Review Article

Genetics of the Cardiomyopathies: A Review for the Cardiologist

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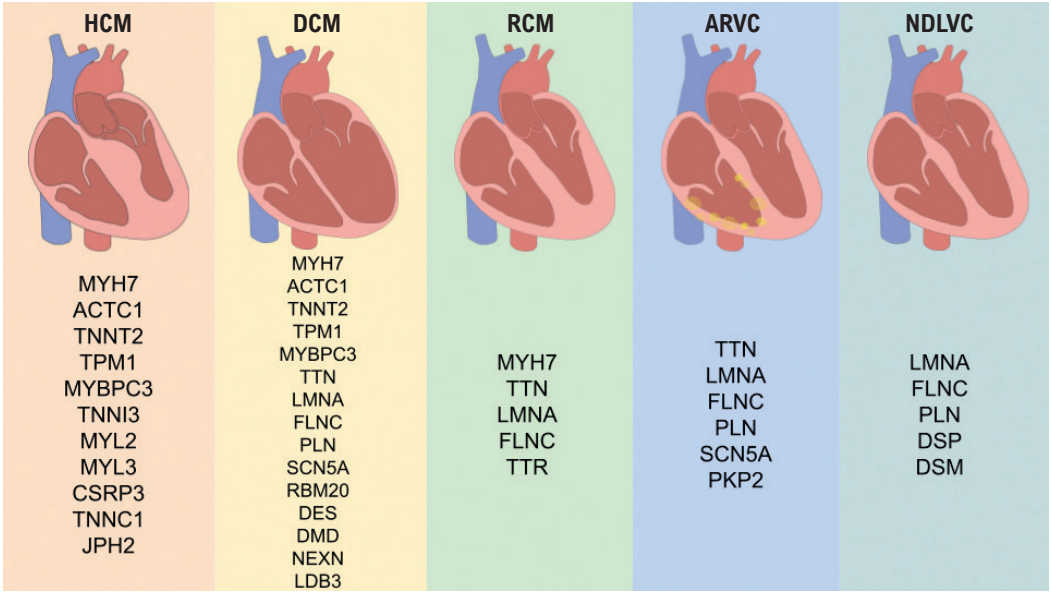
Central Illustration: Genetics of the Cardiomyopathies: A Review for the Cardiologist



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Cardiomyopathies phenotypes and the most common genes associated. Caption: The five most common cardiomyopathies are associated with pathogenic/likely pathogenic germline variants in genes that may be associated with the phenotype. In some cases, the same gene can produce distinct phenotypes. ARVC: arrhythmogenic cardiomyopathy; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; NDLVC: non-dilated left ventricular cardiomyopathy; RCM: restrictive cardiomyopathy.

Keywords

Cardiomyopathies; Genetic Testing; Heart Failure; Phenotype

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Abstract

Cardiomyopathies, myocardial diseases without other causative factors like hypertension or coronary artery disease, were once considered rare but have seen increased diagnoses due to improved imaging and clinical awareness. Recent categorizations based on predominant phenotypes, such as hypertrophic cardiomyopathy, dilated cardiomyopathy, non-dilated left ventricular cardiomyopathy, restrictive cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy highlight their complexity. Phenotype characterization is challenging due to overlapping features among different cardiomyopathies, making

genetic testing indispensable, offering insights into etiology, risks, and guiding treatments. Advancements in testing accessibility and standardized classification guidelines have facilitated early detection, enabling interventions like lifestyle modifications and targeted medication regimens to mitigate risks. Current guidelines recommend genetic testing for all cardiomyopathy patients. This review elucidates genetic variants underlying the distinct cardiomyopathies phenotypes, enabling accurate diagnoses and treatment.

Introduction

Cardiomyopathies denote myocardial diseases resulting from abnormalities in muscle structure and functionality, in the absence of other causes such as hypertension, valvular disease, coronary artery disease, or congenital anomalies.[1,2] Despite being initially described as rare diseases, advances in imaging technics and clinical awareness have led to an increase in its diagnosis.[3,4] Recently, cardiomyopathies have been categorized according to predominant phenotypes, including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), non-dilated left ventricular cardiomyopathy (NDLVC), restrictive cardiomyopathy (RCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC) (Central Illustration).[1]

Initial phenotype characterization is performed by patient's history, family history, electrocardiogram, laboratory evaluation and cardiovascular imaging, but identifying their origins can be complicated due to shared features among various cardiomyopathies.[4,5] Their heterogeneous clinical presentation and phenotypes have made genetic testing to become indispensable, offering insights into the underlying causes, assessing associated risks, and guiding potential treatment strategies.[5-7]

In recent years, significant advances have been made in genetic testing.[8,9] Initially hindered by high costs, advancements in technology and the increasing availability of testing services have rendered genetic testing more accessible.[8] Furthermore, the classification of genetic variants has improved, thanks to enhanced standardization outlined in the 2015 guidelines from the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP).[9] These advancements facilitate early detection of cardiomyopathies, enabling interventions such as lifestyle modifications, anticoagulation therapy, medication regimens, and other interventions aimed at mitigating patient risk.[1,3] In fact, recent guidelines recommend a genetic test for all patients with a cardiomyopathy.[1] The following review aims on helping the cardiologist in the understanding of the genetic variants underlying the different cardiomyopathies.

Genetic testing

Choosing the test

The selection of genetic testing methodology begins with a clinical hypothesis on the underlying disease.[8] Three main sequencing technics can be used: whole genome sequencing (WGS), wherein the whole genome, encompassing coding and non-coding regions are evaluated, but this technic is primarily employed for investigational purposes; whole exome sequencing (WES), which exclusively sequences all exons constituting protein-coding regions; and genetic panels, which target a predetermined set of genes.[10,11] The latter represents the prevailing method for assessing cardiomyopathies as it focuses on a set of established genes associated with the observed phenotype, rendering it more cost-effective compared to WGS and WES.[11] Several companies commercializes pre-set gene panels for specific phenotypes such as dilated cardiomyopathy, hypertrophic cardiomyopathy, arrhythmias, among others. Nevertheless, by defining a specific amount of genes, it may overlook rare or novel variants in untargeted genes.[8,10,11] With the progression in sequencing techniques and the availability of more economical components, the costs of WES are converging with those of genetic panels, rendering it an enticing option due to the potential for sequencing a broader array of genes.[8] However, when WES is selected for evaluating a patient with a cardiomyopathy, it is imperative to acknowledge that several genes unrelated to the specific phenotype will undergo sequencing, potentially uncovering pathogenic or likely pathogenic variants, some of which necessitate reporting (e.g., variants in BRCA1 and BRCA2 genes).[8,10] Furthermore, WES typically employs shallower sequencing depth compared to genetic panels, heightening susceptibility to sequencing errors.[6,8,10,11] These attributes should be thoroughly understood by the cardiologist ordering the test, enabling a balanced consideration of the pros and cons whenever feasible.

Pre-test evaluation

A few steps must be taken before ordering a genetic test. First, a proper family history must be taken with the most affected patients of the family.[1,6] A three generation history should always be assessed with an active screening in which the patient should be asked of how many relatives there are in each side of the family, their ages, which ones may have died of unexpected reasons, those with cardiovascular history, and any details that may unveil a possible genetic disease.[8,9] Special attention should be taken for history of heart failure, sudden cardiac death (SCD), heart surgeries or pacemakers, especially when occurring at younger ages.[8] It is recommended that the physician should not assume a cause of death, especially in cases in which an autopsy was not taken in relatives that died young or suddenly.

In addition, family counseling has always been a fundamental in patient care due to hereditary cardiomyopathies, but currently, its perspective has been modified by genetic evaluation.[1] The identification of a pathogenic or likely pathogenic variant brings a series of repercussions and discussions, from genetic education to implications in the treatment of the disease in the proband and family members who discover themselves affected, involving aspects of lifestyle, psychosocial, and work-related issues. All these points and more should be addressed in pre- and post-test counseling. (Table 1)

In cases where the genetic test is positive, meaning the presence of a pathogenic or likely pathogenic variant causing disease is identified, screening for this variant should be offered to at-risk family members. (Figure 1).

Understanding the genetic test results

Genomic sequencing inevitably unveils variants that must evaluated for its pathogenicity.[9] To discern the clinical

Table 1 – Aspects to be addressed in pre- and post-test counseling

Pre-test	Post-test
Genetic education	Recapitulation of key points from the pre-test session
Explanation of all possible results	Discussion of the results
Implications for clinical care	Specific implications for clinical care
Lifestyle implications, including sports, exercise, and employment	Lifestyle implications, including sports, exercise, and employment
Family members implication	Specific implications for the family and how to address relatives
Variants reclassification risk	Variants reclassification
Psychosocial support	Psychosocial support

significance of these variants, a comprehensive assessment is essential, incorporating multiple criteria such as the variant's frequency within the population, functional characterization through empirical studies, its correlation with the observed phenotype, patterns of segregation and inheritance, mutation type (e.g., missense, frameshift), affected genomic region (e.g., exonic, intronic), and outcomes from in silico analyses utilizing computational algorithms predicting variant impact (e.g., PolyPhen, SIFT).[9] Additionally, consideration of population-specific databases and allele frequencies, such as gnomAD, aids in discerning the rarity or commonality of the variant. Upon identification of a suspected variant, these rigorous criteria are systematically applied, aligning with the guidelines set forth by the ACMG/AMP, culminating in its classification as delineated in Table 2, ranging from pathogenic to benign or of uncertain significance.[9]

Hypertrophic cardiomyopathy

HCM is a monogenic disease with autosomal dominant inheritance characterized by ventricular hypertrophy caused by variants in several sarcomeric genes.[12] HCM is characterized by left ventricular outflow tract obstruction in 40% of patients.[12,13] Exercise intolerance, chest pain and syncope are clinical manifestations related to HCM, whereas atrial fibrillation is the most common arrhythmia.[12] Although a rare event, SCD has been associated with HCM especially in the young.[1,14] The most recent data from the National Center for Catastrophic Sports Injury Research indicate that HCM is responsible for 16.2% of deaths related to cardiovascular diseases in young athletes in the United States.[15]

CLINGEN, a collaborative study group funded by the NIH, identified that of the 33 genes most involved in the etiology of HCM, only 8 (MYBPC3, MYH7, TNNT2, TNNI3, TPM1, ACTC1, MYL2, and MYL3) have definitive evidence, 3 (CSRP3, TNNC1, and JPH2) have moderate evidence, and the remaining genes have limited to no evidence supporting an association with the disease.[16] Delving a little deeper into genetic epidemiology, we can affirm that the MYH7 genes (which encode heavy chain beta myosin) and MYBPC3 (which encode myosin-binding protein C) are responsible for the majority of cases.[17,18] In general, the sensitivity of genetic tests for the identification of the etiology in familial HCM revolves around 30% to 60% of cases.[1] The incomplete gene penetrance and genetic heterogeneity results in variable disease expression.[19] Among clinically unaffected individuals harboring a likely pathogenic or pathogenic variants, diagnosed as part of the familial genetic cascade, 46% developed HCM in a 15-year follow-up study, highlighting a moderate disease penetrance.[20]

HCM prognosis may also be affected by the genetic status. The SHARE registry studied 4,591 patients with HCM and observed that adverse events (ventricular arrhythmia, heart failure, and atrial fibrillation) were more frequent in patients with pathogenic sarcomeric variants.[21] These findings have supported the use of genetic tests in risk stratification by the European Society of Cardiology Treatment of ventricular arrhythmias and prevention of sudden death.[22]

Dilated Cardiomyopathy

DCM is defined as left ventricular or biventricular dilation of systolic dysfunction not explained by valvular disease or significant coronary artery disease.[23] The etiology of the disease is highly heterogeneous and in a significant proportion of patients no cause can be found and a genetics involvement could be associated.[23,24] A plausible genetic etiology can be identified in 10 to 40% of the cases according to clinical characteristics.[25]

Molecular genetics became essential in the evaluation of DCM.[23] The advent of next-generation sequencing has facilitated its widespread adoption, significantly advancing our understanding of the genetic basis of DCM.[24] Numerous genes have been implicated in DCM and exhibit association with various phenotypic presentations.[26] The most common inheritance is autosomal dominant, but autosomal recessive, X-linked, mitochondrial inheritance and de novo mutations are also observed.[24] The penetrance is variable depending on the type of mutation and, in mainly cases, its age-dependent.[23,26-28] Gene-environment interaction, caused by myocarditis, pregnancy, chemotherapy or alcohol, can lead to phenotypic expression in patients with DCM genetic mutations.[29,30] The pre-test probability of identifying a causative gene variant for DCM may change according to specific clinical characteristics. Skeletal myopathy, family history of DCM, low voltage on the electrocardiogram, absence of hypertension and absence of left bundle branch block are all associated with the presence of a pathogenic DCM variant.[25]

Mutations can occur in different DCM genes that encode a range of cellular mechanisms.[31] These include genes involved in cytoskeletal, sarcomeric, desmosomal, nuclear membrane, mitochondrial and RNA-binding proteins.[1,26] The TTN is the largest protein in humans and the most common gene associated with DCM and encodes titin protein.[27] In the heart, it is associated with the regulation of sarcomere contraction.[28] It typically displays an autosomal dominant pattern of inheritance and accounts for approximately 15-25% of familial DCM cases.[27,28,32] TTN mutations in DCM are mainly truncation.[28] Furthermore, two thirds of genetic variants in peripartum cardiomyopathy are found in the TTN gene.[29] Missense TTN variants have been reported in ARVC and in skeletal myopathies.[33,34] LMNA mutations contribute for approximately 8% of genetic DCM and the most common inheritance is autosomal dominant.[1] The LMNA gene encodes lamin A/C. The main characteristics of its mutation in DCM is

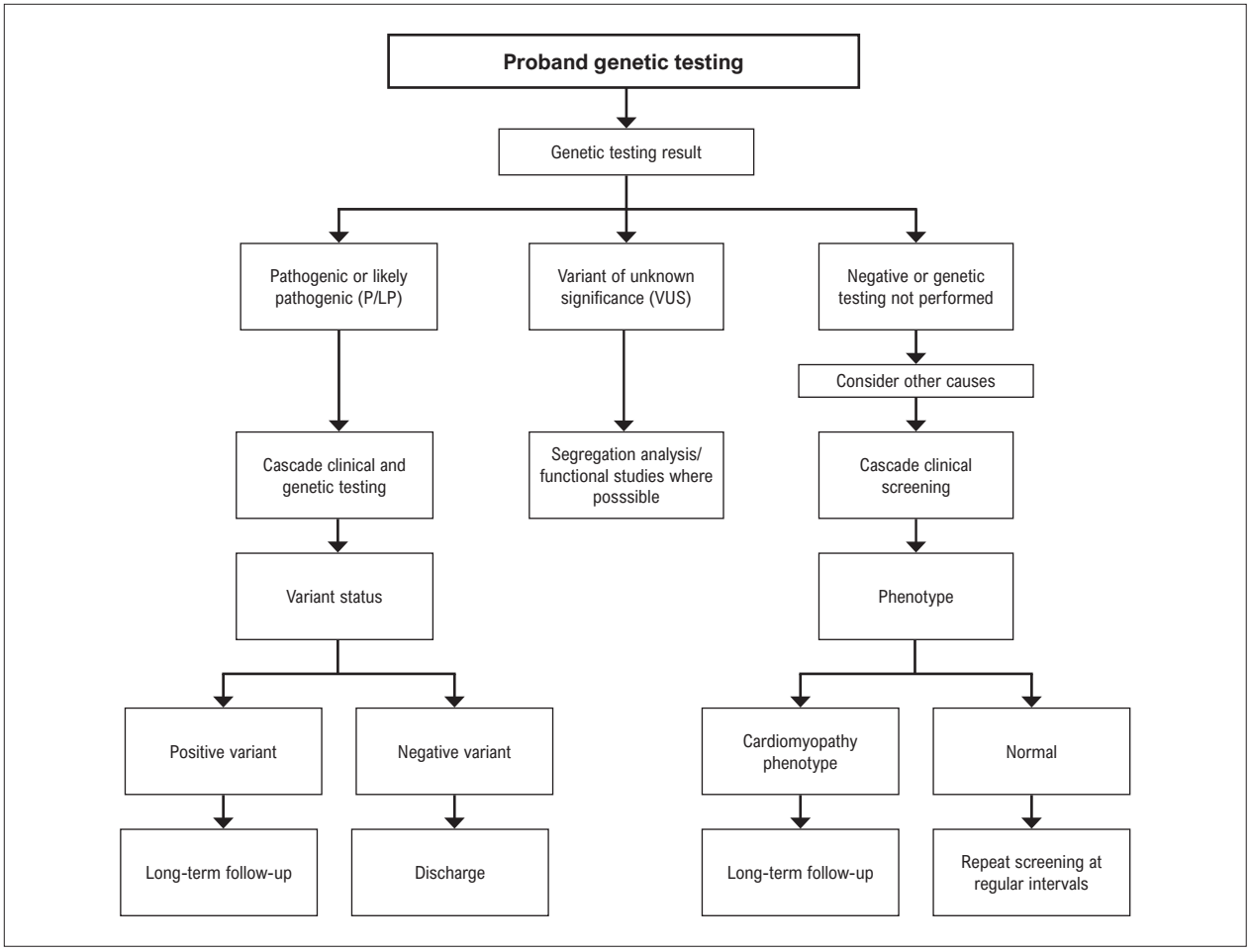

Figure 1 – *Genetic testing and results interpretation*

dysrhythmias.[23,35] Affected individuals are prone to conduction abnormalities, atrial and ventricular arrhythmias and SCD, with an annual rate of 5 - 10%.[1,35,36] Other phenotypic alterations are elevated serum creatine kinase levels and skeletal muscle involvement, such as Emery-Dreifuss muscular dystrophy.[1,23] The RBM20 mutations are presented in 1 - 5% of genetic DCM.[1] This gene encodes the RNA-binding motif 20, and the phenotypic expression associated with RBM20 mutations bears similarity to variants in the TTN gene.[37,38] The SCN5A gene encodes sodium ion channels.[39] Missense mutations within it can predispose individuals to DCM with an increased risk of arrhythmias, being also associated with Brugada and long QT syndrome.[1,39,40]

Various other genes have been linked to DCM.[1] Mutations in genes encoding for sarcomere (MYH7, MYBPC3, ACTC1, TNNT2, TPM1), some of which are also associated with HCM or left ventricular hypertrabeculation.[1,31,41] Cytoskeleton genes (DES, DMD, FLNC, NEXN, LDB3) that include mutations in dystrophin may also express with a DCM with peripheral muscular dystrophy and arrhythmias.[42-44]

Changes in therapeutic management resulting from genetic testing relies mainly on the indications for device implantation. Patients with high-risk gene mutations for SCD (LMNA, RBM20, PLN, FLNC-truncating) should be considered for ICD implantation for primary prevention even if the left ventricular ejection fraction exceeds 35%. This recommendation is particularly pertinent in the presence of additional risk factors (non-sustained ventricular tachycardia, male sex, significant late gadolinium enhancement in the cardiac magnetic resonance).[13]

Non-dilated left ventricular cardiomyopathy

Due to the new imaging and molecular techniques, the knowledge about cardiomyopathies has increased substantially over the last decades.[4] These new phenotypic descriptions created the need for new classification, to simplify terminology and standardize diagnosis and treatment. The most recent ESC statement endorsed the proposal of replacement of the previous term 'hypokinetic non-DCM' for the broader term NDLVC which incorporates what has been previously described as arrhythmogenic left ventricle cardiomyopathy (ALVC), non-dilated hypokinetic cardiomyopathy, left-dominant arrhythmogenic right ventricle cardiomyopathy and the cases of arrhythmogenic DCM which do not fulfill criteria for ARVC.[1,45] NDLVC phenotype is defined as the presence of non-ischemic LV scarring or fatty replacement regardless

Table 2 – 2015 American College of Medical Genetics and Genomics (ACMG) classification of variants

Pathogenic (P)	A genetic alteration supported by various types of evidence, including population frequency, computational and predictive data, functional studies, segregation analysis, de novo occurrences, allelic data, and reputable databases. It's important to note that some pathogenic variants may exhibit reduced penetrance.
Likely Pathogenic (LP)	A genetic alteration with a high probability (greater than 90% certainty) of being classified as pathogenic or disease-causing.
Variant of unknown significance (VUS)	A genetic alteration characterized by limited and/or conflicting evidence regarding its pathogenicity.
Likely benign (LB)	A genetic alteration with a high likelihood (greater than 90% certainty) of being classified as benign.
Benign (B)	A genetic alteration supported by sufficient evidence indicating its lack of pathogenicity.

of the presence of global or regional wall motion abnormalities, or isolated global LV hypokinesia without scarring unexplained by abnormal loading conditions or coronary artery disease.[1,45] Tissue characterization is, therefore, usually key to the diagnosis and it is assessed by cardiac magnetic resonance (CMR) including T2-weighted sequences, T1 mapping and late gadolinium enhancement.[1,46] LV systolic dysfunction is defined by the presence of an ejection fraction < 50% detected preferably by echocardiogram or CMR.[1,47]

Because NDLVC is a recently described entity, its genetic background is not well established yet.[1] Genes currently associated to NDLVC are part of the phenotypic spectrum the condition is understood to comprise, thus often overlapping with DCM and ARVC.[45,48] Desmoplakin (DSP), Filamin C (FLNC), Desmin (DSM), Lamin A/C (LMNA) and Phospholamban (PLN) are the most related genes with NDLVC.[1,49,50] Elucidating genetic etiology is potentially helpful in predicting prognosis, differentiating diagnosis, and guiding therapy e.g implantable cardiac defibrillator (ICD) implantation.[22] LMNA and FLNC-related cardiomyopathies present a rate of 5-10% of SCD each year, while PLN and DSP are right down the list presenting with a 3-5% SCD rate per year.[1,51] Also, genetic counseling and family screening might impact patients' and family members' clinical follow-up and life-changing decisions. Therefore, genetic testing is recommended in all patients identified with a NDLVC phenotype.[1] In genotype-positive phenotype-negative individuals clinical management is still challenging, as well as the precise application of family cascade screening. Further studies are needed to elucidate remaining topics.

Restrictive cardiomyopathies

Amyloidosis

Amyloidosis is an infiltrative disease caused by the extracellular tissue accumulation of protein fibrils in different organs and systems.[52,53] Currently, almost 50 different types of amyloidosis have been identified, and its origin can be genetic, neoplastic, related to renal disease in dialytic state, or chronic inflammatory states.[53] The main affected systems are neurological (especially in the peripheral nervous system, such as in carpal tunnel syndrome), cardiac, renal, ocular, and gastrointestinal.[1,54]

Cardiac Amyloidosis typically presents with a restrictive phenotype and in 98% of cases is caused by either ATTR (Transthyretin) or AL (Light Chains) types.[54] It has a relevant and underdiagnosed prevalence in patients with aortic stenosis, heart failure with preserved ejection fraction, conduction disorders, and atrial fibrillation.[53] Its diagnosis can be made based on clinical findings associated with complementary tests, including hematological evaluation, echocardiography with myocardial strain, cardiac magnetic resonance imaging, and pyrophosphate scintigraphy.[53]

Transthyretin is a protein predominantly synthesized in the liver that functions in the transport of thyroid hormone (thyroxine) and retinol (vitamin A).[53] ATTR amyloidosis can be divided into wild-type (previously known as senile), where there is transthyretin accumulation due to processes associated with aging, and hereditary type, where variants in the TTR gene cause alterations in the structural conformation of the molecule, leading to instability and consequent greater propensity to tissue deposition.[53,55]

The TTR gene is located on chromosome 18, with over 130 mutations already described with an autosomal dominant inheritance with varying levels of penetrance.[56,57] Some of these genetic variants are related to specific regions or ethnic groups, while others are widely distributed.[56-58] The most common variant of the TTR gene is Val50Met, where there is a substitution of valine by methionine, causing a predominantly neurological deposition phenotype but also affecting the heart and other organs. It is especially prevalent in Brazil, Portugal, Japan, the island of Mallorca - Spain, and in Sweden, where it reaches 4% in the regions of Piteå and Skelleftå.[59] Among other identified variants associated with cardiac involvement, we can mention Val142Ile (which occurs in almost 4% of the African-American population) and Thr60Ala.[57,59,60]

In Brazil, TTR gene sequencing is commercially available, with evaluation of the presence of nucleotide variants, insertions, and deletions.[53] In addition to diagnostic assistance, its use can be useful in screening and monitoring family members carrying the gene still in the subclinical phase of the disease.[60] Finally, genetic analysis will also play an important role in the therapeutic evaluation of amyloidosis.[55] Currently, with the introduction of transthyretin stabilizers (Tafamidis) and messenger RNA silencing molecules of TTR (patisiran and inotersen), we can

modify the natural history of these patients.[53,55] In 2021, the positive results of the first study in humans using CRISPR-Cas9 technology for editing mutant genes in patients with ATTR amyloidosis were published.[61] The promising perspective indicates that the future of transthyretin amyloidosis treatment may be based on developing and refining gene editing techniques, bringing a new horizon to the management of this pathology.[62]

Oher restrictive cardiomyopathies

Among other restrictive cardiomyopathies, apart from infiltrative or deposition diseases, we observe a rare spectrum of myocardial disorders.[1] Generally, their prognosis is unfavorable, and mortality rates is high.[1,63] With the increasing availability of genetic sequencing techniques, non-infiltrative restrictive cardiomyopathies, previously referred to as "idiopathic," can now be better understood, being recognized as yet another genetically mediated condition.[1,64] The restrictive phenotype manifests as non-dilated cardiomyopathy, without increased wall thickness, associated with diastolic dysfunction, ventricular relaxation deficit, increased filling pressures, atrial enlargement, and consequently, signs and symptoms of heart failure.[1,65] Similar to the non-ischemic dilated phenotype, the majority of restrictive cardiomyopathies can be attributed to genetic variants.[65] Studies demonstrates that in up to 75% of cases this etiology can be identified, either through active search for evidence among relatives carrying the pathology, or through identification of pathogenic variants.[63,65] Overall, inheritance is autosomal dominant, noting that it is interesting to observe how the same genetic variants can express themselves with different phenotypes - with the intersection between hypertrophic and RCM being very common, but also presenting as dilated phenotype and even as non-compacted myocardium.[1,63,65]

Most of the related genes are responsible for encoding sarcomeric proteins (TTN and MYH7), but variants have also been identified in genes responsible for proteins not directly related to contractile activity, such as filamentous sites (LMNA and FLNC).[64] Although not all mechanisms involved in the loss of ventricular function and diastolic dysfunction are well understood, we can now understand that the consequences of genetic variants are expressed in two main points: calcium homeostasis in cardiomyocytes and the interaction among myocardial proteins related to ventricular contraction.[63]

The first effect is based on the alteration of calcium sensitivity in the sarcomeric unit and the control of its influx and efflux in the sarcoplasmic reticulum. This results from pathological conformational variants of intracellular proteins involved in the contractile process, causing distortion of physiological myocardial relaxation and predisposing the individual to a higher risk of ventricular arrhythmias - a pathophysiological phenomenon shared also with HCM.[66] The second mechanism involved in restrictive phenotypes are mutations affecting proteins directly linked to myocardial contraction. Among sarcomeric variants, the most common involve genes encoding troponin (especially in its I unit - cTnI).[67] The most affected region is the C-terminal portion, where troponin interacts with other proteins involved in muscle contraction, such as actin, tropomyosin, and cMyBP-C (cardiac myosin-binding protein C).[67] cTnI mutations are the most prevalent among patients with RCM. Finally, in addition to mutations related to sarcomeres, we can also mention non-sarcomeric pattern genetic alterations, with the most common phenomenon being protein aggregation, with intracellular deposition of molecules such as desmin, filamin C, and alpha-B crystallin, which due to pathological structural changes, aggregate and deposit within the sarcoplasmic reticulum.[67-69]

Arrhythmogenic right ventricular cardiomyopathy

ARVC is a rare, genetic disorder that is characterized by the replacement of the myocardium, specifically in the right ventricle, with fibrofatty tissue.[1,70-72] This pathological transformation leads to highly arrhythmogenic clinical presentations not explained by ischemic, hypertensive, or valvular heart disease.[71] Although most commonly affects the right ventricle, some cases may present with a left-predominant form.[71,72] Therefore, some authors refer to this entity as arrhythmogenic cardiomyopathy.[71] Clinical presentation may occur between the second and fifth decade of life by ventricular arrhythmias and SCD.[71,72]

The genetic underpinnings of ARVC are often associated with mutations in desmosome-specific genes in 60% of cases.[1,73] Desmosomes are intercellular junctions that are necessary for myocyte stability and integrity.[71] The major components of the desmosome include Plakophilin-2 (PKP2), Desmoglein-2 (DSG2), Desmocollin-2 (DSC2), Desmoplakin (DSP), and Plakoglobin (JUP).[1,73] Although several genes are involved, most cases are caused by pre-mature termination of protein or abnormal splicing of the PKP2 gene.[73,74] Mutations in these genes, usually in autosomal dominant pattern and incomplete penetrance, can lead to defective mechanical bonds that hold heart cells together.[71,74] Desmosome mutations have been associated with some clinical caveats such as inverted anterior pre-cordial T-waves (V1-V3), family history and early onset of the disease with the presence of a causative mutation.[75] However, other genes related to other cardiomyopathies may also present with ARVC phenotype such as TTN, LMNA, PLN, SCN5A, and FLNC.[1] Patients carrying multiple mutations may be more prone to present with ventricular arrhythmias, suggesting a gene-dosage effect in ARVC.[76]

The molecular mechanisms of ARVC are complex, and the genetic architecture is ever-evolving.[1,73,75] Given this, multidisciplinary patient care for the incorporation of genetics and family cardiovascular care is critical. Future work will refine the understanding of gene-specific outcomes in ARVC and implications for tailored therapy.

Conclusion

The pivotal role of genetics in cardiomyopathies cannot be overstated. Through extensive research and technological advancements, genetic factors have emerged as key determinants in shaping the phenotype of cardiomyopathies. By elucidating the genetic underpinnings, clinicians can

better establish accurate diagnoses, leading to more tailored and precise treatment strategies. Furthermore, the evolving landscape of genetic knowledge continues to revolutionize therapeutic approaches, with targeted interventions aimed at mitigating specific genetic abnormalities. Thus, integrating genetic insights into clinical practice not only enhances our understanding of the cardiomyopathies but also holds tremendous promise in optimizing patient care and outcomes.

Author Contributions

Conception and design of the research: Scolari FL, Bittencourt MI; Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for content: Scolari FL, Garbin HI, Beuren TMA, Matheus FC, Mourilhe-Rocha R, Bittencourt MI.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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