Ambry Genetics™

Multi-Gene Testing in a Male Breast Cancer Cohort: Insights and Unexpected Results

Mary Pritzlaff, Pia Summerour, Rachel McFarland, Shuwei Li, Holly Laduca
Ambry Genetics, Aliso Viejo, CA92656

BACKGROUND

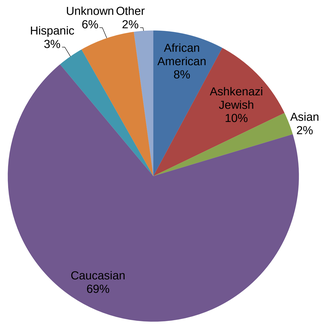
- Approximately 5-10% of female breast cancer is due to an inherited predisposition; however, the epidemiology of male breast cancer (MBC) is less well defined.
- The majority of hereditary MBC has been linked with pathogenic mutations in *BRCA2*.
- The *CHEK2* 1100delC mutation has been linked with MBC, but reports are conflicting, and the role of other *CHEK2* mutations in MBC is not well established.[1,2]
- Data is limited regarding the yield of multi-gene panel testing for male breast cancer patients.
- In a study of 2,158 breast cancer patients who underwent a 25-gene cancer panel, 7/22 MBC cases tested positive for pathogenic mutations or likely pathogenic variants (VLP): *BRCA1* (1), *BRCA2* (3), *PALB2* (1), *CHEK2* (1), *ATM* (1).[3]

METHODS

- Reviewed test results for all MBC patients who underwent breast cancer-associated multi-gene panel testing from March 2012 to March 2015.
  - 7 different breast-cancer associated panels were included, ranging from 2 to 43 genes
- Assessed demographic and clinical histories provided on test requisition forms including ethnicity, personal cancer history, age at diagnosis, and family history.
- Performed statistical analysis using the Wilcoxon Rank Test and Fisher's exact test.

DEMOGRAPHICS

Ethnicity



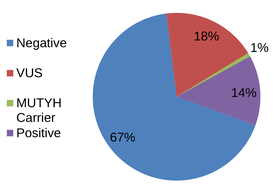
Age at Breast Cancer Diagnosis

Age at Diagnosis	No. of Positive Men (n=38)	No. of Negative/ VUS Men (n=242)
<36y	2	10
≤45y	4	35
<50y	4	49
>50y	33	183
Age not provided	1	10

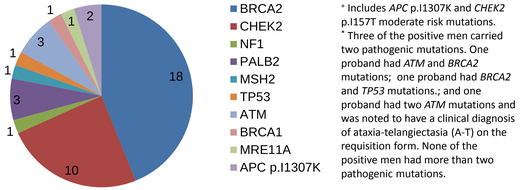
The average age at diagnosis for positive men (62.5 years) was not significantly different from negative men (59.5 years) (p=0.269). However, the average age of diagnosis for men with *CHEK2* 1100delC mutations (n=4) (46.0 years) was significantly lower than in other positive men (p=0.012).

MULTI-GENE PANEL RESULTS FOR MBC PATIENTS

Overall Panel Results (n=280)



Mutations and VLPs+*



+ Includes *APC* p.I1307K and *CHEK2* p.I157T moderate risk mutations.
* Three of the positive men carried two pathogenic mutations. One proband had *ATM* and *BRCA2* mutations; one proband had *BRCA2* and *TP53* mutations.; and one proband had two *ATM* mutations and was noted to have a clinical diagnosis of ataxia-telangiectasia (A-T) on the requisition form. None of the positive men had more than two pathogenic mutations.

Gene-specific Mutation Frequencies[1]

Gene	Positive Rate	Gene	Positive Rate
BRCA2	18/280 (6%)	*MSH2*	1/71 (1%)
CHEK2 (incl. p.I157T)	10/196 (5%)	*NF1*	1/196 (0.5%)
APC p.I1307K	2/59 (3%)	*MRE11A*	1/196 (0.5%)
ATM	3/200 (2%)	*TP53*	1/280 (0.4%)
PALB2	3/200 (2%)	*BRCA1*	1/280 (0.4%)

[1]The men in this cohort were tested via different multi-gene panels; therefore, not all men were tested for all genes. Of note, 84 men (30%) were not tested for *CHEK2*.

ADDITIONAL CANCERS IN POSITIVE MEN[1]

Cancer Site	No. Men	Mutations
MBC only	19	*BRCA1* (1); *BRCA2* (7); *CHEK2* (4); MRE11A (1); *NF1* (1); *PALB2* (1); *ATM/ATM* (1); *BRCA2/TP53* (1)
MBC and one additional cancer:		
Prostate	4	*BRCA2* (3); *MSH2* (1)
Melanoma	3	*BRCA2* (2); *CHEK2* (1)
Skin –SCC	1	*ATM* / *BRCA2*
Thyroid	1	*PALB2*
Bladder	1	*BRCA2*
Renal	1	*CHEK2*
Colon	1	*CHEK2*
MBC and two additional cancers:		
Pancreatic and Prostate	1	*BRCA2*
Pancreatic and Melanoma	1	*BRCA*
Bladder and Esophageal	1	*APC* I1307K

[1]Excluding *MUTYH* mutations

ADDITIONAL CANCERS

- Additional cancers were present in 42% of men with a mutation or VLP; of these, 64% had *BRCA2* and 14% had *CHEK2* mutations.
- None of the positive men had a second primary breast cancer or bilateral breast cancer.
- Additional cancers were present in 26% (64/247) of men who did not test positive.

FAMILY HISTORY OF MBC

- Men with *CHEK2* mutations were significantly more likely to have a family history of MBC compared to other positive men (3/7 compared to 2/26) (p=0.020). Of men with VUS, 3/51 had a family history of MBC, and 10/189 negative men had a family history of MBC.

Test result	No. men with fam hx of MBC[1]
CHEK2 positive	3
BRCA2 positive	1
ATM positive	1
Inconclusive	3
Negative	10

[1] Excluding *MUTYH* mutations

TAKE-HOME POINTS

- Multi-gene testing identified mutations in MBC patients that would not have been identified with a single gene testing approach along with multiple mutation carriers.
- Family history and age of diagnosis are predictive for positive results in *CHEK2* but not for the overall cohort, supporting that individuals with MBC should be tested regardless of age of diagnosis or family history.
- The *CHEK2* mutation rate in this cohort was second in frequency to *BRCA2*, affirming a role for *CHEK2* testing in MBC.

REFERENCES

1. Meijers-Heijboer H et al. *Nat Genet*. 2002 May;31(1)55-9.
2. Ruddy KH and Winer EP *Ann Oncol*. 2013 Jun;24(6):1434-43.
3. Tung N et al. *Cancer*. 2015 Jan 1;121(1):25-33