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Abstract #3406

MAYO CLINIC

Hereditary Risks of Male Breast Cancer in a Multi-Gene Panel Testing Cohort

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BACKGROUND

- Population-based risk for breast cancer in males is relatively low (1:1000).
- Inherited predisposition raises this to as high as 1:10 in men who carry a *BRCA2* mutation.
- Lifetime breast cancer risks of 1-2% have also been reported in men who carry a *BRCA1* mutation.
- Male breast cancer (MBC), as well as elevated risks of prostate, pancreatic, and melanoma cancers, are important to discuss in families diagnosed with hereditary breast and ovarian cancer syndrome, which is often viewed as being clinically relevant only to the women in an affected family.
- Beyond the BRCA*1/2* genes, limited data is available on hereditary predisposition to MBC.

METHODS

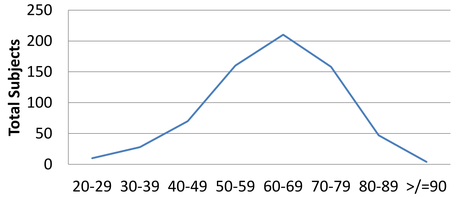
- Clinical histories and molecular results from multi-gene panel testing for cancer predisposition in a cohort of 708 MBC patients eligible for inclusion were assessed.
  - Molecular testing included analysis of 5 to 49 genes for DNA coding sequence by next-generation sequencing and copy number variants by microarray.
- Genetic variants identified were classified by a 5-tier system using previously validated algorithms.[1]
  - Only those variants classified as pathogenic or likely pathogenic were included in the analyses as positive for a mutation.
- Case-control analyses were performed based on sequencing results from 421 Caucasian MBC patients and 26,911 ExAC NFE-non TCGA controls to generate gene specific risk estimates.
- 31.5% of the cohort was known to have prior *BRCA1/2* testing and were analyzed as a subgroup.

DEMOGRAPHICS

Table 1. Ethnicity in Overall Cohort

Ethnicity	N	%
Caucasian	468	66.1%
Ashkenazi Jewish	70	9.9%
African American	58	8.2%
Asian	23	3.2%
Other/Unknown	89	12.6%

Figure 1. Age at Diagnosis of MBC



RESULTS

- 18% overall mutation detection rate among 708 MBC patients
- *BRCA2* and *CHEK2* were the most frequently mutated genes.
- 6 subjects carried a mutation in two different breast cancer predisposition genes.
  - *ATM/BRCA2*(n=2), *BRIP1/BRCA2*(n=1), *BRCA1/CHEK2*(n=1), *BARD1/PALB2*(n=1), *CHEK2/PALB2*(n=1)
- Significantly elevated MBC risks by gene were seen for *BRCA2, CHEK2* and *PALB2.*
- Average age at diagnosis was similar amongst men with and without mutations (63.5±2.7 vs 62.3±1.2 years).
- Clinical and family histories of additional cancers were also similar among men with and without mutations..

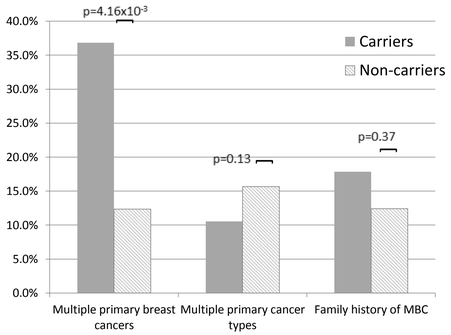
Table 2. Frequency of pathogenic variants in breast cancer genes in overall MBC cohort

	No prior BRCA1/2 testing			All MBC		
Gene	Total P/LP Variants	Total Tested[a]	%	Total P/LP Variants	Total Tested[a]	%
BRCA2	53	480	11.0	55	677	8.1
CHEK2 (all)	16	386	4.1	22	581	3.8
CHEK2 (excluding I157T)	11	386	2.8	16	581	2.8
CHEK2 (I157T only)	5	386	1.3	6	581	1.0
ATM[b]	6	390	1.5	6	586	1.0
BRCA1	6	480	1.3	6	677	0.9
NF1	2	354	0.6	3	512	0.6
PALB2	2	417	0.5	5	621	0.8
RAD51D	1	354	0.3	1	512	0.2
BRIP1	1	370	0.3	1	564	0.2
MRE11A	1	370	0.3	1	564	0.2
NBN	1	370	0.3	1	564	0.2
BARD1	0	370	0.0	2	564	0.4

Table 3. MBC risks associated with pathogenic variants by gene among Caucasians

	Ambry cases		ExAC controls			Cancer Risk		
Gene	Mutated Alleles	Cases	Mutated Alleles	Cases	OR	95%CI lower	95%CI upper	p-value
ATM	2	421	90	26644	1.4	0.3	5.1	0.66
BRCA1	2	394	74	26911	1.8	0.3	6.8	0.30
BRCA2	21	394	105	26791	13.9	8.5	22.5	1.92×10^{-16}
CHEK2 All	17	421	424	25215	2.4	1.4	3.9	1.82×10^{-3}
CHEK2_c.1100delC	8	421	127	25215	3.8	1.7	7.8	1.82×10^{-3}
CHEK2 W/O I157T	12	421	191	25215	3.8	2.1	6.8	1.51×10^{-4}
CHEK2 I157T	5	421	233	25215	1.3	0.5	3.0	0.60
PALB2	3	421	29	26869	6.6	1.7	21.1	0.013

Figure 2. Clinical histories of pathogenic carriers vs. non-carriers



TAKE-HOME POINTS

- The high overall diagnostic yield of 18% suggests the utility of testing all male breast cancer patient regardless of age or family history by multigene panel testing.
- This data provides gene specific risk estimates for MBC among a cohort of high risk families
- This data supports risk-based counseling and medical recommendations for screening and/or prevention in male mutation carriers.

REFERENCES

1. Pesaran T, Karam R, Huether R, et al. Beyond DNA: An Integrated and Functional Approach for Classifying Germline Variants in Breast Cancer Genes. *Int J Breast Cancer* 2016:1-10.

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