# Frequent pathological human mutations: a survey

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**Abstract**: We analyzed some mutations from dbSNP database which were known to be pathological, but are relatively frequent in humans with the intention of testing PolyPhen-2's efficiency on particularly difficult cases. We proved that the majority of these mutations could benefit from a therapeutic approach with pharmacological chaperones.

Exon-sequencing will soon become a common practice in disease diagnoses. All the steps that follow the acquisition of the sequence must be optimized if we wish to find one or more mutations associated to the pathological phenotype. We believe the diagnosis will expand from only working on early onset and severe phenotype diseases to working on late onset and mild phenotype diseases too. Therefore the cases of research on mutations that cause little damage to the mutant protein will get more and more frequent. One of the most common programs used to distinguish pathological mutations is PolyPhen-2[1]. PolyPhen-2 algorithm classifies variations using eight sequence-based and three structure-based predictive features. We analyzed cases that may be found in clinical practice with a relative frequency (minor allele frequency MAF>0). We found that in half of the cases PolyPhen-2 erroneously classifies these mutations as benign or neutral. The percentage of false negatives does not decrease when the 3D structure of the protein is known and PolyPhen-2 can also use three structure-based predictive features. The prediction becomes more precise when

the notation in Swiss-Prot is available. At least one fourth of the cases erroneously classified by PolyPhen-2 are mutations that severely destabilize the protein structure, but approximately 40% are mildly destabilizing as assessed by the program SDM[2]. To check whether the same mutations occurred in ligand binding pockets we used an algorithm developed by us. This tool evaluates the sequence conservation of each pocket on the protein surface. It was named DrosteP because it recursively searches for optimal input sequences to be used to calculate conservation. We proved that the vast majority of pathologic mutations frequently encountered in humans do not occur in the active site or in any other conserved ligand-binding surface pockets. This finding has important practical consequences since mildly destabilizing pathological mutations non occurring at functional sites are likely to be responsive to pharmacological therapy with chemical chaperones[3].


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