Genetic Evaluation of BRCA1 associated A Complex genes with Triple-negative Breast Cancer Susceptibility in Chinese Women

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BACKGROUND: The tumor suppressor BRCA1 plays a pivotal role in maintaining genomic stability and tumor suppression. The BRCA1-A complex is required for recruitment of BRCA1 to DNA damage sites, DNA repair and cell cycle checkpoint control. Since germline mutations of BRCA1 often lead to breast tumors that are triple-negative breast cancer (TNBC) type, we aimed to investigate whether genetic deficiency in genes of the BRCA1-A complex is associated with risk to TNBC development.

HYPOTHESIS: Genetic deficiency in genes of the BRCA1-A complex is associated with risk to TNBC development in Chinese Han women.

METHODS: We investigated associations between the BRCA1-A complex genes and TNBC developing risk in a case-control study of Chinese Han Women population including 414 patients with triple-negative breast cancer and 354 cancer-free controls diagnosed in the Fudan University Shanghai Cancer Center during 2008-2011. We detected 37 common variants in ABRAXAS, RAP80, BRE, BRCC36 and NBA1/MERIT40 genes encoding the BRCA1-A complex and evaluated their genetic susceptibility to the risk of TNBC in Chinese women population. Another study cohort with a total of 652 non-TNBC and 890 normal cases was used to investigate the association between the SNPs genotype and non-TNBC risk. We also did *in silico* analysis and further function examination to the investigated SNPs.

RESULTS: We found that rs7250266 in the promoter region of NBA1 confers a decreased risk to TNBC. The allelic frequency of the G-allele of rs7250266 was 0.19 in controls compared with 0.14 in patients with significant difference (P<0.01). A comparison of genotype frequency between TNBC cases and controls showed that genotypes GC or GG of rs7250266 was associated with a significant decreased risk of TNBC in a co-dominant model (GC genotype, odds ratio (OR) = 0.70, GG genotype, OR = 0.48, P = 0.03). Under a dominant model, it's shown that women with genotypes GC or GG of rs7250266 conferred approximately 33% decreased risk to the development of TNBC (P = 0.01). We also noticed that two NBA1 variants rs2278256 and rs7250266 had a high linkage disequilibrium (LD) with a D' of 0.99 and r^2 of 0.37 in the LD-plot. In addition, the haplotypes containing two polymorphisms rs7250266 and rs2278256 were associated with a lower chance of TNBC development specifically (H3, OR = 0.75, P = 0.04; H5, OR = 0.34, P = 0.02). Further study showed rs7250266 or rs2278256 had no association with risk of non-TNBC breast cancer in Chinese Han women population. Our studies also showed that the protective alleles of rs7250266 (C>G) and rs2278256 (T>C) down-regulate promoter activity of NBA1 in mammary epithelial cells.

CONCLUSIONS: Genetic variants of NBA1 may be an important genetic determinant of developing TNBC. Further investigation and validation of these SNPs in larger cohorts may facilitate in predication and prevention of TNBC and in counseling individuals for risk of TNBC development.