

Atypical laminopathy phenotype: recurrent exertional *hyperCKemia* and metabolic syndrome in a patient with an LMNA c.659g>a [p.(ARG220HIS)] variant

Abstract

Background: Pathogenic variants in *LMNA* cause a heterogeneous spectrum of disorders collectively known as laminopathies, encompassing familial partial lipodystrophy (FPLD), Emery–Dreifuss muscular dystrophy, dilated cardiomyopathy, and accelerated aging syndromes.

Case presentation: An 18-year-old male born to consanguineous parents presented with recurrent, exercise-induced muscle cramps, episodic dark urine, and marked *hyperCKemia* (peak creatine kinase >10,000 U/L), along with profound metabolic syndrome characterized by marked insulin resistance (HOMA-IR >6.85), severe hypertriglyceridemia, and hepatic steatosis. Muscle histopathology revealed striking subsarcolemmal periodic acid–Schiff (PAS)-positive accumulation, strongly mimicking a glycogen storage myopathy such as McArdle disease (GSD V). However, a 210-gene targeted neuromuscular next-generation sequencing panel excluded *PYGM* alterations and identified a heterozygous likely pathogenic *LMNA* c.659G>A [p.(Arg220His)] variant (allele fraction 47%).

Conclusions: Exertional rhabdomyolysis and marked *hyperCKemia* represent atypical clinical manifestations of *LMNA* alterations, especially when occurring alongside severe lipodystrophic metabolic derangements. This case highlights diagnostic overlap between metabolic myopathies and striated muscle laminopathies, demonstrating the clinical utility of comprehensive genomic profiling in resolving complex neuromuscular presentations.

Keywords: laminopathy, familial partial lipodystrophy, *hyperCKemia*, *LMNA*, Rhabdomyolysis, McArdle disease mimic

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Introduction

The *LMNA* gene encodes lamins A and C, intermediate filament proteins of the nuclear envelope that are essential for maintaining nuclear architecture, chromatin organization, gene expression, and cellular mechanical integrity. Pathogenic variants in *LMNA* cause a diverse spectrum of tissue-selective disorders collectively termed laminopathies. These include striated muscle disorders, such as Emery–Dreifuss muscular dystrophy, dilated cardiomyopathy, and limb-girdle muscular dystrophy; partial lipodystrophy, particularly familial partial lipodystrophy type 2 (FPLD2); peripheral neuropathies; and premature-aging syndromes.^{1,2}

Familial partial lipodystrophy type 2 (FPLD2), also known as the Dunnigan variety, is classically characterized by progressive, postpubertal loss of subcutaneous adipose tissue from the limbs and trunk, with relative accumulation of adipose tissue in the face, neck, and visceral compartments. This abnormal adipose tissue distribution is associated with severe insulin resistance and metabolic complications, including diabetes mellitus, dyslipidemia, hypertriglyceridemia, and hepatic steatosis.^{3,4} The clinical phenotype is heterogeneous, and muscular hypertrophy and myalgia are recognized manifestations of FPLD2.^{3,5} However, recurrent exercise-induced rhabdomyolysis and severe episodic *hyperCKemia* are not characteristic features of FPLD2 and may mimic a primary metabolic myopathy, creating a diagnostic challenge. Herein, we report an 18-year-old male presenting with recurrent exertional *hyperCKemia*, dark urine, and metabolic abnormalities, in whom genetic testing identified a heterozygous *LMNA* c.659G>A [p.(Arg220His)] variant.

Case presentation

History and clinical examination

An 18-year-old male born to first-degree consanguineous parents presented with a protracted history of painful, recurrent muscle cramps predominantly localized to the quadriceps and gastrocnemius muscle beds. Episodes were typically precipitated by strenuous physical exertion and occasionally developed during sleep. Ictal episodes were accompanied by dark, cola-colored urine indicative of pigmenturia. In interictal periods, the patient retained functional stamina, climbed stairs without difficulty, walked long distances without premature fatigue, and exhibited no documented “second-wind” phenomenon. Notably, previous empiric administration of systemic corticosteroids had exacerbated the frequency and severity of muscle cramping.

- **Neuromuscular Assessment:** Symmetrical muscle strength was fully preserved (5/5 on the MRC scale throughout all muscle groups). Deep tendon reflexes were normal and symmetric. No joint contractures, rigid spine, calf pseudohypertrophy, or axial weakness were detected.
- **Adipose and Metabolic Phenotype:** Marked peripheral subcutaneous lipodystrophy was evident across the upper and lower extremities with prominent superficial venous patterning, contrasting with preserved facial and truncal adiposity. Acanthosis nigricans was noted over the flexural creases.
- **Systemic Examination:** Slit-lamp biomicroscopy demonstrated early bilateral lenticular opacities (cataracts). Abdominal exami-

nation revealed smooth, non-tender hepatosplenomegaly, corroborated by ultrasound showing diffuse hepatic steatosis.

Diagnostic investigations (Table 1 & 2)

Histopathological and genetic analysis

A skeletal muscle needle biopsy of the vastus lateralis demonstrated preserved architecture with no endomysial inflammatory infiltration,

necrosis, or significant fiber degeneration. However, Periodic Acid–Schiff (PAS) staining (Figure 1) revealed coarse, dense subsarcolemmal PAS-positive deposits forming prominent peripheral crescents and rings beneath the sarcolemma of scattered hypertrophied muscle fibers. These histological features heightened suspicion for a primary glycogenolytic disorder, particularly myophosphorylase deficiency (McArdle disease, GSD V).

Table 1 Diagnostic laboratory investigations and results

Investigation	Patient result	Reference interval	Clinical interpretation
Creatine kinase (Ictal)	~10,000 U/L	20–200 U/L	Severe episodic exertional rhabdomyolysis
Creatine kinase (Interictal)	~200 U/L	20–200 U/L	Near-complete interictal normalization
HOMA-IR	>6.85	<2.0	Severe peripheral insulin resistance
Serum triglycerides	284 mg/dL	<90 mg/dL	Marked atherogenic hypertriglyceridemia
Total cholesterol	162 mg/dL	<170 mg/dL	Normal
Alanine aminotransferase (ALT)	117 U/L	8–22 U/L	Elevated (hepatic steatosis vs. myogenous release)
Aspartate aminotransferase (AST)	58 U/L	13–26 U/L	Elevated (transaminitis / muscle breakdown)
Alkaline phosphatase (ALP)	137 U/L	48–95 U/L	Mild elevation

Table 2 Results of neurological, cardiac and immunological investigations

Investigation	Patient result	Reference interval	Clinical interpretation
Electromyography (EMG)	Normal	—	No myopathic motor units or spontaneous activity
ECG and echocardiography	Normal	—	Normal ejection fraction; no conduction delay or AV block
Autoimmune serology	Negative	—	ANA, ENA, RF, anti-TPO, C3, and C4 normal

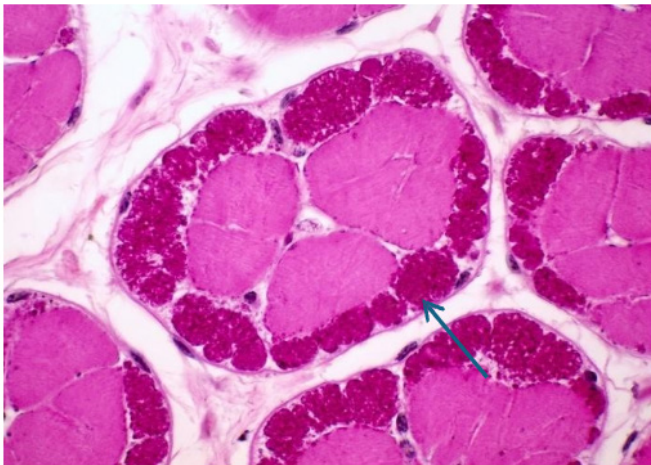


Figure 1 Skeletal muscle biopsy (cross-section, Periodic Acid–Schiff [PAS] stain, original magnification ×400). Granular, intense PAS-positive deposits selectively localized in the subsarcolemmal compartment, forming characteristic peripheral rings and blebs beneath the sarcolemma of hypertrophied muscle fibers.

To establish a definitive diagnosis, a targeted 210-gene next-generation sequencing neuromuscular panel was performed. Genomic analysis excluded pathogenic or likely pathogenic variants in PYGM, PFKM, CPT2, ACADVL, and GAA. Rather, testing revealed a heterozygous missense variant in the LMNA gene: c.659G>A [p.(Arg220His)] with a variant allele frequency of 47%, classified as likely pathogenic.

Discussion

The patient presented with a clinical picture highly suggestive of an exercise-induced metabolic myopathy, particularly McArdle

disease (glycogen storage disease type V [GSD V]), characterized by exertional myalgia, marked episodic hyperCKemia (~10,000 U/L), dark urine, and subsarcolemmal PAS-positive material. McArdle disease classically manifests with exercise intolerance, early muscle pain and contractures, and episodes of rhabdomyolysis, with the characteristic “second-wind” phenomenon reflecting improved exercise tolerance after several minutes of activity.⁶ Nevertheless, several features of our patient diverged from the classic clinical picture of isolated GSD V.

First, the patient demonstrated preserved aerobic walking capacity, tolerating sustained low- to moderate-intensity walking without the early exercise intolerance or contractures typically associated with McArdle disease. Although the second-wind phenomenon is highly characteristic of GSD V, its absence alone does not exclude the diagnosis; rather, the patient’s overall exercise tolerance was considered discordant with a typical presentation.⁶

Second, the histological findings required cautious interpretation. Subsarcolemmal PAS-positive material may suggest abnormal glycogen accumulation and can support a glycogen storage disorder; however, PAS positivity is not by itself diagnostic of McArdle disease and should be interpreted alongside biochemical, enzymatic, and molecular findings. In this case, the histological appearance contributed to the initial metabolic-myopathy impression but did not establish a specific glycogen storage disorder.

Third, the patient exhibited a prominent lipodystrophic-metabolic phenotype, including marked insulin resistance (HOMA-IR >6.85), hypertriglyceridemia, peripheral loss of subcutaneous adipose tissue, and hepatic steatosis. These findings are not readily explained by an isolated metabolic myopathy and instead raised suspicion for an underlying metabolic laminopathy.^{3,4} Importantly, muscular manifestations including myalgia, muscle hypertrophy, cramps, and weakness have previously been reported in patients with LMNA-

associated familial partial lipodystrophy.⁵ Moreover, non-codon 482 LMNA mutations have been associated with severe metabolic abnormalities and muscle manifestations, sometimes in patients without the typical clinically apparent lipoatrophy of Dunnigan-type FPLD2.⁸ This observation is particularly relevant to the atypical phenotype in our patient.

The identification of the LMNA c.659G>A [p.(Arg220His)] variant provided critical diagnostic clarification. Classical Dunnigan-type FPLD2 is most strongly associated with missense variants clustered around codon 482 in the C-terminal globular domain of lamin A/C, although pathogenic variants outside this hotspot are well documented.^{3,4} The p.Arg220His substitution lies within the central α -helical rod domain of lamin A/C. Thus, its location differs from the canonical Arg482 hotspot and may contribute to the atypical clinical phenotype observed in this patient. Previous studies have demonstrated that non-codon 482 LMNA variants can produce overlapping metabolic, muscular, and cardiac phenotypes, highlighting the substantial genotype–phenotype heterogeneity of laminopathies.^{7,8}

The mechanism underlying the patient's marked exertional hyperCKemia remains uncertain. A-type lamins contribute to nuclear mechanical stability and nucleo-cytoskeletal force transmission, particularly in mechanically stressed tissues such as skeletal muscle.^{1,2,7} Experimental studies of LMNA-related muscular disease have demonstrated increased nuclear deformability, impaired nuclear stability, and mechanically induced nuclear-envelope rupture in mutant skeletal muscle cells.⁷ Therefore, it is biologically plausible that an LMNA-associated defect in nuclear mechanotransduction could contribute to susceptibility to muscle injury during strenuous exercise. However, this proposed mechanism remains speculative in the present patient, and a direct causal relationship between the p.Arg220His variant and recurrent exertional hyperCKemia has not been established.

The presence of early-onset bilateral cataracts further supports the multisystem nature of the underlying laminopathy. Given the established association of pathogenic LMNA variants with progressive conduction-system disease, arrhythmias, and dilated cardiomyopathy, a normal baseline cardiac evaluation does not eliminate the need for longitudinal surveillance.^{2,3} Current recommendations for asymptomatic individuals with a pathogenic LMNA variant include periodic cardiovascular assessment with history, physical examination, electrocardiography, and echocardiography every 1–2 years, with more intensive rhythm monitoring when ECG abnormalities or other clinical indications are present.⁹ Accordingly, continued cardiology follow-up is warranted in this patient, with ambulatory rhythm monitoring and cardiac MRI considered according to the evolving clinical and electrocardiographic findings.

Overall, this case illustrates an unusual phenotypic overlap between metabolic myopathy and LMNA-associated lipodystrophy. The combination of exertional myalgia, dark urine, severe episodic hyperCKemia, and subsarcolemmal PAS positivity initially suggested McArdle disease, whereas the associated metabolic abnormalities

and genetic findings supported an LMNA-related disorder. The case emphasizes the importance of integrating clinical phenotype, histopathology, metabolic assessment, and molecular genetic testing when an apparent metabolic myopathy is accompanied by features suggestive of a systemic laminopathy.

Conclusions

This case illustrates an unusual phenotypic manifestation of the LMNA c.659G>A [p.(Arg220His)] variant presenting with exertional rhabdomyolysis and marked hyperCKemia mimicking a metabolic myopathy in the setting of severe lipodystrophic metabolic dysfunction. In patients presenting with exercise-induced hyperCKemia and subsarcolemmal PAS positivity accompanied by systemic metabolic derangements, laminopathies should remain a key differential diagnosis. Broad next-generation sequencing is instrumental in achieving diagnostic accuracy and directing appropriate cardiovascular and metabolic management.

Acknowledgments

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

1. Broers JLV, Ramaekers FCS, Bonne G, et al. Nuclear lamins: laminopathies and their role in premature ageing. *Physiol Rev*. 2006;86(3):967–1008.
2. Rankin J, Ellard S. The laminopathies: a clinical review. *Clin Genet*. 2006;70(4):261–274.
3. Fernandez-Pombo A, Diaz-Lopez EJ, Castro AI, et al. Clinical spectrum of LMNA-associated type 2 familial partial lipodystrophy: a systematic review. *Cells*. 2023;12(5):725.
4. Hussain I, Patni N, Garg A. Lipodystrophies, dyslipidaemias and atherosclerotic cardiovascular disease. *Pathology*. 2019;51(2):202–212.
5. Spuler S, Kalbhenn T, Zabojszcza J, et al. Trembath RC, Shackleton S. Muscle and nerve pathology in Dunnigan familial partial lipodystrophy. *Neurology*. 2007;68(9):677–683.
6. Haller RG, Vissing J. Spontaneous “second wind” and glucose-induced second “second wind” in McArdle disease: oxidative mechanisms. *Arch Neurol*. 2002;59(9):1395–1402.
7. Earle AJ, Kirby TJ, Fedorchak GR, et al. Mutant lamins cause nuclear envelope rupture and DNA damage in skeletal muscle cells. *Nat Mater*. 2020;19(4):464–473.
8. Decaudoain A, Vantyghem MC, Guerci B, et al. New metabolic phenotypes in laminopathies: LMNA mutations in patients with severe metabolic syndrome. *J Clin Endocrinol Metab*. 2007;92(12):4835–4844.
9. Hershberger RE, Jordan E. LMNA-related dilated cardiomyopathy. In: Adam MP, Bick S, Mirzaa GM, et al, editors. *GeneReviews*® [Internet]. University of Washington, Seattle; published June 12, 2008. Updated March 17, 2022.