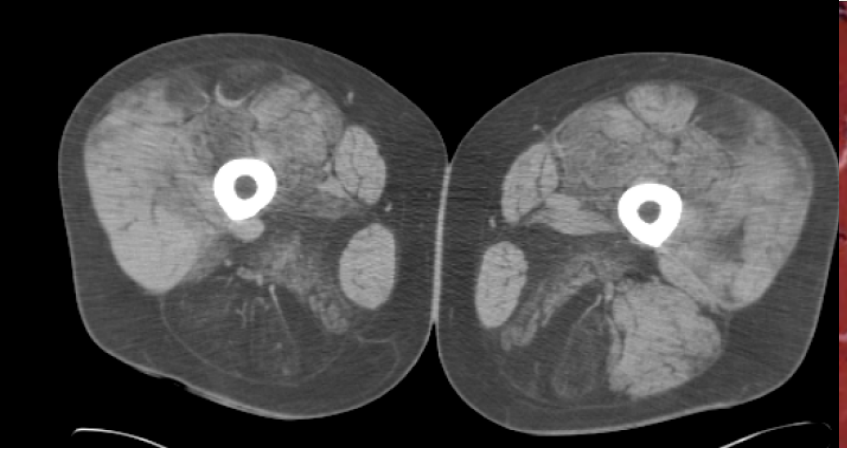
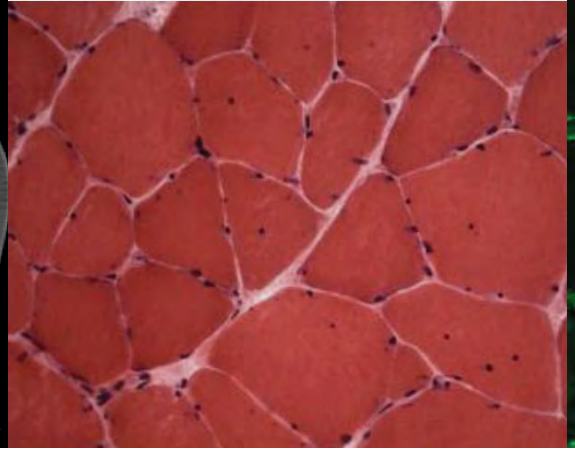
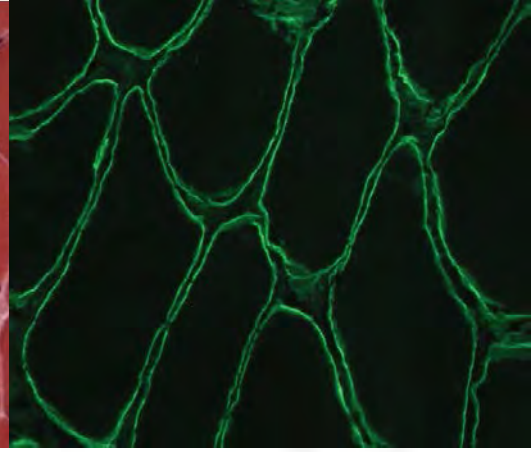
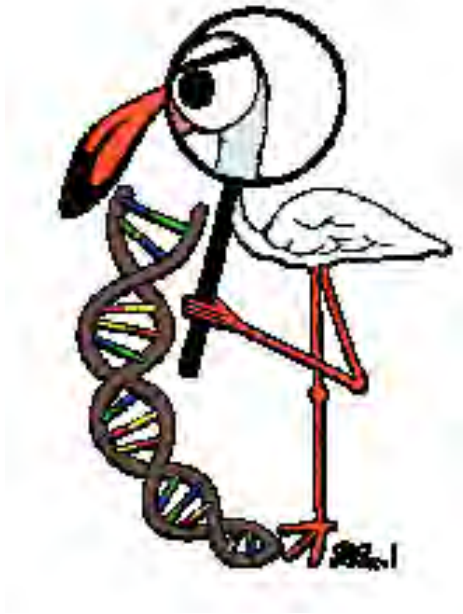




Studio multicentrico sulle Distrofie Muscolari dei Cingoli Telethon-UILDM



Centro Dino Ferrari, Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico, DEPT, UO
Neurologia, Università di Milano

FONDAZIONE IRCCS CA' GRANDA
OSPEDALE MAGGIORE POLICLINICO

UNIVERSITÀ DEGLI STUDI DI MILANO

BRAIN

VOL. 77, PART 2.

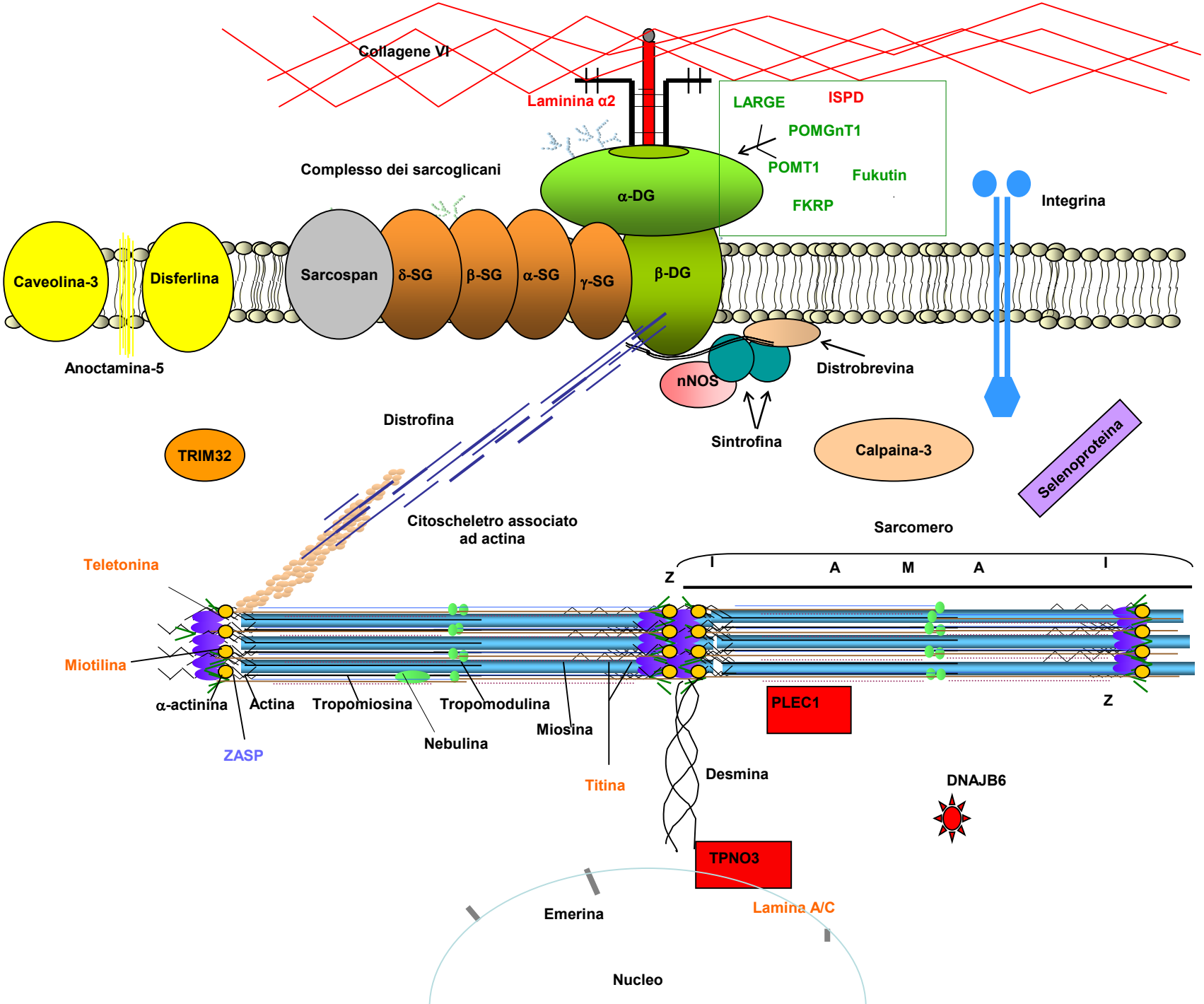
ON THE CLASSIFICATION, NATURAL HISTORY AND TREATMENT OF THE MYOPATHIES

BY

JOHN N. WALTON AND F. J. NATTRASS

(From the Department of Medicine, King's College, University of Durham and the Royal Victoria Infirmary, Newcastle upon Tyne)

In our opinion, these cases should be regarded as a distinct clinical and genetic group and we suggest that they should be called *limb-girdle muscular dystrophy*. Leaving aside certain clinical characteristics which may be added later, we feel that the cardinal features of this type are (*a*) onset usually late in the first or in the second or third decade but sometimes in middle age, (*b*) commencement of muscular weakness in either the shoulder or pelvic girdle, (*c*) transmission usually via an autosomal recessive gene, (*d*) a relatively slow course which nevertheless leads to severe disablement and often death before the normal age.


Collagene VI
Laminina α2
LARGE
ISPD
POMGnT1
POMT1
Fukutin
FKRP
Complesso dei sarcoglicani
α-DG
Integrina
Caveolina-3
Disferlina
Sarcospan
δ-SG
β-SG
α-SG
γ-SG
β-DG
Anoctamina-5
nNOS
Distrobrevina
Distrofina
Sintrofina
Calpaina-3
Selenoproteina
TRIM32
Citoscheletro associato ad actina
Sarcomero
Teletonina
Z
I
A
M
A
I
Miotilina
α-actinina
Actina
Tropomiosina
Tropomodulina
Miosina
Nebulina
ZASP
Titina
PLEC1
Z
Desmina
DNAJB6
TPNO3
Lamina A/C
Emerina
Nucleo

Molecular classification

	Gene	Gene location	Protein
LGMD 1A	MYOT	5q31	Myotilin
LGMD 1B	LMNA	1q21.2	Lamin A/C
LGMD 1C	CAV3	3p25	Caveolin-3
LGMD1D	DES	2q35	Desmin
LGMD 1E	DNAJB6	7q36	DnaJ homolog subfamily B member 6
LGMD 1F	TNPO3	7q32	Transportin3
LGMD 1G	HNRPDL	4p21	Heterogeneous nuclear ribonucleoprotein D-like protein
LGMD 1H	?	3p23-p25	?

- 8 Autosomal Dominat (LGMD1)
- 23 Autosomal Recessive (LGMD2)

30% without a molecular diagnosis

	Gene	Gene location	Protein
LGMD 2A	CAPN3	15q15.1-q21.1	Calpain-3
LGMD 2B	DYSF	2p13.3-913.1	Dysferlin
LGMD 2C	SGCG	13q12	γ-Sarcoglycan
LGMD 2D	SGCA	17q12-q21,33	α-Sarcoglycan
LGMD 2E	SGCB	4q12	ß-Sarcoglycan
LGMD 2F	SGCD	5q33	δ-Sarcoglycan
LGMD 2G	TCAP	17q12	Telethonin
LGMD 2H	TRIM32	9q31-9q34	TRIM32
LGMD 2I	FKRP	19q13,3	Fukutin Related Protein
LGMD 2J	TTN	2q24.3	Titin
LGMD 2K	POMT1	9q34.1	O-Mannosyl transferase-1
LGMD 2L	ANO5	11p12-p13	Anoctamin-5
LGMD 2M	FKNT	9q31-q99	Fukutin
LGMD 2N	POMT2	14q24	O-Mannosyl transferase-2
LGMD 2O	POMGnT1	1p34	Protein O-mannose beta-1,2-N-acetylglucosaminyl-transferase
LGMD 2P	DAG1	3p21	Dystrophin-associated glycoprotein
LGMD 2Q	PLEC1	8q24.3	Plectin
LGMD 2R	LAMA2	6q22	Merosin
LGMD2S	TRAPPC11	4q35	Transport protein particle complex 11
LGMD2T	GMPPB	3p21	GDP-mannose pyrophosphorylase B
LGMD2U	ISPD	7p21	Isoprenoid synthase domain containing protein
LGMD2V	POMK	8p11.21	Protein O-mannose kinase
LGMD2W	PINCH2/LIMS2	2q14.3	Particularly interesting new cys-his protein 2

Clinical and laboratory network for LGMD diagnosis, in view of a national registry Telethon GUP10006

- Department of Neurological Sciences, I.R.C.C.S. Foundation Cà Granda Ospedale Maggiore Policlinico, University of **Milan**
- NeuroMuscular Unit-IRCCS E Medea **Bosisio Parini**,
- Department of General Pathology, University of Naples, **Naples**
- Telethon Institute of Genetics and Medicine, **Naples**
- IRCCS Fondazione "San Camillo" Hospital, Lido di **Venezia**
- Department of Neurosciences, University of **Torino**
- Neuromuscular Diseases and Neuroimmunology Unit, Fondazione IRCCS Istituto Neurologico C. Besta, **Milan**
- Department of Neurosciences, Psychiatry and Anaesthesiology, University of Messina, **Messina**
- Department of Neurological Sciences, **Verona**
- Department of Clinical and Experimental Medicine, University of **Pisa**
- Center of Myology and Neurodegenerative Diseases, Istituto Giannina Gaslini, **Genova**
- Department of Neurology, Policlinico Universitario A. Gemelli, University Cattolica del Sacro Cuore of **Rome**
- Department of Neurosciences, University of **Padua**
- IRCCS Fondazione Stella Maris, Calambrone, **Pisa**

TeleThon
COMBATTI LA DISTROFIA MUSCOLARE E LE ALTRE MALATTIE GENETICHE

Objectives

- Create a national registry of LGMD Italian patients
- Collect clinical data about neuromuscular, respiratory, cardiac, cognitive involvement
- Delineate natural history of each sub-group
- Define outcome measures
- Further investigate patients without molecular diagnosis

Patient Selection

INCLUSION CRITERIA:

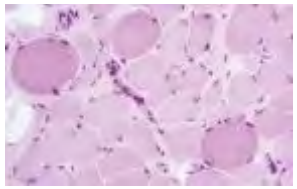
1. limb girdle and proximal upper and lower limb muscle weakness (Proximo-distal phenotypes may be included)
2. dystrophic pattern at muscle biopsy and/or
3. proven deficiency of LGMD proteins at IHC or WB analysis and/or molecular confirmation

EXCLUSION CRITERIA:

Limb Girdle syndrome with identified alternative etiology (inflammatory, metabolic myopathies, congenital myopathies, congenital myasthenic syndromes, SMA type II and III, FSH, dystrophinopathies, DM1, DM2 and mitochondrial myopathies)

Data collection

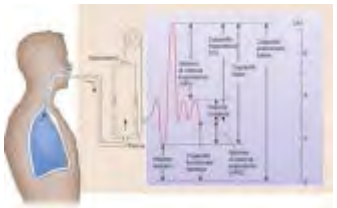
ANAMNESTIC DATA
Familiarity
Onset
CK values
Muscular involvement (distribution)
Tendon retraction
Scoliosis



MUSCLE BIOPSY
Morphology
IHC analysis
WB analysis

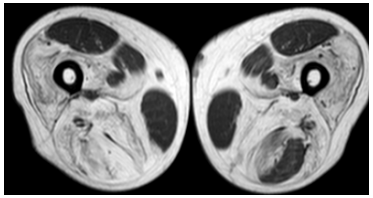
MOLECULAR ANALYSIS

CARDIAC FUNCTION
ECG
Holter ECG
Echocardiogram



RESPIRATORY FUNCTION
Spirometry
Nocturnal saturimetry
NIV

FUNCTIONAL EVALUATIONS
MRC
Walton
MFM
6MWT

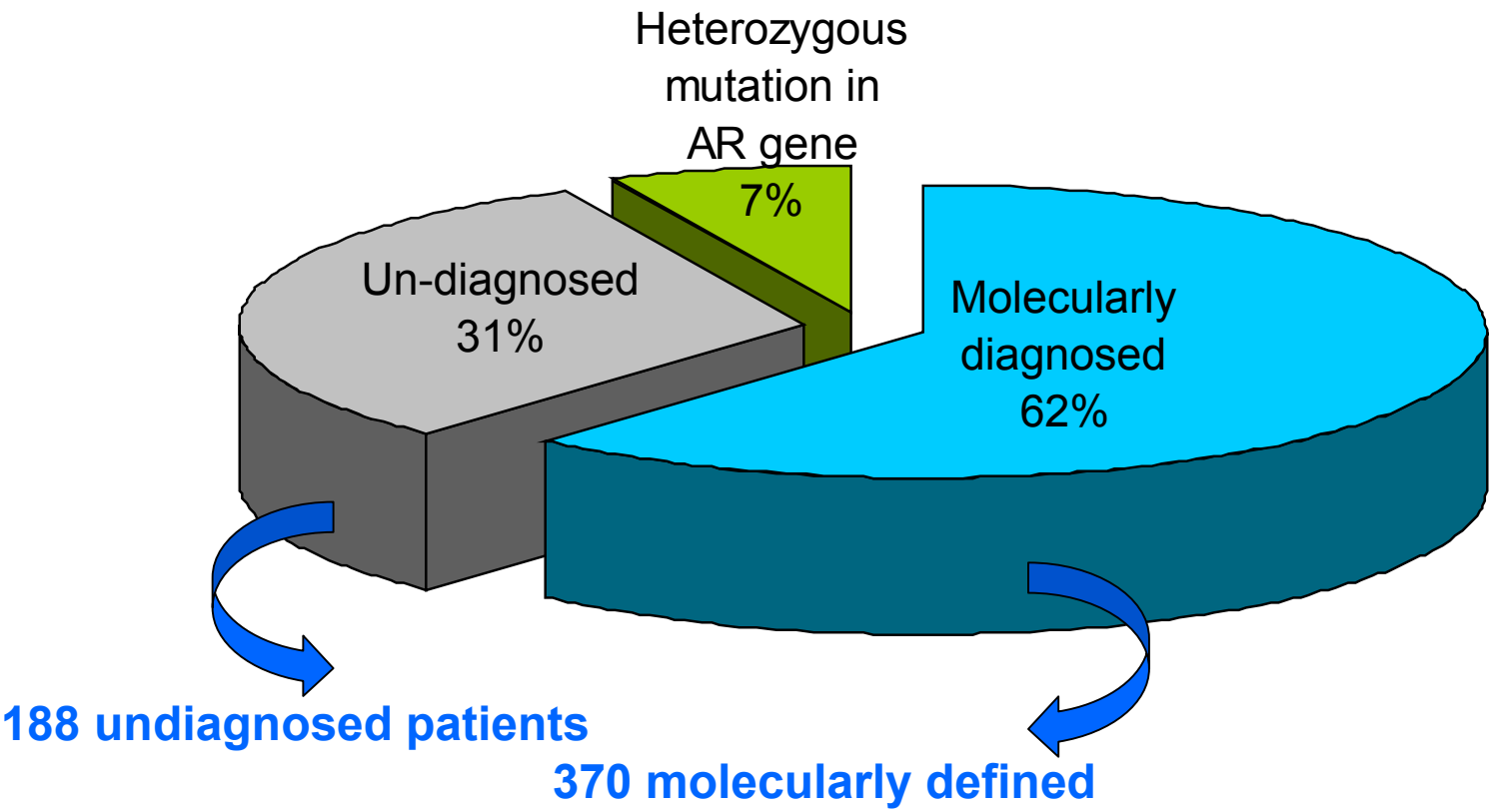


MAGNETIC RESONANCE
Muscular MRI
Brain MRI

DATABASE containing retrospective and prospective data

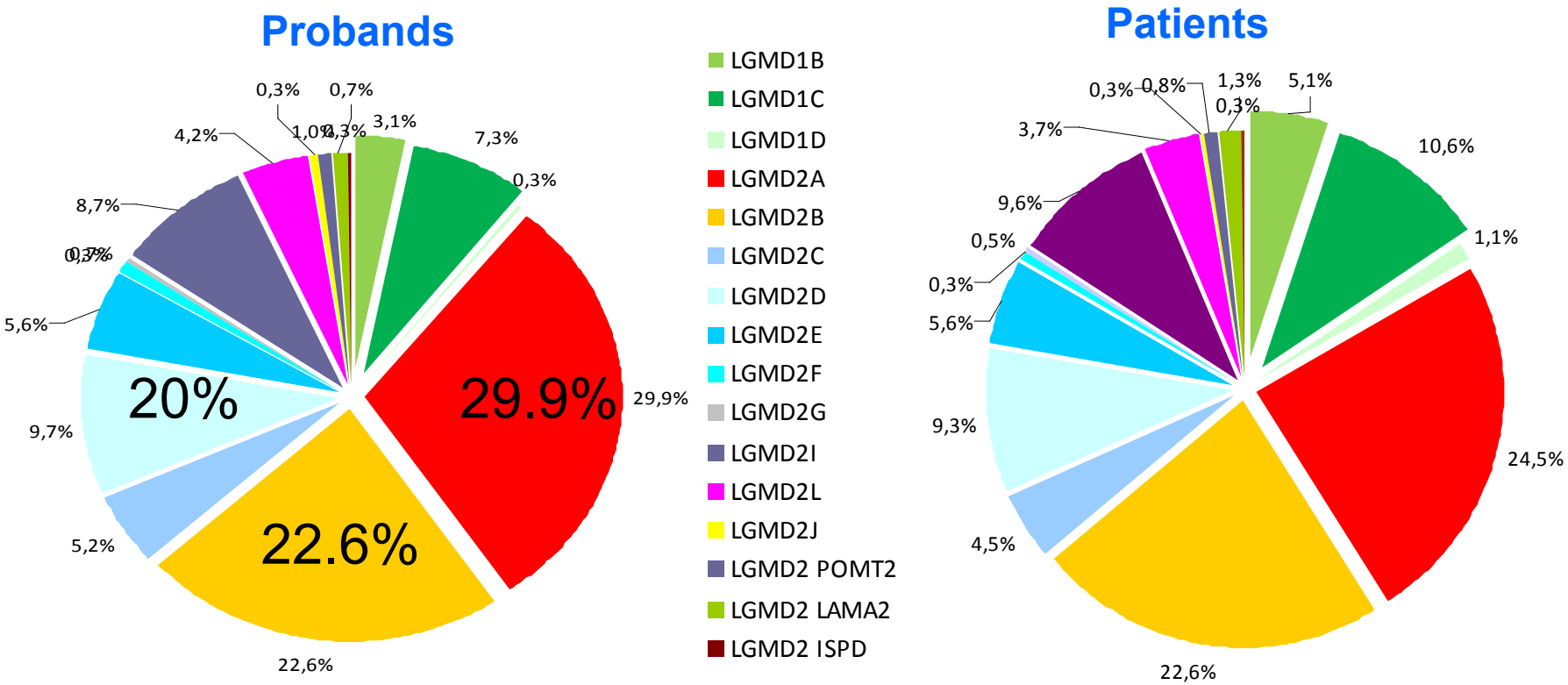
LGMD National registry

599 LGMD patients



LGMD registry

370 molecularly defined

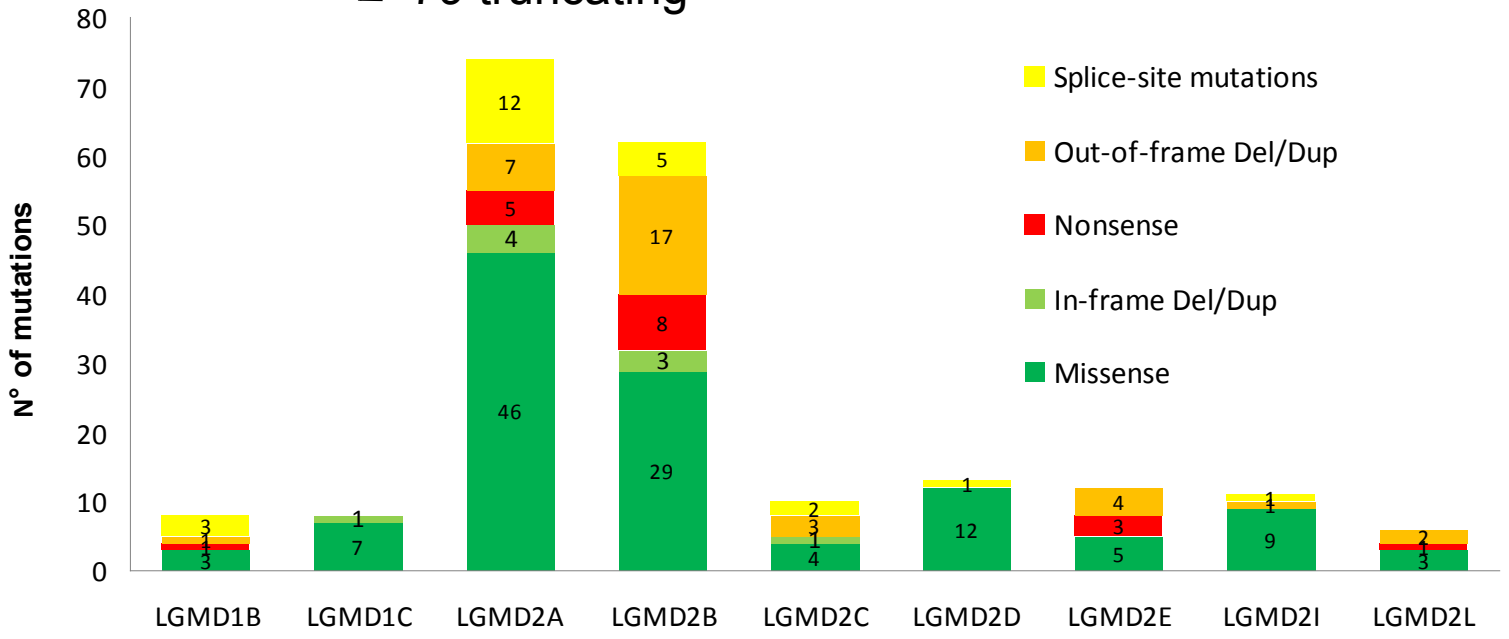


Mean follow-up 17,0 ± 11,6 years

Molecular aspects

207 different mutations ⇨ 128 in-frame

↘ 79 truncating

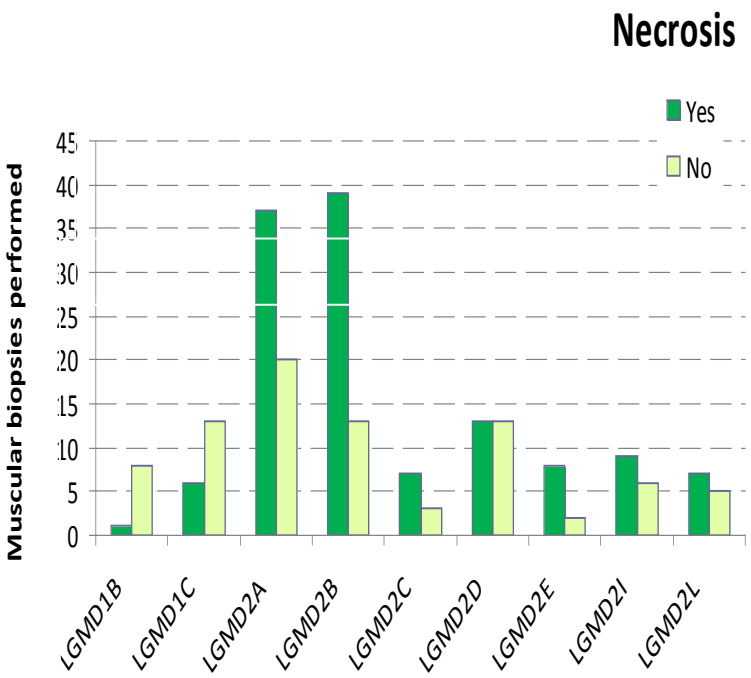


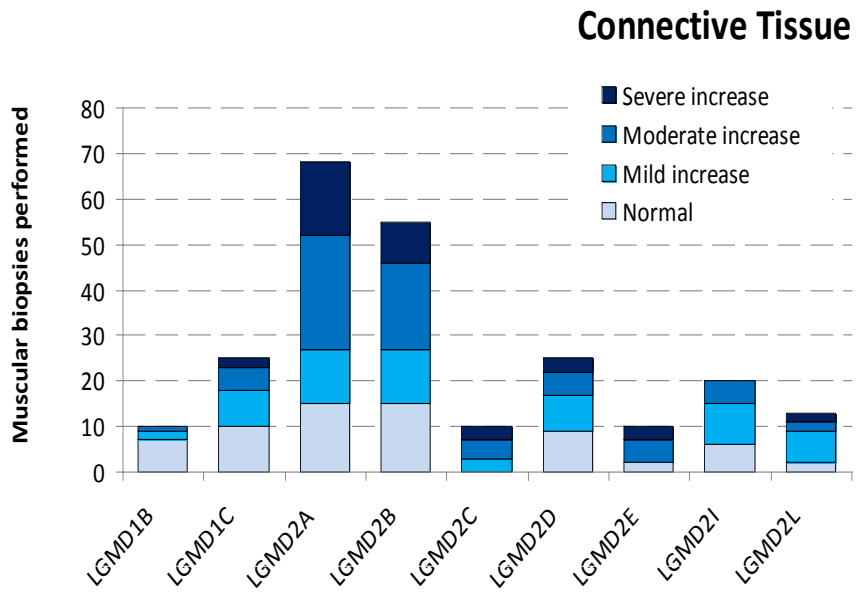
No hot-spots

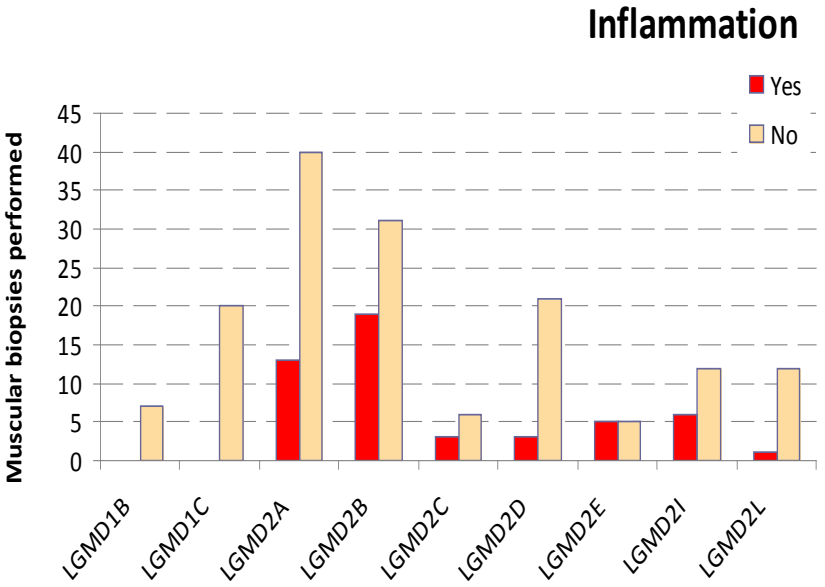
Most frequent mutations:

- **c.826C>A** (p.Leu276Ile) exon 4 (*FKRP*) → 23/38 alleles (60%) LGMD2I
- **c.525delT** (p. Phe175LeufsX20) exon 6 (*SGCG*)→ 8/22 (36%) LGMD2C
- **c.850C>T** (p.Arg284Cys) exon 7 (*SGCA*) → 16/50 (32%) LGMD2D
- **c.377_384dup** (p.Gly128GlnfsX2) exon 3 (*SGCB*)→ 9/30 (30%) LGMD2E

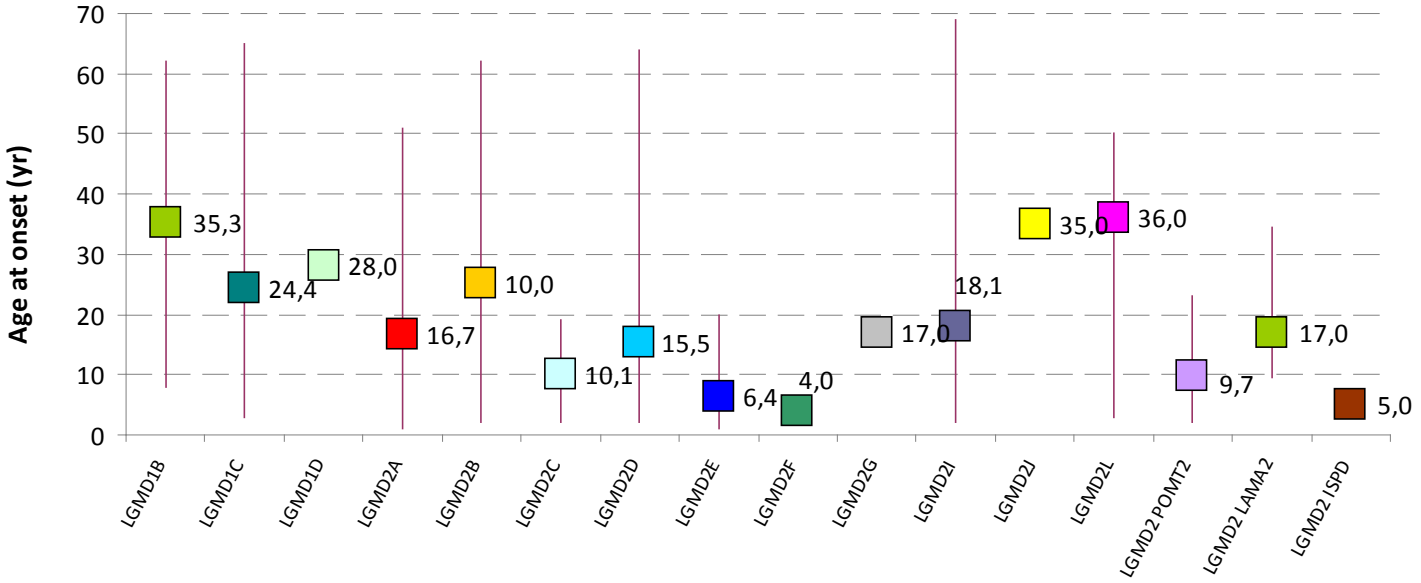
Muscle biopsy

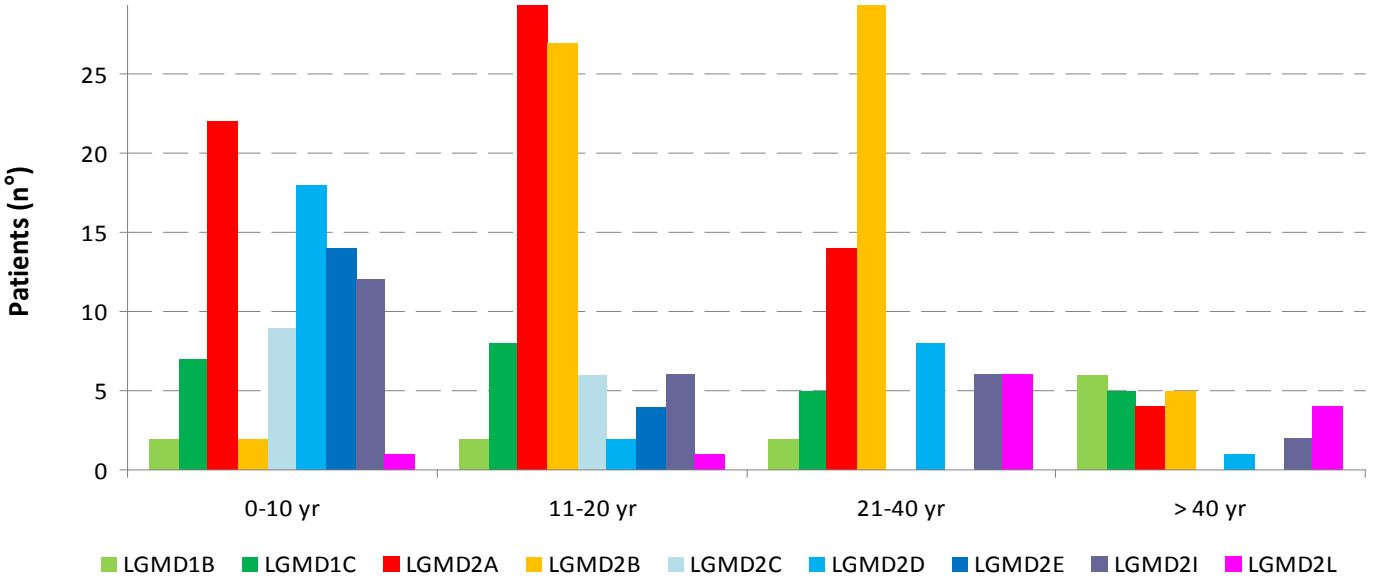




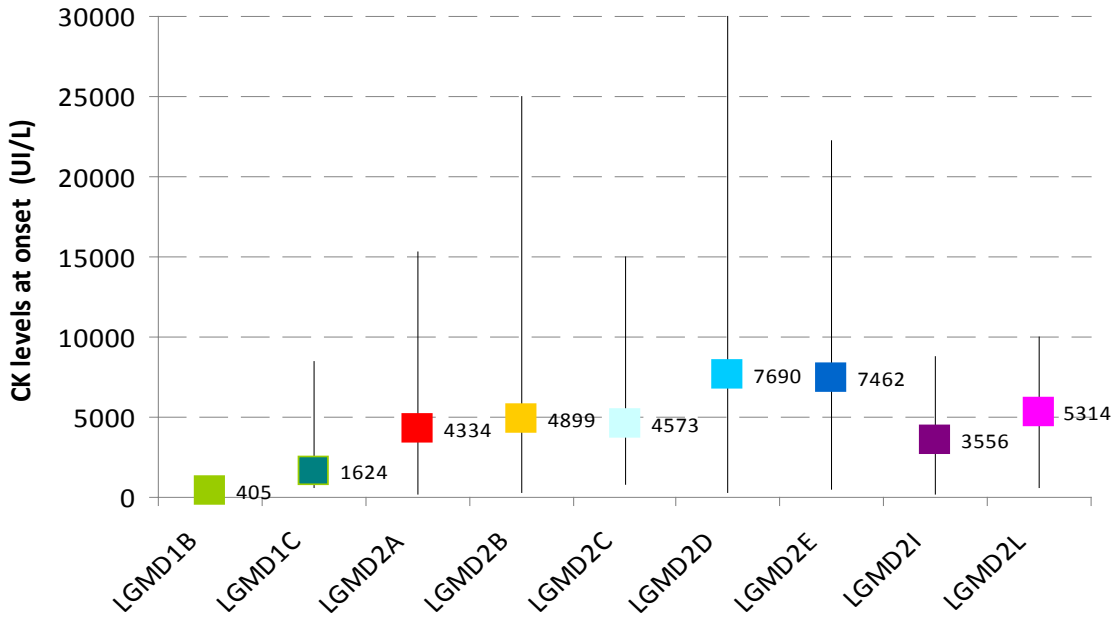


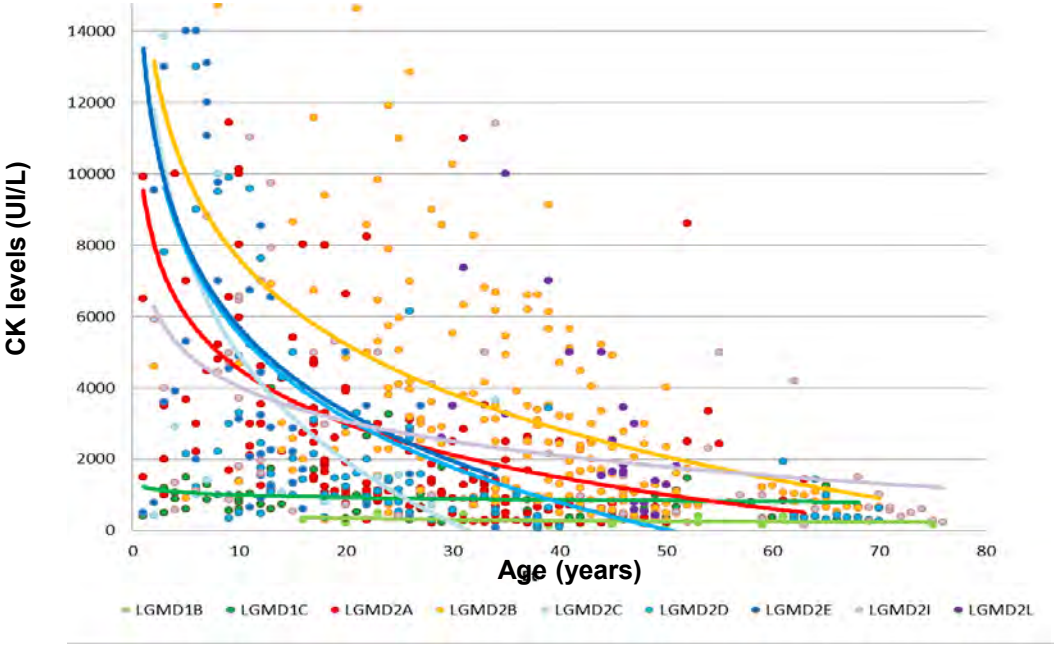
Clinical evolution – Age of onset



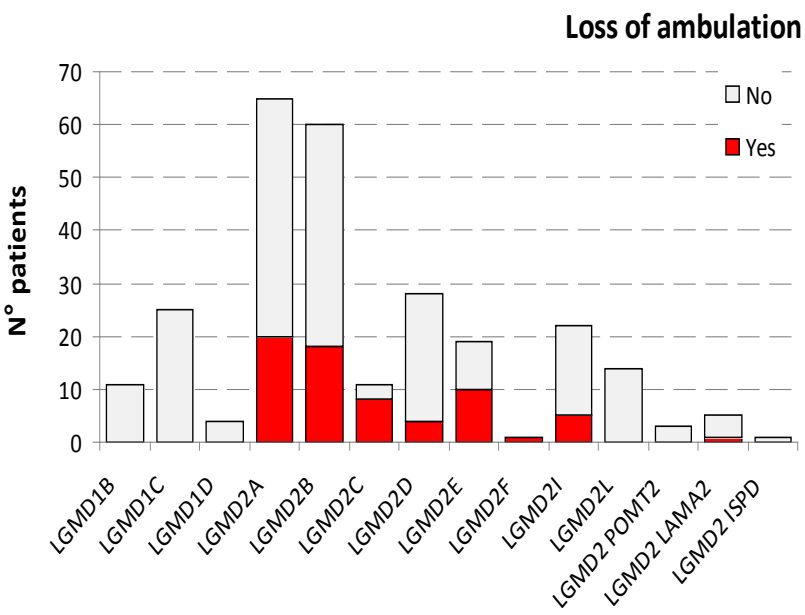


Clinical evolution – CK levels

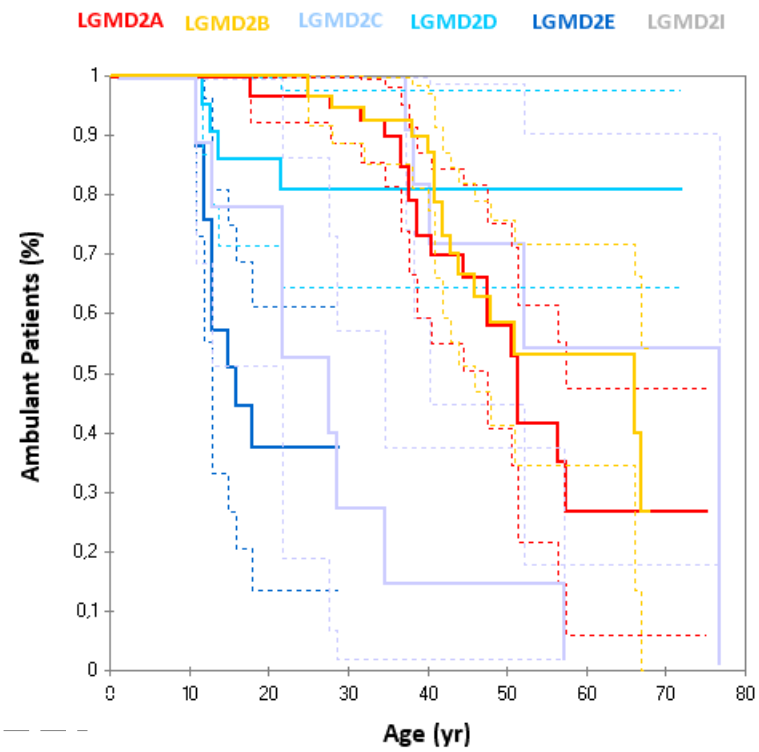


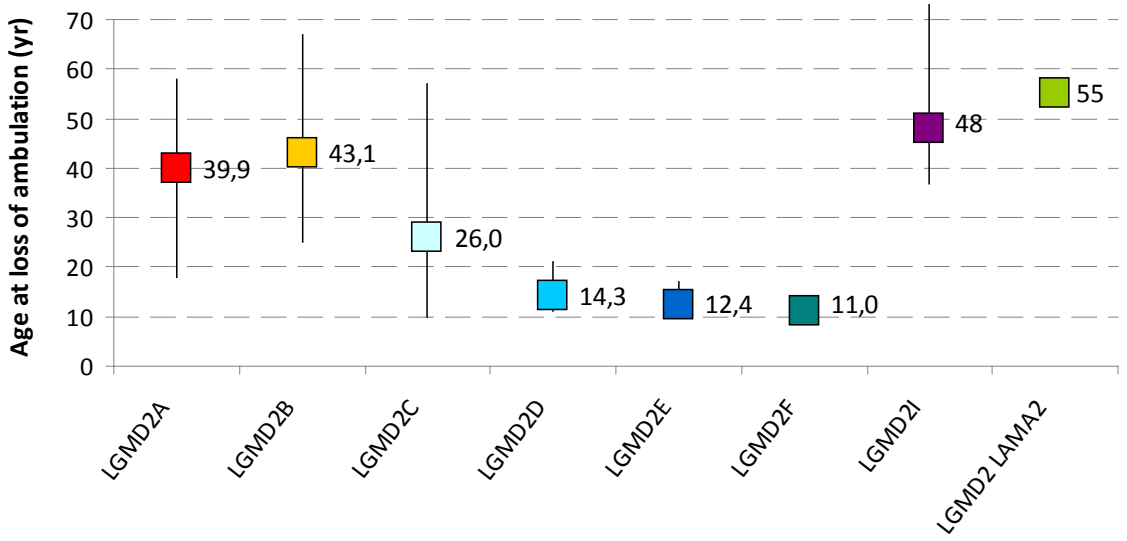


Clinical evolution – Loss of independent ambulation

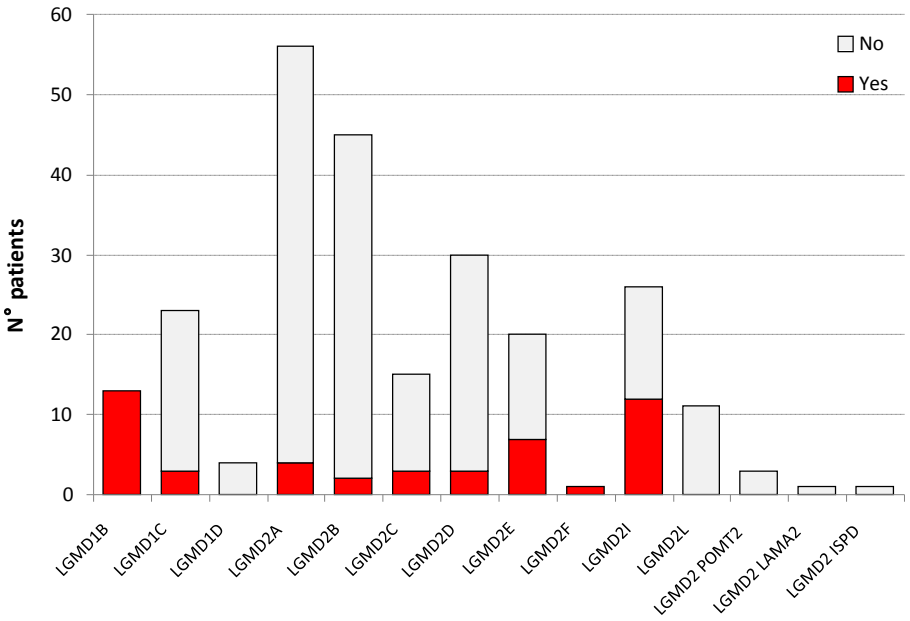


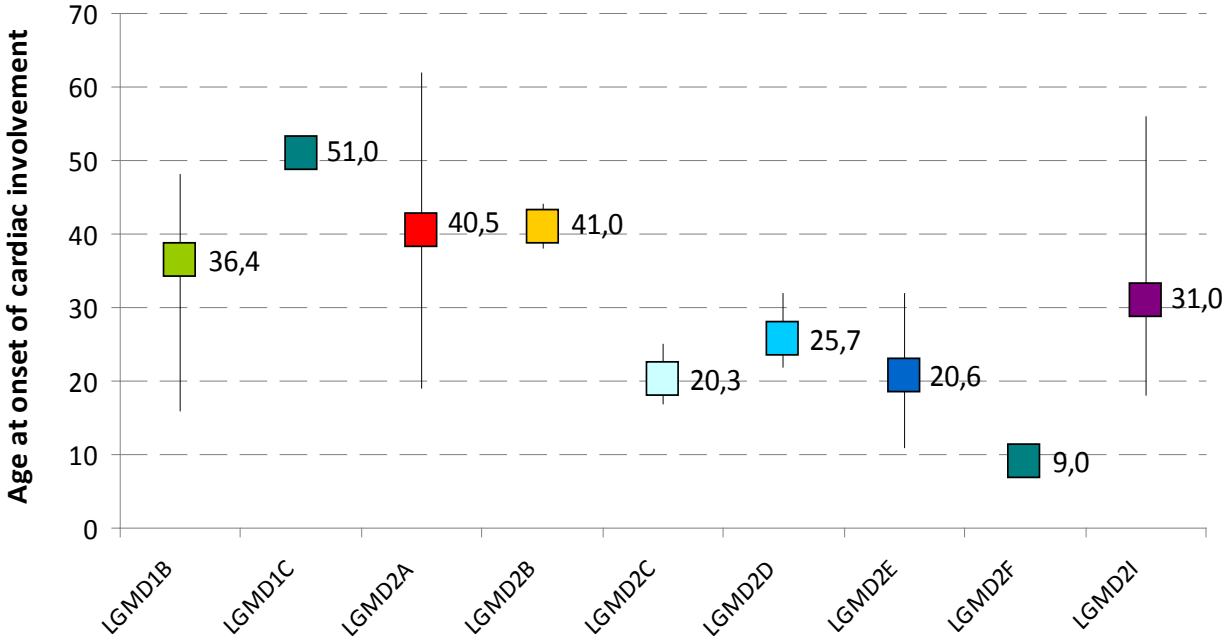
C



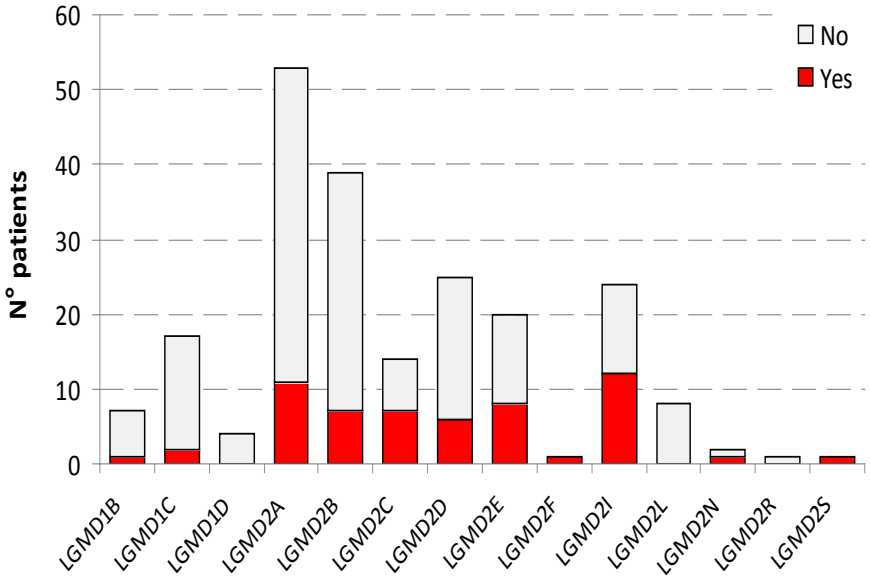


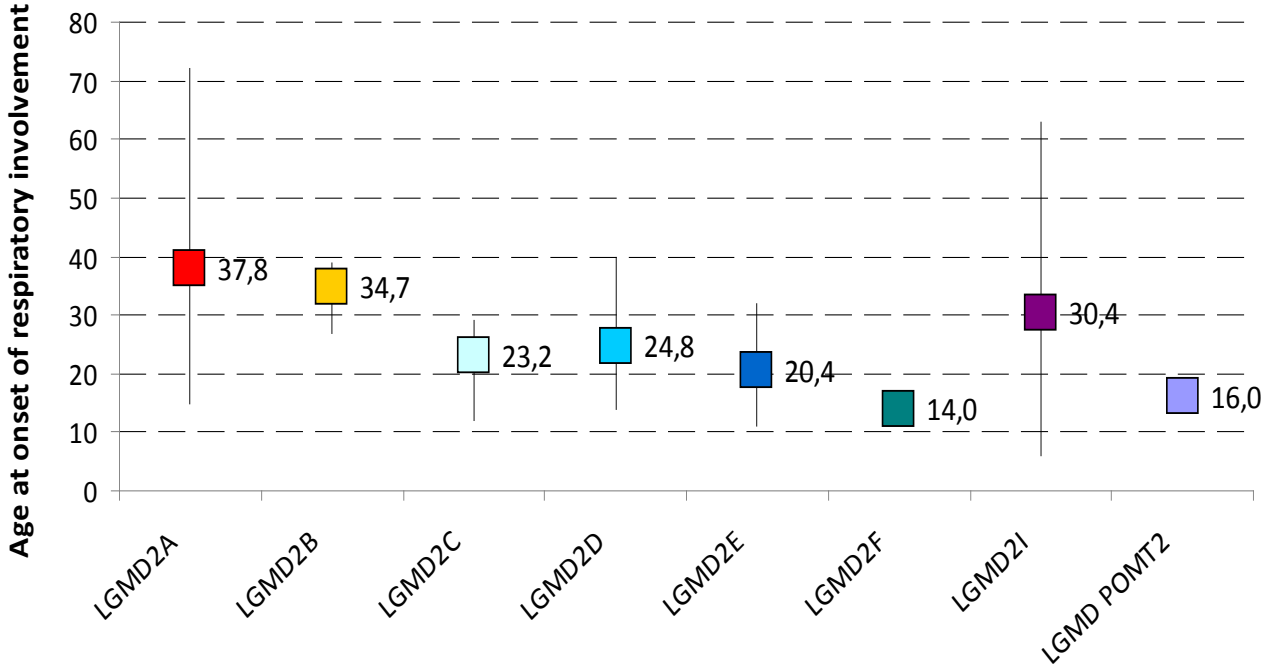
Clinical evolution – Cardiac involvement





Clinical evolution – Respiratory involvement





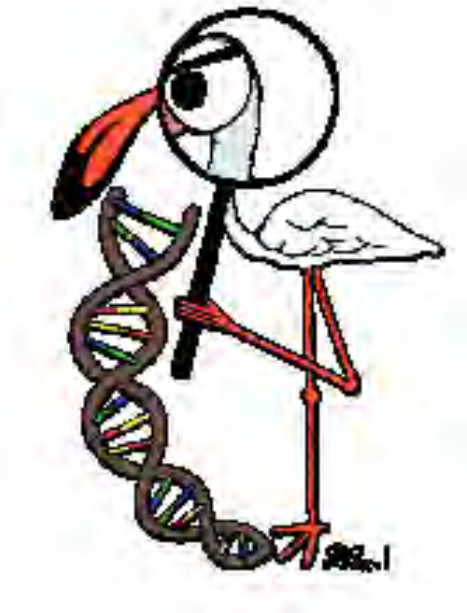
LGMD differential diagnosis

Age at onset	→	Earlier onset in LGMD2C-2E, dystroglycanopathies Later onset LGMD2I and 2L
CK levels	→	High levels in LGMD2B, LGMD2I Low levels in LGMD1B, 1C
Ambulation loss	→	Early in LGMD2D, 2E Late LGMD2A, 2B, 2C
Cardiac involvement	→	LGMD2E , LGMD2C, LGMD2F, LGMD2I, LGMD2M
Respiratory involvement	→	LGMD2A, LGMD2D, LGMD2M
Muscle biopsy analysis	→	LGMD1C, 2A, 2B, sarcoglycanopathies, dystroglycanopathies

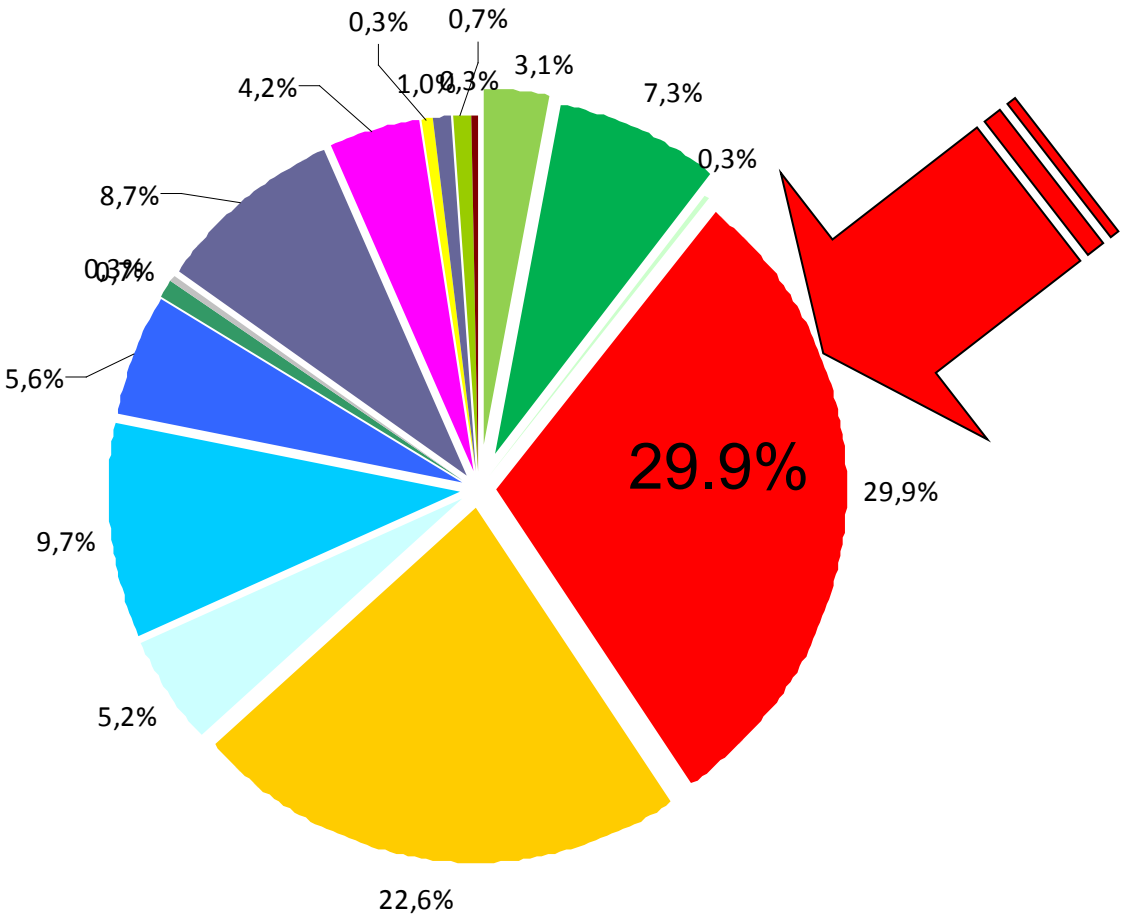
LGMD national registry

- LGMD molecular epidemiology in Italy is extremely heterogenous.
- The relative frequency of the predominant LGMD types differs in Southern Europe from that other Northern countries
- Deacreasing the proportion of genetically undiagnosed cases is probably possible by Next Generation Sequencing.
- New common or rare pahogenetic pathways may emerge from this effort.
- Building an itemised disease natural history database for at least 30 different diseases (often with allelic early onset and late onset phenotypes) is a complex and time consuming task.
- Therapeutic trials involving this population are scarce and reflect into less attention paid to the data collection to establish a reference clinical database for these disorders.

What about LGMD2A?



LGMD2A POPULATION



86 probands
92 patients

F:M= 1.3/1

Mean follow-up

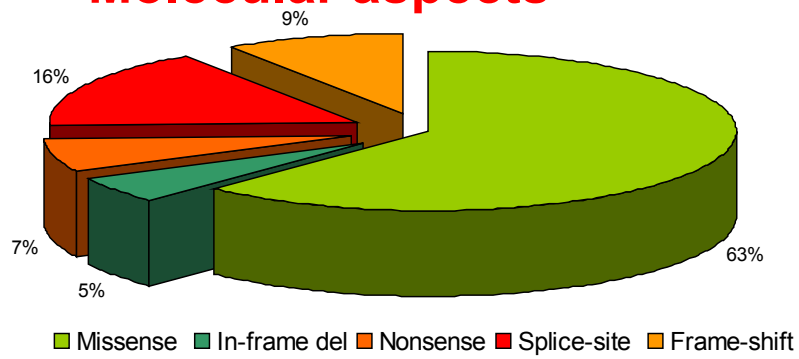
18.8 ± 9.2 years

Age ot last evaluation

37.1 ± 14.2 years

LGMD2A Diagnostic clues

Molecular aspects

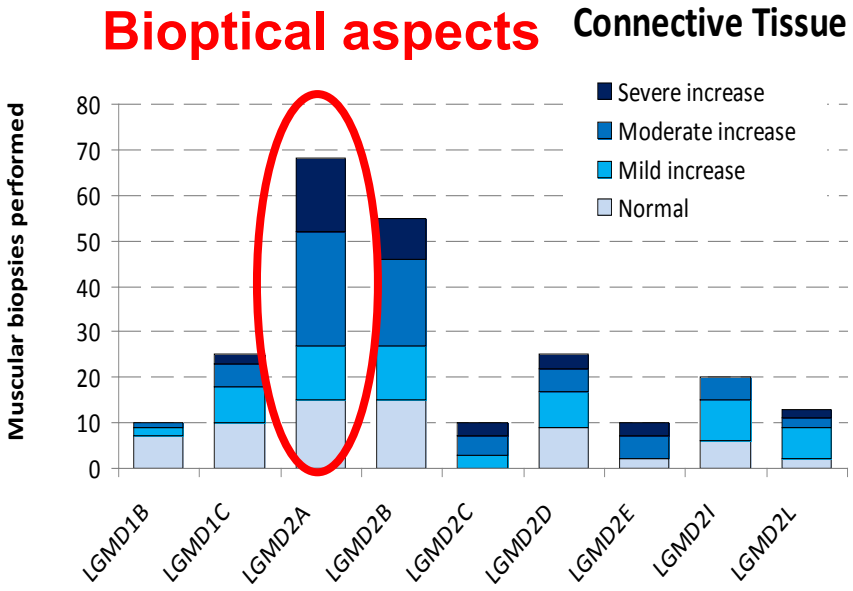


69% of mutations are located in exons 4,11,10,13,1,21,5,6

Most frequent mutations:

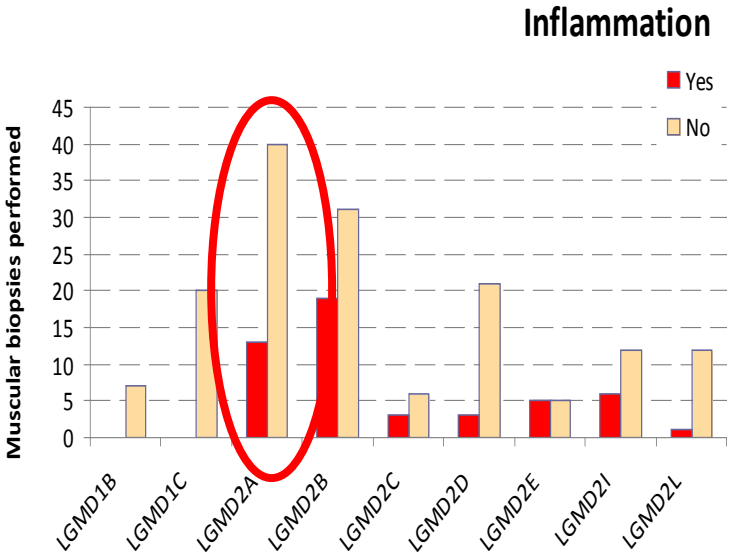
c.550delA	6.8%
c.1469G>A	6.1%
c.2242C>T	4.5%

Bioptical aspects



10 patients without connective tissue increase
(7 quadriceps femori)

No correlation with age or disease duration

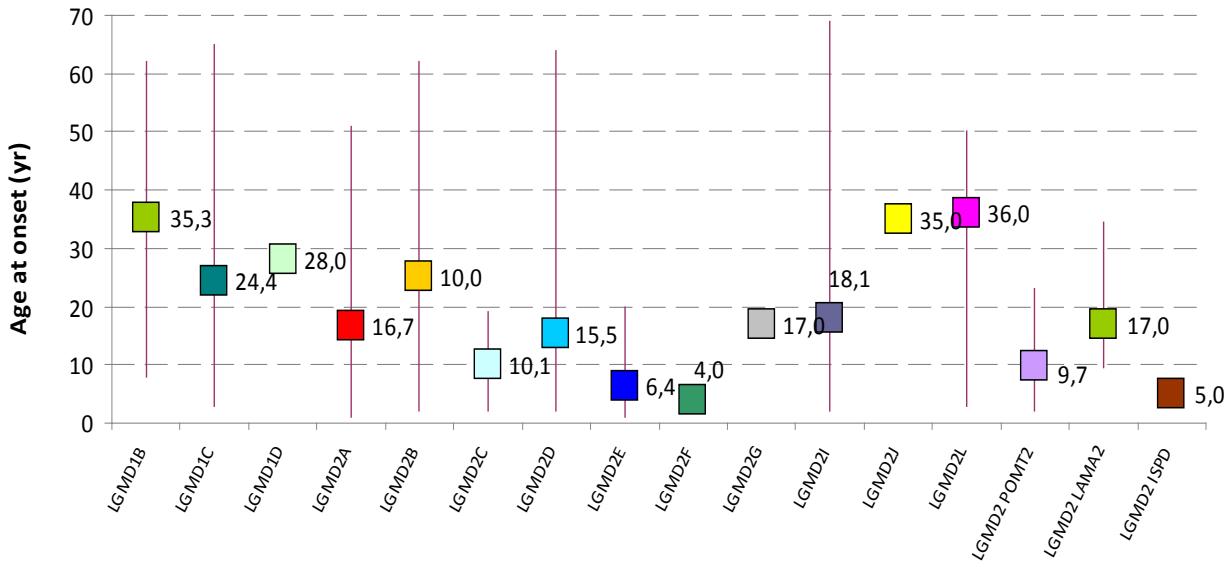


Protein analysis

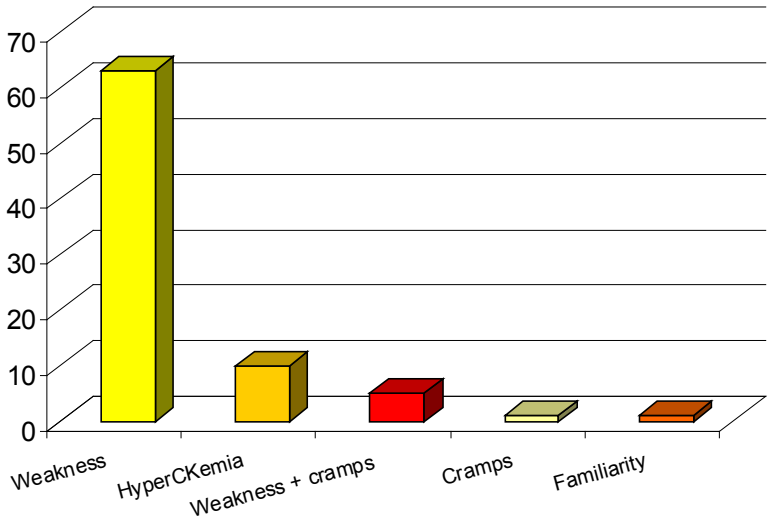
Western-blot analysis: reduction in 57 patients, normal expression in 3 subjects

LGMD2A Clinical evolution 1

Age at onset



Symptoms at onset



Onset of weakness

17.6 ± 11.8 years
(range 1-51).

< 1 years of age	→3 pt (5%)
≤ 20 years of age	→47 pt (75%)
20-40 years of age	→12 pt (19%)
> 40 years of age	→4 pt (6%)

LGMD2A Clinical evolution 2

Distribution of muscular involvement

55 patients pelvic + shoulder girdle
8 patients pelvic girdle (4-75 years old, 3-30 years from onset)
3 patient early distal involvement

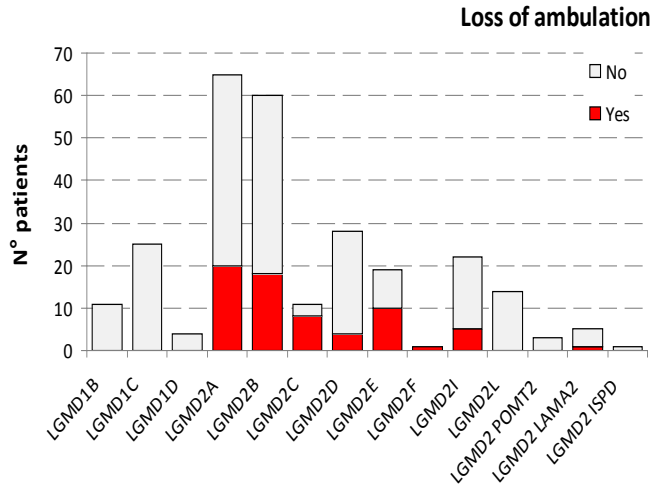
Difficulties in postural changes

27/42 → 31.9 ± 15.9 years
17.2 ± 7.0 years from onset

Loss of ambulation

20/65 → 31% mean age 39.9 ± 11.5 years

Wheelchair-bound patients have earlier onset (15.4 ± 8.3 vs 19.6 ± 12.1 years)



LGMD2A Clinical evolution 3

CK values	4025 ± 3393 UI/L (range 217-15300)
Cardiac involvement	4/56 → 7% Mean age at onset 39 ± 22 years Onset respectively at 19, 20, 55 and 62 years of age Range 8-17 years from disease onset 2 patients with dilatative cardiomyopathy Furthermore 12 patients with rhythm alteration
Respiratory involvement	11/53 → 21% Mean age at onset 37.8 ± 22.8 years Restrictive pattern
Peculiar aspects	Tendon retraction 29/51 64% Sural hypertrophy 15/49 pt Scoliosis 16/44

Thank you

UO Neurologia - IRCCS Ca´Granda– Milano
Prof. Bresolin, Prof. Comi, Dr. Magri, Prof. Corti, Dr. Govoni, Dr. Brusa, Dr. Del Bo, Dr. Ronchi, Dr Piga

UOD Neuromuscolari, IRCCS Ca´Granda, University Milan
Prof Moggio, Dr. Sciacco, Dr. Colombo, Dr Peverelli, Dr Villa
Ist. E. Medea Bosisio Parini – Lecco
Dr. D´Angelo, Dr. Gandossini
Dr. Brighina, Dr. Micoli

Istituto Neurologico C. Besta- Milano
Prof. Mora, Dr. Moroni, Dr Morandi,

Telethon Institute of Genetics and Medicine (TIGEM) – Napoli
Prof. Nigro, Dr Savarese, Dr. Di Fruscio

Dipartimento di Neuroscienze – Padova,l
Prof. Pegoraro, Dr. Semplicini

Dipartimento di Neuroscienze – Torino
Prof. Mongini

Dipartimento di Neuroscienze, Messina
Prof. Toscano, Dr. Musumeci, Dr. Vita, Dr. Messina,
Dipartimento di Scienze Neurologiche, Verona
Dr. Tomelleri, Dr Tonin

Centro di Miologia, Istituto Giannina Gaslini, Genova Prof. Minetti, Dr. Bruno

Dipartimento di neurologia, Università Cattolica del Sacro Cuore, Roma Dr. Ricci, Dr. Monforte, Dr Tasca

Dipartimento di Neuroscienze, Pisa
Prof. Siciliano, Dr. Ricci

IRCCS Fondazione "San Camillo"
Prof. Angelini

IRCCS Fondazione Stella Maris, Calambrone
Dr. Fiorillo