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Gene Section
Mini Review

MLH1 (human mutL homolog 1)

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Identity

Other names: COCA2; FCC2; hMLH1; HNPCC2

HGNC (Hugo): MLH1

Location: 3p21.3

Local order: Between the KIAA0342 and LRRFIP2 genes.

DNA/RNA

Description

The MLH1 gene is composed of 19 exons spanning in a region of 57360 bp.

Transcription

The transcribed mRNA has 2524 bp.

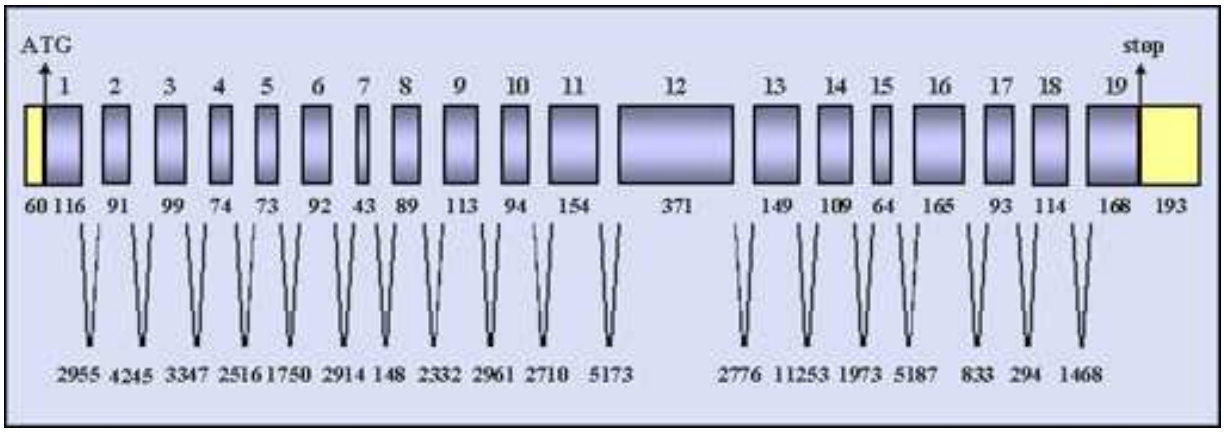

Diagram of the MLH1 gene. Exons are represented by boxes (in scale) transcribed and untranscribed sequences in blue and yellow, with exon numbers on top and number of base pairs at the bottom. Introns are represented by black bars (not in scale) and the number of base pairs indicated. The arrows show the ATG and the stop codons respectively.

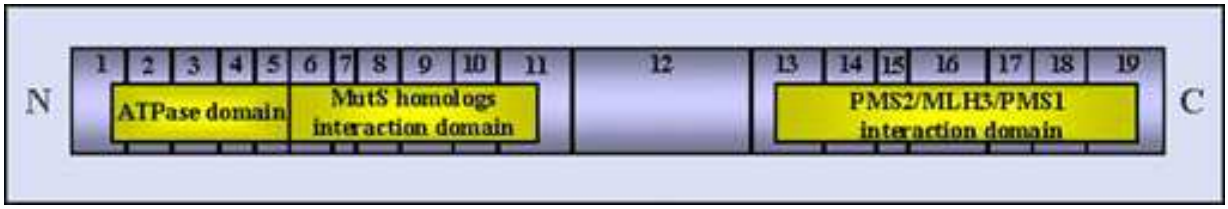

Diagram of the MLH1 protein in scale. Numbers inside the blue boxes indicate the exon from which is translated each part of the protein. The three boxes inside represent the ATPase domain, the MutS homologs interaction domain and the PMS2/MLH3/PMS1 interaction domain; C: Carboxyl-terminal; N: Amino-terminal

Protein

Description

Aminoacids: 756. Molecular Weight: 84.6 kDa. MLH1 is a protein involved in the mismatch repair process after DNA replication. It contains an ATPase domain and two interaction domains, one for MutS homologs (MSH2, MSH3, MSH6) and the other for PMS2, MLH3 or PMS1.

Localisation

Nuclear.

Function

MLH1 has no known enzymatic activity. MLH1 forms a heterodimer with PMS2 known as MutLa, although it can also bind to PMS1 or MLH3. This heterodimeric complex binds to the heteroduplexes MutSa (composed of MSH2 and MSH6) or MutSb (composed of MSH2 and MSH3), which recognize DNA lesions. The heterodimer formed by MLH1 is responsible for the recruitment of the proteins needed for the excision and repair synthesis.

Homology

MLH1 is homologue to the bacterial MutL gene, specially in the N-terminal region, and MLH1 homologues are also present in eukaryotes (for example in Mus musculus, Drosophila melanogaster, Caenorhabditis elegans or Saccharomyces cerevisae).

Mutations

Germinal

There are over 300 MLH1 germline mutations described all along the gene that cause hereditary non-polyposis colorectal cancer (HNPCC, see below). These mutations are not present in any particular hotspot or zone of the gene and include either nucleotide substitutions (missense, nonsense or splicing errors) or insertions/deletions (gross or small). In most of these mutations the resulting protein is truncated.
There are also founding mutations which account for a high proportion of the HNPCC tumours in some specific populations (for example there are two Finnish mutations that delete the exons 16 or 6). Some germline genetic changes have also been described in both exons and introns as non pathogenic.

Somatic

There are described some sporadic mismatch repair deficiency cases (sporadic MSI) with somatic MLH1 mutations, although most of them have MLH1 promoter hypermetilation.

Implicated in

HNPCC (Hereditary Non Polyposis Colorectal Cancer)

Disease

Predisposition to develop cancer, preferentially colorectal, but also in endometrium, ovary, urinary tract, stomach, small bowel, biliary tract and brain.

Oncogenesis

MLH1 mutations in HNPCC account for about 25% of the total cases approximately. These mutations are inherited in one allele and later the other allele is lost by LOH. This leads to mismatch repair deficiency in these patients, which is the cause of the accumulation of mutations along the genome, causing microsatellite instability (MSI) and promoting tumorigenesis. It has been suggested that low levels of MSI characterize MLH1 and MSH2 HNPCC carriers before tumor diagnosis.

MSI (MicroSatellite Instability)

Note

Tumours in which the molecular feature that leads to cancer is the lost of the mismatch repair (MMR) system.

Disease

This phenotype is present in 15% of colorectal, gastric and endometrial cancer, and with lower incidence in some other tissues.

Prognosis

MSI tumours have better prognosis than the MicroSatellite Stable (MSS).

Oncogenesis

Sporadic MSI cases are mostly due to a biallelic hypermetilation of the MLH1 promotor and therefore lack of MLH1 protein expression. Few sporadic cases and about 25% of the HNPCC are due to different mutations in MLH1. These mutations are germline in HNPCC.

Muir-Torre syndrome

Disease

Coincidence of at least one sebaceous adenoma, epithelioma or carcinoma and one internal malignancy.

Oncogenesis

Inherited MLH1 mutations can cause Muir-Torre syndrome (although MSH2 mutations are more present).

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