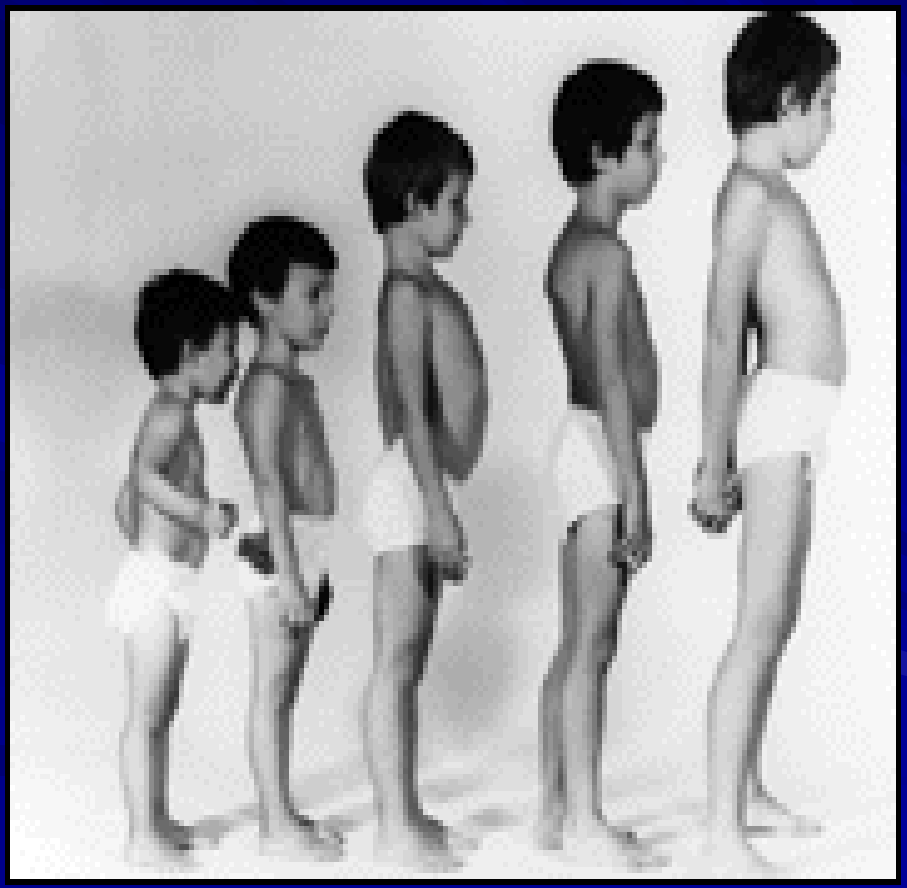
- Duchenne muscular dystrophy
- Genotype: Dystrophin
- 96% with frameshift mutation
- 30% with new mutation
- 10% to 20% of new mutations are gonadal mosaic
- Onset 3 to 5 yrs

BMD

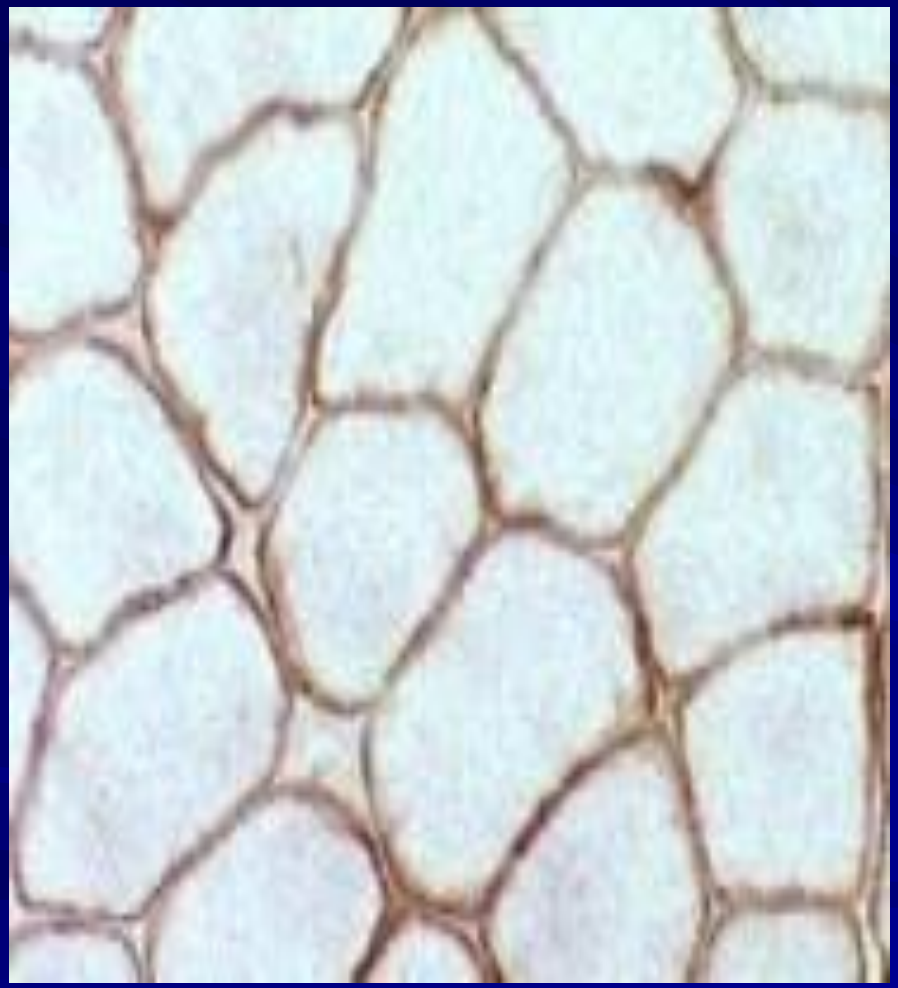
- Genotype: Dystrophin mutations
- 70% of patients: Usually In-frame
- 16% with frameshift mutation
- New mutations rare
- Point mutations > 70 identified
- Mutations in CpG: All C to T; None G to A

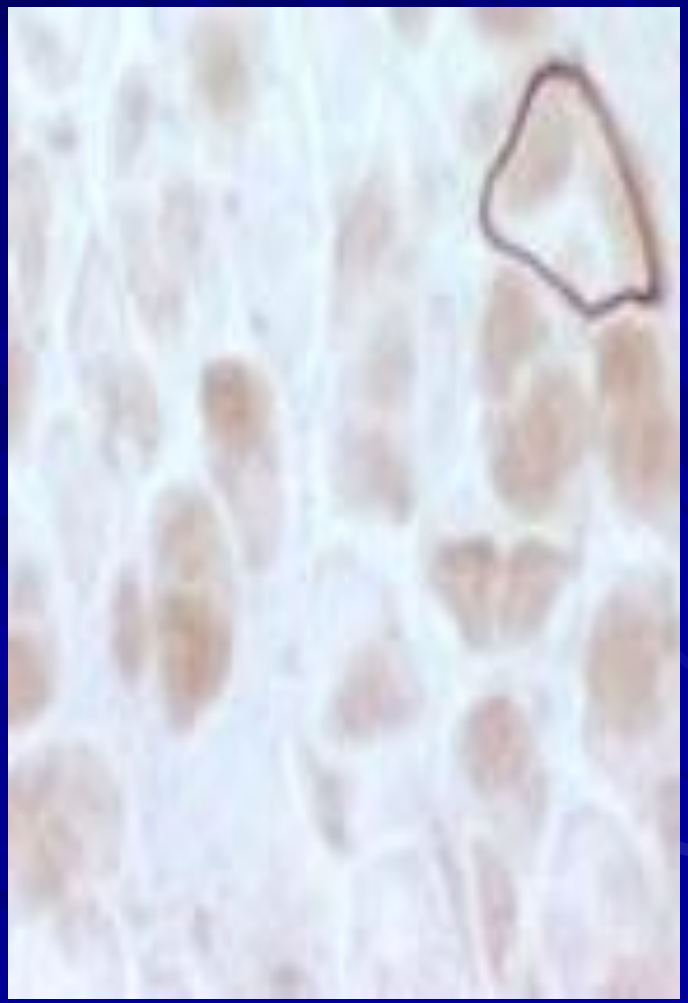
ממצאים קליניים





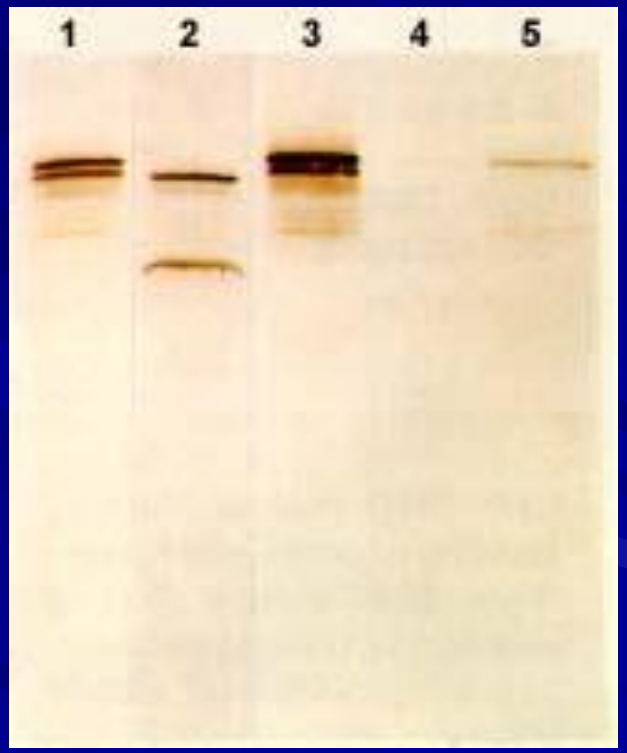
צביעות לדיסטרופין





Western blot of dystrophin

- 1,2 BMD
- 3 NORMAL
- 4 DMD



Myotonia

- Impaired relaxation of muscle after forceful voluntary contraction, due to repetitive depolarization of muscle membrane
- Most commonly patients are symptomatic in hands, but also can affect tongue, eyelids, thighs (walking)
- Complaints of stiffness or tightness, difficulty releasing handshake, unscrewing bottle top, or opening eyes
- Classically improves with repeated exercise and made worse with cold exposure, but considerable variation among patients and disorders

Myotonic Dystrophy

- Myotonic muscular dystrophy is often known simply as *myotonic dystrophy* and is occasionally called *Steinert's disease*, after a doctor who originally described the disorder in 1909.

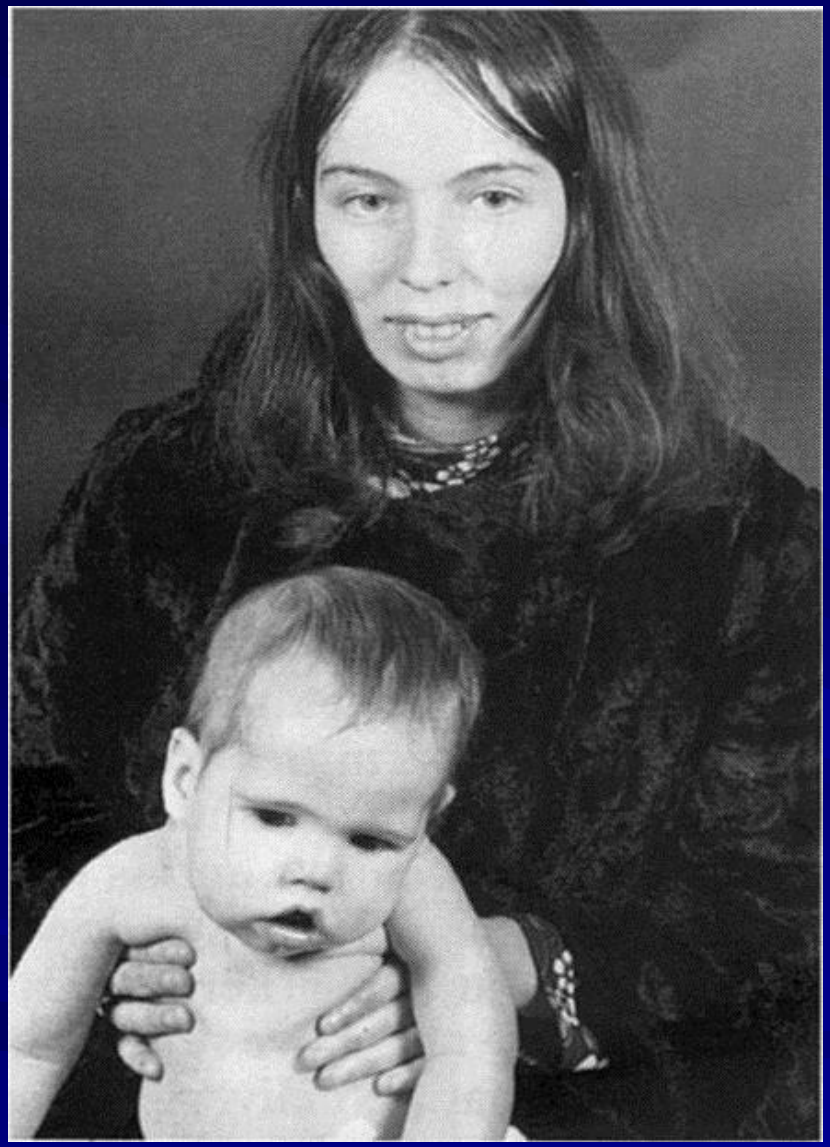
- It's also called *dystrophia myotonica*, a Latin name, and therefore often abbreviated "DM."

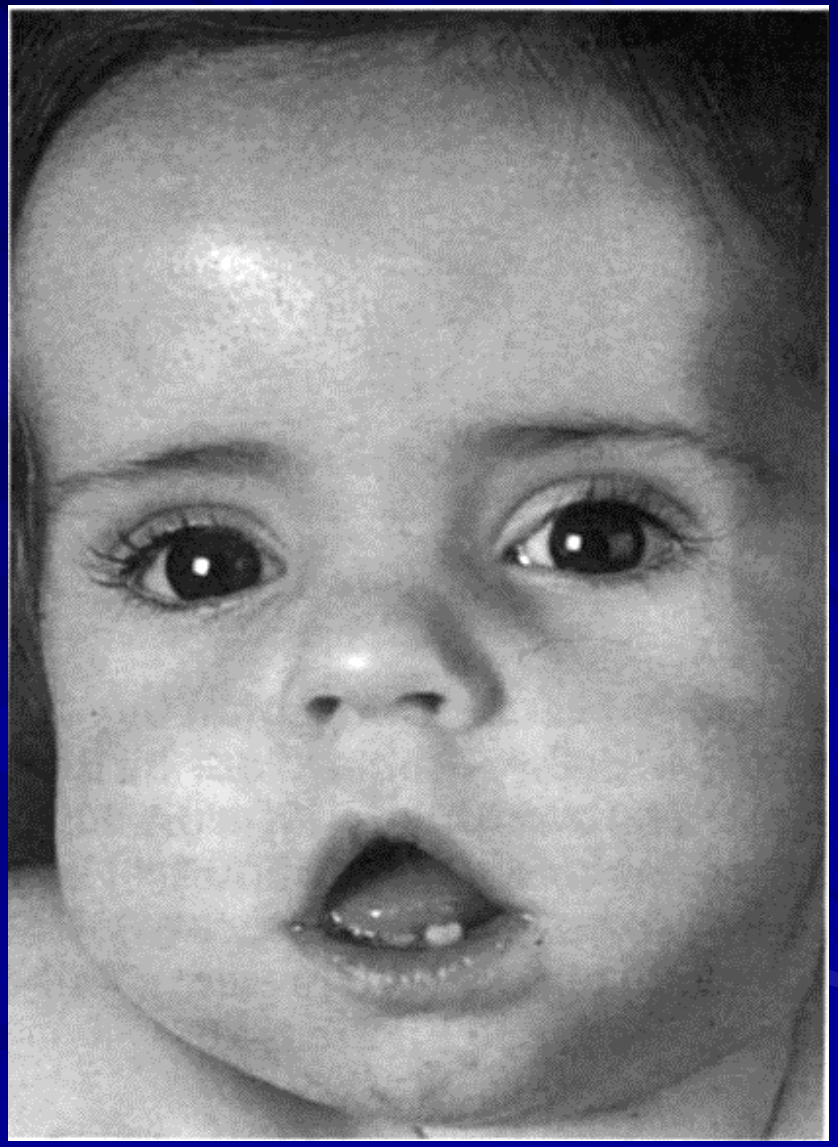
Myotonic Dystrophy

- Autosomal Dominant
  - due to expanded CTG repeat on chromosome 19
  - CTG expansion occurs in the 3’ noncoding region of the myotonic dystrophy protein kinase (*DMPK*) gene
  - the number of repeats correlates positively with disease severity
- Anticipation occurs primarily via maternal transmission
- Pregnancy often associated with polyhydramnious, preterm labour, and breech presentation

Congenital Myotonic Dystrophy

- CNS
  - 70% of congenitally affected children suffer mild-moderate mental retardation
  - Ventriculomegaly
  - affected mothers often report poor school performance (even if never suspected of having MD)





- A child born with congenital myotonic dystrophy is likely to have facial weakness and an upper lip that looks "tented." The eye muscles may also be affected.

Clinical Sings

- A long, thin face with hollow temples, drooping eyelids and, in men, balding in the front.

Myotonic Dystrophy

- Skeletal muscle:
  - neonatal hypotonia, muscle weakness
  - myopathic facies, often with non-fluctuating ptosis
  - poor gag and swallow: at risk for aspiration
  - delayed milestones
  - myotonia elicitable by age 7-8 years
  - scoliosis common

Myotonic Dystrophy

- Cardiac:
  - at risk for cardiac arrhythmias
  - sudden death well documented
  - may develop cardiomyopathy
    - needs yearly cardiology follow-up
- Ocular
  - at risk for cataracts, and retinal degeneration
  - often myopic
    - need yearly ophthalmology examination

Myotonic Dystrophy

- Smooth muscle
  - at risk for small bowel dilatation (acute abdominal pain or distention must be evaluated for megacolon)
  - increased risk of gallstones (due to delayed gallbladder emptying)
  - often have patulous anus (may be mistaken for child abuse in older children)
  - women often have uterine instability (miscarriages, preterm labour)

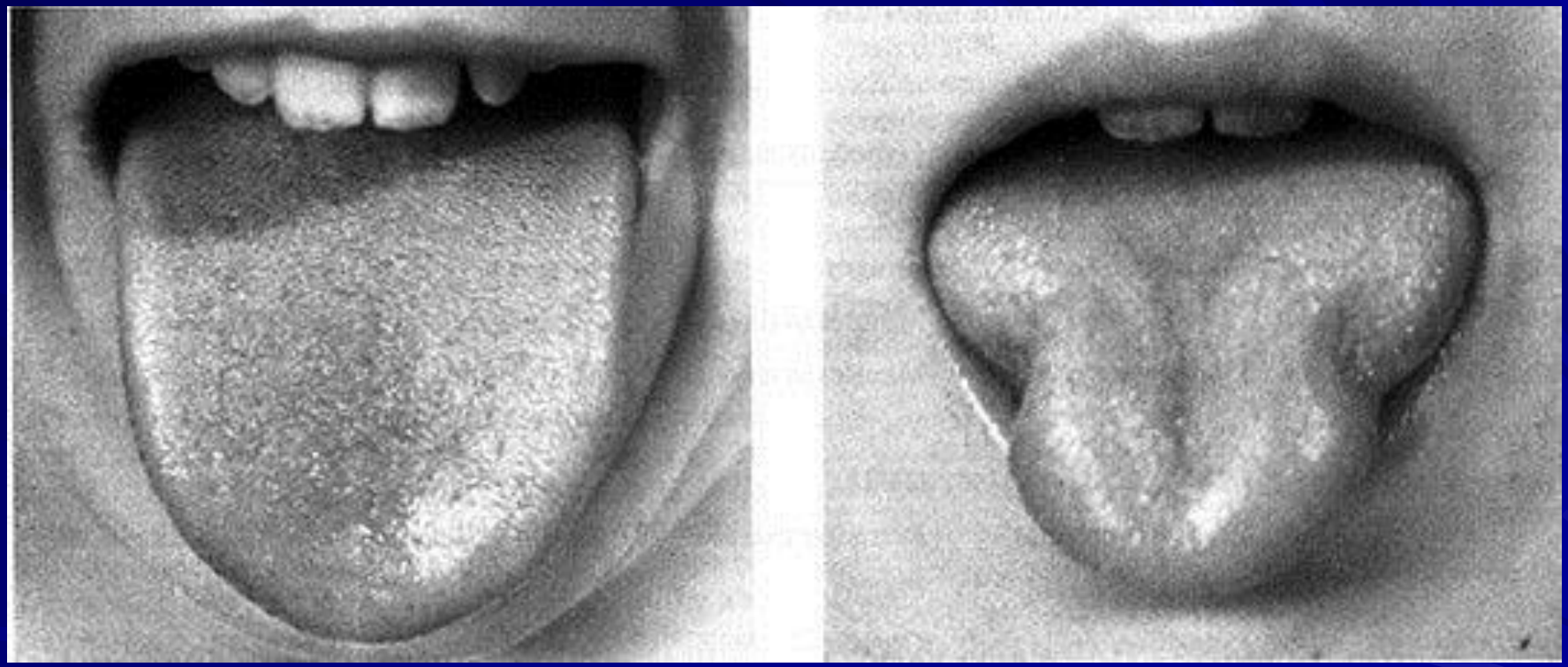
Myotonic Dystrophy

- Fatigue and Hypersomnia
  - very common, etiology unknown
    - some patients respond to Ritalin
- Endocrine
  - at risk for growth failure (abnormal growth hormone), hyperglycemia (rarely severe)
  - may have testicular atrophy, reduced fertility
  - early onset frontal balding

Myotonic Dystrophy

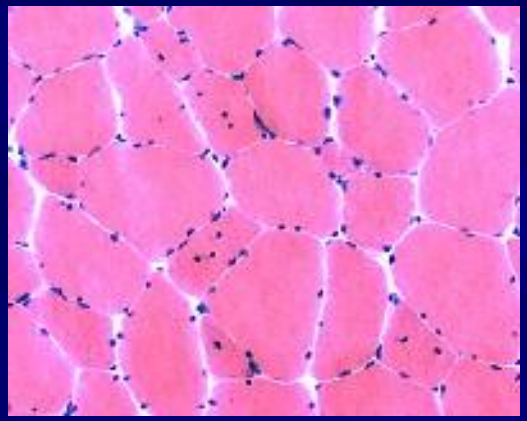
- Anesthesia
  - at risk for poor ventilatory recovery post-anesthetics
  - may develop a malignant hyperthermia-like reaction
    - avoid general anesthesia whenever possible, monitor very closely
    - must wear a medic-alert bracelet

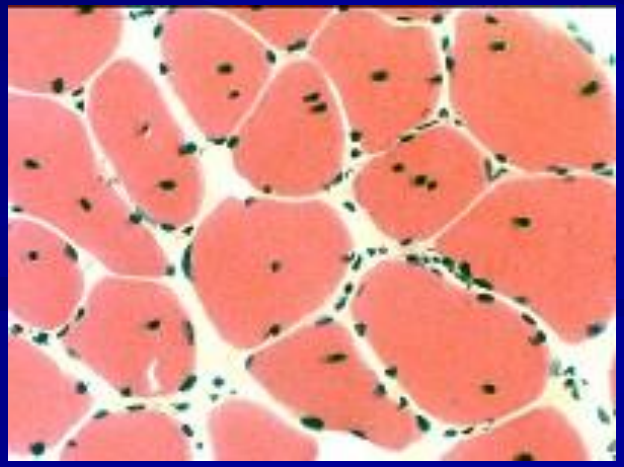
Percussion Myotonia

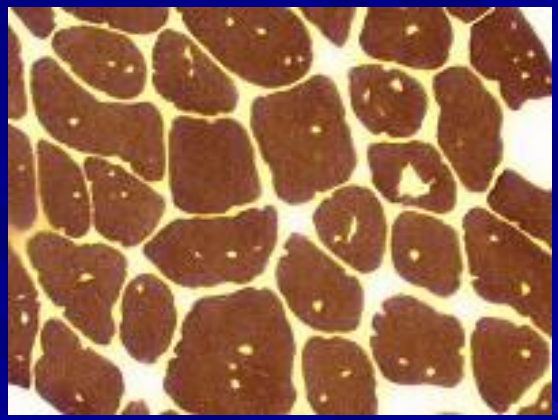


ביופסית שריר

- שינויים לא ספציפיים, גרעינים מרכזיים



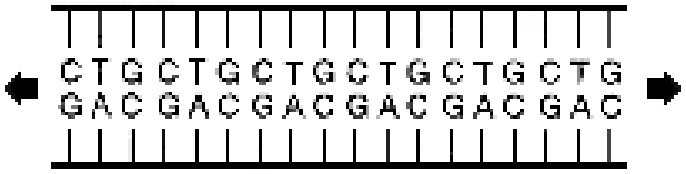




CTG repeats expansion

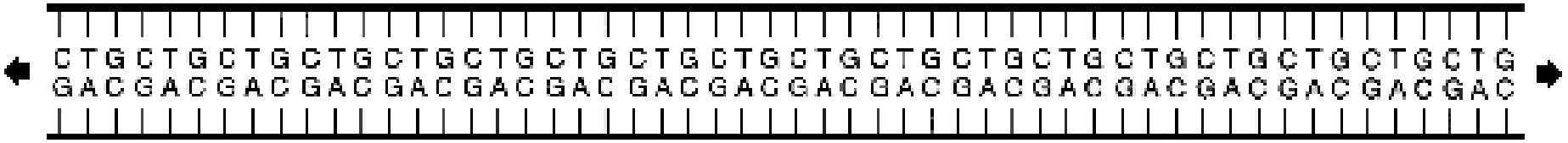
Normal

5 - 30 repeats



Altered

50 - 2000 repeats



DM1: Myotonin protein kinase (DMPK) protein

- The expanded area of DNA is in a gene that carries instructions for a protein known as *myotonin protein kinase*.

- The expanded DNA isn't in the "working" part of the gene -- the part that carries instructions telling cells to make myotonin protein kinase.

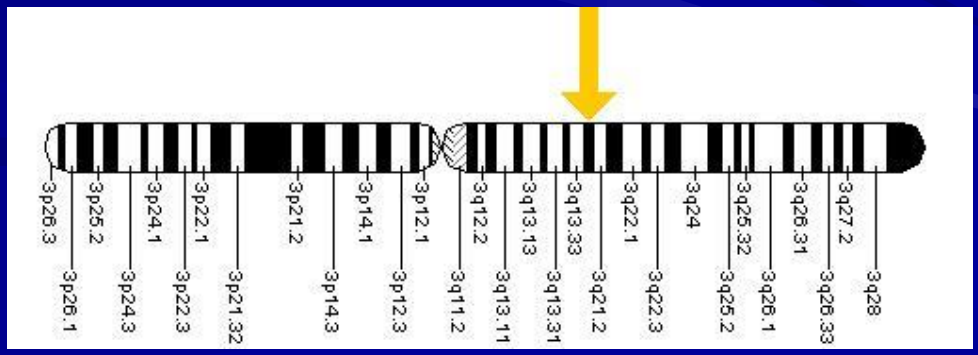
Myotonic Dystrophy

- Characterized by myotonia, muscular dystrophy, cataracts, hypogonadism, frontal balding, and ECG changes
- Dystrophia myotonica protein kinase gene (DMPK)
- Anticipation: Disease manifests earlier and more severely in subsequent generations

DM2

- In DM2 (type 2) patients, CCTG repeats in the first intron of the ZNF9 gene are found expanded.
- The clinical manifestations of DM1 and DM2 are very similar, although there are some differences.
- The signs and symptoms of type 2 myotonic dystrophy typically appear in adulthood.
- Congenital myotonic dystrophy has not been seen in families with type 2.

- The inherited mutation in the ZNF9 gene is an abnormally large segment made up of four repeated DNA bases (CCTG).
- This sequence is copied from 75 to more than 11,000 times in people who have the disease, with an average of about 5,000 repeats.
- messenger RNA from the altered ZNF9 gene can interact with certain proteins to form clumps in the cell nucleus.
- These abnormal clumps prevent cells in muscles and other tissues from functioning normally, leading to the signs and symptoms of type 2 myotonic dystrophy.



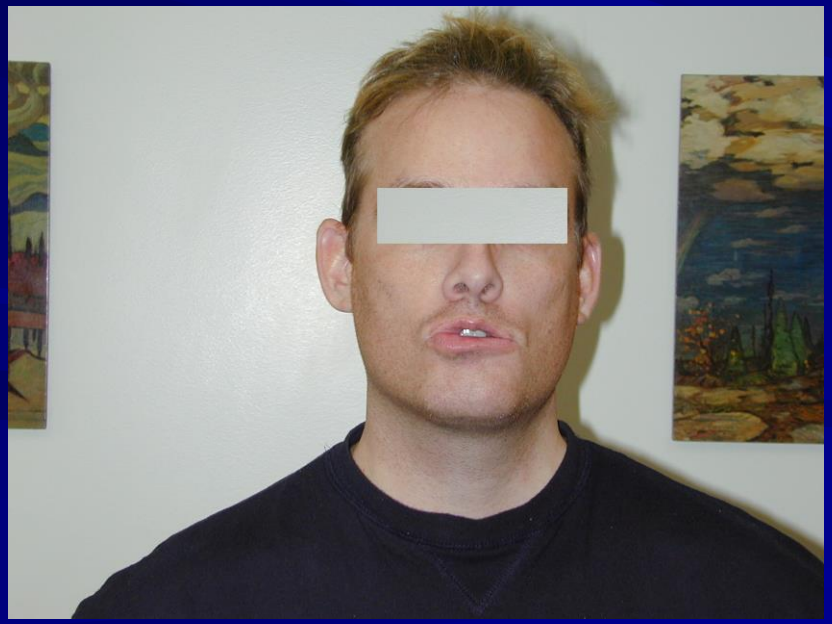
Facioscapulohumeral Dystrophy (FSHD)

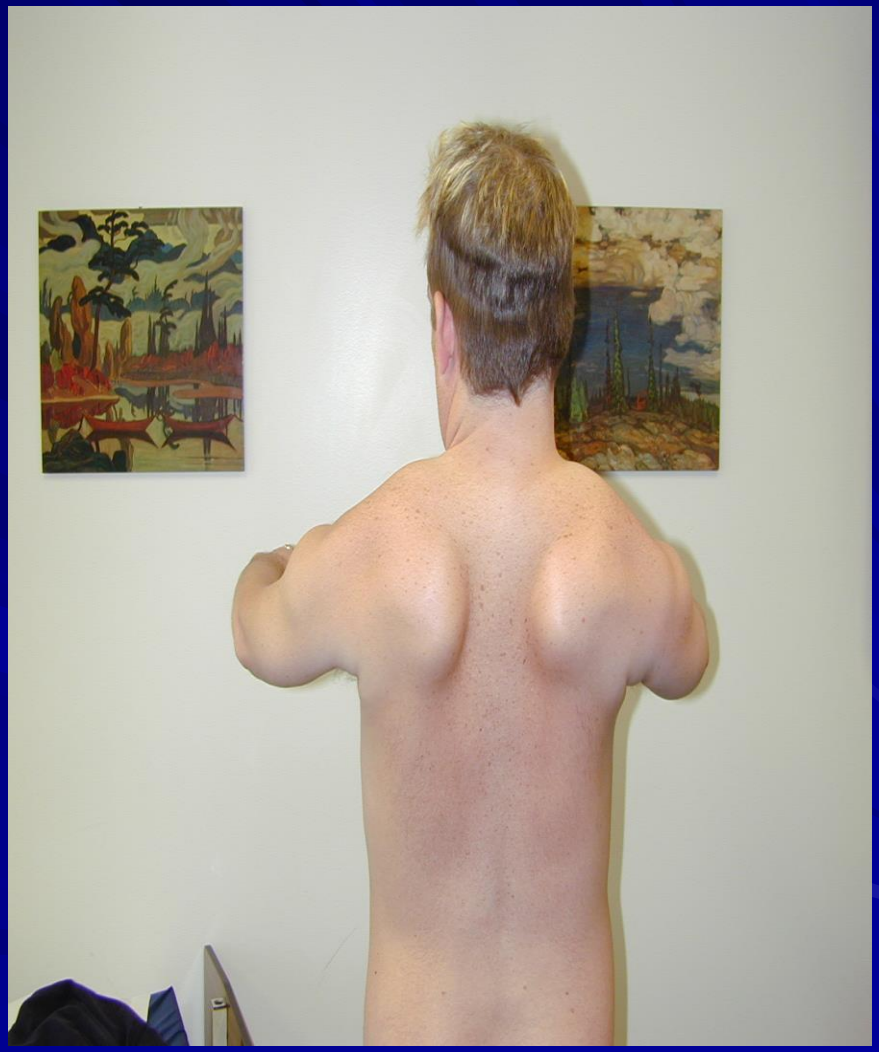
- Third most common familial myopathy (after dystrophinopathies and myotonic dystrophy)
  - Prevalence: 1 in 20,000
- Age of onset can be from the 1st to 6th decade
  - Mean: male 16 years, female 20 years
  - Penetrance is 95% by age 20
- M:F ratio equal in symptomatic patients, but a larger percentage of females tends to be asymptomatic and remains so beyond age 30

Clinical Features of FSHD

- Typical phenotype
  - Early involvement of facial and shoulder girdle muscles with scapular winging, progressing to dorsiflexor and pelvic girdle weakness
  - Weakness often asymmetrical
  - Relative sparing of deltoids is common
- Extramuscular involvement in FSHD
  - Usually subclinical
  - Sensorineural hearing loss (64%)
  - Retinal vasculopathy (49-75%)
  - Pectus excavatum (5%)
  - Mild cardiac conduction defects

Clinical Features of FSHD





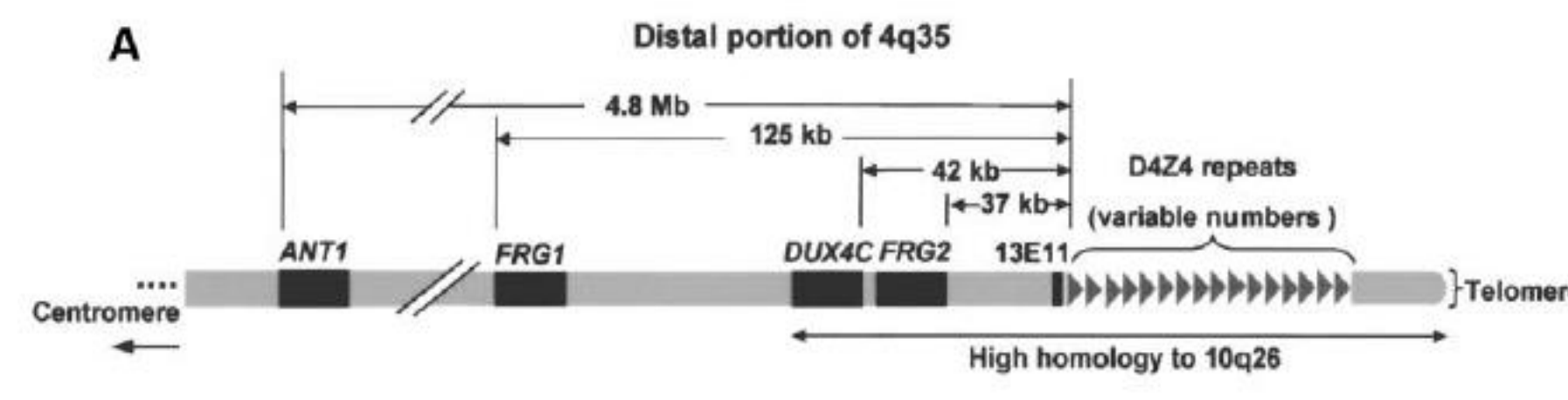
Phenotypic Heterogeneity in FSHD

- Large number of atypical presentations
  - Facial-sparing scapulohumeral dystrophy
  - Limb-girdle muscular dystrophy
  - Distal myopathy
  - Asymmetric brachial weakness
  - Typical FSHD with CPEO

Genetics of FSHD

- Autosomal dominant inheritance in most cases
  - 10% of cases represent new mutations
- Deletion of 3.3 kb D4Z4 repeat units in the subtelomeric (non-coding) region of 4q35
  - Normal individuals: 12-100 copies of D4Z4
  - FSHD: less than 12 copies
  - Deletion alters expression of a more proximally located gene (position-effect variegation)?
- Association with the 4qA allele (distal to the D4Z4 repeat array)
- FSHD gene has not been located yet

Genetics of FSHD



- Clinical severity ranges from asymptomatic carriers to severely affected cases

- Significant interfamilial and intrafamilial variability in age of onset and disease severity (in individuals with the same number of repeats)

Treatment of FSHD

- Supportive
- No effective treatment
  - Negative open-label trial of prednisone
  - Negative randomized-controlled trial of albuterol
- Surgery for ankle contractures, scoliosis, pectus excavatum
- 20% of patients become wheelchair dependent

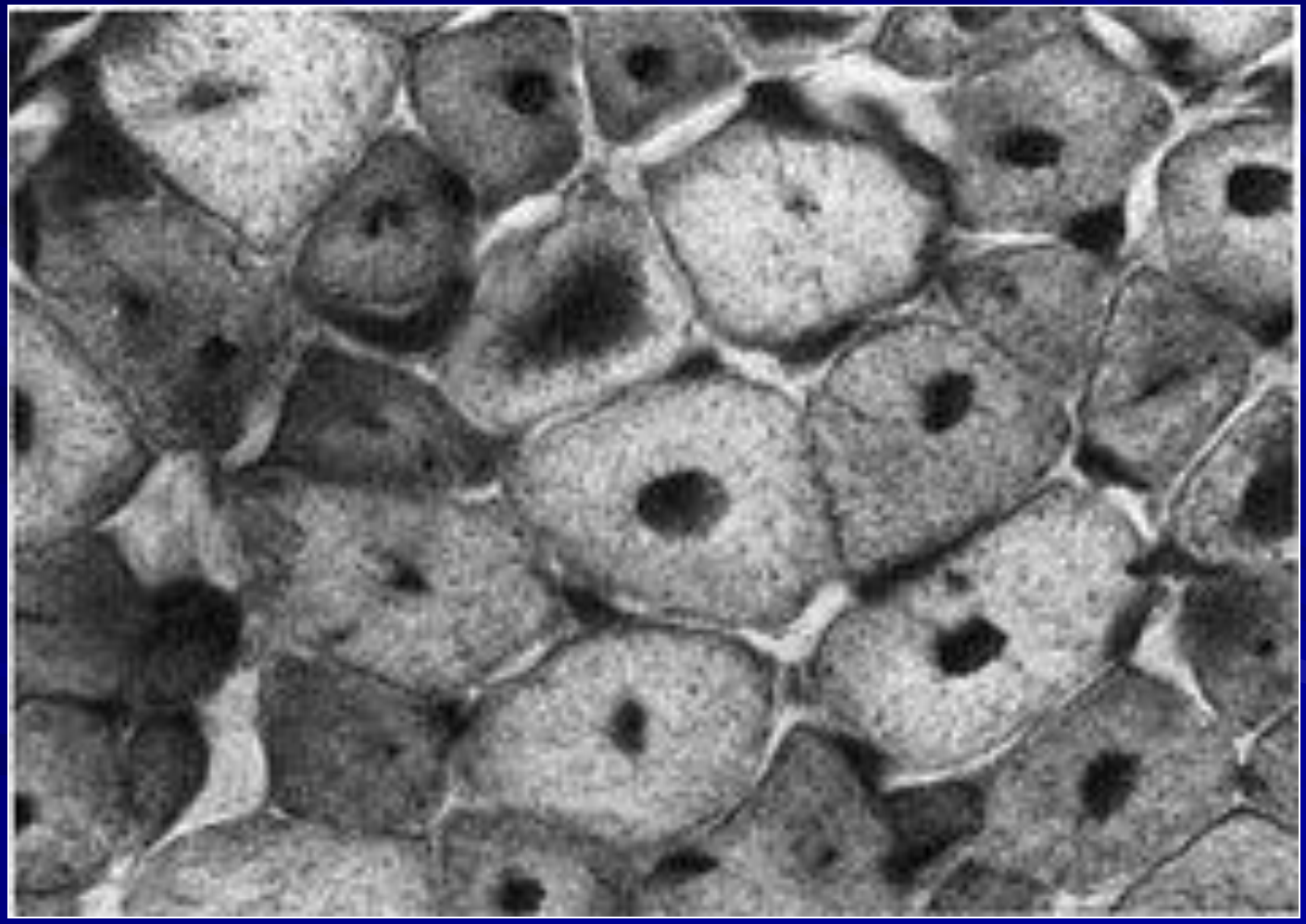
Congenital Myopathies

- Congenital disorders defined by structural aberration in muscle fiber architecture
- Present with neonatal hypotonia and delayed motor milestones
- EMG normal or shows a mild myopathy
- CK often normal or even low
- Children often **improve** as muscle bulk increases
- At risk for pulmonary infections, scoliosis, and cardiomyopathy (some forms only)

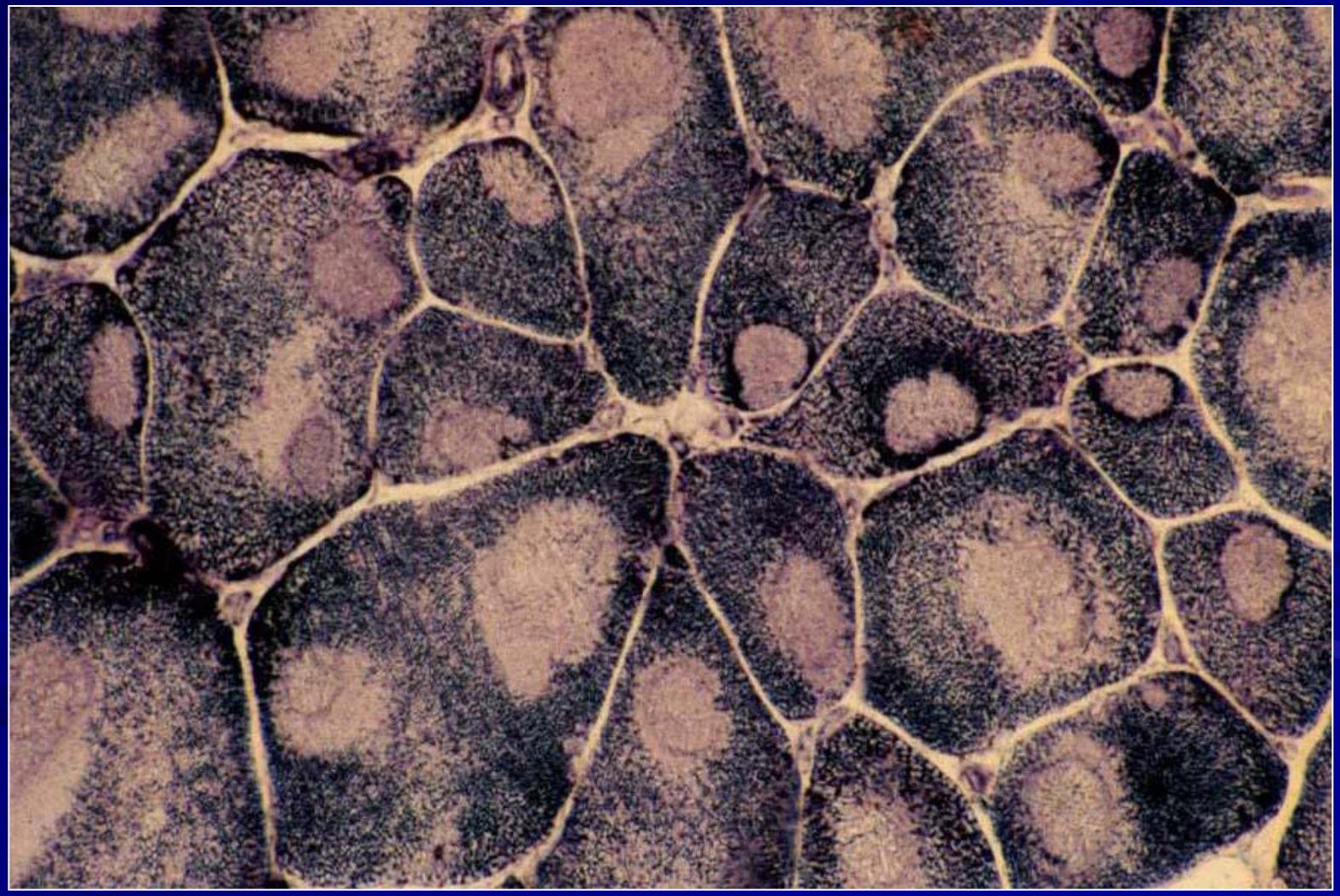
Congenital Myopathies

- Nemaline Myopathy
- Central Core Myopathy
- Central Nuclear (myotubular) Myopathy
- Congenital Fiber Type Disproportion
- Other

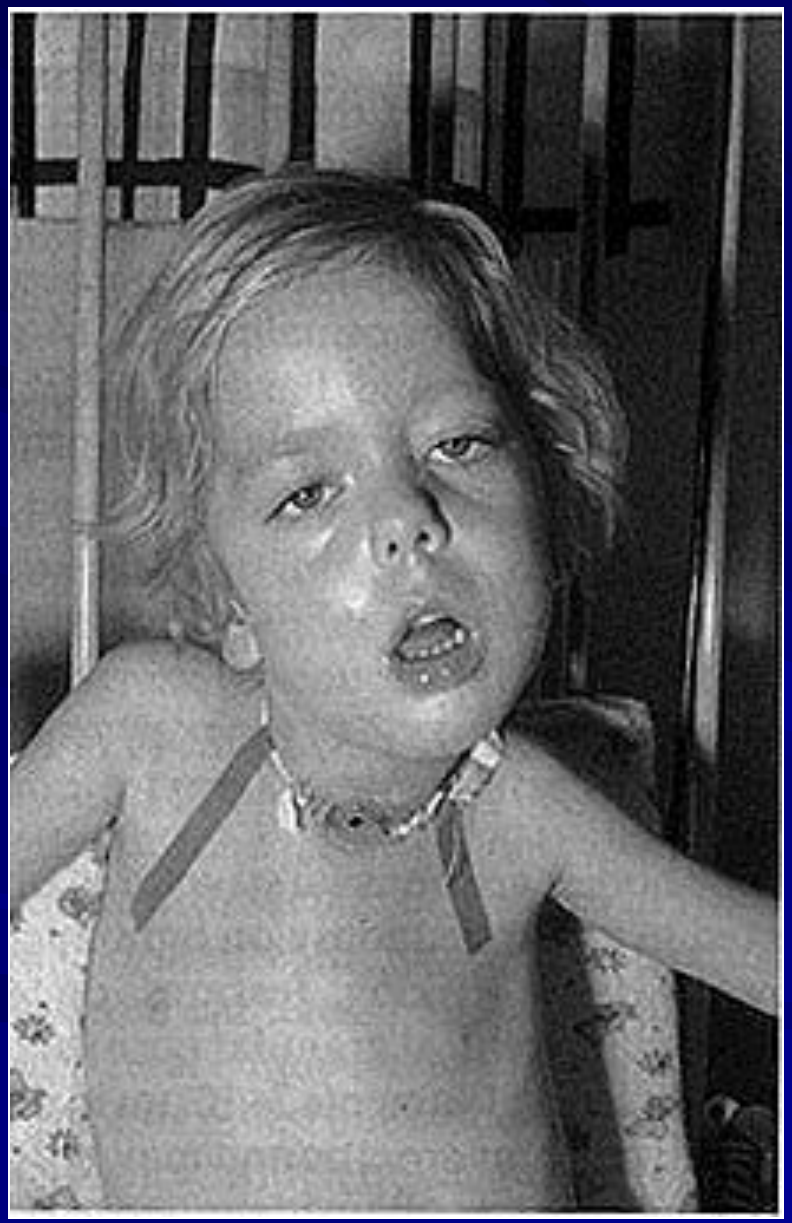
Myotubular (Centronuclear) Myopathy

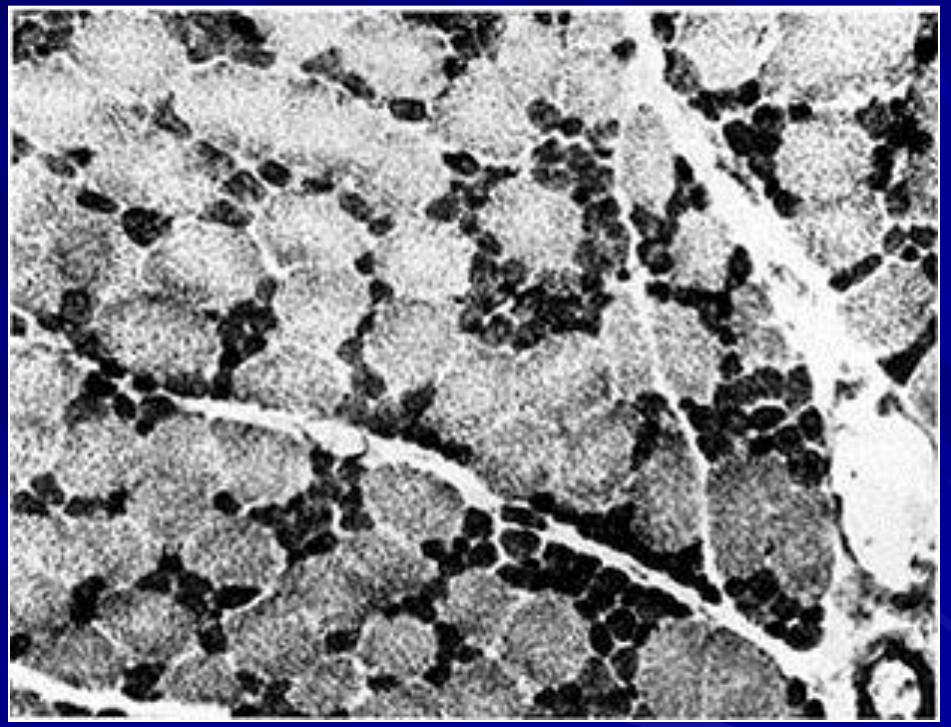


Central Core Myopathy



CFTD





Thank you