SHORT COMMUNICATION

IN SILICO SCORING OF ALPL GENE MUTATIONS HELP TO DISTINGUISH SEVERE AND MODERATE PHENOTYPES IN HYPOPHOSPHATASIA

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An increasing number of studies are dedicated to in silico models predicting the consequences of sequence variations at the DNA level. In combination with clinical and biological data these tools could be useful in hypophosphatasia diagnosis to help to distinguish severe and moderate genotypes in prenatal context or for therapeutic management. They are mostly based on multiple sequence alignments in different species, on the chemical properties of amino acids composing the protein and on alterations of secondary structures. Although they are increasingly used, their prediction results are often discordant and do not take into account some specificities found in the tissue nonspecific alkaline phosphatase, responsible for hypophosphatasia, such as the possible dominant negative effect of mutations. We developed HPRED, an in silico prediction tool for the severity of ALPL gene mutations. A severity score was calculated by multiple linear regression (MLR) or multi-layer perceptron (MLP) of 4 distinct scores, three of them corresponding to existing web servers mostly based onto sequence alignments (SIFT, PMUT and POLYPHEN) and a score that includes 3D modeling and site-directed mutagenesis experiments. We tested our model in a set of 67 missense mutations for which the severity (severe or moderate) was known with certainty. We found that 86.5% and 91.0% of the mutations were correctly assigned with HPRED with MLR and MLP, respectively, while only 55% with PMUT, 68.6% with SIFT and 80.5% with POLYPHEN. The model was tested in a panel of 199 single genotypes homozygote or compound heterozygote for missense mutations characterized in our laboratory or reported in the literature, and resulting in various phenotypes. Each genotype was classified according to the severity of mutations composing it. By using a threshold moderate/severe alleles of 0.75, the model predicts moderate phenotypes (odonto, adult, childhood and prenatal benign hypophosphatasia) with a probability of 91% and severe phenotypes (perinatal and infantile hypophosphatasia) with a probability of 66%. As expected the mildest form ondontohypophosphatasia and the most severe perinatal form have the best predictions (100% and 85%, respectively). We will discuss the possible causes of incorrect assignments and how their identification allows to improve the predictive power. This work was supported by grants from Hypophosphatasie Europe and from French Agency of Biomedicine.