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Characterizing the mutation spectrum in *BRCA1/2*-negative early-onset breast cancer patients undergoing multigene panel testing

Selvi Palaniappan, Holly LaDuca, Shuwei Li, Rachel McFarland, Elizabeth Chao

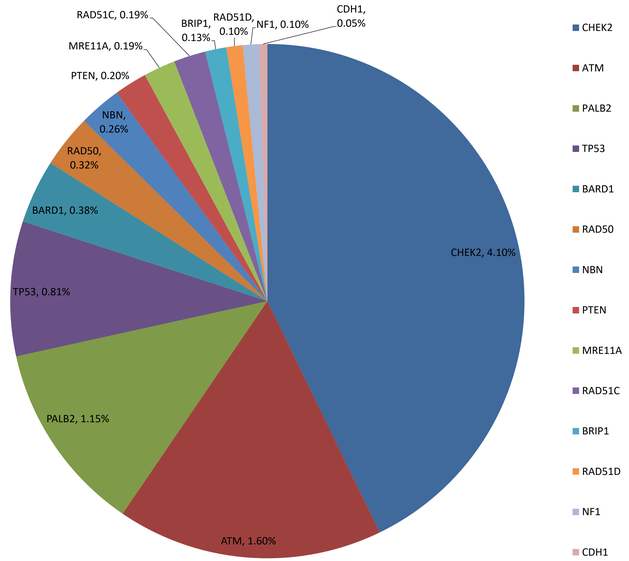
BACKGROUND

- National Comprehensive Cancer Network (NCCN) guidelines support *BRCA1/2* testing for early-onset breast cancer, as one of their testing criteria is breast cancer diagnosed at age 45 or younger.
- Women diagnosed with early-onset breast cancer often seek knowledge from genetic testing for informed decision making with regards to treatment and prevention.
- Panel testing is currently available to provide information about a hereditary cancer susceptibility. [1,2]
- Recent studies on panel testing in cancer patients indicate that there are other genes involved in hereditary breast cancer beyond *BRCA1* and *BRCA2.* [3]
- This study aims to define the mutation spectrum in *BRCA1/2* mutation-negative women diagnosed with breast cancer at age 45 or younger.

METHODS

- Results from Hereditary Breast Ovarian Cancer Syndrome (HBOC) multigene panel testing, performed at our clinical diagnostic laboratory, were retrospectively reviewed for a cohort of 4066 *BRCA1/2* mutation-negative patients diagnosed with breast cancer at age 45 or younger.
- Panels included comprehensive analysis of 6-23 genes, depending on the test ordered (BRCAplus, BreastNext, or OvaNext). Mutation frequencies were calculated for the following breast and/or ovarian cancer genes: *CHEK2, ATM, PALB2, TP53, BARD1, RAD50, NBN, PTEN, MRE11A, RAD51C, BRIP1, RAD51D, NF1*, *CDH1* and mismatch repair (MMR) genes.
- Mutation frequencies were calculated based on the number of times each gene was sequenced in this cohort and then compared with those observed in 4615 breast cancer patients diagnosed after age 45.

Figure 1: Mutation spectrum in patients 45 years of age or younger



RESULTS

- The majority of patients in this study were of Caucasian descent and most underwent BRCAplus testing – a panel comprised of six high-risk breast cancer genes (Table 1).
- The most commonly mutated gene in this cohort was *CHEK2* (4.10%), followed by *ATM* (1.6%), *PALB2* (1.15%), and *TP53* (0.81%). Mutation frequencies for each of the remaining 10 genes was <0.50% (Figure 1).
- Mutations in *ATM*, *CHEK2*, and *TP53* were significantly more frequent among patients diagnosed age 45 or younger when compared to women diagnosed after age 45 (p-value <0.05) (Figure 2). We were not able to perform statically analysis on *BARD1, MRE11A, NF1, NBN, RAD51C, RAD51D*, and *CDH1* due to the small sample size in our cohorts.
- 1100delC was the most common mutation discovered in *CHEK2* (40% of the *CHEK2* positives). The average age of diagnosis in patients with a *CHEK2* mutation was 47 (Table 2). The average age of diagnosis was also similar amongst the carriers of the common 1100delC mutation when compared to other mutations in *CHEK2* (p-value > 0.3).
- The average age at first breast cancer diagnosis for *ATM* and *TP53* mutation carriers was 43 and 38, respectively. While it is known that *TP53* mutations are common amongst women with early-onset breast cancer, our data indicates that *ATM* mutations may also be common in these women.
- Mutations in *BRIP1* were significantly more frequent among patients diagnosed after age 45 when compared to women diagnosed at age 45 or younger (Figure 2). The average age at first breast cancer diagnosis of *BRIP1* mutation carriers was 57.
- Of note all of the mutations found in MMR genes were in patients diagnosed with breast cancer after age 45 with an average age at diagnosis of 52.

Table 1: Demographics

Demographic	≤45 (n)	≤45 (%)	>45 (n)	>45 (%)	Overall (n)	Overall (%)
			Age Group			
African American	348	8.6%	253	5.5%	601	6.9%
Ashkenazi Jewish	147	3.6%	246	5.3%	393	4.5%
Asian	214	5.3%	126	2.7%	340	3.9%
Caucasian	2681	65.9%	3389	73.4%	6070	69.9%
Hispanic	250	6.1%	155	3.4%	405	4.7%
Middle Eastern	22	0.5%	24	0.5%	46	0.5%
Mixed Ethnicity	157	3.9%	123	2.7%	280	3.2%
Native American	2	0.0%	3	0.1%	5	0.1%
Other	8	0.2%	14	0.3%	22	0.3%
Unknown	237	5.8%	282	6.1%	519	6.0%
			Ethnicity			
BRCAplus	2506	61.6%	2661	57.7%	5167	59.5%
BreastNext	1398	34.4%	1580	34.2%	2978	34.3%
OvaNext	162	4.0%	374	8.1%	536	6.2%
Totals	4066		4615		8681	
			Test Ordered			

Figure 2: Gene-specific mutation frequencies

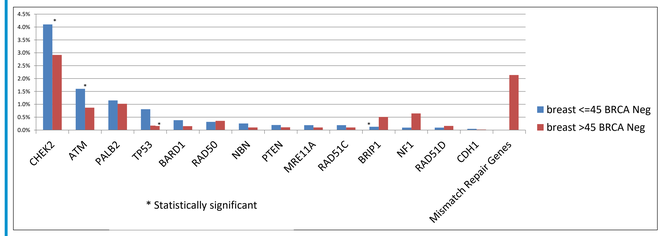


Table 2: Average age at first breast cancer diagnosis

Gene	Average Age at Diagnosis
CHEK2	47
ATM	43
PALB2	49
TP53	39
MMR	52
BRIP1	57
BARD1	41
RAD50	51
CDH1	43
MRE11A	46
NBN	49
NF1	51
PTEN	47
RAD51C	45
RAD51D	46

TAKE-HOME POINTS

- *ATM*, *CHEK2*, *PALB2* and *TP53* are the most commonly discovered mutations in *BRCA1/2* mutation-negative women diagnosed with breast cancer at age 45 or younger. *ATM*, *CHEK2* and *TP53* mutations were significantly more common in early onset patients when compared to women who were diagnosed after age 45.
- Given the frequency of these mutations in this younger population, molecular diagnosis for these genes may be important.
- While NCCN management guidelines exist for *TP53* mutation carriers, this study illustrates to need to define management guidelines for *ATM*, *CHEK2* and *PALB2*.

REFERENCES

1) NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment.
2) Walsh T, Casadei S, Lee MK, et al. Mutations in 12 genes for inherited ovarian cancer, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. PNAS 2011;108(44):18032-7.
3) Maxwell KN, Wubbenhorst B, D'Andrea K, et al. Prevalence of mutations in a panel of breast cancer susceptibility genes in BRCA1/2-negative patients with early-onset breast cancer. Genet Med. 2014 Dec 11.

15 Argonaut, Aliso Viejo, CA 92656 Toll Free 866 262 7943 Fax 949 900 5501 ambrygen.com