Highly frequent gene mutations and co-occurring genes analysis in colorectal cancer (CRC)

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Background

Colorectal cancer (CRC) is the second most leading cause of cancer-related deaths worldwide. Understanding the molecular alterations that drive CRC is critical for improving patient outcomes. Next-generation sequencing (NGS) has revolutionized CRC molecular profiling by simultaneous analysis of multiple genes with high accuracy and sensitivity. In this study, we analyzed a cohort of CRC formalin-fixed paraffin-embedded (FFPE) samples to identify highly frequent gene mutations and co-occurring genes in CRC.

Methods

FFPE samples from CRC patients tested from January 2020 to December 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 Study Workflow

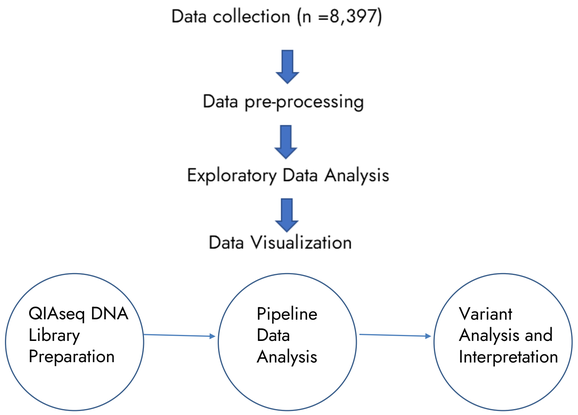

Fig 1A: QIAseq DNA target panel NGS workflow

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

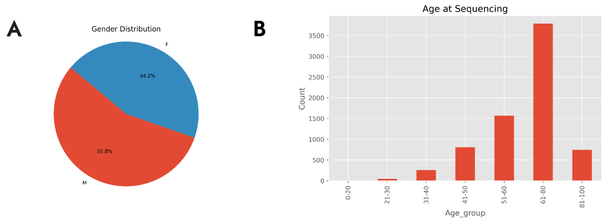

Fig 2: Demographics of cohort testing. A: Gender distribution B: Age at sequencing

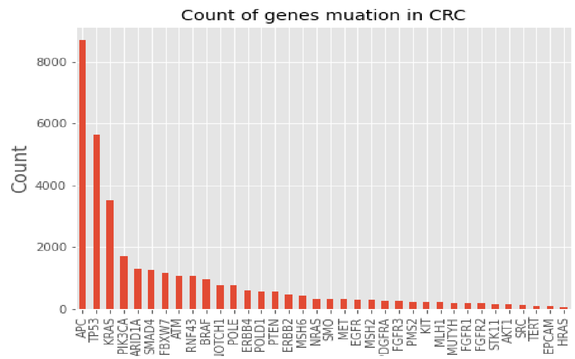

Fig 3: Distribution of Gene mutations. Long tailed distribution of CRC cancer genes

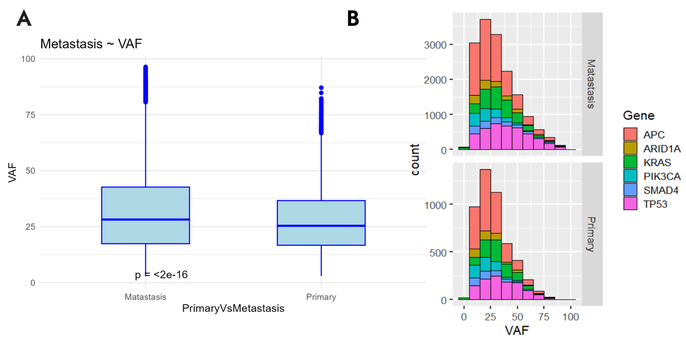

Fig 4: Metastasis vs primary CRC. A: VAF is significantly higher in metastasis CRC group compared to primary group. B: Count of six frequent mutated genes VAF in metastasis vs primary CRC group.

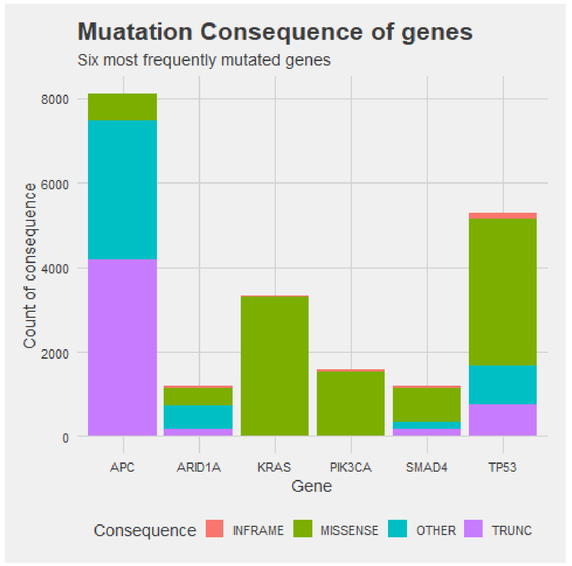

Fig 5: Six most frequently mutated genes consequence counts in CRC cohort. APC genes truncation mutations were the most prevalent while TP53, KARS, PIK3CA and SMAD3 missense mutations were the major mutation category.

A	B	Neither	A Not B	B Not A	Both	Log2 Odds Ratio	p-Value	q-Value	Tendency
APC	KRAS	384	838	202	923	1.066	<0.001	<0.001	Co-occurrence
APC	TP53	236	514	350	1247	0.71	<0.001	<0.001	Co-occurrence
ARID1A	RNF43	1862	229	137	119	2.82	<0.001	<0.001	Co-occurrence
ARID1A	BRAF	1797	237	202	111	2.059	<0.001	<0.001	Co-occurrence
ARID1A	NOTCH1	1832	261	167	87	1.871	<0.001	<0.001	Co-occurrence
ARID1A	POLE	1851	269	148	79	1.877	<0.001	<0.001	Co-occurrence
ARID1A	ATM	1782	264	217	84	1.386	<0.001	<0.001	Co-occurrence
ARID1A	FBXW7	1742	274	257	74	0.872	<0.001	<0.001	Co-occurrence
ATM	RNF43	1868	223	178	78	1.876	<0.001	<0.001	Co-occurrence
ATM	POLE	1887	233	159	68	1.792	<0.001	<0.001	Co-occurrence
ATM	NOTCH1	1857	236	189	65	1.436	<0.001	<0.001	Co-occurrence
ATM	BRAF	1802	232	244	69	1.135	<0.001	<0.001	Co-occurrence
BRAF	NOTCH1	1858	235	176	78	1.809	<0.001	<0.001	Co-occurrence
BRAF	POLE	1869	251	165	62	1.484	<0.001	<0.001	Co-occurrence
FBXW7	RNF43	1825	266	191	65	1.223	<0.001	<0.001	Co-occurrence
FBXW7	ATM	1783	263	233	68	0.984	<0.001	<0.001	Co-occurrence
FBXW7	POLE	1844	276	172	55	1.095	<0.001	<0.001	Co-occurrence
KRAS	PIK3CA	1026	803	196	322	1.07	<0.001	<0.001	Co-occurrence
NOTCH1	POLE	1927	193	166	61	1.875	<0.001	<0.001	Co-occurrence
PIK3CA	ARID1A	1594	405	235	113	0.92	<0.001	<0.001	Co-occurrence
PIK3CA	FBXW7	1604	412	225	106	0.875	<0.001	<0.001	Co-occurrence
PIK3CA	POLE	1676	444	153	74	0.868	<0.001	<0.001	Co-occurrence
PIK3CA	RNF43	1654	437	175	81	0.809	<0.001	<0.001	Co-occurrence
PIK3CA	ATM	1619	427	210	91	0.716	<0.001	<0.001	Co-occurrence
RNF43	BRAF	1917	117	174	139 >3		<0.001	<0.001	Co-occurrence
RNF43	POLE	1941	179	150	77	2.477	<0.001	<0.001	Co-occurrence
RNF43	NOTCH1	1916	177	175	79	2.289	<0.001	<0.001	Co-occurrence

Fig 6: Gene co-occurrence analysis. Co-occurrence analysis performed by pairwise statistical analysis. Fisher's exact test and likelihood ratio methods were used.

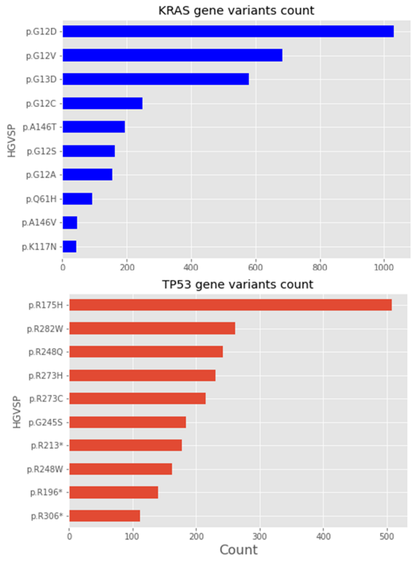

Fig 7: Mutations analysis of KRAS and TP53 genes. KRAS p.G12D and TP53 p.R175H were the most prevalent.

Key findings

- A total of 8,397 patients with CRC were included in this study (44% female, 56% male), with age group 61 to 80 years old exhibiting the highest prevalence.
- APC (39.2%), TP53 (25.%), KRAS (16.1%), and PIK3CA (7.6%) 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 APC mutations showed co-occurrence with KRAS and TP53 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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