

Distinct KRAS Mutation Codons Differentially Associate with Microsatellite Instability in Colorectal Carcinoma

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Background

- MSI/MMR and KRAS are key biomarkers in colorectal carcinomas (CRC) for PD-(L)1 inhibitors, EGFR mAbs, and KRAS G12Ci.
- Although MSI-High/MMRd is reported to be less common in KRAS-mutant CRC; we found rates to vary by KRAS codon in US¹:
 - 14% of KRAS-wt CRCs (p<0.001)
 - 6% of KRAS codon 12/13/61 mut
 - 10% of KRAS codon 146 mut
- Because KRAS mut location influences protein function and CRC pathophysiology, we hypothesized that MSI/MMR also differs by KRAS mutation site.

Methods

- MSI-High/MMR-deficiency prevalence was assessed by KRAS mutation location in CRCs in 3 clinicogenomic databases:
 - MD Anderson (initial)
 - MSK-CHORD² (validation)
 - Caris CODEai³ (validation)
- Testing modalities: MMR by IHC
 - MSI by tissue NGS
 - KRAS status by tissue NGS
- BRAF p.V600E CRCs (associated with sporadic MMRd) were excluded from MSK-CHORD and Caris CODEai subsets to reduce confounding.
- In MSK-CHORD subset, CRCs were further excluded if they had NRAS mutation or prior EGFR-targeted mab, to reduce confounding (i.e. from acquired RAS muts).
- KRAS mutations were assessed by codon and individual nucleotide changes.

Results

1) MD Anderson: 1,857 CRCs (non-BRAF V600E)

KRAS	Total	MSI-H/MMRd		Logistic Regression		
	n	n	%	OR	95%CI	P value
Mutated, codon 12	615	19	3 %	ref		
Mutated, codon 13	173	12	7 %	2.34	(1.11-4.92)	0.03
Mutated, codon 146	66	6	9 %	3.14	(1.21-8.16)	0.02
Mutated, codon 61	43	3	7 %	2.35	(0.67-8.29)	0.18
Mutated, codons 19, 59 or 117	19	3	16 %	5.88	(1.58-21.91)	0.008
Mutated, other codons	20	2	10 %	3.49	(0.75-16.11)	0.11
Wildtype	921	85	9 %	3.19	(1.92-5.30)	<0.001

2) MSK-CHORD: 4,805 CRCs (non-BRAF V600E, NRASwt, no prior EGFRmab)

KRAS	Total n	MSI-H		Logistic regression of MSI-H		
		n	%	OR	(95CI)	p val
MSK-CHORD CRC	4,805	420	8.7			
wt	2,510	222	8.8	1.8	(1.4-2.3)	<0.001
codon 12	1,517	78	5.1	ref		
codon 13	436	59	13.5	2.9	(2-4.1)	<0.001
codon 14	6	3	50.0	18.4	(3.7-92.9)	<0.001
codon 59	10	5	50.0	18.4	(5.2-65.1)	<0.001
codon 61	94	13	13.8	3.0	(1.6-5.6)	0.001
codon 117	26	8	30.8	8.2	(3.5-19.4)	<0.001
codon 146	164	26	15.9	3.5	(2.2-5.6)	<0.001

3) Caris CODEai: 83,532 CRCs (non-BRAF V600E)

KRAS	Total n	MSI-H		Logistic regression of MSI-H		
		n	%	OR	(95CI)	p val
Caris CODEai CRC	83,532	4,545	5.4			
wt	57,657	3,682	6.4	3.6	(3.2-4)	<0.001
codon 12	17,623	330	1.9	ref		
codon 13	4,653	261	5.6	3.1	(2.6-3.7)	<0.001
codon 14	52	10	19.2	12.5	(6.2-25.1)	<0.001
codon 22	54	1	1.9	1.0	(0.1-7.2)	0.99
codon 59	134	36	26.9	19.3	(12.9-28.6)	<0.001
codon 61	1,399	93	6.6	3.7	(2.9-4.7)	<0.001
codon 117	317	18	5.7	3.2	(1.9-5.1)	<0.001
codon 146	1,643	114	6.9	3.9	(3.1-4.9)	<0.001

4) Across all 3 datasets, KRAS codon 12-mut CRCs had the lowest prevalence of MSI-H/MMRd; we next investigated MSI/MMR by specific nucleotide changes in KRAS mutations:

KRAS mutations	Total n	n	MSI-H %
codon 12			
p.G12A (C>G)	104	5	4.8
p.G12C (C>A)	153	3	2.0
p.G12D (C>T)	658	51	7.8
p.G12R (C>G)	24	2	8.3
p.G12S (C>T)	105	4	3.8
p.G12V (C>A)	469	13	2.8
codon 13			
p.G13C (C>A)	19	2	10.5
p.G13D (C>T)	412	55	13.4
codon 59			
p.A59T (C>T)	10	5	50.0
codon 61			
p.Q61H (T>G, T>A)	50	5	10.0
p.Q61K (GA>TT, G>T, GA>TG)	21	8	38.1
p.Q61L (T>A)	7	0	0.0
p.Q61R (T>C, TT>GC)	15	0	0.0
codon 117			
p.K117N (T>A, T>G)	24	8	33.3
codon 146			
p.A146P (C>G)	9	2	22.2
p.A146T (C>T)	128	23	18.0
p.A146V (G>A)	26	1	3.9

5) We next investigated whether similar KRAS codon-associated patterns were observed in Pancreatic adenocarcinomas, which overall are infrequently MSI-H/MMRd:

KRAS	Total n	MSI-H		Logistic regression of MSI-H		
		n	%	OR	(95CI)	p val
Caris CODEai PDAC	40,480	273	0.7			
wt	22,675	168	0.7	1.4	(1.1-1.8)	0.02
codon 12	16,439	89	0.5	ref		
codon 13	103	8	7.8	15.5	(7.3-32.8)	<0.001
codon 61	1,252	5	0.4	0.7	(0.3-1.8)	0.51
codon 146	11	3	27.3	68.9	(18-263.9)	<0.001

Conclusions

- MSI-H/MMRd prevalence consistently varied by KRAS mutation location in CRC across 3 independent, large datasets.
- 6-9% of KRASwt CRCs were MSI-H/MMRd
- Codon 12 mutations (especially C>A) were associated with lowest MSI-H/MMRd rates:
 - 2-5% of KRAS codon 12 muts
 - But mutation context mattered:
 - 2-4% of G12C/S/V
 - vs. ~8% of G12D/R
- KRAS codon 13/61/146 muts – and 14/59 muts -- were enriched among MSI-H CRCs:
 - highest for codon 59 (27-50%).
 - Again, mutation context mattered:
 - 38% of Q61K, but only 10% of Q61H
 - 18-22% of A146P/T vs 4% of A146V
- Similar patterns were observed in PDAC, where overall 0.7% are MSI-H, but 8% of KRAS codon 13 & 27% of codon 146 were.
- Our findings suggest that MSI/MMR mutational processes are associated with distinct codon-resolved KRAS biology,
- These findings warrant further investigation and could refine predictive biomarker interpretation.

References

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- Jee et al. Nature, 2024.
- Caris CODEai

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