Abstract:

Germline mutations in mismatch repair (MMR) genes, tumours with high microsatellite instability (MSI-H) and loss of MMR protein expression are the hallmarks of HNPCC (Lynch syndrome). While somatic MLH1 promoter hypermethylation is generally accepted in the tumorigenesis of sporadic tumours, abnormal MLH1 promoter methylation in normal body cells is controversially discussed as a mechanism predisposing patients to HNPCC. In all 94 patients suspected of HNPCC-syndrome with a mean age of onset of 45.5 years, MLH1-deficiency in their tumours but no germline mutation, underwent methylation-specific PCR-screening for MLH1 promoter methylation. In peripheral blood cells of 12 patients an MLH1 promoter methylation, in seven informative cases allele-specific, was found. Normal colonic tissue, buccal mucosa, and tumour tissue available from three patients also presented abnormal methylation in the MLH1 promoter. The heredity of aberrant methylation is questionable. Pro: MLH1 promoter methylation was found in a patient and his mother giving evidence for a familial predisposition for an epimutation in MLH1. Contra: a de novo set-up of methylation in one patient, a mosaic or incomplete methylation pattern in six
patients, and no evidence for inheritance of MLH1 promoter methylation in the remaining families. Our findings provide strong evidence that MLH1 promoter methylation in normal body cells mimics HNPCC and constitutes a pathogenic pre-lesion in MLH1. The identification of hypermethylation as an epigenetic defect has important implications for surveillance recommendations, as these patients should be treated like Lynch syndrome patients, whereas the heritability of methylation is still under investigation. European Journal of Human Genetics (2008) 16, 804-811; doi:10.1038/ejhg.2008.25; published online 27 February 2008.