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Abstract

TITLE: Prevalence of Germline Mutations in Consecutive, Unselected Patients with Newly Diagnosed Adenocarcinoma of the Pancreas

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ABSTRACT BODY:

Abstract Body: Background: Currently, germline genetic testing among individuals with pancreatic ductal adenocarcinoma (PDAC) is based on family and personal cancer history. Identifying mutation carriers may provide potential targets for personalized treatment with agents such as PARP and immune checkpoint inhibitors and allows for recognition of family members who may benefit from pancreatic and other cancer screening and prevention strategies. The aim of this study is to estimate the prevalence of known heritable germline mutations in patients with newly diagnosed PDAC. Methods: Consecutive, unselected adult patients with histologically-proven PDAC who were diagnosed within the previous 12 weeks and presented to one of three participating centers were enrolled from May 2016 to September 2016 in an ongoing, prospective study. A 3-generation pedigree was elicited for all participants by a genetic counselor. Germline mutations in known pancreatic cancer syndrome genes (APC, ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, TP53) and in genes associated with risk for other cancers (BARD1, BRIP1, BMPR1A, CDH1, CDK4, CHEK2, GREM1, MRE11A, MUTYH, NBN, NF1, POLD1, POLE, PTEN, RAD50, RAD51C, RAD51D, SMAD4, SMARCA4) were identified by next generation sequencing (NGS) and deletion/duplication analysis (del/dup only in EPCAM, & GREM1). Results: Among 128 patients, 58 (45%) are female, 98 (77%) are Caucasian and 15 (12%) are Ashkenazi Jewish. The median (IQR) age at diagnosis is 68 (61,76) years. A total of 54 (42%) patients met criteria for genetic testing based on current National Comprehensive Cancer Network and/or American College of Gastroenterology guidelines. Four patients met criteria for familial pancreatic cancer (FPC) defined as a kindred with >2 PDAC members, at least 2 of whom are directly related. As shown in the Table, 7 pathogenic variants in genes known to contribute to PDAC susceptibility were identified in 7 patients (5.5%); 4 of these met criteria for BRCA1/2 testing; however, none met testing criteria for Lynch syndrome or FPC. CHEK2 mutations were identified in an additional 7 patients; 5 met criteria for genetic testing, one of whom was from an FPC family. Mutation carrier status, whether inclusive of CHEK2 or restricted to variants known to confer risk for PDAC, was not associated with age at diagnosis, personal history of cancers, or meeting criteria for genetic testing (all $p>0.05$). Conclusion: Preliminary results from this prospective study of newly diagnosed, unselected PDAC patients demonstrate that 5.5% carry pathogenic mutations known to contribute to PDAC susceptibility. Future work is required to determine if pathogenic variants in CHEK2 are associated with an increased risk for PDAC, and whether and to what extent changes in PDAC genetic testing criteria are warranted.

TABLE:

Criteria for Genetic Testing

Patient	Gender	Age at Diagnosis	Gene	Mutation	.	BRCA1/2	Lynch	Familial PC
1	male	68	BRCA1	c.68_69delAG	p.E23Vfs*17	Y	N	N
2	male	83	BRCA1	c.181T>G	p.C61G	Y	N	N
3	male	50	MSH6	c.2230dupG	.	N	N	N
4	male	59	ATM	c.5932G>T	p.E1978*	N	N	N
5	male	74	BRCA2	c.1237delC	p.L413Yfs*17	Y	N	N
6	female	68	ATM	c.1564_1565delGA	p.E522Ifs*43	Y	N	N
7	male	66	CDKN2A	c.-34G>T	.	N	N	N
8	male	71	CHEK2	c.470T>C	p.I157T	Y	N	N
9	male	89	CHEK2	c.470T>C	p.I157T	N	N	N
10	male	47	CHEK2	c.470T>C	p.I157T	Y	Y	N
11	male	54	CHEK2	EX8_9del	.	N	N	N
12	male	68	CHEK2	c.1283C>T	p.S428F	Y	N	N
13	male	75	CHEK2	c.1116dupC	p.K373Qfs*22	Y	N	N
14	female	88	CHEK2	c.470T>C	p.I157T	Y	N	Y

(No Image Selected)

DISCLOSURE

The following authors have completed their 2017 DDW disclosure:: Randall Brand: Disclosure completed | Nadine Tung: Disclosure completed | Beth Dudley: Disclosure completed | Eve Karloski: Disclosure completed | Mary Linton Peters: Disclosure completed | Lindsey Stobie: Disclosure completed | Erkut Borazanci: Disclosure completed | A. Moser: Disclosure completed | Arlene Colvin: Disclosure completed | Cynthia Lim: Disclosure completed | Melissa Hogg: Disclosure completed | Kenneth Lee: Disclosure completed | J. Wallis Marsh: Disclosure completed | Allan Tsung: Disclosure completed | Herbert Zeh: Disclosure completed | Amer Zureikat: Disclosure completed | Courtney Grosvenor: Disclosure completed | Brigette Tippin Davis: Disclosure completed | Holly LaDuca: Disclosure completed | Jill Dolinsky: Disclosure completed | Emily Dalton: Disclosure completed | Mary Helen Black: Disclosure completed | Virginia Speare: Disclosure completed