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## Combination of Genetic Screening and Molecular Dynamics as a Useful Tool for Identification of Disease-Related Mutations: ZASP PDZ Domain G54S Mutation Case

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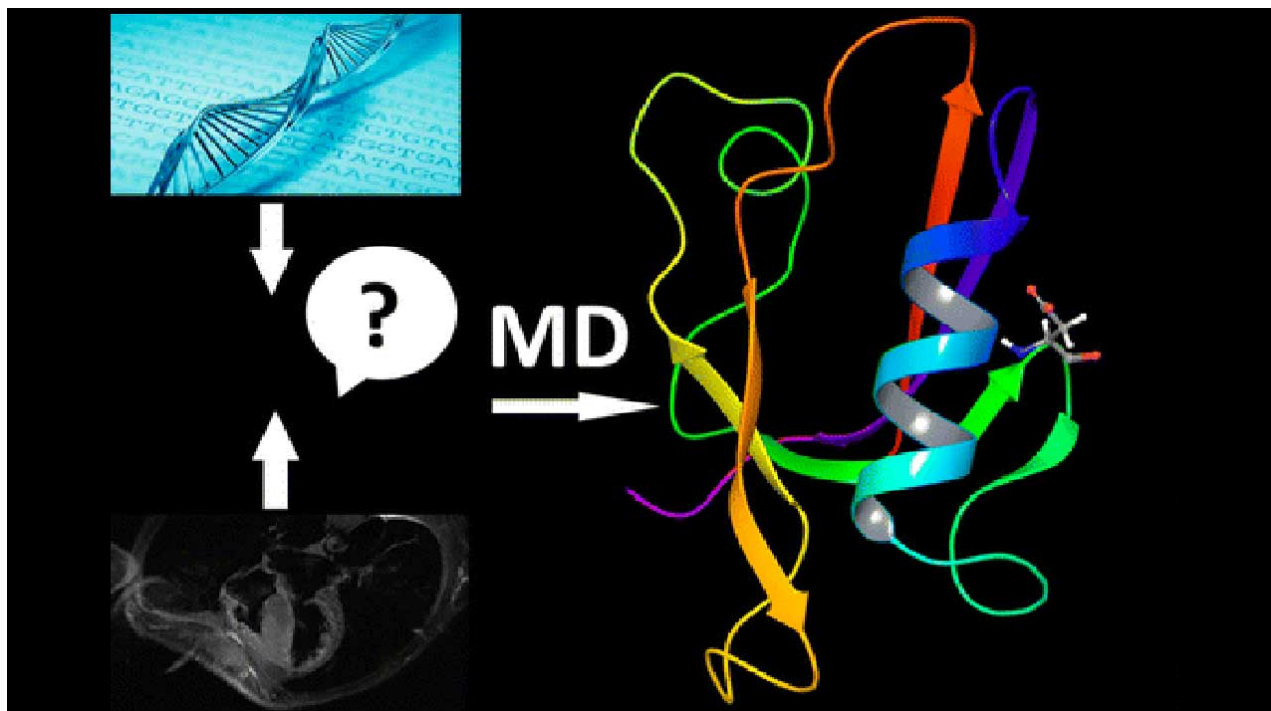
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## Abstract



Cypher/ZASP (LDB3 gene) is known to interact with a network of proteins. It binds to  $\alpha$ -actinin and the calcium voltage channels (LTCC) via its PDZ domain. Here we report the identification of a highly conserved ZASP G54S mutation classified as a variant of unknown significance in a sample of an adult with hypertrophic cardiomyopathy (HCM). The initial bioinformatics calculations strongly evaluated G54S as damaging. Furthermore, we employed accelerated and classical molecular dynamics and free energy calculations to study the structural impact of this mutation on the ZASP apo form and to address the question of whether it can be linked to HCM. Seventeen independent MD runs and simulations of 2.5  $\mu$ s total were performed and showed that G54S perturbs the  $\alpha$ 2 helix position via destabilization of the adjacent loop linked to the  $\beta$ 5 sheet. This also leads to the formation of a strong H-bond between peptide target residues Leu17 and Gln66, thus restricting both the  $\alpha$ -actinin2 and LTCC C-terminal peptides to access their natural binding site and reducing in this way their binding capacity. On the basis of these observations and the adult's clinical data, we propose that ZASPG54S and presumably other ZASP PDZ domain mutations can cause HCM. To the best of our knowledge, this is the first reported ZASP PDZ domain mutation that might be linked to HCM. The integrated workflow used in this study can be applied for the identification and description of other mutations that might be related to particular diseases.

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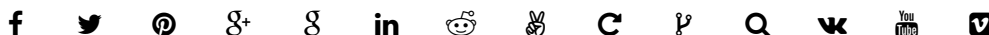
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