BACKGROUND

*BRCA1/BRCA2* testing is uninformative in approximately 80% of families with clinical features of inherited susceptibility to breast/ovarian cancers. DNA repair pathway is a main defense system that eliminates extensive varieties of DNA damage. The aim of this study was to identify the missing heredity associated with DNA repair genes in high-risk families, *BRCA1/BRCA2* WT (BRCAX families), through whole-exome sequencing (WES) of constitutive DNA.

METHODS

We performed WES (Nextera Rapid Capture Exome and Expanded Exome Kit) in 45 *BRCA1/BRCA2* WT individuals with high-risk for breast/ovarian cancer. The criteria for data analysis were: (i) coverage ≥10x, (ii) frameshift and nonsense variants, (iii) variants present in less than 15% (≤7 samples) and (iv) missense, in frame and stop loss variants classified as pathogenic by at least three of six *in silico* prediction programs selected. We analyzed 228 genes involved in DNA repair.

RESULTS

A cohort of 45 Brazilian women at-risk for HBOC (40 breast and 5 ovarian cancers) were included in the study. We identified 82 different variants (55 genes) in DNA repair genes.

The twenty most frequently altered genes can be observed in Figure 1, highlight that many of them have already been associated with hereditary predisposition syndromes to cancer, such as: *ATM, MLH1, MSH6, MUTYH* genes.

CONCLUSIONS

Our data on BRCAX families in DNA repair genes revealed several alterations. These genes are probably implicated in BRCAX cancer development, however, large-scale collaborative efforts will be required to attain sufficient power to understand the missing heredity associated with breast/ovarian cancer development in high-risk families.