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

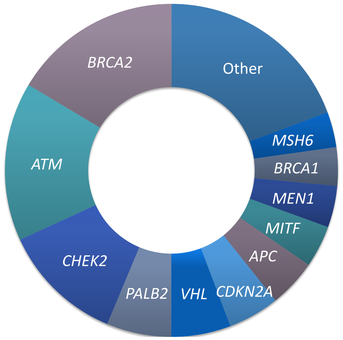
	ExAC Controls	All Caucasian Pancreatic Cancer Cases (n=1390)						Caucasian Pancreatic Cancer Cases with Pancreatic Cancer as First Cancer Diagnosis (n=1010)					
Gene	Control AF	Case AC	Case AN	Case AF	OR	p-value	95% CI	Case AC	Case AN	Case AF	OR	p-value	95% CI
ATM	0.19%	39	2616	1.49%	7.892	9.30E-20	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.

References

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