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THE ASSOCIATION OF GENETIC VARIATION WITHIN THE WNT SIGNALLING PATHWAY WITH COLORECTAL CANCER: A META-ANALYSIS

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Introduction: 35% of colorectal cancer (CRC) risk is attributable to heritable factors, of which a large proportion remains unexplained. Genome wide association studies have conclusively identified several risk variants in the TGF-beta pathway. Both TGF-beta and Wnt pathways are key regulators of colonic crypt homeostasis and colorectal carcinogenesis. The Wnt pathway is deregulated in 93% of CRCs, however the role of Wnt pathway genetic variation in CRC risk is uncertain. A systematic review and meta-analysis to assess the association of polymorphisms within the Wnt signalling pathway and the risk of CRC will be performed

Method: A systematic literature review of the Pubmed and HuGENet databases was conducted. Studies were included/excluded based on pre-specified criteria. In order to assess the risk attributed to each identified variant, the 'per allele' model was utilised to calculate pooled odds ratios. Heterogeneity was investigated by subgroup analyses for ethnicity, gender and tumour location. Publication bias was investigated using funnel plots and Egger's test. Statistical analysis was conducted using the R program (version 3.1.0).

Results: Forty-three polymorphisms across 18 different genes in the Wnt pathway were identified. Meta-analyses were conducted for 12 of these polymorphisms including between 831 to 31,427 cases per polymorphism. 6 polymorphisms were significantly associated with the risk of CRC. Rs1801155 within *APC* (OR= 1.79; 95% CI 1.27-2.52) and rs10505477 at the 8q24.21 locus (OR= 1.15; 95% CI 1.12-1.19) were associated with an increased risk of CRC. rs16260 (OR=0.94; 95% CI 0.89-0.99) and rs9929218 (OR=0.93; 95% CI 0.90-0.95) within *CDH1*; rs6983267 (OR=0.85; 95% CI 0.83-0.87) within *MYC* and rs7014346 (OR=0.87; 95% CI 0.81-0.94) at the 8q24.21 locus, were associated with a decreased risk of CRC. Subgroup analysis revealed gender, ethnicity and tumour location were not sources of heterogeneity.

Conclusion: Six polymorphisms associated with CRC risk account for a significant proportion of familial risk, although are unlikely to account completely for aberrant activation of the Wnt pathway. These polymorphisms are located within *APC*, *CDH1* and *MYC* genes and the 8q24.21 locus. Further research into their precise role in colorectal carcinogenesis is warranted. Meta-association studies of all SNPs in the Wnt pathway should be conducted to identify further risk variants. Rare variants, copy number variations and epigenetic alterations may contribute to the remaining heritability and Wnt pathway activation.

Disclosure of Interest: None Declared