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CASE REPORT

# An atypical presentation of severe congenital contractures and lack of cerebellar involvement in a patient with a novel *LAMA1* mutation

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## ABSTRACT

**Background:** *LAMA1* gene is mutated in patients with Poretti-Boltshauser syndrome, which include mainly the characteristic neuroimaging findings of cerebellar dysplasia and cysts.

**Case Presentation:** We present a novel homozygous *LAMA1* variant that is predicted to cause atypical phenotype of severe arthrogryposis, feeding difficulties, developmental delay, retinopathy, and no cerebellar involvement.

**Conclusion:** Our findings are suggestive of absence of cerebellar involvement in *LAMA1* mutations in some cases and phenotype may include severe arthrogryposis.

**Keywords:** Case report, *LAMA1* gene, arthrogryposis, cerebellum.

## Background

*LAMA1* gene encodes one of the alpha 1 subunits of laminin. The laminins are a family of extracellular matrix glycoproteins that have a heterotrimeric structure consisting of an alpha, beta, and gamma chain. These proteins make up a major component of the basement membrane and have been implicated in a wide variety of biological processes including cell adhesion, differentiation, migration, signaling, and neurite outgrowth (1). Mutations in *LAMA1* gene is associated with Poretti-Boltshauser syndrome (2). The phenotypic spectrum of this syndrome includes mild to moderate neurological phenotypes such as ataxia, intellectual disability, retinal dystrophy, and characteristic neuroimaging findings of cerebellar d y splasia and cysts (3,4). Here, we present a novel homozygous *LAMA1* variant causing an atypical phenotype of severe arthrogryposis, feeding difficulties, developmental delay, retinopathy, and no cerebellar involvement. This is the first report of *LAMA1* mutation from the Middle East. Our finding expands the phenotypic spectrum of the *LAMA1* mutations to include severe congenital contractures.

## Case Presentation

A 29-year-old Saudi mother had an ultrasound scan at 28 weeks of gestation showing polyhydramnios, type III placenta previa and a fetus in breech presentation. An elective cesarean section was performed at 38+1 weeks. The outcome was a term baby girl weighing 2,670 g, length of 49 cm, and occipitofrontal circumference of 34 cm. The Apgar score was 5 and 7 at 1 and 5 minutes, respectively. The baby had dysmorphic features including retrognathia, small anterior fontanel, frontal bossing, high anterior hairline, high arch palate, and severe arthrogryposis involving the upper and lower limbs (elbows, wrists, hands, hips, knees, and ankles), with the upper limbs being more severely affected. Neurological examination revealed truncal hypotonia and absent gag reflex. The baby had breast and formula-feeding problems due to sucking difficulties.

The skeletal survey indicated multiple joint contractures in all limbs and left acetabular dysplasia. Her creatine

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kinase, nerve conduction, and electromyographic studies were normal. However, the neuromuscular transmission was not tested. Interestingly, MRI of the brain showed normal cerebellum, small frontal periventricular cystic changes, and bilateral symmetrical faint high signal in the tegmentum of lower pons and medulla oblongata. Repeated brain MRI at the age of 11 months was unremarkable. MRI of the spine was normal (Figure 1). The electroretinogram at day 7 and 12 months of age showed bilateral retinal involvement. The barium swallow showed severe gastroesophageal reflux. Echocardiogram showed a patent foramen ovale. Of note, the parents are consanguineous and they have a healthy child.

The microarray-based comparative genomic hybridization (aCGH) analysis was unremarkable, whereas the whole exome sequencing detected a novel homozygous splicing variant in the *LAMA1* gene (NM_005559.3: c.5661-2A>G). In order to investigate the effect of this splicing variant, we performed Reverse transcription polymerase chain reaction (RT-PCR) on lymphoblast cell line on the obligate carrier parents (no RNA sample was available from the index, see below). The primers sequence was as follows: c.x 38–39F_ Left primer gatgctctagagcacttagaggatc, and c.x 40–41R_ right primer gattctgagagcaggctcgtc. The product size was 323 bp.

The RT-PCR revealed a complete absence of the wildtype transcript and the creation of at least three aberrant transcripts all of which predicting frameshift and premature truncation (Figures 1 and 2). According to the American College of Medical Genetics and Genomics guidelines, this variant was classified as pathogenic. Of note, other possible genetic causes of arthrogryposis were checked and ruled out.

The patient required a nasal cannula since birth because of the frequent desaturations and recurrent aspirations. Occasionally, she required positive pressure ventilation and continuous positive airway pressure. She also required feeding with a nasogastric tube. She was started on an intensive rehabilitation program. On her last examination at 17 months of age, her head circumference was 47 cm, she showed an improvement in her communication (cooperative and social smile) and motor skills (fine and gross). Additionally, an improvement of the arthrogryposis and muscle strength (upper extremities: 4/5; lower extremities: 2+/5) was noted. The baby survived for 18 months but eventually succumbed to a severe gram-negative septic episode.

## Discussion

The biallelic inactivation of the *LAMA1* gene is known to cause Poretti-Boltshauser syndrome, which includes non-progressive cerebellar ataxia, intellectual disability, language impairment, ocular motor apraxia, and frequent occurrence of myopia or retinopathy. The neuroimaging is usually remarkable for cerebellar dysplasia with cysts and abnormal shape of the fourth ventricle, in the absence of significant supratentorial anomalies and any muscular involvement (3,4). The three patients described

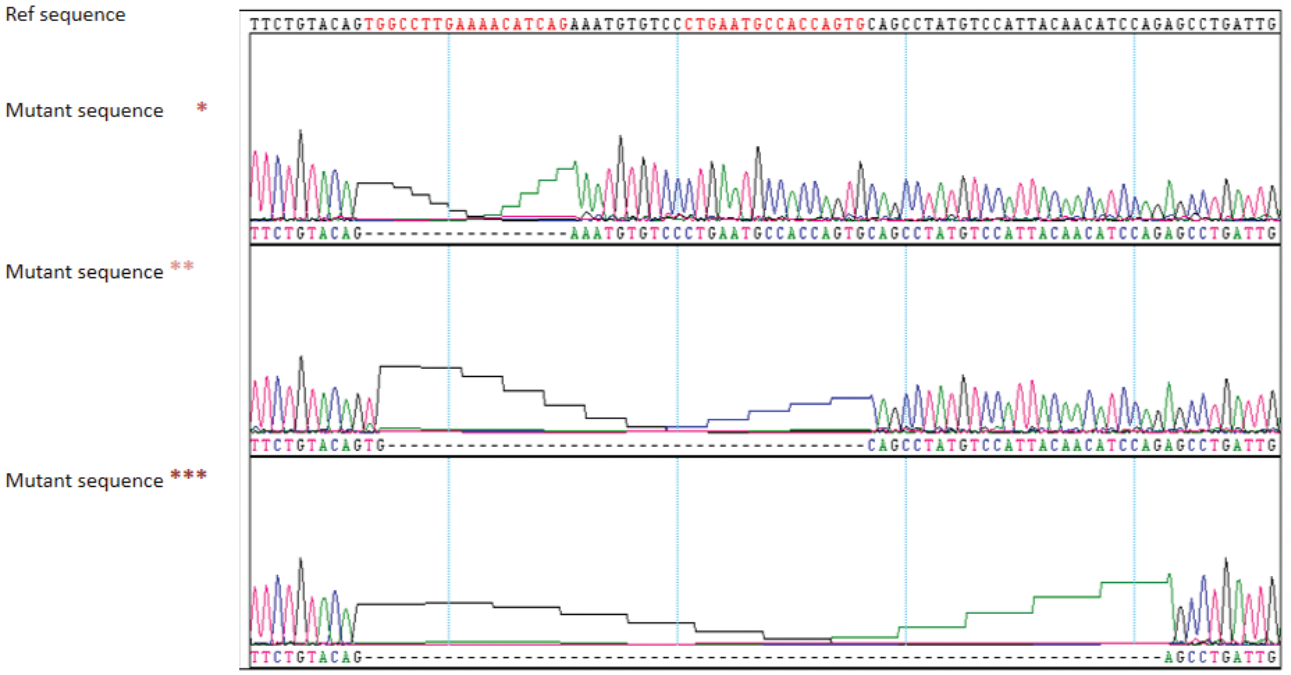


***Figure 1.*** *(a) Pedigree of the study family: affected individual indicated by the black symbol is homozygous for the LAMA1 c.5661-2A > G mutation. (b) Normal sagittal Brain MRI. No cerebellar dysplasia or cyst. (c) RT-PCR on the obligate carrier parents revealed a complete absence of the wildtype transcript and the creation of at least three aberrant transcripts all of which predicting frameshift and premature truncation.*

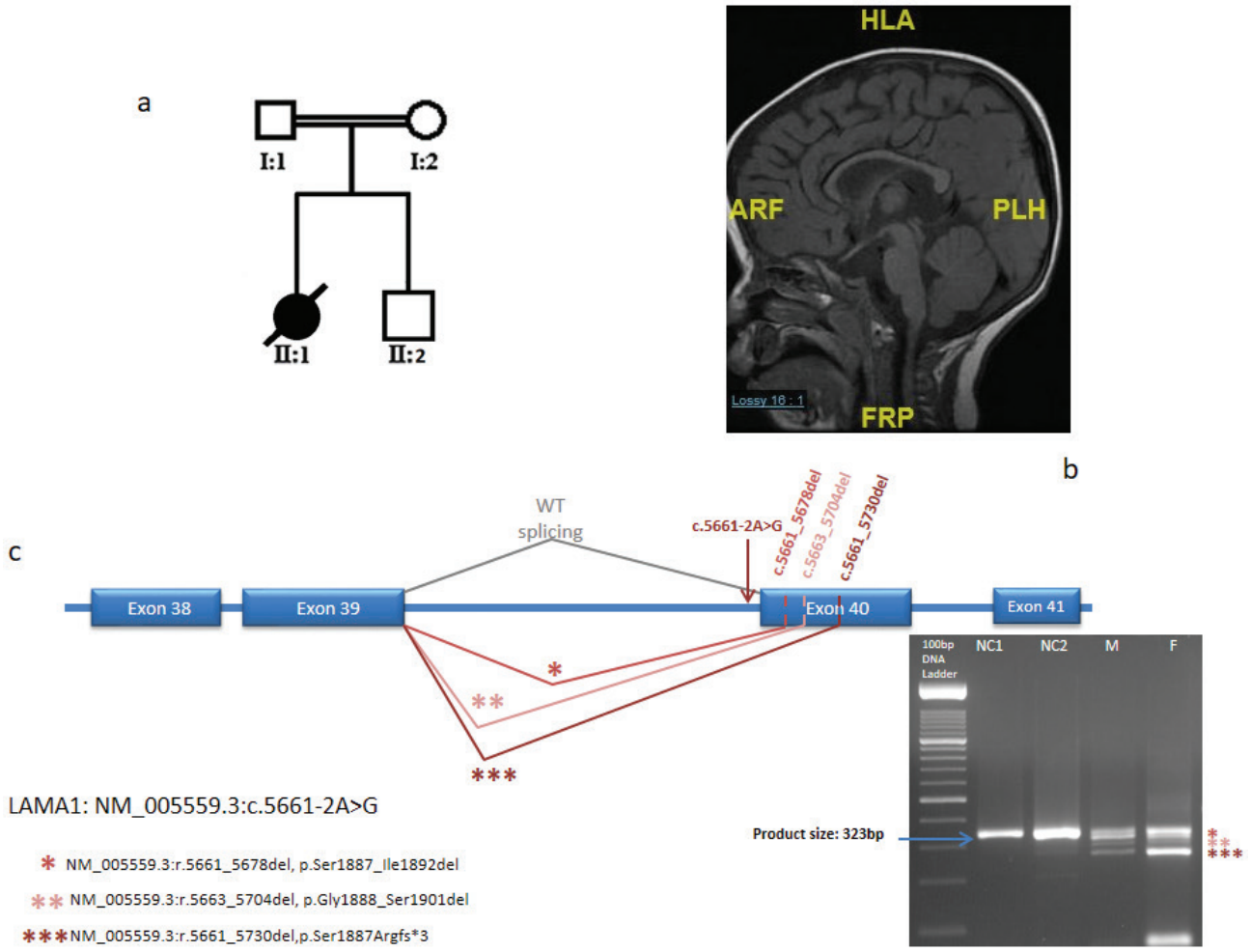


***Figure 2.*** *Sequence chromatogram by using SeqMan alignment program.*

by Viboux et al. manifested, in addition to the classical finding of the tics, obsessive-compulsive features and anxiety (1). Our patient presented with a new phenotype of severe neonatal onset, arthrogryposis, and the absence of the cardinal findings of Poretti-Boltshauser syndrome; cerebellar dysplasia or cyst. This new phenotype can be explained by the fact that one gene can cause multiple phenotypes.

The laminins are one family of the extracellular matrix glycoproteins with a heterotrimeric structure consisting of an alpha, beta, and gamma chains (5). The Laminin subunit alpha (*LAMA1)* gene encodes one of the alpha 1 subunits of the laminins. It was shown that *LAMA1* deficiency leads to altered cell adhesion and migration (5). Using immunohistochemistry and ultrastructural studies, Viboux et al. demonstrated that *LAMA1*-deficient cells lack the filopodia and cytoplasmic projections that are indispensable for the formation of focal adhesions (1). These cellular structures are critical for cell–cell and cell–extracellular matrix adhesions, cell motility, and neuronal development. The severe phenotype of our case due to the biallelic loss of function variant in the *LAMA1* gene is consistent with the severe embryonic phenotype in the *LAMA1*-knockout mice (6,7).

The arthrogryposis phenotype observed in our patient and described in other laminopathies due to variants in other genes is most likely a result of combined central and neuromuscular mechanism. The neuromuscular transmission was not tested in our patient, which is a limitation of our study. Interestingly, the failure of this transmission has been previously reported in a patient with *LAMA5* variant which supports our mechanistic hypothesis (8).

In conclusion, this observation expands the molecular basis of the congenital contractures and the phenotypic spectrum of the *LAMA1* mutations. Such findings are important for establishing the clinical and molecular diagnosis, providing family counseling and reproductive options for unaffected future pregnancies.

## Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human

experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from the patients for being included in the study. No animals were used in this study. A copy of the written consent is available for review by the Editor-in-Chief of this journal**.**

**Acknowledgement**
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**Consent for publication**
A written informed consent was obtained from the parents of the patient for publication of the case report.

**Ethical approval**
Ethical approval is not required at our institute to publish an anonymous case report.

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**Declaration of conflicting interests**
The authors declare that there is no conflict of interests.

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