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Impact of Wnt signaling pathway gene variants in gallbladder cancer genetic predisposition, therapeutic response and survival

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Background: Wnt signaling pathway is a highly complex pathway that is critical for development, differentiation and cellular homeostasis. Dysregulations caused by germ-line genetic variants in Wnt pathway genes are involved in development and expansion of cancers. This study analyzed association of Wnt signaling pathway genes (GLI-1, SFRP2, SFRP4, DKK2, DKK3, WISP3, APC, B-Catenin, AXIN-2) variants in GBC genetic predisposition, treatment outcomes and survival.

Materials & Methods: The study included 550 GBC patients and 250 controls. Out of 550, 200 patients were followed-up for treatment response and survival. Mild to severe toxicity grading was done in 200 patients and tumor response was recorded in 140 patients undergoing non-adjuvant chemotherapy (NACT). Genotyping was done by using PCR-RFLP, ARMS-PCR and Taqman assays. Statistical analysis was done by binary logistic regression, SNPstats, CART and GMDR. In-silco analysis was performed using Bioinformatics tools (F-SNP, FAST-SNP). Survival was assessed by Kaplan Meier survival curve and multivariate Cox-proportional hazard model.

Results: Binary logistic regression showed statistically significant association of GLI-1 rs222826C/G [p-value=0.001], SFRP4 rs1802073G/T [p-value= 0.004], AXIN-2 rs4791171C/T [p-value= 0.001], AXIN-2 rs2240308G/A [p-value=0.003], B-catenin rs4135385A/G [p-value=0.037], APC rs4595552 A/T [p-value=0.021] with increased risk of GBC. Haplotypes of APC Trs459552Trs11954856 [p-value = 0.0450] and AXIN-2 Trs4791171Ars2240308 [p-value = 0.039] significantly associated with increased risk of GBC susceptibility. Gene-gene interaction analysis (GMDR) predicted GLI-1 rs2228226, APC rs11954856 [p-value=0.0054] as significant model with GBC susceptibility. GLI-1 rs2228226, AXIN-2 rs4791171 [p-value= 0.0107, 0.001] predicted as significant model for poor prognosis and moderate-severe gastrointestinal toxicity. CART analysis represents APC rs4595552 (AT), APC rs4595552 (TT) higher risk genotype for GBC susceptibility and GLI-1 rs2228226 (GG), DKK3 rs3206824 (CC) with clinical outcomes. Cox-proportional hazard model showed GLI-1 rs2228226 CG/GG genotype higher mortality and hazard ratio in post-operative and locally advanced GBC cases.

Conclusion: GLI-1 rs2228226 emerged as major genetic variant in WNT signaling pathway influencing susceptibility, treatment outcome and survival in gallbladder cancer.

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