Breast Cancer Gene Panel Testing Among High Risk Individuals: A Single Institution Experience

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Objective

Identifying individuals with a hereditary predisposition to breast cancer has important implications. Next-generation sequencing (NGS) allows for rapid identification of multiple genes responsible for hereditary cancer risk, and is being increasingly utilized in cancer genetics evaluation. This study presents the results of gene panel testing for patients with a significant history of breast cancer seen at Beaumont Health System.

Methods

Patients with suspected hereditary predisposition to breast cancer were evaluated at the Beaumont Cancer Genetics Program. Select patients with strong family histories of breast cancer or those suggestive of more than one cancer syndrome were offered gene panel testing. The panels ranged from six to 26 genes associated with a risk for breast cancer and other cancers. The majority (64 of 92 or 69.6%) of tests consisted of a six gene high risk breast panel. Patients received pre- and post-test genetic counseling and were informed of the implications and limitations of gene panel testing. These genes were analyzed using NGS and microarray technologies.

Results

Ninety-three patients underwent gene panel testing between November 2012 and April 2014. Sixty-two (66.7%) patients tested negative for any mutation. Six (6.5%) tested positive for a deleterious mutation: one PALB2, two PTEN, one BRCA1, one CHEK2, and one MSH6 (Table 1). One of the PTEN carriers did not meet testing criteria for Cowden syndrome (Figure 1). The PALB2 mutation carrier had no personal or family history of pancreatic cancer (Figure 2). One patient had both a CHEK2 deleterious mutation and a BRIP1 variant of uncertain significance (VUS) (Figure 3).

Twenty-seven patients (29.0%) were found to carry at least one VUS, with three patients having two variants, one patient having four variants, and one with a VUS and a deleterious mutation. There were 33 variants identified in 27 patients. Seven variants occurred in BRCA1/2 and twenty-six variants occurred in other genes (Table 2). Two of the CHEK2 variants were interpreted as suspected deleterious by another independent laboratory, bringing the total number of deleterious mutation carriers to 8 (8.6%).

Conclusion

This study demonstrates the finding of five (5.4%) deleterious mutations in genes other than BRCA1/2, which likely would not have been discovered by pedigree analysis alone. Accounting for the two additional CHEK2 variants with discordant interpretations, our rate of deleterious mutations was 8.6%. Our finding of 29.0% VUS rate underscores the challenge of utilizing panel tests in clinical decision making. The use of larger panels will likely lead to a higher proportion of variants as reported in other studies. Further research is needed to better define the broad mutational spectrum of high risk families with breast cancer in order to optimize clinical management.