Dysferlinopathies

LGMD2B, Miyoshi & Others

2B Empowered Conference

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Penn State Health

May 24, 2015

Outline

A. Empower you with knowledge about your diagnosis.

B. Explain why the diagnosis may have been hard for your doctors.

1. Dysferlinopathies, what do they look like?
2. What else looks like dysferlinopathies?
3. How common are dysferlinopathies?
4. How do we diagnose dysferlinopathies?
5. Why remain hooked into your doctor?

Dysferlinopathies, what do they look like?

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY.

Evidence-based guideline summary: Diagnosis and treatment of limb-girdle and distal dystrophies

Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine

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Michael Weiss, MD, FAAN
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ABSTRACT

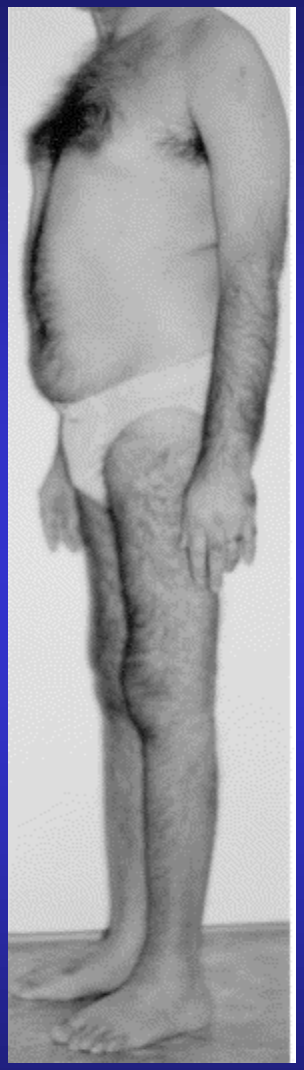
Objective: To review the current evidence and make practice recommendations regarding the diagnosis and treatment of limb-girdle muscular dystrophies (LGMDs).

Methods: Systematic review and practice recommendation development using the American Academy of Neurology guideline development process.

Results: Most LGMDs are rare, with estimated prevalences ranging from 0.07 per 100,000 to 0.43 per 100,000. The frequency of some muscular dystrophies varies based on the ethnic background of the population studied. Some LGMD subtypes have distinguishing features, including pattern of muscle involvement, cardiac abnormalities, extramuscular involvement, and muscle biopsy findings. The few published therapeutic trials were not designed to establish clinical efficacy of any treatment.

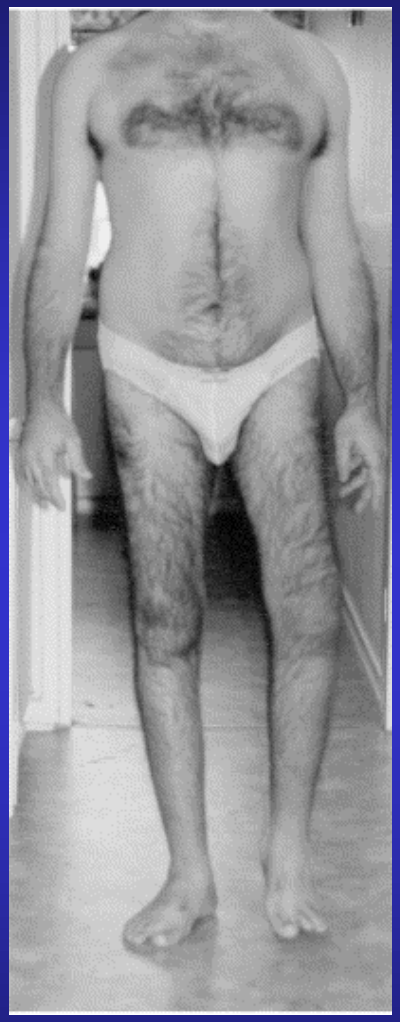
Principal recommendations: For patients with suspected muscular dystrophy, clinicians should use a clinical approach to guide genetic diagnosis based on clinical phenotype, inheritance pattern, and associated manifestations (Level B). Clinicians should refer newly diagnosed patients with an LGMD subtype and high risk of cardiac complications for cardiology evaluation even if they are asymptomatic from a cardiac standpoint (Level B). In patients with LGMD with a known high risk of respiratory failure, clinicians should obtain periodic pulmonary function testing (Level B). Clinicians should refer patients with muscular dystrophy to a clinic that has access to multiple specialties designed specifically to care for patients with neuromuscular disorders (Level B). Clinicians should not offer patients with LGMD gene therapy, myoblast transplantation, neutralizing antibody to myostatin, or growth hormone outside of a research study designed to determine efficacy and safety of the treatment (Level R). Detailed results and recommendations are available on the *Neurology*® Web site at Neurology.org. ***Neurology*® 2014;83:1453–1463**

Dysferlinopathy



- Phenotype (What are the physical characteristics?)
  - Limb girdle pattern (143/293 cases)
  - Also ***distal myopathies***: (150/293 cases)
    - Miyoshi myopathy (gastrosoleus complex)
    - Distal anterior compartment myopathy (tib ant)
  - Scapuloperoneal or proximodistal pattern
  - Biceps atrophy
  - Bent spine syndrome
  - Carriers may be symptomatic
- Identical genetic mutations may present with different phenotypes
  - Even within the same family

Mahjneh et al
Neuromusc Disord 2001;11:20-26



Dysferlinopathy

- Onset – mean 18-32 yrs (range 0-73 yrs)
- Most have:
  - Some ***distal***, calf weakness
  - Calf atrophy common (inability to stand on toes)
  - Asymmetries (side to side differences)
- No scapular winging, dysphagia, dysarthria, contractures or cardiac dysfunction
- PFTs ↓ over decades
  - Rarely symptomatic

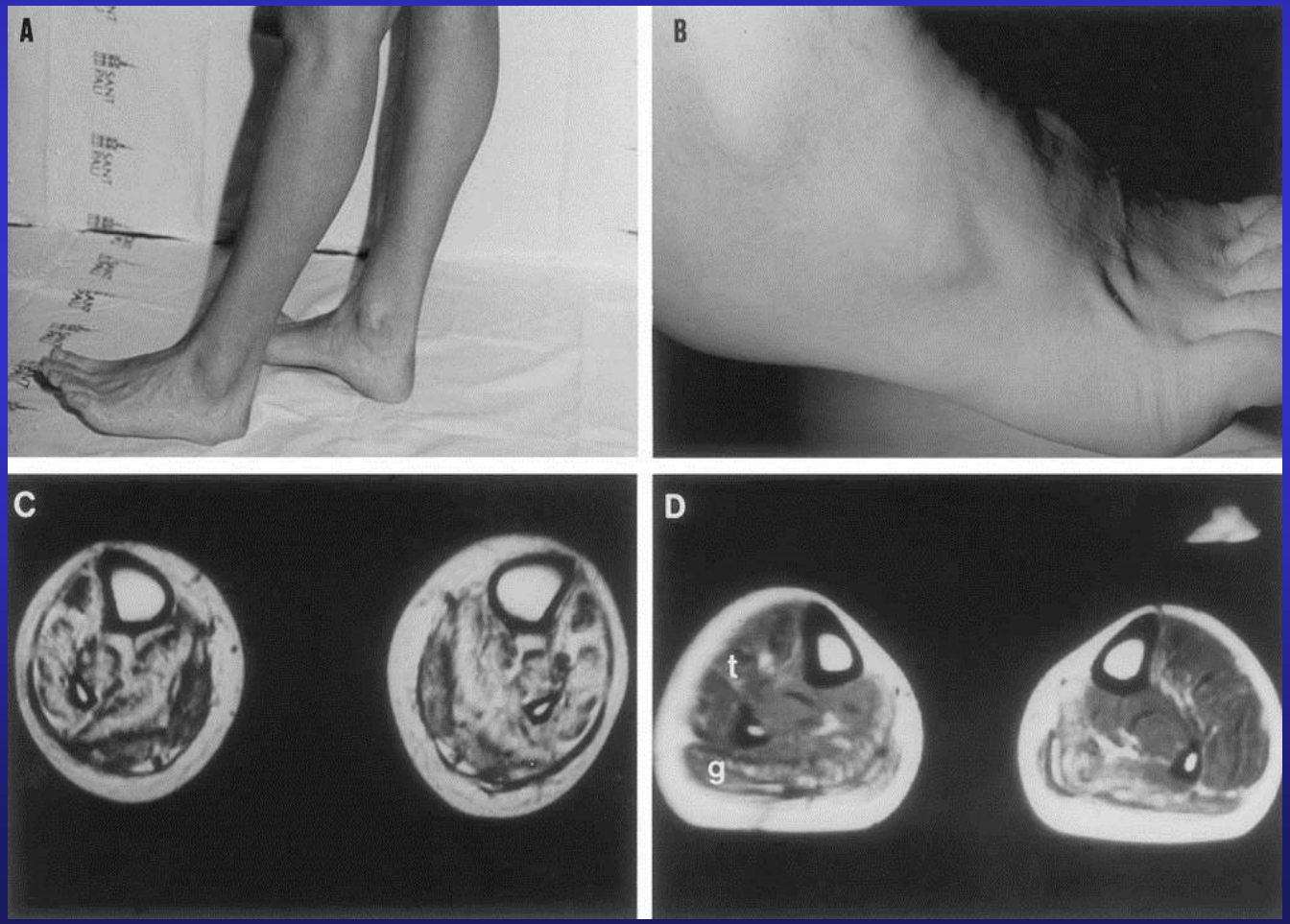
Mahjneh et al
Neuromusc Disord 2001;11:20-26

Dysferlinopathy

- Anterior tibial
  - 13/76 cases

Anterior tibial

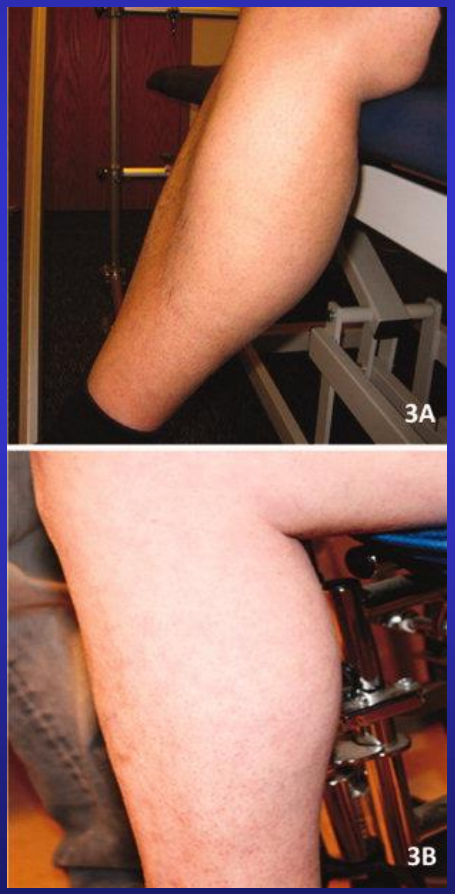
Miyoshi



Illa et al
Ann Neurol 2001;49:130-134

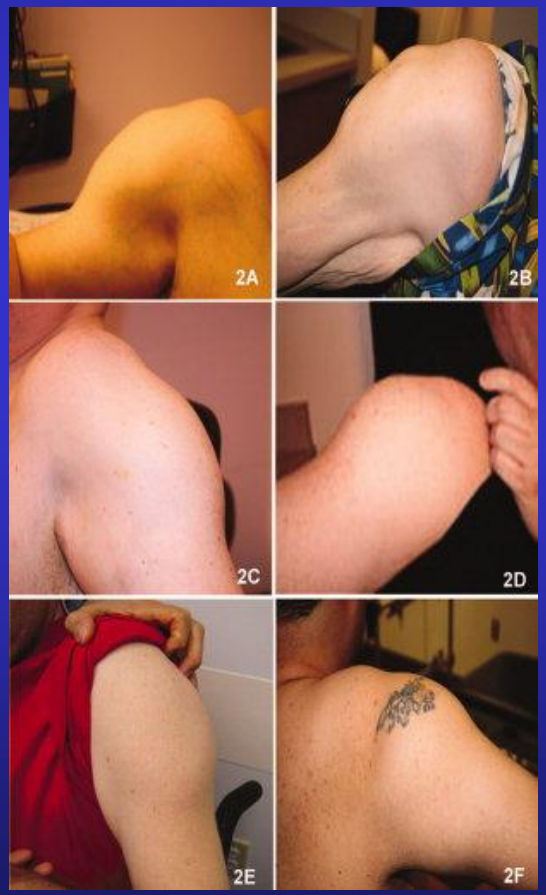
Dysferlinopathy

Calf hypertrophy early in course



Rosales, X
Muscle Nerve 2010;42:14

Prominent deltoids with biceps atrophy

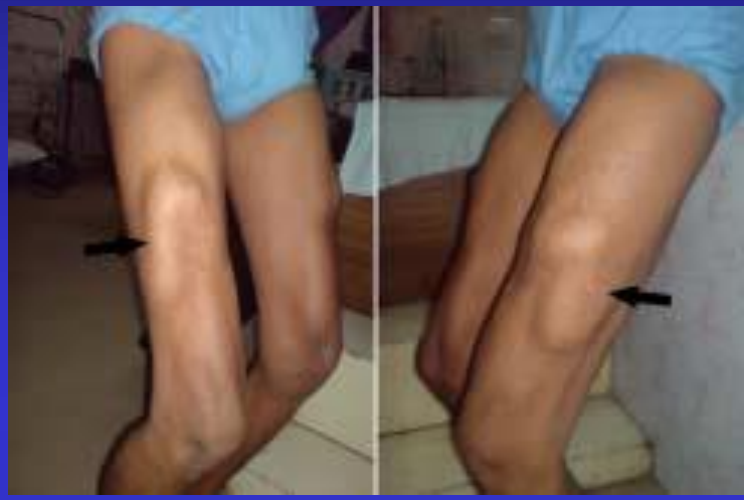


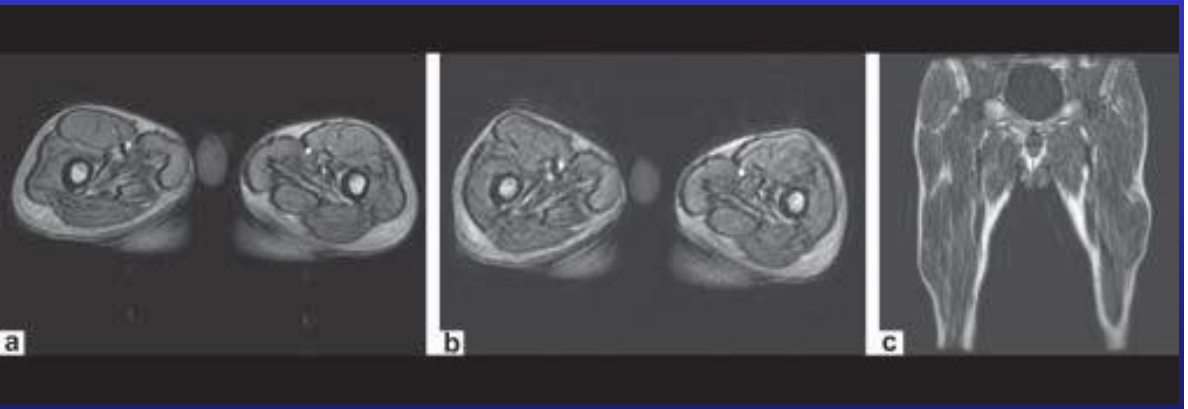
Rosales, X
Muscle Nerve 2010;42:14

Dysferlinopathy

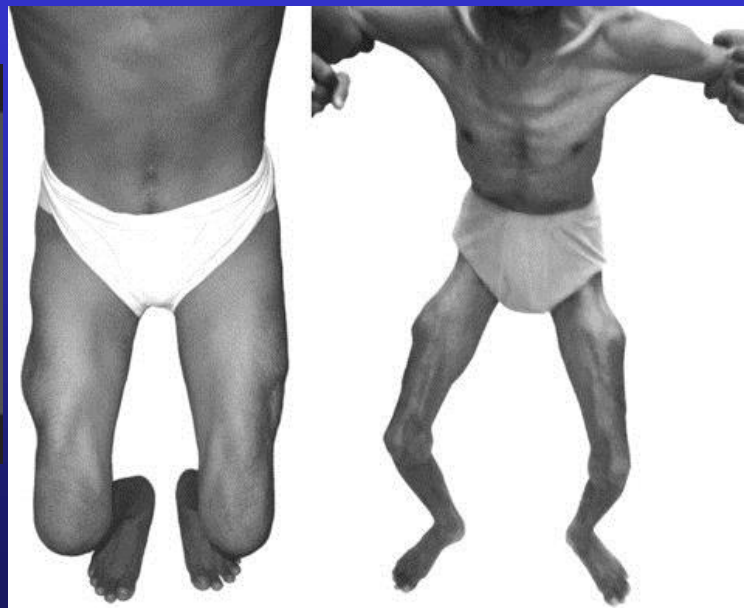
Diamond on Quadriceps Sign

- 21/33 cases



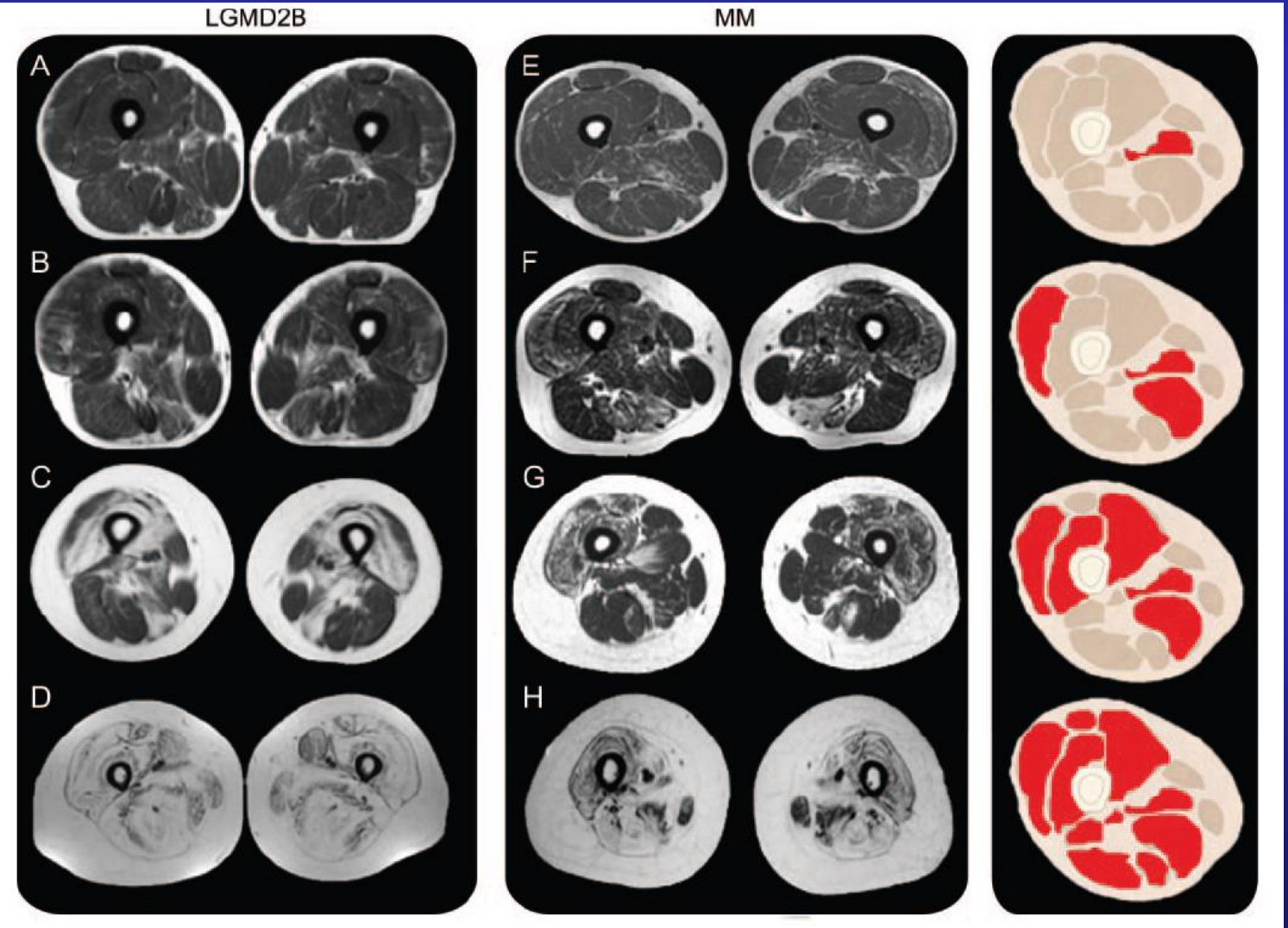


Pradhan, S
Neurology India 2009;57:172



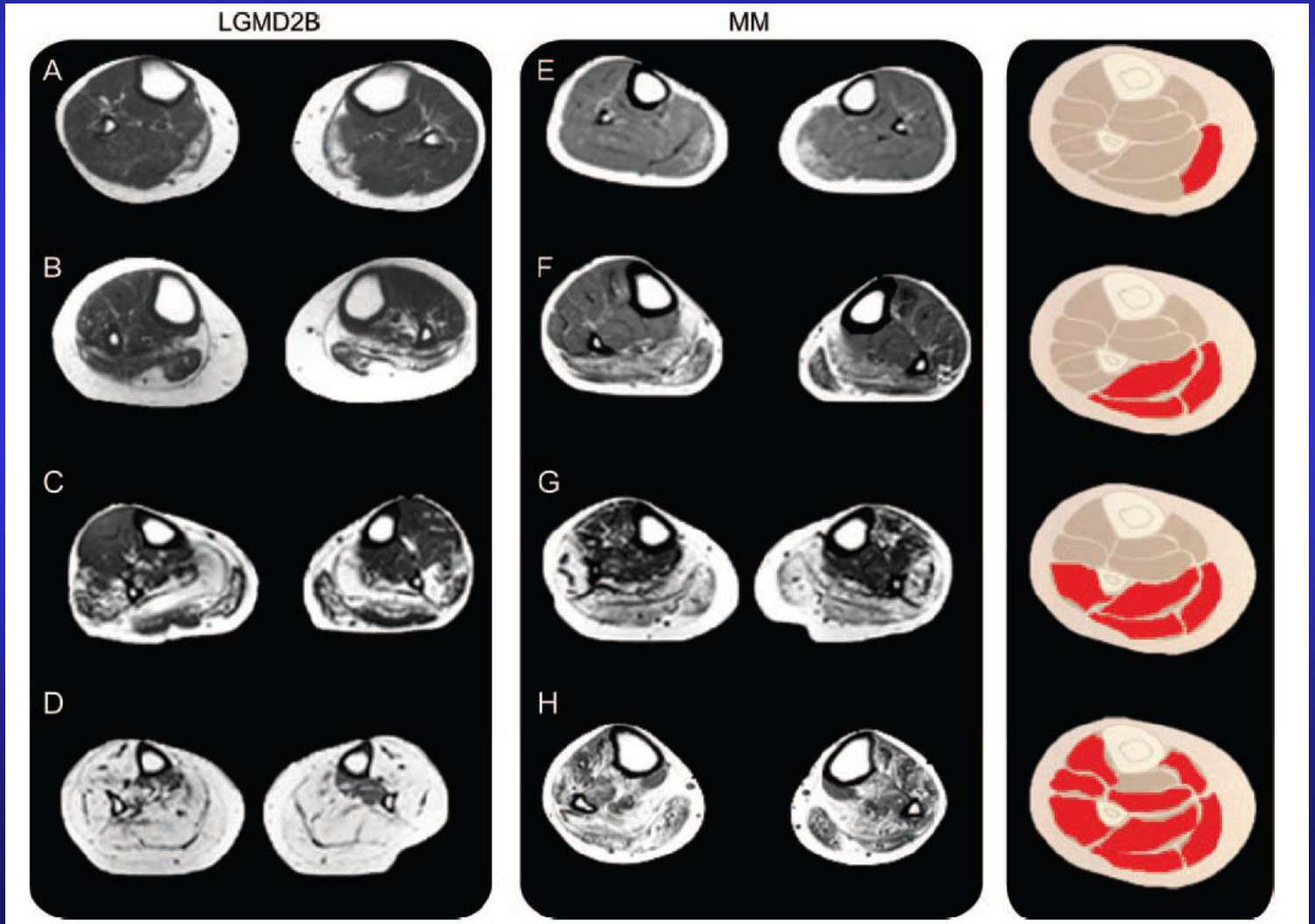
Pradhan, S
Neurology 2008;70:332

Dysferlinopathy



Paradas, C
Neurology 2010;75:316

Dysferlinopathy



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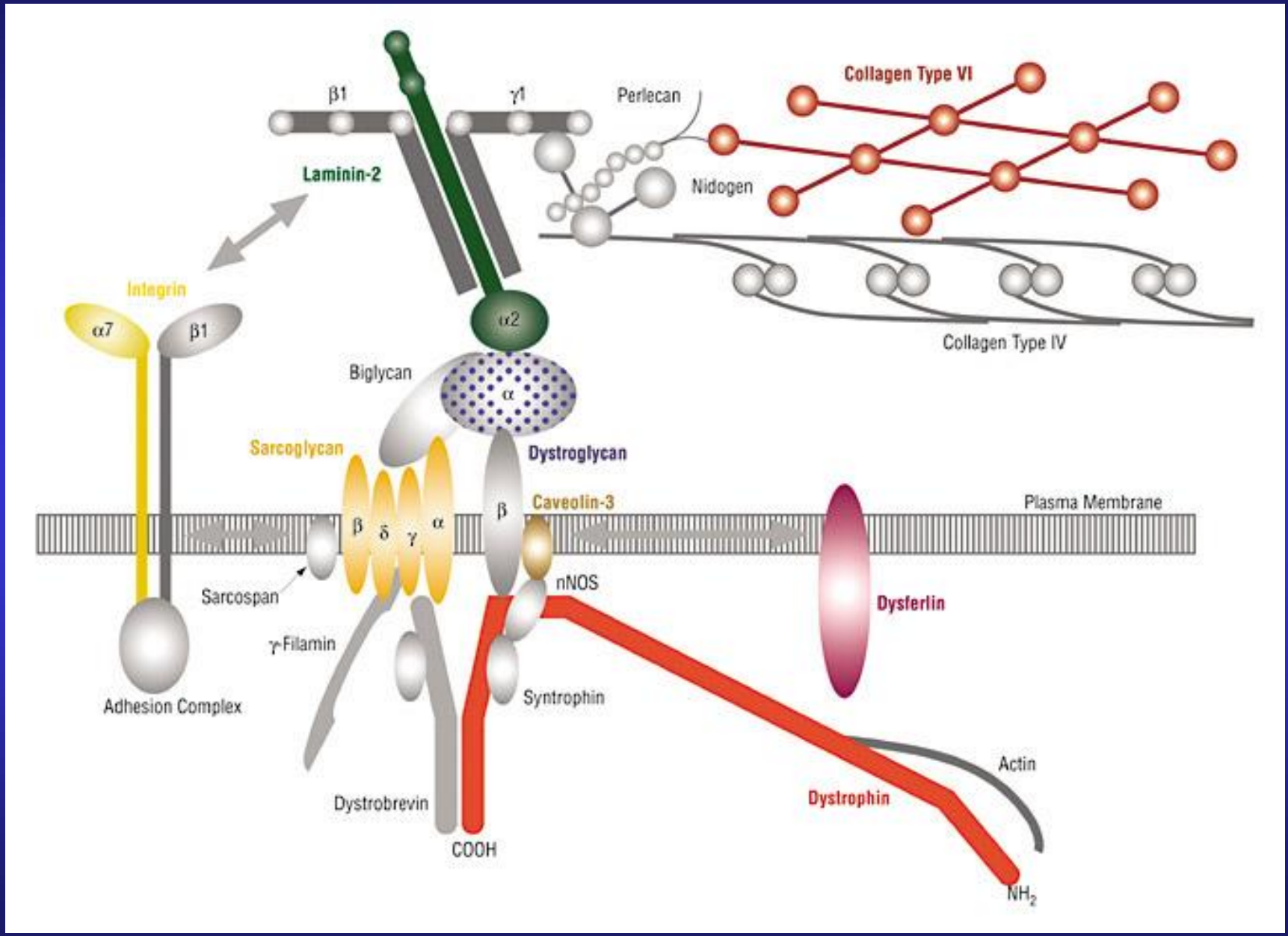
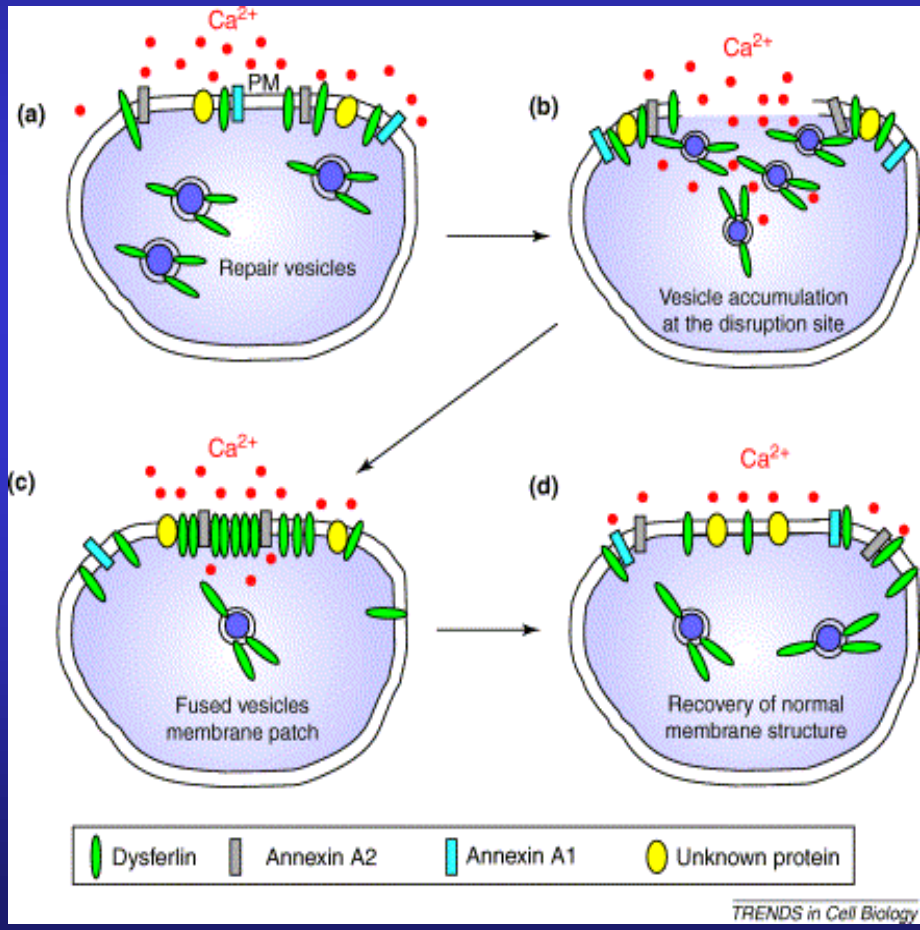

β1
γ1
Laminin-2
Perlecan
Collagen Type VI
Nidogen
Collagen Type IV
Integrin
α7
β1
α2
Biglycan
α
Sarcoglycan
Dystroglycan
β
δ
γ
α
β
Caveolin-3
Plasma Membrane
Sarcospan
nNOS
Dysferlin
γ-Filamin
Adhesion Complex
Syntrophin
Actin
Dystrophin
Dystrobrevin
COOH
NH2

Dysferlinopathy

- Mechanism of action
  - Dysferlin-associated membrane repair
  - Mitochondrial health
  - Stabilizes stress-induced Ca^{2+} signaling in the T-tubule membrane
    - Diltiazem ↓ muscle fiber inflammation & injury

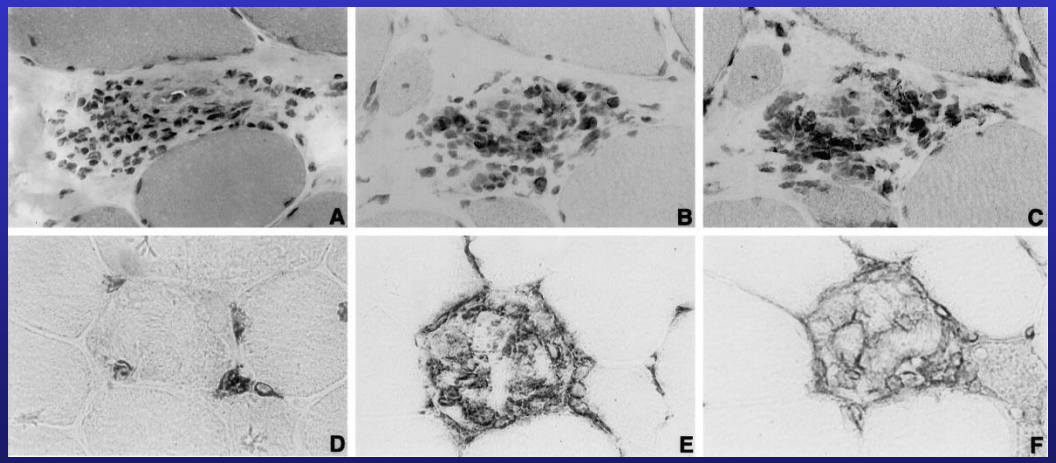


Bansal and Campbell
Trends Cell Biol 2004;14:206-13

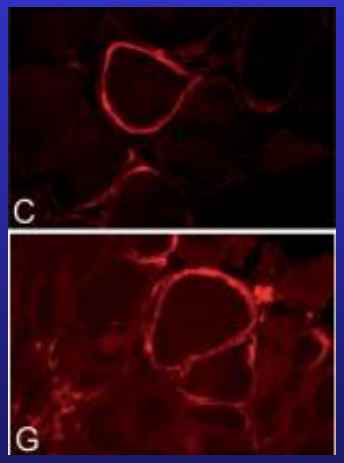
Dysferlinopathy

- CK may be markedly elevated
  - Mean = 3800 U/L
    (generally 1,000-30,000 U/L)

- Biopsies:
  - ***Inflammation*** (common)
    - Treatment refractory polymyositis
    - Deflazacort not effective
  - Amyloid (20-30%)



Gallardo, E
Neurology 2001;57:2136

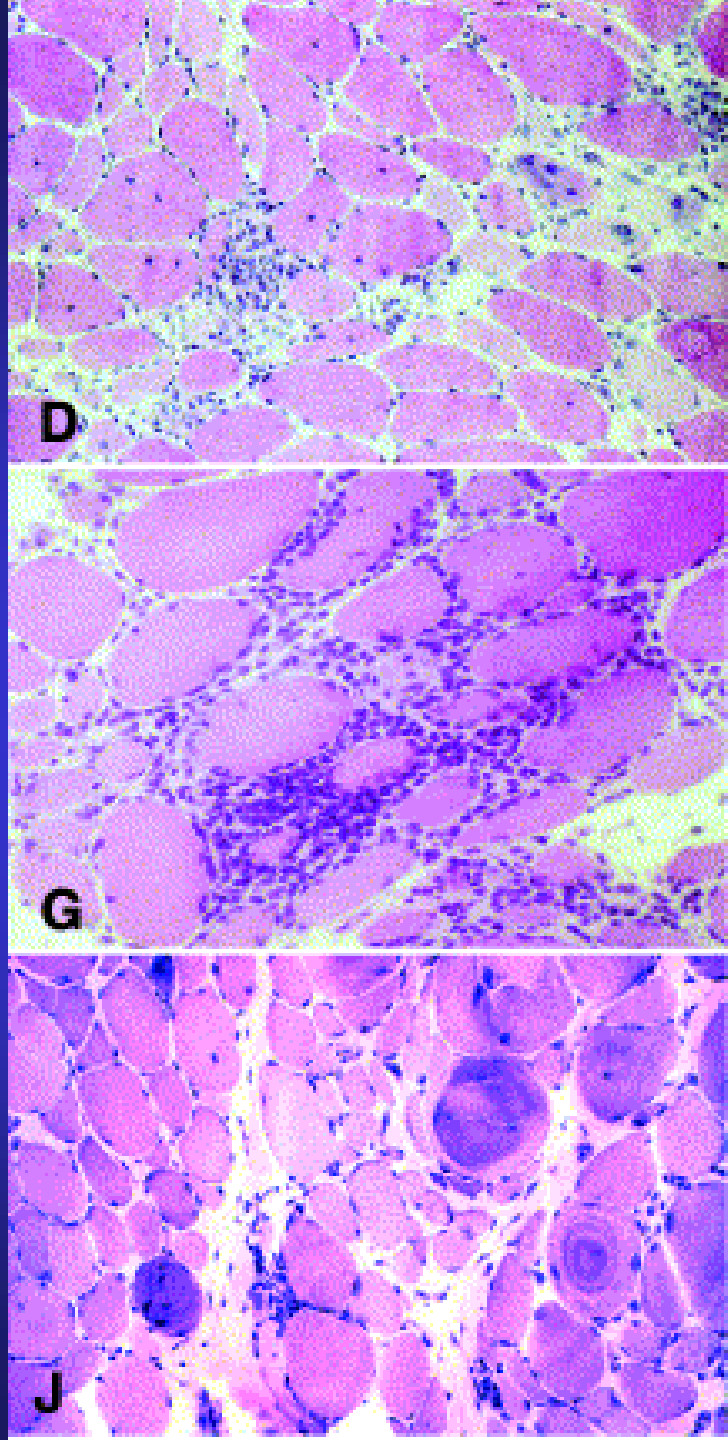


Spuler, S
Ann Neurol 2008;63:323

Dysferlin

Polymyositis

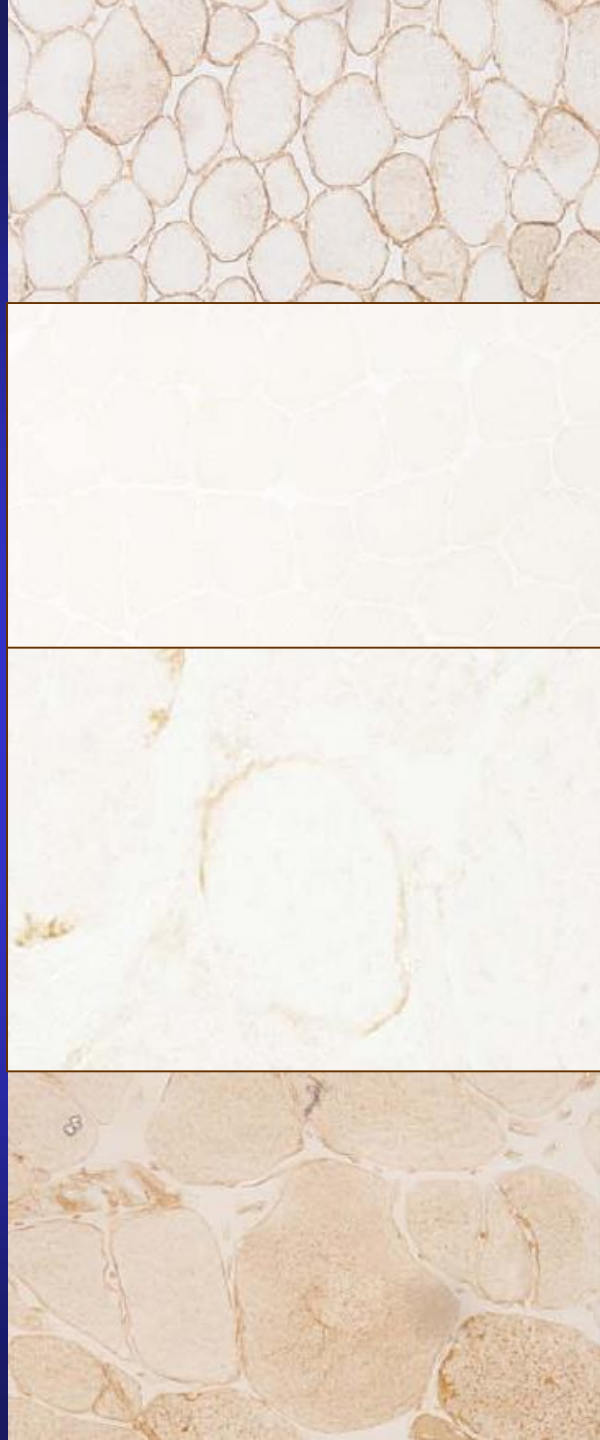
Duchenne Muscular Dystrophy



Dysferlinopathy

- Immunostaining variable in dysferlinopathies
  - Absent
  - Diminished sarcolemmal
  - Sarcoplasmic accumulation

- Abnormal staining in other muscle disorders also



Dysferlinopathy

- Diagnosis
  - Western blot on muscle or monocytes
- Best to use genetic testing
  - Gene sequencing
  - Next generation gene panel
  - Exome/genome sequencing

What else looks like dysferlinopathies?

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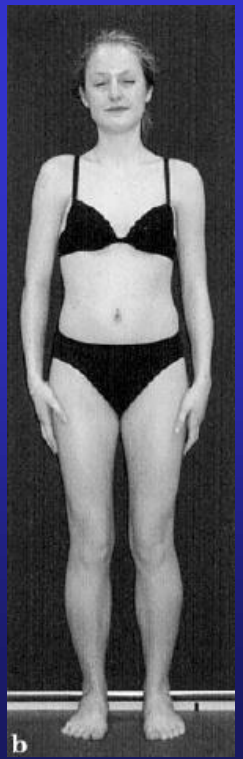
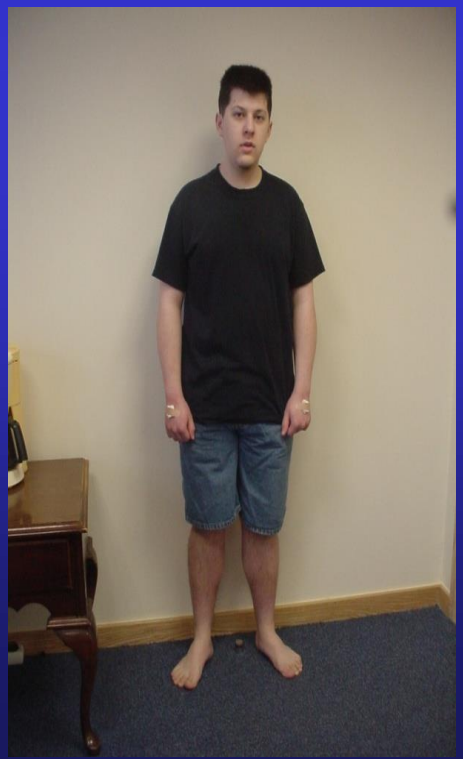
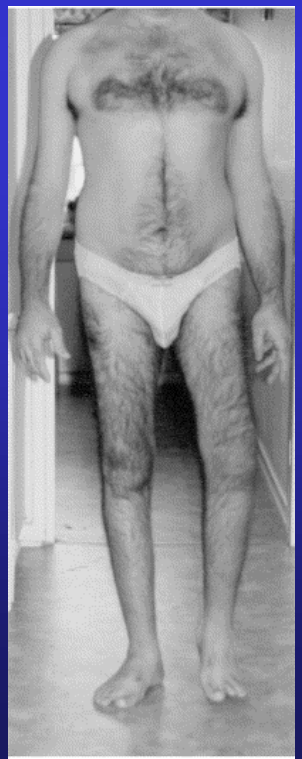
DISEASE	LINKAGE	GENE	GENE PRODUCT
LGMD1A	5q22.3-31.3	*MYOT*	Myotilin
LGMD1B	1q11-21	*LMNA*	Lamin A/C
LGMD1C	3p25	*CAV3*	Caveolin-3
LGMD1D	7q36	*DNAJB6*	Molecular chaperone protein
LGMD1E	2q35	*DES*	Desmin
LGMD1F	7q32.1-32.2	*TNPO3*	Transportin 3
LGMD1G	4p21	*HNRPDL*	RNA-processing protein
LGMD1H	3p23-p25.1		Unknown
LGMD2A	15q15.1-21.1	*CAPN3*	Calpain-3
LGMD2B	**2p13**	***DYSF***	**Dysferlin**
LGMD2C	13q12	*SGCG*	γ-sarcoglycan
LGMD2D	17q12-21.33	*SGCA*	α-sarcoglycan
LGMD2E	4q12	*SGCB*	β-sarcoglycan
LGMD2F	5q33-34	*SGCD*	δ-sarcoglycan
LGMD2G	17q11-12	*TCAP*	Telethonin
LGMD2H	9q31-33	*TRIM32*	E3-ubiquitin-ligase
LGMD2I	19q13	*FKRP*	Fukutin Related Protein
LGMD2J	2q31	*TTN*	Titin
LGMD2K	9q34.1	*POMT1*	O-mannosyltransferase-1
LGMD2L	11p13-p12	*ANO5*	Anoctamin 5
LGMD2M	9q31	*FCMD*	Fukutin
LGMD2N	14q24	*POMT2*	O-mannosyltransferase-2
LGMD2O	19q13	*POMGnT21*	O-mannose-β1,2-N-acetylglucosaminytranferase-1
LGMD2P	3p21	*DAG1*	α-dystroglycan
LGMD2Q	8q24	*PLEC1*	Plectin 1f
LGMD2R	2q35	*DES*	Desmin
LGMD2S	4q35.1	*TRAPPC11*	Transport protein particle complex, subunit 11

Limb Girdle, Distal, or what?

- 19 autosomal recessive LGMDs
- 8 autosomal dominant LGMDs

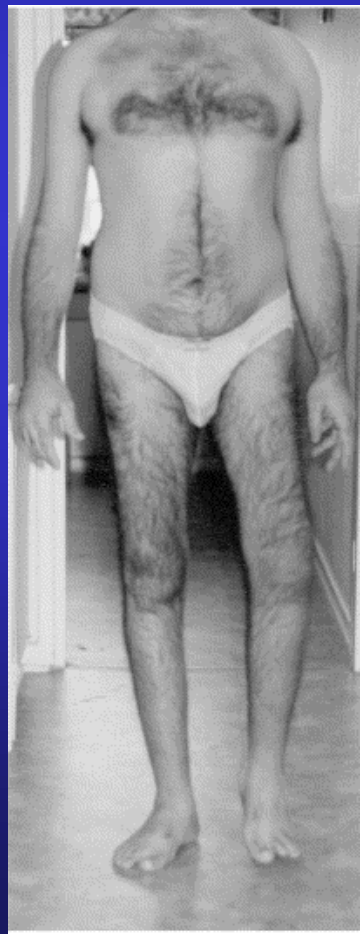







Limb Girdle, Distal, or what?

- 19 autosomal recessive LGMDs
- 6 autosomal dominant LGMDs
- 9 distal myopathies



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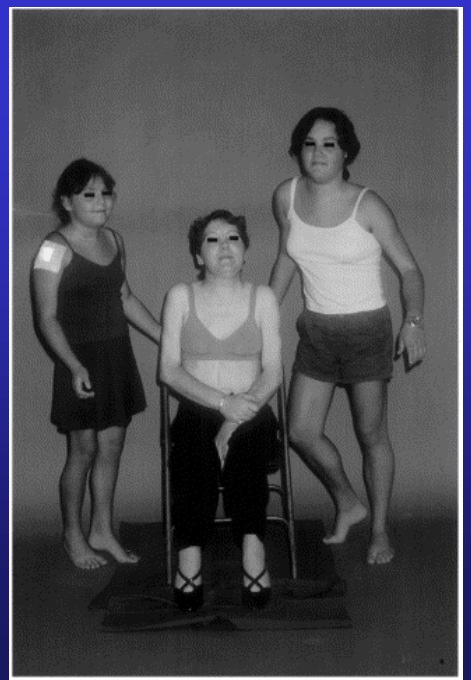
- 6 Emery Dreifuss muscular dystrophies



Limb Girdle, Distal, or what?

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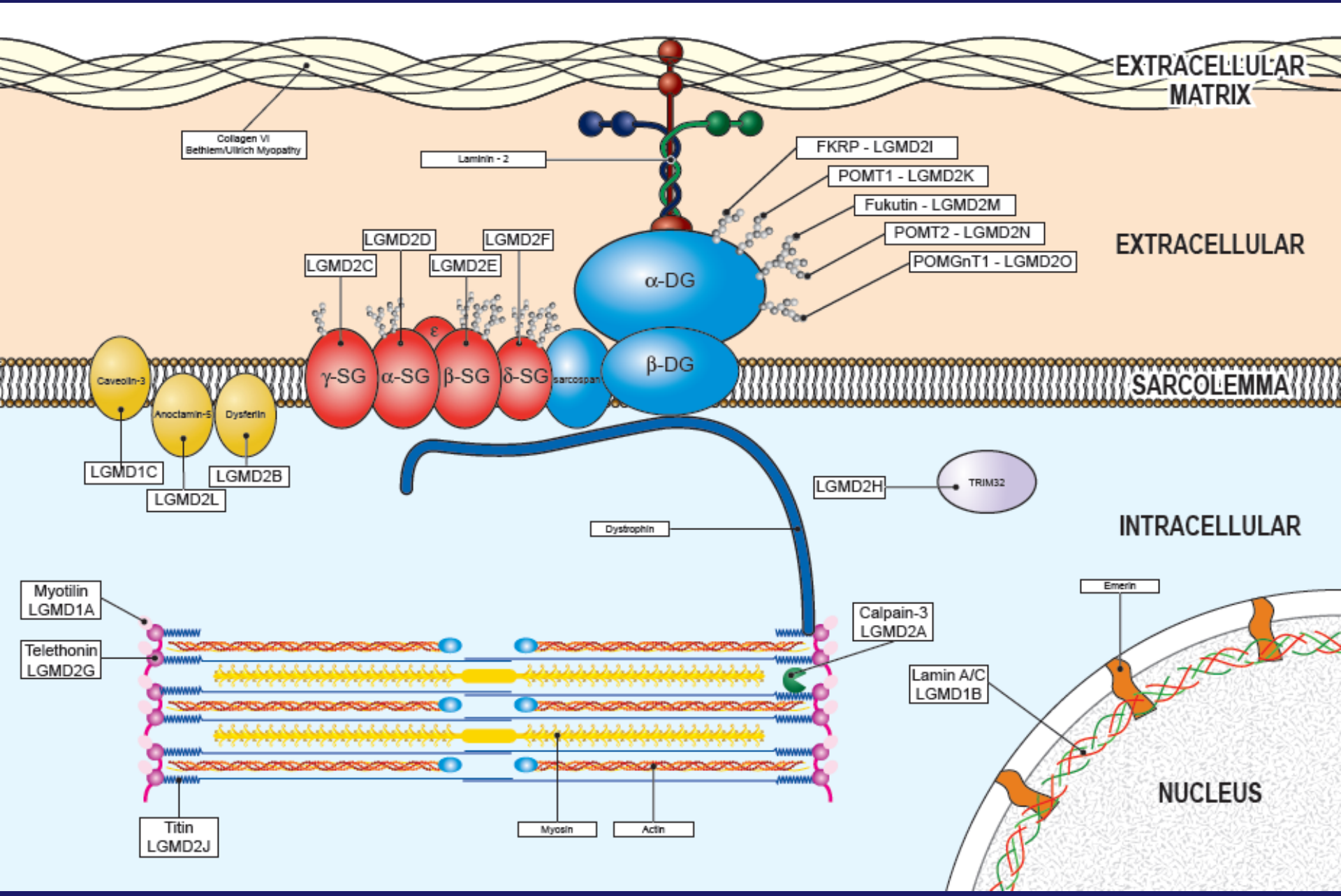
- 6 autosomal dominant LGMDs
- 9 distal myopathies
- 6 Emery Dreifuss muscular dystrophies
- 7 myofibrillar myopathies

Nearly 50 genes in total


EXTRACELLULAR MATRIX
Collagen VI
Bethlem/Ullrich Myopathy
Laminin - 2
FKRP - LGMD2I
POMT1 - LGMD2K
Fukutin - LGMD2M
POMT2 - LGMD2N
POMGnT1 - LGMD2O
EXTRACELLULAR
LGMD2D
LGMD2F
LGMD2C
LGMD2E
α-DG
β-DG
γ-SG
α-SG
β-SG
δ-SG
ε
sarcospan
Caveolin-3
Anoctamin-5
Dysferlin
SARCOLEMMA
LGMD1C
LGMD2L
LGMD2B
LGMD2H
TRIM32
Dystrophin
INTRACELLULAR
Myotilin
LGMD1A
Telethonin
LGMD2G
Calpain-3
LGMD2A
Emerin
Lamin A/C
LGMD1B
NUCLEUS
Titin
LGMD2J
Myosin
Actin

How common are dysferlinopathies?

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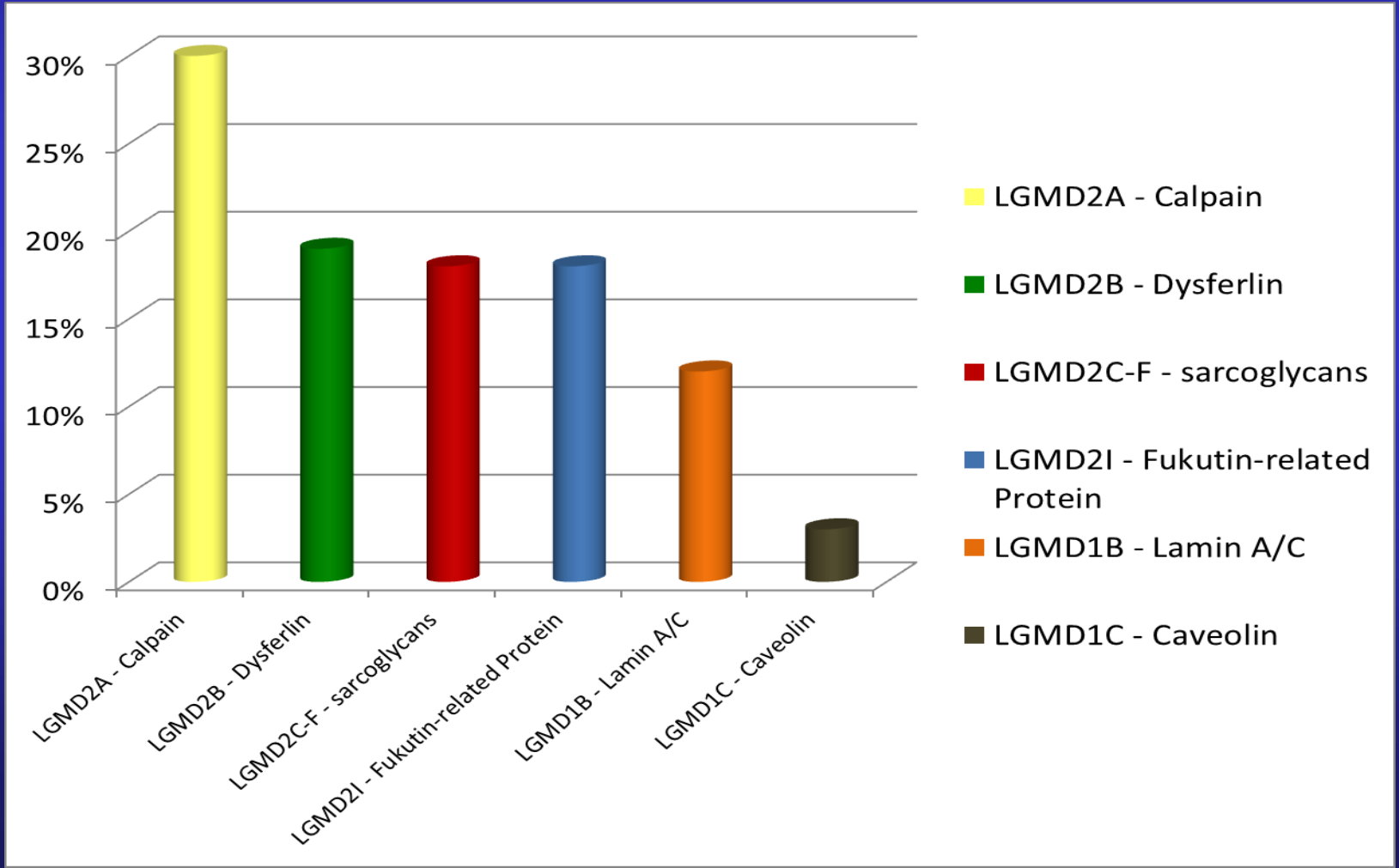
LGMD Regional Variability

- Northern Europe – LGMD 2A, 2I & 2L
- Southern Europe – LGMD 2A
- North Africa – LGMD 2B-F
- Asia – 2B & 2A
- South America – LGMD 2A-F
- North America – LGMD 1B & 2A-F
  - East Coast => LGMD 2A
  - West Coast => LGMD 2B

Relative Prevalence – USA

Dysferlinopathies:

•10-20% (0.6%–33%) of LGMD/distal myopathies



How do we diagnose dysferlinopathies?

JAIN FOUNDATION

Diagnostic Strategies

- If clinically FSHD, DM1 or OPMD => genetic testing
- If “limb-girdle” pattern of weakness
  - Use phenotype, PH, FH, CK & EMG => targeted genetic test(s)
    - Jain Foundation web-based “smart” algorithm (ALDA)
- Dystrophin gene testing
  - Including in women
- Pompe disease testing – *free*

Jain Foundation

LGMD Online Patient Diagnostic Tool

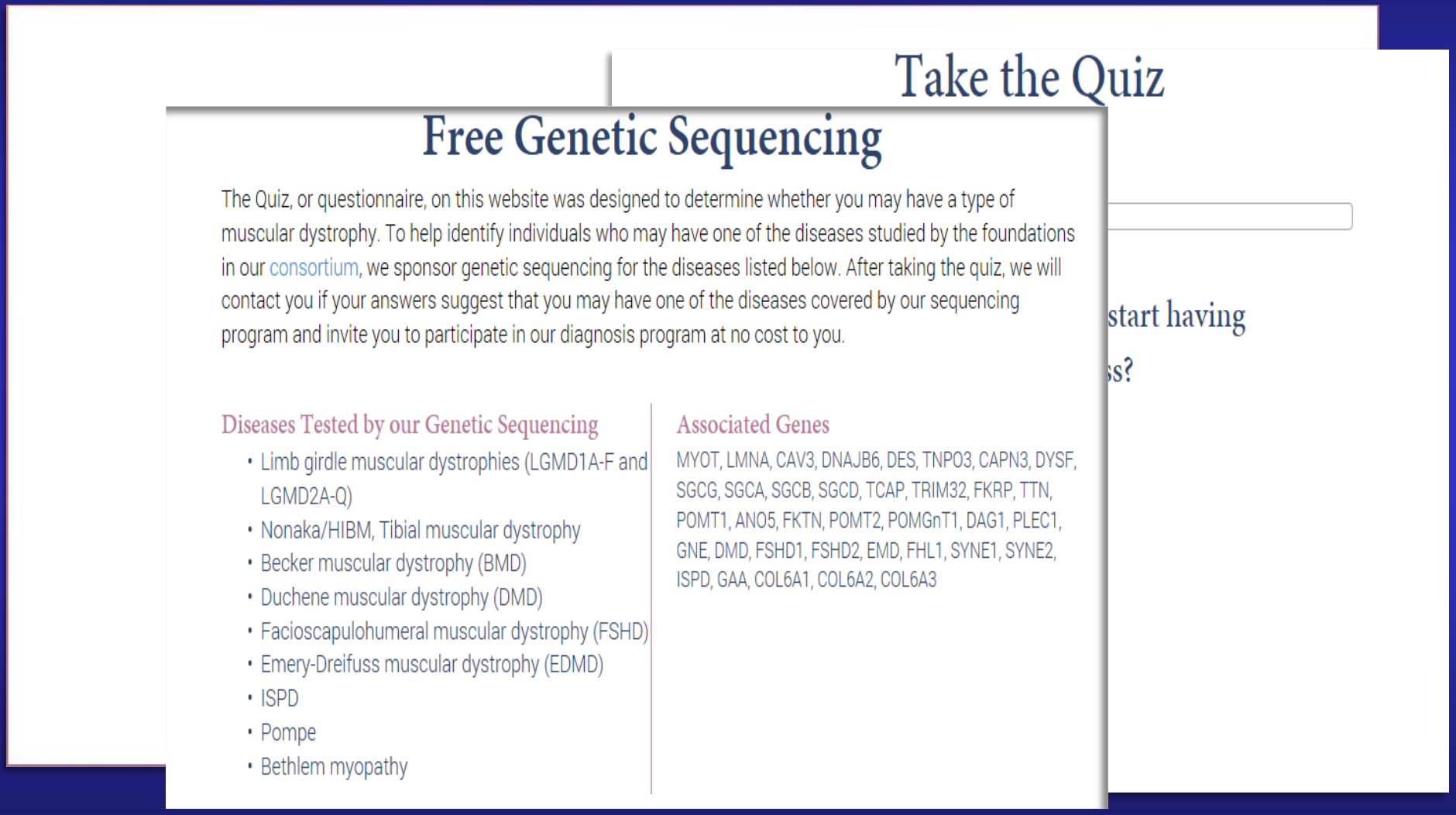


Photo Permission on File: www.jain-foundation.org

Diagnostic Strategies

- Muscle biopsy?
  - Muscle biopsy with immunostains - $7,000-$12,000
  - Or… multiple mutation analyses
    - Commercially available panels (33, 79 & 200+ genes)***
  - Or…
    - Exome sequencing – 3 affected & 3 unaffected family members***
    - Genome sequencing – now raw data available in < 1 week***
      - Cautionary tale…
- “Inverted Diagnosis”

LGMD Genetic Testing

- Jain Foundation in concert with this LGMD consortium now offering same panel of 35 genes to >5,000 LGMD patients registered throughout the USA.
  - An explosion of diagnoses over the upcoming year!
  - Who knows what we'll find???

“Whilst looking down the rabbit hole, all I saw was bunnies. But once my eyes gazed ‘bout the glen, the panoply of species I did see.”

(Old English Fairy Tale)

Why remain hooked into your doctor?

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Methods: Systematic review and practice recommendation development using the American Academy of Neurology guideline development process.

Results: Most LGMDs are rare, with estimated prevalences ranging from 0.07 per 100,000 to 0.43 per 100,000. The frequency of some muscular dystrophies varies based on the ethnic background of the population studied. Some LGMD subtypes have distinguishing features, including pattern of muscle involvement, cardiac abnormalities, extramuscular involvement, and muscle biopsy findings. The few published therapeutic trials were not designed to establish clinical efficacy of any treatment.

Principal recommendations: For patients with suspected muscular dystrophy, clinicians should use a clinical approach to guide genetic diagnosis based on clinical phenotype, inheritance pattern, and associated manifestations (Level B). Clinicians should refer newly diagnosed patients with an LGMD subtype and high risk of cardiac complications for cardiology evaluation even if they are asymptomatic from a cardiac standpoint (Level B). In patients with LGMD with a known high risk of respiratory failure, clinicians should obtain periodic pulmonary function testing (Level B). Clinicians should refer patients with muscular dystrophy to a clinic that has access to multiple specialties designed specifically to care for patients with neuromuscular disorders (Level B). Clinicians should not offer patients with LGMD gene therapy, myoblast transplantation, neutralizing antibody to myostatin, or growth hormone outside of a research study designed to determine efficacy and safety of the treatment (Level R). Detailed results and recommendations are available on the *Neurology*® Web site at Neurology.org.

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Recommendations for Future Research

As the category of LGMDs expands with advances in molecular diagnostics and new disorders are identified, there is need for research in the following areas.

1. **Large prospective, long-term, population-based studies** to establish the prevalence of these disorders, identify the ethnic populations among which they are most prevalent, and evaluate their long-term course, including the incidence of cardiorespiratory complications.
2. **Studies of genotype/phenotype correlation** to establish phenotypic patterns based on genotype, and to describe the phenotypes caused by each genotype.
3. **Optimal management of other organ system involvement** (e.g., frequency and types of screening, effective treatments).
4. Well-designed studies of the **effectiveness of exercise programs, physical therapy, and endurance training**.
5. Studies of treatments, including **symptomatic treatments** such as orthotics for contractures (nonsurgical/surgical) on mobility and quality of life, as well as **disease-modifying treatments** such as gene therapy and stem cell therapy.
6. Preliminary data suggest **corticosteroids** may benefit α-dystroglycanopathies but not dysferlinopathies. These results need replication in larger, controlled studies.

Engagement Empowers

- Encourage diagnosis.
- Engulf education about dysferlinopathies.
- Employ knowledge to optimize quality of life.
- Enable through community efforts.
- Endow all with your enthusiasm.
- Embolden research.
- Envision no dysferlinopathies…

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