ATM mutations contribution to hereditary breast-pancreatic cancer

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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.

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. 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. Patients underwent comprehensive analysis of 5-49 genes, depending on the panel ordered. 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.

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%). Gene-specific mutation frequencies and statistical comparisons may be found in Table 1. *ATM* mutations were significantly more likely to be identified in women with breast and pancreatic cancer compared to breast cancer alone (Table 1). Interestingly, 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 this gene. Of those 13 women with breast and pancreatic cancers who had identified mutations, 11 (85%) had diagnoses of breast cancer over age 50.

Table 1. Mutation Frequencies

Gene	Mutation Frequency n/N (%)		p	OR [95% CI]
	Breast & Pancreatic	Breast Only		
ATM	6/89 (6.74%)	209/17,570 (1.19%)	**0.00076**	**6.00 [2.12, 13.85]**
BRCA1	2/90 (2.22%)	429/26,336 (1.63%)	0.66	1.37 [0.16, 5.14]
BRCA2	4/90 (4.44%)	442/26,336 (1.68%)	0.066	2.72 [0.72, 7.28]
CDKN2A	0/54 (0.00%)	13/3,965 (0.33%)	1	0.00 [0, 24.70]
PALB2	1/89 (1.12%)	175/17,570 (1.00%)	0.59	1.13 [0.03, 6.54]
STK11	0/86 (0.00%)	0/16,931 (0.00%)	1	Inf [0, Inf]

CONCLUSION: 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 such as *BRCA2*, *PALB2* and *STK11*. 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.