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Immunotherapies which target the PD1/PD-L1 checkpoint and thereby block a regulatory pathway that shields tumor cells from the immune system have provided us a new weapon to fight cancer. These therapies have demonstrated durable clinical responses and long-term remissions; however, only in a subset of patients. There is an urgent need to identify predictive biomarkers in order to rationally select patients to achieve optimal drug response. Recent analyses have revealed that tumor mutational landscapes are linked to the neoantigen load and local immune infiltrates within the tumor and may be predictive of clinical response to the immune checkpoint therapy. In this work, we performed integrative analysis of PD-L1 gene expression, somatic mutation and copy number variations (CNV) in bladder, lung, skin and head & neck cancers based on 1,023 whole-exome sequencing and genetically-matched RNA sequencing profiles from The Cancer Genome Atlas (TCGA) project. We developed a quintile model based statistical approach to systematically evaluate the association of all high-frequency somatic mutations and CNVs with PD-L1 gene expression. In our preliminary results, we found that PD-L1 expression is significantly associated with total tumor mutation load. In particular, we established that specific missense and loss of function mutations in tumor suppressors and oncogenes are strongly associated with PD-L1 gene expression in multiple cancer types. For example, mutations in BRAF in skin cancer, PIK3CA in bladder, lung and head & neck cancers, and TP53 in all four cancers screened are all associated with high PD-L1 gene expression. Our results are expected to provide both novel insights into the identification of molecular genetic biomarkers for personalized anti-PD1/PD-L1 therapy and to further our mechanistic understanding of immunogenetic interactions in cancer development.

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