METABOLOME-WIDE ASSOCIATION STUDY OF COLORECTAL CANCER GENETIC TRAITS

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BACKGROUND: Genome-wide association studies (GWAS) have identified over 187 common genetic variants associated with the risk of colorectal cancer (CRC). For the vast majority, the molecular mechanisms implicating these variants in CRC remain unknown. Better understanding of the metabolic pathways through which genetic variants affect CRC risk could provide new insights on cancer pathogenesis and pave the way to novel therapeutic and/or preventive strategies.

METHODS: Metabolome-wide association analyses were performed for each of the 187 CRC genetic variants. We used genomics data, as well as ^{1}H Nuclear Magnetic Resonance (NMR) metabolomics data from urine samples of 1,951 Airwave Health Monitoring Study participants. For each genetic variant, Spearman partial correlation analysis was conducted against the ^{1}H NMR spectral data. All univariate analyses were adjusted for confounders and corrected at 5% False Discovery Rate (for high resolution NMR data) or 5% Bonferroni (for sensitivity analysis of 70 annotated metabolites). rs10411210 knock-out (+/- 27 nucleotides) in CACO-2 cell lines using CRISPR/Cas9 genome editing was performed to experimentally assess the effect of this genomic region on CRC.

RESULTS: Overall, 7 out of 187 examined genetic variants were associated with at least one urinary metabolic trait. The strongest associations were observed for rs10411210 (RHPN2 gene) with sucrose and rs78368589 (SLC6A18 gene) with amino acids. Gut microbial metabolites (p-cresol sulfate, trimethylamine-N-oxide) have also shown strong association with CRC genetic variants (MAP2K5, BMP2 genes). rs10411210 knock-out in CACO-2 cell lines revealed compromised cell growth, altered expression of 643 genes, as well as a trend for increased sucrase-isomaltase expression compared to wild type cells, confirming statistical correlations.

CONCLUSIONS: Our study produces new knowledge on the causal pathways linking genes to CRC, highlighting the importance of an RHPN2 intron region in sucrose metabolism and the role of SLC6A18 gene in amino acid transport.

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