Cleveland Clinic Children's

An Overview of Pediatric Neuromuscular Disease

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Disclosures

- **No disclosures or conflict of interest**

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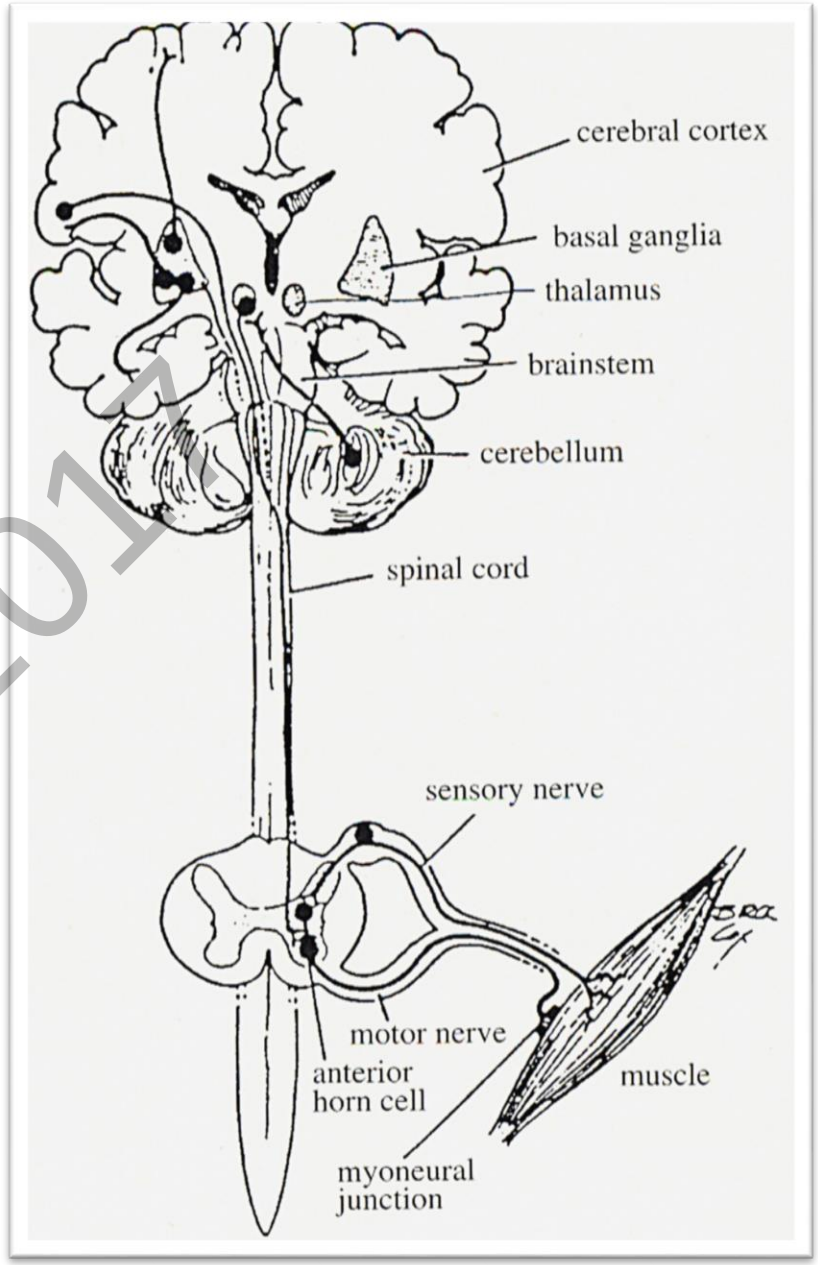
CNS influences the activity of skeletal muscle through two sets of neurons

- Upper motor neuron
- Lower motor neuron



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Relationship of UMN to LMN

- **Upper motor neurons control the lower motor neurons through two different pathways:**
  - **Pyramidal tracts (corticospinal tracts)**
  - **Extrapyramidal tract**

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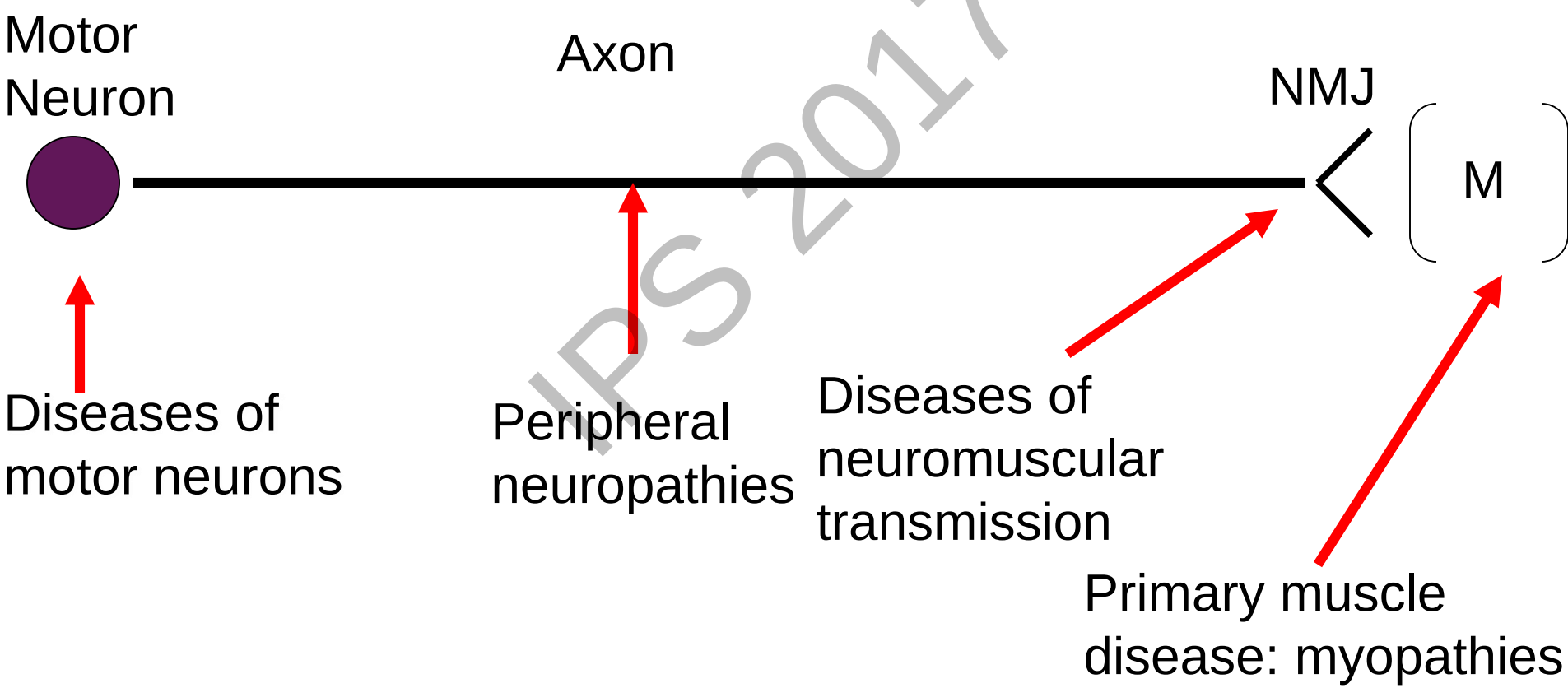
The Motor Unit



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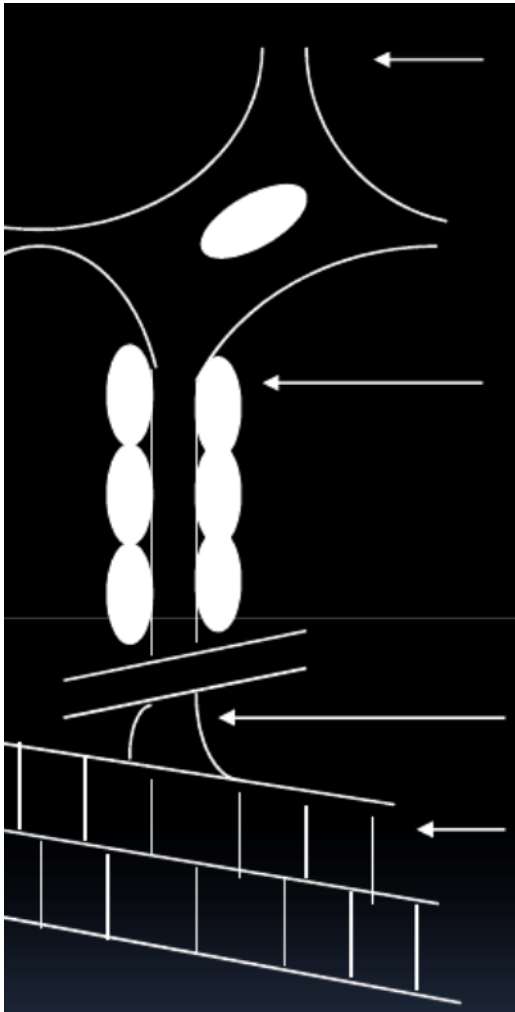

AnteriorHorn Cell

Hereditary

Spinal Muscular Atrophy

Acquired

Poliomyelitis

Nerve Fibre

Neuropathies

a) Demyelinating eg GBS.

b) Axonal, eg lead.

Neuromuscular Junction

Myasthenia gravis

Muscle

Hereditary

1. Muscular Dystrophy
2. Congenital Myopathies

Acquired

1. Dermatomyositis.
2. Endocrine myopathies.

Feature	Neuropathic	Myopathic
Distribution of weakness	Distal (length dependent)	Proximal (may involve face or eyes)
Reflexes	Absent	Usually present/ reduced
Sensory loss	Usually present	Absent
Atrophy	Present	Absent until late (pseudohypertrophy)
Creatine kinase	Normal to mildly elevated	Elevated (may be normal)
Nerve conduction velocity	Usually decreased	Normal
EMG	Fibrillations and fasciculations	Small muscle units
Muscle biopsy	Group atrophy	Irregular necrotic fibers

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Presenting Symptoms

- **Motor developmental delay**
- **Gait characteristics**
- **Functional difficulties**

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Table 2 Symptoms and Signs Associated with Myopathies

Negative	Positive
Weakness	Myalgias
Fatigue	Cramps
Exercise intolerance	Contractures
Muscle atrophy	Myotonia
	Myoglobinuria

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Jackson C. Semin Neurol 2008;28:228–240

Table 12 Functional Assessment of Muscle Weakness

Location	Signs or Symptoms of Weakness
Facial	Inability to ''bury eyelashes,'' ''horizontal smile,'' inability to whistle
Ocular	Double vision, ptosis, dysconjugate eye movements
Bulbar	Nasal speech, weak cry, nasal regurgitation of liquids, poor suck, difficulty swallowing, recurrent aspiration pneumonia, cough during meals
Neck	Poor head control
Trunk	Scoliosis, lumbar lordosis, protuberant abdomen, difficulty sitting up
Shoulder girdle	Difficulty lifting objects overhead, scapular winging
Forearm/hand	Inability to make a tight fist, finger or wrist drop
Pelvic girdle	Difficulty climbing stairs, waddling gait, Gower's sign
Leg/foot	Foot drop, inability to walk on heels or toes
Respiratory	Use of accessory muscles

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Jackson C. Semin Neurol 2008;28:228–240

Signs of Neuromuscular Disease

- Observation
  - Atrophy or hypertrophy
  - Fasciculations
  - Functional abilities
- Palpation
  - Muscle texture
  - Tenderness
  - Nerve thickness
- Examination
  - Joint contractures
  - Myotonia
  - Strength
  - Patterns of weakness
  - Gower sign
  - Tendon reflexes

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Gower Sign

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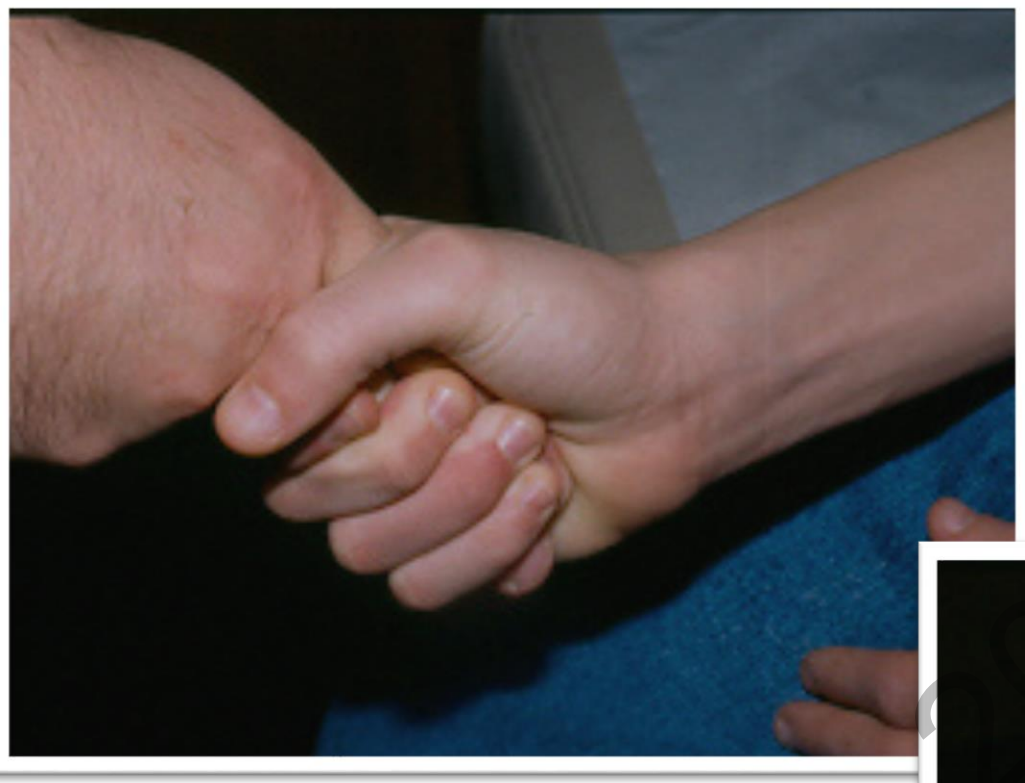

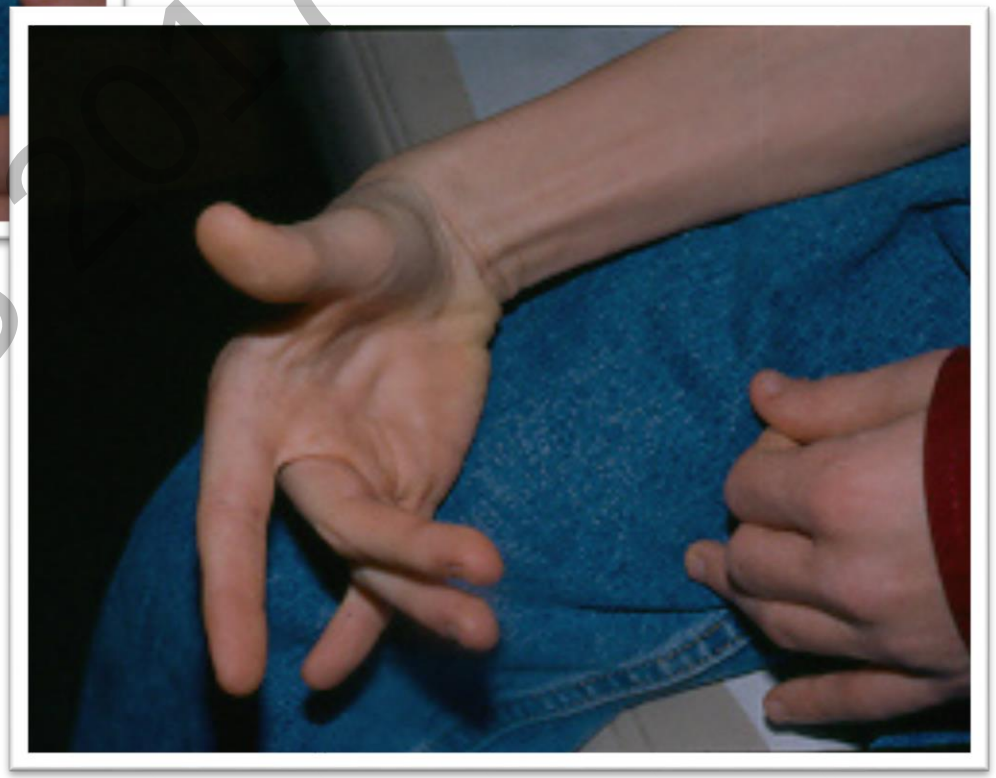

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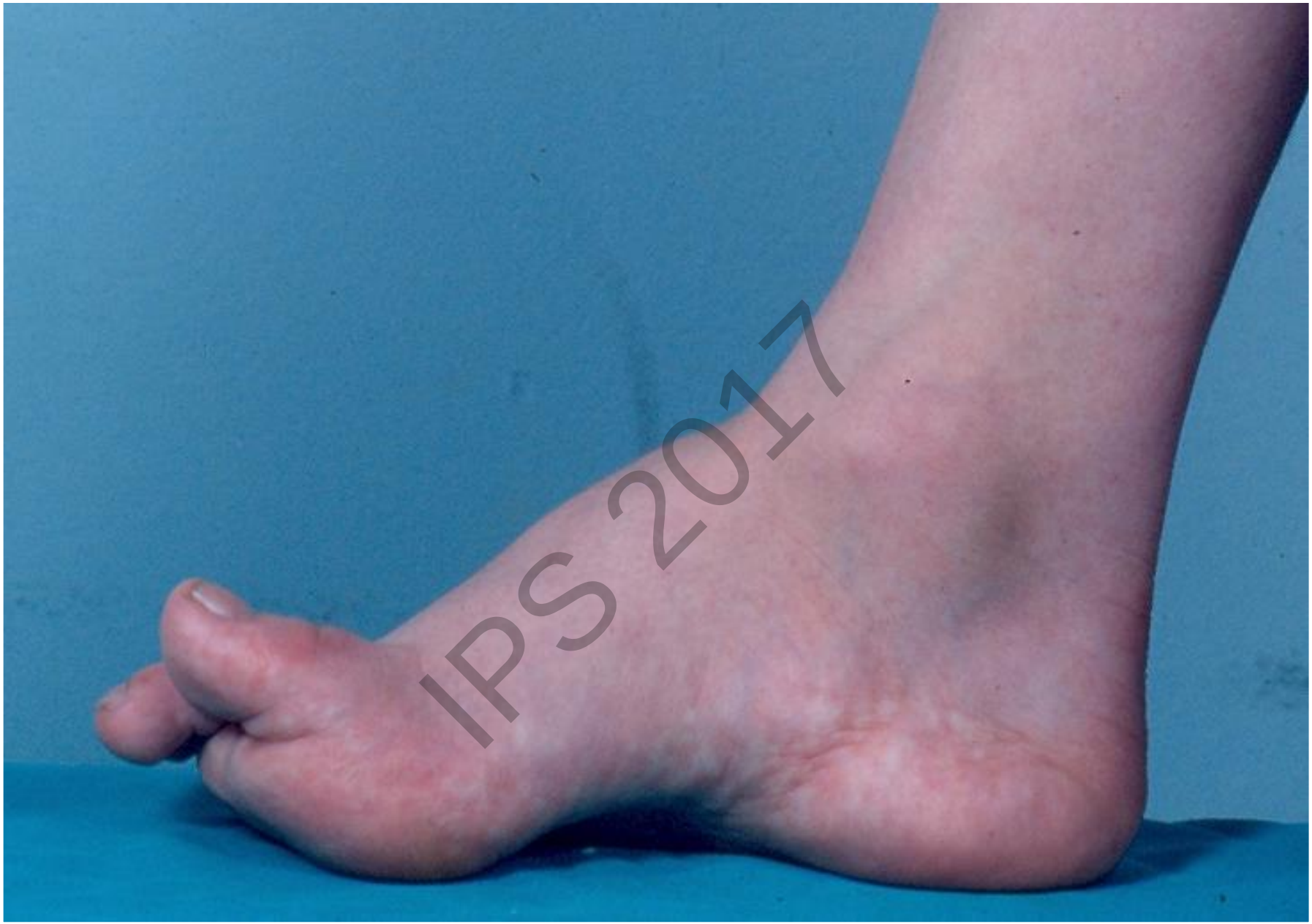
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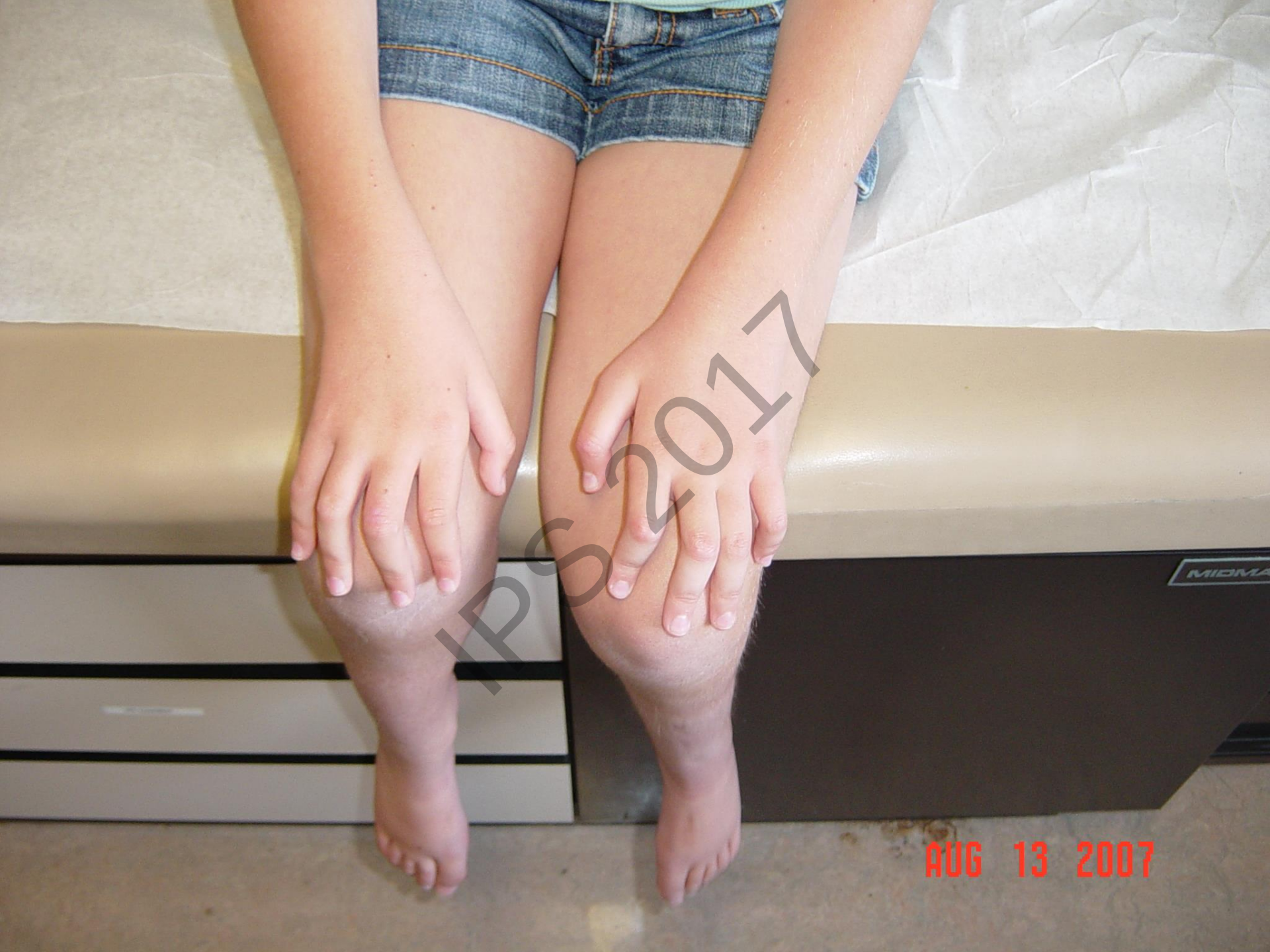
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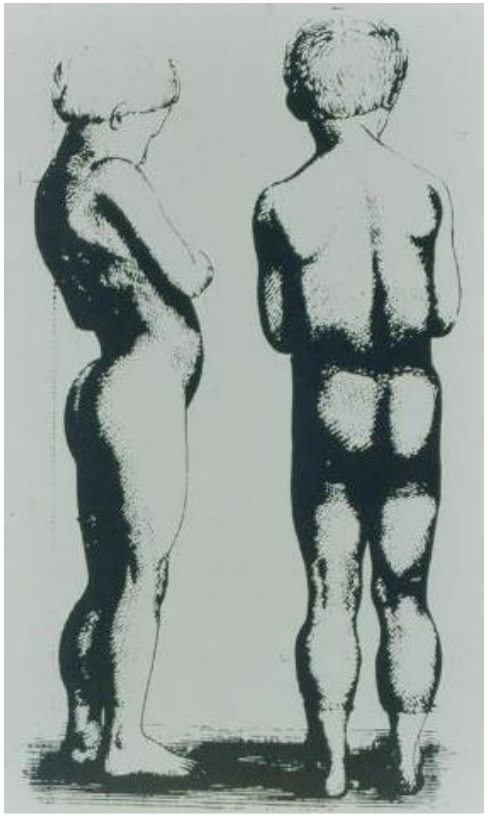
Classification of Pediatric Myopathies

- Muscular dystrophies
- Congenital myopathies
- Inflammatory myopathies
- Metabolic myopathies
- Channelopathies
- Myasthenic syndromes



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Muscular Dystrophy: Classification

X-linked recessive

- Duchenne/Becker muscular dystrophy
- Emery-Dreifuss muscular dystrophy

Autosomal dominant

- Limb girdle muscular dystrophy (type 1)
- Emery-Dreifuss muscular dystrophy
- Myotonic dystrophy
- Facio-scapulo-humeral muscular dystrophy

Autosomal recessive

- Limb girdle muscular dystrophy (type 2)
- Congenital muscular dystrophy

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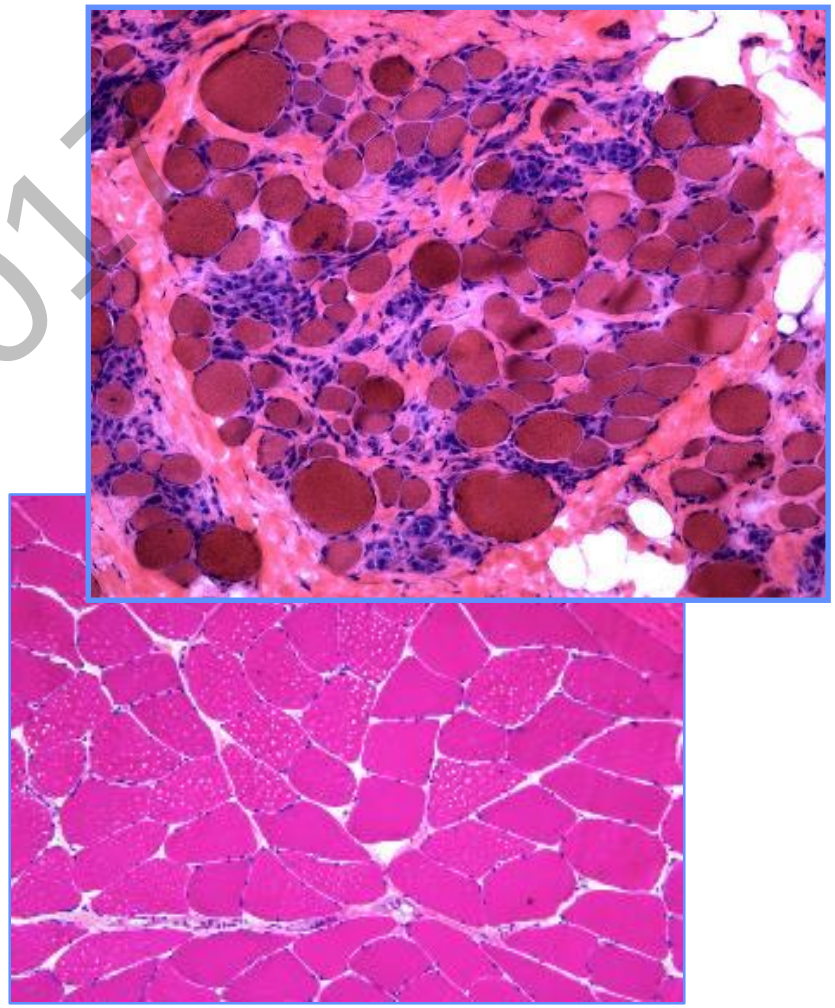
Definition of Muscular Dystrophy

- Group of genetically determined disorders
- Progressive degenerative process in skeletal muscle
- Unifying feature is the histological appearance on muscle biopsy



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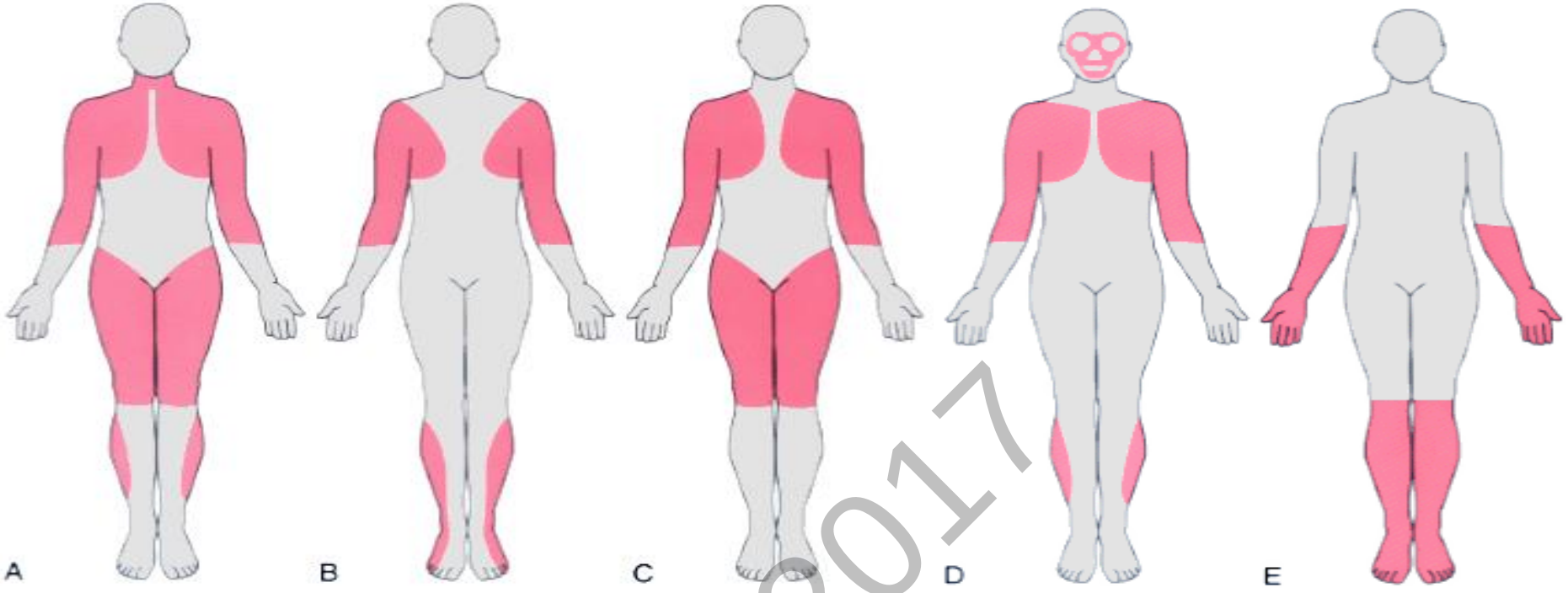
Courtesy of Dr. Susan Stagautis



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A:

B:

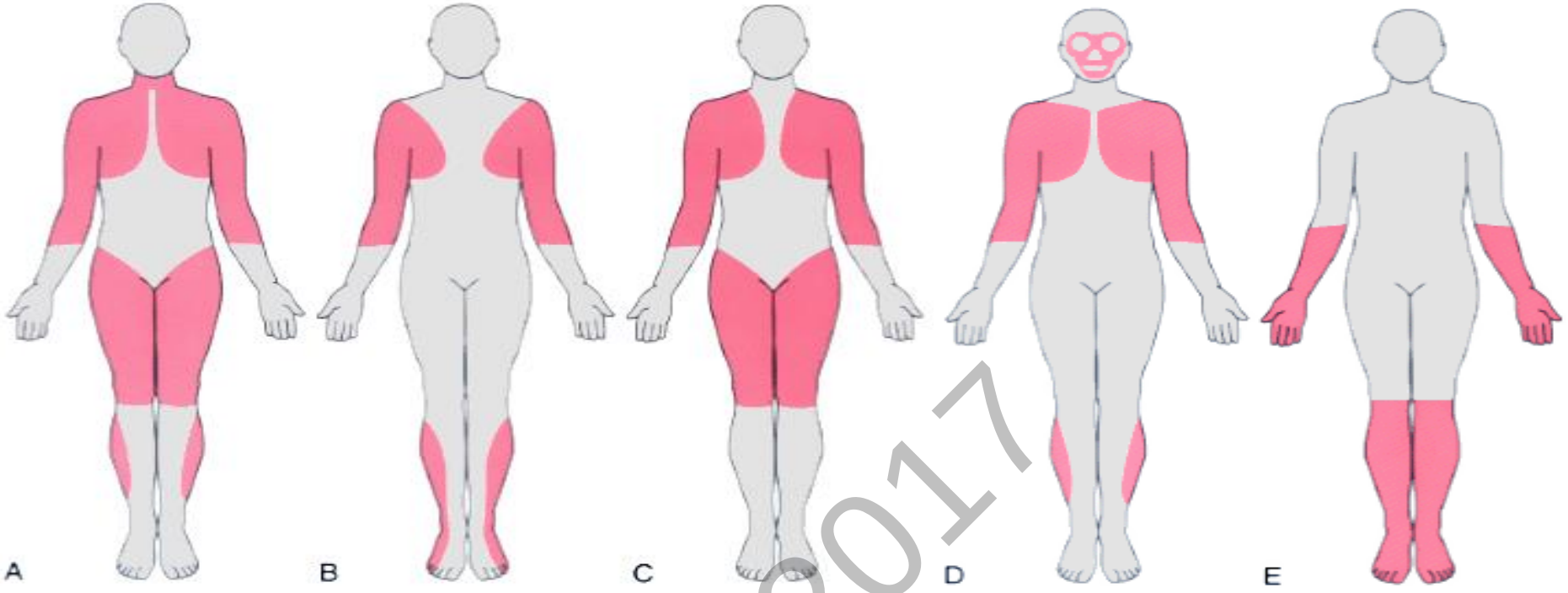
C:

D:

E:

Pattern of Weakness

From Emergy AE: The muscular dystrophies. BMJ 317:991–995, 1998.



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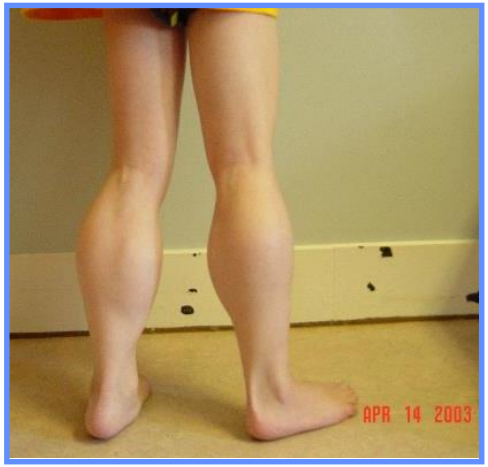
A: Duchenne/Becker
B: Emery-Dreifuss
C: Limb girdle
D: Facioscapulohumeral
E: Distal

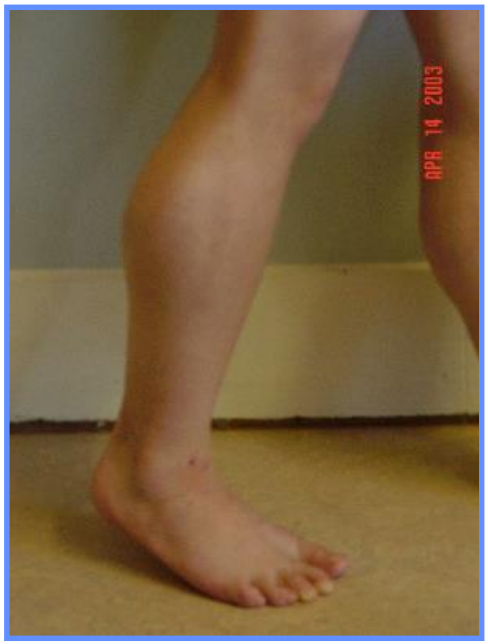
Pattern of Weakness

From Emergy AE: The muscular dystrophies. BMJ 317:991–995, 1998.

Duchenne/Becker Muscular Dystrophy

- Progressive, symmetric proximal weakness
- Calf hypertrophy (pseudohypertrophy)
- Gower sign
- Waddling gait typically with toe-walking
- Hypo/areflexia
- Tendoachilles contractures
- Scoliosis (usually later in disease course)





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	DUCHENNE	BECKER
Incidence	1:3 500 live male births	1:30 000 live male births
Age of presentation	3-5 yrs	5-10 yrs, sometimes adolescence
Loss of ambulation	Before 13th birthday	Beyond 16th birthday
Death	Early 20's – from cardiopulmonary failure	Variable – long term survival possible
CK	Massively elevated > 10-100 X normal	Massively elevated > 10-100 X normal
Cardiomyopathy	Late – end stage	Early, disproportionate to muscle weakness May be presenting feature
Dystrophin	**Absent** (< 5%)	**Reduced in quantity or quality** (> 10%)
Gene deletion	About 97% of cases	About 97% of cases

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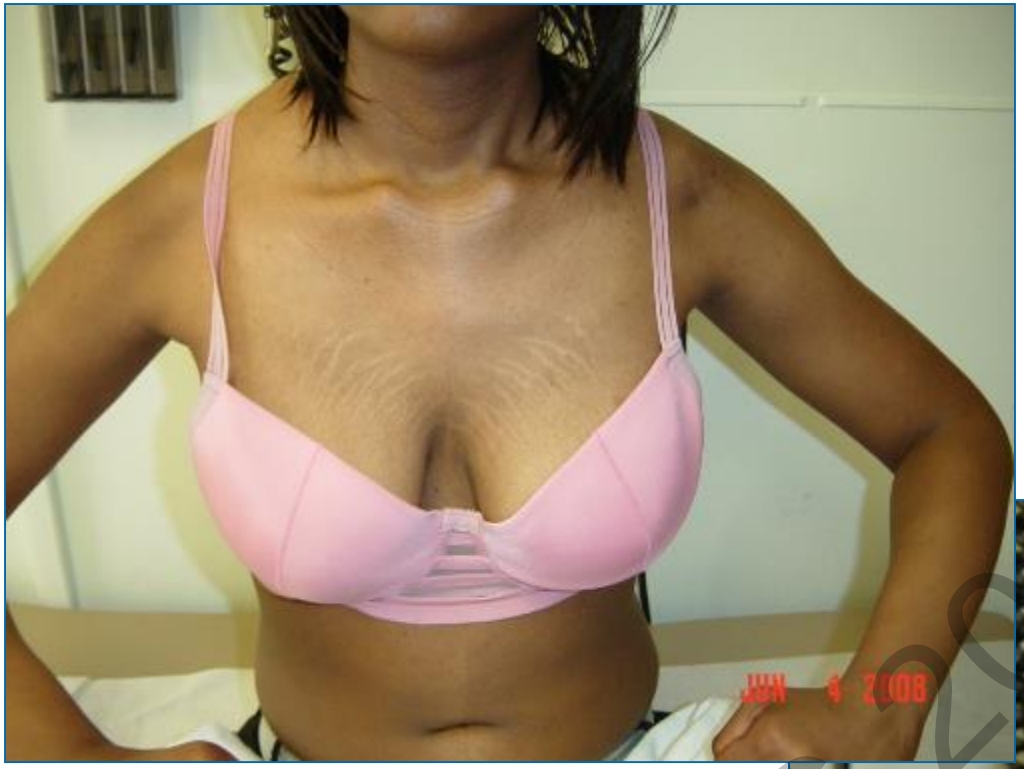

Diagnosis?

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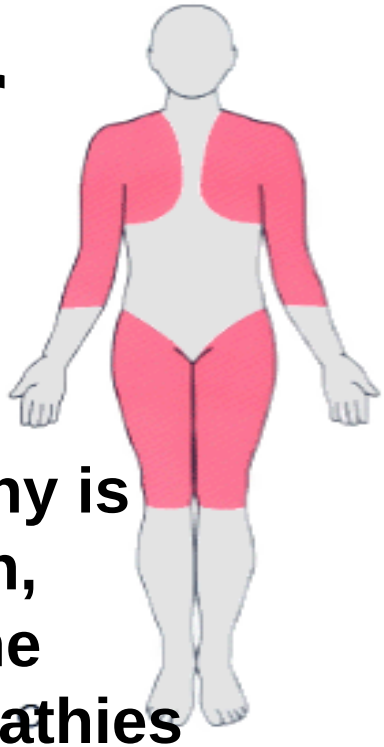
Limb Girdle Muscular Dystrophy



Clinical Presentation

- Variable age of onset – infancy, childhood, adolescence or even adult life.
- Progressive predominant proximal shoulder and hip girdle weakness and wasting.
  - Face typically not involved (may be involved late in disease)
- Calf hypertrophy is frequently seen, especially in the sarcoglycanopathies
- Tendoachilles contractures common
  - other joint contractures usually only occurs in severe or advanced disease.
- Variable cardiac involvement

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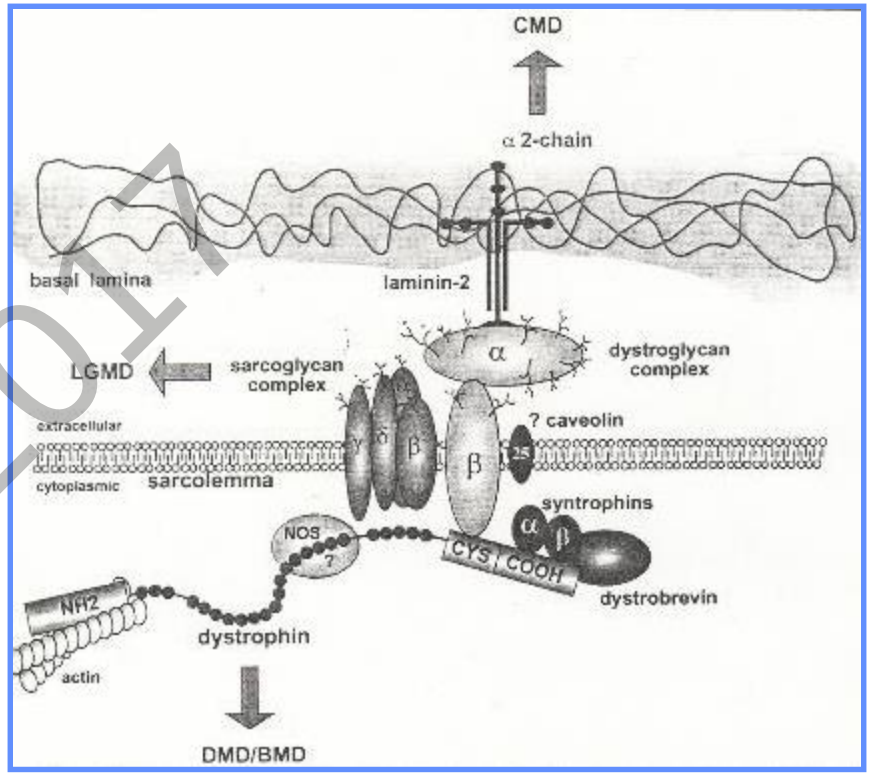
Classification

Autosomal Dominant

LGMD1A	5q31	Myotilin
LGMD1B	1q21.2	Lamin A/C
LGMD1C	3p25	Caveolin*
LGMD1D	7q	HSP
LGMD1E	6q23	Desmin
LGMD1F	7q32	Transportin 3
LGMD1D	4q21	

Autosomal Recessive

LGMD2A	15q	Calpain*
LGMD2B	2p13	Dysferlin*
LGMD2C	13q12	γ-sarcoglycan
LGMD2D	17q 12	α-sarcoglycan
LGMD2E	4q12	β-sarcoglycan
LGMD2F	5q33	δ-sarcoglycan
LGMD2G	17q12	Telethonin
LGMD2H	9q	E3-ubiquitin ligase
LGMD2I	19q13.3	Fukutin-related protein
LGMD2J	2q24.3	Titin2
LGMD2X	6q21	



From Bönneman et al. *Current Opinion in Pediatrics* 1996; 8: 569 – 582

*May preset with “benign hyperCKemia”

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LGMD2A
Calpain
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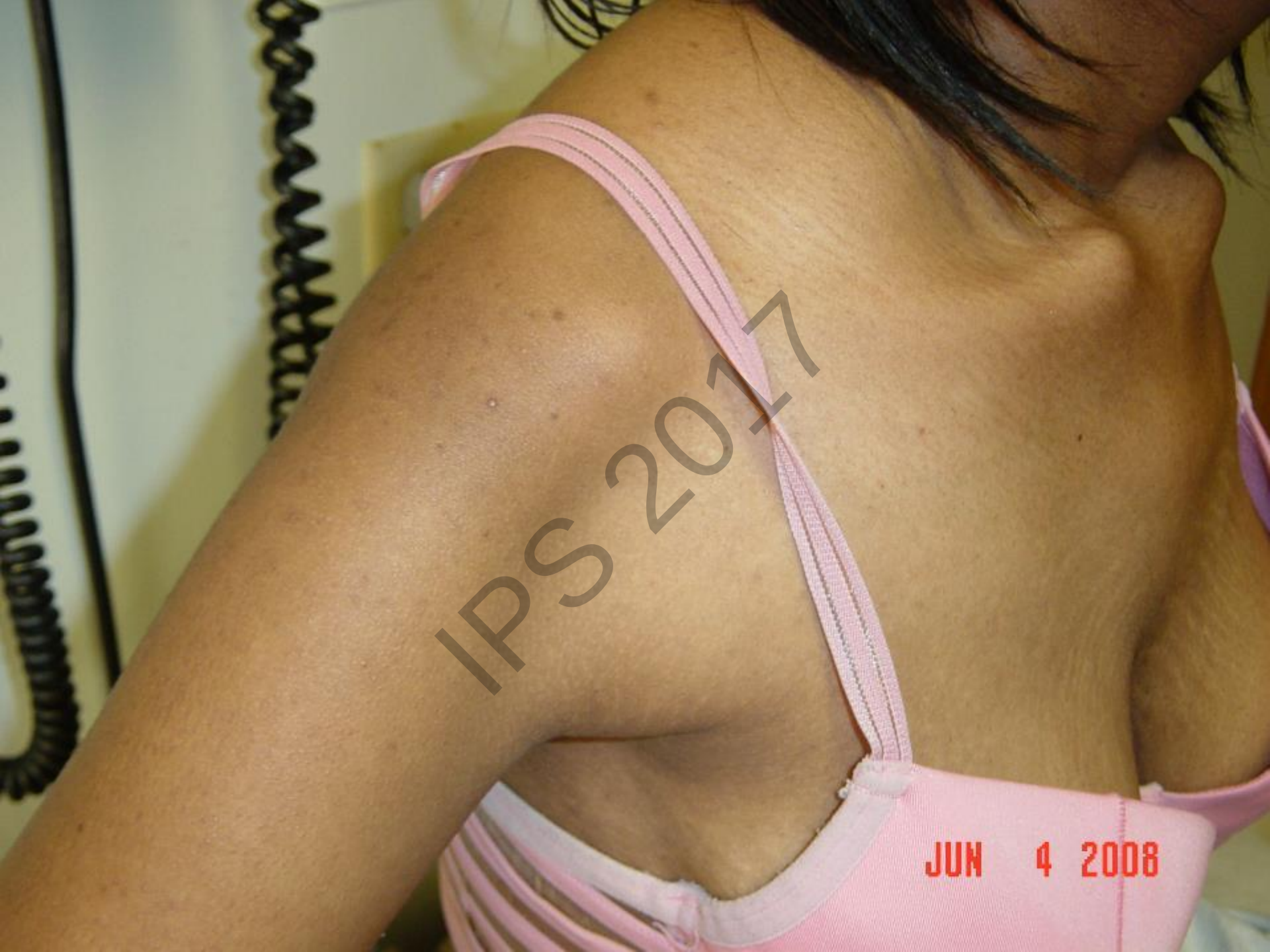
JUN 4 2008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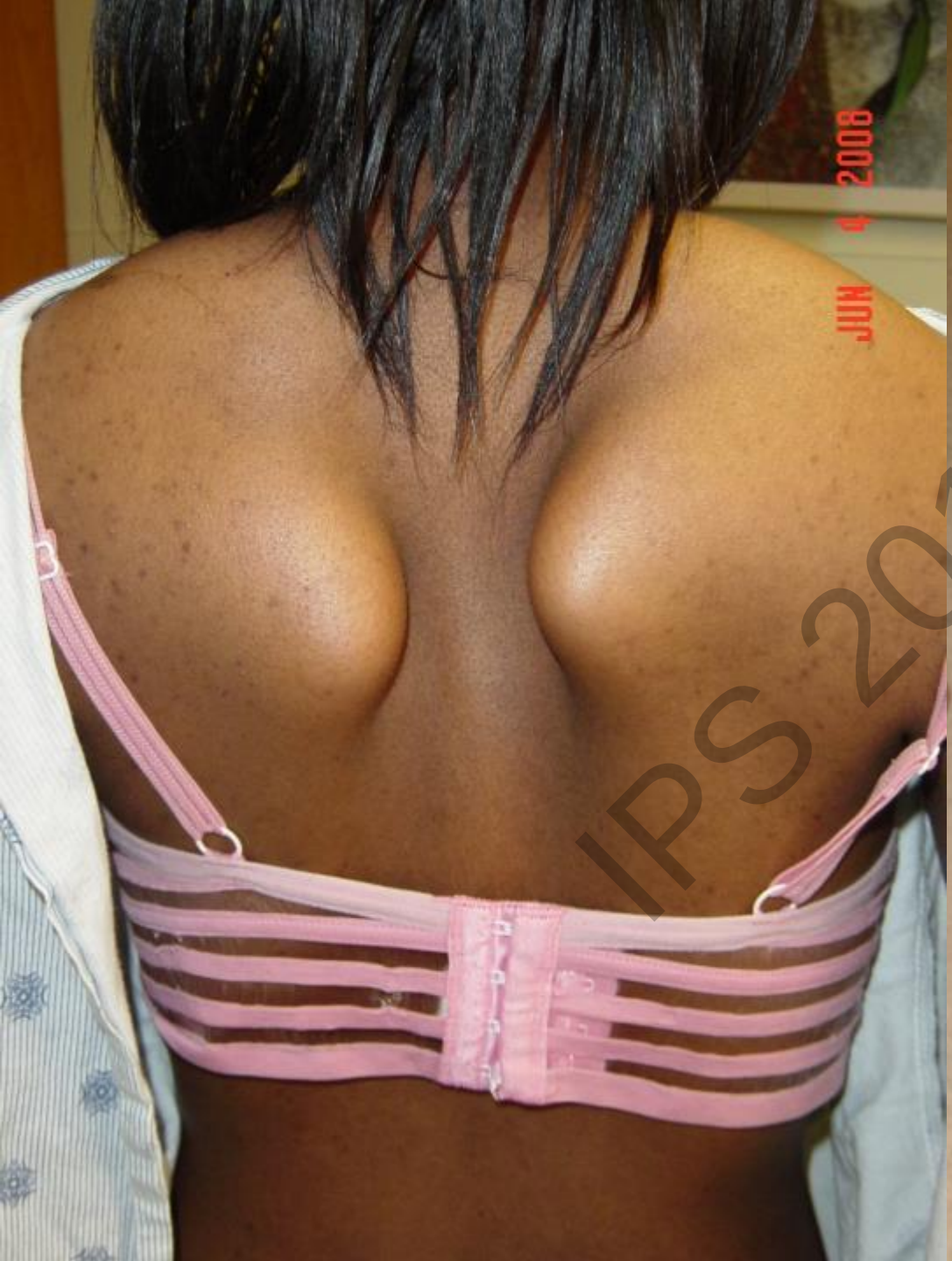

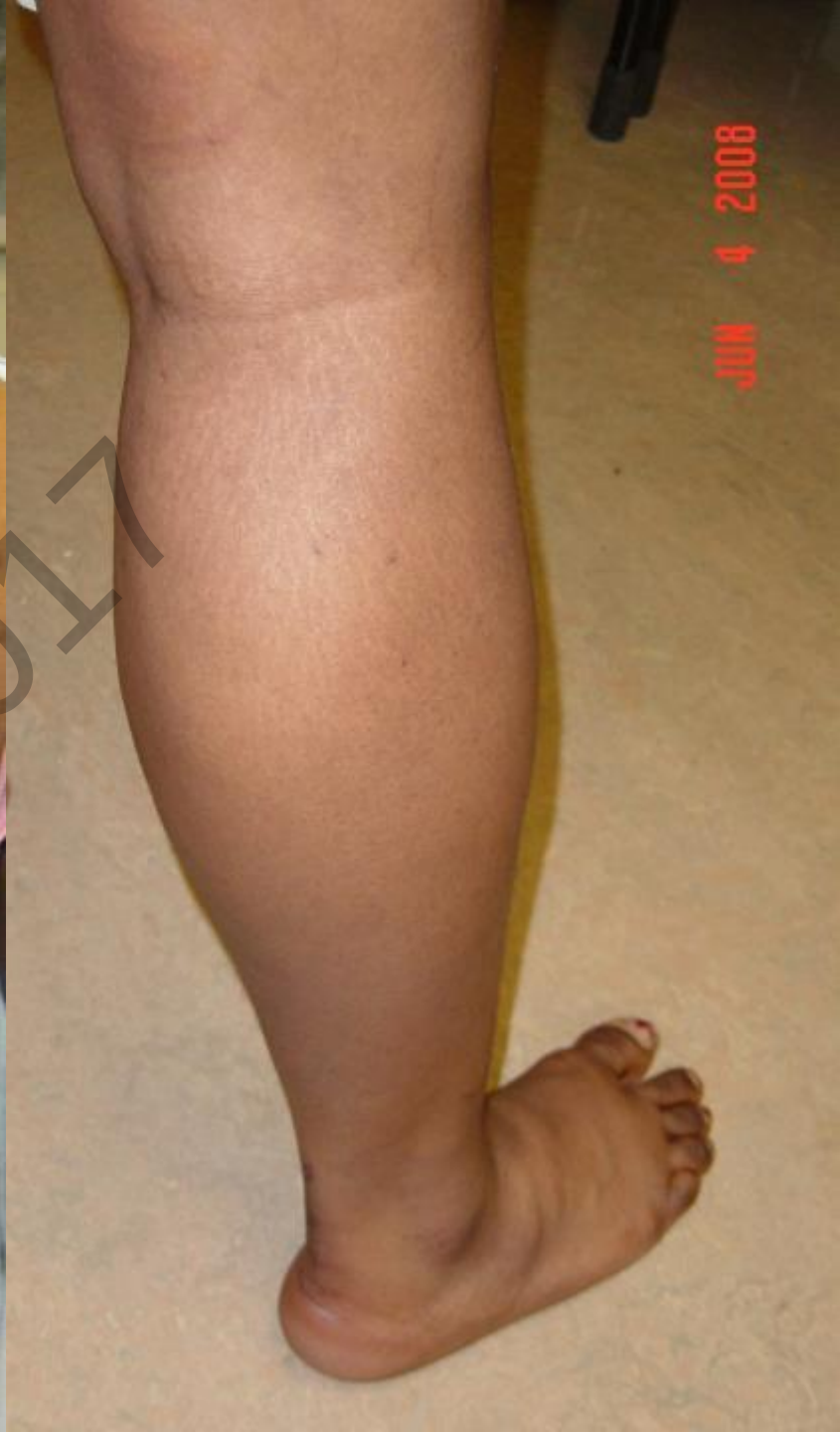

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LGMD2B: Dysferlin

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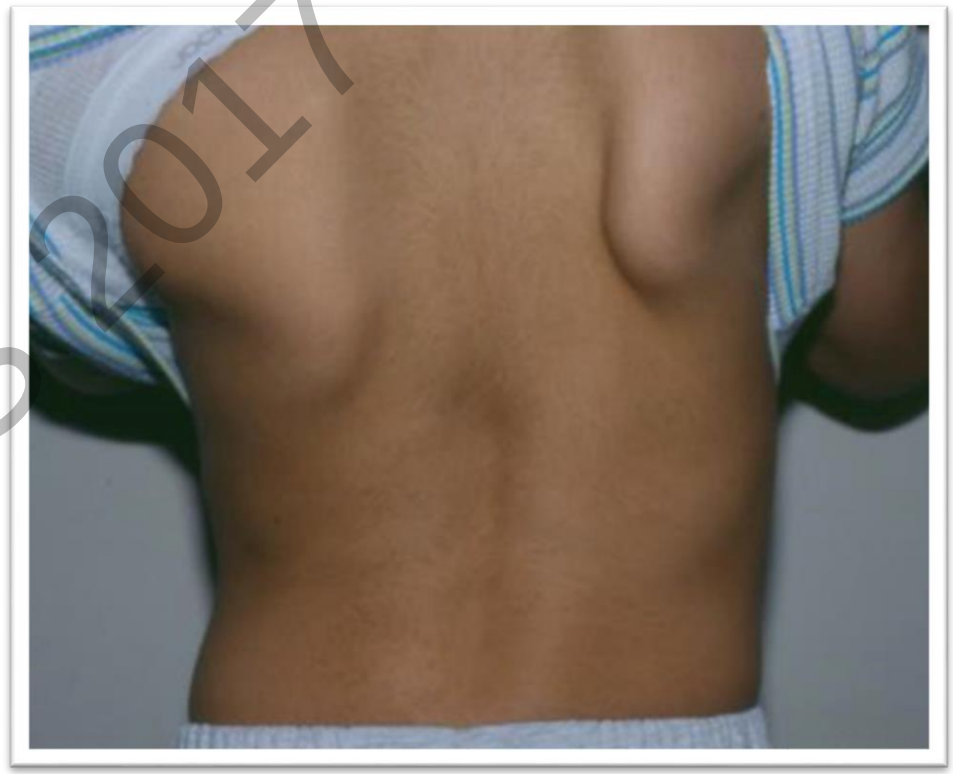
LGMD2C: Gamma-sarcoglycan



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LGMD 2F: Delta sarcoglycan

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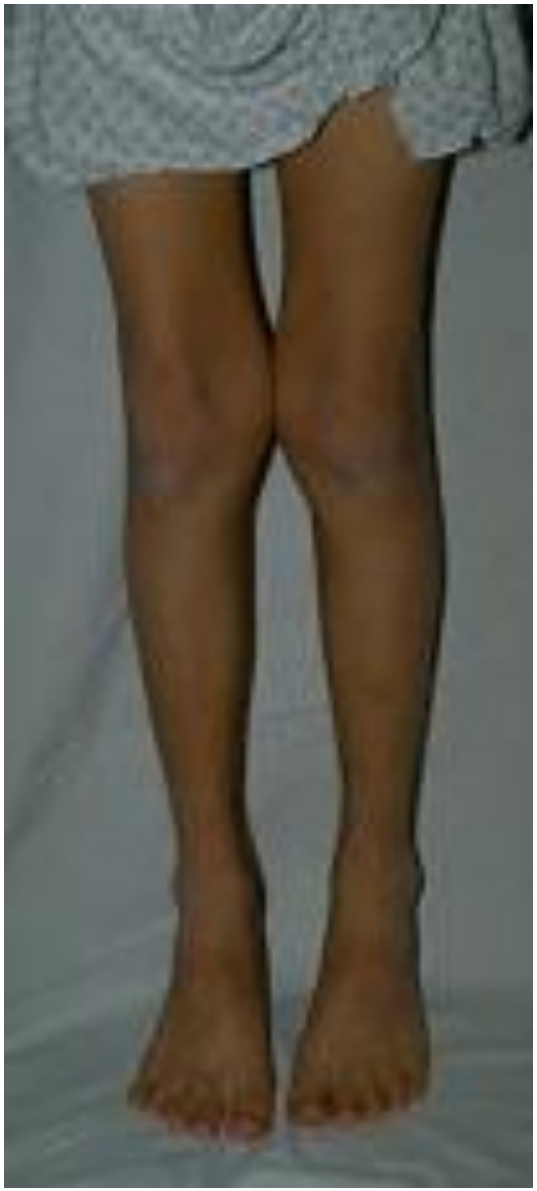
Courtesy of
Dr. Carsten
Bonnemann

Diagnosis?



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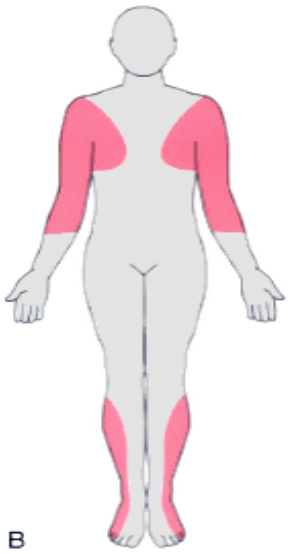
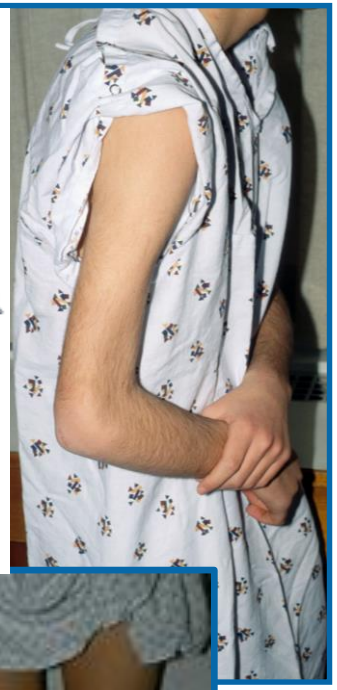
Emery-Dreifuss Muscular Dystrophy





- **Triad:**
  - **Contractures:**
    - **elbows, tendoachilles, spine**
  - **Weakness:**
    - **humeroperoneal pattern/distribution**
  - **Cardiac involvement:**
    - **conduction defects (atrial paralysis, ventricular arrhythmias) and cardiomyopathy**
- **Genetics:**
  - **X-linked and autosomal dominant**

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Diagnosis?

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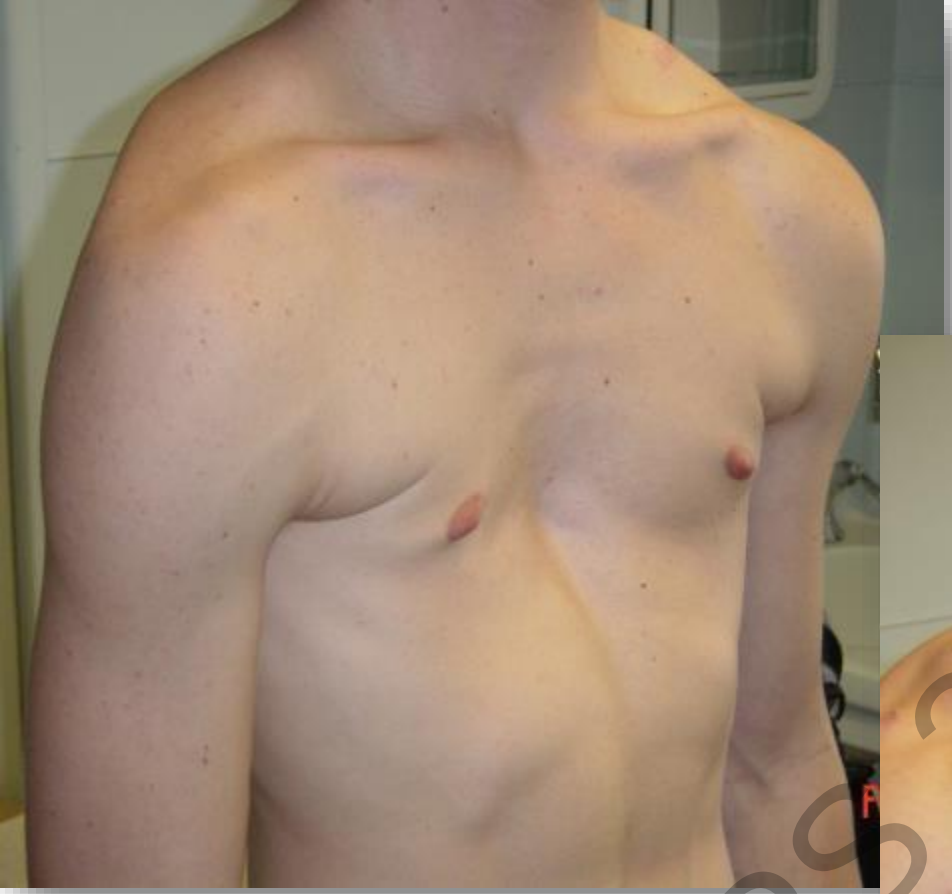

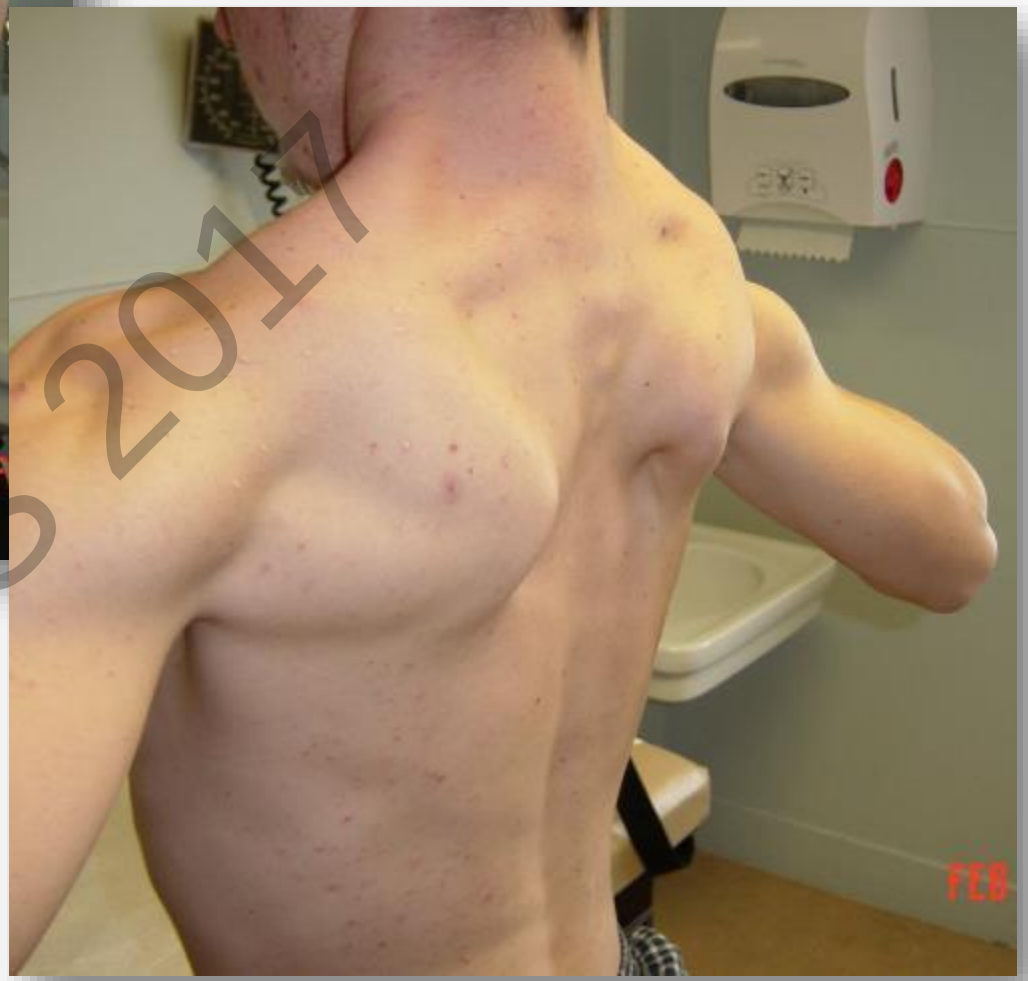

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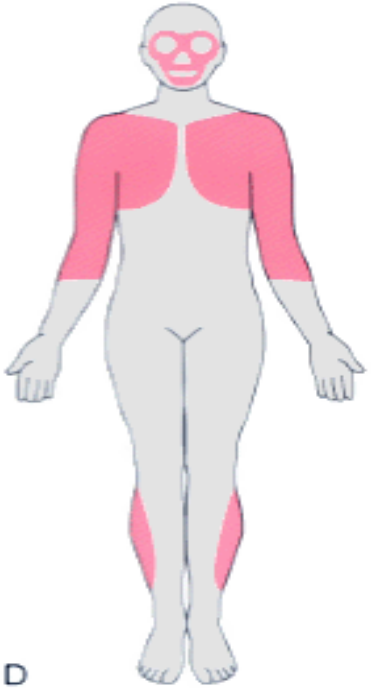
Facioscapulohumeral Muscular Dystrophy

- FSHD is probably the third most common form of muscular dystrophy
- Genetics: partial deletion of a tandem repeat in the subtelomeric region of chromosome 4q .



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Clinical Presentation

- **Age of onset, disease severity and distribution of muscle weakness can be variable both within and between families**
  - **Typically early involvement of facial and scapular muscles, descending to involve biceps, triceps and eventually pelvic girdle muscles.**
  - **The exception to this is the early involvement of the tibialis anterior muscle.**
  - **An asymmetric pattern of muscle involvement is frequent and often striking.**
  - **Bulbar, extraocular, masseter, temporalis and respiratory muscles are usually spared**
- **CK – variable (elevated in about ~50%)**

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Muscular Dystrophy: Classification

X-linked recessive
- Duchenne/Becker muscular dystrophy
- Emery-Dreifuss muscular dystrophy

Autosomal dominant
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- Facio-scapulo-humeral muscular dystrophy

Autosomal recessive
- Limb girdle muscular dystrophy (type 2)
- Congenital muscular dystrophy

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Overview

- Clinically and genetically heterogeneous
- Autosomal recessive inheritance
  - At least 9 genes identified to date
- CK – variable (normal to very high)

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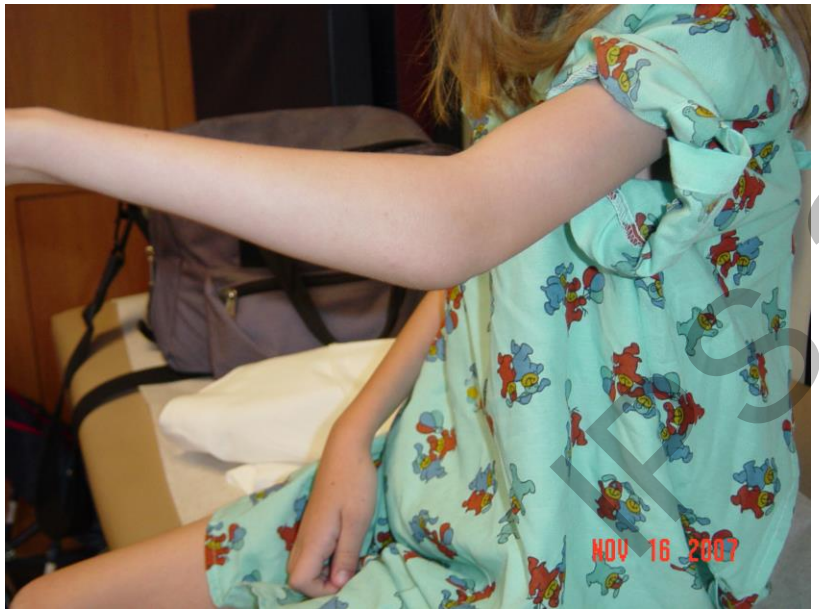
Clinical Presentation



- Typically presents at birth or within first few months of life
- Hypotonia, weakness, hyporeflexia, joint contractures
- May present with delayed motor milestones during infancy

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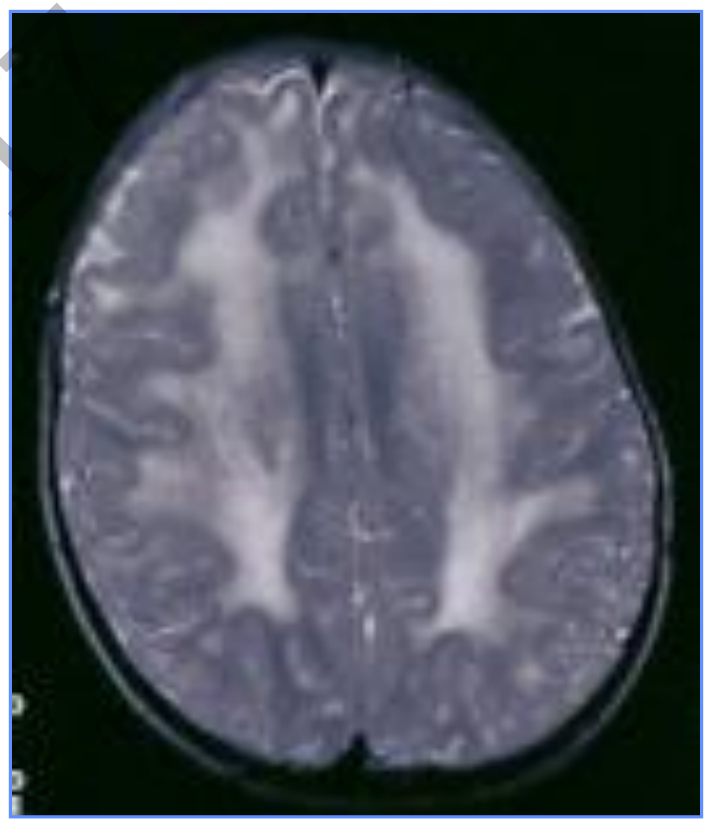
CNS Involvement

- **CNS involvement may occur (CMD +)**
  - **Lissencephaly**
  - **White matter changes**



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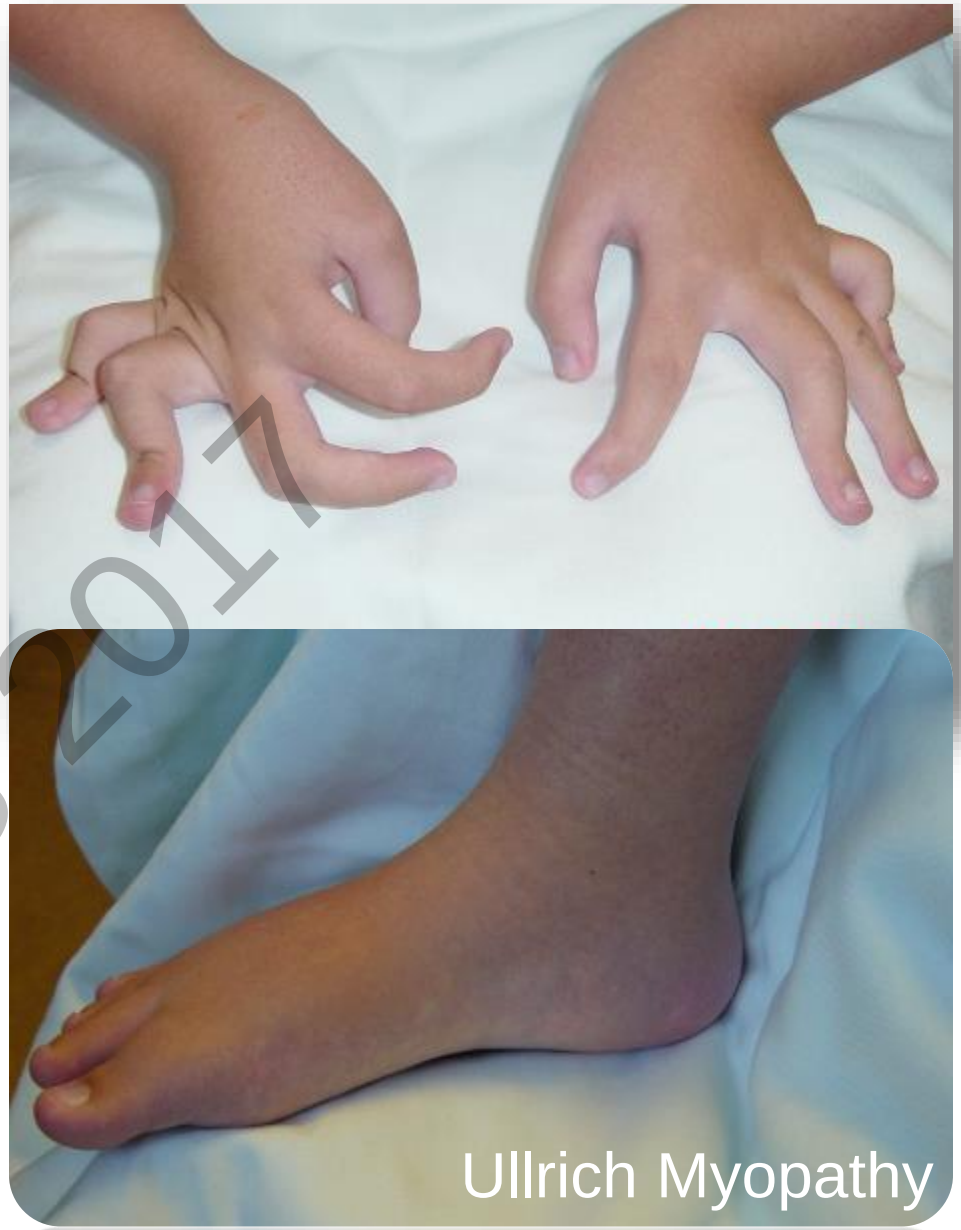

Ullrich Myopathy

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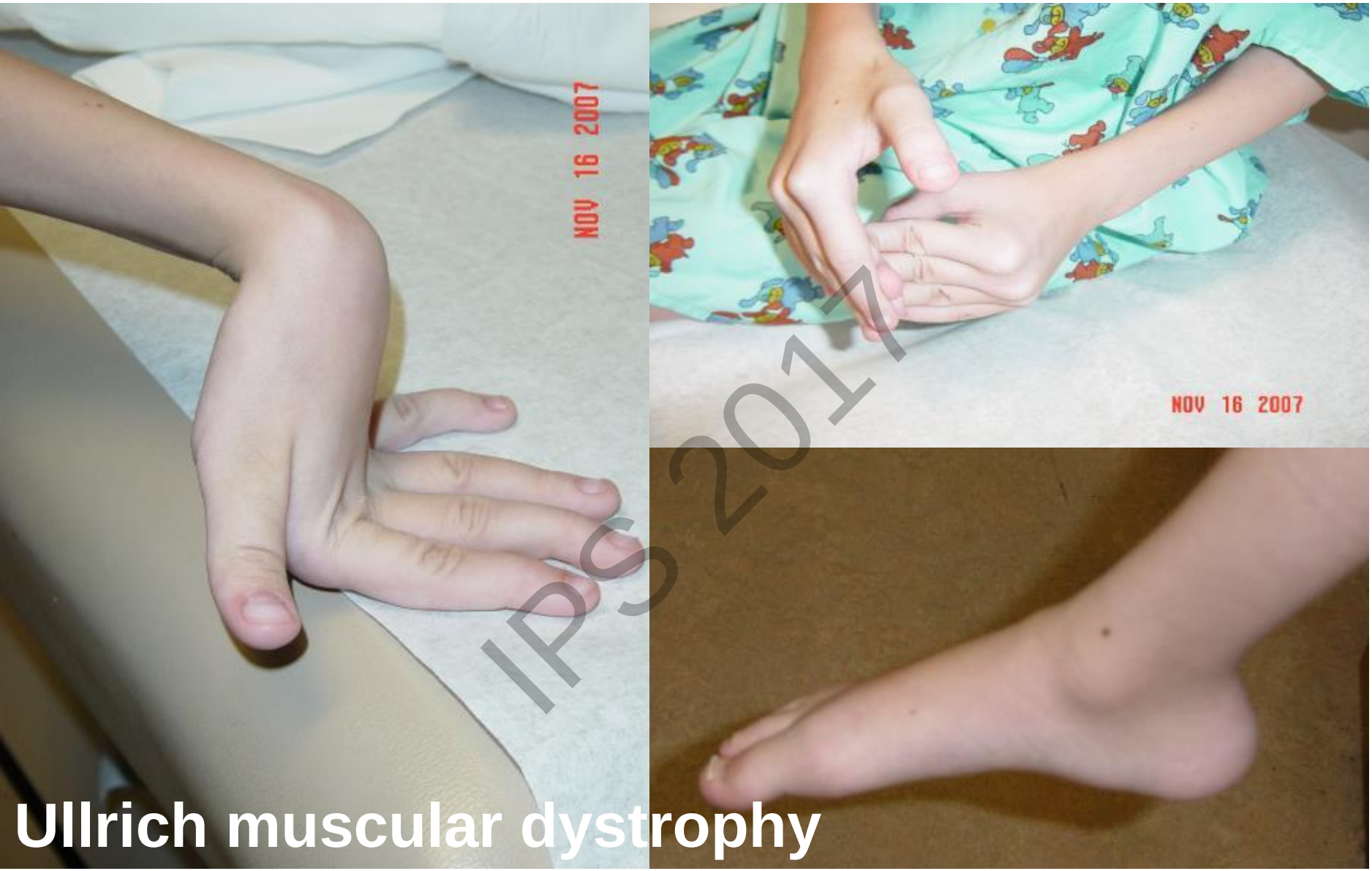

Ullrich muscular dystrophy

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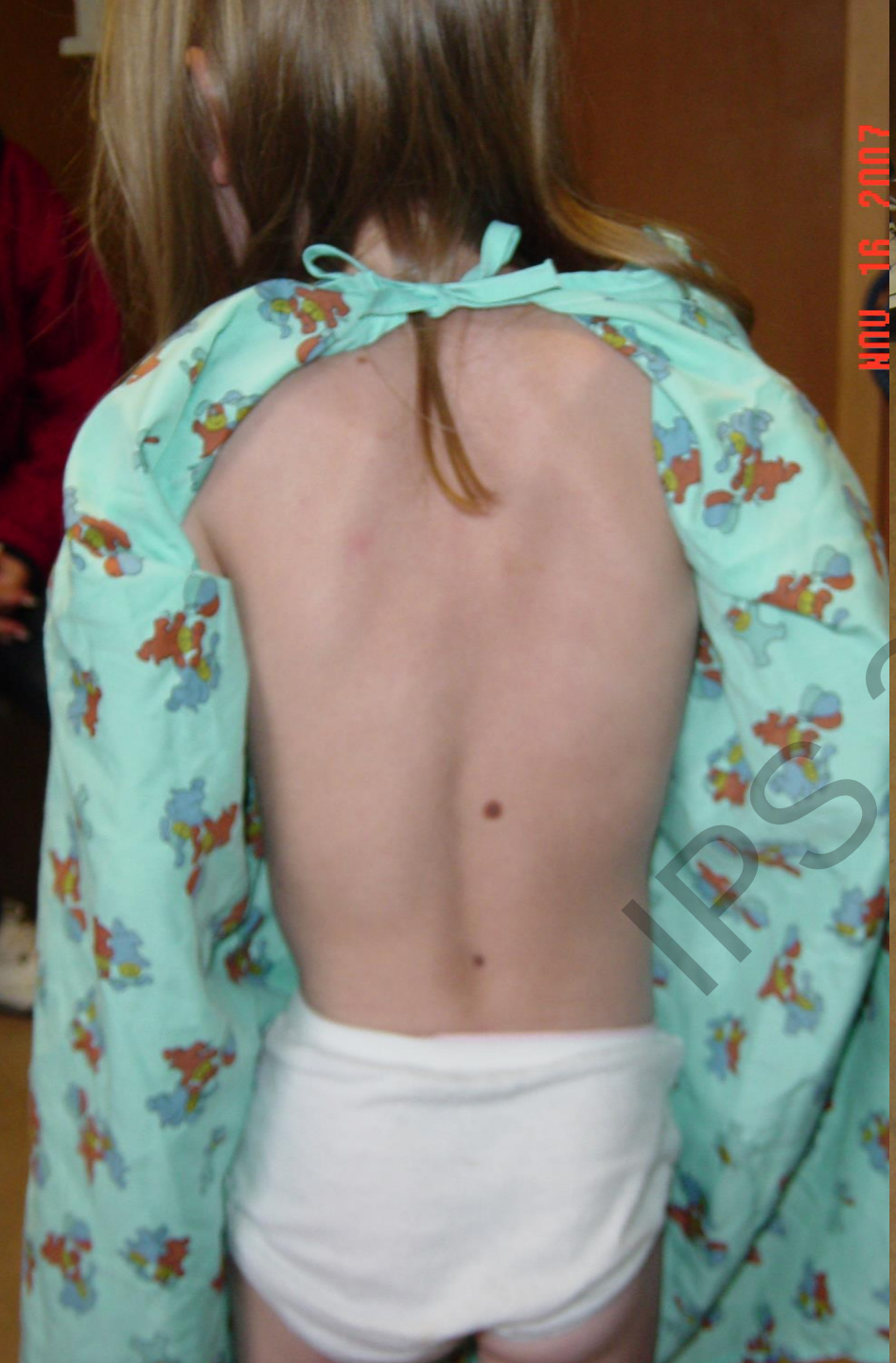

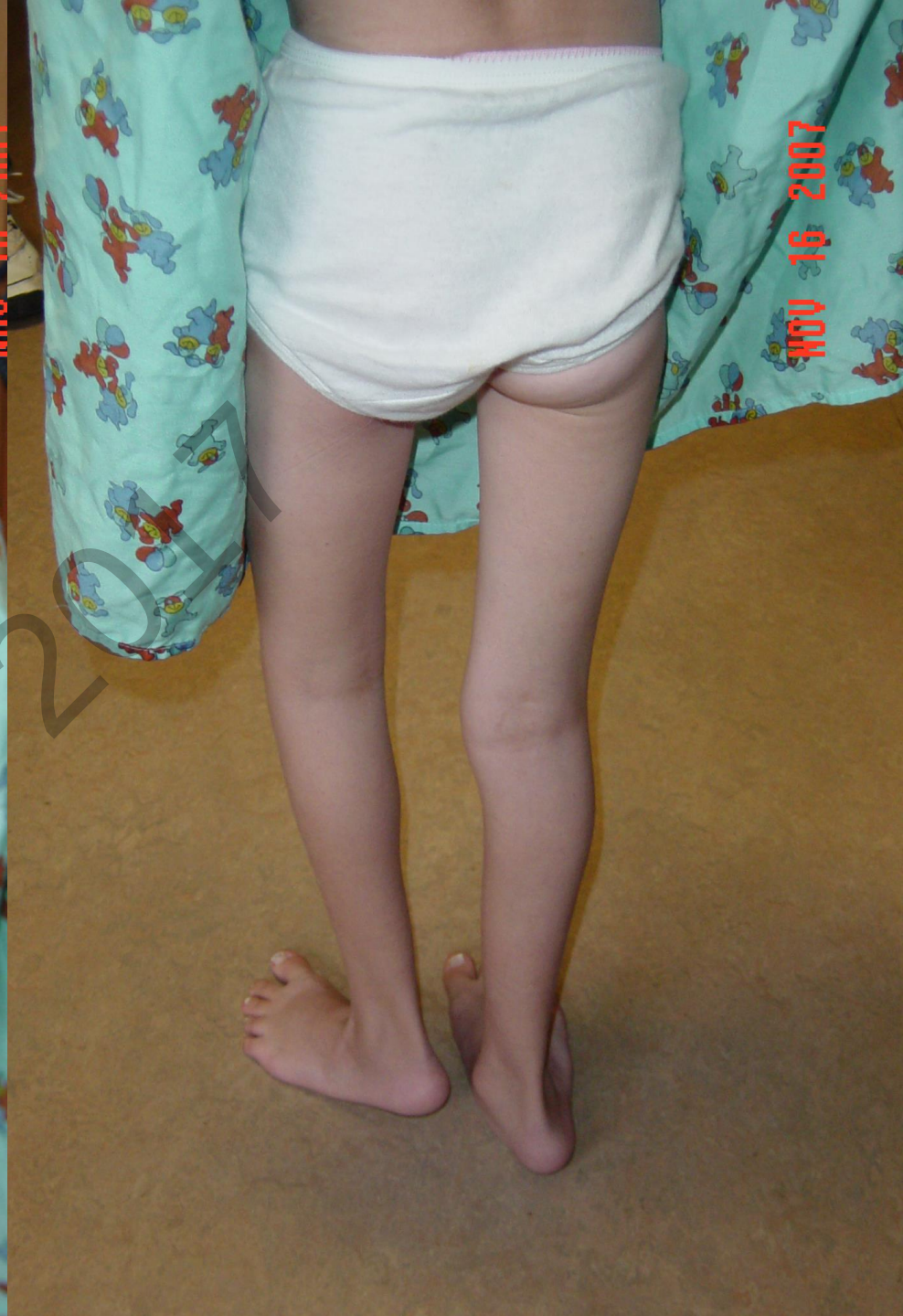

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Cleveland Clinic

Every life deserves world class care.

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