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Linkage to chromosome 2q32.2-q35 in families with serrated neoplasia

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Background

Causative genetic variants have to date been identified for only a small proportion of familial colorectal cancer (CRC). While conditions such as Familial Adenomatous Polyposis (FAP) and Lynch Syndrome (Hereditary Non-polyposis Colorectal Cancer, HNPCC) are caused by well defined genetic defects, the search for variants underlying the remainder of familial CRC is plagued by genetic heterogeneity. The recent identification of families with a heritable predisposition to malignancies arising through the serrated neoplasia pathway provides an opportunity to study a subset of familial CRC in which genetic heterogeneity may be greatly reduced.

Methods

A genome-wide linkage screen was performed on a large family displaying a dominantly inherited predisposition to serrated neoplasia genotyped using the Affymetrix GeneChip Human Mapping 10K Xba 142 Array, with parametric and nonparametric linkage analyses performed using Genehunter. Fine-mapping was undertaken in a further ten families using microsatellite markers spanning a 78 NIb region of interest on chromosome 2, and parametric linkage scores and haplotypes generated using SimWalk. LOD scores were also generated under the assumption of locus heterogeneity (HLOD). Lynch syndrome was excluded in all families using mismatch repair gene (MMR) immunohistochemistry and somatic BRAF mutation testing. Coding and untranslated regions of five primary candidate genes were sequenced.

Results

Genome-wide linkage analysis revealed a region on chromosome 2 with overlapping parametric (maximum LOD score 1.6) and nonparametric (maximum NPL 4.3) peaks. Fine-mapping further localised the region to 2q32.2-q35, with a total LOD score of 1.1 and HLOD of2.8, with 7 of 11 families showing evidence of linkage. Haplotypes segregating with affected status were present in all 7 families. No segregating variants were found in five primary candidate genes.

Conclusions

We have identified an approximately 12 Mb locus on chromosome 2q with linkage to familial CRC arising through the serrated neoplasia pathway. Up to 60% of serrated neoplasia families may be linked to the 2q locus, but a causative gene is yet to be identified.

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