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

Overview of NGS Workflow

Fig 1A: QIAseq DNA target panel NGS workflow

Genes included

AKT1	ARID1A	APC	ATM	BRAF	EGFR
EPCAM	ERBB2	ERBB4	FBXW7	FGFR1	FGFR2
FGFR3	HRAS	KIT	KRAS	MET	MLH1
MSH2	MSH6	MUTYH	NOTCH1	NRAS	PDGFRA
PIK3CA	PMS2	POLD1	POLE	PTEN	RNF43
SMAD4	SMO	SRC	STK11	TERT	TP53

Fig 1B: NeoTYPE ® CRC panel curated content

Results

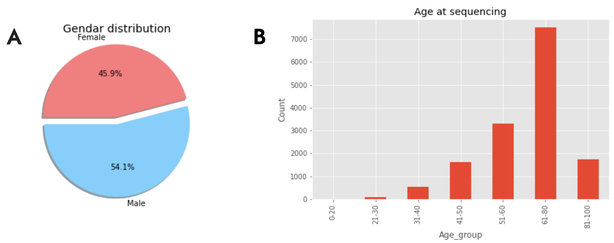

Fig 2: Demographics of cohort testing. A: Gender distribution B: Age at sequencing

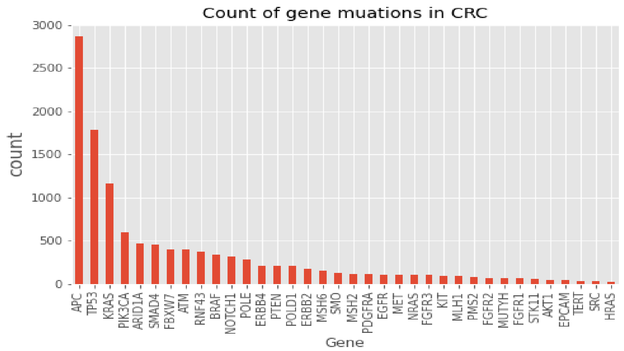

Fig 3: Distribution of Gene mutations. Long tailed distribution of CRC cancer genes

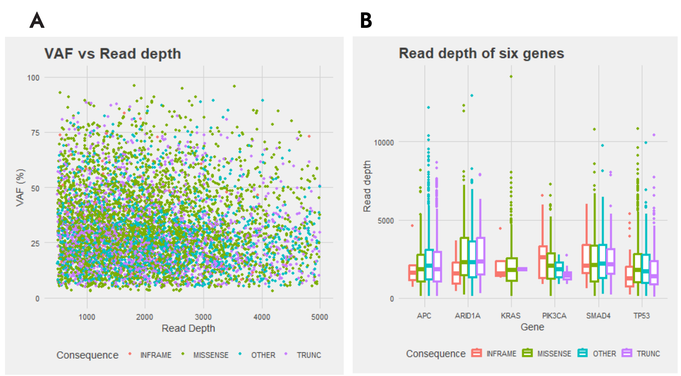

Fig 4: Sequence read depth and VAF. A: No correlation between VAF and read depth. B: Read depth of six frequent mutated genes

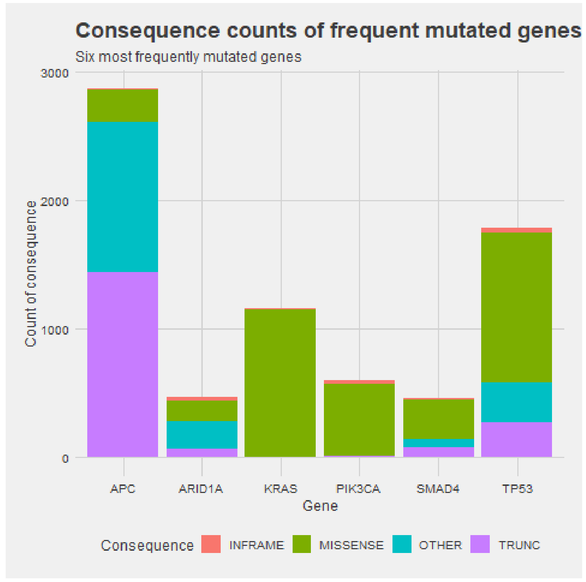

Fig 5: Six most frequently mutated genes consequence counts in CRC cohort. APC genes truncation mutations were the most prevalent while TP53, KARS, PIK3CA and SMAD3 missense mutations were the major mutation category.

A	B	Neither	A Not B	B Not A	Both	Log2 Odds Ratio	p-Value	q-Value	Tendency
APC	RNF43	427	1664	159	97	-2.675	<0.001	<0.001	Mutual exclusivity
APC	BRAF	419	1615	167	146	-2.14	<0.001	<0.001	Mutual exclusivity
APC	ARID1A	458	1541	128	220	-0.969	<0.001	<0.001	Mutual exclusivity
APC	NOTCH1	498	1595	88	166	-0.764	<0.001	<0.001	Mutual exclusivity
KRAS	BRAF	946	1088	276	37	<-3	<0.001	<0.001	Mutual exclusivity
KRAS	RNF43	1018	1073	204	52	-2.048	<0.001	<0.001	Mutual exclusivity
KRAS	ARID1A	1002	997	220	128	-0.774	<0.001	<0.001	Mutual exclusivity
KRAS	NOTCH1	1061	1032	161	93	-0.752	<0.001	<0.001	Mutual exclusivity
KRAS	POLE	1079	1041	143	84	-0.716	<0.001	<0.001	Mutual exclusivity
TP53	PIK3CA	497	1332	253	265	-1.355	<0.001	<0.001	Mutual exclusivity
TP53	ATM	589	1457	161	140	-1.508	<0.001	<0.001	Mutual exclusivity
TP53	KRAS	320	902	430	695	-0.802	<0.001	<0.001	Mutual exclusivity
TP53	ARID1A	589	1410	161	187	-1.043	<0.001	<0.001	Mutual exclusivity
TP53	RNF43	630	1461	120	136	-1.033	<0.001	<0.001	Mutual exclusivity
TP53	NOTCH1	642	1451	108	146	-0.741	<0.001	<0.001	Mutual exclusivity
TP53	POLE	653	1467	97	130	-0.745	<0.001	<0.001	Mutual exclusivity
TP53	BRAF	626	1408	124	189	-0.561	0.002	0.003	Mutual exclusivity

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

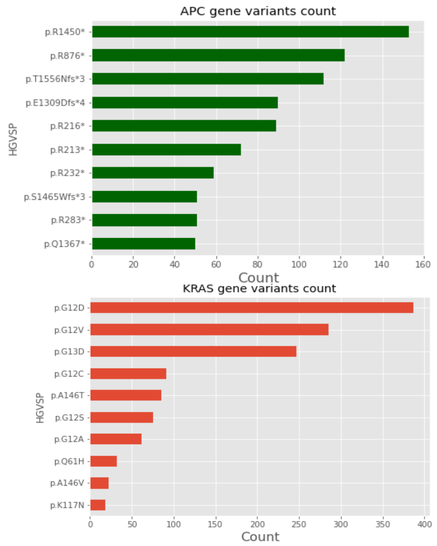

Fig 7: Mutations analysis of APC and KRAS genes. APC p.R1450* and KRAS p.G12D were the most prevalent.

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 and p.G13D, constituted 71% of all 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.

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