From one tumour to many: Distinct genomic signatures in mucinous ovarian tumours

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INTRODUCTION

Mural nodules are an uncommon finding in mucinous ovarian tumours and are classified into sarcoma-like (reactive), anaplastic carcinomatous, and sarcomatous subtypes. Their molecular relationship to the mucinous epithelium remains unclear, as does their distinction from dedifferentiated mucinous ovarian carcinoma (DDMC), an aggressive entity composed of differentiated and undifferentiated elements.

METHODS

Targeted genomic profiling was performed on 38 mucinous ovarian tumours: cystadenomas (n=3), borderline tumours (MBT) (n=13), mucinous carcinomas (MC) (n=10), mucinous tumours with mural nodules (MTMN) (n=11; 7 anaplastic, 1 sarcoma-like, 3 sarcomatous) and DDMC (n=1). The degree of genomic alterations was assessed using variant allele frequency (VAF) and copy number alterations.

Aim: To investigate the molecular alterations underlying MTMN and compare them with mucinous tumours without mural nodules and DDMC.

RESULTS

Figure 1: Comparison of genomic signatures across mucinous ovarian tumour grades. *Bubble size indicates percentage of tumours with mutation; colour indicates mean VAF.*

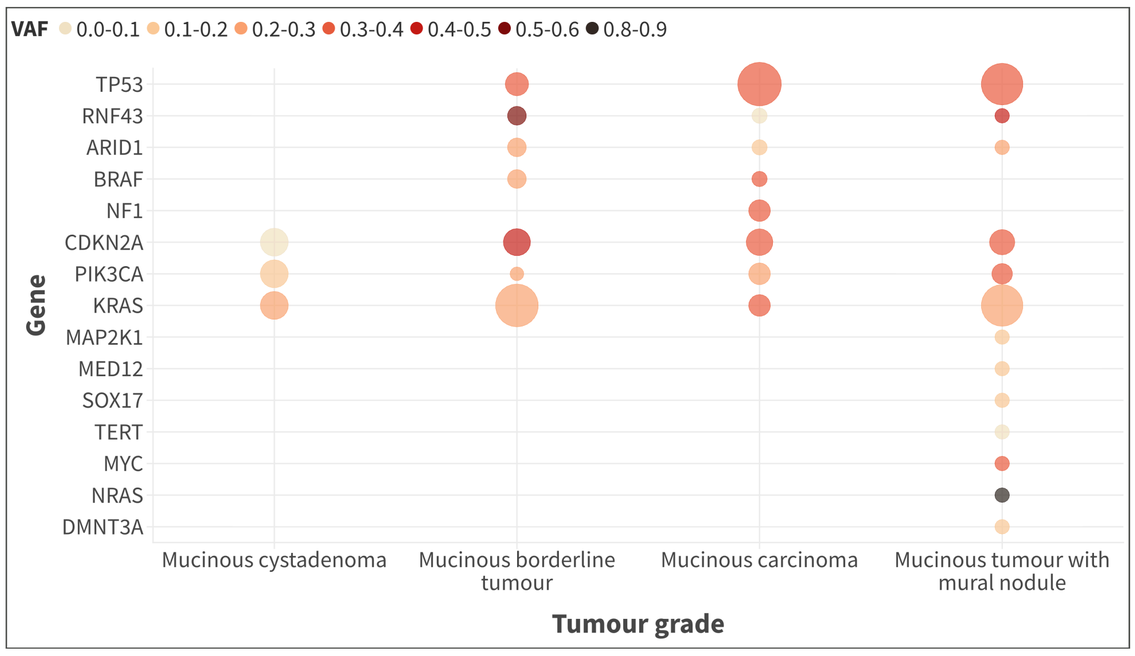

Figure 2: Comparison of copy number gains across mucinous ovarian tumour grades.

Tumour	Gene	Median copy number gain (range)
Mucinous carcinoma with anaplastic nodule (n=1)	MYC	24
	ERBB2	89
Mucinous borderline tumour (n=2)	ERBB2	43 (37-49)
Mucinous carcinoma (n=3)	ERBB2	54 (15-63)

Figure 3: Key histopathological features across tumour grades and components.

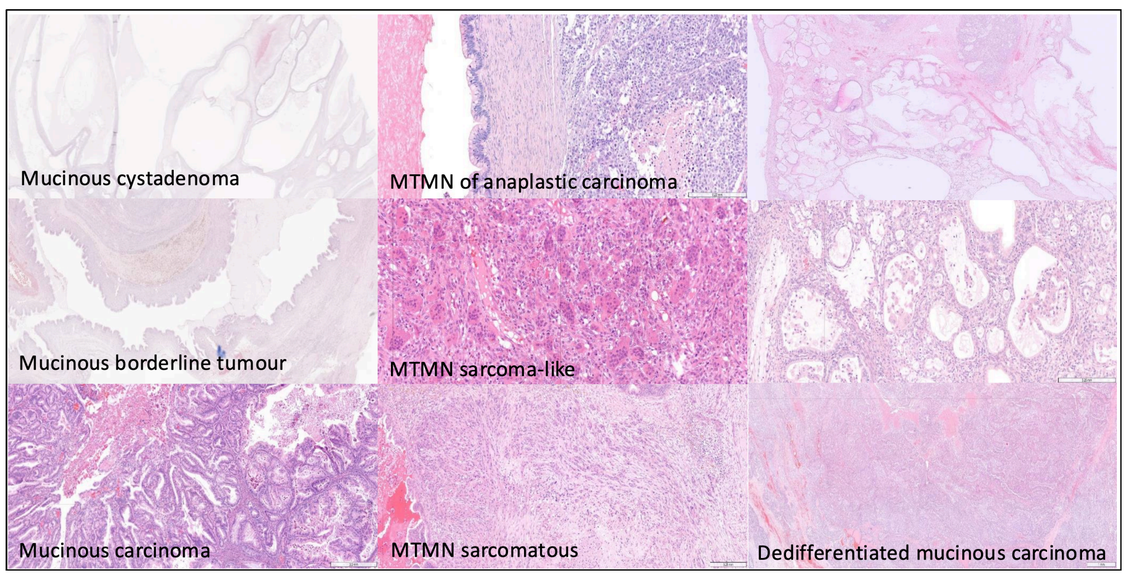

Figure 4a. Comparison of genomic signatures between mucinous ovarian tumours and corresponding mural nodules.

Case	Mucinous	Mural nodule	Gene	Consequence	DNA	Protein	Pathogenecity
Case 1	MC	Anaplastic	TP53	Missense	c.743G>A	p.(arg248Gln)	Pathogenic
			KRAS	Missense	c.35G>T	p.(Gly12Val)	Pathogenic
			PIK3CA	Missense	c.1633G>A	p.(Glu545Lys)	Pathogenic
			ARID1	Stop Gained	c.1011G>A	p.Trp337Ter	Likely pathogenic
Case 2	MBT	Sarcoma	TP53	Missense	c.524G>A	p.(Arg175His)	Pathogenic
			TP53	Frameshift	c.714dup	p.(Asn239Ter)	Pathogenic
			KRAS	Missense	c.182A>G	p.(Gln61Arg)	Pathogenic
			DMNT3A	Frameshift	c.1258_1264del	p.(Lys420TrpfsTer229)	Likely pathogenic
			CDKN2A	Frameshift	c.225del	p.(Ala76Profster70)	Pathogenic
Case 3	MC	Anaplastic	TP53	Missense	c.733G>A	p.(Gly245Ser)	Pathogenic
			KRAS	Missense	c.35G>A	p.(Gly12Asp)	Pathogenic
Case 4	MC	Anaplastic	KRAS	Missense	c.34G>A	p.(Gly12Ser)	Pathogenic
Case 5	MBT	Sarcoma-like	NRAS	Missense	c.182A>G	p. (Gln61Arg)	Pathogenic
			MYC	Missense	c.482C>T	p.(Ser161Leu)	Likely pathogenic

Figure 4b. Comparison of VAF between mucinous ovarian tumours and corresponding mural nodules.

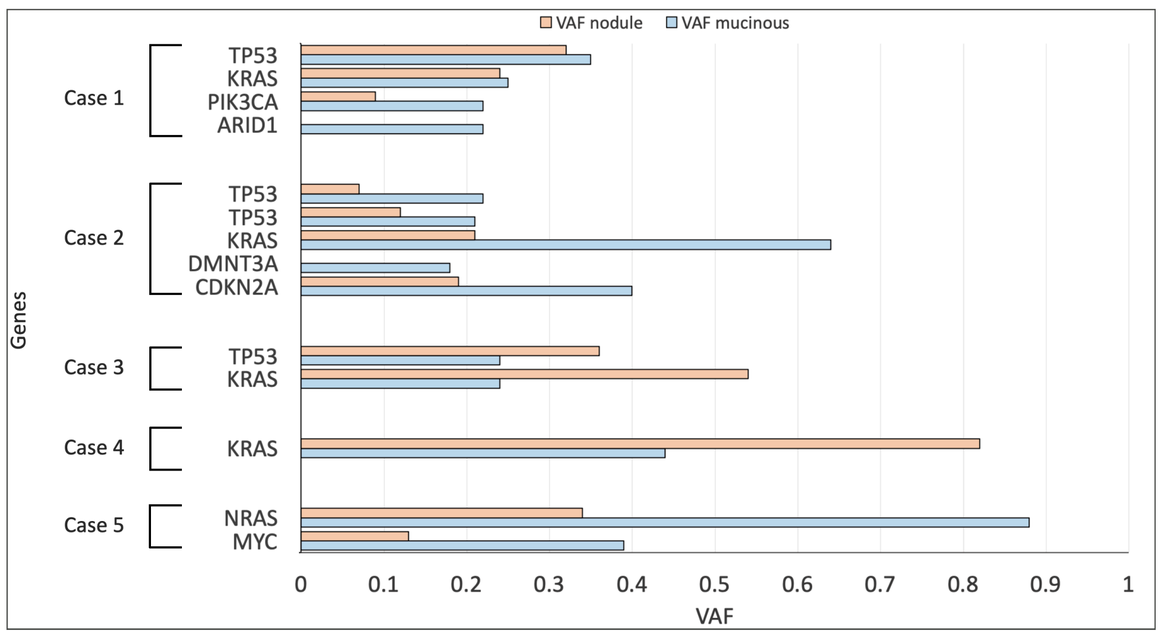

Figure 5: Genomic signatures of one case of DDMC

Gene	Consequence	DNA	Protein	VAF	Pathogenicity
BRCA2	Splice variant	c.8332-2A>C		0.64	Likely Pathogenic
SMARCA4	Nonsense	c.3979G>T	p.(Glu1327Ter)	0.11	Pathogenic
ARID1	Nonsense	c.5152G>T	p.(Glu1718Ter)	0.34	Likely Pathogenic
TP53	Nonsense	c.853G>T	p.(Glu285Ter)	0.53	Likely Pathogenic
STK11	Splice Variant	c.596_597+21del		0.52	Likely Pathogenic
EP300	Missense	c.4241A>G	p.(Tyr1414Cys)	0.5	Likely Pathogenic
KRAS	Amplification (16.3 fold)				
MSI	No evidence				

DISCUSSION

1. Grade-Associated Genomic Accumulation and Molecular Heterogeneity in Mucinous Ovarian Tumours

Across the cohort, early driver alterations (*KRAS*, *CDKN2A*, *PIK3CA*) were identified in cystadenomas and persisted through borderline tumours and mucinous carcinoma, consistent with their role as truncal driver mutations. Higher-grade tumours demonstrated increased mutational burden, including recurrent *TP53* mutations and copy-number gains involving *ERBB2* and *MYC*. Several alterations showed non-linear distribution across grades (*RNF43*, *ARID1A*, *BRAF*, *NF1*), highlighting the molecular heterogeneity of mucinous tumours.

2. Compartment-Specific Molecular Differences Between Mucinous Epithelium and Mural Nodules

The shared presence of key driver mutations, *KRAS* and *TP53*, in mucinous epithelium and mural nodules supports a clonal origin. However, MTMN diverge at two levels. First, they acquire additional genomic alterations; our results further identify novel *TERT*, *MAP2K1*, *MED12*, and *SOX17* mutations in MTMN, which were absent in mucinous tumours without mural nodules. Second, MTMN demonstrate intratumoural divergence; for example, *ARID1* and *DMNT3A* mutations were present in the mucinous component but absent in the mural nodules.

Compartment-restricted alterations (e.g. *DNMT3A*) and differential VAFs (e.g. *CDKN2A*) suggest molecular divergence between components rather than 'collision tumours'.

3. DDMC are distinct from MTMN, driven by triple impairment of DNA repair and chromatin remodelling

DDMC showed concurrent disruption of chromatin-remodelling (*SMARCA4*, *ARID1A*) and homologous recombination repair (*BRCA2*), a combination not previously described in this tumour type [1]. Although emerging data in other tumour contexts demonstrate functional links between SWI/SNF complexes and HRR pathways [2], the relevance of this interaction in mucinous ovarian carcinoma remains to be clarified. The *BRCA2* alteration indicates HRR impairment, which may contribute to genomic instability when occurring alongside SWI/SNF deficiency.

This pattern is distinct from MTMN and supports DDMC as a separate molecular entity. The presence of HRR impairment may raise the possibility of susceptibility to PARP inhibition.

CLINICAL IMPACT

These findings support the value of integrating morphology with targeted genomic profiling, particularly where mucinous and mural components show discordant molecular features. Identifying compartment-specific alterations may assist in distinguishing MTMN from DDMC or sarcoma in diagnostically challenging cases.

The concurrent SWI/SNF disruption and BRCA2-associated HRR impairment observed in DDMC may have therapeutic relevance, including potential sensitivity to PARP inhibitors, although this remains early evidence and should be validated with a larger series.

REFERENCES:
1. Tessier-Cloutier B, Kommoss FKF, Kolin DL, Němejcová K, Smith D, Pors J, et al. Dedifferentiated and undifferentiated ovarian carcinoma: an aggressive and molecularly distinct ovarian tumor characterized by frequent SWI/SNF complex inactivation. Mod Pathol 2024; 37 (1): 100374.
2. Bochar DA, Wang L, Beniya H, Kinev A, Xue Y, Lane WS, et al. BRCA1 is associated with a human SWI/SNF-related complex: linking chromatin remodeling to breast cancer. Cell 2000 21; 102 (2): 257-65.

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