PMS2 Mutations in Childhood Cancer


Until recently, the PMS2 DNA mismatch repair gene has only rarely been implicated as a cancer susceptibility locus. New studies have shown, however, that earlier analyses of this gene have had technical limitations and also that the genetic behavior of mutant PMS2 alleles is unusual, in that, unlike MLH1 or MSH2 mutations, PMS2 mutations show low heterozygote penetrance. As a result, a dominantly inherited cancer predisposition has not been a feature reported in families with PMS2 mutations. Such families have instead been ascertained through childhood-onset cancers in homozygotes or through apparently sporadic colorectal cancer in heterozygotes. We present further information on the phenotype associated with homozygous PMS2 deficiency in 13 patients from six families of Pakistani origin living in the United Kingdom. This syndrome is characterized by café-au-lait skin pigmentation and a characteristic tumor spectrum, including leukemias, lymphomas, cerebrovascular malformations (such as supratentorial primitive neuroectodermal tumors, astrocytomas, and glioblastomas), and colorectal neoplasia with an onset in early adult life. We present evidence for a founder effect in five families, all of which carried the same R802→X mutation (i.e., arginine-802 to stop) in PMS2. This cancer syndrome can be mistaken for neurofibromatosis type 1, with important management implications including the risk of the disorder occurring in siblings and the likelihood of tumor development in affected individuals.

The clinical features of 13 patients with childhood cancer, derived from six consanguineous kindreds of Pakistani origin living in the United Kingdom (one of which, termed kindred 01, has been previously reported (1)) are summarized in Table 1. These families were ascertained through pediatric oncology services in three U.K. cities. We selected patients for analysis who had a history of parental consanguinity, early-onset cancer, and one or more of the following characteristics: affected sibling, multiple tumor types, and café-au-lait patches. Pakistani origin was not specified among the selection criteria for this study, but Pakistanis are the largest consanguineous social group in the United Kingdom. All patients gave written informed consent to participation in the study, which was approved by the internal review board of St James’s Hospital.

It is particularly notable that four of the 13 patients in our study developed supratentorial primitive neuroectodermal tumor, which is a very rare malignancy. Café-au-lait spots or patches were reported in 10 of the 13 patients; no information was available on the other three patients. This cutaneous feature had frequently led to an initial diagnosis of neurofibromatosis type 1. However, the skin lesions did not segregate in a manner that was consistent with dominant inheritance, and the café-au-lait spots or patches had a ragged-edged, slightly diffuse appearance that was not typical of the more sharply delineated café-au-lait spots or patches in neurofibromatosis type 1 (Fig. 1). Two patients had axillary freckling and café-au-lait spots or patches and would therefore have fulfilled the National Institutes of Health consensus criteria for neurofibromatosis type 1, although neither child had Lisch nodules. None of the parents had a history consistent with neurofibromatosis type 1, and none had had cancer. The combined clinical picture of café-au-lait spots or patches, malignancy, and parental consanguinity is now recognized as an indicator of recessive mismatch repair gene defects (2). The tumor types and absence of a history of hereditary nonpolyposis colon cancer in these families were further indicative that the locus in question might be PMS2, as we have reported previously for family 01 (1).

PMS2 sequence analysis was performed on DNA extracted from blood, by use of gene-specific single-exon polymerase chain reaction (PCR) primer pairs and conditions as previously described (1). In four of the five new families, the same homozygous truncating mutation in exon 14 (R802→X, i.e., arginine-802 to stop) was found in affected children. The affected children in the sixth family were homozygous for a single-nucleotide deletion in exon 6 (543ΔT, predicting the protein-truncating Y181→X change, where Y is tyrosine.)

The architecture of the PMS2 locus is complex, with a 100-kilobase (kb) inverted duplication resulting in a pseudogene (PMS2CL, formerly referred to as P0) that corresponds to the 3′ half of PMS2, including exons 9 and 11–15 (1). We have also recently become aware that gene conversion occurs between the two arms of this inverted duplication (B. Hayward, unpublished results). This finding raises a theoretical concern that on some alleles, supposedly gene-specific PCR primers could, in fact, amplify PMS2CL, because gene conversion had occurred at the primer binding sites. If this hypothesis were true, then R802→X could still be a pseudogene variant misinterpreted as PMS2 specific. To eliminate this possibility, we reanalyzed patients 01 and 03 from family 01. A 16-kb gene-specific long-range PCR product was generated with an upstream primer in exon 10. (Exon 10 is deleted from the pseudogene, so that this product can only be derived from PMS2 proper.) Sequencing of this product revealed homozygosity for R802→X, confirming that this mutation does indeed reside in PMS2 and not in the pseudogene PMS2CL.

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See “Notes” following “References.”

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All six families described in this study were of Pakistani origin. All five families that carried the R802→X mutation originated from the Mirpur region of northeastern Pakistan, but these families had no known blood relationship to one another. The sixth family that carried the Y181→X mutation was Pashtun from western Pakistan. To assess a possible common ancestry for the R802→X mutation in the five Mirpuri families, we identified three nearby multiallelic polymorphisms, a (CA)$_n$ sequence that was approximately 205 kb telomeric from PMS2 (i.e., 205 tel), a (TA)$_n$ sequence that was approximately 335 kb centromeric from PMS2 (i.e., 335 cen), and a (CA)$_n$ sequence that is approximately midway between the other two markers and less than 100 kb centromeric from PMS2 (i.e., D7S481) (Table 2). Four of the five families had identical genotypes at all three markers, suggesting an ancestral founder effect giving rise to R802→X in the Mirpuri Pakistanis. Family 06, however, showed concordance with the other five families only at marker D7S481, possibly because of microsatellite mutations at the other two markers or recombination or because the R802→X mutation in this family had an independent origin.

R802X does indeed appear to have arisen independently at least twice, because this mutation was first identified in an established cell line, HEC-1-A, that was derived from an ovarian carcinoma in a Japanese patient (whether germline or somatically acquired is not known) (3). Biochemical studies have shown that R802→X is a null mutation that confers a very severe mismatch repair defect and microsatellite instability (4,5).

Indeed, the mutation rate at the HPRT locus in HEC-1-A cells is fourfold to sevenfold higher than that observed in

![Fig. 1. Café-au-lait skin patches from the PMS2 mutation syndrome and from type 1 neurofibromatosis. A) PMS2 mutation syndrome. B) Type 1 Neurofibromatosis. In café-au-lait skin patches in patient 01 from family 01, the macules are variable in size, shape, and depth of pigmentation, and they have irregular margins. They differ, in these regards, from the café-au-lait patches typically observed in type 1 neurofibromatosis.](https://academic.oup.com/jnci/article-abstract/98/5/358/2522010)
the MLH1-deficient cell lines AN3CA and HCT116 (4). It is therefore to be expected that cells homozygous for the R802→X mutation will be severely compromised in their ability to maintain genome stability. Although we have not characterized germline microsatellite instability in the patients in our study, a very high level of microsatellite instability in normal tissues has indeed been previously demonstrated in compound heterozygous PMS2-deficient individuals (6,7).

A distinctive clinical syndrome emerges from this study. The syndrome is characterized by café-au-lait spots or patches, an unusual tumor spectrum, colonic polyps, and a high risk of second primary malignancies (Table 1). The tumor spectrum is marked by rare types, particularly noteworthy and suggests a specific association with PMS2. Other tumors reported in PMS2-deficient children include intracerebral gliomas and medulloblastoma and, from the second decade on, colorectal cancer and multiple colonic polyps [Table 1 and cases previously cited by De Vos et al. (1)]. But all but two of the children in our study who survived their first cancers went on to develop second primary malignancies. The two oldest patients, both of whom have reached early adult life, have colorectal neoplasia—patient 02 from family 01 has multiple polyps, and patient 01 from family 02 has both polyps and colorectal cancer.

Although heterozygous mutations in DNA mismatch repair genes typically cause hereditary nonpolyposis colon cancer, several reports have recently appeared detailing childhood-onset cancer syndromes that result from homozgyosity or compound heterozygosity for such mutations. The presence of café-au-lait patches is a feature of all these disorders, but clinically significant differences can be discerned that depend on the locus and type of mutation. Null mutations in MLH1, for example, result in hereditary nonpolyposis colon cancer, and children homozygous for such mutations have had a preexisting family history of that disorder (8,9). In contrast, in nine families that are now known with homozgyous or compound heterozygous PMS2 mutations, including the five new families described in this study and the four families previously described by us (1) and others (6,7,10), no history of hereditary nonpolyposis colon cancer (or indeed other cancer predispositions) in heterozygotes has been reported. Despite this fact, heterozygous PMS2 mutations have recently been described in adult patients with familial or sporadic colorectal cancer (11–13). These apparently conflicting observations are most easily reconciled by the idea that heterozygous PMS2 mutations have a high population frequency but a penetrance lower than those in MLH1 or MSH2. Data supporting this possibility have recently been published (12); in a population of patients with sporadic colorectal cancer, although the number of PMS2 mutations was similar to that observed in MLH1 and MSH2, the penetrance of the heterozygous mutations was low (12). Because completely robust methods for comprehensive PMS2 mutation analysis do yet not exist, confirming or refuting this hypothesis may not be a trivial exercise.

The homozygous PMS2 syndrome appears to be an important cause of pediatric malignancy among a population in the United Kingdom that originated from south Asia, and its prevalence in Pakistan itself should therefore also now be investigated. The tumor spectrum is distinctive, and early accurate diagnosis is of considerable importance in view of the 25% risk of the disorder occurring in siblings and the likely differences in therapeutic response of mismatch repair-deficient tumors (14). Given its phenotypic similarities to neurofibromatosis type 1, we also emphasize that the latter diagnosis should be made only with considerable caution in children from consanguineous unions, particularly when neither parent is affected.

References


NOTES

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