# Gene Section
**Review**

# HLTF (helicase-like transcription factor)

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## Abstract

HLTF is a transcription factor - The Helicase-Like Transcription Factor (HLTF/SMARCA3) belongs to the family of SWI/SNF proteins that use the energy of ATP hydrolysis to remodel chromatin in a variety of cellular processes.

Several groups independently isolated HLTF through its capacity to selectively interact with a DNA cis-element in the promoter or enhancer of different genes involved in cardiac development during embryogenesis, cell cycle, collagen biogenesis, cell motility and angiogenesis.

HLTF is a key element in DNA Damage Tolerance pathways - HLTF plays a role in DNA Damage Tolerance, especially in (i) translesion synthesis and (ii) template switching pathways (fork regression and strand invasion).

HLTF is an E3 ubiquitin ligase targeting PCNA (K164) that results in DTT activation.

The E3 ubiquitin ligase, translocase and HIRAN catalytic domain are the HLTF core activities. A key role in DNA repair was confirmed in vivo, in 2 different Hltf null mouse models and showed that Hltf loss compromises error-free DNA replication and modulates mutagenesis by regulating proteins involved in the G2/M phase transition of the cell cycle in mouse heart and brain.

HLTF is a tumor suppressor gene - In cancer, two mechanisms of HLTF inactivation are reported: (i) hypermethylation of its promoter and (ii) expression of truncated protein forms that have lost domains involved in DNA repair.

These data support a role of tumor suppressor gene for HLTF.

The first association between HLTF inactivation and tumorigenesis was shown when hypermethylation of the HLTF promoter was detected in 43% of primary colon tumors and 22-55% of gastric cancers.

Moreover, HLTF deficiency in Apc-/+ mice induced the transition from colon adenocarcinoma to a carcinoma with high chromosomal instability. In head and neck, thyroid and uterus (cervix) cancers, an increased expression of two HLTF protein forms truncated in the carboxyl-terminal domain following alternative mRNA splicing was reported.

These truncated HLTF forms have lost their DNA repair ability and might also have gained functions favouring cancer.

### Keywords

HLTF; Transcription factor; Post-replication DNA Repair; DNA damage tolerance pathways; E3-ubiquitin ligase; Cell Cycle; Cancer; Epigenetics; promoter methylation; Alternative splicing.

## Identity

**HGNC (Hugo):** HLTF

**Location:** 3q24

**Other names:** HIP116, HIP116A, HLTF1, RNF80, SMARCA3, SNF2L3, ZBU1, RUSH
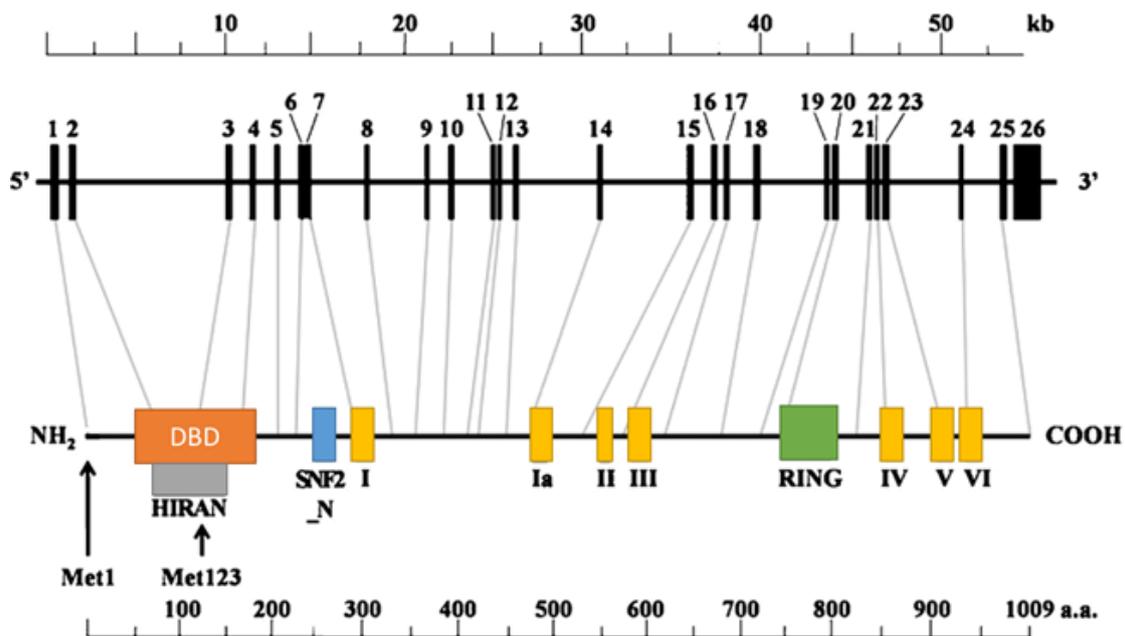
**Figure 1. Graphic representation of HLTF protein with its domains.** Exon/intron structure of the human HLTF gene (upper line, after GenBank no.AJ418064) and domain organisation of the largest encoded protein (lower line after Genbank Z46606) (Debauve et al., 2008). The thin tilted lines link the 3' 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; Lyer 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).

# DNA/RNA

## Description

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

## Transcription

The alternative splicing of intron 25, mapped in the 3'UTR, produces two mRNA of 5.4 and 4.5kb 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).

In the mouse, a transcriptome analysis of the heart and brain revealed the expression of a full-lenght HLTF RNA isoform (exons 1-25) and a spliced isoform (exons 1-21 + intron 21) in a ratio 26 :1 (heart) and 5 :1 (brain) (Helmer et al., 2013 and 2013a).

## Pseudogene

None.

# Protein

**Note**

**Translation of alternatively spliced mRNAs:**
The alternative use of start codons Met1 and

Met123 in the same reading frame generates HLTF proteins of 115kDa and 110kDa, respectively (Ding et al., 1996).

The rabbit orthologue of human HLTFMet123 is the RUSH-1alpha 113kDa protein; RUSH-1beta is a 95kDa truncated version that results from alternative splicing of a 57bp exon (Chilton et al., 2008).

In Hela cells two protein variants resulting from alternative splicing of exon 20 or intron 21 were observed: HLTF1ΔA (83kDa) and HLTF1ΔB (95kDa). These proteins have lost domains needed for DNA repair activity (Capouillez et al., 2009).

## Description

HLTF belong to the SWI/SNF family of chromatin remodelling enzymes.

The protein contains: (a) a HIP116 Rad5p N-terminal (HIRAN) domain embedded in a larger DNA-binding domain, (b) a Sucrose Non-Fermenting 2 (SNF2) amino-terminal dimerization domain, (c) seven conserved DNA helicase/ATPase domains, characteristic of SWI/SNF2 family members and (d) a Really Interesting New Gene (RING) finger domain (Dhont et al., 2015) (see diagram 1). The HLTF1ΔA protein form has lost the RING domain and the last 3 helicase domains. HLTF1ΔB form 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). Sandhu and colleagues built a Hltf -/- mouse by replacing Hltf with LacZ, in order to track Hltf expression during embryogenesis. They found that Hltf was specifically expressed in the heart at an early developmental stage (E8.5 to E9.5). Hltf exhibited a broader expression pattern at E10.5, with LacZ signals detected in somites, branchial arches, limb bud and brain. At later embryonic developmental stages, such as E16.5, Hltf showed wide and strong expression in many tissues, including heart, lung, liver, kidney, spleen and pancreas. This wide-spread expression of Hltf was also observed in adult mice. In both adult intestine and colon, Hltf expression was mainly detected in the crypts and in the intestinal epithelial cells (Sandhu et al., 2012).

**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).

**Protein regulation:**

Kim and colleagues showed that HLTF undergoes a negative regulation by CHFR, a E3 ubiquitin ligase. Both proteins interact in vitro and in vivo and as CHFR levels increase, HLTF levels decrease accordingly. Proteasome inhibitor (MG132) reverts this effect on HLTF stability, suggesting its degradation is mediated by ubiquitin-proteasome system. They also proved that HLTF half-life was shortened in presence of CHFR (Kim et al., 2010).

Qing and colleagues showed that HLTF was positively regulated by USP7, a deubiquitination enzyme, which interacts with HLTF in vitro and in vivo and stabilizes it without any competition with CHFR (Qing et al., 2011).

**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. For a detailed analysis, see Dhont et al., 2015.

## Localisation

Intracellular localisation.

In head and neck, and thyroid 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 (SERPINE1) promoter | Ding et al., 1996 |
| P113 (mouse) | PAI-1 (SERPINE1) 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 SERPINE1 (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).

Two different consensus sequences recognized by HLTF were discovered: (A/G)G(T/C)(G/T)G (Ding

et al., 1996) and (C/A)C(T/A)TN(T/G) (Hayward-Lester et al., 1996). The latter one was used by Genomatix (MatInspector; Cartharius et al., 2005) to develop an algoritm to find putative HLTF binding sites.

HLTF can activate gene transcription either alone or with different protein partners according to the cell type and the target gene (i.e., SP1/ SP3 for SERPINE1 (Ding et al., 1996 and 1999), NONO and SFPQ for PRL (Guillaumond et al., 2011), LEF1 and MITF for OCA2 (Visser et al., 2012)). It binds a promoter (i.e. SERPINE1 or PRL) or an enhancer (i.e., intron 86 of HERC2 for OCA2 expression) and involves a long distance chromatin looping (Visser et al., 2012) for PRL expression (Guillaumond et al., 2011) and its own downregulation mediated by Erg-1 and REL (Hewetson et al., 2008). See also Dhont et al., 2015.

**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. HLTF is 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 PAXIP1 (PTIP) and RPA70,

both involved in DNA replication and repair (MacKay et al., 2009).

When DNA damaged, the replication fork stalls and leads to cell death. DNA damage tolerance pathways are activated through PCNA ubiquitination. RAD6-RAD18 and HLTF control this pathways. HLTF is preferentially recruited when DNA is damaged by UV and inhibits its counterpart SHPRH in that case. However, if DNA is damaged by methyl-methan sulfonate (MMS), HLTF degradation is triggered and SHPRH is activated (Lin et al., 2011). HLTF activates translesion synthesis by monoubiquinating PCNA and by recruiting the error-free DNA polymerase POLH ID: 303> (Polη). HLTF also activates template switching by polyubiquitinating PCNA. Its HIRAN domain is essential in the recognition of stalled DNA replication fork (a 3'-hydroxyl group (3'-OH) on the nascent leading strand, which mimics a site of two unpaired nucleotides) and its restart (Kile et al., 2015), in concert with it helicase domains (Blastyàk et al., 2010). Beside this role, HLTF exhibits an ATP hydrolysis-dependent protein remodeling activity at stalled replication fork: HLTF catalyzes the clearance of roadblocks in replication fork restart (Achar et al., 2011).

HLTF can also promote the intrusion of the newly synthesized strand, stalled by a damage, in the sister chromatid to bypass the lesion (Burkovics et al., 2013). Both RING and helicase domains are critical for this process (Blastyak et al., 2010). Studies on HLTF HIRAN domain revealed how HLTF recognizes a stalled replication fork and restarts it by fork regression (Hishiki et al., 2015; Ikegaya et al., 2015). Stalled replication forks contain a 3'-hydroxyl group (3'-OH) on the nascent leading strand, which mimics a site of two unpaired nucleotides ("lesion"). HLTF specifically recognizes this "lesion" by its HIRAN domain pocket in which (i) the two unpaired nucleotides are stuck between two tyrosines (Y72 and Y93) and (ii) the 3'-OH single DNA (ssDNA) end binds to an aspartate (D94) (Kile et al., 2015; Tsutakawa et al., 2015). Fork reactivation is also promoted via concerted mediation of TP53, POLI (POLɩ), HLTF and ZRANB3 (Hampp et al., 2016).

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*

HLTF promoter methylation is rare in normal colon tissue (3.0-10.2 %). However, it is increased in colon adenoma (25.7-68.5 %) and remains stable or slightly increased in invasive carcinomas (34.3-41.4 %), independently of tumor stage (reviewed in Dhont et al., 2015). Colorectal cancers with a highly methylated panel of genes, including HLTF, are associated with the absence of lymph nodes metastasis and with a poorly differentiated histology (Hibi et al., 2005 and 2006). HLTF promoter hypermethylation alone was significantly less frequent in non-metastatic (Dukes's stages B and C) than in metastatic (Duke's stage D) primary cancers (reviewed in Dhont et al., 2015).

### Prognosis

HLTF promoter hypermethylation alone or with a panel of other genes is an independent pejorative prognostic factor in colorectal cancer, associated with a shorter survival and higher risk of disease recurrence. It also correlated with larger tumor size, higher stage and grade, and metastatic disease (reviewed in Dhont et al., 2015).

## *Gastric carcinoma*

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)*

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*

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).

HLTF immunodetection increased during the oncogenesis in cervical cancer (Capuillez et al., 2011): cervix carcinomas (SCC, AD and AD in situ) exhibited the highest HLTF immunostaining. Truncated protein forms were detected in SCC (no data about AD and AD in situ). No correlation with clinical data was presented in this study. In addition, Cho et al. (2011) showed HLTF overexpression in recurrent cervical carcinoma following radiation treatment compared with patients with former cervical cancer without recurrence; this might confer radiation resistance in cervical cancer, but the HLTF protein form expressed in these cases was not determined. Ye et al. (2015) also showed that HLTF mRNA was a target of MIR145, which is decreased in cervical cancers and is associated with radio-sensitivity. Indeed, MIR145 and HLTF expression levels were inversely correlated in radio-resistant cervical cancers.

### Abnormal protein

In cervix cancer, truncated forms of HLTF proteins were detected. These forms result from an alternative splicing of HLTF mRNA (Exons 19-22).

## *Renal cancer*

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)*

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.

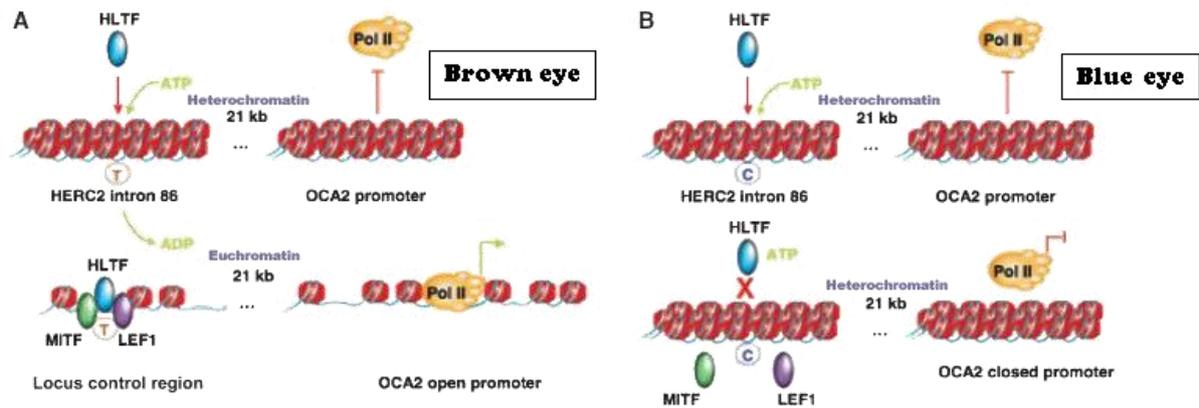### Hybrid/Mutated gene
None

**Figure 2. Model for the determination of the blue-brown eye colour** based upon regulation of OCA2 gene expression (Sturm et al., 2009).

**Abnormal protein**
None

## Head and Neck Cancers

HLTF expression was assessed by immunohistochemistry followed by microscopy computer-assisted quantification and immunodetection on western blots.
In HSCC, HLTF staining increased from tumor-free tissue to carcinoma, associated with a protein shift from the nucleus to the cytoplasm between dyplasias and carcinomas.
In LSCC, HLTF expression decreased from tumor-free tissue to carcinomas, associated with a nucleo-cytoplasmic translocation in dyplasias and carcinomas (Capouillez et al., 2008 and 2009).

**Disease**
Hypopharyngeal (HSCC) and Laryngeal Squamous Cell Carcinoma (LSCC)

**Prognosis**
In HSCC, HLTF detection is an independent prognostic marker of disease recurrence.
In LSCC, there is a trend of a higher risk of recurrence in low-HLTF carcinoma.

**Abnormal protein**
In both HSCC and LSCC, truncated forms of HLTF proteins were detected.
These forms result from an alternative splicing of HLTF mRNA (Exons 19-22).

## Thyroid Cancer

HLTF expression was assessed in two independent cohorts.
In the first cohort (80 patients), HLTF expression was compared among adenoma, papillary carcinoma, follicular carcinoma and anaplastic carcinoma: adenomas presented strong nuclear HLTF immunostaining, whereas carcinomas exhibited HLTF only in the cytoplasm.
In the second cohort (69 patients), benign thyroid lesions (including 10 colloid nodules, 16 follicular adenomas, 7 Hashimoto's thyroiditis, and 7 Grave's disease) and malignant lesions (including 17 papillary carcinomas and 12 follicular variant of papillary carcinomas) were compared.
HLTF staining was strong and primarily located in nuclei in benign lesions, and it was weaker and shifted to the cytoplasm in malignant lesions. Interestingly, thyroid immune diseases (Hashimoto and Graves's diseases) harbored lower HLTF expression within the benign lesion group (Arcolia et al., 2014).

**Disease**
Thyroid adenoma and carcinoma (papillary, follicular, and anaplastic), Hashimoto's thyroiditis and Grave's disease.

**Prognosis**
HLTF was proposed as a biomarker in the differential diagnosis of benign and malignant thyroid lesions.

# To be noted

**Note**
**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| -           | +       | +         |
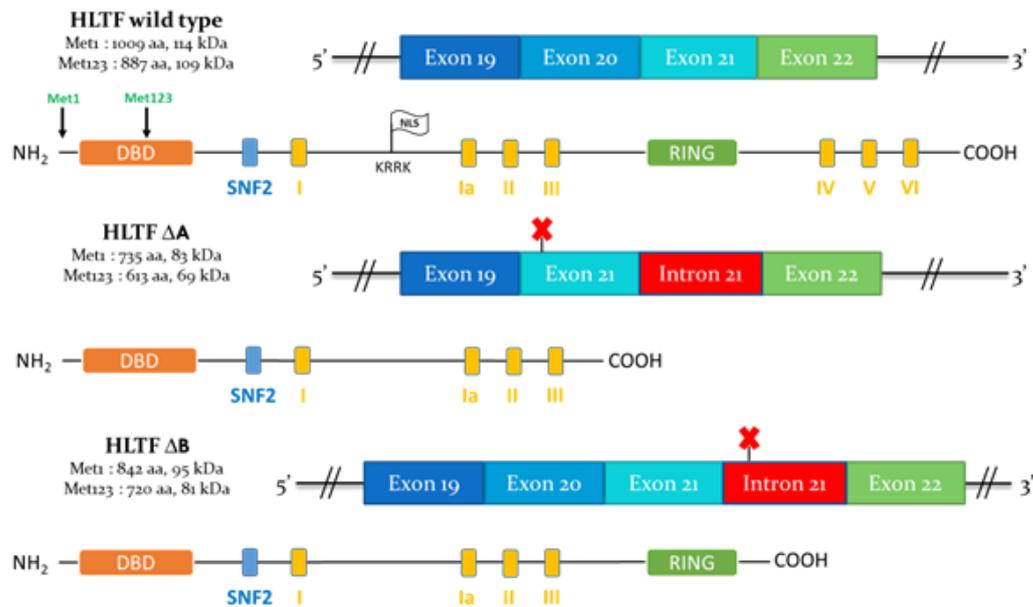
**Figure 3. Alternative splicing and encoded proteins of HLTF.** For each HLTF protein form, the name, number of amino acids and the theoretical molecular weight (kDa) are indicated (left). Met1 is the first methionine, corresponding to the first translation start site, and Met123 is the methionine 123, corresponding to the alternative translation start site (exon 3). The protein domains are indicated as colored boxes. DBD (orange): DNA binding domain. SNF2 (blue): SNF2 domain. Yellow boxes from I to VI: Helicase/ATPase domains. RING (green): RING domain. The white flag "NLS" represents the nuclear localization signal (amino-acids KRRK at position 380 encoded by exons 10-11). Above each protein, the mRNA area of exons 19-22 is represented. This area is subjected to alternative splicing, resulting in protein forms truncated at the carboxyl-terminus. Exons and introns are represented as colored rectangles. The red crosses indicate the early stop codons, resulting from reading frameshifts (Dhont et al., 2015)

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