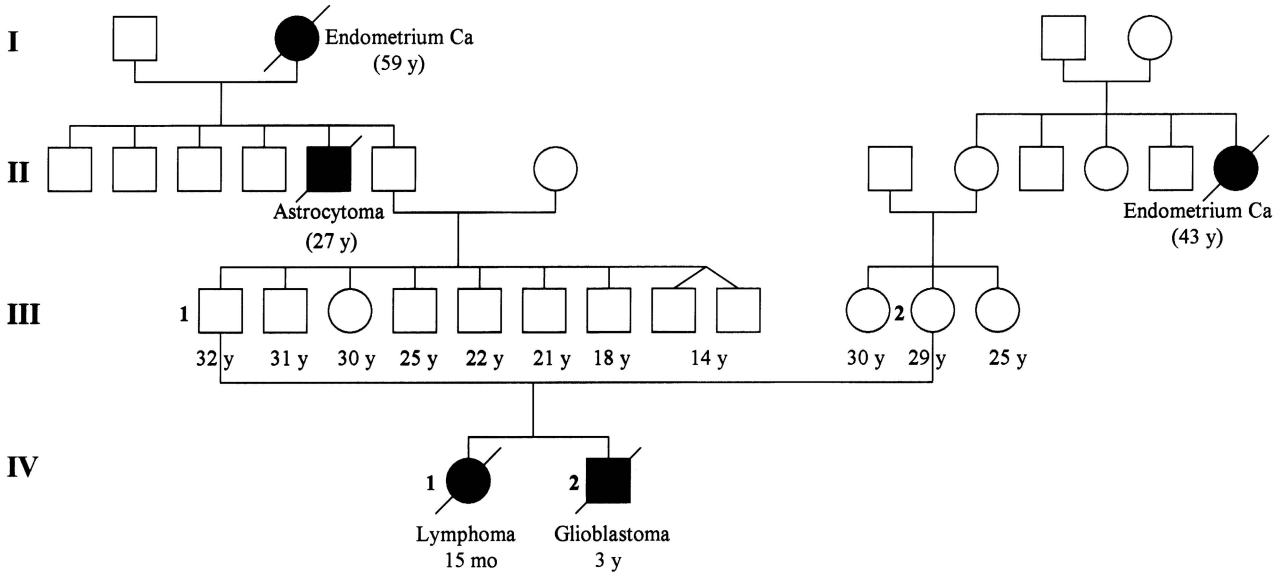

Figure 1 Partial pedigree of the family. Filled symbols denote affected subjects; open symbols denote asymptomatic subjects; oblique line denote deceased. Numbers beside symbols are subject identifiers. The ages of unaffected individuals are indicated. For affected subjects, the tumor type and the age at diagnosis or of death (in parentheses) are indicated. Ca = cancer; y = years; mo = months.

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Early-Onset Brain Tumor and Lymphoma in *MSH2*-Deficient Children

To the Editor:

Homozygous germline mutations of *MLH1* have been reported so far in three families with hereditary nonpolyposis colorectal cancer (HNPCC [MIM 114500]) and have been shown to be associated with leukemia or lymphoma, CNS tumors, and the neurofibromatosis type I phenotype (Ricciardone et al. 1999; Wang et al. 1999; Vilkki et al. 2001). More recently, the first case of a homozygous germline mutation of *MSH2* was described in a child with leukemia and multiple café-au-lait spots (Whiteside et al. 2002). We report here the incidental discovery of a new case of *MSH2* deficiency, which is remarkable because of the presentation of the family and because of the association with an early-onset brain tumor.

The proband (III.2) and her husband (III.1), of French origin, were seen for genetic counseling in the dramatic context of the death of their two children (fig. 1). Individual IV.1 died at age 15 mo from a T mediastinal lymphoma; her brother (IV.2) died at age 4 years from a temporal glioblastoma. Their mother and father, age 29 years and 32 years, respectively, had no personal history of cancer. Although several second-degree relatives of the parents had developed cancers (fig. 1), the presentation of the family did not fulfill the criteria for a Mendelian genetic predisposition to cancer. The development of a CNS tumor and lymphoma in two sibs led us to consider initially the hypothesis of Li-Fraumeni syndrome (LFS) in this family. Since no DNA was available from the affected children, we analyzed the *TP53* gene in both unaffected parents. Sequencing analysis of *TP53* revealed no mutation. Stimulated by our recent finding of a family with LFS with complete heterozygous germline deletion of *TP53* (unpublished data), we completed the analysis of *TP53* by searching for a similar defect using quantitative multiplex PCR of short fluorescent fragments (QMPSF) (Charbonnier et al. 2000,

2002). QMPSF analysis of *TP53* performed in the father (III.1) demonstrated that the *TP53* gene was not affected, but, to our surprise, revealed a heterozygous deletion of *MSH2* exon 3 corresponding to the control amplicon. Therefore, we analyzed, by QMPSF, the 16 exons of *MSH2*, and this analysis showed the presence, in the unaffected father, of a heterozygous genomic deletion of *MSH2* removing exons 1–6 (fig. 2*A*). We then sequenced the *MSH2* gene in the unaffected mother (III.2) and identified a 1-bp heterozygous deletion at codon 153 within exon 3 (fig. 2*B*). In the absence of constitutional DNA from the affected children, we sequenced *MSH2* exon 3 from the glioblastoma DNA of individual IV.2. As shown in figure 2*C*, we detected only the mutant maternal allele, which strongly suggested that individual IV.2 had received from his father the mutant allele harboring the exons 1–6 deletion. Haplotype analysis at the *MSH2* locus confirmed the presence of two parental *MSH2* alleles within the tumor, ruling out a somatic loss of heterozygosity (data not shown).

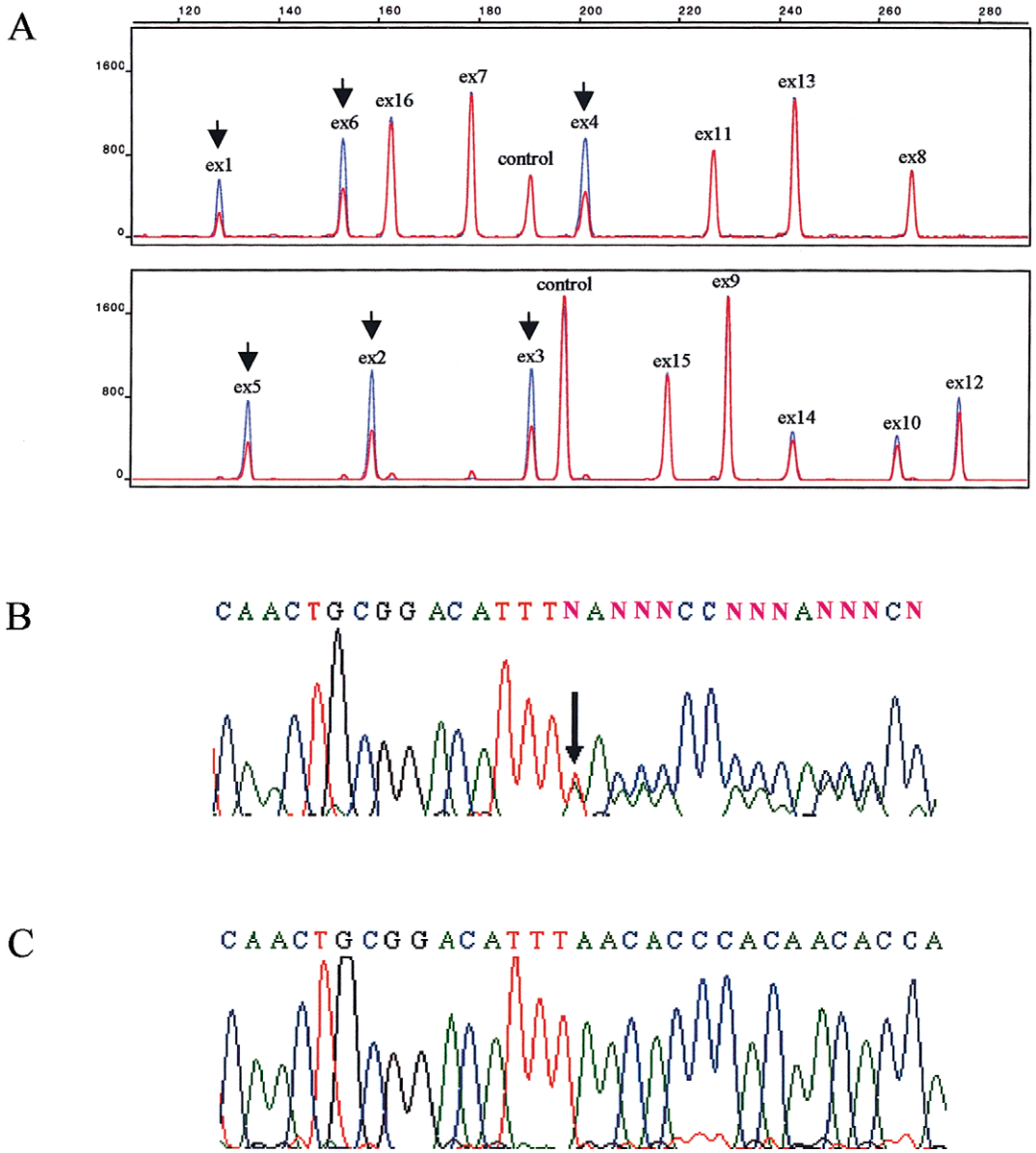

Figure 2 Detection of the *MSH2* alterations. *A*, Heterozygous deletion of *MSH2* exons 1–6 in the father (individual III.1) detected by QMPSF. The electropherogram of the father (*red*) was superposed on that of a control individual (*blue*). The *Y*-axis displays fluorescence in arbitrary units, and the *X*-axis indicates the size in bp. This result was obtained on two independent samples. *B*, Heterozygous 1-bp deletion within exon 3 detected in the mother (individual III.2). *C*, Hemizygous 1-bp deletion within exon 3, detected in the brain tumor developed in individual IV.2. In panels *B* and *C*, sequences correspond to the noncoding strand.

Screening for microsatellite instability (MSI), as recommended by Boland et al. (1998), revealed no replication error (RER) phenotype within the glioblastoma.

This case report shows that *MSH2* deficiency in humans can result in early-onset CNS tumors. Homozygous *MLH1* mutations have been detected in two children who had developed a medulloblastoma (Wang et al. 1999) and a glioma (Vilkki et al. 2001). Compound heterozygous mutations of the *PMS2* gene, which is rarely involved in HNPCC, have been identified in two sisters with early-onset brain and colorectal tumors (De Rosa et al. 2000). These studies, together with the present report, indicate that germline *MMR* deficiency predisposes to primary early-onset neuroepithelial tumors. Turcot syndrome (MIM 276300) was originally defined by the association of CNS malignant tumors with familial polyposis of the colon, but molecular studies have subsequently distinguished two entities, resulting from *APC* and *MMR* gene mutations, respectively (Hamilton et al. 1995; Paraf et al. 1997). It is tempting to speculate, as suggested elsewhere (De Rosa et al. 2000), that, in some families with Turcot syndrome, the association of colorectal neoplasms with childhood brain tumors may be due to a complete MMR deficiency.

We were surprised that we could not detect an RER phenotype in the *MSH2*-deficient brain tumor. It is interesting that MSI was not also detected in the nontumoral DNA of the *MSH2*-deficient patient reported by Whiteside et al. (2002), in contrast to the case of the two *MLH1*-deficient subjects analyzed by Wang et al. (1999) and Vilkki et al. (2001). This result could suggest that, at least in certain tissues, *MSH2* deficiency could lead to tumorigenesis through a mechanism distinct from a defect in the repair of postreplicative mismatches affecting repetitive sequences. Indeed, MSH2, like its bacterial homolog, MutS, has been shown to play additional roles in genetic recombination, since these proteins prevent exchange between divergent DNA sequences (Modrich and Lahue 1996). Furthermore, MSH2 was recently shown to be associated with TP53 within recombinative repair complexes during S phase (Zink et al. 2002).

As in the previous report of a *MSH2* deficiency (Whiteside et al. 2002), the familial history presented in this study was not strongly suggestive of HNPCC, although the young age of the parents and their sibs could explain the absence of cancer within this generation. Therefore, as shown in this report, the presence of homozygous mutations of the different *MMR* genes must be considered in families with early-onset CNS tumors and hematological malignancies, even in the absence of a familial history of HNPCC.

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Gaëlle Bougeard,[1] Françoise Charbonnier,[2] Alexandre Moerman,[3] Cosette Martin,[2] Marie M. Ruchoux,[4] Nathalie Drouot,[2] and Thierry Frébourg[1,2]

[1]INSERM EMI 9906–IFRMP, Faculty of Medicine, and [2]Department of Genetics, Centre Hopitalo-Universitaire of Rouen, Rouen; and Departments of [3]Genetics and [4]Neuropathology, Hôpital Roger Salengro, Centre Hopitalo-Universitaire of Lille, Lille, France

Electronic-Database Information

Accession numbers and URL for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for hereditary nonpolyposis colorectal cancer [MIM 114500] and Turcot syndrome [MIM 276300])

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Address for correspondence and reprints: Dr. Thierry Frébourg, INSERM EMI 9906, Faculty of Medicine, 22 Boulevard Gambetta, 76183 Rouen, France. E-mail: Frebourg@chu-rouen.fr

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