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A COMMON GENE VARIANT IN HEDGEHOG PATHWAY GENE GLI1 IDENTIFIES PATIENTS AT RISK OF RECURRENCE IN STAGE II COLON CANCER

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Background: A paradigm shift is ongoing in how we approach and effectively manage stage II and III colon cancer (CC) patients and it is now widely recognized that a multitude of factors contribute to the success (or failure) of CC treatment. Specifically, the presence of significant heterogeneity among patients and their respective diseases may have a significant impact on the efficacy of treatment and overall disease prognosis. The Wnt, Notch and Hedgehog signaling pathways have recently been shown to play a central role in the development and progression of CC. Germline variants in these pathways may result in heterogeneity among patients by altered gene function and/or gene activity, thereby causing individual differences in tumor recurrence and chemoresistance. We investigated a comprehensive panel of germline polymorphisms in Wnt, Notch and Hedgehog signaling pathways to predict recurrence in stage II and III CC patients.

Methods: A total of 815 patients with histopathologically confirmed stage II and III CC treated at the Division of Clinical Oncology, Department of Medicine, Medical University of Graz were recruited in this retrospective analysis. Genomic DNA was extracted from tissue samples using QIAamp DNA mini Kit (Qiagen) and analysed for potential functional germline polymorphisms in SFRP, DKK2, DKK3, APC, MYC, TCF7L2, NOTCH-2 and GL1 genes by 5'-exonuclease assay (TaqMan).

Results: Overall, the homozygous GG variant of GLI1 rs2228226 C > G was significantly associated with shorter DFS in univariate (79 vs 122 months; HR 1.955, 95%CI 1.236-3.092, p = 0.004) and multivariate Cox regression analysis adjusted for known prognostic markers (HR 1.844, 95%CI 1.161-2.927, p = 0.009). Moreover, the GLI1 rs2228226 GG variant was significantly associated with decreased OS in univariate analysis (94 vs 129 months; HR 1.697, 95%CI 1.009-2.854, p = 0.046). In stage II patients, the homozygous GG variant of GLI1 rs2228226 remained significantly associated with decreased DFS in univariate (70 vs 145 months; HR 3.035, 95% CI 1.262-7.301, p = 0.013) and multivariate analysis (HR 3.874, 95% CI 1.578-9.507, p = 0.003). In stage III patients, the GG genotype of rs2228226 showed a trend for decreased DFS in univariate analysis (71 vs 104 months; HR 1.650, 95% CI 0.962-2.831, p = 0.069). In multivariate analysis, the GG variant was significantly associated with decreased DFS (HR 1.749, 95% CI 1.016-3.010, p = 0.044).

Conclusion: This study provides the first evidence that the germline polymorphism rs2228226 in Hedgehog pathway gene GLI1 is an independent prognostic marker especially for stage II CC patients. GLI rs2228226 may help to identify colon cancer patients at high risk of recurrence who might benefit from adjuvant treatment. Prospective biomarker embedded trials are warranted to validate our findings.