Original Article

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TPM1 Gene Trend among Concentric Hypertrophic Cardiomyopathy Patients in Tertiary Care Hospitals

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Abstract

Background: TPM1 (Alpha Tropomyosin Protein) gene mutations were investigated in concentric HCM (Hypertrophic Cardiomyopathy) patients from tertiary hospitals, focusing on exons 5, 7, and 8—regions harboring a third of known pathogenic variants. HCM is an autosomal dominant disorder with diverse presentations, associated with mutations in genes like MYH7, MyBPC3, TNNT2 and TPM1. Located on chromosome 15q22.2, TPM1 encodes a crucial contractile protein in myocytes; its mutations may disrupt actin-tropomyosin interaction, leading to atypical hypertrophy patterns. The study aimed to identify such mutations in concentric HCM patients within our population.

Material and methods: In this cross-sectional study, ten adult patients diagnosed with concentric HCM (90% male, 10% female, average age 44) were included. Genomic DNA was isolated from peripheral blood samples, and the targeted region of the TPM1 gene (2078 bp fragment encompassing exons 5, 7 and 8) was amplified using PCR and sequenced by Sanger sequencing.

Results: Data analysis using Geneious® R11 and BLAST tool by NCBI revealed no pathogenic variants in the TPM1 gene within the studied region in any of the ten patients.

Conclusion: The absence of mutations in this study may be due to the small targeted region, focus on exonic variants, or low prevalence of TPM1 mutations in the Bangladeshi population. As TPM1 mutations account for only 5% of HCM cases globally, further research using whole-genome sequencing (NGS) is recommended to address these limitations.

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Introduction

From a genetic perspective, HCM shows the autosomal dominant trait pattern of inheritance.[1-3] Several genetic mutations have already been identified as responsible for this disease.[3] Among them, some mutations (Those of MYH7, MyBPC3, TNNT2, TPM1, TNNT3, etc.) are more responsible for the clinical heterogeneity of HCM[4]. The expression of the disease could be ranging from severe hypertrophy with less risk of SCD to mild hypertrophy with a high risk of SCD. The penetrance of this disease-causing mutations are variable and have an increased chance of transmission along with age of the carrier.[5, 6]

Tropomyosin-alpha (TPM1) is the gene which is responsible for synthesizing tropomyosin-alpha protein, which is a thin filament within the myocytes. It is one of the principal components of the contractile system.[7] TPM1 is situated on 15q22.2 position with an exon count of fifteen. Among these fifteen exons 3, 4, 5, 7 and 8 are found in all the splice variants and others are alternatively spliced in different organs.[8] Tropomyosin is composed of two alpha protein arranged in a coil. It is polymerized end to end with the groves of actin providing stability.[7] Mutation of this gene is prevalent in familial HCM. A study by Watkins et al. concluded that variations in the TPM1 cause HCM in about 3% of familial HCM cases.[9] Mutation of TPM1 destabilizes the active state of actin or reduces the binding ability of tropomyosin.[10,11] Patients with thin filament mutations more often show atypically distributed hypertrophy. including the concentric and apical patterns.[12]

The morphology of the diseased heart depends on the variety of genetic mutations. Attempts of studying HCM patients in our country has not got into focus yet. The most common mutation has been found in MyBPC and MYH7 gene. These two whole genes analysis with Next Generation

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Sequencing (NGS) has been carried out in the Department of Anatomy, Bangladesh Medical University, Dhaka.[13] The next common genes found to be mutated in HCM is TPM1, TNNT2, TNNI3, LMN1 etc. The features of the TPM1 gene mutation are similar to the characteristics of the concentric HCM. So, this study was directed to find if there any TPM1 gene mutation in the concentric HCM patients in our population. One-third of the clinically detected pathogenic mutations of the TPM1 gene is situated in the region of the exon 5, 7 and 8 and this area would be the focus of the study. The data of this research could be valuable in the understanding of the disease pattern in our population.

Materials and methods

This cross-sectional study was conducted in the Department of Anatomy at Bangladesh Medical University (BMU) following approval from the Institutional Review Board. Patients were recruited from various hospitals, clinics and private practices over a study period from August 2017 to February 2019. Preliminary selection of the patients was made if the patients had already been diagnosed as a case of concentric HCM by the cardiologists.

A selection checklist was made according to the inclusion and exclusion criteria. HCM, defined as an echocardiographically confirmed left ventricular wall thickness ≥15 mm in any myocardial segment by a registered cardiologist, in adult individuals (≥18 years) of Bangladeshi nationality and Bengali ethnicity, regardless of sex, was considered as the inclusion criteria. Participants with a history of myocardial infarction, poorly controlled hypertension, infiltrative cardiac diseases or valvular disorders that could mimic HCM were excluded. Additionally, individuals with diabetes mellitus, thyroid disorders or pituitary diseases that might influence HCM-related changes were also excluded. After fulfilling the patient selection criteria, informed written consent was obtained from ten participants. Following consent, a detailed HCM-specific data sheet was completed using patient-provided information. Clinical features and echocardiographic measurements were systematically documented. Peripheral blood samples were collected and genomic DNA was isolated from each subject. After quantifying and quality measurement of collected DNAs, targeted region of the TPM1 gene amplicons were procudes by PCR and confirmed by gel electrophoresis.

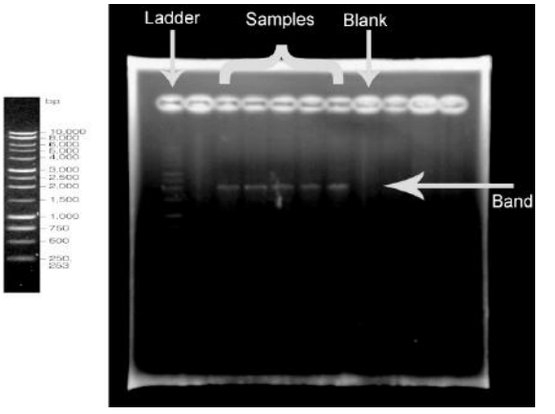

Figure 1 The band is appearing in gel documentation method was between 2000bp to 2500bp marker of the 1kb ladder. The first column of the gel documentation contains standardized 1kb ladder DNA

Sanger's sequencing was used to get electropherogram data. Data was analyzed using the Geneious® R11 software, and revalidated with BLAST tool by NCBI. Statistical Package for Social Science (SPSS) version 23.0 (IBM Corporation) was used to analyze the socio-demographic data.

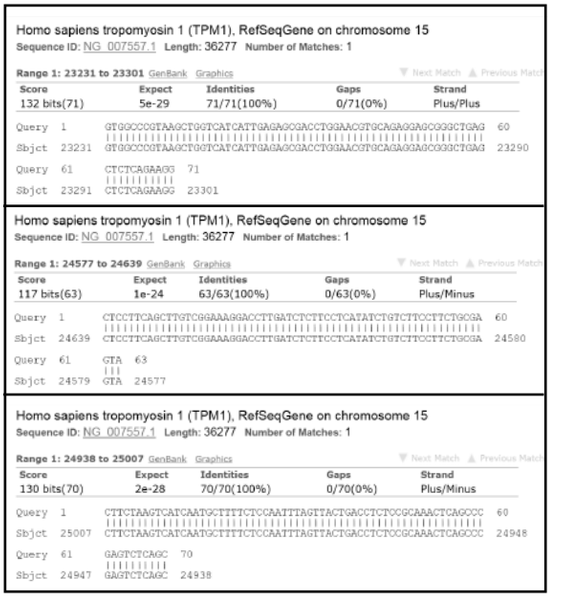

Figure 2 Alignment of sample query sequences of exon 5, 7 and 8 of TPM1 gene from the sample with that of the reference sequence of TPM1 gene given by NCBI, using BLAST tool from NCBI

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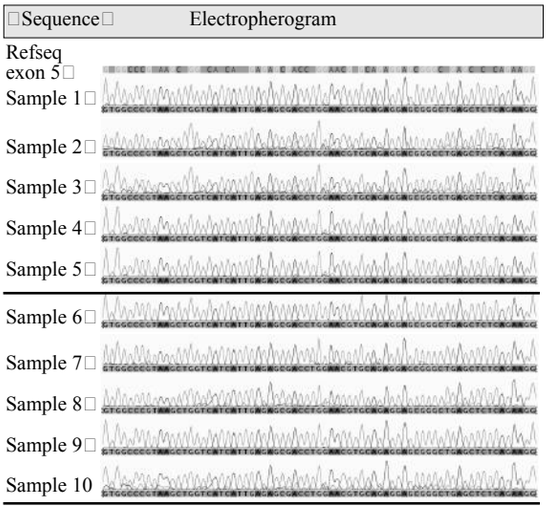

Figure 3 Electropherogram of exon 5 of TPM1 gene of TEN patients

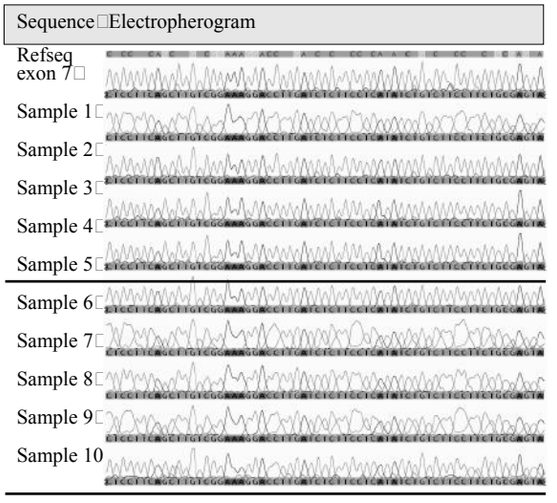

Figure 4 Electropherogram of exon 7 of TPM1 gene of TEN patients

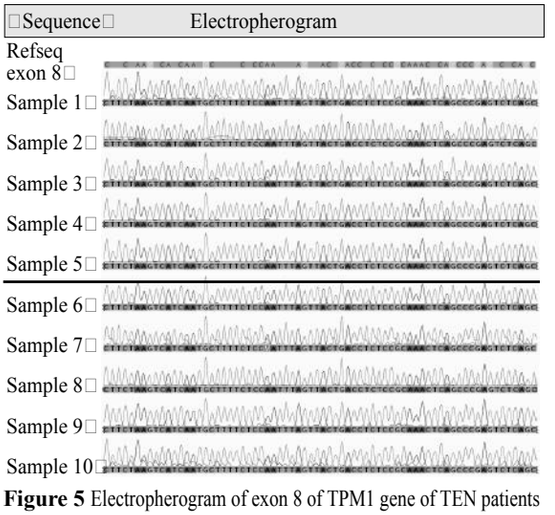

Figure 5 Electropherogram of exon 8 of TPM1 gene of TEN patients

Results

Ten patients was found with diagnosed concentric HCM. Among them 9 (90%) were male, and 1 (10%) were female. All the patients were adults and had an average age was around 44 years. Venous blood was collected from them. Their DNA was analyzed to find mutations in exon 5, 7 and 8 of TPM1 gene.

PCR was done successfully for the desired fragment that included exon 5, 7 and 8 of TPM1 gene. The fragment was 2078 bp in length, and the exons were 71 bp, 60 bp and 70 bp in length respectively.

TPM1 gene is located on the loci 22 of the long arm of chromosome 15. The target region extended from 15:63060778 to 15:63062855 nucleotide region. The fragment was sequenced by capillary electrophoresis in ABI 3730 Sanger sequencer. Raw sequenced data were analyzed with the reference sequence (RefSeq) of TPM1 (Gene ID TPM1–7168) gene from NCBI with the software Geneious® R11 and BLAST tool by NCBI.

The present study showed no pathogenic variant in the ten concentric HCM patients.

Discussion

HCM is predominantly an autosomal dominant inherited disease with sporadic and other inheritance patterns.[1] More than 1400 variants, in 250 genes, in more than 18 chromosomes have already been identified to be responsible for the disease.[14] The most common mutation has been found in MyBPC gene followed by MYH7 gene. Complete sequencing of these two genes with NGS has already been done in the Department of Anatomy, Bangladesh Medical University, Dhaka.[13] They found a total of sixteen known clinically significant variants in these two genes from sixty HCM patients. But, no pathogenic variant was found. The study was done with a span of three years. Following these two genes, the next common genes found to be mutated in HCM is TPM1, TNNT2, TNNI3, LMN1, etc. So, TPM1 was selected as the target gene for this study. The objective of this study was to identify mutations in the TPM1 gene in concentric HCM patients. Ten concentric HCM patients were selected for genetic analysis. Due to time and financial constraints, an area of TPM1 gene was targeted for investigation.

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TPM1 gene mutation plays a significant role in HCM.[15] Eleven missense mutations in the TPM1 gene have been shown to cause hypertrophic cardiomyopathy (HCM). These variations include Asp175Asn and Glu180Gly (Both in exon 5). These mutations show a decrease in the rate of cardiac contraction and relaxation and in HCM Asp175Asn and Glu180Gly mutations are responsible for amino acid substitutions. These amino acid changes are likely to cause a local change in the tropomyosin conformation, which can be a structural alteration.

Only a few TPM1 mutations had been reported, causing either HCM or DCM.[16] Two mutations in exon 5 have been associated with a transition from severe hypertrophy to DCM (Glu180Val) and with mild LV hypertrophy but poor prognosis (Glu180Gly). Also in the same protein domain, a mutational hot spot at position Asp175Asn (Exon 5) has been identified in five unrelated families with HCM. The Asp175Asn mutation was studied in three families and showed full penetrance.

In identified mutations in human TPM1, out of thirty, four (Glu40Lys, Glu54Lys, Asp175Asn, Glu180Gly) have been characterized more than the others.[17] Glu40Lys and Glu54Lys (Exon 3) are DCM-causing. These mutants decrease calcium sensitivity in ATPase and lower tension at high Ca^{2+} concentrations. The HCM-causing mutants Asp175Asn and Glu180Gly (exon 5) show opposite changes to the DCM mutants.

A study found that the TPM1 gene mutation was present in all clinically affected individuals from five families.[18] However, none of these abnormalities were present in over 200 chromosomes from unrelated healthy individuals.

The Glu180Gly and Asp175Asn (Both in exon 5) mutations do show novel features like binding actin with a weaker affinity.[10]

The TPM1 gene, the Asp175Asn (Exon 5) mutation was found in a case of a patient diagnosed at age 41 years with severe hypertrophy (32 mm)[4]. His son and his brother had this mutation and hypertrophy of 27 and 20 mm. Three of six known TPM1 gene mutations involve independent occurrences of the same nucleotide alteration. This may reflect an increased tendency for this particular residue to mutate. The mutation identified in exon 5 (Asp75Asn) of the TPM1 gene, occurs near the calcium-dependent troponin T binding domain.

An experimental mouse model using Glu180Gly for assessing morphological changes in the hearts of the transgenic mouses.[19] An autopsy revealed concentric hypertrophy of left ventricle. Mice started to die from 4 months of age. 70% of the mice died within five months and the maximum period of survival was six months. For contrast, a healthy transgenic mouse he used can live up to two years.

Limitations

Not finding any mutation in this study might be due to several reasons, like-

- A small region was targeted.
- Focusing only on the exonic variants.
- Presence of low prevalence of the TPM1 gene mutation in Bangali Bangladeshi population.

Conclusion

The target region of this study was from 15:63060778 to 15:63062855 nucleotide location. Exon 5, 6, 7 and 8 were present here, in which 5, 7 and 8 were the constantly spliced exons for synthesizing cardiac variant of TPM1 gene. Most commonly found a pathogenic variant of TPM1 gene is located in exon 5, and about one-third of the detected pathogenic variants are present in the exon 5, 7 and 8.

The studies showed TPM1 gene mutation expresses severe HCM with full penetrance while inheriting the disease, but the overall rate of TPM1 gene mutation is rare. Worldwide TPM1 gene mutation is only 5% of the total mutations identified to be responsible for HCM. The highest percentage of occurrence is found in the Finnish.[16]

Some of these limitations could have been overcome by doing a whole genome sequencing with NGS. NGS can handle a much larger segment of DNA at the same time, than that of Sanger sequencing method. It is a cheaper and faster process in case of large DNA sequence. It can gather multiple sample data at once, but the processing of that data can be time-consuming. Moreover, Sanger sequencing is required to fill in the gaps in the data from NGS. Also, it generates a high number of variants of uncertain significance. Though Sanger sequencing is comparatively

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expensive, it is financially feasible for the small sized sample. But, it is accurate and precise. Therefore, Sanger sequencing was the choice of method in this study.

Recommendations

A study with larger population and extended area of TPM1 gene analysis is recommended to see proper trend.

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Contribution of authors

RS-Conception, acquisition of data, data analysis, drafting & final approval.

MM-Design, data analysis, interpretation of data, critical revision & final approval.

JB-Data analysis, critical revision & final approval.

MS-Acquisition of data, interpretation of data, drafting & final approval.

SN-Conception, design, critical revision & final approval.

Disclosure

All the authors declared no competing interests.

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