Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2025**; 30(2): 25714
https://doi.org/10.31083/FBL25714

Review

Hypertrophic Cardiomyopathy: Genes and Mechanisms

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Academic Editor: Natascia Tiso
Submitted: 16 July 2024 Revised: 28 August 2024 Accepted: 10 September 2024 Published: 12 February 2025

Abstract

Hypertrophic cardiomyopathy (HCM) is a hereditary disease of the myocardium characterized by asymmetric hypertrophy (mainly the left ventricle) not caused by pressure or volume load. Most cases of HCM are caused by genetic mutations, particularly in the gene encoding cardiac myosin, such as *MYH7*, *TNNT2*, and *MYBPC3*. These mutations are usually inherited autosomal dominantly. Approximately 30–60% of HCM patients have a family history of similar cases among their immediate relatives. This underscores the significance of genetic factors in the development of HCM. Therefore, we summarized the gene mutation mechanisms associated with the onset of HCM and potential treatment directions. We aim to improve patient outcomes by increasing doctors' awareness of genetic counseling, early diagnosis, and identification of asymptomatic patients. Additionally, we offer valuable insights for future research directions, as well as for early diagnosis and intervention.

Keywords: cardiomyopathy; hypertrophic cardiomyopathy; heredity; genetic mutations

1. Introduction

In 2008, European Society of Cardiology launched a classification method for cardiomyopathies, which not only focused on the pathological morphology and dysfunction of different phenotypes of cardiomyopathies, but also made detailed groupings according to whether they are hereditary or not [1]. In recent years, with the vigorous development and widespread application of new medical imaging and molecular biology technologies, people's understanding of cardiomyopathy has greatly increased. On this basis, the new guidelines divide cardiomyopathy into hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), non-dilated left ventricular cardiomyopathy (NDLVC) and arrhythmogenic right ventricular cardiomyopathy (ARVC). This new classification prompts clinicians to consider cardiomyopathy as the cause of several clinical manifestations (e.g., arrhythmias, heart failure) [2].

HCM is a potential hereditary heart disease characterized by abnormal thickening of the heart muscle, leading to abnormal heart function [3]. The pathogenic genes of HCM mainly involve genes encoding cardiac myofilament proteins, such as *MYH7*, *MYBPC3*, etc. These gene mutations lead to abnormal myocardial contractile function, increase the stress load of myofilaments, and ultimately cause myocardial cell hypertrophy, disordered arrangement and fibrosis, which in turn leads to the occurrence and development of HCM [4,5]. The common causes and outcomes of HCM are shown in Fig. 1. In the early days, due to insufficient diagnostic technology and limited knowledge about HCM, the early prevalence was estimated to be 1/500 [6]. However, a recent study has shown that HCM may be more common than traditionally expected, affecting approximately 1 in 200 patients [7]. In comparison to the general population, individuals with HCM face significantly elevated risks across multiple fronts. Numerous studies have shown that patients with HCM face a significantly increased risk of adverse events compared with the general population. They have a higher risk of death, with twice the risk of sudden death, 2.5 times more likely to have heart failure, and approximately 6 times higher rates of atrial fibrillation than the age-matched general population [8,9]. However, a large international cohort study of HCM patients with long-term follow-up found no difference in mortality, progressive heart failure, or sudden death events between those with and without pathogenic genotypes. This study suggests that genetic test results cannot reliably predict the prognosis of HCM patients or guide management decisions. Although their findings differ from most current research, the authors attribute this to demographic differences and variability in clinical outcomes across different eras [10]. Nowadays, with more and more research on its genetic characteristics and pathogenesis, it has attracted the attention of more and more cardiovascular physicians. Although most patients experience a clinically benign course, some develop complications, including heart failure, left ventricular outflow tract obstruction, atrial and ventricular

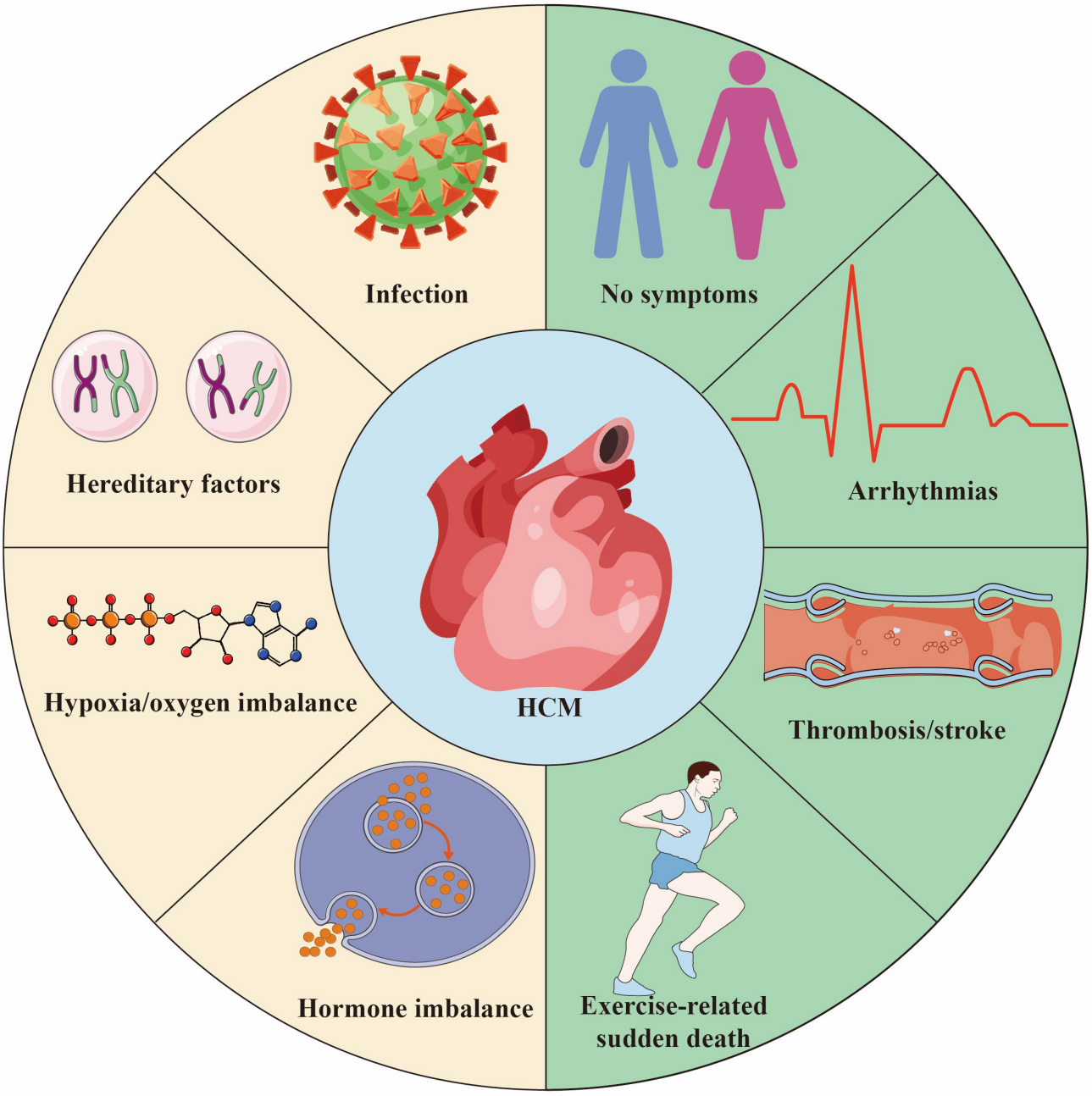

Fig. 1. Hypertrophic Cardiomyopathy (HCM) is a common hereditary heart disease, 30%–60% of the causes are due to genetic factors. Other causes include infection/inflammation, hypoxia/oxygen supply imbalance and endocrine factors. The outcome of HCM varies depending on individual differences and the severity of the disease. Some people are asymptomatic or have mild symptoms throughout their lives and live a normal life. Some patients suffer from thrombosis/stroke secondary to atrial fibrillation. HCM is one of the main causes of sudden death in young athletes. Created by Adobe Illustrator (Adobe Inc., San Jose, CA, USA).

arrhythmias, and sudden death. In addition, different genetic defects can also lead to different clinical phenotypes, such as asymmetric left ventricular hypertrophy [11]. Nevertheless, there is also evidence of nonfamilial forms of HCM, which also needs to be paid enough attention [12].

This review aims to explore the current genetic mechanism of HCM and the correlation between HCM genotype and phenotype. It also discusses new directions in molecular diagnosis, genetic counseling, and personalized treatment. It aims to guide clinical diagnosis and treatment, and the direction of future basic research.

2. HCM and Related Pathogenic Genes

HCM stands out as the predominant hereditary heart condition, typically passed down through generations in an autosomal dominant manner. It often exhibits incomplete penetrance and a degree of variability, with around

30%–60% of cases showing familial ties [10,13]. Presently, there's a prevailing agreement within the medical community to advocate for targeted genetic testing in individuals suspected of HCM [14]. This approach serves to not only confirm the diagnosis but also shed light on the specific molecular causes, facilitating informed decisions regarding family screening and treatment strategies [15]. We used the STRING 12.0 database (https://cn.string-db.org/) to screen genes closely related to HCM, and through in-depth analysis of relevant literature, selected genes with significant roles in HCM, while also focusing on genes that are relatively less studied but potentially important. We focused on genes that have a clear role in HCM and are likely to provide new insights.

2.1 MYBPC3

The *MYBPC3* encodes the cardiac isoform of myosin-binding protein C (cMBP-C). This gene spans a 3.7 kb DNA sequence and contains 34 coding elements, ultimately forming 35 exons. These exons are transcribed to produce a 3824 bp transcript. cMBP-C, a member of the intracellular immunoglobulin superfamily, is encoded by the *MYBPC1* and *MYBPC2* in skeletal muscle and by the *MYBPC3* in the heart. Its structure includes eight immunoglobulin-like domains (C0, C1, C2, C3, C4, C5, C8, C10) and three fibronectin type III domains (C6, C7, C9) [16,17]. The core function of cMBP-C is to precisely regulate cross-bridge recycling in cardiomyocytes through phosphorylation and interaction with other factors, thereby contributing to the assembly of myocardial heavy chains. This regulation is crucial for ensuring that the heart muscle contracts and relaxes properly. Additionally, cMBP-C modulates the sensitivity of fibrin protein to calcium ions, which in turn affects the contractile performance of the myocardium. This discovery offers a new perspective for understanding the mechanisms underlying myocardial contraction [18].

Since the *MYBPC3* was recognized by the scientific community as the main causative gene of HCM in 1995, a large number of studies have focused on this gene and its related mutations. To date, more than 600 mutations related to the *MYBPC3* have been discovered, and these mutations account for approximately 35% of mutation-positive HCM patients. This finding further solidifies *MYBPC3*'s status as a major causative gene in HCM [19–21]. Among the known *MYBPC3* mutations, more than 60% are truncating mutations, including nonsense mutations, insertions or deletions, splicing or branch point mutations, and the *MYBPC3* is tolerant to missense and LoF mutations (LOUEF: 0.96). Truncating mutations often activate nonsense-mediated decay (NMD) and the ubiquitin-proteasome system (UPS), leading to haplodeficiency of the cMBP-C, the production of toxic peptides, and the COOH-terminal truncation of cMBP-C, which in turn causes myosotrophy (Fig. 2). The deletion of the protein or its binding site causes abnormalities in the structure and function of myosin, ultimately leading to haploid protein deficiency. Haploid gene defects are the predominant manifestation of heterozygous deletion mutations, and most *MYBPC3*-related HCM mutations are heterozygous [22,23].

Clinical phenotypes caused by *MYBPC3* mutations often share some common characteristics: disease onset usually occurs after middle age, cardiac hypertrophy is relatively low, and disease progression is slow. Clinically, truncating mutations and double mutations in the *MYBPC3* often lead to more severe clinical phenotypes. In addition to changes in cMBP-C composition that can lead to myasthenia gravis and peptide toxicity, its function is also regulated by a variety of post-translational modifications, including phosphorylation, acetylation, citrullination, and oxidation. Compensatory slowing of calcium processing preserves contractile parameters, whereas faster sarcomere dynamics reduce myocardial contractility [24]. At present, at least three phosphorylation sites have been found to be located in the molecular structure of cMBP-C and targeted by protein kinases. These sites begin at Ser282, which acts as a switch to make Ser273 and Ser302 more susceptible to phosphorylation. Currently known protein kinases that can phosphorylate MBP-C include protein kinase A (PKA), Ca^{2+}/calmodulin-dependent kinase II, p90 ribosomal S6 kinase, protein kinase D and protein kinase C, etc. [25]. Research shows that *MYBPC3* therapy has the potential to restore MBP levels, with the goal of preventing heart failure and reducing mortality in *MYBPC3*-related cardiomyopathy. Each genetic mutation has its own unique clinical manifestations. For example, men with the *MYBPC3* c.2149-1G>A splice variant have an earlier onset of HCM and a higher penetration rate than women. When the pathogenicity of a mutation is confirmed, relatives carrying the mutation are eligible for surveillance to detect early signs of disease, treat it, and prevent its consequences [26]. Although understanding the causative genes of patients with HCM cannot change the current course of treatment, genetic testing can provide probands and relatives with prognostic data. Specific types of mutations can predict likely disease onset and associated clinical outcomes [27]. Through genetic screening, we can conduct regular health monitoring of young mutation carriers in the family who have not yet shown symptoms, thereby enabling early identification and intervention of potential risks. This measure is particularly important in the diagnosis and treatment of HCM. Genetic testing of HCM patients can not only reveal the genetic roots of the disease and provide important basis for the formulation of treatment plans, but also promote the development of family screening, which has far-reaching implications for the early diagnosis of family members and early intervention and treatment of mutation carriers [28].

2.2 MYH7

The *MYH7* is located on chromosome 14q11.2-q13 and contains 40 exons. It encodes the β-myosin heavy chain

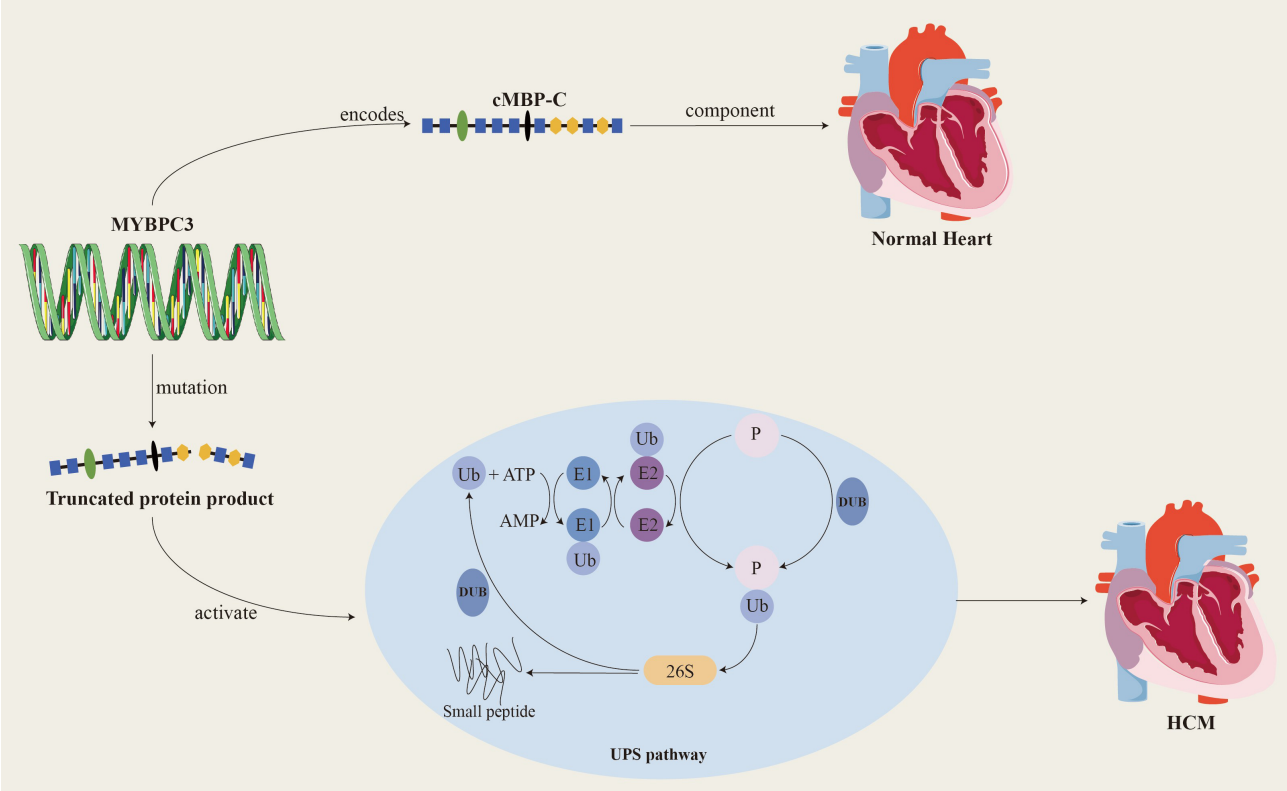

Fig. 2. *MYBPC3* encodes cardiac myosin binding protein-C, which is a key structural protein of the myocardium and plays an important role in the relaxation and contraction of the myocardium. When *MYBPC3* mutates, it produces a truncated protein product that activates the UPS system and ultimately leads to HCM. cMBP-C, cardiac myosin binding protein-C; Ub, ubiquitin; E1, ubiquitin-activating enzyme; E2, ubiquitin-conjugating enzyme; DUB, deubiquitinating enzymes; UPS, ubiquitin-proteasome system; P, phosphonates. Created by Adobe Illustrator (Adobe Inc., San Jose, CA, USA).

(β-MHC), which consists of 1935 amino acids and serves as the core component of ventricular myosin. The protein is composed of two heavy chains and four light chains, forming three functional regions: the head, neck, and tail, which collectively drive muscle contraction. The motor domain S1 of the head binds to actin and ATP, facilitating cardiomyocyte contraction. The tail region comprises S2 and light filament myosin, while the neck region connects the head and tail [29]. *MYH7* plays a key role in the contraction and relaxation of cardiomyocytes. HCM patients with mutations in it are more likely to develop left ventricular outflow tract obstruction than those with *MYBPC3* mutations. They have an earlier age of onset, high clinical phenotype penetrance, severe myocardial hypertrophy, and a high rate of sudden death, the prognosis is poor. There are currently multiple views on the pathogenesis of HCM caused by *MYH7* gene mutations. These mechanisms mainly include changes in mitochondrial function, changes in muscle cell structure and contractility, and abnormalities in the regulation of ATP hydrolysis and ADP release. These changes together lead to insufficient energy supply to the ventricular myocardium, which in turn triggers hypertrophy of the ventricles or interventricular septum. Further research also revealed the important role of mitochondrial function in the pathogenesis of HCM. Metabolic disorders and mitochondrial dysfunction are common pathological features in HCM patients. Experimental data show that in a mouse model of HCM with *MYH7* mutations, fibroblast growth factor 21 levels are significantly increased and the increase in mitochondrial DNA copy number is consistent with changes in mitochondrial activity and the development of cardiomyopathy [30]. In addition, missense mutations in the *MYH7* can also affect the structure and function of cardiomyocytes, leading to the occurrence of HCM. Most of these mutations are located in the globular head and neck regions of the β-MHC protein, affecting binding sites with ATP, actin, and essential or regulatory light chains. Mutations may also lead to disruption of thick filament dimerization, thereby affecting myosin ATP hydrolysis and myofilament sliding [31].

The severity of HCM is closely related to the proportion of abnormal myosin in cardiomyocytes. Mutations in the *MYH7* may cause disease through a dominant-negative "toxic peptide" mechanism, that is, the abnormal myosin produced by the pathogenic mutation will interfere with the normal contractile function of the sarcomere. In addition, *MYH7* gene mutations may also increase the sensitivity of myofibrillar cells to Ca^{2+}, leading to increased

myocardial energy consumption and ventricular diastolic dysfunction, further exacerbating ventricular hypertrophy [32]. The pathogenicity of *MYH7* gene mutations is closely related to its key function in cardiomyocytes. These mutations not only affect the contractile function of cardiomyocytes but may also lead to changes in a complex genetic and epigenetic background. Therefore, an in-depth study of the pathogenic mechanism of *MYH7* gene mutations is of great significance for early diagnosis, precise treatment and prognosis judgment of HCM patients. It is exciting to see that significant progress has been made in the current field of gene therapy research. In particular, the combined application of gene therapy or gene editing technology and human-induced pluripotent stemcell-derived cardiomyocyte (hiPSC-CM) has opened up a new way for individualized cultivation of mature cardiomyocytes. This breakthrough technology may bring unprecedented hope for the treatment of HCM patients caused by *MYH7* gene mutations.

2.3 CAV3

The traditional concept is that caveolae are a rich place for intracellular signaling molecules and can form complexes to regulate ion channels, vesicle transport and signal transduction. But modern molecular biology techniques have revealed more functions of caveolae, such as maintaining cholesterol homeostasis and regulating signaling [33]. However, the regulation of cholesterol homeostasis remains controversial. Caveolae is a key characteristic protein on the caveolae membrane, which is essential for maintaining the morphology, structure and function of caveolae. It also constitutes a special subset of lipid rafts [34]. As the main component of caveolae, caveolin-3 (CAV3) was first cloned and identified in 1996. It consists of 151 amino acids and contains several independent domains: N-terminal domain (residues 1–53), CSD domain (residue 54–73), transmembrane domain (residues 74–106) and c-terminal domain (residues 107–151) [35]. Most of its mutations are concentrated in the caveolin scaffolding domain, which is involved in self-assembly and interaction with signaling molecules. Therefore, CAV3 plays an important role in cell physiology, including regulating ion channels, vesicle transport, cholesterol and calcium homeostasis, and signal transduction. It serves as a molecular chaperone and scaffold through the scaffolding domain to regulate a variety of signaling molecules.

When the *CAV3* mutates, it may lead to varying degrees of lesions in skeletal muscle, myocardium and other tissues through various mechanisms. This type of disease is collectively called caveolin disease. The caveolin-3 protein encoded by the *CAV3* gene is a key component of caveolae. It is expressed in cardiac muscle, skeletal muscle and smooth muscle, and interacts with a variety of molecules related to cardiac hypertrophy signals [36]. In cardiomyocytes, a variety of signaling molecules such as β2-ARs, m2-mAChR and their related G protein subunits, adenylyl cyclase isoforms, G protein-coupled receptor kinase family members (such as GRK2) and catalytic subunit of protein kinase A, etc. will accumulate in caveolae when cells are in a steady state or activated state. This indicates that caveolae are not only a physical gathering place for signaling molecules, but also serve as a scaffold for preassembled membrane-bound oligomer complexes, providing a platform for rapid coupling between receptors and effectors. This rapid coupling process is critical for sympathetic regulation of cardiomyocyte function, ensuring that cardiomyocytes can rapidly respond and adapt to various physiological and pathological conditions [37].

It is worth noting that the distribution of α1-AR in the plasma membrane is not random, but tends to accumulate in caveolae. This means that caveolae may be a key microdomain of α1-AR signaling, which can promote the interaction between α1-AR and other signaling molecules, thereby regulating the function and response of cardiomyocytes. When α1-AR signaling is enhanced, it may accelerate the development of cardiac hypertrophy. As the main component of caveolin, its reduced inhibitory effect on growth factor signaling may also play an important role in the pathogenesis of cardiac hypertrophy. In caveolin-3-deficient transgenic mice, researchers observed that the development of hypertrophic cardiomyopathy is closely related to increased endothelial nitric oxide synthase (eNOS) activity. Myocardial contractility was enhanced in these mice, but NOS expression levels did not change. This finding suggests that loss of NOS inhibition secondary to caveolin-3 deficiency may be a key link in the pathogenesis of hypertrophic cardiomyopathy. Further research showed that the activity of NOS has a significant impact on cardiac function. eNOS and neuronal nitric oxide synthase (nNOS) are localized in caveolae and sarcoplasmic reticulum (SR) respectively, and they exert different effects on cardiac contractility. For example, knockdown of eNOS enhances myocardial contractility, whereas overexpression reduces cardiac size and decreases contractility. Of particular note, mouse hearts with moderately increased eNOS activity exhibit enhanced contractility and features of hypertrophic cardiomyopathy, whereas extremely high activation of eNOS reduces myocardial contractility and heart size [38]. In addition, the contractile response to cardiac tissue produced by exogenous nitric oxide also appears biphasic. Low levels of nitric oxide enhance myocardial contractility, while high levels have an inhibitory effect. This phenomenon further demonstrates that moderate and extremely high activation of eNOS activity have distinct effects on cardiac function [39]. *CAV3* and its encoded proteins play an important role in cell signaling, ion channel regulation, and the pathogenesis of cardiomyopathy, and are of great significance for understanding these complex biological processes and treating related diseases.

2.4 GLA

The *GLA* is a gene in the human genome and is located on the X chromosome. The coding sequence of the *GLA* contains 7 exons and 6 introns, with a total length of approximately 13.5 kb. It includes the transcription start site, coding region, and termination site. This gene encodes a protein called α-galactosidase A (α-Gal A) [40]. α-Gal A is an enzyme composed of 429 amino acids that catalyzes the hydrolysis of α-galacturonide into galactose and fatty acids. This enzyme's activity is crucial for normal metabolism and cellular function. It contains a signal peptide sequence that directs its localization to the cytoplasm, followed by post-translational modification to produce the mature α-Gal A protein. The mature protein has an α/β fold structure and comprises four domains: an N-terminal α-helical domain, a middle β-turn domain, a C-terminal α/β ribbon domain, and a C-terminal α-helical domain. These domains are essential for the function and stability of α-Gal A. Additionally, the α-Gal A protein contains a covalently attached sugar group, which is also necessary for its stability and function.

The mature α-Gal A enzyme is localized in the lysosomes, organelles within cells that are responsible for breaking down and degrading waste products, lipids, and proteins. Within lysosomes, the α-Gal A enzyme binds to α-galacturonide and catalyzes its hydrolysis, breaking it down into galactose and fatty acids. These products can then be further processed and utilized in other metabolic pathways. The enzyme normally plays a crucial role in breaking down a lipid called acylsphingosine trihexoside. However, mutations in the *GLA* alter the enzyme's structure and function, impairing its ability to break down this fat. As a result, acylsphingosine trihexosylglycosides and diposylceramides accumulate in body cells, particularly in blood vessels of the skin, kidneys, heart, and nervous system, which adversely affects the normal functioning of these organs. This abnormal lipid accumulation can lead to tissue and organ damage.

In cardiac cells, this deposition leads to organelle dysfunction, intracellular metabolism and energy production are affected, and ultimately leads to cardiomyocyte hypertrophy and hyperplasia. Deposition of Gb3 leads to the formation of its metabolite lyso-Gb3 [41]. Lyso-Gb3 is a degradation product of Gb3 but also accumulates within cells. The deposition of Gb3 and lyso-Gb3 causes intracellular metabolic abnormalities and lysosomal dysfunction in cardiac cells, leading to hypertrophy, hyperplasia, and fibrosis of cardiac myocytes [42]. Gb3 and Lyso-Gb3 are deposited in various cells of the cardiovascular system, leading to various manifestations including left ventricular hypertrophy, conduction abnormalities, aortic valve and mitral valve insufficiency, etc. [43]. Gb3 is deposited in all types of cells and tissues in the heart, including cardiomyocytes, intramyocardial blood vessels (endothelial and smooth muscle cells), and conductive tissue. In addition to the mechanical effects of deposition, the accumulation of these substances can trigger secondary reactions, damaging cellular endocytosis and autophagy functions, inducing apoptosis, and disrupting mitochondrial energy production. This leads to abnormal energy metabolism and increased oxidative stress, which in turn triggers metabolic changes within cells. These alterations contribute to cellular remodeling and activate pathways that promote cellular hypertrophy. Accumulated Gb3 may also change the expression of ion channels and/or cell membrane transport, thereby changing the electrophysiological properties of cardiomyocytes, leading to an increase in myocardial conduction velocity between the atrium and ventricle, resulting in a shortened PR interval on the patient's electrocardiogram [44]. Gb3 and Lyso-Gb3 can also serve as antigens to activate natural killer T cells, leading to chronic inflammation and autoimmune reactions, leading to pathological damage and fibrosis of cardiomyocytes, further promoting the occurrence of myocardial thickening, and ultimately leading to HCM.

2.5 LAMP2

The *LAMP2* is a gene encoding lysosomal-associated membrane protein 2 (LAMP2). It is located on the X chromosome of the human genome and is also known as a Danon disease-related gene. LAMP2 is one of the main protein components of the lysosomal membrane. There are currently three main subtypes: LAMP2A, LAMP2B and LAMP2C [45]. Its structure includes extracellular domain, transmembrane domain and intracellular domain, which plays an important role in maintaining the structure and function of lysosome. LAMP2 forms a stable structure on the lysosomal membrane and helps maintain lysosome integrity and stability. It participates in regulating the formation, fusion and transport processes of lysosomes, ensuring the normal function of lysosomes within cells [46].

LAMP2 gene mutations can lead to defects in the autophagy function of autophagosomes, disorders in the fusion process of lysosomes and target cells, and loss of organelle motility, ultimately leading to the accumulation of autophagosomes in cardiomyocytes and the storage of glycogen in the cytoplasm [47]. LAMP2B is mainly involved in the biogenesis of lysosomes and macroautophagy, and is indispensable for the fusion of autophagosomes and lysosomes in cardiomyocytes [48]. LAMP2B is indispensable for autophagosome and lysosome fusion in cardiomyocytes. LAMP2B on the lysosomal membrane interacts with autophagy related gene 14 (*ATG14*) and vesicle-associated membrane protein 8 (VAMP8) through its C-terminal domain to mediate autophagosome-lysosome fusion, thereby regulating cardiomyocyte function [45]. *ATG14* is an important factor in the autophagy process. It binds to the Beclin-1 complex (similar to the PI3K complex) and participates in the formation of autophagosomes and the regulation of the autophagy process. LAMP2B

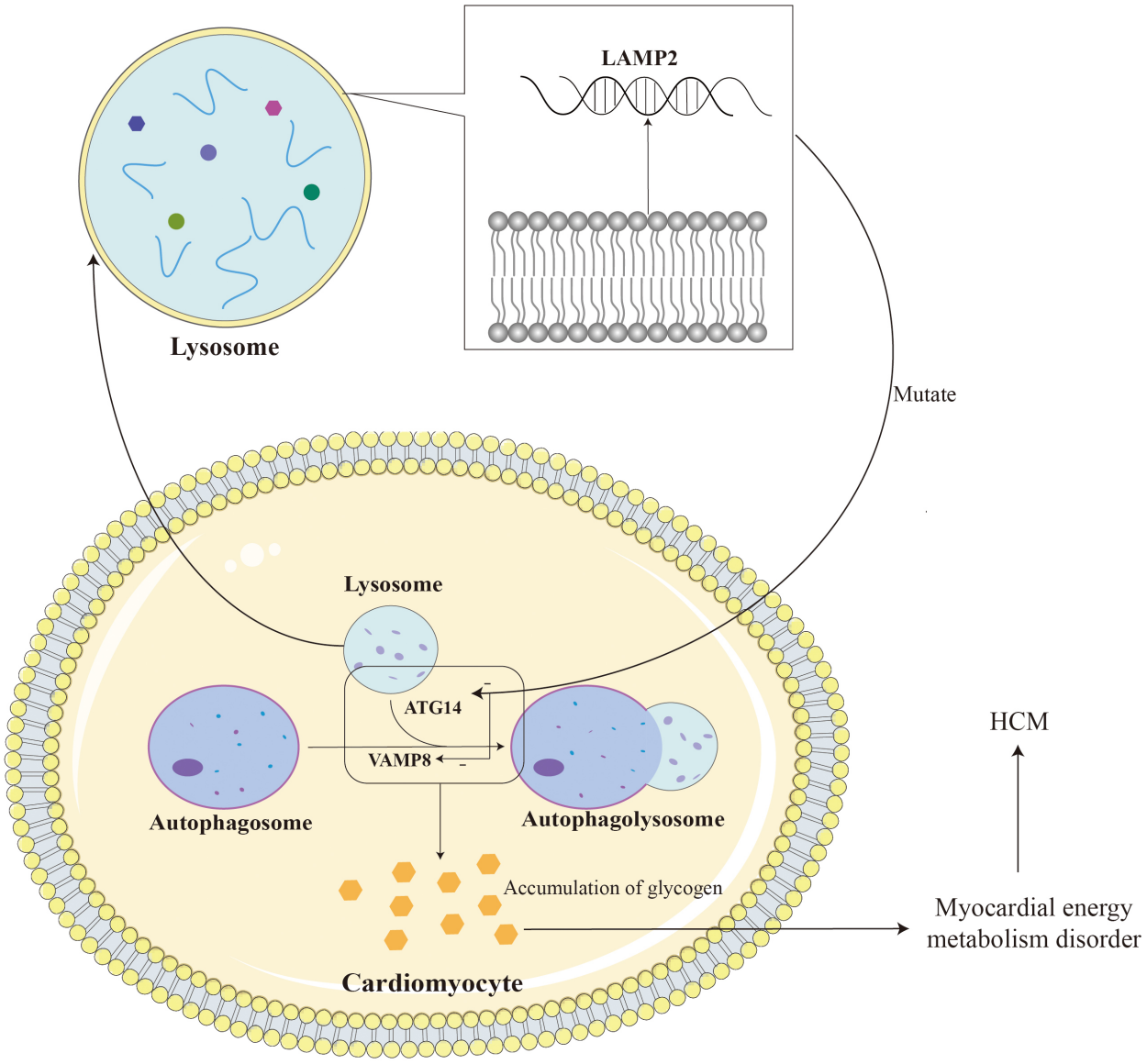

Fig. 3. LAMP2 is located on the lysosomal membrane and assists in the fusion of lysosomes and autophagosomes. The mutation leads to impairment of myocardial autophagy by reducing the fusion of lysosomes and autophagosomes, leading to glycogen accumulation and ultimately HCM. LAMP2, lysosomal-associated membrane protein 2; ATG14, autophagy-related protein 14; VAMP8, vesicle-associated membrane protein 8. Adobe Illustrator (Adobe Inc., San Jose, CA, USA).

helps regulate the formation of autophagosomes and promotes the fusion of autophagosomes and lysosomes by binding to *ATG14*. VAMP8 is a vesicle-associated membrane protein that participates in the process of vesicle trafficking and fusion within cells. During the autophagy process, LAMP2B helps regulate the fusion process between autophagosomes and lysosomes through its interaction with VAMP8, promoting the degradation of the contents in autophagosomes by lysosomes. Loss of LAMP2B leads to autophagy-lysosomal maturation impairment. This dysfunction may cause the autophagic vacuoles within autophagosomes to be unable to effectively fuse with lysosomes, thereby affecting the degradation and clearance of autophagic contents [49]. Due to lysosomal dysfunction, glycogen in autophagosomes cannot be effectively degraded and cleared, resulting in the accumulation of glycogen. This accumulation of glycogen leads to metabolic disorders and energy imbalance within cardiomyocytes. Similarly, lysosomal dysfunction can also lead to the accumulation of other autophagic vacuoles in autophagosomes that cannot be effectively degraded and cleared. The accumulation of autophagic vacuoles and glycogen can lead to metabolic disorders within cardiomyocytes, including disorders of energy metabolism and disorders of waste clearance. This metabolic disorder can lead to intracellular functional abnormalities, including reduced calcium ion processing capabilities, abnormal cell signaling, etc., thereby affecting the structure and function of cardiomyocytes; trig-

Table 1. Summary on M-, T-, and MT-class of human *ACTC1* gene mutations.

Gene	Alternative titles	Class	Variant
ACTC1	ACTC, SMOOTH MUSCLE ACTIN, ACTIN, ALPHA	Myosin/M	E99K
			H88Y
			R95C
			F90Δ
			S271F
		Tropomyosin/T	A230V
			R312C
		Myosin and tropomyosin/MT	P164
			Y166C
			A295S
			A331P
			M305L

gering intracellular stress responses, including inflammatory responses, oxidative stress, etc. These stress reactions will cause the activation of intracellular biochemical pathways and promote the hypertrophy and proliferation of muscle cells; the accumulation of metabolites and waste products will increase the volume of cells and trigger a series of changes in cell signaling pathways, thereby promoting the hypertrophy of cardiomyocytes and hyperplasia. In addition, missing or dysfunctional LAMP2 can lead to obstruction of lysosomal autophagy, which in turn can lead to damage and death of cardiomyocytes, thereby causing fibrosis and granuloma formation during the repair process. These abnormal tissue repair and inflammatory responses may cause cardiac hypertrophy [49–51]. Fig. 3 shows some of the mechanisms by which *LAMP2* mutations cause HCM.

In addition, there is increasing recognition that other rare genetic disorders may mimic the phenotypic and clinical features of HCM but are caused by mutations in different genes. Notable among these conditions are Fabry disease (an X-linked a-galactosidase deficiency with glycosphingolipid deposition), PRKAG2 syndrome (caused by mutations in the regulatory subunit of adenosine monophosphate-activated protein kinase), and *LAMP2* deficiency (a lysosomal storage disorder, also known as Danon disease) [52–55].

2.6 ACTC1

ACTC1 is responsible for encoding α-cardiac actin, which together with tropomyosin and three types of troponins form thin contractile filaments that connect the muscle cell Z-disk to the thick filament protein myosin. The complex is mainly expressed in cardiomyocytes. ACTC1 is the only actin expressed in embryonic cardiac muscle, has a very conserved amino acid sequence, and is critical for multiple cellular functions. In addition to its classic role in muscle contraction, actin also interacts with the actin skeleton, affecting its multiple functions such as polymerization and depolymerization, thus participating in the regulation of gene transcription. Actin also maintains its normal functions such as morphological stability and division by interacting with chromatin remodeling complexes [56,57]. Lack or mutation of *ACTC1* may affect its interaction with actomyosin and binding to regulatory proteins, ultimately exhibiting embryonic lethality and myofibrillar disorganization.

Most cases of HCM are caused by mutations in genes encoding sarcomeric proteins, with less than 3% of pathogenic variants found in the sarcomeric gene *ACTC1* [58]. Currently, 12 different *ACTC1* mutations have been found in HCM patients. *ACTC1* mutations are divided into three categories according to the position of the amino acid changes in actin: ① mutations that only affect the motor binding site of the myosin molecule are called M-type mutations, ② mutations that only affect the tropomyosin binding site, called T-class mutations, and ③ mutations that affect both myosin and tropomyosin binding sites, are called MT-class mutations [59,60] (Table 1).

Symptoms in patients with HCM often include systolic dysfunction and restricted diastole, this may be because mutations in the *ACTC1* associated with HCM alter the structure and function of cardiac actin, thereby affecting myocardial function [61]. A study has found that a non-synonymous mutation (p.Gly247Asp or:G247D) in the *ACTC1* leads to increased cardiomyocyte apoptosis and sarcomeric disorganization, both of which have deleterious effects on contractile function [62]. Studies have found that sarcomeric protein mutations cause intrinsic abnormalities in myofibrillar structure and function. These abnormalities jointly drive invasive structures at the cellular and extracellular levels by interfering with the excitation-contraction coupling process, cardiomyocyte energy metabolism, cardiomyocyte signaling, and other mechanisms. Remodeling, which in turn impairs myocardial systolic and diastolic function, leads to the common occurrence of progressive left ventricular dysfunction in HCM [63,64]. The specific mechanism by which *ACTC1* mutations cause HCM remains unclear. *ACTC1* mutations lead to increased myocar-

Table 2. Mutant types and possible mechanisms of *TNNT2*.

Mutation type	Mechanism
K280N	Affects sarcomere dynamics and energetics, leading to impairment of myocardial contractile function [71,72].
Ile79Asn, Arg92Gln, Glu244Asp, Lys273Glu, Arg278Cys	Maintaining calcium sensitivity of cardiac myofilament proteins under conditions of higher Ca^{2+} [73–76].
Lys210del, Arg141Trp	Causes sarcomeric protein mutations and desensitization to Ca^{2+} [77,78].
E244D, K247R, D270N, N271I, K273E	Weaken the affinity of troponin to thin filaments, cause abnormal protein folding, destroy the stability of troponin complex, enhance calcium ion sensitivity, and enhance the maximum activity level of ATPase [79,80].

dial cell apoptosis and abnormal sarcomeres, resulting in abnormal myocardial systolic and diastolic function, which in turn leads to abnormal cardiac morphology and hemodynamic disorders. This may be a potential mechanism for continued research.

2.7 TNNT2

TNNT2 is located on chromosome 1 (1q32), encoding cardiac troponin T2 (TnT). It mainly regulates actin filament function by binding calcium ions and is crucial for human cardiac muscle contraction and relaxation [65]. TnT interacts with the other two troponin subunits, troponin T (TnT) and troponin C (TnC), through the C-terminus to form a stable trimer core, and the N-terminus interacts with actin filaments. Binding at specific sites anchors the troponin complex to the myofilaments and moves as the muscle contracts and relaxes. 2%–5% of HCM patients are caused by pathogenic mutations in this gene, and abnormal N-terminal splicing and TnT point mutations are possible causes. Abnormal splicing of N-terminal exon 5 can affect the interaction between cTnT and tropomyosin, interfere with the calcium sensitivity of myofibrils, thereby affecting cardiac contraction, ultimately leading to cardiac hypertrophy and HCM [66,67]. More than ten *TNNT2* single mutations causing HCM have been found, such as Ile79Asn, Glu244Asp, etc., but the specific mechanism is still not completely clear. Homozygous mutations are very rare and usually have a more severe phenotype than heterozygous mutations in a gene dose-dependent manner [68,69]. A homozygous mutation K280N (c.804G>T) can 100% cause changes in TnT, leading to an acceleration of the shedding rate of sarcomere cross-bridges and an increase in the energy cost of tension, supporting the pathogenesis of cardiomyopathy caused by inefficient utilization of ATP by myofilaments [70]. Some types of *TNNT2* mutations and corresponding mechanisms are summarized in Table 2 (Ref. [71–80]).

A study has shown that by replacing mutated TnT with wild-type TnT, the rate constants of tension and isometric relaxation generated after maximum Ca^{2+} activation can be reduced, reducing the tension cost to unmutated control values, suggesting that the direct effect of the mutant protein can be reversed. Therefore, the introduction of normal protein remission may be a potential therapeutic strategy to treat this type of HCM patients [70]. Table 3 summarizes all the gene types, functions and phenotypic characteristics mentioned above.

3. Genetic Counseling and Testing in HCM

Genetic counseling is a process designed to help individuals and their families understand and cope with the pathophysiological, psychosocial, and familial implications of genetic disorders [81,82]. It should be performed by health care professionals with specific training, such as clinical/medical geneticists. Genetic counseling includes but is not limited to discussing genetic risks, providing education and clinical assessment, conducting pre- and post-test counseling, identifying variants to be tested, obtaining a three-generation family history, and providing psychosocial support [83,84]. In general, genetic counseling can improve patients and relatives' understanding of the disease, increase decision satisfaction and reduce anxiety [85].

The new guidelines provide more scientific conclusions on the importance of genetic counseling [2]. For genetic counseling of children, the first consideration should be whether they have the ability to independently decide to undergo genetic testing and the issue of informed consent. Obtain family history after fully considering the wishes of the child and his or her family. It should be noted that symptoms of HCM may not become apparent until many years later. It is also necessary to consider the impact this may have on the child's subsequent education, sports activities, etc., and consider the transition from pediatric to adult medical care [86,87]. The latest guidelines in 2024 indicate that for children with HCM, regardless of symptom status, exercise stress testing is recommended to determine functional capacity and provide prognostic information. Exercise stress testing is particularly useful for evaluating overall exercise tolerance and identifying potential exercise-induced left ventricular outflow tract obstruction. This is especially important in young patients, as children might not be able to clearly articulate their symptoms, making routine exercise stress testing a key diagnostic tool in this population. It is also recommended that for most HCM patients, there is no need to generally restrict strenuous physical activity or competitive sports [13]. The guiding prin-

Table 3. Summary of HCM-related genes reviewed in this article.

Gene type	Gene function	HCM phenotype
MYBPC3	Encodes cMBP-C, which is involved in myofilament assembly and stability, regulation of cardiac contraction and calcium sensitivity.	Myocardial hypertrophy (left ventricle, especially the ventricular septum), arrhythmias, cardiac dysfunction, and decreased exercise tolerance.
MYH7	Encodes β-MHC, involved in myocardial contraction, mechanical energy conversion, regulation of the speed and force of cardiac contraction, and adaptive adjustment.	Myocardial hypertrophy (thickening of the left ventricular wall), arrhythmias, heart failure, and familial clustering.
LAMP2	Encodes LAMP2, which is involved in the maintenance of lysosomal function, regulation of autophagy and cell protection.	Myocardial hypertrophy (left ventricular hypertrophy), arrhythmias, premature heart failure, systemic symptoms such as skeletal muscle weakness, liver enlargement and mental retardation, etc., the prognosis is poor.
TNNT2	Encodes cTnT, which is involved in calcium regulation of myocardial contraction, transmission of contractile signals and maintenance of myofilament structure.	Myocardial hypertrophy (thickening of the left ventricular wall, which may be present), left ventricular outflow tract obstruction, arrhythmias, heart failure, and a distinct genetic trait.
ACTC1	Encodes α-cardiac actin, involved in cardiac contraction, cytoskeleton maintenance and mechanotransduction.	Myocardial hypertrophy (asymmetric hypertrophy), arrhythmias, heart failure, exercise intolerance, and familial clustering.
CAV3	Encodes Caveolin-3, which is involved in membrane structure regulation and signal transduction, maintaining muscle cell stability and regulating ion channel function.	Myocardial hypertrophy (symmetric or asymmetric thickening of the left ventricle), arrhythmias, decreased exercise tolerance, heart failure, and familial hereditary.
GLA	Encodes α-galactosidase A, which is involved in glycolipid degradation, maintaining cell stability and regulating cardiac function.	Myocardial hypertrophy (left ventricle), arrhythmia, heart failure, decreased exercise tolerance, and other systemic symptoms such as rash, renal impairment, and neuropathy.

ciple remains that any clinical or genetic testing should be conducted in the best interest of the child. Psychosocial outcomes for children who undergo clinical screening and cascade genetic testing do not differ from those in the general population [88]. Genetic counseling and testing are available for at-risk pregnant women or for fathers with a known pathogenic (familial) variant. Chorionic villus sampling is performed transcervically or transabdominally at 10 to 14 weeks of gestation. The rate of fetal loss associated with the procedure is 0.2%. The fetal loss rate is 0.1% when amniotic fluid is collected directly after 15 weeks of pregnancy [89]. The current non-invasive testing method is mainly to isolate cell-free foetal DNA from maternal plasma samples in early pregnancy (around the 9th week), and the risk of miscarriage will not increase. However, it is still under development and not widely used [90]. For the general population, the guidelines recommend that after investigating disease-related genes associated with a specific phenotype, if a pathogenic or likely pathogenic (P/LP) variant is found in the index patient, cascade genetic testing, including pretest genetic counseling, should be offered to first-degree at-risk relatives. In the event of the death of a first-degree relative, evaluation of the deceased's next of kin (i.e., the index patient's second-degree relatives) should also be considered [91,92].

4. Future Treatments for HCM

Shared decision-making is crucial for delivering the best possible clinical care. It requires a careful conversation between patients, their families, and healthcare teams, where medical professionals outline all available testing and treatment options, explain the associated risks and benefits, and assess the suitability of each option for the patient. This process also ensures that patients communicate their personal preferences and goals, allowing these to guide and inform their treatment plan [13]. The goals of treatment for HCM are to improve symptoms, reduce complications, and prevent sudden death. There is no strict staging of HCM, and there is no specific treatment for non-obstructive HCM. For obstructive HCM, beta-blockers or surgery are required. As people's understanding of the hereditary nature of HCM becomes better, screening and monitoring of family members is becoming more and more important [93].

MYH7 mutations will affect the activity of myosin ATPase and increase myocardial force production, while MYBPC plays a role in sarcomere organization and may act as a brake on the contraction of myofibrils [94,95]. Mavacamten (MyoKardia, Inc., South San Francisco, CA, USA), an oral small molecule allosteric modulator of cardiac β-myosin, directly targets the above mechanisms, resulting in reversible inhibition of actin–myosin cross bridging [96,97]. In animal models, treatment with Mavacamten reduced contractile capacity, eliminated spontaneous myocardial infarction, alleviated left ventricular outflow tract obstruction, and improved myocardial pressure-volume relationships [98].

Sarcomeric mutations in HCM lead to inefficient utilization of adenosine triphosphate (ATP), which may lead to energy depletion and impair myocardial energy metabolism when cardiomyocytes face excessive energy demands [99]. Under this condition, fatty acid utilization increases as a compensatory mechanism, similar to the adaptations of cardiomyocytes during ischemia [100]. Perhexiline, used as an anti-angina treatment in Australia and New Zealand, is an oral carnitine palmitoyltransferase I (CPT-1) inhibitor. Inhibiting CPT-1 reduces mitochondrial uptake of fatty acids [101]. Although there are clinical studies showing beneficial changes in cardiometabolism and improved exercise capacity in the experimental group compared with placebo [102,103], a recent multicenter phase IIb clinical trial (NCT02862600) was terminated due to lack of efficacy and a higher incidence of side effects. Trimetazidine is also a metabolic regulator that can produce reversible inhibition of 3-ketoacyl-coenzyme A. It can be used as a second-line antianginal drug in Europe with fewer side effects, but it has recently been proven to be ineffective in non-hypertrophic cardiomyopathy (NCT01696370) [104].

In recent years, studies of mitochondrial-targeted therapies in HCM have shown that improving the supply of equivalents in the Krebs cycle with nicotinamide adenine dinucleotide supplementation or using elamipretide (a cardiolipin peroxidase inhibitor and mitochondrial targeting peptide) improves respiratory chain function to stabilize cardiolipin in the inner mitochondrial membrane, improves the proximity of the mitochondrial respiratory system, reduces electron leakage and oxidative stress, and enhances ATP regeneration [105–107].

5. Conclusion

HCM is primarily caused by mutations in genes encoding myocardial proteins. The most commonly mutated genes include *MYH7* and *MYBPC3*. Other related genes are *LAMP2*, *TNNT2*, and *ACTC1* [108]. Genetic counseling can help family members understand their risk for HCM. Through genetic testing, it can be determined which family members carry these mutated genes, enabling early preventive measures to improve their quality of life. Additionally, understanding the genetic basis of HCM allows doctors to develop individualized treatment plans. For families planning to have children, genetic counseling can provide advice on risks and options to reduce the likelihood of passing the condition to the next generation. Currently, due to the lack of relevant randomized controlled trials, drug treatment is primarily based on clinical experience to improve functional ability and reduce symptoms [109–111]. For patients with symptomatic left ventricular outflow tract obstruction, the goal is to improve symptoms through septal ablation using medications, surgery, or alcohol. Treatment of symptomatic patients without left ventricular outflow tract obstruction focuses on management of arrhythmias, lowering left ventricular diastolic pressure, and treating angina. Patients with progressive left ventricular systolic or diastolic dysfunction who do not respond to medical therapy should be considered for cardiac transplantation early.

Author Contributions

JLC, YX, JS, YML, ZKL, LZ, and JGY were responsible for the conception, design, and literature analysis. JLC and YX were responsible for most of the manuscript content writing. JS and YML are responsible for writing part of the manuscript content. ZKL and LZ were responsible for the production of charts and data collection. JGY is responsible for reviewing the content and proposing modifications. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This study was supported by the Key Research and Development Programme of Gansu Province (No. 20YF8FA079).

Conflict of Interest

The authors declare no conflict of interest.

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