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Gene Section
Review

HLTF (helicase-like transcription factor)

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Identity

Other names: HIP116; HIP116A; HLTF1; RNF80; SMARCA3; SNF2L3; ZBU1

HGNC (Hugo): HLTF

Location: 3q24

DNA/RNA

Description

The HLTF gene is located at 3q 25.1-26.1 (Lin et al., 1995); it is 56.4 kb long and contains 26 exons.

Transcription

The alternative splicing of intron 25, mapped in the 3'UTR, produces two mRNA of 5.4 and 4.5 kb with identical coding capacity. Additional alternative splicing of exon 20 or intron 21 was observed in HeLa cells (Capouillez et al., 2009). In the rabbit, the RUSH 1alpha and beta protein variants result from progesterone- or estrogen-dependent alternative splicing of the mRNA, respectively (Hayward-Lester et al., 1996).

Pseudogene

None.

Protein

Translation of alternatively spliced mRNAs:
The alternative use of start codons Met1 and Met123 in the same reading frame generates HLTF proteins of 115 kDa and 110 kDa, respectively (Ding et al., 1996). The rabbit orthologue of human HLTFMet123 is the RUSH-1alpha 113 kDa protein; RUSH-1beta is a 95 kDa truncated version that results from alternative splicing of a 57 bp exon (Chilton et al., 2008). In Hela cells two protein variants resulting from alternative splicing of exon 20 or intron 21 were observed: HLTF1ΔA (83 kDa) and HLTF1ΔB (95 kDa). These proteins have lost domains needed for DNA repair activity (Capouillez et al., 2009).

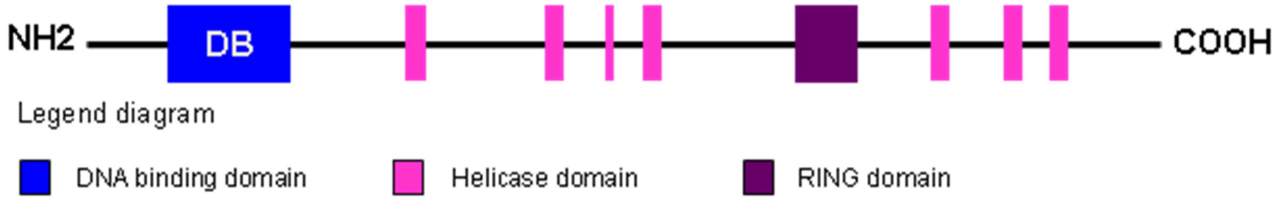


Diagram 1. Graphic representation of HLTF protein with its domains.
Exon/intron structure of the human HLTF gene (upper line, after GenBank no.AJ418064) and domain organisation of the largest encoded protein (lower line after Genbank Z46606) (G. Debauve et al., 2007). The thin tilted lines link the 3' end of each exon to the last amino acid it encodes, except for exons 1 and 25 where they indicate the 1st and last protein residues, respectively. The different protein domains are boxed: DBD (DNA binding domain), HIRAN (Hip116-Rad5 N-terminal domain; Iyer et al., 2006), SNF2_N (SNF2 family N-terminal domain), I to VI (7 helicase domains), RING (zinc finger domain associated with E3 ubiquitin ligase activity).

Description

HLTF belong to the SWI/SNF family of chromatin remodelling enzymes. The protein contains a DNA binding domain, 7 helicase domains and one RING domain (see diagram 1). The HLTF1ΔA variant has lost the RING domain and the last 3 helicase domains. HLTF1ΔB has only lost the last 3 helicase domains (Capouillez et al., 2009). Both proteins are predicted to have lost DNA repair activity.

Expression

Development:

During mouse embryogenesis, Zbu1 (mouse HLTF) transcripts are detected relatively late in foetal development and increase in neonatal stages, whereas the protein accumulates asynchronously in heart, skeletal muscle, and brain. In adult human tissues, alternatively spliced Zbu1 transcripts are ubiquitous with highest expression in the same tissues (Gong et al., 1997).

Expression profile:

Find link to expression profile: HLTF (T1D database)

Transcription regulation:

In the uterus rabbit HLTF expression is repressed by estrogens and induced by progesterone (Hayward-Lester et al., 1996).

The rabbit HLTF (RUSH) promotor has no TATAA box and the transcription start site maps on an initiator/downstream element (Inr-DPE). Two Sp1/Sp3 binding sites in the proximal promoter repress basal transcription. These features are conserved in the human gene promoter. In addition the rabbit HLTF promoter is repressed by NF-Y and HLTF itself and activated by progesterone (Hewetson and Chilton, 2003). In response to progesterone the HLTF (RUSH 1alpha) protein binds to a distal site in the promoter of its own gene and is involved in DNA looping by interaction with Egr-1/c-Rel bound to one of the Sp1/Sp3 sites mentioned above. This interaction represses progesterone induction (Chilton and Hewetson, 2008).

Cancer:

Two lines of evidence have lead to the conclusion that HLTF was a tumor suppressor gene. A first set of publications showed aberrant hypermethylation of the HLTF promoter leading to its silencing in various cancer types. Then two publications demonstrated that the HLTF protein was involved in post replication DNA repair and that its inactivation leads to chromosome rearrangements.

The HLTF promotor is hypermethylated in 43% of primary colon cancer (Moinova et al., 2002) and is frequently methylated in adenomas and hepatocarcinomas. Kim et al. (2006) found that the HLTF inactivation by promoter hypermethylation was associated with the first stages of carcinogenesis. In laryngeal cancer progression the immunolabeling intensity of HLTF decreased with malignancy (Capouillez et al., 2008).

Localisation

Intracellular localisation.

In hypopharynx cancer progression a significant shift of HLTF expression from the cytoplasm toward the nuclear compartment was observed (Capouillez et al., 2008).

Function

DNA-binding protein: HLTF was isolated independently (and given different names) by different groups based on its interaction with different genes (see table below).

Name	Target gene	Reference
HIP116 (human)	HIV promoter; SV40 enhancers	Sheridan et al., 1995
HLTF (human)	PAI-1 promoter	Ding et al., 1996
P113 (mouse)	PAI-1 promoter	Zhang et al., 1996
RUSH (rabbit)	Uteroglobin promoter	Hayward-Lester et al., 1996
Zbu1 (mouse)	Myosin light chain enhancer	Gong et al., 1997
HLTF (human)	B-globin locus control region	Mahajan and Weissman, 2002

Transcriptional activity: the HLTFMet123 variant activates the PAI-1 promoter in synergy with Sp1 or Sp3. This synergy involves protein/protein and protein/DNA interactions (Ding et al., 1996; Ding et al., 1999).

Chromatin remodelling: similarly to other SNF/SWI proteins, HLTF could play a role in chromatin remodelling. It has the 7 helicase domains and presents a DNA-dependent ATPase activity (Sheridan et al., 1995; Hayward-Lester et al., 1996; MacKay et al., 2009).

E3 ubiquitin ligase activity: the RING domain insures protein-protein interactions in E3 ubiquitin ligases. It allows specific targeting of the substrate proteins for transfer of ubiquitin by the associated E2 ubiquitin ligase. The HLTF RING domain is situated between helicase domains III and IV and is strongly conserved in evolution. HLTF and its homologue SHPRH are the functional orthologues of Rad5 in S. cerevisiae, which mediates the polyubiquitination of PCNA lysine 63 when damage is detected on the lagging DNA strand during replication (Unk et al., 2008; Motegi et al., 2008). The HLTF E3 ubiquitin ligase activity was confirmed with a range of E2 ubiquitin ligases (MacKay et al., 2009).

DNA repair: the SNF2 domain is situated between the HLTF DBD and the first helicase domain. It is present in a large variety of proteins implicated in DNA repair, recombination, chromatin remodelling and transcription (Eisen et al., 1995; Linder et al., 2004). In addition, part of the HLTF DNA binding domain is conserved in SWI2/SNF2 proteins such as Rad5p: this domain was named HIRAN based on one of the HLTF alternatives names (HIP116) and the Rad5p N-terminal domain. This domain was predicted to recognize features associated with damaged DNA or stalled replication forks (Iyer et al., 2006). HLTF was indeed recently shown to be involved in post replication DNA repair (Unk et al., 2008; Motegi et al., 2008). HLTF can complement the ultraviolet (UV) sensitivity of rad5- yeast cells, thus strongly supporting a role in postreplication DNA repair (Unk et al., 2008). Hltf-deficient mouse embryonic fibroblasts show elevated chromosome breaks and fusions after methyl methane sulfonate treatment (Motegi et al., 2008). In addition the HLTF protein interacts with PTIP and RPA70, both involved in DNA replication and repair (MacKay et al., 2009).

Isoforms of RUSH (rabbit HLTF) interact with a RING-finger binding protein (RFBP), which is a splice variant of the Type IV P-type ATPase, ATP11B. This protein is a putative phospholipid pump, located in the inner nuclear membrane and the interaction with the HLTF RING domain is conserved in humans (Mansharamani et al., 2001; Hewetson et al., 2008).

Homology

SMARCA3 (chimpanzee: 99%; dog: 93%; cow: 91% identity)

RUSH-1-alpha and RUSH-1-beta (rabbit: 91% and 90% identity)

P113 (rat and mouse: 83% identity)

MGC131155 (Xenopus leavis: 63% identity)

RAD5B (Saccharomyces cerevisiae: 25, 7% identity)

Implicated in

Colorectal cancer

Note

HLTF promoter methylation was initially reported by Moinova et al., 2002 and shown to be linked to transcription inhibition. All the analyzed colon cancer cell lines that lacked HLTF gene expression demonstrated methylation of CpG sites within the putative promoter, identified upstream of the HLTF coding sequence. Such a promoter methylation wasn't detected in the HLTF expressing cell lines. Hibi et al., 2005 also demonstrated that HLTF methylation was aberrant in colorectal cancer without lymph node metastasis. HLTF gene hypermetymation was found in 34% of patients with primary colorectal cancer in another study (Kang et al., 2007).

Prognosis

Hibi and Nakao (2006) demonstrated that colon cancer associated with highly methylated HLTF gene was significantly correlated with a poorly differentiated histology.

Moinova et al., 2002 showed that the HLTF silencing may confer a growth advantage on some colon cancers and that this gene could be considered like a colon cancer tumor suppressor gene.

No difference between adenomas, primary cancers and liver metastases were noticed, even if the HLTF promoter hypermethylation increased drastically between normal colonic tissues and adenomas (Kym et al., 2006).

The hypermethylation of the HLTF promoter could be observed not only in tumor tissue but also in serum and stool samples, using a methylation-specific PCR to detect small quantities of methylated DNA (Leung et al., 2007).

Detection of HLTF promoter hypermethylation in patient sera was significantly associated with tumor size, stage and poor prognosis (Wallner et al., 2006). These authors proposed that the hypermethylation of the HLTF and HPP1/TPEF genes could also be used as independent prognostic serum markers of recurrence after curative surgery (Herbst et al., 2009).

In the azoxymethane colon cancer model in rodents, the HLTF gene was unmethylated in both the tumor and the normal colon mucosa (Borinstein et al., 2009).

A search for epigenetic molecular markers in plasma of patients with colorectal cancer. Using methylation-specific PCR HLTF gene hypermethylation was detected in 32% of patients (Lee et al., 2009).

Gastric carcinoma

Note

The HLTF promoter hypermethylation has been detected in approximately 20-55% of primary gastric cancers (Hibi et al., 2003; Hamai et al., 2003; Kim et al., 2006; Leung et al., 2003; Oue et al., 2006). For patients with family histories HLTF gene silencing is probably an early stage of gastric carcinogenesis. HLTF mRNA expression has been studied in different gastric carcinoma cell lines and Hamai et al., 2003 have shown that the KATO-III cells present loss of HLTF expression associated with its promoter methylation. A chromatin immunoprecipitation assay revealed that the acetylation levels of histones H3 and H4 in the 5' CpG island of the HLTF gene were inversely associated with DNA methylation status. These findings support a model in which methyl-CpG-binding proteins act as anchors on methylated DNA, recruiting accessory proteins, such as HDAC, that contribute to build a repressive chromatin structure.

Esophageal squamous cell carcinoma (ESCC)

Note

The HLTF promoter was found methylated in 1 case out of 40, suggesting that it is not a common target for epigenetic gene silencing in ESCC (Hibi et al., 2003).

Prognosis

This cancer is very aggressive and with a poor prognosis.

Uterine cancer

Note

HLTF promoter hypermethylation was found in 22% of uterine cancers, but it was more frequently methylated in cervical adenocarcinomas (43%) and in endometrial adenocarcinomas. These findings suggest that HLTF promoter hypermethylation may predispose to the development of specific types of human uterine cancer (Kang et al., 2006).

Renal cancer

Note

Experimental model of estrogen-induced carcinogenesis in hamster.

Early overexpression of HLTF in tumor buds (Debauve et al., 2006).

Determination of human iris colour (blue/brown eye colour)

Note

See Sturm et al., 2008 and Sturm et al., 2009.

Disease

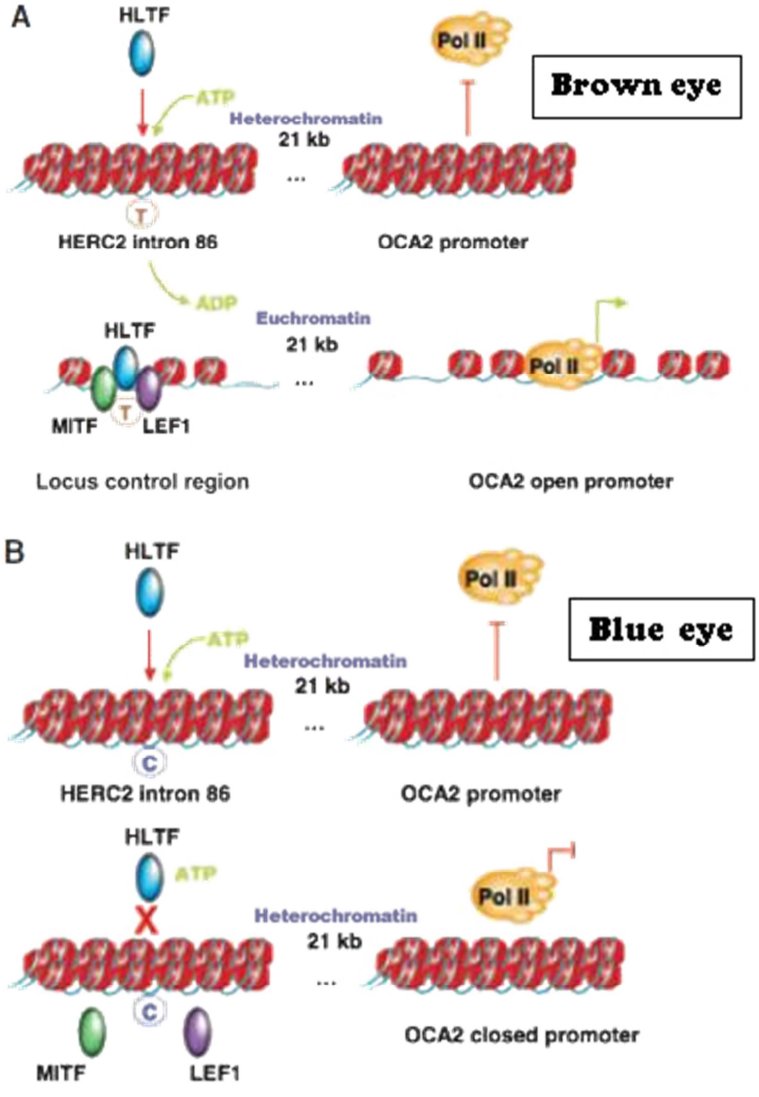
None

Cytogenetics

The identified SNP (rs 12913832 T/C) in the OCA2 intron 86 of the HERC2 locus serve as a target for the SWI/SNF family member HLTF.

Hybrid/Mutated gene

None.



Model for the determination of the blue-brown eye colour based upon regulation of OCA2 gene expression (Sturm et al., 2009).

Abnormal protein
None.

To be noted

Alternative splicing variants: Ref: Capouillez et al., 2009.

	Exons 1 & 2	Exon 20	Intron 21
Met1	+	+	-
Met1 ΔA	+	-	+
Met1 ΔB	+	+	+
Met123	-	+	-
Met123 ΔA	-	-	+
Met123 ΔB	-	+	+

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