Systematic investigation of predicted effect of nonsynonymous SNPs in human prion protein gene: a molecular modeling and molecular dynamics study.

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Abstract

Nonsynonymous mutations in the human prion protein (HuPrP) gene contribute to the conversion of HuPrP(C) to HuPrP(Sc) and amyloid formation which in turn leads to prion diseases such as familial Creutzfeldt-Jakob disease and Gerstmann-Straussler-Scheinker disease. In order to better understand and predict the role of HuPrP mutations, we developed the following procedure: first, we consulted the Human Genome Variation database and dbSNP databases, and we reviewed literature for the retrieval of aggregation-related nsSNPs of the HuPrP gene. Next, we used three different methods - Polymorphism Phenotyping (PolyPhen), PANTHER, and Auto-Mute - to predict the effect of nsSNPs on the phenotype. We compared the predictions against experimentally reported effects of these nsSNPs to evaluate the accuracy of the three methods: PolyPhen predicted 17 out of 22 nsSNPs as "probably damaging" or "possibly damaging"; PANTHER predicted 8 out of 22 nsSNPs as "Deleterious"; and Auto-Mute predicted 9 out of 20 nsSNPs as "Disease". Finally, structural analyses of the native protein against mutated models were investigated using molecular modeling and molecular dynamics (MD) simulation methods. In addition to comparing predictor methods, our results show the applicability of our procedure for the prediction of damaging nsSNPs. Our study also
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elucidates the obvious relationship between predicted values of aggregation-related nsSNPs in HuPrP gene and molecular modeling and MD simulations results. In conclusion, this procedure would enable researchers to select outstanding candidates for extensive MD simulations in order to decipher more details of HuPrP aggregation. An animated interactive 3D complement (I3DC) is available in Proteopedia at http://proteopedia.org/w/Journal:JBSD:34.

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