

The evolving spectrum of LAMA2 related congenital muscular dystrophy (MDC1)-Case series and review of literature

Rahul Sinha^{a,*}, Sonali Singh^b, Mona Tiwari^c, Zulfikar Luhar^d, Ankit Kumar Meena^e, Arvinder Wander^e, Dharmesh Soneji^f

^a Department of Pediatrics and Pediatric Neurology, Command Hospital, Chandimandir, Panchkula, India

^b Hospital for Sick Children, University of Toronto, Toronto, Canada

^c Institute of Neurosciences, Kolkata, India

^d Apex Child Neurology and Epilepsy Centre, India

^e All India Institute of Medical Sciences, Bhatinda, Punjab, India

^f Department of Medicine and Medical Oncology, Command Hospital, Chandimandir, Panchkula, India

ARTICLE INFO

Keywords:

Muscular dystrophy
LAMA 2
Laminin
Hypotonia
Creatinine phosphokinase
White matter

Introduction

Laminin α 2-related muscular dystrophy (LAMA2-MD) Or Non Syndromic Congenital muscular dystrophy is a congenital muscular dystrophy with a spectrum of clinical presentations from the severe type 1A congenital muscular dystrophy (MDC1A), characterized by complete merosin deficiency, to a milder, later-onset form associated with partial merosin deficiency [1]. The cardinal features include weakness in axial and proximal muscles, delayed motor development, early spinal rigidity, joint contractures, scoliosis and respiratory difficulties. In addition, patients may experience different seizures semiology and exhibit characteristic diffuse white matter lesions on magnetic resonance imaging (MRI) [2]. The severe form of LAMA2-MD includes weak cry at birth, marked hypotonia and decreased movements with the involvements of facial weakness, tongue and limited extraocular movements which gradually develops later on in life. In contrast, most patients with a mild form of LAMA2-MD present with delayed motor milestones during early childhood. The clinical diagnosis of LAMA2-MD is confirmed by the presence clinical and neuroimaging features along with genetic testing for pathogenic variants in the LAMA2 gene. Currently, no curative treatments exist for LAMA2-MD, but preclinical studies are ongoing [3].

We describe five genetically proven cases of LAMA2 related congenital muscular dystrophy (MDC1) with atypical and varied presentation. Our goal is to provide varied spectrum in LAMA2-related muscular dystrophy and to establish a well-characterized baseline cohort of patients with LAMA2-MD for future studies.

Patient description

Case-1

A 3.9-years-old male, born to consanguineous parents, presented with motor developmental delay, feeding difficulties, and respiratory complaints, gradually improving with age. Comprehension and language were relatively preserved. Child had no history of seizure. He could sit without support and recite poems. He had hypotonia with diminished deep tendon reflexes (DTRs). Serum creatine phosphokinase (CPK) level was measured at 1416 IU/L. The whole exome sequencing (WES) was done suspecting congenital myopathy or muscular dystrophy and revealed homozygous variant c.7586_7589dup, [p. (Phe2531X)] on exon 55 in LAMA2 gene, reported as a causative variant in the literature [4] After getting the genetic diagnosis, MRI brain was done which

* Corresponding author.

E-mail address: dr Rahul_2000@yahoo.com (R. Sinha).

<https://doi.org/10.1016/j.dscb.2025.100181>

Available online 20 January 2025

2666-4593/© 2025 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC license (<http://creativecommons.org/licenses/by-nc/4.0/>).

Table 1

Characteristics of patients.

Clinical features	Case 1	Case 2	Case 3	Case 4	Case 5
Age/Gender	3.9y/ M	7y/F	6y/F	3y/M	1yr/F
Age of onset	Early infancy	Early infancy	Early infancy	Early infancy	Early infancy
Tone	Hypotonia	Hypotonia	Hypertonia (R > L)	Hypotonia	Hypotonia
Contractures	+	-	-	-	-
Cognition	N	Mild ID	Mild ID	N	N
Feeding/ respiratory complaints	++	+	-	+	-
Seizures	-	++ (Eyelid myoclonia)	+ (GTCS)	-	-
EEG (Sleep)	-	Slow waves in occipital region	Bilateral temporal discharges	-	-
Ambulation (A/NA)	NA	A	A	NA	NA
Motor	Sits without support	Independent ambulation	Independent ambulation	Sits without support	Sits with support
Neuropathy	No	Yes (axonal)	No	No	No
Nerve conduction study	Normal	Motor axonal polyneuropathy	Normal	Normal	Normal
EMG study	Myopathic pattern	Myopathic pattern	Myopathic pattern	Myopathic pattern	Normal
CPK (Normal range 100- 180 IU/L)	1416	1918	501	325	120
MRI Brain	Symmetrical, confluent involvement of WM- SC, PV, Deep BS- MB, Pons Cerebellar peduncle	Symmetrical, confluent involvement of WM- PV, deep Cerebellar peduncle CC	Symmetrical, confluent involvement of WM- SC, PV (cystic), deep CC, thalamus BS- MB, Pons Cerebellar peduncle	Asymmetrical, patchy involvement of WM- SC, PV, Deep CC	Symmetrical, confluent involvement of WM- SC, PV (cystic), deep CC, thalamus BS- MB
Genetic (LAMA2)	Homozygous nonsense pathogenic variant c.7586_7589dup (p. Phe2531X) mutation on exon 55 in LAMA2 gene	Homozygous Missense novel variant, c.2054T>G p.Leu685Arg on Exon 14, in LAMA2 gene.	Compound heterozygous missense likely pathogenic variant, c.2131_2134dup p. Pro712LeufsTer4 on Exon 15 and variant c.8396C>G p. Ser2799Cys on Exon 60 in LAMA2 gene.	Homozygous pathogenic variant, c.1306+2T>G (5'Splice-site) on the intron 9 in LAMA2 gene.	Homozygous nonsense pathogenic variant, c.7732C>T (p. Ser315Trp) on Exon 55 in LAMA2 gene

NA- Non Ambulatory; A- Ambulatory; WM-white matter; PV- periventricular; SC- subcortical; BS- brainstem; MB- midbrain; CC- corpus callosum; MRI- magnetic resonance imaging; CPK- creatinine phosphokinase; ID- intellectual disability; GTCS- generalized tonic clonic seizure; EEG- electroencephalography; EMG- Electromyography.

demonstrated symmetrical confluent signal alterations in subcortical, periventricular, and deep white matter regions, as well as in the midbrain, pons, and cerebellar peduncle.

Case-2

A female child born to consanguineous parents, aged 7 years, presented with delayed achievement of motor milestones and floppiness which improved with age. She had mild intellectual disability and recent onset frequent eyelid myoclonia. She walked without support. She had a myopathic facies, positive Gower sign and bilateral tendo-achilles contracture. She had hypotonia with diminished DTRs. Serum CPK level was elevated at 1918 IU/l with arterial lactate being 2.4 mmol/L. Electroencephalography (EEG) showed multifocal polyspike-and-waves. Her seizures were well controlled on single medicine, lamotrigine. Nerve conduction study (NCS) showed motor axonal neuropathy involving all four limbs. MRI brain revealed symmetrical confluent signal alterations in the periventricular and deep white matter, cerebellar peduncle, and corpus callosum. With suspicion of congenital muscular dystrophy or mitochondrial disorder WES and mitochondrial genome sequencing (MGS) was advised. WES identified a homozygous missense novel variant, c.2054T>G on Exon 14, in LAMA2 gene reported in Clinvar data base as variant of unknown significance. It is predicted that the p. (Leu685Arg) might alter its composition and physico-chemical properties. MGS was negative.

Case-3

A 6-year-old female child born to non-consanguineous parents presented complaints of motor developmental delay and progressively

worsening asymmetric spastic gait. She had mild intellectual disability and history of an episode of generalized tonic-clonic seizure with normal EEG. On examination, she had average intelligence, spastic speech and hypertonic of upper and lower limbs with brisk DTRs. Serum CPK level was 501 IU/l (Normal range 100-180 IU/L). She had a normal NCS. MRI brain imaging revealed symmetrical confluent signal alterations in the subcortical and deep white matter, periventricular cystic changes, involvement of the midbrain, pons, cerebellar peduncle, and corpus callosum. Leukodystrophy, mitochondrial disorders with cystic leukoencephalopathy were suspected. WES and MGS was done which revealed compound heterozygous novel variants, c.2131_2134dup on Exon 15 and c.8396C>G on Exon 60 in LAMA2 gene. MGS was negative. Neither of the reported variants is reported in ClinVar database. The variant c.2131_2134dup is novel and causes a frameshift starting with codon Proline 712, changes this amino acid to Leucine residue and creates a premature stop codon at position 4 of new reading frame. LOF variants have been previously reported to be disease causing and classified as likely pathogenic. The variant c.8396C>G leads to amino acid change from Ser to a Cys at position 2799 which might alter its composition and physico-chemical properties.

Case-4

A 3-year-old female born to consanguineous parents, symptomatic since early infancy, presented with delayed attainment of motor milestones and floppiness, along with a history of feeding and respiratory issues. She was cognitively age appropriate without history of seizure. She could sit but not stand. She had myopathic face and nasal intonation of voice. Serum CPK level was 325 IU/L and NCS was normal. She was suspected to have congenital myopathy or spinal muscular atrophy

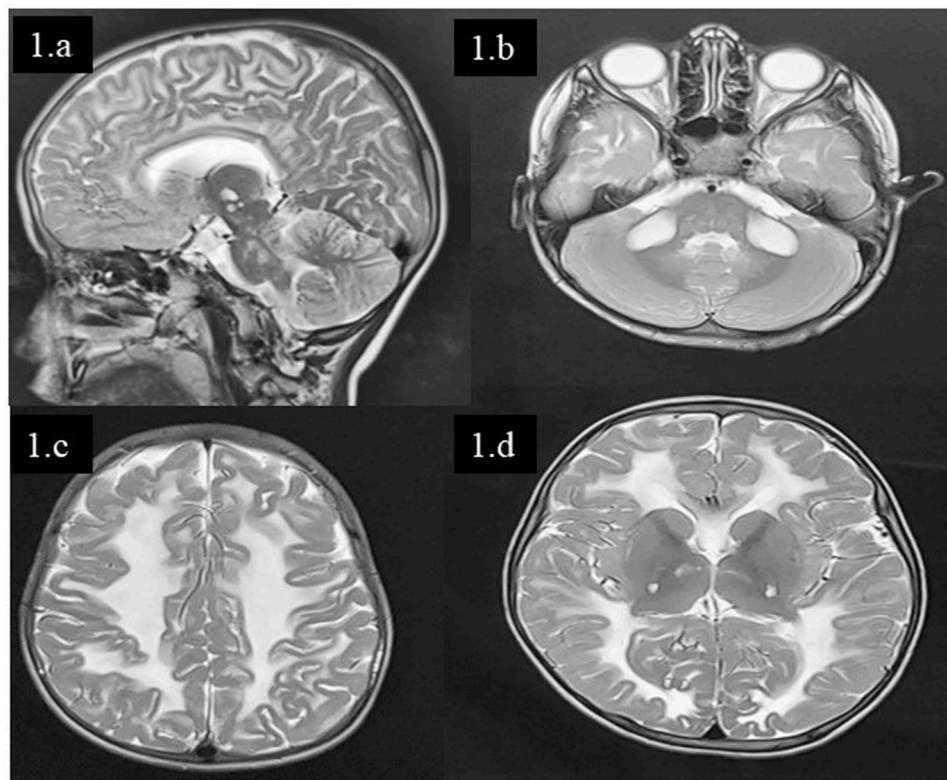


Fig. 1. MRI Brain T2 weighted Sagittal (1a) and axial (1b-d) images of case 3 showing bilaterally symmetrical, confluent involvement of subcortical (SC), deep and periventricular (PV) white matter (WM), corpus callosum (CC), midbrain (MB), pons, thalamus, cerebellar peduncle.

(SMA). SMA for deletion/duplication analysis by MLPA revealed heterozygous duplication in exon 7 and 8 of SMN1 gene and heterozygous deletion in exon 7 and 8 of SMN2 gene. With SMA ruled out, WES was ordered which identified a homozygous pathogenic variant, c.1306+2T>G(5'Splice-site) on the intron 9 in LAMA2 gene, classified as pathogenic in the ClinVar database. MRI brain was done, and it showed asymmetrical patchy signal changes in the subcortical and deep periventricular white matter, as well as in the corpus callosum.

Case 5

A 1-year-old female born to consanguineous parents presented with gross motor delay, tongue fasciculations, generalized hypotonia with diminished DTRs. She had more of proximal limb weakness. She could sit with support and could utter bisyllables. Blood CPK level was 120 IU/L and NCS was normal. SMA was ruled out by MLPA testing. The whole exome sequencing revealed homozygous nonsense pathogenic variant, c.7732C>T on Exon 55 in LAMA2 gene. This results in a stop codon and a premature truncation of the protein at codon 2578 p. (Arg2578Ter) and classified as pathogenic by ACMG recommendations. MRI (Brain) revealed symmetrical, confluent signal changes in subcortical, periventricular white matter changes along with involvement of corpus callosum, thalamus and midbrain. The reference codon is conserved across species. All case details are tabulated in [Table 1](#). The detailed ACMG scores and evidence are tabulated in a supplementary Table 1 for reference.

Common points to all:

1. No positive family history
2. Normal value for serum CPK= 100-180 UI/L
3. Parental testing was not done in any of the patients due to financial constraints
4. Functional study or muscle biopsy was not performed in any of the patients

Discussion

Laminin alpha2 (merosin negative) congenital muscular dystrophy (CMD) is among the most commonly seen muscular dystrophies and accounts for approximately 25 % of cases of non-syndromic CMDs. LAMA2 gene encodes 64 exons with variants distributed through 9.5 kbase sequences. The Laminin protein functions in cell adhesions, cell migration and cellular growth. The expression of laminin is present in basement membranes of Schwann cells and in neuromuscular junctions [5]. The severity of phenotype depends on partial or complete absence of merosin. In LAMA2-related dystrophy, both the central nervous system (CNS) and peripheral nervous system are frequently involved. Complete absence of merosin deficiency patients present in the neonatal period with severe hypotonia and generalized weakness of trunk and limb muscles. Upper limbs are generally more involved than lower limbs, and multiple joint fractures are frequently observed. Sometimes, muscle hypertrophy is also observed in the initial months, respiratory function and feeding are well preserved. Patients usually gain slow milestones during infantile age, and the maximum milestone attained is independent sitting in these children, however, some patients exceptionally attain standing with support and independent walking. Children develop flexion contractures, and in due course of time, they develop rigid kyphoscoliosis. Dysphagia and respiratory insufficiency develop slowly, which necessitates feeding tubes and non-invasive ventilation requirements [6,7]. The serum creatine phosphokinase (CPK) levels are in the range of thousands during in neonatal period which gradually decrease over time.

In our series, the children presented with clinical features that suggested varied differential diagnosis like SMA, congenital myopathy or muscular dystrophy, white matter degenerative brain diseases (WMDs) or leukodystrophy or mitochondrial disorders. This reflects the wide variation in which the patients with mutation in LAMA2 present. These patients do not fit into a typical clinical presentation despite early onset of symptoms noted in all the five patients. Motor symptoms were

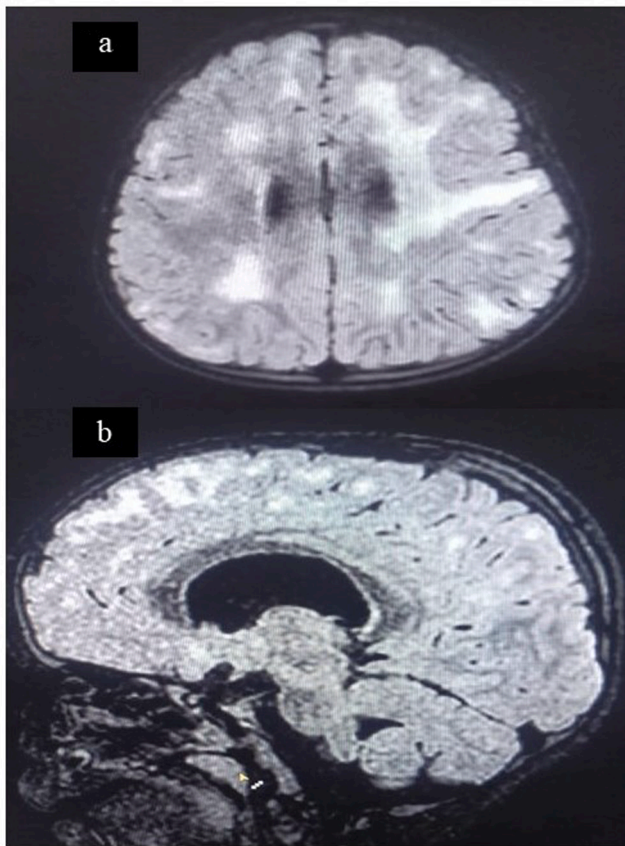


Fig. 2. MRI Brain Flair axial (2a) and sagittal (2b) images of case 4 showing asymmetrical, patchy involvement of SC, deep, and PV WM along with CC involvement.

common to all with relative preservation of language and intelligence. Seizure was present in 2/5, however well controlled. Epilepsy occurs in approximately 30 % patients with seizure semiology varying from focal to generalized, myoclonic, typical or atypical absences [8,9]. The prevailing hypothesis concerning the aetiology of these seizures is that abnormal neuronal firing results from deficient neuronal migration in specific cortical areas, which may not be evident on neuroimaging [10]. Case 2 and 3 could achieve independent ambulation which is contrary to belief that all cases having onset in early infancy will have severe outcome which is interesting in this study.

Electrodiagnostic tests shows nonspecific findings of myopathic pattern with needle electromyography. Nerve conduction velocities are usually slow in these children [11]. One of our cases (Case-2) had motor axonal polyneuropathy. Electromyography (EMG) was done in all our cases which showed myopathic pattern except case no 5 which had normal findings. Mild sensorimotor demyelinating neuropathy is frequently observed in patients, although its contribution to muscle weakness is minimal in humans. In contrast, this neuropathy plays a significant role in muscle weakness in mouse models of LAMA2 deficiency. As laminin- α 2 is also expressed in Schwann cells, there is a range of clinical features related with peripheral nerve involvement in LAMA2-MD patients. The serum CPK level was in the range of 120 to 1900 IU/L in our patients while case 5 had normal CPK.

Muscle biopsy studies show dystrophic changes, and on immunohistochemistry, the absence of staining with laminin alpha two chain on frozen muscles or skin tissues confirms the diagnosis. Partial merosin deficiency is also observed among young onset or adult-onset patients, but these patients present with less severe phenotypes [12]. Similarly secondary merosin deficiency is also seen in MDC1 B, muscle eye brain disease, fukutin-related protein gene (FKRP) related CMD and LGMD 21

[13].

In our series, the neuroimaging pattern of all patients had typical white matter signal changes. Cases 3 and 5 had periventricular cystic changes, and Cases 2,3,5 have corpus callosum affected (Figs. 1,2). The corpus callosum and cerebellar involvement is less common in LAMA 2 related congenital muscular dystrophy which is again interesting finding in our series as all cases had corpus callosum involvement except one. Characteristic neuroimaging features include brain white matter (WM) hypointensity on T1-weighted magnetic resonance imaging and increased T2 signal in the periventricular and subcortical WM, which are invariably observed in most patients older than 6 months regardless of clinically evident central nervous system (CNS) involvement [14,15]. The underlying pathogenesis of white matter changes is still unclear. One hypothesis is that white matter contains increased water content due to impaired selective filtration of blood-brain barrier caused by laminin- α 2 deficiency [16]. Another hypothesis is that these white matter changes indicate structural changes because interactions between laminin- α 2 and integrins on developing oligodendrocytes (myelinating cells of the CNS) enhance the myelin membrane's development [17]. The corpus callosum (CC) involvement in mitochondrial disease includes cystic changes mostly involving middle blade of CC along with, symmetric abnormalities in deep gray matter structures which is generally unusual in LAMA2 [18]. Additionally, cerebral atrophy and neuronal migration defects, such as focal cortical dysplasia, polymicrogyria, or cortical anomalies typically affecting the occipital regions, are observed in approximately 10 % to 40 % of patients across various series.

Genetic confirmation is always necessary. The most frequent reported genotypes include variants that create premature termination codons (PTC) in both disease alleles and are associated with complete deficiency of laminin- α 2 in muscle biopsy as well as a MDC1A phenotype. In contrast, missense variants are present in a smaller number of cases and usually correlate with partial laminin- α 2 deficiency giving rise to milder phenotypes. The asymmetrical proportion between truncating and non-truncating variants, explains the higher prevalence of MDC1A as compared with other emerging LAMA2-related phenotypes [19]. In our series, muscle biopsy was not done due to resource constrain, however all cases had undergone genetic testing (exome analysis) which clearly highlighted that nonsense mutation had severe outcomes (cases 1,4 and 5).

The most appealing treatments can be therapies aimed at providing constructs that could compensate for the lack of specific compounds (e. g., use of linker proteins in LAMA2-RD) [20,21]. Probably in a near future, we will witness a new generation of laminin-binding proteins that, depending on the underlying genetic defects, are able to replace defective domains of laminin and promote the assembly of a stable and fully functional basement membrane.

Limitations: This case series had small cohort of patients with varied spectrum in LAMA2-related muscular dystrophy. The muscle biopsy, parental testing and functional studies could not be done due to limited resource setting.

Conclusion

MDC1 typically represents the severe end of the spectrum of LAMA2-related muscular dystrophy. Normal IQ, peripheral neuropathy, and borderline CPK values do not argue against the diagnosis of MDC1. Also, onset of clinical features in early infancy may not have severe outcome which is interesting in our study. Neuroimaging findings play a crucial role in the diagnosis of MDC1. The presence of corpus callosum (CC) involvement in MDC1 may resemble the CC pattern seen in mitochondrial disorders. MDC1 should also be considered as a potential differential diagnosis in cases of cystic leukoencephalopathy. Both clinical and imaging findings in MDC1 can exhibit variability, and it's essential to acknowledge that this data is continually evolving.

Statements and declarations

Funding: The authors did not receive support from any organization for the submitted work.

Ethical compliance statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

CRediT authorship contribution statement

Rahul Sinha: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Sonali Singh:** Formal analysis, Data curation, Conceptualization. **Mona Tiwari:** Investigation, Data curation. **Zulfikar Luhar:** Resources, Methodology, Data curation. **Ankit Kumar Meena:** Writing – original draft, Validation. **Arvinder Wander:** Writing – review & editing, Investigation. **Dharmesh Soneji:** Writing – review & editing, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.dscb.2025.100181](https://doi.org/10.1016/j.dscb.2025.100181).

References

- [1] A. Sarkozy, A.R. Foley, A.A. Zambon, C.G. Bönnemann, F. Muntoni, LAMA2-related dystrophies: clinical phenotypes, disease biomarkers, and clinical trial readiness, *Front. Mol. Neurosci.* 13 (2020 Aug 5) 123.
- [2] F. Geranmayeh, E. Clement, L.H. Feng, C. Sewry, J. Pagan, R. Mein, et al., Genotype–phenotype correlation in a large population of muscular dystrophy patients with LAMA2 mutations, *Neuromuscul. Disord.* 20 (4) (2010 Apr 1) 241–250.
- [3] P. Barraza-Flores, C.R. Bates, A. Oliveira-Santos, D.J. Burkin, Laminin and integrin in LAMA2-related congenital muscular dystrophy: from disease to therapeutics, *Front. Mol. Neurosci.* 13 (2020) 1.
- [4] S.H.S. Chan, A.R. Foley, R. Phadke, A.A. Mathew, M. Pitt, C. Sewry, et al., Limb girdle muscular dystrophy due to LAMA2 mutations: diagnostic difficulties due to associated peripheral neuropathy, *Neuromuscul. Disord.* 24 (8) (2014 Aug) 677–683.
- [5] P.H. Vachon, F. Loechel, H. Xu, et al., Merosin and laminin in myogenesis; specific requirement for merosin in myotube stability and survival, *J. Cell Biol.* 134 (1996) 1483–1497.
- [6] J. Philpot, A. Bagnall, C. King, et al., Feeding problems in merosin deficient congenital muscular dystrophy, *Arch. Dis. Child* 80 (1999) 542–547.
- [7] M. Fardeau, F.M. Tome, A. Helbling-Leclerc, et al., Congenital muscular dystrophy with merosin deficiency: clinical, histopathological, immunocytochemical and genetic analysis], *Rev. Neurol.* 152 (1996) 11–19.
- [8] C.G. Bönnemann, C.H. Wang, S. Quijano-Roy, N. Deconinck, E. Bertini, A. Ferreira, et al., Diagnostic approach to the congenital muscular dystrophies, *Neuromuscul. Disord.* 24 (4) (2014 Apr) 289–311.
- [9] P. Prandini, A. Berardinelli, M. Fanin, F. Morello, E. Zardini, A. Pichiecchio, et al., LAMA2 loss-of-function mutation in a girl with a mild congenital muscular dystrophy, *Neurology.* 63 (6) (2004 Sep 28) 1118–1121.
- [10] E. Pegoraro, H. Marks, C.A. Garcia, et al., Laminin alpha2 muscular dystrophy: genotype/phenotype studies of 22 patients, *Neurology.* 51 (1998) 101–110.
- [11] H.J. Gilhuis, H.J. ten Donkelaar, R.B. Tanke, et al., Nonmuscular involvement in merosin-negative congenital muscular dystrophy, *Pediatr. Neurol.* 26 (2002) 30–36.
- [12] E. Tan, H. Topaloglu, C. Sewry, et al., Late onset muscular dystrophy with cerebral white matter changes due to partial merosin deficiency, *Neuromuscul. Disord.* 7 (1997) 85–89.
- [13] M. Brockington, Y. Yuva, P. Prandini, et al., Mutations in the fukutin-related protein gene (FKRP) identify limb girdle muscular dystrophy 2I as a milder allelic variant of congenital muscular dystrophy MDC1C, *Hum. Mol. Genet.* 10 (2001) 2851–2859.
- [14] L. Farina, L. Morandi, I. Milanesi, E. Ciceri, M. Mora, I. Moroni, et al., Congenital muscular dystrophy with merosin deficiency: MRI findings in five patients, *Neuroradiology.* 40 (12) (1998 Dec 1) 807–811.
- [15] C.C. Leite, L.T. Lucato, M.G.M. Martin, L.G. Ferreira, M.B.D. Resende, M. S. Carvalho, et al., Merosin-deficient congenital muscular dystrophy (CMD): a study of 25 Brazilian patients using MRI, *Pediatr. Radiol.* 35 (6) (2005 Jun 1) 572–579.
- [16] S. Saredi, S. Gibertini, L. Matalonga, L. Farina, A. Ardisson, I. Moroni, et al., Exome sequencing detects compound heterozygous nonsense LAMA2 mutations in two siblings with atypical phenotype and nearly normal brain MRI, *Neuromuscul. Disord.* 29 (5) (2019) 376–380.
- [17] J. Relucio, M.J. Menezes, Y. Miyagoe-Suzuki, S. Takeda, H. Colognato, Laminin regulates postnatal oligodendrocyte production by promoting oligodendrocyte progenitor survival in the subventricular zone, *Glia* 60 (10) (2012) 1451–1467.
- [18] S.D. Roosendaal, T. van de Brug, C.A.P.F. Alves, S. Blaser, A. Vanderver, N.I. Wolf, M.S. van der Knaap Imaging Patterns Characterizing Mitochondrial Leukodystrophies, *American Journal of Neuroradiology* Jul 2021, 42 (7) 1334–1340; [10.3174/ajnr.A7097](https://doi.org/10.3174/ajnr.A7097).
- [19] J. Oliveira, A. Gruber, M. Cardoso, LAMA2 gene mutation update: toward a more comprehensive picture of the laminin- α 2 variome and its related phenotypes, *Hum. Mutat.* 39 (10) (2018 Oct.) 1314–1337, <https://doi.org/10.1002/humu.23599>, Epub 2018 Aug 10. PMID: 30055037.
- [20] B.E. Deverman, B.M. Ravina, K.S. Bankiewicz, S.M. Paul, D.W.Y. Sah, Gene therapy for neurological disorders: progress and prospects, *Nat. Rev. Drug Discov.* 17 (2018) 641–659.
- [21] P.N. Valdmantis, M.A. Kay, Future of rAAV gene therapy: platform for RNAi, gene editing, and beyond, *Hum. Gene Ther.* 28 (2017) 361–372.