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Gallbladder cancer predisposition: A multigenic and multianalytical approach to genetic variants of steroidal, inflammatory and tumor suppressor genes

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Introduction: Gallbladder cancer (GBC) is a violent neoplasm associated with late diagnosis, unsatisfactory treatment and poor prognosis. The disease shows complex interplay between multiple genetic variants. 15 polymorphisms in 9 genes involved in various pathways to find out combinations of genetic variants contributing to GBC risk were analyzed.

Methods: The genes included in the study were *(MMP-2, 7, 9) TIMP-2, CYP1A1, CYP1B1, PLCE1, LXR-alpha* and *LXR-beta*. Genotypes were determined by PCR-RFLP and Taqman probes. Statistical analysis was done by SPSSver16. Multilocus analysis was performed by Classification and Regression Tree Analysis (CART) and Multifactor dimensionality reduction (MDR) for higher order gene-gene interactions in modifying GBC risk. *In-silico* analysis was done using various bioinformatics tools (F-SNP, FAST-SNP).

Results: Single locus analysis showed association of *MMP2* (-735 C>T, -1306 C>T), *MMP7* -181 A>G, *MMP-9* (P574R, R668Q), *TIMP2*-418 G>C, *CYP1A1*-MspI, *CYP1A1*-Ile462Val, *PLCE1* (rs2274223 A>G, rs7922612 T>C) and *LXR-beta* T>C (rs3546355 G>A, rs2695121 T>C) polymorphisms with GBC risk ($p<0.05$) whereas *CYP1B1* and *LXR-α* variants were not associated with GBC risk. Multidimensional reduction analysis revealed *LXR-β* (rs3546355 G>A, rs2695121 T>C), *MMP-2* (-1306C>T), *MMP-9* (R668Q) and *PLCE1* rs2274223A>G to be key players in GBC causation ($p<0.001$, CVC=7/10). The results were further supported by independent CART analysis (($p<0.001$). Sub-group analysis based on gender and gallstone status showed distinct subsets of genetic signatures in GBC susceptibility. *In-silico* analysis of associated variants suggested change in splicing, transcriptional and translational regulation. Interactome and String analysis showed network of associated genes.

Conclusion: The study found *PLCE1* rs2274223, *LXR-β* (rs35463555, rs2695121), MMP-2(1306C>T) and *MMP* 9 R668Q variations and their interactions contributing to GBC risk.

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