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LOW-PENETRANCE SUSCEPTIBILITY GENES FOR COLORECTAL CANCER IN THE INSULIN/INSULIN GROWTH FACTOR 1 AXIS

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Low-penetrance mutations account for much of the predisposition resulting in `sporadic´ CRC and contribute to a large amount of CRC-associated morbidity.

The presented case-control studies were performed on a Czech or a German study population and focussed on low-penetrance variants which may lead to an increase in CRC risk. The SNPs were selected on the basis of their suggested effect on the gene expression or the protein function or because they were in LD with a putatively functional polymorphism with a strong prior probability to be involved in CRC carcinogenesis. Due to a relatively large sample size we achieved a power to detect variants with a moderate individual effect.

We examined genes that are involved in the INS/IGF1 axis (INS, INSR, IGFBP1, IRS1, IRS2, IGF1 and IGFBP3). This pathway regulates two different signaling cascades, the Ras/MAPK pathway that stimulates cell growth and differentiation and the PI-3K pathway that regulates apoptosis as well as metabolism of glucose, proteins, and lipids.

Our results suggested a reduced CRC risk for carriers of the INSR -603G allele. The protective effect was even stronger in the carriers of both the INSR -603G and the IRS1 972Arg alleles. Because of a relationship between insulin-related diseases and CRC, SNPs in the insulin pathway genes may have a more prominent effect on CRC risk in diabetic and obese individuals, which warrants further studies.

Our findings of the polymorphisms in the IGF1 and the IGFBP3 genes provide reasonably strong support indicating that the common variants or haplotypes in the IGF1 and the IGFBP3 genes are not independently associated with the risk of the CRC nor is there any effect of the gene-gene interaction. However, it remains possible that there are other factors, such as interactions of other genes with the IGF1 and the IGFBP3 genes or

gene-life style interactions that modify the genetic association of the IGF1 and the IGFBP3 and the risk of the CRC.

In all our studies, to observe a dominant effect, we had an 80 % and more power to detect an OR of 1.4.

In conclusion, the identification of CRC susceptibility genes and low-penetrance variants associated with disease risk in addition to the environmental risk factors is essential for understanding the etiology of CRC and is of importance for developing new prevention strategies.