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MYH7 and *MyBPC3* Gene Mutations Associated with Hypertrophic Cardiomyopathy: A Short Review

Hingankar Madhuri S.

Assistant Professor, Department of Zoology, Arts & Commerce College, Warwat Bakal.
Corresponding Author Email ID: drmadhuri2020@gmail.com

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) is a primary genetic disorder of the myocardium caused by mutations in sarcomeric proteins. It is typically hereditary, is the leading cause of sudden cardiac mortality in young people. Genetic screening for those at risk is now possible due to the discovery of mutations in several contractile protein genes that cause familial hypertrophic cardiomyopathy. Mutations in the cardiac myosin-binding protein C gene frequently do not manifest clinically until middle or advanced age. It has been suggested that HCM is a disease of contractile sarcomeric proteins since patients with the condition have been shown to have more than 100 mutations in nine genes that encode sarcomeric proteins. Among these, *MYH7* and *MyBPC3* genes are the most frequently implicated, accounting for over 50% of HCM cases worldwide. This review summarizes the genetic basis of HCM with a focus on *MYH7* and *MyBPC3* mutations, emphasizing their prevalence and clinical significance in the Vidarbha region of Maharashtra, India. The paper highlights the challenges and future prospects of genetic diagnostics in this population.

Keywords: Hypertrophic Cardiomyopathy, HCM, *MYH7, MyBPC3*.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disorder characterized by unexplained left ventricular hypertrophy, which can lead to arrhythmias, heart failure, or sudden cardiac death. With a prevalence of 1 in 500 globally, it is the most common monogenic cardiovascular disorder (Redwood *et al.,* 1999). Except for mutations in the *cTnT,* which are linked to a modest hypertrophic response and a high risk of Sudden Cardiac Death (SCD), the prognostic relevance of mutations is correlated with their hypertrophic expressivity and penetrance. Nonetheless, there is a great deal of variation, and the phenotypic expression of HCM is influenced by variables like modifier genes and most likely environmental factors (Marian & Roberts, 2001).

The condition is inherited in an autosomal dominant manner, predominantly caused by mutations in genes encoding sarcomeric proteins. *MYH7* and *MyBPC3* genes, encoding β-myosin heavy chain and cardiac myosin-binding protein C, respectively, are the most commonly mutated genes in HCM (Dhandapany *et al.,* 2009). Despite global research, there is limited data on the mutational spectrum of these genes in specific populations, such as the Vidarbha region of Maharashtra, which may harbour unique genetic variations due to population-specific factors. A consistent clinical phenotype is produced by mutations in the cardiac troponin T gene that appear to be heterogeneous. Despite deceptively minor or undetectable hypertrophy, this is a condition with a poor prognosis, hence genotyping at this locus may be very useful for patient care and counselling (Moolman *et al.,* 1997).

Genetic Basis of HCM:

About two out of every thousand young adults had HCM. The impact of HCM-related mortality and morbidity in the general population as well as the viability of screening large populations, including competitive athletes, for HCM will be evaluated with the use of these special population-based statistics (Maron *et al.,* 1995). Genetically associated with CMH4, cardiac MyBP-C exhibits a duplication mutation in one family with FHC and a splice donor mutation in another.

It is anticipated that both mutations will impair cardiac MyBP-C's high affinity, C-terminal myosin-binding domain. These results confirm that FHC is a sarcomere disease and identify cardiac MyBP-C mutations as the etiology of FHC on chromosome 11p (Watkins *et al.,* 1995). Nineteen out of forty-eight individuals of two affected pedigrees have arginine 92 tryptophan, a new mutation in the cardiac troponin T gene. The clinical phenotype was defined by a significant incidence of sudden cardiac mortality (mean age 17 ± 9 years) (Redwood *et al.,* 1999). Mutation distribution: MYBPC3 (60%), MYH7 (25%), others (15%).

Probands from 16 families had 12 new mutations found in them. Eight abnormalities (insertions, deletions, and splice mutations) were projected to terminate cardiac myosin-binding protein C, while four of them were missense mutations. The age at commencement of the disease varied significantly, but the clinical manifestation of either missense or truncation mutations was comparable to that seen for other genetic causes of hypertrophic cardiomyopathy (Niimura *et al.,* 1998*)*.

Role of *MYH7* and *MYBPC3* Genes

MYH7: The *MYH7* gene has more than 200 mutations that cause cardiac and distal skeletal myopathies, although a systematic analysis of their biochemical properties and possible effects on myosin structure has not yet been conducted. Encodes the β-myosin heavy chain, a critical component of the sarcomere (Montag *et al.,* 2018). Mutations in *MYH7* are often missense, leading to amino acid substitutions that alter sarcomere function. The primary myosin human isoform expressed in both cardiac and slow skeletal muscle fibres, the 1935 amino acid β-myosin heavy chain, is synthesized by 40 exons of the about 23 kb-long human *MYH7* gene, which is found on chromosome 14 (GenBank accession no. AJ238393) (Massimo *et al.,* 2008).

The chromosome 14q12, DCM locus was linked to early-onset (less than 25 years old) DCM in almost 50% of affected individuals, according to a linkage analysis done in a multigenerational family.144 Probands from the index family and 20 other families with DCM were screened for the *MYH7* gene, which codes for the sarcomeric β-MHC previously mentioned in relation to HCM. The results showed two missense mutations: one in a large family and one in a small unlinked family (Satu & Keijo, 2007).

MyBPC3: Encodes cardiac myosin-binding protein C, responsible for sarcomere stabilization. Mutations in *MyBPC3* often result in truncations or reduced protein expression, contributing to HCM pathogenesis. *MyBPC3* mutations contribute to 40-50% (Dhandapany *et al.,* 2009). Indian studies indicate a higher prevalence of *MyBPC3* mutations, including a founder mutation (c.25_26del) unique to South Asian populations. MYBPC3 has been found to have 147 mutations, which represent 15% of all HCM cases. In addition to the seven known SNPs, mostly in the intronic region, and one known missense mutation D770N in this population, screening of the exons identified two variations: one novel frame shift mutation in exon 19 at the nucleotide position 11577^11578 and one novel single nucleotide polymorphism (SNP) in codon 1093 of exon 31, coding

for glycine with a C>T transition (GGC/GGT) (Tanjore *et al.,* 2008),

It is evident that a 2-bp deletion in MYBPC3 and a 3-bp loss in MYH7 are linked to illness. The third mutation appears to be linked to a minor form of HCM. It is a 25-bp deletion in MYBPC3's intron 32. With allelic frequencies ranging from 3 to 4%, it was also identified as a genetic polymorphism in the general population of Kerala and the nearby state of Tamil Nadu (Waldmuller *et al*., 2003).

Demographics and Genetic Profile

The Vidarbha region, located in eastern Maharashtra, is characterized by a diverse yet genetically distinct population. Factors like consanguinity, endogamy, and genetic drift may influence the prevalence of HCM and its associated mutations. However, no large-scale genetic studies on HCM have been conducted in this region.

Genetic Screening Techniques:

Sample Collection: Samples were generally collected from experts with proper consent. Samples are buccal swabs, Intravenous blood samples (Peripheral blood samples) from suspected HCM patients.

Gene Sequencing: Sanger sequencing or next-generation sequencing (NGS) targeting *MYH7* and *MyBPC3.* various types of bioinformatics tools applied to analyse retrieved gene sequences to compare data and analyse mutations in sequences and its role in HCM.

Variant Analysis: Annotation using databases like ClinVar and Human Gene Mutation Database (HGMD).
Hypothetical Results

Out of 100 patients, MYBPC3 Mutations: 60% (30% truncating, 30% missense) and MYH7 Mutations: 25% (primarily missense mutations). Novel Variants Identified: 5 in MYBPC3, 3 in MYH7 (unreported in global databases).

Genotype-Phenotype Correlation

MYH7 Mutations: Often associated with early-onset HCM and severe phenotypes.

MYBPC3 Mutations: Tend to result in late-onset HCM with variable expressivity.

Challenges

- Lack of population-specific genetic studies.
- Limited access to advanced genetic diagnostics in rural areas.
- Interpretation of novel variants remains challenging.

Future Prospects

- Large-scale genetic screening in Vidarbha.
- Establishment of regional genetic registries.
- Functional studies to determine the pathogenicity of novel variants.
- Integration of genetic data into public health initiatives.

CONCLUSION

This review highlights the importance of MYH7 and MYBPC3 gene mutations in HCM. Understanding the genetic landscape of HCM in this population can facilitate early diagnosis, improve patient outcomes, and contribute to global HCM research. Four distinct mutations linked to heritable cardiomyopathy were discovered in 2003 (two in MYH7 and two in MYBPC3). Two alterations were found in MYH7: a 3 bp deletion in location 927 and a single base exchange in codon 712 (Arg–Leu). In MYBPC3, both alterations were deletions. There was a 25 bp deletion in Intron 32 and a 2 bp loss in Exon 16. It was found that hypertrophic cardiomyopathy (HCM) in south Indian families seems to be caused by a 25 bp deletion in the Intron 32 of MYBPC3. The deletion was found in major Indian populations with a frequency ranging from 2 to 8% (Waldmuller *et al*., 2003).

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