LATS1 (LATS, large tumor suppressor, homolog 1 (Drosophila))

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Published in Atlas Database: May 2009
Online updated version: http://AtlasGeneticsOncology.org/Genes/LATS1ID41127ch6q25.html
DOI: 10.4267/2042/44735

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Identity

Other names: EC 2.7.11.1; WARTS; h-warts; wts
HGNC (Hugo): LATS1
Location: 6q25.1
Local order: KATNA1 - LATS1 - LOC645967 - NUP43

DNA/RNA

Description
The LATS1 gene contains 8 exons, ranging in size from 106 bp to 1513 bp. The mRNA transcript spans 4756 bp.

Transcription
An alternatively spliced variant was identified in vertebrate retina and testis. This smaller variant has deletions of exon 6, 7, and 8. The functional significance of this splice variant is not known.

Protein

Description
LATS1 is a highly conserved Ser/Thr kinase that belongs to the AGC (Protein kinase A/G/C) family of protein kinases. Within the C-terminal kinase domain lie two conserved residues, Ser909 and Thr1079, which are phosphorylated upon activation. The N-terminus of LATS1 contains two PPxY motifs, which bind to WW-domain transcriptional co-activators TAZ and YAP, as well as a protein binding domain (PBD) that has been shown to bind to MOB1 and cytoskeletal proteins LIMK1 and Zyxin. In addition, an ubiquitin binding domain (UBA) and a proline-rich region (P-stretch) have been identified in the N-terminal region of LATS1, although the functional significance of these domains has not yet been determined.

Expression
LATS1 is ubiquitously expressed.

Localisation
LATS1 is primarily localized within the cytoplasm. However, LATS1 possesses functions that require its translocation to the nucleus. The mechanism of translocation is not yet understood.

Function
As a tumor suppressor, LATS1 functions as a key regulator of cell cycle progression, apoptosis, and cell migration. As cell cycle regulator, LATS1 is able to modulate multiple aspects of the cell cycle, including G2/M arrest, mitotic exit, activation of
the G1 tetraploidy checkpoint, and regulation of cytokinesis. LATS1 also promotes apoptosis by inducing expression of pro-apoptotic proteins BAX, caspase 3 and tumor suppressor p53. Finally, loss of LATS1 has been shown to enhance the rate of cell migration.

**HIPPO-LATS Signaling Pathway:** LATS1 is a key player in the conserved Hippo-LATS signaling pathway. Components of this pathway include the adaptor proteins WW45 and MOB, which aid in bringing LATS in contact with the kinase MST1/ MST2. MST1/2 can then phosphorylate and activate LATS1. Upstream of MST1/2 lay FERM domain proteins Willin/FRMD6 and Merlin/NF2, as well as a protocadherin FAT4. The molecular mechanisms regulating this pathway have not yet been delineated in a mammalian system. Down-stream of LATS1 lay two transcriptional co-activators, YAP and TAZ, which are phosphoryla-ted and inhibited by LATS1, thereby sequestering them in the cytoplasm. Finally, YAP and TAZ have been shown to act through the TEAD/TEF family of transcription factors to modulate the expression of a variety of genes (See figure below). Function-ally, the Hippo-LATS pathway has been implicated in cell proliferation, apoptosis, the epithelial mesenchymal transition, and cell migration.

**Homology**
The LATS1 kinase domain is conserved across species. Human homologs include LATS2 and the nuclear Dbf2-related kinases, NDR1 and NDR2.

**Mutations**

**Note**
There have been no reports of mutations in LATS1.

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<th><strong>Implicated in</strong></th>
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<td><strong>Cancers</strong></td>
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**Disease**
There is increasing evidence that LATS1 is downregulated in a variety of human tumor types. To date, loss of LATS1 has been found in soft tissue sarcomas, particularly myxoid liposarcoma, leiomyosarcoma, and malignant fibrous histocyto-mas, as well as ovarian cancer, breast cancer, acute lymphoblastic leukemia, and astrocytoma. Prima-rily downregulation of LATS1 expression is due to hypermethylation of the promoter region.

**Prognosis**
Decreased LATS1 expression in breast cancer is associated with large tumor size, high lymph node metastasis, and estrogen and progesterone nega-tivity. Thus, loss of LATS1 is associated with poor prognosis in breast cancer. Furthermore, loss of LATS1 expression, in addition to other genes, can be used as a prognostic factor in predicting disease-free survival for acute lymphoblastic leukemia.

**References**


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Lei QY, Zhang H, Zhao B, Zha ZY, Bai F, Pei XH, Zhao S, Xiong Y, Guan KL. TAZ promotes cell proliferation and epithelial-mesenchymal transition and is inhibited by the hippo pathway. Mol Cell Biol. 2008 Apr;28(7):2426-36


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