Comprehensive Characterization of *KRAS* Mutations and Interrelation With Primary Tumor Location In Colorectal Cancers

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INTRODUCTION

- Kirsten rat sarcoma (*KRAS*) is one of the most frequently mutated oncogenes in Colorectal Cancer (CRC).
- The recent development of *KRAS* G12C inhibitors underscores the potential to target *KRAS* mutations.
- Right-sided and left-sided colon tumors (RT and LT) exhibit different molecular features.
- Herein, we aimed to characterize the prevalence of *KRAS*-variants, interrelation with primary tumor location, and association with immune biomarkers in CRC

METHODS

- We retrospectively reviewed CRC tumors of all stages (with sidedness) that underwent NGS with Tempus xT assay (DNA-seq of 648 genes at 500x coverage, full transcriptome RNA-seq)
- Bivariate analyses were performed to compare *KRAS* alterations, immune biomarkers, and co-mutations by tumor location
- *P*-values comparing individual co-mutations between groups were adjusted for false discovery (FDR)

Bivariate analyses were performed to compare (**LT vs Transverse vs RT**):

- ***KRAS* alterations**
- **Immune biomarkers**
- **Co-mutations**

Note – **Left-sided**: Rectosigmoid junction, descending colon, splenic flexure of colon, sigmoid colon, rectum, overalpping lesion of rectum, anus and anal canal
Right-sided: Ascending colon, hepatic flexure of colon, cecum, **Transverse colon**: transverse colon

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SUMMARY

- **Our study suggests that RT CRC** tumors harbored **more *KRAS* alterations** than **transverse and LT tumors**
- Across *all KRAS*-altered CRC tumors, the **most frequent *KRAS* alterations** were **G12D, G12V, G13D,** and **G12C**
- There was **no significant difference** in the distribution of *KRAS* alteration types between tumor locations
- CRC tumors that harbored **G13D variants** were **significantly more likely** to be associated with **MSI-H and TMB-H status**
- Future studies will provide more insights into the related mechanisms and observed associations

RESULTS

Table 1: Demographic/Clinical characteristics of the patient cohort

Characteristic	Right, N = 442[1]	Transverse colon, N = 116[1]	Left, N = 2833[1]	p-value[2]
Age at Diagnosis	65 (55, 75)	64 (54, 75)	59 (49, 67)	**<0.001**
Unknown	19	6	165	
Gender				**<0.001**
Male	213 (48%)	63 (54%)	1717 (61%)	
Female	228 (52%)	53 (46%)	1106 (39%)	
Unknown	1	0	10	
Race				**0.003**
White	181 (74%)	50 (72%)	1,184 (77%)	
Black or African American	45 (18%)	6 (8.7%)	173 (11%)	
Other	20 (8.1%)	13 (19%)	188 (12%)	
Unknown	196	47	1,288	
Ethnicity				**0.3**
Not Hispanic or Latino	123 (85%)	40 (85%)	792 (80%)	
Hispanic or Latino	22 (15%)	7 (15%)	198 (20%)	
Unknown	297	69	1843	
***KRAS* alt status**				**<0.001**
KRAS wild-type	210 (48%)	69 (59%)	1626 (57%)	
KRAS altered	232 (52%)	47 (41%)	1207 (43%)	

[1] Median (IQR); n (%)
[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

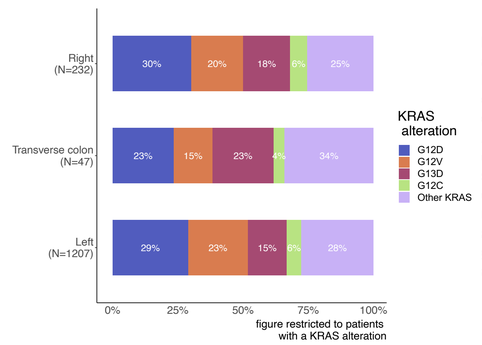

Figure 1 - Most common *KRAS* alterations by tumor location.
No significant difference in the distribution of *KRAS* alterations was detected between tumor locations. *KRAS* alterations were defined as either a pathogenic or likely pathogenic short variant, copy number loss, or copy number amplification (copy number >=8). All copy number aberrations fall into the 'other *KRAS*' group and make up <3% of *KRAS* alterations overall.

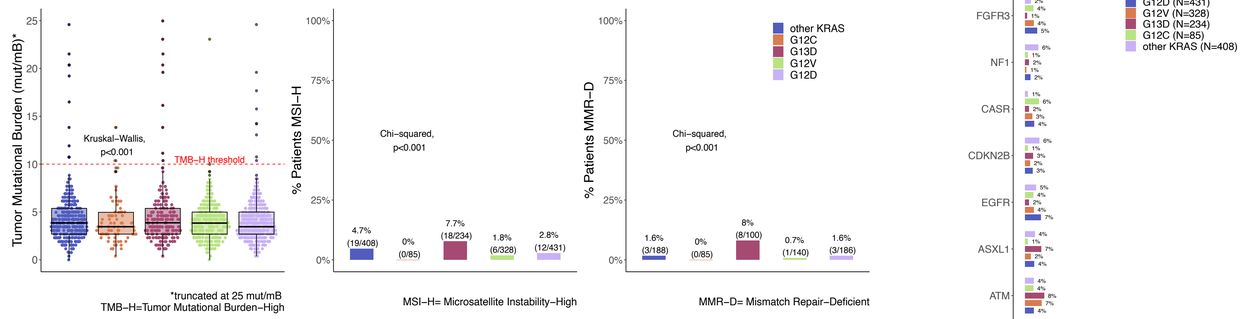

Figure 2 - Comparisons of TMB, % patients MSI-H, and % patients MMR-D between *KRAS* alteration groups. For all metrics, global significance between groups was detected. *KRAS* G13D tumors exhibited highest median TMB compared to G12D, G12V, and G12C tumors (4.23 vs. 3.84 vs. 3.84 vs. 3.46, respectively). Analogously, G13D tumors exhibited significantly increased TMB-H (8.5% vs. 3.9% vs 2.1% vs 2.4%), MSI-H (7.7% vs 2.8% vs 1.8% vs 0%), and MMR-D (8% vs 1.6% vs 0.7% vs 0%).

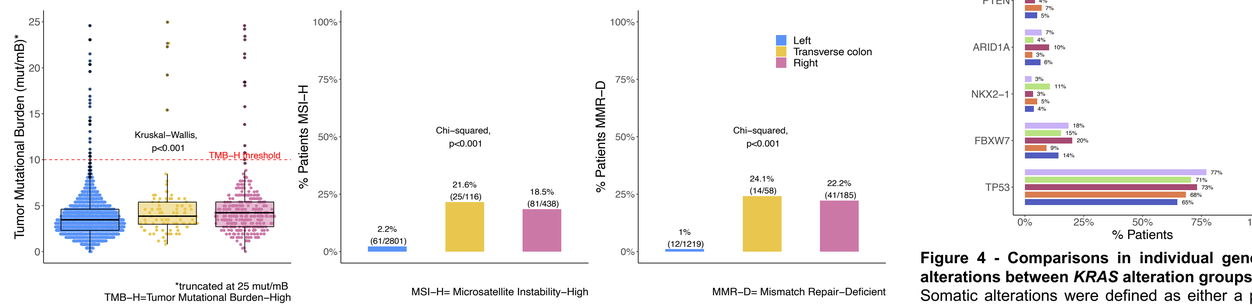

Figure 3 - Comparisons of TMB, % patients MSI-H, and % patients MMR-D between tumor location groups.
For all metrics, global significance between groups was detected. Transverse and RT sided tumors exhibited similar behavior compared to LT sided tumors. LT tumors exhibited significantly lower median TMB compared to transverse and RT tumors (3.5 vs. 4.6 vs. 4.6, respectively). Analogously, LT tumors exhibited significantly decreased TMB-H (3% vs. 22% vs. 20%), MSI-H (2.2% vs. 22% vs. 18%), and MMR-D (1% vs. 24% vs. 22%).

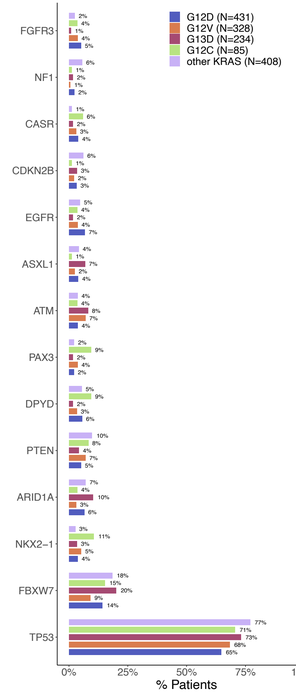

Figure 4 - Comparisons in individual gene somatic alterations between *KRAS* alteration groups.
Somatic alterations were defined as either a pathogenic or likely pathogenic short variant, copy number loss, or copy number amplification (copy number >=8). Genes of interest are shown although p-values come from comparing all genes altered. No significant differences were identified after false-discovery correction.