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Novel Single Residue Mutation in the B-*MYH7* gene and their impact in Cardiomyopathies

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Background:

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

Methods:

We sequenced the B-*MYH7* gene in 101 HCM and 147 DCM patients along with 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 3 splice-sites variations; [(IVS17+2T) T>G, (IVS7-1G) G>A, (IVS19-1G) G>A], and 3 frame-shifts mutations; [Asn602 (A-ins), Asn676 (T-del), Gln789 (A-del)]. Interestingly, we observed 9 missense mutations; [p.His358Leu, p.Met362Leu, p.Ser384Tyr, p.Ala423Thr, p.Val431Met, p.Phe510Leu, p.Glu525Lys, p.Arg723His, p.Asp896Asn]. Except p.Ala423Thr remaining 7 missense mutations in the head motor domain of B-*MYH7* were evolutionarily conserved across many species. These 7 mutants 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 root-mean-square deviation (RMSD) of ~2.55A0, ~1.85A0, ~1.24A0, ~1.17A0, ~3.90A0, ~3.36A0, ~0.77A0, and ~3.86A0, respectively.

Conclusion:

In the present study, we detected numerous novel, unique, and rare mutations in the B-*MYH7* gene exclusively in Indian cardiomyopathy patients. Here, we demonstrate how each mutant (missense) uniquely disrupts a critical network of non-bonding interactions at the mutation site (molecular level) and may contribute to cardiomyopathy (CM). Therefore, our findings may provide insight to understand the molecular bases of disease, diagnosis and promote novel therapeutic strategies (personalized medicine).

Keywords:

"B-*MYH7*", "Cardiomyopathy", "homology models", "3D structure", "Sarcomere genes" "HCM", "DCM".

Recent Publications:

Deepa Selvi Rani, Kumar AV, Nallari P, Sampathkumar K, Dhandapany PS, Narasimhan C, Rathinavel A, Thangaraj K. (2021). Novel mutations in B-*MYH7* gene in Indian patients with dilated cardiomyopathy, CJC Open. DOI: 10.1055/s-0039-1694829.

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Biography

Dr. 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. She has a 22 h-index with a total of 1602 citations

https://scholar.google.co.in/citations?hl=en&user=qUgZf-kAAAAJ&view_op=list_works&sortby=pubdate.

WIN CARS has recently awarded her "Servier Women Researchers Award" in 2019

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