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Abstract Topic:- Complex traits and polygenic disorders

Abstract Title:- Genome-wide association study and protective role of CSMD1 gene in cervical cancer patients of Gangetic plain.

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Aims:-In terms of prevalence among women worldwide, cervical cancer is the fourth most common, and emerging countries like India are the main contributors. The main risk factor for cervical cancer is HPV, which infects virtually all women. However, different women react differently to HPV infection, with only a small percentage of them going on to develop malignancy while the majority recover. This is because there are differences in the genetic architecture that control host response variability. HLA and numerous non-HLA loci have long been recognised as the primary loci responsible for increased cervical cancer susceptibility. The current study is an attempt to do an association study in North Indian women.

Methods:- Patients with histologically confirmed cervical cancer were enrolled in the case control study.

The control sample data was obtained from ancestrally matched female samples from a previously published population study, which generally considers collecting samples from random healthy individuals. We used the previously established genome-wide significance level of 5x10-8 to account for multiple testing. Only SNPs with a minor allele frequency (MAF) larger than 1% were evaluated to avoid any genotyping error introducing false association of rarer variants. After confirming with the principal component analysis (PCA), we obtained the ancestrally matched control samples of women from the published dataset. The Plink v1.9 tool is used to determine the odds ratio (OR), p value by operating association testing (—assoc), to filter out alleles with values less than the minor allele frequency (MAF) and preferably maintained the quality score above 98, and to remove all variants with missing call rates greater than 0.03. The Manhattan plot was created with HaploviewHaploview v4.2, and the LD plot of the CSMD1 gene with the most significant lowest p value, including other neighbouring SNPs was created from both the case and control samples using Haploview v4.2 Expression analysis was done using the GEPIA2.

Results:- We found few SNPs on different chromosomes that are found to be significantly associated with cervical cancer susceptibility (or resistance) rs4478597 is an SNP that has crossed the genome wide threshold with a p value of 4.82 x 10-8 (OR=0.1206), and three other SNPs with rsIDs- rs435293(p=5.53x10-6, OR=0.2099, chr 15), rs8091665(p=6.9x10-6, OR=4.545, chr 18), and rs493795(p=8.08x10-6, OR=0.162 chr 3) attained the suggestive association threshold. rs4478597 is on chromosome 8p.23 and has been linked to the tumour suppressor gene CSMD1- Cub and Sushi multiple domain 1. We cross validated our findings with the expression variation from GEPIA2 and GTEx portal, which represents significantly lower expression for the AA genotype, whose frequency is significantly higher in cases, increasing susceptibility, and highest expression for the GG genotype, whose frequency is higher in controls, providing a protective advantage.

Conclusions:- The study concludes that rs4478597 is a SNP associated with cervical tumorigenesis because the G allele of this SNP is much more common in control samples than cases. This SNP is in the CSMD1 gene, which has been associated to several cancers, but its involvement in cervical cancer remains to be reported in the literature and yet to be explored. CSMD1 gene has higher expression in healthy people but drops significantly in cervix cancer patients, which is coherent with its role as a tumor suppressor.

Keywords:- cervical cancer, GWAS, CSMD1, linkage disequilibrium, HPV