UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE:
CARDIOLOGIA E CIÊNCIAS CARDIOVASCULARES

THAÍS MARIEL ANDARA BEUREN

CARACTERIZAÇÃO GENÉTICO-CLÍNICA DE PACIENTES COM CARDIOMIOPATIA HIPERTRÓFICA NO SUL DO BRASIL

Porto Alegre

2024

THAÍS MARIEL ANDARA BEUREN

CARACTERIZAÇÃO GENÉTICO-CLÍNICA DE PACIENTES COM CARDIOMIOPATIA HIPERTRÓFICA NO SUL DO BRASIL

Tese apresentada ao Programa de Pós-Graduação em Cardiologia e Ciências Cardiovasculares da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul como requisito parcial para a obtenção do título de Doutor em Cardiologia.

Orientador: Prof. Dr. Ricardo Stein

Porto Alegre

2024

CIP - Catalogação na Publicação

Andara Beuren, Thais Mariel
CARACTERIZAÇÃO GENÉTICO-CLÍNICA DE PACIENTES COM CARDIOMIOPATIA HIPERTRÓFICA NO SUL DO BRASIL / Thais Mariel Andara Beuren. -- 2024.
108 f.
Orientador: Ricardo Stein.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares, Porto Alegre, BR-RS, 2024.

1. Cardiomiopatia hipertrófica. 2. Genética. 3. Cardiologia. I. Stein, Ricardo, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

THAÍS MARIEL ANDARA BEUREN

CARACTERIZAÇÃO GENÉTICO-CLÍNICA DE PACIENTES COM CARDIOMIOPATIA HIPERTRÓFICA NO SUL DO BRASIL

Tese apresentada ao Programa de Pós-Graduação em Cardiologia e Ciências Cardiovasculares da Universidade Federal do Rio Grande do Sul como requisito parcial para a obtenção do título de Doutor em Cardiologia.

BANCA EXAMINADORA

Prof. Dr. Felipe Costa Fuchs
Prof. Dr. Fernando Luis Scolari
Prof. Dr. Mário Wiehe

Aos meus pais Ricardo e Eliane que, ao meu lado incondicionalmente e atravessando continentes, me ensinaram a nunca desistir e a levantar após cada queda.

Ao meu marido Lucas pelo apoio incondional, paciência e amor.

Aos meus irmãos Athos, Stéphanie e meu sobrinho-irmão Eduardo pelo incansável esforço de tornar o caminho sempre mais leve e colorido.

Às minhas avós Nazi (in memoriam) e Ivone, as mulheres mais corajosas que já conheci, que me ensinaram determinação e resiliência, sem nunca perder a ternura.

AGRADECIMENTOS / ACKNOWLEDGMENTS

À Deus, que está sempre à frente da minha caminhada.

Ao meu orientador, Prof. Ricardo Stein, pela dedicação e confiança em abraçar a ideia de um projeto difícil e inovador.

Ao meu orientador e mentor durante o tempo de PhD na Universidade de Amsterdam, Prof. Peter van Tintelen, por dividir comigo ensinamentos de sua mente brilhante e também de seu coração incrivelmente bondoso, acolhedor e humilde.
Aan mijn supervisor and mentor tijdens mijn PhD aan de Universiteit van Amsterdam, Prof. Peter van Tintelen, voor het delen met mij van de leringen van je briljante geest en ook van je ongelooflijk vriendelijke, gastvrije en nederige hart.

Ao Dr. Fernando Scolari, por me apoiar durante todo o período do programa, me receber e incluir nas atividades do ambulatório de cardiomiopatia hipertrófica e demais atividades de cardiogenética.

Aos mestres e colegas cardiologistas do Hospital São Lucas da PUCRS, em especial Prof. Mário Wiehe e Prof. Luiz Carlos Bodanese, que me incentivaram e me apoiaram nesse projeto em meio ao cenário desafiador da residência médica de cardiologia.

Aos meus colegas e amigos da Universidade de Amsterdam, da Medicina Nuclear do Hospital Moinhos de Vento e da UTI cardiovascular do Hospital Unimed Vale dos Sinos, por me apoiarem e ajudarem em momentos cruciais, os quais possibilitaram a conclusão desse projeto.

Ao Programa de Pós-Graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares, na pessoa de sua coordenadora Carisi Anne Polanczyk e vice-coordenadora Andreia Biolo

Finalmente, aos pacientes e suas famílias, que aceitaram e se dispuseram a participar desse projeto inovador, por vezes me recebendo e se deslocando para viabilizar coletas de material e/ou dados.

ABBREVIATIONS

ACC	American College of Cardiology
ACMG	American College of Medical Genetics
AHA	American Heart Association
ACP	Artificial Cardiac Pacing
CAAE	Certidão Apresentação Apreciação Ética
CMH	Cardiomiopatia hipertrófica
CRT	Cardiac resynchronization therapy
ECG	Eletrocardiogram
ESC	European Society of Cardiology
HCM	Hypertrophic cardiomyopathy
ICD	Implantable cardioverter defibrillator
LGE	Late gadolinium enhancement
LV	Left ventricle
LVED	Left ventricle end diastolic
LVEF	Left ventricle ejection fraction
LVES	Left ventricle end systolic
LVOTO	Left ventricle outflow tract obstruction
MYBPC3	Myosin binding protein C3
MYH7	Myosin heavy chain 7
NNT	Number needed to treat
SCD	Sudden cardiac death

RESUMO

Introdução - A cardiomiopatia hipertrófica (CMH) é a doença cardiovascular hereditária mais prevalente no mundo e a identificação da sua etiologia genética primária é essencial para adequada assistência a pacientes e seus familiares. Apesar disso, o Brasil ainda se encontra em fase de desenvolvimento na área da cardiogenética e são poucas as informações disponíveis relacionadas ao perfil genético dos pacientes com CMH. **Objetivo -** Caracterizar o perfil genético-clínico de uma amostra populacional de pacientes com CMH do sul do Brasil. **Métodos –** Estudo observacional transversal conduzido uma em coorte de 80 pacientes diagnosticados com CMH, incluindo alguns de seus familiares. Nesse estudo, foi realizado sequenciamento massivo paralelo para a genotipagem utilizando painel genético que abrange 100 genes. Além disso, foram coletadas variáveis clínicas para possibilitar análise detalhada de prevalência e comparação entre os dados obtidos. **Resultados –** Os genes que apresentaram maior prevalência de alterações na população estudada foram o *MYH7* e *MYBPC3*. Embora não tenha sido identificada diferença significativa nas comparações realizadas, observou-se maior frequência de arritmias ventriculares em indivíduos com variantes no gene *MYBPC3.* Além disso, os pacientes com genótipo positivo apresentaram mais desfechos clínicos desfavoráveis quando comparados àqueles com genótipo negativo. **Conclusão –** A etiologia genética dos pacientes genotipados apresenta padrão semelhante ao observado em coortes internacionais, destacando-se uma prevalência ligeiramente maior no gene *MYH7*. Esse resultado é consistente com o perfil genotípico identificado nas outras poucas coortes brasileiras.

Palavras-chave: Cardiomiopatia; teste genético; genótipo-fenótipo

ABSTRACT

Introduction – Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disease and identifying its primary genetic causes is essential for providing appropriate support to patients and family members. Despite that, the field of cardiogenetics in Brazil is still emerging, resulting in limited information regarding the genetic profile of HCM patients. **Objective –** To characterize the genotype – phenotype relationships in a sample of HCM patients and family members from southern Brazil. **Methods –** A cross-sectional observational study was conducted involving a cohort of 80 patients with HCM and some of their relatives. Genotyping was performed using a genetic panel that included 100 genes, simultaneously with the collection of clinical variables for prevalence analysis and comparison. **Results –** The most prevalent genes identified were *MYH7* and *MYBPC3*. Even though no significant differences were found between the groups, a higher frequency of ventricular arrhythmias was observed in patients with variants in the *MYBPC3* gene. Additionally, patients with a positive genotype exhibited a higher frequency of worse clinical outcomes compared to those with a negative genotype. **Conclusion –** The genetic etiology of genotyped patients presents a similar pattern to that observed in international cohorts, with a slightly higher prevalence of *MYH7* gene. This finding is consistent with the genotypic profiles reported in the few other Brazilian samples.

Keywords: cardiomyopathy; genetic test; phenotype-genotype

TABLE OF CONTENTS

1. INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a primary cardiac disease, most often caused by sarcomeric gene pathogenic variants that follow an autosomal dominant inheritance pattern (1). It has a prevalence – once considered rare – currently estimated to be as high as 1 in 500 to 1 in 200 individuals (2), with a worldwide distribution and already identified in at least 50 countries (3). The disease is defined in index patients by an increase in the ventricular myocardium thickness of 15 mm or greater, measured by any imaging technique (echocardiography, cardiac magnetic resonance or computed tomography) that is not explained by abnormal loading conditions (4). It may lead to complications such as left-ventricle outflow tract obstruction (LVOTO), diastolic dysfunction and increased risk of ventricular arrhythmias (5). In first-degree relatives a ventricular wall thickness of 13 mm or greater already defines HCM diagnosis (6). The rise of research effort in the last decades evolved the perception of HCM exponentially. The first descriptions of Braunwald referred to the condition as a ‘functional aortic stenosis not amenable to surgical correction’ (7). The understanding of numerous aspects made HCM be recognized nowadays as the most common monogenic heart disease characterized by complex pathophysiology, heterogeneous phenotype and variable clinical course (8). It can be expressed in a wide spectrum that might range from a benign stable condition with normal life expectancy, progress to restrictive or dilated heart failure or to present with malignant arrhythmia and sudden cardiac death risk. So far, there are no tools able to predict which pathway the disease will course in each individual (2). Even though HCM pathophysiology is primarily determined by genetic abnormalities, not enough evidence supports the use of specific

genotypes to predict phenotype expression nor potentially devastating clinical outcomes. To improve patients and family members' assistance, further studies including extensive genetic profiling are needed worldwide. In Brazil, few data is available, therefore our main goal is to contribute to our population genetic and clinical characterization through massive parallel genotyping, done for the first time in a Brazilian HCM patients cohort.

2. JUSTIFICATION AND OBJECTIVES

Patients with genetic cardiomyopathies are poorly characterized in Brazil. Assistance to these patients and their family members still occurs in an incomplete and delayed manner, since the condition is often identified in a symptomatic and potentially advanced stage. Genetic screening is not routinely part of the clinical arsenal of cardiologists in our country, whether due to lack of financial resources and/or limited experience/knowledge/incentive in the area. Reinforcing its relevance, countries like the Netherlands already include genetic testing in the basic approach of the patient with a genetic cardiomyopathy and their families, as recommended by the guidelines. The prevalence of HCM in Brazil is comparable to other countries, so it deserves attention commensurate with its social impact. Our main goal is to characterize genetically and clinically, using massive parallel sequencing for the first time, patients with HCM and variant carriers followed in one of the main healthcare centers in southern Brazil. In parallel, we aim to create a database containing clinical characteristics to enable additional genotype-phenotype analysis. We believe this study could represent an important step towards a cardiogenetics advance in Brazil, opening doors for future projects to improve care of HCM patients and family members.

3. METHODS

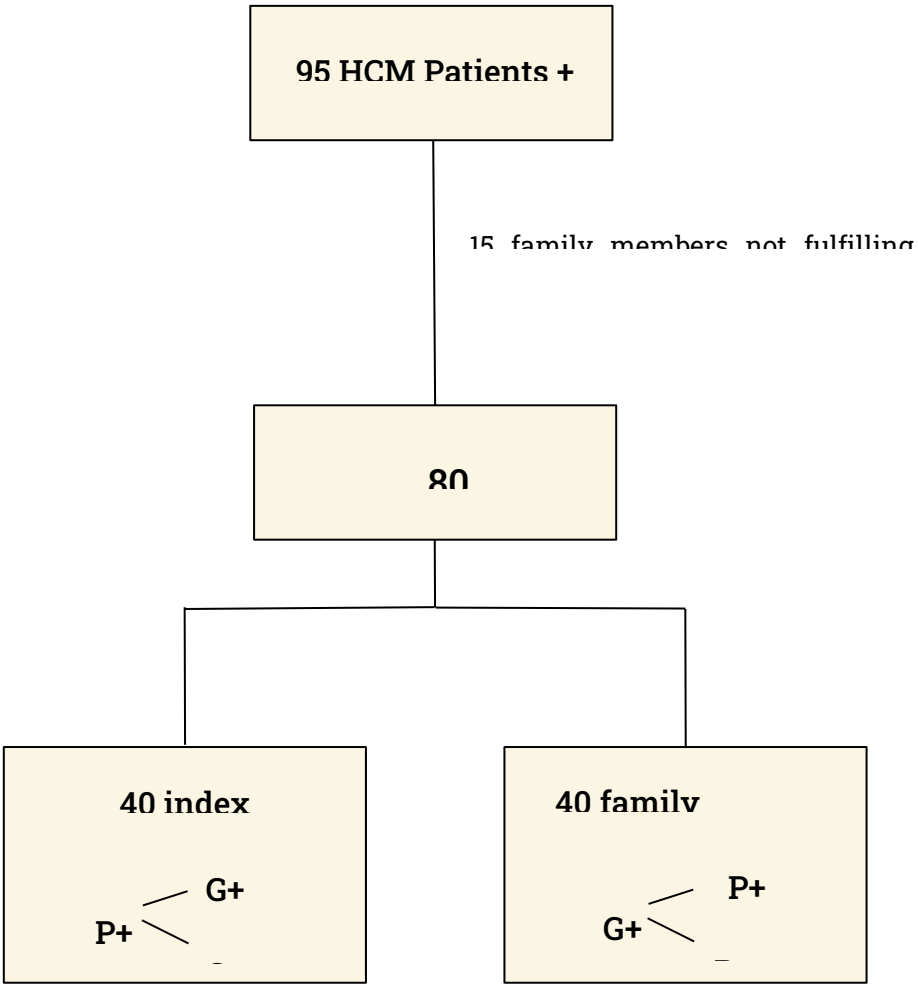
3.1 Ethics committee approval

This study was approved by the ethics committee of Plataforma Brasil, with the Ethical Appraisal Presentation Certificate (CAAE) number : 554413421.4.1001.5327.

3.2 Participants

Participants were selected from outpatients cardiology clinics of Hospital de Clínicas de Porto Alegre (HCPA) in Porto Alegre, Brazil. Initially, 95 individuals amongst HCM affected patients and their relatives were selected. After genetic screening, family members not fulfilling criteria for HCM or genetic variant identification were excluded (n=15). In total, 80 HCM patients and some of their relatives were included, being 40 non-related index patients (HCM affected, variant carriers or not) and 40 family members (HCM affected or carriers). Cohort selection process can be appreciated in the flowchart (figure 1). Inclusion criteria were: HCM diagnosis (left ventricle wall thickness ≥ 15mm not explained by abnormal loading conditions in index patients or ≥ 13mm in genetic variant carriers) or be an asymptomatic carrier with an age of minimum 18 years old. Exclusion criteria were: diagnosis of HCM phenocopy, presenting both a negative phenotype and genotype and/or age less than 18 years old. The study was explained to all potential participants and informed consent was obtained prior to their inclusion. Genetic counseling was provided both before and after every genetic test.

Figure 1 - Selection process flowchart



Index: first identified case in the family; G+: genotype positive; G-: genotype negative; P+: phenotype positive; P-: phenotype negative.

3.3 Database

The variables collected included:

- Date of birth
- Gender

- Age of HCM diagnosis
- Family history of HCM
- Family history of SCD
- Aborted SCD
- Ventricular arrhythmia (sustained and nonsustained ventricular tachycardia and ventricular fibrillation) observed in 24-hour Holter monitoring, resting ECG or exercise testing
- Baseline pharmacological treatment
- Comorbidities
- Atrial fibrillation (detected in 24-hour Holter monitoring or resting ECG)

Electrocardiogram measures:

- Heart rate
- Heart rhythm
- Presence of atrioventricular or ventricular conduction alterations
- Presence of ventricular overload criteria
- ST interval and T wave alterations
- PR, QRS and QTc intervals
- Axis

Echocardiography measures:

- Left ventricular ejection fraction (LVEF)
- Left ventricular end-diastolic (LVED) and end-systolic (LVES) diameters
- Left ventricular wall thickness
- Presence of left ventricular outflow tract obstruction (LVOTO)
- Maximum outflow tract gradient

- Left atrial size

Cardiac magnetic resonance measurements:

- LVEF
- LVED and LVES volumes
- Left atrial volume
- Presence of late gadolinium enhancement (LGE)

- Implantable cardiac defibrillator implantation
- Mortality status

3.4 Genetic sequencing

Genomic DNA was extracted from saliva samples and genetic testing was performed with commercial hypertrophic cardiomyopathy panels containing 100 genes: *ABCC9 ACADVL ACTC1 ACTN2 AGL ALMS1 ALPK3 BAG3 BRAF CACNA1C CACNA1D CALM1 CALM2 CALM3 CASQ2 CBL CDH2 CPT2 CRYAB CSRP3 DES DMD DNAJC19 DOLK DSC2 DSG2 DSP ELAC2 EMD EYA4 FHL1 FKRP FKTN FLNC, GAA, GATA4, GATA5, GJA5, GLA, HCN4, HRAS, JUP, KCNE1, KCNH2, KCNJ2, KCNQ1, KRAS, LAMP2, LMNA, LZTR1, MAP2K1, MAP2K2, MRAS, MTO1, MYBPC3, MYH7, MYL2, MYL3, MYL4, MYLK3, NF1, NKX2-5, NRAS, PCCA, PCCB, PKP2, PLN, PPA2, PPCS, PPP1CB, PRKAG2, PTPN11, RAF1, RASA1, RBM20, RIT1, RYR2, SCN5A, SDHA, SGCD, SHOC2, SLC22A5, SOS1, SOS2, SPRED1, TAZ, TBX20, TCAP, TMEM43, TMEM70, TNNC1, TNNI3, TNNI3K, TNNT2, TPM1, TRDN, TRPM4, TTN, TTR, VCL*. Full-gene sequencing was performed using massive parallel sequencing covering clinically important regions of each gene, including coding exons and 10 to 20 base pairs of adjacent intronic sequences on either side of

the coding exons in the transcript and non-coding variants.This assay achieves >99% analytical sensitivity and specificity for single nucleotide variants, insertions and deletions <15bp in length, and exon-level deletions and duplications.

3.5 Statistical Analysis

A confidential and secure database was created in RedCap software. Statistical analysis was performed in R software version 4.3.0. Categorical variables were analyzed with a chi-square test. For continuous variables with normal distribution t test was used and variables without normal distribution Wilcoxon test. The level of significance considered to all analysis was 5%.

4. LITERATURE REVIEW

4.1 Hypertrophic cardiomyopathy pathogenesis

Around 30 genes have been related to HCM, in different degrees, with over 2000 variants identified so far (9, 10). The majority are sarcomeric or sarcomere-related protein genes encoding for elements of the cardiac contractile machinery (see figure 2). The two most commonly affected proteins, together being accountable for more than 50% of the cases, are the cardiac myosin-binding protein C (MYBPC3) expressed in the intermediate filament of the sarcomere and β-myosin heavy chain (MYH7) expressed in the thick filament of the sarcomere (11). The gene *MYH7* is located in the long arm of chromosome 14 and hosts around 200 already described variants, of which, 96% are missense. Seventy per cent of these variants are located in the globular head and neck domains of the protein coding regions, while 30% are located in the rod domain. The gene *MYBPC3* is located in the short arm of chromosome 11 and has around 150 variants identified, located along the entire gene: 70% of them are nonsense, leading to a putative null allele (termination codon, splice site mutations, small deletions, or insertions disrupting the reading frame), while 30% of them are missense (12). Less common genetic variants, also identified as causes of HCM, encode for thin filament proteins, such as troponin T (TNNT2), troponin I (TNNI3), myosin light chain (MYL2 and MYL3) and actin (ACTC1), together accounting for less than 10% of cases. Other genes like *TTN*, *ALPK3*, *ACTN1*, *ACTN2*, *TNNC1*, *RYR2*, *MYH6*, *FLNC* and *PLN* have also been described in patients with HCM, in some cases being considered causal and others only associated with the disease (13). Variants in genes like *GLA*, *LZTR1* and *LAMP2* are found in ~2% of misdiagnosed HCM cases, enabling phenocopies diagnosis, in which

hypertrophy mechanisms are not necessarily due to functional defects in myocytes, like in HCM (14).

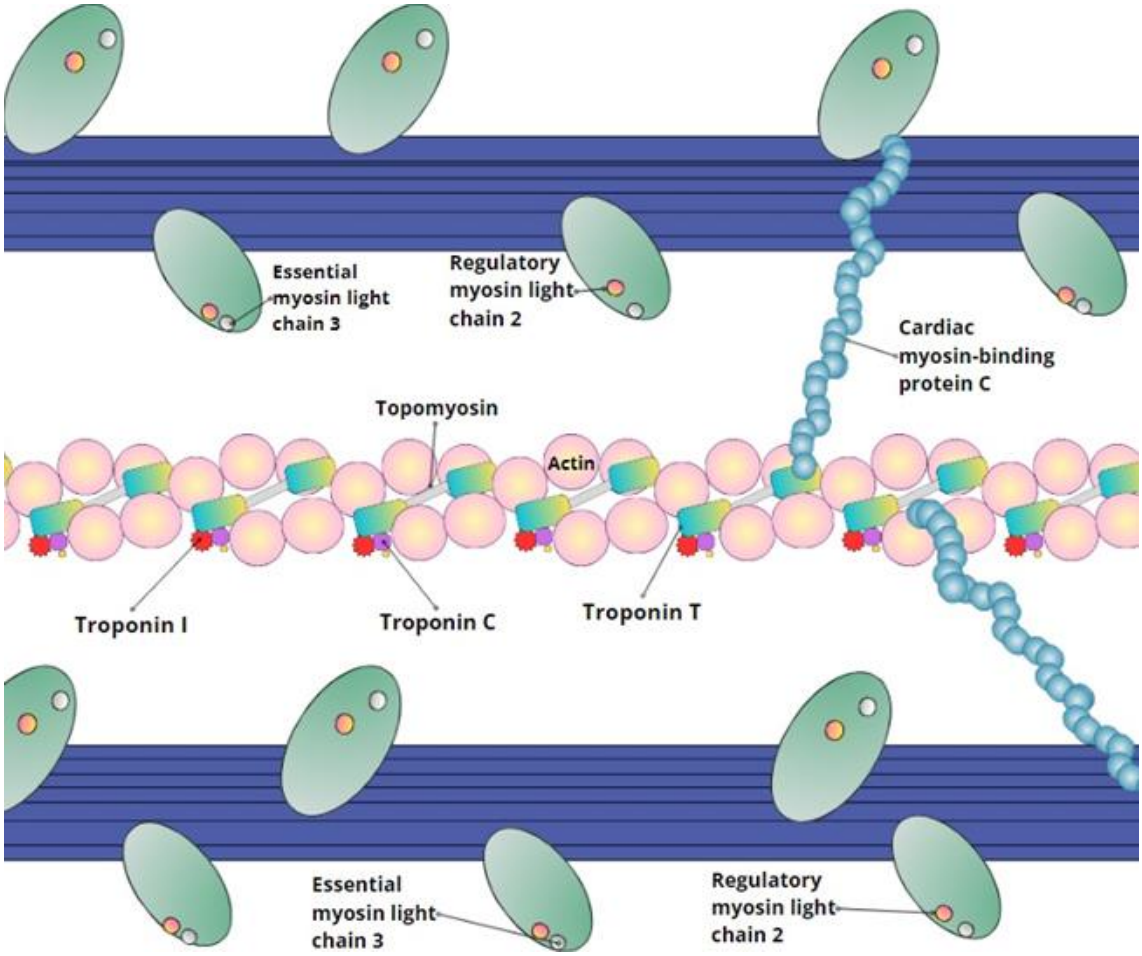


Figure 2 - – Cardiomyocyte sarcomere proteins

At the cellular level, cardiomyocytes are disorganized, hypertrophied and permeated with interstitial fibrosis in different degrees (10). The mechanism mutant proteins incorporate into myofilaments do not seem to follow a specific pattern and may disarrange sarcomeric function in variable manners, being considered more or less pathogenic (11, 15). The pathogenicity classification of variants is defined by criteria of the American College of Medical Genetics and

Genomics (ACMG) that estimates the impact in organic function and the extension with which they are considered disease causative. These criteria are mainly based on: 1) how the variant cosegregates in family members, 2) how frequent the variant is in the healthy and sick population, 3) the impact it has on protein function by *in vivo, in vitro and in silico* analysis, 4) allelic data and 5) variant previous description (16). In general, one pathogenic variant is sufficient to cause HCM, however variable penetrance and other genetic and non-genetic factors are responsible for heterogeneous phenotypic expression in which different degrees of myocardial hypertrophy, hypercontractility, reduced compliance, myofibrillar disarray and fibrosis can be developed (9, 17). Complex genotypes, presenting with more than one possible causing variant, in the same or other genes, are not common, but have been described in around 5% of HCM cases (18).

Macroscopically, clinical profiles range from a stable benign disease, to left ventricle outflow obstruction with possible progression to heart failure, arrhythmic sudden cardiac death (SCD) risk, progression to atrial fibrillation or a non-obstructive heart failure end-stage profile (19) (figure 3). Only 10% of patients experience one of the adverse pathways. However, there are currently no criteria to predict if or how variant carriers and early-stage disease will progress (20) and SCD prediction models for later disease can provide different recommendations (21).

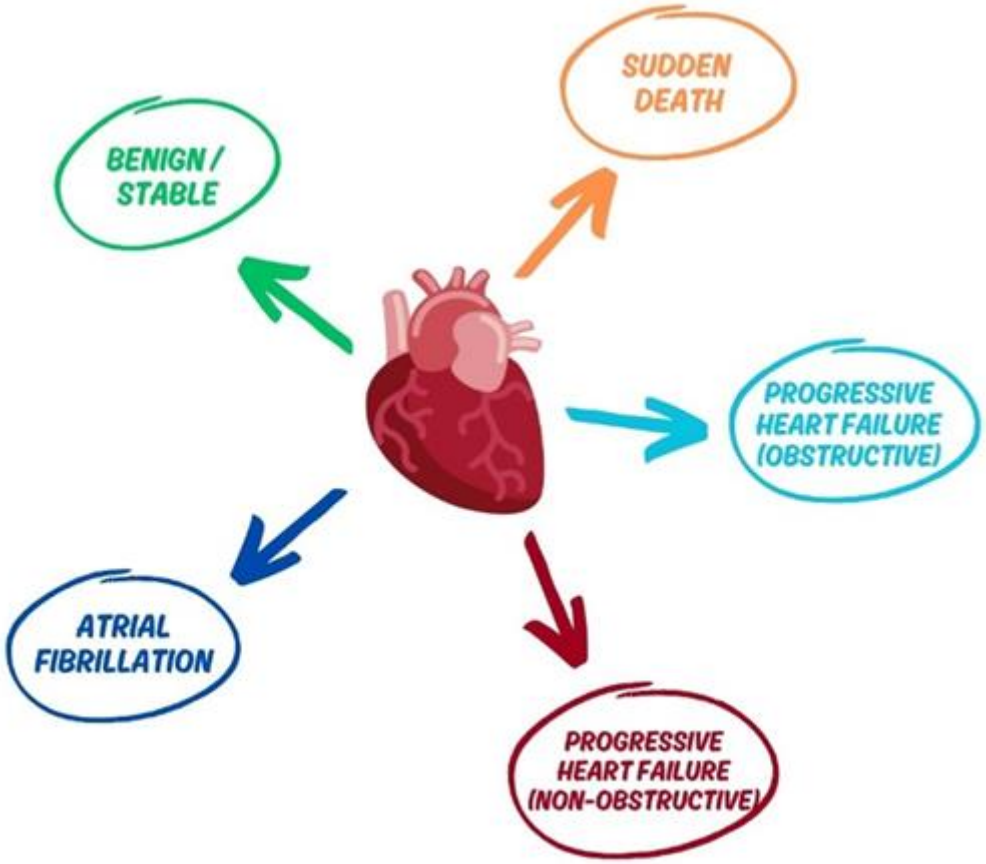


Figure 3 – Hypertrophic cardiomyopathy clinical pathways

4.2 Genotype as a phenotype predictor

Besides the influence of multiple molecular elements in the pathogenic pathways of HCM, phenotype prediction is also hampered by genotype heterogeneity between families. It is estimated that more than half of identified variants are considered ‘private’, meaning they are found in a single family (9). Still, associations between genotype and the expressed disease have been assessed and suggested in previous studies (22, 23). In a HCM cohort, Watkins et. al. described a lower life expectancy of individuals presenting with *MYH7* missense variants (24). Similar findings, correlating *MYH7* variants with worse

prognosis, were recently described by Jansen et al (25). Pathogenic variants in *MYBPC3* have been associated with delayed and elderly-onset and a higher rate of incomplete penetrance than *MYH7* variants (26). Certain *TNNT2* variants (Arg92Trp, Arg92Gln, Ile79Asn) have also been associated with an increased risk of sudden death in certain families (27).

Nevertheless, findings remain controversial. Despite genetic analysis being strongly recommended in current guidelines for all HCM patients (1,4, 6), its utility does not yet include phenotype prediction or SCD risk estimation in adults, which contributes to its underemployment in medical routine practice. The usefulness of genetic testing must be clear so it can be adequately employed in HCM follow-up. Genotyping is valuable to predict the chance of developing HCM in family members at risk of inheriting the pathogenic variant, it is helpful in differential diagnosis of HCM phenocopies and to guide offspring and fertilization matters. Also, it helps planning patients' and family members' cardiological follow-up and may impact on crucial lifetime decisions (28). It is important to point out that accessing genetic information must be always done in parallel to patient and family counseling, by a habilitated member of the healthcare team (6).

Estimating SCD risk remains one of the biggest challenges in HCM (29). Even though substantial efforts to identify SCD predictors are being made throughout the last decades, this devastating complication still strikes unpredicted cases. Individuals identified as pathogenic variants carriers without fulfilling HCM criteria (genotype-positive / phenotype-negative) are also at risk for SCD, since non-hypertrophied ventricles can also be electrically unstable (30). HCM is one of the most common causes of SCD in young individuals (31), a dramatic statistic that deserves attention from the scientific community. So far,

the major risk factors found to significantly influence malignant arrhythmic events are very much based on advanced disease characteristics: left ventricle mass, outflow tract gradient, fibrosis extension, contractile function, presence of apical aneurysm, family history of sudden death, personal history of unexplained syncope, evidence of ventricular arrhythmia and age of disease presentation (i.e. disease penetrance) (32, 33). These elements were rigorously selected, following large prospective studies, and compose current ESC and AHA/ACC SCD risk prediction models. However, recommendations based on these models may vary amongst individuals. A validation study in a German cohort estimated a sensitivity of 29% and a specificity of 83% of the ESC calculator, while the AHA/ACC calculator presented with a sensitivity of 93% and a specificity of 28% (21). That means there is still a substantial margin for unnecessary implantable cardioverter defibrillators (ICD) placement - which can bring significant impact in mental health, especially in younger people (34) - and for SCD in patients with no apparent risk factors. Genetic status, rather than specific genetic variants, have been also assessed for SCD prediction with findings that consistently point in the same direction. Several studies report worse outcomes in patients carrying disease-causing variants than patients without genetic variants identified: younger age at diagnosis, more ventricular arrhythmia, more ventricular dysfunction and higher incidence of cardiovascular death (35, 36, 37, 38). In the same validation study aforementioned, the authors tested the inclusion of genetic status as an additional variable to the ESC calculator resulting in an increase to 86% in sensitivity and a decrease to 69% in specificity. That lowered the number needed to treat (NNT) initially estimated as 13 to 9. The AHA/ACC model was not tested with additional genetic status, presenting with a NNT of 28. For pediatric

patients genotype status was validated and included in the SCD risk assessment tool of the newest 2024 AHA/ACC guideline for the management of hypertrophic cardiomyopathy (39).

At the same time robust data supporting the inclusion of specific genotypes in phenotype or SCD risk prediction is still lacking, genetic information grows in evidence as relevant markers for HCM comprehensive clinical evaluation. Furthermore, it is one of the few detectable factors in early-stage cases and the only marker present in carriers who do not yet express the disease. This highlights the need for further research, to attempt phenotype prediction, to improve risk stratification tools and potentially prevent disease development.

4.3 Therapeutic Management

Pharmacological therapy is administered empirically focusing on improvement of functional capacity, symptom control and preventing disease progression (40). In patients with LVOTO, septal reduction therapy (alcohol ablation or surgical myectomy) is also available. Until recently, pharmacological therapy relied mainly on negative inotropes like beta-blockers, nondihydropyridine calcium channel blockers and disopyramide to improve LV filling pressures (6). In 2020, the first specific-HCM therapy demonstrated to ameliorate significantly NYHA class in combination with outflow tract gradient decrease in patients with obstructive disease (41). Mavacamten is an allosteric modulator of **β**-myosin heavy chain that reduces actin-myosin affinity and is currently part of the arsenal for patients with refractory obstructive symptoms (42).

A better understanding of disease-causing genetic variants has led to advancements in therapeutic targeting and renewed hope for the cure of HCM. Preclinical research yielded promising results with gene therapy strategies (43). Recent studies have tested gene editing approaches using CRISPR/Cas9, which allows for the replacement of mutated alleles with normal alleles. The research group led by Chai demonstrated a transcript level correction of 35% in a *MYH7* mutated mice model (44), while Reichart et. al reached a transcription level correction of 26% in ventricular myocytes of another HCM mouse model (45). Additionally, techniques like allele-specific silencing, gene replacement and modulation of signaling pathways have been explored in HCM murine models, yielding promising results (46, 47, 48, 49). However, despite the excitement regarding genetic therapy, several challenges need to be addressed before human use viability. Especially within safety and efficacy areas, science needs further effort in order to evolve to a clinical scenario.

4.4 Cardiogenetics in Brazil

In a significant part of the world – mostly developing and underdeveloped countries - the general population and medical community do not include cardiovascular genetics as an essential part of HCM management. Multiple factors contribute to this fact: the financial cost of a genetic diagnosis, deficient knowledge about the subject and its usefulness and consequently little of interest in changing health professionals' mindset. In Brazil, few data are available regarding characterization of HCM in the population. Marsiglia et al. conducted a study in the state of São Paulo, Brazil, where they screened a cohort of 268 index patients for variants in three genes associated with HCM: *MYH7*, *MYBPC3* and *TNNT2*. The study found a high prevalence of pathogenic variants in the *MYH7*

gene (59,5%), followed by 38,2% in *MYBPC3* and 2,3% in *TNNT2* (50). In a tertiary center in the south of Brazil, Mattos et. al also studied *MYH7, MYBCP3* and *TNNT2* in 10 index HCM patients and 33 family members, observing the same distribution pattern (*MYH7* > *MYBPC3* > *TNNT2*) (51). In American and European cohorts *MYH7* and *MYBP3* appear to also share the first position of most common affected genes, however with a slightly higher prevalence of *MYBPC3* (1,2,3,4). To gain a deeper understanding of HCM in Brazil, a more comprehensive genetic characterization is necessary. This would involve genomic methods as larger gene panels and studying a broader population sample. Unveiling the genetic etiology of HCM is not only crucial for improving the management of diagnosed patients, but it also has significant impact for family members which may be affected, carriers or be at risk of passing along the next generation. HCM's autosomal dominant inheritance pattern represents a risk of 50% for carriers' children, impacting heavily in daily routine, life-time decisions and medical follow-up. Therefore, normalizing a complete adequate evaluation that includes genetic characterization is pivotal to achieve progress in general HCM prognosis worldwide. Expert global leaders' initiatives like the SHaRe Registry (52) multiply exponentially HCM knowledge and advances. In order to enhance our Brazilian HCM patients' care, we joined efforts to characterize and advise the biggest number of patients and families possible in a sample of the South - Brazilian population. Counting with the expertise and large experience of the Genetics team of the University Medical Center Utrecht, the Netherlands, we also focused on multidisciplinary cases discussions to incentivize assistant teams and enable better comprehension of such a relevant cardiologic condition.

5. REFERENCES

1 - ARBELO, E.; PROTONOTARIOS, A.; GIMENO, J. R.; ARBUSTINI, E.; BARRIALES-VILLA, R.; BASSO, C.; BEZZINA, C. R.; BIAGINI, E.; BLOM, N. A.; DE BOER, R. A.; DE WINTER, T.; ELLIOTT, P. M.; FLATHER, M.; GARCIA-PAVIA, P.; HAUGAA, K. H.; INGLES, J.; JURCUT, R. O.; KLAASSEN, S.; LIMONGELLI, G.; LOEYS, B.; MOGENSEN, J.; OLIVOTTO, I.; PANTAZIS, A.; SHARMA, S.; VAN TINTELEN, J. P.; WARE, J. S.; KASKI, J. P.; ESC SCIENTIFIC DOCUMENT GROUP. 2023 ESC Guidelines for the management of cardiomyopathies. *European Heart Journal*, v. 44, n. 37, p. 3503-3626, 2023. DOI: 10.1093/eurheartj/ehad194.

2 – MARON, B. J.; DESAI, M. Y.; NISHIMURA, R. A.; SPIRITO, P.; RAKOWSKI, H.; TOWBIN, J. A.; ROWIN, E. J.; MARON, M. S.; SHERRID, M. V. Diagnosis and Evaluation of Hypertrophic Cardiomyopathy. *Journal of the American College of Cardiology*, v. 79, n. 4, 2022.

3- MARON, B. J.; MARON, M. S. Hypertrophic cardiomyopathy. *The Lancet*, v. 381, n. 9862, p. 242-255, 2013.

4 – OMMEN, S. R.; MITAL, S.; BURKE, M. A.; DAY, S. M.; DESWAL, A.; ELLIOTT, P.; EVANOVICH, L. L.; HUNG, J.; JOGLAR, J. A.; KANTOR, P.; KIMMELSTIEL, C.; KITTLESON, M.; LINK, M. S.; MARON, M. S.; MARTINEZ, M. W.; MIYAKE, C. Y.; SCHAFF, H. V.; SEMSARIAN, C.; SORAJJA, P. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*, v. 142, n. 25, p. e533-e557, 2020. DOI: 10.1161/CIR.0000000000000938.

5 - ZAMPIERI, M.; BERTEOTTI, M.; FERRANTINI, C.; TASSETTI, L.; GABRIELE, M.; TOMBERLI, B.; CASTELLI, G.; CAPPELLI, F.; STEFÀNO, P.; MARCHIONNI, N.; COPPINI, R.; OLIVOTTO, I. Pathophysiology and Treatment of Hypertrophic Cardiomyopathy: New Perspectives. *Current Heart Failure Reports*, v. 18, n. 4, p. 169-179, 2021. DOI: 10.1007/s11897-021-00523-0.

6 - 3 – ELLIOTT, P. M.; ANASTASAKIS, A.; BORGER, M. A.; BORGGREFE, M.; CECCHI, F.; CHARRON, P.; HAGEGE, A. A.; LAFONT, A.; LIMONGELLI, G.; MAHRHOLDT, H.; MCKENNA, W. J.; MOGENSEN, J.; NIHOYANNOPOULOS, P.; NISTRI, S.; PIEPER, P. G.; PIESKE, B.; RAPEZZI, C.; RUTTEN, F. H.; TILLMANNS, C.; WATKINS, H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *European Heart Journal*, v. 35, n. 39, p. 2733-2779, 2014. DOI: 10.1093/eurheartj/ehu284.

7 - MORROW, A. G.; BRAUNWALD, E. Functional aortic stenosis: a malformation characterized by resistance to left ventricular outflow without anatomic obstruction. *Circulation*, v. 20, p. 181-189, 1959.

8 - MARON, B. J. Clinical Course and Management of Hypertrophic Cardiomyopathy. *New England Journal of Medicine*, v. 379, n. 20, p. 1977, 2018.

9 - TEEKAKIRIKUL, P.; ZHU, W.; HUANG, H. C.; FUNG, E. Hypertrophic Cardiomyopathy: An Overview of Genetics and Management. *Biomolecules*, 16 dez. 2019. Disponível em: https://www.mdpi.com/2218-273X/9/12/878. Acesso em: 18 ago. 2024.

10 - MARIAN, A. J.; BRAUNWALD, E. Hypertrophic Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. *Circulation Research*, v. 121, n. 7, p. 749-770, 2017. DOI: 10.1161/CIRCRESAHA.117.311059.

11 - BURKE, M. A.; COOK, S. A.; SEIDMAN, J. G.; SEIDMAN, C. E. Clinical and Mechanistic Insights Into the Genetics of Cardiomyopathy. *Journal of the American College of Cardiology*, v. 68, n. 25, 2016.

12 - RICHARD, P.; VILLARD, E.; CHARRON, P.; ISNARD, R. The Genetic Bases of Cardiomyopathies. *Journal of the American College of Cardiology*, v. 48, n. 9 Suppl A, 2006.

13 - GLAVAŠKI, M.; VELICKI, L.; VUCINIC, N. Hypertrophic Cardiomyopathy: Genetic Foundations, Outcomes, Interconnections, and Their Modifiers. *Medicina*, v. 59, p. 1424, 2023.

14 - INGLES, J.; GOLDSTEIN, J.; THAXTON, C.; CALESHU, C.; CORTY, E. W.; CROWLEY, S. B.; DOUGHERTY, K.; HARRISON, S. M.; MCGLAUGHON, J.; MILKO, L. V.; MORALES, A.; SEIFERT, B. A.; STRANDE, N.; THOMSON, K.; VAN TINTELEN, J. P.; WALLACE, K.; WALSH, R.; WELLS, Q.; WHIFFIN, N.; WITKOWSKI, L.; SEMSARIAN, C.; WARE, J. S.; HERSHBERGER, R. E.; FUNKE, B. Evaluating the Clinical Validity of Hypertrophic Cardiomyopathy Genes. *Circulation: Genomic and Precision Medicine*, v. 12, n. 2, 2019.

15 - MARIAN, A. J.; BRAUNWALD, E. Hypertrophic Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. *Circulation Research*, v. 121, n. 7, p. 749-770, 2017. DOI: 10.1161/CIRCRESAHA.117.311059.

16 - RICHARDS, S.; AZIZ, N.; BALE, S.; BICK, D.; DAS, S.; GASTIER-FOSTER, J.; GRODY, W. W.; HEGDE, M.; LYON, E.; SPECTOR, E.; VOELKERDING, K.; REHM, H. L. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine*, v. 17, n. 5, p. 405-424, 2015. DOI: 10.1038/gim.2015.30.

17 - BURKE, M. A.; COOK, S. A.; SEIDMAN, J. G.; SEIDMAN, C. E. Clinical and mechanistic insights into the genetics of cardiomyopathy. Journal of the American College of Cardiology, v. 68, p. 2871–2886, 2016.

18 - CUI, Y.; LIU, C.; LUO, J.; LIANG, J. Dysfunctional Network and Mutation Genes of Hypertrophic Cardiomyopathy. *Journal of Healthcare Engineering*, 28 jan. 2022, p. 8680178. DOI: 10.1155/2022/8680178.

19 - MARON, B. J.; DESAI, M. Y.; NISHIMURA, R. A.; SPIRITO, P.; RAKOWSKI, H.; TOWBIN, J. A.; ROWIN, E. J.; MARON, M. S.; SHERRID, M. V. Diagnosis and Evaluation of Hypertrophic Cardiomyopathy. *Journal of the American College of Cardiology*, v. 79, n. 4, 2022.

20 - ROWIN, E. J.; MARON, M. S.; CHAN, R. H.; HAUSVATER, A.; WANG, W.; RASTEGAR, H.; MARON, B. J. Interaction of Adverse Disease Related Pathways in Hypertrophic Cardiomyopathy. *American Journal of Cardiology*, v. 120, n. 12, p. 2256-2264, 2017. DOI: 10.1016/j.amjcard.2017.08.048.

21 - AMR, A.; KOELEMEN, J.; REICH, C.; SEDAGHAT-HAMEDANI, F.; KAYVANPOUR, E.; HAAS, J.; FRESE, K.; LEHMANN, D.; KATUS, H. A.; FREY, N.; MEDER, B. Improving sudden cardiac death risk stratification in hypertrophic cardiomyopathy using established clinical variables and genetic information. *Clinical Research in Cardiology*, v. 113, n. 5, p. 728-736, 2024. DOI: 10.1007/s00392-023-02310-4.

22 - ROBERTS, R.; SIGWART, U. New concepts in hypertrophic cardiomyopathies, part I. *Circulation*, v. 104, n. 17, p. 2113-2116, 2001. DOI: 10.1161/hc4201.097429.

23 - MARIAN, A. J.; ROBERTS, R. Molecular genetic basis of hypertrophic cardiomyopathy: genetic markers for sudden cardiac death. *Journal of Cardiovascular Electrophysiology*, v. 9, n. 1, p. 88-99, 1998. DOI: 10.1111.

24 - WATKINS, H.; ROSENZWEIG, A.; HWANG, D. S.; LEVI, T.; MCKENNA, W.; SEIDMAN, C. E.; SEIDMAN, J. G. Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy. *New England Journal of Medicine*, v. 326, n. 17, p. 1108-1114, 1992. DOI: 10.1056/NEJM199204233261703.

25 - JANSEN, M.; DE BROUWER, R.; HASSANZADA, F.; SCHOEMAKER, A. E.; SCHMIDT, A. F.; KOOIJMAN-REUMERMAN, M. D.; BRACUN, V.; SLIEKER, M. G.; DOOIJES, D.; VERMEER, A. M. C.; WILDE, A. A. M.; AMIN, A. S.; LEKANNE DEPREZ, R. H.; HERKERT, J. C.; CHRISTIAANS, I.; DE BOER, R. A.; JONGBLOED, J. D. H.; VAN TINTELEN, J. P.; ASSELBERGS, F. W.; BAAS, A. F. Penetrance and Prognosis of MYH7 Variant-Associated Cardiomyopathies: Results From a Dutch Multicenter Cohort Study. *JACC: Heart Failure*, v. 12, n. 1, p. 134-147, 2024. DOI: 10.1016/j.jchf.2023.07.007.

26 - HO, C. Genetics and clinical destiny: improving care in hypertrophic cardiomyopathy. *Circulation*, v. 122, p. 2430-2440, 2010.

27 - MOOLMAN, J. C.; CORFIELD, V. A.; POSEN, B.; NGUMBELA, K.; SEIDMAN, C.; BRINK, P. A.; WATKINS, H. Sudden death due to troponin T mutations. *Journal of the American College of Cardiology*, v. 29, p. 549-555, 1997.

28 - MARON, B. J.; MARON, M. S.; SEMSARIAN, C. Genetics of Hypertrophic Cardiomyopathy After 20 Years. *Journal of the American College of Cardiology*, v. 60, n. 8, 2012

29 - PARATZ, ED.; STUB, D.; SUTHERLAND, N.; GUTMAN, S.; LA GERCHE, A.; MARIANI, J.; TAYLOR, A.; ELLIMS, A. The challenge of risk stratification in hypertrophic cardiomyopathy: Clinical, genetic and imaging insights from a quaternary referral centre. Int J Cardiol. 2024 Jan 15;395:131416. doi: 10.1016/j.ijcard.2023.131416. Epub 2023 Oct 4. PMID: 37802298.

30 - CHRISTIAANS, I.; LEKANNE DIT DEPREZ, R. H.; VAN LANGEN, I. M.; WILDE, A. A. Ventricular fibrillation in MYH7-related hypertrophic cardiomyopathy before onset of ventricular hypertrophy. *Heart Rhythm*, v. 6, p. 1366-1369, 2009.

31 - SALZILLO, C.; SANSONE, V.; NAPOLITANO, F. Sudden Cardiac Death in the Young: State-of-the-Art Review in Molecular Autopsy. *Current Issues in Molecular Biology*, v. 46, n. 4, p. 3313-3327, abr. 2024.

32 - DONG, Y.; YANG, W.; CHEN, C.; JI, J.; ZHENG, W.; ZHANG, F.; YANG, B.; LI, X.; ZHOU, X. Validation of the 2020 AHA/ACC Risk Stratification for Sudden Cardiac Death in Chinese Patients With Hypertrophic Cardiomyopathy. *Frontiers in Cardiovascular Medicine*, 17 ago. 2021. DOI: 10.3389/fcvm.2021.691653.

33 - O'MAHONY, C.; JICHI, F.; PAVLOU, M.; MONSERRAT, L.; ANASTASAKIS, A.; RAPEZZI, C.; BIAGINI, E.; GIMENO, J. R.; LIMONGELLI, G.; MCKENNA, W. J.; OMAR, R. Z.; ELLIOTT, P. M. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD). *European Heart Journal*, v. 35, p. 2010–2020, 2014.

34 - GHEZZI, E. S.; SHARMAN, R. L. S.; SELVANAYAGAM, J. B.; PSALTIS, P. J.; SANDERS, P.; ASTLEY, J. M.; KNAYFATI, S.; BATRA, V.; KEAGE, H. A. D. Burden of mood symptoms and disorders in implantable cardioverter defibrillator patients: a systematic review and meta-analysis of 39,954 patients. *Europace*, v. 25, n. 6, 2023. DOI: 10.1093/europace/euad130.

35 - HO, C. Y.; DAY, S. M.; ASHLEY, E. A.; MICHELS, M.; PEREIRA, A. C.; JACOBY, D.; CIRINO, A. L.; FOX, J. C.; LAKDAWALA, N. K.; WARE, J. S.; CALESHU, C. A.; HELMS, A. S.; COLAN, S. D.; GIROLAMI, F.; CECCHI, F.; SEIDMAN, C. E.; SAJEEV, G.; SIGNOROVITCH, J.; GREEN, E. M.; OLIVOTTO, I. Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy: Insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). *Circulation*, v. 138, n. 14, p. 1387-1398, 2018. DOI: 10.1161/CIRCULATIONAHA.117.033200.

36 - LOPES, L. R.; SYRRIS, P.; GUTTMANN, O. P.; O'MAHONY, C.; TANG, H. C.; DALAGEORGOU, C.; JENKINS, S.; HUBANK, M.; MONSERRAT, L.; MCKENNA, W. J.; PLAGNOL, V.; ELLIOTT, P. M. Novel genotype-phenotype associations demonstrated by high-throughput sequencing in patients with hypertrophic cardiomyopathy. *Heart*, v. 101, n. 4, p. 294-301, 2015. DOI: 10.1136/heartjnl-2014-306387.

37 - SEDAGHAT-HAMEDANI, F.; KAYVANPOUR, E.; TUGRUL, O. F.; LAI, A.; AMR, A.; HAAS, J.; PROCTOR, T.; EHLERMANN, P.; JENSEN, K.; KATUS, H. A.; MEDER, B. Clinical outcomes associated with sarcomere mutations in hypertrophic cardiomyopathy: a meta-analysis on 7675 individuals. *Clinical Research in Cardiology*, v. 107, n. 1, p. 30-41, 2018. DOI: 10.1007/s00392-017-1155-5.

38 - VAN VELZEN, H. G.; VRIESENDORP, P. A.; OLDENBURG, R. A.; VAN SLEGTENHORST, M. A.; VAN DER VELDEN, J.; SCHINKEL, A. F. L.; MICHELS, M. Value of Genetic Testing for the Prediction of Long-Term Outcome in Patients With Hypertrophic Cardiomyopathy. *American Journal of Cardiology*, v. 118, n. 6, p. 881-887, 2016. DOI: 10.1016/j.amjcard.2016.06.038.

39 - OMMEN, S. R.; HO, C. Y.; ASIF, I. M.; BALAJI, S.; BURKE, M. A.; DAY, S. M.; DEARANI, J. A.; EPPS, K. C.; EVANOVICH, L.; FERRARI, V. A.; JOGLAR, J. A.; KHAN, S. S.; KIM, J. J.; KITTLESON, M. M.; KRITTANAWONG, C.; MARTINEZ, M. W.; MITAL, S.; NAIDU, S. S.; SABERI, S.; SEMSARIAN, C.; TIMES, S.; WALDMAN, C. B. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*, v. 149, n. 23, p. e1239-e1311, 2024. DOI: 10.1161/CIR.0000000000001250.

40 - SPOLADORE, R.; MARON, M. S.; D'AMATO, R.; CAMICI, P. G.; OLIVOTTO, I. Pharmacological treatment options for hypertrophic cardiomyopathy: high time for evidence. *European Heart Journal*, v. 33, n. 14, p. 1724-1733, 2012. DOI: 10.1093/eurheartj/ehs150.

41 - OLIVOTTO, I.; OREZIAK, A.; BARRIALES-VILLA, R.; ABRAHAM, T. P.; MASRI, A.; GARCIA-PAVIA, P.; SABERI, S.; LAKDAWALA, N. K.; WHEELER, M. T.; OWENS, A.; KUBANEK, M.; WOJAKOWSKI, W.; JENSEN, M. K.; GIMENO-BLANES, J.; AFSHAR, K.; MYERS, J.; HEGDE, S. M.; SOLOMON, S. D.; SEHNERT, A. J.; ZHANG, D.; LI, W.; BHATTACHARYA, M.; EDELBERG, J. M.; WALDMAN, C. B.; LESTER, S. J.; WANG, A.; HO, C. Y.; JACOBY, D.; EXPLORER-HCM STUDY INVESTIGATORS. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*, v. 396, n. 10253, p. 759-769, 2020. DOI: 10.1016/S0140-6736(20)31792-X.

42 - HEITNER, SB.; JACOBY, D.; LESTER, SJ.; OWENS, A.; WANG, A.; ZHANG, D.; LAMBING, J.; LEE, J.; SEMIGRAN, M.; SEHNERT, AJ.; Mavacamten Treatment for Obstructive Hypertrophic Cardiomyopathy: A Clinical Trial. Ann Intern Med. 2019 Jun 4;170(11):741-748. doi: 10.7326/M18-3016. Epub 2019 Apr 30. PMID: 31035291.

43 - PARATZ, E. D.; MUNDISUGIH, J.; ROWE, S. J.; KIZANA, E.; SEMSARIAN, C. Gene Therapy in Cardiology: Is a Cure for Hypertrophic Cardiomyopathy on the Horizon? *Canadian Journal of Cardiology*, v. 40, p. 777-788, 2024.

44 - CHAI, A. C.; CUI, M.; CHEMELLO, F.; LI, H.; CHEN, K.; TAN, W.; ATMANLI, A.; MCANALLY, J. R.; ZHANG, Y.; XU, L.; LIU, N.; BASSEL-DUBY, R.; OLSON, E. N. Base editing correction of hypertrophic cardiomyopathy in human cardiomyocytes and humanized mice. *Nature Medicine*, v. 29, n. 2, p. 401-411, 2023. DOI: 10.1038/s41591-022-02176-5.

45 - REICHART, D.; NEWBY, G. A.; WAKIMOTO, H.; LUN, M.; GORHAM, J. M.; CURRAN, J. J.; RAGURAM, A.; DELAUGHTER, D. M.; CONNER, D. A.; MARSIGLIA, J. D. C.; KOHLI, S.; CHMATAL, L.; PAGE, D. C.; ZABALETA, N.; VANDENBERGHE, L.; LIU, D. R.; SEIDMAN, J. G.; SEIDMAN, C. Efficient in vivo genome editing prevents hypertrophic cardiomyopathy in mice. *Nature Medicine*, v. 29, n. 2, p. 412-421, 2023. DOI: 10.1038/s41591-022-02190-7.

46 - MERKULOV, S.; CHEN, X.; CHANDLER, M. P.; STELZER, J. E. In vivo cardiac myosin binding protein C gene transfer rescues myofilament contractile dysfunction in cardiac myosin binding protein C null mice. *Circulation: Heart Failure*, v. 5, p. 635-644, 2012.

47 - MEARINI, G.; STIMPEL, D.; GEERTZ, B.; WEINBERGER, F.; KRÄMER, E.; SCHLOSSAREK, S.; MOUROT-FILIATRE, J.; STOEHR, A.; DUTSCH, A.; WIJNKER, P. J.; BRAREN, I.; KATUS, H. A.; MÜLLER, O. J.; VOIT, T.; ESCHENHAGEN, T.; CARRIER, L. Mybpc3 gene therapy for neonatal cardiomyopathy enables long-term disease prevention in mice. *Nature Communications*, v. 5, p. 5515, 2014. DOI: 10.1038/ncomms6515.

48 - GEDICKE-HORNUNG, C.; BEHRENS-GAWLIK, V.; REISCHMANN, S.; GEERTZ, B.; STIMPEL, D.; WEINBERGER, F.; SCHLOSSAREK, S.; PRÉCIGOUT, G.; BRAREN, I.; ESCHENHAGEN, T.; MEARINI, G.; LORAIN, S.; VOIT, T.; DREYFUS, P. A.; GARCIA, L.; CARRIER, L. Rescue of cardiomyopathy through U7snRNA-mediated exon skipping in Mybpc3-targeted knock-in mice. *EMBO Molecular Medicine*, v. 5, n. 7, p. 1128-1145, jul. 2013. DOI: 10.1002/emmm.201202168.

49 - YADAV, S.; YUAN, C. C.; KAZMIERCZAK, K.; LIANG, J.; HUANG, W.; TAKEUCHI, L. M.; KANASHIRO-TAKEUCHI, R. M.; SZCZESNA-CORDARY, D. Therapeutic potential of AAV9-S15D-RLC gene delivery in humanized MYL2

mouse model of HCM. *Journal of Molecular Medicine (Berlin)*, v. 97, n. 7, p. 1033-1047, jul. 2019. DOI: 10.1007/s00109-019-01791-z.

50 - MARSIGLIA, J. D. C.; CREDIDIO, F. L.; DE OLIVEIRA, T. G. M.; REIS, R. F.; ANTUNES, M. O.; DE ARAUJO, A. Q.; PEDROSA, R. P.; BARBOSA-FERREIRA, J. M.; MADY, C.; KRIEGER, J. E.; ARTEAGA-FERNANDEZ, E.; PEREIRA, A. C. Screening of MYH7, MYBPC3, and TNNT2 genes in Brazilian patients with hypertrophic cardiomyopathy. *American Heart Journal*, out. 2013.

51 - MATTOS, B. P. e; SCOLARI, F. L.; TORRES, M. A. R.; SIMON, L.; FREITAS, V. C. de; GIUGLIANI, R.; MATTE, Ú. Prevalence and Phenotypic Expression of Mutations in the MYH7, MYBPC3 and TNNT2 Genes in Families with Hypertrophic Cardiomyopathy in the South of Brazil: A Cross-Sectional Study. *Arquivos Brasileiros de Cardiologia*, v. 107, n. 3, p. 257-265, 2016. DOI: 10.5935/abc.20160133.

52 - SHaRe Registry. Disponível em: https://www.thesharegistry.org/. Acesso em: 18 ago. 2024.