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Where do we stand in trial readiness for autosomal recessive limb girdle muscular dystrophies?

Volker Straub *, Marta Bertoli

The John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK

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Abstract

Autosomal recessive limb girdle muscular dystrophies (LGMD2) are a group of genetically heterogeneous diseases that are typically characterised by progressive weakness and wasting of the shoulder and pelvic girdle muscles. Many of the more than 20 different conditions show overlapping clinical features with other forms of muscular dystrophy, congenital, myofibrillar or even distal myopathies and also with acquired muscle diseases. Although individually extremely rare, all types of LGMD2 together form an important differential diagnostic group among neuromuscular diseases. Despite improved diagnostics and pathomechanistic insight, a curative therapy is currently lacking for any of these diseases. Medical care consists of the symptomatic treatment of complications, aiming to improve life expectancy and quality of life. Besides well characterised pre-clinical tools like animal models and cell culture assays, the determinants of successful drug development programmes for rare diseases include a good understanding of the phenotype and natural history of the disease, the existence of clinically relevant outcome measures, guidance on care standards, up to date patient registries, and, ideally, biomarkers that can help assess disease severity or drug response. Strong patient organisations driving research and successful partnerships between academia, advocacy, industry and regulatory authorities can also help accelerate the elaboration of clinical trials. All these determinants constitute aspects of translational research efforts and influence patient access to therapies. Here we review the current status of determinants of successful drug development programmes for LGMD2, and the challenges of translating promising therapeutic strategies into effective and accessible treatments for patients.

Keywords: LGMD2; Translational research; Outcome measures; Clinical trials; Patient registries

1. Introduction

The term limb girdle muscular dystrophy (LGMD) includes a heterogeneous group of genetic disorders characterised by progressive muscle weakness and wasting involving mainly the pelvic, shoulder girdle and proximal limb muscles. LGMDs were first described as a distinct nosological entity in 1954 by John Walton and Frederick Nattrass [1]. The first responsible gene was identified in 1994 in the laboratory of Kevin Campbell [2]. Since then, at least 8 different forms of autosomal dominant LGMD (LGMD1) and more than 20 distinct forms of autosomal recessive LGMD (LGMD2) (Table 1) have been characterised that also encompass other allelic disorders.

The overall frequency of LGMD, autosomal dominant and autosomal recessive, has been shown to vary within different populations and has been estimated to be around 20–40/1.000.000 [18].

The most frequent presentation is proximal weakness with onset in the second decade of life. However, a broadening phenotypic spectrum highlights the importance of considering LGMD2 as a differential diagnosis in almost any patient presenting with primary muscle weakness. A precise genetic diagnosis is critical, as it allows more accurate follow-up, the prevention of known possible complications, and appropriate genetic counselling for family members. Although new therapeutic concepts are rapidly developing, there is currently no licenced treatment for any form of LGMD, except for LGMD2V, which is generally referred to as Pompe disease. It is therefore important to review the translational research pathway for LGMD2 in order to identify bottlenecks that may currently be hindering the development of promising treatments. The key stages of translational research are outlined in Fig. 1, demonstrating how basic science research, clinical research and clinical care are distinct but interdependent stages of translational research. The

* Corresponding author. The John Walton Muscular Dystrophy Research Centre, MRC Centre for Neuromuscular Diseases at Newcastle, Institute of Genetic Medicine, Newcastle University, Central Parkway, Newcastle upon Tyne NE1 3BZ, UK. Tel.: +44 (0)1912418762/8655; fax: +44 (0)1912418770.
E-mail address: volker.straub@ncl.ac.uk (V. Straub).

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Table 1
Molecular genetics and main clinical features of LGMD2s [3–5]. DGC: Dystrophin glycoprotein complex. UL: upper limbs. LL: Lower limbs.

Disease name/gene	Protein function	Populations with founder mutations	CK	Onset	Progression (wheelchair bound)	Main clinical features	Complications		
							Contractures	Respiratory involvement	Cardiomyopathy (or other cardiac involvement)
LGMD2A – CAPN3	Calcium-sensitive protease involved in muscle re-modelling	Amish [6], Basque (Spain) [7], Northern Italy [8], Germany and eastern Europe [9]	5–80× but can be normal	2–40 yrs (8–15 yrs)	Moderate-rapid (11–28 years after onset)	Posterior thigh and scapular weakness common; often hip abductor sparing – calf atrophy	Yes	Rare	Rare
LGMD2B – DYSF	Structure and signalling function, involved in membrane repair	Libyan Jewish [10]	Often >100×	17–23 yrs	Slow	Proximal and/or distal weakness, little shoulder involvement – calf hypertrophy rare	Yes (ankles)	Rare	Not frequent
LGMD2C – SGCG	Structural components of the DGC	North Africans; Gypsies [11,12]	10–70×	3–15 yrs (8.5 yrs) Complete deficiency: difficulty run, walk	Rapid (~15 years after onset)	Proximal weakness – calf hypertrophy and scapular winging common	Yes	Yes (frequent)	Yes (rare in 2D)
LGMD2D – SGCA									
LGMD2E – SGCB		Amish [13]		Adolescent – young adulthood Partial deficiency: cramps, exercise intolerance					
LGMD2F – SGCD		Brazilian [7]							
LGMD2G -TCAP	Structural protein of the sarcomere		3–17×	9–15 yrs	Slow-moderate (~18 y after onset)	Prominent distal involvement (UL proximal, LL proximal and distal)			Yes
LGMD2H – TRIM32	E3 ubiquitin ligase involved in the differentiation of muscle stem cells and in muscle regeneration	Manitoba Hutterites [14]	4–30×	1–9 yrs	Slow (late in life)	Proximal LL, neck and facial weakness – muscle wasting			No
LGMD2I – FKRP	Involved in the glycosylation of alpha-dystroglycan		10–20×	1.5–27 yrs (11.5 yrs)	Slow-moderate (23–26 y after onset)	Mainly proximal weakness, muscle hypertrophy, BMD/DMD-like	Rare (scoliosis in childhood onset)	Yes	Yes
LGMD2J – TTN	Structural protein of the sarcomere.	Finland [15]	10–40×	5–25 yrs	Slow-moderate (20 y after onset)	Proximal weakness, ankle contractures	No	Yes	No
LGMD2K – POMT1	Involved in the glycosylation of alpha-dystroglycan	Turkish [16]	20–40×	1–3 yrs	Slow (1 patient – 17 y)	Mild weakness, proximal > distal – hypertrophy of calves and thighs	Yes (ankles, neck scoliosis)	Yes	Not frequent
LGMD2L – ANO5	Calcium activated chloride channel localised in the endoplasmic reticulum, function unknown	Northern European [17]	10–50×	3rd decade	Slow	Proximal pelvic – femoral or distal weakness in lower limbs, atrophy of quadriceps, hamstrings and biceps	Yes (wrist, fingers, ankles)	No	No
LGMD2M – FKTN	Involved in the glycosylation of alpha-dystroglycan		4–50×	Early childhood	Moderate	Proximal weakness, LL > UL – calves, thighs and triceps hypertrophy	Yes (scoliosis in childhood onset)	Yes	Not frequent
LGMD2N – POMT2	Involved in the glycosylation of alpha-dystroglycan		4–50×	Early childhood	Moderate (20 years – 1 patient)	No weakness – scapular winging and mild lordosis; intellectual disability – calf hypertrophy	Yes (scoliosis)	Yes	Not frequent
LGMD2O – POMGNT1	Involved in the glycosylation of alpha-dystroglycan		Normal to 2×	10–15 years	Moderate (19 y – 1 patient)	Weakness proximal > distal – hypertrophy of calves and quadriceps; wasting of hamstrings and deltoids	Yes (ankles)		No
LGMD2P – DAG1	Structural component of the DGC, basement membrane receptor		20×	Early childhood	Moderate (24 y – 1 patient)	Developmental delay without structural brain anomalies	Yes (ankles, lumbar lordosis)		No
LGMD2Q – PLEC	Component of intermediate filaments providing mechanical strength to cells		10–50×	2–3 yrs	Slow	Proximal weakness and generalised muscle atrophy	Yes		
LGMD2R – DES	Member of the intermediate filament protein family		Normal	Young adulthood	Slow	Proximal weakness and generalised muscle atrophy	No		Not frequent (conduction defects)
LGMD2S – TRAPPC11	Component of a protein complex involved in intracellular vesicle trafficking		9–16×	Childhood	?	Shoulder girdle more affected than hip girdle, possible hyperkinetic movement disorder, ataxia and developmental delay	Scoliosis	Possible restrictive	Not frequent
LGMD2T – GMPPB	Involved in the glycosylation of alpha-dystroglycan		Normal to 2×	Early childhood to young adulthood	Slow	Developmental delay, exercise intolerance, possible seizures	Ankles	Mild	
LGMD2U – ISPD	Involved in the glycosylation of alpha-dystroglycan		6–50×		?	Proximal weakness and muscle pseudo hypertrophy		Yes	Yes
LGMD2V – GAA	Lysosomal enzyme involved in the hydrolysation of glycogen		Normal to 20×	Variable	Variable	Proximal weakness, respiratory insufficiency	No	Yes	Not frequent in adults
LGMD2W – LIMS2	Mediates adhesion between cells and the extracellular matrix		10×	Childhood	?	Proximal weakness, macroglossia, calf hypertrophy			Yes

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