MOLECULAR PROFILING OF PATIENTS WITH COLORECTAL CANCER AND THEIR CLINICAL IMPLICATIONS

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**Background** Colorectal cancer (CRC) is a complex disease with heterogeneous molecular characteristics and targeted therapy is often used in the clinical management of the disease. Comprehensive molecular profiling has become an essential tool to uncover the underlying genomic alterations, providing valuable insights into CRC tumor biology and potential therapeutic targets. Multiplex genetic testing and targeted next-generation sequencing (NGS) allow simultaneous testing of a large cohort of potentially actionable genetic aberrations using a relatively small amount of genetic materials. Here, we aimed to identify the mutational spectrum, mutation hotspots of genes and their clinical association in patients diagnosed with CRC.

**Methods** FFPE samples from CRC patients tested from January 2020 to May 2023 using NeoTYPE® Colorectal Tumor Profile NGS assay were analyzed. NeoTYPE® CRC profile NGS is a targeted next-generation sequencing focusing on a panel of 36 genes known to be frequently mutated in CRC. Gene mutations frequency, co-occurring genes and clinical significance were explored and analyzed. In addition, immunotherapy markers, Microsatellite Instability (MSI) and Tumor Mutation Burden (TMB) were assessed.

**Results** A total of 7,317 patients (3,909 men and 3,408 women) with CRC were included in this study. One or several gene mutations are identified in 6,206 (84.8%) patients with CRC. We found that APC (24.9%), TP53 (16.2%), KRAS (10.2%), and PIK3CA (5.0%) were the most frequently mutated genes. APC mutations were not biased in a particular domain, the vast majority of them were truncation mutations. APC p. R1450* were the most common mutations. KRAS p. G12D/V/C and p.G13D were the most recurrent variant in our cohort. Furthermore, we identified several less commonly mutated genes that co-occurred with PIK3CA gene, including ATM, ARID1A, BRAF, NOTCH1, FBXW7, and ERBB4. The presence of TP53 mutations showed mutual exclusivity with that of PIK3CA mutations. These findings are line with that PIK3CA and TP53 alterations tend to be mutually exclusive in diverse tumors. Likewise, TP53 and EGFR alterations was mutually exclusive in our cohort. TP53 and BRAF alterations also showed mutually exclusiveness. In addition, we found right colon cancers harbor more genetic aberrations than left colon cancers.

**Conclusions** Our results suggest that the mutational landscape of CRC is complex, with multiple genes being affected in a coordinated manner. These findings have important implications for understanding the molecular mechanisms underlying CRC and may inform the development of novel therapeutic approaches for the treatment of CRC.

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