Central Manchester University Hospitals NHS
NHS Foundation Trust

Muscular dystrophies Overview

Dr Imelda Hughes
Consultant Paediatric Neurologist
Royal Manchester Children's Hospital

Declarations

- PI in clinical trials for PTC Therapeutics, Summit
- Consultancy for Santhera and Biogen
- Conference fees and travel by PTC therapeutics

Topics covered

- Definition
- Prevalence of muscular dystrophies
- Clinical features of the more common muscular dystrophies
- Diagnostic process
- Complications of muscular dystrophies

Muscular dystrophies

- Group of genetically heterogeneous conditions
- Progressive muscle weakness with mostly a proximal onset
- Range of severity
- Raised CK
- Muscle biopsy myopathic-dystrophic
- Frequent cardiorespiratory involvement

Disease group	No. of cases based on clinical diagnosis	No.of cases confirmed according to diagnostic standard (Table 1)	Proportion (%) of clinic population affected (with 95% confidence intervals)	Estimated point prevalence per 100 000 (with 95% confidence intervals)
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Brain 2009: 132; 3175-86 Norwood et al

- DBMD
- Limb girdle muscular dystrophy
- Congenital muscular dystrophies
- FSHD
- EDMD

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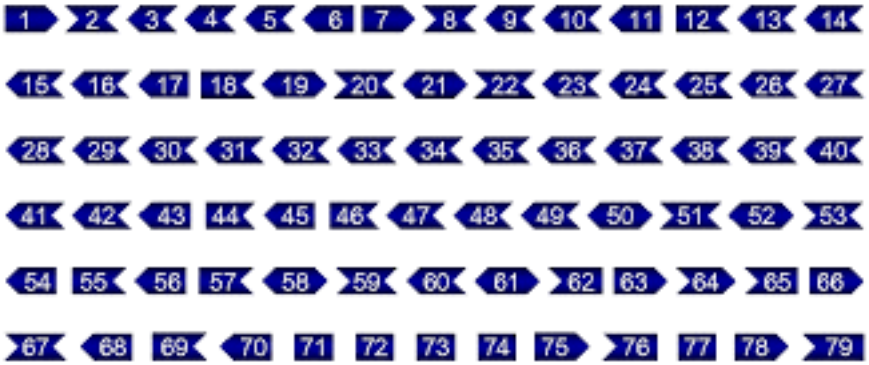
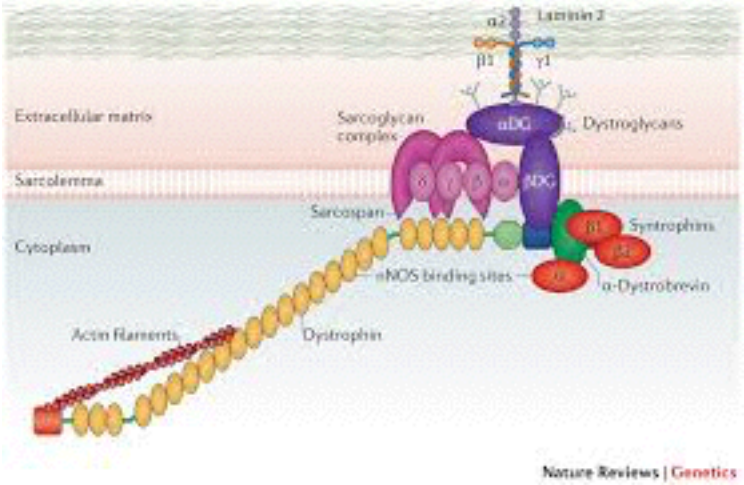




- Deletion 65% DMD, 85% BMD
- 5% duplication
- other mutations, point mut. small del or ins
- 30% new mutations
- 20% germ line mosaicism (with new mutations)

Dystrophinopathy – the clinical spectrum

- Duchenne MD 1:3 300
- Becker MD 1:18 000-31 000
- X-linked dilated cardiomyopathy
- Quadriceps myopathy
- Muscle cramps with myoglobinuria
- Asymptomatic elevation of CK
- Manifesting female carrier

DBMD

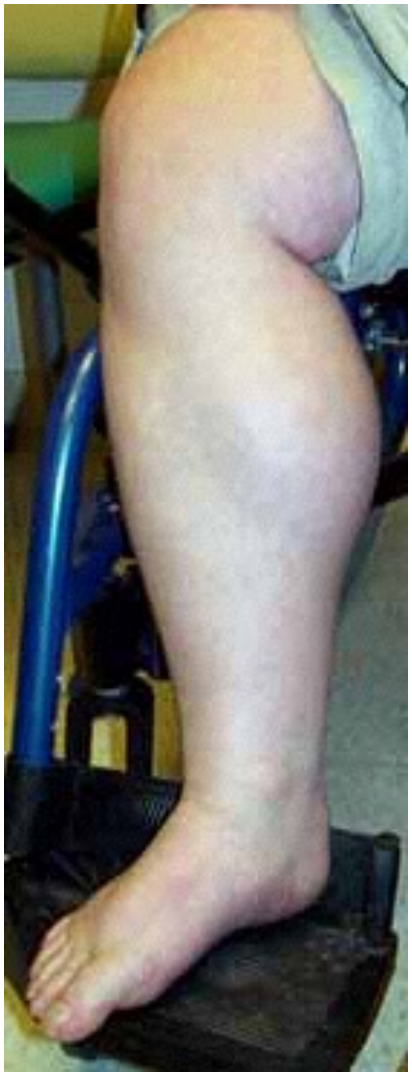
- DMD Early onset, loss of ambulation by 13 years
- Intermediate/outlier loss of ambulation 13-16 years
- BMD loss of ambulation after 16 years

DBMD – clinical presentation

- Delayed motor development
- Global developmental delay
- Poor motor skills/abnormal gait
- Toe walking
- Speech & language delay
- Family history
- Abnormal biochemistry CK LFTs

Clinical features – Gower’s manoeuvre

Clinical features – calf hypertrophy, toe walking



Dystrophinopathy – diagnostic process

- CK
- Deletion/duplication testing
- Muscle biopsy
- Point mutation testing

Female carriers

Neuromuscular disorders 2011;21:172-177 N Seemann et al

Pediatric Neurology (2015), doi: 10.1016/ j.pediatrneurol.2015.11.004 Papa R et al.

- Proximal muscle weakness 6/9 7/15
- Calf pseudohypertrophy 5/9 8/15
- Abnormal gait 5/9
- Myalgia 5/9
- Toe walking 3/9
- Behaviour/learning issues 5/9 4/15

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LGMD 1 AD

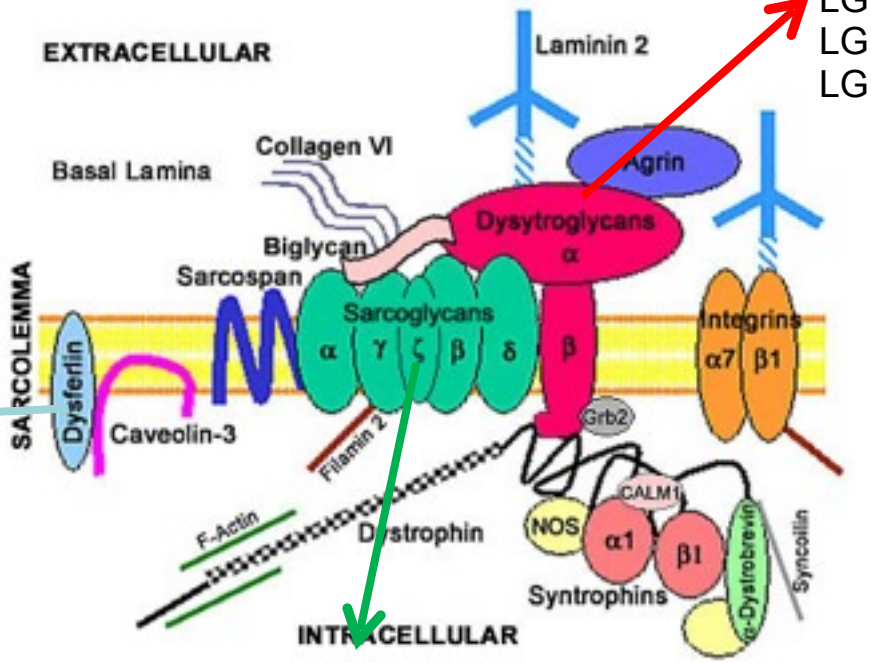
- LGMD1 A-G 6 genes
- Less common than recessive
- 1B LMNA mutations, cardiac dysrythmia and cardiomyopathy

- 1C Caveolinopathy, rippling muscles

LGMD 2 A-Y

LGMD 2A calpainopathy

LGMD 2I FKRP
LGMD 2K POMT1
LGMD 2M FKTN
LGMD 2N POMT2
LGMD 2O POMGnT1



LGMD 2B

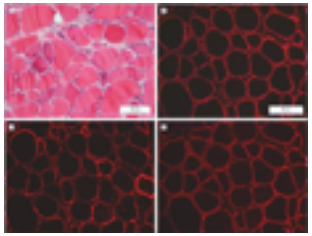
LGMD 2C γ
LGMD 2D α
LGMD 2E β
LGMD 2F δ

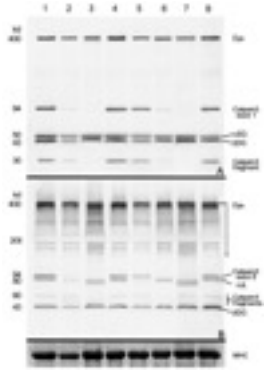
LGMD 2 diagnosis

- 75% genetic diagnosis
- Reasons to pursue precise diagnosis
  - Genetic counselling
  - Prediction of risks
  - Potential future specific treatment

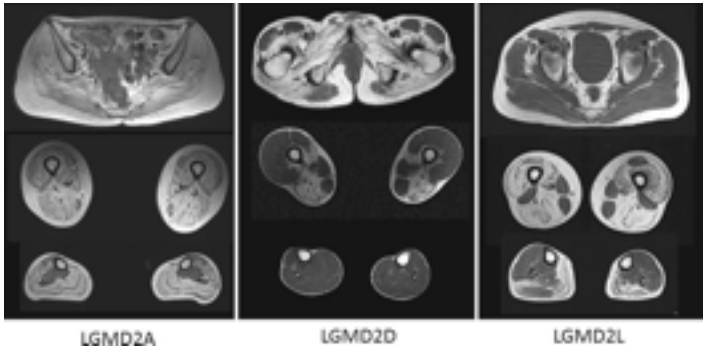
Approach to Diagnosis

Clinical features + Muscle biopsy immunohistochemistry & immunoblot





MRI +



Guide genetic testing

LGMD protein analysis

- Calpain
  - Degrades easily
  - Secondary deficiency in 2B, 2I, 2J
  - Normal in 23% with CAPN3 mutations
- Sarcoglycans
  - Residual expression highly variable, does not predict genotype
  - Abnormal dystrophin frequent
- Dysferlin
  - Secondary deficiency common, 1C

LGMD 2 - α-dystroglycanopathies

LGMD 2A calpainopathy

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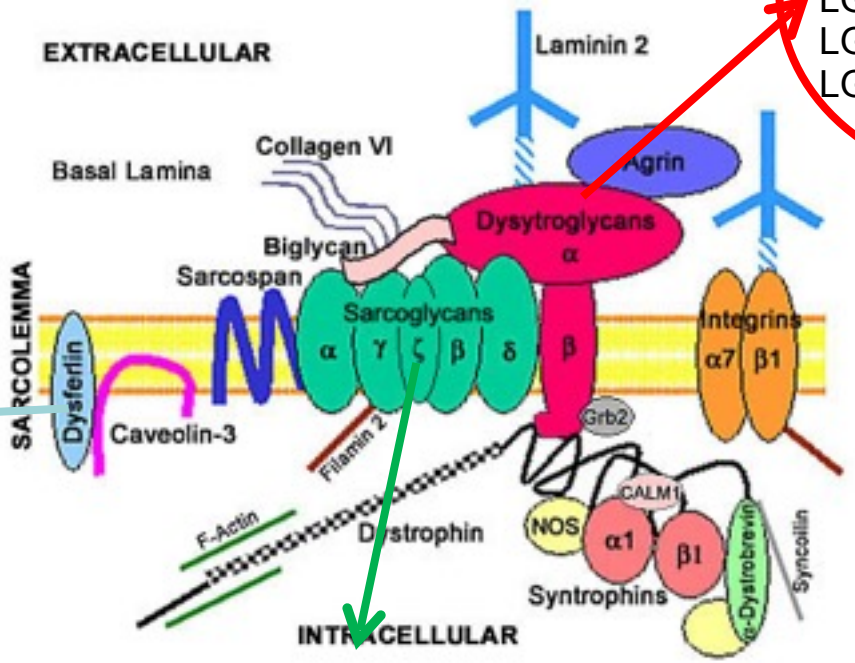

LGMD 2B

LGMD 2C γ
LGMD 2D α
LGMD 2E β
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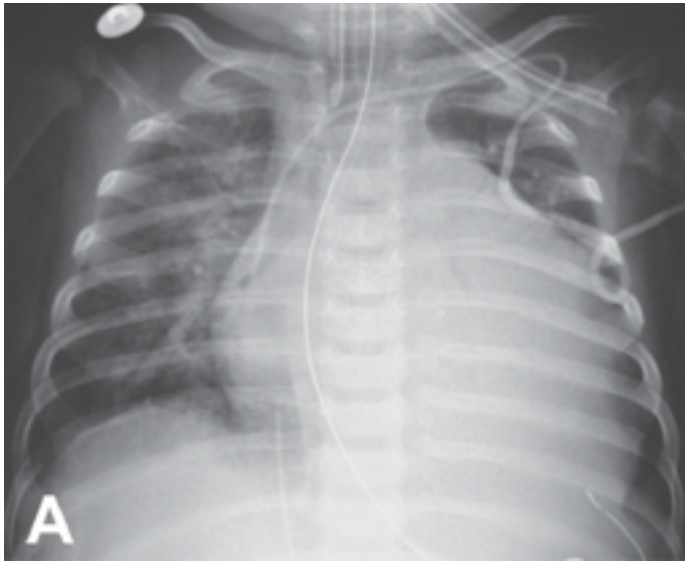
LGMD 2I FKRP

- North Europeans including UK
- 61% muscle pain/cramps
- 27% at least 1 episode myoglobinuria
- Calf hypertrophy common
- Common mutation C826A, homozygous less severe than compound heterozygotes
- Global IQ not impaired
- Specific impairment executive function, visuo-spatial planning
- Various MRI brain abnormalities; non-specific white matter changes, ventricolomegaly, enlarged subarchnoid spaces

LGMD2I

Cardiac involvement may be out of proportion to skeletal muscle weakness
Surveillance recommended



Respiratory impairment common

Other α-dystroglycanopathies

- LGMD 2K POMT1
  - Learning difficulty
- LGMD 2M FKTN
  - Not usually associated with structural brain abnormality or LD
  - cardiomyopathy
- LGMD 2N POMT2
- LGMD 2O POMGnT1
- 1 patient reported with DAG1 mutation

LGMD 2A Calpainopathy

- Toe walking, scapular winging
- Contractures especially TA also finger flexion, elbow flexion, wrist flexion
- Wasting
- Occasional mild facial weakness
- Mild scoliosis
- Cardiomyopathy rare
- Respiratory function preserved
- Dominant inheritance of an in-frame deletion associated with mild weakness with slow progression

LGMD 2 - Sarcoglycanopathy

LGMD 2A calpainopathy

LGMD 2I FKRP
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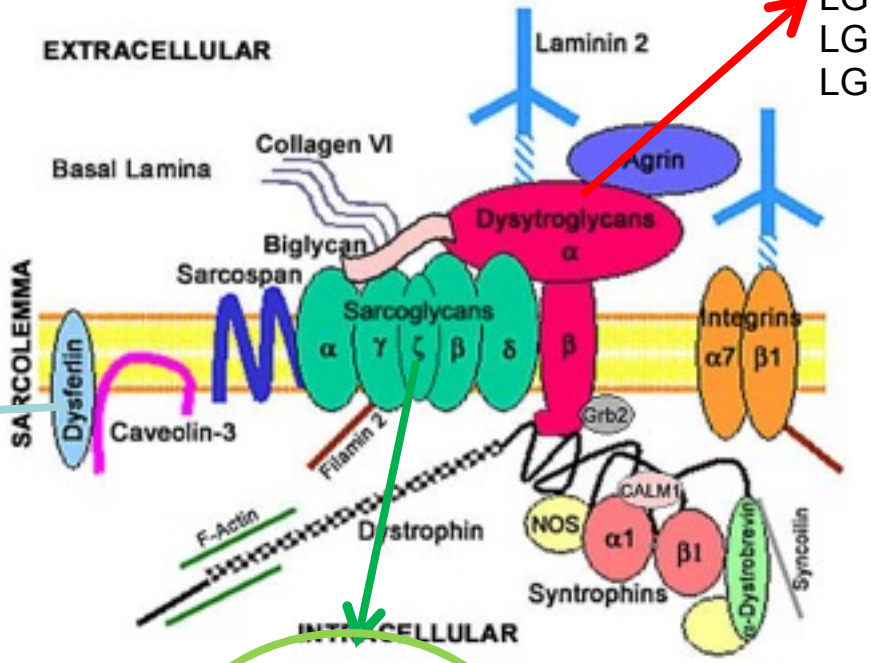
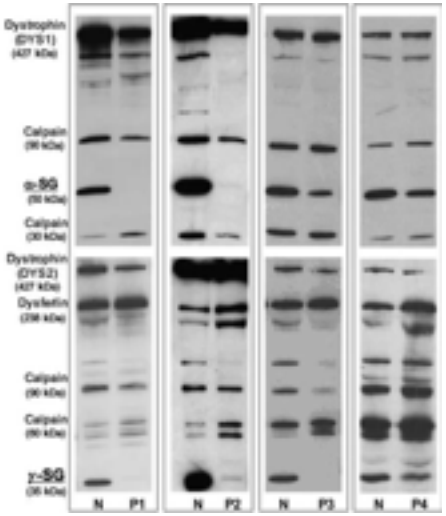


LGMD 2B

LGMD 2C γ
LGMD 2D α
LGMD 2E β
LGMD 2F δ

Sarcoglycanopathy

- Most likely to have childhood onset
- β Amish, γ North Africa, δ Brazil
- Ratio 2Dα:2Eβ:2Cγ:2Fδ 8:4:2:1
- Calf hypertrophy & scapular winging common
- Cardiac & respiratory involvement
- Some SCGA heterozgotes mildly symptomatic, scapular winging/calf hypertrophy



LGMD 2L

- ANO5 anoctamin 5
- CK may be markedly raised at onset
- Founder mutation c.191dupA
- Proximal lower limb weakness/distal myopathy
- Adult onset
- Male predominance
- 20-25% undiagnosed LGMD N Europe

LGMD 2A

LGMD 2A calpainopathy

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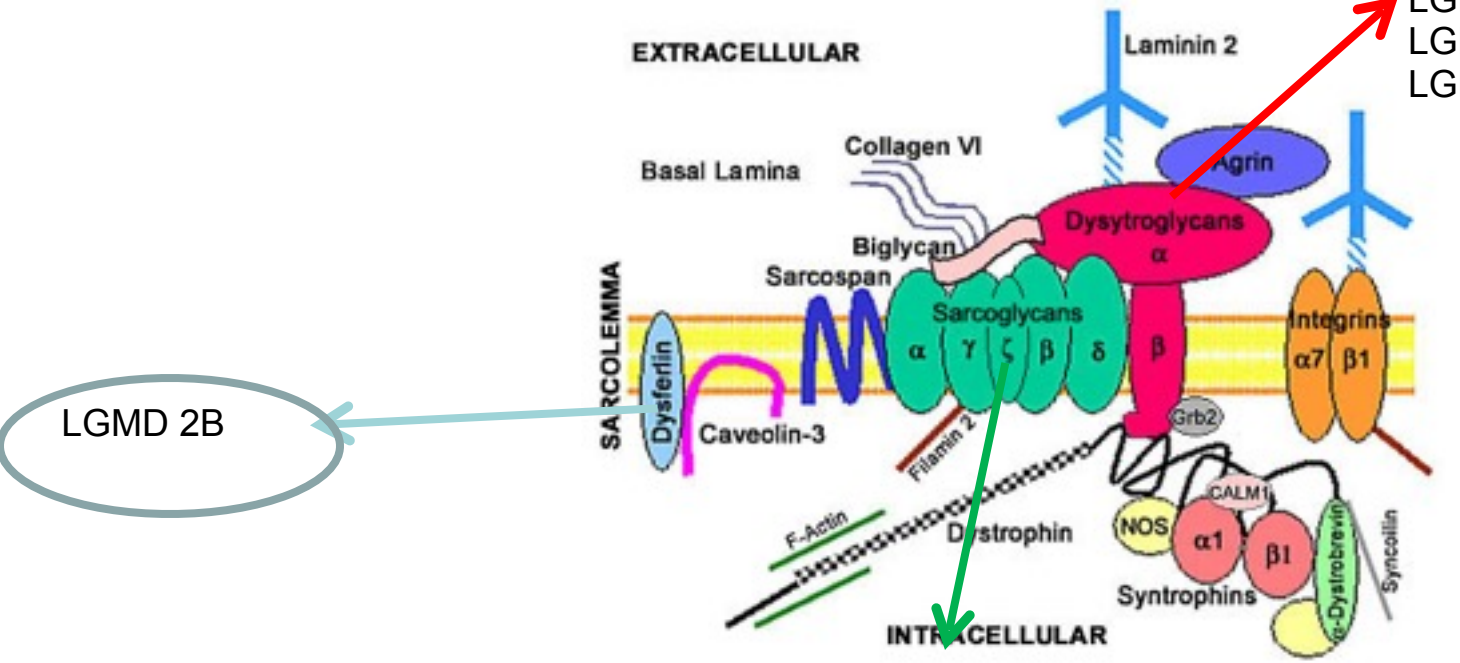

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LGMD 2B Dysferlinopathy

- Distal weakness present at onset, unable to stand on toes
- Preservation of deltoid, wasting of other upper arm muscles
- Posterior peroneal wasting
- Previous good sporting achievement
- Often abrupt onset with very high CK and inflammatory change on biopsy
- Similar phenotype with ANO5 mutations

Muscle Nerve 2010;42: Rosales et al

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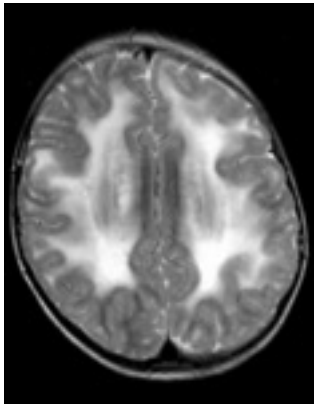
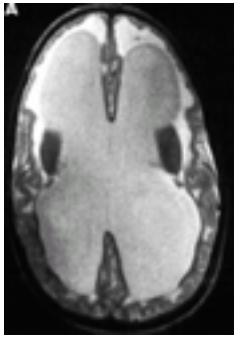
Congenital muscular dystrophy

Laminin α2 related LAMA2



αDystroglycan related

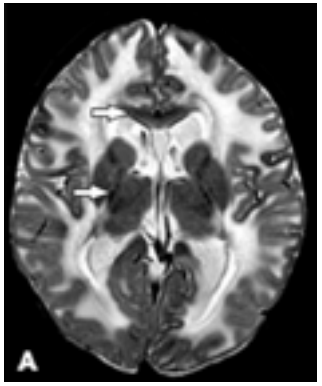


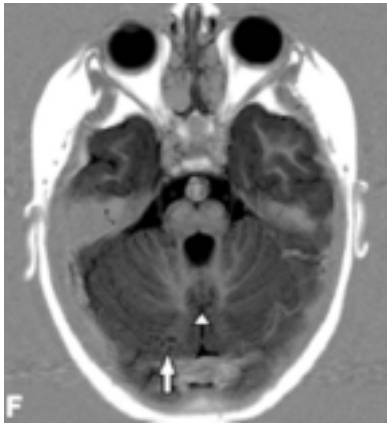
Collagen VI related

SEPN1, RYR1, LMNA related

MDC1A Laminin α2 related
Merosin deficient LAMA2

- Complete-partial deficiency
- CK>x5N
- MRI white matter abnormality, cerebellar cysts, cortical dysplasia
- Facial weakness, later ortodontic problems
- Ophthalmoplegia
- Majority normal cognition
- 30% epilepsy





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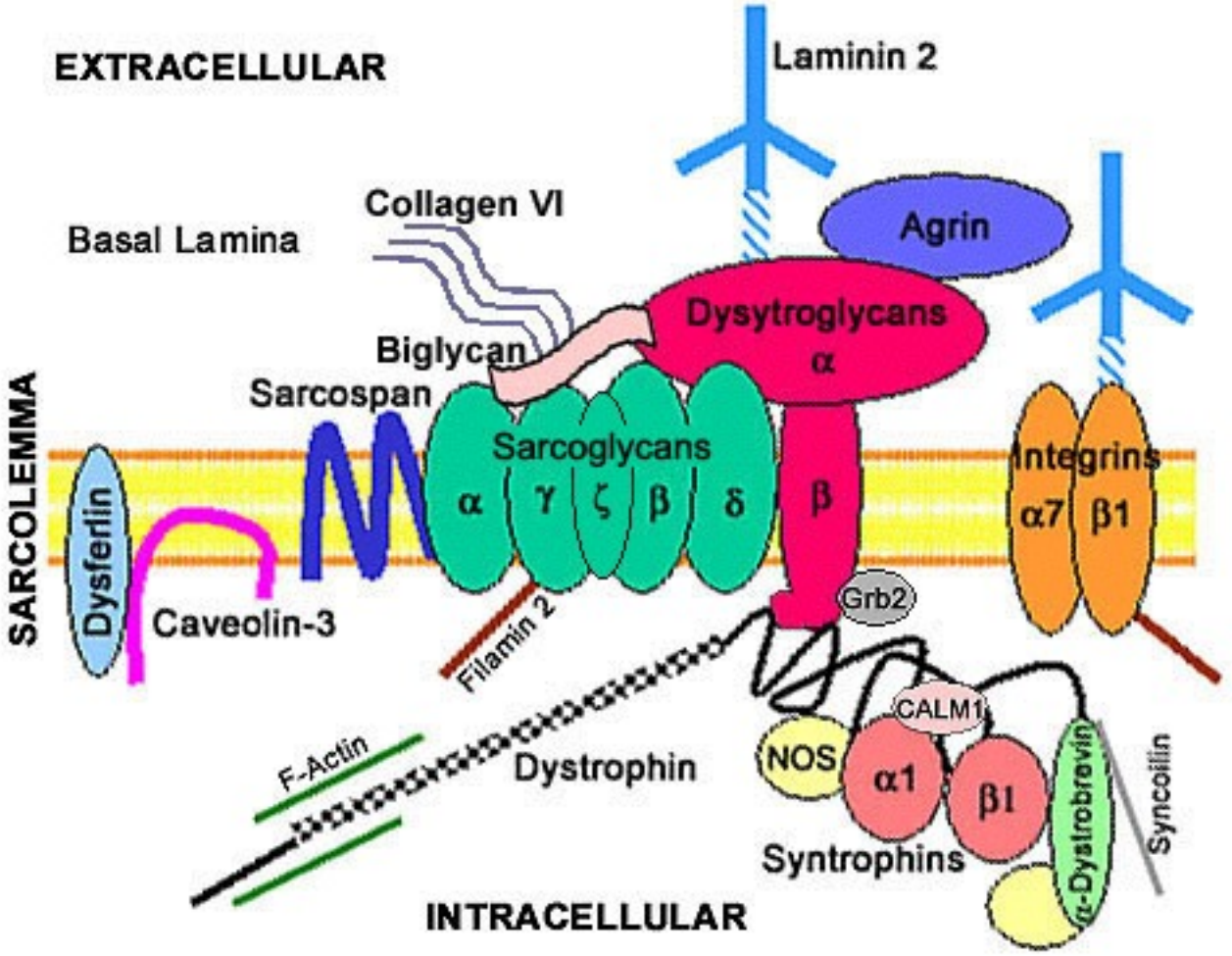
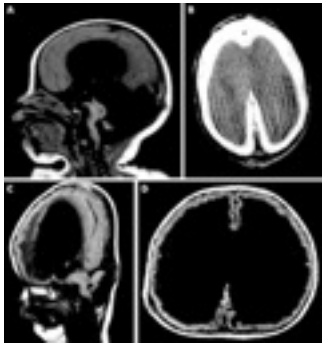
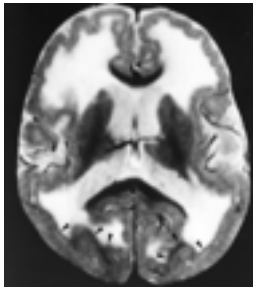


Clinical spectrum





Genetic heterogeneity
16 genes

Walker-Warburg	MEB	FCMD	CMD +/- LD	LGMD +/- LD
POMT1, POMT2, FKRP, FKTN, ISPD, CTDC2, TMEM5, POMGnT1, B3GALNT2, GMPPB, B3GNT1, POMK	POMGnT1, FKRP, FKTN, ISPD, TMEM5	FKTN	+LD FKRP, POMT1, POMT2, ISPD, GMPPB -LD FKRP, FKTN, ISPD, GMPPB	

Collagen VI related COL6A1,COL6A2, COL6A3

- Proximal contractures
- Distal laxity
- Hyperkeratosis pilaris
- Prominent calcanei
- Congenital hip dysplasia
- Torticollis
- Kyphoscoliosis

Disease group	No. of cases based on clinical diagnosis	No.of cases confirmed according to diagnostic standard (Table 1)	Proportion (%) of clinic population affected (with 95% confidence intervals)	Estimated point prevalence per 100 000 (with 95% confidence intervals)
Muscular dystrophies				
Duchenne (DMD)	124	124	11.2 (9.4–13.1)	8.29[a] (6.8–9.8)
Intermediate (IMD)	7	7	0.6 (0.2–1.1)	0.47[a] (0.1–0.8)
Becker (BMD)	109	109	9.9 (8.1–11.6)	7.29[a] (5.9–8.7)
Manifesting carriers	13	13	1.2 (0.5–1.8)	0.43 (0.2–0.7)
Total	253	253	22.9 (20.4–25.4)	8.46 (7.4–9.5)
Facioscapulohumeral muscular dystrophy (FSHD)	118	116	10.7 (8.9–12.5)	3.95 (3.2–4.7)
LGMD1B (AD EDMD)	6	6	8.8[b] (2.1–15.6)	0.20 (0–0.4)
LGMD2A	18	15	26.5[b] (16.0–37.0)	0.60 (0.3–0.9)
LGMD2B	4	2	5.9[b] (0.3–11.5)	0.13 (0–0.3)
LGMD2C	4	4	5.9[b] (0.3–11.5)	0.13 (0–0.3)
LGMD2D	2	2	2.9[b] (0–7.0)	0.07 (0–0.2)
LGMD2E	2	2	2.9[b] (0–7.0)	0.07 (0–0.2)
LGMD2I	13	12	19.1[b] (9.8–28.5)	0.43 (0.2–0.7)
LGMD unconfirmed	19	NA	27.9[b] (17.3–38.6)	0.64 (0.4–0.9)
Total LGMD	68	43	6.15 (4.7–7.6)	2.27 (1.7–2.8)
Emery–Dreifuss muscular dystrophy X-linked (EDMD-X)	4	4	0.36 (0–0.7)	0.13 (0–0.3)
Oculopharyngeal muscular dystrophy	4	4	0.36 (0–0.7)	0.13 (0–0.3)
CMD				
MDC1A	18	18	1.62 (0.9–2.4)	0.60 (0.3–0.9)
Walker–Warburg syndrome	1	1 (POMGnT1)	0.09 (0-0.3)	0.03 (0.01)
UCMD	4	3	0.36 (0–0.7)	0.13 (0–0.3)
RSMD	4	1	0.36 (0–0.7)	0.13 (0–0.3)

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Emery-Dreifuss MD

- LMNA AD, emerin X-linked
- Scapuloperoneal weakness
- Early contractures TA, elbows
- Spinal rigidity
- Cardiac involvement

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Facioscapulohumeral MD

- D4Z4 repeat DNA deletion
  4q
- 2-5% infantile onset
  - Severe facial weakness
  - Generalised weakness
  - Sensorineural hearing loss
  - Coat's disease
  - Remarkable lumbar lordosis

Important differential diagnoses

- SMA III
- Pompe disease
- Collagen 6 myopathy
- Inflammatory myopathy especially SRP

Summary

- Muscular dystrophies are clinically and genetically heterogeneous
- Genetic diagnosis is guided by clinical, imaging, histological & histochemical correlation