

CASE REPORT

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Early versus late diagnosis of *LAMA2* congenital muscular dystrophy: a distinct consequence

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Abstract

Background Laminin subunit alpha 2 (*LAMA2*)-related muscular dystrophy (*LAMA2* MD) is caused by homozygous or compound heterozygous mutations in *LAMA2* (OMIM#156225), located on chromosome 6q22.

Case presentation We describe two patients with *LAMA2* MD treated at a Taiwanese hospital. Both presented with gradual hypotonia starting in early infancy. A targeted muscular dystrophy/myopathy panel and whole-exome sequencing were used as diagnostic tools in both patients. In Patient 1, a maternally inherited variant (NM_000426.3:c.7525_7528dupCTCA/ p.Ser2510ThrfsTer3) and a paternally inherited variant (c.112+2 T>C) were revealed. In Patient 2, compound heterozygote mutations in *LAMA2* were identified: 1) c.1583dupA(p.S529Efs*18) in exon 11, inherited paternally, and 2) c.A6931T:p.K2311X in exon 49, inherited maternally. The discovery of these four mutations enriches the genetic spectrum of *LAMA2* MD.

Conclusions We suggest that comprehensive genetic investigations be performed as early as possible in patients with suspected muscular dystrophy to provide appropriate treatment.

Keywords Early diagnosis, *LAMA2* mutations, Muscular dystrophy, Whole-exome sequencing, Periventricular white matter abnormalities, Asphyxia

Background

Laminins are a family of glycoproteins that serve as major components of all basement membranes. Laminin-211, previously known as merosin, is a laminin isoform and cell adhesion molecule that is strongly expressed in the

basement membrane of skeletal muscle [1]. Mutations in the laminin subunit alpha 2 gene (*LAMA2*) can lead to laminin $\alpha 2$ chain deficiencies, causing skeletal muscle dysfunction, resulting in *LAMA2*-related muscular dystrophy (*LAMA2* MD), which is also known as merosin-deficient congenital muscular dystrophy [2, 3].

LAMA2 MD is characterized by generalized hypotonia and muscle weakness at birth. Patients typically develop motor delays, proximal joint contractures, the inability to walk, and high levels of creatine phosphokinase (CPK). Brain magnetic resonance imaging (MRI) may also reveal clinically asymptomatic abnormalities of the central white matter [4, 5].

Cardiomyopathy, respiratory insufficiency, demyelinating sensory and motor neuropathy, and (late) external ophthalmoplegia have also been reported as symptoms in *LAMA2* MD patients in the literature [3, 5]. The present study reports two cases of *LAMA2* MD, diagnosed at

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different stages of life, resulting in different trajectories. The patients' genetic features, phenotypes, clinical presentations, and outcomes are described here.

Case presentation

Patient 1 A 7-year-old girl (P1, twin A born to a G1P1 mother at the gestational age of 37 weeks, with a body weight of 2440 g at birth) exhibited poor sucking strength and hypotonia from early infancy. When the patient arrived at the China Medical University Hospital's Neurological Outpatient Department at three months old, her physical and neurological examination revealed no specific findings except hypotonia and spinal muscular atrophy, which was initially suspected but later excluded through genetic testing. Her parents had no consanguinity; her family pedigree is shown in Fig. 1A. The patient's CPK level was 2217 IU/L (normal range: 38–234 IU/L). Respiratory insufficiency and *sleep* apnea episodes were evident starting at 6 months of age. Significant axial and proximal muscle weakness were observed, causing feeding difficulties and choking episodes. Therefore, the patient received a nasojunal tube insertion for nutritional support, and intensive respiratory care was

administered using biphasic positive airway pressure during sleep. Periodic pulmonary function testing and pulmonary follow-ups were conducted. A genetic study revealed a compound heterozygous mutation in *LAMA2* at the age of 8 months, confirming a diagnosis of *LAMA2* MD. Brain MRI at 8 months exhibited extensive white matter abnormalities (Fig. 2A). Cardiac echocardiography revealed normal cardiac function but multiple aortopulmonary collateral arteries and mild aortic regurgitation. Motor nerve conduction velocity (NCV) showed normal amplitude but mild to moderate decreases in conduction velocity in the upper extremities. Sensory NCV showed a mild to moderate decrease in conduction velocity. F response showed borderline abnormal latency and conduction velocity over both lower extremities.

The patient is currently 7 years old; ambulation has not been achieved, active rehabilitation is ongoing, and mental development is normal.

Patient 2 A male infant (P2) died suddenly, ostensibly of pneumonia and respiratory failure, at the age of 1 year and 2 months. His parents had no consanguinity; his family pedigree is shown in Fig. 1B. A blood sample was sent to China Medical University Hospital for the genetic

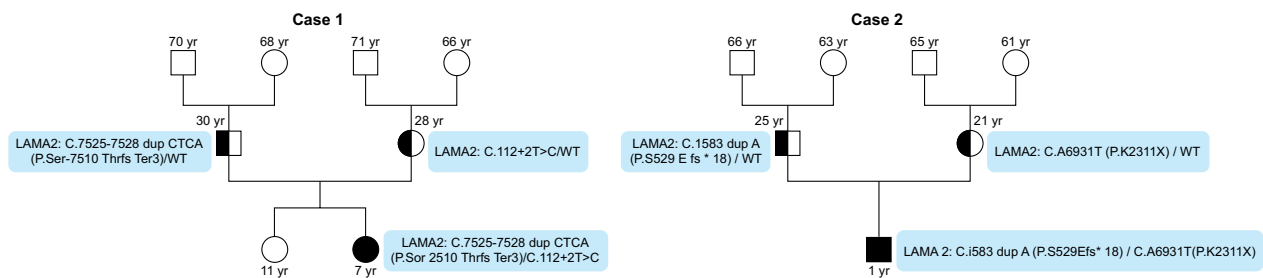


Fig. 1 Family pedigree of **A** Patient 1 and **B** Patient 2

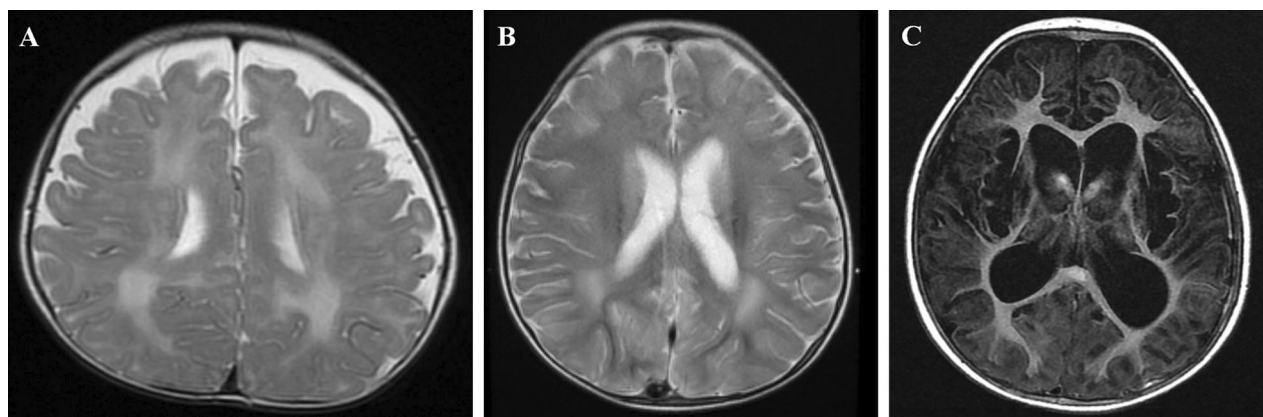


Fig. 2 Cerebral magnetic resonance imaging (MRI; T2-weighted/fluid-attenuated inversion recovery [FLAIR]) of our patients. **A** Imaging in P1 (T2-weighted) at 8 months exhibited widespread T2 hyperintensity of the periventricular white matter. **B** Imaging in P2 (T2-weighted, 10 months) revealed mild ventricular dilatation and myelination delay. **C** Imaging in P2 (T2-weighted/FLAIR, 12 months) exhibited ventriculomegaly, cystic encephalomalacia, extensive subcortical and periventricular white matter loss, and hyperintense white matter with atrophy

investigation of a possible neuromuscular disorder. The patient's genetic history revealed a healthy mother (the patient was born at gestational age 39+2 weeks, with a body weight of 3675 g at birth). The patient exhibited hypotonia, decreased deep tendon reflex, and a weak cry soon after birth. During the first 6 months of life, frequent respiratory infections and dyspnea were reported, in addition to substantial motor delay and a slight delay in cognitive and language development. His cardiac echocardiography showed mild mitral valve collapse and mild tricuspid regurgitation. A series of biochemical and molecular tests (including for *SMNI*) were negative, except for the observation of mildly elevated CPK levels at 548 IU/L.

Despite an intensive rehabilitation course, neither a pulmonary function test nor respiratory assistance was administered in the patient's medical setting. At 10 months, the patient experienced sudden-onset respiratory distress, requiring cardiopulmonary resuscitation in an emergency room. Brain MRI at that time disclosed mild ventricular dilatation and myelination delay (Fig. 2B). After another 2 months, the patient experienced a second, longer asphyxia event, and the brain MRI performed during hospital admission revealed extensive cystic cavities in the bilateral parietal, frontal, and temporal lobes and insular cortex with marked neuronal loss. Abnormal signal intensity was present within the bilateral basal ganglia and white matter (Fig. 2C). Therefore, brain damage due to asphyxia was diagnosed, and the patient exhibited a persistent vegetative state. Following a third respiratory distress event at 1 year and 2 months, the patient died because the family requested no further resuscitation.

In P1, a muscular dystrophy/myopathy gene panel comprising 77 genes revealed compound heterozygous variants in trans in *LAMA2*. One variant was maternally inherited (NM_000426.3:c.7525_7528dupCTCA/

p.Ser2510ThrfsTer3), and one variant was paternally inherited (c.112+2 T>C). In P2, we conducted WES and Sanger sequencing to validate the results of WES on DNA samples from the proband and his parents, leading to the identification of the following compound heterozygote mutations in *LAMA2*: (1) c.1583dupA(p.S529Efs*18) in exon 11, inherited from the father; and (2) c.A6931T:p.K2311X in exon 49, inherited from the mother. The four variants in our patients were extremely rare and were not listed among known Genome Aggregation Database exomes; all of the identified mutations were expected to be damaging to the protein structure, resulting in the premature termination of translation.

We present two cases of *LAMA2* MD, one in which the patient was diagnosed early and achieved a good prognosis, and another in which the patient died before diagnosis. The clinical presentations and prognoses of these two patients are compared in Table 1. The early diagnosis of *LAMA2* MD and disease management by a multidisciplinary team can improve the quality of life and prolong the life span of a patient. Although spinal muscular atrophy is a commonly considered diagnosis among infants presenting with hypotonia and motor delays, many cases of congenital muscular dystrophy involve genetically determined conditions that are evident at birth (such as mutations in *LAMA2*, *SEPN1*, *COL6A1*, *COL6A2*, *COL6A3*, *LMNA*, *POMT1*, *POMT2*, *POMGNT1*, *FKTN*, *FKRP*, *LARGE*, *ISPD*, *GTDC2*, *TMEM5*, *B3GALNT2*, *POMK*, *B3GNT1*, or *GMPPB*) [6, 7]. This clinical report underlines the importance of early diagnosis in cases of *LAMA2* MD, which may lead to more favorable results, as was observed in these two patients.

Most patients with *LAMA2* MD display periventricular white matter abnormalities on brain imaging, but mental retardation and seizures are rare occurrences [8–10]. However, the case of P2 raises two questions. (1) What changes occur on brain MRI in patients with

Table 1 Genetic and Clinical Findings in Patients with *LAMA2* MD

Patient	Age/Sex	Age at diagnosis	<i>LAMA2</i> mutations	Initial presentation	Initial CPK level (IU/L)	Brain MRI	Clinical course and outcome
1	7 y/F	8 mo	c.7525_7528dupCTCA(p.Ser2510ThrfsTer3)/c.112+2 T>C	Hypotonia and feeding difficulties from early infancy	2217	At 8 mo: Abnormal periventricular and subcortical white matter signals	Mental activity and cognition were normal, but ambulation was not achieved
2	14 mo/M	1 mo after death (14 mo)	c.1583dupA(p.S529Efs*18)/c.A6931T(p.K2311X)	Hypotonia, respiratory muscle weakness, and feeding difficulties from birth	548	First (10 mo): Ventricular dilatation and myelination delay. Second (12 mo): Extensive cystic cavities and marked neuronal tissue loss in both hemispheres	OHCA twice and death from respiratory failure

CPK creatine phosphokinase; F female; *LAMA2* laminin alpha-2; M male; MD muscular dystrophy; Mo month; OHCA out-of-hospital cardiac arrest; y year

LAMA2 MD who experience concurrent hypoxic/ischemic events? (2) Can the typical clinical manifestation of *LAMA2* MD be masked or distorted by hypoxic events? P2 entered a vegetative state after two prolonged asphyxia events, resulting in a delayed diagnosis due to a distorted clinical presentation [11, 12].

The diagnostic algorithm for early-onset congenital muscular dystrophy has recently undergone considerable change [13, 14], and many currently available molecular diagnostic tools, such as WES, whole-genome sequencing, and targeted panel sequencing for myopathy diseases, can facilitate the early diagnosis of muscular diseases [10]. All cases of hypotonia in infants without determined causes should proceed to comprehensive genetic screening, and WES should be considered as a first choice for cases with clear causal indications. These less invasive techniques have partially replaced muscle biopsies as the first diagnostic step [15].

In addition to being clinically significant, the four variants identified in these two patients are novel *LAMA2* mutations. In particular, the c.7525_7528dupCTCA(p.Ser2510ThrfsTer3), c.112+2 T>C, c.1583dupA(p.S529Efs*18), and c.A6931T(p.K2311X) mutations enrich the genetic spectrum of *LAMA2* MD.

Conclusions

In summary, we report two cases of *LAMA2* MD diagnosed that were diagnosed at different stages of life, resulting in opposite outcomes. We suggest that a comprehensive genetic investigation for patients with suspected muscular dystrophy be performed as early as possible to facilitate correct diagnosis and the provision of appropriate treatment. Moreover, four novel mutations in *LAMA2* were discovered, enriching the genetic spectrum of *LAMA2* MD.

Abbreviations

CPK	Creatine phosphokinase
<i>LAMA2</i>	Laminin subunit alpha 2
MRI	Magnetic resonance imaging
MD	Muscular dystrophy
WES	Whole-exome sequencing

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Author contributions

SYH provided treatment to the patient, collected the data, and wrote the draft. CHL, SSL, and ICL participated in the design of the case report and wrote the manuscript. CHC and ICC provided recommendations for the patients' treatment. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Consent for discussion of the clinical history was provided by the families. The study protocol was approved by the Ethics Review Board of the China Medical University ethics committee (Approval # CMUH107-REC2-017). Written informed consent for participation was obtained from the legal guardians.

Consent for publication

Consent for publication was obtained from the legal guardians.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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References

- Ehrig K, Leivo I, Argraves WS, Ruoslahti E, Engvall E. Merosin, a tissue-specific basement membrane protein, is a laminin-like protein. *Proc Natl Acad Sci USA*. 1990;87:3264–8.
- Vachon PH, Loechel F, Xu H, Wewer UM, Engvall E. Merosin and laminin in myogenesis; specific requirements for merosin in myotubal stability and survival. *J Cell Biol*. 1996;134:1483–97.
- Helbling-Leclerc A, Zhang X, Topaloglu H, Cruaud C, Tesson F, Weisenbach J, et al. Mutations in the laminin alpha 2-chain gene (*LAMA2*) cause merosin-deficient congenital muscular dystrophy. *Nat Genet*. 1995;11:216–8.
- Philpot J, Sewry C, Pennock J, Dubowitz V. Clinical phenotype in congenital muscular dystrophy: correlation with expression of merosin in skeletal muscle. *Neuromuscul Disord*. 1995;5:301–5.
- Geranmayeh F, Clement E, Feng LH, Sewry C, Pagan J, Mein R, et al. Genotype-phenotype correlation in a large population of muscular dystrophy patients with *LAMA2* mutations. *Neuromuscul Disord*. 2010;20:241–50.
- Kang PB, Morrison L, Iannaccone ST, Graham RJ, Bönnemann CG, Rutkowski A, et al. Evidence-based guideline summary: evaluation, diagnosis, and management of congenital muscular dystrophy: report of the guideline development subcommittee of the American academy of neurology and the practice issues review panel of the American association of neuromuscular & electrodiagnostic medicine. *Neurology*. 2015;84:1369–78.
- Bönnemann CG, Wang CH, Quijano-Roy S, Deconinck N, Bertini E, Ferreira A, et al. Diagnostic approach to the congenital muscular dystrophies. *Neuromuscul Disord*. 2014;24:289–311.
- Xiong H, Tan D, Wang S, Song S, Yang H, Gao K, et al. Genotype/phenotype analysis in Chinese laminin- α 2 deficient congenital muscular dystrophy patients. *Clin Genet*. 2015;87:233–43.
- Nguyen Q, Lim KRQ, Yokota T. Current understanding and treatment of cardiac and skeletal muscle pathology in laminin- α 2 chain-deficient congenital muscular dystrophy. *Appl Clin Genet*. 2019;12:113–30.
- Camacho A, Núñez N, Dekomien G, Hernández-Lain A, de Aragón AM, Simón R. *LAMA2*-related congenital muscular dystrophy complicated by West syndrome. *Eur J Paediatr Neurol*. 2015;19:243–7.
- Woodward KE, Murthy P, Mineyko A, Mohammad K, Esser MJ. Identifying genetic susceptibility in neonates with hypoxic-ischemic encephalopathy: a retrospective case series. *J Child Neurol*. 2023;38:16–24.
- Russ JB, Simmons R, Glass HC. Neonatal encephalopathy: beyond hypoxic-ischemic encephalopathy. *Neoreviews*. 2021;22:e148–62.
- Vill K, Blaschek A, Gläser D, Kuhn M, Haack T, Alhaddad B, et al. Early-onset myopathies: clinical findings, prevalence of subgroups and diagnostic approach in a single neuromuscular referral center in Germany. *J Neuro-muscul Dis*. 2017;4:315–25.

14. Chae JH, Vasta V, Cho A, Lim BC, Zhang Q, Eun SH, et al. Utility of next generation sequencing in genetic diagnosis of early onset neuromuscular disorders. *J Med Genet*. 2015;52:208–16.
15. Haskell GT, Adams MC, Fan Z, Amin K, Guzman Badillo RJ, Zhou L, et al. Diagnostic utility of exome sequencing in the evaluation of neuromuscular disorders. *Neurol Genet*. 2018;4: e21.

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