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 variants 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® CRC panels 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. Patient demographics, sequence coverage, gene mutation frequency, exclusive mutation genes and clinical significance were explored and analyzed.

Overview of NGS Workflow

Key findings
• A total of 2,349 patients with CRC were included in this study (46% female, 54% male), with age group 61 to 80 years old exhibiting the highest prevalence.
• APC (24.9%), TP53 (16.2%), KRAS (10.2%), and PIK3CA (5.0%) were the most frequently mutated genes.
• KRAS mutations, specifically p.G12D/V/C, were the most frequently mutated KRAS mutations.
• The presence of TP53 mutations showed mutual exclusivity with PIK3CA, ATM, KRAS, BRAF, RNF43 and ARID1A in our cohort.

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

Fig 1: NeoTYPE® CRC panel curated content

Fig 2: Demographics of cohort testing. A: Gender distribution  B: Age at sequencing

Fig 3: Distribution of Gene mutations. Long tailed distribution of CRC cancer genes

Fig 4: Sequence read depth and VAF. A: No correlation between VAF and read depth. B: Read-depth of six frequent mutated genes

Fig 5: Six most frequently mutated genes consequence counts in CRC cohort. APC gene truncation mutations were the most prevalent while TP53, RARX, PIK3CA and SMAD3 missense mutations were the major mutation category.

Fig 6: Gene mutual exclusivity analysis. Mutual exclusivity analysis performed by pairwise statistical analysis. Fisher’s exact test and likelihood ratio methods were used.

Fig 7: Mutations analysis of APC and KRAS genes. APC p.R1456* and KRAS p.G12D were the most prevalent.