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## **The impact of genetic heterogeneity in fatty acid metabolizing genes in the etiology of colorectal cancer**

Geboren am 05.07.1977 in Ludwigshafen am Rhein  
Diplom der Fachrichtung Biotechnologie am 15.04.2005 an der Hochschule Mannheim

Promotionsfach: Deutsches Krebsforschungszentrum  
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Colorectal cancer (CRC) is a complex disease with genetic, epigenetic, and environmental influences. Evidence suggests that diet has an important impact on its development. North American and European diets contain high amounts of the  $\omega$ -6 polyunsaturated fatty acid arachidonic acid (AA), whose metabolic pathway is a key pathway in the production of pro-inflammatory prostaglandins and has been previously implicated in colon tumorigenesis. Initial evidence suggests that polymorphisms of some key genes involved in the AA metabolism may modulate the risk of colorectal carcinomas, yet a comprehensive analysis of this pathway has not been published to date. Therefore, the present work was motivated to complete and broaden existing information on how polymorphic alleles of genes in the fatty acid pathway alter CRC susceptibility.

In the context of a large European cohort study, the “European prospective Investigation into Cancer and Nutrition” (EPIC) study, 1225 CRC cases and 2032 matched controls were explored in a nested case-control design for the association of genes directly and indirectly involved in AA metabolism with CRC risk. A total of 392 variants in 43 selected genes were genotyped with the Golden Gate® assay and the 5'-nuclease allelic discrimination assay (TaqMan®). Odds ratios (OR) and 95% confidence intervals (CI) for colorectal cancer, adjusted for potential confounders, were calculated using conditional logistic regression models. The genotype distribution and their contributions to CRC risk were analyzed assuming a dominant and recessive model of inheritance. The test for a trend was performed by modeling the number of rare alleles as a continuous variable. Haplotype analysis was performed at the level of haplotype blocks within a gene using the method haplo.glm. Statistical interaction was evaluated with the likelihood-ratio test by including an interaction term of the variables of interest.

In total, 38 SNPs in 18 candidate genes demonstrated statistically significant associations with CRC risk, all with a minor allele frequency (MAF) > 5%. After correction for multiple comparisons by means of Bayesian false-discovery probability (BFDP), noteworthy associations with CRC risk were seen for hydroxyprostaglandin dehydrogenase 15-(NAD) (*HPGD*) (rs2612656, rs8752), phospholipase A2, group VI (*PLA2G6*) (rs4821737), prostaglandin E receptor 2 (*PTGER2*) (rs17831718) and transient receptor potential vanilloid (*TRPV3*) (rs11078458). Compared to non-carriers, homozygotes for the minor alleles of the two *HPGD* polymorphisms were at 36% and 66% increased risk of CRC respectively ( $p_{\text{trend}} \leq 0.003$ ; 95%CI = [1.10-1.67]; [1.20-2.30], respectively). The minor allele frequencies of these two SNPs were 0.26 and 0.44 in CRC cases compared to 0.22 and 0.40, respectively, in the EPIC controls. The homozygote minor *PLA2G6* rs4821737 C-allele conferred an increased CRC risk (OR = 1.26, 95%CI = [1.06-1.50]  $p_{\text{recessive}} = 0.008$ ), while a tagging SNP located downstream of *PTGER2* (rs17821718) was inversely associated with CRC risk (OR = 0.21, 95%CI = [0.05-0.95]). A notable positive disease association was observed for a synonymous-coding *TRPV3* SNP (rs11078458) (OR = 1.32; 95%CI = [1.1-1.59],  $p_{\text{recessive}} = 0.003$ ).

On the haplotype level, the *HPGD*-AGGGA-haplotype was significantly ( $p < 0.001$ ) associated with a 33% increased risk of CRC. A significant inverse association ( $p < 0.006$ ) was found for a *PTGER2* haplotype while a *PLA2G3* haplotype was associated with 17% increased CRC risk ( $p = 0.003$ ).

Furthermore, significant evidence for strong statistical interaction was evident for the joined analysis of *PLA2G2A* (rs1891320) and *PTGER2* (rs17125318) as well as for *PPARGC1A* (rs2970884) and *TBXA2R* (rs17348907) variants.

In conclusion, the present study strongly suggests a relevance of genetic variation in fatty acid metabolism-related genes, particularly of genes implicated in prostaglandin metabolism (*HPGD*, *PTGER2*, *PLA2G6*) and *TRPV3* in colon carcinogenesis. Interestingly, all of the genes with noteworthy results are directly involved in prostaglandin signaling. Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) is found throughout the gastrointestinal tract and seems to play an important role in modelling apoptosis, proliferation, angiogenesis, and colorectal cancer development. Clearly, the replication of these findings in further independent epidemiological studies is essential.