Hereditary non-polyposis colorectal cancer: clinical and molecular evidence for a new entity of hereditary colorectal cancer.

BACKGROUND: Hereditary non-polyposis colorectal cancer (HNPCC) is clinically defined by familial clustering of colorectal cancer and other associated tumours.

METHODS: By thorough molecular and clinical evaluation of 41 families, two different groups were characterised: group 1, 25 families with truncating mutations in MLH1 or MSH2 (12 novel mutations); and group 2, 16 Amsterdam positive families without mutations in these genes and without microsatellite instability in their corresponding tumours. RESULTS: Significant clinical differences between these two groups were found. Firstly, earlier age of onset for all colorectal cancers (median 41 v 55 years; p< 0.001) and all tumours (median 43 v 56 years; p = 0.022) was observed, comparing groups 1 and 2. Secondly, 68% of the index colorectal cancers were localised proximally of the splenic flexure in group 1 compared with 14% in group 2 (p< 0.010). Thirdly, more synchronous and metachronous colorectal (p = 0.017) and extracolorectal tumours (p< 0.001) were found in group 1. Fourthly, a higher colorectal adenoma/carcinoma ratio (p = 0.030) and a tendency towards more synchronous or metachronous adenomas in group 2 (p = 0.084) was observed, indicating a slower
progression of adenomas to carcinomas. As three mutation negative tumours revealed chromosomal instability after comparative genomic hybridisation, these tumours may be caused by one or more highly penetrant disease alleles from the chromosomal instability pathway. CONCLUSION: These data show that HNPCC includes at least two entities with clinical and molecular differences. This will have implications for surveillance programmes and for cancer research.