

Gene Section

Review

HTRA3 (HtrA serine peptidase 3)

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Published in Atlas Database: April 2012

Online updated version : <http://AtlasGeneticsOncology.org/Genes/HTRA3ID45757ch4p16.html>
DOI: 10.4267/2042/47534

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Identity

Other names: Prsp, Tasp

HGNC (Hugo): HTRA3

Location: 4p16.1

Local order: Genes flanking HTRA3 in telomere to centromere direction:

- GMPSP1: guanine monophosphate synthetase pseudogene 1
- SH3TC1: SH3 domain and tetratricopeptide repeats 1
- **HTRA3**
- ACOX3: acyl-CoA oxidase 3
- METTL19: methyltransferase-like 19

Note

Deletions and translocations of the 4p16.1 region are associated with the development of Wolf-Hirschhorn Syndrome (Iwanowski et al., 2011). The neocentromere from a giant supernumerary chromosome in the well-differentiated liposarcoma cell line (94T778) is originated from a region at 4p16.1, which shows high frequency of AT sequences and contains a long interspersed nucleotide element (LINE)1 (Italiano et al., 2009).

DNA/RNA

Description

The HTRA3 gene encompasses 37350 bases of DNA. The coding part is composed of ten exons (Figure 1).

Transcription

Two alternatively spliced variants of HTRA3 mRNA have been sequenced, a long variant, length of 2543 bases, and a short form mRNA, length of 1953 bases (Figure 1).

The long HTRA3 variant has an open frame of 1362 bases and lacks exon 7.

It encodes a 49 kDa protein of 453 amino acid residues. The short form HTRA3 mRNA has an open frame of 1074 bases, and lacks three exons: 8, 9 and 10. It encodes a 38 kDa protein of 357 amino acid residues (Nie et al., 2003).

The 5' promoter region of HTRA3 is methylated in some cases of cervical carcinomas but not in normal cervix tissues (Ongenaert et al., 2008). Expression of HTRA3 is regulated through methylation in the first exon.

This epigenetic modification causes downregulation of HTRA3 expression in human lung cancer cell lines.

Moreover, low levels of HTRA3 expression in primary lung tumors strongly correlate with heavy smoking history (Beleford et al., 2010a). It was also shown that expression of HTRA3 is stimulated through an indirect mechanism involving the MEK/ERK pathway in clear cell renal carcinoma (Theoleyre et al., 2010). However, transcription factors for HTRA3 are unknown.

Pseudogene

No pseudogenes have been identified.

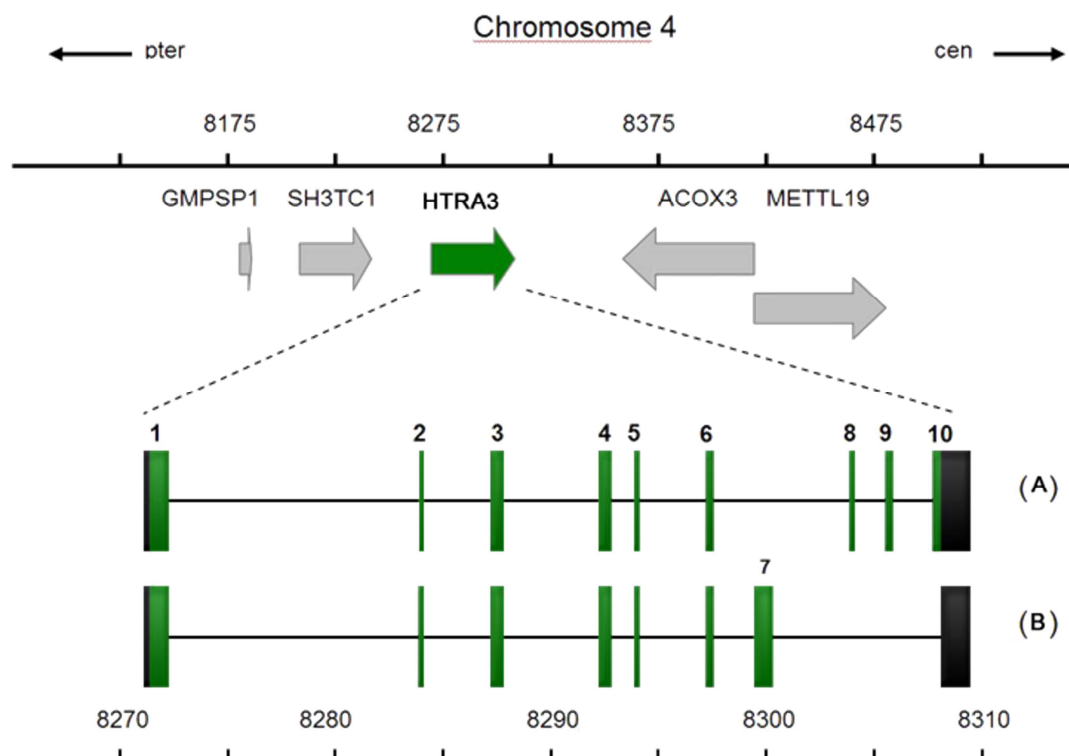


Figure 1. Localization and schematic organization of the HTRA3 gene on chromosome 4. The numbers indicate the length in kilo bases. Green boxes represent exons. Exons present in the long variant of HTRA3 mRNA (A) and in the short form HTRA3 mRNA (B) are shown. Black boxes indicate untranslated regions.

Protein

Note

HtrA3 belongs to the HtrA family of ATP-independent serine proteases, homologues of the HtrA serine protease from the bacterium *Escherichia coli*.

HtrA proteins are very well conserved in evolution. Structurally, they are characterized by the presence of a trypsin-like protease domain with the catalytic triad His-Asp-Ser and at least one PDZ domain at the C-terminal end. General function of the HtrA proteins is the defense against cellular stresses (such as heat shock, oxidative stress) causing aberrations in protein structure. At least, four human HtrA proteins have been identified. They are involved in important physiological processes including maintenance of mitochondrial homeostasis, cell death (apoptosis, necrosis, anoikis) and cell signaling. Disturbances in their functions may contribute to the development of several disorders such as cancer, arthritis and neurodegenerative disorders (reviewed by Chien et al., 2009a; Zurawa-Janicka et al., 2010; Clausen et al., 2011).

Description

The open reading frame (ORF) of the long splice variant of HTRA3 mRNA encodes a polypeptide of 453 aa, mass of approximately 49 kDa. The long isoform of HtrA3 (HtrA3-L) contains a signal secretory peptide at the N-terminus (1-17), a domain with

homology to the insulin-like growth factor binding proteins (29-94 aa) and a Kazal-type inhibitor motif (89-126) followed by a serine protease domain (176-341 aa) with the catalytic triad His191-Asp219-Ser305 and one PDZ domain (384-440 aa) at the C-terminal end.

Domain with homology to the insulin-like growth factor binding proteins and a Kazal-type inhibitor motif shares homology with Mac25 protein.

The PDZ domain mediates specific protein-protein interactions (Figure 2).

The ORF of the short splice variant of HTRA3 mRNA encodes a polypeptide of 357 aa, mass of about 38 kDa. Contrary to HtrA3-L, the short isoform of HtrA3 (HtrA3-S) lacks the PDZ domain. Moreover, the last seven C-terminal residues of HtrA3-S (APSLAVH) are completely different from the corresponding residues in HtrA3-L (DWKKRFI) (Figure 2) (Nie et al., 2003).

Under treatment of lung cancer cell lines with chemotherapeutic agents (cisplatin, etoposide) a removal of the N-terminal Mac25 domain has been observed (Beleford et al., 2010b).

The proteolytic processing is believed to be an autocatalytic process since the catalytically inactive mutant did not undergo such modification. Substitution of the serine residue belonging to the protease catalytic site with alanine abolished autocatalytic degradation (Singh et al., 2012). Solely the structure of PDZ domain of HtrA3 was determined by the X-ray crystallography (Runyon et al., 2008).

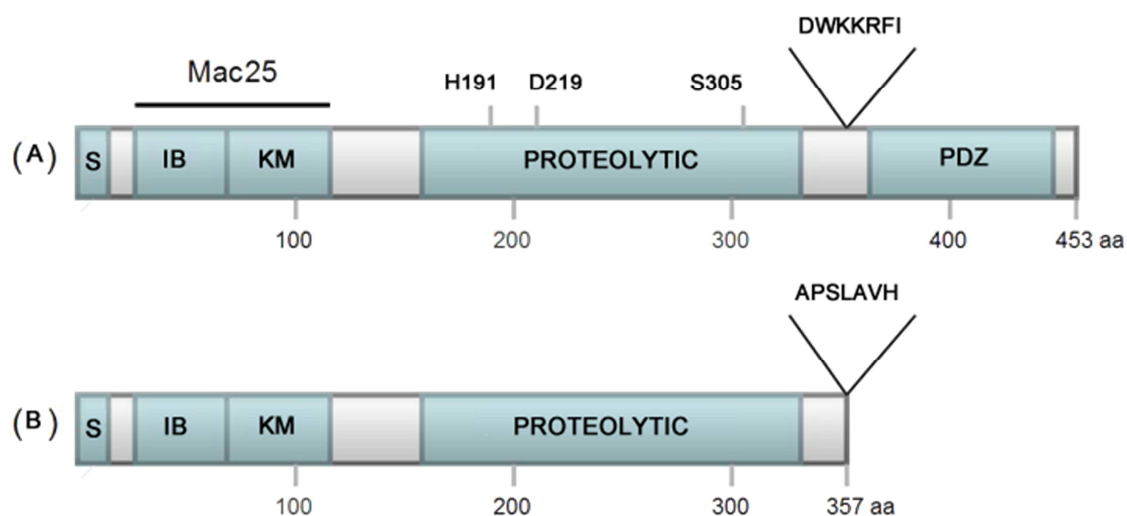


Figure 2. Domain organization of human HtrA3 protein. Schematic organization of the long (A) and short (B) isoform of HtrA3 is presented. S: signal peptide, IB: domain with homology to insulin-like growth factor binding proteins, KM: Kazal type serine protease inhibitor motif, PROTEOLYTIC: trypsin-like domain, PDZ: PDZ domain, DWKKRFI/APSLAVH: amino acid residues different in the HtrA3 variants. The insulin-like growth factor binding domain (IB) and Kazal type inhibitor motif (KM) are homologous to Mac25 protein. Amino acid residues of the HtrA3 catalytic triad are marked (numbers indicate the position of the given residue in a polypeptide chain).

The Myosin-9 was identified as a first endogenous binding protein of HtrA3 in the placenta (Singh et al., 2012).

Expression

Both variants of HTRA3 transcripts are widely expressed in the human body with variable levels in different organs (Nie et al., 2003). Reciprocal ratio of the long HTRA3 mRNA to short HTRA3 mRNA is dependent on the type of tissue. The highest expression of HTRA3 was observed in heart tissues and reproductive organs (ovary, uterus and placenta) (Nie et al., 2003).

HTRA3 is expressed predominantly in the glandular epithelium, endometrium and decidual cells during preparation of endometrium for embryo implantation in the early pregnancy. The maximal expression of placental HTRA3 is observed during the first trimester and then it decreases dramatically (Nie et al., 2005; Nie et al., 2006a; Li et al., 2011). Placental HtrA3 expression is negatively regulated through oxygen tension in the placenta (Li et al., 2011). It was clearly demonstrated that expression of HTRA3 is up-regulated during folliculogenesis and luteinisation in the rhesus monkey ovary (Bowden et al., 2008). These data indicate an important role of HTRA3 in placenta development and function.

Transcription of HTRA3 gene is stimulated through an indirect mechanism involving the MEK/ERK pathway in clear cell renal carcinoma (Theoleyre et al., 2010). In vitro transcriptional studies revealed that infection of chicken chondrocytes by bacterium *Mycoplasma synoviae* up-regulates of HTRA3 gene as an apoptosis-like event (Dusanic et al., 2012).

Beleford with co-workers showed that expression of HTRA3 is silenced by cigarette smoke-mediated

methylation in lung tumors. This epigenetic modification increased the resistance of lung cancer cell lines to etoposide- and cisplatin-induced cytotoxicity (Beleford et al., 2010a). These results suggest that cigarette smoke-induced down-regulation of HTRA3 could contribute to the development of chemoresistant lung cancer.

Localisation

HtrA3 is a nuclear-encoded mitochondrial protease (Chien et al., 2009b). Localisation of HtrA3 in the mitochondrion depends on the presence of Mac25 domain and is regulated by protease function of HtrA3 (Beleford et al., 2010b). Processed forms of HtrA3 have been also found in the cytoplasm (Beleford et al., 2010b). However, HtrA3 is also classified as a secreted protein (Nie et al., 2003).

Function

HTRA3 functions as an ATP-independent serine protease.

HtrA3 has been shown to act as an inhibitor of TGF-beta signaling. HtrA3 binds to several members of the TGF-beta proteins family, including BMP4, TGF-beta1, TGF-beta2, GDF5, and suppresses signal transduction mediated by these extracellular cytokines (Tocharus et al., 2004). The proteolytic activity of HtrA3 is indispensable for this inhibitory function (Tocharus et al., 2004).

HtrA3 plays a significant role during embryo implantation and formation of placenta in mammals in the early stage of pregnancy (Nie et al., 2005; Nie et al., 2006a; Nie et al., 2006b; Bowden et al., 2008). Placental HtrA3 is secreted into the maternal circulation and distinctly detectable in serum of pregnant women in the first trimester (Nie et al.,

2006a). At this stage of pregnancy cellular and serum level of HtrA3 is the highest and then HtrA3 level is dramatically down-regulated by an increase of placental oxygen tension at 13-14 week of pregnancy (Li et al., 2011). HtrA3, due to its proteolytic activity, negatively regulates trophoblast invasion during placental development (Singh et al., 2010; Singh et al., 2011).

HtrA3 is involved in the programmed cell death, apoptosis. It has been demonstrated that stable small hairpin RNA- and epigenetic-mediated down-regulation of HTRA3 expression attenuates cisplatin- and etoposide-induced cytotoxicity in lung cancer cell lines while HTRA3 re-expression of proteolytic active HtrA3 promotes etoposide and cisplatin cytotoxicity (Beleford et al., 2010a, Beleford et al., 2010b).

Homology

The HtrA3 protein is evolutionarily conserved among mammalian species.

At the amino acid level homology between human HtrA3 and its orthologs from rat and mouse reaches 92,3 and 92,7 %, respectively.

At least three paralogs of human HtrA3 have been identified: HtrA1 (L56, ORF480, PRSS11, ARMD7), HtrA2 (Omi) and HtrA4. HtrA3 shares the 76, 74 and 72 % homology with HtrA1, HtrA2 and HtrA4, respectively. The identity between HtrA3 and its paralogs reaches 59, 52 and 53 %, respectively.

Mutations

Germinal

Not known.

Somatic

Not known.

Implicated in

Various cancers

Note

Expression of HTRA3 varies according to the tumor type. The variable expression of HTRA3 is manifested in hematologic malignancies and depends on specific molecular alterations. For instance, expression of HTRA3 is up-regulated in pro-B Acute Lymphoblastic Leukemia with hyperploidy but down-regulated in B-cell Acute Lymphoblastic Leukemia and acute myeloid leukemia (reviewed by Chien et al., 2009a). HTRA3 is up-regulated in esophageal adenocarcinoma (Hao et al., 2006), pancreatic adenocarcinoma (Iacobuzio-Donahue et al., 2003) and seminoma (Korkola et al., 2006). In contrast, its diminished expression was observed in ovarian (Narkiewicz et al., 2008), endometrial (Bowden et al., 2006; Narkiewicz et al., 2009) and lung cancers (Beleford et al., 2010a; Beleford et al., 2010b). In endometrial cancer the HTRA3 mRNA and protein levels were reduced with the increasing tumor staging.

Moreover, a significant negative correlation between HtrA3 and TGF-beta1 protein levels found in endometrial cancer suggests that HtrA3 is involved in regulation of the TGF-beta1 signaling pathway in this type of cancer (Narkiewicz et al., 2009).

It was demonstrated that HtrA3 is involved in the induction of apoptosis in response to cytotoxic stress induced by chemotherapeutic agents in lung cancer cell lines (Beleford et al., 2010b). Resistance of cancer cells to cisplatin- and etoposide-mediated cytotoxicity is suggested to be a consequence of disturbances in the HtrA3 pro-apoptotic activity (Beleford et al., 2010b).

Oncogenesis

Several studies argue the involvement of HtrA3 in oncogenesis. HtrA3 acts as a proapoptotic protein and is suggested to function as a tumor suppressor (Beleford et al., 2010a; Beleford et al., 2010b). However, variable expression of HTRA3 depending on cancer type makes unambiguous definition of the HtrA3 role in carcinogenesis difficult.

HtrA3 involvement in regulation of TGF-beta signaling (Tocharus et al., 2004) forms another link between HtrA3 and carcinogenesis. At early stages of tumorigenesis, TGF- β proteins act as tumor suppressors, inhibiting tumor outgrowth, but in advanced phases they stimulate tumor progression, invasion and metastasis.

Preeclampsia

Note

Li et al. (2011) showed that placental HtrA3 level and secretion of the protein into the maternal circulation is regulated by oxygen tension in the placental tissue.

Abnormally high level of HtrA3 in the maternal serum at the 13-14 week of gestation is associated with the development of preeclampsia (Li et al., 2011).

Disease

Preeclampsia is a severe disorder of human pregnancy. It is a multifactorial disease characterized by hypertension with proteinuria and is responsible for about 18% of maternal deaths and up to 40% of fetal mortality.

Every year, 8,5 millions cases of preeclampsia are reported.

Defective remodeling of the maternal vessels in the early stage of pregnancy is recognized as important factors in the initiation of the disorder (Anderson et al., 2012; Mary et al., 2012).

Breakpoints

Note

No breakpoints described so far.

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This article should be referenced as such:

Glaza P, Zurawa-Janicka D, Lipinska B. HTRA3 (HtrA serine peptidase 3). *Atlas Genet Cytogenet Oncol Haematol*. 2012; 16(9):644-648.
