Supplemental table 1. Pancreatic cancer-related genes listed by gene classification set

Classification Set	**Genes**
Mismatch repair (MMR)	*MSH2, MSH6, MLH1, PMS2*
Autosomal dominant [AD] disorders	*APC, BRCA1, BRCA2, CDKN2A, MEN1, PALLD, STK11, TP53, VHL*
Autosomal Recessive [AR]/AD disorders	*ATM, FANCA, FANCC, PALB2, XRCC2*
Hereditary/chronic pancreatitis	*PRSS1, CTRC, CPA1, CFTR, CASR, SPINK1*

Supplementary table 2. Source population, patients, families, *CDKN2A* mutation status, and study references for contributing studies

Study Population	Source	*CDKN2A* Mutation	Number of PC Patients	Number of Families	Study References
American	Melanoma family study	p.V126D	5	3	Goldstein et al, 2000; 2005
		p.R87P	1	1	
		p.R80fs	1	1	
		None	1	1	
		TOTAL:	**8**	**6**	
Dutch	Melanoma family study	c.225-243del19	17	9	Bergman et al, 1992; Gruis et al, 1995; de Snoo et al, 2008; Research Protocol: P00.117
Italian[a]	Melanoma family study and PC case-control study, Genoa [University and IRCCS AOU San Martino-IST	p.G101W (n=7), p.E27X (n=3), p.A127P, p.L65P, p.G67R, p.R144C, 201ACTC>CTTT	15[b]	15	Ghiorzo et al, 2006; 2012
		None	16[c]	16	
	Clinical Study of PC/Melanoma, Turin (University)	p.E27X, p.Q50X, p.G101W	3	3	
	Clinical Study of PC/Melanoma, Monza	None	1	1	
	Clinical Study of PC/Melanoma, Bologna (University and Policlinico Sant'Orsola)	None	2	2	
		TOTAL:	**37**	**37**	
Swedish	Melanoma family study, Stockholm	p.112dupArg	3	3	Borg et al, 1996; Platz et al, 1997; Hashemi et al, 2001; Hansson et al, 2007
	Melanoma and cancer family study, Lund	p.112dupArg	4	3	
		None	6[d]	6	
		TOTAL:	**13**	**12**	

[a]All Italian PC patients in the study are unrelated, thus number of patients = number of families

[b]Patients with CDKN2A mutation: Personal/family history of melanoma (n=5), probands of multiplex PC families (n=6), or sporadic PC (n=4)

[c]Patients without CDKN2A mutation: Personal (n=7) or family history of melanoma (n=7) or family history of PC (n=2)

[d]Patients are from families with aggregations of pancreatic cancer

PC, pancreatic cancer

Supplementary table 2 Study References (summarized)

Bergman W, Gruis NA, Frants RR (1992) Cytogenet Cell Genet 59:161-164
Borg A et al. (1996) Cancer Res 56:2497-2500
de Snoo FA et al. (2008) Clinical Cancer Res 14:7151-7157
Ghiorzo P et al. (2006) Hum Mol Genet 15:2682-2689
Ghiorzo P et al. (2012) J Med Genet 49:164-170
Goldstein AM, Struewing JP, Chidambaram A, Fraser MC, Tucker MA (2000) J Natl Cancer Inst 92:1006-1010
Goldstein AM, Landi MT, Tsang S, Fraser MC, Munroe DJ, Tucker MA (2005) Cancer Epidemiol Biomarkers Prev 14:2208-2212
Gruis NA et al. (1995) Nat Genet 10:351-353
Hansson J et al. (2007) J Clinical Oncol 25:2819-2824
Hashemi J et al. (2001) Genes, Chromosomes & Cancer 31:107-116
Platz A et al. (1997) J Natl Cancer Inst 89:697-702

Supplemental table 3. Number of pancreatic cancer patients and families from each study population

	CDKN2A +		*CDKN2A* -		All	
Study Populations	No. PC Patients	No. Families	No. PC Patients	No. Families	No. PC Patients	No. Families
American	7	5	1	1	8	6
Dutch	17	9	0	0	17	9
Italian	17	17	18	18	35	35
Swedish	7	6	6	6	13	12
TOTAL	48	37	25	25	73	62
Total for Analysis	43	33	23	23	66	56

No., Number; PC, pancreatic cancer

Supplemental table 4. Detailed information about variants observed in PC patients including type of variant, allele frequency in various databases, evidence for deleteriousness/pathogenicity, *CDKN2A* mutation carrier status, history of smoking, and patient/family ID

GENE	CHROM	LOCATION	rsID	REF	VAR	AA/protein change	Technivally validated (Y, N, ND)*1	1000 Genome European Allele Freq	ESP European Allele Freq	ExAC (All) Allele Freq	ExAC Non-Finnish European Allele Freq	Meta LRP*2	HGMD*3	CLINVAR Clinical Significance Classification	Ingenuity Variant Analysis Classification	Align GVGD Score*4	Gene-specific Database classification	Number of cases with variant	*CDKN2A* mutation carrier	History of smoking (yes/no/unk)	Family/Patient ID
MSH2	chr2	47630331	rs267607911	A	G	M1V	ND			8.31E-06	0	D	DM	Uncertain	Uncertain	C15	Class 3*#	1	yes	no*5	LUMC6_019
MSH2	chr2	47637248	rs145649774	C	G	L128V	Y		0.000349	3.54E-04	1.35E-04	D		Uncertain	Uncertain	C25	Class 3	1	yes	no	P147
MSH2	chr2	47641430	rs34136999	C	T	A272V	Y		0.000581	2.39E-04	3.76E-04	D	DM	Uncertain	Uncertain	C0	Class 3	1	no	no	P149
MSH6	chr2	48026852	rs376220212	G	A	R577H	Y		0.000116	4.12E-05	5.99E-05	D		Uncertain	Uncertain	C25		1	yes	no	P176
MSH6	chr2	48027269		C	G	T716R	Y					T			Uncertain	C0		1	yes	unk	K_1001
MSH6	chr2	48030747	rs587781609	G	A	E1121K	ND					T		Uncertain	Uncertain	C0		1	no	unk	P1
MLH1	chr3	37089053	rs587782621	G	C	S592T	ND			8.24E-06	1.50E-05	T		Uncertain	Uncertain	C0		1	yes	unk	M799
CASR	chr3	121994847		C	A	F522L	ND			8.24E-06	1.50E-05	T			Uncertain			1	no	unk	DK1810
PALLD	chr4	169433083	rs149345491	G	A	R143H	ND	0	0.000116	9.88E-05	9.04E-05	T			Uncertain			1	yes	unk	T2427
APC	chr5	112177694		A	G	I2135V	ND			1.65E-05	3.00E-05	T			Uncertain			1	yes	unk	LUMC19_015
PMS2	chr7	6013060	rs371673459	G	C	I853M	Y		0.000247	1.58E-04	2.96E-04	T		Uncertain	Uncertain	C0		1	yes	no	M402
PMS2	chr7	6013076		G	A	P848L	Y					D		Uncertain	Uncertain	C65		1	no	unk	P1
PMS2	chr7	6022617	rs587780046	G	A	T671M	ND			1.80E-04	6.34E-04	D		Uncertain	Uncertain	C0		1	no	yes	P282
PMS2	chr7	6026397	rs587780045	C	T	E667K	Y			5.77E-05	9.10E-05	T		Uncertain	Uncertain	C15		1	no	no	M595
PMS2	chr7	6027156	rs370752614	C	A	D414Y	ND		0.000116	8.24E-06	0	T		Uncertain	Uncertain	C0		1	yes	unk	LUMC22_004
CFTR	chr7	117171037	rs201958172	G	A	A120T	Y			1.15E-04	1.36E-04	D	DM		Uncertain		Pancreatitis, CF	1	yes	no	M402
CFTR	chr7	117171152	rs397508725	G	C	S158T	Y			1.65E-05	1.73E-05	D	DM?		Uncertain			1	yes	no	P61
CFTR	chr7	117243784	rs151048781	G	C	M952I	Y		0	9.06E-05	1.20E-04	D	DM		Uncertain			1	no	yes	P115
CFTR	chr7	117250625	rs149279509	A	G	Y1014C	Y	0.001	0.000349	2.72E-04	4.06E-04	D	DM	Uncertain	Uncertain		Pancreatitis, CF	2	yes	unk	K_1001, K_1002
CPA1	chr7	130023239		C	T	T164M	ND			6.59E-05	0	T			Uncertain			1	no	yes	P100
CPA1	chr7	130023275		C	T	T176M	Y			1.65E-05	3.03E-05	T			Uncertain			1	no	unk	RU7185
ATM	chr11	108122581		T	G	L542W	Y					D			Uncertain	C55		1	no	no	P268
ATM	chr11	108155142		AG		E1313fs	Y								Likely Pathogenic			1	no	no	M595
ATM	chr11	108183151	rs587779852	G	T	E1978*	Y			6.59E-05	1.05E-04		DM	Pathogenic	Pathogenic			1	no	unk	AJ7379
ATM	chr11	108196797	rs567060474	G	A	A2274T	Y	0.001		1.07E-04	1.96E-04	D	DM?	Uncertain	Uncertain	C55		1	no	yes	P115
ATM	chr11	108216600		T	C	L2850S	Y					T			Uncertain	C65		1	no	no	P140
BRCA2	chr13	32907000	rs56403624	A	G	E462G	ND		0.000349	2.39E-04	4.07E-04	T	DM?	Benign	Benign	C0	Uncertain	1	no	unk	LM1534-MA3432
BRCA2	chr13	32907418		A	C	K601N	ND			4.94E-05	9.26E-05	T			Uncertain	C0		1	no	unk	UA6685
BRCA2	chr13	32914288	rs80359537	AT		H1932fs	QC						DM		Pathogenic			1	no	yes	P153
BRCA2	chr13	32954034	rs80359164	A	G	Q3034R	ND			1.65E-05	3.15E-05	T	DM	Uncertain	Uncertain	C0	Uncertain	1	yes	yes	P93
PALB2	chr16	23646627	rs180177100	G	A	R414*	Y						DM	Pathogenic	Pathogenic			1	no	unk	AJ7379
FANCA	chr16	89858430		CTT		E377del	Y								Uncertain			1	no	yes	P282
TP53	chr17	7576911	rs145151284	G	C	T312S	ND	0	0	9.06E-05	8.99E-05	D		Uncertain	Uncertain	C0		1	no	no	P268
BRCA1	chr17	41256266	rs28897673	T	C	Y105C	ND		0.000116	5.77E-05	1.05E-04	D	DM?	Benign	Likely Benign	C15	Benign	2	yes	no, yes	LUMC19_013, LUMC19_016
BRCA1	chr17	41276071	rs80357031	T	G	I15L	ND					T		Uncertain	Uncertain	C0	Uncertain	1	no	yes	P100

*1 Y=yes, N= no, ND= not done
*2 D=deleterious, T=tolerated
*3 DM=disease causing mutation; DM?= questionable disease causing mutation
*4 Classified from least likely (C0) to most likely to interfere with function (C65)
*# Class 3 = uncertain, insufficient evidence to classify as pathogenic or benign
*5 Extensive passive smoking exposure

CHROM, chromosome; REF, referent; VAR, variant; AA, amino acid; LRP, likelihood ratio prediction; HGMD, Human Gene Mutation Database
Freq, frequency; ESP, Exome Sequencing Project; CF, cystic fibrosis; ExAC, Exome Aggregation Consortium; GVGD, Grantham Variation and Grantham Deviation