INVITED REVIEW

Genetics of hypertrophic cardiomyopathy: A review of current state

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Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disease. HCM is a highly complex and heterogeneous disease regarding not only the number of associated mutations but also the severity of phenotype, symptom burden, and the risk of complications, such as heart failure and sudden death. The penetrance is incomplete and it is age and gender dependent. It is accepted as a disease of the sarcomere. Sixty percent of HCM cases carry mutations in 1 of 8 sarcomere protein genes, mainly non-sense MYBPC3 and missense MYH7 variants. Young patients with severe phenotype and other clinical features are included in proposed scores for prediction of high positive genetic result. The number of genes reported as disease-causing has increased in the last few years, in some cases without robust evidence. Currently available in silico tools are not always useful for differentiation between benign and deleterious variants. There is enough information on genotype-phenotype correlations to start understanding the mechanisms of the disease. Genetic and environmental modifiers have been explored with some interesting insights from miRNA studies with potential as biomarkers and therapeutic agents. There is an additional value of genetic testing in HCM for prognosis. Knowledge about genetics and functional studies are the basis of near future therapies.

KEYWORDS
cardiomyopathy, genetics, hypertrophy, sudden death

1 | INTRODUCTION

Cardiomyopathies are a very heterogeneous group of diseases affecting the heart muscle characterized by alterations in the size of the cardiac chambers, ventricle wall thickness, or abnormal contraction in the absence of coronary artery disease, hypertension, valvular or congenital heart disease. There are 3 major cardiomyopathies based on population prevalence: hypertrophic (HCM, 1:500), dilated (DCM, 1:2500) and arrhythmogenic (1:5000).1,2

In the last 5 years, the advances in molecular technology, mainly high-throughput sequencing, have allowed reducing costs and increasing yield, identifying novel cardiomyopathy genes.3 High-throughput sequencing technologies have become part of the clinical work-up of cardiomyopathies and are recognized in clinical guidelines. Genetic cause in cardiomyopathies is attributed to more than 40 genes (many of them shared by different categories).

This review aims to address current knowledge on the molecular basis of HCM with insights into phenotypic modifiers and future directions of therapies.

1.1 | Definition and clinical features

HCM is the most common inherited cardiovascular disease characterized by increased wall thickness (hypertrophy), not explained by abnormal loading conditions. The risk of sudden cardiac death (SCD) is high in young patients, including athletes, and it may be the first manifestation of the disease.1–4

The clinical manifestations of HCM are highly variable. Many patients are asymptomatic and are diagnosed incidentally, others may manifest shortness of breath, chest pain, palpitations or syncope, triggered by left ventricle hypertrophy (LVH), arrhythmias or heart failure. Moreover, phenotypic expression can vary even within the same family.
At least 1 in 4 people with HCM present intracavitary obstruction at rest, which is associated with more severe symptoms. Another 25% can develop outflow tract obstruction with provocation or exercise.\textsuperscript{5–7} Approximately, 5%-10% of patients with HCM progress to end-stage disease with impaired systolic function and dilatation.

2 | HISTOPATHOLOGICAL FINDINGS

Histologically, it is characterized by a chaotic spatial arrangement of myocytes ("disarray") which are hypertrophied. The combination of myocardial disarray and replacement fibrosis is considered a malignant arrhythmogenic substrate. An additional feature that is often encountered is the presence of dysplastic coronary arterioles. The abnormal arteries exhibit thickened walls because of proliferation of the intimal and medial smooth muscle cells and collagen, which results in luminal narrowing.\textsuperscript{8}

Myocardial bridge involving an epicardial artery is often seen in HCM, which implies an abnormality in development of the heart in embryonic stages. Although the typical phenotype develops with age, some features like myocardial bridging and endomyocardial hypertrabeculation are seen in asymptomatic carriers from birth.\textsuperscript{9,10}

Due to the small number of pathological series and the significant genetic heterogeneity of HCM, there is little information on the correlation between histological findings and sarcomeric mutations.\textsuperscript{11} On the contrary, histology is valuable for correct identification of phenocopies (lysosomal and storage diseases).\textsuperscript{12}

3 | GENETICS OF HCM

Over the past 25 years, HCM has been considered mainly an autosomal dominant disease although some cases are explained by de novo mutations, and less commonly, autosomal recessive inheritance. Often, mutations are shared by only 1 or a few families. The penetrance is incomplete and varies with age and gender.

HCM is frequently described as a disease of the sarcomere, with pathogenic variants detected in almost all sarcomeric proteins, which are responsible for generating the molecular force of myocyte contraction, mainly the ones encoded by MYBPC3 and MYH7 genes (70% identified mutations). The other genes include TNNT2, TNNI3, TPM1, MYL2, MYL3, and ACTC1 with a much lower frequency of pathogenic variants (1%-5% each). A recent study showed that sarcomeric variants are mostly associated with female gender and younger age of presentation, presenting an asymmetric septal hypertrophy and family history of HCM and SCD.\textsuperscript{13}

Despite the private nature of most variants, there are some common ones and "hot spots" in main genes have been recognized such as Arg403Gln, Arg453Cys and Arg663His in MYH7; Arg92Gln, Arg92Trp and Arg104Val in TNNT2, and Arg495Gln, Arg502Trp and c.1928-2A>G in MYBPC3.\textsuperscript{14–17}

4 | IMPACT OF HIGH-THROUGHPUT SEQUENCING

High-throughput sequencing represents a major advance for diagnosis of genetic diseases. Whole-exome studies are currently feasible at a reasonable time and cost. New technologies have evidenced a number of variants previously associated with cardiomyopathy that in fact are common in control populations. Early publications led to question the pathogenicity of up to 14% of HCM mutations.\textsuperscript{18} In a recent publication with a larger population, 12% of individuals from Exome Aggregation Consortium (ExAc) had reported HCM variants, which is far in excess of disease prevalence.\textsuperscript{19}

The most important databases including the frequencies of variants of the general population include the 1000Genomes Project (www.1000genomes.org), the Exome Sequencing Project (evs.gs.washington.edu/EVS/), dbSNP (www.ncbi.nlm.nih.gov/SNP), and the ExAc (exac.broadinstitute.org).

The analysis of gene panels with multiple genes involved in HCM implies the identification of a large number of variants of uncertain clinical significance (VUS).\textsuperscript{20} Therefore, the "background noise" of human genetic variation has increased with VUS in genes whose pathogenicity has not been tested. Figure 1 presents the odds ratios for missense and non-sense variants for the main genes in patients with HCM compared to control population.\textsuperscript{19} Interestingly, the higher odds ratio values were for truncating MYBPC3, TNN1C and TTR variants followed by non-truncating variants TPM1, MYH7 and TNNI3. On the contrary and surprisingly, despite being statistically significant, the odds ratios of truncating variants in MYH7 and non-truncating variants in TTR and PRKAG2 or TNN1C were particularly low. Odds ratios for a given type of mutation in a particular gene provide valuable information for relative measurement of "background noise" and should be taken into consideration in the pathogenicity process.

Higher proportions of complex genotypes, such as compound heterozygous, double heterozygous patients and homozygous patients, have also been recently reported using high-throughput sequencing technologies. On the contrary, large deletions and duplications seem to be a rare cause of HCM. Copy number variations have been showed in less than 1% of HCM cases.\textsuperscript{21}

The impact of high-throughput sequencing has been notable in the diagnostic yield in some cardiomyopathies such as DCM (14%-50%), in contrast, it has been more modest in HCM (45%-72%)\textsuperscript{14,22} (Table 1). New-sequencing technologies have led to a striking reduction of costs, by 80%-90%, in all cardiomyopathies and valuable time savings. The spectrum of genes associated with HCM has been expanded to dozens of genes encoding various non-sarcomeric proteins (Z-disc, Ca\textsuperscript{2+}-handling proteins). Insight that a significant proportion of HCM patients carry variants in desmosomal and ion channel genes (up to 43%) or in Titin (up to 64%), often associated with mutations in classical sarcomeric genes and with complex or mixed phenotypes.\textsuperscript{14,23}

It has been suggested that these rare variants may act as "modifiers" of the disease phenotype and prognosis. Statistically, ANK2 variants have been associated with a more severe hypertrophy, SCN5A variants were associated with a higher proportion of obstruction and left atrial enlargement and phospholamban gene (PLN)
variants with a higher risk of ventricular arrhythmias. These findings could have clinical implications for risk stratification of patients in the future. Nevertheless, these associations have to be taken very cautiously as causality is not proven and pathogenicity of SCN5A, ANK2 and PLN in HCM has been questioned.¹⁹

5 | NEW GENES ASSOCIATED WITH HCM

Genetic testing has been incorporated to the clinical practice for some time but over the last few years, the number of genes involved in HCM has increased (Table 2).

Some of these genes are CSRP3, PLN, CRYAB, TNNC1, MYOZ2, ACTN2, ANKRD1 FLNC,²²–²⁷ and FHL1.²³,²⁸ The patients with mutations in these genes might present atypical or mixed cardiomyopathy, often with mild hypertrophy and without obstruction. It is clinically important to identify them as, although the phenotype is apparently mild, the arrhythmic prognosis could be particularly poor. Despite this apparently association, other authors have failed to show increase frequency of variants in some of these new candidate genes in cases compared to general population datasets.²³ Further studies are warranted to dilucidate their pathogenic role.

Titin (TTN) is a sarcomeric gene which has been difficult to sequence due to its large size and unknown structure. Since 2012, when Herman et al²⁹ identified a high frequency of variants in TTN in dilated and HCM populations, a significant percentage of TTN radical variants in affected patients and in control populations have been identified. TTN has become the most prevalent mutation gene in patients with DCM, being numerous the related reports published³⁰–³⁹; in contrast, the reports about defect in TTN as a cause of HCM¹³,⁴⁰ are practically non-existent.

6 | PHENOCOPIES OF HCM

There are some recognized HCM phenocopies, which can masquerade HCM, caused by mutations in LAMP2 (Danon disease), PRKAG2 (Wolff-Parkinson-White syndrome), GLA (Anderson-Fabry disease),

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Impact of high-throughput sequencing in the main cardiomyopathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition</td>
<td>Sanger sequencing</td>
</tr>
<tr>
<td></td>
<td>No of genes</td>
</tr>
<tr>
<td>HCM</td>
<td>2–4</td>
</tr>
<tr>
<td>DCM</td>
<td>14–19</td>
</tr>
<tr>
<td>ACM</td>
<td>5–8</td>
</tr>
</tbody>
</table>

Abbreviations: ACM, arrhythmogenic cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy.

Estimated cost taken from average costs of sequencing from 3 commercial high-volume laboratories (Health in Code [HIC], Harvard partners and Blueprint genetics) 2016.

Estimated number of genes and yield taken from large published series (Refs. 63, 106 and 107 for Sanger sequencing and Refs. 13 and 19 for high-throughput sequencing).

The cost per positive genotyping was calculated as the cost of sequencing divided by the number of patients with positive genotyping.

*a Estimated costs/gen (~25 amplicons) (€) = 500.
TABLE 2 The main HCM disease causing genes are summarized

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Locus</th>
<th>HCM frequency (%)</th>
<th>Number (pb)</th>
<th>dbSNP</th>
<th>Number of pathogenic/likely pathogenic variants</th>
<th>% Variants per pb</th>
<th>% Pathogenic variants per pb</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTC1</td>
<td>Actin α-cardiac muscle 1</td>
<td>NG_007553</td>
<td>&lt;1</td>
<td>7630</td>
<td>826</td>
<td>27</td>
<td>10.8</td>
<td>0.4</td>
</tr>
<tr>
<td>CSR3P</td>
<td>Cysteine and glycine rich protein 3</td>
<td>NG_011932.2</td>
<td>&lt;1</td>
<td>28541</td>
<td>2050</td>
<td>10</td>
<td>7.2</td>
<td>0.0</td>
</tr>
<tr>
<td>DES</td>
<td>Desmin</td>
<td>NG_008043</td>
<td>&lt;1</td>
<td>8360</td>
<td>896</td>
<td>56</td>
<td>10.7</td>
<td>0.7</td>
</tr>
<tr>
<td>FHL1</td>
<td>Four and a half LIM domains 1</td>
<td>NG_015895.1</td>
<td>&lt;1</td>
<td>63959</td>
<td>9157</td>
<td>32</td>
<td>14.3</td>
<td>0.1</td>
</tr>
<tr>
<td>FLNC</td>
<td>Filamin C</td>
<td>NG_011807</td>
<td>&lt;1</td>
<td>28846</td>
<td>3636</td>
<td>7</td>
<td>12.6</td>
<td>0.0</td>
</tr>
<tr>
<td>GLA</td>
<td>Galactosidase alpha</td>
<td>NG_007119</td>
<td>&lt;1</td>
<td>10223</td>
<td>1291</td>
<td>164</td>
<td>12.6</td>
<td>1.6</td>
</tr>
<tr>
<td>LAMP2</td>
<td>Lysosomal associated membrane protein 2</td>
<td>NG_007995</td>
<td>&lt;1</td>
<td>43202</td>
<td>1846</td>
<td>36</td>
<td>4.3</td>
<td>0.1</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Myosin binding protein C cardiac</td>
<td>NG_007667</td>
<td>40</td>
<td>21297</td>
<td>2600</td>
<td>422</td>
<td>12.2</td>
<td>2.0</td>
</tr>
<tr>
<td>MYH7</td>
<td>Myosin heavy chain 7</td>
<td>NG_007884</td>
<td>40</td>
<td>22949</td>
<td>3190</td>
<td>359</td>
<td>13.9</td>
<td>1.6</td>
</tr>
<tr>
<td>MYL2</td>
<td>Myosin light chain 2</td>
<td>NG_007554</td>
<td>&lt;1</td>
<td>9782</td>
<td>1052</td>
<td>29</td>
<td>10.8</td>
<td>0.3</td>
</tr>
<tr>
<td>MYL3</td>
<td>Myosin light chain 3</td>
<td>NG_007555</td>
<td>1</td>
<td>5617</td>
<td>608</td>
<td>15</td>
<td>10.8</td>
<td>0.3</td>
</tr>
<tr>
<td>PLN</td>
<td>Phospholamban</td>
<td>NG_009082</td>
<td>&lt;1</td>
<td>12146</td>
<td>890</td>
<td>3</td>
<td>7.3</td>
<td>0.0</td>
</tr>
<tr>
<td>PTKA2G</td>
<td>AMP-activated protein kinase subunit-γ-2</td>
<td>NG_007486</td>
<td>&lt;1</td>
<td>321117</td>
<td>20621</td>
<td>17</td>
<td>6.4</td>
<td>0.0</td>
</tr>
<tr>
<td>PTPN11</td>
<td>Protein tyrosine phosphatase non-receptor type 11</td>
<td>NG_007459</td>
<td>&lt;1</td>
<td>91182</td>
<td>4418</td>
<td>86</td>
<td>4.8</td>
<td>0.1</td>
</tr>
<tr>
<td>TNNC1</td>
<td>Troponin C1. slow skeletal and cardiac type</td>
<td>NG_008963</td>
<td>&lt;1</td>
<td>2951</td>
<td>1338</td>
<td>74</td>
<td>45.3</td>
<td>2.5</td>
</tr>
<tr>
<td>TNNI3</td>
<td>Troponin I3 cardiac type</td>
<td>NG_007866</td>
<td>3-5</td>
<td>5966</td>
<td>886</td>
<td>61</td>
<td>14.9</td>
<td>1.0</td>
</tr>
<tr>
<td>TNNT2</td>
<td>Troponin T2 cardiac type</td>
<td>NG_007556</td>
<td>3-5</td>
<td>18664</td>
<td>1801</td>
<td>70</td>
<td>9.6</td>
<td>0.4</td>
</tr>
<tr>
<td>TPM1</td>
<td>Tropomyosin 1 (alpha)</td>
<td>NG_007557</td>
<td>&lt;5</td>
<td>23455</td>
<td>2466</td>
<td>47</td>
<td>10.5</td>
<td>0.2</td>
</tr>
<tr>
<td>TTR</td>
<td>Transthyretin</td>
<td>NG_009490</td>
<td>&lt;1</td>
<td>7258</td>
<td>710</td>
<td>43</td>
<td>9.8</td>
<td>0.6</td>
</tr>
</tbody>
</table>


RAF1 and PTPN11 (LEOPARD syndrome and Noonan’s syndrome), GAA (Pompe’s disease), TTR (amyloidosis) and FXN (Friederich’s ataxia). From those syndromic or metabolic cases, Fabry disease is particularly common in a 1%-3% of adult HCM male series. Age at diagnosis is a key point to know the etiology of cardiomyopathies. Inborn errors of metabolism are more commonly diagnosed in infants than in adults.

HCM is also prevalent in patients with cardio-facio-cutaneous syndrome, which is a genetic disorder characterized by mutations in genes involved in the RAS/MAPK pathway. RASopathies (Noonan, Costello and LEOPARD syndromes) are also a cause of HCM in children that could justify some cases of adults that could pass unnoticed (part of morphotype may be lost with development).

Identification of causative mutations in a proband with HCM facilitates presymptomatic diagnosis of family members, clinical surveillance and reproductive advice. For these reasons, the European Society of Cardiology (ESC) guidelines (2014) recommended genetic testing in patients meeting the diagnostic criteria for HCM to enable cascade genetic screening of their relatives.

It is very important to make a correct classification of the variants for an appropriate use of genetic testing in clinical practice.

Genetic testing for the screening of healthy populations or for hypertensive patients with mild hypertrophy is not recommended, as the diagnostic yield is very low in these cases and the absence of variants would not rule out the presence of the disease. Only exceptionally, it can be justified in borderline cases. There are important implications of genetic testing not only for affected but also for asymptomatic carriers. A positive genetic testing in athletes would have an impact on their sports career and might lead to cessation of competitive sport, even in the absence of overt disease.

The attempts to develop a clinical tool to determine a priori the yield of genetic testing have been continuous. Two genotype predictor scores have been published recently, which, based on 7 clinical variables, estimate the yield of genetic testing in patients with HCM, thus helping the patients and their clinicians to decide whether to undergo genetic testing (Table 3). Clinical predictors of positive genetic test, according to these studies, were early age of diagnosis, the degree and asymmetry of the hypertrophy, a peculiar septal morphology, presence of family history of HCM, familial SCD and lack of hypertension.

8 PROGNOSTIC VALUE OF GENETICS

In contrast to DCM, in which some genes and mutations have been clearly associated with a poor prognosis (LMNA, PLN), in HCM, this issue remains controversial. Multiple attempts to identify genes with an unfavorable impact on prognosis have been made without much success. It seems clear that patients in which it is possible to identify a mutation have a worse prognosis than those with negative genetic testing. Traditionally, TNNT2 mutations were associated with a mild phenotype but a high risk of SCD. Despite some mutations in TNNT2 seem to fit this paradigm, others like p.Arg278 have
been recently degraded as they have been identified with low frequency in general population (Exome Sequencing Project).55,56

The radical mutations are very common in the MYBPC3 and do not seem to pose a more unfavorable prognosis than missense mutations.57−60

Gene dosage probably also influences prognosis in HCM. Although several reports support that patients with double or triple mutations have a more severe phenotype and adverse prognosis, the impact of the number of mutations on severity is weaker than expected. The analysis of series of SCD or transplant cases identified a modest increase of 12% in the proportion of multiple mutations vs 5% of a non-selected HCM cohort.51,62

9 | TOOLS FOR PATHOGENICITY STUDIES

Making a correct classification to predict variants pathogenicity and their functional relevance is essential for a proper use of genetic testing in the clinical management of patients and their family. In silico studies are limited and a multiparametric approach including information from functional studies and cosegregation has been used in the cardiomyopathy setting.13,63,64 Figure 2 summarizes the process, which consists of 6 items. (1) Frequency of variants in control population in international database (Exome Sequencing Project, 1000Genome or ExAc). (2) Published variant. It is important to know whether the variant has been reported previously as associated with disease (HGMd, ClinVar, Ensembl). However, this evidence needs careful evaluation in absence of functional study or clinical cosegregation. (3) In silico pathogenicity scores using different software (eg, MutationTaster, Polyphen2, SIFT, Pmut, ESEfinder) to predict the potential impact of the variant on protein structure or function. (4) Conserved domain: determining if the involved nucleotide and amino acid residue are conserved among species and isoforms and if they are located in a strategic functional domain. (5) Cosegregation study. Cosegregation of a variant with the disease in large families usually provides strong evidence for causation. (6) Functional studies. In most cases, it is unavailable because it is difficult and expensive.

Due to the increased complexity of analysis and interpretation of genetic tests, general guidelines for the interpretation of variants have been published recently.65 Two sets of classification criteria were proposed in this expert’s document: one for pathogenic or likely pathogenic variants and the other one for classification of benign or likely benign variants. By applying the proposed score, variants can be classified into 5 main groups: pathogenic, likely pathogenic, uncertain significance (VUS), likely benign and benign.

10 | EFFECT OF THE MUTATION

The effect of a mutation depends not only on the mutated gene but also on the location of the mutation within the gene. The mutations occurring in most sarcomeric genes are missense-type, with a dominant negative effect resulting in the formation of poison peptides, which can be incorporated into the sarcomere, with consequences for its function.66

Protein-truncating variants and which are not incorporated into the sarcomere cause HCM by haploinsufficiency. The most MYBPC3 mutations result in frame shift a and often in protein truncation.67 mRNAs containing premature termination codons as a result of mutation are degraded through the non-sense-mediated mRNA decay system.68 Nevertheless, truncating mutations are not always pathogenic,
11 | GENOTYPE-PHENOTYPE CORRELATION

As mentioned above, HCM is a highly complex and heterogeneous disease in terms not only of the number of associated mutations but also of the variable degree of LVH, symptoms, and risk of SCD or heart failure.46

The genotype-phenotype relationship might not be obvious. This is the case of family members with the same mutation and different manifestations of the disease.

At gene level, MYBPC3 mutations have been associated with an elderly onset, and a lower penetrance than MYH7 mutations. Founder mutations are more frequent in MYBPC3, due to its late onset the reproductive age is not affected. In MYBPC3 missense-type mutations are more common in children, whereas truncation mutations predominate in adults.46,57

The presence of some electrocardiogram (ECG) findings suggesting the presence of accessory atrioventricular pathways is more common in PRKAG2 mutations. Serum markers like creatine kinase elevation might be indicative of a LAMP2 mutation. It is generally accepted that mutations in PRKAG2 and LAMP2, which often cause atypical distribution of hypertrophy, are associated with higher rate of heart failure and arrhythmia related complications.42 Right atrial enlargement in HCM patients has been associated with a poor prognosis and with a higher prevalence of sarcomeric mutations, TNNT2 mutations and complex genotypes.47 Restrictive phenotype in HCM has been associated with TNNI3 and MYH7 mutations.70 Apical hypertrophy and left ventricular non-compaction have been associated with ACTC1 mutations.71

12 | ENVIRONMENTAL AND GENETIC MODIFIERS

The clinical heterogeneity and different phenotypic expression seen in the carriers of the same mutation could be explained by other factors, such as environmental and genetic modifiers.

12.1 | Impact of gender, obesity, hypertension and exercise

There is little data on the impact of gender, obesity, hypertension and exercise on the clinical expression in genotyped cohorts.72-75 Gender has proven to be an important variable in the natural history of characterization and management of a variety of acquired cardiovascular conditions.76,77 It has been hypothesized to be one of the important modifying factors in HCM. Females tend to develop the disease later in life, but when the disease appears, affected females are more symptomatic.76,77 Obesity seems to increase the thickness of the myocardium and promote the development of the disease.78

Hypertension is supposed to enhance the degree of LVH in a similar way to intense physical exercise, via the induction of molecular pathways leading to cardiomyocyte hypertrophy.77 There is a general belief, based on indirect data or from small series, that hypertension should be associated with an increase in LVH in HCM patients,75,77 and that intense exercise is associated with an increase in LVH and is a trigger of malignant arrhythmias and hence a cause of SCD in HCM.80,81

The impact of exercise in the penetrance of HCM has not been studied in depth. The clinician is confronted with HCM patients or even non-affected mutation carriers seeking advice on physical activity. Discerning whether lifestyle choices can modify penetrance is crucial. The diagnosis of HCM is included in the current guidelines as a disqualifying cause in competitive sports.92,83

12.2 | Renin angiotensin aldosterone system polymorphisms

In addition to sarcomeric mutations which have a role in the myocyte function, there are some non-sarcomeric polymorphisms which increase the LVH and modify the phenotype in HCM patients. In these terms, the study of Renin Angiotensin Aldosterone System (RAAS) polymorphisms has a special interest. RAAS activation and receptor function could be modified by polymorphisms in angiotensin converting enzyme (ACE), angiotensin II, receptor type I (AGTR1), aldosterone synthase (CYP11B2), angiotensinogen (AGT), and in cardiac Chimaera A (CMA). These polymorphisms have been studied as disease modifiers in HCM (Table 5). ACE DD genotype has been associated with the magnitude of LVH in HCM patients46 and its influence depends on the mutation.55 The polymorphism of AGT T235 has been described as a predisposing factor for cardiac hypertrophy in patients with HCM and carries an approximately 2-fold increased risk (Table 5). Patients with higher number of different polymorphisms seem to present a higher risk of developing a severe
phenotype. Despite interesting information, the issue on the clinical role of RAAS polymorphism in HCM remains controversial.86

12.3 | Epigenetics

The epigenetics include DNA methylation and histone acetylation, which regulate the expression of different genes. The heart is composed primarily of terminally differentiated mature cardiomyocytes. The transcriptional profile and protein post-transcriptional modifications seem to be important in the development of HCM.87,88 Evaluation of DNA methylation requires the examination of heart tissue. Despite sample limitations, there is evidence that differential methylation exists in human end-stage cardiomyopathic hearts. Cardiac hypertrophy has been linked with histone acetylation implicating both histone acetyltransferases and histone deacetylases.89,90

12.4 | Micro RNAs

MiRNAs, small non-coding short RNAs, regulate gene expression by directly targeting mRNA for degradation or translational repression. An increasing list of miRNAs has been associated with different stages of HCM in animal models and human samples (Table 4). MiRNA profile can lead to the understanding of the pathophysiology of the disease from hypertrophy or inflammation to fibrosis and dilatation.91,92 Some miRNAs have been reported as useful biomarkers of the disease.93 There is expectation on whether miRNAs might have a role as future therapeutic agents in inherited cardiac diseases, because some miRNAs seem to be heart tissue specific.

12.5 | Mitochondrial DNA variants

The heart is a high energy demanding structure. Hundreds of mitochondrias are included in a single cardiomyocyte. Mutations in mitochondrial DNA have been associated with HCM in children.94 Moreover, an association between clinical progression of cardiomyopathies and several mitochondrial haplotypes has been showed (Table 5). Some studies support the hypothesis that polymorphisms in mitochondrial genes leading to reduced energy efficiency would have an impact on disease expression in HCM.95 It has been described that haplogroup H has higher mitochondrial oxidative damage because this haplogroup is the highest VO2max consumer, in contrast with haplogroup J, which it is the lowest. Therefore, haplogroup H constitutes a susceptibility factor while haplogroup J constitutes a protective factor for HCM.96

13 | THERAPEUTIC IMPLICATIONS

Current therapeutics for HCM patients are based on symptomatic alleviation and depend on the clinical features. The pharmacotherapy is mainly based on beta-blockers, calcium channel blockers and disopyramide.97 A small percentage of HCM patients with severe symptoms require surgical myectomy and alcohol ablation to relieve left ventricular obstruction. The implantation of an internal cardioverter defibrillator is generally limited to avoid the possibility of SCD and hence extend the lifespan of the patient.97

Exon skipping is emerging as a genetic-correction strategy of clinical usefulness. The antisense oligonucleotides (ASO) used for exon skipping are designed to restore reading frame disruption and it is currently being tested in humans with dystrophin gene mutations causing Duchenne muscular dystrophy.98,99 Exon skipping approach could be useful in HCM where the disease is caused as a consequence of a truncating mutation.100

ASO could also be used as tools to shift alternative splicing.29,100 It is the case of progeria syndrome cause by a mutation of lamin gene (LMNA) which produces a shift in splicing, increasing truncated lamin A production. A morpholine ASO used in fibroblast cultures has proven successful in restoring normal splicing101 and, in a murine model of progeria, it was able to reverse most phenotypical abnormalities.102

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Finding</th>
<th>Model</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{miRNA}) 1</td>
<td>Control Notch1 receptor</td>
<td>Drosophila</td>
<td>108</td>
</tr>
<tr>
<td>22</td>
<td>Induce hypertrophy in cardiomyocytes. Regulator of survival, cardiomyocyte hypertrophy remodeling in response to stress in vivo</td>
<td>In vitro and in vivo</td>
<td>109,110</td>
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<tr>
<td>21, 23a, 24, 125, 129, 132, 195, 199, 208, 212 and 222</td>
<td>Upregulated in hypertrophy</td>
<td>Mice and human heart</td>
<td>92,111</td>
</tr>
<tr>
<td>1, 133a, 29, 30b and 150</td>
<td>Downregulated in hypertrophy</td>
<td>Mice and human heart</td>
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<tr>
<td>27a, 29a, 199a-5p</td>
<td>Circulating miRNAs. Correlated with left ventricular mass</td>
<td>Human</td>
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<tr>
<td>27a</td>
<td>Circulating miRNAs. Regulates HCM gene expression by targeting thyroid hormone receptor in cardiomyocyte</td>
<td>Human</td>
<td>112</td>
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<tr>
<td>29a</td>
<td>Circulating miRNAs correlated with fibrosis</td>
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<td>150, 181b</td>
<td>Downregulated in hypertrophy in vitro overexpression reduces cardiomyocyte cell size</td>
<td>In vitro</td>
<td>93</td>
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<td>155</td>
<td>Control macrophage activity, involved in inflammation of hypertrophy</td>
<td>Mice</td>
<td>113</td>
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<tr>
<td>195</td>
<td>In vitro overexpression leads to cardiac growth and progressive to dilated cardiomyopathy</td>
<td>Transgenic mice</td>
<td>93</td>
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<tr>
<td>208a</td>
<td>Encoded in intron of (\alpha)-HCM and expressed only in cardiac muscle</td>
<td>Mouse</td>
<td>109</td>
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</tbody>
</table>

Abbreviation: HCM, hypertrophic cardiomyopathy.
TABLE 5  Previous studies of correlation between clinical variables and RAAS polymorphisms and mitochondrial haplogroups

<table>
<thead>
<tr>
<th>Previous studies</th>
<th>RAAS polymorphisms</th>
<th>Mitochondrial haplogroups</th>
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<tbody>
<tr>
<td>Karjalainen et al115</td>
<td>p.M235T ACE AGTR1</td>
<td>H,J,T,HV,O</td>
</tr>
<tr>
<td>Kozhevnikova et al120</td>
<td>AGTR1</td>
<td>H,V,U,K,J,T,I,W,X</td>
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<td>Hagen et al96</td>
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<table>
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<tr>
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<td>Genetic diagnosis</td>
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<thead>
<tr>
<th>RAAS SNPs/ mitochondrial haplogroups</th>
<th>HTN</th>
<th>Age at diagnosis</th>
<th>Symptoms</th>
<th>Syncope</th>
<th>LV mass</th>
<th>Max LVH</th>
<th>Obstruction</th>
<th>LVEDd</th>
<th>LA</th>
<th>Systolic impairment</th>
<th>Diastolic function</th>
<th>FHSCD</th>
<th>AF</th>
<th>NSVT</th>
<th>Score proLVH</th>
<th>LVEF</th>
<th>Survival</th>
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<tr>
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<td>p.M235T ACE AGTR1, CPYP11B2 CMA1</td>
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Abbreviations: ACE, angiotensin converting enzyme; AF, atrial fibrillation; AGT, angiotensinogen; CMA, cardiac quimase A; FHSCD, family history of sudden cardiac death; HTN, hypertension; LA, left atrium; LV, left ventricle; LVEDd, left ventricular end diastolic diameter; LVEF, left ventricle ejection fraction; Max LVH, maximal left ventricular hypertrophy (mm); NSVT, non-sustained ventricular taquicardia; RAAS, renin angiotensin aldosterone system; SNPs, single nucleotide polymorphisms.
Recent advances in genetics, molecular mechanisms and physiopathology are leading to the development of new interesting therapeutic agents in HCM. This is the case of ranolazine, which is currently being evaluated in different studies on HCM patients, and also of a promising small molecule MYK-461, which suppresses the HCM development and attenuates hypertrophic gene expression in mice harboring heterozygous human mutations in MYH7. This indicates that contraction inhibitors could be valuable therapeutic targets for HCM.

14 | CONCLUSIONS AND FUTURE PERSPECTIVE

HCM is the main genetic heart condition. Mutations in sarcomere protein genes are the most common cause of the disease. New technologies are increasing the number of candidate genes with an impact in costs and diagnostic yield. In silico studies are limited and cosegregation and functional studies are essential to discern the causality of the different variants. New genetic biomarkers are necessary to understand this complex and heterogeneous disease. Genetic information would guide the development of therapeutic agents.

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Conflict of interest

None declared.

REFERENCES


