Systematic Literature Review of Clinical Outcomes and Disease Burden in Limb-Girdle Muscular Dystrophy Subtype 2I/R9

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OBJECTIVE

- This SLR examined the association between glycosylated α-dystroglycan (αDG) and clinical outcomes in individuals living with limb-girdle muscular dystrophy subtype 2I/R9 (LGMD2I/R9), and the clinical, humanistic, and economic burden of LGMD2I/R9

BACKGROUND

- LGMD2I/R9 is a rare, progressive muscular disorder caused by loss-of-function mutations in the fukutin-related protein gene, reducing glycosylation of αDG, a key protein for muscle integrity[1,2]
- Individuals living with LGMD2I/R9 experience irreversible muscle weakness and loss of ambulation, and cardiac and respiratory involvement is common[1,3]
- LGMD2I/R9 is among the more commonly studied LGMD subtypes, although prevalence varies geographically[4]
- Individuals living with LGMD2I/R9 experience substantial clinical, humanistic, and economic burden; however, evidence describing these outcomes remains fragmented and has not been comprehensively synthesized[5,6]

METHODS

Study Design

SLR Workflow

Protocol/Standards
PRISMA 2020
PROSPERO

Literature Search
MEDLINE
Embase
Cochrane library

Screening/Eligibility
Title/abstract screening
Full-text review
Two independent reviewers

Data Extraction/Synthesis
Study characteristics
Outcomes
Qualitative synthesis

SLR conduct and governance

- SLR conducted in accordance with PRISMA 2020 guidelines
- Protocol registered in PROSPERO (CRD42025640843)

Data sources and search strategy

- **Databases:** MEDLINE (via PubMed), Embase, Cochrane library
- **Search date:** December 13, 2024
- **Full-text publications:** English language, January 2004–December 2024
- **Congress abstracts:** 2021–2024
- Free-text and controlled vocabulary (MeSH/Emtree) terms

Study selection and eligibility

- **Population:** LGMD2I/R9
- **Outcomes:** epidemiology; clinical, functional, and surrogate/biomarker; humanistic; and economic
- **Eligible designs:** observational, registry, retrospective cohort, cross-sectional, and clinical studies and meta-analyses
- **Excluded:** case studies and case reports

Screening and data extraction

- Two independent reviewers
- Data extracted by one reviewer and validated by a second

Risk of bias assessment

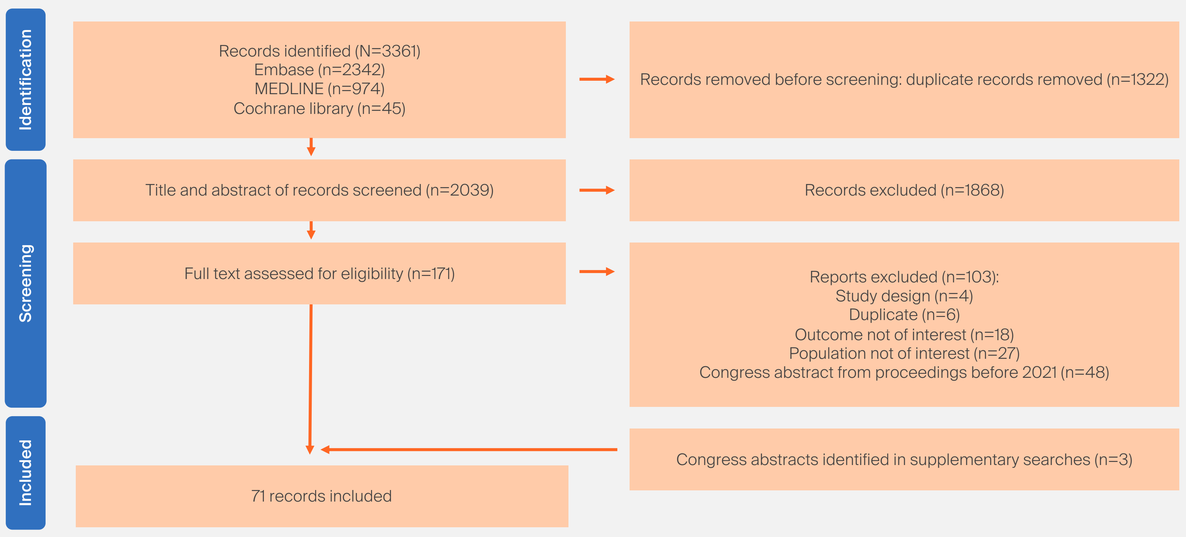
- Randomized trials (n=1): Cochrane RoB 2[a]
- Non-randomized/single-arm studies: ROBINS-I[a]
- Poor-quality studies were not excluded

[a]RoB 2 and ROBINS-I tools were used to systematically assess the strength of evidence and potential risk of bias in the included studies.

RESULTS

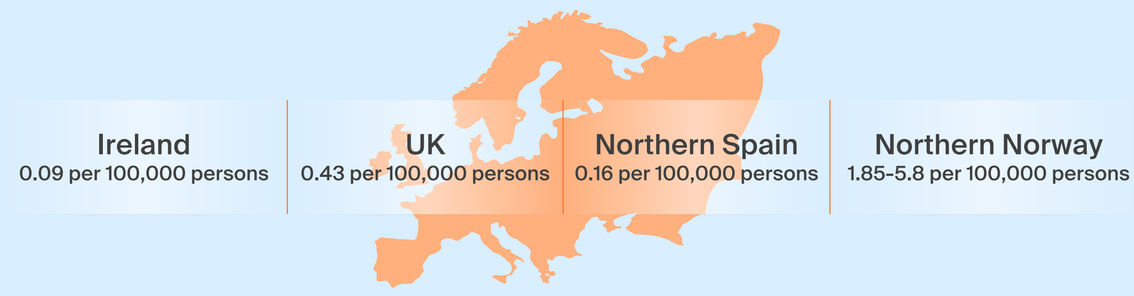
- A total of 2039 records were screened; 71 studies were included in the SLR (62 full-text publications; 9 congress abstracts) **(Figure 1)**

Figure 1. PRISMA flow diagram of study selection



- Prevalence of LGMD2I/R9 ranged from 0.09 to 5.8 per 100,000 persons (Ireland, UK, Northern Spain, and Northern Norway), and LGMD2I/R9 comprised 1.2%–45.2% of the total LGMD population across studies **(Figure 2)**

Figure 2. Population-based prevalence of LGMD2I/R9 in selected European countries



RESULTS (cont'd)

- Five studies (6 articles) reported reduced αDG levels in LGMD2I/R9, with evidence suggesting that lower αDG glycosylation is associated with poorer clinical outcomes and genotype, although findings were limited and largely cross-sectional **(Figure 3)**
- Muscle function was reported in 28 studies, with muscle weakness prevalence ranging from 17.6% to 100% across varied assessments and populations; hypertrophy, atrophy, and contractures were also documented **(Figure 4)**

Figure 3. Reported associations between glycosylated αDG and outcomes in LGMD2I/R9[a]

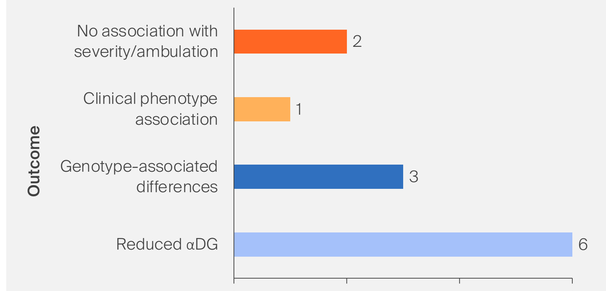
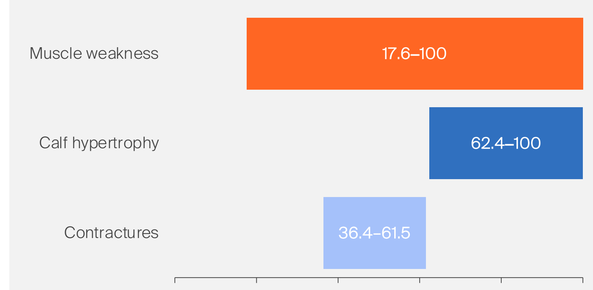


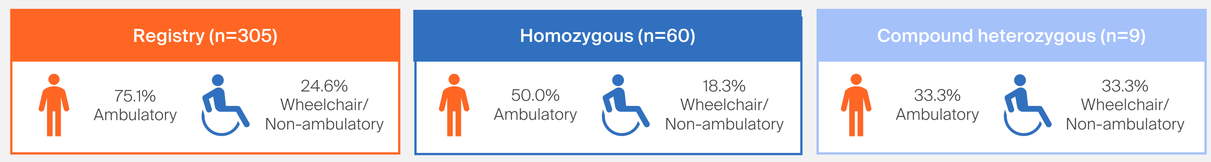
Figure 4. Range of reported prevalence of muscle function in LGMD2I/R9



[a]Sproule et al and Rajasingham et al represent preliminary and final analyses of the same study and were counted as 1 study.

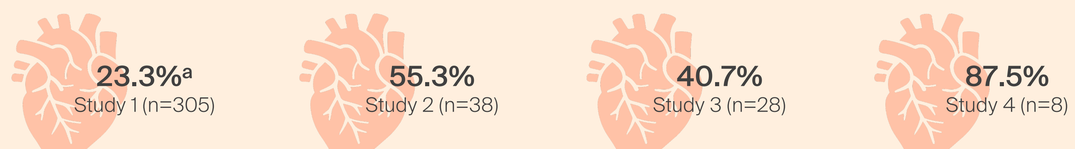
- Most individuals with LGMD2I/R9 were ambulatory, and in the largest registry (n=305), 75.1% were currently ambulatory and 24.6% were non-ambulatory, with wheelchair dependence more frequent among those with c.826C>A compound heterozygosity compared with those with homozygosity **(Figure 5)**
- In the largest registry cohort (n=305), cardiac involvement was reported in 23.3% of individuals with available cardiac data (30/129)
- Separate genotype-stratified studies reported earlier onset of cardiac abnormalities with non-c.826C>A genotypes compared with c.826C>A homozygosity **(Figure 6)**

Figure 5. Ambulatory status and wheelchair dependence in LGMD2I/R9[a]



[a]Percentages represent reported categories only; remaining patients were not further described.

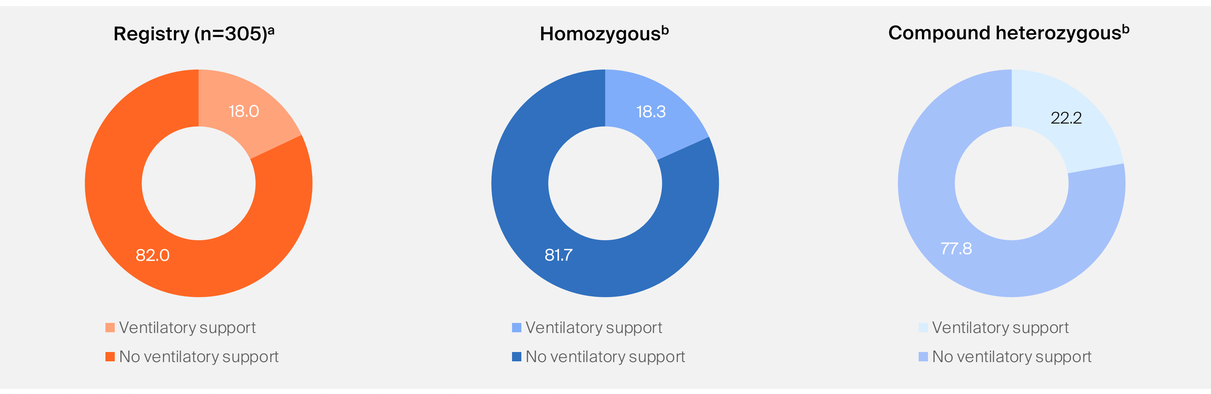
Figure 6. Cardiac involvement in individuals with LGMD2I/R9



[a]23.3% reflects 30/129 patients with available cardiac data within the 305-patient registry cohort.

- In the largest registry cohort (n=305), 18.0% of individuals required ventilatory support (15.1% non-invasive; 2.9% invasive)
- In a separate cohort (n=88), higher ventilatory support needs were reported among c.826C>A compound heterozygotes than homozygotes **(Figure 7)**

Figure 7. Ventilatory support in LGMD2I/R9



[a]Registry cohort data. [b]Percentages reflect genotype-specific proportions reported in an 88-patient cohort.

- Nine studies showed poorer quality of life in individuals with LGMD2I/R9 compared with healthy controls, with fatigue, pain, and poor sleep quality contributing to impaired well-being
- Fatigue prevalence ranged from 17.6% to 82.0% and was more frequently reported in individuals who were compound heterozygous
- Pain severity was associated with ambulatory status, with the highest burden being in individuals who were able to walk but not run
- Economic evidence was limited to 1 study that showed substantial productivity burden: 36.2% of individuals were completely unable and 18.8% were partially unable to work or study, with work impairment associated with greater pain and poorer general health
- No studies evaluated caregiver experience

CONCLUSIONS

- LGMD2I/R9 is associated with substantial clinical, functional, and humanistic burden
  - Disease severity and progression differ by genotype; individuals with c.826C>A compound heterozygosity show earlier loss of ambulation and greater cardiopulmonary involvement than those with homozygosity
- Major evidence gaps include economic burden, caregiver impact, and long-term outcomes
- Longitudinal studies are warranted to evaluate the relationship between glycosylated αDG levels and functional outcomes to better understand disease progression

LIMITATIONS

- Most evidence is observational and cross-sectional, and because LGMD2I/R9 is rare, studies are often small and heterogeneous, with potential risk of bias

STRENGTHS

- This study follows a PRISMA-compliant, PROSPERO-registered systematic approach, synthesizing evidence from 71 studies, including large registry and natural history cohorts

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ABBREVIATIONS: αDG, α-dystroglycan; ECG, electrocardiogram; LGMD, limb-girdle muscular dystrophy; LGMD2I/R9, limb-girdle muscular dystrophy subtype 2I/R9; LVEF, left ventricular ejection fraction; MeSH, Medical Subject Headings; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RoB 2, version 2 of the Cochrane risk-of-bias tool for randomized trials; ROBINS-I, Risk of Bias in Non-Randomized Studies - of Interventions; SLR, systematic literature review

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DISCLOSURES: K Bartley is a full-time employee and shareholder of BridgeBio Pharma, Inc., and a shareholder of Roche. **O Evuarherhe and G Carter** are full-time employees of Oxford PharmaGenesis Ltd, and G Carter is a shareholder. **A Talaga** is a full-time employee and shareholder of BridgeBio Pharma, Inc. **JM Statland** received grant funding from ALSA, CDC, Friends of FSH Research, FSHD Canada, FSHD Society, MDA, NCATS, and NINDS; consulted or served on scientific advisory boards for Alnylam, Armatus, Avidity, Dyne, Kate Therapeutics, Merck, Novartis, RegenXBio, Roche, Sarepta, Scholar Rock, and Vertex; and received stock options from Dyne.