THE AETIOLOGY OF HYPERPLASTIC POLYPOSIS SYNDROME IN A LARGE FAMILY FROM THE WEST OF IRELAND

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Introduction: We have identified a family with a dominantly inherited predisposition to mixed histology multiple polyps and colorectal cancer. The family meet WHO criteria for hyperplastic polyposis syndrome. We have attempted to elucidate the gene which predisposes to this condition.

Aims & Methods: Mutations in *APC*, *MYH*, *SMAD4* and genes which cause HNPCC were excluded by direct sequencing and other methods. Somatic mutations were screened in genes often mutated in colorectal cancers. Genome wide genotypes were obtained for over 10000 SNPs using Affymetrix 10k plus 2 arrays and linkage analysis was performed. Genome wide copy number variation analysis was also performed using the Goldengate SNP platform. Whole genome expression analysis profiles were obtained on cell line RNA using the Affymetrix U133 Plus 2.0 GeneChip oligonucleotide arrays.

Results: The polyps appear to follow a hyperplastic/serrated polyp to mixed serrated/adenomatous (see figure) to adenocarcinoma sequence. Linkage analysis shows a maximum parametric LOD score of 2.71 at 8p22–21.3. Genome wide copy number and loss of heterozygosity (LOH) studies reveal LOH at 8p and 17p in the cancers. A number of genes at that locus including *BMP1* and *MTUS1* have been screened, the latter gene having more than a fivefold up-regulation in expression.

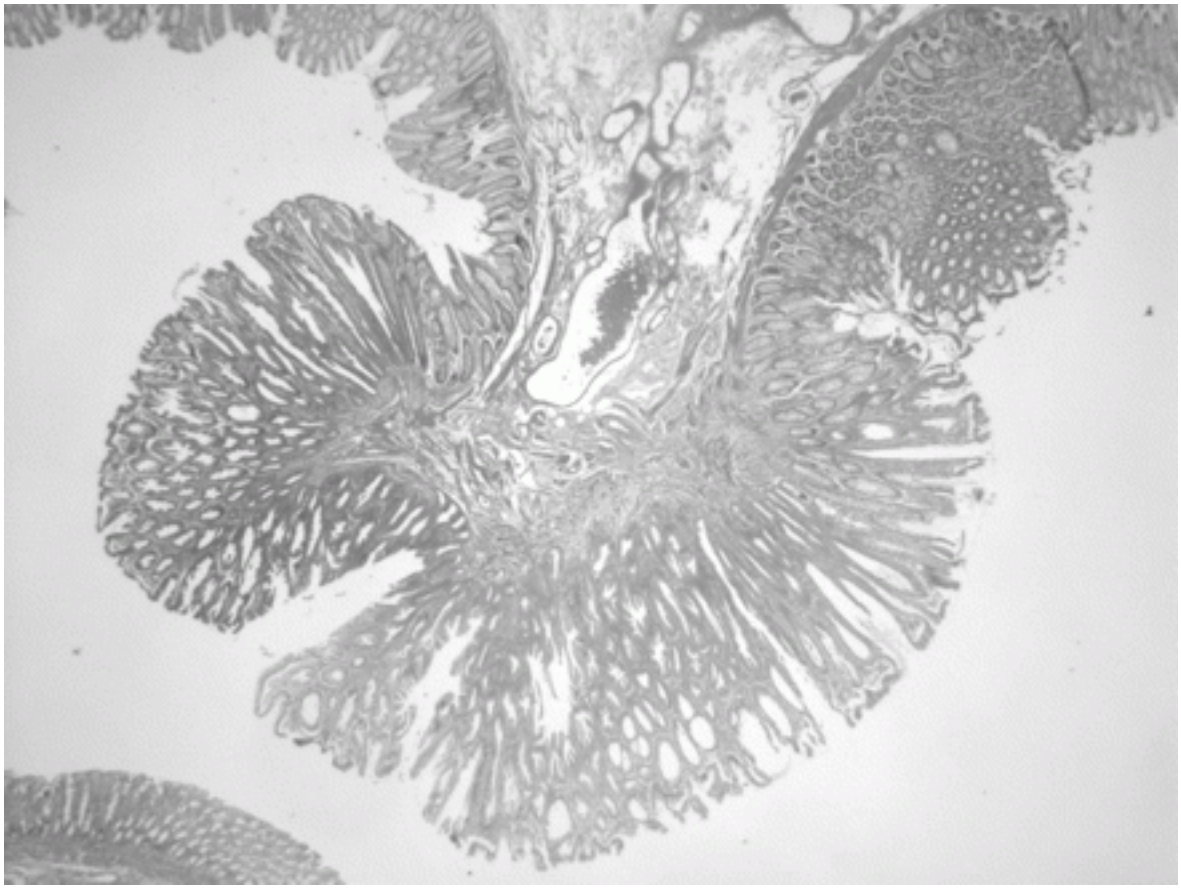

Figure: Mixed hyperplastic/adenomatous polyp with high grade dysplasia

Conclusion: We have identified a locus on chromosome 8p which predisposes to hyperplastic polyps and colorectal cancer in a large family from the West of Ireland. This is the first time such an association has been identified and may be useful in screening families at risk of colorectal neoplasia.

References

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