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Ancestral Susceptibility to Colorectal Cancer

Promotionsfach: Molekulargenetische Epidemiologie
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The aim of the presented thesis was the investigation and validation of new candidate genes and polymorphisms contributing to the risk of colorectal cancer (CRC). Further knowledge about CRC susceptibility variants may provide new insights into the genetic background and underlying biology of CRC.

One specific intention of the studies was to investigate a possible association of polymorphisms in the putative WNT signalling gene CTNNBL1 with the risk of CRC. For this purpose, eight tagging SNPs within CTNNBL1 were analyzed for a possible association with CRC. A further specific goal was to investigate possible associations of polymorphisms known to be associated with nutrition-related diseases such as obesity, type 2 diabetes, hypertension and metabolic syndrome with the risk of CRC. Therefore, 29 SNPs located in 15 genes were appraised to be promising candidates and were analyzed for a possible association with CRC. In particular, these studies were intended to assess the influence of the ancestral alleles of these polymorphisms on CRC susceptibility and to identify variants under selective pressure. The association studies were mainly carried out in a hospital-based case-control population from the Czech Republic containing more than 1.900 CRC cases and controls. Additionally, a German case-control population, containing more than 1.000 family-based CRC cases and blood donor controls, was used to investigate the effect of polymorphisms in CTNNBL1 on the risk of CRC.

The results of the presented study suggest that polymorphisms in CTNNBL1, AGT, CYP3A7 and ENPP1 may be associated with CRC, possibly through a gene-environment interaction. Carriers of the ancestral alleles in rs2344481, rs699 and rs10211 (CTNNBL1, AGT, CYP3A7, respectively) had an increased risk of CRC, whereas carriers of the ancestral allele in rs1044498 (ENPP1) had a decreased risk. Additionally, the presented study indicated that all four genes were shaped by selection. The SNPs that were found to be associated with CRC and the genes harbouring the SNPs, respectively, have been previously reported to be associated with the nutrition-related diseases obesity (CTNNBL1), hypertension (AGT and CYP3A7) and insulin resistance (ENPP1).

Nutrition-related traits and their consequences, intertwining several environmental factors and a so far unknown number of genetic variants, are great challenges for medical science, disease prevention, therapy and healthcare policy. A better understanding of the extent of the influence of risk factors on the individual risk or on the risk of a population might make it possible to improve treatment and prevention.