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SNP ANALYSIS IN BRCA POSITIVE AND BRCA NEGATIVE SUBJECTS WITH AND WITHOUT BREAST CANCER (BRCA) REVEAL CENTRAL ROLE OF ALK SNPS AND TGFBETA SUPERFAMILY IN MALIGNANT TRANSFORMATION

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10.1136/jim-2016-000080.42

Purpose of Study Over 240,000 individuals are diagnosed with breast cancer each year in the USA. Outcomes depend on DNA deregulations in tumors. Carriers of deleterious BRCA1 and BRCA2 mutations are predisposed to 30 fold higher lifetime risks of breast and ovarian cancer.

Aims:

1. To check for differences in SNPs of genomic DNA obtained in BRCA+/− with and without BrCa.
2. Analyze correlates of molecular mechanisms occurring in BRCA mutant patients.

Methods Used We analyzed 94 subjects (41 BRCA positive) with or without BrCa to detect SNPs whose expression is significantly differentially expressed between breast cancer and controls. DNA samples were extracted from PBMCs. Samples were measured for DNA concentration using an Invitrogen QuBit Fluorometer, and diluted to 50 ng/μL.

All samples were collected between 2010 and 2014 and survival data was known in all cancer patients. Processed samples were sequenced using an Illumina MiSeq Sequencer with a 300 cycle kit to detect SNPs. Variant Call Files were analyzed in Microsoft Excel using Fisher's Exact Test.

Summary of Results ALK SNPs were commonly found in cancer relative to control. Significant associations of ALK SNPs were seen in BRCA mutation subjects. ALK protein was overexpressed in 47% of BRCA mutations cases, which was significantly higher than in non-BRCA cases. Our results show that the ALK signaling pathway possibly is more common in early onset of breast cancer as seen with BRCA mutations. Coremine analysis showed SNPs identified in cancer were most commonly associated with deregulation of Transforming Growth Factor-Beta Superfamily protein synthesis and binding function.

Conclusions Differences in the associations of the modifying polymorphisms with BrCarisk for BRCA1 and BRCA2 mutation carriers are likely to reflect differences in the biology of tumor development in these two groups of women at high risk of breast cancer. The identification of modifying polymorphisms could therefore lead to a better understanding of the etiology of tumors in mutation carriers and also to the development of effective and more specific therapies for BrCa in mutation carriers.