Deepa Selvi Rani

CSIR-Centre for Cellular and Molecular Biology
India

Novel amino acid substitutions in β-Myosin and their impact in disease phenotype

Abstract:

Background: Heart failure is a hallmark of severe hypertrophic (HCM) and dilated (DCM) cardiomyopathies. Mutations in the β-MYH7 gene are the known cause of cardiomyopathies (CM), yet the mechanism is not fully understood.

Methods: We sequenced the β-MYH7 gene in 101 HCM and 147 DCM patients and 207 ethnically matched healthy controls to detect the frequency of mutations and their association.

Results: Our study revealed 45 variations, of which 29 were novel, including three splice-sites variations [(IVS17+2T) T>G, (IVS7-1G) G>A, (IVS19-1G) G>A], and three frame-shifts mutations; [Asn602 (A-ins), Asn676 (T-del), Gln789 (A-del)]. In the present study, we observed nine missense mutations [p.His358Leu, p.Met362Leu, p.Ser384Tyr, p.Ala423Thr, p.Val431Met, p.Phe510Leu, p.Glu525Lys, p.Arg723His, p.Asp896Asn]. Except for the p.Ala423Thr, eight other amino acids in the head motor domain of β-MYH7 are evolutionarily conserved across many species. All eight variations were predicted pathogenic by Polymorphism phenotyping v2 (Polyphen-2) and Sorting Intolerant From Tolerant (SIFT) bioinformatics tools. In addition, these mutants; p.His358Leu, p.Met362Leu, p.Ser384Tyr, p.Ala423Thr, p.Val431Met, p.Phe510Leu, p.Glu525Lys, p.Arg723His, displayed rootmean-square deviation (RMSD) of ~2.55A0, ~1.85A0, ~1.24A0, ~1.17A0, ~3.90A0, ~3.36A0, ~0.77A0, and ~3.86A0, respectively.

Conclusion: In our study, we have identified numerous novel, unique, and rare mutations in the βMYH7 gene, a finding that is exclusive to Indian cardiomyopathy patients. We have shown how each mutant (missense) uniquely disrupts a critical network of non-bonding interactions at the mutation site (molecular level), potentially contributing to the cardiomyopathy (CM) disease phenotype. These findings not only deepen our understanding of the molecular bases of the disease but also hold promise for improved diagnosis and the development of novel therapeutic strategies (personalized medicine).

Biography

Deepa Selvi Rani is from CCMB-CSIR, 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, M.Sc. in Biochemistry and M.Sc. in Biotechnology. Her Ph.D. work was on "Molecular Studies in Cardiomyopathies and Noonan Syndrome." She identified several mutations in sarcomere protein genes causing cardiomyopathies and sudden cardiac arrest. To understand the disease specifically, she studied their molecular mechanisms, which are relevant to pharmacogenomic studies and personalized medicine. Dr. Rani is an enthusiastic, dedicated, outstanding researcher and published 50 papers in peer-reviewed International Journals.