HOW TO APPROACH LIMB GIRDLE AND NON-LIMB GIRDLE WEAKNESS

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CONTENT

Clinical approach in NM disease and phenotype

Common and uncommon LGMDs

Common and uncommon non-LGMD

Time dependent changes in phenotype

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- Genotype phenotype correlations

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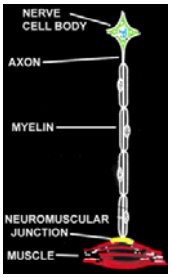
ANATOMIC LOCI OF NM DISEASE



CLINICAL HISTORY IN NEUROMUSCULAR DISEASES

- **Weakness**
  - Anatomic distribution / pattern of weakness
  - Focal wasting or hypertrophy of muscle groups (arms versus legs, proximal versus distal, symmetric versus asymmetric).
  - Myopathies have weakness that is usually proximal greater than distal with rare exceptions
- **Course of weakness**
  - Acute onset (days to weeks)
  - Chronic (months to years)
  - Episodic
  - Is the weakness getting worse, staying the same, or getting better?
  - Ascertain the rate of progression (days, weeks, months, or years).

• FUNCTIONAL DIFFICULTIES

- ambulatory distances
- frequency of falls
- transitions from the floor to standing
- problems climbing stairs
- problems dressing
- problems reaching overhead
- difficulty lifting
- running ability, problems in physical education, and recreational or athletic performance

ASSOCIATED FEATURES

- Onset age
  - Neonatal, childhood, teen, adult [20–60 years], or geriatric)
- Identify factors which worsen or help primary symptoms
- History of recent illnesses (e.g. recent viral illnesses, respiratory difficulties, pneumonia, pulmonary infections)
- Pain
- Feeding difficulties, dysphagia, nutritional status, and body composition

- Fatigue or lack of endurance
- Muscle cramps or stiffness
- Lack of sensory loss
- Gait characteristics
  - Toe walking, excessive lordosis, trendelenburg or gluteus maximus, lurch, etc.

SYSTEMIC FEATURES

- Cardiac symptoms (dizziness, syncope, chest pain, orthopnea, cardiac complaints with exertion)
- Pulmonary symptoms (breathing difficulties, sleep disturbance, morning headaches)
- Anesthetic history (e.g. malignant hyperthermia)
- History regarding the child's acquisition of developmental milestones
- History regarding language acquisition, mental development and school performance
- History regarding pregnancy and neonatal period

LGMD- INTRODUCTION

Limb girdle muscular dystrophy (LGMD) is a broad term

Denominator: *chronic progressive weakness of the limb girdles*

The advances in the previous two decades in immunocytochemistry and genetic studies have catapulted the knowledge on this subject

Presently, so many types have been described, that it is difficult for the clinician to decipher the clinical syndrome of LGMDs.

NON-LIMB GIRDLE WEAKNESS

Hereditary	Acquired
Muscular dystrophies	Inclusion body myositis
Distal myopathies	
Congental myopathies	
Myofibrillar myopathies	
Metabolic myopathies	

CLINICAL FEATURES

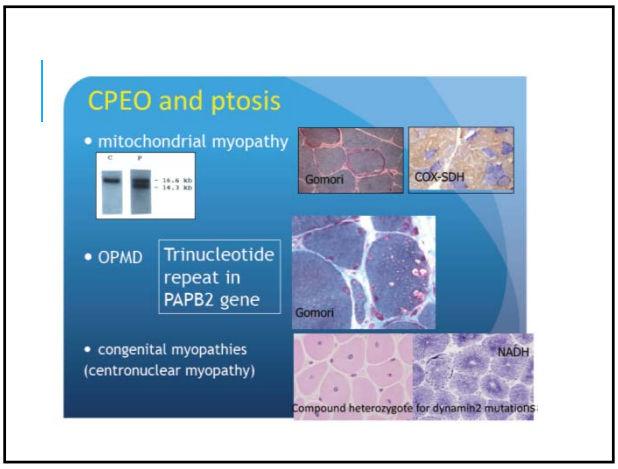
External ophthalmoplegia and or ptosis

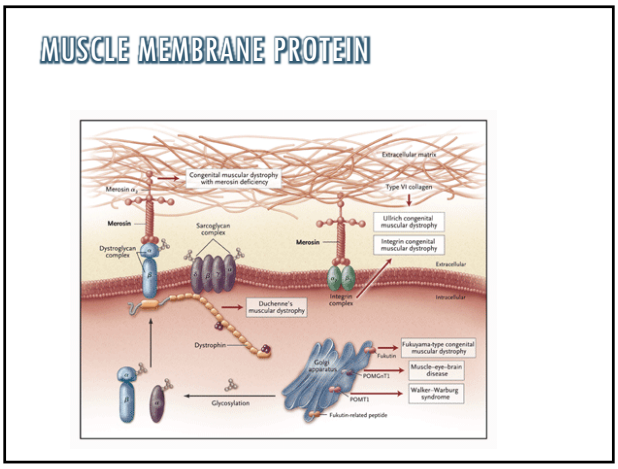
Facial/bulbar involvement

Limb-girdle syndrome

Distal muscle weakness
- Symmetrical or asymmetrical muscle weakness

Floppy infant syndrome





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

AMERICAN ACADEMY OF NEUROLOGY

Background

- The LGMDs are classified into 2 main groups depending on the inheritance pattern:
  - LGMD1, autosomal dominant, and
  - LGMD2, autosomal recessive.
- Appended to this numeric division is a letter designating the order of discovery for each chromosomal locus.[2,3]

AMERICAN ACADEMY OF NEUROLOGY

Clinical Question 1

- **What is the frequency of genetically confirmed LGMD subtypes?**

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Q1. Clinical Context

- Overall, LGMDs are uncommon disorders.[6]
  - The most common adult-onset muscular dystrophies presenting with limb-girdle weakness are
    - BMD (dystrophin),
    - LGMD2A (calpain 3),
    - LGMD2I (fukutin-related protein), and
    - LGMD2L (anoctamin 5)
  - The most common distal myopathy is Miyoshi myopathy (dysferlin and anoctamin 5).
  - Of those, BMD is the most common, with an estimated prevalence of 2.38 to 7.29 per 100,000.[6–10]
  - Most LGMDs are rare, with estimated prevalences ranging from 0.07 (LGMD2D and LGMD2E) to 0.43 (LGMD2I) per 100,000.

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Q2. Clinical Context: Clinical Features

- Features common to most LGMDs:
  - Presentation of slowly progressing symmetrical weakness
  - Age at onset adolescence to early adulthood (can range from early childhood to late adult life)
  - Most common weakness pattern of limb-girdle weakness affecting proximal muscles of the arms and legs
  - *Other patterns include scapuloperoneal weakness and distal weakness*
  - One genotype can present with different phenotypes; one phenotype can result from more than one genotype

Q2. Clinical Context: Distinguishing Features

- Distinguishing features of LGMD disorders include:
  - Early development of foot drop (e.g., myofibrillar myopathies [MFM])
  - Asymmetry in muscle weakness (e.g., LGMD1A, LGMD2L, MFM)
  - Limb contractures (lamin A/C myopathies, Emery–Dreifuss muscular dystrophy [EDMD], *BAG3*)
  - Prominent muscle cramps (LGMD1C)
  - Ancestry (e.g., northern European for LGMD2I)

Q2. Clinical Context: Distinguishing Features

- Family or personal history of frontotemporal dementia, Paget disease of bone, or motor neuron disease (h1BMPFD)
- Scapular winging (e.g., sarcoglycanopathies, LGMD2A)
- Calf hypertrophy (BMD, LGMD2I)
- Cardiac conduction system abnormalities (e.g., laminopathy, desminopathy)
- Cardiomyopathy (e.g., LGMD2I)
- Rippling muscle phenomenon and percussion-induced muscle contractions in LGMD1C

Q2. Clinical Context: Distinguishing Features

- EMG features in MFM (e.g., myotonic and pseudomyotonic discharges, the latter characterized by runs of decrescendo positive sharp-wave discharges without the typical waxing and waning of amplitudes and frequencies)
- Muscle biopsy features that distinguish between muscular dystrophies include:
  - Rimmed vacuoles
  - Reducing bodies/cytoplasmic bodies
  - Derangement of myofibrils consistent with MFM
  - Nemaline rods in distal myopathies due to nebulin mutations
  - Reductions of specific proteins on immunohistochemistry suggestive of deficiencies (need to confirm the diagnosis with genetic testing)

CLINICAL APPROACH

- Age at onset
- Genetic transmission, region and ethnicity
- Clinical features and case studies
- Time dependent issues
- Genotype phenotype issues

AGE AT ONSET

Most patients present from adolescence to early adulthood

Early childhood presentations (DMD mimics)

- **LGMD 2 (C-F): Sarcoglycanopathies**
- **LGMD2N : Dystroglycanopathy :POMT**
- **LGMD2P : DAG 1**
- **LGMD1E : Desminopathy and dilated cardiomyopathy**
- **FHL1: In the spectrum of Emery Dreifuss dystrophy**

Late Presentations

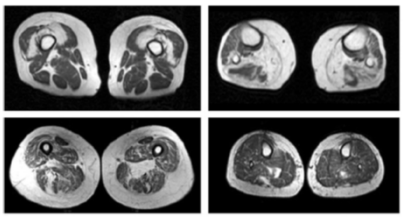
- **Udd myopathy**
- **Welander myopathy**

REGION AND ETHNICITY

The prevalence of limb girdle muscular dystrophies varies as per studied populations

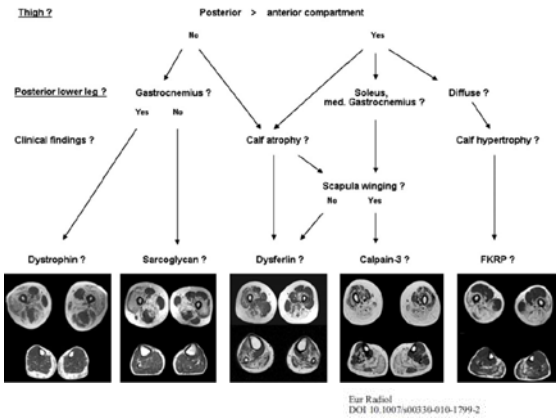
1. Dysferlinopathy is common in Japan
2. GNE myopathy is common in Israel
3. Anoctaminopathy is common in Europe
4. Welander and Udd myopathies are common in Finland
5. Calpainopathies and dysferlinopathies are common in Asia
6. Sarccoglycanopathies are common in Tunisia

MUSCLE IMAGING

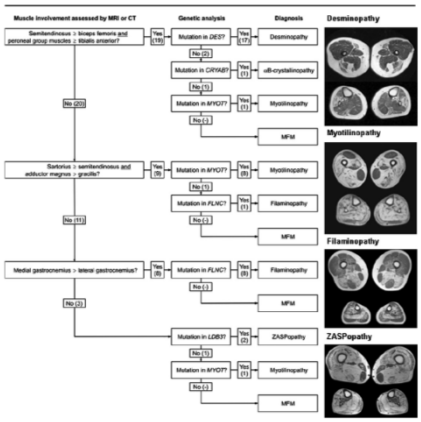


(a) DM1 is typically characterised by distal more than proximal muscle involvement showing predominant affliction of the soleus, medial gastrocnemius and proximally the anterior thigh compartment with relative sparing of the rectus femoris.

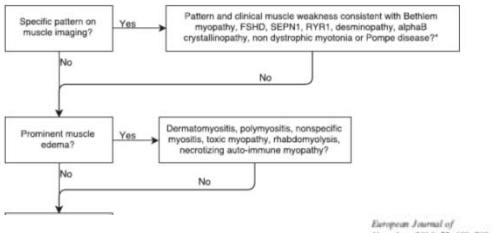
(b) DM2 (PROMM) are often less affected and show no fatty degeneration. Affected patients show more involvement of the proximal muscles with affliction of the quadriceps and sparing of the rectus femoris and gracilis muscles.



Eur Radiol
DOI 10.1007/s00330-010-1799-2



FLOW CHART FOR DIAGNOSIS OF MUSCLE DISORDERS BASED ON MR MUSCLE IMAGING.



European Journal of Neurology 2016, **23**: 688–703

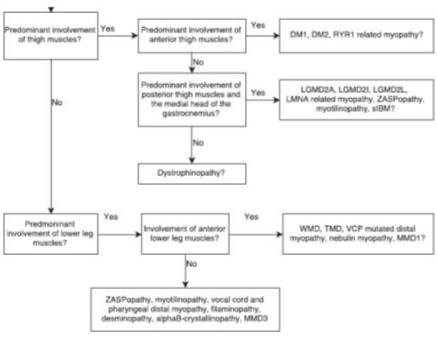
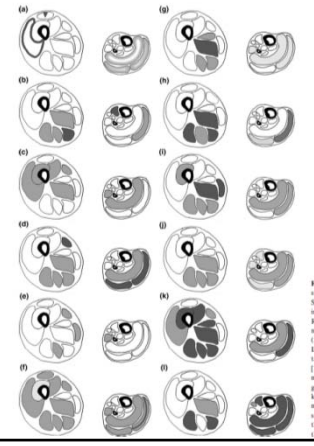


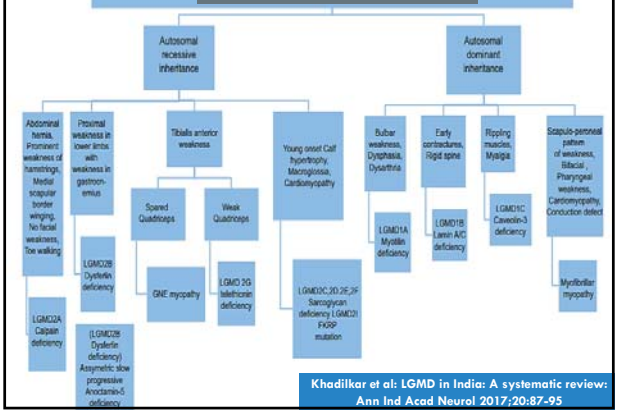
Figure 5 Flow chart for diagnosis of muscle disorders based on MR muscle imaging.



European Journal of Neurology 2016, 23: 688–703

Figure 2 Schematic representation of specific patterns of muscle involvement. Specific patterns of muscle involvement in Bethlem myopathy (a), FSHD (b), RYR1 (c), SEPN1 (d), alpha-B-crystallinopathy (e), non-dystrophic myotonia (f), GSDII (g), dystrophinopathy (h), LGMD2A (i), LGMD2I (j), anoctaminopathy (k), dysferlinopathy (l) [1,7,20,23,58,67,78]. The replacement of muscle tissue by fat is reflected by the grey colour of (part of) the muscle. Darker grey represents more replacement of muscle tissue by fat. The first column shows a cross-section at the level of the thigh, the second shows cross-sections through the lower leg.

LGMD "Phenotips"



Khadilkar et al: LGMD in India: A systematic review: Ann Ind Acad Neurol 2017;20:87-95

Almost half of LGMD patients do not exhibit any important diagnostic clues on clinical examination and in these, help from investigations is required

TIME DEPENDANT PHENOTYPE

Is a single assessment comprehensive enough??

GENOTYPE VS PHENOTYPE ISSUES

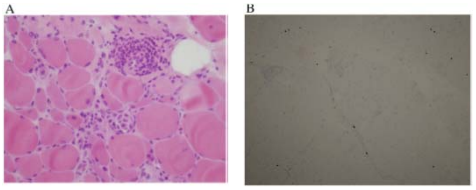
Case example

Brother: 14 years old with hip and distal leg weakness

- CK 13,678
- Muscle biopsy: necrotic and regenerative fiber, absent dysferin

Younger brather: 13 years old, asymptomatic

- CK 12131



Letter to the Editor

Kulkantrakor K, Sangruchi T.

Discordant manifestation in brothers with Miyoshi myopathy

Journal of the Neurological Sciences 373 (2017) 86–87


FIVE YEARS FOLLOW UP

Elder brother

- CK 9000-29000
- progressive atrophy and weakness in both hips and ankles
- ambulation by wheel chair, relatively normal upper limb

Younger brother:

- CK 12,000-26,000
- Minimally symptomatic

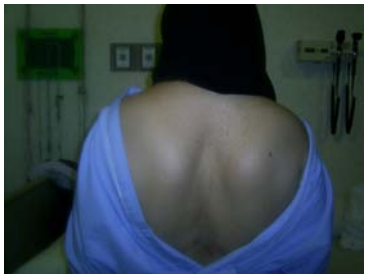
GENOTYPE PHENOTYPE ISSUES

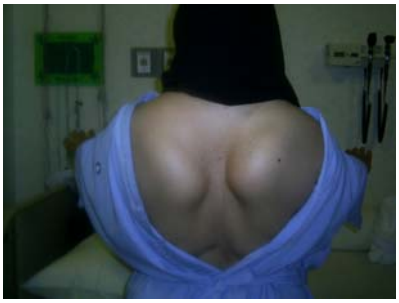
One phenotype can be the result of many genotypes

E.g. Foot drop can be the result of

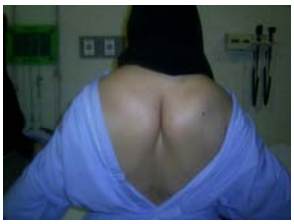
- Myofibrillary myopathy
- GNE myopathy
- Anoctaminopathy
- calpainopathy

A LADY WITH PROXIMAL MUSCLE WEAKNESS

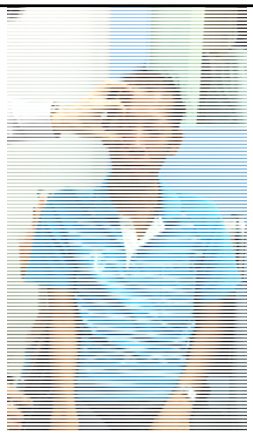


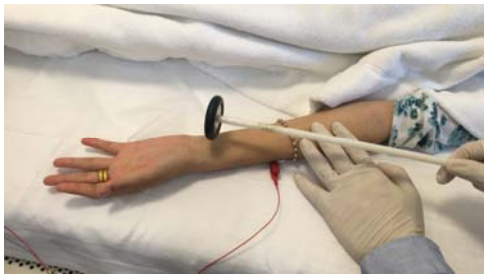


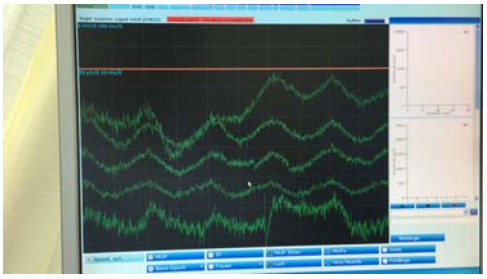
LOCALIZATION

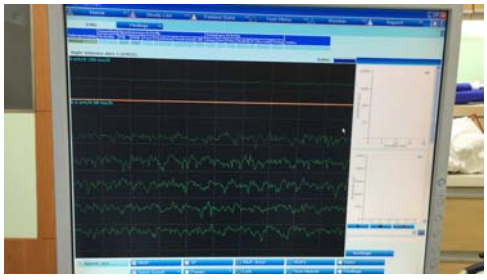


A MAN WITH GENERALIZED WEAKNESS









MYOTONIC DISORDERS

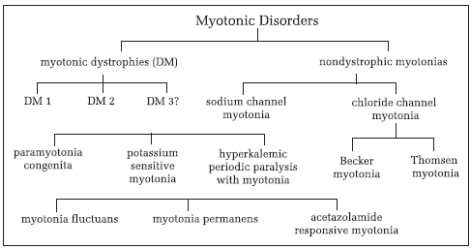


Table 1. Differential diagnosis of myotonic disorders.

- Clinical Myotonia and Electrical Myotonia
  - Myotonic dystrophy type 1
  - Myotonic dystrophy type 2 (proximal myotonic myopathy)
  - Myotonia congenita
  - Schwartz–Jampel syndrome
- Clinical Paramyotonia and Electrical Myotonia
  - Hyperkalemic periodic paralysis
  - Paramyotonia congenita
- Electrical Myotonia without Clinical Myotonia
  - Acid maltase deficiency
- Uncommon Causes of Myotonia
  - Myopathy
  - Denervation
  - Drug-induced hypothyroidism

FIGURE 1. (A) Myotonia of the orbicularis oculi. In this series of photographs the patient is initially looking straight ahead (left), then forcibly closing her eyes (center), and finally is attempting to open her eyes as wide as possible (right). Note that the patient is unable to open her eyes because of myotonia of the orbicularis oculi muscle. This figure demonstrates classic myotonia, in which the myotonia is most severe after the first contraction. If the patient had repeated the forcible eye closures the myotonia would have "warmed up" or lessened with repeated closures. **(B)** Paradoxical orbicularis oculi myotonia. In this series of photographs the patient has been asked to forcibly close her eyes and then to open them fully as quickly as possible. Each photograph was taken immediately after the patient was told to open her eyes. After the first forcible eye closure (left) the patient has no difficulty in opening her eyes. Note the progressive difficulty in fully opening her eyes. After the fourth forcible eye closure (right) the patient is unable to open her eyes. (Reproduced with permission from Pourmand R, editor: Neuromuscular diseases: expert clinicians' views. Boston: Elsevier; 2001. © Elsevier.)

PERCUSSION MYOTONIA

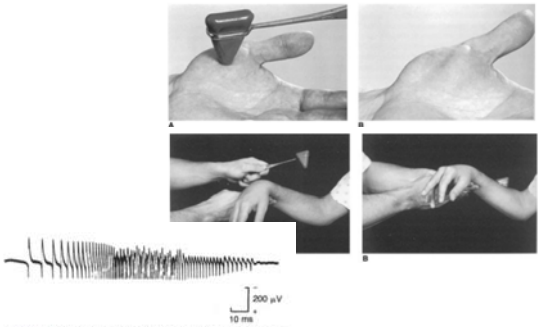
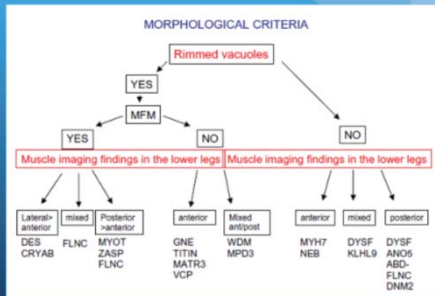


FIGURE 4. Myotonic discharge. EMG of typical myotonic discharge demonstrating waxing and waning of both amplitude and frequency.

Distal muscle weakness

- Myofibrillar myopathies
- Hereditary inclusion body myopathy (*GNE-pathy*)
- Myopathies associated with defects in the genes encoding dysferlin, anoctamin 5, nebulin, slow myosin and titin
- Others, e.g. sIBM, myotonic dystrophy, FSHD

Distal muscle weakness



Udd, Neuromusc Disord 2012; 22:5

DD Distal muscle weakness

- Calf muscle atrophy/weakness + high CK
  - Miyoshi-(like) myopathy (dysferlin or ANO5 mutation)
- Symmetric foot extensor weakness
  - MD1 (myotonia), caveolinopathy (high CK, rippling muscles), Laing myopathy
- Asymmetric foot extensor weakness
  - FSHD (axillar folds, facial weakness), sIBM
- Miscellaneous: hereditary IBM, myofibrillar myopathy, glycogenosis (debranching enzyme def.)

http://neuromuscular.wustl.edu/musdist/distal.html#distal

A LADY WITH LEG WEAKNESS AND DIFFICULTY GETTING UP FROM THE FLOOR

A LADY WITH ABNORMAL WALKING

Evidence-based Guideline Summary:

Evaluation, Diagnosis, and Management of

Facioscapulohumeral Dystrophy

Report by:
Guideline Development, Dissemination, and Implementation Subcommittee
of the American Academy of Neurology (AAN)
Practice Issues Review Panel
of the American Association of Neuromuscular & Electrodiagnostic Medicine

AMERICAN ACADEMY OF NEUROLOGY

INTRODUCTION

- Third most common form of muscular dystrophy (MD)
  - Prevalence of appx. 1:15,000–1:20,000.[1,2]
- Autosomal dominant disorder
  - Up to 30% of cases are sporadic, arising from de novo mutations

Development and Progression

- Symptoms typically develop in the second decade of life
  - Can begin at any age[1]
- FSHD typically progresses slowly but variably.[4,5]
  - About 20% of individuals with FSHD become wheelchair dependent after age 50.[1]

Development and Progression

- Characterized by distinctive, initially regional distribution of muscle involvement
  - Typically facial, periscapular, and humeral muscles[3]
- Extramuscular manifestations can include:
  - Respiratory compromise
  - Retinal vascular disease
    - Rarely leads to exudative retinopathy and visual loss
  - Hearing loss

Types of FSHD

FSHD type 1 (FSHD1)
- Appx. 95% of cases
- Deletion of critical number of D4Z4 repeats on the A allele[9,10]

FSHD type 2 (FSHD2)
- Appx. 5% of cases[13,14]
- No contractions in the 4q35 D4Z4

Both types
- Identical molecular basis
  - Results from the aberrant expression of the double homeobox 4 (*DUX4*) gene in skeletal muscle[15,16]

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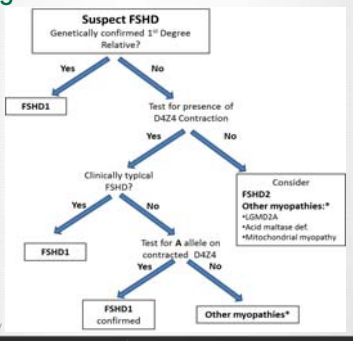
Practice Recommendations
1. Diagnosis: Clinical Context



Slide 87

Practice Recommendations
1. Diagnosis

Clinicians should obtain genetic confirmation of FSHD1 in patients with atypical presentations and no first-degree relatives with genetic confirmation of the disease (Level B).

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Practice Recommendations
2. Predictors of Severity: Clinical Context

- Factors that predict disease severity are important for:
  - Counseling patients
  - Screening for and managing potential complications
- The D4Z4 deletion size appears to be somewhat predictive of the overall rate of disease progression.
  - D4Z4 deletion size should be used cautiously for predicting disease progression rate in any particular individual due to other sources of variation affecting disease severity, including intrafamilial factors.
- Clinical experience suggests that patients with severe childhood-onset disease almost invariably have very large deletions.
  - This suggests a much more robust correlation between disease severity and large deletions.

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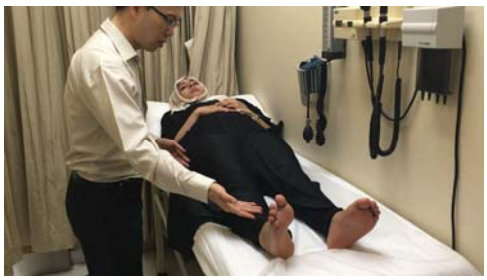
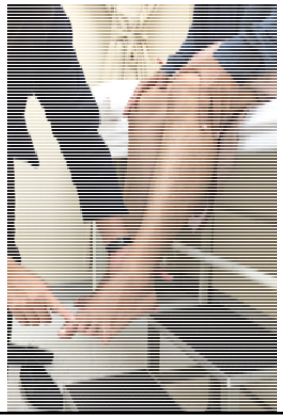
Practice Recommendations
2. Predictors of Severity

Large D4Z4 deletion sizes (contracted D4Z4 allele of 10–20 kb) should alert the clinician that the patient is more likely to develop more significant disability and at an earlier age. Patients with large deletions are also more likely to develop symptomatic extramuscular manifestations (Level B).

Slide 90

AN ARABIC LADY WITH LEG WEAKNESS



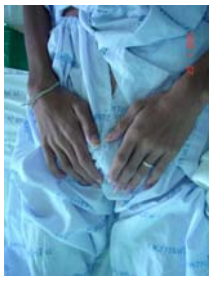


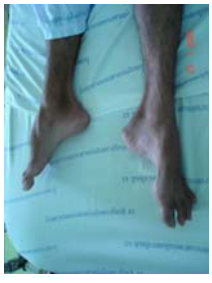
A TEENAGER CAME IN WITH DIARRHEA

Found to be short stature

Generalized, easily fatigue while working in a department store

HAND AND FEET





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PTOSIS

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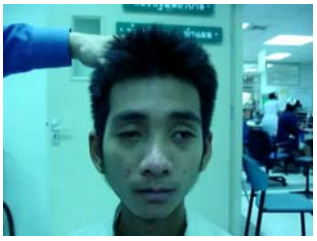
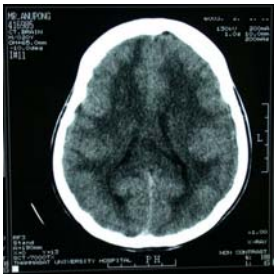
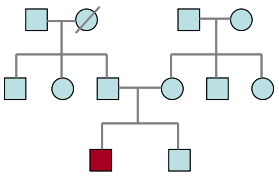
EYE MOVEMENT VIDEO



CT BRAIN AND PEDIGREE





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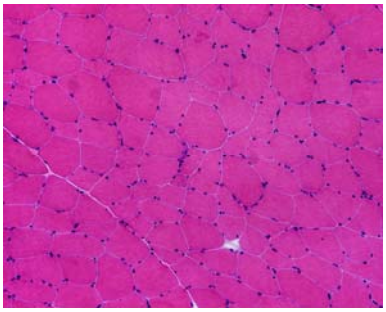
H&E



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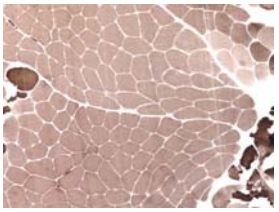
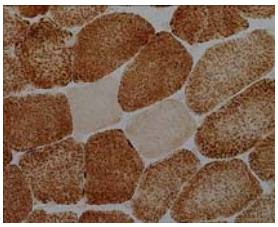
MUSCLE BIOPSY



ATPase stain at pH 4.6
showing fiber type grouping



COX stain showing absent staining
(COX negative fibers)

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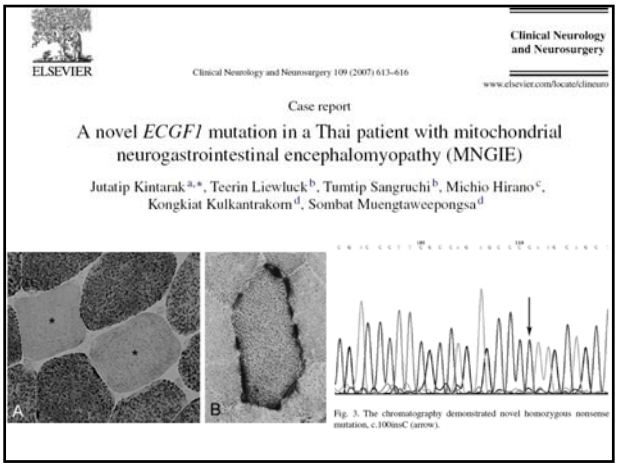

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Case report

A novel *ECGF1* mutation in a Thai patient with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)

Jutatip Kintarak[a,*], Teerin Liewluck[b], Tumtip Sangruchi[b], Michio Hirano[c], Kongkiat Kulkantrakorn[d], Sombat Muengtaweepongsa[d]

A

B

Fig. 3. The chromatography demonstrated novel homozygous nonsense mutation, c.100insC (arrow).

KEY POINTS

- Phenotype
  - Limb girdle
  - Non- limb girdle
- Additional features:
  - Ptosis, EOM deficit
  - Distal weakness, etc
- Extramuscular manifestation: multisystem disorders
- Investigations: muscle imaging, biopsy and genetic diagnosis
- Case examples: LGMD 2A, LGMD2B/Miyoshi, FSHD, Myotonic dystrophy, GNE myopathy, MNGIE