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Non-neutral nonsynonymous single nucleotide polymorphisms in human ABC transporters: the first comparison of six prediction methods

Da Cheng Hao[1], Yao Feng[1], Rongrong Xiao[1], Pei Gen Xiao[2]

[1]Laboratory of Biotechnology, College of Environment, Dalian Jiaotong University, Dalian 116028, China

[2]Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100193, China

Correspondence: Da Cheng Hao, e-mail: hao@djtu.edu.cn; Pei Gen Xiao, e-mail: xiaopg@public.bta.net.cn

Abstract:
Nonsynonymous single nucleotide polymorphisms (nsSNPs) in coding regions that can lead to amino acid changes may cause alteration of protein function and account for susceptibility to disease and altered drug/xenobiotic response. Abundant nsSNPs have been found in genes coding for human ATP-binding cassette (ABC) transporters, but there is little known about the relationship between the genotype and phenotype of nsSNPs in these membrane proteins. In addition, it is unknown which prediction method is better suited for the prediction of non-neutral nsSNPs of ABC transporters. We have identified 2,172 validated nsSNPs in 49 human ABC transporter genes from the Ensembl genome database and the NCBI SNP database. Using six different algorithms, 41 to 52% of nsSNPs in ABC transporter genes were predicted to have functional impacts on protein function. Predictions largely agreed with the available experimental annotations. Overall, 78.5% of non-neutral nsSNPs were predicted correctly as damaging by SNAP, which together with SIFT and PolyPhen, was superior to the prediction methods Pmut, PhD-SNP, and Panther. This study also identified many amino acids that were likely to be functionally critical but have not yet been studied experimentally. There was significant concordance between the predicted results of SIFT and PolyPhen. Evolutionarily non-neutral (destabilizing) amino acid substitutions are predicted to be the basis for the pathogenic alteration of ABC transporter activity that is associated with disease susceptibility and altered drug/xenobiotic response.

Key words:
phenotype, SNAP, PolyPhen, SIFT, Panther, Pmut, SNP, ABC transporter