Characteristics of Deleterious Mutations in Tumor Suppressor Genes

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The objective of this study was to identify characteristics of deleterious mutations in human tumor suppressor genes. More specifically, this study used the BRCA1 gene as an example and focused on coding non-synonymous single-base nucleotide polymorphisms (nsSNPs) affecting one of the four functional domains in the BRCA1 protein. The BRCA1 protein is responsible for cell cycle regulation and DNA repair. Previous studies suggest that mutations such as nsSNPs in the BRCA1 gene could disrupt the protein functions and lead to elevated cancer risk. Despite the fact that nsSNPs of unknown clinical significance have been found in many BRCA1-gene screening subjects, there is no reliable method to assess the clinical impact of novel nsSNPs at present time in a timely fashion. This computer-based project utilized various public online databases, retrieved nsSNP data, synthesized the mutant proteins, examined the resulting changes in physicochemical properties of residues, performed protein structure and folding analyses, and subsequently formulated an unsupervised machine learning function to identify patterns that could be utilized to differentiate deleterious mutations from benign ones. A classifier was constructed from the above machine learning function to evaluate novel BRCA1 nsSNP mutations and generate a quantitative assessment. It was validated with cases reported in published work, and exhibited high sensitivity (82%), good accuracy (81%), and relatively low false-alarm rate (22%). The performance of this classifier is on par with those developed by major studies reported in the literature. Clinical applications involve identification of disease-causing alleles, optimized assay prioritization, and deep analysis of population genomics.

Awards Won:

Intel ISEF Best of Category Award of $5,000

First Award of $5,000