Case Report

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Genetic variant affecting the myosin light chain 2 related to familial hypertrophic cardiomyopathy

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SUMMARY Familial hypertrophic cardiomyopathy (FHCM) is a genetic disease characterized by left ventricle (LV) or interventricular septum hypertrophy. FHCM is a common heart disease (affecting 1 out of 500 individuals) associated with genetic variants in genes related to the sarcomere, including the *MYL2* (myosin light chain 2) gene that is affected in 1 to 3% of the cases. As described in this report, the genetic mutation p.Gly87Ala, rs 397516399 in the *MYL2* gene is likely pathogenic. Reported here is the case of a 37-year-old Colombian man with asymmetric septal hypertrophic cardiomyopathy and ventricular tachycardia. The man had progressive symptomatology, a family history of FHCM with a dominant inheritance pattern, a mother and 2 brothers with FHCM, and 2 brothers who died suddenly before the age of 35. A molecular panel of 17 genes for hypertrophic cardiomyopathy identified a heterozygous variant, p.Gly87Ala, of the *MYL2* gene. This variant can be found in Ensembl, dbSNP, and ClinVar, where it has conflicting interpretations: it either has an uncertain significance or it is likely pathogenic. This is the first report of a Colombian case of FHCM secondary to a mutation in the *MYL2* gene, highlighting the importance of molecular diagnosis, genetic counseling, and bioinformatic analysis in these patients.

Keywords heart diseases, cardiomyopathy, hypertrophic, familial, hypertrophy, left ventricle

1. Introduction

Familial hypertrophic cardiomyopathy (FHCM) is a hereditary disease characterized by left ventricle (LV) or interventricular septum thickening in the absence of a secondary cause; myofibrillar disarray and interstitial fibrosis may be observed microscopically, and an asymmetric pattern of wall thickening is evident macroscopically, with localized hypertrophy of the interventricular septum being the most common pattern of hypertrophy. The phenotype is heterogenous, even within the same family, and ranges from being asymptomatic to manifesting as dyspnea, arrhythmia, progressive heart failure, and even sudden death (*1*). The frequency of FHCM is approximately 1 in 500 individuals (*2*).

FHCM is a monogenic disease that exhibits an autosomal dominant inheritance pattern, with incomplete penetrance and variable expressivity. The mutations affect genes that code for proteins involved in sarcomere activity: *MYH7* and *MYBPC3* are affected in 50% of cases, though *TNNT2*, *TPM1*, *MYL2*, *MYL3*, *ACTC1*, and *TNNI3* may be affected in some cases. In cases of recessive inheritance, other genetic conditions like Noonan syndrome and LEOPARD syndrome should be considered; in addition, non-genetic disorders such as amyloidosis can mimic FHCM (*3-5*). The *MYL2* (myosin light chain 2) gene is affected in only 1 to 3% of FHCM cases (*6,7*).

The introduction of next-generation sequencing and its integration with bioinformatic tools, which are constantly evolving, has facilitated the application of advances in molecular biology to the identification of genetic diseases in clinical practice. However, decision-making based on molecular tests is still a challenge.

This case report adds to the medical literature by presenting a new case of FHCM secondary to a mutation in the *MYL2* gene, the first such case reported in Colombia, and it highlights the importance of molecular diagnosis in patients with FHCM in order to facilitate genetic counseling.

2. Case Report

A 37-year-old man from Tuluá, Valle del Cauca,

Colombia worked in agriculture and construction, which demanded considerable physical effort. At the age of 25, his symptomatology started, including intense fatigue and mild thoracic pain due to physical activity. Three years later, a routine checkup revealed an abnormal heart murmur. Supplementary electrocardiography revealed hypertrophy of the myocardium but no other abnormalities. Over the next two years, the man's symptoms worsened even with less physical effort. At the age of 32, an echocardiogram revealed asymmetric septal hypertrophic cardiomyopathy (Figure 1). The thickness of the interventricular septum was 19.5 mm in the basal third, 22 mm in the middle third, and 23 mm in the apical third, and ventricular tachycardia was also present. Given the previous diagnosis, alcohol septal ablation was performed. However, ventricular tachycardia and disabling symptoms he persisted, so he required an implantable cardioverter-defibrillator at the age of 35.

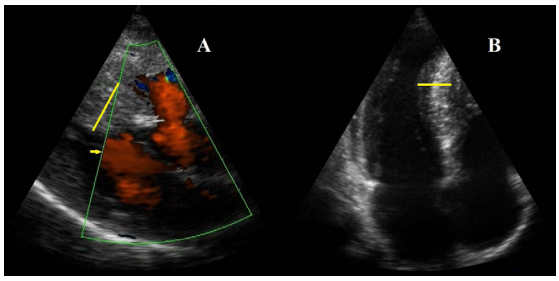

Figure 1. Patient's echocardiogram. (A), In a long-axis view of the heart, asymmetric septal hypertrophy is evident, as identified by the yellow line. Doppler ultrasound suggests a partial obstruction of the left ventricular outflow tract, the yellow arrow indicates the obstruction; **(B)**, Four-chamber cardiac view, the yellow line depicts the thickness of the septum.

During genetic assessment, a family history of hypertrophic cardiomyopathy (HCM) was detected. The patient's mother had HCM and died at the age of 66; two living brothers have MCH (51 and 60 years of age). In addition, two of his brothers under the age of 35 died suddenly, two more brothers died from an unknown cause before the age of 5, and yet another brother is being examined for possible heart disease. Findings indicated a dominant inheritance pattern for HCM in this family (Figure 2).

In light of the clinical diagnosis of FHCM, a molecular panel for HCM including 17 genes (*ACTC1*, *DES*, *FLNC*, *GLA*, *LAMP2*, *MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *BLN*, *PRKAG2*, *PTPN11*, *TNNC1*, *TNNI3*, *TNNT2*, *TPM1*, and *TTR*) was performed. This panel identified a heterozygous variant of the *MYL2* gene, p.Gly87Ala, dbSNP: rs397516399, that is likely pathogenic (Figure 3).

A routine echocardiogram at the age of 36 yielded the following findings: an LV of normal size, mild hypertrophy of the septum, normal systolic function, and diastolic dysfunction with slow LV relaxation. The patient still suffers dyspnea during physical effort and occasionally thoracic pain with palpitations.

A search of the literature in PubMed, Embase, Lilacs, ScienceDirect, Ovid Medline, and the Cochrane Central

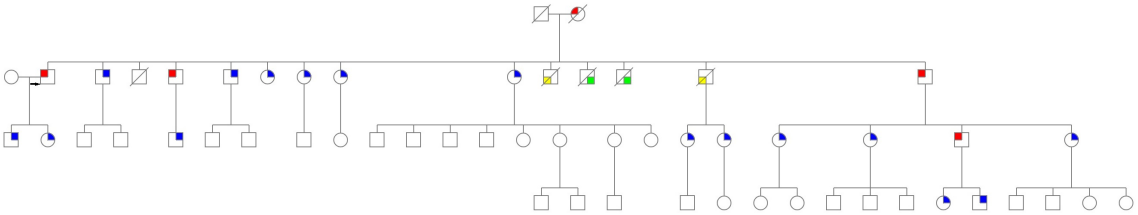

Figure 2. Patient's genogram. Genogram of three generations suggesting an autosomal dominant inheritance pattern of familial hypertrophic cardiomyopathy. **(Black arrow)**, the proband; **(red)**, patient with hypertrophic cardiomyopathy; **(blue)**, genetic testing advised; **(green)**, sudden death before the age of 5; **(yellow),** sudden death.

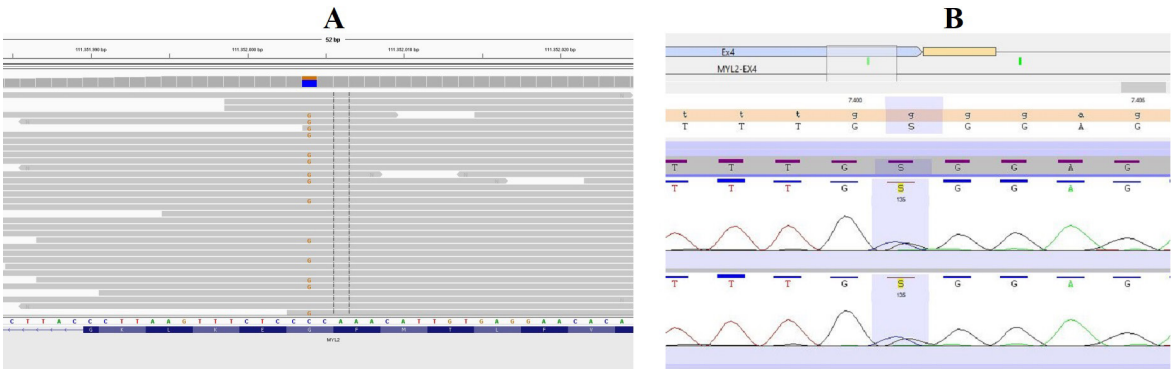

Figure 3. Variation identified in the fourth exon of *MYL2*. (A), Next-generation sequencing alignment of *MYL2*; **(B)**, Sanger sequencing chromatogram focusing on the targeted region including the variation.

Register of Controlled Trials was conducted using combinations of the following keywords: "Colombia" or "Colombian," "hypertrophic cardiomyopathy" or "familial hypertrophic cardiomyopathy," "MYL2" or "MCL2" or "CMH10." The terms were expressed in the respective language of the database, and the thesaurus of each database was used. No language nor year of publication restrictions were imposed. The search returned no results related to a Colombian case of HCM secondary to MYL2 mutations. Thus, the current case is the first reported case of FHCM secondary to a mutation in the *MYL2* gene in Colombia.

3. Discussion

The *MYL2* gene, with a locus at 12q24.11 on chromosome 12 (110,910,819-110,921,443:-1), codes for the ~19 kDa sarcomeric protein MYL2, which is involved in the contraction force of the heart by increasing the stiffness of the myosin lever arm, improving myosin head diffusion with actin. During embryogenesis, *MYL2* facilitates the assembly of cardiac myofibrils, which are important in early contractibility (*8*). Associated phenotypes with mutations in the *MYL2* gene are congenital myopathy with fiber-type disproportion (OMIM# 255310) and FHCM (OMIM# 608758) (*9*).

The frequency of mutations in the *MYL2* gene in FHCM is low, if the frequency of this disease is taken into account (1 in 500 individuals) (*2*). Álvarez *et al.* (2011), reported that among 124 patients with FHCM, only 3 (2.4%) exhibited consequences of mutations in the *MYL2* gene (*6*). Walsh *et al.* (2019) analyzed 4,185 probands with HCM and found that 43 (1.03%) had mutations in the *MYL2* gene (*7*). Lopes *et al.* (2015) identified 6 patients (1.6%) with HCM secondary to *MYL2* mutations out of 383 patients with HCM (*10*). Based on these data, the estimated prevalence of FHCM secondary to mutations in *MYL2* should be between 1 in 20,000 individuals and 1 in 50,000 individuals.

Patients with FHCM are usually asymptomatic during the first two decades of their lives (*3*). This pathology is frequently diagnosed incidentally *via* cardiac auscultation, thorax imaging, or *via* a thorough analysis of family history. The current patient was diagnosed as a result of incidental identification of a heart murmur at the age of 28; when asked, however, he reported experiencing symptoms since the age of 25.

FHCM has a broad symptomatology, from mild to moderate cases with mild dyspnea, thoracic pain, and fatigue upon exertion to more severe cases with angina, palpitations secondary to auricular fibrillation or ventricular tachycardia, syncope, ventricular fibrillation, and even sudden death (*1,3*).

A physical exam may reveal a crescendo-decrescendo murmur at the mitral auscultation site; an electrocardiogram may reveal inversion of the T wave below 0.5 mV, depression of the ST segment above 0.1 mV, or a left bundle branch block (*5,11*). These findings may suggest FHCM, but an echocardiogram is the cornerstone for diagnosing that condition. In adults, a myocardial wall thicker than 15 mm in one or more segments of the LV is a diagnostic criterion for HCM. In first-degree relatives of patients with HCM, the diagnostic criterion for LV thickness decreases to 13 mm (*3,5,12*).

HCM has a heterogeneous etiology. About 70% of cases are explained by genetic causes and the remaining 30% are idiopathic. In patients with HCM, cardiologists and geneticists should design a genogram to search for a family history of cardiomyopathies or sudden deaths of parents or siblings; if evident, a diagnosis of FHCM should considered, and treatment should proceed to molecular studies including the genes that code for proteins involved in cardiac sarcomere performance (*3*).

The current patient meets the clinical criteria for FHCM, and a molecular study identified a missense variant of the *MYL2* gene, NM_000432.3:c.260G>C dbSNP: rs397516399, in which a cytosine nucleotide is replaced by a guanine, substituting glycine for alanine at amino acid 87 of the protein.

This variant is reported in Ensembl, dbSNP and ClinVar, where it has two conflicting interpretations: it either has an unknown significance or is likely pathogenic.

The variant of the *MYL2* gene reported here was also identified in 2015 by Lopes *et al.* in a proband from a cohort of 383 patients with FHCM; 6 of those patients had variants associated with *MYL2* (*10*). It was also reported by Captur *et al.* (2020), which found this variant in 1 of 3 patients with *MYL2* mutations out of 110 patients with HCM (*13*). The current case of FHCM associated with the rs397516399 variant would be a new case involving this association.

The variant NM_000432.3:c.260G>C p.Gly87Ala has not been reported in controls in large population databases (GnomAd and the 1000 Genomes Consortium). It has not been identified in EF-hand domains, which are critical for protein function. A functional impact analysis of different in silico predictors yielded varied results (Table 1).

The variant has only been reported when patients with FHCM are index cases, it has not been found in population controls, and some in silico predictors classify it as deleterious. Given these facts, the current case corroborates the contention that the variant NM_000432.3:c.260G>C p.Gly87Ala is likely pathogenic.

In cases of FHCM with a pathogenic or likely pathogenic genetic mutation, individuals should be tested for the identified mutation and receive genetic counseling in order to predict outcomes for patients (*3*). In the current case, individuals shown in blue in the genogram should be tested (Figure 2).

Table 1. In silico prediction of the functional impact of the variation

Gene	Type	Mutation	Prediction tool	Predicted pathogenicity	Score
MYL2	Missense	p.Gly87Ala rs397516399	Mutation Assessor	NEUTRAL	0.6
			PROVEAN	DELETERIOUS	-4.44
			SIFT	TOLERATED	0.091
			PolyPhen-2	LIKELY HARMFUL	1.0
			SUSPECT	Score 15 (0-100)	15

A considerable number of individuals with HCM die without being diagnosed. Molecular testing and genetic counseling of affected individuals and their relatives allow recognition of the etiology, early interventions in asymptomatic individuals, and decrease sudden deaths of undiagnosed individuals, thus improving the prognosis for asymptomatic carriers.

This report of a case of FMCH secondary to a mutation in the *MYL2* gene adds to the medical literature and Colombian epidemiology. The medical community, and especially cardiologists, is encouraged by the molecular testing and genetic counseling of patients with FMCH. Moreover, the current report corroborates the contention that the variant p.Gly87Ala, rs 397516399 in the *MYL2* gene is likely pathogenic, contributing to the clinical significance of the identification of this genetic variant.

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