Abstract # 4286

Germline mutation spectrum and cancer risk: what we've learned from pancreatic cancer patients undergoing multigene panel testing

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Background

- The relevance of inherited pathogenic variants in cancer predisposition genes to pancreatic cancer (PC) is not well understood.
- Several small studies have identified pathogenic variants in 4% to 14% of unselected PC patients using multigene panels of predisposition genes,[1,2] but only *BRCA2*, *ATM*, and *PALB2* have been clearly implicated in this disease.[3-5]
- We aimed to assess the clinical and molecular characteristics of PC patients referred for hereditary cancer genetic testing and to estimate the risk of PC associated with pathogenic variants in panel-based cancer predisposition genes.

Methods

- PC patients (n=1819) were ascertained from a large cohort of over 140,000 patients undergoing multigene panel testing (MGPT) of 5 to 49 hereditary cancer predisposition genes between March 2012 and June 2016 at a single diagnostic laboratory.
- Clinical histories and molecular results were reviewed and summarized (Table 1).
- Gene-level pathogenic/likely pathogenic variant frequencies among Caucasian and Ashkenazi Jewish PC cases were compared to those from the Exome Aggregation Consortium (ExAC) Non-Finnish European (NFE) population (excluding The Cancer Genome Atlas (TCGA) exomes) to calculate gene-specific PC risk ratios.

Table 1. Demographics & Clinical History

Characteristic	N (%)	Characteristic	N (%)
Gender		Family history of cancer (1st or 2nd degree)	
Male	745 (41.0)	PC	684 (37.6)
Female	1074 (59.0)	Breast	865 (47.6)
Ethnicity		Ovarian	237 (13.0)
Caucasian	1202 (66.1)	Uterine/endometrial	150 (8.2)
Ashkenazi Jewish	188 (10.3)	Colorectal	506 (27.8)
African American/Black	88 (4.8)	FPC*	57 (3.1)
Asian	52 (2.9)	No family history of PC	1014 (55.7)
Hispanic	70 (3.8)	Personal history of cancer	
Mixed Ethnicity	56 (3.1)	Primary PC	1358 (74.7)
Others/Unknown	163 (9.0)	Breast	296 (16.3)
Age at diagnosis of PC		Ovarian	42 (2.3)
Mean (±SD)	60.4 (±12.3)	Uterine/endometrial	40 (2.2)
Range	13-90	Colorectal	56 (3.0)
		No cancer other than PC	1214 (66.7)

*FPC; familial pancreatic cancer, defined as kindreds containing at least two affected first-degree relatives

Table 3. Case Control Analysis

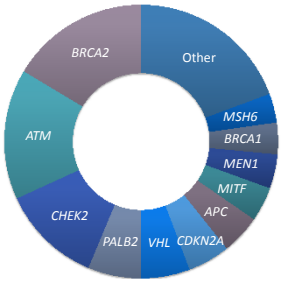
	ExAC Controls	All Caucasian Pancreatic Cancer Cases (n=1390)						Caucasian Pancreatic Cancer Cases with Pancreatic Cancer as First Cancer Diagnosis (n=1010)					
Gene	Control AF	Case AC	Case AN	Case AF	OR	p-value	95% CI	Case AC	Case AN	Case AF	OR	p-value	95% CI
ATM	0.19%	39	2616	1.49%	7.892	9.30E-20	5.419-11.55	21	1930	1.09%	5.735	1.90E-09	3.527-9.2
*BRCA1**	0.15%	10	2560	0.39%	2.570	0.00894	1.295-4.929	7	1890	0.37%	2.436	0.0318	1.11-5.284
BRCA2	0.20%	43	2560	1.68%	8.381	1.75E-22	5.847-12.087	27	1890	1.43%	7.109	1.28E-13	4.607-10.957
CDKN2A	0.02%	12	2274	0.53%	28.649	1.24E-11	11.771-70.998	8	1752	0.46%	24.772	3.87E-08	9.432-69.271
*CHEK2**	0.52%	13	1280	1.02%	1.980	0.0278	1.081-3.47	7	792	0.88%	1.721	0.203	0.798-3.656
MSH2	0.01%	3	2588	0.12%	9.796	0.00772	2.122-41.049	2	1922	0.10%	8.793	0.0323	1.282-46.035
MSH6	0.07%	11	2588	0.43%	6.560	5.75E-06	3.258-12.896	6	1922	0.31%	4.813	0.00269	1.969-11.604
PALB2	0.06%	19	2624	0.72%	13.059	2.27E-13	7.252-23.388	11	1936	0.57%	10.230	1.05E-07	5.047-20.783
TP53	0.03%	5	2720	0.18%	5.480	0.00425	1.945-15.118	2	1978	0.10%	3.012	0.158	0.498-12.782

**BRCA1* p.R1699Q and *CHEK2* p.I157T and were excluded from analysis.

Table 2. Gene-specific Mutation Frequencies

Gene	N, positive (N, tested)	% positive	Gene	N, positive (N, tested)	% positive
BRCA2	66 (1704)	3.9	*SDHB*	1 (220)	0.5
ATM	63 (1733)	3.6	*TP53*	8 (1807)	0.4
CHEK2	23 (822)	2.8	*NBN*	3 (797)	0.4
PALB2	26 (1755)	1.5	*NF1*	2 (691)	0.3
VHL	3 (220)	1.4	*MLH1*	5 (1729)	0.3
CDKN2A	18 (1530)	1.2	*MSH2*	5 (1729)	0.3
APC	18 (1642)	1.1	*BRIP1*	2 (797)	0.3
MITF	2 (208)	1.0	*BARD1*	2 (797)	0.3
MEN1	2 (210)	1.0	*PMS2*	4 (1729)	0.2
BRCA1	15 (1704)	0.9	*MRE11A*	1 (797)	0.1
MSH6	14 (1729)	0.8	*CDH1*	1 (850)	0.1
BAP1	1 (143)	0.7	*EPCAM*	2 (1729)	0.1
RAD50	5 (797)	0.6			

Figure 1. Proportion of Mutations by Gene



Results

- Overall, 15.4% (n=280) of PC patients were found to have at least one pathogenic/likely pathogenic variant in panel-based predisposition genes.
- Genes with the highest frequencies of pathogenic/likely pathogenic variants included *BRCA2* (3.9%), *ATM* (3.6%), *CHEK2* (excluding p.Ile157Thr) (2.0%) and *PALB2* (1.5%) (Fig 1, Table 2).
- Pathogenic variants in *ATM*, *BRCA2*, *CDKN2A*, *MSH6*, and *PALB2* were significantly associated with high PC risks (RR>5), and pathogenic variants in *BRCA1* were associated with a moderate risk of PC (RR=2.6) (Table 3).
- Pathogenic variants in *TP53* and *CHEK2* were associated with increased PC risk when assessing all Caucasian PC cases; however, the association was no longer significant when the analysis was restricted to cases with PC as their first cancer.
- Clinical histories were not always consistent with the corresponding syndrome:
  - 22.2% (n=18/81) of *BRCA1* and *BRCA2* carriers did not meet *BRCA1/2* testing criteria.
  - 64.3% (n=9/14) of *MSH6* carriers did not meet Lynch syndrome testing criteria.
  - No *CDKN2A* families met diagnostic criteria for familial atypical multiple mole melanoma syndrome, and 38.9% (7/18) did not report any personal or family history of melanoma.

Conclusions

- These findings shed light on the yield (15.4% at minimum) and spectrum of mutations that can be expected for PC patients referred for cancer predisposition testing.
- The results confirm the associations of pathogenic *CDKN2A* and *BRCA2* variants with PC and suggest that *ATM*, *PALB2*, and *MSH6* may be high-risk PC genes, warranting further investigation in case-control and family-based studies.
- A subset of PC patients with *BRCA1/2* and *MSH6* mutations did not meet respective testing criteria and a subset of *CDKN2A* mutation carriers did not have a personal or family history of melanoma, suggesting utility of an MGPT approach for PC patients.

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Category: EP01 Epidemiology

- Familial and hereditary cancers
- Next-generation sequencing in epidemiology studies (whole genome, exome, targeted, or fine mapping)
- Pathway and candidate gene studies of risk or prognosis

Research type: Epidemiological research

Key words/indexing: Pancreatic cancer, Genetic susceptibility, Epidemiology

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Short title (35 characters with spaces): Hereditary multigene panel testing for pancreatic cancer

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Purpose: The relevance of inherited pathogenic variants in cancer predisposition genes to pancreatic cancer (PC) is not well understood. Several small studies have identified pathogenic variants in 4% to 14% of unselected PC patients using multigene panels of predisposition genes, but only BRCA2, ATM, and PALB2 have been clearly implicated in this disease. We aimed to assess the clinical and molecular characteristics of PC patients referred for hereditary cancer genetic testing, and to estimate the risk of PC associated with pathogenic variants in panel-based cancer predisposition genes.

Methods: PC patients (n=1,819) were ascertained from a large cohort of over 140,000 patients undergoing multigene panel testing (MGPT) of predisposition genes between March 2012 and June 2016 at a single diagnostic laboratory. Clinical histories and molecular results were reviewed and summarized. Gene-level variant frequencies among PC cases were compared to those from the Exome Aggregation Consortium (ExAC) to calculate gene-specific pancreatic cancer risk ratios.

Results: PC patients were predominantly Caucasian (76.5%) and female (58.9%), with a median age at diagnosis of 61 years (51.7). Of these, 33.5% reported additional cancer primaries, and 44.8% reported a family history of PC. Overall, 15.4% of PC patients were found to have at least one pathogenic/likely pathogenic variant in panel-based predisposition genes. Genes with the highest frequencies of pathogenic/likely pathogenic variants included BRCA2 (3.9%), ATM (3.6%), CHEK2 (excluding p.Ile157Thr) (2.0%), PALB2 (1.5%), VHL (1.4%), CDKN2A (1.2%), BRCA1 (0.8%), and MSH6 (0.8%). 21.8% of BRCA1 and BRCA2 carriers did not meet BRCA1/2 testing criteria and 61.5% of MSH6 carriers did not meet Lynch syndrome testing criteria. No CDKN2A families met diagnostic criteria for familial atypical multiple mole melanoma syndrome, and 44% did not report any personal or family history of melanoma. To estimate associations between pathogenic variants and pancreatic cancer, Caucasian PC cases were compared to non-Finnish European, non-TCGA ExAC reference controls. Pathogenic variants in ATM, BRCA2, CDKN2A, MSH6, and PALB2 were significantly associated with high

PC risks (RR>5). Pathogenic variants in BRCA1 were associated with a moderate risk of PC (RR=2.7).

Conclusions: These findings shed light on the spectrum of mutations that can be expected for PC patients referred for cancer predisposition testing. The results confirm the associations of CDKN2A and BRCA2 variants with PC, and expand on the phenotypic spectrum associated with these variants. Furthermore, these results suggest that ATM, PALB2, and MSH6 may be high-risk PC genes, warranting further investigation in case-control and family-based studies.