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Whole genome association study of familial colorectal cancer in the German population

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Colorectal cancer is one of the most common forms of neoplasia in the Western and industrial countries, with 71,400 annual new cases (over 16% of all cancers) in Germany. Colorectal cancer is a multifactorial disease, in which genetic and non-genetic risk factors contribute to the onset of the disease. Highly penetrant causative mutations are the main genetic risk factor in familial adenomatous polyposis, Lynch syndrome and other familial forms of colorectal cancer. However, such genetic syndromes represent only 3% of the inherited colorectal cancer cases associated with genetic predisposition and can not explain the increased risk observed in first-degree relatives of the sporadic colorectal cancer patients. The increased risk in sporadic cases suggests a mild genetic predisposition, i.e., the involvement of low-penetrance genes. The last is inline with the hypothesis of 'common disease-common variant', and suggest that part of the genetic risk in sporadic colorectal cancer susceptibility can be caused by common, low penetrance alleles. To identify low-penetrance gene in familial colorectal cancer cases, in addition to those already reported, we conducted a genome-wide association study in 371 familial cases and 1,263 healthy controls from a German cohort. The genotyping was done by using a new technology – the GeneChip Human Mapping 6.0 K Array - which allowed us to analyse a total of 906,600 SNPs simultaneously. The results of the association study indicated top 875 single nucleotide polymorphisms with p-value < 10^{-4} to be associated with risk of colorectal cancer. Two of the associated single nucleotide polymorphisms were located on chromosomes 8q24 and 11q23 - loci that have been reported in previous genome-wide association study to be associated with increased risk of colorectal cancer. The results from the genome-wide association study are in the process of being validated and one of the techniques used, which is based on mass array spectrometry (Sequenom) has been described

in this dissertation. The emergence of 8q24 locus in various genome-wide association study in different cancers is difficult to interpret and the only gene of any consequence located close to the associated loci has been *C-MYC*. This extensive ongoing research into low-penetrance, multifactorial predisposition to colorectal cancer is now beginning to bear fruit, with important implications for understanding disease aetiology and developing new diagnostic, preventive and therapeutic strategies.