

Introduction

Little is known about the etiology of male breast cancer (MBC); however, single-gene hereditary factors, particularly variants in BRCA2, are estimated to account for ~10% of cases. Germline variants in other genes including BRCA1, CHEK2, PALB2, PTEN, and TP53 have been reported in MBC, but there are fewer data regarding their role in hereditary MBC assessment. Herein, we describe our experience with testing for hereditary causes of MBC and define the role of multi-gene panel testing in patients with MBC.

Methods

- A case series of 245 consecutive patients with MBC undergoing commercial testing for hereditary cancer risk were identified.
- Germline DNA was tested with next-generation sequencing for read through and copy number variation. The genes analyzed were selected at the discretion of ordering clinicians on the basis of each patient's clinical indication.
- De-identified information from requisition forms or medical records was reviewed to determine whether clinical criteria for genetic testing were met. A personal history of MBC was not included as a criterion.

Results

Germline Genetic Findings in MBC Patients

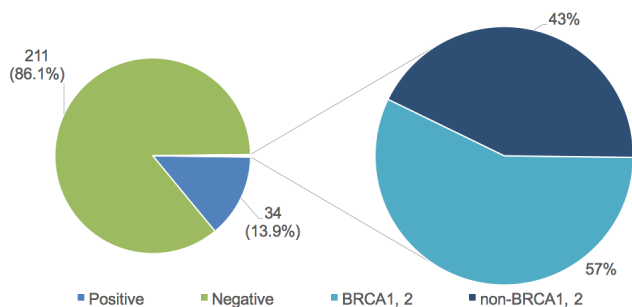


Figure 1: Results of germline genetic testing in MBC patients undergoing testing for hereditary risk.

Pathogenic or likely pathogenic (P/LP) variants were identified in 34 of 245 (13.9%) patients. Of 37 total P/LP variants identified, 21 (57%) occurred in BRCA2 and 16 (43%) in genes other than BRCA1/2 (Figure 1; Table 1). Among the patients with P/LP variants, three patients had variants in two genes including BRCA2/PTEN (Figure 2), BRCA2/MUTYH, and ATM/MUTYH. The identified CHEK2 variants included the P variant c.1100delC (p.Thr367Metfs) in three patients, the LP variant c.349A>G (p.Arg117Gly), and the -low-penetrance P variant c.1283C>T (p.Ser428Phe).

Requisitioned tests included BRCA1/2 in 21 patients, resulting in P/LP findings in 9.5%, and panel testing ranging from three to 79 genes in 224 patients, resulting in P/LP findings in 16%. Family history or previous personal history met established criteria for BRCA1/2 testing in 67 of 245 (27%) patients, and of those, 14 (21%) had P/LP findings.

Results (continued)

Gene	Number of patients in which gene was requisitioned	Pathogenic or likely pathogenic finding
ATM	180	3 (1.7%)
BRCA1	246	0 (0.0%)
BRCA2	246	21 (8.5%)
CHEK2	202	5 (2.5%)
FANCA	2	1 (50%)
MUTYH	121	4 (3.3%)
PALB2	218	1 (0.5%)
PTEN	204	1 (0.5%)
TP53	213	1 (0.5%)

Table 1: Requisitioned genes and findings in 245 patients with a personal history of MBC.

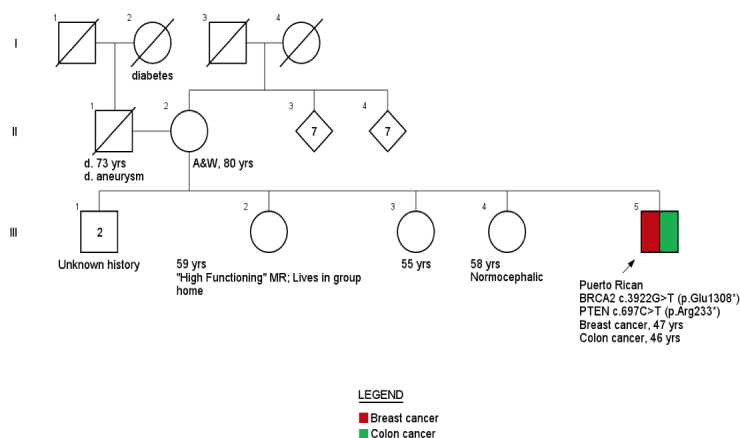


Figure 2: Patient with MBC and colorectal cancer found to have pathogenic variants in both BRCA2 and PTEN.

Conclusions

- Our data support previously described associations of BRCA2, CHEK2, PALB2, PTEN, and TP53 with MBC as well as the finding that BRCA1 is a rare cause of hereditary MBC.
- Many (73%) MBC patients lacked family histories suggestive of hereditary risk, including 59% of those who tested positive, which reinforces current recommendations to offer genetic testing to all MBC patients regardless of family history.
- ATM variants in MBC patients have not been previously reported and warrant further study.
- As in female breast cancer, the use of multi-gene panel testing in MBC increases yield compared with testing for only BRCA1/2.
- Further research is needed to determine the optimal prevention and treatment options for hereditary MBC as more individuals with genetic risk are identified.

References

- Silvestri, V, et al. *Breast Cancer Res*. 2016;18:15.
 Basham, VM, et al. *Breast Cancer Res*. 2002;4(1):R2.
 Ding, YC, et al. *Breast Cancer Res Treat*. 2011;126(3):771-8.
 De Juan, I, et al. *Fam Cancer*. 2015;14(4):505-13.
 Hagelstrom, RT, et al. *Pediatr Blood Cancer*. 2016;63(3):544-6.