

Case Report

Early Death of 2 Siblings Related to Mutations in *LMOD2*, a Recently Discovered Cause of Neonatal Dilated Cardiomyopathy

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ABSTRACT

We report a family with 2 neonatal deaths related to dilated cardiomyopathy (DCM) and compound heterozygous loss-of-function variants (c.1243_1244del, p.Leu415Valfs*108 and c.1537C > T, p.Arg513*) in *Leiomodin 2* (*LMOD2*), a recently documented cause of early DCM. The phenotype in mice and humans consists of early, severe cardiac dilation and dysfunction related to decreased functional *LMOD2*, which results in abnormal actin filaments and abnormal myocardial contractility. Our cases confirm mutations in *LMOD2* as a cause of DCM in humans and highlight the rapid changes occurring in cardiac genetics and the importance of reviewing previously negative genetic test results in the context of emerging literature.

RÉSUMÉ

Notre compte rendu concerne une famille dont deux nouveau-nés sont décédés des suites d'une cardiomyopathie dilatée (CMD) et qui présentaient une perte hétérozygote composite de variants fonctionnels (c.1243_1244del, p.Leu415Valfs*108 et c.1537C > T, p.Arg513*) du gène *Leiomodin 2* (*LMOD2*), une cause récemment avérée de CMD précoce. Chez la souris et l'humain, le phénotype de cette anomalie consiste en une dilatation et une dysfonction cardiaques sévères précoces liées à une diminution de la fonction du gène *LMOD2* entraînant des anomalies dans les filaments d'actine et la contractilité du myocarde. Nos cas permettent de confirmer que les mutations du gène *LMOD2* sont une cause de CMD chez l'humain. Ils mettent en évidence les modifications rapides se produisant dans la génétique cardiaque et l'importance de revoir les résultats négatifs d'anciens tests génétiques à la lumière des nouvelles données publiées.

The female proband was the first child for this family and was delivered at 40 weeks' gestational age via emergency caesarean section for a nonreassuring fetal heart rate. Her mother was 34 years of age, and the father was 37. The parents are of Vietnamese background, are nonconsanguineous, and have no known significant health issues. Following delivery, the baby

Novel Teaching Points

- Mutations in *LMOD2* cause dilated cardiomyopathy in humans.
- Rapid changes in cardiac genetics affect variant classification.
- Timely review of previously negative genetic test results in the context of emerging literature is important.

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Ethics Statement: This research report had adhered to the relevant ethical guidelines.

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showed signs of cardiogenic shock, and an echocardiogram found severe biventricular dysfunction. With inadequate response to intubation and multiple inotropes, the baby was cannulated onto venoarterial extracorporeal membrane

oxygenation (ECMO). She was decannulated after 6 days but with worsening end-organ injury related to severe cardiac dysfunction (left ventricular ejection fraction [LVEF] 15% by cardiac magnetic resonance imaging with no ventricular dilation), she was placed back onto ECMO. Complications included bleeding and clot formation, and the family elected for withdrawal of life-sustaining therapies. The patient died shortly after removal from the ECMO circuit at 24 days of age.

A myocardial biopsy was negative for any signs of myocarditis. Cardiomyocytes showed a perinuclear halo and some cytoplasmic vacuoles with interstitial fibrosis. Transmission electron microscopy found patchy dense mitochondrial matrix, mitochondrial swelling, and loss of cristae with intact outer double membranes and some inclusions (Fig. 1). Myofibril misalignment, broad Z-discs, sarcoplasmic reticulum dilation, and increased convolutions of intercalated discs were also observed. A 184-gene panel through Blueprint Genetics (Helsinki, Finland) reported only a variant of unknown significance in *LZTR1*. Both parents had normal echocardiograms with the father demonstrating right bundle branch block (QRS duration, 154 msec) on his electrocardiogram. A genetic cause was not identified for this child's DCM, and fetal echocardiography was recommended for future pregnancies.

Approximately 1 year later this family presented with another singleton female pregnancy. Fetal echocardiograms at 17-, 26-, and 31-weeks' gestational age found normal anatomy and function. However, at 37 weeks' gestational age, the right atrium and right ventricle were qualitatively dilated, and there was mildly reduced right ventricular systolic function and severe tricuspid regurgitation. Because of the concerning echocardiogram and a nonreassuring stress test, the baby was delivered by caesarean section. An echocardiogram at a few hours of age found mildly decreased biventricular systolic function with a right ventricular fractional area change of

29% (normal, > 35%) and a LVEF of 47% (normal, > 50%). The baby was placed on noninvasive ventilation and started on milrinone at 0.25 $\mu\text{g}/\text{kg}/\text{min}$. DNA was sent for chromosomal microarray and cardiomyopathy panel sequencing with regions of interest targeted using hybridization-based target capture methodology (Blueprint Genetics). By 3 days of age, there was severe biventricular dysfunction with an LVEF of 22% and a right ventricular fractional area change of 28%. Milrinone was increased to 0.9 $\mu\text{g}/\text{kg}/\text{min}$, and she was started on inhaled nitric oxide. She went on to have atrial ectopic tachycardia and was unable to tolerate trophic feedings. Parents declined ECMO, placement of a ventricular assist device, or heart transplantation and elected for withdrawal. She was extubated and passed away 12 hours later at 31 days of age.

Updated cardiomyopathy panel testing (using identical methodology) for this child found 2 loss-of-function variants in *Leiomodin 2* (*LMOD2*), a frameshift mutation (c.1243_1244del, p.Leu415Valfs*108) and a nonsense mutation (c.1537C > T, p.Arg513*) with a variant inherited from each parent. The *LMOD2* c.1243_1244del variant deletes 2 base pairs in exon 2 (of 3 total exons) resulting in a frameshift and a premature stop codon at position 108. The *LMOD2* c.1537C > T variant generates a premature stop codon in exon 2. Both variants are predicted to lead to loss of normal protein function. Subsequent testing confirmed that the first child also carried both variants. Based on a recently published case report, functional evidence from mice, variant type, absence of homozygotes from variation databases and segregation data, both variants were classified as likely pathogenic, and the family counselled that their daughters had died from autosomal recessive *LMOD2* deficiency.¹ The publication of the *LMOD2* case report occurred between the testing of the first and second child, indicating how rapidly the field of cardiogenetics continues to evolve.

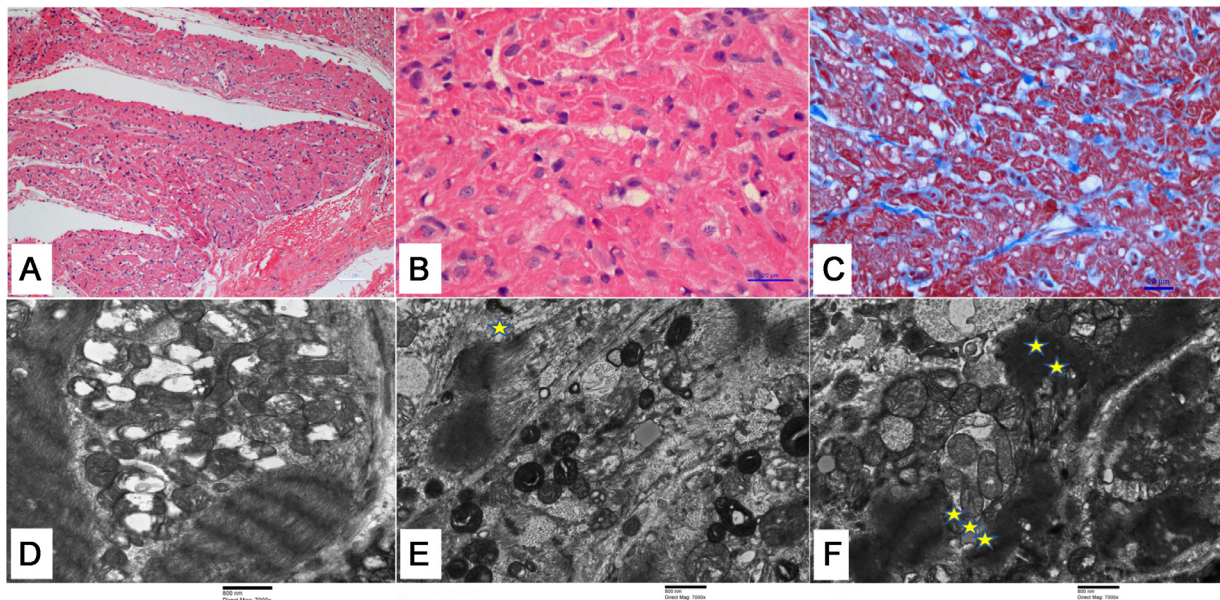


Figure 1. Hematoxylin and eosin staining at (A) low power (10 \times) and (B) higher magnification highlights abnormal myocardial architecture with fibre distortion and vacuolation (scale bar = 20 μm). (C) Masson's trichrome staining shows extensive interstitial fibrosis (scale bar = 20 μm). Transmission electron microscopy at (D) lower and (E, F) higher resolution shows focal misalignment (1 star), patchy dense mitochondrial matrix (2 stars), and mitochondrial swelling and loss of cristae (3 stars) (scale bar = 800 nm).

Discussion

LMOD2 is an actin-binding protein that functions to elongate actin filaments in the heart and generate myocardial contraction.^{2,3} Mice lacking LMOD2 exhibit DCM and abnormal myocardial pathology findings.² Myocardium from a patient with a truncating mutation (c.1193G > A, p.Trp398*) in LMOD2 found myofibrillar disarray, wide Z-discs, and thin filaments that were approximately 70% shorter than normal.¹ Reported patient pathology findings documented somewhat disorganized and hypertrophic myocytes with perinuclear clearing and extensive fibrosis,¹ as seen in our patient. No evidence of skeletal muscle myopathy has been found, and heterozygotes are asymptomatic with no detectable cardiac phenotype.^{1,2}

Our report confirms mutations in *LMOD2* as a cause of neonatal severe DCM. The recurrence of disease in a family with an initially comprehensive but uninformative genetic evaluation emphasizes the importance of reviewing previously negative results in a timely manner and linking research and clinical findings as new disease genes are identified.

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Disclosures

The authors have no conflicts of interest to disclose.

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