Pancreatic intraductal tubulopapillary neoplasm is genetically distinct from intraductal papillary mucinous neoplasm and ductal adenocarcinoma

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胰腺导管腺癌

- WHO 定义：一种几乎完全发生于成人的肿瘤，可能来自胰腺导管上皮，并且在表现上与之类似，可产生黏液，并表达特征的细胞角蛋白。

- 癌前病变

导管上皮内瘤变（PanIN）

胰腺导管腺癌

- 分子遗传学

*KRAS*密码子12的激活点突变，最常见

*p16*和*TP53*抑癌基因的基因改变

*BRCA2*和*DPC4*的缺失

- 胰腺导管内肿瘤，包括导管内乳头状黏液性肿瘤（IPMN）和导管内管状乳头状肿瘤（ITPN），是胰腺导管系统内原发并大体可见（囊性或实性）的上皮性肿瘤，伴有导管上皮分化

胰腺导管内乳头状黏液性肿瘤（IPMN）

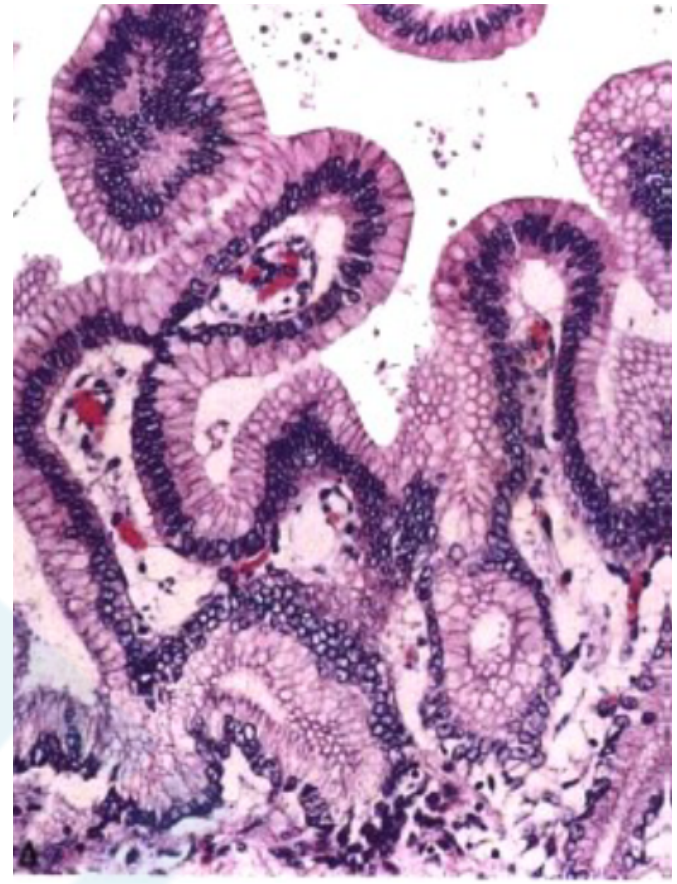
- WHO 定义：大体可见导管内产黏液的上皮性肿瘤，主要发生在胰腺的主胰管及其分支内。肿瘤上皮通常乳头状生长，黏液分泌及导管扩张程度不等，及不同程度的上皮异型增生。

- ICD-O编码：

IPMN伴轻度或中度异型增生	8453/0
IPMN伴高度异型增生	8453/2
IPMN相关浸润性癌	8453/3

组织病理学

- 导管内柱状黏液细胞增生为特点。典型病变上皮形成乳头状或假乳头状结构，部分肿瘤可以由非乳头状上皮构成。



胰腺导管内乳头状黏液性肿瘤（IPMN）

- 基因改变
- KRAS 突变在IPMN是最常见的突变，且在大多数肿瘤中可检测到
- TP53 突变 发生在具高度不典型增生的肿瘤
- 可检测到CDKN2A 突变

胰腺导管内乳头状黏液性肿瘤（IPMN）

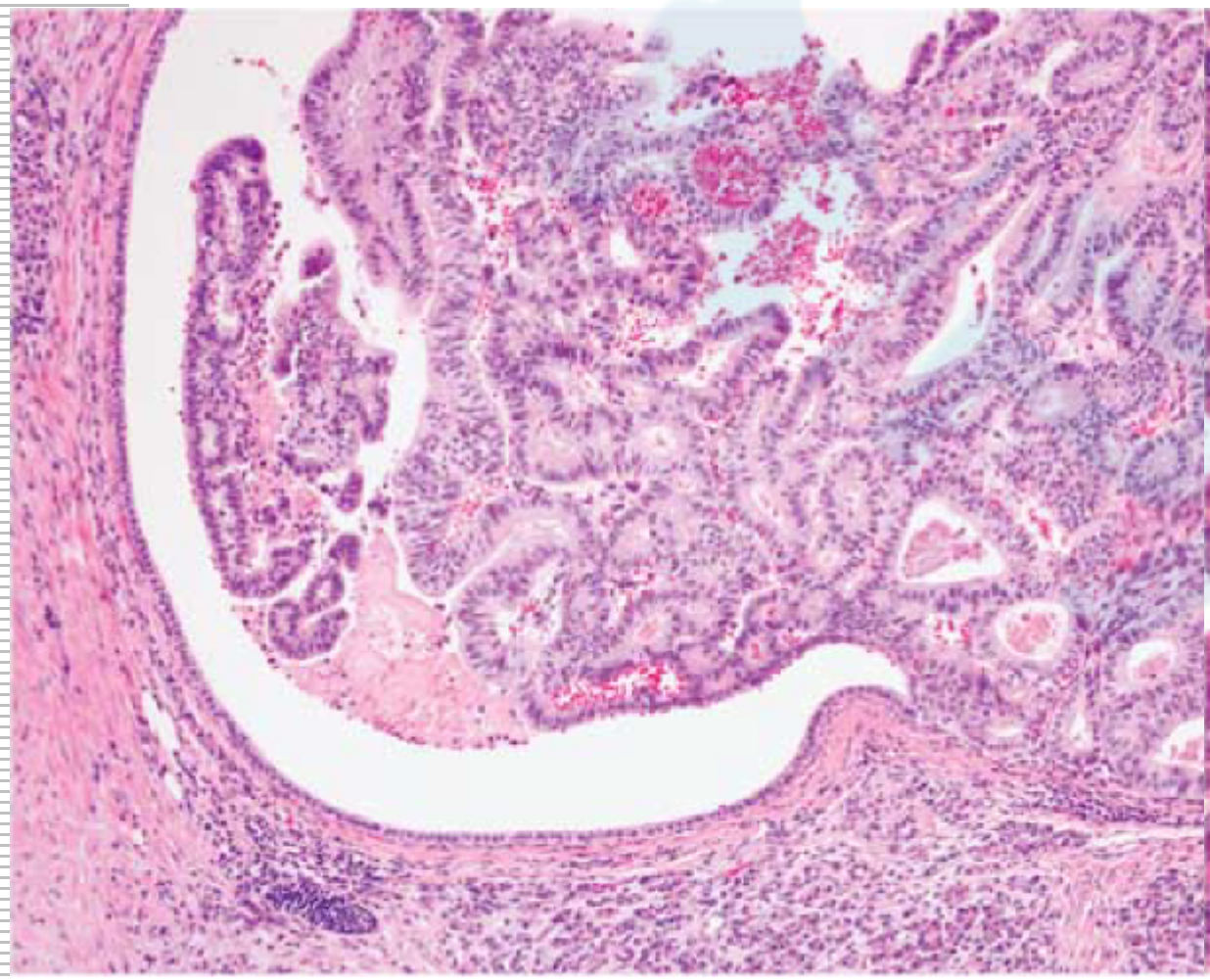
- 基因改变
- GNAS 突变已在将近一半的 IPMN中得到证实，尤其是肠型IPMN
- RNF43 的突变在IPMN常见
- 少见改变包括PIK3CA, SMAD4,BRAF,CTNNB1/β-catenin, IDH1, STK11, PTEN, ATM, CDH1, FGFR3, SRC

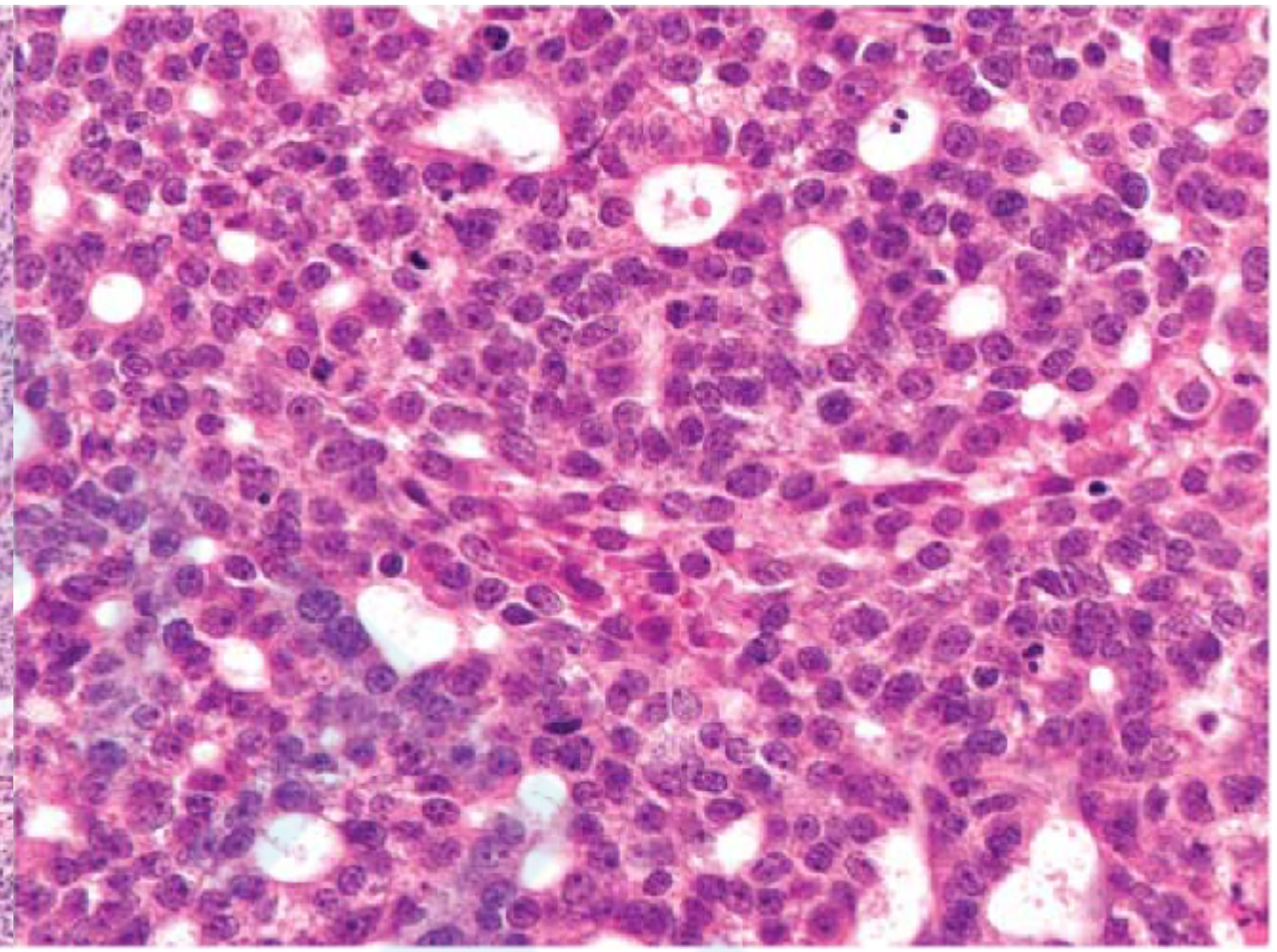
胰腺导管内管状乳头状肿瘤(ITPN)

- WHO 将ITPN 定义为:导管内生长并大体可见的上皮性肿瘤，小管状结构伴上皮重度异型增生，无黏液过度分泌，局灶管状乳头状生长方式可见
- 如伴有浸润性癌成分则命名为导管内管状乳头状肿瘤伴浸润性癌
- ITPN少见，不足胰腺外分泌肿瘤的1%，仅占导管内肿瘤的3%。目前病例数有限，男女比例均等，35-84岁均可发生，平均年龄56岁

病理特点

- 结节内小管状“背靠背”的排列，偶可见乳头状结构，在扩张的大胰管内呈筛状
- 大部分ITPN以小管状结构为主，甚至仅有小管结构，少许病例可见乳头。实性区可见杂乱的腺体
- 部分肿瘤结节梗阻管腔，形成表面被覆纤维间质的边界清楚的细胞巢。
- 无或很少的黏液样分泌
- 主要为相对均一的立方上皮构成，中等量的胞浆嗜酸性或双嗜性胞浆
- 核分裂（0-9个/10HPF）和坏死(偶见粉刺样坏死)
- CK7和CK19阳性，但缺乏MUC5AC、腺泡细胞或神经内分泌标志物





IPMN和ITPN的异同

均形成大体及影像学检查可见的导管内生长的肿块
都可以有管状和乳头状生长方式

病理参数	IPMN	ITPN
中位发病年龄	60 岁	64 岁
男:女	2.38:1	1.11:1
发生部位 (胰头部:胰体尾部)	3.26:1	2:1
临床表现	腹痛、呕吐等消化道症状,体重减轻,梗阻性黄疸	腹痛、呕吐等消化道症状,体重减轻,梗阻性黄疸
大体特征	中央型:主胰管内乳头状或菜花样隆起,见黏液分泌;周围型:多囊性改变,囊内可见乳头样隆起,见黏液分泌	导管内实性多结节状占位,罕见黏液分泌。
组织学特征	以分支乳头状排列为主,可见腺管及筛孔结构,大部分病例肿瘤细胞胞质内含黏液,可伴有浸润性癌成分	以腺管样及筛孔样排列为主,罕见乳头结构,细胞内无黏液,胞核异型明显,可伴有浸润性癌成分
免疫表型	MUC2(+),MUC5AC(+)	MUC2(-),MUC5AC(-)
K-ras 基因突变	半数病例可出现[3-4]	少见
预后	一般较好,若出现浸润性癌成分则较差	一般较好,若出现浸润性癌成分则较差

胰腺导管内管状乳头状肿瘤(ITPN)

- 有关ITPN的基因遗传学数据有限，因为肿瘤罕见
- 首次报道ITPN，对其进行转录谱分析和聚类分析，ITPN的转录谱与胰腺导管腺癌和其他胰腺囊性肿瘤的转录谱明显不同。

Aimed

- further define the genetic underpinnings of intraductal tubulopapillary neoplasm and analyzed 22 cases by targeted next-generation sequencing or whole-exome sequencing

Materials and methods

- patients with diagnoses of pancreatic intraductal tubular carcinoma or intraductal tubulopapillary neoplasm.
- the major genes known to be altered in pancreatic ductal adenocarcinoma and intraductal papillary mucinous neoplasm, including KRAS,TP53, CDKN2A, SMAD4, GNAS, and RNF43

Materials and methods

- Targeted Next-Generation Sequencing
- Targeted Cancer Gene Panel Sequencing
- Whole-Exome Sequencing
- Whole-Genome Sequencing

Results–Clinicopathologic Features

Table 1 Clinicopathologic features of the cases

Mean age (range) (years)	58 (21–75)
Male/female	1.4
Type of specimen	*n* (%)
Pancreaticoduodenectomy	10 (48)
Distal pancreatectomy	7 (33)
Total pancreatectomy	3 (14)
Biopsy	1 (5)
Unknown	1
Tumor location	*n* (%)
Head	9 (47)
Body	2 (11)
Tail	5 (26)
Diffuse	3 (16)
Unknown	3
Median overall tumor size (range)	3.3 cm (0.9–16)
Invasive component	*n* (%)
Present	17 (81)
Absent	4 (19)
Unknown (biopsy case)	1
Lymphovascular invasion	*n* (%)
Yes	7 (39)
No	11 (61)
Unknown	4

Results-Clinicopathologic Features

Resection margin	*n* (%)
R0	15 (100)
R1	0
Unknown	7
Lymph node status	*n* (%)
N0	16 (94)
N1	1 (6)
Unknown	5
Median follow-up (months) (range)	48.5 (1–173)
Status of known 18 cases	
Died of perioperative complications	1
Died of other disease(s)	1
Died of disease	3
Alive WITH disease	6
Alive WITHOUT disease	7

Results-Molecular Features

Table 2 High confidence mutations and recurrent copy number variants identified by MSK-IMPACT, Ion AmpliSeq, or whole-exome sequencing

Case #	*Analysis*	*Gene*	*Type of mutation*	*Protein*	*MCL amplification*	*CDKN2A loss*
1	MSK-IMPACT	JAK	Missense mutation	p.V1009D	Yes	No
		DNMT3A	Missense mutation	p.R181H		
		TET2	Missense mutation	p.E755K		
		ARHGAP26	Missense mutation	p.R103Q		
		ROR2	Missense mutation	p.R522Q		
		MLL2	Nonsense mutation	p.E3587*		
2	MSK-IMPACT	MLL2	Nonsense mutation	p.R2471*	No	No
		MLL2	Frame_Shift_Ins	p.L4518fs		
3	MSK-IMPACT	NOTCH2	Missense mutation	p.N832S	Yes	No
		IRF4	Missense mutation	p.E130G		
		DNMT3B	Missense mutation	p.G511C		
		BCOR	Frame_Shift_Ins	p.E1484fs		
4	MSK-IMPACT	None	None	None	No	No
5	MSK-IMPACT	MAP2K1	Missense mutation	p.E51G	Yes	No
		FAM123B	Splice_Site	p.Q2048fs		
		MLL3	Frame_Shift_Del			
		MAP2K1	In_Frame_Ins	p.59_60insQK		
6	MSK-IMPACT	EPHA2	Missense mutation	p.A112T	Yes	No
		BRCA2	Missense mutation	p.G1771D		
7[a]	MSK-IMPACT	PTEN	In_Frame_Del	p.T319	No	Yes
		NPM1	Missense mutation	p.S125L		
		MLL3	Missense mutation	p.K992M		
8	MSK-IMPACT	None	None	None	Yes	No
9	MSK-IMPACT	BAP1	Splice_Site	p.E577_splice	No	No
10	MSK-IMPACT	INPP4A	Missense mutation	p.N308T	No	Yes
		KDR	Missense mutation	p.M559I		
11[a]	MSK-IMPACT	AXIN1	Missense mutation	p.E195*	No	No
		BAP1	Missense mutation	p.R213H		
		FLT4	Splice_Site	p.P1023R		
		PBRM1	Missense mutation			
12	MSK-IMPACT	XPO1	Missense mutation	p.L660F	No	No
13	MSK-IMPACT	PIK3CA	Missense mutation	p.G1049R	No	No
		EBD	Missense mutation	p.N194S		
		FGFR4	Frame_Shift	p.R464Pfs*32		
14	MSK-IMPACT	PIK3CA	Missense mutation	p.H1047R	No	No
		BAP1	Nonsense mutation	p.S319*		
		ATRX	Missense mutation	p.I47V		
		CRKL	Missense mutation	p.G136E		
		MLL1	Missense mutation	p.I962V		
		SPEN	Missense mutation	p.A3060V		
15	MSK-IMPACT	SMARCA4	Missense mutation	p.R885C	No	Yes
		NTRK1	Missense mutation	p.G181E		
16 intraductal & invasive tumor	MSK-IMPACT	ZFHX3	Deletion	p.G3517_G3527del	No	No
17[a]	MSK-IMPACT	None	None	None	Yes	No
18 primary pancreatic tumor	MSK-IMPACT	CEBPA	Missense mutation	p.R86P	No	No
18 recurrent pancreatic tumor	MSK-IMPACT	CDKN2A	Nonsense mutation	p.Y129*	No	No
		RET	Missense mutation	p.L80R		
18 celiac LN metastasis	MSK-IMPACT	None	None	None	No	No

Results–Molecular Features

Table 2 High confidence mutations and recurrent copy number variants identified by MSK-IMPACT, Ion AmpliSeq, or whole-exome sequencing

Case #	*Analysis*	*Gene*	*Type of mutation*	*Protein*	*MCL amplification*	*CDKN2A loss*
19	Ion AmpliSeq	TRIP11	Missense mutation	p.L872H	Not applicable	Not applicable
20	Ion AmpliSeq	AXL	Missense mutation	p.R190H	Not applicable	Not applicable
		PIK3CB	Missense mutation	p.L35V		

Results–Molecular Features

Table 2 High confidence mutations and recurrent copy number variants identified by MSK-IMPACT, Ion AmpliSeq, or whole-exome sequencing

Case #	*Analysis*	*Gene*	*Type of mutation*	*Protein*	*MCL amplification*	*CDKN2A loss*
21	Whole-exome seq	SYCP1	Splice site mutation	—	Yes	Yes
		USH2A	Missense mutation	p.R878C		
		SLC4A10	Missense mutation	p.D208H		
		CTNNB1	Missense mutation	p.S45F		
		CBLB	Missense mutation	p.G259V		
		PIK3CA	Missense mutation	p.E545K		
		EPHB3	Missense mutation	p.Y855H		
		ETFDH	Missense mutation	p.G75D		
		FAT1	Missense mutation	p.E2401K		
		FAM170A	Missense mutation	p.R65C		
		HIST1H4K	Nonsense Mutation	p.E64*		
		MYB	Missense mutation	p.R73Q		
		MUC12	Missense mutation	p.N4428D		
		EHBP1L1	Missense mutation	p.R1138H		
		UBASH3B	Missense mutation	p.E257K		
		KCNA5	Missense mutation	p.A50V		

Results–Molecular Features

Table 2 (Continued)

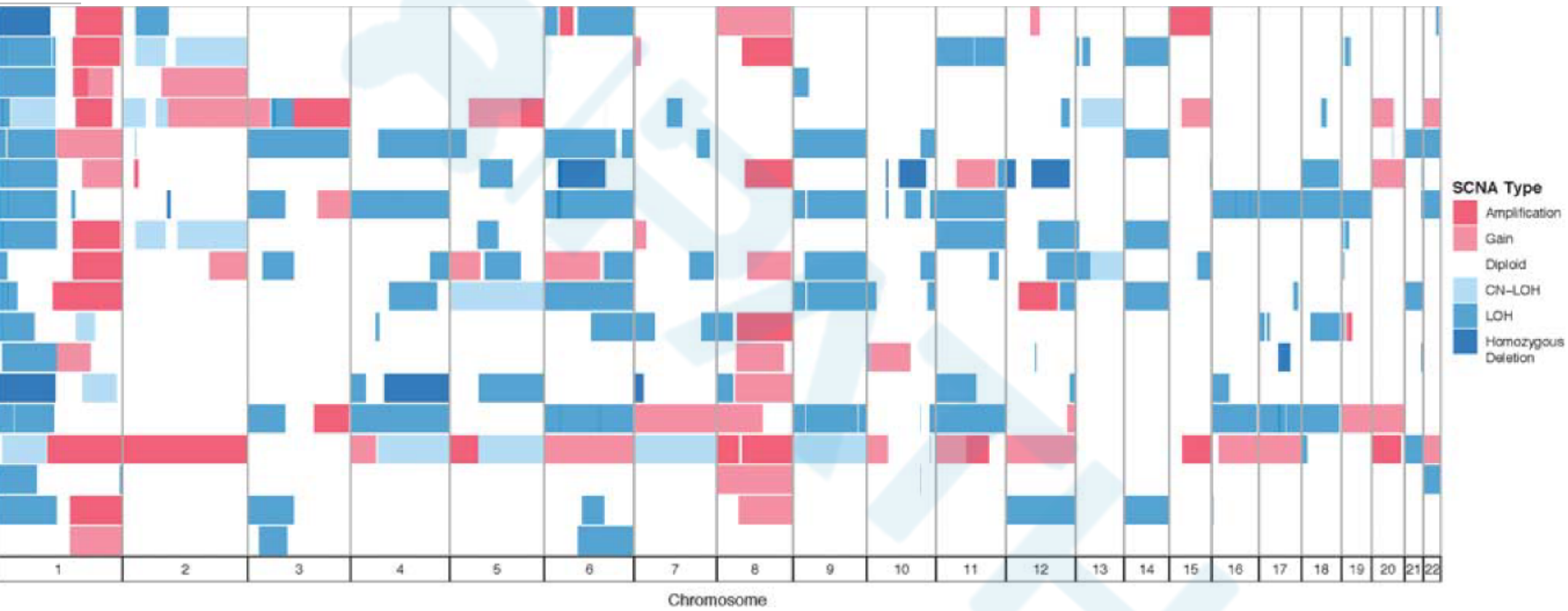
Case #	*Analysis*	*Gene*	*Type of mutation*	*Protein*	*MCL amplification*	*CDKN2A loss*
		TM7SF3	Frameshift Insertion	p.S246fs		
		CNTN1	Missense mutation	p.P271L		
		OSBPL8	Missense mutation	p.R318Q		
		CLK3	Nonsense Mutation	p.Y36*		
		TP53	Missense mutation	p.P113L		
		MYH13	Missense mutation	p.G203R		
		MYH8	Missense mutation	p.R1715H		
		KRT26	Missense mutation	p.R93C		
		JMJD6	Missense mutation	p.R95G		
		NOL4	Missense mutation	p.T119M		
		LTBP4	Missense mutation	p.G283D		
		ARHGAP35	Nonsense mutation	p.S975*		
		FAM71E2	Missense mutation	p.L329M		
22[b]	Whole-exome seq	CYR61	Missense mutation	p.C39*		
		CHML	Missense mutation	p.D210Y		
		SCN9A	Missense mutation	p.S1594T		
		KALRN	Missense mutation	p.A364T		
		COL6A6	Nonsense mutation	p.R1502H		
		PRR14L	Nonsense mutation	p.E658*		
		APC	Missense mutation	p.A2T		
		HIST1H3G	Missense mutation	p.M448K		
		WRN	Missense mutation	p.E226K		
		MUC2	Missense mutation	p.A59E		
		KRAS	Missense mutation	p.S286T		
		DNASE1L2	Missense mutation	p.S82F		
		NF1	Missense mutation	p.K1111T		
		ZNF208	Missense mutation	p.V30L	**YES**	**YES**

Results-Molecular Features

copy number analysis

- amplifications and deletions in 80% of ITPN(16/20)
- amplification of MCL1 in 40% of ITPN (8/20)
- loss of CDKN2A in 25% of ITPN (5/20).
- One case (Case #21)revealed amplification of MCL3 as well as hemizygous loss of MLL2 and BAP1.

Results-Molecular Features



染色体1p全部或部分杂合性缺失或中性杂合性缺失；
染色体1q 和染色体8 重新获得/扩增

Results-Molecular Features

- chromatin remodeling pathway (MLL1, MLL2, MLL3, BAP1, PBRM1 ,EED , ATRX)
- WNT-β catenin pathway (CTNNB1, APC, AXIN1)
- GAS6-AXL pathway(AXL)
- Rho pathway (ARHGAP26, ARHGAP35, ROR2 , KALRN)
- tyrosine kinase pathway (KDR , FLT4 , NTRK ,RET)
- ephrin pathway (EPHA2 ,EPHB3)

Results–Molecular Features

Table 3 Rearrangements identified in our series

Case #	*Gene 1*	*Gene 2*	*Site 1 description*	*Site 2 description*	*Fusion*
FGFR2 fusions					
#11	FGFR2	CEP55	Exon 17 of FGFR2	Exon 2 of CEP55	Protein fusion: in frame (FGFR2-CEP55)
#12	FGFR2	SASS6	Intron of FGFR2(−): 80 bp after exon 16	Intron of SASS6(−): 586 bp before exon 7	Protein fusion: in frame (FGFR2-SASS6)
#14	FGFR2	DISP1	Intron of FGFR2(−): 276 bp before exon 17	Intron of DISP1(+): 9Kb after exon 2	Protein fusion: out of frame (DISP1-FGFR2)
#14	FGFR2	TXLNA	Intron of FGFR2(−): 687 bp before exon 17	Intron of TXLNA(+): 1kb before exon 5	Protein fusion: in frame (FGFR2-TXLNA)
#15	VCL	FGFR2	Exon 13 of VCL(+)	Intron of FGFR2(−): 535 bp before exon 17	Protein fusion: mid-exon (FGFR2-VCL)
ALK fusion[a]					
#18	STRN	ALK	Exon 3 of STRN (NM-003162)	Exon 20 of ALK (NM-004304)	Protein fusion: in frame (STRN-ALK)

[a]Identified in the primary and recurrent pancreatic tumors as well as in the celiac lymph node metastasis

22% (4/18,)of ITPN revealed FGFR2 fusions and 5.5% (1/18) revealed an ALK fusion

Results-Molecular Features

Whole-Genome Sequencing

- Cases #7 and #17 were found to have multiple copy number gains and losses in multiple chromosomes. No significant copy number alterationswere identified in Case #11
- a total of 129 mutations within these three tumors
  - 67 mutations in Case #7, 28 in Case #11, and 34 in Case #17

DISCUSSION

Recent studies

- IPMN with low-grade dysplasia , intraductal papillary mucinous neoplasm with associated invasive carcinoma- progression

- accompanied by a high number of molecular alterations (about 26 mutations per neoplasm), the most frequent mutations in KRAS, GNAS,and RNF43.

DISCUSSION

Reported

1.one case with IPMN and ITPN: GNAS mutation in both lesions and the ITPN also had NRAS mutation

2.PIK3CA mutation:ITPN (3 ,27%), IPMN(none); immunoexpression of phosphorylated AKT;

KRAS mutation: ITPN(none),IPMN(26,52%)

3.ITPN:PIK3CA(3,21%),KRAS(1,7%),BRAF(1,7%),

IPMN:PIK3CA(none),KRAS(12,80%),GNAS(9,60%)

DISCUSSION

In this study

- loss of CDKN2A in ITPN (25%)
- Eight (40%) had MCL1 amplification
- six (27%) phosphatidylinositol pathway mutations (threePIK3CA, one PIK3CB, one INPP4A, and one PTEN mutation)
- seven (32%) chromatin remodeling genes mutated (MLL1, MLL2, MLL3, BAP1, PBRM1, EED, ATRX)

DISCUSSION

Reported

- Somatic mutations of MLL2 and MLL3 in 20% of pancreatic ductal adenocarcinoma patients who have prolonged overall and progression-free survival
- improved outcome patients with DAXX/ATRX alterations in metastatic pancreatic neuroendocrine, primary tumors with DAXX/ATRX mutations appear to have a poorer outcome

DISCUSSION

Reported

- FGFR fusions show enhanced sensitivity to the FGFR inhibitors

In this study

- FGFR2-TXLNA fusion in four (22%) ITPN

FGFR fusions -a useful biomarker of tumor response to FGFR inhibitors

In summary

- validate the morphologic distinction of ITPN from other types of pancreatic neoplasms
- it demonstrates potentially targetable genetic alterations in ITPN
- will likely shed new light on the mechanisms of intraductal tumor formation in the pancreas andreveal new therapeutic targets

Thank you