









## ORIGINAL ARTICLE

# Genomic study of dilated cardiomyopathy in a group of Mexican patients using site-directed next generation sequencing

Alessandra Carnevale<sup>1</sup>  | Sandra Rosas-Madrigal<sup>1</sup>  |  
 Rigoberto Rosendo-Gutiérrez<sup>1</sup> | Enrique López-Mora<sup>2</sup> | Sandra Romero-Hidalgo<sup>1</sup>  |  
 Nydia Avila-Vazzini<sup>2</sup> | Leonor Jacobo-Albavera<sup>1</sup>  | Mayra Domínguez-Pérez<sup>1</sup>  |  
 Gilberto Vargas-Alarcón<sup>2</sup>  | Fernando Pérez-Villatoro<sup>1</sup>  | Juana Inés Navarrete-Martínez<sup>3</sup> |  
 María Teresa Villarreal-Molina<sup>1</sup> 

<sup>1</sup>Instituto Nacional de Medicina Genómica, Mexico City, Mexico

<sup>2</sup>Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico

<sup>3</sup>Hospital Central Sur PEMEX, Mexico City, Mexico

**Correspondence**

María Teresa Villarreal-Molina, Instituto Nacional de Medicina Genómica, Mexico City, Mexico.

Email: mvillarreal@inmegen.gob.mx

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**Abstract**

**Background:** Dilated cardiomyopathy (DCM) is a major cause of nonischemic heart failure and death in young adults. Next generation sequencing (NGS) has become part of the diagnostic workup in idiopathic and familial DCM. More than 50 DCM genes have been identified, revealing great molecular heterogeneity and variable diagnostic yield. Interpretation of variant pathogenicity is challenging particularly in under-represented populations, as pathogenic variant databases include studies mainly from European/Caucasian populations. To date, no studies on genomic diagnosis of DCM have been conducted in Mexico.

**Methods:** We recruited 55 unrelated DCM patients, 22 familial (F-DCM), and 33 idiopathic (I-DCM), and performed site-directed NGS seeking causal mutations. Diagnostic yield was defined as the proportion of individuals with at least one pathogenic (P) or likely pathogenic (LP) variant in DCM genes.

**Results:** Overall diagnostic yield was 47.3%, and higher in F-DCM (63.6%) than in I-DCM (36.4%,  $p = 0.047$ ). Overall, NGS disclosed 41 variants of clinical interest (61.0% novel), 27 were classified as P/LP and 14 of unknown clinical significance. Of P/LP variants, 10 were A-band region *TTN* truncating variants, five were found in *DSP* (18.5%), five in *MYH7* (18.5%), two in *LMNA* (7.4%), and one in *RBM20*, *ABCC9*, *FKTN*, *ACTA1*, and *TNNT2*. NGS findings suggested autosomal recessive inheritance in three families, two with *DSP* loss of function mutations in affected individuals. The increasing number of mutation reports in DCM, increasing knowledge on the functional consequences of mutations, mutational hotspots and functional domains of DCM-related proteins, the recent refinement ACMG/ClinGen Guidelines, and cosegregation analysis in DCM families helped increase the diagnostic yield.

Alessandra Carnevale and Sandra Rosas-Madrigal contributed equally to this work.

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**Conclusion:** This is the first NGS study performed in a group of Mexican DCM patients, contributing to understand the mutational spectrum and complexity of DCM molecular diagnosis.

**KEY WORDS**

diagnostic yield, dilated cardiomyopathy, Mexican population, NGS

## 1 | INTRODUCTION

Dilated cardiomyopathy (DCM) is a nonischemic heart muscle disease with structural and functional myocardial abnormalities, characterized by dilatation and systolic dysfunction of the left or both ventricles (Schultheiss et al., 2019). It is a major cause of nonischemic heart failure and death in young adults and represents the most frequent indication for cardiac transplantation (Taylor et al., 2007). DCM has an estimated prevalence >0.4% in the general population (Hershberger, Hedges, & Morales, 2013; Redfield et al., 2003). In the absence of family history of the disease (familial DCM or F-DCM), it is considered idiopathic (I-DCM) after excluding an array of potential causes such as ischemic heart disease, hypertension, metabolic disorders, congenital heart disease or infections. Clinical screening of first-degree relatives (ECG and echocardiography) has revealed that up to 20%–35% of I-DCM cases may in fact be F-DCM (Sweet, Taylor, & Mestroni, 2015). Most F-DCM cases show autosomal dominant inheritance (90%), while 1%–2% are autosomal recessive and 5%–10% are X-linked. Age of onset and clinical findings vary, including insidious progressive heart failure, thromboembolism, arrhythmias, and sudden cardiac death. The etiology may be genetic in more than 50% of I-DCM cases and to date more than 50 genes have been associated with the disease (McNally & Mestroni, 2017). These genes encode a wide variety of proteins involved in the normal cardiomyocyte development and function, mainly sarcomeric, cytoskeletal, nuclear membrane, dystrophin-associated glycoprotein complex, desmosome, z-disk proteins, and ion channels (Sweet et al., 2015). Most of these genes account for only a small proportion of cases and many mutations are private to a single family (van Spaendonck-Zwarts et al., 2013).

While next generation sequencing (NGS) has improved our understanding of the molecular basis of the disease and led to the identification of new mutations and causal genes, it has also evidenced the complexity, genetic heterogeneity, and overlap of DCM with other cardiomyopathies. Mutation frequencies vary among different populations (Haas et al., 2015), and the presence of new variants of uncertain significance (VUS) further complicate the interpretation of sequencing results. Hershberger et al. (2018) pointed out the ongoing challenges of variant interpretation in non-Caucasian populations, as most repositories of known pathogenic variants

come from studies in Caucasian or Northern European populations. Moreover, in spite of the inclusion of other population groups in large population databases such as gnomAD (gnomad.broadinstitute.org), genetic test interpretation of variant alleles from underrepresented ethnic groups in reference data sets is extremely challenging and must be approached with considerable caution (Hershberger et al., 2018). Nevertheless, genetic testing has become part of the diagnostic workup of I-DCM and F-DCM, as it may be of prognostic value, have clinical implications according to the affected gene and offers the possibility of presymptomatic diagnosis and early treatment for other mutation carriers in the family (Paldino et al., 2018; Rosenbaum, Agre, & Pereira, 2019).

To date, there are no reports on the clinical and genetic characteristics of Mexican patients with I-DCM or F-DCM. We thus aimed to identify causative DCM mutations and variants in a group of Mexican patients with I-DCM or F-DCM using site-directed NGS. This is the first NGS study performed in a group of Mexican DCM patients, contributing to understand the mutational spectrum and complexity of DCM molecular diagnosis.

## 2 | MATERIALS AND METHODS

### 2.1 | Ethical compliance

The Ethics Committees of the Instituto Nacional de Cardiología, the Instituto Nacional de Medicina Genómica, and Hospital Central Sur PEMEX (Mexico City) approved the study and all participants provided written informed consent.

Unrelated patients diagnosed with I-DCM and F-DCM recruited over a 2-year period at the Instituto Nacional de Cardiología “Ignacio Chávez” and the Hospital Central Sur PEMEX in Mexico City, were included in the study. All index cases identified themselves as Mexican mestizos, both parents and all grandparents had been born in Mexico. All participants underwent medical assessment including full medical history, pedigree, chest X-rays, ECG, and transthoracic echocardiography. Diagnostic criteria for DCM were left ventricular ejection fraction <45% associated with left ventricular end-diastolic dimensions >117% of the predicted value corrected for age and body surface area (Elliott, 2000).

Available relatives of index cases were examined to determine whether cases were idiopathic (I-DCM) or familial (F-DCM). When more than one affected relative was found or sudden cardiac death (SCD) occurred in at least one relative aged <35 years, the patient was classified as F-DCM, while patients with no affected relatives were classified as I-DCM. Patients with metabolic, infectious or systemic causes of DCM, or with age of onset above 60 years were excluded from the study. A total of 124 first-degree relatives of the 55 index cases were included in the study.

Genomic DNA was extracted from peripheral blood leukocytes using the DNeasy Blood Kit (Qiagen, USA). All patients were sequenced using the Trusight Cardio sequencing panel (Illumina), in a MiSeq System (Illumina). Post-run sequencing quality was assessed with FastQC (Babraham Bioinformatics, UK). Sequence reads were aligned with BWA Enrichment v2.1.0 and variant calling was performed using GATK v4.0. Variants were annotated with ANNOVAR (wannovar.wglab.org).

All novel or very low frequency variants (MAF <0.0005) found in DCM-related genes were classified according to the criteria described by the American College of Medical Genetics and Genomics as benign, likely benign, of unknown clinical significance (VUS), likely pathogenic (LP) or pathogenic (P) (Richards et al., 2015). All variants classified as VUS, LP, or P were confirmed by capillary sequencing and screened in all available first-degree relatives. Variants were also analyzed with the help of Varsome (Kopanos et al., 2018) and further curated considering the refinement of ACMGM/ClinGen Guidelines for DCM (Morales et al., 2020). Diagnostic yield was estimated based on the finding of at least one pathogenic or likely pathogenic variant per patient. Differences between I-DCM and F-DCM were compared using Student's *t* test or the chi-square test as appropriate and *p* values <0.05 were considered significant.

### 3 | RESULTS

A total of 55 unrelated patients were recruited, 33 diagnosed as I-DCM and 22 as F-DCM. Table 1 compares clinical

findings in F-DCM and I-DCM. Overall, 69.1% of the patients were male, and sex ratio did not differ in I-DCM and F-DCM. Age of onset, mean left ventricular ejection fraction (LVEF%) and frequency of arrhythmia did not differ significantly in I-DCM and F-DCM cases. Implantable cardioverter defibrillator (ICD) implantation was significantly more frequent in F-DCM as compared to I-DCM (*p* = 0.037). Over the course of the study, a total of 11 patients (18.9%) died. Although death occurred more frequently in F-DCM cases, the difference did not reach statistical significance. Among F-DCM cases, the pedigree was compatible with autosomal dominant inheritance in 18/22 (81.8%).

NGS disclosed the presence of a total of 41 variants of interest in DCM-associated genes (P, LP, or VUS) in 37/55 patients (Tables 2 and 3). Overall, 25/41 (61.0%) variants were novel, 27 variants were classified as P or LP (63.0% novel), and 14 as VUS (57.1% novel). All P/LP variants (*n* = 27) were found in established DCM genes: 10 were *TTN* truncating variants (*TTN<sub>tr</sub>*) found in the A-band region, accounting for 37.0% of P/LP variants and for 18.2% of all DCM cases, 5 in *DSP* (18.5%), 5 in *MYH7* (18.5%), 2 in *LMNA* (7.4%), and 1 in *RBM20*, *ABCC9*, *FKTN*, *ACTA1*, and *TNNT2* (Table 2). NGS results were compatible with autosomal recessive inheritance in three families: one with two siblings homozygous for a very low frequency *FKTN* variant, a family with two siblings who were compound heterozygous for *DSP* mutations (one loss of function and one missense), and a third family where the index case was initially considered as I-DCM but found to be homozygous for a frameshift *DSP* mutation. Diagnostic yield for DCM (the proportion of patients with pathogenic or likely pathogenic variants in DCM genes) was 47.3% and was higher in F-DCM (63.6%) than in I-DCM (36.4%, *p* = 0.047).

Screening of first-degree relatives identified a total of 19 individuals with LP/P mutations in DCM families compatible with autosomal dominant inheritance. Most of these individuals were asymptomatic when the mutation was identified and are currently under clinical vigilance. In DCM families compatible with autosomal recessive inheritance, molecular diagnosis confirmed DCM in two individuals, and a total of six healthy recessive mutation

**TABLE 1** Comparison of clinical features in familial and idiopathic DCM cases

	All DCM n = 55	F-DCM n = 22	I-DCM n = 33	<i>p</i>
Gender (% male)	69.1	68.2	69.7	NS
Early age of onset	39 (70.9%)	17 (77.3%)	22 (66.7%)	NS
LVEF (%)	28.04 ± 8.41	27.00 ± 7.65	28.73 ± 8.93	NS
Heart transplantation	2 (3.64%)	2 (9.1%)	0 (0%)	NS
ICD implantation	12 (21.82%)	8 (36.4%)	4 (12.1%)	0.037
Arrhythmia	33 (60.0%)	15 (68.2%)	18 (54.5%)	NS
Diagnostic yield (%)	26 (47.3%)	14 (63.6%)	12 (36.4%)	0.047

TABLE 2 Pathogenic/likely pathogenic variants found in Mexican DCM patients

DCM Type	Gene	Transcript	cDNA	Protein	Cyosity	ID dbSNP	ACMG Class
I	<i>TTN</i>	NM_001267550.2	c.51285_51286insTA	p.P17096Yfs*13	Ht		P
F	<i>TTN</i>	NM_001267550.2	c.C52903T	p.R17635X	Ht		P
F	<i>TTN</i>	NM_001267550.2	c.53391delA	p.G17798Afs*17	Ht		P
I	<i>TTN</i>	NM_001267550.2	c.58571_58574del	p.K19524Tfs*5	Ht		P
F	<i>TTN</i>	NM_001267550.2	c.C60733T	p.R20245X	Ht		P
I	<i>TTN</i>	NM_001267550.2	c.62312_62316del	p.L20771Pfs*15	Ht		P
I	<i>TTN</i>	NM_001267550.2	c.66524dupT	p.S22176Ifs*7	Ht		P
I	<i>TTN</i>	NM_001267550.2	c.T71421A	p.Y23807X	Ht		P
F	<i>TTN</i>	NM_001267550.2	c.80691dupA	p.G26822Rfs*2	Ht		P
I	<i>TTN</i>	NM_001267550.2	c.C100825T	p.R33609X	Ht	rs1057518195	P
I	<i>DSP</i>	NM_004415.4	c.A1333T	p.I445F	Ht	rs934142779	LP
F	<i>DSP</i>	NM_004415.4	c.2179dupA	p.D728Rfs*9	Comp Ht		P
	<i>DSP</i>	NM_004415.4	c.T6902C	p.I2301T	Comp Ht	rs772381363	LP
F	<i>DSP</i>	NM_004415.4	c.C6496T	p.R2166X	Ht	rs141026028	P
I	<i>DSP</i>	NM_004415.4	c.8495_8496insATCTC	p.R2834Hfs*50	Homo		LP
I	<i>MYH7</i>	NM_000257.4	c.T1174A	p.S392T	Ht	rs1555338377	LP
F	<i>MYH7</i>	NM_000257.4	c.C2058A	p.N686K	Ht		LP
F	<i>MHY7</i>	NM_000257.4	c.2896_2898del	p.K966del	Ht		LP
F	<i>MYH7</i>	NM_000257.4	c.C2710T	p.R904C	Ht	rs727503253	LP
F	<i>MYH7</i>	NM_000257.4	c.G3149A	p.R1050Q	Ht		LP
F	<i>LMNA</i>	NM_001282625.2	c.C391T	p.Q131X	Ht		P
F	<i>LMNA</i>	NM_001282625.2	c.C1292A	p.S431X	Ht		P
I	<i>RBM20</i>	NM_001134363.3	c.C1913T	p.P638L	Ht	rs267607003	P
I	<i>ABCC9</i>	NM_005691.3	c.4517_4527del	p.R1506fs	Ht	rs1272651352	P
I	<i>FKTN</i>	NM_001198963	c.G1270A	p.G424S	Homo	rs752358445	P
F	<i>ACTA1</i>	NM_001100.4	c.G472A	p.G158S	Ht		LP
F	<i>TNNT2</i>	NM_001276345.2	c.C451T	p.R151W	Ht	rs74315379	P

carriers were identified (four parents and two siblings). Finally, only one asymptomatic sibling with a *TTN* truncating variant was identified in families initially classified as idiopathic.

Variants of unknown clinical significance found in patients where molecular diagnosis was not achieved are described in Table 3. At least one VUS in nonsyndromic or syndromic DCM genes was found in 14 patients, 3 of which had two VUS. Of note, three VUS were found in the *RYR1*, two in *TPM1* and two in *MYH6*. Failure to find any variant of clinical interest (VUS, LP or P) was more frequent in I-DCM (57.6%) than in F-DCM cases (18.2%), but the difference did not reach statistical significance ( $p = 0.06$ ). Moreover, among the 27 pathogenic/likely pathogenic variants, 16 were loss of function (nonsense or frameshift), and only 4 were missense. In contrast, 1/14 VUS was an in-frame-deletion and the remainder 13 were missense variants ( $p < 0.001$ ).

## 4 | DISCUSSION

Although Next Generation Sequencing (NGS) has transformed clinical genetic screening of both F-DCM and I-DCM by sequencing large numbers of genes in a cost-effective way and in a short time, interpretations of the pathogenicity of variants has become increasingly complex, and diagnostic yield is relatively low both in F-DCM and I-DCM. Moreover, criteria for curation of potentially causal variants require constant refinement and updating, and variants may need to be reclassified over time. Regardless of these problems, NGS has become part of the diagnostic workup of I-DCM and F-DCM.

Diagnostic yield in both F-DCM and I-DCM cases was higher in this group of Mexican patients (47.3%) than that found in previous reports (10%–40%) (Hershberger et al., 2010, Lakdawala et al., 2012, van Spaendonck-Zwarts et al., 2013, Pugh et al. 2014, Walsh et al., 2017, Fatkin, Huttner,

**TABLE 3** Variants of unknown clinical significance in DCM-associated genes, found in Mexican patients with idiopathic and familial dilated cardiomyopathy

DCM TYPE	GENE	Transcript	cDNA	Protein	ID dbSNP
I	<i>TPM1</i>	NM_001018005.2	c.A650G	p.K217R	
	<i>MYH6</i>	NM_002471.4	c.G2658C	p.K886N	rs749609972
F	<i>TPM1</i>	NM_001018005.2	c.G238A	p.D80N	
I	<i>TNNC1</i>	NM_003280.3	c.A241T	p.M81L	
I	<i>RYR1</i>	NM_000540.3	c.G2659A	p.E887K	rs766827383
I	<i>RYR1</i>	NM_000540.3	c.12950_12958del	p.R4321_L4323del	
F	<i>RYR1</i>	NM_000540.3	c.C12322G	p.Q4108E	rs774414325
F	<i>ACTC1</i>	NM_005159.5	c.G116A	p.R39H	
I	<i>MYH6</i>	NM_002471.4	c.C3476T	p.T1159M	rs780305056
	<i>VCL</i>	NM_014000.3	c.C3089T	p.T1030I	
I	<i>DMD</i> <sup>a</sup>	NM_004006.3	c.G446A	p.R149H	rs771307588
	<i>KCNJ2</i>	NM_000891.3	c.C322G	p.L108V	rs371331394
F	<i>DLG1</i>	NM_004087.1	c.T1455A	p.D485E	
I	<i>CAV3</i>	NM_033337.3	c.T335C	p.I112T	

<sup>a</sup>All variants were found in heterozygous form, except for DMD p.R149H which was found in hemizygous form.

Kovacic, Seidman, & Seidman, 2019). Higher diagnostic yield could be expected in more recent studies because of the increasing number of reports of mutations in DCM patients, the increasing knowledge on the functional consequences of mutations, mutational hotspots and functional domains of some DCM-related proteins, and the refinement ACMG/ClinGen Guidelines, which particularly helped reclassify *MYH7* and *DSP* mutations in the present study. Moreover, co-segregation analyses in a few families were of help to increase diagnostic yield.

The prevalence of *TTN*<sub>IV</sub> was close to 20%, as observed in other populations, and all affected the A band region, known to be overrepresented in DCM (Gigli et al., 2016, Akinrinade et al., 2019). While several patients had between 1 and 4 rare or novel *TTN* missense variants predicted as damaging by bioinformatic means, they were not considered as variants of interest as comparable frequencies of rare predicted deleterious *TTN* missense variants have been observed in DCM patients and reference populations, suggesting they are not independently causative for DCM (Akinrinade et al., 2019; Morales et al., 2020).

The relatively high frequency of patients with loss of function *DSP* mutations in this group of patients is noteworthy. One patient with severe and early onset DCM was homozygous for a novel frameshift mutation (R2384Hfs\*50); another was compound heterozygous for a novel frameshift (D728Rfs\*9) and a missense (I2301T) variant, where co-segregation and family history helped define the pathogenicity of the latter. A third patient was heterozygous for a *DSP* nonsense mutation (R2166X). While *DSP* mutations have been found in patients with arrhythmogenic right ventricle dysplasia, non-missense *DSP* mutations have been specifically

associated with left domain arrhythmogenic cardiomyopathy forms (Castelletti et al., 2017). Moreover, variant interpretation criteria have very recently been adapted indicating that *DSP* loss of function variants should be assigned a moderate degree of pathogenicity in DCM, although the variant must have been observed in at least one unrelated DCM case (Morales et al., 2020).

Among the 27 pathogenic/likely pathogenic variants found in the present study, 16 were loss of function (nonsense or frameshift), and only 4 were missense. In contrast, 1/14 VUS was an inframe-deletion and the remainder were missense variants. This exemplifies the problem of defining pathogenicity for missense mutations, partly due to the difficulty of performing appropriate functional studies in a wide array of genes. While the AMGC considers co-segregation of disease with multiple family members as a supporting criterion of pathogenicity, there are no clear criteria as to what number of members can be considered as multiple, and co-segregation is not always easy to establish because other family members may not be available or willing to undergo diagnostic workup. This illustrates the importance of structured family screening and the yield of genetic testing in suspicion of an inherited cardiac disease. Unfortunately, not enough family members were available to seek co-segregation in several of our families.

Finally, because of the probabilistic nature of genetic results and because information and knowledge change over time, periodic reclassification of variants should always be considered (Hershberger et al., 2018; Ingles, Bagnall, & Semsarian, 2018; Richards et al., 2015). This study contributes to increase the number of genetic screening studies in the Mexican and other populations of Latin America, which may



eventually have an impact on the reclassification of variants of unknown clinical significance.

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## CONFLICTS OF INTEREST

All authors declare there are no conflicts of interest or competing interests.


## ETHICS APPROVAL

The Ethics Committees of the Instituto Nacional de Medicina Genómica, the Instituto Nacional de Cardiología and Hospital Central Sur PEMEX approved the protocol.

## CONSENT TO PARTICIPATE

All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki (1964).

## ORCID

Alessandra Carnevale  <https://orcid.org/0000-0003-4511-4557>

<https://orcid.org/0000-0003-4511-4557>

Sandra Rosas-Madrigal  <https://orcid.org/0000-0002-9980-6658>


<https://orcid.org/0000-0002-9980-6658>

Sandra Romero-Hidalgo  <https://orcid.org/0000-0003-3077-7825>

<https://orcid.org/0000-0003-3077-7825>

Leonor Jacobo-Albavera  <https://orcid.org/0000-0001-5129-8108>

<https://orcid.org/0000-0001-5129-8108>

Mayra Domínguez-Pérez  <https://orcid.org/0000-0002-6049-0430>


<https://orcid.org/0000-0002-6049-0430>

Gilberto Vargas-Alarcón  <https://orcid.org/0000-0001-7916-5163>

<https://orcid.org/0000-0001-7916-5163>

Fernando Pérez-Villatoro  <https://orcid.org/0000-0002-5419-8484>

<https://orcid.org/0000-0002-5419-8484>

María Teresa Villarreal-Molina  <https://orcid.org/0000-0003-4450-7690>

<https://orcid.org/0000-0003-4450-7690>

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