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Mutations in Troponin I (TNNI3) gene and their association in Indian HCM patients

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Background: Troponin I (TNNI3) is the inhibitory subunit of the thin filament regulatory complex Troponin, which confers calcium sensitivity to striated muscle actomyosin ATPase activity. Mutations (2-7%) in this gene were reported in Hypertrophic Cardio Myopathy (HCM) patients. However, the frequencies of mutations and associated clinical presentation have not been established in Indian cardiomyopathy patients, hence we have undertaken this study.

Methods: We have sequenced all the exons, including the exon-intron boundaries of TNNI3 gene in 101 HCM patients, along with 160 healthy controls, inhabited in the same geographical region of southern India.

Results: Our study revealed a total of 16 mutations. Interestingly, we have observed Arginine to Glutamine (R to Q) mutation at 3 positions 98,141 and 162, exclusively in HCM patients with family history of sudden cardiac death. The novel R98Q was observed in a severe Hypertrophic Obstructive Cardio Myopathy patient (HOCM). The R141Q mutation was observed in two familial cases of severe Asymmetric Septal Hypertrophy (ASH++). The R162Q mutation was observed in a ASH++ patient with mean septal thickness of 29 mm and have also consists of allelic heterogeneity by means of having one more synonymous (E179E) mutation at g.4797:G A: in the same exon 7, which replaces a very frequent codon (GAG: 85%) with a rare codon (GAA: 14%). Screening for R162Q mutation in all the available family members revealed its presence in 9 individuals, including 7 with allelic heterogeneity (R162Q and E179E) of which 4 were severely affected. We also found 2 novel SNPs, (g.2653; G A and g.4003 C T) exclusively in HCM and in silico analysis of these SNPs have predicted to cause defect in recognition/binding sites for proteins responsible for proper splicing.

Conclusion: Our study has provided valuable information regarding the prevalence of TNNI3 mutations in Indian HCM patients and its risk assessment; these will help in genetic counselling and to adopt appropriate treatment strategies.

Keywords: TNNI3-Troponin I, Cardiomyopathy, SNPs, HCM, Indians, Mutations.

Biography

Deepa Selvi Rani is from CSIR-Centre for Cellular and Molecular Biology, Hyderabad, India. She is interested in understanding the Genetic basis of Cardiovascular Diseases, Male infertility, Mitochondrial disorders and the Origin of Modern Humans. She has two master's degrees, MSc in Biochemistry and MSc in Biotechnology. Her PhD work was on "Molecular Studies in Cardiomyopathies and Noonan Syndrome." She identified several mutations in sarcomere protein genes causing cardiomyopathies and sudden cardiac arrest in Indian patients. To understand the disease specifically, she studied DNA sequence variations and their association in patients, their molecular mechanisms, which are relevant to pharmacogenomic studies and personalized medicine. She is an enthusiastic, dedicated, outstanding researcher and published more than 60 papers in peer-reviewed International Journals. She has a 23 h-index, 41 i10-index and a total of 1800 citations.

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