Mutations in the homologous recombination (HR) pathway in 13 cancer types

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Background: The HR pathway is important in DNA double-strand break repair. HR defects promote carcinogenesis and are associated with selective sensitivity to PARP inhibitors and DNA-damaging agents like platinum.

Method: We used next-generation sequencing (NGS) to survey genes in the HR pathway in 1020 tumors in 13 cancer types. NGS on 501 genes was performed using formalin-fixed paraffin-embedded samples on the Illumina NextSeq platform (Caris Life Sciences, AZ). All variants were detected with ≥99% confidence and with the analytical sensitivity of 5%. Deletions larger than 27bp may not be detected by this method. Pathogenic or presumed pathogenic variants are counted as mutations.

Results: The table shows mutation rates of 7 key genes in the homologous recombination pathway in 13 cancer types. PALB2, CHEK2, BRC2, ATM, BRCA2, ATR, and PTEN were included in this pilot study. Analysis of 17 additional HR genes (ATM, ATR, BARD1, BLM, BRIP1, FANCA, FANCC, FANCD2, FANCN, FANCJ, FANCQ, FANCW, FANCE, FANCD, FANCG, FANCI, FANCL, MRE11A, MRE12, RAD50, RAD51, RAD52) is ongoing. PTEN mutations were seen in 6.3% of tumors, ATM in 5.3%, BRCA2 in 2%, PALB2 in 1% and CHEK2 in 1% of cancers. CHEK2 mutations were not seen in 5 of the 13 tumors, including 3 cancers with more than one mutation in the HR pathway. PALB2 and CHEK2 mutations were seen in cholangiocarcinoma, ovarian and endometrial tumors, respectively. Tumor profiling on the biopsy of a 53-year old patient with metastatic poorly-differentiated adenocarcinoma of the stomach revealed a PALB2 nonsense mutation (S326*). Ovarian cancers (23%) had the highest rates of ATM, BRCA2 and PALB2 mutations. The highest BRCA1 deleterious mutations was seen in ovarian cancer (7%) and 2% of BRCA2 deleterious mutations were seen in pancreatic cancer. PTEN mutations were seen in 6.3% of tumors, ATM in 5%, BRCA1 in 2%, and ATR in 2.5%. CHEK2 and ATRX mutations were seen in 1.6% of tumors.

Conclusions: Thus, mutation rates of at least 8 to 43% in the HR pathway are reported from 13 cancer types. This method can potentially identify responders to DNA-damaging agents including platinum.

References