

## Molecular basis of hereditary cardiomyopathy: A systematic review

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### Abstract

Hereditary cardiomyopathies include a diverse spectrum of myocardial disorders characterized by mechanical and electrical abnormalities, among which hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) are distinguished. This paper dives into the genetic foundations of these conditions, with a focus on mutations in genes encoding sarcomere proteins, thin filament proteins, and calcium homeostasis regulators. The familial aggregation of cardiomyopathies underscores the substantial genetic component, with autosomal dominant inheritance patterns predominant in some cases. Genetic testing and counseling emerge as pivotal tools for early diagnosis, risk assessment, and the formulation of personalized treatment strategies. The integration of genetic insights into clinical management holds promise for improving patient outcomes and reducing disease burden. Further analysis of the molecular mechanisms underlying hereditary cardiomyopathies is critical for identifying novel therapeutic targets and advancing precision medicine approaches. By comprehensively exploring the genetic underpinnings of cardiomyopathies, this paper contributes to our understanding of these complex diseases and highlights the potential for innovative interventions to enhance patient care in the field of cardiovascular medicine.

**Keywords:** Hereditary Cardiomyopathies; Hypertrophic Cardiomyopathy; Dilated Cardiomyopathy.

### 1. Introduction

Heart is an organ that consists of a sophisticated structure comprising various cell types, including cardiomyocytes, endothelial cells, vascular smooth muscle cells, fibroblasts, pericytes, and immune-related cells, among others. Cardiomyocytes specifically, are responsible for the contractile function of the myocardium, enabling the heart to effectively pump blood throughout the body [1]. Cardiomyopathies represent a diverse range of myocardial diseases characterized by mechanical and electrical abnormalities. Typically, they involve improper enlargement or dilation of the ventricles and can stem from various factors, often with a genetic component [2]. Cardiomyopathy arises from abnormalities in cardiac muscle function and can be categorized into primary and secondary forms. Primary cardiomyopathy diagnosis involves ruling out secondary causes and encompasses various clinical types, while secondary cardiomyopathy results from external factors like ischemia, hypertension, and metabolic disorders [3]. Mutations in the structural or regulatory proteins of cardiomyocytes can result in cardiomyopathy. Cardiomyopathies include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic cardiomyopathy (ACM), and left ventricular noncompaction (LVNC), which can be either genetic or acquired forms [3,4,5].

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HCM, is affecting approximately 1 in 500 individuals, and is a leading cause of sudden cardiac death in youth. It is marked by left ventricular hypertrophy without apparent hemodynamic stresses and can manifest with preserved systolic function but impaired relaxation, eventually leading to ventricular dilation and systolic dysfunction. Autosomal dominant mutations in sarcomeric protein genes are commonly implicated in HCM [3,8].

### 1.1. Genetics behind cardiomyopathy

Primary cardiomyopathy's origins were previously unknown, but from 2000s, scientists have unearthed various genetic abnormalities linked to the condition. More than fifty percent of individuals with hypertrophic cardiomyopathy (HCM) have a familial history of the disorder, suggesting a dominant genetic trait is involved.

Based on research from 2010, between twenty to thirty-five percent of patients with dilated cardiomyopathy (DCM) have familial cases, predominantly showing autosomal dominant inheritance, though some cases may adhere to autosomal recessive or X-linked recessive patterns. Familial occurrences are also noted in restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and left ventricular noncompaction (LVNC) [4].

The presence of a familial history indicates a genetic predisposition, prompting investigations in families with multiple affected individuals to pinpoint disease loci. These investigations have led to the identification of mutations in genes located within these loci. Further analyses, focusing on genes encoding proteins linked to or interacting with products of the disease genes, have unveiled additional disease genes [6].

Progress in understanding the genetic underpinnings of cardiomyopathy enables clinicians to precisely categorize affected individuals based on their molecular profiles, identifying even asymptomatic individuals at heightened risk of developing cardiomyopathy. Genetic testing is now recommended for various cardiomyopathy types, including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and left ventricular noncompaction (LVNC) [7].

### 1.2. Hereditary cardiomyopathies

The exploration of the genetic basis of hypertrophic cardiomyopathy (HCM) marks a significant achievement in cardiovascular research [9]. Familial forms of cardiomyopathies, particularly HCM, have been recognized for decades, with early studies establishing their genetic origins. Subsequent investigations, supported by echocardiography, revealed familial incidence rates of approximately 50%. Recent genetic research has revealed that some cases initially thought to be sporadic are actually linked to inheritable mutations. While most cases exhibit autosomal dominant inheritance, other patterns such as autosomal recessive or X-linked inheritance have been observed [8]. While traditionally viewed as a single-gene disorder predominantly inherited in an autosomal dominant manner, HCM has now been extensively studied in large families showing clear inheritance patterns. Pioneering research by scientists such as Christine Seidman and Jonathan Seidman identified the first mutation associated with familial HCM, shedding light on the role of the MYH7 gene in encoding the sarcomere protein MYH7.

Subsequent studies have revealed numerous other genes implicated in familial HCM, greatly expanding our understanding of its genetic mechanisms. However, comprehending the genetic basis of HCM in cases where the disease occurs sporadically or in small families presents significant challenges. Approximately half of HCM cases fall into this category, where limited family size or sporadic presentation complicates genetic analysis. Establishing causal relationships in such cases is particularly challenging. To address these complexities, further exploration of genome-wide variations, their frequencies in populations, and their functional implications is warranted [9].

Dilated cardiomyopathy (DCM) also exhibits familial clustering, with around 20% of cases having a genetic basis. However, DCM presents greater genetic complexity, with evidence suggesting polygenic or multifactorial inheritance patterns. Genetic studies have identified several disease loci and mutations associated with familial cardiomyopathies. Notably, mutations in genes encoding cardiac sarcomeric proteins, such as  $\beta$ -myosin heavy chain ( $\beta$ -MHC), troponin T, and  $\alpha$ -tropomyosin, have been implicated in HCM. Similarly, defects in the dystrophin gene have been linked to X-linked forms of DCM. Additionally, a gene on chromosome 1p1-1q1 has been implicated in an autosomal dominant form of DCM with atrioventricular conduction defects. These findings underscore the genetic complexity of familial cardiomyopathies and emphasize the importance of genetic screening and counseling in affected families [8].

Given the intricate nature of the clinical characteristics, numerous genes play a role in the development of HCM and DCM. Early genetic studies primarily linked HCM to abnormalities in sarcomeres, the organized structures within striated muscles composed of thick and thin filaments. These filaments undergo ATP-dependent interactions to facilitate muscle contraction [9].

### 1.3. Genes encoding Thick Filament Proteins of the Sarcomere

The thick filament proteins of the sarcomere, crucial in hypertrophic cardiomyopathy (HCM), primarily involve MYH7 and MYBPC3 genes, responsible for muscle force generation. MYH7, also known as  $\beta$ -MYH, constitutes a significant portion of sarcomere proteins, predominantly found in cardiac myocytes. Structurally, it comprises distinct domains facilitating ATP binding and interaction with actin, crucial for muscle contraction [9].

Numerous pathogenic variants (PVs) in MYH7, mostly missense mutations, have been identified in HCM patients, particularly in familial cases [9].

MYBPC3, which binds to MYH7 and cardiac actin, regulates actomyosin interactions. Mutations in MYBPC3, notably truncating mutations, are also implicated in HCM, with rare population frequencies except for certain founder mutations. Additionally, genes encoding MYL2, MYL3, and TTN, involved in muscle contraction and expressed in cardiac myocytes, have been linked to HCM, albeit less frequently. Conversely, MYH6, encoding a minor myosin isoform, shows limited association with HCM due to its smaller contribution to sarcomere MYH protein [9].

### 1.4. Genes Encoding Thin Filament Proteins of the Sarcomere

The thin filaments within cardiac myocytes consist of ACTC1 (cardiac  $\alpha$ -actin 1) and the troponin/tropomyosin complex. This complex includes TNNC1 (cardiac troponin C), TNNI3 (cardiac troponin I), and TNNT2 (cardiac troponin T) anchored by TPM1 (tropomyosin 1), ultimately forming the thin filaments [8,9].

TNNT2, constituting approximately 5% of sarcomere proteins, was among the first genes implicated in HCM through genetic linkage studies. Numerous pathogenic variants (PVs), primarily missense mutations, have been identified in TNNT2, indicating its importance in cardiac myocyte function. Additionally, mutations in TNNI3, TNNC1, and TPM1 genes, though less common, are associated with HCM, highlighting their potential role in the disease. ACTC1, a critical component of thin filaments, interacts with the troponin/tropomyosin complex and MYH7 protein to facilitate muscle contraction. Mutations in ACTC1 are rare but significant causes of HCM due to its essential function in cardiac myocyte contraction [9].

#### 1.4.1. Genes Encoding the Protein Constituents of the Z Lines (or Z Discs or Z Bands)

Genes responsible for encoding the protein constituents of the Z lines, crucial structures anchoring the end of thin filaments in cardiac muscle, play a pivotal role in providing mechanical stability during muscle contraction and relaxation. Among these genes are ACTN2 ( $\alpha$ -actinin 2), MYOZ2 (myozenin 2), CSRP3 (cysteine and glycine-rich protein 3), TCAP (TTN capping protein), and FHL1 (four and a half LIM domain 1) [10].

MYOZ2, expressed exclusively in cardiac and skeletal muscles, interacts with ACTN2 and other proteins, likely regulating myofibrillogenesis and calcium-dependent signaling pathways. While MYOZ2 exhibits tolerance to loss-of-function (LoF) and missense variants, pathogenic and likely pathogenic variants (PVs and LPVs) have been implicated in both sporadic and familial cases of hypertrophic cardiomyopathy (HCM), exerting moderate effects on disease expression. ACTN2, predominantly expressed in cardiac and skeletal muscles, interacts with actin, contributing to the regulation of sarcomere function. Despite its intolerance to LoF variants, PVs in ACTN2 have been linked to skeletal myopathy and various cardiomyopathies, including sporadic HCM [9,10].

CSRP3, formerly known as MLP (muscle lim protein), is highly expressed in cardiac and skeletal muscles, interacting with various sarcomere and cytoskeletal proteins as well as cardiac transcription factors. While mutations in CSRP3 are implicated in HCM, the gene displays tolerance to missense and LoF variants, suggesting that PVs in CSRP3 may act in conjunction with PVs in other relevant genes rather than independently causing HCM [8].

TCAP, encoding TTNcap, regulates the assembly of the TTN protein in cardiac and skeletal muscle. Despite rare variants reported in HCM patients, TCAP is tolerant to missense but intolerant to LoF variants. However, it does not appear to be a major cause of HCM. FHL1, located on the X chromosome, encodes the FHL1 protein expressed predominantly in various muscle cells. Although FHL1 mutations are predominantly associated with skeletal myopathy, sporadic cases of HCM have been reported. PVs in FHL1 are expected to exert modest effects on HCM expression and are unlikely to cause HCM without concurrent skeletal myopathy [9].

#### 1.4.2. Genes Coding for Proteins Located at the M Line (M Band)

Genes responsible for encoding proteins located at the M line, which serve as anchors for thick filaments within the sarcomere, play crucial roles in muscle structure and function. Alongside structural proteins, several enzymatic proteins

are localized to the M lines, including OBSCN (obscurin), MYOM2 (myomesin 2), and TRIM63 (tripartite motif containing 63). OBSCN, a large protein primarily expressed in skeletal muscle with lesser expression in cardiac and tongue muscles, interacts with TTN and MYBPC3 while also possessing signaling functions and kinase activity.

While somewhat tolerant to loss-of-function (LoF) variants and tolerant to missense variants, a few pathogenic variants (PVs) in the OBSCN gene have been linked to various forms of cardiomyopathies, including hypertrophic cardiomyopathy (HCM) [12].

TRIM63, also known as MuRF1 (muscle ring finger 1), is predominantly expressed in cardiac and skeletal myocytes. Acting as an E3 ubiquitin ligase, it tags thick filament proteins for degradation via the ubiquitin-proteasome system. The gene is tolerant to LoF and missense variants. LoF variants in TRIM63 have been associated with HCM in small families and sporadic cases, with mechanisms involving impaired ubiquitination of MYH7 and MYBPC3 and activation of the MTOR-S6K pathways. Homozygous LoF in TRIM63 has also been linked to an autosomal-recessive form of familial HCM. Overall, data suggests modest-to-moderate effect sizes of PVs in the TRIM63 gene in HCM. MYOM2, which cross-links TTN and MYH7 at the M line and is involved in sarcomerogenesis, is predominantly expressed in cardiac and skeletal muscle. Variants in the MYOM2 gene have been associated with HCM [13].

#### 1.4.3. Gene Regulating Calcium Homeostasis in Cardiac Muscle

A key aspect of cardiac muscle function is the regulation of intracellular calcium concentration, which in turn governs actomyosin interaction and the generation of muscle force. JPH2, encoding junctophilin 2, plays a vital role in calcium homeostasis and excitation-contraction coupling as a major component of the junctional membrane complex. Its expression is particularly enriched in cardiac, skeletal, and smooth muscles, including those in organs like the colon and urinary bladder. The gene is intolerant to loss-of-function (LoF) and missense variants. Pathogenic variants (PVs) in JPH2 are more common in patients with sporadic hypertrophic cardiomyopathy (HCM) compared to the general population, and they are expected to have a moderate effect on the phenotypic expression of HCM [9,10].

PLN, encoding phospholamban, is mainly expressed in cardiac myocytes, where it regulates calcium homeostasis by inhibiting the activity of ATP2A2 (SERCA2a), a calcium pump responsible for sequestering calcium into the sarcoplasmic reticulum. Consequently, phospholamban acts as a negative regulator of cardiac contraction. While PVs in the PLN gene are primarily associated with dilated cardiomyopathy, a rare truncating variant has been reported in HCM [9].

### 1.5. Genes Encoding Sarcomere-Associated Proteins

Several genes indirectly involved in regulating sarcomere structure and function have been implicated as causes of hypertrophic cardiomyopathy. FLNC, although more prominently associated with dilated cardiomyopathy, has been recently linked to HCM as well. Highly intolerant to loss-of-function (LoF) variants, FLNC is expressed abundantly in cardiac and skeletal muscle. It interacts with actin, likely playing a role in organizing cytoskeletal proteins in response to stress. While FLNC variants have been found in sporadic HCM cases and small families, they are not as common as in dilated cardiomyopathy [14].

ALPK3, coding for  $\alpha$ -kinase 3, is primarily expressed in cardiac and skeletal muscle and is involved in myocyte differentiation. It is tolerant to missense and LoF variants. PVs, including homozygous truncating variants, have been observed in patients with HCM, either alone or alongside other PVs. CAV3 encodes caveolin 3, a component of caveolae in the cytoplasmic membrane. It is expressed in cardiac and skeletal muscle, where it interacts with various cellular components. While tolerant to missense and LoF variants, CAV3 PVs have been linked to skeletal myopathy, long QT syndrome 9, and various forms of cardiomyopathies, including HCM [14].

CRYAB, encoding crystalline  $\alpha$ B, a small heat shock protein with chaperone-like activity, is expressed in multiple cell types but enriched in cardiac and skeletal muscles. It is tolerant to LoF and missense variants. Although most commonly associated with dilated cardiomyopathy, PVs in the CRYAB gene have also been reported in sporadic HCM cases. However, they are not expected to be major contributors to the phenotypic expression of HCM [9] [10] [14].

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## 2. Materials and methods

This review paper was conducted by reviewing professional and scientific literature available on reliable internet databases. Most of the materials were analyzed on the "Google Scholar" database, where numerous scientific articles and books can be found. Besides Google Scholar, PubMed and NCBI databases were also of use. Additionally, since the research was based on information from around the world, all sources were available in English. Nine scientific articles

from various parts of the world, published between 2002 and 2023, were cited, and one article from the year 1995. The method of work is review-based and descriptive.

The key words used to find information on the mentioned platforms were: Cardiomyopathy, Hereditary cardiomyopathy, familial cardiomyopathy, molecular basis of cardiomyopathy, genetics of cardiomyopathy.

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### 3. Results

The results of the literature review shed light on the genetic and molecular underpinnings of hereditary cardiomyopathies, a diverse group of myocardial diseases characterized by mechanical and electrical abnormalities. These conditions, including hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM), stem from various genetic factors and can have significant implications for patient outcomes. Familial clustering of cardiomyopathies, particularly HCM, has been well-documented, with a notable proportion of cases demonstrating autosomal dominant inheritance patterns. Genetic studies have identified mutations in key genes encoding sarcomere proteins, thin filament proteins, and proteins involved in calcium homeostasis as central players in the pathogenesis of these conditions [14].

The exploration of the genetic basis of cardiomyopathies, as outlined in the introduction of the seminar paper, highlights the complex interplay between genetic abnormalities and disease manifestation. The identification of mutations in genes such as MYH7, MYBPC3, TNNT2, and ACTC1 underscores the role of sarcomere dysfunction in the development of hereditary cardiomyopathies. Moreover, the recognition of familial incidence rates and the involvement of multiple inheritance patterns emphasize the importance of genetic testing and counseling in affected families [13] [14],

Early detection through genetic risk assessment enables proactive intervention, potentially altering disease trajectory and improving patient outcomes. Overall, the results underscore the critical role of genetics in the management of hereditary cardiomyopathies and emphasize the need for further research to elucidate the complexities of these conditions [14].

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### 4. Discussion

The exploration of cardiomyopathies, encompassing various genetic and acquired forms, underscores the complex interplay between genetic predisposition and environmental factors in cardiovascular diseases. Understanding the genetic basis of cardiomyopathies, particularly hereditary forms like hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM), has witnessed significant advancements in recent years [15].

Familial clustering of these conditions highlights the importance of genetic factors in disease pathogenesis, with a substantial proportion of affected individuals harboring identifiable mutations in genes encoding sarcomere and cytoskeletal proteins. HCM, characterized by left ventricular hypertrophy without hemodynamic stress, exemplifies the intricate genetic landscape underlying cardiomyopathies [16].

Studies have identified mutations in genes encoding thick filament proteins like MYH7 and MYBPC3, emphasizing the role of sarcomeric dysfunction in HCM pathogenesis. Additionally, variants in thin filament proteins such as ACTC1 and TNNT2 contribute to disease susceptibility, highlighting the multifaceted genetic architecture of HCM. Understanding the functional implications of these mutations is crucial for delineating their role in disease manifestation and progression [16] [17].

In contrast, DCM presents with ventricular dilation and systolic dysfunction, often unrelated to external factors like hypertension or coronary artery disease. Genetic studies have revealed a diverse array of mutations associated with familial DCM, ranging from defects in sarcomeric proteins to abnormalities in cytoskeletal and transcriptional regulators. The polygenic nature of DCM underscores the complexity of its genetic underpinnings, necessitating comprehensive genetic screening and counseling for affected families [18].

Evidences implicate genes encoding proteins located at the Z lines and M lines of the sarcomere in cardiomyopathy pathogenesis. These proteins play critical roles in sarcomere structure and function, with mutations in genes like MYOZ2, ACTN2, and TRIM63 contributing to disease susceptibility. Clarifying the molecular mechanisms underlying the involvement of these genes in cardiomyopathies is essential for uncovering novel therapeutic targets and personalized treatment strategies [18] [19].

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## 5. Conclusion

Overall, the integration of genetic insights into the clinical management of hereditary cardiomyopathies holds immense promise for personalized medicine approaches. Genetic testing and counseling facilitate early diagnosis, risk stratification, and targeted interventions, ultimately improving patient outcomes and reducing disease burden [20]. Continued research efforts aimed at unraveling the genetic complexities of cardiomyopathies will pave the way for innovative therapeutic strategies and precision medicine interventions in the field of cardiovascular medicine.

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## Compliance with ethical standards

### *Disclosure of conflict of interest*

The authors declare that they have no conflict of interest.

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