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MSH2 Sequence Variations and Inherited Colorectal Cancer Susceptibility

N.J. Froggatt,[1] J.A. Joyce,[1] D.G.R. Evans,[2] P.W. Lunt,[3] D.J. Koch,[1] B.J. Ponder[4] and E.R. Maher[1]

[1]Human Molecular Genetics Group, Department of Pathology, Cambridge University; [2]Department of Medical Genetics, Medical Genetics, St Mary's Hospital, Manchester; [3]Clinical Genetics, Bristol Royal Hospital for Sick Children, Bristol; and [4]CRC Human Cancer Genetics Group, Cambridge University Department of Pathology, Cambridge, U.K.

THE IDENTIFICATION of germline mutations causing colorectal cancer susceptibility is important for understanding the genetic pathogenesis of this common cancer and may enhance the management of affected patients and relatives. Therefore, we read with interest the article of Hall and associates [1] concerning the significance of the intronic splice acceptor site variation in the hereditary non-polyposis colon cancer (HNPCC) gene *MSH2*. Like Hall and colleagues [1], we have investigated the possible association between colorectal cancer and the T→C substitution at position 6 of the 5′ exon 13 splice site. Our results lend further support to the conclusion of Hall and colleagues [1] that this sequence variation represents a polymorphism rather than a mutation. Although we initially detected this change by single-strand conformational polymorphism (SSCP) analysis of *MSH2* in a chromosome 2-linked HNPCC family [2], the sequence variation did not segregate with colon cancer in the family. Furthermore, using a *XmnI* restriction site assay, we found no significant difference between the heterozygote frequency of this variant in 30 HNPCC probands (1/30) and normal controls (2/16).

Nevertheless, sequence variants in *MSH2* remain candidates for low penetrance cancer susceptibility mutations, and we have investigated a further variant for a possible association with familial or early onset colorectal cancer. We initially detected a GGC→GAC substitution (glycine→aspartic acid) at codon 322 in exon 6 of *MSH2* by SSCP analysis, in an individual with multiple primaries including colorectal cancer at age 36 years, and endometrial and ovarian cancers at age 45 years. The glycine at codon 322 is highly conserved and is present in yeast and human *MSH2* homologues [3, 4]. To investigate whether this change was likely to be a polymorphism or a pathogenic mutation, we designed a *HinfI* restriction site assay to specifically detect this variant and screened (i) 45 patients with early onset colorectal cancer (age <45 years); (ii) 50 patients with late onset colorectal cancer (>45 years); and (iii) 30 probands from HNPCC families and 72 normal controls. A further isolated patient with early onset colorectal cancer (age 19 years), whose parents are consanguineous, was found to be homozygous for G322D. Although none of the late onset patients or the HNPCC probands were positive for G322D, one of the 72 normal controls was heterozygous for this variant. This individual had no personal history of cancer at age 84 years, but further investigation of her family history revealed that two of her siblings were reported to have colorectal cancer at ages 41 and 80 years, respectively. However, we have not been able to establish whether either of these relatives had the G322D variant. Thus, although the G322D variant may represent a rare polymorphism, it is also a candidate for a low penetrance mutation or a modifying effect in patients with an inherited susceptibility to colorectal cancer. We hope that this report will encourage other groups to investigate the significance of this sequence variation.

Correspondence to E.R. Maher at the University of Cambridge, Box 134, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, U.K.
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Chemotherapy with Doxorubicin, Etoposide and Cyclophosphamide (DEC) in Ovarian Cancer Persistent after Platinum-based Treatment

G. Zanetta, S. Lo Monico, A. Gabriele, D. Miceli and C. Mangioni

Department of Obstetrics and Gynaecology, Ospedale S. Gerardo Monza, III Branch of the University of Milan, Italy

SECOND-LINE treatments for persistent ovarian cancers provide discouraging results and investigation of new cytotoxic drugs

Correspondence to G. Zanetta.
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