Determining the clinical value of germline genetic testing coupled with tumor mutation profiling

Background

Somatic mutation analysis by next-generation sequencing (NGS) is an expanding clinical assessment offered to cancer patients. Studies report that 4–12% of patients have a positive tumor mutation profiling (TMP) result in a known cancer predisposition gene also identified in their germline, which has potential implications for the patient’s acute treatment, ongoing surveillance, and the screening of family members. We report a series of patients with TMP coupled with germline genetic testing and include yield of pathogenic germline mutations, discordance between germline and TMP findings, and potential clinical impact.

Methods

Our study used de-identified data from 100 consecutive patients who underwent TMP followed by germline testing with an NGS-based hereditary cancer gene panel.

Results

In 64/100 (64%) cases, one or more TMP variants in genes associated with hereditary cancer syndromes or genes conferring increased cancer risk were seen somatically but were not seen in the germline test. In 36/100 (36%) cases, one or more germline variants were found (Figure 1).

Germline Origin of Tumor variants in Cancer patients

- 64% TMP Variant excluded from Germline origin
- 36% Germline variants-high penetrance genes
- 21% Germline variants-moderate penetrance genes
- 15% Germline variants-low penetrance genes

In 5 cases out of the 36, the germline variants we identified were discordant with TMP results (Figure 3). In two cases, the discordance was of interpretation, i.e. what was considered a positive TMP variant was interpreted as a variant of uncertain significance (VUS) in the germline report.

Clinically Actionable Discordance: Germline vs. Somatic

- Concordance 86%
- Actionable Discordance 14%

Two of the remaining discordant cases involved RAD51C, and FANCC, where germline testing discovered a LP/P germline variant not reported in the TMP (the genes were not on the TMP panel).

Conclusions

- In TMP patients, 50 of 182 had a medically actionable germline mutation with established management guidelines. This high rate may be influenced by clinician selection bias. Among these 50, 12 (24%) met neither current personal or family criteria nor the latest NCCN guidelines for germline testing in patients with TMP. Also striking were nine patients whose germline LP/P mutations were absent in TMP results. These data suggest that indications for germline testing of cancer patients must be expanded to avoid missing important germline findings in patients undergoing TMP.

References

1. Schrader et al. JAMA Oncol. 2016, PMID 26556299