Role of MSH6 and PMS2 in the DNA Mismatch Repair Process and Carcinogenesis

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• MSH6 • PMS2 • Mismatch repair • Penetrance

The fidelity of DNA synthesis during cell replication is maintained by the mismatch repair system, which detects and repairs DNA mismatches—point mutations caused by base substitutions, insertions, or deletions.[1] Loss of mismatch repair function can result in the accrual of mismatches with subsequent replication leading to the mutator phenotype. Cancers consequent to this mutator phenotype are characterized by microsatellite instability (MSI) due to the inability of the mismatch repair system to repair commonly occurring mismatches in repeat sequences.

The mismatch repair system in humans and other eukaryotes is initiated by a heterodimer most commonly comprising MSH2 and MSH6 (MutSα), two mismatch repair proteins made by the mismatch repair genes *MSH2* and *MSH6* respectively. Once the MutSα heterodimer is bound to the mismatch, a second heterodimer (MutL), most commonly comprising MLH1 and PMS2, made by the genes *MLH1* and *PMS2*, interacts with Mutsα to excise and repair the mismatch.[2]

Some DNA mismatches may be able to be repaired even in the absence of MSH6 or PMS2. Initiation of the mismatch repair process can be initiated with MutSβ, the heterodimer of MSH2 and MSH3, which can share the role of mismatch recognition with MutSα, especially of single-base insertions.[1] Similarly, a homolog of the MutL, MutLγ (MLH1–MLH3) is thought to repair insertions or deletions.[3] Therefore, some DNA mismatches may be repaired in the absence of MSH6 and PMS2.

Loss of mismatch repair function in a cell can occur via a variety of mechanisms, including germline mutation of a mismatch repair followed by somatic loss of the second allele or by somatic loss of both alleles. Somatic loss appears to be a function of age.

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DISCOVERY OF INHERITED MUTATIONS IN *MSH6* AND *PMS2*

The first reports of inherited mutations in *MSH6* and *PMS2* were studies of DNA samples from colorectal cancer patients who had a strong family history of colorectal and other cancers, and in whom mutations in *MLH1* and *MSH2* could not be found.

The first reported inherited mutation in *MSH6* was identified in a Japanese woman diagnosed with colorectal cancer and endometrial cancer in her 50s. She had two sisters diagnosed with endometrial cancer, one sister with ovarian cancer, and a brother with pancreatic cancer, all diagnosed before age diagnosed 70.[4]

The first report of an inherited mutation in *PMS2* was identified in a cancer patient (site unreported) who had a family history of colorectal cancer meeting the Amsterdam criteria for HNPCC.[5]

NUMBER OF MUTATIONS IN *MSH6* AND *PMS2*

It is difficult to describe the spectrum of mutations in *MSH6* and *PMS2* because: (1) there are no ''hotspots'' as the variants are spread across the coding and regulatory regions of the genes; (2) it is often difficult to determine the pathogenicity of any variant; (3) many variants are not reported or published; and (4) use of nomenclature of genetic variants has been inconsistent.

There are several databases of genetic variants of mismatch repair genes. These include the Leiden Open Variation Database managed from Leiden University Medical Center (www.lovd.nl); the Mismatch Repair Genes Variant Database,[6] which is a database of ''only those variants which have been published in peer-reviewed journals'' using a standard nomenclature; and the MMR Gene Unclassified Variants database (www.mmrmissense.net/), which contains information from functional assays and other types of data to support the interpretation of the unclassified variants of the MMR gene. As of March 2009, the combined databases contained 377 distinct *MSH6* variants and 176 distinct variants in *PMS2* (as compared to 1004 for *MLH1* and 888 for *MSH2*). According to the Mismatch Repair Genes Variant Database,[6] of the *MSH6* variants, 37% were insertions/deletions, 27% were missense, 21% were silent, 11% were nonsense, 2% were large genomic deletions/duplications, and 2% were splicing variants. In contrast, for *PMS2*, the most commonly described variants were missense (49%), followed by large genomic deletions/duplications (19%), silent (15%), insertions/deletions (9%), and nonsense (7%).

The apparent lower proportion of mismatch repair gene mutations due to *PMS2* compared to the other mismatched repair genes may not be due to a lower mutation frequency. Testing for germline mutations in *PMS2* is not as straightforward as for *MSH6* or the other mismatch repair genes. There are at least 13 highly homologous *PMS2* pseudogenes, the majority of which have some homology with at least some of the 10 exons at the 3' end of the gene.[7–10] Long-range polymerase chain reaction, in which primers are selected from regions with no pseudogene homology, has been shown to avoid the amplification of pseudogene sequences.[11–13] Due to these issues, testing for *PMS2* has been limited to a few laboratories, possibly limiting the rate of testing and therefore identification of new mutations.

Although these databases describe the variety of variants identified in *MSH6* and *PMS2*, they do not provide information on the frequency of variants in the population. In the only published study to date reporting the estimated prevalence of mismatch repair gene mutations in the population, it is estimated that 1 in 3139 (95% CI, 1 in 1247 to 1 in 7626) 15- to 74-year-olds carry a mutation in *MLH1* or *MSH2*.[14] There have been no published estimates of the comparative figures for *MSH6* or *PMS2*.