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CASE REPORT
Arrhythmias/electrophysiology

A case report of a novel mutation in lamin A/C gene related with risk of sudden death

Carlos Andres Sanchez Vallejo [1,2]*, Carlos Daniel Rodriguez Ariza [3], Jose Alfredo Restrepo Urbina[1], and Santiago Callegari Osorio [2]

[1]Hospital Univesitario Fundación Santa Fe - Internal medicine department - Cardiology section, Carrera 7 #117-15, Bogotá 111071, Colombia; [2]Universidad de los Andes, Faculty of Medicine, Carrera 1 #18a-12, Bogotá 111711, Colombia; and [3]Hospital Univesitario Fundación Santa Fe - Internal medicine department, Carrera 7 #117-15, Bogotá 111071, Colombia

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Background Lamin A/C-associated heart disease is a group of clinical entities characterized by a mutation in the *LMNA* gene. Multiple cardiac phenotypes have been described, including a higher risk of sudden death.

Case summary A 23-year-old asymptomatic patient with an extensive history of heart disease in the family consulted the clinic. He had a genetic test performed when he was born revealing a new frameshift mutation in the *LMNA* gene. Numerous cardiac function tests were ordered, which initially were normal. After a year of follow-up, Holter monitoring was positive for episodes of nonsustained ventricular tachycardia (NSVT). Because of the risk factors and higher likelihood of sudden death, a decision was made to offer an implantable cardiac defibrillator (ICD), which was performed without complications. The patient continues the follow-up with cardiology and electrophysiology consisting of yearly cardiac imaging and device recordings.

Discussion Lamins are nuclear proteins involved in various cellular processes in myocardial cells. Therefore, mutations are associated with wide phenotypic alterations. The mutation described here was not previously reported in the literature. In the face of an undescribed mutation, the decision to use an ICD for primary prevention of sudden death is challenging. Because of the episodes of NSVT and a higher likelihood of risk of sudden death due to male sex and first-degree atrioventricular block, the decision to use an ICD was made for this patient, with no complications.

Keywords Case report • Lamin A/C • Sudden death • Frame-shift mutations • Implantable cardiac defibrillator

ESC Curriculum 5.10 Implantable cardioverter defibrillators • 6.1 Symptoms and signs of heart failure • 6.5 Cardiomyopathy

Learning points

- A new frameshift mutation with an autosomal dominant inheritance pattern of the lamin A/C gene has been described.
- Patients with lamin A/C gene mutations should be evaluated for the risk of ventricular arrhythmias and sudden death in order to choose which patients could benefit from an implantable cardiac defibrillator.

* Corresponding author. Tel: +57 321 8310388, Email: car.sanch1@gmail.com
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Introduction

Lamin A/C-associated heart disease comprises a group of clinical entities characterized by a mutation in the *LMNA* gene, which codes for the synthesis of nuclear proteins called lamins A and C.[1] These are involved in DNA replication, regulation of the cell cycle, among others.[1]

Cardiac phenotypic involvement is variable. Common clinical presentations include isolated ventricular dilatation, arrhythmic cardiomyopathy, non-hypokinetic dilated cardiomyopathy, sudden death, or ventricular and supraventricular arrhythmias.[1]

We report a case of a previously undescribed mutation of the *LMNA* gene in a patient with a phenotype of lamin A/C-associated heart disease.

Timeline

Infancy	Genetic sequencing revealing new frameshift mutation of *LMNA 1* gene
Presentation	First evaluation in the cardiology consult
Month 4	No lamin phenotype was found
Month 12	Holter revealed the presence of NSVT and first-degree atrioventricular block
Month 13	Recommendation of the interdisciplinary meeting for an ICD as primary prevention for sudden death
Month 13	Implantation of ICD without complications
2 years	No discharges from the ICD reported

Case presentation

A 23-year-old asymptomatic man with no past medical history, who had a family history of structural heart disease and arrhythmias in various members of his paternal family line (*Figure 1*), decided to consult the clinic. The patient presented with a genetic analysis revealing sequencing of the exon 1 of the *LMNA* 1 gene, describing a new genetic variant F113LfsX116 g551delT; a Frame Shift type heterozygous mutation done in infancy because of his extensive family history. After the death of the patient's father, and considering the extensive family history in cardiac pathologies, the family physician recommended performing genetic analysis to evaluate for genetic cardiomyopathies. Because the results showed an unknown mutation, with uncertain clinical significance, the patient was counselled to have a cardiac evaluation when he was an adult.

The physical examination was uneventful. Complementary studies were normal, including electrocardiogram, NT-proB-type natriuretic peptide blood test, a 24 h electrocardiographic Holter, and a transthoracic echocardiogram (TTE), with a normal left ventricular ejection fraction (LVEF) and global longitudinal strain of −18.5% (*Figure 2*). A cardiac magnetic resonance imaging (MRI) showed no structural or functional alterations or abnormalities in late gadolinium enhancement.

Four months later, the patient remained asymptomatic, and the outpatient evaluation was carried out without pathological findings. Twelve months after the first visit, a nonsustained ventricular tachycardia (NSVT) and first-degree atrioventricular block were identified in a 24 h electrocardiographic Holter (*Figure 3*). The patient remained asymptomatic with a normal physical examination. The TTE revealed a normal LVEF and a global longitudinal strain of −19%.

The case was discussed with a multidisciplinary committee. We considered a male patient carrier of a frameshift type heterozygous mutation of the *LMNA* exon 1 gene (genetic variant F113LfsX116 g551delT). Because of the presence of NSVT and first-degree atrioventricular block (which are two high-risk features for sudden death), the final decision was to carry out an ICD. The clinical scenario and the recommended intervention were discussed with the patient, who agreed with the procedure, which later was performed without complications. A follow-up plan consisted of device analysis every 6 months, yearly echocardiograms, and MRI depending on the results. The patient is not interested in having children. A year after the procedure, there has not been any documented discharges from the device.

Discussion

Lamins are nuclear proteins involved in various cellular processes in the myocardial cell. They are encoded by the *LMNA* gene, which can undergo mutations of various types, including missense, frameshift, nonsense mutations, and intragenic deletion or duplications. Mutations in this gene are responsible for about 10% of hypertrophic cardiomyopathy cases. However, the phenotypic range of 'lamin A/C-associated heart disease' is wide, ranging from alterations in the cardiac conduction system and ventricular arrhythmias to established structural heart disease.[1]

The main cardiac manifestation of lamin A/C mutations is the presence of dysrhythmias such as atrioventricular block, atrial fibrillation, and ventricular arrhythmias.[2] Previous data from carriers of lamin A/C mutations have determined that heart disease-related laminopathies confer a high risk of sudden death, with data of up to 46% of sudden death episodes in carrier patients, regardless of the presence of structural heart disease.[2] Other clinical variables (dilated cardiomyopathy, sporadic family history of dilated cardiomyopathy or cardiac conduction, cardiac conduction system disease, or atrial fibrillation) confer a particular pretest probability for the presence of lamin A/C-associated heart disease.[3–5]

Regarding the known risk of sudden death in carriers of *LMNA* gene mutations, the variables that are related to a higher cumulative risk are NSVT, LVEF <45%, and male sex. These characteristics have an additive effect on the risk. The more risk factors a patient has with the mutation, the lower the cumulative probability of survival free of sudden death events.[6] Other studies include the prolongation of the PR interval as an independent risk factor for the development of ventricular arrhythmias, corroborating the compromise in the LVEF as a risk factor.[7]

Based on the available data, it is considered that an ICD may be useful in adult patients diagnosed with a progressive disease of the cardiac conduction system with a mutation of the lamin A/C gene presented with ventricular dysfunction and/or NSVT (Class IIa recommendation)[8] or in the presence of two or more risk factors such as non-missense mutations, male sex, NSVT, or LVEF <45% (Class IIa recommendation, Level of evidence B).[9–12] The patient

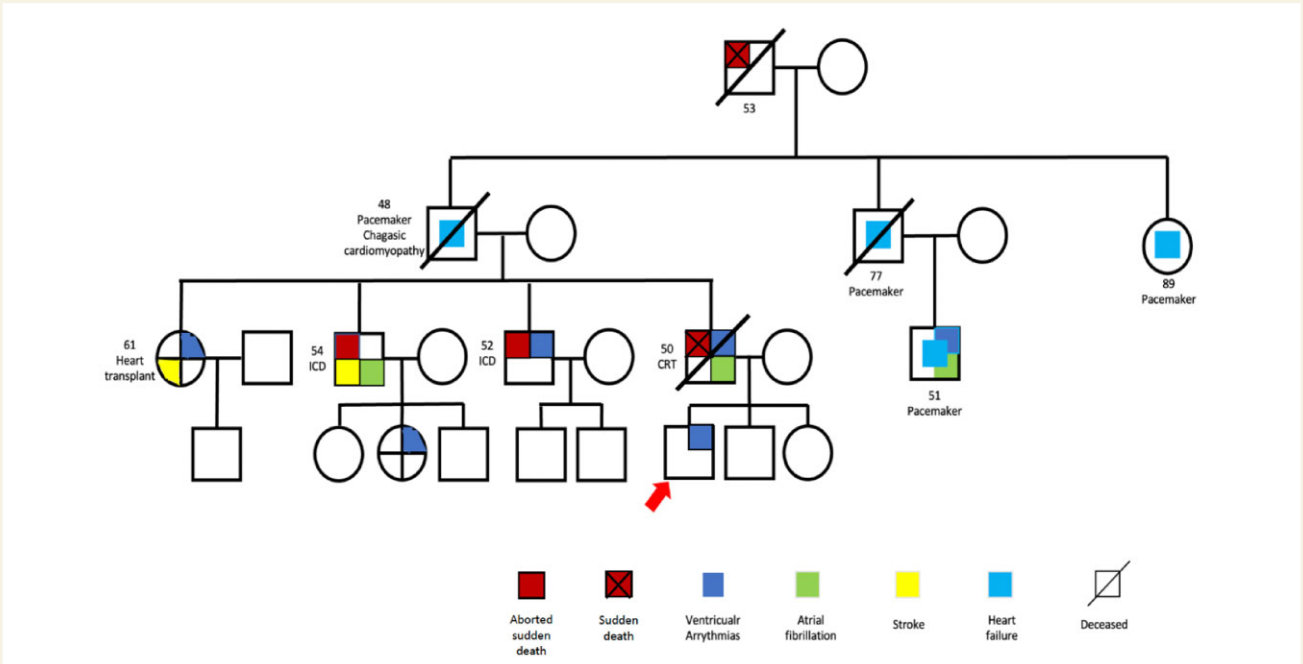

Figure 1 Summary of the family history of the patient (pointed out with the red arrow). The mutation had an evident autosomal dominant inheritance and various phenotypic expressions. No other family members have performed genetic screening, and they are not interested in performing any genetic analysis.

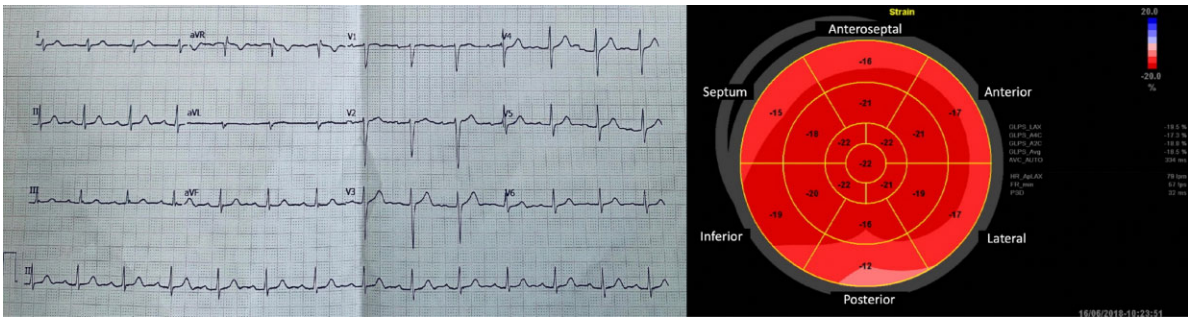

Figure 2 Results of the tests ordered in the first cardiology consult. There are no pathological alterations revealed in the electrocardiogram, echocardiogram, or magnetic resonance (Magnetic resonance and echocardiogram can be found in the supplementary figures).

had two of these characteristics, which conferred him a high risk of sudden death. An ICD subcutaneous pacemaker is also a viable option, but because the lamin mutations are also associated with heart conduction disturbances, which will increase the likelihood of needing a pacemaker, a transvenous ICD was chosen, because it can act as a pacemaker if needed in the future. Unfortunately, there are no effective prophylactic therapies that impact the outcomes in these patients. Angiotensin-converting enzyme inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and other medical therapies have not been shown to consistently reduce the risk of sudden death unless heart failure is established.

Finally, the follow-up plan should include genetic counselling for the patient as well as the family. In the face of a newly described mutation, and taking into account the inheritance pattern and the possible implications, once identified a mutation with these characteristics, all members of the family should be screened. Also, the cascade screening and the possible prognosis should also be discussed with the patient.

This case illustrates the current established management of an asymptomatic patient with a phenotype of heart disease associated with a new mutation not described in the literature of the lamin A/C gene. In whom the indication for an ICD was justified by the

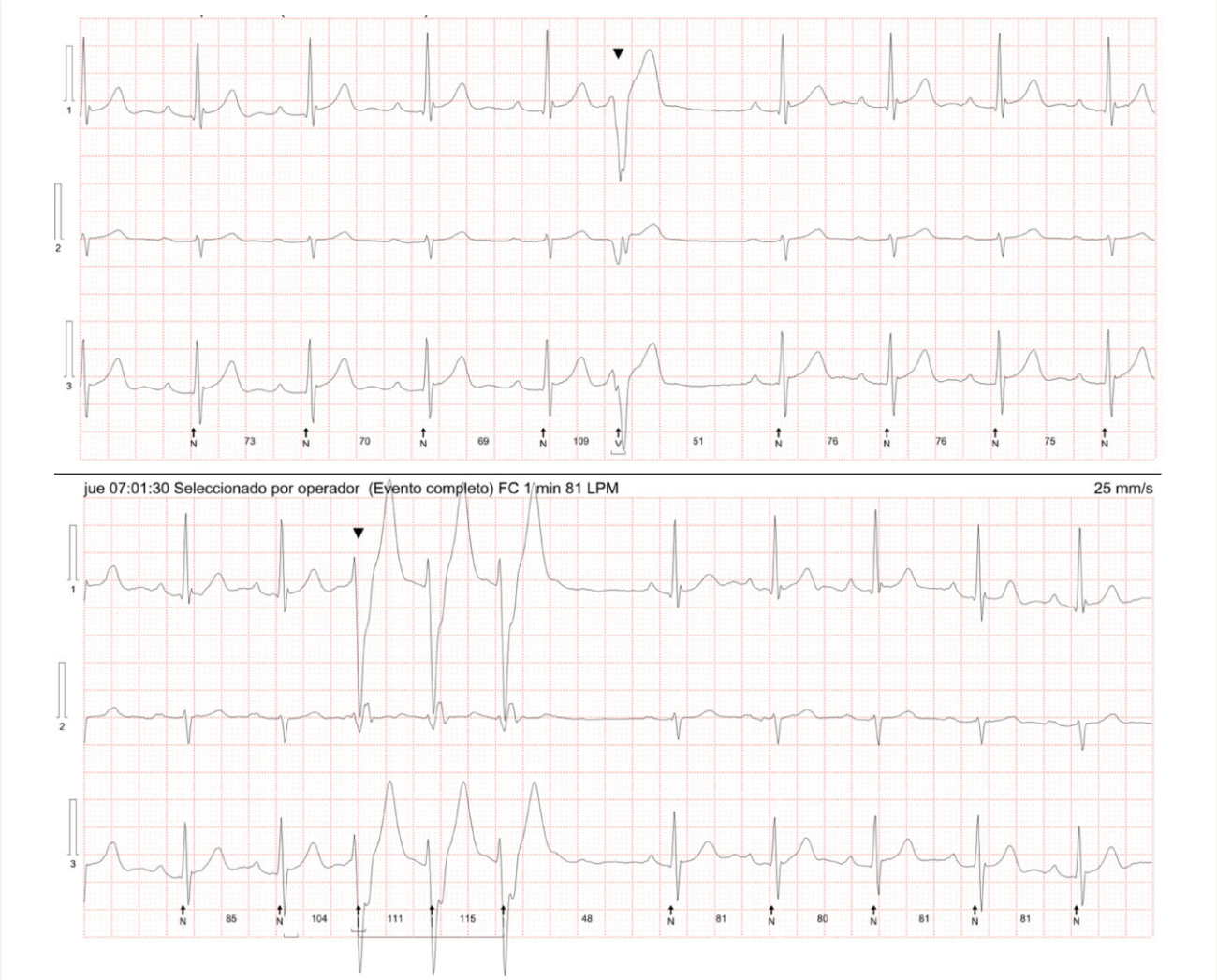

Figure 3 Holter monitoring showing the episode of nonsustained ventricular tachycardia and occasional ventricular and atrial extrasystoles.

documentation of an episode of NSVT, atrioventricular block, and the male gender. The additional risk factors that confer a greater probability of sudden death have not yet been fully clarified in large cohorts, and further knowledge of this entity will undoubtedly allow its greater detection in the future.

Lead author biography

Carlos Andrés Sánchez, MD, is a clinical cardiologist at Hospital Universitario Fundación Santa fe de Bogota. Dr Sánchez completed his medical education at Universidad de los Andes, Bogotá-Colombia. Later, he graduated as a specialist in internal medicine and as cardiologist at Universidad el Bosque. Currently, he is completing an epidemiology master's degree.

Supplementary material

Supplementary material is available at the *European Heart Journal – Case Reports* online.

Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

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