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A new mathematical model for the interpretation of translational research evaluating six CTLA-4 polymorphisms in high-risk melanoma patients receiving adjuvant interferon.

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Abstract

Adjuvant therapy of stage IIB/III melanoma with interferon reduces relapse and mortality by up to 33% but is accompanied by toxicity-related complications. Polymorphisms of the CTLA-4 gene associated with autoimmune diseases could help in identifying interferon treatment benefits. We previously genotyped 286 melanoma patients and 288 healthy (unrelated) individuals for six CTLA-4 polymorphisms (SNP). Previous analyses found no significant differences between the distributions of CTLA-4 polymorphisms in the melanoma population vs. controls, no significant difference in relapse free and overall survivals among patients and no correlation between autoimmunity and specific alleles. We report new analysis of these CTLA-4 genetic profiles, using Network Phenotyping Strategy (NPS). It is graph-theory based method, analyzing the SNP patterns. Application of NPS on CTLA-4 polymorphism captures allele relationship pattern for every patient into 6-partite mathematical graph P. Graphs P are combined into weighted 6-partite graph S, which subsequently decomposed into reference relationship profiles (RRP). Finally, every individual CTLA-4 genotype pattern is characterized by the graph distances of P from eight identified RRP's. RRP's are subgraphs of S, collecting equally frequent binary allele co-occurrences in all studied loci. If S topology represents the genetic "dominant model", the RRP's and their characteristic frequencies are identical to expectation-maximization derived haplotypes and maximal likelihood estimates of their frequencies. The graph-representation allows showing that patient CTLA-4 haplotypes are uniquely different from the controls by absence of specific SNP combinations. New function-related insight is derived when the 6-partite graph reflects allelic state of CTLA-4. We found that we can use differences between individual P and specific RRPs to identify patient subpopulations with clearly different polymorphic patterns relatively to controls as well as to identify patients with significantly different survival.