Frequency of Somatic TP53 Mutations in Combination With Known Pathogenic Mutations as Identified by Next-Generation Sequencing

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The tumor suppressor gene TP53 encodes p53, a DNA-binding transcription factor that regulates multiple genes involved in DNA repair and cell cycle arrest. TP53 is associated with human cancer by (1) mutations that lead to a loss of wild-type p53 function or (2) mutations that promote invasion, metastasis, proliferation, and cell survival. Identifying TP53 mutations in tumor cells may lead to directed therapies and improved clinical outcomes. In this study, we used Next-generation sequencing (NGS) technology to identify which TP53 somatic mutations predominated across the following tumor types: glioma/glioblastoma, colon adenocarcinoma, and non-small cell lung carcinoma (NSCLC). We also identified somatic mutations in numerous actionable genes including BRAF, EGFR, KRAS, NRAS, PIK3CA, IDH1, and CDKN2A that occurred concurrently with these TP53 variants. DNA was extracted from formalin-fixed paraffin-embedded sections and used to prepare barcoded libraries using the Ion Torrent Cancer 50 gene Hotspot Panel v2. Samples were multiplexed and sequenced using Ion Torrent 318v2 chips on the PGM Sequencing Platform. Variants were identified using the Variant Caller Plugin (v4.0.2) available in the Torrent Suite, and Golden Helix SVS (v7.7.8) was used to assess quality and functional predictions. Of the 530 tumors examined that contained 1 or more mutations in the TP53 gene, 222 were colon adenocarcinomas, 215 were NSCLS, 46 were gliomas/glioblastomas, and 47 were classified as other (including melanoma, breast and sarcoma). 100 of 215 NSCLC patients positive for TP53 mutations also showed a variant located in a pathogenic gene (KRAS 27.5%, EGFR 11.6%, PIK3CA 4.2%, and BRAF 3.3%). The most common TP53 variants identified in these patients were V157 (7/215, 3.3%) and R158 (8/215, 3.7%). Among the patients positive for TP53 mutations diagnosed with colon adenocarcinoma, 109 out of 222 also showed a mutation in a pathogenic gene (BRAF 13.5%, KRAS 32.4%, and NRAS 3.2%). The most common TP53 variants observed in this cohort were R273 (14/222, 6.3%) and R248 (18/222, 8.1%). 7 of the 46 cases diagnosed with glioma/glioblastoma were positive for the R273 variant located in the TP53 gene. Variants located in pathogenic genes were also observed in this cohort (IDH1 41.3%, CDKN2A 8.6%, and PIK3CA 10.9%). Efforts to develop drugs that could activate or restore the original p53 pathway have reached clinical trials; hence, identifying the particular TP53 mutation as well as concurrent known actionable genes present in these tumors could lead to more effective cancer therapies.