

MLH1 (human mutL homolog 1)

Identity

Other names

COCA2

FCC2

hMLH1

HNPCC2

Hugo

MLH1

Location

3p21.3

Between the KIAA0342 and LRRFIP2 genes

DNA/RNA

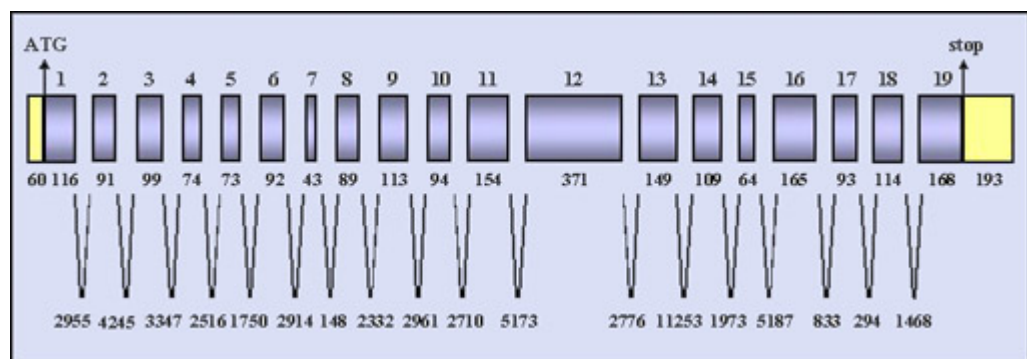


Diagram of the MLH1 gene. Exons are represented by boxes (in scale) transcribed and untranscribed sequences in blue and yellow, with exon numbers on top and number of base pairs at the bottom. Introns are represented by black bars (not in scale) and the number of base pairs indicated. The arrows show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

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

Transcription The transcribed mRNA has 2524 bp

Protein

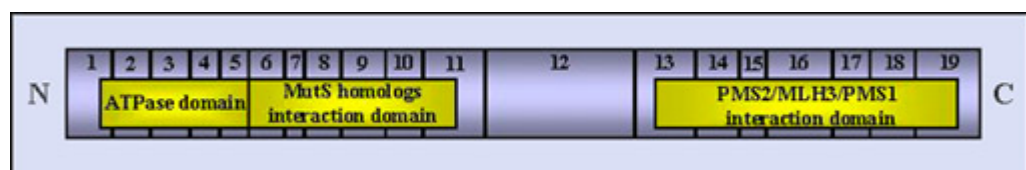


Diagram of the MLH1 protein in scale. Numbers inside the blue boxes indicate the exon from which is translated each part of the protein. The three boxes inside

represent the ATPase domain, the MutS homologs interaction domain and the PMS2/MLH3/PMS1 interaction domain; C: Carboxyl-terminal; N: Amino-terminal

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 <i>Mus musculus</i> , <i>Drosophila melanogaster</i> , <i>Caenorhabditis elegans</i> or <i>Saccharomyces cerevisiae</i>)

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 hypermethylation.

Implicated in

Entity	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.
Entity	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 hypermethylation 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.

Entity 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).

External links

Nomenclature

[Hugo](#)

[MLH1](#)

[GDB](#)

[MLH1](#)

[Entrez_Gene](#)

[MLH1_4292](#) mutL homolog 1, colon cancer, nonpolyposis type 2 (E. coli)

Cards

[Atlas](#)

[MLH1ID149ch3p21](#)

[GeneCards](#)

[MLH1](#)

[Ensembl](#)

[MLH1](#)

[CancerGene](#)

[MLH1](#)

[Genatlas](#)

[MLH1](#)

[GeneLynx](#)

[MLH1](#)

[eGenome](#)

[MLH1](#)

[euGene](#)

[4292](#)

Genomic and cartography

[GoldenPath](#) [MLH1 - 3p21.3](#) [chr3:37009983-37067341 + 3p22.3](#) (hg17-May_2004)

[Ensembl](#)

[MLH1 - 3p22.3 \[CytoView\]](#)

[NCBI](#)

[Genes Cyto](#) [Gene Seq](#) [Map View - NCBI]

[OMIM](#)

[Disease map \[OMIM\]](#)

[HomoloGene](#)

[MLH1](#)

Gene and transcription

[Genbank](#)

[AY217549](#) [SRS] [AY217549](#) [ENTREZ]

Genbank	AY344475 [SRS] AY344475 [ENTREZ]
Genbank	AY706914 [SRS] AY706914 [ENTREZ]
Genbank	U17839 [SRS] U17839 [ENTREZ]
Genbank	U17840 [SRS] U17840 [ENTREZ]
RefSeq	NM_000249 [SRS] NM_000249 [ENTREZ]
RefSeq	NT_086636 [SRS] NT_086636 [ENTREZ]
AceView	MLH1 AceView - NCBI
TRASER	MLH1 Traser - Stanford
Unigene	Hs.195364 [SRS] Hs.195364 [NCBI] HS195364 [spliceNest]
Protein : pattern, domain, 3D structure	
SwissProt	P40692 [SRS] P40692 [EXPASY] P40692 [INTERPRO]
Prosite	PS00058 DNA_MISMATCH_REPAIR_1 [SRS] PS00058 DNA_MISMATCH_REPAIR_1 [Expasy]
Interpro	IPR003594 ATPbind_ATPase [SRS] IPR003594 ATPbind_ATPase [EBI]
Interpro	IPR002099 DNA_mis_repair [SRS] IPR002099 DNA_mis_repair [EBI]
Interpro	IPR011186 MLH1 [SRS] IPR011186 MLH1 [EBI]
CluSTr	P40692
Pfam	PF01119 DNA_mis_repair [SRS] PF01119 DNA_mis_repair [Sanger]] pfam01119 [NCBI-CDD]
Pfam	PF02518 HATPase_c [SRS] PF02518 HATPase_c [Sanger]] pfam02518 [NCBI-CDD]
Blocks	P40692
Polymorphism : SNP, mutations, diseases	
OMIM	120436 [map]
GENECLINICS	120436
SNP	MLH1 [dbSNP-NCBI]
SNP	NM_000249 [SNP-NCI]
SNP	MLH1 [GeneSNPs - Utah] MLH1 [SNP - CSHL] MLH1 [HGBASE - SRS]
General knowledge	
Family Browser	MLH1 [UCSC Family Browser]
SOURCE	NM_000249
SMD	Hs.195364
SAGE	Hs.195364
Amigo	function ATP binding
Amigo	process mismatch repair
Amigo	process negative regulation of cell cycle
Amigo	component nucleus

[PubGene](#)

[MLH1](#)

Other databases

Probes

[Probe](#)

[MLH1 Related clones \(RZPD - Berlin\)](#)

PubMed

[PubMed](#)

[94 Pubmed reference\(s\) in LocusLink](#)

Bibliography

Mutation in the DNA mismatch repair gene homologue hMLH 1 is associated with hereditary non-polyposis colon cancer

Bronner CE, Baker SM, Morrison PT, Warren G, Smith LG, Lescoe MK, Kane M, Earabino C, Lipford J, Lindblom A, Tannergard P, Bollag RJ, Godwin AR, Ward DC, Nordenskjold M, Fishel R, Kolodner R, Liskay RM
Nature 1994; 368: 258-261.

Medline [8145827](#)

Microsatellite instability in inherited and sporadic neoplasms.

Eshleman JR, Markowitz SD.

Curr Opin Oncol 1995; 7: 83-89. (REVIEW).

Medline [7696368](#)

The genetic basis of Muir-Torre syndrome includes the hMLH1 locus.

Bapat B, Xia L, Madlensky L, Mitri A, Tonin P, Narod SA, Gallinger S.

Am J Hum Genet 1996; 59: 736-739.

Medline [8751876](#)

Biallelic inactivation of hMLH1 by epigenetic gene silencing, a novel mechanism causing human MSI cancers.

Veigl ML, Kasturi L, Olechnowicz J, Ma AH, Lutterbaugh JD, Periyasamy S, Li GM, Drummond J, Modrich PL, Sedwick WD, Markowitz SD.

Proc Natl Acad Sci USA 1998; 95: 8698-8702.

Medline [9671741](#)

hMLH1 promoter methylation and lack of hMLH1 expression in sporadic gastric carcinomas with high-frequency microsatellite instability.

Leung SY, Yuen ST, Chung LP, Chu KM, Chan AS, Ho JC.

Cancer Res 1999; 59: 159-164.

Medline [9892201](#)

DNA mismatch repair defects: role in colorectal carcinogenesis.

Jacob S, Praz F.

Biochimie 2002; 84: 27-47. (REVIEW)

Medline [11900875](#)

DNA mismatch repair and mutation avoidance pathways.

Marti TM, Kunz C, Fleck O.
J Cell Physiol 2002; 191: 28-41. (REVIEW).
Medline [11920679](#)

Mismatch repair genes hMLH1 and hMSH2 and colorectal cancer: a HuGE review.

Mitchell RJ, Farrington SM, Dunlop MG, Campbell H.
Am J Epidemiol 2002; 156: 885-902. (REVIEW)
Medline [12419761](#)

Low levels of microsatellite instability characterize MLH1 and MSH2 HNPCC carriers before tumor diagnosis.

Alazzouzi H, Domingo E, Gonzalez S, Blanco I, Armengol M, Espin E, Plaja A, Schwartz S, Capella G, Schwartz S Jr.
Hum Mol Genet 2005; 14: 235-239.
Medline [15563510](#)

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[BiblioGene - INIST](#)

Contributor(s)

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