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Letters

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MSH2 Codon 322 Gly to Asp Seems Not to Confer an Increased Risk for Colorectal Cancer Susceptibility

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HEREDITARY NONPOLYPOSIS colorectal cancer (HNPCC) is an autosomal dominantly inherited disease, also known as Lynch syndrome, that is characterised by an increased risk of colorectal cancer and other cancers, as well as an earlier age of onset than the corresponding sporadic cases. Recent studies have suggested that an increased risk of HNPCC is associated with mutations in five genes (*hMSH2*, *hMLH1*, *hPMS1*, *hPMS2*, *hMSH6*). The protein products of these genes are involved in the DNA mismatch repair pathway. A malfunction of this pathway can lead to replication errors and cause tumours.

We have used denaturing gradient gel electrophoresis (DGGE) to perform mutation screening in *hMSH2* according to conditions detailed previously [1]. In total, 170 patients with a family history of colorectal cancer were studied. 9 were found to be carrying *hMSH2* exon 6, codon 322 G to A, changing Gly to Asp, first reported by Liu and colleagues [2]. This alteration was further studied by Froggatt and associates [3] who suggested that it could either be a rare polymorphism, a low penetrance mutation or even an alteration with a modifying effect on patients with an already inherited susceptibility [3]. Another investigation suggested this alteration to be a mutation [4].

The 9 cases detected represented different categories. Three were found in 3 affected individuals from two different HNPCC families, where *hMLH1* and *hMSH2* mutations were known to segregate with disease (2 were mother and son in family 2 with a known *hMLH1* mutation and the third was 1 affected in family 6 with a known *hMSH2* mutation) and this exon 6 alteration did not segregate in other affected members of the families. The other six were found in six probands from six different families where no mutation has been found in either of *hMLH1* or *hMSH2*. The first case was a man with colorectal cancer at the age of 44 years in family 152. He presented a family with 2 known cases of colorectal cancer, he and his mother. The mother shared this alteration with her son. The second case was from a woman with one adenoma, representing an HNPCC family (family 155). This alteration was not shared by 1 affected sister with colorectal cancer at the age of 55 years. The third case was from a man with colorectal cancer at the age of 44 and 59 years (family 117). He represented an HNPCC family, but his daughter with colorectal cancer at the age of 25 years did not share this alteration. The fourth case was a man with colorectal cancer at the age of 76 years, representing a family with hereditary colorectal cancer at an older age (family 157). This alteration was not shared by his brother with colorectal cancer at the age of 69 years or his niece with colorectal cancer at the age of 55 years. The fifth case was a man with colorectal cancer at the age of 34 years whose grandmother had colorectal cancer at the age of 63 years and possibly some of her siblings (family 116) and the last case was a man with an adenoma whose brother had colorectal cancer at the age of 25 years (family X2). From these two last families, no additional samples were available.

We also used a HinfI restriction enzyme assay to screen normal samples and sporadic colorectal cancer cases for this alteration. A part of exon 6 containing codon 322 (f:5′-CACTAATGAGCTTGCCATTC, r:5′-CCACTGGITAA-CAAGTCT) was amplified using the same conditions as in the DGGE polymerase chain reaction (PCR) [3]. The product was then digested using the enzyme HinfI overnight and finally run on an ethidium bromide stained 2% agarose gel.

In summary, we found this exon 6 mutation in 9 of 170 colorectal cancer patients (5.3%) from high risk families and in 6 of those this alteration was shown not to segregate with disease. We also found this alteration in 12 of 192 normal controls (6.3%) and in none of 104 sporadic colorectal cancer cases. Based on these results, we conclude that this alteration is rather a common polymorphism than a disease-causing mutation.

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