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MYH7 in cardiomyopathy and skeletal muscle myopathy

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Abstract
Myosin heavy chain gene 7 (*MYH7*), a sarcomeric gene encoding the myosin heavy chain (myosin-7), has attracted considerable interest as a result of its fundamental functions in cardiac and skeletal muscle contraction and numerous nucleotide variations of *MYH7* are closely related to cardiomyopathy and skeletal muscle myopathy. These disorders display significantly inter- and intra-familial variability, sometimes developing complex phenotypes, including both cardiomyopathy and skeletal myopathy. Here, we review the current understanding on *MYH7* with the aim to better clarify how mutations in *MYH7* affect the structure and physiologic function of sarcomere, thus resulting in cardiomyopathy and skeletal muscle myopathy. Importantly, the latest advances on diagnosis, research models in vivo *and* in vitro and therapy for precise clinical application have made great progress and have epoch-making significance. All the great advance is discussed here.

Keywords *MYH7* · Hypertrophic cardiomyopathy · Cardiomyopathy · Myosin myopathy · Genetic variant

Introduction

Myosin which makes up the backbone of the sarcomere thick filament, plays a key role in the process of muscle cell contraction. Emerging evidence proved that hereditary myosin myopathies are caused by mutations in skeletal muscle myosin heavy chain (*MYH*) gene family, including *MYH1*, *MYH2*, *MYH3*, *MYH4*, *MYH8*, and *MYH13* on chromosome 17 expressed in skeletal muscles, as well as *MYH6* and *MYH7* on chromosome 14, encoding two main types of cardiac muscle, alpha isoform and beta isoform, respectively [1]. Myosin is highly sensitive to the mutation of *MYH* gene family [2]. Consistent with the locations and predominate muscles of myosin, pathogenic variants in the respective genes are associated with distinctive phenotypes of cardiac and skeletal myopathies.

Myosin heavy chain (myosin-7), the same substance with cardiac muscle beta isoform as mentioned above, is a slow ATPase myosin and is encoded by *MYH7* gene. Myosin-7 is located in both ventricular muscle fibers and slow/type 1 skeletal muscle fibers. Therefore, pathogenic mutations in *MYH7* gene could cause cardiomyopathy, skeletal muscle myopathy, and both of them. Known human cardiomyopathy includes hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restricted cardiomyopathy (RCM), left ventricular non-compaction cardiomyopathy (LVNC), and other less common congenital cardiomyopathies. The common skeletal muscle myopathy includes myosin storage myopathy (MSM), Laing distal myopathy (LDM), and congenital fiber-type disproportion (CFTD). Compound *MYH7* mutations increase the severity of disease and the risk of sudden cardiac death (SCD). The variable clinical phenotypes and coexisting multiple mutations increase the difficulty and complexity of clinical work.

In this review, we summarized the structure of *MYH7* and provide a brief overview of the relationship between the mutations in *MYH7* and its disorders, as well as updating the latest research progress on diagnose methods and target therapy.

Structure

The structure and sequence of *MYH7* (MIM:160760) have been completely discovered in 1990 [3], which is 22,883 bp long and located on chromosome 14q11.2, 3.6 kb upstream from the *MYH6* (MIM:160710) in a head-to-tail tandem fashion [4, 5]. *MYH7* is composed of 39 introns and 40 exons, including 38 coding. The 5-prime untranslated

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region, 86 bp long, is split by 2 introns and the 3-prime untranslated region (UTR) is 114 bp long. The translation start codon (ATG) is located in nucleotide position 9 of the third exon. Three Alu repeats (–GATC–) were identified within the gene and the fourth one is in the 3-prime flanking intergenic region [3] (Fig. 1a).

Myosin-7 (P12833), a protein of 1935 amino acids and a chemical mass of 223,097 Da, is encoded by the *MYH7* gene. It is also known as heart muscle beta-myosin heavy chain, myosin heavy chain 7, myosin heavy chain slow isoform. According to Geeves et al. [6], myosin-7 is composed of a Src homology 3-like (SH3-like) domain, a head motor

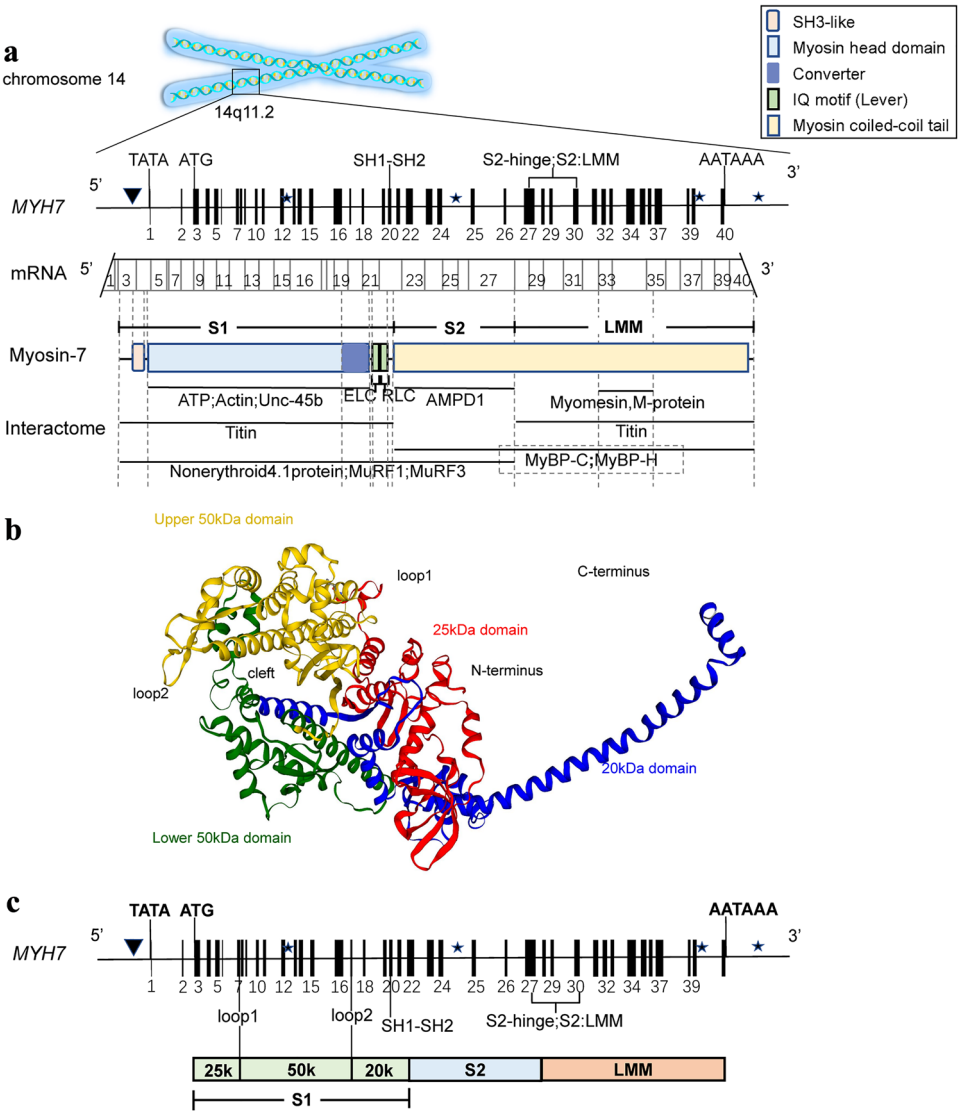

Fig. 1 **a** Schematic of *MYH7* gene, mRNA and protein, its interactomes. *MYH7* is composed of 39 introns and 40 exons, whose 38 are translated into a 223,097 Da peptide called myosin-7, containing 1935 amino acids. The exons are drawn as black boxes. Locations of the TATA box, translation start codon (ATG), and poly (A) signal (AATAAA), two "active thiols" (SHl, SH2), and the S2-hinge, S2:LMM are illustrated, in addition to promoter indicated by a triangle and 4 Alu repeats by asterisks in *MYH7*. **b** Representation of S1 constructed by Swiss Model. Using amino acid sequence of human myosin-7 as target (sequence identity: 78.88%), the N-terminal 25 kDa, central 50 kDa which are functionally divided into upper 50 kDa and lower 50 kDa domains, and C-terminal 20 kDa, are indicated with corresponding colors. Loop1 connecting the 25 kDa and 50 kDa, loop 2 connecting the 50 kDa and 20 kDa, and the cleft formed by numerous α-helix surrounding a 7-stranded β-sheet core are illustrated. (https://swissmodel.expasy.org/). **c** The proteolytic cleavage form of S1. It contains the N-terminal 25 kDa, central 50 kDa, and C-terminal 20 kDa. The locations of loop1 and loop2 are indicated. *SH3-like domain* Src homology 3-like domain, *IQ motif* isoleucine–glutamine motif, *HMM* heavy meromyosin, *LMM* light meromyosin, *S1* subfragment 1, *S2* subfragment 2, *ELC* essential light chain subunit, *RLC* regulatory light chain subunit, *Unc-45* uncoordinated mutant number-45, *MyBP-C* myosin binding protein-C, *MyBP-H* myosin binding protein-H, *AMPD1* adenosine monophosphate deaminase 1, *MuRF1* muscle RING dinger protein1, *MuRF3* muscle RING dinger protein3, *Interactome* interaction partner

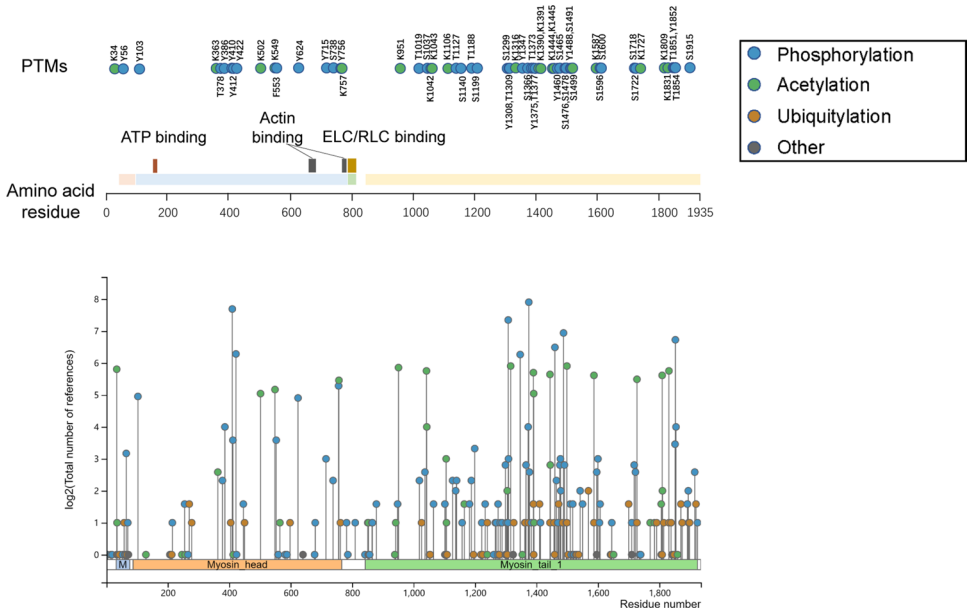

Fig. 2 Sites of PTMs in myosin-7. The many PTMs published in papers, which affect myosin-7 are represented by variously colored circles, and the PTMs with more than 5 references are shown in detail, required from PhosphatePlus database (https://www.phosphosite.org/homeAction). *PTMs* posttranslational modifications, *Other O*-glycosylation, and methylation sites

domain, a lever arm, and a coiled-coil "tail." Proteolytic cleavage yields myosin-7 into two parts: heavy meromyosin (HMM) and light meromyosin (LMM). HMM can be further digested into subfragment 1 (S1) and subfragment 2 (S2). S1 contains the SH3-like domain in N-terminus, the motor head domain containing a converter segment in the C-terminus via a relay helix, and the lever arm compounded from two isoleucine–glutamine (IQ) motifs. The two IQ motifs extend to the "tail" structure of myosin molecular, containing S2 and LMM. S2 and LMM contain the NH2- and COOH-terminal regions of the α-helical rod domain, respectively, and these two α-helical heavy chains dimerize to form a coiled-coil in the "tail" (Fig. 1a). The motor head region has the actin binding site and the ATP binding site. And the region is composed of a 7-stranded β-sheet core surrounding by numerous α-helices, which forms a cleft stretching between these two binding sites. Furthermore, S1 can be cleaved to 3 subdomains by trypsin, the central 50 kDa, the N-terminal 25 kDa, and the C-terminal 20 kDa [7]. The N-terminal 25kD contains the SH3-like domain. The central 50 kDa domain is further functionally divided into upper and lower 50 kDa regions [8]. The ATP binding site is located in the cleft which is formed between the upper and lower 50 kDa subregions, and the actin binding site is in the central 50 kDa domain, mostly the lower 50 kDa subregion [9, 10] (Fig. 1b). Moreover, these two binding procedures are implemented in a well-defined coupling process in which when the ATP binds to the head region, the actin binding cleft is controlled to open, which is the pre-requisite for functioning effectively [11]. In addition to two active thiols (SH1 and SH2), the ATP and actin binding sites, are all well conserved, and there are also several variable subregions, including N-terminus of S1, the hypervariable loop1 and loop2, the S2-hinge and the S2:LMM junction. Loop1, which connects the 25 kDa and 50 kDa, sets above the nucleotide binding pocket, and is suggested to be essential in modulating the ATPase kinetics. Loop 2, connecting the 50 kDa and 20 kDa, involves in actin binding step [12]. The S2 hinge and the S2:LMM junction are located in the linking area between the head and the rod, and exert to mediate the flexibility between them [3] (Fig. 1c).

In addition to ATP and actin binding sites, myosin-7 also react with several interaction partners (interactomes) in stable or transient forms to properly complete its functions, including essential light chain subunit (ELC) and regulatory light chain subunit (RLC) binding to the NH2- and COOH-terminal IQ motifs of lever arm, respectively, myosin binding protein-C (MyBP-C) and MyBP-H binding to the coiled-coil tail containing both S2 and LMM [13, 14], myomesin and M-protein binding to the LMM [15, 16], titin binding to S1 and LMM [17, 18], nonerythroid 4.1 protein, MuRF1 and MuRF3 binding to HMM [19, 20], AMPD1 binding to S2 [19], and Unc-45 binding to the head domain [21] (Fig. 1a). There are also multiple posttranslational modifications (PTMs) in myosin-7, most of which are phosphorylation sites, followed by acetylation, ubiquitylation, and a limited O-glycosylation and methylation sites (Fig. 2).

In striated muscles, two myosin heavy chain subunits (myosin-7), along with 4 light chain subunits, 2 of which are ELC subunits and the others are RLC subunits, compose the sarcomeric myosin, the main component of thick myosin filament. A number of highly ordered bipolar thick myosin filaments, together with thin actin filaments, in addition to several accessory proteins, comprises the sarcomere, the fundamental contractile unit of striated muscle containing both cardiac and skeletal muscle. Thousands of sarcomeres

make up myofibrils, which come together to form myofibers that give rise to mature muscles (Fig. 3). Consequently, the thick filaments slide past the thin filaments orderly, consuming ATP and phosphate and driving the contraction of muscles.

MYH7 and inherited cardiomyopathies

Sarcomere is the basic unit of the contraction in cardiac muscles. Genetic mutation in genes coding sarcomeric proteins can exactly cause the impairment of the integrity of structure or function of sarcomere. Those disorders can hinder myocardial contraction greatly and are predominant with family clustering, thus classified as inherited cardiomyopathy. The two majors of *MYH7*-related inherited cardiomyopathy include HCM and DCM. RCM, LVNC, congenital heart defects (CHD), arrhythmia, etc., can be affected as well.

MYH7 and hypertrophic cardiomyopathy

HCM (MIM#192,600), the most common family cardiovascular disease, with a prevalence of at least 1:500 in global population [22, 23], is characterized by significant ventricular hypertrophy, usually asymmetric and frequently involving interventricular septum, with disorganized myocytes and diastolic dysfunction but without elevated loading conditions. The symptoms between inter- and intra-family vary exceedingly from benign to malignant kinds with a considerable risk of heart failure and SCD in younger adults and athletes [24]. Majority of HCM are single-gene hereditary, in an autosomal dominant mode or a de novo mutation fashion displaying family HCM or sporadic HCM, and more than 1500 mutations involved in at least 11 cardiac sarcomeric genes have been identified [25]. The missense variant p.R403Q in *MYH7* is the firstly found pathogenic gene related to family HCM [5, 26]. Gradually, other genes, which are mostly sarcomeric protein encoding genes, have been successively found and *MYH7* ranks the second frequently pathogenic gene in HCM followed *MyBP-C3* [27, 28]. Besides, *MYH7* variants are highly related to evolute toward impaired systolic function and end-stage HCM [29]. The disease-relevant missense variants are enriched in S1 and S2 [9], and it is supported by a recent study, which showed the converter domain and residues in myosin mesa, a single flat surface on myosin head, are the common sites of *MYH7*-associated HCM mutations [30]. Moreover, patients with variants in these enriched regions tend to develop an earlier-onset disease compared with HCM patients carrying mutations in elsewhere of *MYH7* [30]. Furthermore, mutants in converter region are associated with adverse prognosis and overlapping phenotypes of other cardiomyopathies [31]. The phenotypic diversity and the relationship between variation and clinical characteristics are described herein after.

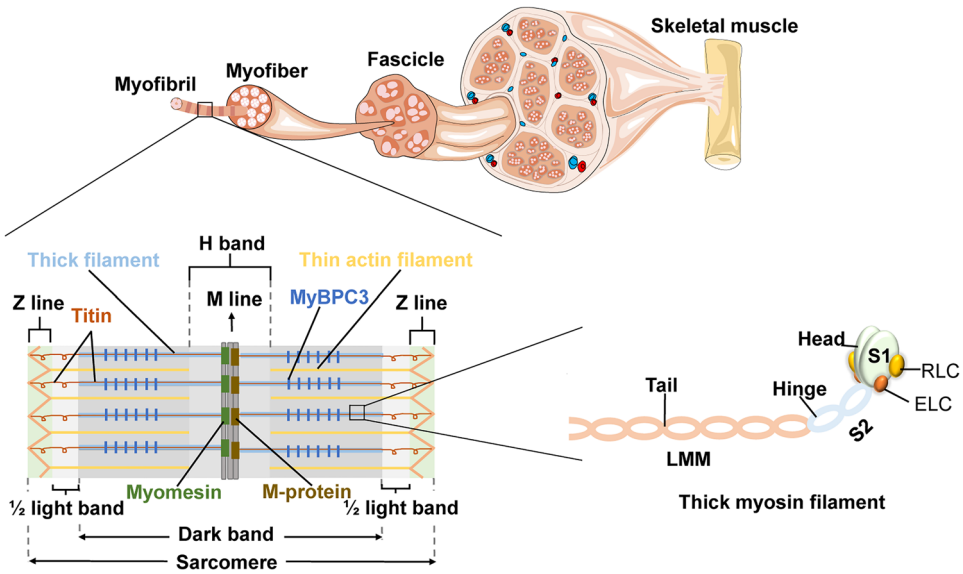

Fig. 3 The composition of striated muscle, the schematic drawing of sarcomere and thick myosin heavy chain. The thick myosin filaments and thin actin filaments, together with the binding proteins of myosin are represented in corresponding colors. The area between two adjacent Z lines is called a sarcomere, which consists of a dark band chiefly containing thick myosin filaments (myosin-7, MyBP-C, etc.) anchored to M line in center and two 1/2 light bands only containing part of thin actin filaments anchored to Z line in lateral sides. The M line, which contains myomesin and M-protein et al., is the center of the dark band and the H band is the relatively bright region in dark band as a result of consisting of only thick filaments. The schematic illustration of a thick myosin heavy chain composed of two myosin-7 and 4 light chain subunits (2 ELC and 2 RLC) is indicated in different colors

MYH7 mutations

The groupwork enrolling the American College of Medical Genetics and Genomics (ACMG), the Association for Molecular Pathology (AMP), and the College of American Pathologists (CAP), recommended a guideline, giving five classifications of variants transmitted in Mendelian inherited pattern in addition to mitochondrial variants, "pathogenic (P)," "likely pathogenic (LP)," "uncertain significance (VUS)," "likely benign," and "benign" [32]. This classification framework has been applied universally in *MYH7*-associated cardiomyopathies. The major known "P" and "LP" mutations of *MYH7* associated with HCM are missense variants [33], with a small proportion of nonsense, frameshift, and splice variants which are predicted to produce loss-of-function (LOF) proteins or unstable transcripts. These missense mutations have been reported in numerous cases and recoded in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) with variable degree of confidence (Table 1), and they occur more common in the head and neck than the tail of *MYH7* [34]. Despite the knowledge of LOF variants in *MYH7* is still incomplete, reports of its potential pathogenicity have sprung up. To date, the ClinVar records a total of 25 LOF variants in *MYH7* tabbed as "P" or "LP," among which 7 are considered to be related with HCM (Table 2). Additionally, two protein-truncating variants in *MYH7* were found. c.3562_3574delACTGCCGCGGCCC/p.T1188Cfs*22 is a sporadic 13 base pairs deletion variant in the tail domain and is predicted to produce a truncated protein resulting in dysfunction to dimerize to coiled-coil tail, manifesting both HCM and RCM [35]. And p.Lys1173ArgfsTer41 is a frameshift variant found in 2 HCM carriers and is considered to lead to a truncated protein [36].

Furthermore, several founder mutations which are not common in *MYH7* have been discovered in specific communities and nations, where they account for a sizable proportion of HCM instances. The missense variant p.G584R found in two families in 1993 with a putative Portuguese ancestor is the first mutation believed to have a founder impact [37]. The missense variants p.A797T and p.R403W, accounting for 25% and 5% HCM cases of a subpopulations in Western and Eastern Cape provinces in South Africa, respectively, in addition to p.R249Q, p.R719Q, and p.Glu499Lys accounting for 7.5% altogether, are assumed to exert founder effects, originating from mixed ancestors [38]. The variant p.N1918K is the first founder mutation found in Dutch, causing a variable phenotype, with a relatively early-onset age in period of childhood but with a generally benign outcome [39]. The missense variant p.A797T is a founder mutation, accounting for 25% probands in the panel of South Africa, resulting in a poor outcome and a high risk of SCD [40]. The missense variant p.E894G has been found in 6 unrelated families worldwide [41–44], a novel missense variant p.R652K, a significant methylation site, was found in Spain [45], and the deletion variant p.K847del found in Manaus [46]. Whether they are founder mutations is still an unsolved issue. Therefore, these founder genes are more frequently sequenced in individual communities and the existence of them would play a key role in saving cost and time in the program of molecular diagnose.

Mutation of *MYH7* in pediatric cardiomyopathy

Variants found in childhood are largely associated with early-onset age, complicated manifestations, and high risk of adverse cardiovascular events [47, 48]. A hebetic girl, identified a "P" missense variant p.R719W, experienced combined symptoms, including non-obstructive HCM, RCM, complete left bundle branch block and intermittent third-degree atrioventricular block [49]. A 7-year-old boy with a "P" missense variant p.R453C, presented HCM and WPW with increased likelihood of SCD syndrome [50]. A 9-month female newborn carrying a "LP" missense variant p.Y386C suffered SCD with the diagnose of RCM companied with coronary artery bridging [51]. Moreover, childhood with *MYH7* variants-related CHD would manifest more complexly, displaying a couple forms of CHD and other cardiovascular diseases simultaneously, including ventricular septal defect (VSD), Ebstein anomaly (EA), hypoplastic left heart syndrome, Taussig–Bing type double-outlet right ventricle, LVNC, arrhythmias, and so forth [52]. The complex clinical phenotypes and adverse cardiovascular events are associated with the onset of disease in childhood.

Compound *MYH7* mutations

Evidence has proved that compound variants with more than one allelic mutation often develop a more complex and severe phenotypes. In comparison to compound heterozygous diallelic mutations with double mutations in two alleles, the clinical manifestation, severity of disease, and prognosis of monoallelic double mutations illustrated in a cis-manner in *MYH7* are thought to be better [53, 54]. Cumulative effect is thought to exist when another mutation occurs, presenting a more severe clinical phenotype, such as an earlier-onset age, a higher chance of SCD, and a worse prognosis in *MYH7*-related HCM, than that generated by each of the single one [55–67]. A mouse model reconfirmed the addictive effect that mouse with single missense variant p.Val606Met manifested a relatively benign phenotype, but when mouse model was introduced by dual "P" variants p.V606M & p.R453C or p.V606M & p.R719W, it developed a more hypertrophic phenotype [, 67, 68]. In the same family, the members carrying homozygotes variant p.R869G developed a more severe phenotype than it in heterozygous individuals, also

Table 1 The "P" and "LP" missense variants in *MYH7*-related cardiomyopathy recorded in ClinVar

Disease	Pathogenicity	Confidence	Variant
HCM	P	***	R1712Q, T1377M, E1356K, R1053Q, L908V, D906G, E894G, R870H, K847E, G741W, G741R(c.2221G>C), I736T, R723G, R723C, R719Q, R719W, G716R(c.2146G>A), R663H, G584R, R453H, R453S, R453C, R403Q, R403W, I263T
		**	E930K, R904C, D778E, G768R(c.2302G>A), R694H, R663C, R652G, R442C, K351E, G256E
		*	L1793P, E1752K, Q1865P, L1805P, E1801K, L1597P, R1500P, R904P, R904H, P838L, G823R, M822V, A820D, L804P, D778V, G768R(c.2302G>C), F764L, G741E, G716R(c.2146G>C), R712H, L601F, F540L, S532P, E525K, I467N, R403L, R369Q, A254E, I201T
	LP	***	R1712W, R1420W, R1193H, G1057S, R1045L, E949K, R870C, R869H, A868P, K865E, P710H, I457T, V440M, V338M, D239N, R143Q
		**	E927K, L915P, R869C, M849T, R719P, I702N, Y609C, H576R, G407V
		*	Q1794K, T1760R, A1603P, Q1598P, S1550P, R1500W, R1434P, E1120K, E965K, E924G, E921K, D896, V878A, M877I, M877K, L859P, R858P, M852R, A843T, S842G, P838Q, K837R, F834L, R807P, A797P, R783P, S782N, F764Y, Q734P, Q734E, I730N, I730T, G641A, K615T, D587H, G584C, M539L, L517M, M515R, M515T, I511L, M493I, M493V, L476F, K450N, R442L, M439V, R403G, K397E, D382Y, F341I, E328G, V320E, T318P, L267V, F252C, R249L, F247L, A199T, R169S
	P/LP	**	A1379T, E930Q, D928N, E924K, Q882E, K865R, R858C, M852T, E848G, A797T, G741R(c.2221G>A), P731S, N696S, V606M, G584S, E497D, N479S, D394E, A355T, V320M, R249Q, R243C, A199V, K146N, R143W
DCM	P	***	R904H, R904C, S532P
		**	R719W
	P	*	E930Q, E924K, D906G, E894G, P838L, A797T, G741R(c.2221G>C), I736T, R723C, R694H, R663H, R663C, L655M, R453C, R403Q, R403W, R249Q
	LP	***	E1914K, E1801K, R369Q
		**	R1500P, R1500W, E921K, E525K
		*	A1906G, R1712Q, R1420W, T1377M, R1193H, R1045L, Q882E, L881R, R870C, R869H, K865E, R858C, R783P, R783G, C705Y, G641A, P600S, N597K, H576R, C520F, L517M, M515T, E497D, I457T, K397E, F341I, R243C, D239N, I201T, Q172E, R143Q
RCM	P	***	P838L
		*	G768R(c.2302G>A)
LVNC	P	*	E1801K, E924K, R369Q, R281T
	LP	*	A428D, Y350N, Y283D
Cardiovascular phenotype	P	**	R663H, V606M, R369Q
		*	A1379T, T1377M, R1053Q, E924K, L908V, D906G, R904H, R904C, E894G, K847E, A797T, D778E, G768R(c.2302G>C), G768R(c.2302G>A), G741R(c.2221G>A), G741R(c.2221G>C), G741W, I736T, R723C, R719Q, R719W, D717A, R663C, R652K, R652G, G584R, S532P, E497D, R453H, R453C, R403L, R403Q, R403W, A355T, I263T, G256E, R249Q, D239N
	LP	**	R1712Q
		*	R1712W, R1500W, E1356K, G1057S, R1045L, E930K, D928N, E927K, E921K, R904P, R904L, M877I, R870C, R869H, R869C, A868P, R858P, R858C, M852T, M849T, S782N, D778H, L749Q, P710H, R694H, A649V, Y609C, G584D, G584S, H576R, F540L, M493V, N479S, I457T, R442C, G407V, G407C, K351E, V338M, V320M, R281T, R249L, F247L, R243C, I201T, A199V, R143Q, R143W

The confidence of pathogenicity is classified into 4 degrees, ***reviewed by expert panel; **reviewed by two or more submitters with ascertain criteria and evidence providing the same interpretation; *reviewed by multiple submitters with assertion criteria and evidence but existing conflicting interpretations, or one submitter providing an interpretation with assertion criteria and evidence; None: reviewed with no ascertain criteria

The variants related to more than one cardiomyopathy and/or skeletal myopathy are indicated by underlines

indicating a dose-dependent effect [69]. All evidence indicate that compound variations are related with poor prognosis, thus comprehensive and precise genetic sequencing is necessary in patients with complex and severe clinical manifestations.

Table 2 The "P" and "LP" LOF variants including frameshift, nonsense, and splice in *MYH7*-related disorders with different degrees of confidence

Consequence	Name	Protein change	Condition(s)	dbSNP ID
Frameshift	c.5659del (p.Glu1887fs)	E1887fs	Not provided (LP*)	rs730880892
	c.3985dup (p.Leu1329fs)	L1329fs	*MYH7*-Related Disorders (LP*)	rs1566526391
	c.2563_2656del (p.Glu855fs)	E855fs	HCM(LP*)	rs1892625481
			BVNC(LP*)	
	c.2366del (p.Gln789fs)	Q789fs	Familial cardiomyopathy(P)	rs606231337
	c.2028del (p.Asn676fs)	N676fs	Familial cardiomyopathy(P)	rs606231331
	c.1858_1859del (p.Leu620fs)	L620fs	DCM(LP)	rs1566533919
Nonsense	c.3349G>T (p.Glu1117Ter)	E1117*	Cardiomyopathy (LP*)	rs141735183
	c.2443C>T (p.Gln815Ter)	Q815*	Not provided (LP*)	rs1064797184
	c.195T>G (p.Tyr65Ter)	Y65*	*MYH7*-Related Disorders(P)	rs934278063
Splice	c.5655+1G>T	–	HCM(LP*)	–
	c.5655+1G>C	–	MSM(LP*)	rs1892079951
	c.5560-2A>C	–	*MYH7*-related skeletal myopathy (LP*)	rs1566521710
		–	CFTD(LP*)	
	c.4954-15_4958del	–	Not provided (LP*)	-
	c.4522_4524del	–	HCM(P*)	rs397516220
		–	Cardiovascular phenotype(P*)	
		–	LDM(P*)	
		–	*MYH7*-related skeletal myopathy (LP*)	
	c.3336+1G>C	–	Not provided (LP*)	rs1892449432
	c.2163-1G>A	–	DCM(P*)	rs606231334
	c.1956+2T>G	–	Familial cardiomyopathy(P)	rs606231329
	c.1000-1G>A	–	LVNC(LP)	rs113392527
	c.732+2T>G	–	HCM(P*)	rs1555338658
		–	LVNC(LP)	
	c.732+1G>T	–	HCM(P*)	–
	c.732+1G>C	–	HCM(P*)	rs730880850
	c.732+1G>A	–	LVNC(P**)	rs730880850
		–	HCM(P*)	
	c.640-1G>A	–	Familial cardiomyopathy (LP)	rs606231315
	c.640-2A>T	–	DCM(LP)	–
	c.346-1G>A	–	Not provided (LP*)	rs1057519221

MYH7-associated pathomechanisms

The molecular pathogenic mechanisms of HCM have been detailed described in a review by Norbert Frey et al. [25], including impaired calcium cycling and calcium sensitivity, increased myocardial fibrosis, disturbed biomechanical stress sensing, and altered cardiac energy homeostasis. *MYH7*-associated pathomechanisms also have been gradually revealed, but it has not been completely elucidated. Increased actin-activated ATPase activity, higher average force generation and faster actin filament sliding velocity [70, 71], diastolic dysfunction [72] and impaired cardiac relaxation [73], abnormal Ca^{2+} response [74], cardiac fibrosis and remodeling [75], and a series of differences in gene transcription factors [76] were all observed in mouse models harboring p.R403Q, which is a known "P" variant. As mentioned above, the major "P" and "LP" mutations in *MYH7*-related HCM are missense variants, which encode stable proteins which are anticipated to be integrated into sarcomeres, disturb normal motor function, and trigger pathologic signals. The motor activity is predicted to be either enhanced [77] or reduced [78] in *MYH7*-related HCM. Currently, the gain-of-function pathophysiologic mechanism associated missense variants in *MYH7* is widely accepted, which proposed the poison peptides produced by *MYH7* incorporating into the sarcomere and perturbing the formation of proper and functional sarcomere, leading to elevated contractility and relayed relaxation. As a result, destabilization of interacting-heads motif (IHM) irregulates the balance of increased numbers of myosin in disordered relaxed

state (DRX) and decreased number of it in super relaxed state (SRX), consequently excessing mitochondrial quantity, energetic consumption, metabolic stress, and remodeling of cardiomyocytes with hypertrophy [79]. The IHM has already been found in all human muscle myosins, and is definitely a conserved motif, playing an important role in conserving ATP consumption [80]. Myosin in DRX conformation consumes five times energy than it in SRX state [81, 82].

HCM patients with "P" and "LP" variants in *MYH7* are sequenced that those variants are significantly enriched in the interacting region with IHM [83]. Two human-induced pluripotent stem cell-cardiomyocyte (iPSC-CM) models harboring missense variant p.P710R and p.R723C, respectively, and both of them are located in converter domain, observed prolonged myosin working time and slowed relaxation, emphasizing the key role of dysregulated SRX state in hypercontractility [84, 85]. The hypercontractility has also been verified in molecular level by using microscale thermophoresis technique based on four variants p.R249Q, p.H251N, p.D382Y, and p.R719W [86]. Mutations in S2 domain are assumed to interfere the normal interaction of this domain with C0-C2 domain of MyBP-C by decreasing the phosphorylation lever of MyBP-C, eventually inhibiting myosin transforming into the SRX state, thereby leading to sarcomeric hypercontractility, impaired full relaxation and increased energy consumption, in a vitro test using three known variants associated with HCM in this region, p.R870H, p.E924K, and p.E930del [87].

Furthermore, it has long been believed that the quantity of toxic peptides acts as a significant risk factor for the severity of disease. However, recently, this hypothesis has gradually rectified, as the variable genotype–phenotype relationship emerged, even exhibiting heterogeneity in a family with the same mutation. The latest studies about the mechanism of genotype–phenotype relationship of different mutations in heterozygous HCM patients highlight the allelic expression imbalance of mutant and wildtype mRNA in cell level, in a stochastic switch on–off, burst-like transcription pattern, resulting in imbalance of proteins eventually, which generate distinct contractile force from cell to cell, leading to different force generation in myofibril level and developing to cardiac hypertrophy in different degrees [88–90]. A pair of monozygotic twins with the same "P" variant p.G768R demonstrated different clinical manifestations and tissue characteristics increase the credibility of the mechanism [91]. Another possible intrinsic process involved in the allelic imbalance is presumed that different mutations in coding regions of *MYH7* could alter the secondary structure of mRNA, affecting its stability and lifetime and leading to allelic imbalance, which was proposed from an experiment in vivo according to a "P" variant p.R723G [92].

Besides, the variable clinical phenotypes demonstrated by patients from SCD to lifetime survival, and even asymptomatic, with the same variant, indicated diverse additional mechanisms should have taken part in the regulation of allelic imbalance, including environment factors, epigenetic factors, etc. [40, 93–98]. The considerable phenotypic heterogeneity of HCM has been explained by a number of moderating factors, including lifestyle [99], gender [100], genetic background [, 94, 101], and so on. Additionally, the discrepancy of level between the protein/gene and their regulatory factors, such as microRNAs, probably plays a conceivable role in diversity of genotype–phenotype [102]. *MyBP-H* is validated to be a modifier gene in HCM patients with the "P"/"LP" missense variant p.A797T [103]. The genetic polymorphism of renin–angiotensin–aldosterone system is predicted as a modifier factor for the penetrance and severe degree of HCM [104, 105]. The conceivable pathogenetic mechanisms correlated in patients carrying a same variant, suffered from HCM to DCM, and even heart failure, are proposed to include impaired energy generation, dose addictive effect of the poison proteins, environmental factors, the modifier factors of gene, and so on [106, 107]. Virus infection is also considered to deteriorate the condition of a patient with HCM [108]. The factors involved in the diversity of genotype–phenotype needs further exploration for clarifying the mechanism of clinical phenotypic variability.

Several assumptions for the mutations in specific regions of *MYH7* have risen. The mutations in the promoter region of the gene are presumed to perturb the formation of triple-stranded G-quadruplex, which is enriched in this region and nears a variety of transcription factors, affecting the process of protein expression [109]. And the mutations located in the promoter domain are predicted to be a hazard to develop HCM, nevertheless no evidence of disease-causing effect for mutations in the introns and 3-prime UTR has been found [110]. Mutations located close to the SH1 or SH2 cysteine are speculated to generate disulfide crosslinking, resulting in non-functional proteins [111]. More researches about the specific regions-related pathogenic mechanism and clinical characteristic are needed.

Diagnosis tools for *MYH7*-associated HCM

Genetic testing, predominantly whole-exome sequencing (WES), next genetic sequencing (NGS), has been widely used in HCM. For the past 20 years, the estimated prevalence of *MYH7*-related HCM was about 0.2% in adult [112]. Moreover, with the widespread application of genetic testing, in addition to taking the analysis of family information, sex, specific ethnic, and locational backgrounds into account, the detectable rate in general population is elevated to 1:250 [113]. The most common sequence variants in human are single-nucleotide polymorphisms (SNPs) [114]. Primer extension technique by labeling the dideoxynucleotides

(ddNTPs) is proposed an appropriate tool to detect disease-specific SNPs with individual mutation [115]. Recently, a novel platform using ferrocene-labeled oligonucleotides was validated on the basis of primer elongation to electrochemically detect SNPs in *MYH7*, just depending 10 µL fingerprick blood sample, which facilitates the efficiency of detecting SNP [116]. Those novel detection techniques are important impetus for genetic testing and worth further developing.

Although the category provides convenience for clinical experts to make good judgment and offer useful advice for patients and their families, variants of VUS still cause misjudgment and delayed judgment, leading to delay in treatment. A new PE-MYH7-ACMG tactics which adds the phenotype-enhanced criteria (PE-ACMG) using the HCM Genotype Predictor Score (HGPS) on the basis of the MYH7-specific ACMG guidelines is considered as available criteria for the designation of VUS in order to better use genetic testing, with a considerably reduced VUS of 30 to 16 in a cohort of Australia and 49 to 27 in Mayo Clinic [117]. Moreover, the modified ClinGen's guideline confirms a professional guidance for clinical experts to give more accurate classification diagnose of the variants than ACMG/AMP framework, with increased variants of 65% contrast to 54% and a decreased VUS number of 30% compared to 42% [118]. While about 181 missense variants have been recorded in ClinVar database classified as "P" or "LP" variants, REVEL score sets a threshold with 0.05 REVEL that warrants a new predicting index for recognizing deleterious variants of *MYH7* associated with HCM [119]. Diagnose criteria mentioned above provide a new efficient idea to identify VUS for early treatment.

Researchers also devoted to pursue the difference methods for *MYH7* and other sarcomere encoding gene-associated HCM to simplify the process of diagnosis. In spite of different onset age, the degree of cardiac hypertrophy and prognosis in adult, *MyBP-C3* and *MYH7* variant carriers are observed with no significant difference not only in the echocardiographic parameters reflecting the degree of myocardial deformation, of both right and left ventricle, but also CMR imaging [46, 120–124]. Nevertheless, Radiomic Analysis of Native T1 Mapping Images makes it possible to distinguish these two genotypes with subtle clinical phenotypic difference, and importantly, it could be a potential tool to predict and provide prescient treatment [125]. The level of circulating miR-499a-5p in the plasma of patients with "P" or "LP" *MYH7* mutation is considered to be a potential biomarker as well, with higher level than both non-HCM patients and *MyBP-C3*-related HCM patients [126]. Whether there is significant clinical target difference to distinguish *MYH7* and *MyBP-C3* needs large-scale study in future.

Clinical manifestations and auxiliary examinations also provide useful information for physicians to evaluate the severity of disease and prognosis of patients, and to offer proper and timely treatment. Patients with the variants located in the enriched mutation region suffered from higher incidence of AF than those with not-enriched region. Moreover, patients with mutations are in higher risk of SCD when they suffered AF at an early age [127]. Pediatric patients with *MYH7*-related HCM always suffered from severe phenotype and a higher risk of SCD, so an implantable cardioverter defibrillator (ICD) placement is suggested to be a feasible intervention treatment and should be adopted in early stage [128]. Due to the adverse effect of this gene mutations, left ventricular global longitudinal strain, using 3D speckle tracking imaging technique is considered as a valuable parameter to predict adverse cardiovascular event of HCM patients carrying *MYH7* mutations [129]. The changes of parameters in ECG appear earlier than that in echocardiography, divulging the importance of using ECG to assist in diagnosing the mutations carriers in early stage and screen condition progression [130, 131]. Two cases of patients carrying variant p.Leu517Arg and p.Arg858Leu, respectively, both suffered from cardiac arrest caused by ventricular fibrillation before demonstrating HCM, and a case with identified "P" / "LP" p.A1379T variant presented AF and atrial fibrosis as the first clinical manifestation, all emphasizing the significance of ECG [132, 133]. All cases above proved that highly efficient use of clinical manifestation and auxiliary inspection could facilitate the diagnosis and treatment.

Besides, researchers identified a promising hallmark for inherited cardiomyopathy, including genetic HCM and DCM, that the shortened telomere is an abnormal feature of CMs, which is illustrated in iPSC-CM models in vitro harboring mutations associated with both HCM and DCM, significantly decreased by 26% and 40%, respectively [134]. The shortening of telomeres is proposed to be essential in developing into the dysfunction of mitochondria, which is the important pathogenic link in HCM and DCM [135]. Although there is no difference between *MYH7* and other genetic variants, the important role of telomere is undoubtable and needs to be further elucidated.

MYH7-targeting therapy for HCM

Therapies according HCM have been systematically reviewed by Ali J. Marian, M.D et al. [136]. Nowadays, many novel ideas about *MYH7* gene or base targeting therapy for HCM patients have been put on. Experimental data from a cell and mice model indicated that YTHDF2, which is a m6A reader protein, plays a protective role in the regulation of cardiac hypertrophy and heart failure, expression upregulating in a self-regulation mechanism, by interacting with m6A site of *MYH7* mRNA via its YTH domain, and promoting its degradation to alleviate cardiomyocyte

hypertrophy [137]. As the switch from fetal dominant *MYH7* phenotype to *MYH6* is considered to be completed during the maturation period, the *MYH7* gene targeting therapy to delete the re-expressed *MYH7* is supposed to be effective after its transformation [138], and it is proved available by an iPSC model harboring *MYH7*/*MYH6* mutations [58]. An mice experiment both in vitro *and* in vivo provided a feasible targeting therapeutic option, selective knocking down of rs7157716, which is a common SNP with high heterozygosity using antisense oligonucleotides technique [139]. And another group identified it in a further human-cell model, which also studied the short hairpin RNA method in this hiPSC-CM model [140]. Moreover, cationic porphyrins are speculated to destabilize the G-quadruplex as said before, by binding to the structure, which proposes a sight in drug designation [141]. The telomere shortening as previously stated is also a challenging drug target. For a fetus suffered from high risk of familial HCM accompanied by diastolic dysfunction, intrauterine treatment using beta-receptor blockers is recommended as an optional treatment [142]. Although more and more new notions emerged and have been validated to be feasible and effective, *MYH7* gene therapy has not been used clinically. Whether those therapies are practically available needs further research.

Models for studying *MYH7*-associated HCM

A number of animal models have been used for studying the pathogenic mechanism of *MYH7*-associated HCM. The first animal model is a transgenic mouse model according to a missense variant, p. R403Q, the first found mutation related to HCM, also the most common used [143]. For a long time, researchers preferred mice model to imitate human HCM cases and investigate the possible pathogenic mechanisms. However, a significant limitation has also merged that human express slow beta-myosin heavy chain but mouse models encode fast alpha-myosin, which do not result in the typical phenotype found in human with HCM [144]. Therefore, several alternative models have been found. Transgenic rabbit carrying the variant p.R403Q precedes the understanding of molecular mechanism in human HCM [145]. The genetic editing pig model with the knock-in orthologous "P" point variant p.R723G based on somatic cell nuclear transfer technique provided a more suitable large animal model to investigate the pathogenic mechanism of human HCM than mouse model, with more similar cardiovascular physiology to human [146]. Another group proved that zebrafish is also an alternative animal model for the study of cardiomyopathy caused by the mutant of *MYH7*, and confirmed that the inhibition of mTOR and MAPK signal pathway had a therapeutic effect using the zebrafish homolog of human *MYH7*-based cardiomyopathy model [147]. A human orthologous "VUS" variant p.E1883K has been found in a cat suffered from HCM, making it possible that the cat with HCM is an optional model as well [148]. Those new animal models are all alternative to study the molecular pathogenic mechanism and therapeutic tools in future.

Meanwhile, a number of iPSC-CM HCM models, harboring a number of well-known HCM-causing heterozygote variants, including "P" p.R403L, p.R719Q, p.Ala355Thr, p.R723G, p.R663H, p.E1356K, p.R1712Q, p.R723C, and "VUS" p.M659I and p.E1462K, using CRISPR/Cas-9 editing protocol, could be an useful tool for the future study of the molecular mechanism of HCM [149–159]. Also, using the same editing tool, a homozygous knockout human embryonic stem cell (hESC) line of *MYH7* gene has been produced [160]. Genome-editing technique combining with iPSC-CMs provides a practical platform to guide the understanding of mechanism and evaluation of precision drug. Isogenic genome-edited human pluripotent stem cell-cardiomyocytes (hPSC-CMs) using CRISPR/Cas-9 editing protocol, produced 11 isogenic variants centered on "P" p.R453C and comprehensively phenocopied the features of adult hypertrophic cardiomyocytes [161]. Ioannis Karakikes et al. produced a transcription activator-like effector nucleases (TALEN)-instructed knocking out iPSC-CMs line [162]. Those iPSC lines models provide an available, valuable, and validated opportunity for studying the pathogenic mechanisms and therapeutic tools of HCM in vitro in future.

MYH7 and other cardiomyopathies

Increasing evidence has revealed that *MYH7* could also lead to many other kinds of cardiomyopathies except HCM, including DCM, RCM, LVNC, arrhythmogenic cardiomyopathy, and other types of CHD. Majority of them are identified in family cases, also predominantly in an autosomal dominant transmitted Mendel pattern, and also involving autosomal recessive, X-linked, and mitochondrial inherited mode [163–166].

DCM and RCM are two well-known cardiomyopathies. DCM (MIM#613,426) is a kind of relatively rare cardiomyopathy, about 1:2500 [167], with the characteristics of ventricular enlargement predominantly in left ventricular with systolic dysfunction [168]. *MYH7* gene is ranked the third common pathogenic gene of idiopathic DCM [169] and most of them are non-truncating variants with a high penetrance in family, with a relatively high proportion of pediatric patients [170–172]. Fifty-nine "P" and "LP" missense variants are recorded in ClinVar with at least one submitter, among which 6 are with high confidence (Table 1), in addition to 3 LOF variants (Table 2). DCM is the leading reason for congestive heart failure and patients are at high risk of SCD [173, 174], predominantly in working people with early age [175]. Unlike HCM, *MYH7* mutations associated

with DCM are scattered throughout entire length of the gene without a significant enriched region, like IHM interacting residues. The biological mechanism in DCM is opposite to HCM, with a decreased sarcomeric contractility as a result of impaired ATPase activity and reduced velocity sliding along actin filaments [176], ultimately triggering the process of remodeling, which is tested in mouse models by knocking in the "P" missense variant p.S532P in actin binding domain and "P" p.F764L in converter domain which are recognized pathogenic *MYH7* mutation in human DCM [177]. Same with HCM, digenetic mutations involving a variant in *MYH7* gene and the other gene predispose to a severe phenotype of DCM, leading to an addictive effect [178–180]. Furthermore, the variable manifestations of DCM patients with a causative-variant in *MYH7* are also presumed to attribute to environmental and genetic modifiers [166]. RCM, least common cardiomyopathy with unknown prevalence [181, 182], with the estimated 5% in pediatric cardiomyopathies [183, 184], is characterized by diastolic dysfunction but without impaired systolic function, in the condition of stiffed ventricular walls but not necessary for thickening, leading to lower the appropriate filling of ventricular [185, 186]. Idiopathic RCM is predominantly an inherited ailment [187]. Most of mutations in *MYH7*-related RCM are inherited in an autosomal dominant pattern and are missense variants [185]. There are 2 "P" and "LP" missense variants in ClinVar with more than one submitter, and 1 of them has high confidence with a number of references (Table 1). Unexpectedly, RCM is related with the worst prognosis among cardiomyopathy [188].

LVNC (MIM#613,426), resulting of the incomplete or arrested development and compaction of human myocardium during the 5^{th} to 8^{th} week of embryonic development [181], is the third common genetic cardiomyopathy, characterized by the presence of numerous thickened trabeculations and deep recesses, prominent in the left ventricular with a spongy like, with a risk of developing to HCM and DCM [189–191]. *MYH7* is one of the pathogenic gene for LVNC [192]. Unlike HCM and DCM, except point mutation, truncating variants in *MYH7* are thought to be pathogenic in LVNC [193], with a relatively high proportion of pediatric patients [194]. In addition to 7 "P" and "LP" missense variants (Table 1), 4 "LP" LOF mutants (Table 2) are documented in ClinVar. Patients in LVNC with *MYH7* mutations are prone to have a low risk of adverse cardiovascular events [195], and the proportion of asymptomatic individuals accounts for a significant ratio, about 8% subjects meeting the criteria for LVNC in high-trained athletes from UK and France [196]. The risk of adverse cardiovascular event is also considered lower in LVNC with *MYH7* mutations compared with patients carrying other gene variants [197]. The potential mechanism for the development of irregular trabeculations and deepened recesses is interpreted by the notion that variants in *MYH7* may increase apical–basal polarization, resulting in the delamination of compact layer cardiomyocytes [198]. Moreover, the too-early isoform switch from *MYH7* to *MYH6* which are programed to be finished at birth may trigger pathological remodeling and abnormal sarcomere assembly, leading to impaired trabeculation and compaction of myocardium, possibly accompanied by specific modulator of gene expression, such as G-quadruplex resolvase RNA helicase associated with AU-rich element [199]. Like HCM, coexistence of digenic mutations is prone to develop an early-onset age, severe phenotype, and poor outcome [200]. Although LVNC is often exist individually, it sometimes coexists with several CHD [191], most common one of which is EA [201], a relatively rare kind of CHD, with a prevalence of 1:200,000 in births [202], characterized by a lower position of tricuspid and malformed leaflets [203], leading to an enlarged right atrium, tricuspid regurgitation, and eventually heart failure [204, 205]. Moreover, variants in *MYH7* are increasingly identified as the disease-causative of the combination of LVNC and EA, sometimes incorporated with other CHD, also in a dominant autosomal pattern, and patients presenting variable manifestations too, significantly from asymptomatic, mild symptomatic to fetal [65, 206, 207]. Many other types of CHD and malformations also have been found in combination with LVNC, including bicuspid aortic valve, single umbilical artery [208, 209].

Besides, limited cases of rare CHD independently associated with *MYH7* have been reported, such as double-chambered right ventricle and double-chambered left ventricle [205, 210]. Additionally, a single variant also could develop to a complicated clinical phenotype, such as a young female identified with a novel missense "VUS" variant p.F252S manifested both RCM and left ventricular hypertrophy [211]. The phenotypes of patients with those kinds of cardiomyopathies present variably and the conceivable mechanism of genotype–phenotype is still unclear [209, 212]. Meanwhile, pediatric patients suffered from a more severe degree of cardiomyopathies with more severe malformations or more coexist cardiomyopathies or poor prognosis [49, 209, 213]. Interestingly, *MYH7* variants in pediatric patients with both DCM and LVNC are totally located in residues among 1 to 600 found in a large pediatric cohort [214]. A few cases of fetus with LVNC identified in the third trimester by using prenatal ultrasound technique, carrying mutations in *MYH7,* elucidate the importance of seeking the pathogenic gene and investigating the family disease history of suspicious fetus [215, 216].

Although the application of experimental models in these cardiomyopathies is relatively countless, human iPSC models and animal models also extended to this field, including the iPSC model according to systolic cardiomyopathy derived from "P"/"LP" variant p.E848G, and zebrafish model which is considered an available animal platform to

investigate the pathogenic molecular mechanism of LVNC [198, 217]. Zebrafish has been found corresponding homologues according to 96% genes associated with DCM, therefore, zebrafish is a promising animal model for future research of cardiomyopathy [218]. To find more experimental models is necessary for better understanding the pathogenic mechanism and clinical application.

MYH7 and skeletal muscle myopathy

MYH7 and Laing distal myopathy

LDM (MIM#160,500), a predominantly autosomal dominant condition, as a result of heterozygous mutations enriched in C-terminus of *MYH7* [219], which affects the anterior compartment of the legs, with the characteristics of progressively progressing distal weakness, results in the recognizable "hanging big toe" sign [220]. It is well recognized that the typical LDM phenotype exhibits an early-onset age but could also range from infancy to adult up to 45 years old [220–223], development of the foot dorsiflexors and big toe extensors, then a weakening of the proximal upper and lower limbs, cervical flexor muscles and finger extensor muscles, even respiratory and cardiovascular system diseases, moreover, with substantial variability in clinical presentations and frequent histological morphologic changes in different instances [220, 224–227]. However, the footdrop is valid not a specific feature, the weakening of finger extension is thought to be more specific [226]. CFTD, cores and minicores, dystrophic alterations, and moderate unspecified abnormalities are only a few examples of the variety in muscle histology in LDM [, 228, 229].

Often these LDM patients possess mutations in the mid-rod domain of *MYH7* gene within 32–36 exons including p.E1508del, p.R1500P, p.Lys1617del, p.Ala1663Pro, p.Leu1706Pro, and p.Lys1729del, etc. [219, 224, 227], which interfere the normal process of tail forming coiled-coil, whereas in a few limited cases, the globular head region has also been linked to the condition, including p.Tre441Met, p.R783P, and p.V606M [230–232]. The "P" and "LP" missense variants (Table 3) and LOF variants (Table 2) are recorded in ClinVar. The phenotype spectrum is also significantly variable, and the case in point is deletion variant p.E1508del [224], which is a susceptible residue [233], and missense variant p. Leu1551Pro, located in the exon 34 of the *MYH7* [234]. Furthermore, missense variant p.L1453P, located in exon 32, was found related to brain white matter lesions on imaging, but whether the mutation in *MYH7* gene is to blame for the neurologic abnormalities requires further research [235]. Moreover, patients with LDM, having the fatty atrophies and substitutions of the proximal or paraspinal muscles could be more severe and illness progression more quickly compared with that of the lower thigh muscles [236]. All cases above broadened the phenotype spectrum of *MYH7*-related LDM.

There are also founder-effect mutations which have been found in several regions. Geographically restricted to the South of Spain, the missense "LP" variant p.R1560P was confirmed to be a novel founder mutation linked to LDM [237]. The deletion variant p.K1729del was assumed to be a founder mutation in Safor of Spanish, being brought into the population around the start of the seventeenth century, having an origination of Italian, according to the mathematical method [238].

Table 3 The "P" and "LP" missense variants in *MYH7*-related skeletal myopathy recorded in ClinVar

Disease	Pathogenicity	Confidence	Variant
MSM	P	*	E930Q, E924K, D906G, E894G, A797T, G741R(c.2221G>C), R723C, R719W, R694H, R663H, R663C, R403Q, R403W, R369Q, R249Q
	LP	*	E1801K, R1712Q, R1500W, R1420W, T1377M, R1045L, R870C, R869H, K865E, R858C, H576R, M515T, I457T, R243C, D239N, R143Q
CFTD	P	*	E930Q, E924K, D906G, E894G, A797T, G741R(c.2221G>C), R723C, R719W, R694H, R663H, R663C, R403Q, R403W, R249Q
	LP	**	R858C
		*	R1712Q, R1500W, R1420W, T1377M, R1045L, M877I, R870C, R869H, K865E, P731R, H576R, I457T, R243C, D239N, R143Q
MYH7-related late-onset scapuloperoneal muscular dystrophy	P	*	E930Q, E924K, D906G, E894G, A797T, G741R(c.2221G>C), R723C, R719W, R694H, R663H, R663C, R403Q, R403W, R249Q
	LP	*	R1712Q, R1500W, R1420W, T1377M, R1045L, R870C, R869H, K865E, R858C, H576R, M515T, I457T, R243C, D239N, R143Q
Other *MYH7*-related skeletal myopathy	P	*	E1801K, E930Q, E924K, D906G, E894G, A797T, G741R(c.2221G>C), R723C, R719W, R694H, R663H, R663C, R403Q, R403W
	LP	*	R1712Q, L1629P, R1500W, R1420W, T1377M, R1045L, R870C, R869H, K865E, R858C, H576R, M515T, I457T, R243C, D239N, R143Q

The variants related to more than one cardiomyopathy and/or skeletal myopathy are indicated by underlines

A fly model harboring the known LDM variant p.K1729del imitated the morphological feature and impaired muscle function as seen in human LDM, using CRISPR/Cas-9 genome engineering protocol, indicated that the severity of disease is explained by the number of mutated alleles, illustrating a dose-dependent effect, and increasing the expression of protein Abba/Thin which are instrumental in maintaining the integrity of sarcomere could alleviate the phenotype [239]. It provides a potential treatment tool.

MYH7 and myosin storage myopathy

MSM (MIM#608358) was first listed in 2003 [240], the first skeletal muscle myopathy found to be caused by *MYH7* gene, previously named as hyaline body myopathy due to sluggish myosin hyaline body accumulation seen in type 1 muscle fibers in subsarcolemmal tissues displayed in histopathologic features, perturbing the assembly of thick filaments. Clinical features include mainly early-onset age predominantly in infancy and childhood, prominent axial and proximal weakening, spinal stiffness, severe scoliosis, accompanied by or without respiratory and cardiac involvement. Variants of *MYH7*-related MSM are mostly in an autosomal dominant inherence pattern with mutations in the distal rod region corresponding to 37–40 exons of *MYH7* gene, including missense variant p.Arg1845Trp, p.His1904Leu, p.Leu1793Pro, p.Glu1883Lys [240–245], in-frame deletion variant p.K1784del [246] and a missense variant p.X1936WfsX32 changing the TAG to tryptophan (W), which leads to the elongation of the C-terminus [244]. Additionally, countless occurrences of recessive inheritance have been documented, such as homozygous variant p.R1712W, heterozygous variant of truncating p.Gln1567*, and missense p.E1555G [247]. The clinical manifestations of *MYH7*-related MSM are incredibly varied from asymptomatic to severe weakness [241, 248–252]. The mechanism of pathology could be interpreted by mutations perturbing the process of proteins to assemble to proper, stable, and functional thick filaments, corresponding to variants enriched in distal rod [253, 254]. Different mutations interfere distinct steps in assembling process, including two α-helices properly folded into coiled-coils, then assembling to bundles of coiled-coils, and ultimately into thick filaments. An uncommon missense variant p.Ile457Arg is located in the head domain, performing pronounced thigh weakness as well as respiratory and cardiac impairment, indicating the correlation of variants location and its functional region [255]. The exact mechanism needs further exploration.

MYH7 and congenital myopathy with fiber-type disproportion

CFTD (MIM#255,310), is an uncommon myopathy, defined by the characteristic pattern with a predominance of slowly contracting type I fibers in skeletal muscles seen by histological analysis [256]. *MYH7* is one of the pathogenic genes of CFTD, inherited in autosomal dominant, recessive or X-linked forms. Also, CFTD presents a variable range of clinical manifestations [257]. Moreover, the stop-loss variant p.X1936WfsX32 linked to CFTD is speculated to eventually develop to MSM later, as a result of the absence of stop signal and producing an elongated protein, leading to disturb the degradation of the protein, protein buildup, and accumulation in sarcomere, which caused the weakness of axial muscles, prominent neck muscle [244, 258].

MYH7 and other myopathies

MYH7 mutations were also identified in many other forms of myopathies, including usually scapuloperoneal myopathy, axial stiffness, drop-head syndrome, congenital core myopathy, and asymptotic hyperCKemia accompanied by or without hyaline bodies [259–262]. The variable phenotypes and muscle biopsy findings are postulated to have a relationship with Ca^{2+} regulatory process by interfering the charge of residuals, leading to assembly destabilization or structural alterations, eventually perturbing the normal structure and stability of myosin [227].

There are also a variety of animal models used to study the molecular pathogenic mechanism of human myopathy related with *MYH7* gene, including nematode model with the ortholog (unc-54) of human *MYH7*, pig model carrying an in-frame insertion variant [263, 264].

MYH7 with clinical phenotypic diversity

The clinical phenotype of patients with mutations in *MYH7* gene significantly vary from person to person, even with the same variant within a family, presenting either cardiomyopathy or skeletal muscle myopathy independently, also showing an overlapping complex form of both of them, possibly accompanied by other complications [265], such as nonsense "VUS" variant p.Q1916* [266], deletion variant p.Glu1508del [267], and missense variant p.E1801K [268], p.E1856K [269], p.R1820W [270], p.R783P [231], p.V606M [232], p.R249Q [271], p.Arg1820Gln [272], p.Glu1883Lys [245], p.Leu1467Val, p.Arg1588Pro [273], and so on. The existence of clinical phenotypic diversity in *MYH7*-related diseases adds difficulty to clinical practice, so it is very important to find out the regular pattern between

mutation and phenotype, which needs more exploration in future.

MYH7 with tumorigenesis diseases

Additionally, *MYH7* is also found in many tumorigenesis diseases. *MYH7* has been found highly expressed in lung cancer, especially in cigarette smoking-associated lung adenocarcinoma patients, 12% of which experiencing *MYH7* mutation. High expression of *MYH7* is also considered to be related to cancer progression and poor prognosis, which indicated that *MYH7* is a potential biomarker for smoking-related lung cancer and a promising targeting-therapy point [274]. *MYH7* is ranked in the top ten hub gene of prostate cancer as well [275]. *MYH7* is also found enriched in the biological processes of oral cancer [276]. A large-scale research held in China identified *MYH7* mutations in Epstein–Barr virus-associated intrahepatic cholangiocarcinoma [277]. Both gene mutations and changes in expression can affect the occurrence and development of cancer. All the above results show the possible influence of *MYH7* on tumorigenesis.

Conclusion

MYH7 is one of the most important sarcomere protein encoding genes, and its variants are disease-causative for a series of cardiomyopathy and skeletal myopathy, which sometimes exhibit clinical overlap. *MYH7* can also affect a limited number of tumorigenesis diseases from expression change to base change. Better understanding of the structure of *MYH7* and the functional regions of myosin-7 can improve the insight into its related disorders. Genetic testing provides and accelerates the accurate and early diagnosis of inherited diseases, especially in families. Deeper comprehension to the pathogenic mechanisms of cardiomyopathy and/or skeletal myopathy as well as the investigation of variable genotype–phenotype is necessary. It is essential to extend application of iPSC models and animal models in all forms of *MYH7*-associated diseases and establish more suitable animal models to study the disease mechanisms and morphological performances. There are still several urgent questions to be resolved. More precise and cost-effective sequencing technology are needed to distinguish the VUS and missing variants, and re-evaluation is necessary probably, in addition to more sophisticated management of pediatric patients. In conclusion, *MYH7* is a potential biomarker to predict disease. Further work in the development of base- and gene-specific therapies are required for the pinpoint management of patients.

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Data availability Enquiries about data availability should be directed to the authors.

Declarations

Competing interests The authors declare no competing interests.

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