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REVIEW ARTICLE

Genetic Testing in Cardiomyopathy: Decoding Molecular Underpinnings and Influencing Treatment Decisions

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Abstract

Cardiomyopathy is characterized by structural and functional abnormalities in the heart muscle that are not influenced by coronary disease, hypertension, valve disease, or congenital heart defects. Genetic testing, which helps diagnose the molecular bases of cardiomyopathy, can affect prognostication and clinical decisions. Recent guidelines advocate classifying cardiomyopathies based on phenotypic categories, which encompass a range of clinical presentations, underlying causes, and outcomes. Beyond deepening our grasp of the disease, genetic testing can distinguish between diseases with similar presentations, known as genocopies, which can profoundly influence treatment decisions. Genetic testing is also essential for reproductive counseling and risk evaluation among family members. Combined with advanced imaging techniques such as magnetic resonance imaging, genetic investigation offers a comprehensive understanding of the disease. Thus, as the nature of cardiomyopathies continues to be unraveled, cardiologists must stay updated on advances in genetic testing and their practical applications.

Introduction

Cardiomyopathy is a myocardial disorder in which the heart muscle undergoes structural and functional abnormalities when other diseases, such as coronary disease, hypertension, valve disease, or congenital heart disease, cannot account for these changes.[1] Nevertheless, cardiomyopathies can coexist with other conditions, including ischemic, valve, and hypertensive diseases.[2]

The most recent European Society of Cardiology guidelines emphasized the importance of genetic testing after phenotypic characterization for cardiomyopathies. Such testing could be highly valuable for diagnosis, revealing etiology after phenotypic evaluation, clarifying uncertain cases, and identifying genocopies.[2] It also contributes to prognostic evaluation, guides individuals toward specific treatments, refines risk assessment for sudden cardiac death, informs decisions about implantable cardioverter defibrillators, and provides information for reproductive decisions and family assessments.[2,3]

Although the foremost step in classifying cardiomyopathies is phenotype assessment, it should be noted that various phenotypes can exist within the same family, and an individual's phenotype may change over time. Genetic insight can clarify these situations.[2] Additionally, a comprehensive family history spanning 3 or 4 generations is invaluable for understanding inheritance patterns, disease etiology, and identifying at-risk family members.[2,4,5]

European Society of Cardiology guidelines recommend genetic counseling and testing for patients who fullfill cardiomyopathy criteria (class of recomendation I, level of evidentece B). It also suggests post-mortem genetic analysis if it could improve the treatment and survival of family members (level of

Keywords

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Central Illustration: Genetic Testing in Cardiomyopathy: Decoding Molecular Underpinnings and Influencing Treatment Decisions

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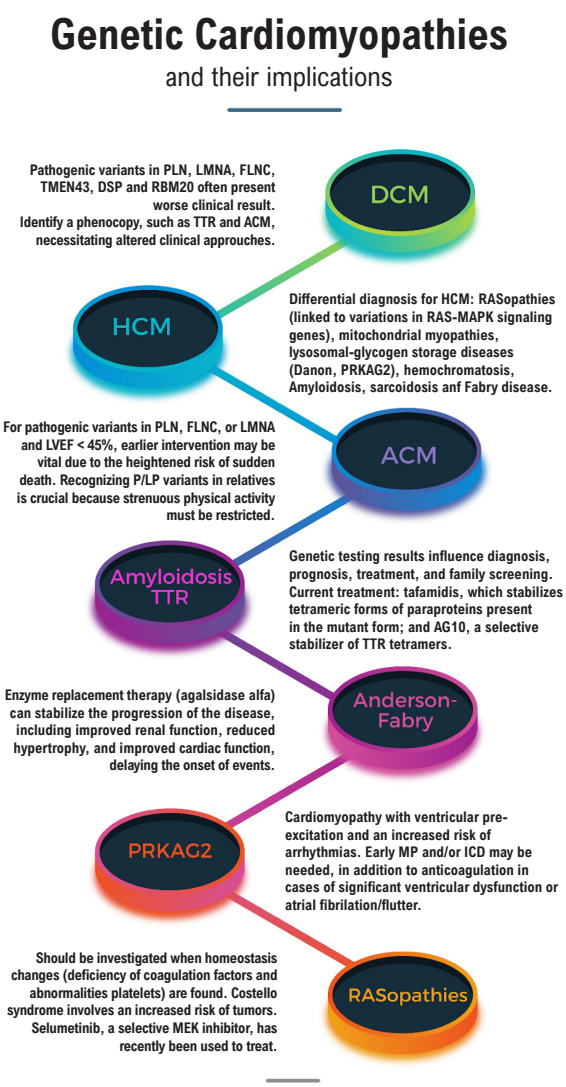

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Genetic implications of cardiomyopathies. Genes. PLN: phospholamban; LMNA: lamin A/C; FLNC: filamin C; TMEM43: transmembrane protein 43; DSP: desmoplakin; RBM20: RNA binding motif protein 20; TTR: transthyretin; PRKAG2: protein kinase AMP-activated non-catalytic subunit gamma 2; DCM: dilated cardiomyopathy; ACM: arrhythmogenic cardiomyopathy; HCM: hypertrophic cardiomyopathy; LVEF: left ventricular ejection fraction; P/LP: Pathogenic/likely pathogenic; ICD: implantable cardioverter defibrillator; AG10: acoramidis; MEK: MAPK-ERK kinase.

evidence C).[2]

This review will explore the phenotypes of cardiomyopathies, their genetic assessment, rare cases, and conclude with a discussion on genocopies and their clinical relevance.

Dilated Cardiomyopathy (DCM)

DCM is characterized by dilation of the left ventricle and reduced ejection fraction that is unexplained by secondary causes such as myocardial ischemia, arterial hypertension, or primary valve and congenital heart diseases.[1,2,5-7] Its prevalence ranges between 1 in 250 to 1 in 500 in the broader population.[7,8] Inherited and sporadic DCM must be differentiated. For instance, hereditary DCM is when ≥ 2 members of the same family meet the criteria for DCM, or when the proband has a first-degree relative who died suddenly before 35 years of age or

whose DCM was confirmed through autopsy. Genetic testing is more fruitful in hereditary DCM scenarios.[7,9-11]

DCM has many causes, both genetic and environmental.[2,6] These include genetic variants, toxin exposure, infections, autoimmune responses, storage diseases, and tachyarrhythmias. Monogenic variants associated with DCM have remarkable diversity, involving multiple genes and multiple biological pathways. Disease modifiers can worsen the DCM phenotype, such as epigenetic factors and acquired modifiers, including pregnancy, hypertension, and excessive consumption of alcohol and other toxic substances.[2,6,12] Various genetic factors may play a role, and it is essential to consider the interplay between genetic and acquired causes during diagnosis.[2,13-15]

Selecting the right test is paramount. Given the variety of genes linked to DCM, whole exome or specific panel sequencing can be used. While whole exome sequencing could offer a broader analysis, a specialized cardiomyopathy panel ensures focus on DCM-related genes. Whole exome sequencing analyzes a large number of genes, including genes unrelated to cardiac pathologies, and could lead to secondary findings, for which the assistance of a geneticist is instrumental. The cardiomyopathy panel consists of DCM-related genes and is available in different configurations[16,17] (Table 1).

The current genetic testing yield for DCM varies from 15% to 40%.[5] A recently proposed scoring system, the Madrid score, can estimate the likelihood of pathogenic variants in DCM. This score considers the presence of skeletal myopathy, family history of DCM, electrocardiogram voltage, history of hypertension, and an absence of left bundle branch block in electrocardiography. When ≥ 4 of these factors are present, the test's positivity rate can reach 79%. However, the absence of such variants does not nullify DCM diagnosis or risk among close relatives.[18] Nevertheless, only selected cases should undergo genetic evaluation.[4,5]

Genetic insights can profoundly influence DCM management, assisting in differential diagnosis, prognosis, and personalized treatment. Patients carrying pathogenic or likely pathogenic variants often experience worse clinical outcomes, particularly concerning malignant arrhythmias and severe heart failure.[19] Some of these variants, such as those in *PLN*, *LMNA*, *FLNC*, *TMEM43*, *DSP*, and RBM20, with other risk factors, can support the use of implantable cardioverter defibrillators as a primary preventive measure.[2,3] Moreover, these variants have been associated with a lower likelihood of reverse cardiac remodeling, even when optimal clinical treatments are provided.[19] In certain instances, genetic testing identifies a genocopy, such as *TTR*-related amyloidosis or arrhythmogenic cardiomyopathy (ACM), requiring alternate clinical approaches and specialized treatment.[20,21]

Genetic analysis also influences detection rates among first-degree relatives. It can uncover individuals at risk of DCM or those who already have the disease but no evident symptoms. Among patients who received a heart transplant due to DCM, a study discovered pathogenic or likely pathogenic variants in 39.6% of their family members. Notably, 52.6% of these family members showed no clinical manifestations of the disease.[22] Timely identification of DCM in a family is crucial, since it facilitates early intervention, which prevents disease advancement and reduces the risk of sudden death.[5,7,23]

Hypertrophic Cardiomyopathy (HCM)

HCM is characterized by abnormal heart wall thickening due to genetic factors, excluding secondary causes like hypertension, amyloidosis, intense physical exercise, metabolic disorders, and heart valve diseases. Hypertrophy, the enlargement of the cardiac muscle, predominantly occurs in the septal wall. It is asymmetric in up to 95% of cases, but it can also be evenly distributed (symmetric hypertrophy), although the septal variant is more common. In approximately 75% of patients, this condition can lead to partial obstruction of left ventricle blood flow during rest or when induced by the Valsalva maneuver.[24,25]

Because the term HCM has been used interchangeably with other nomenclatures in the past, genuine HCM must be distinguished from conditions with similar symptoms. In the 6 decades since HCM was first clinically described, the disease has been referred to by various names, including idiopathic hypertrophic subaortic stenosis and obstructive HCM. Given that obstruction of the left ventricular outflow tract is evident or emerges in the majority of HCM patients but remains absent in approximately one-third, the consensus is to use HCM to denote cases both with and without left ventricular outflow tract obstruction. Using HCM when there is left ventricular wall thickening due to systemic conditions or secondary causes of ventricular hypertrophy can be misleading. Systemic conditions encompass a range of metabolic and multisystemic disorders, including

Table 1 - Main genes related to cardiomyopathies.

DCM		
TTN	TNNT2	ACTN2
BAG3	DES	JPH2
DSP	DMD	NEXN
FLNC	PLN	TNNI3
LMNA	SCN5A	TPM1
MYH7	TNNC1	VCL
RBM20	ACTC1	
HCM		
MYBPC3	TNNT2	MYL2
MYH7	TPM1	MYL3
TNNI3	ACTC1	CSRP3
TNNC1	JPH2	
ACM		
PKP2	DES	TGFB3
DSP	LMNA	TTN
DSG2	TMEM43	CDH2
DSC2	PLN	SCN5A
JUP	CTNNA3	
Amyloidosis		
TTR		
Rare Cardiomyopathies		
PRKAG2	LAMP2	GLA
GAA		

RASopathies (BRAF, KRAS, MAP2K1, MRAS, NRAS, PTPN11, RAF1, RASA2, RIT1, RRAS2, SOS1, SOS2, LZTR1, MAP2K2, HRAS, SHOC2, PPP1CB, NF1, SPRED1, SPRED2, CBL, A2ML1)
DCM: dilated cardiomyopathy; ACM: arrhythmogenic cardiomyopathy; HCM: hypertrophic cardiomyopathy.

RASopathies (linked to variants in RAS-MAPK signaling pathway), mitochondrial myopathies, glycogen/lysosomal storage diseases in children, and conditions like Danon disease, amyloidosis, and Fabry disease in adults. While the extent and pattern of left ventricular wall thickening in these conditions might mirror that of isolated HCM due to sarcomeric gene variations, the underlying mechanisms, progression, and therapeutic approaches differ. Therefore, it is essential to recognize that cardiac or systemic diseases which can lead to ventricular hypertrophy should not be classified as HCM.[24-26]

Further investigation of cardiomyopathies requires an imaging test, such as echocardiography, but cardiac magnetic resonance imaging is the gold standard (Figure 1). Diagnostic challenges can arise in various situations, particularly conditions that lead to secondary ventricular hypertrophy, which may resemble HCM. Examples of such conditions include heart remodeling due to athletic training ("athlete's heart") and morphological alterations stemming from chronic

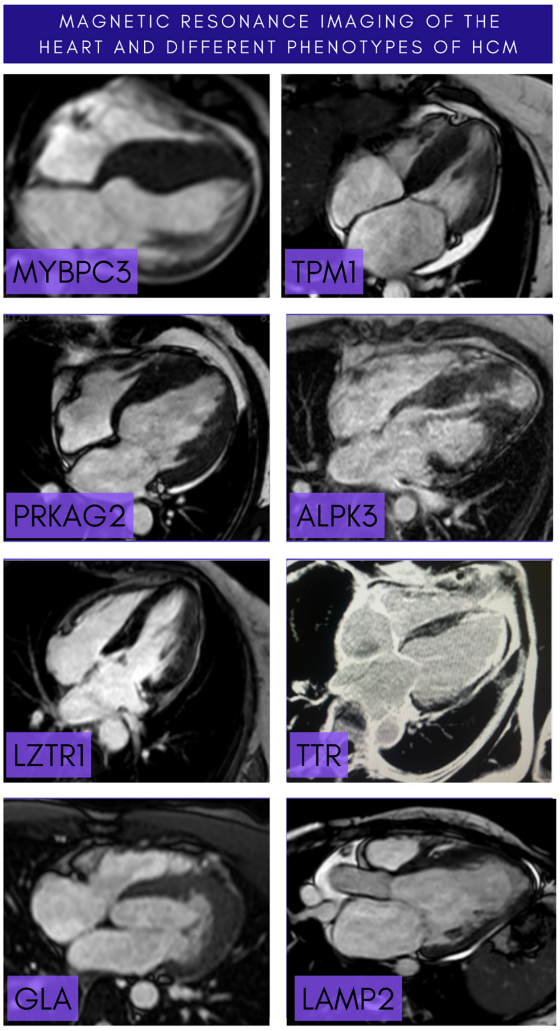

Figure 1 – Eight phenotypes of left ventricular hypertrophy. HCM due to(myosin binding protein C3 (MYBPC3). HCM due to tropomyosin 1 (TPM1) and PRKAG2 syndrome. HCM due to alpha kinase 3 (ALPK3). Noonan syndrome with HCM due to leucine zipper-like post translational regulator 1 (LZTR1). TTR amyloidosis. Fabry disease due to galactosidase alpha (GLA). Danon disease due to lysosomal associated membrane protein 2 (LAMP2).

systemic hypertension (hypertensive cardiomyopathy). Furthermore, left-sided obstructive abnormalities, whether due to valvular or subvalvular stenosis, or even gradients secondary to non-pathological situations, such as a sigmoid-shaped septum, can also create diagnostic ambiguities.

While it is challenging to conclusively exclude HCM in these scenarios, a combination of clinical indicators and testing methods can help distinguish HCM from physiologically-induced ventricular hypertrophy.[27]

HCM is generally inherited in a Mendelian pattern, primarily as an autosomal dominant trait.[28] For individuals suspected of HCM, advanced sequencing techniques, such as genetic panels, are advised. These panels typically include at least the 8 primary sarcomeric genes, with *MYH7* and *MYBPC3* being particularly significant, since they comprise approximately 70% of diagnosed cases. This approach often reveals pathogenic or likely pathogenic variants identified as disease-causing in roughly 30% of sporadic cases and 60% of family cases. Notably, certain variants in genes such as *TNNC1* and others not directly linked to the sarcomere, such as *CSRP3*, *JPH2*, *ALPK3*, and *FHOD3*, have been highlighted due to the moderate-to-strong evidence of pathogenicity.[16] It is crucial that competent medical laboratories or teams assess the pathogenicity of this genetic variant, and such assessment should adhere to American College of Medical Genetics and Genomics standards. Specifically for the *MYH7* gene, there is an adapted pathogenicity classification system overseen by a ClinGen expert panel. The test yield is roughly 60%, and the disease penetrance is estimated at around 80%.[29]

ACM

ACM is a genetic disorder characterized by cardiomyocyte death and fibro-fatty replacement. Myocardial scarring increases the risk of sudden cardiac death, particularly in youth and athletes.[2,30] Previously described only in the right ventricle, new insights have changed our understanding of the disease, and it is now recognized that ACM can also affect the left ventricle or both ventricles simultaneously, leading to the broader term "arrhythmogenic cardiomyopathy".[21]

Patients with ACM can present a heterogeneous range of clinical symptoms, from asymptomatic to sudden cardiac death or severe heart failure requiring heart transplantation. Some ACM presentations can mimic myocarditis, with symptoms such as chest pain, electrocardiographic changes, and increased troponin levels, despite no obstructive coronary disease. The diagnostic criteria for the form with predominant right ventricle involvement are based on the 2010 International Task Force criteria for arrhythmogenic right ventricle cardiomyopathy.[31] However, these criteria lack the necessary sensitivity and specificity to diagnose the form with predominant left ventricle involvement. The 2020 international (Padua) criteria for ACM updated the imaging and structural criteria for the right-dominant form

and introduced new criteria for the left-dominant form. Diagnosing the left-dominant form requires confirmation of a related pathogenic or likely pathogenic variant.[32]

Several genes, primarily those that encode cardiac desmosome proteins, are linked to ACM. These include *PKP2, DSP, DSG2, DSC2*, and *JUP*. ACM can also be linked to non-desmosomal genes, such as *PLN, FLNC, DES, TMEM43*, and *LMNA*.[21,33] Genotype-phenotype studies suggest that genes such as *DSP, PLN*, and *FLNC* are often associated with left-dominant ACM, while genes like *PKP2, DSC2*, and *DSG2* are typically associated with right-dominant ACM.[16,21]

For patients in whom a pathogenic ACM variant is identified, genetic screening for first-degree relatives is recommended.[2] Recognizing pathogenic or likely pathogenic variants in relatives is crucial because strenuous physical activity must be restricted in these patients, given the association with early symptom onset and increased arrhythmic burden.[2,34,35]

Patient risk should be stratified according to specific guidelines to determine the need for a cardioverter defibrillator, thus reducing the risk of sudden death. For patients with pathogenic variants in *PLN, FLNC, or LMNA* and an LVEF < 45%, early cardioverter defibrillator implantation may be considered due to the high risk of sudden death.[21]

Restrictive Cardiomyopathy (RCM)

RCM is characterized by a pattern of increased ventricular filling pressure, even in small volumes, which is attributed to increased myocardial stiffness. This condition may manifest as uni- or biventricular diastolic or systolic dysfunction. Biatrial enlargement commonly presents as a notable feature of RCM. Individuals with end-stage hypertrophic or DCM can also present restrictive physiology, with the preferred terms being "HCM" or "DCM with restrictive physiology."' Restrictive physiology can also arise from pathologies such as fibrosis, fibroelastosis, and thrombosis, which adversely affect diastolic function.[1,2]

Although its exact prevalence is still unknown, it is likely the least common type of cardiomyopathy.[1,36] RCM may arise idiopathically, manifest as a family condition, or result from systemic disorders such as amyloidosis, sarcoidosis, carcinoid heart disease, scleroderma, or anthracycline toxicity.[36]

Familial RCM is frequently characterized by autosomal dominant inheritance. In some families, this inheritance pattern is linked to mutations in the troponin I gene (*TNNI3*) and other sarcomeric subunits, including troponin T (*TNNT2*), α-actin (*ACTC*), and B-myosin heavy chain (*MYH7*). Alternatively, in certain cases, familial RCM is associated with conduction defects stemming from mutations in the desmin gene, typically involving skeletal myopathy. In rare cases, familial RCM may have an autosomal recessive inheritance pattern, as observed in conditions such as hemochromatosis due to mutations in the *HFE* gene or glycogen storage diseases, such as Danon disease and protein kinase, AMP-activated, noncatalytic, gamma 2 subunit cardiac (*PRKAG2*) syndrome. X-linked inheritance, such as in Anderson-Fabry disease, is another rare association with familial RCM.[1,36]

Moreover, restrictive ventricular physiology can result from endocardial pathologies, including fibrosis, fibroelastosis, and thrombosis, thereby compromising diastolic function. The fundamental therapeutic approach is based on treating an identified cause, combined with traditional heart failure management. Advances in interactive genomic analysis and biomarkers, such as transcriptome and microRNAs, have enabled the characterization of different phenotypes, providing valuable information about treatment options and prognosis.[36]

Amyloidosis

Systemic amyloidosis involves the extracellular deposition of fibrillar proteins. These proteins, when stained with Congo red, have emerald green birefringence under polarized light and can be found in multiple organs, including the heart and nervous system.[37]

Once deemed rare, cardiac amyloidosis is being detected with increasing frequency as diagnostic methods evolve. Some studies show that 13% of patients with heart failure with preserved ejection fraction and 25% of autopsied older adults show amyloid transthyretin (ATTR) deposits in the heart. In other words, it is a relevant and underdiagnosed disease. Significant treatment advancements have also emerged with the discovery of novel disease-modifying medications.[20]

Although over 30 proteins can induce amyloidosis, only 9 lead to cardiac manifestations. Of these, the immunoglobulin light chain and ATTR types account for the majority of cardiac amyloidosis cases.[37]

Immunoglobulin light chain amyloidosis is a

hematologic clonal disease in which abnormal plasma cells or B lymphocytes produce immunoglobulin light chains,[38] which is not the focus of this article.

The ATTR form is characterized by a misfolding of TTR, a protein that transports thyroxine and retinol. This misfolding can occur due to mutations in the *TTR* gene, leading to the variant form (ATTRv). In wild-type ATTR, the amino acid sequence is normal, but the wild-type protein becomes unstable for unclear reasons, likely related to aging, leading to aggregation into amyloid fibrils.[20,37]

ATTRv is due to variants in the *TTR* gene. Over 140 *TTR* variants have been documented, with most being pathogenic and having autosomal dominant inheritance.[39] Clinical manifestations affecting the heart and nervous system, age of onset, and geographical distribution vary based on the specific variant (Table 2).[40] In the United States, the most common variants are Val142Ile, Thr80Ala, and Val50Met, while Val50Met, Val142Ile, and Glu89Gln are the most frequent worldwide. Although the worldwide prevalence of Val142Ile is higher than that of Val50Met, the penetrance of Val30Met appears to be higher, making the incidence of Val50Met-related cardiac ATTRv amyloidosis higher. The predominant phenotype of the Val142Ile variant is cardiac, with manifestations such as left ventricular hypertrophy, RCM, heart failure, atrial fibrillation, and conduction disorders. However, approximately 60% of these individuals also present with sensory neuropathy. Patients with Val50Met and early disease onset predominantly present with polyneuropathy, but those with later onset also often have cardiomyopathy. Leu131Met and Ile88Leu are variants reported in Denmark and Italy, respectively, and present with a predominantly early-onset cardiac phenotype and a more severe course.[41]

Genetic testing must be performed for all ATTR amyloidosis patients, since the results influence diagnosis, prognosis, treatment, and family screening.[40,42] Genetic counseling should be offered, including explanation of the implications and an offer to test immediate relatives.[43]

Clinical monitoring of at-risk patients (ie, those with a pathogenic *TTR* gene variant but no manifestation of disease) is primarily guided by expert recommendation. Once this gene variant is identified, forecasting the onset of the disease relies on both populational data and family trends.[42] Clinical monitoring should begin a decade prior to the anticipated age of disease onset (≤ 60 years, depending on family history), including annual assessment. This interval can be reduced for variants known to progress more rapidly.[44] Initial tests typically include electrocardiography, transthoracic strain-imaging echocardiography, cardiac magnetic resonance, pyrophosphate scintigraphy, and certain lab tests, such as BNP, troponin, renal function assessment, as well as serum and urinary protein electrophoresis. For patients with specific variants like Thr80Ala and Val50Met, neurological evaluation with baseline electroneuromyography might be beneficial. Subsequent visits should include clinical evaluation (focused on neuropathy assessment) and electrocardiography. Other tests can be determined based on patient needs.[42,43] If changes indicating disease progression are observed in clinical or supplemental tests, treatment options must be promptly evaluated. However, for asymptomatic patients who only possess the gene variant and show no signs of disease, targeted treatment is not recommended due to a lack of evidence regarding its efficacy and safety.[40,42]

Rare Cardiomyopathies and Genocopies

Rare cardiomyopathies encompass a diverse array of phenotypes that resemble 'classic' morphologic subgroups such as HCM, DCM, ACM, RCM, and non-dilated left ventricular cardiomyopathy. Notably, these differ substantially in causation, pathophysiology, risk stratification, and therapeutic approaches.[2]

The term "phenocopies" denotes conditions that outwardly mirror the presentation of another disorder yet stem from distinct pathophysiological roots. While often used to describe any cardiomyopathy-like condition with a differing etiology, its core definition, albeit debated, refers to non-genetic diseases with phenotypes akin to genetic disorders. In HCM, for instance, phenocopies may include acquired conditions such as hypertensive heart disease, athlete's heart, or myocardial hypertrophy due to aortic stenosis. Interestingly, the European Society of Cardiology has designated genetically-based phenocopies as "genocopies".[2]

Accurate identification of a cardiomyopathy's etiology profoundly influences patient management and prognosis, especially when targeted treatments exist.[45] Establishing a "phenotypic diagnosis" requires delving deeper for a precise etiological diagnosis. This involves spotting diagnostic red flags, with age being a primary indicator for rare cardiomyopathies.[46] Here, symptoms, family history, complementary examinations, and, especially, genetic testing, guide this diagnostic journey.

Table 2 - Key differences among pathogenic variants of ATTRv amyloidosis

Pathogenic variant in TTR gene (NM_000371.4)	Geographic distribution	Prevalence	Age onset	Phenotype	Penetrance	Survival
Val50Met	Portugal, Spain, France, Switzerland, Sweden, Germany, Japan, and Brazil	Most common world-wide variant, prevalence can approach 1:1000 in endemic areas	30–40 years in endemic areas, 50–60 years in nonendemic areas.	Cardiomyopathy: 26.9% Sensory neuropathy: 89.5% Motor neuropathy: 38.9% Autonomic neuropathy: 69.3%	Variable according to geographic locale and age at disease onset	Death within 10 to 20 years of disease onset
Val142Ile	Western Africa, USA, Caribbean, and Europe	3–4% of African-Americans	>65 years	Cardiomyopathy: 96.6% Sensory neuropathy: 60.3% Motor neuropathy: 19% Autonomic neuropathy: 27.1%	Low, but undefined and age-dependent	Death within 5-6 years of disease onset
Thr80Ala	Appalachia (USA), UK, Ireland, and Japan	1% North-west Republic of Ireland	>60 years	Cardiomyopathy: 90.5% Sensory neuropathy: 80% Motor neuropathy: 25% Autonomic neuropathy: 40%	Low penetrance	Death within 6.6 years of disease onset
Ile88Leu	Central-northern Italy	Unknown	>60 years	Cardiomyopathy: ~100% Carpal tunnel syndrome: 42% Peripheral neuropathy: <10%	Unknown	Unknown
Leu131Met	Denmark	Unknown	>30 years	Cardiomyopathy: 100% Carpal tunnel syndrome: common	Unknown	Unknown

Comprehensive diagnostic assessment requires a 3-generation pedigree to determine inheritance patterns. DCM, for instance, can involve different inheritance patterns, such as autosomal dominant, X-linked, autosomal recessive, and matrilineal. Physical examinations should monitor for signs such as hepatomegaly, ataxia, muscle weakness, and scoliosis. Routine laboratory evaluations can help pinpoint systemic causes, including assessing serum creatinine, creatine phosphokinase enzyme, myoglobinuria, transaminases, and blood lactate. For instance, elevated creatine phosphokinase levels may indicate glycogen storage disorders or muscular dystrophies, such as Duchenne, Becker, and Emery-Dreifuss, while proteinuria hints at Anderson-Fabry disease.[47] Muscular dystrophies (Duchenne, Becker, and Emery-Dreifuss) often correlate with DCM, including a heightened risk of atrioventricular block and ventricular arrhythmias.[48] Electrocardiography findings might show ventricular preexcitation in mitochondrial disorders or Pompe disease, high-amplitude QRS complexes in Pompe disease, or right-axis deviation indicative of RASopathies. In children, significant symmetrical left ventricular hypertrophy could suggest metabolic or storage disorders. When concentric left ventricular hypertrophy is combined with systolic dysfunction, it indicates potential underlying conditions, such as storage disorders, mitochondrial anomalies, or metabolic disorders, including beta-oxidation disorders.[49]

- ***Dystrophinopathies***

Dystrophinopathies arise from pathogenic variants in the dystrophin gene, leading to muscle weakness, especially in the girdle muscles, which often manifests as gait abnormalities. These disorders can also show signs of developmental delay and DCM. Becker muscular dystrophy is linked to in-frame mutations of the *DMD* gene, which result in diminished dystrophin protein

levels. On the other hand, Duchenne muscular dystrophy patients commonly have a complete lack of dystrophin and usually develop symptoms during childhood.[50] Glucocorticoids are advised for Duchenne muscular dystrophy patients experiencing deteriorating motor function. There is also evidence that steroids have beneficial effects in maintaining cardiac function. However, this evidence comes exclusively from observational studies, making the recommendation inapplicable to isolated dystrophin-deficient cardiomyopathy.[51]

- ***Mitochondrial disorders***

Mitochondrial disorders involve a broad range of clinical and genetic variations. Due to their systemic nature, they predominantly affect organs with high-energy needs, especially the heart. While the majority of these disorders stem from nuclear DNA mutations related to the mitochondrial respiratory chain, which are inherited in classic Mendelian patterns, a smaller percentage are traced back to mitochondrial DNA pathogenic variants. These mitochondrial DNA variants lead to diverse systemic effects with varying severity. In some cases, cardiac anomalies, particularly HCM, can be the primary or even the sole manifestation of a mitochondrial disorder. One notable example is mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome. Caused by mitochondrial DNA mutations that affect transfer RNA, MELAS is linked to HCM, DCM, ventricular pre-excitation, and conduction disease.[52]

- ***Friedreich ataxia***

Friedreich ataxia is an autosomal recessive inherited condition, mostly resulting from a biallelic GAA triplet repeat expansion in the first intron of the frataxin gene. This disease is a significant cause of HCM in children and often manifests with muscular weakness and ataxia. Some patients may develop diabetes mellitus. Given the severe prognosis, early diagnosis is crucial, with clinical markers aiding in identification. Electrocardiography may reveal supraventricular arrhythmias like atrial fibrillation, echocardiography might show concentric hypertrophy, and magnetic resonance imaging might indicate fibrosis, a potential negative prognostic factor. A hallmark of this condition is mitochondrial iron accumulation. Although various clinical markers can facilitate diagnosis and multiple diagnostic criteria have been suggested, definitive diagnosis relies on genetic testing.[51] Open-label studies have linked idebenone, a coenzyme Q10 analogue, with improved cardiac outcomes, but 4 randomized controlled trials found no significant cardiac or neurological benefits. Currently, no specific treatment exists for Friedreich ataxia.[53]

- ***RASopathies***

RASopathies in infants typically present with HCM and biventricular obstruction, which may occur as a primary finding or due to pulmonary valve or subvalvular stenosis. For instance, Noonan syndrome, the most prevalent RASopathy, is a leading cause of infantile HCM and is linked to early mortality.[48] RASopathies are also frequently related to tumors and neoplasia, although not all diseases from this group have a specific tumor screening guideline, such as Costello syndrome, in which screening for rhabdomyosarcomas and neuroblastomas is recommended through physical examination, ultrasonography of the abdomen and pelvis, and thoracic radiography every 3 to 4 months until the age of 10 years. After this point, hematuria, which could indicate bladder cancer, is screened through annual urinalysis (Roberts, 2001; Ney et al., 2022). While specific treatments for RASopathies have not yet been established, animal studies have shown promising results with trametinib (a MEK inhibitor), including potential reversal of left ventricular hypertrophy and outflow tract obstruction in patients with Noonan Syndrome.[54] Rapamycin and everolimus have also shown encouraging results.[54] Another selective MEK inhibitor, selumetinib, has been approved to treat symptomatic plexiform neurofibromas that cannot be completely removed surgically in individuals with type 1 neurofibromatosis.[55]

- ***Anderson-Fabry***

Anderson-Fabry (or Fabry) disease is an X-linked disorder characterized by tissue lipid accumulation due to a deficiency in the lysosomal enzyme alpha-galactosidase A. Manifesting typically in childhood or early adolescence, especially in boys, symptoms of Fabry disease can include cardiomyopathy, stroke, skin lesions, and kidney failure. Additional symptoms may include painful acroparesthesia, decreased sweating (hypohidrosis), gastrointestinal issues (such as abdominal cramping and diarrhea), and skin manifestations (such as angiokeratomas). Diagnosis is based on identifying deficient alpha-galactosidase A enzyme activity (measured in plasma, isolated leukocytes, and/or cultured cells) and/or through genetic testing to identify a pathogenic variant in the GLA gene. Family screening is recommended to identify individuals at risk.[56]

Treatment is based on supportive therapies, such as managing cardiomyopathy/heart failure and symptom relief through medications like carbamazepine or gabapentin to alleviate pain (acroparesthesia), as well as chronic hemodialysis and/or kidney transplantation, depending on the stage of renal failure, in addition to a multiprofessional team. Primary complications can be prevented through targeted therapies, including enzyme replacement with or without chaperone therapy (eg, migalastat) to prevent and/or delay the progression of renal, cardiac, and cerebrovascular manifestations. This specific therapy, which has been associated with improved prognosis and quality of life, should be initiated as early as possible in all males with Fabry disease and in females with clinical manifestations.[57]

- ***Glycogen storage disease***

Some patients with cardiomyopathy, especially those with the hypertrophic phenotype, may be misdiagnosed with sarcomeric HCM. Although magnetic resonance imaging can help indicate glycogen storage disease in some cases, genetic testing is usually required for differential diagnosis. Such testing involves identifying variants in genes that regulate glycogen metabolism, such as PRKAG2 syndrome, LAMP2 (Danon disease), and GAA (Pompe disease).[58]

Danon disease is an X-linked autophagic vacuolar cardioskeletal myopathy associated with severe heart failure. It can also present with extracardiac manifestations, including neurological/psychiatric symptoms (such as learning disabilities or mild cognitive defects and anxiety or mood disorders), skeletal symptoms (myalgia and proximal muscle weakness), and ophthalmologic manifestations (retinopathy). The condition is caused by loss-of-function variants in the LAMP2 gene and is among the most severe and penetrant of the genetic cardiomyopathies, especially in males, often leading to heart transplantation or sudden death.[58]

PRKAG2 syndrome is an autosomal-dominant inherited disease caused by pathogenic variants in the *PRKAG2* gene, which can cause dysregulation of adenosine monophosphate kinase, leading to myocyte hypertrophy and an accumulation of vacuoles with glycogen stores. It is characterized by ventricular pre-excitation, supraventricular arrhythmias, and cardiac hypertrophy. Clinical symptoms usually appear between 30 and 50 years of age and have varying phenotypes, from severe infantile presentations to mild left ventricular hypertrophy in later life. Atrial fibrillation is common and typically appears about a decade earlier than in sarcomeric HCM. Unlike Danon disease, muscle weakness or myalgia is rare (only 2% of patients), and PRKAG2 disease does not lead to retinal or intellectual impairment. The prognosis is often unfavorable, with many patients experiencing early-onset conduction disease, advanced heart failure, and life-threatening arrhythmias.[59]

Pompe disease is an autosomal recessive genetic disorder caused by pathogenic variants in the GAA gene (which encodes acid α-glucosidase), resulting in lysosomal glycogen accumulation primarily in skeletal and cardiac muscles. The phenotypic expression depends on residual enzymatic activity, which is lower in patients who present in infancy and can be higher in patients presenting in later life.[58]

While clinical assessments and tests can provide valuable insights, some cardiomyopathies may remain unidentified without a molecular diagnosis, especially rare types. Genetic testing is crucial for refining diagnoses and guiding genetic counseling, and it can be essential for conditions requiring specific treatments, which can influence prognosis.[60,61]

- ***Key Takeaways***

A comprehensive family history spanning 3 to 4 generations is essential for all patients with potential cardiomyopathies.

Expert genetic counseling is a valuable tool for patients with suspected or confirmed cardiomyopathies.

Genetic testing is advised for patients fitting the criteria for cardiomyopathies.

If the proband has an identifiable pathogenic or likely pathogenic variant, cascade genetic testing in family members is recommended.

It is vital to understand the implications of the discovered variant since they influence prognosis, device recommendations, counseling, and prospective targeted treatments.

Conclusions

Classifying cardiomyopathies by phenotype is a recommended first step, although a thorough assessment further pinpoints their etiology and prognosis and results in more personalized treatment. Genetic testing is thus an invaluable tool, and its growing prevalence in

daily medical practice underscores its importance. By effectively applying its results, cardiologists can offer profound benefits to patients and their families.

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Conception and design of the research: Furquim SR; acquisition of data: Furquim SR, Lipari LFVP, Andrade FA, Correia VM, Olivetti NQS, Sacilotto L, Fernandes F; analysis and interpretation of the data: Lipari LFVP, Andrade FA, Correia VM, Olivetti NQS, Sacilotto L, Krieger JE, Pires LVL; writing of the manuscript: Furquim SR, Lipari LFVP, Andrade FA, Correia VM, Olivetti NQS, Sacilotto L, Krieger JE, Pires LVL; critical revision of the manuscript for intellectual content: Furquim SR, Lipari LFVP, Andrade FA, Correia VM, Olivetti NQS, Sacilotto L, Fernandes F, Krieger JE.

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