Objective

Individuals of Ashkenazi Jewish (AJ) ancestry are at risk for carrying a mutation in one of three specific locations in BRCA1/BRCA2 (187delAG and 5385insC in BRCA1, 6174delT in BRCA2) (Figure 1). These founder mutations account for the vast majority of all deleterious BRCA mutations in this ethnic group. There is some debate on whether proceeding to reflex BRCA1/2 full sequencing and deletion/duplication analyses is warranted in certain AJ families. Due to the markedly increased risk of cancer and significant management implications, it is important to elucidate whether reflex testing provides additional yield in AJ families. This study presents the results of AJ families identified to carry a non-founder mutations in BRCA1/2.

Methods

BRCA genetic test results of Ashkenazi Jewish individuals who presented for genetic counseling between May 2008 and December 2013 were reviewed (N=529). Based on their AJ ancestry, BRCA1/2 testing was performed in a stepwise fashion, starting with analysis of the three AJ founder mutations. Certain individuals with strong family histories who tested negative for the three AJ founder mutations proceeded to BRCA full sequencing. Excluding their AJ ancestry, each of these families still met National Comprehensive Cancer Network (NCCN) guidelines for BRCA1/2 genetic testing.

Results

A total of 75 (14.2%) individuals were found to carry a deleterious mutation, and of those, three families (4.0%) had mutations located outside the AJ founder sites. One tested positive for a BRCA1 mutation (4035delTT) (Figure 2), and two tested positive for a BRCA2 mutation (3036del4 and 4075delGT) (Figures 3 and 4). Each family had a significant history of cancer, including early onset breast cancer, male breast cancer, and/or ovarian cancer.

Conclusion

This study demonstrates the occurrence of non-AJ founder mutations in select patients with significant family histories undergoing testing for the BRCA genes. Of the deleterious mutations identified, 4.0% occurred in non-AJ mutation sites. These mutations were identified in patients who had a significant family history and met criteria for BRCA testing, independent of their AJ ancestry. These results have implications for the evaluation of families who test negative for the AJ founder mutations, but whose family history is still suggestive of hereditary risk.