

Genetic Association and Functional Significance of Matrix Metalloproteinase-14 Promoter Variants rs1004030 and rs1003349 in Gallbladder Cancer Pathogenesis

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Abstract : Gallbladder cancer (GBC) is rare but highly malignant cancer; its prevalence is more in certain geographical regions and ethnic groups, which include the Northern and Eastern states of India. Previous studies in India have reported genetic predisposition as one of the risk factors in GBC pathogenesis. Although the matrix metalloproteinase-14 (MMP14) is a well-known modulator of the tumor microenvironment and tumorigenesis and TCGA data also suggests its upregulation yet, its role in the genetic predisposition for GBC is completely unknown. We elucidated the role of MMP14 promoter variants as genetic risk factors and their implications in expression modulation. We screened MMP14 promoter variants association with GBC using Sanger's sequencing in approximately 300 GBC and 300 control subjects and 26 GBC tissue samples of Indian ethnicity. The immunohistochemistry was used to check the MMP14 protein expression in GBC tissue samples. The role of promoter variants on expression levels was elucidated using a luciferase reporter assay. The variants rs1004030 (p-value = 0.0001) and rs1003349 (p-value = 0.0008) were significantly associated with gallbladder cancer. The luciferase assay in two different cell lines, HEK-293 (p = 0.0006) and TGBC1TKB (p = 0.0036) showed a significant increase in relative luciferase activity in the presence of risk alleles for both the single nucleotide polymorphisms (SNPs). Similarly, genotype-phenotype correlation in patients samples confirmed that the presence of risk alleles at rs1004030 and rs1003349 increased MMP14 expression. Overall, this study unravels the genetic association of MMP14 promoter variants with gallbladder cancer, which may contribute to pathogenesis by increasing its expression.

Keywords : gallbladder cancer, matrix metalloproteinase-14, single nucleotide polymorphism, case control study, genetic association study

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