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Journal of Clinical Cardiology and Cardiovascular Interventions

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Case Report

Perspective of Two Genetic Variants Causing Hypertrophic Cardiomyopathy and Dilated Cardiomyopathy, Report of Two Cases

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Received date: September 05, 2025; Accepted date: February 10, 2026; Published date: February 23, 2026

Citation: Andrea D. Sampayo, Paul Lerma, Rodrigo Huerta, Ernesto Hernández, Miguel A, et al., (2026 Perspective of Two Genetic Variants Causing Hypertrophic Cardiomyopathy and Dilated Cardiomyopathy, Report of Two Cases, *J Clinical Cardiology and Cardiovascular Interventions*, 9(3); **DOI:10.31579/2641-0419/516**

Abstract

The following two cases to be described are from patients who were admitted to our unit in the same clinical context, due to functional class deterioration (dyspnea), with structural alterations in echocardiogram consistent with cardiomyopathies, both with a family history of death due to heart failure in first-degree relatives, however once the genetic study was obtained from both patients, it was shown that, as well as the clinical context and history, the prognosis was not the same. The first case consists of a genetic variation of TMP1, a gene that encodes tropomyosin, causing asymmetric septal cardiomyopathy; Alterations in these proteins interfere with the mechanical properties of the sarcomere leading to hypertrophy and myocyte disorder; However, they are mutations with a good prognosis. The second clinical case involved a greater approach due to the more aggressive progression of the disease, finding in the genetic test a mutation in the LMNA gene causing dilated cardiomyopathy, mutations in the LMNA gene producing laminopathies, a more malignant genetic variant that other common DCMs due to high rates of adverse events such as sudden cardiac death, even when left ventricular failure is mild. Currently both are undergoing medical treatment, however in the case of the patient with the mutation in the LMNA gene, rapid progression has led to ICD placement and adjustment of pharmacological treatment, in addition to being in the waiting line for heart transplant.

Key Words: hypertrophic cardiomyopathy; dilated cardiomyopathy; genetic variation; LMNA gene; TMP1 gene

Introduction

Cardiomyopathies are disorders of the heart muscle that lead to structural and functional failure, and are not primarily caused by coronary artery disease, hypertension, valvular disease, or congenital heart disease. Currently, it has been shown that several forms of cardiomyopathy, previously considered secondary to external factors, have genetic etiologies. The diagnostic approach to cardiomyopathy is based on the interpretation of clinical and instrumental findings to suspect and thus generate an etiological diagnosis to guide specific treatment of the disease. First, a detailed clinical history is necessary, since the presence of family members with heart disease, sudden deaths, or heart transplants can point to a genetic or hereditary etiology. The presence of ventricular and atrial arrhythmia and conduction disorders can aid in the diagnosis, suggest specific causes, and monitor disease progression and risk stratification. This approach should result in a timely and accurate diagnosis that allows for early treatment of symptoms and prevention of disease-related complications. We present two cases of hypertrophic and dilated cardiomyopathies, their suspected diagnosis, management, and treatment.

Evolution of Cases

The first case, with a benign course and good prognosis, involved a 57-year-old female patient with a family history of hypertrophic heart disease, a 45-year-old sister being treated for heart failure, and healthy family members. The patient had cardiovascular risk factors characterized

by a sedentary lifestyle, type 2 diabetes, and systemic arterial hypertension, both of which were at target levels with pharmacological treatment. The patient had a history of cardiovascular functional class decline for approximately 5 years. The reason for consultation was due to worsening of symptoms for approximately 6 months, upon questioning he was in NYHA functional class I, his primary physician performed a first approach with a chest x-ray and electrocardiogram where criteria for left ventricular hypertrophy and cardiomegaly grade III respectively were evident, he was referred to the cardiology of our unit where on physical examination we found the patient with rhythmic heart sounds of adequate intensity, without murmurs, with apex displaced to the anterior axillary region, a transthoracic echocardiogram was performed where non-obstructive asymmetric septal hypertrophic cardiomyopathy was documented without obstructive gradient (5mmHg), nor significant increase in it after the Valsalva maneuver, diastolic dysfunction with a restrictive pattern and increased filling pressures, the myocardium with a honeycomb image suggestive of an infiltrative pattern, the left ventricle with increased internal diameters and indexed volumes, with preserved systolic function of 61% by Simpson biplanar method. Due to family history, genetic screening was performed, finding a mutation in the tropomyosin 1 gene, variant c.841A>G;p. (Met281Val), classified as of uncertain significance, is associated with hypertrophic cardiomyopathy (OMIM: 115196), in addition to dilated cardiomyopathy and non-compact myocardium, all with a benign course, with autosomal dominant inheritance. Therefore, management was established with ACEI and Beta-blockers, with functional class monitoring, last assessment in December 2024 without functional class progression, currently without surgical criteria, continues without obstructive gradient.

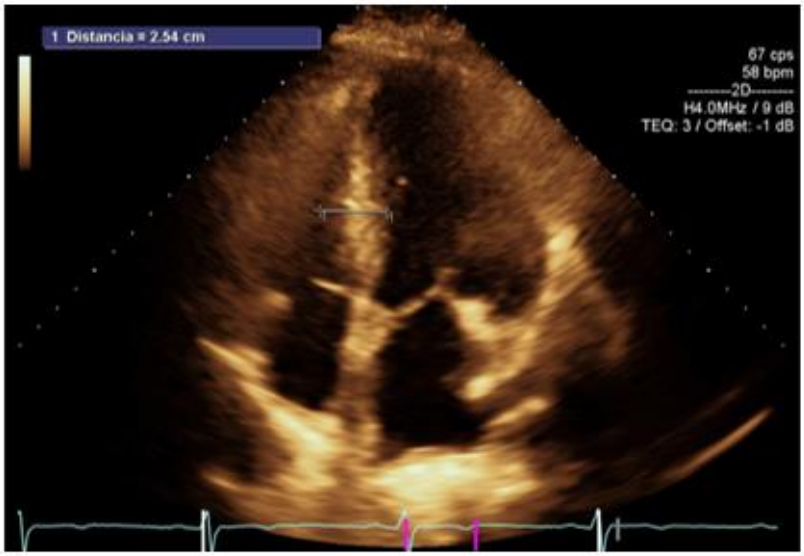

Figure 1: Apical 4-chamber axis showing asymmetric septal hypertrophy

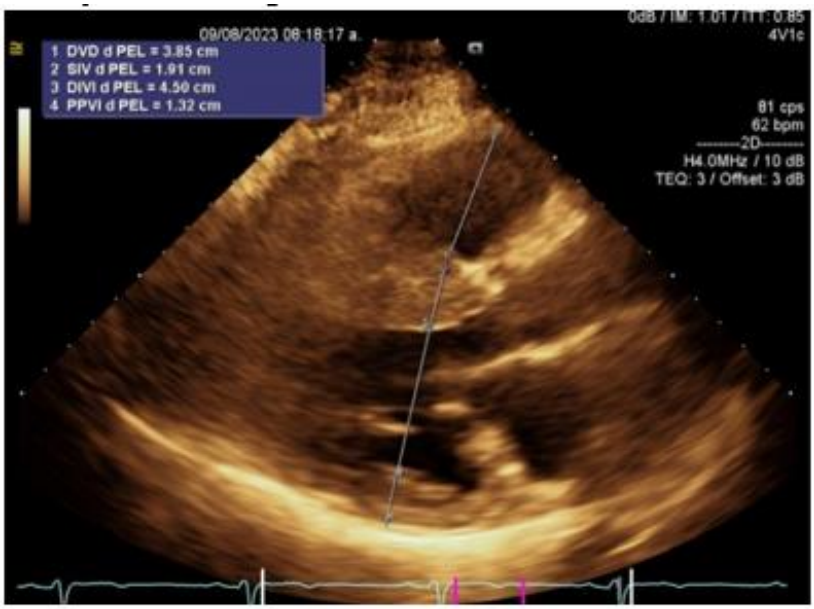

Figure 2: Long parasternal axis showing increased basal septal thickness

The second case is a course of worse prognosis of aA 47-year-old female patient with a family history of a deceased brother due to heart failure and a living sister with the same clinical syndrome who has currently undergone a transplant. She had a cardiovascular history of mitral valve replacement in 2016 and is currently undergoing treatment for heart failure. She attended the cardiology consultation for the first time due to

dyspnea when climbing stairs that had been developing for six months. She denied DPN or orthopnea. Cardiovascular physical examination revealed rhythmic heart sounds of adequate intensity. S1 and S2 were unchanged, and S3 or S4 showed a prosthetic click in the mitral valve focus of adequate intensity, with no additional acoustic phenomena, and no pleuropulmonary syndrome. As part of the protocol, diagnostic aids were requested. A chest x-ray showed a mitral valve prosthesis in position, grade II cardiomegaly, and an electrocardiogram showed complete right bundle branch block. A transthoracic echocardiogram showed a dilated left ventricle with a 57mm end-diastolic diameter and 44mm end-systolic diameter, with a normofunctioning prosthesis with a mean gradient of 3.8 mmHg and an area of 1.5 cm2. A dilated left atrium had an indexed volume of 32 mm. Generalized hypokinesia, with reduced systolic function of 36%, and LVEF due to longitudinal global strain of 40%. Moderate secondary functional TR with an indexed ring of 37 mm. Treatment was started with loop diuretics, ACEIs, beta-blockers and VKAs. Due to family history, a genetic test was requested, which documented a mutation in the LMNA gene, on chromosome 1q22: c.568c> t (p.arg190trp), which allowed establishing the prognosis and prompt referral to the heart failure service with a path to heart transplant, however with progressive clinical presentation (persistence of dyspnea, NYHA functional class II and episodes of DPN), with a new echocardiogram two years later with respect to the initial one that reported dilated cardiomyopathy with reduced biventricular function, normofunctional mechanical mitral prosthesis, LVEF of 25% by biplane Simpson, right ventricle with dilated diameters, severe tricuspid regurgitation secondary to annulus dilation. Heart failure treatment was adjusted by adding complete neurohumoral blockade, with sequential dose adjustment, electrocardiogram in sinus rhythm QRS 140 ms RBBB morphology, ergospirometry was requested to objectively determine functional class, patient with MAGGIC prognosis of 10 points, mortality at 1 year of 3.9% and at 3 years of 10.2, with rapid progression of the disease despite complete treatment of heart failure for which the patient was taken to ICD for prevention of sudden cardiac death, currently undergoing heart transplantation.

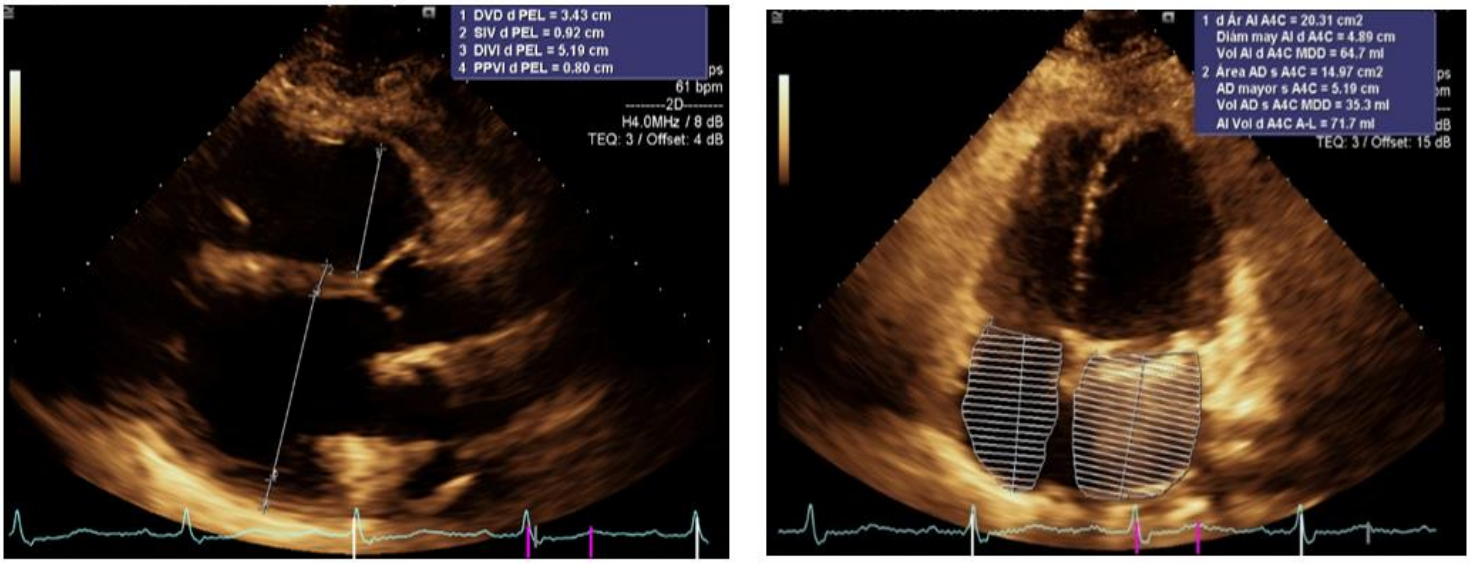

Figure 3: Apical 4-chamber axis showing dilation of the left atrium.

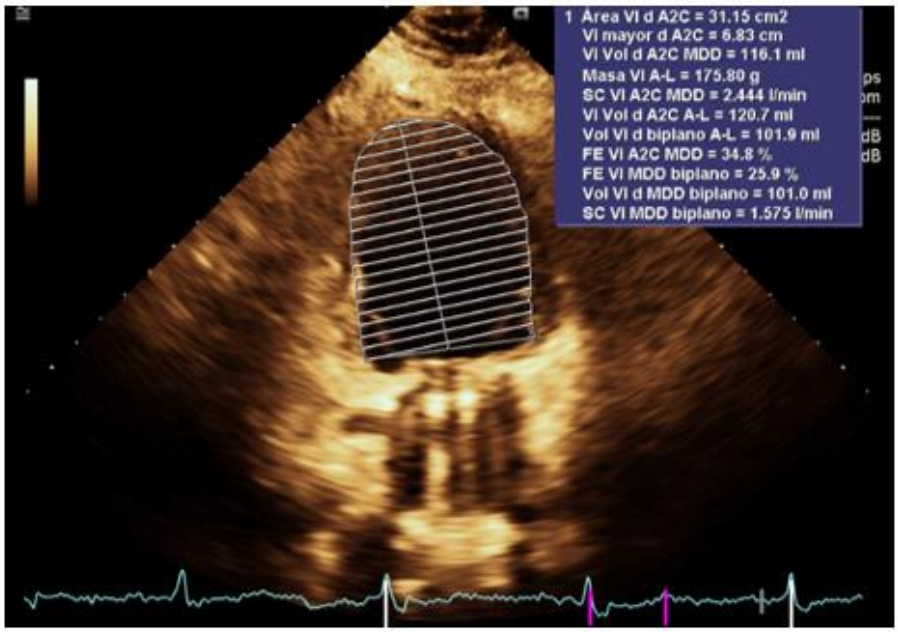

Figure 4: Apical 2-chamber axis showing the ejection fraction and end-diastolic volume of the left ventricle, the acoustic shadow generated by the mechanical mitral prosthesis is observed (red arrow)

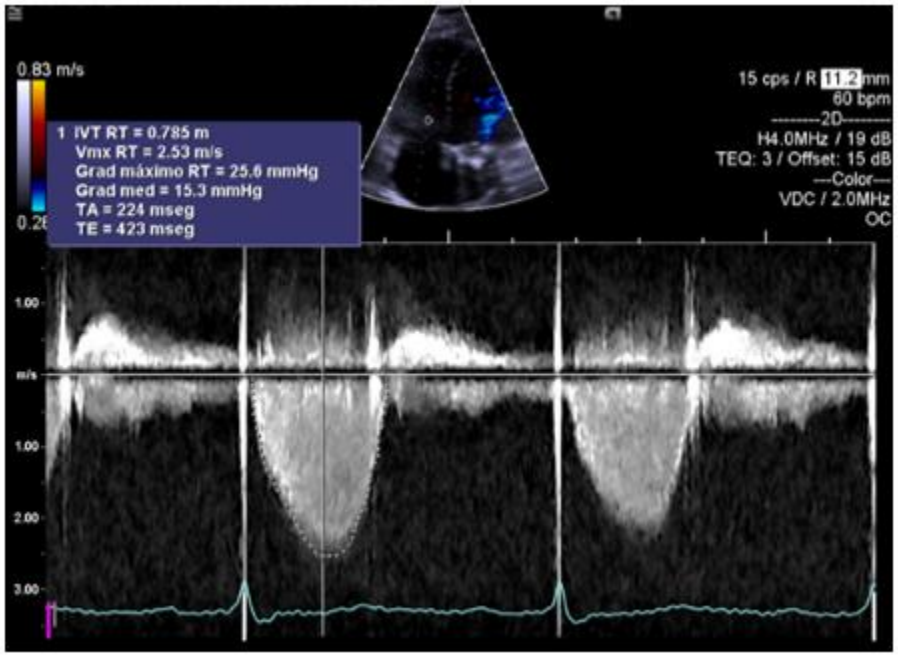

Figure 4: Continuous Doppler in the tricuspid valve showing the regurgitation spectrum.

Relevance of the Cases

Cardiomyopathies vary in their expression throughout life. Relatively recently, they were considered a grim pathological entity with few effective treatment options; however, management has evolved substantially [1]. In most hypertrophic cardiomyopathies, approximately 70% of patients have disease-causing variants in myosin-binding protein C3 (MYBPC3) or myosin heavy chain 7 (MYH7). The remaining 30% harbor variants in other regions of the sarcomere, including myosin light chain 2 (MYL2), myosin light chain 3 (MYL3), troponin T2 (TNNT2), troponin I3 (TNNI3), tropomyosin 1 (TPM1), and alpha cardiac muscle actin 1 (ACTC1) [2,3]. Alterations in cardiac muscle proteins interfere with the mechanical properties of the sarcomere and lead to myocyte hypertrophy and disarray, diastolic dysfunction, and myocardial fibrosis. Over time, these changes affect overall cardiac function and can cause hypercontractility, atrial and ventricular arrhythmias, and heart failure [4]. HCM manifests genetic heterogeneity, with multiple loci (8 genes), with multiple mutations identified for each gene, approximately 70% of patients have disease-causing variants in myosin-binding protein C3 (MYBPC3) or myosin heavy chain 7 (MYH7). The remaining 30% harbor variants in other regions of the sarcomere, including tropomyosin (Tpm) encoded by the TPM1 gene, an important player in calcium regulation, serving as a guardian of actin-myosin interaction, the variant presented by

our patient is associated with dilated cardiomyopathy, with autosomal dominant inheritance, it is considered to have a benign course and good prognosis [3,4]. Mutations in the LMNA gene (laminin gene) number up to 41, of which 8 are known to cause dilated cardiomyopathy, which causes variable phenotypes. Characterized by progressive conduction system disease, arrhythmia, and systolic failure, laminar A/C heart disease is more malignant than other common DCMs due to the high rates of adverse events, even when left ventricular failure is mild [5,6]. The pathological mechanisms of laminopathies are not clear, it is known that the lamina is a mesh-like structure that supports the integrity of the nucleus, acts as a mechanosensor capable of detecting external stimuli, and as a mechanotransducer that converts information into other cellular responses. The general cellular response is mainly governed by type A lamins encoded by the human gene LMNA through the modulation of nuclear stiffness and chromatin remodeling, influencing the nuclear influx of transcription factors and modulating the amount of external aggressions transmitted to the nucleus with consequences on nuclear damage, nuclear positioning, cell migration, differentiation and apoptosis [7,8,9]. Current clinical management of cardiomyopathies focuses on two main aspects: symptom management, risk assessment, and prevention of SCD. Pharmacological therapy remains the cornerstone of treatment to relieve symptoms, reduce heart rate, increase diastolic filling time, and restore cardiac filling pressure [1]. The evolution from pharmacological treatment to interventional and device therapies capable of interrupting and altering the natural history has reduced mortality while substantially improving quality of life [4]. Surgical techniques beyond heart transplantation continue to evolve and now frequently address the mitral valve. Looking into the distant future, there is even the possibility of addressing the genetic mutations responsible for the disease and preventing transmission to future generations [10].

Conclusion

These clinical cases demonstrate that diagnostic suspicion is essential for guiding the diagnosis. Understanding the genetic etiology, while unlikely to alter the prognosis of cardiomyopathy, could modify the urgency of the approach to preventing early adverse events due to rapid disease progression. It can also reduce the risk of sudden death, as is the case with rapidly developing and high-risk genetic variants. It also provides information on family members who may benefit from testing. Currently, pharmacological treatment and devices such as defibrillators and cardiac resynchronization devices, indicated according to international guidelines, are the cornerstone of treatment, with the goal of achieving heart transplantation whenever possible.

Declarations:

Acknowledgement: None to declare

Financial disclosure: The authors declare that they do not have a financial relationship to disclose.

Conflict of interest: The authors declare that they do not have any conflict of interest

Competing interests: The authors declare that they have no competing interests.

Informed consent: Verbal consent is obtained from patient.

Author contributions: All authors were involved in various portions of the article. SO helped with literature review, planning, writing, and editing. MR helped in literature review, writing, and editing. LP helped in literature review and editing. RP helped in planning and editing. RW helped in planning and editing.

Data availability: The authors declare that data supporting the findings of this case report are available within the article.

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DOI:10.31579/2641-0419/516