Genomic profiling of epithelial neoplasms of the appendix: insights across histological subtypes and histological grades

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INTRODUCTION

The biological behavior of appendiceal epithelial neoplasms (AENs) depends on histological subtype and grade. Due to their rarity, previous molecular analyses have grouped diverse biological types together. We aimed to examine genomic and outcomes differences among distinct biological subgroups of appendiceal cancer.

METHODS

Tempus Lens was used to analyze de-identified clinical genomic, and transcriptomic information for patients diagnosed with AENs (N = 807): mucinous adenocarcinomas (MA) (N = 282), enteric-type adenocarcinomas (N = 311), signet-ring cell carcinoma (SRC) (N = 46), and goblet cell adenocarcinoma (GCA) (N = 168). Patients were stratified by *GNAS/KRAS* co-mutations (N = 151) or wild-type (wt) (N = 231). RNA-seq data were normalized and quantified as transcripts per million (TPM) and reported as log2(TPM+1). Immune infiltration was estimated via quanTIseq and enrichment via single sample gene set enrichment analysis (ssGSEA). Real-world overall survival (rwOS) was defined as the time from sample collection to death or loss to follow up. Median OS (mOS) was estimated using Kaplan-Meier curves and compared using log-rank tests.

SUMMARY

- AENs show unique DNA alterations by histological subtype
- Grade 2 MA closely resembling Grade 1, not Grade 3, in survival and genomics, supporting a three-tier grading system over a high-grade (G2/G3) grouping
- *KRAS* G12D represented 37% of *KRAS* mutations in patients with MA.
- Patients with *KRAS/GNAS* co-mutations had better survival and a favorable immune profile, supporting further immunotherapy research in low-grade MA.

RESULTS

Table 1: Patient demographics and clinical characteristics

Characteristic	Overall N = 807[1]	Mucinous Adeno carcinoma N = 282[1]	Enteric-type Adeno carcinoma N = 311[1]	Signet-Ring Cell Carcinoma N = 46[1]	Goblet Cell Carcinoma N = 168[1]
Age a diagnosis					
Median (Q1, Q3)	61 (51, 69)	58 (48, 68)	63 (52, 70)	60 (47, 72)	62 (53, 68)
Min, Max	20, 88	27, 84	23, 88	20, 82	31, 84
Unknown	196	77	71	9	39
Sex					
Female	432 (54%)	160 (57%)	151 (49%)	26 (57%)	95 (57%)
Male	375 (46%)	122 (43%)	160 (51%)	20 (43%)	73 (43%)
Race					
White	290 (79%)	90 (78%)	119 (75%)	18 (82%)	63 (90%)
African American	37 (10%)	12 (10%)	20 (13%)	1 (4.5%)	4 (5.7%)
Other Race	30 (8.2%)	12 (10%)	15 (9.5%)	2 (9.1%)	1 (1.4%)
Asian	8 (2.2%)	1 (0.9%)	4 (2.5%)	1 (4.5%)	2 (2.9%)
Unknown	442	167	153	24	98
Ethnicity					
Not Hispanic/Latino	261 (91%)	81 (87%)	119 (93%)	8 (80%)	53 (95%)
Hispanic/Latino	26 (9.1%)	12 (13%)	9 (7.0%)	2 (20%)	3 (5.4%)
Unknown	520	189	183	36	112
Grade					
Grade 3	242 (48%)	46 (25%)	85 (44%)	25 (100%)	86 (83%)
Grade 2	169 (34%)	59 (32%)	96 (49%)	0 (0%)	14 (14%)
Grade 1	93 (18%)	77 (42%)	13 (6.7%)	0 (0%)	3 (2.9%)
Unknown	303	100	117	21	65
Stage					
Stage IV	463 (87%)	164 (92%)	166 (81%)	32 (89%)	101 (88%)
Stage III	38 (7.1%)	6 (3.4%)	17 (8.3%)	3 (8.3%)	12 (10%)
Stage II	32 (6.0%)	9 (5.0%)	20 (9.8%)	1 (2.8%)	2 (1.7%)
Stage I	2 (0.4%)	0 (0%)	2 (1.0%)	0 (0%)	0 (0%)
Unknown	272	103	106	10	53

[1]n (%)

Table 2. Commonly mutated genes across histological subtypes

	Mucinous Adeno carcinoma N = 282[1]	Enteric-type Adeno carcinoma N = 311[1]	Signet-Ring Cell Carcinoma N = 46[1]	Goblet Cell Carcinoma N = 168[1]	p-value[2]
KRAS	212(75%)	172(55%)	9 20%)	23(14%)	<0.001
TP53	124(44%)	185(59%)	8(17%)	57(34%)	<0.001
SMAD4	67(24%)	82(26%)	14(30%)	26(15%)	0.034
GNAS	117 (41%)	46 (15%)	3 (7%)	13 (8%)	<0.001
APC	23 (8%)	71 (23%)	2 (4%)	3 (2%)	<0.001
RHOA	1 (0.5%)	9 (3%)	2 (4%)	13 (8%)	<0.001
KDM6A	6 (2%)	8 (3%)	7 (15%)	7 (4%)	0.002
PIK3CA	21 (7%)	42 (14%)	5 (11%)	7 (4%)	0.004

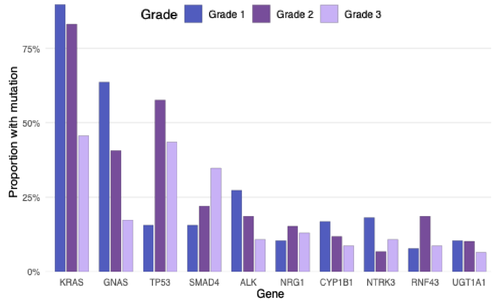
[1]n (%); [2]Fisher's exact test or Pearson's Chi-squared test when appropriate

Table 3. Common *KRAS* alterations in MA and NMA

Characteristic	Mucinous Adeno carcinoma N = 282[1]	Enteric-type Adeno carcinoma N = 311[1]	Signet-Ring Cell Carcinoma N = 46[1]	Goblet Cell Carcinoma N = 168[1]	p-value[2]
KRAS_p.G12D	104 (37%)	77 (25%)	3 (6.5%)	4 (2.4%)	<0.001
KRAS_p.G12V	57 (20%)	42 (14%)	2 (4.3%)	6 (3.6%)	<0.001
KRAS_p.G12A	0 (0%)	7 (2.3%)	1 (2.2%)	1 (0.6%)	0.028
KRAS_p.G13D	20 (7.1%)	18 (5.8%)	1 (2.2%)	3 (1.8%)	0.057
KRAS_p.G12C	13 (4.6%)	11 (3.5%)	1 (2.2%)	2 (1.2%)	0.3
KRAS_p.G12S	4 (1.4%)	4 (1.3%)	0 (0%)	1 (0.6%)	0.7
KRAS_p.Q61H	3 (1.1%)	1 (0.3%)	0 (0%)	0 (0%)	0.2
KRAS_p.A146T	5 (1.8%)	5 (1.6%)	0 (0%)	1 (0.6%)	0.8
KRAS_other	6 (2.1%)	7 (2.3%)	0 (0%)	4 (2.4%)	>0.9

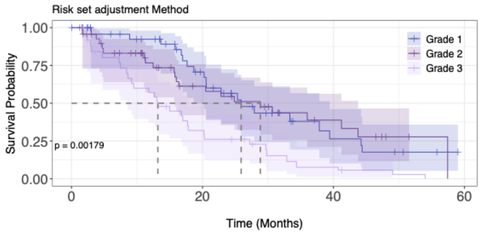
[1]n (%); [2]Fisher's exact test or Pearson's Chi-squared test when appropriate

Figure 1. Most commonly mutated genes across Grade 1, 2, and 3 MA



Grade 2 MA was genomically more like Grade 1 than Grade 3, with KRAS and GNAS rates for G1/2/3 of 90%/83%/46% and 64%/41%/17%, respectively. Top 10 most commonly mutated genes are shown.

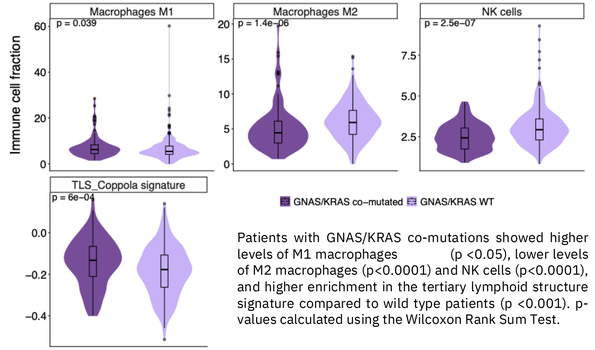
Figure 2. Comparison of OS between Grade 1, 2, and 3 MA



At Risk				
Grade 1	4	20	6	0
Grade 2	23	18	7	0
Grade 3	21	11	4	0
Events				
Grade 1	0	8	18	20
Grade 2	0	12	18	21
Grade 3	0	20	27	30

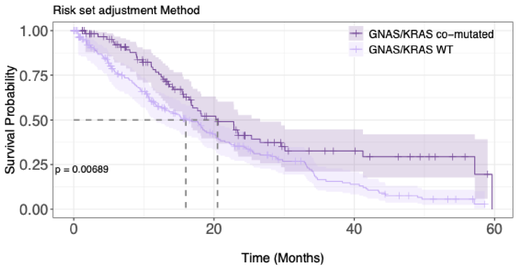
mOS was 25.9 months for Grade 1, 28.8 months for Grade 2, and 13.2 months for Grade 3 disease. p=0.002, log-rank test.

Figure 3. Comparison of immune profiles between *GNAS/KRAS* co-mutated vs. WT patients



Patients with GNAS/KRAS co-mutations showed higher levels of M1 macrophages (p <0.05), lower levels of M2 macrophages (p<0.0001) and NK cells (p<0.0001), and higher enrichment in the tertiary lymphoid structure signature compared to wild type patients (p <0.001). p-values calculated using the Wilcoxon Rank Sum Test.

Figure 4. Comparison of OS between GNAS/KRAS-mutant vs. WT patients



GNAS/KRAS co−mutated				
At Risk	7	34	10	0
Events	0	33	44	47
GNAS/KRAS WT				
At Risk	34	55	16	0
Events	0	75	108	119

mOS was 20.5 months for GNAS/KRAS co-mutated disease vs. 16 months for GNAS/KRAS WT disease. p=0.007, log-rank test.

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