ATM mutations contribution to hereditary breast-pancreatic cancer

Ora K Gordon[1], Kimberly Childers[1], Rachel McFarland[2], Holly LaDuca[2]

[1]Providence Health and Services Southern California; [2]Ambry Genetics

Background

- Germline mutations in *PALB2*, *BRCA2* and *STK11* are well established as increasing risk of both breast and pancreatic cancer. More recently, *ATM* and *BRCA1* mutations have also been associated with risk, but literature is limited.
- We investigated the prevalence of pathogenic mutations and likely pathogenic variants ("mutations") in *BRCA1/2*, *PALB2*, *STK11* and *ATM*, comparing mutation occurrence in individuals with diagnoses of breast cancer alone to those with both breast and pancreatic cancer primaries.
- Prevalence of *CDKN2A* (p16) mutations was also evaluated in the breast-pancreatic cohort because of its contribution to hereditary pancreatic cancer.

Demographics & Clinical Characteristics

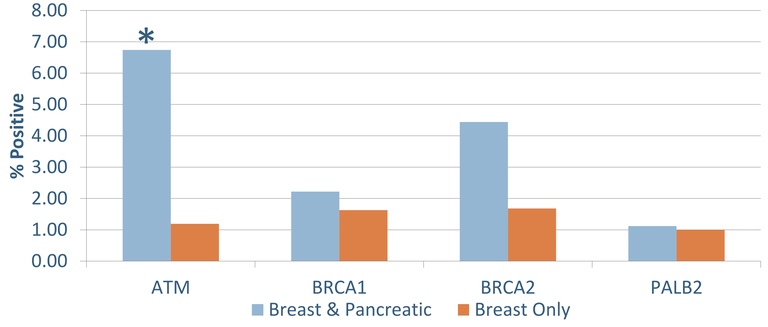
	Breast & Pancreatic		Breast Only	
	N	%	N	%
Ethnicity				
Caucasian	73	75.3%	17928	65.0%
African American/Black	3	3.1%	2012	7.3%
Ashkenazi Jewish	9	9.3%	1424	5.2%
Asian	2	2.1%	1229	4.5%
Hispanic	3	3.1%	1642	6.0%
Mixed Ethnicity	3	3.1%	1195	4.3%
Other	0	0.0%	298	1.1%
Unknown	4	4.1%	1845	6.7%
Panel Ordered				
BRCAplus	7	7.2%	9163	33.2%
BreastNext	20	20.6%	10508	38.1%
CancerNext	42	43.3%	3704	13.4%
CancerNext Expanded	3	3.1%	555	2.0%
GYNplus	2	2.1%	768	2.8%
OvaNext	5	5.2%	2724	9.9%
PancNext	19	19.6%	79	0.3%
Other			72	0.3
Age at Cancer Diagnosis				
Breast cancer – median	56 years		46 years	
Breast under age 50	34	36.6%	16953	63.0%
Breast age 50+	59	63.4%	9962	37.0%
Pancreatic cancer - median	65 years		n/a	n/a

Methods

- Clinical histories and test results were reviewed for patients undergoing multi-gene panel testing at one clinical laboratory between April 2012 and June 2015. Patients underwent comprehensive analysis of 5-49 genes, depending on the panel ordered.
- The study population was limited to women with breast cancer only (n=27,573) and women with both breast and pancreatic cancer (n=97) without other primaries.
- Demographic and clinical information was provided by clinicians on test requisition forms and pedigrees/clinic notes if provided.
- Gene-specific mutation frequencies were compared between women with breast cancer only and women with breast and pancreatic cancer using Fisher's exact test.

Mutation Frequency Comparisons

Gene	Breast & Pancreatic (n=97)		Breast Only (n=27,573)		p-value	OR	95% CI
	n, positive	n, tested	n, positive	n, tested			
ATM	6	89	209	17570	**<0.001**	**6**	**2.12, 13.85**
BRCA1	2	90	429	26336	0.66	1.37	0.16, 5.14
BRCA2	4	90	442	26336	0.07	2.72	0.72, 7.28
CDKN2A	0	54	13	3965	1	0	0, 24.70
PALB2	1	89	175	17570	0.59	1.13	0.03, 6.54
STK11	0	86	0	16931	1	Inf	0, Inf



*95% CI does not include 1.0

Results

- Mutations were identified in *BRCA1*, *BRCA2*, *PALB2* or *ATM* in 13 of the 97 breast - pancreatic cancer probands (13.4%) and 1,255 of the 27,573 breast cancer probands (4.6%).
- Of those 13 women with breast and pancreatic cancers who had identified mutations, 11 (85%) had diagnoses of breast cancer over age 50.
- *ATM* mutations were significantly more likely to be identified in women with breast and pancreatic cancer compared to breast cancer alone.
- *BRCA2* mutations were also more frequent among women with breast and pancreatic cancer compared to breast cancer alone, however this was not statistically significant (p=0.07). Prior *BRCA1/2* testing in this cohort may have confounded the analysis.
- No *CDKN2A* or *STK11* mutations were identified in the breast plus pancreatic cohort, although this may have been limited by the small number of individuals tested for *CDKN2A* (n=54). The absence of *STK11* mutations is not surprising, as patients with a clinical diagnosis of Peutz-Jeghers syndrome are likely to be referred for single gene analysis of *STK11* rather than multi-gene panel testing.

Conclusions

- This exploratory study substantiates the association of deleterious germline *ATM* mutations with predisposition to both breast and pancreatic cancers.
- These results also suggest that mutations in *ATM* may account for a larger portion of inherited breast and pancreatic cancer kindreds than mutations in other well-described genes.
- A personal history of breast and pancreatic cancer may warrant the expansion of current NCCN testing criteria as a single indicator for germline testing, and that pancreatic screening consortia (CAPS) consider inclusion of *ATM* mutations in screening recommendations.

References

1) National Comprehensive Cancer Network. **Genetic/Familial High-Risk Assessment: Colorectal (Version 1.2016).** https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. Accessed September 19, 2016.