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Limb-girdle Muscular Dystrophy Type 2I/R9: Future Gene Therapy Options of an Extremely Rare Fukutin Protein-related Dystroglycanopathy

Stefan Bittmann [a,b++*], Elisabeth Luchter [a] and Elena Moschüring-Alieva [a]

[a] Department of Pediatrics, Ped Mind Institute, Department of Pediatrics, Hindenburgring 4, D-48599 Gronau, Germany.
[b] School of Medicine, Shangluo Vocational and Technical College, Shangluo, 726000, Shaanxi, China.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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Abstract

Limb-girdle muscular dystrophy type 2I, now designated R9 (LGMD2I/R9), is an autosomal recessive dystroglycanopathy caused by biallelic pathogenic variants in the fukutin-related protein (FKRP) gene. Loss of FKRP glycosyltransferase activity disrupts the ribitol-phosphate-mediated glycosylation of alpha-dystroglycan, reducing matriglycan formation and weakening the link between the sarcolemma and the extracellular matrix. The resulting phenotype ranges from mild, adult-onset limb-girdle weakness to a severe congenital muscular dystrophy, and frequently includes dilated cardiomyopathy and restrictive respiratory failure. No disease-modifying treatment is currently licensed, and management remains supportive. Over the

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[++] *Honorary Professor (Hon.Prof.);*
**Corresponding author: E-mail: stefanbittmann@gmx.de;*

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past decade, three broad experimental strategies have moved toward clinical evaluation: adeno-associated virus (AAV)-mediated gene replacement, small-molecule substrate supplementation with ribitol, and combinatorial approaches that pair gene replacement with muscle-anabolic transgenes such as follistatin. Registered early-phase AAV-FKRP programmes and the placebo-controlled FORTIFY trial of oral ribitol provide important translational context, but peer-reviewed clinical efficacy and long-term safety data remain limited; interim registry, conference and sponsor-reported findings should therefore be interpreted cautiously. This narrative review synthesises the molecular pathophysiology of FKRP-related dystroglycanopathy, appraises the natural history and outcome measures relevant to trial design, and critically evaluates the preclinical and early clinical evidence for gene-based and substrate-based therapies. It concludes with a discussion of unresolved translational barriers and a forward-looking assessment of the therapeutic pipeline for this ultra-rare neuromuscular disorder.

Keywords: Limb-girdle muscular dystrophy; LGMDR9; fukutin-related protein; dystroglycanopathy; gene therapy; adeno-associated virus; ribitol; matriglycan.

1. Introduction

Limb-girdle muscular dystrophies constitute one of the largest and most genetically heterogeneous groups of inherited myopathies encountered in neuromuscular practice, and among the recessively inherited forms, dystroglycanopathy caused by biallelic variants in the fukutin-related protein gene represents one of the more frequently diagnosed subtypes in populations of Northern European descent. Unlike the dystrophinopathies, in which the causative protein sits within a single, well-defined structural complex, the dystroglycanopathies arise from disruption of a multistep post-translational glycosylation pathway, a biochemical architecture that has profoundly shaped the therapeutic strategies now under active clinical investigation. This narrative translational review addresses limb-girdle muscular dystrophy type 2I, redesignated R9 under current nomenclature (LGMD2I/R9), with particular emphasis on gene-based therapeutic strategies and ribitol substrate supplementation that have moved from murine proof-of-concept studies into registered human trials over the past five years.

1.1 Nosology and Historical Context

Limb-girdle muscular dystrophies (LGMDs) comprise a heterogeneous group of inherited myopathies characterised by predominantly proximal muscle weakness affecting the shoulder and pelvic girdles. The clinical entity was first delineated by Walton and Nattrass in the mid-twentieth century, and its molecular classification has been repeatedly revised as causative genes have been identified (Bouchard & Tremblay, 2023; Straub et al., 2018). The 2017 European Neuromuscular Centre nomenclature replaced the older numeric system, distinguishing dominant (LGMDD) from recessive (LGMDR) subtypes and ordering each by chronology of gene discovery (Straub et al., 2018). Under this scheme, the disorder historically known as LGMD2I is now designated LGMDR9, reflecting biallelic pathogenic variants in the gene encoding fukutin-related protein (FKRP) (Johnson & Statland, 2022). Both nomenclatures remain in clinical and scientific use, and this review employs the combined designation LGMD2I/R9 throughout, consistent with contemporary practice. A recent scoping review similarly emphasised that marked inter-subtype variability necessitates individually tailored rehabilitation and respiratory support rather than uniform management protocols across LGMDs (D'Este et al., 2025).

1.2 Molecular Basis of Disease

FKRP encodes a Golgi-resident ribitol-5-phosphate transferase that acts within the multistep glycosylation pathway responsible for building the laminin-binding polysaccharide matriglycan on α-dystroglycan (Cataldi et al., 2023). Matriglycan, a repeating disaccharide of glucuronic acid and xylose, allows α-dystroglycan to bind extracellular matrix ligands containing laminin-G domains, thereby completing the physical linkage between the intracellular cytoskeleton and the basement membrane (Kanagawa, 2021). Loss-of-function variants in *FKRP* impair the transfer of ribitol-phosphate onto the core glycan of α-dystroglycan, truncating matriglycan synthesis and reducing laminin-binding capacity. The resulting hypoglycosylation compromises sarcolemmal stability during repeated contraction–relaxation cycles, rendering myofibres vulnerable to contraction-induced injury, chronic degeneration and fibro-fatty replacement (Lu et al., 2024). Cardiac myocytes and respiratory

musculature share this dependence on glycosylated α-dystroglycan, which accounts for the frequent, and sometimes dissociated, occurrence of cardiomyopathy and ventilatory failure in affected individuals (Libell et al., 2020). Metabolomic profiling of *FKRP*-mutant muscle further indicated that ribitol and ribose produce distinct metabolic effects despite both supporting increased CDP-ribitol availability and matriglycan synthesis, highlighting the need to evaluate long-term metabolic consequences when selecting substrate-based therapies (Cataldi & Lu, 2025).

A single founder missense variant, c.826C>A (p.Leu276Ile), accounts for a large proportion of LGMD2I/R9 alleles in populations of Northern European ancestry and is associated with a comparatively attenuated phenotype when present in the homozygous state; compound heterozygosity for L276I and a second, more disruptive variant typically produces earlier and more severe disease (Libell et al., 2020). Because L276I retains partial residual enzymatic activity, it has provided the biochemical rationale for substrate-based therapeutic strategies that seek to potentiate the mutant enzyme rather than replace it outright. Recent preclinical work in an L276I homozygous mouse model showed that long-term ribitol administration enhanced matriglycan expression and attenuated muscle pathology, supporting the premise that treatment response may depend partly on residual mutant FKRP activity (Wu et al., 2025).

Diagnosis of LGMD2I/R9 typically proceeds from a clinical suspicion of limb-girdle weakness with markedly elevated serum creatine kinase, prompting molecular genetic testing by targeted gene panel or whole-exome sequencing that identifies biallelic *FKRP* variants. Historically, diagnosis relied on muscle biopsy with immunohistochemical staining for glycosylated α-dystroglycan using the IIH6 monoclonal antibody, which demonstrates reduced or absent membrane staining in affected muscle, together with dystrophic histopathological features including fibre size variation, central nucleation, necrosis and endomysial fibrosis. With the widespread availability of next-generation sequencing, molecular confirmation has increasingly supplanted biopsy as the primary diagnostic step, although muscle biopsy retains a role where genetic results are equivocal or where a quantitative biomarker of glycosylation status is required to inform prognosis or to support enrolment in a therapeutic trial (Vissing et al., 2026). This shift from a primarily histopathological to a primarily molecular diagnostic pathway has been an important enabling development for gene-therapy trial recruitment, since it allows earlier and more definitive genotypic confirmation of eligibility.

1.3 Clinical Phenotype

The clinical spectrum of *FKRP*-related dystroglycanopathy is wide, extending from asymptomatic hyperCKaemia and mild calf hypertrophy to a severe congenital muscular dystrophy (MDC1C, the historical abbreviation for congenital muscular dystrophy type 1C) with early loss of independent ambulation. The more common LGMD2I/R9 phenotype typically presents in the first to third decade of life with proximal lower-limb weakness, calf pseudohypertrophy, exercise intolerance and markedly elevated serum creatine kinase (CK). Progressive weakness leads to loss of ambulation in a substantial minority of patients over one to several decades, while cardiac and respiratory involvement often progress independently of skeletal muscle strength and require separate, longitudinal surveillance (Libell et al., 2020). Scapular winging, lumbar hyperlordosis and a waddling gait are frequently observed clinical signs, and a subset of patients, particularly those homozygous for the L276I variant, present initially with exercise-induced myalgia and recurrent episodes of myoglobinuria rather than fixed weakness, occasionally leading clinicians to suspect a primary metabolic myopathy before genetic testing clarifies the underlying dystroglycanopathy. Pain, fatigue and reduced health-related quality of life (HRQoL) are increasingly recognised as clinically important, patient-relevant features that are not adequately captured by strength or ambulation measures alone (Jensen, Friborg, et al., 2024; Reelfs et al., 2023). Reproductive health also merits specific mention, since pregnancy in women with LGMD2I/R9 is generally achievable but has been associated with a measurable risk of peripartum respiratory and cardiac complications, underscoring the systemic rather than purely musculoskeletal nature of this disorder and the importance of multidisciplinary reproductive counselling alongside any future gene-based intervention. A recent genetically confirmed Chinese cohort further documented substantial clinical, imaging and pathological heterogeneity and associated null *FKRP* variants with more severe phenotypes than missense or in-frame variants (Yuan et al., 2025).

1.4 Scope, Research Gap and Objectives

Despite growing mechanistic understanding of matriglycan biosynthesis and considerable preclinical progress in murine models of FKRP deficiency, no disease-modifying therapy for LGMD2I/R9 has yet received regulatory

approval, and current care remains limited to symptomatic management, cardiopulmonary surveillance and rehabilitation. Two experimental disease-modifying approaches, AAV-mediated *FKRP* gene replacement and oral ribitol substrate therapy, have progressed to early-phase and pivotal human trials over the past three years, while combinatorial gene-therapy constructs pairing *FKRP* with muscle-anabolic transgenes remain at the preclinical stage. A comprehensive narrative synthesis integrating the molecular pathophysiology, the maturing natural-history and outcome-measure literature, and the fragmented preclinical and clinical gene-therapy evidence base has not, to the authors' knowledge, been recently undertaken for this specific and extremely rare disorder. This review therefore aims to (i) summarise the pathophysiological basis of FKRP-related dystroglycanopathy as it pertains to therapeutic target selection; (ii) critically appraise the natural-history data and clinical outcome assessments that underpin contemporary trial design; (iii) evaluate the preclinical and early clinical evidence for AAV gene replacement, ribitol substrate therapy and combinatorial gene-based strategies; and (iv) identify the principal translational barriers that will determine whether gene-based therapies can be safely and durably delivered to this patient population.

2. Methods for Literature Selection

2.1 Databases and Search Strategy

A narrative literature search was conducted across Web of Science, Scopus, Google Scholar and PubMed, supplemented by field-specific resources relevant to neuromuscular disease and gene therapy research. These included the Cochrane Neuromuscular Disease register, ClinicalTrials.gov and EU clinical-trial registries, the TREAT-NMD global registry network literature index, and the Orphanet bibliographic database for rare disease research. Search strings combined the terms "FKRP", "LGMD2I", "LGMDR9", "limb-girdle muscular dystrophy", "dystroglycanopathy", "matriglycan", "alpha-dystroglycan", "ribitol", "gene therapy" and "adeno-associated virus" using Boolean operators, restricted to English-language records. The literature search covered publications from 1 January 2016 to 1 April 2026, chosen to capture the period following elucidation of the ribitol-phosphate glycosylation pathway; a small number of earlier, field-defining publications were retained where they established foundational genetic, nomenclature or pathophysiological concepts still in active clinical use. Clinical-trial registries and sponsor communications (See: BridgeBio Pharma, Inc., 2026) were used only to contextualise the therapeutic pipeline and were not treated as equivalent to peer-reviewed efficacy evidence.

2.2 Rationale for a Narrative Approach

A narrative rather than systematic review methodology was adopted because the evidence base for LGMD2I/R9 spans heterogeneous study designs, including animal pharmacology, early-phase clinical trials, natural-history cohorts, mechanistic biochemistry, registry records and conference or sponsor-reported pipeline updates. A single systematic protocol with fixed inclusion criteria would be poorly suited to synthesising this translational evidence into a coherent clinical framework. The review therefore does not claim PRISMA-level record counts, pooled estimates or formal risk-of-bias grading; instead, it uses explicit source-selection criteria to distinguish peer-reviewed evidence from contextual trial-registry and sponsor-reported information. This approach follows the precedent of comparable recent narrative syntheses of limb-girdle muscular dystrophy classification and therapeutics (Bouchard & Tremblay, 2023).

2.3 Screening and Study Selection

Titles and abstracts identified through the search strategy were screened for relevance to FKRP-related dystroglycanopathy, its pathophysiology, natural history, or experimental therapeutics. Duplicate records retrieved across databases were removed using reference-management software before full-text screening, but formal database-by-database retrieval and exclusion counts were not generated because the manuscript was designed as a narrative translational review rather than a systematic review. Non-English-language records, unpublished theses, patents and trade publications were excluded. Conference abstracts, trial-registry entries and company communications were retained only where they clarified the current development stage of a therapy and were clearly separated from peer-reviewed evidence. Case reports of fewer than five patients were generally excluded unless they addressed a clinically relevant issue, such as pregnancy or severe cardiopulmonary management, for which cohort-level evidence in LGMDR9 is limited. Full texts of the remaining records were reviewed for methodological transparency and relevance; studies employing validated animal models of FKRP

deficiency were prioritised for the preclinical therapeutics sections, while multicentre natural-history and outcome-measure studies were prioritised for the clinical sections.

2.4 Data Synthesis

Extracted information was organised thematically around pathophysiology, natural history and outcome measures, and therapeutic modality (AAV gene replacement, substrate therapy, combinatorial gene therapy, and adjunctive genome-editing approaches). Because the number of dedicated LGMD2I/R9 gene-therapy publications remains small, relevant preclinical and safety literature from the wider AAV gene-therapy field was incorporated where it directly informed interpretation of FKRP-specific findings, particularly vector immunogenicity and hepatotoxicity. Throughout the synthesis, peer-reviewed clinical and preclinical studies were weighted more strongly than registry descriptions, sponsor press releases or conference abstracts.

3. Epidemiology and Genetic Architecture

Limb-girdle muscular dystrophies collectively represent the fourth most common inherited myopathy after the dystrophinopathies, myotonic dystrophies and facioscapulohumeral muscular dystrophy (Bouchard & Tremblay, 2023). FKRP-related dystroglycanopathy is disproportionately represented among LGMDR subtypes in Northern Europe: a Norwegian nationwide cohort study identified 153 genetically confirmed subjects, yielding a national prevalence of 2.84 per 100,000, the highest figure reported for this disorder worldwide (Jensen et al., 2023). The disease is inherited in an autosomal recessive pattern, and numerous distinct pathogenic *FKRP* variants have been catalogued, though the founder missense variant c.826C>A (p.Leu276Ile) predominates in populations of Northern European descent (Libell et al., 2020). Genotype exerts a marked influence on phenotype: homozygosity for L276I is generally associated with later onset and slower progression, whereas compound heterozygosity for L276I with a second, functionally more disruptive allele, or homozygosity for non-L276I variants, tends to produce earlier and more rapidly progressive disease, including higher rates of early cardiomyopathy (Libell et al., 2020). This genotype–phenotype relationship carries direct implications for gene-therapy trial design, since disease severity, age at intervention and residual enzymatic activity are all liable to modify treatment response.

Table 1. Genetic and clinical features relevant to LGMD2I/R9 gene-therapy trial design

Feature	Description	Clinical/trial relevance	Source
Gene and inheritance	*FKRP*, autosomal recessive	Defines eligibility for gene-replacement and substrate therapies; parental carriers unaffected	Cataldi et al. (2023)
Founder variant	c.826C>A (p.Leu276Ile), retains partial residual activity	Basis for ribitol substrate-therapy rationale; genotype stratification in trials	Libell et al. (2020)
Prevalence	Highest reported figure 2.84/100,000 (Norway)	Confirms ultra-rare, geographically clustered disease; informs trial feasibility and recruitment planning	Jensen et al. (2023)
Cardiomyopathy	Present in approximately 45% of a US cohort; later onset in L276I homozygotes	Mandates baseline and longitudinal cardiac surveillance in gene-therapy trials	Libell et al. (2020)
Molecular defect	Truncated matriglycan synthesis on α-dystroglycan	Defines the biochemical endpoint (glycosylated α-dystroglycan) used as a trial biomarker	Kanagawa (2021); Vissing et al. (2026)

Beyond Northern Europe, FKRP-related dystroglycanopathy has been reported in genetically diverse cohorts and case series, including populations in North America and Asia, but the available evidence is less uniform than the Norwegian registry-based data and often reflects differences in ascertainment, sequencing access and referral patterns. This international variability in allelic architecture has practical consequences for trial recruitment: programmes anchored in Northern European or Scandinavian centres, where the L276I founder variant predominates, are likely to enrol a genetically and phenotypically narrower population than multinational trials drawing on more genetically admixed cohorts, and outcome data generated in one genetic context may not generalise directly to patients carrying different, non-founder FKRP alleles. Because

LGMD2I/R9 remains an ultra-rare disease even within the already rare LGMD category, systematic epidemiological ascertainment is inherently difficult, and prevalence estimates are likely to be conservative in regions lacking comprehensive neuromuscular genetic testing infrastructure or national disease registries comparable to the Norwegian cohort. Table 1 summarises the principal genetic and clinical features of LGMD2I/R9 that bear most directly on eligibility criteria and stratification strategies for gene-therapy trials.

As Table 1 indicates, genotype, prevalence and cardiac status are not independent considerations for trial design but interact directly with one another, a point developed further in the pathophysiology and natural-history sections that follow.

4. Pathophysiology of α-Dystroglycan Hypoglycosylation

4.1 The Matriglycan Biosynthetic Pathway

α-Dystroglycan is a heavily glycosylated, peripheral membrane component of the dystrophin–glycoprotein complex encoded by *DAG1*, subsequently cleaved into extracellular α- and transmembrane β-subunits (Kanagawa, 2021). Functional glycosylation proceeds through a multistep pathway: initial *O*-mannosylation by POMT1/POMT2 is extended by POMGNT2 and B3GALNT2 to form a core trisaccharide, which is then phosphorylated by protein *O*-mannose kinase and further modified with a ribitol-phosphate unit contributed sequentially by fukutin and FKRP. This ribitol-primed intermediate is extended by TMEM5 and B4GAT1 before the bifunctional glycosyltransferase LARGE1 polymerises the repeating xylose–glucuronic acid disaccharide that constitutes mature matriglycan (Kanagawa, 2021). Matriglycan is the sole ligand recognised with high affinity by laminin-G domain-containing extracellular matrix proteins, including laminin-211, agrin and perlecan, and its loss disrupts the mechanical continuity between the sarcolemmal cytoskeleton and the basement membrane (Beltrán et al., 2019). Unlike most linear glycan structures, matriglycan is unusual in being synthesised with an essentially unbounded, tissue- and developmentally regulated chain length, so that the degree of hypoglycosylation, rather than its simple presence or absence, correlates with residual laminin-binding capacity and, by extension, with clinical severity (Lu et al., 2024). This graded relationship between glycan chain length and function carries practical implications for therapeutic monitoring, since even partial restoration of matriglycan synthesis, as might be achieved through submaximal AAV dosing or substrate supplementation of a hypomorphic allele, could in principle confer meaningful functional benefit without requiring full normalisation to wild-type glycosylation levels.

4.2 Consequences of FKRP Deficiency

Because FKRP acts near the proximal end of this pathway, its loss produces a truncated, non-functional glycan that abolishes laminin binding regardless of downstream enzymatic capacity. The resulting sarcolemmal fragility renders myofibres susceptible to contraction-induced membrane microtears, triggering a cycle of degeneration, incomplete regeneration, inflammatory infiltration and progressive replacement of contractile tissue by fibrous and adipose tissue (Cataldi et al., 2023). Skeletal, cardiac and diaphragmatic muscle are all dependent on adequately glycosylated α-dystroglycan, which accounts for the tripartite pattern of skeletal, cardiac and respiratory involvement characteristic of LGMD2I/R9, and for the observation that cardiorespiratory decline can occur independently of, and sometimes precede, overt limb-girdle weakness (Libell et al., 2020).

4.3 Residual Enzymatic Activity as a Therapeutic Opportunity

A distinguishing feature of FKRP-related, as opposed to fukutin- or POMT-related, dystroglycanopathy is that the common founder variant retains measurable residual catalytic activity rather than representing a complete null allele. This partial function underlies two complementary therapeutic rationales that dominate the current pipeline: substrate supplementation with ribitol, which increases availability of the rate-limiting precursor and thereby drives flux through the residual mutant enzyme, and AAV-mediated gene replacement, which restores wild-type enzymatic capacity independent of residual mutant function (Cataldi et al., 2023). Because these mechanisms act at different points in the same pathway, preclinical evidence indicates that they may be complementary rather than mutually exclusive, a concept discussed further in Section 7.

4.4 Secondary Pathological Consequences and their Relevance to Trial Endpoints

Chronic sarcolemmal fragility in FKRP-deficient muscle initiates a cascade of secondary pathology that extends well beyond the primary glycosylation defect and carries direct relevance to the selection of clinically

meaningful trial endpoints. Repeated microtears activate calcium-dependent proteolytic pathways and chronic low-grade inflammation, driving progressive replacement of contractile tissue with fibrous and adipose tissue, a process that is readily visualised on fat-fraction muscle magnetic resonance imaging and that, once established, is unlikely to be reversed by restoration of glycosylation alone (Willis et al., 2013). This observation underlies the rationale, discussed in Section 8, for combinatorial gene-therapy strategies that pair correction of the primary molecular defect with muscle-anabolic transgenes capable of rebuilding lost contractile mass. In cardiac muscle, analogous fibro-fatty remodelling contributes to the dilated cardiomyopathy phenotype observed in a substantial proportion of patients, while in the diaphragm and accessory respiratory musculature, similar pathology underlies the restrictive ventilatory pattern that can develop independently of, and occasionally in advance of, limb-girdle weakness (Libell et al., 2020). The tripartite, tissue-specific expression of the consequences of a single underlying molecular defect is a recurring theme throughout this review and one that any gene-based therapy must address across all three organ systems to achieve comprehensive disease modification.

5. Natural History and Clinical Outcome Assessment

Longitudinal characterisation of disease course is a foundational requirement for any interventional trial in a slowly progressive, ultra-rare disorder, since without a well-defined natural-history comparator it becomes exceedingly difficult to distinguish a genuine treatment effect from the ordinary heterogeneity of untreated disease trajectories. The following subsections review the principal natural-history cohorts, the outcome measures that have been validated within them, and the cardiorespiratory surveillance data that together inform contemporary gene-therapy trial design for LGMD2I/R9.

5.1 Longitudinal Cohort Studies

Robust natural-history data are a prerequisite for interpretable clinical trials in an ultra-rare disease, and several multicentre cohorts have substantially advanced this evidence base over the past five years. The Norwegian LGMDR9 cohort study, drawing on the national prevalence estimate described above, has characterised disease burden, health-related quality of life, sleep and pain across the adult LGMD2I/R9 population using validated patient-reported outcome instruments including the Individualized Neuromuscular Quality of Life questionnaire and the 36-item Short Form (Jensen, Friborg, et al., 2024). In the United States, a University of Iowa-based cohort has separately reported on cardiomyopathy prevalence and timing (Libell et al., 2020), pregnancy outcomes (Libell et al., 2021), and pain interference and fatigue trajectories (Reelfs et al., 2023), while the multinational Genetic Resolution and Assessments Solving Phenotypes in LGMD (GRASP) consortium has established a prospective natural-history platform explicitly designed to validate clinical outcome assessments for future interventional trials (Alfano et al., 2025). Complementing these prospective clinical cohorts, sleep-related morbidity has emerged as a further, previously underappreciated dimension of disease burden: a dedicated analysis of the Norwegian LGMDR9 cohort identified substantial rates of insomnia and sleep-disordered breathing, both of which were linked to health-related quality of life, heart failure markers or fatigue-related pulmonary measures (Jensen, Abeler, et al., 2024). Collectively, these cohorts have transformed LGMD2I/R9 from a disease characterised largely by small, single-centre case series into one with an increasingly robust, multidimensional natural-history evidence base spanning motor function, cardiorespiratory status, imaging, biomarkers and patient-reported outcomes, a transformation that has been instrumental in enabling the design of the interventional trials discussed in Sections 6 and 7.

5.2 Functional and Biomarker Outcome Measures

The GRASP consortium's cross-sectional analysis of 101 participants with FKRP-related LGMD2I/R9 evaluated the North Star Assessment for limb-girdle-type dystrophies (NSAD), the 100-metre timed test and the Performance of Upper Limb 2.0 (PUL) scale, finding that most functional assessments correlated strongly with one another, with the notable exception of the nine-hole peg test, which behaved as a relatively independent measure of distal hand function (Alfano et al., 2025). Quantitative fat-fraction muscle magnetic resonance imaging has independently demonstrated sensitivity to disease progression over a twelve-month interval even when conventional strength and timed-function testing failed to detect significant change, underscoring the value of imaging-based biomarkers in a slowly progressive disease (Willis et al., 2013). Most recently, the GRASP-LGMD consortium has validated glycosylated α-dystroglycan measured by quantitative immunohistochemistry in serial tibialis anterior muscle biopsies as a biomarker that is both consistently lower in affected individuals than in unaffected controls and stable over six to twelve months, supporting its qualification

as a target-engagement biomarker for interventional trials, including gene-replacement and substrate-therapy studies (Vissing et al., 2026). Sampling variability nonetheless remains a recognised limitation of biopsy-based glycosylation biomarkers, since fatty and fibrotic replacement in more advanced disease can bias tissue sampling toward myocyte-poor regions, a caveat that trial designers must weigh when selecting biopsy timing and site relative to disease stage. Table 2 summarises these principal outcome measures alongside their key validated properties.

Table 2. Principal clinical outcome assessments used in contemporary LGMD2I/R9 trials and natural-history studies

Outcome measure	Domain assessed	Key finding	Source
North Star Assessment for limb-girdle dystrophies (NSAD)	Gross motor function	Correlated with other functional measures in a prospective GRASP cohort; useful for gross motor assessment in LGMD2I/R9 trial design	Alfano et al. (2025)
100-metre timed test	Ambulatory endurance	Correlated with NSAD; sensitive to gradual decline	Alfano et al. (2025)
Performance of Upper Limb 2.0 (PUL)	Upper-limb function	Validated cross-sectionally in LGMD2I/R9; useful in non-ambulatory patients	Alfano et al. (2025)
Quantitative muscle MRI (Dixon fat fraction)	Structural muscle change	Detected significant 12-month fat-fraction increase when functional tests did not	Willis et al. (2013)
Glycosylated α-dystroglycan (muscle biopsy)	Molecular target engagement	Reduced versus controls; stable over 6–12 months; used as surrogate endpoint	Vissing et al. (2026)
INQoL / SF-36	Health-related quality of life	HRQoL domains compromised, particularly with compound-heterozygous c.826C>A genotype	Jensen, Friborg, et al. (2024)
PROMIS pain interference and fatigue	Patient-reported symptom burden	Fatigue elevated in adults, correlated with declining motor and pulmonary function	Reelfs et al. (2023)

As Table 2 illustrates, the outcome-measure landscape for LGMD2I/R9 now spans function, imaging, molecular biomarkers and patient-reported experience, a breadth that reflects the multisystem nature of the disease and offers trial designers a correspondingly wide choice of primary and supportive endpoints.

5.3 Patient-reported Burden

Beyond objective motor, cardiac and imaging measures, patient-reported outcome data have increasingly demonstrated that the subjective burden of LGMD2I/R9 is not fully explained by conventional strength or ambulation metrics. Health-related quality of life, assessed longitudinally over fourteen months in the Norwegian cohort using the Individualized Neuromuscular Quality of Life questionnaire and the SF-36, was found to be measurably compromised relative to population norms, with compound heterozygotes for the c.826C>A variant showing significantly greater impairment than homozygotes, mirroring the genotype-severity gradient observed in motor and biomarker domains (Jensen, Friborg, et al., 2024). In a separate United States cohort followed for up to six years using the Patient-Reported Outcomes Measurement Information System (PROMIS) pain interference and fatigue instruments, fatigue was found to be elevated in adults but not children, to correlate inversely with both motor and pulmonary function in adults, and to fluctuate substantially over time without a clear directional trend, a pattern that carries direct implications for the choice and timing of patient-reported endpoints in interventional trials (Reelfs et al., 2023). These findings, together with the cardiac data discussed below, are summarised in Table 3.

Taken together, the domains in Table 3 indicate that disease burden in LGMD2I/R9 extends well beyond the neuromuscular system narrowly defined, reinforcing the case for multidomain, rather than single-endpoint, evaluation of any future gene-based therapy.

Table 3. Multisystem and patient-reported disease burden in LGMD2I/R9

Domain	Key finding	Implication for gene-therapy development	Source
Health-related quality of life	Compromised relative to population norms; worse in compound heterozygotes	Supports inclusion of HRQoL instruments as secondary trial endpoints	Jensen, Friborg, et al. (2024)
Pain interference	Elevated above general population in a majority of patients; episodic rather than fixed	Argues for repeated-measures rather than single time-point assessment	Reelfs et al. (2023)
Fatigue	Elevated in adults; correlates with declining motor and pulmonary function	Candidate patient-relevant endpoint sensitive to systemic disease progression	Reelfs et al. (2023)
Cardiomyopathy	Present in ~45% of a US cohort; weak correlation with ambulatory function	Mandates cardiac assessment independent of motor endpoints	Libell et al. (2020)
Reproductive health	Pregnancy generally achievable in reported LGMDR9 cohort; weakness may worsen during pregnancy or postpartum, and assisted vaginal delivery/induction rates may be increased	Relevant to reproductive counselling and long-term safety counselling for gene-therapy recipients of reproductive age	Libell et al. (2021)

5.4 Cardiorespiratory Surveillance

Cardiac and respiratory involvement in LGMD2I/R9 warrants dedicated surveillance independent of skeletal muscle strength assessment. In a retrospective United States cohort of 56 subjects with 157 echocardiograms, cardiomyopathy was identified in 45% of participants, with the median age at first abnormal echocardiogram substantially later in individuals homozygous for c.826C>A (54.2 years) than in those with other genotype combinations (18.1 years); correlation between cardiac ejection fraction and ambulatory function was weak, reinforcing the need for independent cardiac monitoring rather than reliance on motor status as a surrogate (Libell et al., 2020). These findings carry direct implications for gene-therapy trial design, since cardiac outcomes constitute both an efficacy endpoint of clinical importance and a domain requiring careful safety monitoring given the cardiotropism of several AAV serotypes under clinical investigation.

6. AAV-Mediated Gene Replacement Therapy

6.1 Rationale and Vector Design

AAV-mediated gene replacement seeks to restore wild-type FKRP expression in skeletal, cardiac and respiratory muscle through a single systemic administration of a recombinant AAV vector carrying a codon-optimised human *FKRP* transgene under the control of a muscle-specific promoter. This approach offers the theoretical advantage of restoring full enzymatic function independent of the mutant allele's residual activity, and, unlike small-molecule substrate therapy, requires only a single administration to achieve durable transgene expression in post-mitotic muscle tissue (Benasutti et al., 2023). Vector design choices, including capsid serotype, promoter selection and untranslated-region architecture, materially influence both the magnitude of transgene expression and the biodistribution profile across skeletal, cardiac and hepatic tissue, and each of these parameters has been iteratively optimised across successive generations of preclinical FKRP vectors, as summarised in Table 4.

6.2 Preclinical Efficacy in Murine Models

Systemic delivery of AAV9-*FKRP* to the FKRP-deficient (FKRP^P448L) mouse model demonstrated dose-dependent rescue of functional α-dystroglycan glycosylation together with measurable improvement in muscle pathology and function, providing a proof-of-concept foundation later built upon by combination studies pairing AAV-*FKRP* with ribitol substrate therapy, discussed in Section 7.2 (Cataldi et al., 2023). Subsequent optimisation work using an AAV6 vector with untranslated-region modifications to increase transgene

expression demonstrated dose- and time-dependent improvements in grip strength, a three- to five-fold reduction in serum creatine kinase, partial stabilisation of exercise-induced respiratory changes, and improved treadmill running capacity with reduced exercise-induced muscle damage in the aged FKRP^P448L mouse model (Benasutti et al., 2023). These preclinical data collectively established proof of concept for the biodistribution, dose-dependence and functional efficacy of AAV-*FKRP* gene replacement, forming the basis for subsequent early-phase human trials. Notably, across independent studies from different research groups, the dose–response relationship for functional benefit was not strictly linear: modest AAV doses produced measurable improvements in histopathology and biochemical glycosylation, whereas the higher doses required to approach wild-type levels of matriglycan restoration and to achieve durable, body-wide correction of cardiac and respiratory muscle fell into a dose range associated with heightened immunogenicity risk in the wider AAV gene-therapy field, a tension discussed further in Section 6.4.

6.3 Early Clinical Experience

Peer-reviewed human efficacy data for AAV-FKRP therapy remain limited, and the registered clinical programmes should be distinguished carefully. ATA-100, formerly GNT0006 (ClinicalTrials.gov identifier NCT05224505), is a Phase 1 multicentre study evaluating the safety, pharmacodynamics and immunogenicity of an intravenous AAV9 vector encoding FKRP in participants with genetically confirmed FKRP-related LGMDR9/LGMD2I; the registry describes actual enrolment of six participants and long-term follow-up extending beyond the initial dosing period (ClinicalTrials.gov, 2025a). AB-1003, previously LION-101 (NCT05230459), is a separate Phase 1/2 two-part multicentre study using a randomized, double-blind, placebo-controlled dose-escalation and adaptive design in adults with LGMD2I/R9 mutations in FKRP (ClinicalTrials.gov, 2026). Preliminary safety or pharmacodynamic findings reported in congress presentations or sponsor communications are useful for understanding the therapeutic pipeline but should be interpreted as interim, non-peer-reviewed evidence until full trial data are published. Trial eligibility criteria across AAV-FKRP programmes generally require genetically confirmed biallelic FKRP variants, defined residual motor function and screening for pre-existing anti-AAV capsid neutralising antibodies, reflecting lessons drawn from the wider AAV gene-therapy field regarding the exclusionary effect of pre-existing humoral immunity on transduction efficiency (Shen et al., 2022).

6.4 Vector Immunogenicity and Systemic Safety

The principal barrier to widespread clinical translation of high-dose systemic AAV gene therapy is host immunity directed against the viral capsid and, in some cases, the transgene product. A meta-analysis of 255 AAV clinical trials encompassing 7,289 planned participants found that AAV2 remained the most frequently used serotype, that fewer than half of trials employed prophylactic or reactive immunosuppression, and that considerable heterogeneity existed in neutralising-antibody eligibility thresholds across programmes, complicating cross-trial comparison of immunogenicity outcomes (Shen et al., 2022). Pre-existing anti-capsid antibodies exclude a proportion of otherwise eligible patients from systemic AAV trials, while cellular and humoral responses mounted after dosing can attenuate transgene expression over time and, in serious cases, precipitate complement activation and hepatotoxicity (Bradbury et al., 2023). High-dose systemic administration has been associated with severe, occasionally fatal, hepatotoxicity in other neuromuscular gene-therapy programmes, and preclinical toxicology in non-human primates has confirmed dose-dependent transaminase elevation and hepatocellular injury following systemic self-complementary AAV9 administration that was not consistently ameliorated by prophylactic corticosteroid or B-cell-depleting immunosuppression (Hudry et al., 2023). These findings are directly relevant to FKRP gene-therapy development, since the vector doses required to achieve therapeutically meaningful matriglycan restoration in preclinical FKRP models fall within ranges associated with immunogenicity and hepatotoxicity risk in other systemic AAV programmes (Cataldi et al., 2023). Beyond hepatotoxicity, the broader meta-analytic literature on AAV clinical trials indicates that durability of transgene expression varies substantially by target tissue, with muscle-directed trials generally achieving more sustained expression than ocular-directed programmes, a reassuring observation for muscle-targeted FKRP vectors, though it does not eliminate the possibility of gradual immune-mediated attenuation of expression over years of follow-up (Shen et al., 2022). The absence, at present, of an approved strategy for safe AAV vector redosing further constrains the field: because neutralising antibodies generated in response to an initial administration typically preclude effective retreatment with the same serotype, patients who receive a suboptimal initial dose, or whose transgene expression declines over time, currently have limited recourse to a

second corrective administration, a limitation that reinforces the clinical importance of achieving durable benefit from a single, carefully optimised initial dose.

Table 4. Preclinical and translational evidence relevant to AAV-based therapy in FKRP-related dystroglycanopathy

Study/programme	Model or population	Vector/design	Key finding	Source
Dose-dependent AAV9-*FKRP* efficacy	FKRP-deficient (FKRP^P448L) mouse model	Systemic AAV9-*FKRP*	Dose-dependent rescue of α-dystroglycan glycosylation and muscle function	Cataldi et al. (2023)
UTR-optimised AAV6-*FKRP*	Aged FKRP^P448L mice	AAV6 with 5′/3′ UTR modification	Improved grip strength, reduced CK, improved treadmill performance	Benasutti et al. (2023)
Ribitol + AAV-FKRP combination	FKRP^P448L mice, long-term follow-up	AAV-FKRP ± oral ribitol	Combination superior to either monotherapy; improved lifespan and matriglycan induction	Cataldi et al. (2023)
Dual FKRP/FST vector	FKRP^P448L mice	Single AAV bicistronic FKRP + follistatin	Supranormal muscle strength; normalised ambulation endurance	Lam et al. (2024)
Cross-programme AAV safety review	255 AAV clinical trials, 7,289 patients	Multiple serotypes and indications	High variability in immunosuppression practice and antibody eligibility criteria	Shen et al. (2022)

Table 4 illustrates a clear preclinical progression from single-gene, dose-optimised AAV-FKRP constructs toward combination and dual-gene strategies designed to address the dosing and durability limitations identified in the cross-programme safety literature. The table should be interpreted as a preclinical and translational summary rather than as evidence of established human clinical efficacy; the registered ATA-100 and AB-1003 clinical programmes described in Section 6.3 have not yet produced comprehensive peer-reviewed long-term efficacy and safety datasets.

7. Ribitol Substrate Therapy

7.1 Mechanistic Basis

Ribitol is a naturally occurring five-carbon sugar alcohol that serves as the metabolic precursor for CDP-ribitol, the nucleotide-sugar donor used by FKRP and fukutin to attach ribitol-phosphate to the core glycan of α-dystroglycan. Because the common founder FKRP variant retains partial catalytic activity, increasing intracellular ribitol availability can drive residual enzymatic flux toward greater matriglycan synthesis without requiring gene replacement (Cataldi et al., 2023). Ribitol supplementation has demonstrated the capacity to enhance matriglycan expression in cultured human cell lines expressing hypomorphic FKRP activity, providing direct biochemical support for this substrate-based strategy (Cataldi et al., 2023). As an orally bioavailable small molecule rather than a biologic or viral construct, ribitol is chemically and regulatorily distinct from AAV gene therapy, and its development pathway has accordingly followed conventional small-molecule pharmacokinetic and dose-escalation principles rather than the biodistribution and immunogenicity considerations that dominate AAV programme design.

7.2 Preclinical and Combinatorial Evidence

In the FKRP^P448L mouse model, long-term oral ribitol supplementation alone improved pathology, muscle function and survival relative to untreated controls, while combination with AAV-*FKRP* gene therapy produced synergistic benefit exceeding either intervention alone: high-dose AAV-FKRP combined with ribitol produced the greatest matriglycan restoration, and low-dose AAV-FKRP combined with ribitol achieved comparable benefit to considerably higher AAV doses given alone, suggesting that substrate supplementation may allow

dose reduction and thereby mitigate AAV-related immunogenicity and hepatotoxicity risk (Cataldi et al., 2023). This dose-sparing potential represents one of the more clinically significant preclinical findings in the field, since it directly addresses the principal safety liability of systemic AAV gene therapy identified in Section 6.4.

7.3 Clinical Development

Oral ribitol (BBP-418) has progressed to the registered FORTIFY trial (ClinicalTrials.gov identifier NCT05775848), a Phase 3 randomized, placebo-controlled, double-blind study evaluating efficacy and safety in adolescents and adults with genetically confirmed LGMD2I/R9 (ClinicalTrials.gov, 2025b). The trial is designed to assess glycosylated alpha-dystroglycan, functional outcomes and safety over a longer treatment period. Sponsor-reported interim Phase 3 findings and subsequent regulatory communications, including reported FDA acceptance and priority review of the BBP-418 new drug application with a target action date in November 2026, are important pipeline developments but remain distinct from fully peer-reviewed trial publications (BridgeBio Pharma, Inc., 2026). As an oral, non-viral small molecule, ribitol carries a fundamentally different risk profile from AAV gene therapy, without the same capsid-immunity, redosing and high-dose hepatotoxicity concerns associated with systemic viral vectors. Its efficacy is mechanistically contingent on the presence of at least partial residual FKRP enzymatic activity and may therefore be less applicable to genotypes with minimal residual function. This genotype dependence contrasts with AAV gene replacement, which in principle restores function irrespective of the specific mutant allele present, and suggests that the two modalities may ultimately occupy complementary rather than directly competing positions within the therapeutic landscape.

8. Combinatorial and Muscle-Anabolic Gene Therapy Strategies

A distinguishing translational challenge in LGMD2I/R9, as in other muscular dystrophies, is that gene replacement alone halts further deterioration but does not readily reverse muscle mass and strength already lost prior to treatment. To address this limitation, a bicistronic AAV vector co-expressing human *FKRP* under a muscle-specific promoter alongside human follistatin, a myostatin antagonist that promotes muscle hypertrophy, was evaluated in the FKRP^P448L mouse model. This dual-gene construct not only restored glycosylation but produced muscle strength and mass exceeding wild-type levels, normalised ambulation endurance in a one-hour walk test, and showed more balanced increases in muscle mass with amplified expression of both transgenes relative to either single-gene vector administered alone (Lam et al., 2024). This combinatorial platform illustrates a broader conceptual shift in neuromuscular gene therapy, from purely corrective strategies aimed at halting progression toward regenerative strategies capable of rebuilding lost muscle capacity within a single vector administration, though clinical translation will require additional safety characterisation given the systemic metabolic effects of myostatin pathway inhibition. Follistatin-based muscle-anabolic gene therapy has been explored independently in other neuromuscular indications, and the accumulated safety experience from those programmes, encompassing considerations of off-target tissue growth, lipid metabolism and long-term cardiac loading under conditions of supraphysiological muscle mass, will be directly relevant to risk assessment for any dual FKRP/follistatin construct that advances toward human evaluation. A further open question concerns the optimal stoichiometry between the two transgenes packaged within a single bicistronic vector, since preclinical data indicate that the ratio of FKRP to follistatin expression achieved by a given promoter and vector architecture materially influences the balance between glycosylation correction and muscle hypertrophy, and this ratio may require disease-stage-specific optimisation rather than a single fixed formulation.

9. Genome Editing and Emerging Approaches

Although no CRISPR-Cas9 or base-editing programme specific to *FKRP* has yet advanced to preclinical efficacy publication, genome-editing platforms developed for other muscular dystrophies illustrate potential future directions applicable to dystroglycanopathy. In Duchenne muscular dystrophy, AAV-delivered CRISPR-Cas9 approaches employing antisense oligonucleotide-mediated exon skipping alongside gene-editing correction have demonstrated the capacity to restore reading-frame integrity and produce truncated but partially functional protein in preclinical and early clinical settings, with AAV-delivered CRISPR-Cas9 offering the theoretical advantage of a single, potentially permanent genetic correction compared with the repeated dosing required by oligonucleotide-based exon-skipping drugs (Solberg et al., 2020). For LGMD2I/R9, where the disease-causing mechanism is predominantly a hypomorphic missense variant rather than a large structural deletion, base-editing or prime-editing strategies designed to correct the founder c.826C>A variant directly at the genomic level represent a conceptually attractive, though currently unrealised, therapeutic avenue.

Homology-directed repair-based correction remains constrained in this context by its dependence on active cell division, which limits efficiency in post-mitotic mature myofibres (Solberg et al., 2020), a limitation that applies equally to any future FKRP-directed editing strategy and that AAV-delivered gene replacement and substrate therapy do not share. Base editors and prime editors, which do not require a double-strand break or a donor repair template, are in principle better suited than classical homology-directed repair to correcting single-nucleotide missense variants such as L276I in post-mitotic tissue, but their application to muscle in vivo remains at an early preclinical stage across the muscular dystrophy field generally, and substantial work on muscle-tropic delivery vehicles, editing efficiency in terminally differentiated myonuclei, and off-target risk assessment will be required before an FKRP-directed editing programme could reasonably progress toward clinical evaluation.

10. Cardiorespiratory and Multidisciplinary Management Considerations for Gene-Therapy Candidates

Because cardiomyopathy and respiratory insufficiency in LGMD2I/R9 can progress independently of skeletal muscle weakness and are not reliably predicted by ambulatory status, candidates for gene-based therapy require comprehensive baseline and longitudinal cardiopulmonary assessment incorporating echocardiography, electrocardiography and spirometry, irrespective of apparent skeletal muscle severity (Libell et al., 2020). This requirement carries particular weight for AAV gene-replacement programmes, given the cardiotropism of commonly used AAV serotypes and the need to monitor cardiac safety as well as skeletal-muscle target engagement. Any hypothesis that molecular restoration in fibrotic myocardium could alter myocardial mechanics remains unproven in human recipients and should be treated as a safety question for longitudinal follow-up rather than as an established risk. Multidisciplinary input from cardiology, respiratory medicine, physiotherapy and psychosocial support services accordingly remains integral to safe trial conduct and to post-approval care pathways, complementing rather than being superseded by any future gene-based intervention.

Table 5. Comparative features of the principal therapeutic modalities under development for LGMD2I/R9

Feature	AAV gene replacement	Ribitol substrate therapy	Combinatorial (dual-gene) therapy	Genome editing (prospective)
Mechanism	Delivers functional *FKRP* transgene	Increases substrate flux through residual mutant enzyme	Gene replacement plus muscle-anabolic transgene (e.g., follistatin)	Direct correction of the pathogenic variant
Administration	Single systemic infusion	Chronic oral dosing	Single systemic infusion	Prospectively single administration
Genotype dependence	Largely genotype-independent	Requires residual FKRP activity	Largely genotype-independent	Variant-specific (e.g., targets L276I)
Principal safety concern	Capsid immunogenicity, hepatotoxicity, high-dose risk	Favourable safety profile typical of small molecules	Compounded by myostatin-pathway effects	Off-target editing, delivery to post-mitotic muscle
Redosing feasibility	Limited by anti-capsid immunity	Readily repeatable	Limited by anti-capsid immunity	Currently unestablished
Clinical development stage	Early-phase registered human trials; comprehensive peer-reviewed efficacy data pending	Registered Phase 3 FORTIFY trial; regulatory review supported by interim sponsor-reported data	Preclinical (murine)	Preclinical, extrapolated from DMD
Representative evidence	Cataldi et al. (2023); Benasutti et al. (2023); ClinicalTrials.gov (2025a, 2026)	Cataldi et al. (2023); ClinicalTrials.gov (2025b); BridgeBio Pharma, Inc. (2026)	Lam et al. (2024)	Solberg et al. (2020)

Beyond cardiopulmonary monitoring, several additional practical considerations bear on the multidisciplinary management of individuals enrolled in or considering gene-based therapy for LGMD2I/R9. Rehabilitation and physiotherapy programmes tailored to the fluctuating pattern of pain and fatigue described in Section 5.3 are likely to remain relevant even after successful molecular correction, since restoration of glycosylation does not instantaneously reverse established fibro-fatty muscle remodelling, and a period of supervised, graded exercise rehabilitation may be required to translate biochemical improvement into functional gain. Psychological and social support similarly warrants continued attention, given the demonstrated impact of LGMD2I/R9 on health-related quality of life independent of genotype (Jensen, Friborg, et al., 2024); patients and families entering gene-therapy trials often carry substantial expectations regarding functional recovery, and realistic, iteratively updated counselling regarding the anticipated trajectory and limitations of investigational therapy is an important, though frequently under-resourced, component of trial conduct in this population. Finally, genetic counselling for reproductive planning remains relevant throughout the treatment pathway, both for prospective parents considering future pregnancies and for extended family members identified as carriers through cascade testing, since autosomal recessive inheritance means that unaffected sibling carriers are common within affected families. Table 5 draws together the modalities discussed in Sections 6 through 9 to compare their mechanisms, safety considerations and developmental maturity, providing a single reference point before the forward-looking discussion in Section 11.

As Table 5 makes clear, no single modality currently combines genotype-independence, a favourable safety profile and clinical maturity; this trade-off is the central problem that the future-directions priorities outlined below are intended to address.

11. Future Directions

The maturing pipeline for LGMD2I/R9 points toward several priorities for the coming decade. Dose optimisation strategies that combine lower AAV doses with adjunctive ribitol substrate supplementation warrant dedicated clinical evaluation, building directly on preclinical evidence of synergy and potential dose-sparing benefit, since reducing the administered AAV dose while preserving efficacy would directly mitigate the immunogenicity and hepatotoxicity risks that currently constrain systemic gene therapy across the neuromuscular field. Capsid engineering to reduce hepatotropism and pre-existing seroprevalence, alongside more standardised immunosuppression protocols informed by cross-programme meta-analytic data, should improve the therapeutic index of future AAV constructs. Combinatorial regenerative approaches, exemplified by dual FKRP/follistatin vectors, merit continued preclinical refinement and careful early-phase safety evaluation given the systemic consequences of myostatin pathway modulation. Validated biomarkers, including biopsy-based quantitative glycosylated alpha-dystroglycan and quantitative muscle magnetic resonance imaging, should be further qualified as surrogate or supportive endpoints capable of informing expedited regulatory pathways appropriate to an ultra-rare disease population in which large, conventionally powered pivotal trials are difficult to conduct. Finally, extension of genome-editing platforms validated in other muscular dystrophies toward direct correction of the FKRP founder variant represents a longer-term but still hypothetical avenue, should efficient, muscle-directed in vivo editing become feasible in post-mitotic tissue. Sustained international collaboration through consortia such as GRASP and coordinated natural-history registries will remain essential to achieving adequately powered, comparable trial data across this geographically dispersed and numerically small patient population.

Several additional considerations are likely to shape the field over the coming years. First, the question of optimal timing of intervention warrants dedicated study: preclinical data indicating attenuated benefit when treatment is initiated at advanced disease stages suggest that early intervention may maximise therapeutic benefit, but any movement toward pre-symptomatic testing or newborn-screening models would require careful ethical, counselling and health-economic evaluation. Second, as multiple therapeutic modalities mature in parallel, sequential-combination or adaptive trial designs may ultimately be required to determine whether substrate therapy administered before or alongside a reduced-dose AAV vector can achieve superior efficacy-to-risk ratios relative to either intervention given alone, building directly on the preclinical synergy data described in Section 7.2. Third, regulatory pathways for ultra-rare diseases may depend on biomarker-supported evidence, but acceptance of such endpoints will require continued validation against meaningful functional, respiratory and patient-reported outcomes. Finally, post-approval pharmacovigilance infrastructure, potentially integrated

with existing natural-history registries, will be essential to capture long-term safety and durability signals that inherently cannot be fully characterised within the time-limited follow-up windows of pivotal trials, particularly for one-time gene-replacement interventions whose durability may only become fully apparent after many years of real-world observation.

12. Conclusions

LGMD2I/R9 is a rare but geographically clustered autosomal recessive dystroglycanopathy whose molecular basis, disruption of ribitol-phosphate-primed matriglycan synthesis on alpha-dystroglycan, has become sufficiently well characterised to support rational, mechanism-based therapeutic development. Preclinical AAV-mediated gene replacement restores glycosylation and improves muscle structure and function across disease stages, while oral ribitol substrate therapy exploits the residual activity of the common founder variant to achieve biochemical and functional signals through a fundamentally different and complementary mechanism. However, definitive peer-reviewed clinical efficacy and long-term safety data remain incomplete for the major human programmes, and interim registry, conference or sponsor-reported findings should not be interpreted as equivalent to final published trial results. Combinatorial gene-therapy constructs that pair correction of the primary glycosylation defect with muscle-anabolic transgenes offer a possible route toward reversing, rather than merely halting, established muscle disease, but this concept remains preclinical. Substantial translational barriers remain, foremost among them AAV vector immunogenicity and hepatotoxicity at the doses required for therapeutic efficacy, together with the need for further validated biomarkers and outcome measures suited to a slowly progressive, phenotypically heterogeneous, ultra-rare disorder. Continued integration of natural-history data, biomarker qualification and iterative preclinical refinement will be essential if gene-based therapies for LGMD2I/R9 are to reach patients safely and durably. The disease occupies a distinctive position within the broader neuromuscular therapeutics landscape: its underlying biochemistry is unusually well defined relative to many rare myopathies, its principal founder variant retains partial residual function that has opened a complementary substrate-based treatment avenue alongside gene replacement, and its patient community has generated an evidence base disproportionately rich for a disorder of its rarity. Whether AAV gene replacement, ribitol substrate therapy, combinatorial regenerative gene therapy, or some sequential or combined use of these modalities ultimately proves most effective, the trajectory of the past five years indicates that LGMD2I/R9 may be among the earlier dystroglycanopathies to move from purely supportive care toward mechanism-directed therapy, provided that the immunogenicity, dosing, durability and evidence-quality challenges outlined in this review can be adequately resolved.

13. Limitations

This review is subject to several limitations. As a narrative rather than systematic review, formal risk-of-bias assessment, PRISMA-style record counts and quantitative synthesis were not undertaken, and selection of source material, while conducted according to explicit criteria, retains an element of author judgement. The literature specific to FKRP-directed gene therapy remains small given the rarity of the disorder, necessitating selective incorporation of evidence from the broader AAV gene-therapy field to contextualise immunogenicity and safety considerations; such extrapolation may not fully capture disease- or tissue-specific factors unique to dystroglycanopathy. Trial-registry entries, conference abstracts and sponsor communications were used only to contextualise the therapeutic pipeline and should not be interpreted as substitutes for peer-reviewed efficacy or long-term safety publications. Peer-reviewed efficacy and long-term safety data from ongoing human AAV-FKRP and ribitol programmes were not yet fully available at the time of writing, limiting the depth of clinical evaluation possible for these specific programmes. Finally, the rapidly evolving nature of this field means that findings reported after the literature search cut-off date may not be fully reflected in this synthesis, and readers are encouraged to consult primary trial registries and subsequent peer-reviewed publications for the most current evidence.

Declaration of AI Use

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contributions or scholarly judgment of the author(s). All AI-assisted outputs, including content, references, and interpretations, were carefully reviewed, revised, verified, and approved by the author(s). The author(s) accept full responsibility for the accuracy, integrity, and final content of the manuscript.

Competing Interests

Authors have declared that no competing interests exist.

References

Alfano, L. N., James, M. K., Grosfjeld Petersen, K., Rudolf, K., Vissing, J., Augsburger, R., Mozaffar, T., Jones, A., Butler, A., Laubscher, K. M., Mockler, S. R. H., Mathews, K. D., Iammarino, M. A., Reash, N. F., Pietruszewski, L., Lowes, L. P., Strahler, T., Wicklund, M., … Johnson, N. E. (2025). Prospective observational study of FKRP-related limb-girdle muscular dystrophy R9: A GRASP consortium study. *Annals of Clinical and Translational Neurology, 12*(2), 332–344. https://doi.org/10.1002/acn3.52276

Beltrán, D., Anderson, M. E., Bharathy, N., Settelmeyer, T. P., Svalina, M. N., Bajwa, Z., Shern, J. F., Gultekin, S. H., Cuellar, M. A., Yonekawa, T., Keller, C., & Campbell, K. P. (2019). Exogenous expression of the glycosyltransferase LARGE1 restores α-dystroglycan matriglycan and laminin binding in rhabdomyosarcoma. *Skeletal Muscle, 9*, Article 11. https://doi.org/10.1186/s13395-019-0195-0

Benasutti, H., Maricelli, J. W., Seto, J., Hall, J., Halbert, C., Wicki, J., Heusgen, L., Purvis, N., Regnier, M., Lin, D. C., Rodgers, B. D., & Chamberlain, J. S. (2023). Efficacy and muscle safety assessment of fukutin-related protein gene therapy. *Molecular Therapy: Methods & Clinical Development, 30*, 65–80. https://doi.org/10.1016/j.omtm.2023.05.022

Bouchard, C., & Tremblay, J. P. (2023). Limb–girdle muscular dystrophies classification and therapies. *Journal of Clinical Medicine, 12*(14), Article 4769. https://doi.org/10.3390/jcm12144769

Bradbury, A., Markusic, D. M., Muhuri, M., & Ou, L. (2023). Editorial: Immunogenicity and toxicity of AAV gene therapy. *Frontiers in Immunology, 14*, Article 1227231. https://doi.org/10.3389/fimmu.2023.1227231

BridgeBio Pharma, Inc. (2026, May 27). *BridgeBio announces FDA acceptance and priority review of NDA for BBP-418 for LGMD2I/R9* [Press release]. U.S. Securities and Exchange Commission. https://www.sec.gov/Archives/edgar/data/1743881/000114036126022979/ef20074977_ex99-1.htm

Cataldi, M. P., & Lu, Q. L. (2025). Ribitol and ribose treatments differentially affect metabolism of muscle tissue in FKRP mutant mice. *Scientific Reports, 15*, Article 1329. https://doi.org/10.1038/s41598-024-83661-4

Cataldi, M. P., Vannoy, C. H., Blaeser, A., Tucker, J. D., Leroy, V., Rawls, R., Killilee, J., Holbrook, M. C., & Lu, Q. L. (2023). Improved efficacy of FKRP AAV gene therapy by combination with ribitol treatment for LGMD2I. *Molecular Therapy, 31*(12), 3478–3489. https://doi.org/10.1016/j.ymthe.2023.10.022

ClinicalTrials.gov. (2025a, October 6). *ATA-100 (formerly GNT0006) gene therapy trial in patients with LGMDR9* (NCT05224505) [Clinical trial registration]. U.S. National Library of Medicine. https://clinicaltrials.gov/study/NCT05224505

ClinicalTrials.gov. (2025b, September 29). *Study to evaluate the efficacy and safety of BBP-418 (ribitol) in patients with limb girdle muscular dystrophy 2I (LGMD2I) (FORTIFY)* (NCT05775848) [Clinical trial registration]. U.S. National Library of Medicine. https://clinicaltrials.gov/study/NCT05775848

ClinicalTrials.gov. (2026, February 20). *A study to evaluate the safety of AB-1003 (previously LION-101) in subjects with genetic confirmation of LGMD2I/R9 (Part 1)* (NCT05230459) [Clinical trial registration]. U.S. National Library of Medicine. https://clinicaltrials.gov/study/NCT05230459

D'Este, G., Spagna, M., Federico, S., Cacciante, L., Cieślik, B., Kiper, P., & Barresi, R. (2025). Limb-girdle muscular dystrophies: A scoping review and overview of currently available rehabilitation strategies. *Muscle & Nerve, 71*(2), 138–146. https://doi.org/10.1002/mus.28284

Hudry, E., Aihara, F., Meseck, E., Mansfield, K., McElroy, C., Chand, D., Tukov, F. F., & Penraat, K. (2023). Liver injury in cynomolgus monkeys following intravenous and intrathecal scAAV9 gene therapy delivery. *Molecular Therapy, 31*(10), 2999–3014. https://doi.org/10.1016/j.ymthe.2023.07.020

Jensen, S. M., Friborg, O., Mellgren, S. I., Müller, K. I., Bergvik, S., & Arntzen, K. A. (2024). Health-related quality of life in FKRP-related limb-girdle muscular dystrophy R9. The Norwegian LGMDR9 cohort study (2020). *Journal of Neuromuscular Diseases, 11*(1), 59–74. https://doi.org/10.3233/JND-221629

Jensen, S. M., Müller, K. I., Mellgren, S. I., Bindoff, L. A., Rasmussen, M., Ørstavik, K., Jonsrud, C., Tveten, K., Nilssen, Ø., Van Ghelue, M., & Arntzen, K. A. (2023). Epidemiology and natural history in 101 subjects with FKRP-related limb-girdle muscular dystrophy R9. The Norwegian LGMDR9 cohort study (2020). *Neuromuscular Disorders, 33*(2), 119–132. https://doi.org/10.1016/j.nmd.2022.11.005

Jensen, S., Abeler, K., Friborg, O., Rosner, A., Olsborg, C., Mellgren, S. I., Müller, K. I., Rosenberger, A. D., Vold, M. L., & Arntzen, K. A. (2024). Insomnia and sleep-disordered breathing in FKRP-related limb-girdle muscular dystrophy R9. The Norwegian LGMDR9 cohort study (2020). *Journal of Neurology, 271*, 274–288. https://doi.org/10.1007/s00415-023-11978-7

Johnson, N. E., & Statland, J. M. (2022). The limb-girdle muscular dystrophies. *Continuum (Minneapolis, Minn.), 28*(6), 1698–1714. https://doi.org/10.1212/CON.0000000000001178

Kanagawa, M. (2021). Dystroglycanopathy: From elucidation of molecular and pathological mechanisms to development of treatment methods. *International Journal of Molecular Sciences, 22*(23), Article 13162. https://doi.org/10.3390/ijms222313162

Lam, P., Zygmunt, D. A., Ashbrook, A., Bennett, M., Vetter, T. A., & Martin, P. T. (2024). Dual FKRP/FST gene therapy normalizes ambulation, increases strength, decreases pathology, and amplifies gene expression in LGMDR9 mice. *Molecular Therapy, 32*(8), 2604–2623. https://doi.org/10.1016/j.ymthe.2024.06.028

Libell, E. M., Bowdler, N. C., Stephan, C. M., Zimmerman, M. B., Gedlinske, A. M., & Mathews, K. D. (2021). The outcomes and experience of pregnancy in limb-girdle muscular dystrophy type R9. *Muscle & Nerve, 63*(6), 812–817. https://doi.org/10.1002/mus.27184

Libell, E. M., Richardson, J. A., Lutz, K. L., Ng, B. Y., Mockler, S. R. H., Laubscher, K. M., Stephan, C. M., Zimmerman, M. B., Edens, E. R., Reinking, B. E., & Mathews, K. D. (2020). Cardiomyopathy in limb girdle muscular dystrophy R9, FKRP related. *Muscle & Nerve, 62*(5), 626–632. https://doi.org/10.1002/mus.27052

Lu, Q. L., Holbrook, M. C., Cataldi, M. P., & Blaeser, A. (2024). Break down of the complexity and inconsistency between levels of matriglycan and disease phenotype in FKRP-related dystroglycanopathies: A review and model of interpretation. *Journal of Neuromuscular Diseases, 11*(2), 275–284. https://doi.org/10.3233/JND-230205

Reelfs, A. M., Stephan, C. M., Mockler, S. R. H., Laubscher, K. M., Zimmerman, M. B., & Mathews, K. D. (2023). Pain interference and fatigue in limb-girdle muscular dystrophy R9. *Neuromuscular Disorders, 33*(6), 523–530. https://doi.org/10.1016/j.nmd.2023.05.005

Shen, W., Liu, S., & Ou, L. (2022). rAAV immunogenicity, toxicity, and durability in 255 clinical trials: A meta-analysis. *Frontiers in Immunology, 13*, Article 1001263. https://doi.org/10.3389/fimmu.2022.1001263

Solberg, M. H., Shariatzadeh, M., & Wilson, S. L. (2020). Gene modification strategies using AO-mediated exon skipping and CRISPR/Cas9 as potential therapies for Duchenne muscular dystrophy patients. *Engineering Biology, 4*(3), 37–42. https://doi.org/10.1049/enb.2020.0017

Straub, V., Murphy, A., Udd, B., & LGMD Workshop Study Group. (2018). 229th ENMC international workshop: Limb-girdle muscular dystrophies—Nomenclature and reformed classification, Naarden, the Netherlands, 17–19 March 2017. *Neuromuscular Disorders, 28*(8), 702–710. https://doi.org/10.1016/j.nmd.2018.05.007

Vissing, J., Mozaffar, T., Johnson, N. E., Mathews, K. D., Wicklund, M. P., Weihl, C., Leung, D. G., Statland, J. M., Kang, P. B., Zingariello, C. D., Lowes, L. P., Desai, U., Bates, K., Alfano, L. N., Xie, H., St Romain, J., Blankenbiller, T., McLendon, G., Rajasingham, T., … Sproule, D. (2026). Quantitative measurement of glycosylated α-dystroglycan as a biomarker for disease severity in limb-girdle muscular dystrophy type 2I/R9. *Neurology Genetics, 12*(2), Article e200370. https://doi.org/10.1212/NXG.0000000000200370

Willis, T. A., Hollingsworth, K. G., Coombs, A., Sveen, M. L., Andersen, S., Stojkovic, T., Eagle, M., Mayhew, A., de Sousa, P. L., Dewar, L., Morrow, J. M., Sinclair, C. D. J., Thornton, J. S., Bushby, K., Lochmüller, H., Hanna, M. G., Hogrel, J. Y., Carlier, P. G., Vissing, J., & Straub, V. (2013). Quantitative muscle MRI as an assessment tool for monitoring disease progression in LGMD2I: A multicentre longitudinal study. *PLOS ONE, 8*(8), Article e70993. https://doi.org/10.1371/journal.pone.0070993

Wu, B., Lu, P. J., Drains, M., Shah, S., Blaeser, A., Leroy, V., Killilee, J., Holbrook, M., & Lu, Q. L. (2025). Ribitol treatment rescues dystroglycanopathy mice with common L276I mutation. *PLOS ONE, 20*(8), Article e0325239. https://doi.org/10.1371/journal.pone.0325239

Yuan, Q., Xie, Z., Lu, Y., Liu, C., Lu, Y., Han, X., Li, Z., Zhang, W., Wang, Z., Yuan, Y., & Xie, Z. (2025). New genotype–phenotype correlations and transcriptomic findings in limb-girdle muscular dystrophy R9. *Journal of Neurology, 272*, Article 516. https://doi.org/10.1007/s00415-025-13252-4

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