Spectrum and frequencies of mutations in MSH2 and MLH1 identified in 1,721 German families suspected of hereditary nonpolyposis colorectal cancer.

Mutations in DNA MMR genes, mainly MSH2 and MLH1, account for the majority of HNPCC, an autosomal dominant predisposition to colorectal cancer and other malignancies. The evaluation of many questions regarding HNPCC requires clinically and genetically well-characterized HNPCC patient cohorts of reasonable size. One main focus of this multicenter study is the evaluation of the mutation spectrum and mutation frequencies in a large HNPCC cohort in Germany; 1,721 unrelated patients, mainly of German descent, who met the Bethesda criteria were included in the study. In tumor samples of 1,377 patients, microsatellite analysis was successfully performed and the results were applied to select patients eligible for mutation analysis. In the patients meeting the strict Amsterdam criteria (AC) for HNPCC, 72% of the tumors exhibited high microsatellite instability (MSI-H) while only 37% of the tumors from patients fulfilling the less stringent criteria showed MSI-H; 454 index patients (406 MSI-H and 48 meeting the AC of whom no tumor samples were available) were screened for small mutations. In 134 index patients, a pathogenic MSH2 mutation, and in 118 patients, a
A pathogenic MLH1 mutation was identified (overall detection rate for pathogenic mutations 56%). One hundred sixty distinct mutations were detected, of which 86 are novel mutations. Noteworthy is that 2 mutations were over-represented in our patient series: MSH2,c.942+3A>T and MLH1,c.1489_1490insC, which account for 11% and 18% of the MSH2 and MLH1 mutations, respectively. A subset of 238 patients was screened for large genomic deletions. In 24 (10%) patients, a deletion was found. In 72 patients, only unspecified variants were found. Our findings demonstrate that preselection by microsatellite analysis substantially raises mutation detection rates in patients not meeting the AC. As a mutation detection strategy for German HNPCC patients, we recommend to start with screening for large genomic deletions and to continue by screening for common mutations in exon 5 of MSH2 and exon 13 of MLH1 before searching for small mutations in the remaining exons.