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NLM Citation: Oliveira J, Parente Freixo J, Santos M, et al. *LAMA2* Muscular Dystrophy. 2012 Jun 7 [Updated 2020 Sep 17]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

LAMA2 Muscular Dystrophy

Synonym: Laminin α2 Chain-Deficiency

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Created: June 7, 2012; Updated: September 17, 2020.

Summary

Clinical characteristics

The clinical manifestations of *LAMA2* muscular dystrophy (*LAMA2*-MD) comprise a continuous spectrum ranging from severe congenital muscular dystrophy type 1A (MDC1A) to milder late-onset *LAMA2*-MD. MDC1A is typically characterized by neonatal profound hypotonia, poor spontaneous movements, and respiratory failure. Failure to thrive, gastroesophageal reflux, aspiration, and recurrent chest infections necessitating frequent hospitalizations are common. As disease progresses, facial muscle weakness, temporomandibular joint contractures, and macroglossia may further impair feeding and can affect speech.

In late-onset *LAMA2*-MD onset of manifestations range from early childhood to adulthood. Affected individuals may show muscle hypertrophy and develop a rigid spine syndrome with joint contractures, usually most prominent in the elbows. Progressive respiratory insufficiency, scoliosis, and cardiomyopathy can occur.

Diagnosis/testing

The diagnosis of *LAMA2* muscular dystrophy is established in a proband with suggestive findings and biallelic (homozygous or compound heterozygous) pathogenic variants in *LAMA2* identified by molecular genetic testing.

Management

Treatment of manifestations: It is recommended that multidisciplinary care be provided by specialists in neurology, gastroenterology, nutrition, orthopedics, occupational and physical therapy, speech and language therapy, education, psychiatry, pulmonary medicine, cardiology, ophthalmology, and social work.

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Surveillance: Routine follow up of nutritional status and safety of oral intake, neurologic status, pulmonary function, developmental/educational progress, cognitive abilities, psychiatric issues, mobility and activities of daily living, cardiac status, vision, and social needs.

Agents/circumstances to avoid: Succinylcholine in induction of anesthesia because of risk of hyperkalemia and cardiac conduction abnormalities; statins, cholesterol-lowering medications, because of the risk of muscle damage.

Genetic counseling

LAMA2-MD is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *LAMA2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *LAMA2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

GeneReview Scope

LAMA2 Muscular Dystrophy: Included Phenotypes
• Congenital muscular dystrophy type 1A (MDC1A) • Late-onset *LAMA2* muscular dystrophy

For synonyms and outdated names see Nomenclature.

Diagnosis

The phenotypic spectrum of *LAMA2* muscular dystrophy (*LAMA2*-MD) ranges from congenital muscular dystrophy type 1A (MDC1A) to *LAMA2*-MD with onset ranging from early childhood to adulthood (referred to as late-onset *LAMA2*-MD).

No consensus clinical diagnostic criteria for *LAMA2*-MD have been published.

Suggestive Findings

LAMA2-muscular dystrophy **should be suspected** in individuals with the following clinical findings by age of onset; laboratory and neuroimaging findings regardless of age; and family history.

Clinical Findings by Age of Onset

Congenital muscular dystrophy type 1A (MDC1A)

- Onset at birth or within the first six months of life: profound hypotonia with muscle weakness
- Poor spontaneous movements with contractures of the large joints
- Feeding difficulties with failure to thrive, aspiration, and recurrent chest infections
- Delayed motor development milestones: the majority of affected individuals are able to sit but rarely achieve independent ambulation.
- Axial weakness, difficulties in head control (mainly due to flexor muscles of the neck); progressive scoliosis starting in childhood
- Absence of findings that could suggest lower motor neuron disease (i.e., tongue fasciculation and areflexia)
- Usually normal intellect
- Less common findings:
  - Weak cry often associated with respiratory failure

- Epilepsy, including of a refractory nature
- Cardiac involvement
- Demyelinating progressive sensorimotor neuropathy

Late-onset *LAMA2*-MD (clinically heterogeneous group)

- Onset during childhood or even adulthood
- Proximal muscle weakness with or without muscle hypertrophy, as seen in limb-girdle muscular dystrophies
- Delayed motor milestones in childhood, but independent ambulation usually achieved
- Less common findings:
  - Rigid spine syndrome with joint contractures usually most prominent in the elbows
  - Childhood-onset seizures
  - Progressive respiratory insufficiency and scoliosis
  - Cardiomyopathy with or without conduction defect

Laboratory and Neuroimaging Findings

Serum creatine kinase (CK) concentration

- **MDC1A.** In the first years of life, serum CK concentration may be more than fourfold normal values [Hayashi et al 2001, Oliveira et al 2008]. In children with MDC1A who do not achieve walking, serum CK concentration is usually more than 1000 IU/L in the first two years of life, after which it progressively decreases.
- **Late-onset *LAMA2*-MD.** Maximum serum CK concentrations range from 593 IU/L to 6987 IU/L (normal 200-400 depending on laboratory) [Oliveira et al 2008]. In adults, CK levels could be only mildly or slightly elevated [Rajakulendran et al 2011, Oliveira et al 2018].

Brain MRI findings (regardless of age)

- **Abnormal white matter signals** (in nearly all individuals with *LAMA2*-MD) include hyperintensity on T_2-weighted and FLAIR MRI, and hypointensity on T_1-weighted images in areas myelinated in the developing brain (i.e., subcortical and periventricular areas) with sparing of areas myelinated later in life (i.e., corpus callosum and internal capsule) [Geranmayeh et al 2010]. These findings, consistently documented in the first year of life, do not represent areas of demyelination but rather are likely secondary to leaky basal laminar connections giving rise to increased water content in the brain [Menezes et al 2014]. Although these white matter changes are mostly diffuse, focal and more subtle changes are seen in a small subset of affected individuals [Leite et al 2005, Chan et al 2014, Oliveira et al 2018]. Of note, two sibs with a late-onset phenotype were reported to have a nearly normal brain MRI [Saredi et al 2019].
- **Structural brain abnormalities** (secondary to neuronal migration defects) include cortical dysplasia [Mercuri et al 1999], lissencephaly (agyria or pachygyria) [Geranmayeh et al 2010], and polymicrogyria [Vigliano et al 2009].

  Polymicrogyria-like patterns (bilaterally in the temporal and occipital lobes) were reported in the majority of 25 individuals. When extensive, the polymicrogyria correlated with epilepsy [Natera-de Benito et al 2020].

Immunohistochemistry (IHC) of muscle or skin biopsy

- Complete or partial laminin α2 deficiency (muscle and skin)
- Increased expression of laminin α4 and α5

Muscle MRI findings. Muscle imaging, including whole-body MRI, is being increasingly used in the diagnostic workup of hereditary myopathies. Although the appearance of muscle on MRI in *LAMA2*-MD is similar to that of the collagen VI myopathies (see Differential Diagnosis), with bands of sparing and affected muscles [Nelson et al 2015, Harris et al 2017], the anterior thigh muscles are more frequently involved in *LAMA2*-MD. Sparing of the gracilis, sartorius, vastus medialis, and rectus femoris muscles has also been described [Nelson et al 2015]. Individuals with rigid spine syndrome had sparing of temporal muscles, except in those associated with biallelic *LAMA2* pathogenic variants [Tordjman et al 2018].

Family History

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *LAMA2* muscular dystrophy **is established** in a proband with suggestive findings and biallelic (homozygous or compound heterozygous) pathogenic (or likely pathogenic) variants in *LAMA2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *LAMA2* variants of uncertain significance (or identification of one known *LAMA2* pathogenic variant and one *LAMA2* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, a variety of multigene panels) and **comprehensive genomic testing** (exome sequencing, exome array, chromosomal microarray (CMA), genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas comprehensive genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with later onset or with an atypical phenotype, in whom the diagnosis of *LAMA2*-muscular dystrophy has not been considered, are more likely to be diagnosed using a larger multigene panel (Option 2) or even comprehensive genomic testing (see Option 3).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *LAMA2*-MD, molecular genetic testing approaches can include **single-gene testing**. Sequence analysis of *LAMA2* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found perform gene-targeted deletion/duplication analysis (e.g. multiplex-ligation dependent probe amplification or CMA) to detect intragenic large deletions or duplications that may be missed by Sanger sequencing.

Option 2

A muscular dystrophy multigene panel that includes *LAMA2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with

the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 3

When the diagnosis of *LAMA2*-MD is not considered because an individual has atypical phenotypic findings, **comprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, is most likely to lead to diagnosis. **Exome sequencing** is most commonly used [Oliveira et al 2018, Saredi et al 2019]; **genome sequencing** may also be considered if clinically available.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *LAMA2* Muscular Dystrophy

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
LAMA2	Sequence analysis [3]	~80% [4]
	Gene-targeted deletion/duplication analysis [5]	~20% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Oliveira et al [2018]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Oliveira et al [2014], Oliveira et al [2018]

Clinical Characteristics

Clinical Description

The clinical manifestations of *LAMA2* muscular dystrophy (*LAMA2*-MD) comprise a continuous spectrum ranging from severe congenital muscular dystrophy type 1A (MDC1A) to milder late-onset *LAMA2*-MD.

Those with congenital muscular dystrophy type 1A (MDC1A) typically have neonatal profound hypotonia, poor spontaneous movements, and respiratory failure [Jones et al 2001]. Failure to thrive, gastroesophageal reflux, aspiration, and recurrent chest infections necessitating frequent hospitalizations are common. As disease progresses, facial muscle weakness, temporomandibular joint contractures, and macroglossia may further impair feeding and can affect speech.

Late-onset *LAMA2*-MD is characterized by later onset of manifestations, ranging from early childhood to adulthood. Affected individuals may show muscle hypertrophy and develop a rigid spine syndrome with joint

contractures, usually most prominent in the elbows. Progressive respiratory insufficiency and scoliosis can occur [He et al 2001] along with cardiomyopathy [Carboni et al 2011, Marques et al 2014].

Congenital Muscular Dystrophy Type 1A (MDC1A)

Respiratory involvement is caused by a progressively restrictive chest wall that first involves weakness of the intercostal and accessory muscles. Early in childhood, the thorax becomes stiff and chest wall compliance decreases, further contributing to alveolar hypoventilation, atelectasis, and mucous plugs with bronchial obstruction. These changes manifest as low lung volumes. Poor secretion clearance resulting from weak cough leads to recurrent chest infection. Swallowing difficulties and gastroesophageal reflux may increase the risk of aspiration. Chest infections may cause atelectasis, which along with limited pulmonary reserve, increases the risk of acute respiratory failure in the setting of infection.

The need for ventilatory support is most likely to occur during two time periods [Geranmayeh et al 2010]:

- Between birth and age five years in the most severely affected children mainly due to respiratory muscle weakness, hypotonia, and fatigue. Depending on age, total hours of ventilatory support required, frequency of hospitalizations, and institutional practice patterns, ventilatory support may be noninvasive or mechanical with tracheostomy. Respiratory issues in these infants and young children often stabilize in the first years, likely as a result of improved muscle tone.
- Between ages ten and 15 years due to progressive restrictive lung disease leading to respiratory insufficiency [Wallgren-Pettersson et al 2004]. Most children in this age group with the early-onset form do not have typical signs/symptoms of hypercapnia (i.e., headaches, attention difficulties, and drowsiness) but rather the more subtle findings including recurrent respiratory infections, failure to thrive, poor cough, and fatigue with feeding.

Feeding difficulties, consistent with poor weight gain, failure to thrive, and precipitous drop in weight with infections and hospitalizations are common. Philpot et al [1999a] reported weight below the third centile and feeding difficulties including swallowing abnormalities, difficulty chewing, and prolonged feeding time. In a study of 46 individuals with *LAMA2*-MD, 17 required enteral feeding, usually within the first year [Geranmayeh et al 2010]. Of note, children with early-onset *LAMA2*-MD do not attain normal weight (see Management, Treatment of Manifestations).

Joint contractures that are present in the first year of life progress slowly even in children receiving intensive daily physical therapy. Contractures tend to occur early in the shoulders, elbows, hips, and knees and later in the temporomandibular joints, distal joints, and cervical spine. Contractures often result in significant morbidity and interfere with activities of daily living.

Hyperlaxity of the distal phalanges of the fingers is observed in a number of affected children.

Motor developmental milestones are delayed and often arrested. Most affected children do not acquire independent walking; Geranmayeh et al [2010] reported that only 15% of individuals acquired independent ambulation. A smaller proportion gained the ability to walk with assistance but subsequently lost the ability.

Axial weakness

- **Neck weakness,** especially of the flexor muscles, impairs moving the head from the back to neutral position or performing neck flexion and lifting head from the lying position [Oliveira et al 2018]. This weakness may progress to a severe cervical lordosis in late adolescence, affecting the capacity to swallow and increasing the risk of food aspiration.
- **Scoliosis** is aggravated by thoracic and lumbar lordosis and frequently observed from the first decade of life [Bentley et al 2001]. It is often slowly progressive and may contribute to respiratory insufficiency due to thoracic restriction and airway compression.

Facial muscle weakness and **macroglossia** may become significant in toddlers and children, resulting in typical elongated myopathic facies, with an open mouth and tongue protrusion.

Limitation of eye movements (ophthalmoparesis) may be evident as early as age two years.

Central nervous system. Cognitive abilities are normal in the majority of affected individuals and do not correlate with brain MRI abnormalities [Messina et al 2010]; however, in a small proportion of individuals, intellectual disability and epilepsy were associated with bilateral occipital pachygyria [Jones et al 2001] or dysplastic cortical changes affecting predominantly the occipital and temporal regions [Sunada et al 1995, Pini et al 1996, Philpot et al 1999b, Leite et al 2005, Geranmayeh et al 2010, Natera-de Benito et al 2020].

Cognitive impairment, reported in fewer than 7% of individuals [Jones et al 2001, Geranmayeh et al 2010], ranged from mild intellectual disability to communication difficulties.

Epilepsy occurs in 8%-35% of affected individuals. Epilepsy is more prevalent in persons with more extensive cortical malformation. Seizures are mainly focal and visual aura; autonomic signs are common. Atypical absence, atonic, motor, and focal seizures with clonic bilateralization can also occur. In some individuals epilepsy is controlled with mono- or polytherapy, whereas in others epilepsy can be refractory, leading to a progressive deterioration of cognition [Vigliano et al 2009, Geranmayeh et al 2010, Natera-de Benito et al 2020].

A progressive sensorimotor neuropathy with signs of dysmyelinization may be detected in childhood [Di Muzio et al 2003]. These abnormalities are usually mild or clinically not significant. In contrast, needle EMG, even when performed early in infancy, shows myopathic signs in a majority of individuals [Quijano-Roy et al 2004].

Cardiac involvement has been described in persons with late-onset *LAMA2*-MD. There are only a few reports of cardiac involvement in individuals with MDC1A [Abdel Aleem et al 2020]; however, as improved medical care prolongs life expectancy, cardiac involvement may become more prevalent, and thus a management concern [Nelson et al 2015].

Secondary pulmonary hypertension may be observed as a complication of respiratory insufficiency [Geranmayeh et al 2010].

Late-Onset *LAMA2* Muscular Dystrophy

The onset of this milder phenotype ranges from early childhood to adulthood. Although children may have delayed motor milestones, they acquire independent ambulation. Proximal muscle weakness is slowly progressive in a pattern similar to that of other limb-girdle muscular dystrophies. Long-term consequences include wheelchair dependence, scoliosis, and respiratory problems [Oliveira et al 2018].

Weakness is also associated with marked contractures (mainly in the elbows and Achilles tendon) [Harris et al 2017, Saredi et al 2019] and heart involvement that can be clinically significant (particularly in individuals with phenotypes resembling Emery-Dreifuss muscular dystrophy or collagen VI diseases); however, subclinical abnormal echocardiograms and/or EKG-Holter findings are more common [Nelson et al 2015, Harris et al 2017].

Some individuals have rigid spine syndrome and/or muscle pseudohypertrophy [Nelson et al 2015].

Peripheral nerve demyelination may be detected with nerve conduction studies; however, most commonly there are no significant clinical consequences [Chan et al 2014].

Severe epilepsy and intellectual disability are described in some individuals.

Genotype-Phenotype Correlations

Prognostication of clinical severity depends on several variables including age at onset of first manifestations, *LAMA2* pathogenic variant type, and, if known, the effect of the variant on protein function [Geranmayeh et al 2010, Oliveira et al 2018]. See Table 6 for the phenotypes associated with several commonly reported pathogenic variants.

Complete absence of laminin α2 and the phenotype of congenital muscular dystrophy type 1A (MDC1A) in general are caused by loss-of-function *LAMA2* variants [Pegoraro et al 1998, Oliveira et al 2008, Oliveira et al 2018]; however, exceptions occur, including an individual homozygous for a pathogenic nonsense *LAMA2* variant who achieved ambulation [Geranmayeh et al 2010]. Intrafamilial variation has also been observed [Geranmayeh et al 2010, Oliveira et al 2018].

Partial deficiency of laminin α2. The phenotypes associated with partial deficiency of laminin α2 tend to be less severe, with slower disease progression [Allamand & Guicheney 2002, Tezak et al 2003, Oliveira et al 2018]. Some missense, splice site, and in-frame variants have been associated with partial deficiency as well as pathogenic missense variants in conserved cysteine residues on the short arm of the laminin α2 protein [Allamand & Guicheney 2002, Tezak et al 2003, Oliveira et al 2018]. Late-onset *LAMA2*-MD has been observed in multiple individuals with the variant c.2461A>C (p.Thr821Pro) in homozygosity or compound heterozygosity with another variant [Oliveira et al 2018].

Nomenclature

Individuals with early-onset *LAMA2*-MD were often categorized in the past as having **complete or partial laminin α2 deficiency** (or **complete or partial merosin deficiency** before it was known that the defect was laminin α2 deficiency) based on immunochemistry (IHC) staining of muscle. These IHC-based terms are less relevant now, given that the diagnosis of *LAMA2* muscular dystrophy can be made with certainty by the detection of biallelic *LAMA2* pathogenic variants. Moreover, laminin α2 deficiency can be secondary to defects in other proteins involved in the dystroglycan complex or pathway (e.g., in dystroglycanopathies; see Differential Diagnosis) [Bönnemann et al 2014, Endo 2015].

The abbreviation **MDC1A** is derived from the designation *m*erosin-*d*eficient *c*ongenital *m*uscular *d*ystrophy type *1A*.

Based on a nomenclature system that describes which chains are present in each laminin isoform, merosin was given the name **laminin-211** because it comprises chains α2, β1, and γ1.

Late-onset *LAMA2* muscular dystrophy may also be referred to as **LGMDR23** [Straub et al 2018].

Prevalence

Exact prevalence of congenital muscular dystrophy type 1A (MDC1A) is still unknown. The prevalence of congenital muscular dystrophies (CMD) has been estimated between 0.563:100,000 (in Italy [Graziano et al 2015]) and 2.5:100,000 (in western Sweden [Darin & Tulinius 2000]).

Geographic prevalence of MDC1A is also quite variable:

- In Europe it accounts for about 30% of CMD, whereas in Japan it accounts for only 6% [Allamand & Guicheney 2002].
- In the United Kingdom it accounts for 37.4% of CMD, making it the most common cause [Sframeli et al 2017].
- In Italy it accounts for 24.1% of CMD, making it the second most common cause [Graziano et al 2015].
- In Australia it accounts for 16% of CMD, making it the third most common cause [O'Grady et al 2016].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with biallelic pathogenic variants in *LAMA2*.

Differential Diagnosis

Congenital muscular dystrophy type 1A (MDC1A) must be distinguished from other disorders that may present with profound hypotonia (with frog leg posture of the legs), chest deformity, and breathing and feeding problems. The disorders included in the differential diagnosis are other congenital muscular dystrophies, congenital myopathies, congenital myasthenic syndromes, and spinal muscular atrophy. Of note, these disorders are not typically associated with: (1) laminin-α2 deficiency detected by immunohistochemical staining of muscle or skin biopsy, or (2) white matter changes on brain MRI. Additional distinguishing features include:

- Progressive improvement of tone and strength (in some affected individuals), CK levels near normal range values, diagnostic structural abnormalities on muscle biopsy (by light and electron microscopy), and an absence of joint contractures (even when the disease is severe) in the congenital myopathies;
- Multisystemic presentation (e.g., liver and cardiac involvement besides muscle weakness) in congenital metabolic myopathies.

Table 2a. Selected Genes of Interest in the Differential Diagnosis of MDC1A

Gene(s)	Disorder	MOI	Distinguishing Clinical Features [1]
B3GALNT2 *B4GAT1* *CRPPA* *DAG1* *FKRP* *FKTN* *GMPPB* *LARGE1* *POMGNT1* *POMGNT2* *POMK* *POMT1* *POMT2* *RXYLT1*	Dystroglycanopathies, congenital (OMIM PS236670)	AR	Wide variety of brain & eye structural & functional abnormalities (may be more severe in Walker Warburg syndrome & muscle-eye-brain disease)
COL6A1 *COL6A2* *COL6A3*	Collagen type VI disorders (Ullrich CMD) [2]	AR [3]	Characterized by triad of myopathic features, hyperlaxity, & typical skin changes (keratosis pilaris, keloids, striae)
BIN1 *CCDC78* *DNM2* *MAP3K20* *MTM1* *MTMR14* *SPEG*	Centronuclear/myotubular myopathy [4] (See X-Linked Myotubular Myopathy.)	XL AR AD	Ophthalmoplegia; facial bulbar weakness

Table 2a. continued from previous page.

Gene(s)	Disorder	MOI	Distinguishing Clinical Features [1]
ACTA1 *CFL2* *KBTBD13* *KLHL40* *KLHL41* *LMOD3* *NEB* *TNNT1* *TPM2* *TPM3*	Nemaline myopathy [4] (OMIM PS161800)	AR AD	Facial & bulbar weakness
RYR1	Central core disease (OMIM 117000) & multiminicore disease (OMIM 255320) [4]	AR AD [5]	Malignant hyperthermia in some affected individuals
SELENON	Congenital myopathy w/fiber-type disproportion	AD AR	Insulin resistance
	Rigid spine (congenital) muscular dystrophy (OMIM 602771)	AR	Restrictive respiratory syndrome (nocturnal hypoventilation)
CHAT *CHRNE* *COLQ* *DOK7* *GFPT1* *RAPSN* [6]	Congenital myasthenic syndromes	AR AD	Facial & bulbar weakness; striking motor variability; decremental EMG response or abnormal single-fiber EMG
SMN1 [7]	Spinal muscular atrophy	AR	Relatively rapid motor impairment & tongue fasciculations; EMG & muscle biopsy findings suggest denervation-reinnervation profile; normal nerve conduction studies

AD = autosomal dominant; AR = autosomal recessive; CMD = congenital muscular dystrophy; MOI = mode of inheritance; XL = X-linked

1. In addition to absence of brain white matter changes

2. Immunohistochemical analysis of muscle or skin biopsies can be diagnostically useful, showing variable reduction of antibody labeling against collagen VI or glycosylated α-dystroglycan.

3. The Ullrich congenital muscular dystrophy phenotype is usually inherited in an autosomal recessive manner; however, exceptions occur.

4. Selected examples of congenital myopathies are included in Table 2a; other congenital myopathies may also be relevant to the differential diagnosis of MDC1A.

5. Minicore disease is most often inherited in an autosomal recessive manner. The report of minicore disease in two generations in a few families also suggested autosomal dominant inheritance.

6. Most commonly associated of ~30 known genes; pathogenic variants in one of multiple genes encoding proteins expressed at the neuromuscular junction are currently known to be associated with subtypes of congenital myasthenic syndromes.

7. The detection of the genetic defect causing spinal muscular atrophy (deletion involving *SMN1* exons 7 and 8) requires specific methodologies.

Late-onset *LAMA2* muscular dystrophy (*LAMA2*-MD) is in the differential diagnosis of childhood-onset weakness of the limb-girdle type.

Table 2b. Genes of Interest in the Differential Diagnosis of Late-Onset *LAMA2*-MD

Genes	Differential Disorder	MOI	Clinical Features of the Differential Disorder	
			Overlapping w/*LAMA2*-MD	Distinguishing from *LAMA2*-MD
EMD *FHL1* *LMNA*	Emery-Dreifuss muscular dystrophy [1]	XL AR AD	Elbow contractures, high serum CK concentrations, prominent spinal rigidity	• Cardiac disease (in all affected persons) w/conduction defects & arrhythmias • Absence of the characteristic brain MRI findings assoc w/*LAMA2*-MD
COL6A1 *COL6A2* *COL6A3*	Collagen type VI disorders (Bethlem myopathy) [2]	AR AD	Elbow or Achilles tendon contractures; mildly ↑ serum CK concentrations	• Contractures, present early in disease, can be more disabling than muscle weakness & usually → persistent severe flexion contractures. • If no typical skin changes (e.g., keloids), differential diagnosis is difficult. • Suggestive findings on muscle MRI

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked

1. Immunofluorescence and/or western blot in fresh muscle biopsies (or from other affected tissues) can be used to detect changes in emerin or FHL1 proteins.

2. Immunohistochemical (IHC) analysis of muscle or skin biopsies can be diagnostically useful, showing variable reduction of antibody labeling against collagen VI.

Management

Published consensus clinical practice guidelines for congenital muscular dystrophies list recommendations for the following six clinical care areas: neurology, pulmonary, gastrointestinal/nutritional/oral care, orthopedics and rehabilitation, cardiology, and palliative care [Wang et al 2010] (full text).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of a child diagnosed with *LAMA2* muscular dystrophy (*LAMA2*-MD), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *LAMA2* Muscular Dystrophy

System/Concern	Evaluation	Comment
Constitutional	Height, weight, & nutritional status	
Neurologic	Complete exam by experienced neurologist	To incl assessment of strength
	For seizures or unexplained fainting or loss of consciousness	To incl EEG
Musculoskeletal	Multidisciplinary neuromuscular clinic assessment by orthopedist, physical medicine, OT/PT	To incl assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, & kyphoscoliosis • Need for adaptive devices • Need for PT (for improving gross motor skills) &/or OT (for improving fine motor skills)

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Feeding	Gastroenterology / nutrition / feeding team	Assessment of: • Nutritional status • For GERD • Constipation • Secretion management, aspiration risk • Optimal position for feeding • Bone health (serum concentrations of vitamin D & calcium)
Oral health	Dental exam	Before age 2 yrs (or at diagnosis) w/attention to enamel defects secondary to GERD, dry mouth, malocclusion/dental crowding interfering w/daily dental care
Respiratory	By pulmonologist	• Assess pulmonary function. • Evaluate for evidence of nocturnal hypoventilation esp in children w/recurrent respiratory infections, FTT, poor cry, or feeding fatigue.
Neurodevelopmental	Developmental assessment	• To incl motor, speech/language eval, & general cognitive skills • Eval for early intervention/special education in least restrictive educational environment
Cognitive/ Psychiatric	As determined by developmental pediatrician / mental health consultant	To determine if there are concerns about learning or mood, behavior, or other psychiatric issues
Cardiac	By cardiologist	For evidence of cardiomyopathy &/or arrhythmia
Ophthalmologic	By ophthalmologist	For evidence of ophthalmoparesis
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *LAMA2*-MD to facilitate medical & personal decision making
Family/Community	Assess: • Social work involvement to connect families w/local resources, respite, & support; • Use of online resources such as Parent to Parent; • Care coordination to manage multiple subspecialty appointments, equipment, medications, & supplies; • Need for palliative care.	

FTT = failure to thrive; GERD = gastroesophageal reflux disease; MOI = mode of inheritance; OT = occupational therapist/therapy; PT = physical therapist/therapy

1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Management ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

Table 4. Treatment of Manifestations in Individuals with Congenital Muscular Dystrophy Type 1A

Manifestation/Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Poor weight gain / FTT	Gastroenterology / nutrition / feeding team incl speech-language specialists	• Low threshold for radiographic swallowing study if evidence of dysphagia • Gastrostomy tube placement may be required for persistent feeding issues.
Epilepsy	Routine mgmt of seizures by experienced pediatric neurologist	While seizures are generally well-controlled w/routine ASM, refractory seizures in those w/cortical dysplasia may require polytherapy.
Musculoskeletal	Multidisciplinary neuromuscular clinic incl orthopedics, physical medicine, OT/PT	To focus on: • Maintenance of function & mobility • Prevention or treatment of joint & neck contractures & spine deformities • Activities to improve respiratory function • Adequate seating & wheelchair support • Appropriate conservation vs surgical management of spine, hips, & ankles
Respiratory	Pulmonologist	• Goals are clearance of secretions & assisted ventilation as needed to maintain oxygenation & avoid hypercapnia. • Aggressive treatment of respiratory infections • Consider positive-pressure ventilation & tracheostomy in individuals w/severe bulbar involvement & chronic aspiration & pneumonia.
Psychiatric	Referral to psychologist/ psychiatrist	If concerns about mood, behavior
Cardiac	By pediatric cardiologist	Early detection & treatment of myocardial dysfunction
Abnormal vision &/or strabismus	Standard treatment(s) per ophthalmologist	

ASM = anti-seizure medication; DD = developmental delay; FTT = failure to thrive; ID = intellectual disability; OT = occupational therapist; PT = physical therapist

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States (US); standard recommendations may vary significantly from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - As required by special education law, children should be in the least restrictive environment feasible at school and included in general education as much as possible and when appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Communication Issues

Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications such as medication used to treat attention-deficit/hyperactivity disorder when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Late-Onset *LAMA2*-MD

The care measures are similar to those described for children but adapted to age and phenotype. A multidisciplinary approach includes respiratory and orthopedic care due to the risk for progressive respiratory insufficiency and joint and spinal deformities. Cardiac surveillance is necessary due to cardiomyopathy and

cardiac conduction defects. Regular physical therapy for stretching limbs, shoulder and pelvic girdle, and spine is mandatory. Anti-seizure medication is used to treat seizures.

Surveillance

Table 5. Recommended Surveillance for Individuals with *LAMA2* Muscular Dystrophy

System/Concern	Evaluation	Frequency
Constitutional & feeding	Height, weight, nutritional status, & safety of oral intake	At least 2x/yr in 1st 5 yrs
Neurologic	Neurologic assessment for progression of weakness	Annually or more often for acute exacerbation
	EEG	If concerns for new seizure activity or progression of seizures
Respiratory	Assessment by pulmonologist of pulmonary function & aspiration risk	At least annually
Neurodevelopmental	Assessment of general developmental progress incl speech-language eval	At least 2x/yr in 1st 5 yrs
	Cognitive/psychiatric assessment; referral to (pediatric) psychiatry if needed	Annually
Musculoskeletal	Physical medicine, OT/PT assessment of strength, joint range of motion, mobility, self-help skills	Annually
	Eval of spine for scoliosis	• At least annually • More often during periods of rapid growth, loss of function, or respiratory compromise
Cardiac	Eval by cardiologist	• For persons w/severe respiratory insufficiency: at least annually • For those w/palpitations, ↑ fatigue, or loss of consciousness w/o clear neurologic origin • If no cardiac symptoms: at age 5 yrs, 10 yrs, & then every 2 yrs
Ophthalmologic	By ophthalmologist	Annually
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Care coordination to manage multiple subspecialty appointments, equipment, medications, & supplies	According to individual needs

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Avoid the following:

- Succinylcholine in induction of anesthesia because of risk of hyperkalemia and cardiac conduction abnormalities
- Statins, cholesterol-lowering medications, because of the risk of muscle damage

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

New treatment strategies are being investigated for *LAMA2*-MD [Yurchenco et al 2018, Nguyen et al 2019].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

LAMA2 muscular dystrophy (*LAMA2*-MD) is an autosomal recessive disorder caused by biallelic *LAMA2* pathogenic variants.

Risk to Family Members

Parents of a proband

- In most families, both parents of an affected child are carriers of one *LAMA2* pathogenic variant.
- Accurate recurrence risk counseling relies on carrier testing of both parents to determine if each is heterozygous for a *LAMA2* pathogenic variant. If the variant is detected in only one parent (and parental identity testing has confirmed biological maternity and paternity) and the child:
  - Appears to have homozygous *LAMA2* pathogenic variants, possible explanations include: a large deletion on one allele (if not previously tested for); and uniparental (segmental) isodisomy for chromosome 6 [Andrade et al 2014];
  - Has compound heterozygous *LAMA2* pathogenic variants, the child may have one inherited variant and one *de novo* variant [Zhou et al 2018].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *LAMA2* pathogenic variant each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- If only one parent is heterozygous for a *LAMA2* pathogenic variant, each sib of an affected individual has at conception a 50% chance of being an asymptomatic carrier and a 50% chance of being unaffected and not a carrier (the risk to the sibs of being affected with *LAMA2*-MD is not increased over that of the general population).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with *LAMA2*-MD are obligate heterozygotes (carriers) for a *LAMA2* pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *LAMA2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *LAMA2* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *LAMA2* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Association Francaise contre les Myopathies (AFM)**
  1 Rue de l'International
  BP59
  Evry cedex 91002
  France
  Phone: +33 01 69 47 28 28
  Email: dmc@afm.genethon.fr
  www.afm-telethon.fr
- **Cure CMD**
  Phone: 562-444-5656
  www.curecmd.org
- **European Neuromuscular Centre (ENMC)**
  Netherlands
  Phone: 31 35 5480481
  Email: enmc@enmc.org
  www.enmc.org
- **Japan Muscular Dystrophy Association**

Japan

Phone: 03-6907-3521

www.jmda.or.jp

- **Muscular Dystrophy Association (MDA) - USA**

  Phone: 833-275-6321

  www.mda.org

- **Muscular Dystrophy UK**

  United Kingdom

  Phone: 0800 652 6352

  www.musculardystrophyuk.org

- **Congenital Muscle Disease International Registry (CMDIR)**

  The CMDIR is a global partnership of patient advocacy organizations, researchers, and clinicians, all working toward the same goal: to find treatments for congenital muscle disease.

  CMDIR/Cure CMD

  www.cmdir.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. LAMA2 Muscular Dystrophy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
LAMA2	6q22.33	Laminin subunit alpha-2	LAMA2 homepage - Leiden Muscular Dystrophy pages	LAMA2	LAMA2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for LAMA2 Muscular Dystrophy (View All in OMIM)

156225	LAMININ, ALPHA-2; LAMA2
253900	MUSCULAR DYSTROPHY, CONGENITAL, PRODUCING ARTHROGRYPOSIS
254100	MUSCULAR DYSTROPHY, CONGENITAL, WITH RAPID PROGRESSION; MDRP
607855	MUSCULAR DYSTROPHY, CONGENITAL MEROSIN-DEFICIENT, 1A; MDC1A

Molecular Pathogenesis

LAMA2-MD is caused by defects in the α2 chain (encoded by *LAMA2*) of laminin-211 (previously known as laminin type 2 or merosin) and also laminin-221 (laminin type 4 or s-merosin).

Laminins are a group of heterotrimeric glycoproteins, composed of a heavy α chain and two light chains, β and γ, each encoded by separate genes. To date, five α chains (designated α1 to α5), three β chains (β1 to β3), and three γ chains (γ1 to γ3) have been identified, which combine to form 15 laminin isoforms [Aumailley et al 2005], each with tissue and/or developmental stage-specific expression [Suzuki et al 2005]. The biologic

functions of laminins are diverse and include cell-cell recognition, growth, differentiation, cell shape, and migration [Suzuki et al 2005].

The link between the sarcolemma of muscle fibers and the extracellular matrix is established by laminin-211, being a major component of the extrasynaptic skeletal muscle basement membrane [Durbeej 2015]. Laminin-211 binds the glycosylated residues of α-dystroglycan and also self-assembles (polymerizes) into networks through its N-terminal domain [Yurchenco 2015]. This supramolecular network connects to collagen IV and to perlecan (heparan sulfate proteoglycan) through nidogen cross-linking [Jones et al 2000]. Laminin-211 expression is not limited to skeletal muscle but has also been detected in a variety of other tissues, most importantly peripheral nerve (Schwann cells) and brain [Yurchenco 2015, Yurchenco et al 2018].

Mechanism of disease causation. Biallelic pathogenic loss-of-function variants in *LAMA2* are associated with complete deficiency of laminin-α2, and give rise to the severe end of the *LAMA2*-MD spectrum with congenital or very early onset.

Partial laminin-211 deficiency, caused by missense or in-frame variants in at least one of the mutated disease alleles, is associated with later onset and a milder phenotype.

***LAMA2*-specific laboratory considerations.** Most of the pathogenic variants reported in *LAMA2* are single-nucleotide variants or small deletions or duplications dispersed along the gene. However, copy number variants should also be considered, such as deletions involving exon 56 or exon 4 – common pathogenic variants in specific populations (see Table 6).

Table 6. Notable *LAMA2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000426.3 NP_000417.2	c.397-4337_639+877del [1]	p.(?)	Common pathogenic deletion in Chinese Han [Xiong et al 2015, Ge et al 2019]
	c.1580G>A	p.Cys527Tyr	Partial laminin α2 deficiency caused by disruption of a conserved cysteine residue [Tezak et al 2003]
	c.1854_1861dup	p.Leu621HisfsTer7	Common pathogenic variant [Allamand & Guicheney 2002]
	c.2049_2050delAG	p.Arg683SerfsTer21	Common pathogenic variant [Guicheney et al 1998, Hayashi et al 2001]
	c.2461A>C	p.Thr821Pro	Late-onset variant [Oliveira et al 2018]
	c.2584T>C	p.Cys862Arg	Partial laminin α2 deficiency caused by disruption of a conserved cysteine residue [Tezak et al 2003]
	c.2901C>A	p.Cys976Ter	Italian founder variant [Guicheney et al 1998, Di Blasi et al 2005]
	c.2986T>C	p.Cys996Arg	Partial laminin α2 deficiency caused by disruption of a conserved cysteine residue [Tezak et al 2003]
	c.3085C>T	p.Arg1029Ter	Common pathogenic variant [Allamand & Guicheney 2002]
	c.3924+2T>C	p.Leu1246_Glu1308del	Middle East or Sudan; founder variant [Di Blasi et al 2011]
	c.3976C>T	p.Arg1326Ter	Common pathogenic variant [Allamand & Guicheney 2002]
	c.7750-1713_78899-2153del [2] (5-kb deletion)	p.Ala2584HisfsTer8	Common pathogenic deletion [Oliveira et al 2008, Oliveira et al 2014]

Table 6. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
	c.7881T>G	p.His2627Gln	Found in large Kenyan family of Asian descent [Geranmayeh et al 2010]
	c.8556_8558del	p.Ile2852del	Partial laminin α2 deficiency [Oliveira et al 2018]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Deletion of exon 3

2. Deletion of exon 56

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Chapter Notes

Author Notes

JO maintains the *LAMA2* locus-specific database (in collaboration with Prof Johan T den Dunnen, Leiden University Medical Center) with the aim to further expand the mutational spectrum and genotype-phenotype correlations in *LAMA2* muscular dystrophies.

Acknowledgments

The authors would like to thank the extensive list of collaborators who over the years contributed to improve the current scientific knowledge about *LAMA2* muscular dystrophies.

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Revision History

- 17 September 2020 (bp) Comprehensive update posted live
- 7 June 2012 (me) Review posted live
- 16 March 2010 (ss) Initial submission

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