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Germline variants in targeted tumor sequencing

Genomic sequencing of tumors can be used clinically to identify acquired somatic mutations in cancer-related genes. In an era of personalized medicine, tumor-specific mutational status can be used to acquire prognostic information and guide molecular targeted therapies. However, many patients also have germline variants in these genes, which not only can make it difficult to identify the tumor-specific somatic mutations, but may also affect the biological mechanism of tumorigenesis. The clinical role of germline mutations is not well defined, and while many of the observed variants are likely benign, some may cause a hereditary neoplastic syndrome or predispose people to certain types of cancers. Although most germline mutations, with a few exceptions, may not be directly targetable, identifying them in a clinical setting may help guide tumor-specific therapy and direct preventative care of family members. The authors conducted a study in which 1,566 consecutive patients with advanced disease underwent genetic profiling with the MSK-Impact assay from March 2014 to October 2014. Targeted sequencing of all exons and selected introns of a panel of 341 cancer-related genes was performed in both DNA from formalin-fixed paraffin-embedded tumor and matched “normal” DNA from a blood sample. Of the 341 cancer-related genes in the panel, 187 were associated with Mendelian-inherited genetic disorders, and 93 of these were associated with a genetic susceptibility to cancer. In the 187 genes associated with genetic disease, a mean of 63 variants per individual were identified. While the vast majority of these were classified as benign mutations, 16 percent of subjects had at least one pathogenic or likely pathogenic variant identified in these genes. In addition, 198 subjects (12.6 percent) had a mutation in one of the 93 genes associated with cancer susceptibility. If the germline variant identified was retained in the tumor, somatic alteration of the other allele was seen in 21 percent of cases, suggesting that these germline mutations played a mechanistic role in tumor development. In almost 60 percent of cases in which a germline mutation was identified, patients were phenotypically discordant, in that they developed a type of cancer that is not typically associated with the mutation. Overall, this study highlights the importance of determining germline mutational status in parallel with sequencing tumor tissue. The reasons go beyond simply obtaining a normal control to which to compare tumor somatic mutations. This study demonstrates that germline mutations may play a vital role in tumorigenesis and be more prevalent than previously thought. Therefore, they should be routinely reported. In addition, understanding germline mutational status may reveal novel correlations between germline variants and cancer types or novel underlying syndromic associations.

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