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Title Of Thesis: "**Mutational and Epigenetic studies of *FHIT* and *Caveolin-1* genes in Breast Cancer Patients of Kashmir"**

Abstract

Breast cancer is one of the most common malignancies in women. Development of breast cancer is a multi step process arising from genetic alterations that drive the transformation of normal mammary epithelial cells into highly malignant derivatives. The present study displays the complexity of candidate intermediate and low penetrance genes involved in breast cancer pathway. In the present study, a total of 40.7% breast tumors were mutated in one or more hot spot exons of *FHIT* gene. The significant feature of the study were the seven nonsense mutations that lead to the truncation of *FHIT* protein and hence reduced expression level of *FHIT* gene. *FHIT* gene mutations were found statistically significant with histopathological grade, nodal status, and menopausal status of breast cancer patients. Hypermethylation of *FHIT* promoter was detected in 45.3% of breast tumors. *FHIT* hypermethylation was statistically significant with age, menopausal status, smoking status nodal status and tumor stage. The important feature of this study was the significant association of *FHIT* mutation with promoter hypermethylation that results in complete loss of expression of *FHIT* gene.

We also found 29.2% mutations in *CAV-1* gene, where 57.8% were missense, 31.5% were frameshift and 10.5% were nonsense mutations .We found statistically significant correlation between mutational status of *CAV-1* gene with histopathological grade and tumor stage, suggesting that *CAV-1* may be up regulated during metastasis which would result in a distinctive mechanism responsible to inactivate the tumor suppressor function of *CAV-1* gene.*CAV-1* mutation was also statistically significant with lymph node involvement, dwelling and breast involved. The promoter region of *CAV-1* gene was hypermethylated in 21.5% of breast cancer samples. Our findings suggest that *CAV-1* promoter hypermethylation

is an important molecular signature in the development of breast cancer.CAV-1 gene hypermethylation was significantly associated with poorly differentiated histopathological grade suggesting that down regulation of *CAV-1* gene in breast cancer cells is a metastasis promoting event.

We further planned our current study to analyse the role of DNA repair genes that might contribute to breast cancer susceptibility. We found 28 patients that were heterozygous and 13 patients carried *IVS10-6G-T* mutations, this mutation leads to incorrect splicing of exon 11 and exon skipping resulting in a frameshift starting at codon 355 and subsequent truncation of the protein at amino acid 419, this overall effect leads to the increased risk for development of breast cancer.

NBS1 657del was found in 25 breast cancer patients, *NBS1 657del5* was significantly associated with tumor grade (III+IV) and poorly differentiated histopathology grade, suggesting that *NBS1 657del5* is a hypomorphic mutation carriers have an increased risk of malignant tumor development and increased cell invasiveness.

CHEK21100delC mutation was found in 12 breast cancer patients. The *CHEK21100delC* polymorphism results in a frameshift starting at starting at codon 366 with subsequent premature protein truncation at amino acid 380. *CHEK21100de*lC was statistically significant with histopathological grade.