Genetic variants in Colombian patients with inherited cardiac conditions

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Abstract

Background: Clinical and molecular diagnosis of inherited cardiac conditions is key to find at-risk subjects and avoid preventable deaths. This study aimed to identify genetic variants in a sample of Colombian patients diagnosed with inherited cardiac conditions.

Methods: Next-generation sequencing (Illumina platform) using a 231 gene panel was performed in blood samples of 25 unrelated patients with age disease onset between 9 and 55 years.

Results: Genetic testing yield was 52%. Two novel likely pathogenic/pathogenic variants were found: a DSP nonsense variant in a patient with arrhythmogenic cardiomyopathy and a KCNE1 frameshift variant in two patients with long QT syndrome. Younger individuals (<18 years) had the highest genetic testing yield (66.6%) compared to 50% and 20% in young adults and patients over 40 years, respectively. All subjects affected with long QT syndrome with a severe event while exercising had a positive genetic test. They also had four times more loss of consciousness events and, resuscitated sudden cardiac arrest was more representative.

Conclusion: This study is the first one undertaken in Colombia to evaluate inherited cardiac conditions. It highlights the need to perform mutational analysis to provide adequate genetic counseling and to be able to identify patients at risk of severe events.

KEYWORDS

arrhythmogenic cardiomyopathy, Brugada syndrome, Colombia, hypertrophic cardiomyopathy, long QT syndrome

1 | INTRODUCTION

Sudden cardiac death is the most relevant outcome of channelopathies and cardiomyopathies (Dainis & Ashley, 2018). Over the past 20 years, individuals at risk of several genetic conditions including inherited cardiac diseases have been identified (Earle et al., 2019). A clear benefit of genetic testing in long QT syndrome (LQTS) is allowing for proper interventions, reducing the risk of arrhythmia, and discharging test-negative kinship from
follow up (Marcondes et al., 2018). For some forms of hypertrophic cardiomyopathy (HCM), gene-specific treatments are being developed (Prondzynski et al., 2019). While understanding in the field is growing, knowledge in Colombia is scarce. The purpose of his study was to determine genetic variants in a pilot sample of Colombian subjects diagnosed with inherited cardiac conditions.

2 | METHODS

2.1 | Ethical compliance

This study has ethical approval from Universidad Nacional de Colombia (N° 018-301-17) and Fundación Clínica Shaio (N° 261). Written consent was obtained from every subject. For minors, written formal consent was obtained from the parent/guardian.

2.2 | Participants and procedures

A total of 25 cases were selected from the Department of Cardiology, Fundación Abood Shaio and other referrals in Bogotá, Colombia. These patients were <61 years of age and were diagnosed with long QT syndrome, Brugada syndrome, hypertrophic cardiomyopathy, and arrhythmogenic cardiomyopathy. Our scope also included catecholaminergic polymorphic ventricular tachycardia and short QT syndrome, however, patients with these conditions were not found.

DNA was isolated using the Qiagen DNA Blood Minikit kit (Qiagen) following the manufacturer’s recommendations (Qiagen Cat No./ID: 51106). Quantification of DNA samples was carried out in a Nanodrop 2000, as well as, in a Qbit system following manufacturer’s recommendations (ThermoFisher Scientific).

Analysis of the samples depending on the diagnosis was carried out by next-generation sequencing (NGS) using a 231 Gene Panel (Cardio Gene Profile panel Sistemas Genómicos®, Paterna, Valencia Spain) and filtering for predefined genes based on the cardiac conditions.

3 | RESULTS

A total of 25 unrelated patients were analyzed. Structural cardiomyopathies represented 52%, while channelopathies accounted for 48% of the sample (Table 1). The mean age was 40.4 years, ranging from 14 to 61 years across all conditions. HCM had the highest average age with 46.4 years. Patients were predominantly male (60%); the only group where the proportion of women was higher was LQTS.

3.1 | Genetics

NGS analysis was performed in all patients as described before. The overall diagnostic yield was 52% (13/25

| Condition | No. of probands | Age, years | Age range, years | Female | Male | Family history |
|-----------|-----------------|------------|-----------------|--------|------|---------------|
| ACM       | 2 (8)           | 34 ± 28.2  | 14–54           | 1 (50) | 1 (50)| 1 (50)        |
| HCM       | 11 (44)         | 46.4 ± 8.7 | 30–61           | 4 (36.4) | 7 (63.6) | 9 (81.8) |
| BrS       | 4 (16)          | 39.2 ± 7.7 | 29–47           | 0 (0)  | 4 (100)| 3 (75)        |
| LQTS      | 8 (32)          | 34.5 ± 13.1| 14–57           | 5 (62.5) | 3 (37.5) | 6 (75)        |
| Total     | 25              | 40.4 ± 13  | 14–61           | 10 (40) | 15 (60) | 19 (76)       |

Note: Values are n, mean ± SD, or n (%).

Abbreviations: ACM, arrhythmogenic cardiomyopathy; BrS, Brugada syndrome; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome.
patients) for pathogenic and likely pathogenic variants using criteria defined by the ACMG (Richards et al., 2015). Variants of uncertain significance (VUS) were detected in 12% of patients (3/25) and negative results in 36% of patients (9/25) (Table 2). Patients were grouped by age, in three groups: underage (<18 years), young adults (18–40 years), and above 40 years. A trend was evidenced with a higher yield of the genetic test when symptoms started at a younger age (8/12 (66.6%); 4/8 (50%); 1/5 (20%), respectively) but not statistically supported.

Of the 13 patients in whom a pathogenic or likely pathogenic variant was identified, 10 patients had missense variants, one patient had a nonsense variant, and two patients had the same frameshift variant. Channelopathies had a better diagnostic yield (58.3%, 7/12 positive patients), implicating the KCNE1 (OMIM #176261) (two patients), KCNH2 (OMIM #152427) (two patients), KCNQ1 (OMIM #607542) (1 patient), SCNA5 (OMIM #600163) (two patients) genes, compared to cardiomyopathies (46.2%, 6/13 patients) with the MYH7 (OMIM #160760) (2 patients), TNNT2 (OMIM #191045) (1 patient), DSP (OMIM #125647) (1 patient), MYL3 (OMIM #160790) (1 patient), and PRKAG2 (OMIM #602743) (1 patient) genes. The diagnostic yield for HCM was 45.5% (5/11 patients).

All pathogenic or likely pathogenic variants identified in HCM patients were missense variants and four of them involved the sarcomere (TNNT2, MYH7, MYL3). Three patients had VUS, of which two were missense variants in the LAMP2 (OMIM #309060) and FLNC (OMIM #102565) genes (patients MC06, MC21) and an intronic variant in the TNNT2 gene (patient MC10). For ACM, one patient (MC17) was positive with a nonsense pathogenic variant (p.Q595Ter) in the desmoplakin gene (DSP), while an additional patient was negative (MC13) (Table 2).

The yield for the LQTS was 62.5% (5/8 patients). For positive patients, three genes were implicated. KCNH2 variants were found in two patients, with a different nucleotide substitution in the same codon that resulted in a different amino acid; patient MC18 with p.S818L and MC24 with p.S818W. Additionally, the same variant was identified in two unrelated patients for the KCNE1 gene that involves a deletion, with subsequent frameshift and a premature stop codon (c.18-131del, p.P11AfsTer24) in patients MC01 and MC23. Finally, a missense variant in the KCNQ1 gene was evinced in MC04. In three of the eight subjects with LQTS (37.5%), no variant was identified.

For Brugada syndrome, a 50% yield was obtained, with two missense variants in the SCNA5 gene (MC11 and MC25) and two patients without molecular findings.

For the HCM group, asymmetric hypertrophy was more prevalent, occurring in nine of 11 patients. Five patients had a positive result in the gene panel, involving sarcomeric genes (TNNT2 c.418C>T, p.R140C; MYH7 c.1208G>A, p.R403Q; MYL3 c.451G>A, p.A151T) and one patient in the PRKAG2 gene (c.1203C>A, p.H401Q). Two patients with VUS (FLNC c.1934A>C, p.D645A and TNNT2 c.851+5G>A genes); and two patients with negative results. The centric pattern was present in two subjects, the first was a VUS in the LAMP2 (c.1091C>T, p.T364I) gene (non-sarcomeric) and the second was negative in the panel. Regarding maximum wall thickness, subjects with a positive result had a mean of 20.2 mm, VUS with 19.6 mm, and negative with 17.6 mm.

3.2 | Diagnosing inherited cardiac conditions

An analysis of conditions, time of diagnosis, and interval of time between the first symptoms and time to diagnosis is presented in Table 3. Brugada syndrome was diagnosed within the first year of symptom’s onset. HCM had a mean of 2 years to diagnose. Long QT syndrome had a mean diagnostic interval of 10.1 years. Among these eight long QT patients, seven patients started to show symptoms before the age of 15. A subject who had a 22-year interval between onset of symptoms and diagnosis (MC18), experienced multiple syncope episodes in early teenage years, and at age 14, was diagnosed with high blood pressure and was medicated. At age 20, he was diagnosed with dyslipidemia; for this reason, he was followed up regularly. At age 32, he was diagnosed with HCM and in subsequent consultation showed prolonged QT interval. At age 40, he had an episode of resuscitated sudden cardiac arrest (RSCA), followed by a placement of an implantable cardioverter-defibrillator (ICD). This patient had a likely pathogenic variant in KCNH2 (c.2453C>T) which is compatible with a diagnosis of type 2 LQTS. There was a significant difference in time of diagnosis for hypertrophic cardiomyopathy compared to long QT syndrome, taking less time for HCM (p = 0.00544; Mann–Whitney).

Arrhythmogenic cardiomyopathy had the longest time interval for diagnosis. In our series, only two patients were affected with this condition. The diagnosis of ACM is sometimes difficult, with multiple criteria in the Task Force scale (Marcus et al., 2010). The patient with the longest time interval for diagnosis (33 years) also had a difficult clinical course. At age 17, he presented chest pain and syncope, and was followed up, apparently with abnormal studies, but nothing conclusive. He had an asymptomatic time interval for more than 30 years. At age 50, he had an episode of RSCA, diagnosis of ACM and ICD implantation as secondary prevention. In addition, he had dyslipidemia, kidney failure, gout, apnea–hypopnea syndrome, and psoriasis with non-significant coronary disease. This
| Code  | Condition | Gene   | Nucleotide       | Exon | Amino acid          | Variant type | Class       | ACMG          | RefSeq         | dbSNP         |
|-------|-----------|--------|------------------|------|---------------------|--------------|-------------|---------------|----------------|---------------|
| MC01  | LQTS      | KCNE1  | c.31_118del      | 3/3  | p.P11AfsTer24       | Frameshift   | LP          | PVS1, PM2     | NM_001270402.2 |              |
| MC02  | BrS       | ND     |                  |      |                     |              |             |               |                |               |
| MC03  | BrS       | ND     |                  |      |                     |              |             |               |                |               |
| MC04  | LQTS      | KCNQ1  | c.1027C>T        | 7/16 | p.P343S             | Missense     | P           | PP1, PM1, PM2, PM5, PP2, PP3 | NM_000218.2 | rs199472762 |
| MC05  | HCM       | TNNT2  | c.418C>T         | 10/16| p.R140C             | Missense     | P           | PS3, PM1, PM2, PP2, PP3, PP5 | NM_001276345.2 | rs397516463 |
| MC06  | HCM       | LAMP2  | c.1091C>T        | 8/9  | p.T364I             | Missense     | VUS         | PM1, PP3, BS1 | NM_013995.2    | rs183781327  |
| MC07  | LQTS      | ND     |                  |      |                     |              |             |               |                |               |
| MC08  | HCM       | ND     |                  |      |                     |              |             |               |                |               |
| MC09  | HCM       | PRKAG2 | c.1203C>A        | 11/16| p.H401Q             | Missense     | LP          | PM1, PM2, PP3, PP5 | NM_016203.3 |              |
| MC10  | HCM       | TNNT2  | c.851+5G>A       |      |                     | Intron       | VUS         | PM2, PP3      | NM_001276345.2 | rs193922620 |
| MC11  | BrS       | SCN5A  | c.362G>A         | 3/28 | p.R121Q             | Missense     | LP          | PM1, PM2, PP1, PP3 | NM_001160160.1 | rs199473058 |
| MC12  | HCM       | MYH7   | c.1208G>A        | 13/40| p.R403Q             | Missense     | P           | PS3, PS4, PM1, PM2, PM5, PP3 | NM_000257.3 | rs121913624 |
| MC13  | ACM       | ND     |                  |      |                     |              |             |               |                |               |
| MC14  | HCM       | ND     |                  |      |                     |              |             |               |                |               |
| MC15  | HCM       | ND     |                  |      |                     |              |             |               |                |               |
| MC16  | HCM       | MYH7   | c.4130C>T        | 30/40| p.T1377M            | Missense     | P           | PS1, PM2, PP3, PP5 | NM_000257.3 | rs397516201 |
| MC17  | ACM       | DSP    | c.1783C>T        | 14/24| p.Q595Ter           | Nonsense     | P           | PVS1, PM2, PP3 | NM_004415.3    |              |
| MC18  | LQTS      | KCNH2  | c.2453C>T        | 10/15| p.S818L             | Missense     | LP          | PM1, PM2, PP2, PP3, PP5 | NM_000238.3 | rs121912510 |
| MC19  | LQTS      | ND     |                  |      |                     |              |             |               |                |               |
| MC20  | LQTS      | ND     |                  |      |                     |              |             |               |                |               |
| MC21  | HCM       | FLNC   | c.1934A>C        | 12/48| p.D645A             | Missense     | VUS         | PM2, PP3      | NM_001458.4    |              |
| MC22  | HCM       | MYL3   | c.451G>A         | 4/6  | p.A151T             | Missense     | VUS         | PM2, PP3      | NM_000258.3    | rs869025486  |
| MC23  | LQTS      | KCNE1  | c.31_118del      | 3/3  | p.P11AfsTer24       | Frameshift   | LP          | PVS1, PM2     | NM_001270402.2 |              |
| MC24  | LQTS      | KCNH2  | c.2453C>G        | 10/15| p.S818W             | Missense     | LP          | PM1, PM2, PP2, PP3, PP4 | NM_000238.3 |              |
| MC25  | BrS       | SCN5A  | c.845G>A         | 6/28 | p.R282H             | Missense     | LP          | PM1, PM2, PM5, PP2, PP3, PP5 | NM_000335.5 | rs199473083  |

Abbreviations: LP, likely pathogenic; ND, none detected; P, pathogenic; VUS, variant of uncertain significance.
The patient had a nonsense variant classified as pathogenic in the DSP gene (MC17).

3.3 Severe events

Different severe events such as RSCA, appropriate ICD discharge, flutter and atrial fibrillation (AF), chest pain, dyspnea, syncope, and seizures were reported by several patients. Some of them presented a combination of the above, especially associated with syncope; some patients having up to three different events. In total, there were 33 events in 22 patients. Three patients did not have any severe event (12%). The most frequent events were RSCA and syncope, both with 30.3% (10 subjects), followed by appropriate ICD discharge in 15.15% (5), 6% for seizures, dyspnea and chest pain (2 subjects each), and finally 3% presented flutter or AF (1 subject each).

Symptoms and severe events were grouped based on loss of consciousness (Table 4). Loss of consciousness is present in RSCA, syncope, and convulsive events, whereas it is absent in other events. In the loss of consciousness group of patients, the mean age was 19.3 years compared to 33 years in the non-loss of consciousness group (p = 0.00288, Mann–Whitney). Patients with long QT syndrome were characterized by having most of the events, as well as the most severe events (Figure 1).

| Condition | Loss of consciousness | No loss of consciousness |
|-----------|-----------------------|--------------------------|
| ACM       | 33.5 ± 23.3           |                          |
| HCM       | 14.4 ± 8.9            | 37.6 ± 8                 |
| BrS       | 28.5 ± 4.9            | 32 ± 2.6                 |
| LQTS      | 17.5 ± 15.1           | 26.3 ± 6.1               |
| Total     | 19.3 ± 14.4           | 33 ± 7.7                 |

Note: Values are mean ± SD.
*Denotes a statistically significant difference.

TABLE 4 Age of presentation for severe events with and without loss of consciousness.

FIGURE 1 Severe events with or without loss of consciousness. Events with loss of consciousness were more representative for LQTS patients than other inherited cardiac conditions.

4 DISCUSSION

This study aimed to find the genetic variants responsible for channelopathies and cardiomyopathies in a sample of Colombian patients. Previously, a study in long QT syndrome in Colombia had been reported (Burgos et al., 2016). That study aimed to evaluate the performance of semiconductor whole-exome sequencing in a cohort of 21 patients clinically diagnosed with LQTS. They reported a 57% diagnostic yield which is similar to our report. We have used an extensive gene panel to analyze these conditions, since different publications suggest gene overlapping (Hertz et al., 2015, 2016) between channelopathies and cardiomyopathies including dilated cardiomyopathy, and that energy and matter interact to have a spectrum of clinical manifestation in patients (Olivotto & Coppini, 2018). In fact, one of our subjects was followed up by the cardiology department under a HCM diagnosis, with a prolonged QT interval subsequently found in the electrocardiogram, and a variant in KCNH2 identified.

Family history is always of great importance in genetic evaluation requiring a minimum of a three generations pedigree. It can raise the suspicion of a genetic condition, helps to identify an inheritance pattern and, to determine
at-risk relatives in gene-positive patients (Waddell-Smith et al., 2016). Nonetheless, a positive family history is not a requisite to request molecular testing. This decision should be made evaluating each individual case, particularly in those patients with a negative family background. In our study six of 25 subjects had a negative family history; of these, 33.3% had a positive genetic test, and 66.7% had a negative result. Among subjects with family history (19/25), 57.9% had a positive genetic test, 15.8% had VUS and 26.3% were negative. This supports the assumption that patients with a family history are more likely to have a likely pathogenic or pathogenic variant but does not exclude probands who do not have a positive family history.

Two likely pathogenic / pathogenic variants not previously reported at the time in the literature or in databases (gnomAD/ ClinVar), were found in three patients. A non-sense variant of the DSP gene (c.1783C>T) found in a patient with ACM. He presented a dilated right ventricle with preserved function identified by echocardiography. Left cardiac catheterization reported ventricular dysfunction, global hypokinesia and normal coronaries. This is consistent with reports of biventricular compromise in DSP-related disease (Austin et al., 2019; Castelletti et al., 2017).

Two patients had a likely pathogenic variant identified in the KCNE1 gene (c.31_118del p.P11AfsTer24), being considered a LQTS type 5. This 87 nucleotide deletion changes a proline for alanine at amino acid 11 in the protein (p.P11AfsTer24) with a frameshift and a stop codon at position 24. The KCNE1 protein functions as a regulatory subunit of KCNQ1 forming a complex with calmodulin and the lipid PIP2 that modulates the biophysical properties of the potassium channel. Recently, some genes involved in LQTS have been disputed as disease-causing, one of them being KCNE1. Adler et al. (2020) classified KCNE1 as limited support for congenital LQTS, while it was given a strong support rating for acquired LQTS. However, KCNE1 has been associated with LQTS since the 1990s. The fact that these conditions have incomplete penetrance is not unknown and this varies from gene to gene. In the multicenter international evaluation of LQT5, it was concluded that loss of function variants had low penetrance (20%) and phenotype-positive individuals with a variant in this gene probably have other genetic or environmental factors that predispose to QT prolongation. In contrast to KCNE2 (OMIM #603796), KCNE1 QT prolongation and clinical events occurred in most individuals in the absence of a QT-prolonging stressor, suggesting that LQT5 should be considered a primary arrhythmic condition of low penetrance rather than an exclusively provoked syndrome (Roberts et al., 2020). This KCNE1 variant (p.P11AfsTer24) was classified as likely pathogenic since there are no population frequencies reported and because loss of function is a known mechanism for this disease. It would be important to determine the penetrance for this variant by performing family segregation studies. Patient MC23 had a paternal cousin with LQTS diagnosis and another cousin with torsades de pointes on the maternal side. Given the positive family history on both sides of her family, the low penetrance of LQTS type 5 and higher prevalence and penetrance in other genes, we recommended a gene panel for her cousin diagnosed with LQTS instead of a point mutation analysis, since the absence of the variant will not be enough to rule out a genetic component.

A male patient (MC09) carrying a PRKAG2 (p.H401Q) variant was originally classified as a VUS. However, recently, the same variant has been identified through segregation analysis in a family from Brazil, and an additional report has been published involving the same codon but with different amino acid change (H401D); (Albernaz Siqueira et al., 2020; Hu et al., 2020). Therefore, we classified this variant as likely pathogenic. Porto et al. (2016), described the red flags to suspect a non-sarcomeric cardiac hypertrophy associated with PRKAG2, several of them present in our proband: diagnosis between the first and fourth decades of life, bradycardia, high-voltage electrocardiogram, supraventricular arrhythmias (flutter), signs of chronotropic incompetence (tachycardia-bradycardia syndrome) and early-onset high blood pressure. Concentric hypertrophy is more related to non-sarcomeric hypertrophy; however, our patient had an obstructive asymmetric pattern.

Three patients with HCM had VUS. One of them could be a candidate for genetic testing cascade, a female with an intronic variant in TNNT2 (c.851 + 5G > A). This change is presumed to alter a conserved nucleotide located near a canonical splicing site and thus could affect the splicing of messenger RNA, resulting in a significantly altered protein sequence. Functional studies are difficult to perform for TNNT2 due to the cardiac tissue specificity, which would require a ventricular biopsy. She had an asymmetric hypertrophy and has had flutter episodes. A meta-analysis observed that 33% of patients with variants in TNNT2 showed supraventricular tachycardias, including atrial fibrillation and flutter (Sedaghat-Hamedani et al., 2018). Family history is significantly predominant in men; her father had AF, and a paternal uncle and cousin are diagnosed with HCM (Figure 2). There is a predominance of male patients described in the literature with mutations in the cardiac troponin T gene, suggesting the existence of susceptibility factors to HCM associated with gender that may include hormonal, lifestyle, or endocrine characteristics. In mouse models, it has been studied that estrogen can inhibit cardiac hypertrophy through epigenetic modifications,
which may explain a delay in the onset of the disease or less affected in this reduced penetrance condition (Pedram et al., 2013). The Patient has a healthy child and four subsequent pregnancy losses without a known cause.

Although the sample size analyzed in this report was small, it is important to note that even though patients diagnosed with LQTS are the ones with most clinical events, and all individuals presented loss of consciousness at some point, their diagnosis was significantly delayed (10.1 years) compared to HCM (2 years) ($p < 0.01$). Patients with likely pathogenic and pathogenic variants presented twice as many events of any kind and twice as many RSCA compared to patients with a negative test in the panel. The association between LQTS and events during exercise is well known (Cheung et al., 2016; Mascia et al., 2018). In our study, all patients with LQTS who presented any event while exercising, had a pathogenic or likely pathogenic variant.

To our knowledge, this is the first study to investigate patients with cardiomyopathies and channelopathies in Colombia. Overall, most of our patients had HCM; however, LQTS presented most of the severe events and were more likely to have a RSCA or other loss of consciousness events occurring during exercise or everyday-like activities. Time to properly diagnose LQTS was significantly higher compared to other conditions. Our pilot results show the importance and impact that a cardiogenetic registry could have in our country to identify individuals at risk and avoid preventable deaths.

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**AUTHOR CONTRIBUTIONS**

Cynthia Rucinski: Conceptualization, Investigation, Methodology, Formal Analysis, Writing-Original Draft Preparation, Writing-Review & Editing. Luz Karime Yunis: Conceptualization, Investigation, Methodology. Fernando Rosas: Conceptualization, Resources, Methodology, Supervision. David Santacruz: Conceptualization, Methodology. Juan Manuel Camargo: Conceptualization, Methodology. Juan José Yunis: Conceptualization, Funding Acquisition, Project Administration, Resources, Supervision, Visualization, Writing-Review & Editing.
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CONFLICT OF INTEREST
The authors, CR, LKY, FR, DS, JMC, and JJY do not have any conflicts of interest to declare.

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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