Clinicogenetic lessons from 370 patients with autosomal recessive limb-girdle muscular dystrophy

Jonas Alex Morales Saute
Medical Genetics Service
Hospital de Clinicas de Porto Alegre (HCPA)
Coordinator of the Reference Center in Rare Diseases - HCPA
PI of NeMuG – Neuromuscular Genetics Research Group
Universidade Federal do Rio Grande do Sul
Brazil

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GENÉTICA
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NEUROMUSCULAR GENETICS

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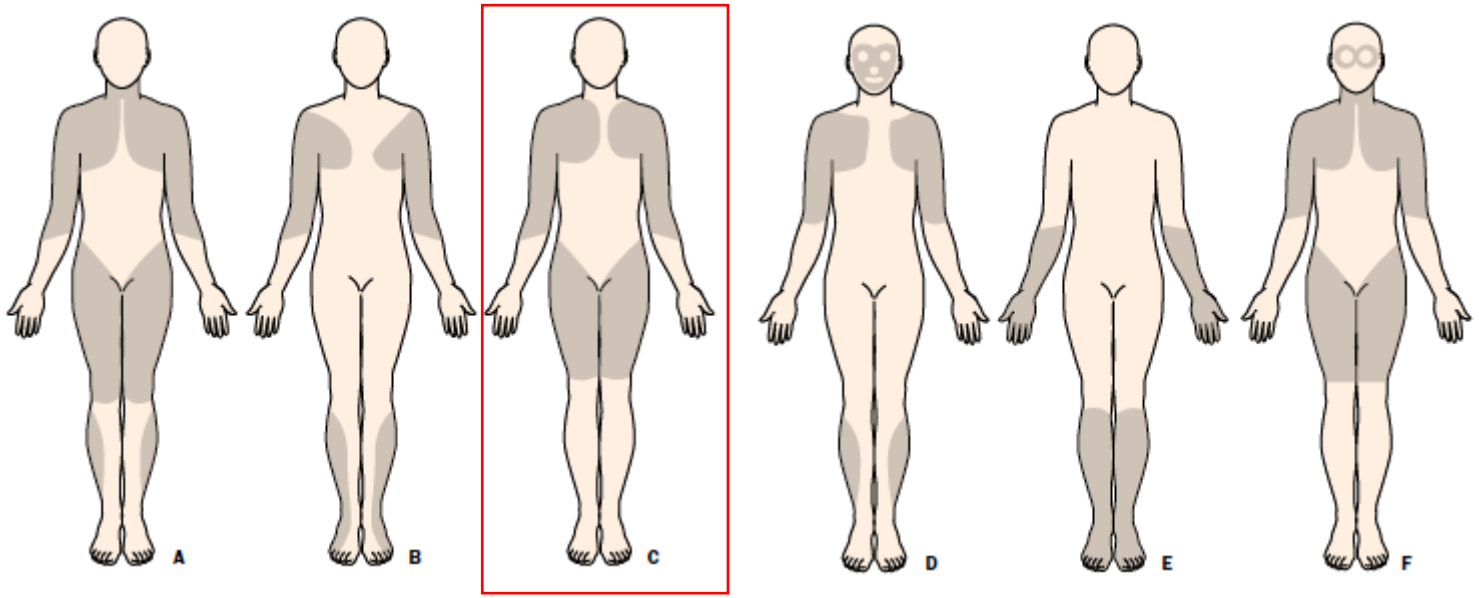
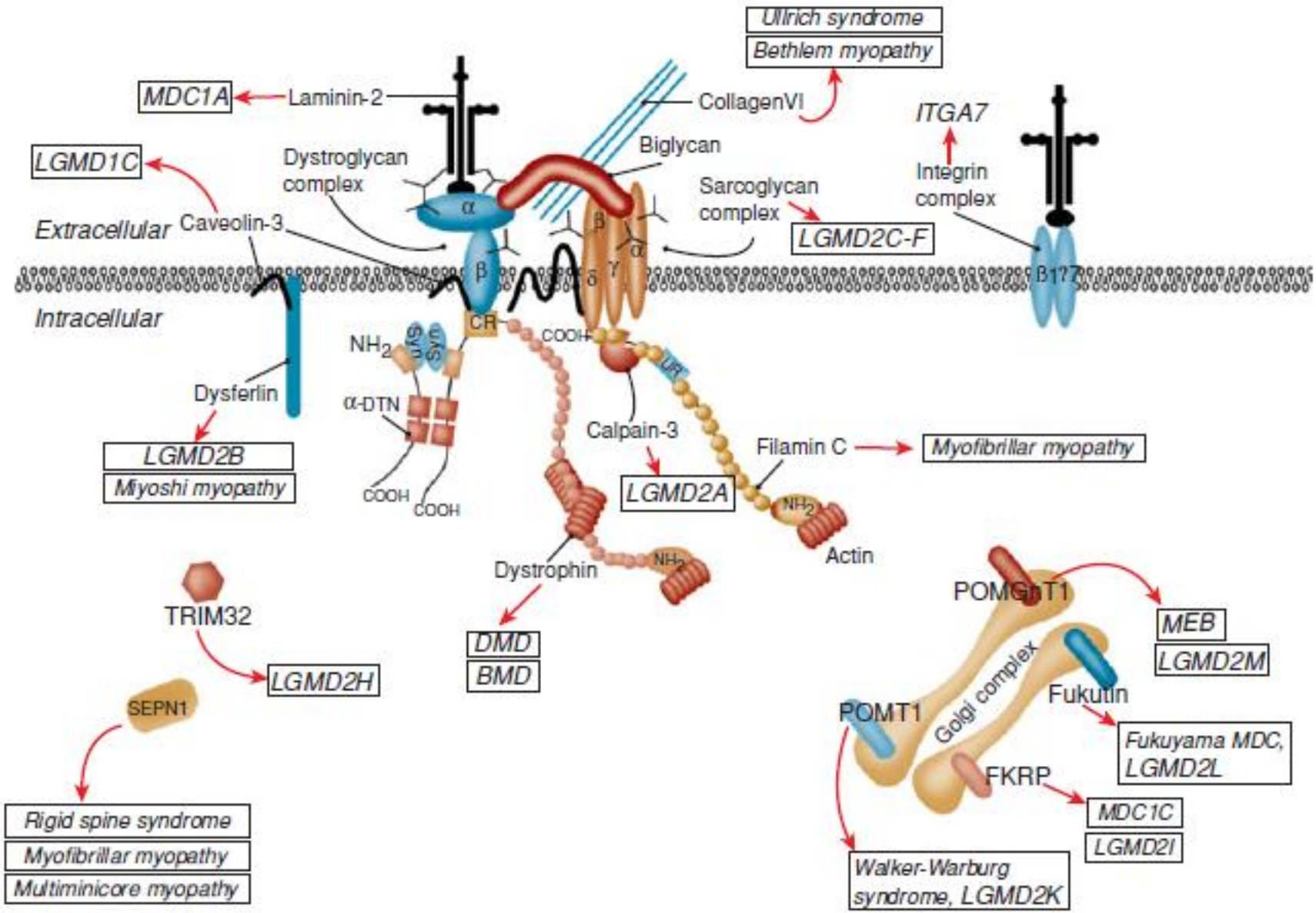
Limb girdle muscular dystrophies (LGMD)

- Heterogeneous group of genetic disorders
- Predominant proximal muscle weakness starting after independent ambulation is attained



Mercuri & Muntoni. Lancet. 2013 Mar 9;381(9869):845-60.
Shieh PB. Neurol Clin. 2013;31:1009-29.
Bastian A, et al. Rom J Intern Med. 2015;53:13–24.


Ullrich syndrome
Bethlem myopathy
MDC1A
Laminin-2
CollagenVI
ITGA7
Integrin complex
LGMD1C
Dystroglycan complex
Biglycan
Sarcoglycan complex
LGMD2C-F
Extracellular
Caveolin-3
Intracellular
Dysferlin
LGMD2B
Miyoshi myopathy
α-DTN
NH2
COOH
CR
Calpain-3
LGMD2A
Filamin C
Myofibrillar myopathy
Actin
Dystrophin
DMD
BMD
TRIM32
LGMD2H
SEPN1
Rigid spine syndrome
Myofibrillar myopathy
Multiminicore myopathy
POMGnT1
MEB
LGMD2M
POMT1
Golgi complex
Fukutin
Fukuyama MDC, LGMD2L
FKRP
MDC1C
LGMD2I
Walker-Warburg syndrome, LGMD2K

Amato A, 2008

Clinical variability in LGMD

Severe ⟵ **Moderate** ⟶ **Mild**

- Duchenne-like

- Ling-girdle weakness

- Asymptomatic increase of CK
- Exercise intolerance

Cortesy of Dr. Zanoteli E

Pergamon

Neuromusc. Disord., Vol. 5, No. 4, pp. 337–343, 1995

0960–8966/95 $9.50 + 0.00

0960–8966(95)00005–4

WORKSHOP REPORT

THE LIMB-GIRDLE MUSCULAR DYSTROPHIES — PROPOSAL FOR A NEW NOMENCLATURE

30TH AND 31ST ENMC INTERNATIONAL WORKSHOPS, NAARDEN, THE NETHERLANDS, HELD 6–8 JANUARY 1995

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 28 (2018) 702–710

www.elsevier.com/locate/nmd

Workshop report

229th ENMC international workshop: Limb girdle muscular dystrophies – Nomenclature and reformed classification Naarden, the Netherlands, 17–19 March 2017

Volker Straub[a,*], Alexander Murphy[a], Bjarne Udd[b,c,d], on behalf of the LGMD workshop study group

Old name	Gene	Proposed new nomenclature	Reason for exclusion
LGMD 1A	*Myot*	Myofibrillar myopathy	Distal weakness
LGMD 1B	*LMNA*	Emery–Dreifuss muscular dystrophy (EDMD)	High risk of cardiac arrhythmias; EDMD phenotype
LGMD 1C	*CAV3*	Rippling muscle disease	Main clinical features rippling muscle disease and myalgia
LGMD 1D	*DNAJB6*	LGMD D1 DNAJB6-related	
LGMD 1E	*DES*	Myofibrillar myopathy	Primarily false linkage; distal weakness and cardiomyopathy
LGMD 1F	*TNP03*	LGMD D2 TNP03-related	
LGMD 1G	*HNRNPDL*	LGMD D3 HNRNPDL-related	
LGMD 1H	?	Not confirmed	False linkage
LGMD 1I	*CAPN*	LGMD D4 calpain3-related	
LGMD 2A	*CAPN*	LGMD R1 calpain3-related	
LGMD 2B	*DYSF*	LGMD R2 dysferlin-related	
LGMD 2C	*SGCG*	LGMD R5 γ-sarcoglycan-related[a]	
LGMD 2D	*SGCA*	LGMD R3 α-sarcoglycan-related	
LGMD 2E	*SGCB*	LGMD R4 β-sarcoglycan-related	
LGMD 2F	*SGCD*	LGMD R6 δ-sarcoglycan-related	
LGMD 2G	*TCAP*	LGMD R7 telethonin-related	
LGMD 2H	*TRIM32*	LGMD R8 TRIM 32-related	
LGMD 2I	*FKRP*	LGMD R9 FKRP-related	
LGMD 2J	*TTN*	LGMD R10 titin-related	
LGMD 2K	*POMT1*	LGMD R11 POMT1-related	
LGMD 2L	*ANO5*	LGMD R12 anoctamin5-related	
LGMD 2M	*FKTN*	LGMD R13 Fukutin-related	
LGMD 2N	*POMT2*	LGMD R14 POMT2-related	

~10%

~90%

Straub V, et al, 2018

LGMD Epidemiology - Worldwide

- 1.63 per 100,000 individuals - Systematic review
- 0.56 in Italy to 6.9 per 100,000 in Spain
- Variable regional frequencies of LGMD2
- LGMD2A and LGMD2B → most common subtypes in Italy and USA
- LGMD2B → most common in China
- LGMD2I (FKRP) → most common in Denmark

Mah JK, et al. Can J Neurol Sci. 2016;43:163–77.
Magri F, et al. Muscle Nerve. 2017;55:55–68
Nallamilli BRR, et al. Ann Clin Transl Neurol. 2018 Dec 1;5(12):1574-1587
Yu M, et al. PLoS One. 2017 Apr 12;12(4):e0175343
Sveen ML, et al. Ann Neurol. 2006;59:808

Lack of studies in Latin America

- Few single center studies reporting sarcoglycanopathies as the most frequent subtypes in Brazil
- Case reports or small series of specific subtypes in other Latin American countries

Passos-Bueno MR, et al. Am J Med Genet. 1999 Feb 19;82(5):392-8.
Comerlato EA, et al. Arq Neuropsiquiatr. 2005 Jun;63(2A):235-45.
Albuquerque, MAV. Arquivos de Neuro-Psiquiatria, 72(6), 481.

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ORIGINAL ARTICLE

CLINICAL GENETICS WILEY

Clinicogenetic lessons from 370 patients with autosomal recessive limb-girdle muscular dystrophy

Pablo B. Winckler[1,2] | André M.S. da Silva[3] | Antônio R. Coimbra-Neto[4,5] | Elmano Carvalho[6] | Eduardo B.U. Cavalcanti[7] | Cláudia F.R. Sobreira[8] | Carlo D. Marrone[9,10] | Marcela C. Machado-Costa[11] | Alzira A.S. Carvalho[12] | Raimunda H.F. Feio[13] | Cleonísio L. Rodrigues[14] | Marcus V.M. Gonçalves[15] | Renata B. Tenório[16] | Rodrigo H. Mendonça[3] | Ana Cotta[6] | Júlia F.O. Paim[6] | Cynthia Costa e Silva[7] | Camila de Aquino Cruz[8] | Marjory I. Benâ[8] | Daniel F.A. Betancur[9] | Antonette S. El Husny[13,17] | Isabel C.N. de Souza[13] | Regina C.B. Duarte[18,19] | Umbertina C. Reed[3] | Márcia L.F. Chaves[1,2,20] | Edmar Zanoteli[3] | Marcondes C. França Jr[4,5] | Jonas A. Saute[1,2,16,20]

- To characterize the clinical, molecular and epidemiological information regarding LGMD2 in Brazil
- To provide genotype-phenotype correlation, prognostic and natural history information of most frequent subtypes
- To understand better disease natural history and to design better clinical trials for LGMD2

Winckler et al, 2019 accepted for publication, Clinical Genetics

Methods

- **Design:** multicenter, historical cohort study at 13 neuromuscular disorders centers in Brazil: 3 centers from South, 5 centers from Southeast, 1 center from Midwest, 2 centers from Northeast, and 2 centers from the North region.
- **Period:** Index cases and affected relatives data from consecutive families were reviewed from July 2017 to August 2018

Methods

➢ **Eligibility criteria:**

- Inclusion criteria:

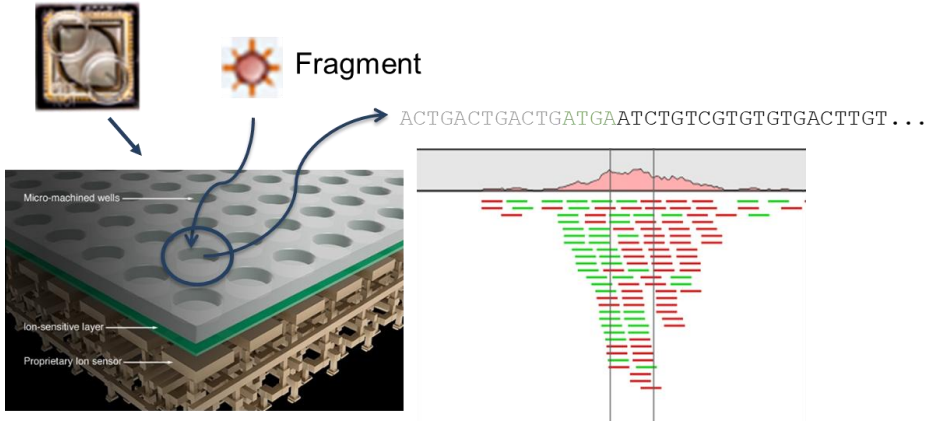
Clinical suspicion of LGMD and the presence of at least one of the following criteria

- presence of at least a likely pathogenic variant in a LGMD2 gene
- LGMD2 subtype diagnosis based on muscle immunohistochemistry (IHC) or western blot (WB) analysis.

- Exclusion criteria:

- Patients with *GAA* pathogenic variants

Methods



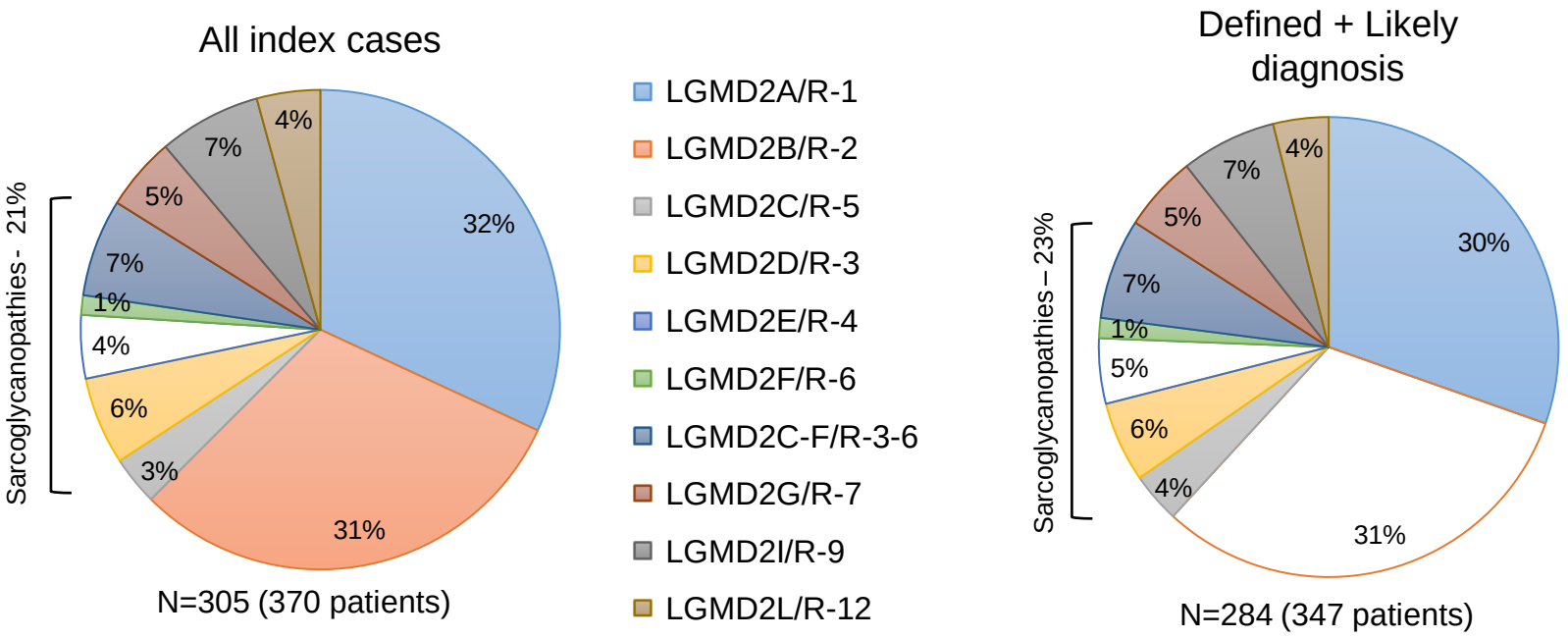
➢ **Molecular Analysis**

- Most centers → commercial targeted NGS panel including *ANO5, CAPN3, DYSF, FKRP, SGCA, SGCB, SGCD, SGCG* and *TCAP*.

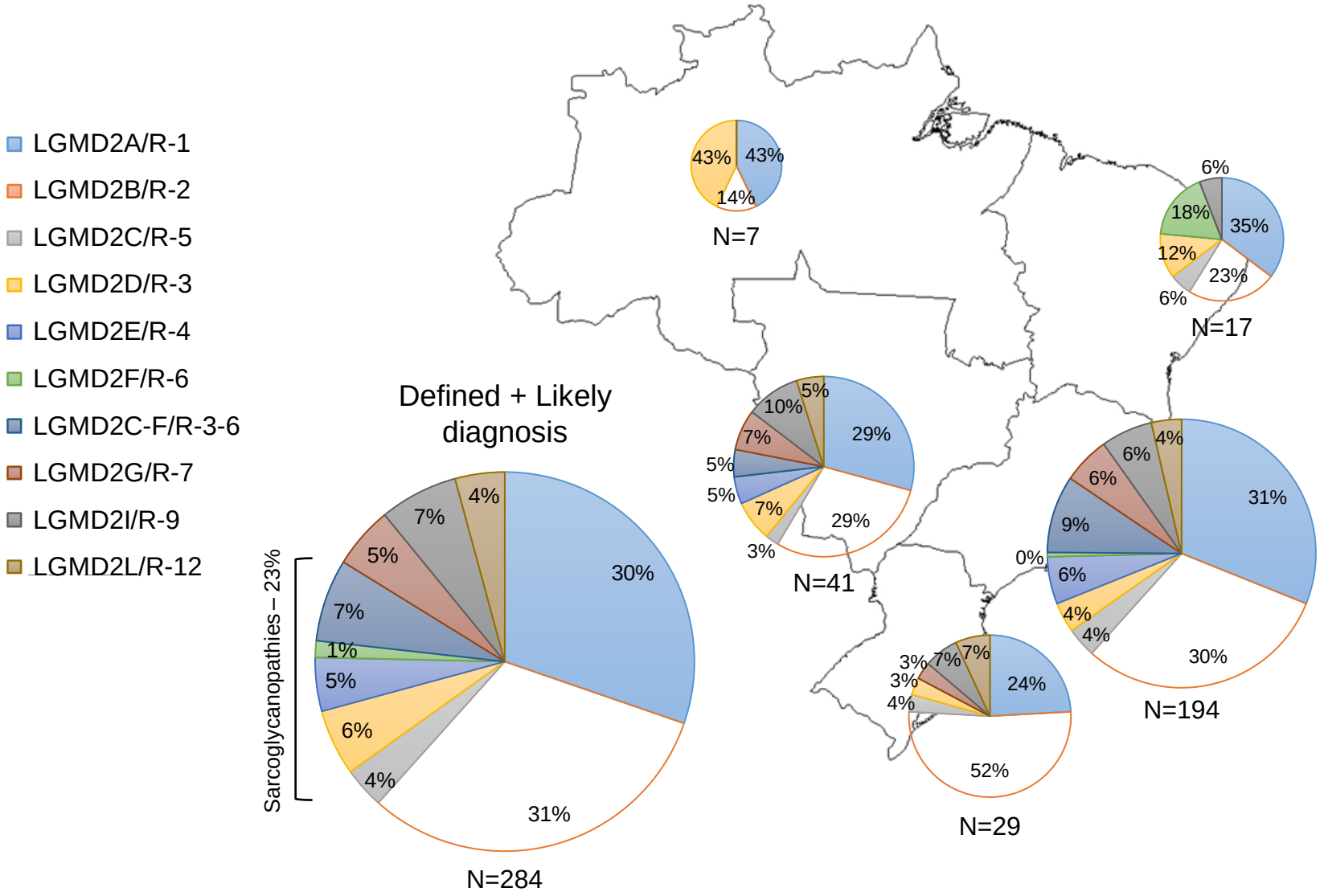
➢ **Ethics**

- GPPG-HCPA/17-0340; HGF-1.347.489

Results – 370 LGMD2 patients



Results


LGMD2A/R-1
LGMD2B/R-2
LGMD2C/R-5
LGMD2D/R-3
LGMD2E/R-4
LGMD2F/R-6
LGMD2C-F/R-3-6
LGMD2G/R-7
LGMD2I/R-9
LGMD2L/R-12
Defined + Likely diagnosis
Sarcoglycanopathies – 23%
30%
31%
4%
6%
5%
1%
7%
7%
5%
4%
N=284
43%
43%
14%
N=7
6%
35%
23%
6%
12%
18%
N=17
29%
29%
3%
7%
5%
5%
10%
7%
5%
N=41
31%
30%
4%
4%
6%
0%
6%
9%
6%
4%
N=194
24%
52%
4%
3%
3%
7%
7%
N=29

Results – molecular Analysis

- 119 different disease-related variants identified
- 37 novel variants

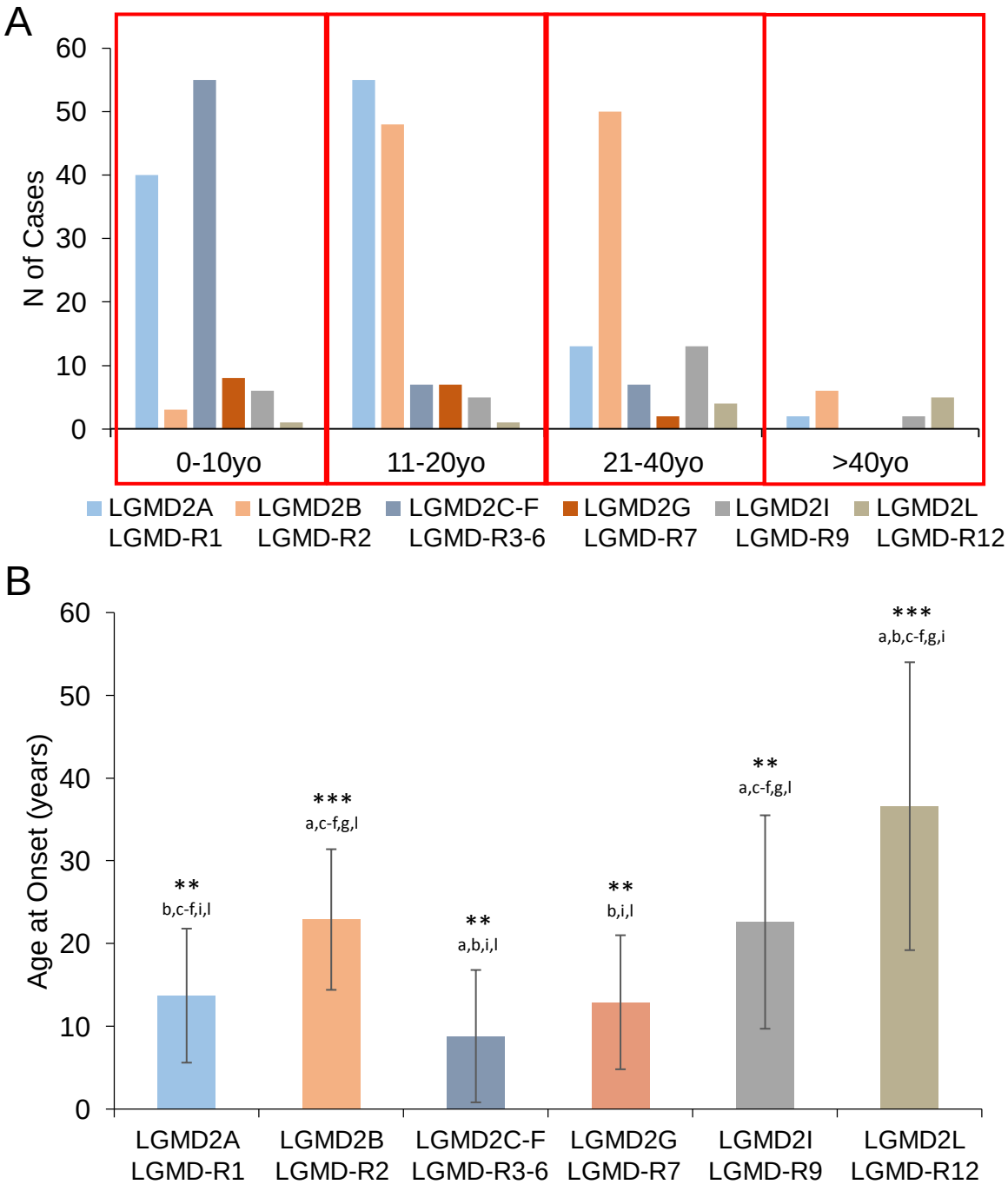
Table 2 – Novel variants in LGMD2/LGMD-R genes

Gene	Nucleotide change	AA change	Mutation type	AF[1]	AF[2]	SIFT	Poly Phen2	MT	CADD	MCAP	GERP ++[3]	Segregation	Functional Evidence	Fam	N[4]	Leiden	ClinVar	ACMG criteria[5]	Classification
DYSF	c.855+1G>A	-	Splice Site	0	0	NA	NA	1	31	NA	4.46	Yes	Yes (dysferlin absent)	1	2	No	No	PVS1,PS3, PM2	Pathogenic
DYSF	c.1163_1165dupCCG	p.Ala388dup	Small Duplication	0	0	NA	NA	0.99	NA	NA	5.47	NA	NA	1	1	No	No	PM1,PM2, PM4	Likely Pathogenic
DYSF	c.1165G>T	p.Glu389*	Nonsense	0	0	NA	NA	1	48	NA	5.47	NA	NA	1	1	No	No	PVS1,PM2	Likely Pathogenic
DYSF	c.2218delC	p.Leu740Cysfs*9	Frameshift	0	0	NA	NA	1	NA	NA	3.54	NA	NA	1	1	No	No	PVS1,PM2	Likely Pathogenic
DYSF	c.2901dupC	p.Met968Hisfs*3	Frameshift	0	0	NA	NA	1	NA	NA	3.37	NA	Yes (dysferlin reduced)	3	2	No	No	PVS1,PS3, PM2	Pathogenic
DYSF	c.2996G>A	p.Trp999*	Nonsense	0	0	NA	NA	1	41	NA	4.64	Yes	Yes (dysferlin absent)	1	2	Yes	No	PVS1,PS3, PM2	Pathogenic
DYSF	c.3071C>T	p.Pro1024Leu	Missense	0.00009	0	0.01	1	0.99	24	0.231	4.14	NA	NA	1	1	No	Yes (1 VUS)	PM2,PP3	VUS
DYSF	c.3115C>T	p.Arg1039Trp	Missense	0.00002	0	0.02	1	0.99	25.5	0.472	3.27	NA	NA	1	1	Yes (dysferlin absent - IHC)	Yes (2 VUS)	PS3,PM2, PP3	Likely Pathogenic
DYSF	c.3235_3236insAGGCGG	p.Phe1079*	In-frame Insertion (Nonsense)	0	0	NA	NA	1	NA	NA	5.6	NA	NA	1	1	No	No	PVS1,PM2	Likely Pathogenic
DYSF	c.3280T>C	p.Trp1094Arg	Missense	0	0	0.01	0.997	0.99	29.9	0.205	5.6	NA	NA	1	1	No	No	PM2,PP3	VUS
DYSF	c.3486_3487delGG	p.Asp1163Profs*11	Frameshift	0	0	NA	NA	1	NA	NA	3.37 (1.15-5-59)	NA	NA	1	1	No	No	PVS1,PM2	Likely Pathogenic
FKRP	c.1403T>C	p.Phe468Ser	Missense	0	0	0	0.879	0.99	29.1	0.730	5.44	NA	NA	1	1	NA	No	PM2,PP3	VUS
SGCA	c.502G>A	p.Gly168Arg	Missense	0.00001	0	0.09	0.755	0.99	24.1	0.551	4.58	NA	NA	1	1	No	Yes (1 VUS)	PM2	VUS
SGCB	c.753+5G>A	-	Intronic	0	0	NA	NA	1	21.7	NA	5.12	NA	NA	1	1	Yes (1 case)	No	PM2,PP3[7]	VUS
SGCG	c.629A>G	p.His210Arg	Missense	0.00001	0	0.13	0.012	0.99	14.29	0.079	4.44	NA	Yes (γ-sarcoglycan deficient)	1	1	Yes (2 cases)	No	PS3,PM2, PP3	Likely Pathogenic

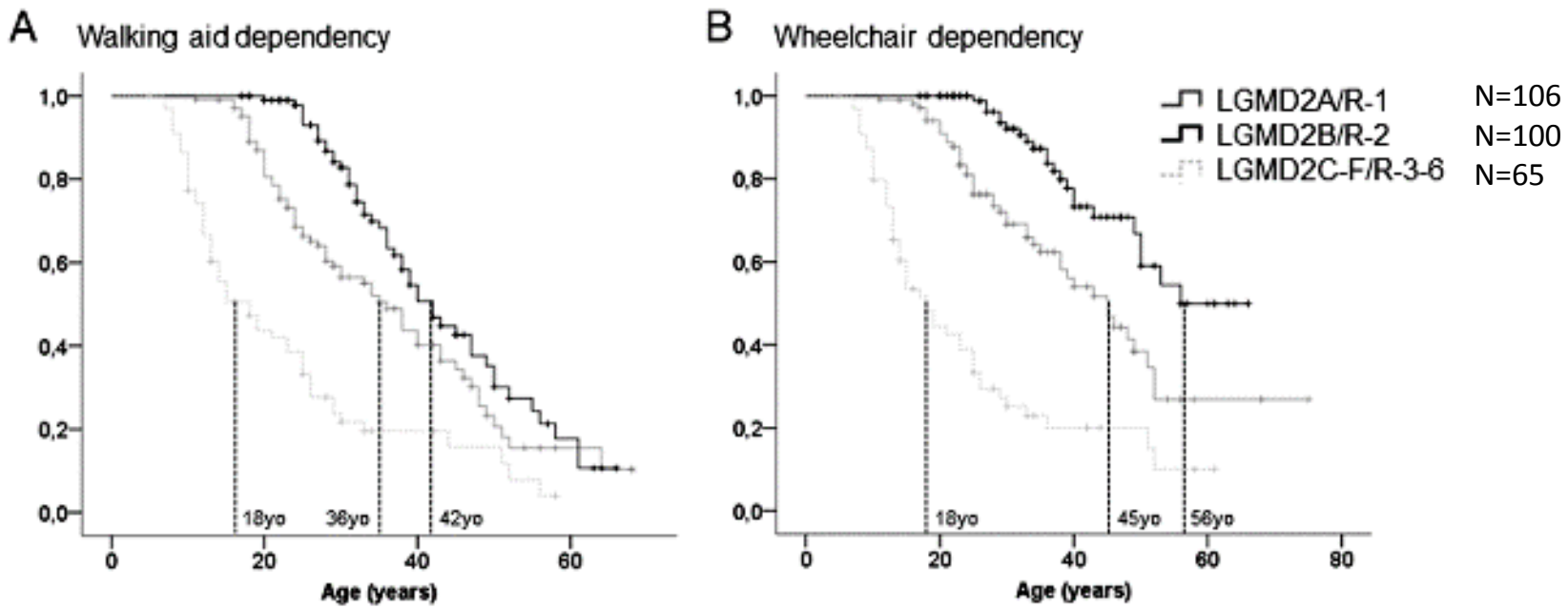
Allele frequencies on [1]gnomAD and [2]1000 genomes browsers; [3] GERP++ data is shown as mean (standard deviation) or raw value;[4] total number of individuals; [5] American College of Medical Genetics and Genomics criteria, Richards et al, 2015; [6] polymorphism prediction; [7] alteration of the WT donor site on Human Splicing Finder 3.1 (http://www.umd.be/HSF3/). AA, amino acid; AF, allele frequency; Fam, families; IHC, immunohistochemistry; MT, Mutation Taster; NA, not available; VUS, variant of unknown significance; alteration of the WT donor site (HSF 3.0); WB, Western Blot.

Results

Age at Onset



Results – Disease Progression
LGMD2A, LGMD2B and sarcoglycanopathies

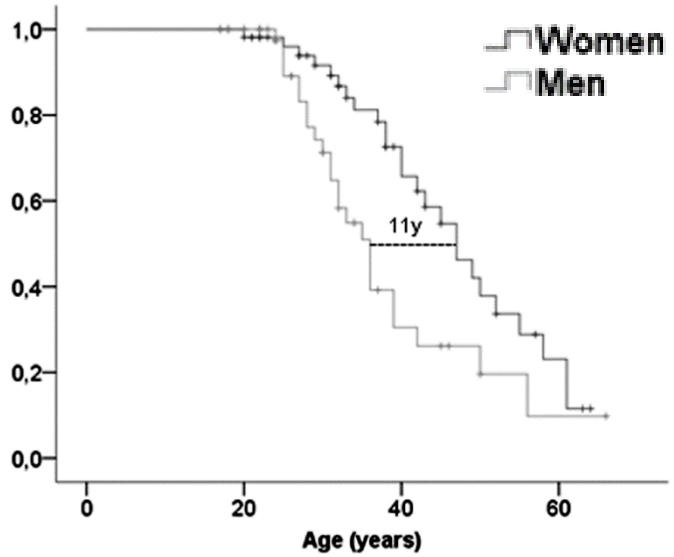

A
Walking aid dependency
1,0
0,8
0,6
0,4
0,2
0,0
18yo
36yo
42yo
0
20
40
60
Age (years)
B
Wheelchair dependency
LGMD2A/R-1
LGMD2B/R-2
LGMD2C-F/R-3-6
N=106
N=100
N=65
18yo
45yo
56yo
80

Results

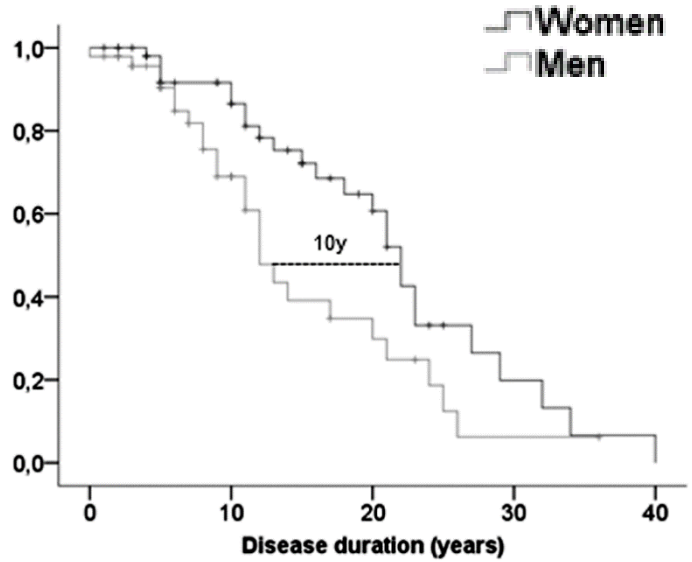
Sex-related effect on disease progression

LGMD2B

A Walking aid dependency



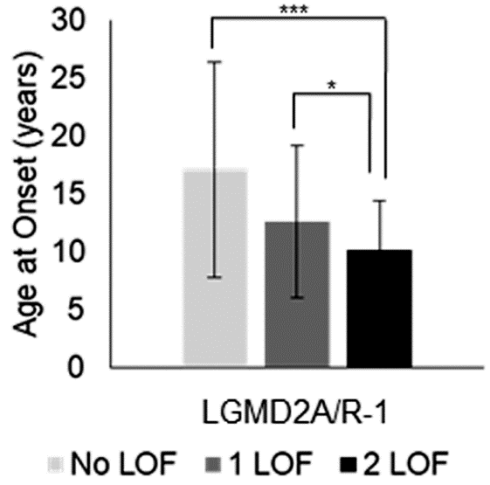
C Walking aid dependency



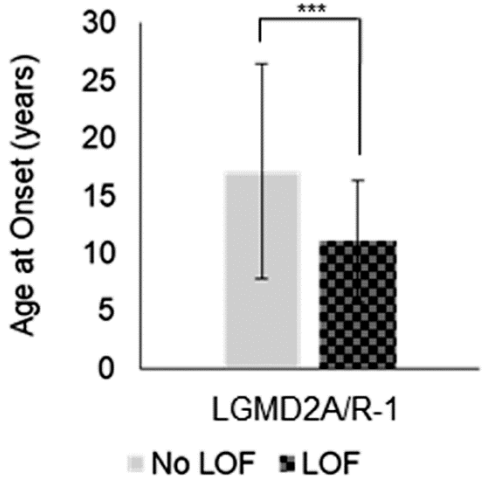
Results - Genotype–Phenotype Correlations LGMD2A

N=110

A



B



No diferences for LGMD2B/LGMD-R2-dysferlin-related (N=45) and sarcoglycanopathies (N=46)

Results - Cardiac and Respiratory Involvement

	LGMD2A/R1	LGMD2B/R2	LGMD2C-F/ R3-6	LGMD2G/R7	LGMD2I/R9	LGMD2L/R12
Affected gene	*CAPN3*	*DYSF*	*SGCA-B-G-D*	*TCAP*	*FKRP*	*ANO5*
Heart conduction disorder (%)	1/105 (1%)	1/83 (1.2%)	0/53 (0%)	0/17 (0%)	6/20 (30%)	0/11 (0%)
Structural heart disease (%)	0/91 (0%)	1/83 (1.2%)	3/51 (5.8%)	0/17 (0%)	8/20 (40%)	0/11 (0%)
Respiratory Involvement (%)	22/102 (21.5%)	13/80 (16.2%)	22/39 (56.4%)	3/13 (23.1%)	9/14 (64.3%)	2/9 (22.2%)
Lung restriction severity[d]						
Mild	16/100 (16%)	9/79 (11.4%)	9/35 (25.7%)	2/13 (15.4%)	4/11 (36.4%)	1/9 (11.1%)
Moderate	6/100 (6%)	2/79 (2.5%)	3/35 (8.6%)	1/13 (7.7%)	0/11 (0%)	0/9 (0%)
Severe	2/100 (2%)	1/79 (1.3%)	6/35 (17.1%)	0/13 (0%)	5/11 (45.5%)	1/9 (11.1%)
Ventilatory Support (%)	2/104 (1.9%)	1/105 (1%)	4/38 (10.5%)	0/15 (0%)	2/22 (9.1%)	0/8 (0%)

Discussion - Epidemiology

- LGMD2A and LGMD2B are the most frequent subtypes in Brazil → 30% of families each
- Epidemiology

- ≤ 10 years-old: sarcoglycanopathies
- 11 and 20 years-old: LGMD2A followed by LGMD2B
- 21 and 40 years-old: LGMD2B
- > 40 years-old: LGMD2B and LGMD2L

Discussion – Epidemiology

- Similar profile to recent large cohorts from Italy and USA

Magri F, et al. Muscle Nerve. 2017;55:55–68.
Nallamilli BRR, et al. Ann Clin Transl Neurol. 2018 Dec 1;5(12):1574-1587.

- Differed from previous Brazilian reports

- São Paulo (Genoma), single center, 37 children → 40.5% sarcoglycanopathies
- Curitiba, single center, 56 patients, IHQ only → 32% sarcoglycanopathies, followed by LGMD2B 14.3%
- São Paulo (USP), single center, 40 families → 55% sarcoglycanopathies, followed by LGMD2B 25%

- Brazil, multicentric, 115 families → 20% sarcoglycanopathies (other forms not evaluated

Passos-Bueno MR, et al. Am J Med Genet. 1999 Feb 19;82(5):392-8.
Comerlato EA, et al. Arq Neuropsiquiatr. 2005 Jun;63(2A):235-45.
Albuquerque, MAV. Arquivos de Neuro-Psiquiatria, 72(6), 481.
Vainzof M, et al. J Neurol Sci. 1999 Mar 15;164(1):44-9.

Discussion – Epidemiology

- 5% of our families had LGMD2G → ultra rare subtype worldwide

- all families were homozygous for the p.Gln53* variant in *TCAP – NMD therapies?*

Moreira ES, et al. Limb-girdle muscular dystrophy type 2G is caused by mutations in the gene encoding the sarcomeric protein telethonin. Nat Genet. 2000 Feb;24(2):163-6.

Discussion - disease progression and its modifiers – sex-effect in LGMD2B

- Earlier ages and disease durations at walking aid dependency for men than for women
- Higher fiber atrophy factor in males than females with LGMD2B → male patients had lower muscle fiber diameter and cross-sectional area and higher atrophic factor than male controls → affected and control females did not differ in this parameters
- Future clinical trials in LGMD2B should consider to control the randomization by sex

Fanin M, Nascimbeni AC, Angelini C. Clin Neuropathol. 2014; 33(3):179-85.

Discussion - disease progression and its modifiers - genotype

- LGMD2A patients with one or two truncating variants started earlier and progressed faster than patients without truncating variants.
- Similar findings for age at onset in a large Italian cohort. Effect on disease progression not tested.
- Another large sample study in LGMD2A (113 patients) found that patients with at least one missense variant started the disease later than patients with two truncating mutations. Inadequate analysis for effect on disease progression.
- Future clinical trials in LGMD2A/LGMD-R1-calpain3-related should consider to control randomization according to genotype

Magri F, et al. Muscle Nerve. 2017;55:55–68.
Sáenz A, et al. Brain. 2005 Apr;128(Pt 4):732-42.

Conclusion

- LGMD2A (111 patients) and LGMD2B (109 patients) → most frequent subtypes of LGMD2 in Brazil.
- Females with LGMD2B had a less severe progression to handicap than males
- LGMD2A patients with truncating variants had earlier disease onset and more severe progression to handicap
- Results of great importance to understand the epidemiology of LGMD2 in Brazil and Latin America
- Paramount to better design future natural history studies and clinical trials for LGMD2

SAREPTA PIPELINE

JAIN FOUNDATION

Coalition to Cure Calpain 3

Overcoming Weakness with Strength

https://www.sarepta.com/our-pipeline - accessed June 19, 2019

Thank you!

Genetic profile of Brazilian patients with dystrophinopathies

Paula Abreu Ducceschi de Almeida[1], Marcela Câmara Machado-Costa[2], Gabrielle Novais Manzoli[2], Leticia Sauma Ferreira[1], Maria do Carmo de Souza Rodrigues[4], Larissa Souza Mario Bueno[2,3], Jonas Alex Morales Saute[5], Filippo Pinto Vairo[5], Ursula da Silveira Matte[5,6], Marina Siebert[5,6], Silvia Liliana Cossio[5,6], Gabriel S. Macedo[5], Pablo Brea Winckler[7], Michele Michelin Becker[8], Lucas Vilas Boas Magalhães[9], Marcus Vinicius Magno Gonçalves[10], Carlo Domenico Marrone[11], Anamarli Nucci[1], Marcondes C. França Jr[1]

Brazilian Task force on NMDs

Pablo Brea Winckler, MD, MSc[1,2]; André Macedo Serafim da Silva, MD[3]; Antônio Rodrigues Coimbra Neto, MD[4,5]; Elmano Carvalho, MD, PhD[6]; Eduardo Boiteux Uchôa Cavalcanti, MD, MSc[7]; Cláudia Ferreira da Rosa Sobreira, MD, PhD[8]; Carlo Domenico Marrone, MD, Phd[9]; Marcela Câmara Machado-Costa, MD, MSc[10]; Alzira Alves de Siqueira Carvalho, MD, PhD[11]; Raimunda Helena Ferreira Feio, MD, MSc[12]; Cleonísio Leite Rodrigues, MD, PhD[13]; Marcus Vinicius Magno Gonçalves, MD[14]; Renata Barreto Tenório, MD[15]; Rodrigo de Holanda Mendonça, MD[3]; Ana Cotta, MD, PhD[6]; Júlia Filardi de Oliveira Paim, MD, MSc[6]; Cynthia Costa e Silva[7]; Camila de Aquino Cruz, MD, MSc[8]; Marjory Irineu Benâ, MSc[8]; Daniel Fernando Arias Betancur, MD[9]; Antonette Souto El Husny, MD, PhD[12,16]; Isabel Cristina Neves de Souza, MD, PhD[12]; Regina Célia Beltrão Duarte, MD, MsC[17,18]; Umbertina Conti Reed, MD, PhD3; Márcia Lorena Fagundes Chaves, MD, PhD[1,2,19]; Edmar Zanoteli, MD, PhD[3]; Marcondes Cavalcante França Junior, MD, PhD[4,5]; Jonas Alex Morales Saute, MD, PhD[1,2,15,19,*]

Title: Clinical and molecular findings in a cohort of Brazilian patients with *ANO5*-related myopathy

Authors: André Macedo Serafim da Silva, MD[1]; Antônio Rodrigues Coimbra-Neto, MD[2]; Paulo Victor Sgobbi Souza, MD[3]; Pablo Brea Winckler, MD, MSc[4]; Marcus Vinicius Magno Gonçalves, MD[5]; Eduardo Boiteux Uchôa Cavalcanti, MD[6]; Alzira Alves de Siqueira Carvalho, MD, PhD[7]; Cláudia Ferreira da Rosa Sobreira, MD, PhD[8]; Clara Gontijo Camelo, MD[1]; Rodrigo de Holanda Mendonça, MD[1]; Eduardo de Paula Estephan, MD[1]; Umbertina Conti Reed, MD, PhD[1]; Marcela Câmara Machado-Costa, MD, MSc[9]; Mario Emilio Teixeira Dourado-Junior, MD, PhD[10]; Vanessa Caldeira Pereira, MD[11]; Marcelo Maroco Cruzeiro, MD, PhD[12]; Paulo Victor Partezani Helito, MD[13]; Laís Uyeda Aivazoglou, MD, MSc[14]; Wladimir Bocca Vieira de Rezende Pinto, MD[3]; Bruno Mattos Lombardi Badia, MD[3]; Luiz Henrique Libardi, MD[3]; Mario Teruo Yanagiura, MD[3]; Acary Souza Bulle Oliveira, MD, PhD[3]; Jonas Alex Morales Saute, MD, PhD[1,15]; Marcondes Cavalcante França-Junior, MD, PhD[2]; Edmar Zanoteli, MD, PhD[1].

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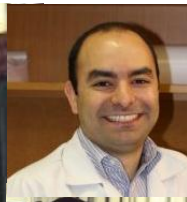

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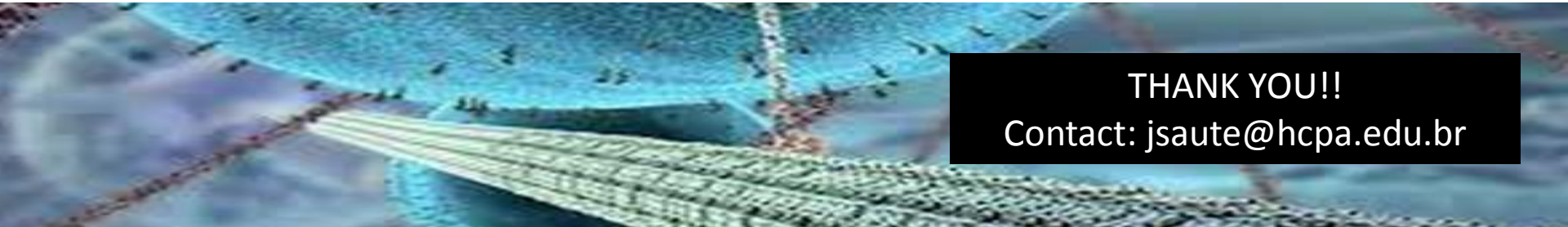

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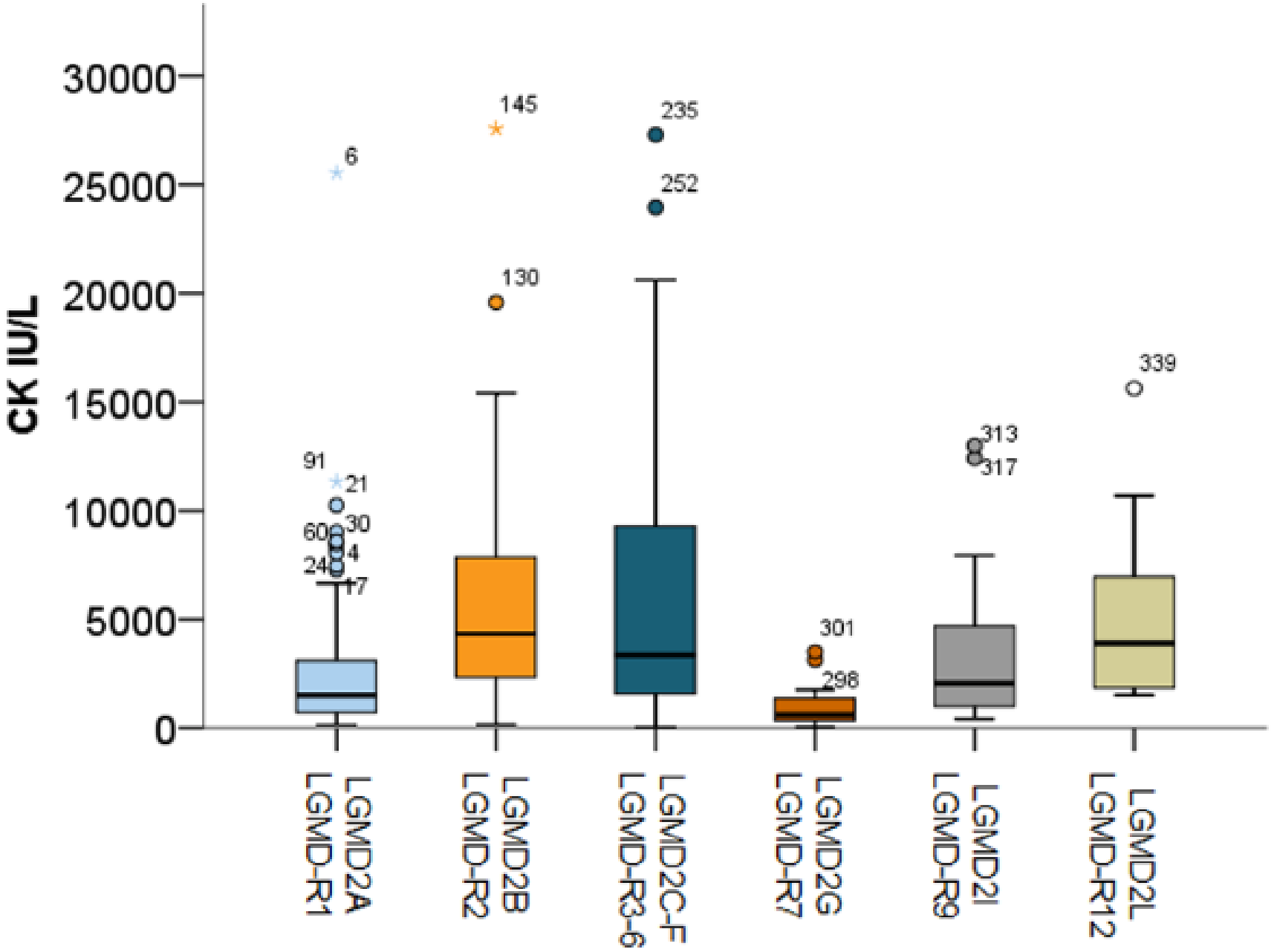
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