Table S1: Primary antibodies used for immunohistochemistry.			
Antibody	**Manufacturer**	**Clone (animal)**	**Dilution**
Anti-p16^{INK4A}	Diagnostic BioSystems (Pleasanton, CA, USA)	Clone JC2 (mouse)	1:200
Anti-p53	Calbiochem (San Diego, CA, USA)	Clone DO-1 (mouse)	1:200
Anti-Smad4	Zeta Corporation (Arcadia, CA, USA)	Clone B-8 (mouse)	1:50

Table S2: Correlation analysis between immunohistochemical expression status of p53, p16 and Smad4 and clinicopathological variables. Mann-Whitney U test was used to test for significance (*p*-value < 0.05 indicates significance).

	Histomorphology Classical vs. rest Mann-Whitney-U test *p*-value
Gender (female vs. male)	0.157
T stage (T1/T2 vs. T3/T4)	0.207
N stage (N0 vs. N1/N2)	0.928
Grading (G2 vs. G3)	0.099
Pn (Pn0 vs. Pn1)	0.849
L (L0 vs. L1)	0.354
V (V0 vs. V1)	0.293
p53 (aberrant vs. normal)	0.180
p16 (normal vs. negative)	0.290
Smad4 (normal vs. negative)	0.308

Pn: perineural invasion; L: lymphatic invasion; V: venous invasion

Table S3: Correlation analysis between clinicopathological variables, immunohistochemical expression status of p53, p16 and Smad4 and histomorphology (classical vs. rest). Mann-Whitney U test was used to test for significance (*p*-value < 0.05 indicates significance).

	p53	p16	Smad4
		Mann-Whitney-U test	
	p-value	*p*-value	*p*-value
Histomorphology (classical vs. rest)	0.483	0.539	0.986
Gender (female vs. male)	0.564	0.931	0.781
T stage (T1/T2 vs. T3/T4)	0.633	**0.011**	0.883
N stage (N0 vs. N1/N2)	0.633	0.903	0.806
Grading (G2 vs. G3)	0.882	0.227	0.731
Pn (Pn0 vs. Pn1)	0.560	0.733	0.892
L (L0 vs. L1)	0.202	0.872	0.813
V (V0 vs. V1)	0.681	0.733	0.685

Pn: perineural invasion; L: lymphatic invasion; V: venous invasion

Table S4: Correlation analysis between *KRAS* and *TP53* mutations; *n* = 39. Statistical significance was calculated by Mann-Whitney U test and Fisher's exact test (*p*-value < 0.05 indicates significance). Distribution of different mutations across *KRAS* and *TP53* was similar. Correlation analysis between 3rd mutations, *KRAS* and *TP53* mutations; *n* = 39. There was a homogenous distribution between *KRAS* and *TP53* mutations and 3rd evident mutation. Statistical significance was calculated by Mann-Whitney-U test and Fisher's exact test (*p*-value < 0.05 indicates significance).

	KRAS mutation NGS							*p*-value
	G12D	G12V	G12R	G12C	Q61H	D57N	WT	
TP53 mutation								0.740
WT	6	3	1	1	1	0	2	
NS	1	1	0	0	0	0	0	
FS/SS	0	3	0	0	0	0	0	
MS	7	9	0	0	1	1	2	

	3rd driver mutations								*p*-value
	No	APC	ATM	BRAF	CDKN2A	CTNNB1/ERBB2	PIK3CA	SMAD4	
TP53 mutation									0.580
WT	9	1	1*	0	1*	1	1	1	
NS	1	0	0	0	0	0	0	1	
FS/SS	2	0	0	0	0	0	0	1	
MS	14	0	0	1*	4*	0	0	2	
KRAS mutation									0.915
G12D	9	1	0	0	1	0	1	2	
G12V	12	0	0	0	2	0	0	2	
G12R	1	0	0	0	0	0	0	0	
G12C	0	0	1*	0	1*	0	0	0	
Q61H	1	0	0	0	0	0	0	1	
D57N	0	0	0	1*	1*	0	0	0	
WT	3	0	0	0	0	1	0	0	

*FS/SS: frameshift/splice-site; NGS: next generation sequencing; NS: non-sense; MS: miss-sense; WT: wild-type; *: one patient*

Table S5: Correlation analysis between *KRAS/TP53* allele frequency rate and histomorphological as well as clini-copathological subgroups. Mann-Whitney-U test was used to test for significance (*p*-value < 0.05 indicates significance).

	Mutational frequency rate	
	KRAS	TP53
	Mann-Whitney-U test	
	p-value	*p*-value
Histomorphology (classical vs. rest)	0.254	0.574
Gender (female vs. male)	***0.011***	0.434
T stage (T1/T2 vs. T3/T4)	0.258	0.211
N stage (N0 vs. N1/N2)	0.398	0.152
Grading (G2 vs. G3)	0.630	***0.029***
Pn (Pn0 vs. Pn1)	0.500	0.061
L (L0 vs. L1)	0.504	0.697
V (V0 vs. V1)	0.619	0.082
p53 (Aberrant vs. Normal)	0.668	0.560
p16 (Normal vs. Loss)	0.499	1.000
Smad4 (Normal vs. Loss)	0.707	0.640

*Pn: perineural invasion; L: lymphatic invasion; V: venous invasion*
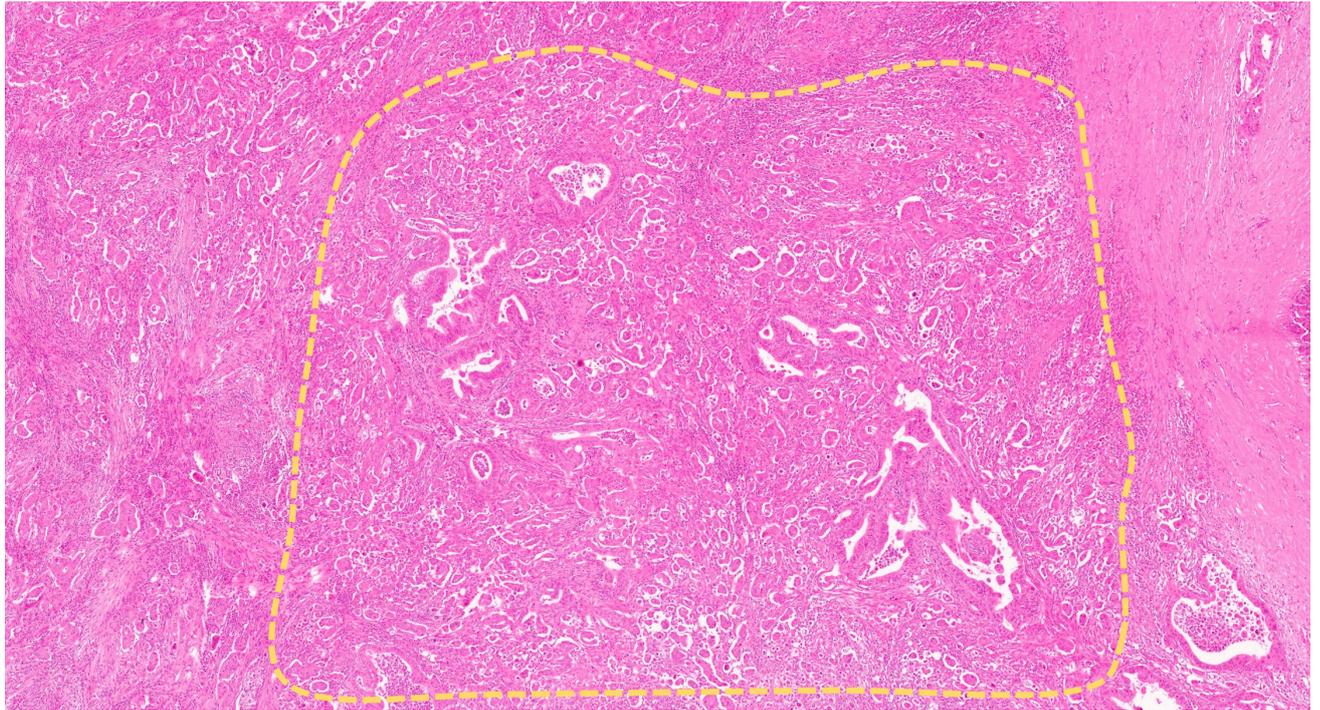
Figure S1. Histomorphology of an exemplary PDAC case from our cohort. An area with adequate tumor cellularity (≥ 80%) was marked for manual macrodissection (yellow dotted line) (H&E, 30x).
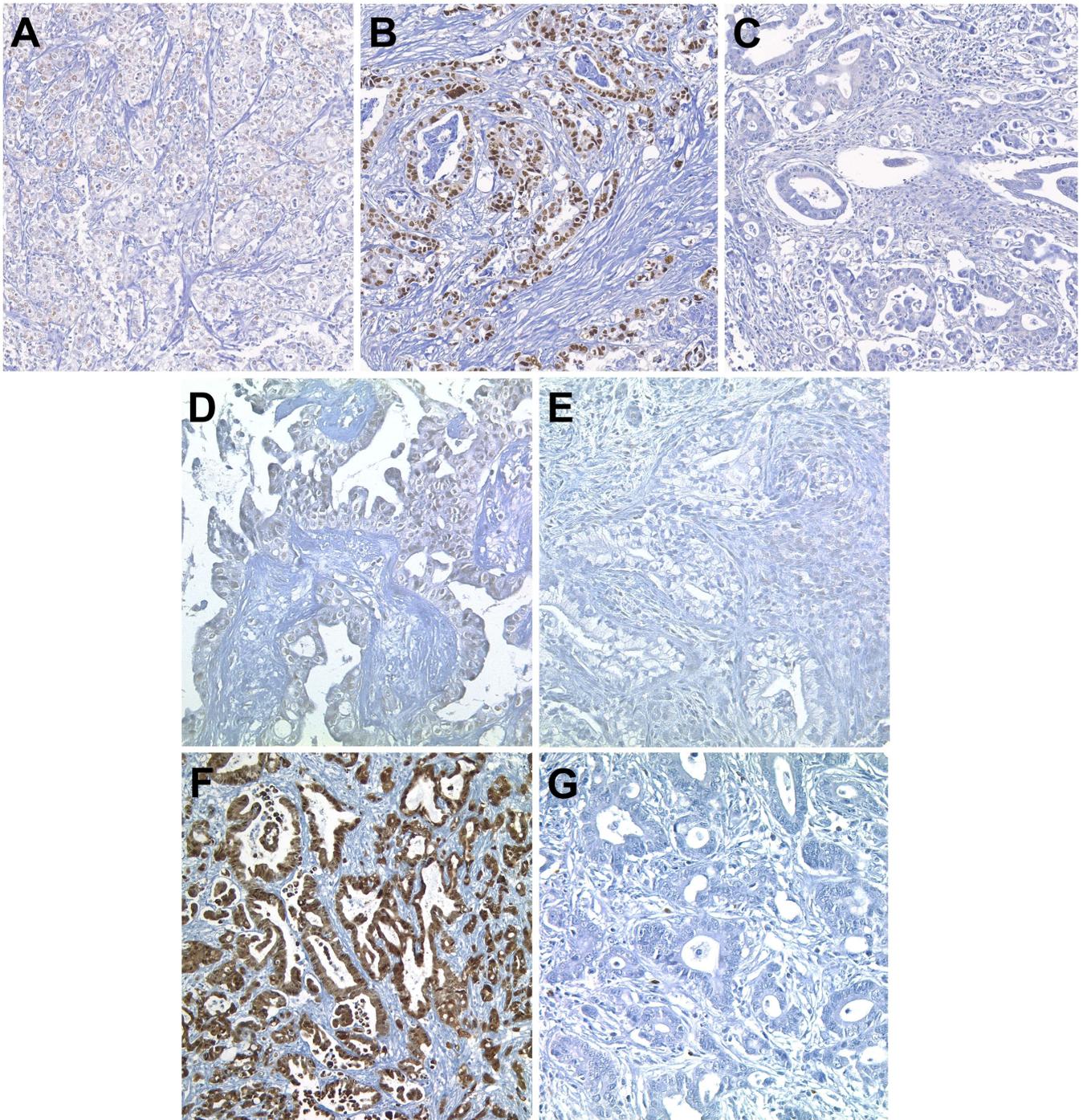
S2. Immunohistochemical (IHC) analyses. A-C: IHC of p53. Wild-type expression pattern with staining of weak intensity in some of the tumor cell nuclei (A), aberrant expression in the form of overexpression (B) and aberrant expression in the form of complete loss of expression are shown (100x, respectively). **D & E.** IHC of Smad4. Wild-type expression pattern with nuclear positivity of Smad4 in PDAC cells (D) and aberrant expression in the form of complete loss of Smad4 expression in PDAC cell nuclei (E) are shown (100x, respectively). **F & G.** IHC of p16. Wild-type expression pattern with cytoplasmic and nuclear p16 positivity of PDAC cells (F, 100x) and aberrant expression in the form of complete loss of p16 expression in PDAC cells (G, 200x) are shown. In E. and G., Smad4- and p16-positive stromal cells serve as internal positive controls, respectively.