Histomorphology of pancreatic cancer in patients with inherited atm serine/threonine kinase pathogenic variants

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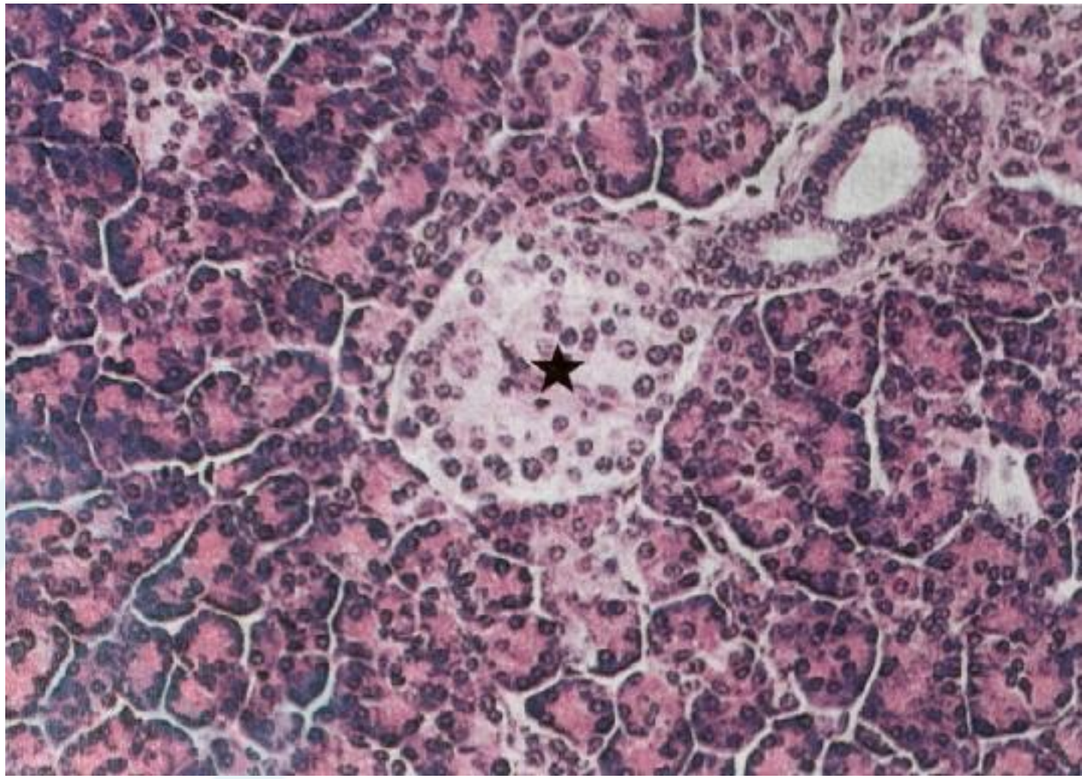
Pancreas

- 胰腺主要由腺泡和导管组成
- 外分泌部（腺泡）是重要的消化腺，分泌胰液经导管排入十二指肠，参与食物消化
- 内分泌部称胰岛，分泌激素进入血液或淋巴，参与调节糖代谢



Pancreatic Cancer

- Pancreatic cancer is a particularly lethal form of cancer with a 5-year survival rate of only 9%.
- To date, pathogenic variants in ATM, BRCA1, BRCA2, CPA1, CPB1, TP53, and the mismatch repair genes (MLH1, MLH2, PMS2, MSH6) are known to be associated with an increased risk of pancreatic ductal adenocarcinoma.
- Identification of these variants are important for targeted treatment, screening and prevention of other cancers, and genetic counseling of families.

Pancreatic Cancer

Malignant epithelial tumours

8500/3	Duct adenocarcinoma NOS
8480/3	Colloid carcinoma
8490/3	Poorly cohesive carcinoma
8490/3	Signet-ring cell carcinoma
8510/3	Medullary carcinoma NOS
8560/3	Adenosquamous carcinoma
8576/3	Hepatoid carcinoma
8014/3	Large cell carcinoma with rhabdoid phenotype
8020/3	Carcinoma, undifferentiated, NOS
8035/3	Undifferentiated carcinoma with osteoclast-like giant cells
8550/3	Acinar cell carcinoma
8551/3	Acinar cell cystadenocarcinoma
8154/3	Mixed acinar-neuroendocrine carcinoma
8154/3	Mixed acinar-endocrine-ductal carcinoma
8552/3	Mixed acinar-ductal carcinoma
8971/3	Pancreatoblastoma
8452/3	Solid pseudopapillary neoplasm of the pancreas
	Solid pseudopapillary neoplasm with high-grade carcinoma

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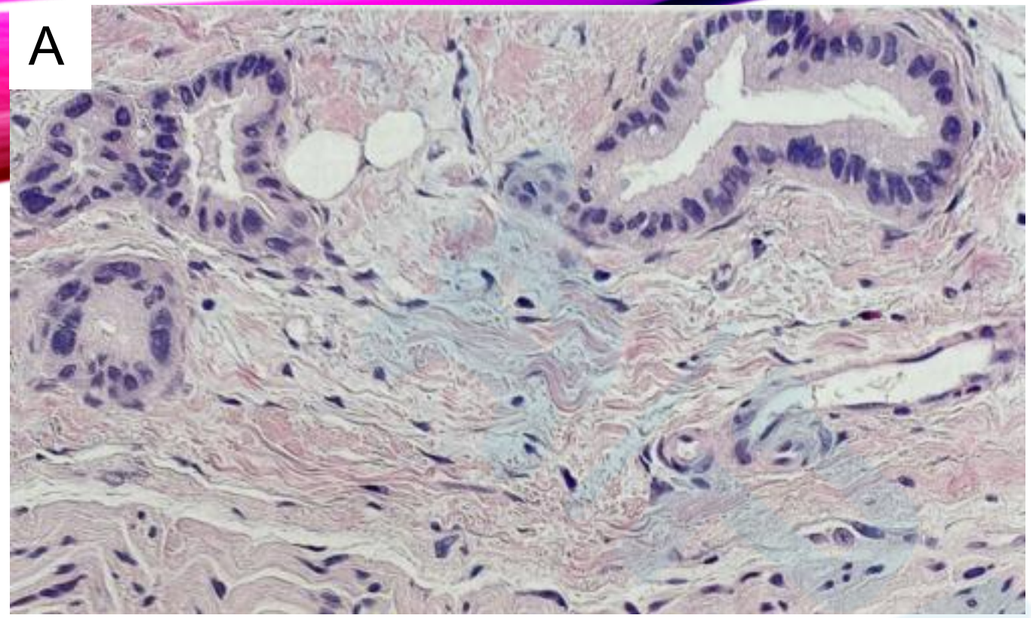

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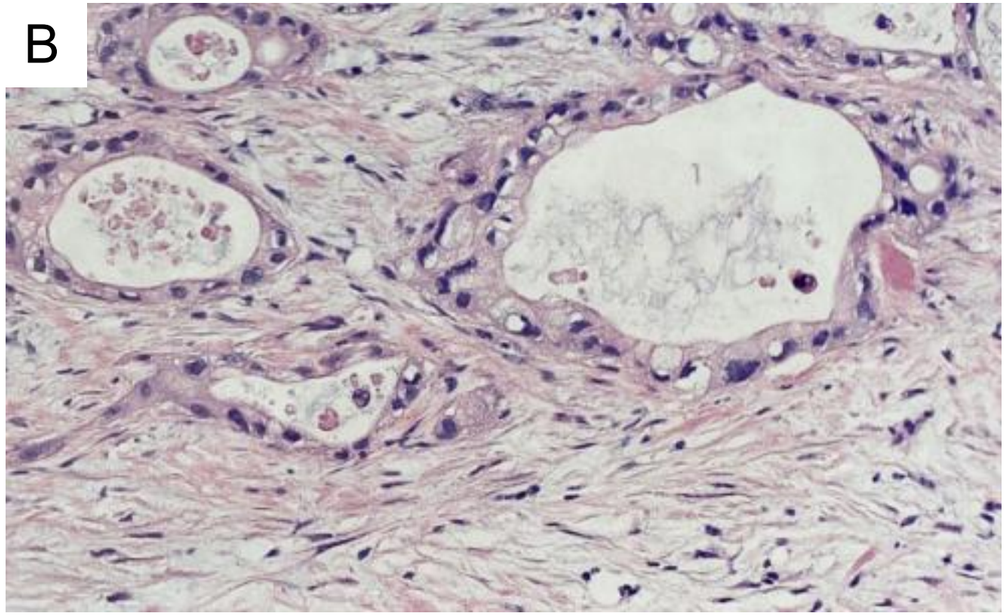

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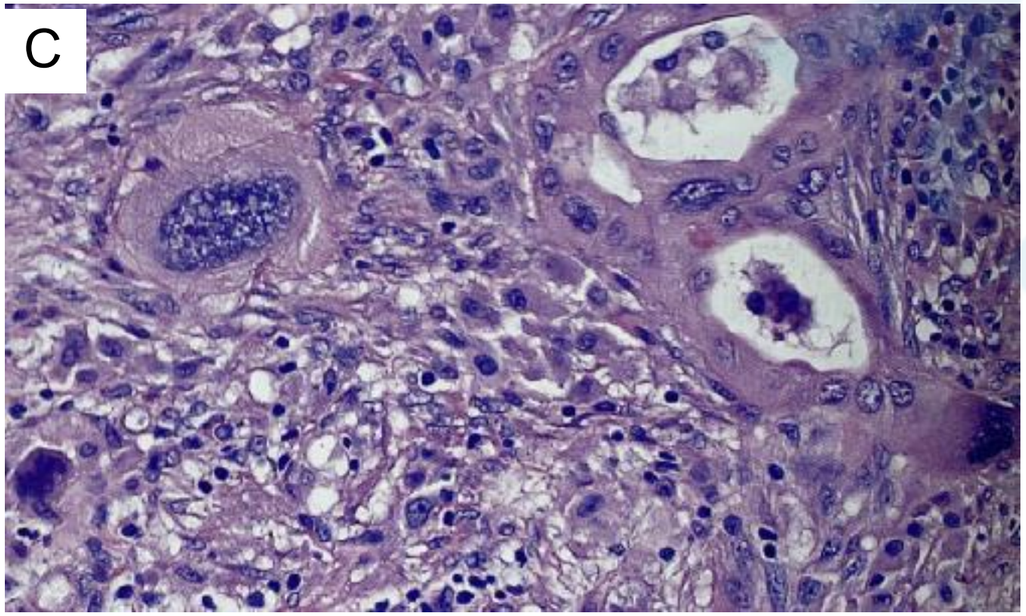

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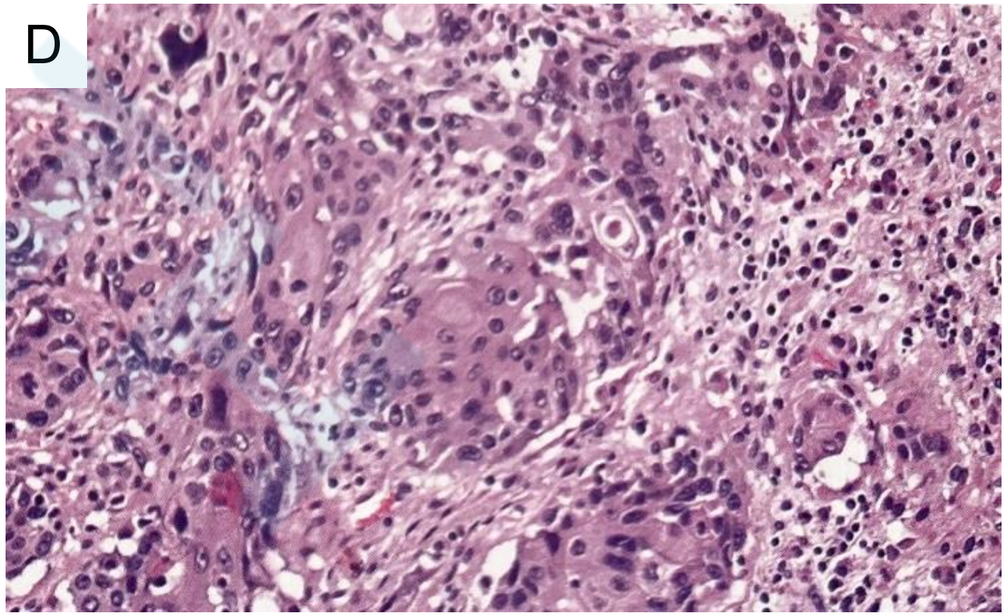


ATM Serine/Threonine Kinase (ATM) Gene

- The ATM (ataxiatelangiectasia mutated gene) serine/threonine kinase (ATM) gene .
- It was subsequently discovered that carriers of germline ATM pathogenic variants are at significantly increased risk of breast cancer （*Ahmed M, Rahman N. ATM and breast cancer susceptibility.Oncogene 2006;25:5906–11.*）

ATM Serine/Threonine Kinase (ATM) Gene

- Roberts *et al.* first described ATM as a pancreatic cancer susceptibility gene in familial pancreatic cancer patients in 2012. *(Roberts NJ, et al. ATM mutations in patients with hereditary pancreatic cancer. Cancer Discov. 2012;2:41–46)*
- Cancers with loss of ATM are important to identify for treatment purposes as they are potentially targetable with poly(ADP-ribose) polymerase 1 inhibitors, ATR serine/threonine kinase inhibitors, DNA-protein kinase catalytic subunit inhibitors, and radiation therapy.
- The identification of a germline pathogenic ATM variant would also have obvious implications for the patient's other family members.

Materials and Methods--Patient Selection

- For each patient, demographic data including age, sex, and race were obtained from pathology records.
- The electronic medical records were searched for clinical information including family history of cancer, personal history of other cancers, treatment with neoadjuvant and/or adjuvant chemotherapy and/or radiation, disease recurrence, and patient survival.

Pathologic Review

- For each patient, all available hematoxylin and eosin stained slides were reviewed from resection and/or biopsy specimens.
- Pancreatic carcinomas were classified by histologic subtype according to World Health Organization criteria.
- Cases were reviewed for the presence or absence of neoplastic precursor lesions, such as pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasm, which when present were classified and graded for dysplasia based on consensus recommendations.

Pathologic Review

- The area of pancreas uninvolved by tumor was measured and the number of duct profiles containing neoplastic precursor lesions were counted. The density of precursor lesions per square centimeter (cm2) of pancreatic parenchyma was calculated.

Pathologic Review

- Treatment effect
- No residual tumor was considered complete response, single cells or rare small groups of cells in a fibrotic background a marked response, residual cancer outgrown by fibrosis was moderate response, and extensive residual cancer was poor response.

Table 1 Clinicopathologic characteristics of pancreatic cancer patients with inherited *ATM* pathogenic variants

Patient	*ATM* mutation (NP_000042.3)	Age	Sex	Race	Histologic subtype	Treatment	Pathologic stage	Pathologic response	Follow-up
1	p.Ser1799MetfsTer8	50–59	M	White	Ductal adenocarcinoma	Adjuvant chemotherapy and radiation therapy	pT1c pN1	N/A	Alive with disease (112 mos.)
2	Splicing	50–59	M	White	Ductal adenocarcinoma	Adjuvant chemotherapy	pT1a pN0	N/A	No evidence of disease (28 mos.)
3	p.Leu2077PhefsTer5	60–69	F	No data	Ductal adenocarcinoma	None	pT1c pN0	N/A	No evidence of disease (2 mos.)
4	p.Gln284Ter	70–79	M	White	Ductal adenocarcinoma	Adjuvant chemotherapy	pT2 pN1	N/A	Deceased of unrelated cause (69 mos.)
5	p.Lys2756Ter	<50	F	White	Ductal adenocarcinoma	Adjuvant chemotherapy and radiation therapy	pT2 pN1	N/A	Deceased of unrelated cause (149 mos.)
6	p.Ala911ArgfsTer19	60–69	M	White	Ductal adenocarcinoma	Adjuvant chemotherapy and radiation therapy	pT2 pN1	N/A	Deceased of unknown cause (60 mos.)
7	p.Met1Ile	60–69	M	White	Ductal adenocarcinoma	Adjuvant chemotherapy	pT2 pN2	N/A	Alive with disease (18 mos.)
8	Splicing	50–59	M	No data	Ductal adenocarcinoma	ND	pT2 pN2	N/A	No data
9	p.Glu522IlefsTer43	60–69	M	White	Ductal adenocarcinoma	None	pT2 pN0	N/A	No evidence of disease (4 mos.)
10	p.Gln2729Ter	70–79	F	No data	Ductal adenocarcinoma	None	pT2 pN1	N/A	No evidence of disease (4 mos.)
11	p.Phe2799LysfsTer4	<50	M	White	Colloid (mucinous non-cystic) carcinoma	No data	pT1a pN0	N/A	No data
12[a]	p.Glu1072Ter	60–69	F	No data	Ductal adenocarcinoma	No data	N/A	N/A	No data
13	Splicing	50–59	M	White	Colloid (mucinous non-cystic) carcinoma	None	pT3 pN2	N/A	Alive with disease (38 mos.)
14	p.Gln1970Ter	70–79	F	Other	Adenosquamous carcinoma	None	pT1c pN0	N/A	No evidence of disease (31 mos.)
15	Splicing	60–69	F	White	Ductal adenocarcinoma	Neoadjuvant chemotherapy	ypT2 ypN2	Poor	Deceased of unrelated cause (24 mos.)
16	Splicing	60–69	F	White	Ductal adenocarcinoma	Neoadjuvant chemotherapy and adjuvant chemotherapy	ypT2 ypN2	Poor	No evidence of disease (30 mos.)
17	p.Arg457Ter	70–79	F	White	Ductal adenocarcinoma	Neoadjuvant chemotherapy and adjuvant chemotherapy	ypT2 ypN2	Moderate	No evidence of disease (40 mos.)
18	p.Glu522IlefsTer43	<50	M	White	Ductal adenocarcinoma	Neoadjuvant chemotherapy, adjuvant chemotherapy and radiation therapy	ypT2 ypN2	Poor	Deceased of disease (10 mos.)
19	Splicing	70–79	F	White	Ductal adenocarcinoma	Adjuvant chemotherapy	pT2 ypN0	N/A	No evidence of disease (98 mos.)
20	p.Arg2443Ter	50–59	M	White	Ductal adenocarcinoma	Neoadjuvant chemotherapy and radiation therapy	ypT1b ypN0	Marked	Alive with disease (58 mos.)

Results--Patient Characteristics

Table 1 (continued)

Patient	*ATM* mutation (NP_000042.3)	Age	Sex	Race	Histologic subtype	Treatment	Pathologic stage	Pathologic response	Follow-up
21	p.Arg2993Ter	70–79	F	Other	Ductal adenocarcinoma	Neoadjuvant chemotherapy and adjuvant chemotherapy	ypT1c(m) ypN2	Poor	Alive with disease (32 mos.)
22	p.Glu2807Ter	50–59	F	White	Ductal adenocarcinoma	Neoadjuvant chemotherapy and adjuvant chemotherapy	ypT2 pN1	Poor	Alive with disease (61 mos.)
23	p.Tyr2791GlyfsTer14	<50	F	White	Colloid (mucinous non-cystic) carcinoma	Adjuvant chemotherapy	pT2 pN2	N/A	No evidence of disease (10 mos.)

N/A not applicable

[a]Indicates biopsy specimen

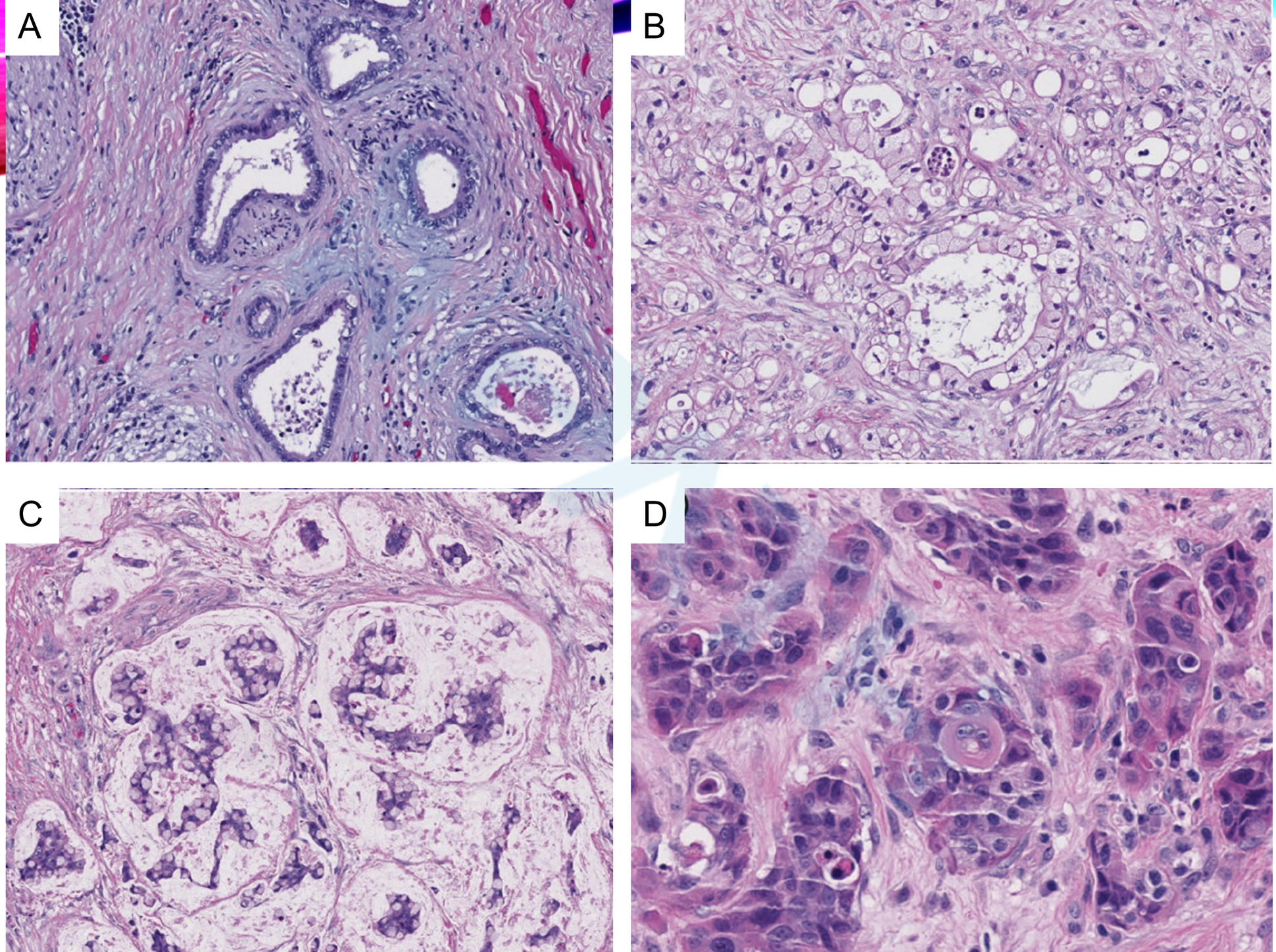
Table 2 Gross and histomorphologic characteristics of pancreatic cancers in patients with germline *ATM* pathogenic variants

Tumor size, median ($n = 22$)	2.8 cm (range 0.1–4.8 cm)
Tumor site ($n = 22$)	
Head, *n* (%)	16 (72)
Body, *n* (%)	3 (14)
Tail, *n* (%)	3 (14)
Histologic subtype ($n = 23$)	
Ductal adenocarcinoma, *n* (%)	19 (83)
Colloid (mucinous non-cystic) carcinoma, *n* (%)	3 (13)
Adenosquamous carcinoma, *n* (%)	1 (4)
Perineural invasion ($n = 22$)	
Absent, *n* (%)	2 (9)
Present, *n* (%)	20 (91)
Angiolymphatic invasion ($n = 22$)	
Absent, *n* (%)	9 (41)
Present, *n* (%)	13 (59)
Lymph node metastasis ($n = 22$)	
None, *n* (%)	7 (32)
1–3, *n* (%)	6 (27)
4 or more, *n* (%)	9 (41)

Table 3 Comparison of histologic subtype between patients with germline *ATM* pathogenic variants and familial or sporadic pancreatic cancer patients

Histologic subtype	Patients with germline *ATM* pathogenic variants ($n = 23$)	Familial pancreatic cancer patients ($n = 519$)	*p*-value	Sporadic pancreatic cancer patients ($n = 651$)	*p*-value
Colloid carcinoma, *n* (%)	3 (13)	4 (1)	0.002	10 (2)	0.008
Other (non-colloid) carcinoma, *n* (%)	20 (87)	515 (99)		621 (98)	

Data for familial and sporadic pancreatic cancer patients from Singhi et al. [27]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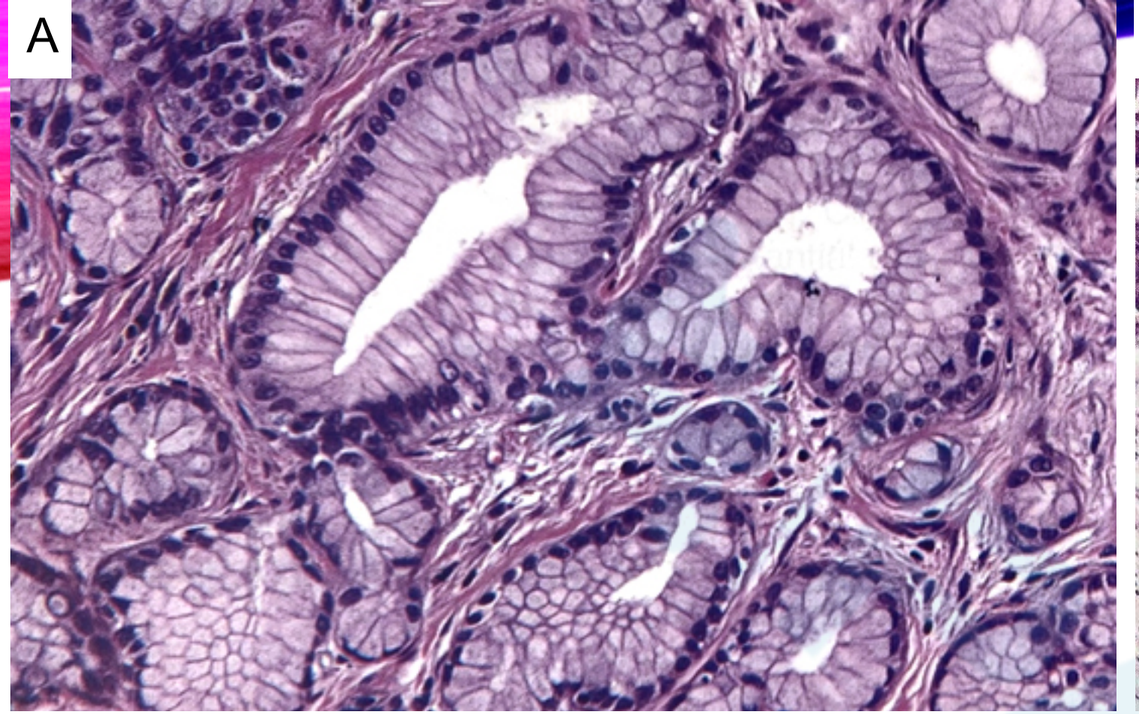
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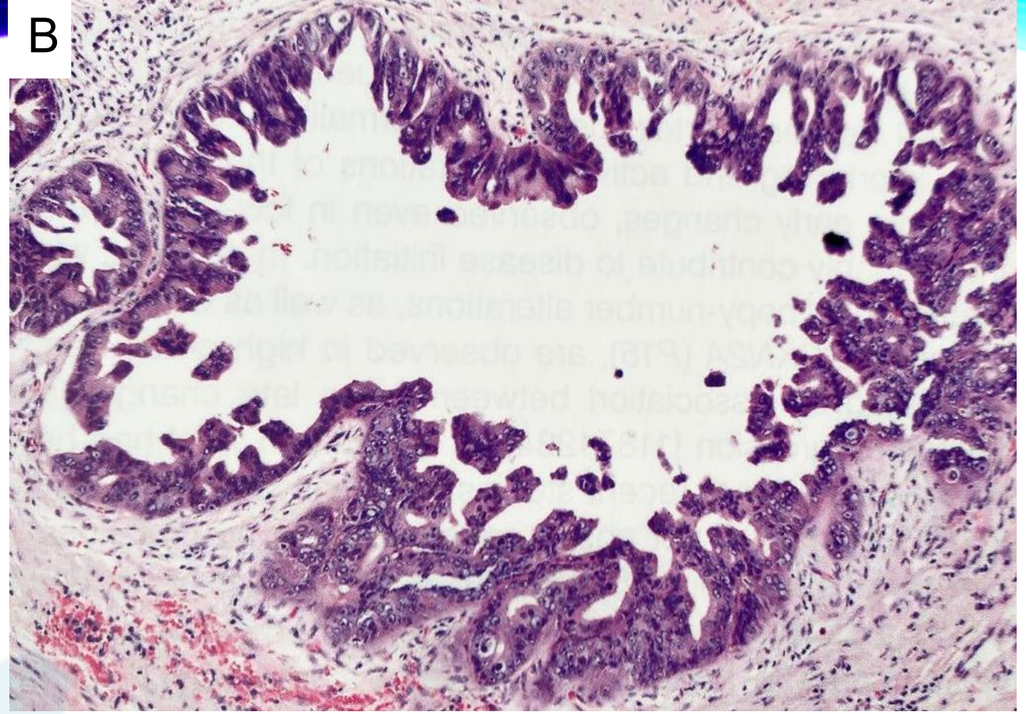
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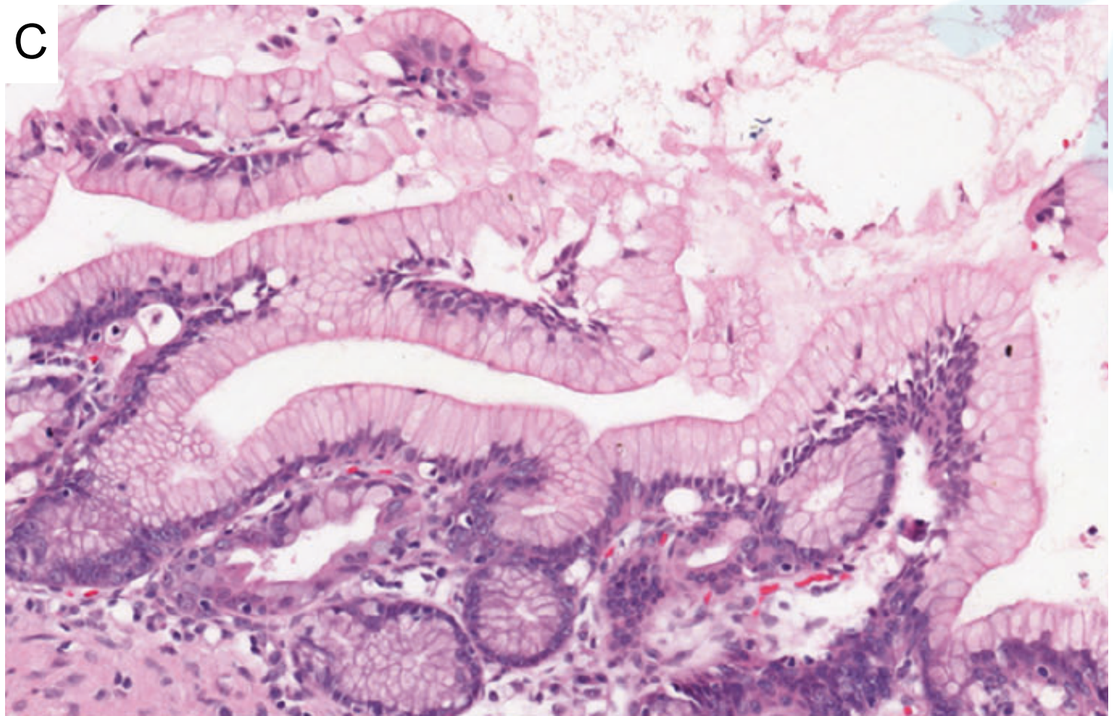
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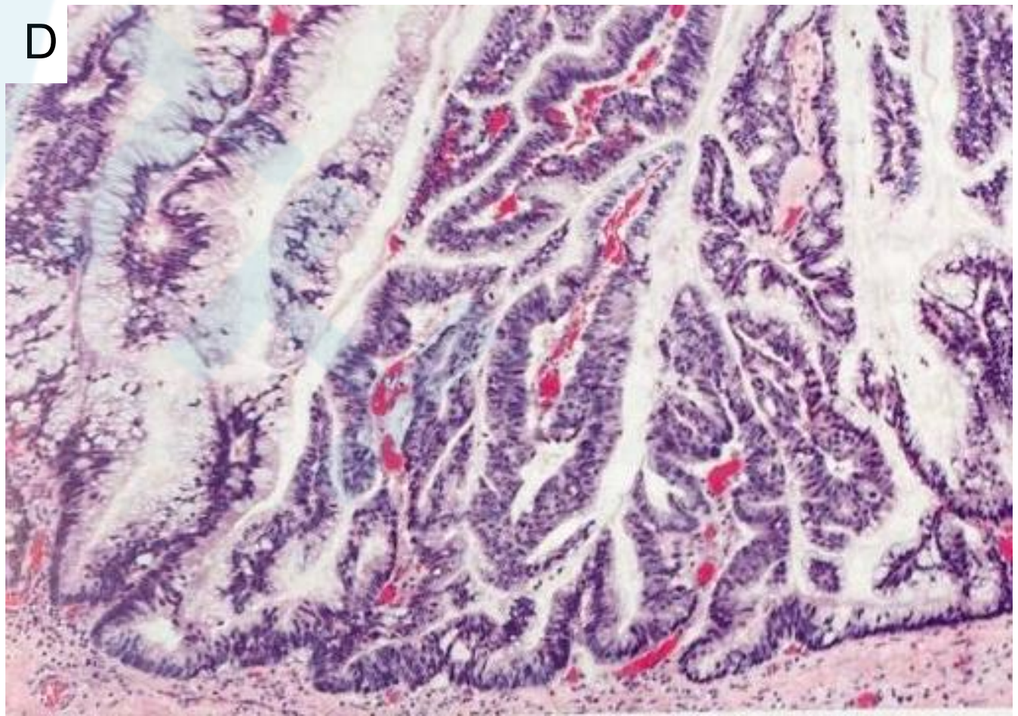
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Table 4 Precursor lesions in patients with germline *ATM* pathogenic variants

	Average number per cm^2 ($n = 18$)[a]
Total precursors	2
Low-grade incipient intraductal papillary mucinous neoplasms	0
Low-grade pancreatic intraepithelial neoplasia	2

[a]Average number per cm^2 rounded to nearest whole number

Discussion

- The identification of germline pathogenic variants in patients with pancreatic cancer is crucial to improving treatment and prevention of this deadly disease.
- In some situations, certain pathologic features may prompt germline testing.

Discussion

- In this study, we examined the histomorphology of pancreatic cancers in patients with germline ATM pathogenic variants and found that the majority of patients (83%) had conventional ductal adenocarcinoma.
- Interestingly, patients with a germline ATM pathogenic variant had more cancers with colloid (mucinous non-cystic) carcinoma histology.

Discussion

- One patient received neoadjuvant combination chemotherapy/radiation and had a more significant pathologic treatment response than patients treated with chemotherapy alone. This appears consistent with evidence that ATM deficient pancreatic cancer cells are more susceptible to radiation.

Discussion

- However, there was no statistically significant difference in progression-free survival for patients receiving neoadjuvant and/or adjuvant treatment compared to those treated with surgery alone.

Summary

- We present the clinicopathologic characteristics of pancreatic cancers in 23 patients with germline ATM pathogenic variants, the largest series to date.
- We found significantly more patients had colloid (mucinousnon-cystic) carcinoma histology compared to previously published data from sporadic and familial pancreatic cancer patients.

THANKS FOR YOUR ATTENTION!