Computational Characterization Of MYH7 And MYBPC3 Pathogenic Variants In Hypertrophic Cardiomyopathy And Their Potential For CRISPR- Based Gene Editing

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***Abstract*—Hypertrophic cardiomyopathy (HCM) is a genetically heterogeneous cardiac disorder, which is marked by unexplained heart muscle thickening, atypical heart function, and increased risk of arrhythmia, heart failure, and sudden cardiac death. A key mechanism underlying HCM is genetic changes in genes encoding cardiac contractile proteins. In this context, MYH7 and MYBPC3 are strongly implicated genes that code for the β-myosin heavy chain and cardiac myosin-binding protein C, respectively. HCM caused by MYH7 is often attributed to missense mutations that alter myosin motor organization and function, whereas MYBPC3-related HCM is mostly caused by deleterious mutations that prevent functional protein expression due to haploinsufficiency. This distinction makes these two genes appropriate models for exploring genotype-dependent disease mechanisms. In support of HCM studies, computational technologies can pinpoint known variants, verify allele frequencies, predict their effects on protein structure and function, and rank variants for experimental validation. Genome editing is one possible method of correcting or changing the pathogenic variants. The classical CRISPR-Cas9 system can take advantage of homology-directed repair and non-homologous end joining, while base editing and prime editing can achieve more accurate correction for certain sequences. Preclinical research using patient-derived iPSC cardiomyocytes has shown that pathogenic variants can be added or corrected in genetically controlled areas. Nevertheless, applying this method in treatment faces obstacles related to delivering gene-editing technologies to cardiomyocytes, editing efficiency, off-target editing and unintended on-target alterations, immunogenicity, long-term safety, manufacturing complexity, and cost.**

***Index Terms*—Hypertrophic cardiomyopathy; MYH7; MYBPC3; CRISPR; Precision medicine**

I. INTRODUCTION

The prevalence of cardiovascular diseases (CVDs) is a problem worldwide, as they include a large category of disorders related to the heart and blood vessels. The major diseases under this category are coronary artery diseases, heart failure, arrhythmias, cardiomyopathies, congenital heart diseases, and hereditary cardiovascular disorders. Although some common risk factors strongly influence the occurrence of CVDs, the role of genetic risk factors cannot be ignored. Nevertheless, molecular genetics research shows that pathogenic gene variations affect heart function and contribute to disease development (Marian, 2021).

The term genetic cardiovascular disorders refers to disorders caused by genetic mutations that affect genes involved in cardiac function and structure. This disorder encompasses inherited cardiomyopathies, cardiac channelopathies, familial dyslipidemias, and inherited aortic diseases. Hypertrophic cardiomyopathy (HCM) is the most commonly inherited cardiomyopathy and has a strong genetic association, along with significant clinical diversity. HCM is characterized by unexplained thickening of the ventricular myocardium, mainly of the left ventricle. It can cause impaired ventricular relaxation, left ventricle outflow tract obstruction along with the possibility of cardiac arrhythmias, heart failure and the increase of the sudden cardiac death risk. The cellular mechanisms of HCM include cardiomyocyte hypertrophy, myocyte disarray, and myocardial fibrosis. (Marian & Braunwald, 2021; Ommen et al., 2024).

Hypertrophic cardiomyopathy (HCM) is closely linked to defects in genes that code for proteins in cardiac muscle. Genetic defects in sarcomeric genes are a well-established cause of HCM. Some significant genes causing HCM are MYH7, MYBPC3, TNNT2, TNNI3, TPM1, ACTC1, MYL2, and MYL3 (Ingles et al., 2019). Nonetheless, it should be noted that the contribution of these genes is not the same for each gene. Thus, MYH7 and MYBPC3, the most commonly present genes in sarcomeric HCM, account for the vast majority of HCM cases (Marian, 2021). Recent work has focused on incomplete penetrance and variable expressivity because disease manifestation varies by variant class.

The MYH7 gene encodes the β-myosin heavy chain, a key player in the cardiac sarcomere's thick filament. It functions as a motor protein and directly contributes to actin-myosin interactions responsible for contraction. Pathogenic variants of MYH7 variants are usually missense variants that can disrupt protein structure, ATPase activity, cross-bridge kinetics, or force production (Marian, 2021). In contrast, MYBPC3 encodes cardiac myosin-binding protein C (cMyBP-C), a protein that helps regulate the sarcomere and modifies actin-myosin interactions. MYBPC3 has a higher rate of truncating mutations, resulting in reduced functional cMyBP-C due to haploinsufficiency. (Helms et al., 2014; Carrier et al., 2022).

Other relevant genes involved in HCM include TNNT2, which encodes cardiac troponin T, and TNNI3, which encodes cardiac troponin I. Both proteins belong to the troponin complex and participate in the calcium-dependent processes of cardiac muscle contraction and relaxation (Marian, 2021). Understanding the consequences of mutations in these genes is crucial for linking genotype to phenotype and applying precision medicine.

Current methods of HCM treatment focus mainly on symptom relief and management of symptoms and complications rather than solving the genetic flaw. Therefore, advances in genome-editing techniques, particularly CRISPR, have sparked interest in the possibility of correcting the underlying DNA mutations. Computational analysis could support this developing direction of science by identifying abnormal mutations, predicting their effects on protein structure and function, and defining possible candidates for experimentation. In view of the above, this paper focuses on MYH7 and MYBPC3 mutations, their molecular background, and computational analyses and perspectives on using CRISPR-based gene editing to correct them.

II. MOLECULAR BASIS OF HCM

Hypertrophic cardiomyopathy has a molecular basis that is closely linked to defects in cardiac sarcomeres. As the main structural and functional unit, the sarcomere contributes to cardiomyocyte contraction. The sarcomere contains thick and thin filaments that interact to generate mechanical force. The thin filament is composed of actin, tropomyosin, and the troponin complex, whereas myosin and other regulatory proteins make up the thick filament. Heart muscle contraction involves myosin heads interacting with actin through cross-bridge cycling, using energy from ATP hydrolysis to produce mechanical work (Marian & Braunwald, 2021; Carrier et al., 2022).

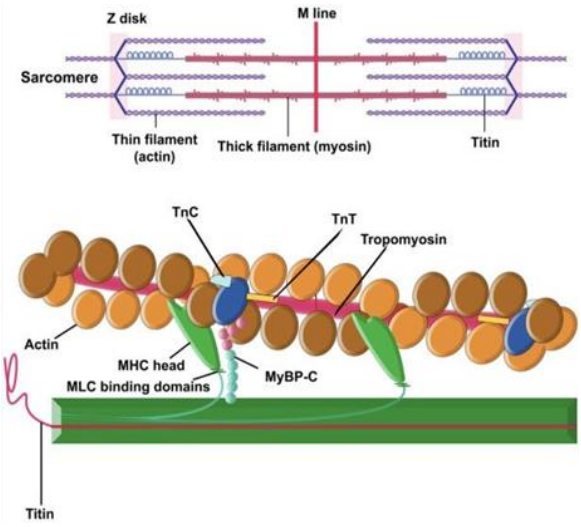


Figure 1: Simplified organization of the cardiac sarcomere, showing the contractile and regulatory proteins with MYH7 and MYBPC3

The β-myosin heavy chain (β-MHC) is encoded by the MYH7 gene, and its product plays an essential role in the thick filament machinery of heart muscle. Myosin is a protein that contains a motor domain capable of hydrolyzing ATP and converting chemical energy into mechanical energy. Repeated interactions of myosin with actin generate the force needed for contraction of cardiomyocytes. Mutations in MYH7 can alter properties of β-MHC, including ATPase activity, actin binding, cross-bridge kinetics, and force generation.

MYH7 mutations may disrupt cardiomyocyte function, leading to pathological remodeling (Marian, 2021). According to a study, most MYH7 mutations linked to hypertrophic cardiomyopathy are missense mutations that substitute one amino acid in β-MHC. Thus, the effect of a specific MYH7 variant on its function depends on the mutation site.

The MYBPC3 gene codes for cardiac MyBP-C (cMyBP-C), a component of the thick filament. The cardiac MyBP-C helps with the structural organization of the sarcomere part of the muscle cells, regulates interaction between myosin and actin, thus contributing to heart function (Carrier et al., 2022). MYBPC3 has a high mutation rate in hypertrophic cardiomyopathy and many pathological variants. Many MYBPC3 variants are truncating, including nonsense, frameshift, and splice-site mutations. These mutations may cause aberrant transcripts, premature termination of protein synthesis, and degradation of abnormal RNA, reducing cMyBP-C levels in cardiomyocytes (Helms et al., 2014; Carrier et al., 2022).

The decreased level of cMyBP-C is associated with haploinsufficiency, in which one functional copy of the gene produces insufficient protein to maintain sarcomere function (Helms et al., 2014). However, some MYBPC3 mutations do not cause truncations but still adversely alter cMyBP-C protein properties. Thus, both MYH7 and MYBPC3 have different mechanisms of action on sarcomeres in the case of hypertrophic cardiomyopathy: MYH7 mutations lead to aberrations of the contractile protein itself, while MYBPC3 truncating variants frequently reduce the amount of functional c MyBP-C through haploinsufficiency, whereas some missense variants may alter the protein's function.

Sarcomeric dysfunction at the cellular level can impact force generation, calcium sensitivity, energy consumption, and cardiomyocyte signaling. This might lead to compensatory hypertrophy, myocyte disarray, fibrosis, and various pathologies typical of HCM. Therefore, understanding these gene-specific molecular mechanisms is crucial for identifying pathogenic mutations and determining whether they can be eliminated using tools such as CRISPR-based gene editing (Marian, 2021).

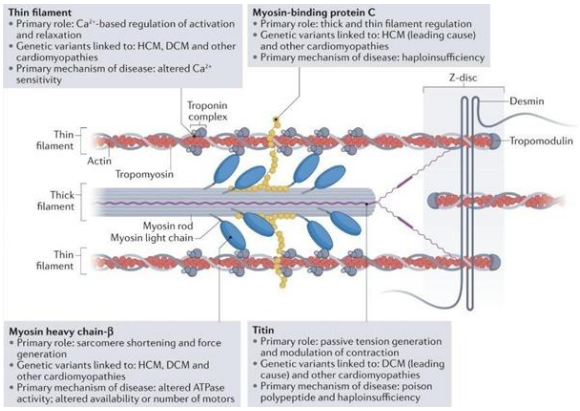


Figure 2: Comparison of common molecular mechanisms underlying MYH7- and MYBPC3-associated hypertrophic cardiomyopathy

III. MAJOR HCM- ASSOCIATED VARIANTS

Missense variants result from nucleotide substitutions that change an amino acid in the encoded protein. Their functional consequences depend on the substituted amino acid's location and biochemical properties. Pathogenic MYH7 variants associated with HCM are predominantly missense variants and may affect β-myosin heavy-chain structure, ATPase activity, actin–myosin interactions, or force generation (Marian, 2021). One example is MYH7 p.Arg403Leu (R403L).

Fontaine et al. (2021) generated an induced pluripotent stem cell (iPSC) line from a patient carrying this variant and used CRISPR/Cas9 to produce an isogenic, gene-corrected control line. These cell lines provide a model to investigate the variant's consequences while controlling for genetic background differences.

Nonsense mutations create an early termination codon, which may generate truncated proteins or trigger transcript degradation via nonsense-mediated decay. In MYBPC3, truncating mutations are common and include nonsense, frameshift, and intronic mutations. Reduced functional cMyBP-C is one mechanism by which MYBPC3 leads to HCM and supports a haploinsufficient model (Helms et al., 2014). One example is the MYBPC3 truncating variant, which has been studied both clinically and experimentally. iPSC-derived cardiomyocytes from patients with this variant have been utilized to address the genotype–phenotype relationship, and during this research, CRISPR/Cas9 was applied to generate isogenic controls that lacked

the pathogenic variant (Gifford et al., 2023).
Rather than relying on computational prediction alone, variant interpretation uses multiple types of evidence. Based on criteria such as population frequency, computational evidence, functional information, and inheritance, the ACMG/AMP framework classifies variants into five categories: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign (Richards et al., 2015). Public databases such as ClinVar contain information on variants and their classifications. Researchers can use this information to compare classifications and to determine the presence of uncertainties in existing classifications (NCBI, 2026). Based on these findings, in the case of the MYH7 and MYBPC3 article, the variants are expected to have strong clinical or laboratory confirmation, unambiguous HGVS nomenclature, and ample information for further analysis.

IV. CURRENT HCM TREATMENTS

Currently, HCM management focuses on alleviating symptoms, treating complications, preventing sudden cardiac death in selected patients, and relieving obstruction or other heart problems. The first-line drug therapy for patients with symptomatic obstructive HCM is usuallynon–vasodilating beta blockers. If these are ineffective or not tolerated, non-dihydropyridine calcium channel blockers such as verapamil or diltiazem may be added. If symptoms persist, clinicians can administer more advanced treatments, including cardiac myosin inhibitors, disopyramide, or the septal reduction procedure, depending on the case (Ommen et al., 2024).

Moreover, cardiac myosin inhibitors are particularly interesting from a mechanistic standpoint because they mitigate processes occurring in the sarcomere rather than simply changing loading conditions. Mavacamten reduces actin-myosin interaction, which lowers contractility and obstruction of the left ventricular outflow tract in adult patients with obstructive HCM. Nevertheless, the use of the drug requires additional monitoring, as excessive decrease in contractility can negatively impact systolic function. Thus, pharmacological treatment provides crucial symptom control but usually does not address the underlying inherited DNA variant associated with sarcomeric HCM.

At experienced centers for hypertrophic cardiomyopathy (HCM), invasive procedures such as septal reduction may be carried out on patients with advanced, drug-resistant obstructive disease. While surgical removal of a part of the hypertrophied septum is termed surgical septal myectomy, the targeted damage of myocardial tissue to alleviate the obstruction is referred to as alcohol septal ablation. The management may also incorporate treatment of arrhythmia, prevention of thromboembolic complications in patients with atrial fibrillation, and evaluation of implantable cardioverter-defibrillator (ICD) use based on individual risk for sudden death (Ommen et al. 2024).

V. GENE EDITING TECHNOLOGIES

CRISPR, or CRISPR-Cas9 genome editing, began as a research laboratory tool, but over time its applications have broadened as researchers explored its capabilities. The central CRISPR-Cas9 technique involves providing a guide or regulatory RNA that partially supplements the Cas9 enzyme's function by directing it to a specific site in the human genome. Cas9 can break DNA strands at specific sites, leading to further editing events. This is significant in HCM because the type of editing depends on the mutation present and whether it needs to be corrected or disrupted.
The two traditional pathways involved in editing after Cas9 acts are non-homologous end joining (NHEJ) and homology-directed repair (HDR). Non-homologous end joining (NHEJ) repairs DNA double-strand breaks without requiring a donor template and can generate insertions or deletions at the target site. Although it is commonly used for gene disruption, its outcomes are less predictable than precise sequence correction."

In this regard, CRISPR-based editors are highly relevant. For example, base editing uses modified Cas proteins fused to DNA-modifying enzymes that convert some bases without inducing DSBs. Depending on the particular editor and target, transitions such as C-to-T or A-to-G can occur. This means base editing can be applicable in certain missense alterations, but its use is limited by the chemistry of the target base substitution and the genome in which it occurs.

On the other hand, prime editing takes this process further by combining a Cas9 nickase, a reverse transcriptase, and a prime-editing guide RNA, which carries the target sequence. This enables base and base-pair substitutions or insertions. This means prime editing can be used for genome editing without DSBs or donor DNA (Anzalone et al., 2019). Recent review papers confirm progress in genome-editing efficiency but also highlight considerable differences across experimental systems.

For HCM, these technologies should be viewed as a spectrum rather than interchangeable tools. Conventional Cas9 with HDR could theoretically correct a specific mutation when an efficient repair template and delivery system are available. NHEJ-based approaches may be better suited to disrupting a harmful allele or regulatory sequence, although uncontrolled indels can complicate therapeutic use. Base editing is attractive for appropriate single-base substitutions, whereas prime editing has broader theoretical editing capacity. The correct platform therefore depends on the exact pathogenic variant, surrounding sequence, desired genetic outcome, editing efficiency, and safety profile.

Using CRISPR editing as a research tool, without the need to be a form of treatment, is just as important. Creating isogenic cell lines involves either correcting a pathological mutation in patient-derived cells or introducing a mutation into healthy genes. By comparing genetically identical edited and unedited cardiomyocytes, researchers can identify the cause-and-effect relationship resulting from the mutation. Several studies on hypertrophic cardiomyopathy involving the genes MYH7 and MYBPC3 have already adopted this technique (Villard et al., 2021; Gifford et al., 2023).

Advances in CRISPR technology link computational variant evaluation with experimental disease modeling. The variation chosen through computation will be examined based on its ability to be modified, the area for guide-RNA preparation, the potential for unintentional changes, and the presence of an effective method for editing.

Experimental correction can be assessed by sequencing and by testing cardiomyocyte characteristics. This workflow is especially relevant to HCM because the condition involves several different types of pathogenic variants with different mechanisms of action.

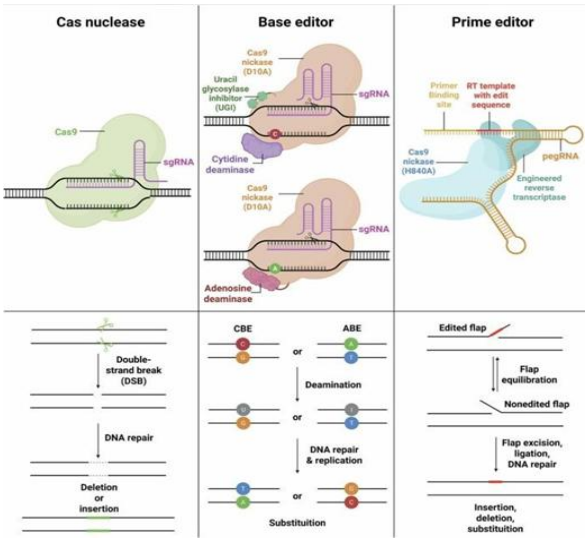


Figure 3: Overview of CRISPR- based genome-editing approaches being investigated for correction of selected pathogenic variants

VI. GENE EDITING STRATEGIES FOR HCM

A gene-editing approach for HCM can be outlined as multiple steps: detecting the disease-causing variant, choosing the right editing tool, delivering to targeted cardiac cells, editing the region of interest, and proving the efficiency of editing. Because HCM is genetically complex, a unified approach is unlikely to work for every patient. Instead, therapy is expected to be customized based on the type of mutation.

CRISPR intervention can in principle be modelled, in the case of a suitable pathogenic variant, as pathogenic variant → targeted editing → corrected DNA → restored protein function → phenotype improvement in cardiomyocytes, but the link between DNA correction and phenotype is not necessarily straightforward, as HCM is influenced by other genetic modifiers, cell characteristics, and subsequent remodeling. This is demonstrated by research on iPSCs from people with the same MYBPC3 truncation variant, which displayed different phenotypes, and by evidence that additional genetic variation appears to impact disease manifestation (Gifford et al., 2023).

MYBPC3 is an important target for investigating variant-specific correction strategies because many of its pathogenic variants are truncating and can cause haploinsufficiency. A theoretical approach could involve precise correction of a specific truncating

mutation through HDR and prime editing, either by restoring the normal coding sequence or, for certain mutation types, by using methods that restore active transcript or protein production.

Patient-derived iPSC-cardiomyocytes are a suitable platform to test whether correction restores cMyBP-C expression and normalizes cellular phenotypes. In research involving brothers with MYBPC3 truncating mutations, isogenic controls generated with CRISPR/Cas9 technologies allowed us to conclude that the mutation causes the disturbance in mitochondrial bioenergetics and excitation-contraction coupling (Gifford et al., 2023).

MYH7 presents a different editing dilemma because many pathogenic mutations are missense mutations, which produce a modified protein rather than simply inhibiting gene expression. Performing a precise repair of the nucleotides seems to be appealing from the theoretical point of view. One known practical case involved using an iPSC line with an MYH7 mutation and applying CRISPR/Cas9 for mutant codon repair, resulting in an isogenic model that could be converted into cardiomyocytes (Fontaine et al., 2021). Such models demonstrate the feasibility of correcting a selected MYH7 variant in cultured iPSCs, but do not establish the safety or efficacy of gene editing as a treatment for HCM.

Recent cardiovascular genome-editing reviews cite preclinical studies using base editing to target disease-causing variants in MYH7 and MYBPC3 and highlight the potential of RNA-targeting methods for selectively inhibiting mutant transcripts (Sami et al., 2025). These new approaches may enable indirect correction when DNA correction is not possible. In general, MYBPC3 and MYH7 illustrate two complementary situations: MYBPC3 focuses on restoring missing protein function, while MYH7 involves correcting an altered protein sequence. Ultimately, computational assessment is essential for identifying variants of biological importance and suitability for editing.

VII. BIOINFORMATICS APPROACHES

Bioinformatics provides a framework for connecting clinical genetic data with molecular interpretation and gene-editing design. In HCM research, the first step is to identify genes with sufficiently strong evidence for disease association. Current evidence supports a core group of sarcomeric genes, with MYH7 and MYBPC3 being particularly important. Gene-level evidence should be distinguished from historical gene lists that may contain genes with limited or disputed evidence, because accurate gene selection is essential for downstream variant analysis.

The next step is variant identification and annotation. Variants can be obtained from clinical databases, published studies, sequencing datasets, or curated disease resources. ClinVar provides a public archive of submitted human genomic variants and their asserted relationships to disease, including supporting evidence and classification information (NCBI, 2026). Standardize variant records using HGVS nomenclature and map them to a consistent reference transcript and genome assembly. For MYH7 and MYBPC3, annotation should include nucleotide change, protein consequence, variant type, exon or domain location, population frequency, and reported HCM phenotype.

Population frequency is a crucial filter. A mutation common in a large population may be less compatible with a highly penetrant, rare Mendelian illness; however, frequency limits must be understood in a gene- and disease-specific way. Tools like gnomAD can give population allele frequency information, while ClinVar can provide clinical classifications. Computational analysis should not rely exclusively on database classifications, because submissions may contain conflicting interpretations and the underlying evidence requires independent evaluation (Richards et al., 2015; NCBI, 2026). To determine a mutation's pathogenicity, computational analysis must integrate information on sequence conservation, biochemical properties, population data, clinical segregation, experimental data, and computational mutation-analysis data. The ACMG/AMP structure classifies mutations as pathogenic (or probably pathogenic), of unknown significance, probably non-pathogenic, or non-pathogenic (Richards et al., 2015). In the review paper focused on MYH7 and MYBPC3, it is clear that computational predictions are only one part of the evidence framework, not stand-alone evidence proving that this mutation is pathogenic.

Analyzing the protein level adds another layer of information. The location of the MYH7 variant can place it in the β-myosin motor domain, actin-

interacting regions, or other functionally important regions. Structure modeling can visualize how amino-acid swaps affect local interactions or stability. Advances in protein structure prediction have improved access to structural protein models, although one should interpret predicted models carefully (Jumper et al., 2021). For MYBPC3 assessment, it is important to examine the organization of functional domains, the truncation site, conserved regions, etc.

As a last step in the bioinformatics process, gene editing feasibility needs to be analyzed. For each variant selected for gene editing, assess the guide RNA efficiency by checking whether it targets the variant properly (i.e., whether it is compatible), off-target sites, and distance from the pathogenic nucleotide. The required correction type determines which approach is applicable. For example, for a transition missense variant, it may be appropriate to use a compatible base editor, while a complex insertion/deletion variant might require prime editing or another approach. Candidate guide calculation is needed before any experimental testing; however, these calculations do not guarantee safe and efficient editing in human cardiomyocytes.

Thus, the workflow can be summarized in the following way: HCM gene identification → variant selection → standard annotation → outlining the relevant population → assessment of the pathogenicity → protein/structure analysis → assessment of editing feasibility → experimental prioritization. The pipeline is especially useful for MYH7 and MYBPC3, which include many variants that can be identified using different molecular mechanisms.

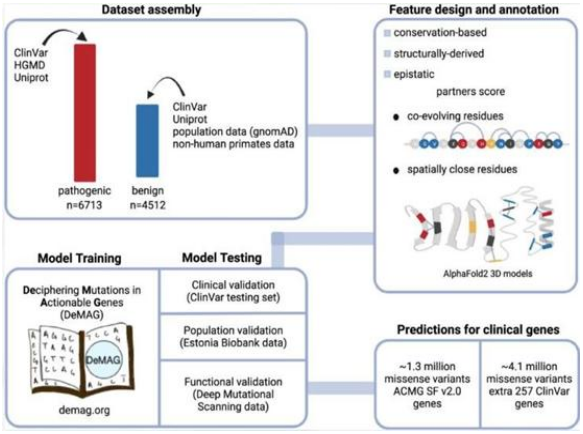


Figure 4: Proposed computational workflow for prioritizing MYH7 and MYBPC3 variants for functional investigation and gene- editing research

VIII. CHALLENGES & LIMITATIONS

Although CRISPR-based methods hold promise for effective HCM therapy, many obstacles still hinder their implementation. One obstacle is delivering gene-editing tools. Specifically, cardiomyocytes are difficult to target; therefore, a sufficiently large proportion of relevant cells must be reached. Different delivery systems, such as viral vectors and lipid nanoparticles, each have pros and cons regarding transport, payload, immunogenicity, delivery timing, and manufacturing.

The second challenge is off-target effects, unintended changes at sites that were not supposed to be edited. The frequency and nature of unintended modifications depend on the editing system, target sequence, delivery method, and experimental conditions. To address this, researchers rely on computational guide design, high-fidelity Cas proteins, delivery system optimization, and sequencing. Prime and base editing can avoid the risks associated with double-stranded break technology but may increase fears of unintended changes to the target DNA.

On-target unintended effects are also important. A correctly targeted double-strand break can generate unexpected insertions, deletions, rearrangements, or large genomic alterations. Base editors may produce bystander edits within the editing window, while prime editors may show variable editing outcomes. Consequently, measuring only the intended nucleotide change is insufficient; therapeutic development requires broader genomic and functional characterization.

Another limitation is editing efficiency. An editing method that works well in cultured cells may perform differently in mature human cardiomyocytes or intact heart tissue. HCM is also heterogeneous, and the same gene may contain variants that require entirely different editing mechanisms. In MYBPC3, for example, correcting a truncating variant and correcting a missense variant are fundamentally different technical problems. MYH7 missense variants similarly require careful consideration of whether precise correction, allele-specific suppression, or another strategy is most appropriate.

The safety of any therapy remains a significant unresolved issue. HCM patients may need treatment at a young age, so corrected cells could survive for many years. Hence, researchers must consider long-term

genomic stability, immune response, unintended biological effects, and the possibility that correcting one gene may not restore the parameters of remodeled cardiac tissue. Manufacturing and costs, however, can also prove to be major translational obstacles. Personalized or variant-specific gene-editing therapies could be technically challenging, requiring highly individualized development and manufacturing and raising the cost of the procedure. Lastly, computational predictions and cell models cannot replicate human heart physiology. Thus, CRISPR-based therapies for HCM should still be regarded as a promising research avenue rather than an established strategy (Ommen et al., 2024; Sami et al., 2025).

IX. FUTURE PERSPECTIVES

Future HCM research will likely integrate genomics, computational biology, stem-cell disease modeling, and precision genome editing. Large-scale variant databases and improved gene-validity frameworks can help distinguish well-established pathogenic variants from variants with limited evidence. At the same time, iPSC-derived cardiomyocytes and isogenic gene-edited controls provide increasingly useful systems for testing the functional consequences of individual MYH7 and MYBPC3 variants. These models link genotype to measurable cellular phenotypes and help identify genetic modifiers that contribute to variable disease expression (Gifford et al., 2023).

Future developments in base editing, prime editing, RNA-targeting systems, advanced delivery systems, and high-fidelity nucleases will broaden the range of variants associated with hypertrophic cardiomyopathy (HCM). Novel computational pipelines that integrate pathogenicity analysis, protein structure, compatibility of the editing window with the disease-causing variant, guide RNA efficiency, predicted off-target activity, and patient-specific genomic information may help prioritize candidates for therapies aimed at correcting congenitally defective genes. However, the clinical application of this approach will require extensive testing under standard laboratory conditions. The objective is not simply gene editing but finding a reproducible correlation between genetic repair, normal sarcomere function, and disease prevention.

X. CONCLUSION

Hypertrophic cardiomyopathy is a genetically complex cardiac disorder in which pathogenic variants affecting sarcomeric proteins can disrupt cardiomyocyte contractile function and contribute to myocardial hypertrophy and associated complications. MYH7 and MYBPC3 are particularly important HCM genes but represent distinct molecular mechanisms: MYH7 variants commonly alter the function of β-myosin heavy chain, whereas MYBPC3 truncating variants frequently reduce functional cardiac myosin-binding protein C. This distinction provides a useful framework for variant-specific computational and experimental investigation. Bioinformatics can help identify and prioritize pathogenic variants, evaluate protein-level consequences, and assess potential CRISPR editing strategies. CRISPR-Cas9, base editing, and prime editing offer increasingly precise tools to investigate and potentially correct disease-associated variants, while patient-derived iPSC-cardiomyocytes provide a powerful platform for functional validation.
Nevertheless, delivery, editing efficiency, off-target and unintended on-target effects, long-term safety, manufacturing, and cost remain significant barriers. Therefore, CRISPR-based correction of MYH7 and MYBPC3 variants should currently be regarded as a promising preclinical research direction. Continued integration of computational genomics, molecular biology, stem-cell models, and genome-editing technologies may help move HCM research toward more individualized and mechanism-based therapeutic strategies.

REFERENCES

[1] V. Anzalone, P. B. Randolph, J. R. Davis, A. A. Sousa, L. W. Koblan, J. M. Levy, P. J. Chen, C. Wilson, G. A. Newby, A. Raguram, and D. R. Liu, “Search-and-replace genome editing without double-strand breaks or donor DNA,” Nature, vol. 576, no. 7785, pp. 149–157, 2019, doi: 10.1038/s41586-019-1711-4.
[2] Circulation Research, vol. 133, no. 2, pp. 108–119, doi: 10.1161/CIRCRESAHA.122.321951.
[3] V. Fontaine, L. Duboscq-Bidot, C. Jouve, M. Hamlin, A. Curjol, V. Briand, P. Janiak, J.-S. Hulot, M.-P. Pruniaux-Harnist, P. Charron, and E.

Villard, "Generation of an iPSC line from an MYH7 R403L mutation carrier with severe hypertrophic cardiomyopathy and isogenic CRISPR/Cas9 corrected control," Stem Cell Research, vol. 52, Art. no. 102245, 2021, doi: 10.1016/j.scr.2021.102245.

[4] A. S. Helms, F. M. Davis, D. Coleman, S. N. Bartolone, A. A. Glazier, F. Pagani, J. M. Yob, S. Sadayappan, E. Pedersen, R. Lyons, M. V. Westfall, R. Jones, M. W. Russell, and S. M. Day, "Sarcomere mutation-specific expression patterns in human hypertrophic cardiomyopathy," Circulation: Cardiovascular Genetics, vol. 7, no. 4, pp. 434–443, 2014, doi: 10.1161/CIRCGENETICS.113.000448.

[5] J. Ingles et al., "Evaluating the clinical validity of hypertrophic cardiomyopathy genes," Circulation: Genomic and Precision Medicine, vol. 12, Art. no. e002460, 2019, doi: 10.1161/CIRCGEN.119.002460.

[6] "iPSC-based modeling of variable clinical presentation in hypertrophic cardiomyopathy." [Author, publication year, journal, and DOI not provided.]

[7] S. Jiménez-Delgado, A. Morillas-García, M. Ortiz-Genga, J. P. Ochoa, D. Carreras, G. J. Pérez, J. L. de la Pompa, R. Brugada, L. Monserrat, R. Barriales-Villa, and A. Raya, 2023. [Title, publication details, and DOI not provided.]

[8] J. Jumper et al., "Highly accurate protein structure prediction with AlphaFold," Nature, vol. 596, no. 7873, pp. 583–589, 2021, doi: 10.1038/s41586-021-03819-2.

[9] K. C. Evanovich, L. Ferrari, V. A. Joglar, J. A. Khan, S. S. Kim, J. J. Kittleson, M. M. Krittanawong, M. W. Martinez, S. Mital, S. S. Naidu, S. Saberi, C. Semsarian, S. Times, and C. B. Waldman, "2024 AHA/ACC/AMSSM/HRS/PACES/SCMR guideline for the management of hypertrophic cardiomyopathy: A report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines," Circulation, vol. 149, no. 23, pp. e1239–e1311, 2024, doi: 10.1161/CIR.0000000000001250.

[10] A. J. Marian, "Molecular genetic basis of hypertrophic cardiomyopathy," Circulation Research, vol. 128, no. 10, pp. 1533–1553, 2021, doi: 10.1161/CIRCRESAHA.121.318346.

[11] National Center for Biotechnology Information (NCBI), "ClinVar: Public archive of reports of relationships among human variations and phenotypes," National Library of Medicine, 2026. [Online]. Available: NCBI ClinVar

[12] S. Richards, N. Aziz, S. Bale, D. Bick, S. Das, J. Gastier-Foster, W. W. Grody, M. Hegde, E. Lyon, E. Spector, K. Voelkerding, and H. L. Rehm, "Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology," Genetics in Medicine, vol. 17, no. 5, pp. 405–424, 2015, doi: 10.1038/gim.2015.30.

[13] N. Sami, M. A. Parikh, W. H. Frishman, and S. J. Peterson, "Clustered regularly interspaced short palindromic repeats genome editing for cardiovascular disease: The future is here," Cardiology in Review, 2025, doi: 10.1097/CRD.0000000000001087.

[14] C. Suay-Corredera and J. Alegre-Cebollada, "The mechanics of the heart: Zooming in on hypertrophic cardiomyopathy and cMyBP-C," *FEBS Letters*, vol. 596, no. 6, pp. 703–746, 2022, doi: 10.1002/1873-3468.14301.