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Gene Section
Review

MSH6 (mutS homolog 6 (E. Coli))

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Identity

Hugo: MSH6
Other names: GTBP; HSAP; HNPCC5
Location: 2p16
Local order: Genes flanking MSH6 in centromere to telomere direction on 2p16 are:
HTLF (2p22-p16) (human T-cell leukemia virus enhancer factor).
FBXO11 (2p16.3) (F-box protein 11).
MSH6 (2p16) (mutS homolog 6 (E. coli)).
LOC285053 (2p16.3) (similar to ribosomal protein L18a).
KCNK12 (2p22-p21) (potassium channel, subfamily K, member 12).
MSH2 (2p22-p21) (mutS homolog 2, colon cancer, nonpolyposis type 1 (E. coli)).

DNA/RNA

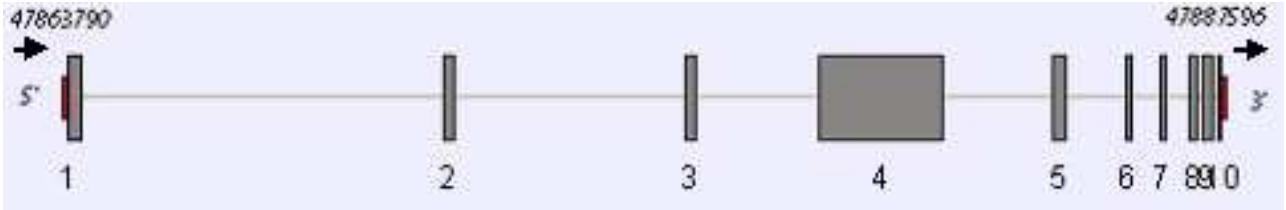
Note: The genes for MSH2 and MSH6 which form the major mismatch recognition MutSalpha complex functional in the mismatch repair (MMR) pathway are located within 1 Mb of each other. MSH2 and MSH6 may have been produced by duplication of a primordial mutS repair gene.

Description

MSH6 gene maps to NC_000002.10 and spans a region of 23.8 kilo bases. MSH6 has 10 exons, the sizes being 347, 197, 170, 2545, 266, 119, 89, 155, 200 and 176 bps.

Transcription

Human MSH6 gene is transcriptionally upregulated 2.5 fold at late G1/early S phase while the amount of protein remains unchanged during the whole cell cycle.
The promoter region has a high GC content, as well as multiple start sites. Sequence analysis of 3.9 kb of the 5'-upstream region of the MSH6 gene revealed the absence of TATAA- or CAAT-boxes. Seven consensus binding sequences for the ubiquitous transcription factor Sp1 were found in the promoter region. This factor is implicated in positioning the RNA polymerase II complex at the transcriptional start sites of promoters lacking TATA- and CAAT-boxes. The proximal promoter region of MSH6 gene also contains several consensus binding sites of the embryonic TEA domain-containing factor ETF. This transcription factor has also been reported to stimulate transcription from promoters lacking the TATA box. In addition, the trancription of MSH6 gene is downregulated by CpG methylation of the promoter region.
Three common polymorphic variants (-557 T G, -448 G A, and -159 C T) of the MSH6 promoter have been identified in which different Sp1 sites were inactivated by single-nucleotide polymorphisms (SNPs) resulting in altered promoter activity.



Exons are represented by gray boxes (in scale) with exon numbers on the bottom. The arrows show the ATG and the stop codons respectively.

Pseudogene

No pseudogene has been reported for the MSH6 gene.

Protein

Note: Eukaryotic MutSalpha is a heterodimer of the 100-kDa MSH2 and the 160-kDa MSH6 that participates in the mismatch repair pathway. The proteins are required for single base and frameshift mispair specific binding, a result consistent with the finding that tumour-derived cell lines devoid of either protein have a mutator phenotype.

Description

The MSH6 protein maps to NP_000170 and has 1360 amino acids. The molecular weight is 152786 Da. The protein contains a highly conserved helix-turn-helix domain associated with a Walker-A motif (an adenine nucleotide and magnesium binding motif) with ATPase activity.
The breast cancer 1 gene (BRCA1) product is part of a large multisubunit protein complex of tumor suppressors, DNA damage sensors, and signal transducers. This complex is called BASC, for 'BRCA1-associated genome surveillance complex and the mismatch repair protein MSH6 was found to be a part of this complex.

Localisation

The subcellular localisation of MSH6 is the nucleus.

Function

hMSH6 gene product with hMSH2, hMSH3 gene products play role in strand specific repair of DNA replication errors. Studies show that hMSH2-hMSH6 complex functions in the recognition step of the repair of base-base mismatches or single frameshifts.
The ADP/ATP binding domain of the heterodimer and the associated ATPase activity function to regulate mismatch binding as a molecular switch. Both MSH2 and MSH6 can simultaneously bind ATP. The MSH6 subunit contains the high-affinity ATP binding site and MSH2 contains a high-affinity ADP binding site. Stable binding of ATP to MSH6 results in a decreased affinity of MSH2 for ADP, and binding to mispaired DNA stabilizes the binding of ATP to MSH6. Mispair binding encourages a dual-occupancy state with ATP bound to Msh6 and Msh2; following which there is a hydrolysis-independent sliding along DNA. Subsequent steps result in the excision of the mispaired region followed by DNA synthesis and ligation.

Homology

H.sapiens: MSH6 (mutS homolog 6 (E. coli)).
C.familiaris: LOC474585 (similar to mutS homolog 6).
M.musculus: Msh6 (mutS homolog 6 (E. coli)).
C.elegans: msh-6 (MSH (MutS Homolog) family).
S.pombe: SPCC285.16c (hypothetical protein).
S.cerevisiae: MSH6 (Mismatch repair protein).
A.thaliana: MSH6 (MSH6).

Mutations

Note: The MSH6 gene plays a role in the development of inherited cancers, especially the colorectum and endometrial cancers.

Germinal

MSH6 germline mutations have variable penetration. Atypical hereditary non polyposis colorectal cancer (HNPCC) can result from germline mutations in MSH6; however, disease-causing germline mutations of MSH6 are rare in HNPCC and HNPCC-like families. Other studies have indicated that germline MSH6 mutations may contribute to a subset of early-onset colorectal cancer.

Somatic

The involvement of somatic or epigenetic inactivation of hMSH6 is rare in colorectal cancer and missense mutations in MSH6 are often clinically innocuous or have a low penetrance. However, somatic mutations of MSH6 have been shown to confer resistance to alkylating agents such as temozolomide in malignant gliomas in vivo. This concurrently results in accelerated mutagenesis in resistant clones as a consequence of continued exposure to alkylating agents in the presence of defective mismatch repair. Therefore, when MSH6 is inactivated in gliomas, there is a change in status of the alkylating agents from induction of tumour cell death to promotion of neoplastic progression.

Implicated in

Hereditary non polyposis colorectal cancer

Disease

Mutations in the mismatch repair genes MSH2, MSH6, MLH1 and PMS2 results in hereditary non polyposis colorectal cancer (HNPCC, Lynch syndrome). Individuals predisposed to this syndrome have increased lifetime risk of developing colorectal, endometrial and other cancers. The resulting mismatch repair deficiency leads to microsatellite instability which is the hallmark of tumors arising within this syndrome, as well as a variable proportion of sporadic tumors.
Clinically, HNPCC can be divided into two subgroups:
Type I: a young onset age for hereditary colorectal cancer, and carcinoma of the proximal colon.
Type II: patients are susceptible to cancers in tissues such as the colon, uterus, ovary, breast, stomach, small intestine and skin.
Diagnosis of classical HNPCC is based on the Amsterdam criteria:

- 3 or more relatives affected by colorectal cancer, one a first degree relative of the other two;
- 2 or more generation affected;
- 1 or more colorectal cancers presenting before 50 years of age; exclusion of hereditary polyposis syndromes.

Turcot Syndrome

Disease

Turcot syndrome is a condition whereby central nervous system malignant tumours are associated with familial colorectal cancer. A homozygous mutation in MSH6 has been reported in a family with childhood-onset brain tumour, lymphoma, colorectal cancer, and neurofibromatosis type 1 phenotype.

Colorectal cancer

Disease

Mutations in four mismatch repair genes MSH2, MLH1, MSH6, and PMS2, have been convincingly linked to susceptibility of hereditary nonpolyposis colorectal cancer (HNPCC)/Lynch syndrome. Of the 500 different HNPCC-associated MMR gene mutations known, approximately 10% are associated with mutations in the MSH6 gene.

Endometrial cancer

Disease

Germline mutations in the MSH6 gene are often observed in HNPCC-like families with an increased frequency of endometrial cancer. Sequence analysis of the MSH6 coding region revealed the presence of three putative missense mutations in patients with atypical family histories that do not meet HNPCC criteria. MSH6 mutations may contribute to the etiology of double primary carcinomas of the colorectum and endometrium.

Ovarian cancer

Disease

Late-onset endometrioid type of ovarian cancer can be linked to MSH6 germline mutations.

Lung cancer

Disease

Early onset lung cancer (before age 50) has been associated with polymorphisms in the MSH6 gene. Cadmium, an environmental and occupational carcinogen associated with lung cancer development was shown to inhibit the ATPase activity of MSH2-MSH6 heterodimer.

Breast cancer

Disease

Mutations in the MSH6 gene are not usually connected with breast cancer, even when associated with endometrial or colorectal cancer.

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