

HUMAN TP53 POINT MUTATIONS: STRUCTURAL ANALYSIS BY MOLECULAR MODELING

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TP53 encodes p53, a nuclear phosphoprotein with cancer-inhibiting properties. Mutations in the p53 are associated with more than 50% human cancers, and 90% of these affect p53-DNA interactions, resulting in a partial or complete loss of transactivation functions.

In theory, it should be possible to restore at least some functional activity of p53 mutants by enhancing the stability of the protein in its folded state, and/or providing additional DNA contacts. However, so far, the exploitation of the available clinical data has been hampered by our limited understanding of the structural and functional characteristics of the individual p53 mutants.

The work presented here is the first attempt to exploit the knowledge available on p53 protein structure and the power of sophisticated molecular modeling techniques to classify the various types of mutants into specific categories. To this purpose, we obtained a 3D molecular model of p53 starting from the relevant human p53 crystal structure by applying a relaxation procedure based on AMBER force field and GB/SA continuum solvation model. Accordingly, the following 20 cancer-associated mutants that are distributed throughout the core domain and are representative of the p53 mutation database have been considered and modeled: R175H M237I C238Y C242S R248Q R273H F134L G245S R249S R282W R282G V143A L145Q P151S V157F I195T Y220C I232T I255F F270C

The results obtained so far revealed that, in agreement with the experimental findings, all mutants are destabilized with respect to the WT, and allowed us to rationalize the data set of mutations considered into 4 different classes, characterized by well-defined patterns of energy-structure relationship.

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