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New Doctorial Cancer Research

Genetic Studies of Colorectal Cancer

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Colorectal cancer is the third most commonly diagnosed cancer worldwide with an incidence rate of over 1 million cases per year. A genetic contribution has been suggested to be involved in around 35% of all colorectal cancer cases. However, mutations in single high-penetrance genes have been identified in only approximately 5% of all cases, leaving the majority of the genetic burden unexplained. Some of this might be attributable to additional high-penetrance genes, however, it is of general belief that low- to moderate-penetrance alleles are responsible for a large proportion of the remaining genetic predisposition for colorectal cancer.

In an attempt to identify novel colorectal cancer predisposing loci, genome-wide linkage analysis was performed in 18 non-FAP/non-HNPCC colorectal cancer families. No common susceptibility locus was identified, thus providing evidence for locus heterogeneity. Analysis assuming locus heterogeneity revealed three regions of interest; one region on chromosome 22q12 was suggested from parametric linkage analysis and two regions on chromosomes 11q and 14q from both parametric and nonparametric linkage analyses. Fine mapping of chromosomes 11q and 14q reduced the LOD scores, but remained suggestive for linkage. Haplotype analysis in families with disease linked to chromosomes 11 and 14 gave the overlapping regions 11q13.2-13.4, 11q22.1-23.1, and 14q23.1-24.1.

A novel susceptibility locus for adenoma and colorectal cancer on chromosome 9q22.2-31.2 has been suggested from sib-pair studies. Analysis of an extended Swedish colorectal cancer family, which had in a previous genome screen shown suggestive linkage to this region, gave evidence of linkage of adenoma and colorectal cancer to chromosome 9q22.32-31.1 with a multipoint LOD score of 2.4. Haplotype analysis defined the region to 7.9 cM between the markers D9S280 and D9S277. Hence, these data support the evidence of a susceptibility locus predisposing to adenoma and colorectal cancer at this chromosomal region.

Genotyping additional 19 non-FAP/non-HNPCC colorectal cancer families for the chromosome 9q22.32-31.1 region revealed suggestive linkage of disease in seven other families. In an attempt to identify the disease-causing gene, the coding regions of a total of nine putative candidate genes were screened for germline mutations. One candidate gene within this region, *TGFBR1*, was also

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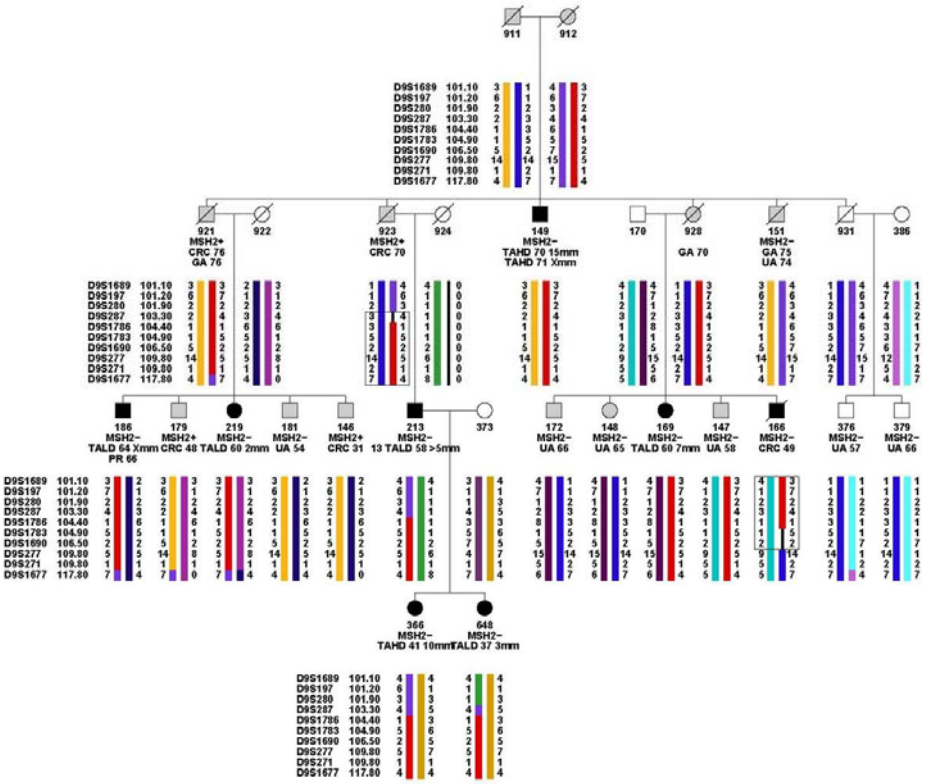

FIGURE 1. Pedigree of family 24 showing haplotypes across the chromosome 9q region. Markers and map positions according to the Généthon genetic map are shown to the left of the pedigree. A black symbol indicates that the individual was coded as affected in the linkage analysis, a gray symbol indicates that the individual was coded as unknown, and a white symbol indicates unaffected. Patient number, *MSH2*-mutation status, clinical manifestation, and age at diagnosis of adenoma/colorectal cancer or last colonoscopy are indicated above each symbol. A red haplotype bar symbolizes the chromosome carrying the linked haplotype. DNA from subjects whose patient number starts with nine was not available and genotypes are inferred from the offspring. The proximal border is determined by individual 923, and the distal border is determined by individual 166 (boxed). A black line indicates that the marker is not informative. Abbreviations: CRC, colorectal cancer; TAHD, tubular adenoma with high-grade dysplasia; TALD, tubular adenoma with low-grade dysplasia; GA, gastric cancer; BR, breast cancer; UA, unaffected at colonoscopy.

investigated for genomic deletions, insertions, and rearrangements with no aberrations or structural variations detected.

A common variant, *TGFBR1**6A, of the *TGFBR1* gene has been reported to be associated with an increased risk for colorectal cancer. Most recently, this variant has been proposed to be directly causally responsible for a proportion of familial colorectal cancer. To further clarify the role of the *TGFBR1**6A variant in colorectal cancer predisposition, a case-control study of 1042 unselected colo-

rectal cancer cases and 856 population controls was performed. The frequency of *TGFBR1**6A was not significantly different between cases and controls. A subsequent meta-analysis of all published case-control studies on the *TGFBR1**6A variant and colorectal cancer risk gave an odds ratio of 1.13 (95% CI: 0.98-1.30) for *TGFBR1**6A carriers. In conclusion, these data provide little evidence to support the hypothesis that *TGFBR1**6A acts as a colorectal cancer susceptibility allele.

Comment by Professor Holger Luthman

The introductory part of the thesis summarizes the literature on genetic predisposition for colorectal cancer in a clear and accessible way. The experimental foundation of the work is presented in four separate papers, two of which are already published and one of which is in the process of being printed. The candidate and her coauthors have used several molecular and genetic approaches to identify and confirm susceptibility loci for colorectal cancer—genome-wide linkage analysis in families, directed linkage analysis in a large pedigree, and candidate gene analysis in case-control materials.

The studies resulted in the identification and confirmation of several novel putative colorectal cancer predisposing loci on chromosomes 9, 11, and 22, and hence strengthen the support and increase the knowledge about genetic predisposition to colorectal cancer. Furthermore, mutational investigation of *TGFBR1*, a candidate gene in the 9q22.32-31.1 region, could rule out this gene as disease causing in the studied families. A common variant in the *TGFBR1* gene, *TGFBR1*6A*, previously reported to increase the risk for colorectal cancer, was also investigated using the case-control design. This material is the largest material of colorectal cancer cases and controls used for studies of this variant. However, no association with colorectal cancer was found. This result emphasizes the importance of a large patient sampling in the genetic analysis of common variants in these types of diseases.