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Prevalence of Genetic Variants Associated with Sudden Cardiac Death in a Population Sample in Colombia

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Abstract

Cardiac channelopathies and cardiomyopathies are a group of cardiac disorders, they can be of both heritable and acquired genetic origin, which predispose affected individuals to sudden death as a result of changes in the expression or posttranslational modification of ion channels or alterations in associated proteins within the heart. 68 cases associated with sudden cardiac death were analyzed using the TruSight™Cardio sequencing panel, which contains 174 genes associated with heart disease. Variant filtering was performed taking into account the recommendations of ACC/AHA/ESC 2006, HRS/EHRA 2011 and HRS/EHRA/APHRS 2013. The study found a prevalence of cardiomyopathies of (40.6%), familial hypercholesterolemia with (5.4%), and cardiac channelopathies with (54%), in addition to the total of variants, 1.82% present conflict of interpretation of pathogenicity and 2.19% of uncertain significance, which should be studied in more detail in the future.

Keywords: Heart diseases, Molecular autopsy, NGS and Prevalence

Introduction

Cardiac channelopathies and cardiomyopathies are a group of cardiac disorders, they can be of both heritable and acquired genetic origin, which predispose affected individuals to sudden death as a result of changes in the expression or post-translational modification of ion channels or alterations in associated proteins within the heart [1-4].

It has been estimated that the prevalence of these types of disorders ranges from 1 in 2,000 to 1 in 3,000 people [5] and that they represent approximately one third of unexplained diseases in cases of sudden cardiac death (SCD) [2,6]. However, these rates may be an underestimate because many people are misdiagnosed, as channelopathies can occur at the brain level as in cases of epilepsy [7] or are not diagnosed before death from sudden cardiac arrest [8].

SCD can occur in children, adolescents, and young adults within minutes of the onset of cardiac symptoms [9]. Recent studies have found that about 30% of negative autopsies in young individuals (<15 years) could possibly be explained by pathogenic variations in channelopathies-related genes [10]. Additionally, it has been found that approximately two-thirds of survivors of sudden cardiac arrest are subsequently diagnosed with a channelopathy condition [6]

The most prevalent cardiac channelopathies are long QT syndrome (LQTS) [11], Brugada syndrome (BrS) [12], short QT syndrome (SQTS) [13] and catecholaminergic polymorphic ventricular tachycardia (CPVT) [14].

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In recent years, technological advances in the field of genetics have facilitated the implementation of gene panels for the detection of mutations, in a short period of time [15]. The application of this technology to cardiology has facilitated the identification of several key genes associated with SCD. As a result, genetic testing has been progressively incorporated into clinical diagnosis, helping to identify the cause of disease in clinically affected patients and in unresolved postmortem cases, as well as to identify risk factors in asymptomatic carriers [10].

In Colombia, there are no studies to determine the molecular basis of deaths that occur due to cardiac arrhythmias, therefore, there is a lack of information on the prevalence of specific mutations capable of producing sudden cardiac death due to this cause, so research in this field is of utmost importance.

In the first place, epidemiologically, it will contribute to refine the diagnosis of hereditary diseases capable of causing lethal arrhythmias, with the consequent genetic counseling that can be derived from this fact for family members. Secondly, it will generate knowledge for teaching and to help the diagnosis of carriers of these conditions; and thirdly, it will establish the bases and parameters for molecular tests in medical-legal autopsies [16] or hospital autopsies that fail to clarify morphologically the cause of sudden cardiac death, to provide a much more accurate diagnosis. The objective is to indirectly determine the genetic prevalence of channelopathies from cases of sudden death by analyzing the distribution of variants identified by the exome study, as well as those reported in other populations.

Methodology

A systematic review of 511 necropsy protocols (years 2015 to 2020) was carried out, taking into account they were negative in structural coronary heart diseases, microscopically normal cardiomyocytes, negative for toxicology and virology. Finally, 68 cases were selected for analysis.

DNA extraction from blood was performed using the QIAamp®DNA Blood Midi/Maxi kit, following the manufacturer's recommendations. The quantification of DNA and libraries was performed using the Quantitating dsDNA kit using the Quantus™ Fluorometer instrument and following the manufacturer's recommendations.

The sequencing panel used was the TruSight™Cardio, which contains 174 genes associated with heart disease. Following the manufacturer's specifications.Four alignment algorithms Bowtie2, BWA-MEM and NovoAlign and three variant call analysis tools (HaplotypeCaller (GATK-HC), Samtoolsmpileup and Freebayes) were used.

The annotation of detected variants was carried out using the bioinformatic tools SnpEff and ANNOVAR, and in silico predictors: SIFT, PolyPhen2, LRT, Mutation Taster, MutationAssesor, FATHMM, MetaSVM) and the conservation of residues between species (GERP++, PhyloP, SiPhy).Variant filtering taking into account the recommendations of the ACC/AHA/ESC [17], HRS/EHRA [1], and HRS/EHRA/APHRS [18].

Haplotype Estimation

The estimation of possible haplotypes from genotype data was performed using the EM algorithm of the haplo.stats library of R's SNPassoc. The genotypes were encoded in make.geno format. The haplo.em function was used to calculate the frequency of haplotypes in the Variants of Interest data. The other analyses were carried out by creating pivot tables in Excel allowing the summary of the information through graphs.

Results and Discussion

It was constructed in hetmap in R, in order to better observe the typification of each of the variants associated with cardiovascular diseases (Figure 1). The variation observed is given by the age spectrum of individuals, with ranges from 2 months to 40 years.

Estimation of haplotypes

When observing the distribution plot of variants (Figure 1), I draw attention to four variants to which an estimation of haplotypes was made, (rs181494964, rs3741315 and rs7124127) of the SCNAB gene, slightly benign, associated with Brugada syndrome type 4 and cardiovascular phenotype; LQTS syndrome and Romano-Ward syndrome; and (rs743547) TAZ gene, benign associated with Barth syndrome Noncompact cardiomyopathy of the left ventricle, Dilated cardiomyopathy 3B. Mutations in TAZ, leads to severe cardiolipin deficiency leading to respiratory chain dysfunction, pathogenic variants can be lethal and that is why this gene has been included within the group of genes associated with sudden cardiac death in children under 2 years, the age of survival to Barth syndrome is between 3 years and 13 years of age [19].

In table 1, common alleles and variants are coded as 1 and 2, the presence of several possible haplotypes can be seen among the subjects and listed with an estimated frequency of haplotypes. Clearly, haplotypes are not as likely as expected from the high DL among the Variants. The most likely haplotypes are highlighted in gray. *Haplo.em* estimates for each subject the probability of a given haplotype on each of the subject's chromosomes.

Detected variants

Once the different filters were made and taking into account a MAF ≤ 0.05, for population frequencies in a thousand genomes, Emone_AD and Genome_AD, and following the recommendations to classify the variants according to the ACMG, 29 variants were found in 19 genes.

The following variants are observed: exonic (12), UTR3 (7), UTR5 (2) and Splicing (2). Additionally, the exonic stop variant (c.C20497T:p. R6833X) is observed.

The TMEM43 gene (NM_024334:c.-142G>A), was found in 13 cases, this variant is interesting. TMEM43 is a transmembrane protein with four domains and variants in this gene have been reported to cause arrhythmogenic cardiomyopathy (ACM) [20,21]. Recently, an exome study identified the autosomal dominant TMEM43:p.S358L variant in a family with MCA in which 10 affected individuals had died suddenly [22],suggesting that more comprehensive functional studies of these variants should be conducted in MSME4.

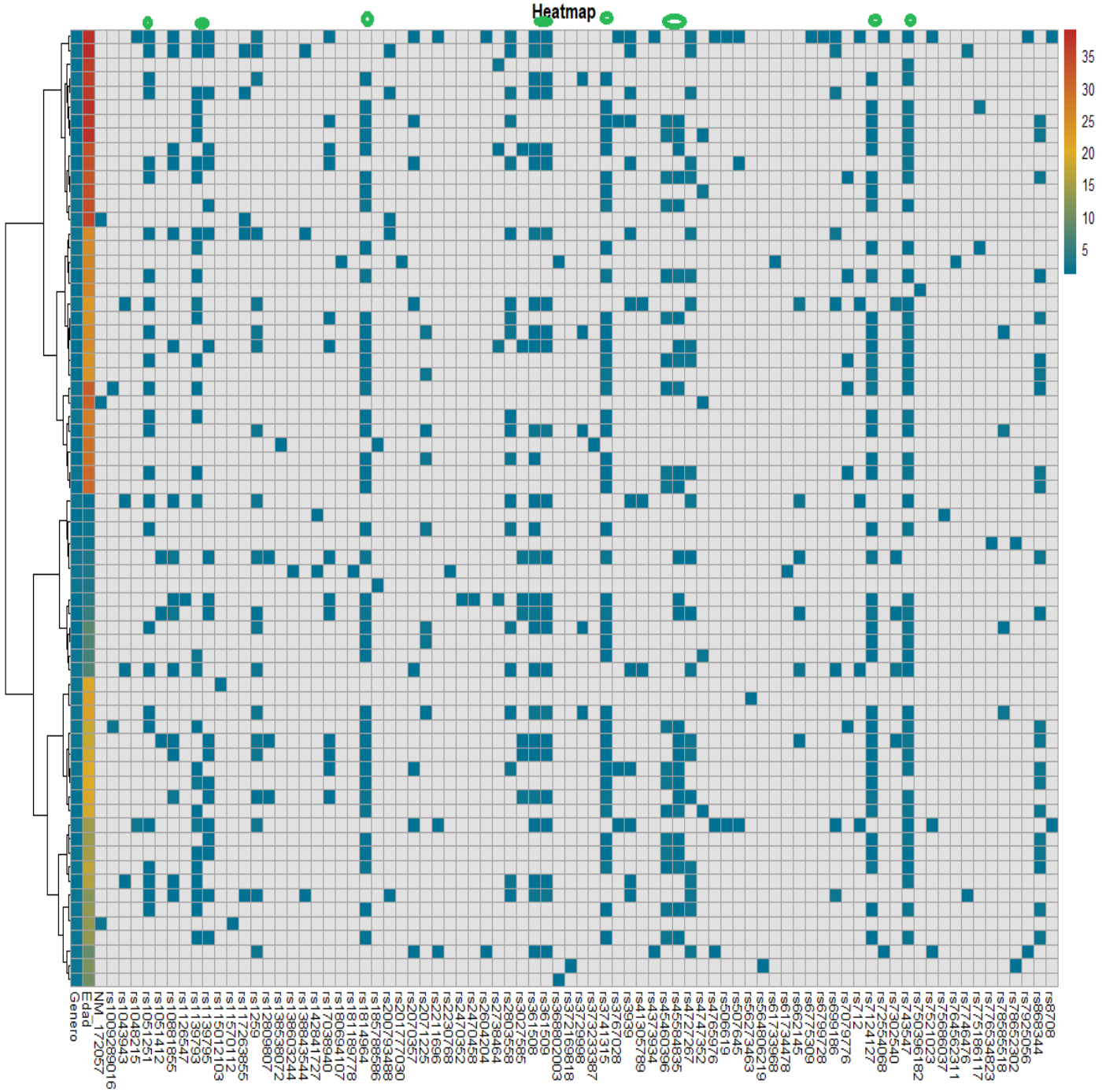

Figure 1: Distribution of the typified variants for each of the individuals analyzed.

The TMPO gene (NM_001032283:c.*1A>G) in three cases, TMPO encodes the LAP2 proteinα, β which contributes to the regulation of the cell cycle and the organization/expression of the genome [23]. Variants in this gene are associated with cardiomyopathies [24]. In the study conducted by Vadrot N. et al., they found the rare variants TMPO (p.(Gly395Glufs*11), p.(Leu124Phe), p. (Ala240Thr) and the frequent variant (p.Arg690Cys) and within silico studies validated the pathogenicity of the three rare variants [25]. With the above, it is confirmed that the variants in POMT are associated with cardiomyopathies, and the gene should be taken into account in the analysis of cases associated with sudden cardiac death.

In the SELENON gene (NC_000001.11:25809790:C>T) in one case, SELENON is a transmembrane protein located in the endoplasmic reticulum [26], variants in this gene have been associated with congenital myopathies, systolic dysfunction of the right ventricle secondary to pulmonary insufficiency and arrhythmias [27,28]. In Zhang S,'s study. et al., evidenced three new SELENON variants (c.1286_1288 of CCT, c.1078_1086dupGGCTACATA and c.785 G>C), additionally suggest that this gene should be considered as differential diagnosis in adult patients with delayed respiratory compromise [29].

Table 1: Estimation of haplotypes for the variants: rs1814964, rs3741315, rs7124127, and rs743547 using the *haplo.em* library in R.

Haplotypes					
a)	**rs1814964**	**rs3741315**	**rs7124127**	**hap.freq**	**Details**
1	1	1	1	0.37805	lnlike = -3993803
2	1	1	2	0.00000	lr stat for no LD = 193.2914
3	1	2	1	0.00000	df = -1
4	1	2	2	0.02439	p-val = NA
5	2	1	1	0.00000	
6	2	1	2	0.00000	
7	2	2	1	0.00000	
8	2	2	2	0.59756	
b)	**rs1814964**	**rs7124127**	**rs743547**	**hap.freq**	
1	1	1	1	0.07809	lnlike = -69.41279
2	1	1	2	0.27870	lr stat for no LD = 68.84967
3	1	2	1	0.01445	df = 2
4	1	2	2	0.01046	p-val = 0
5	2	1	1	0.00000	
6	2	2	1	0.57401	
7	2	2	2	0.04429	
c)	**rs3741315**	**rs7124127**	**rs743547**	**hap.freq**	
1	1	1	1	0.08036	lnlike = -62.95481
2	1	1	2	0.27737	lr stat for no LD = 98.32257
3	1	2	1	0.00000	df = 0
4	2	1	1	0.00000	p-val = NA
5	2	2	1	0.58525	
6	2	2	2	0.05701	
d)	**rs3741315**	**rs1814964**	**rs743547**	**hap.freq**	
1	1	1	1	0.07829	lnlike = -69.47916
2	1	1	2	0.27925	lr stat for no LD = 70.2575
3	1	2	1	0.00000	df = 2
4	2	1	1	0.01396	p-val = 0
5	2	1	2	0.01016	
6	2	2	1	0.57406	
7	2	2	2	0.04428	

The TNNT2 gene (NM_001001432:c.*66G>A) in five cases, TNNT2 synthesizes cardiac troponin T, variants of this gene are the third cause of HCM, increases the sensitivity of Ca^{2+} myofilaments and causes arrhythmogenesis [30]. Additionally, variants in TNNT2 are also associated with an increased risk of ventricular arrhythmogenesis and sudden death despite causing little or no cardiac hypertrophy especially in youth and young adults [31].

In TPM1 (NM_001018020:c.*119T>C) in three cases, TPM1 produces α-tropomyosin, important in the assembly of sarcomeric actin, is found in cardiac muscle tissue and plays a key role in allowing muscles to contract, variants in this gene have been associated with DCM, HCM, LVNCM and RCM [32-34]. For this gene more than 30 variants have been reported that include nonsense, reading change due to deletion variants. In the study by Man YMS., et al., report the novel heterozygous c.340G>C variant in a Chinese family [34], the authors comment that this mutation increases the local positive charge in a negatively charged and highly conserved region of the molecule.

In SCN4B (NM_001142349:c.*1071T>C) in five cases, sub-unit β4 of the sodium channel, it is a regulatory protein in cardiac tissue and plays a crucial role in cell adhesion, signal transduction, channel expression in the sarcolemma and channel gate voltage dependence [35,36].Variants in this gene have been associated with LQTS, BrS and familial atrial fibrillation.

In KCNE3 (NM_005472:c.*1383C>T) in two cases, KCNE3 is a transmembrane subunit expressed in the heart and linked to cardiac arrhythmias mainly as LQTS and BrS; Present together with other subunits in the formation of potassium channel pores [37,38].

In CASQ2 (NM_001232:c.*503G>A) in two cases, CASQ2 is a calcium-binding protein located in the sarcoplasmic reticulum of cardiac cells and slow skeletal muscle. Variants in this gene cause stress induced CPVT [39,40].

For the CASQ2, KCNE3, SCN4B, SNTA1, TMEM43, TMPO, TNNT2 and TPM1 genes, although the variants found were in 3UTR and 5UTR, genetic variations in these regions can modify the regulatory elements that affect the interaction of UTRs with proteins and microRNAs. General functional consequences include modulation of mRNA transcription, secondary structure, stability, localization, translation, and access to regulators such as microRNAs and RNA-binding proteins [41-43], these alterations modify molecular pathways and cellular processes, which can lead to pathological processes. These regions turn out to be important for investigating the impact of changes in the function of ion channels and associated proteins on genetic predisposition to the risk of sudden unexpected death.

It is observed in figure 2, that the slightly benign variants (56.10%) were the most found, followed by variants with benign (20.77%), variants with benign / slightly benign (17.30%) among the most representative.

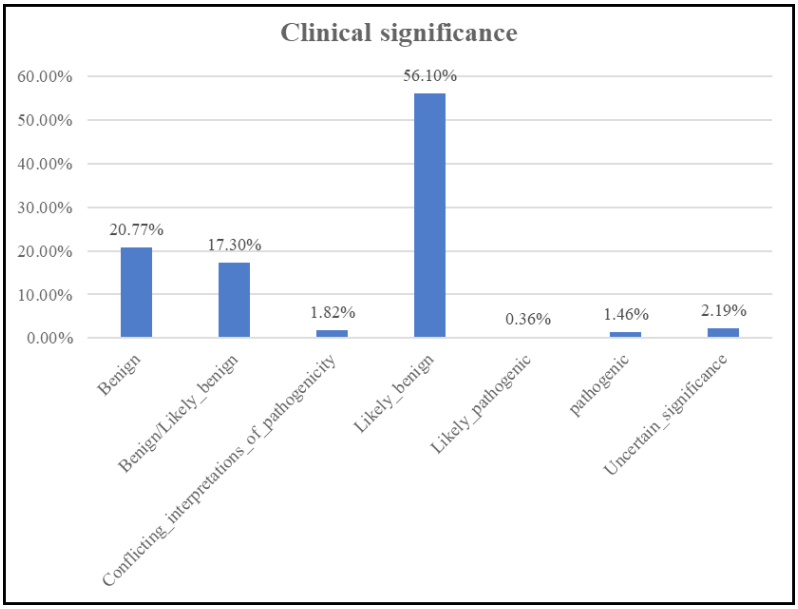

Figure 2: Percentage of clinical significance of the typified variants that passed the filters.

With respect to variants of uncertain significance they represent about 40% of the total variants [44], they are a great challenge and generate dilemma for clinicians and uncertainty about how to provide advice to patients and this is further complicated when addressing complex diseases such as cardiac channelopathies [45].

Oulas, A and collaborators, developed the software VariantClassifier (VarClass), which selects informational variants of uncertain significance through associations based on gene networks, which allows: a) provide new associations between variants previously cataloged as of uncertain significance and the disease, b) allows the detection of variants that act synergistically, Providing a more realistic view of the variability of complex diseases, c) allows for more accurate risk prediction for cohorts of genetic variation of diseases, with the selection of variants of uncertain significance that may be informative [46].

Regarding the variants that present conflict of interpretation of pathogenicity, in silico studies should be carried out with the different pathogenicity prediction algorithms, functional prediction algorithms, evolutionary conservation data that allow the identification of highly conserved functional regions, protein-protein interaction analysis, among others [47-49].

Regarding the different phenotypes, figure 3, there is great genetic heterogeneity and variable expression in heart disease. This may be due to the

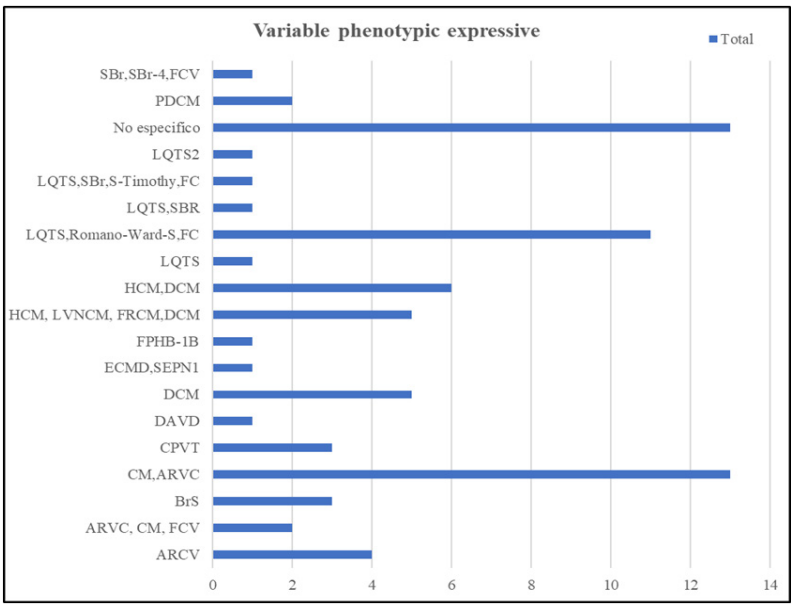

Figure 3: Phenotypes of the different variants found.

involvement of numerous cell types and complex combinations of interacting molecular species, and the manifestation of interrelated diseases such as HCM which has more than 200 variants in at least 11 genes encoding cardiac sarcomere proteins [50]. Additionally, it has been estimated that the prevalence of HCM is approximately 2.5 times higher than that observed clinically in echocardiographic studies [51,52]. On the other hand, studies show that some HCM mutations considered causal are observed with different frequencies compared to controls in certain ethnic groups [53].

On the other hand, HCM encompasses a broad spectrum of diverse endophenotypes that do not depend on the pathobiology of sarcomeres. An example may be mitral valve lengthening, myocardial replacement fibrosis, and hypertrophic remodeling of intramural coronary arteries, among other abnormalities involving cell types that do not express cardiomyocyte sarcomere proteins, which have been observed to varying degrees in individual patients with HCM [54]. Other examples of genetic heterogeneity in the pathogenicity of dilated left ventricular cardiomyopathy and left ventricular noncompaction cardiomyopathy caused by variants in the TTN gene have also been found [55,56].

It has been estimated that the cumulative effect of common variants interacts with environmental factors and determines susceptibility as occurs in heart failure which is a multifactorial disease [57]. The different phenotypes of cardiomyopathies can be caused by mutations in the numerous genes described, however, even mutations in the same gene associated with the disease can cause a distinct quantitative variability in the expression of the cardiomyopathy phenotype [58,59]. Therefore, different mutations within a specific gene can cause different functional effects, producing different phenotypes (variable expressiveness and penetrance imply that factors beyond individual pathogenic mutations (genetic, epigenetic or environmental modifiers) can influence the phenotype and is an as yet unexplored field that should be taken into account in future work.

In our study, we found different variants associated with heart diseases such as hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia, and cardiac channelopathies such as long QT syndrome (LQTS), short QT syndrome (TCTS), Brudaga syndrome (SBr), catecholaminergic polymorphic ventricular tachycardia (CPVT), which have been reported in other studies [17,18,60-62].

On the other hand, it has been studied that ion channels can function as parts of large macromolecule complexes that play crucial roles in transcription, translation, post-translational modification, degradation of all cardiac ion channels, multiprotein assemblies, among others, hence the large number of variants reported give rise to the genetic heterogeneity of this type of arrhythmogenic diseases as they are generally known [63-65].

After performing additional filters taking into account the frequencies with a MAF < 0.05 in the database of one thousand genomes, a total of 43 variants in 27 genes were found in this study in 45 cases from which some variant(s) associated with heart disease (cardiomyopathies and channelopathies) were obtained, being the TTN gene (11), AKA3 (3), KCNH2, DSP, CACNA1C and AKAP9 with 2 variants respectively.

For the KCNH2 gene, in two cases a variant was found in heterozygous state (NM_172057:exon7:c.1672+2T), for this gene was reported in a previous case study in Colombia the homozygous variant (exon2:c.G275C:p.R92P) associated with SQTC [48].

Although, the phenotype and risk depend on the gene, with current knowledge it has been seen that there are groups of variants that share similar characteristics and functional effects, hence the importance of conducting other complementary studies, although in cases of sudden cardiac death, co-segregation studies are proposed to confirm the presence of the variant, In the case of molecular autopsies, there is no access to relatives, making it difficult to deal with these cases, however computational tools can overcome this limitation [66].

Taking into account that 68 cases were processed in total, it was found that 39.7% of cases presented some variant for cardiomyopathies and 26.47% of variant cases for cardiac channelopathies. In a 2016 study by Bagnall R., et al, in 490 cases analyzed, they found that 24% were due to coronary artery disease, 16% of cases to hereditary cardiomyopathy and 40% to sudden unexplained death [67]. The pathogenicity of the variants was evaluated, using multiple tools, such as databases of the 1000gemomas project and Genome and exome AD, bioinformatics tools and different pathogenicity prediction algorithms.

Limitations in this study include the lack of postmortem lipid profiles, the inability to functionally test the pathogenic or probably pathogenesis variants found and the ability to perform complementary studies of co-segregation due to lack of relatives.

Conclusion

In this study, a prevalence of variants in the main genes associated with heart disease, cardiomyopathies with (40.6%), familial hypercholesterolemia with (5.4%), and cardiac channelopathies with (54%) was found, in addition to the total of variants, 27% present conflicts of interpretation of pathogenicity that should be studied in more detail in the future.With the retrospective cohort study of sudden death, a relatively high incidence of unknown genetic heart disease can be determined, and even more so if they have a familial component. With this research, the foundation is laid for the importance of including molecular autopsy in all victims of SUD. Additionally, it should be established with an interdisciplinary group, for genetic counseling that can be provided to family members in order to prevent future cases of SUD. There are several issues that need to be addressed in the future, including the implementation of national guidelines for the investigation of sudden cardiac death autopsies in forensic medicine, the recommendation of a molecular genetic screening panel, and the implementation of a standardized approach to the collection of epidemiological data in cases of sudden unexpected death.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics Statement

Ethical approval for this study was granted by the local committee of the Faculty of Sciences of the National University of Colombia. Principles contained in the updated Declaration of Helsinki were followed, and the use of forensic samples for the purposes of research and teaching of the National Institute of Legal Medicine and Forensic Sciences.

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Author Contributions

All authors researched data for the article, discussed its content, and wrote, edited, and reviewed the manuscript.

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