Deletions account for 17% of pathogenic germline alterations in MLH1 and MSH2 in hereditary nonpolyposis colorectal cancer (HNPCC) families.

Abstract:
Hereditary nonpolyposis colorectal cancer (HNPCC) is due to defects in DNA mismatch repair (MMR) genes MSH2, MLH1, MSH6, and to a lesser extent PMS2. Of 466 suspected HNPCC families, we defined 54 index patients with either tumors of high microsatellite instability (MSI-H) and/or loss of expression for either MLH1, MSH2, and/or MSH6, but without a detectable pathogenic point mutation in these genes. This study cohort was augmented to 64 patients by 10 mutation-negative index patients from Amsterdam families where no tumors were available. Deletion/duplication screening using the multiplex ligation-dependent probe amplification (MLPA) revealed 12 deletions in MSH2 and two deletions in MLH1. These deletions constitute 17% of pathogenic germline alterations but elucidate the susceptibility to HNPCC in only 22% of the mutation-negative study cohort, pointing towards other mutation mechanisms for an inherited inactivation of MLH1 or MSH2. We describe here four novel deletions. One novel and one known type of deletion were found for three and two unrelated families, respectively. MLPA analysis proved a reliable method for the detection of genomic deletions in MLH1 and MSH2; however, sequence
variations in the ligation-probe binding site can mimic single exon deletions.