Review Article

Exploring MYH7 in Cardiomyopathies: Genetic Drivers and Clinical Outcomes

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Abstract

The MYH7 gene, which encodes the beta-myosin heavy chain, is a critical component in the structural and functional integrity of cardiac and skeletal muscle cells. Variants in MYH7 are among the most common genetic causes of cardiomyopathies, particularly hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM), and have also been implicated in restrictive cardiomyopathy (RCM) and left ventricular hypertrabeculation (LVHT). This review explores the molecular mechanisms by which MYH7 variants lead to these diverse phenotypes, focusing on the genotype-phenotype correlations that underlie the clinical manifestations of each condition. MYH7 variants are primarily missense variants concentrated in the myosin head domain, affecting the contractile function of the protein. These variants lead to a wide spectrum of cardiac abnormalities, from thickening of the myocardial walls to dilation of the cardiac chambers. The review also addresses the broader implications of MYH7 mutations, including their role in skeletal myopathies and potential associations with cancer. Understanding the pathogenic mechanisms of MYH7 variants not only increases diagnostic accuracy but also informs the development of targeted therapies. As the integration of genetic knowledge into clinical practice continues to evolve, the MYH7 gene remains a critical focus for advancing the management and treatment of cardiomyopathies, offering patients hope for improved clinical outcomes through precision medicine.

Keywords

MYH7; Hypertrophic cardiomyopathy; Dilated Cardiomyopathy; Genetic Cardiomyopathies; Sarcomeric Genes.

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Integrating genetics and cardiology: the role of MYH7 in cardiomyopathies

In recent years, the advent of next-generation sequencing (NGS) has revolutionized genetic testing, leading to a closer integration of genetics and cardiology in medical practice. As our understanding of the human genome and its relationship to cardiovascular health deepens, numerous genotype-phenotype associations are being identified, providing essential insights for the diagnosis and treatment of genetic heart disease (GHD). Among the several genes implicated in GHD, MYH7 stands out as one of the most frequently associated, especially in large cohorts involving cardiomyopathies. 1-3 Along with the genes MYBPC3, TNNT2, TNNI3, TPM1, MYL2, MYL3 and ACTC1, the MYH7 gene is part of the group of sarcomeric genes, which are predominantly associated with hypertrophic cardiomyopathy (HCM). In this group, MYH7 and MYBPC3 are the main genes involved.4 Furthermore, MYH7 contributes significantly to dilated cardiomyopathy (DCM) and has also been identified in restrictive cardiomyopathy (RCM) and left ventricular hypertrabeculation (LVHT).5-7 This review explores the convergence of clinical and molecular approaches in the treatment of MYH7-related disorders. By examining the molecular mechanisms underlying these conditions, we aim to advance our understanding of the disease spectrum and its application to clinical practice.

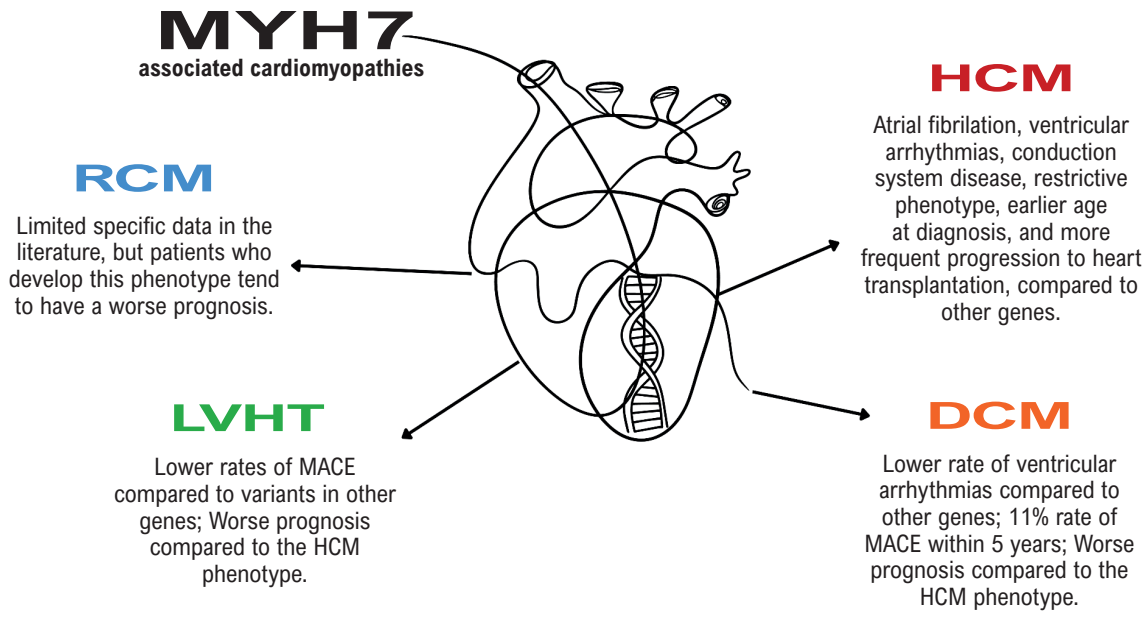
Gene structure and function MYH7

Gene: structure, domains, and functional significance in muscle contraction

The MYH7 gene (OMIM:160760) encodes the beta-myosin heavy chain, a protein predominantly expressed in cardiac and skeletal muscle cells. Located on chromosome 14q12, the gene spans 22,883 base pairs and comprises 41 exons, with the first two being noncoding and exons 37 and 38, forming a unique fused structure. The full-length protein consists of 1,935 amino acids.[8,9] Myosin is an actin-based motor protein with ATPase activity essential for muscle contraction in both cardiac and skeletal muscles. Together with actin thin filaments, myosin constitutes the fundamental contractile unit in muscles (Figure 1).[10]

MYH7 is structurally divided into three major domains: the Myosin N-terminal SH3-like domain (amino acids 31-81); the

Central Illustration: Exploring MYH7 in Cardiomyopathies: Genetic Drivers and Clinical Outcomes



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MYH7 cardiomyopathy spectrum. DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; LVHT: left ventricular hypertrabeculation; MACE: major cardiovascular events; RCM: restrictive cardiomyopathy.

myosin-head domain, which contains the motor unit (amino acids 85-778) and the IQ domain (amino acids 781-810); and the myosin-tail domain (amino acids 839-1935), which consists of repeating 28-amino-acid patterns forming an alpha-helical coiled-coil structure.[10,11] The myosin-head domain is particularly significant, as it contains the actin-binding regions (amino acids 655-667 and 757-771) and is responsible for the protein's contractile power. The myosin-tail domain ensures the proper attachment of myosin to the sarcomere. Within this domain, four specific amino acids, known as "skip" residues (Thr1188, Glu1385, Glu1582, and Gly1807), disrupt the repetitive sequence. These skips modify the coiled-coil structure in their surroundings, with the last skip playing a crucial role in myosin incorporation into the sarcomere structure.[10] Figure 2 highlights the structure of MYH7.

Pathogenic variants in MYH7: clinical implications

Numerous genetic variants affecting MYH7 have been documented in the medical literature and have been associated with a variety of phenotypes, including CHD (primarily cardiomyopathies and some congenital disorders such as Ebstein anomaly) and skeletal myopathies. The mechanisms leading to these diverse phenotypes are not yet fully understood. Analysis of variants reported in public databases of genetic variation (e.g., ClinVar, DECIPHER, GnomAD) suggests that loss-of-function variants may not be disease-causing for this gene. In 2018, the ClinGen Hereditary Cardiomyopathy Expert Panel adapted the ACMG/AMP Variant Classification Criteria specifically targeting MYH7 variants in cardiomyopathies. The panel downgraded the PVS1 criteria (predicted null variant in a gene where loss of function is a known disease mechanism) to moderate strength due to the lack of sufficient evidence linking such variants to CHD.[12,13] The predominant type of disease-causing variants in MYH7 are missense mutations, particularly clustered in amino acids 167–931, which largely overlap the myosin head domain. This region exhibits a statistically significant clustering of pathogenic variants.[13]

Genotype-phenotype correlation

Correlating MYH7 variants with cardiomyopathy phenotypes

The MYH7 gene encodes the beta-myosin heavy chain, a protein expressed in both cardiac and skeletal muscle cells. Genetic variants in MYH7 can lead to a wide array of phenotypes, encompassing various forms of cardiomyopathies and skeletal myopathies[14] (Central Illustration).

MYH7-related hypertrophic cardiomyopathy: Genetic drivers and clinical presentation

HCM is an inherited cardiac disease characterized by hypertrophy of the left ventricular wall, which may extend into the right ventricle. This occurs in the absence of

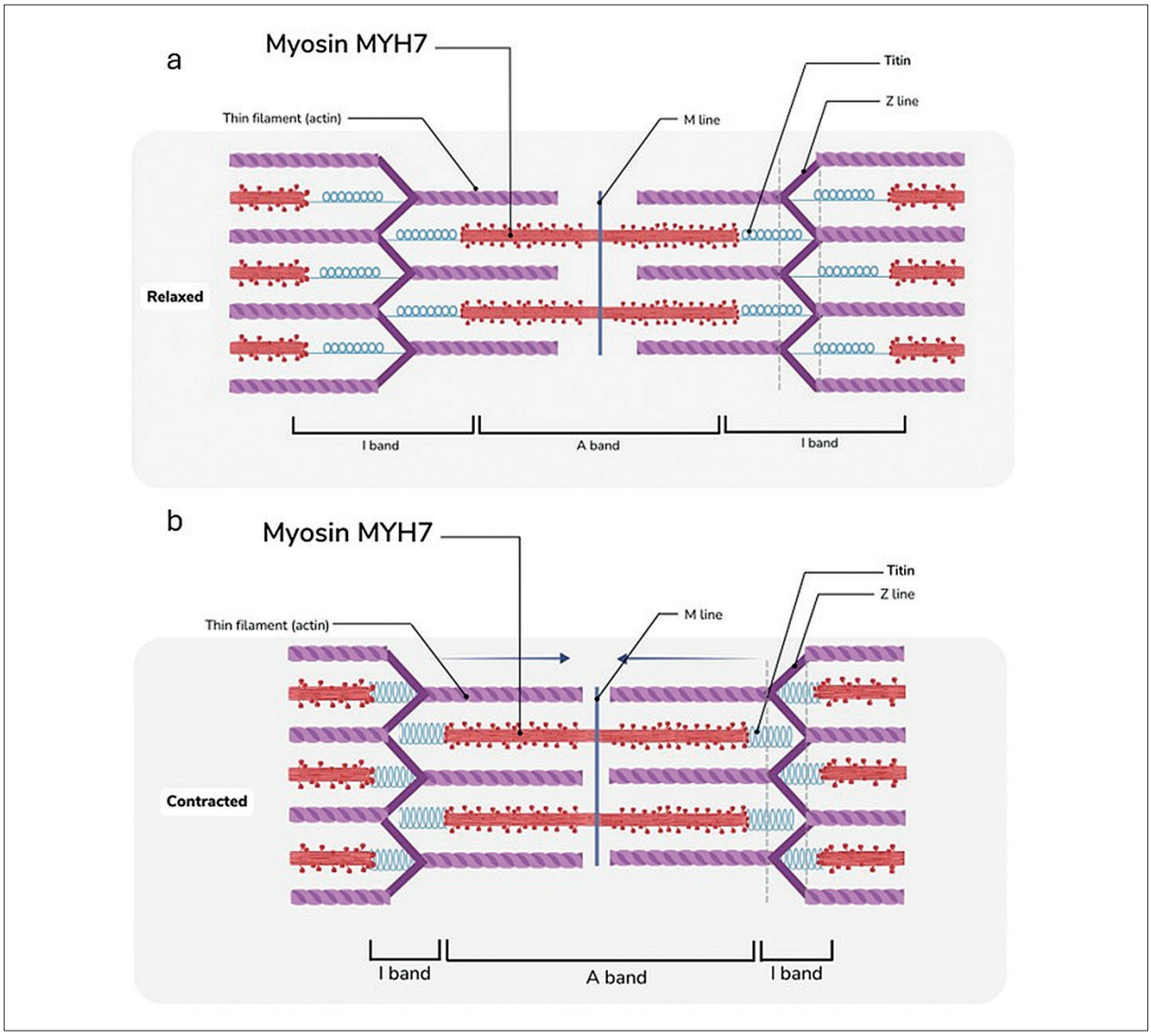

Figure 1 – *Sarcomere structure, relaxed (a) and contracted (b), highlighting the relation between thin filament (actin) and thick filament (Myosin), compounding the major contractile structure of muscle cells.*

other conditions that can cause pressure overload, such as hypertension or aortic stenosis, or conditions that lead to thickening of the ventricular wall, such as Fabry disease or cardiac amyloidosis.[6] In the United States, the prevalence of HCM with an overt phenotype is approximately 1 in 500 individuals. This prevalence increases to 1 in 200 when individuals with both a positive genotype and a negative phenotype are included.[4,15] Diagnosis relies primarily on imaging techniques, such as echocardiography or cardiac magnetic resonance imaging.6,16 HCM is characterized by myocardial dislocation that leads to sarcomere hypertrophy and symptoms including dyspnea, chest pain, palpitations, and sudden death.[17,18] The disease usually follows an autosomal dominant pattern of inheritance, although some cases result from de novo mutations.[19] MYH7 variants are associated with severe phenotypes, including atrial fibrillation, ventricular arrhythmias, conduction system disorders, and earlier age at diagnosis.[15,17] Genetic testing, typically conducted using panels that include MYH7 and other sarcomeric genes, has a diagnostic yield ranging from 30% in sporadic cases to 60% in familial cases.[5,16] Approximately 181 missense variants in MYH7 are classified as "likely pathogenic" or "pathogenic" for HCM in ClinVar.[14] Furthermore, recent evidence links specific variants to expected phenotypes in HCM[15,17] (Figure 3).

MYH7-Related dilated cardiomyopathy: Pathogenesis and phenotypic expression

DCM is characterized by left ventricular dilation and systolic dysfunction, defined by an ejection fraction below 50%.[6] This condition cannot be solely attributed to valvular heart diseases, systemic hypertension, or coronary artery

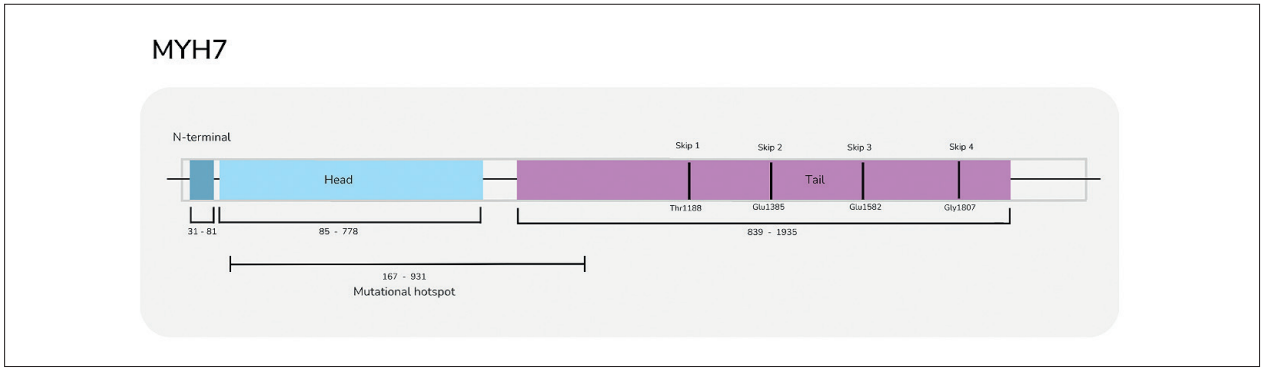

Figure 2 – *Schema of the MYH7 gene highlighting key structural subunits and functional domains*

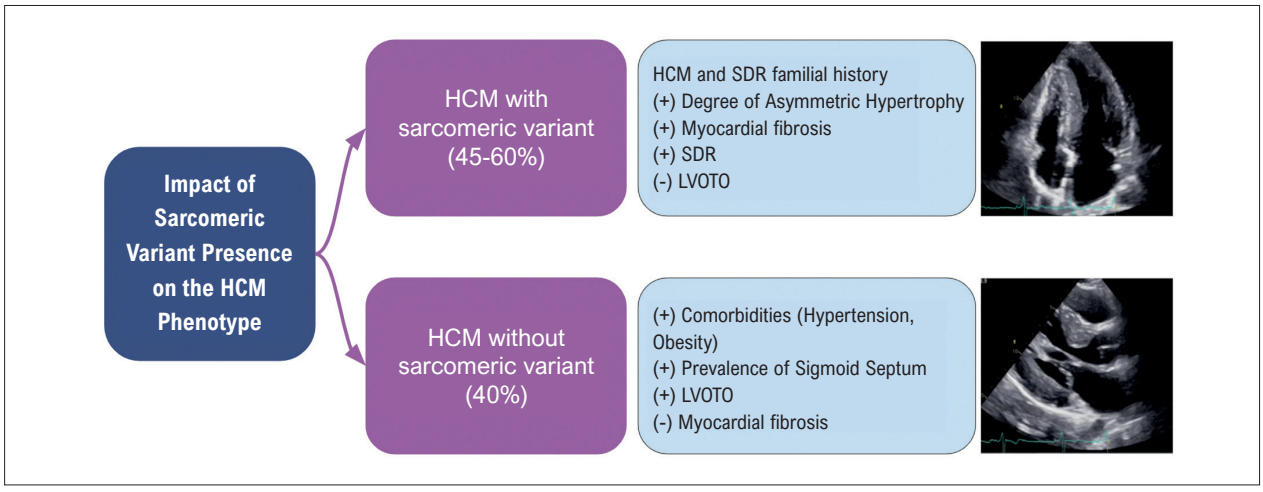

Figure 3 – *Impact of the Presence of Sarcomeric Variant on the HCM Phenotype. HCM: Hypertrophic cardiomyopathy; LVOTO: left ventricular outflow tract obstruction; SDR: sudden death rate.*

disease.[6] Various factors, including viral infections, alcohol abuse, and anabolic steroid use, can contribute to DCM, along with genetic variants that may act independently or within a multifactorial context.[6] DCM often represents the end pathway for various cardiomyopathies.[18]

Etiologically, DCM can be divided into genetic and non-genetic causes. Non-genetic causes include myocarditis (from viruses, bacteria, fungi, parasites); toxins (e.g., alcohol, cocaine, amphetamines, anabolic steroids, hemochromatosis); endocrine disorders (hypo/hyperthyroidism, Cushing's syndrome, pheochromocytoma, acromegaly, diabetes mellitus); nutritional deficiencies (selenium, thiamine, zinc, copper, carnitine); electrolyte disturbances (hypocalcemia, hypophosphatemia); peripartum conditions; autoimmune diseases (giant cell myocarditis, eosinophilic granulomatosis with polyangiitis, systemic lupus erythematosus, sarcoidosis, rheumatoid arthritis, celiac disease, inflammatory bowel diseases); and medications (chemotherapeutics, psychiatric medications, antiretrovirals).[6]

Pathogenic or likely pathogenic genetic variants are present in approximately 20-40% of familial DCM cases and 15-25% of unselected DCM cases.[20] The most commonly associated genes include LMNA, MYH7, TNNT2, TTN, RBM20, and BAG3.[21-25] Most genetic variants related to DCM follow an autosomal dominant inheritance pattern, although autosomal recessive, X-linked, and mitochondrial inheritance modes have also been reported.[26,27]

MYH7 is the third most frequently associated gene with DCM.[22] Most variants in this gene are non-truncated and exhibit high penetrance in familial cases, with a significant proportion of pediatric patients.[28-30] Approximately 59 missense variants and three loss-of-function variants in MYH7 are classified as "likely pathogenic" or "pathogenic" for DCM in ClinVar.[14] The pathogenic mechanism of MYH7 variants in DCM contrasts with that in HCM, involving reduced sarcomeric contractility due to impaired ATPase activity and decreased sliding velocity along actin filaments.[31,32] This leads to ventricular dilation and cardiac remodeling.[31,32]

MYH7-related restrictive cardiomyopathy: Genetic underpinnings and clinical features

RCM is characterized by restrictive ventricular physiology with normal or reduced systolic and diastolic

diameters, preserved left ventricular ejection fraction, and normal ventricular wall thickness.[6] Biatrial dilation is commonly observed, even with normally sized ventricles.[6] RCM often represents an early stage of certain diseases and may progress to DCM.[6]

Causes of RCM are divided into two main categories:

- **Intrinsic myocardial dysfunction:** Includes genetic cardiomyopathies (e.g., sarcomeric variants, filamin A, titin); storage diseases (e.g., Fabry disease, Danon disease, glycogen storage diseases, PRKAG2 syndrome, hemochromatosis); and medications (e.g., hydroxychloroquine).[6,33]
- **Extracellular matrix disorders:** Includes infiltrative diseases (e.g., amyloidosis, sarcoidosis, hyperoxaluria) and fibrotic diseases (e.g., radiation, chemotherapy, systemic sclerosis, diabetic cardiomyopathy).[6,33]

It is essential to differentiate RCM from endocardial diseases that present restrictive physiology, such as endomyocardial fibrosis, hypereosinophilia, carcinoid syndrome, neoplasms, and radiation-induced conditions.[6,33]

Familial RCM is typically inherited in an autosomal dominant manner.[34] The primary genes involved include TNNI3, TNNT2, ACTC1, and MYH7.[34] In some cases, familial RCM may be associated with conduction defects resulting from variants in the DES gene, often accompanied by skeletal myopathy.[34] Other less common inheritance patterns include autosomal recessive (e.g., variants in HFE and PRKAG2) and X-linked inheritance (e.g., Anderson-Fabry disease).[34]

Specifically, MYH7-related RCM variants are predominantly autosomal dominant and missense in nature.[34] In the ClinVar database, two missense variants are classified as "pathogenic" or "likely pathogenic" with high confidence, supported by multiple references.[14]

MYH7 and left ventricular hypertrabeculation (LVHT): A controversial phenotype

LVHT, previously known as noncompaction of the myocardium, remains a controversial topic, with some experts classifying it as a genetic cardiomyopathy and others viewing excessive trabeculation as a morphological feature present in several pathological processes and therefore not constituting a distinct disease.35 The main feature of LVHT is the presence of prominent trabeculae in the left ventricle and deep intertrabecular recesses that are continuous with the LV cavity and distinct from the epicardial coronary arteries.[35]

Variants associated with LVHT involve a diverse array of proteins, including those related to the sarcomere, cytoskeleton, mitochondria, desmosomes, storage, and ion channels, all of which have been implicated in different cardiac diseases.[36] Approximately one-third of LVHT cases involve a pathogenic variant, with the majority following an autosomal dominant inheritance pattern.[37] The most frequently implicated genes include MYH7, MYBPC3, ACTC1, TTN, LMNA, RBM20, ACTN2, and PRDM16, although these genes are not unique to LVHT.[35,37] Unlike HCM and DCM, truncating variants in MYH7 are considered pathogenic in LVHT.38 In ClinVar, seven missense variants and four loss-of-function variants in MYH7 are classified as "pathogenic" or "likely pathogenic."[14] Patients with LVHT and MYH7 variants generally have a lower risk of adverse cardiovascular events when compared to those with variants of other genes.[39]

Expanding the MYH7 spectrum: Skeletal myopathies and other phenotypic associations

Patients with MYH7 variants can present a wide range of clinical phenotypes, including isolated cardiomyopathy, isolated skeletal muscle myopathy, or a combination of both.[40] While this review focuses on cardiomyopathies, MYH7-related skeletal muscle diseases are predominantly autosomal dominant and can manifest from childhood to adulthood, exhibiting considerable clinical and prognostic variability.[41] The main skeletal myopathies associated with MYH7 include Laing distal myopathy, myosin storage myopathy, congenital myopathy with fiber-type disproportion, and MYH7-related late-onset scapuloperoneal muscular dystrophy.[14]

Additionally, MYH7 appears to play a role in tumorigenesis. In patients with smoking-associated lung adenocarcinoma, 12% harbor MYH7 variants, which are associated with cancer progression and poorer prognosis.[42] MYH7 has also been linked to prostate cancer, oral cancer, and Epstein-Barr virus-associated intrahepatic cholangiocarcinoma.[43-45] Both "pathogenic" or "possibly pathogenic" variants and alterations in gene expression can influence cancer onset and progression.[41-45]

Prognostic factors and clinical implications of MYH7 variants in cardiomyopathies

Beyond the diverse phenotypic associations, various studies have identified significant prognostic factors related to MYH7 variants (Figure 4). A Dutch multicenter cohort study, involving 581 individuals (30.1% index patients, 48.4% male, median age 37 years) diagnosed with HCM, LVHT, or DCM, found that early penetrance and major cardiovascular events (MACE) were more prevalent in carriers of MYH7 variants associated with LVHT and DCM compared with those with HCM. Specifically, MACE occurred in 21.2% and 12.0% of LVHT and DCM carriers, respectively, versus 2.9% and 2.1% of HCM carriers.[46] The risk of MACE was significantly higher in individuals with a family history of early MACE (adjusted HR: 1.82; 95% CI: 1.15-2.87; $p = 0.010$) or those with LVHT or DCM phenotypes diagnosed at ≤5 years of age (adjusted HR: 38.82; 95% CI: 5.16-291.88; $p < 0.001$).[46] These findings suggest the need for early screening, especially for carriers of LVHT or DCM-associated variants, as well as those with a family history of MACE before age 12 years. 46Another multicenter cohort study with a median follow-up of 4.5 years examined 147 patients with MYH7 variants associated with DCM, of whom 72.1% had DCM at baseline. 47 During follow-up, 23.7% of initially phenotype-negative carriers developed DCM, and 28% exhibited reverse left ventricular remodeling. 47 The incidence of MACE at 5 years was 11.6%, including five deaths from advanced heart failure and five

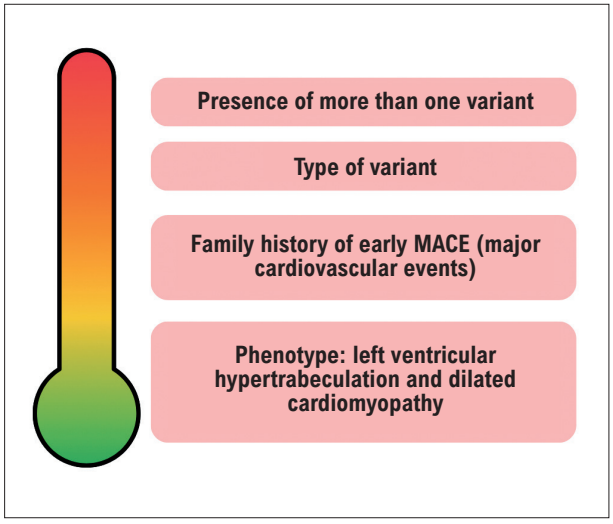

Figure 4 – *Prognostic factors of MYH7 cardiomyopathies. MACE: major cardiovascular events.*

heart transplants. 47 The incidence of ventricular arrhythmias was low (1% at 5 years, increasing to 5% with LVEF ≤35%), which is lower when compared with DCM associated with LMNA gene variants. [47]

The type of MYH7 variant also influences clinical outcomes. A case series reported that the MYH7 R453C and R453H variants were associated with severe HCM phenotypes requiring advanced heart failure interventions. 48 Missense variants in MYH7 relevant to the development of HCM are predominantly located in the S1 and S2 regions of the gene. 49 Recent studies have confirmed that variants in the converter domain and residues within the myosin "table" are common sites for HCM-associated MYH7 variants, which tend to appear earlier, progress more rapidly, and overlap with other phenotypes, compared with variants in other regions of the gene.[50]

Furthermore, the cumulative effect of multiple MYH7 variants exacerbates the severity of HCM, leading to an earlier onset, a higher risk of sudden cardiac death (SCD), and a poorer prognosis.[51-63] A mouse model demonstrated this additive effect: mice with a single missense variant (p.Val606Met) exhibited a relatively benign phenotype, whereas mice with double pathogenic variants (p.V606M & p.R453C or p.V606M & p.R719W) developed a more pronounced hypertrophic phenotype.[64]

Conclusion

MYH7 is a sarcomeric gene essential for the pathophysiology of cardiomyopathies, particularly HCM and DCM, and contributes to less common phenotypes such as CMR and LVHT. In addition, certain MYH7 variants are associated with skeletal myopathies, sometimes overlapping with cardiomyopathies. Advances in the understanding of MYH7 genetic variants and their functional impacts have significantly increased our knowledge of the molecular mechanisms underlying these conditions.

Integrating genetic diagnosis with clinical assessment is essential for effective patient management, enabling a personalized approach that considers both genetic profiles and individual clinical manifestations. Emerging technologies, including gene editing and molecular therapies, promise more targeted and effective interventions. The success of these approaches depends on continued collaboration between cardiologists, geneticists, and researchers, emphasizing the importance of clinical practice aligned with robust genetic discoveries.

Looking ahead, the management of MYH7-associated cardiomyopathies and related genetic conditions will increasingly rely on the intersection of cutting-edge genetic research and meticulous clinical application. This integration aims to improve patient outcomes and quality of life through personalized medicine and advanced therapeutic strategies.

Author Contributions

Conception and design of the research; Writing of the manuscript and Critical revision of the manuscript for content: Pires LVL, Correia VM, Lipari LFVP, Andrade FA, Fernandes F, Madrini Junior V, Carvalho MLP, Napolitano G, Silva EA, Vilalva KH, Val VP, Krieger JE.

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Ethics approval and consent to participate

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

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