Unexpected germline mutations in a pan-cancer analysis including sarcoma, renal, and other cancers.

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Background

Multi-gen e-testing for cancer predisposition is being utilized more frequently in clinical care. Technological advances in next-generation sequencing have allowed broader panels of genes to be tested in diagnostics settings. The testing of more genes results in the reporting of in a greater number of variants of uncertain significance (VUS); however, more actionable pathogenic or likely pathogenic variants may be found in genes other than those traditionally analyzed based on a patient’s clinical presentation.

In this study, we retrospectively analyzed de-identified data from 39,147 patients referred for hereditary cancer syndrome testing for pathogenic germline variants in 80 cancer risk genes. Among these patients, 14.3% of patients (5,589) carried germline PI/PLP mutations in 80 cancer risk genes.

Results

Overall, 14.3% of patients (5,589) carried germline PI/PLP mutations in 80 cancer risk genes. Among them, 12.3% (866) had pathogenic/likely pathogenic variants in the genes initially requisitioned by the ordering provider.

These 5,589 patients carried positive germline findings totaling 5,840 PI/PLP variants in 67 cancer genes. PI/PLP variants in BRCA2 were the most prevalent, with a 2.4% positive rate, followed by BRCA1, CHEK2, ATM, PMS2 and PALB2. The high prevalence in BRCA1 and BRCA2 in the patient population was likely driven by the large number of HBOC patients included.

We found that 0.68% of patients (266) had two or more PI/PLP variants in the 80 pan-cancer genes.

Conclusions

In this series of patients, we show that the yield of positive findings (pathogenic or likely pathogenic variants) in less common cancer types is comparable to, if not higher than, that seen in cancers often associated with hereditary risk. This result suggests that germline genetic testing is warranted in patients with renal cancer, pancreatic cancer, sarcoma, melanoma, or paraganglioma.

We estimate that ~12% of PI/PLP variants are unexpected—i.e., in genes other than those commonly tested for these cancer types. The variants we observed most frequently (CHEK2, ATM, BRCA2, and PMS2) are common in both breast and colon cancer patients. These variants may be generally common and unrelated to the indication for testing, or they may correlate to additional tumor types in the family history.

Given that most of the results were associated with actionable medical management — independent of whether the gene was associated with the tumor indication — clinicians should consider germline testing using expanded panels for patients with personal histories of rare tumors.