Racial and Ethnic Differences in Hereditary Cancer Multi-Gene Panel Testing Results Among Breast Cancer Patients

Hermela Shimelis,[1] Eric C. Polley,[2] Jenna Lilyquist,[2] Jie Na,[1] Chunling Hu,[1] Kun Y. Lee,[1] Steven Hart,[2] Raymond Moore,[2] David E. Goldgar,[3] Amal F Yussuf,[4] Brigette Tippin-Davis,[4] Tina Pesaran,[4] Jill S. Dolinsky,[4] Fergus J. Couch,[1,2] Holly LaDuca [4]

[1]Dept of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; [2]Dept of Health Sciences Research, Mayo Clinic, Rochester, MN; [3]University of Utah School of Medicine, Huntsman Cancer Institute, Salt Lake City, UT; [4] Ambry Genetics, Aliso Viejo, CA

Background

- Recently, the use of next-generation sequencing panels to aid in the diagnosis of hereditary breast cancer (BC) predisposition has increased.
- The discovery of pathogenic and likely pathogenic variants (herein referred to as 'PVs') in known susceptibility genes leads to focused screening and prevention strategies of individuals at increased risk of BC.
- Studies supporting the utility of multi-gene panel testing have focused on Caucasian individuals, therefore we aimed to explore inherited BC susceptibility in non-Caucasian BC cases.

Figure 1. Pooled PV and VUS Frequencies in 12 Breast Cancer Susceptibility Genes†

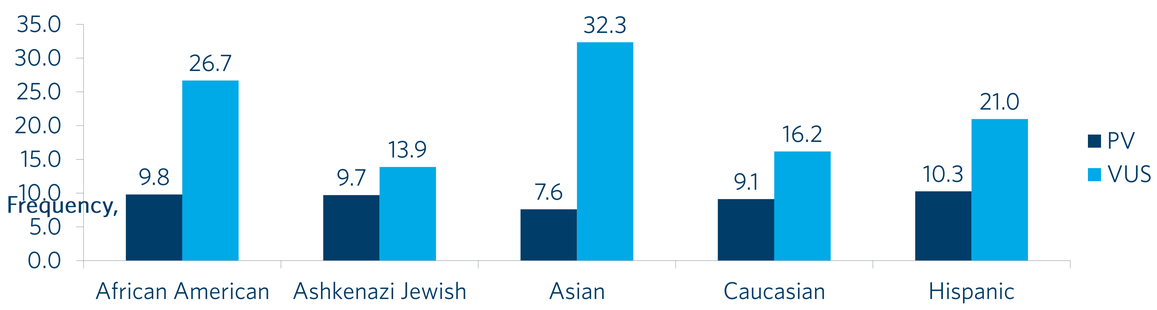

Table 2. Gene-specific PV and VUS Frequencies†

Gene	PV frequency (%)					VUS frequency (%)				
	African American	Ashkenazi Jewish	Asian	Caucasian	Hispanic	African American	Ashkenazi Jewish	Asian	Caucasian	Hispanic
ATM	0.8	1.0	0.6	1.3	0.9	8.7	3.9	5.7	3.8	5.3
BARD1	0.5	0.1	0.3	0.2	0.5	1.6	1.3	2.7	1.2	1.1
BRCA1	2.9	2.6	2.2	1.7	3.1	2.1	0.5	3.0	0.8	1.3
BRCA2	2.9	1.9	2.2	2.0	2.6	4.1	0.6	4.7	1.8	3.1
BRIP1	0.4	0.2	0.0	0.3	0.3	1.8	1.7	3.0	1.5	1.7
CDH1	0.1	0.0	0.1	0.1	0.1	1.3	0.4	1.8	0.7	1.3
CHEK2	0.3	3.3	0.3	2.1	0.8	1.1	2.3	1.9	1.8	2.9
PALB2	1.1	0.3	1.2	0.9	1.1	1.8	1.0	5.0	1.3	1.2
PTEN	0.1	0.0	0.1	0.1	0.1	1.8	0.8	1.8	0.9	1.5
RAD51C	0.3	0.1	0.1	0.2	0.5	1.1	0.8	0.5	1.3	0.5
RAD51D	0.2	0.2	0.1	0.1	0.1	0.9	0.2	1.0	0.6	0.5
TP53	0.2	0.1	0.3	0.2	0.3	0.5	0.4	1.2	0.4	0.4

†Excludes BC cases reporting prior *BRCA1/2* and/or Lynch syndrome testing

Table 3. PV Frequencies Relative to Caucasians†

	African American		Ashkenazi Jewish		Asian		Hispanic	
Gene	OR	P-value	OR	P-value	OR	P-value	OR	P-value
ATM	0.6	7.5E-03	0.8	0.29	0.4	2.28E-03	0.7	2.5E-04
BARD1	1.9	0.02	0.5	3.2E-01	1.4	0.38	2.1	0.01
BRCA1	1.4	1.0E-04	1.8	9.9E-06	1.1	0.29	1.5	8.0E-05
BRCA2	1.4	2.0E-04	1.0	0.74	1.0	0.96	1.2	0.05
BRIP1	1.4	0.27	0.5	0.21	ND	ND	1.1	0.81
CDH1	1.6	0.33	ND	ND	2.4	0.10	0.5	0.47
CHEK2	0.2	1.34E-11	0.6	2.0E-02	0.2	3.49E-07	0.4	5.4E-06
CHEK2 (S428F)	ND	ND	66.9	2.0E-16	0.0	0.99	1.3	0.82
PALB2	1.2	0.17	0.3	9.2E-03	1.5	0.03	1.3	0.16
PTEN	1.6	0.31	ND	ND	0.4	0.43	1.5	0.48
RAD51C	1.3	0.42	0.5	0.37	0.5	0.27	2.2	0.01
RAD51D	1.8	0.18	2.4	0.10	1.7	0.40	0.9	0.85
TP53	1.0	0.86	0.6	0.42	1.2	0.59	1.1	0.86

†Excludes BC cases reporting prior *BRCA1/2* and/or Lynch syndrome testing; logistic regression model assumes no family history and average age at diagnosis is 50
ND: Not determined due to insufficient number of carriers

Methods

Study population: Female BC patients undergoing hereditary cancer panel testing of 5 to 49 genes at Ambry Genetics between 2012 and 2016

Statistical analysis:

- The distribution of age at testing and age at BC diagnosis among non-Caucasians was compared to Caucasians using the Kolmogorov-Smirnov test (Table 1)
- The frequency of PVs and variants of unknown significance (VUS) in African American, Ashkenazi Jewish, Asian, Caucasian and Hispanic BC cases was assessed for 12 genes associated with >2.0 fold risks of overall BC[1] and/or triple-negative BC[2]: *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, PALB2, PTEN, RAD51C, RAD51D, TP53* (Figure 1, Table 2)
- Gene-specific BC risk associations were estimated for each population by comparing PV frequencies between BC cases and gnomAD African/African American, East Asian, non-Finnish European and Latino reference controls, respectively (data not shown)
- Logistic regression analysis was used to compare gene-specific PV frequencies among African American, Ashkenazi Jewish, Asian, and Hispanic BC cases to Caucasians, adjusting for age at BC diagnosis and family history of breast and ovarian cancer (Table 3)

[1]Couch et al *JAMA Oncol.* 2017 Sep 1;3(9):1190-1196; [2]Couch et al. *Cancer Res* 2018;78(4 Suppl):Abstract nr PD1-01

Table 1. Clinical Characteristics of Female Breast Cancer Cases

	Characteristic	African American (n=6722)	Ashkenazi Jewish (4798)	Asian (n=4183)	Caucasian (n=57,003)	Hispanic (n=5194)
		n (%)	n (%)	n (%)	n (%)	n (%)
	Median age at testing (range)	50 (18-90)	60 (21-90)	47 (22-90)	56 (18-90)	49 (20-90)
C	Median age at dx (range)	47 (18-90)	53 (21-90)	45 (20-19)	50 (18-90)	45 (18-86)
C	dx ≤36	1194 (17.8)	346 (7.2)	752 (18.0)	5972 (10.5)	888 (17.1)
C	dx ≤45	3232 (48.1)	1395 (29.1)	2364 (56.5)	21,040 (36.9)	2717 (52.3)
C	dx ≤50	4420 (65.8)	2298 (47.9)	3187 (76.2)	32,228 (56.5)	3718 (71.6)
C	dx ≤60	5878 (87.4)	3593 (74.9)	3802 (90.9)	46,214 (81.1)	4651 (89.5)
B	dx >60	844 (12.6)	1205 (25.1)	381 (9.1)	10,789 (18.9)	543 (10.5)
B	Multiple Breast Cancers	812 (12.1)	626 (13.0)	455 (10.9)	7015 (12.3)	417 (8.0)
Person	Ovarian	79 (1.2)	78 (1.6)	56 (1.3)	1207 (2.1)	61 (1.2)
Person	Endometrial	92 (1.4)	101 (2.1)	56 (1.3)	1241 (2.2)	71 (1.4)
Oth	Colorectal	90 (1.3)	74 (1.5)	36 (0.9)	931 (1.6)	43 (0.8)
Oth	Pancreatic	18 (0.3)	28 (0.6)	5 (0.1)	242 (0.4)	9 (0.2)
Fam	Breast (no ovarian)	3385 (50.4)	2733 (57.0)	1553 (37.1)	31,857 (55.9)	2113 (40.7)
Fam	Breast & Ovarian	458 (6.8)	307 (6.4)	206 (4.9)	4874 (8.6)	329 (6.3)
Fam	Ovarian (no breast)	297 (4.4)	203 (4.2)	190 (4.5)	2653 (4.7)	282 (5.4)
Fam	Colorectal	1161 (17.3)	1168 (24.3)	594 (14.2)	14,156 (24.8)	674 (13.0)
Fam	Endometrial	312 (4.6)	321 (6.7)	183 (4.4)	4352 (7.6)	391 (7.5)
Fam	Pancreatic	538 (8.0)	592 (12.3)	259 (6.2)	5660 (9.9)	390 (7.5)
Fam	No family history of cancer†	1617 (24.1)	827 (17.2)	1360 (32.5)	9633 (16.9)	1518 (29.2)

†1st or 2nd degree relatives with family history of breast, ovarian, colorectal, pancreatic and endometrial cancer

Results

- Ages at testing and breast cancer diagnosis were significantly different among non-Caucasians relative to Caucasians ($p<0.0001$) (Table 1), with younger ages observed in African American, Asian, and Hispanic BC cases and older ages observed in Ashkenazi Jewish cases
- African American, Asian, and Hispanic BC cases were less likely to report a family history of cancer than Ashkenazi Jewish and Caucasian cases (Table 1)
- PV frequency was highest in Hispanic BC cases (10.3%) and lowest in Asian cases (7.6%), whereas VUS frequency was lowest in Ashkenazi Jewish BC cases (13.9%) and highest in Asian cases (32.3%, Fig 1)
- *ATM* and *CHEK2* PVs were significantly less frequent among African American, Asian, and Hispanic BC cases compared to Caucasian BC cases (Table 3)
- *BARD1*, *BRCA1*, and *BRCA2* PVs were significantly more frequent among African American BC cases compared to Caucasian BC cases, which is likely due to the association of these genes with triple negative BC (TNBC) in combination with increased incidence of TNBC in the African American population (Table 3)
- Consistent with these findings, PVs in *BRCA1*, *BRCA2*, and *PALB2* were associated with high risk of BC across all groups in an exploratory analysis of population-specific BC risk associations (data not shown). However, PVs in *ATM*, *CHEK2*, *BARD1*, *BRIP1*, *RAD51C* and *RAD51D* showed population-specific associations with BC.

Conclusions

- Results from this study suggest the presence of population-specific differences in hereditary cancer panel testing referrals for BC patients and further our understanding of population-specific mutation spectra and BC cancer risk associations.
- These findings demonstrate the need for continued investigation of population-specific factors contributing to inherited BC risk.

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