Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section

Review

LZTS1 (leucine zipper, putative tumor suppressor 1)

Andrea Vecchione, Luca Lavra, Carlo M Croce

Department of Molecular Virology, Immunology and Medical Genetics and Comprehensive Cancer Center, Ohio State University, OH, USA; Division of Pathology and Medical Oncology, Department of Clinical and Molecular Medicine, Faculty of Medicine and Psychology, University "Sapienza", Santo Andrea Hospital, Rome, Italy (AV), Division of Pathology and Medical Oncology, Department of Clinical and Molecular Medicine, Faculty of Medicine and Psychology, University "Sapienza", Santo Andrea Hospital, Rome, Italy (LL), Department of Molecular Virology, Immunology and Medical Genetics and Comprehensive Cancer Center, Ohio State University, OH, USA (CMC)

Published in Atlas Database: June 2012

Online updated version : http://AtlasGeneticsOncology.org/Genes/LZTS1ID367ch8p21.html
DOI: 10.4267/2042/48360

Identity

Other names: F37, FEZ1

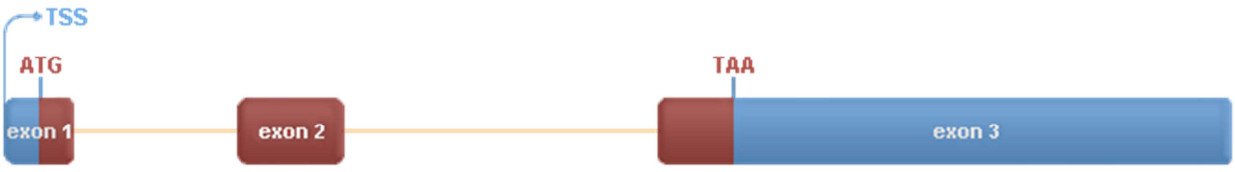
HGNC (Hugo): LZTS1

Location: 8p21.3

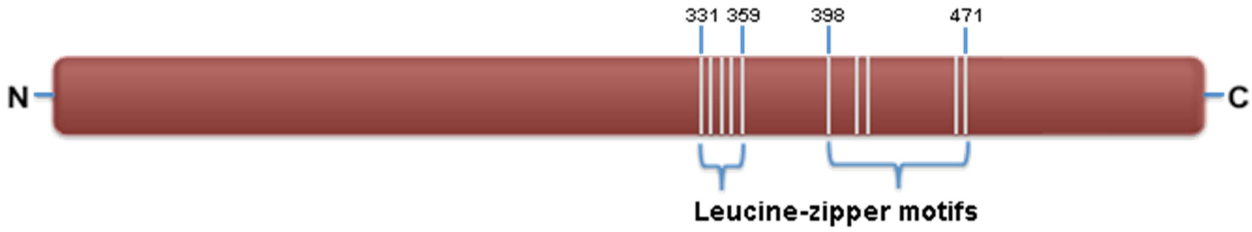
Local order: According to the NCBI map viewer, genes flanking LZTS1 from centromere to telomere are:
- CLU (8p21-p12): clusterin
- PTK2B (8p21.1): protein tyrosine kinase 2 beta
- LPL (8p22): lipoprotein lipase
- NAT2 (8p22): N-acetyltransferase 2 (arylamine N-acetyltransferase)
- CTSB (8p22): cathepsin B
- ANGPT2 (8p23.1): angiopoietin 2.

Note

The human LZTS1 gene maps on chromosome 8p22 and encodes a leucin zipper protein with a region homologue to cAMP-responsive transcription factor Atf-5, and with different potential phosphorylation sites. It is ubiquitously expressed in normal human tissues and is implicated in cell cycle control by modulating the activity of the Cdk1/cyclin B1 complex. LZTS1 chromosomal locus is frequently deleted in tumors (Ishii et al., 1999) and LZTS1 gene and protein expression is reduced or lost in different human malignancies. The reintroduction of LZTS1 expression into LZTS1 null cancer cell lines suppresses cell growth at the G2/M phase of the cell cycle and inhibits migration and invasion. In conclusion, LZTS1 loss is involved in the neoplastic transformation of different types of tumors indicating that LZTS1 can be considered an important tumor suppressor gene and a potential diagnostic and therapeutic target (Ishii et al., 2001; Vecchione et al., 2002; Vecchione et al., 2007a).



Genomic structure of the human LZTS1 gene.



Schematic representation of LZTS1 protein. The leucine residues position of leucine-zipper motifs are indicated by the gray bars.

DNA/RNA

Note

NC_000008.10: 20103676 - 20112803 bp (Entrez-Gene).

Description

According to Entrez-Gene, LZTS1 gene extends over 9 kb (9128 bases) and consists of 3 exons.

Transcription

mRNA size: 5459 bp (NM_021020.2); open reading frame: 1791 bp (NP_066300.1).

LZTS1 mRNA is highly expressed in testis, prostate, spleen, thymus, ovary and brain. It has been detected at lower levels in heart, placenta, small intestine, colon, liver, kidney, skeletal muscle and pancreas. LZTS1 gene is not expressed in primary tumors from breast and prostate and in different cancer cell lines (Ishii et al., 1999).

Pseudogene

No LZTS1 pseudogenes have been reported.

Protein

Description

LZTS1 gene encodes a 596-aa protein of 67 kDa. The protein contains two leucine-zipper motifs, multiple potential phosphorylation sites for different kinases (e.g. PKA, CDC2 and PKC) and a domain with 32% identity to the DNA binding domain of the cAMP-responsive transcription factor Atf5. LZTS1 lacks the DNA recognition domain usually found in transcription factors carrying a leucine-zipper motive (Ishii et al., 1999; Ishii et al., 2001; Vecchione et al., 2007b).

Expression

LZTS1 is ubiquitously expressed in all normal human tissues. LZTS1 protein expression is lost or reduced in different primary tumors.

Localisation

Main sub-cellular localizations: plasma membrane and cytoplasm.

Additional localizations: nucleoli (observed in U2-OS cells) and Golgi apparatus (observed in A-431 cells) (Barbe et al., 2008).

Function

Cell cycle regulation. It has been demonstrated that Lzts1$^{-/-}$ mouse embryonic fibroblasts (MEF) have a faster M phase, associated with a lower cyclin B1/Cdk1 activity. During prophase the interaction between LZTS1 and Cdc25C, a phosphatase implicated in regulation of Cdk1 activity, allows the expression of high levels of Cdc25C and enhances its activity, resulting in normal progression from prophase to metaphase.

In Lzts1 deficient cells during prophase Cdc25C is rapidly ubiquitinated and degraded, thus determining a lower activity of the cyclin B1/Cdk1 complex. This results in a faster cellular progression through prophase and prometaphase and, frequently, in chromosome missegregation (Vecchione et al., 2007b).

Homology

The LZTS1 gene is conserved in the organisms listed below:

- Pan troglodytes (LZTS1) (Gene ID: 464034)
- Macaca mulatta (LZTS1) (Gene ID: 705724)
- Mus musculus (Lzts1) (Gene ID: 211134)
- Rattus norvegicus (Lzts1) (Gene ID: 266711)
- Bos taurus (LZTS1) (Gene ID: 539634)
- Equus caballus (LZTS1) (Gene ID: 100053630)
- Canis lupus familiaris (LZTS1) (Gene ID: 486136)
- Monodelphis domestica (LZTS1) (Gene ID: 100030407)
- Ornithorhynchus anatinus (LZTS1) (Gene ID: 100073437)
- Gallus gallus (LZTS1) (Gene ID: 431331)
- Danio rerio (si:dkey-63d15.13) (Gene ID: 569281).

Mutations

Note

Sequence analysis of LZTS1 ORF, performed in different type of cancers revealed the presence of the somatic point mutations listed hereinafter (Vecchione et al., 2001; Knowles et al., 2005):

- S29P: (TCC->CCC) reported in a primary esophageal tumor
- K119E: (AAG->GAG) reported in a primary esophageal tumor
- Q501Stop: (CAG->TAG) reported in PC3 (prostate cancer cell line)

- H17R: (CAC->CGC) reported in a diffuse-type gastric carcinoma
- L113P: (CTA->CCA) reported in a bladder tumor sample
- G374S: (GGC->AGC) reported in A1698 (bladder cancer cell line)
- L475V: (CTG->GTG) reported in SCaBER (bladder cancer cell line).

Internally truncated transcripts described in different cancers (Ishii et al., 1999):
- Frameshift deletion 1546-1542 (exons affected: 1,2,3) reported in esophagus cancer
- In-frame deletion 558-1715 (exons affected: 2,3) reported in esophagus cancer
- In-frame deletion 1366-1641 (exon affected: 3) reported in prostate cancer
- In-frame deletion 1402-1578 (exon affected: 3) reported in esophagus and prostate cancer and in acute lymphoblastic leukemia
- In-frame deletion 1417-1515 (exon affected: 3) reported in melanoma
- In-frame deletion 1516-1584 (exon affected: 3) reported in melanoma.

A detailed DNA sequence analysis of LZTS1 gene performed in germline DNA extracted from a screening panel of sporadic and hereditary prostate cancers revealed the presence of 24 SNP. The four SNP listed below have a statistically significant association with sporadic prostate cancer (Hawkins et al., 2002):
- A allele of WF101-010 (2812G → A)
- C allele of WF101-012 (2883T → C)
- C allele of WF101-031 (3329C → T)
- G allele of WF101-014 (4361C → T).

Implicated in

Prostate cancer

Note

The DNA sequence analysis of LZTS1 performed on sporadic and hereditary prostate cancer (HPC) samples and unaffected controls revealed the presence of several SNPs associated with prostate cancer (Hawkins et al., 2002). Over-expression of LZTS1 cDNA modulates colony-forming efficiency and proliferation in different prostate cancer cell lines (Cabeza-Arvelaiz et al., 2001).

Ovarian cancer

Note

An immunohistochemical analysis of LZTS1 protein expression performed in ovarian carcinomas tissue samples demonstrated that cytoplasmic staining for FEZ1 protein was absent or drastically reduced in 38% of cases (Califano et al., 2010). In addition, homozygous deletions at LZTS1 locus has been detected in advanced ovarian clear cell carcinomas (Kuo et al., 2010).

Oral squamous cell carcinoma

Note

Reduced LZTS1 gene expression has been reported in 35% of oral squamous cell carcinoma (SSC) samples and in oral SSC-derived cell lines (Ono et al., 2003).

Uveal melanoma

Note

A gene expression profiling performed on 53 primary uveal melanomas by array-based comparative genomic hybridization demonstrated that LZTS1 expression was reduced in rapidly metastasizing and metastatic uveal melanomas but not in slowly metastasizing and non metastasizing uveal melanomas.

Moreover overexpression of LZTS1 in metastasizing uveal melanoma-derived cells inhibited their motility and invasion (Onken et al., 2008).

Lung carcinoma

Note

The immunohistochemical analysis of LZTS1 expression in 103 primary lung cancer specimens demonstrated absence or strong reduction in respectively in more that 42% of cases. A positive correlation between loss of LZTS1 and tumor grading, and between strong LZTS1 expression and mortality rate reduction was also observed (Nonaka et al., 2005). Moreover reduced LZTS1 expression was also detected in several lung cancer derived cell lines (Toyooka et al., 2002).

Gastric carcinoma

Note

The immunohistochemical analysis of LZTS1 expression, performed in 88 gastric cancer specimens demonstrated that it is lost or significantly reduced in more than 44% of cases. In addition, DNA allelotyping analysis at the LZTS1 locus showed LOH and microsatellite instability respectively in 18% and 23,5% of cases (Vecchione et al., 2001).

Breast carcinoma

Note

LZTS1 gene expression was reduced in breast primary tumors and breast cancer cell lines. The immunohistochemical analysis of LZTS1 expression demonstrated that LZTS1 was absent or down-regulated in primary breast carcinomas compared with normal breast. Moreover, reduced LZTS1 expression was significantly correlated with high histologic grade, lymph node metastasis, and poor prognosis. In addition, DNA methylation analysis demonstrated that LZTS1 loss of expression in breast tumors is correlated with gene methylation. Moreover, overexpression of LZTS1 in breast cancer cell lines inhibits cell proliferation, migration and invasion, and induces morphological and molecular changes characteristic of mesenchymal-to-epithelial transition (Chen et al., 2009; Wang et al., 2011).

Bladder cancer

Note

LZTS1 protein expression is reduced in bladder tumor samples and bladder cancer derived cell lines. Reintroduction of LZTS1 expression in TCC derived cell line inhibited cell growth, altered cell cycle progression and suppressed subcutaneous tumor growth in nude mice. Several LZTS1 somatic point mutations have also been reported in bladder cancers tissues and cell lines (Vecchione et al., 2002; Knowles et al., 2005). Moreover, it has been demonstrated by treating heterozygous and nullizygous Lzts1 mice with a classical bladder carcinogen (N-butyl-N-(4-hydroxybutil) nitrosamine, BBN), that the loss of one or both Lzts1 alleles favored development of bladder cancer. These results demonstrated that LZTS1 could represent an important therapeutic target for bladder tumor treatment.

References

Ishii H, Baffa R, Numata SI, Murakumo Y, Rattan S, Inoue H, Mori M, Fidanza V, Alder H, Croce CM. The FEZ1 gene at chromosome 8p22 encodes a leucine-zipper protein, and its expression is altered in multiple human tumors. Proc Natl Acad Sci U S A. 1999 Mar 30;96(7):3928-33

Cabeza-Arvelaiz Y, Sepulveda JL, Lebovitz RM, Thompson TC, Chinault AC. Functional identification of LZTS1 as a candidate prostate tumor suppressor gene on human chromosome 8p22. Oncogene. 2001 Jul 12;20(31):4169-79

Ishii H, Vecchione A, Murakumo Y, Baldassarre G, Numata S, Trapasso F, Alder H, Baffa R, Croce CM. FEZ1/LZTS1 gene at 8p22 suppresses cancer cell growth and regulates mitosis. Proc Natl Acad Sci U S A. 2001 Aug 28;98(18):10374-9

Vecchione A, Ishii H, Shiao YH, Trapasso F, Rugge M, Tamburrino JF, Murakumo Y, Alder H, Croce CM, Baffa R. Fez1/lzts1 alterations in gastric carcinoma. Clin Cancer Res. 2001 Jun;7(6):1546-52

Hawkins GA, Mychaleckyj JC, Zheng SL, Faith DA, Kelly B, Isaacs SD, Wiley KE, Chang BL, Ewing CM, Bujnovszky P, Bleecker ER, Walsh PC, Meyers DA, Isaacs WB, Xu J. Germline sequence variants of the LZTS1 gene are associated with prostate cancer risk. Cancer Genet Cytogenet. 2002 Aug;137(1):1-7

Toyooka S, Fukuyama Y, Wistuba II, Tockman MS, Minna JD, Gazdar AF. Differential expression of FEZ1/LZTS1 gene in lung cancers and their cell cultures. Clin Cancer Res. 2002 Jul;8(7):2292-7

Vecchione A, Ishii H, Baldassarre G, Bassi P, Trapasso F, Alder H, Pagano F, Gomella LG, Croce CM, Baffa R. FEZ1/LZTS1 is down-regulated in high-grade bladder cancer, and its restoration suppresses tumorigenicity in transitional cell carcinoma cells. Am J Pathol. 2002 Apr;160(4):1345-52

Ono K, Uzawa K, Nakatsuru M, Shiiba M, Mochida Y, Tada A, Bukawa H, Miyakawa A, Yokoe H, Tanzawa H. Down-regulation of FEZ1/LZTS1 gene with frequent loss of heterozygosity in oral squamous cell carcinomas. Int J Oncol. 2003 Aug;23(2):297-302

Knowles MA, Aveyard JS, Taylor CF, Harnden P, Bass S. Mutation analysis of the 8p candidate tumour suppressor genes DBC2 (RHOBTB2) and LZTS1 in bladder cancer. Cancer Lett. 2005 Jul 8;225(1):121-30

Nonaka D, Fabbri A, Roz L, Mariani L, Vecchione A, Moore GW, Tavecchio L, Croce CM, Sozzi G. Reduced FEZ1/LZTS1 expression and outcome prediction in lung cancer. Cancer Res. 2005 Feb 15;65(4):1207-12

Baldassarre G, Croce CM, Vecchione A. Take your "M" time. Cell Cycle. 2007 Sep 1;6(17):2087-90

Vecchione A, Baldassarre G, Ishii H, Nicoloso MS, Belletti B, Petrocca F, Zanesi N, Fong LY, Battista S, Guarnieri D, Baffa R, Alder H, Farber JL, Donovan PJ, Croce CM. Fez1/Lzts1 absence impairs Cdk1/Cdc25C interaction during mitosis and predisposes mice to cancer development. Cancer Cell. 2007a Mar;11(3):275-89

Vecchione A, Croce CM, Baldassarre G. Fez1/Lzts1 a new mitotic regulator implicated in cancer development. Cell Div. 2007b Aug 24;2:24

Baffa R, Fassan M, Sevignani C, Vecchione A, Ishii H, Giarnieri E, Iozzo RV, Gomella LG, Croce CM. Fez1/Lzts1-deficient mice are more susceptible to N-butyl-N-(4-hydroxybutil) nitrosamine (BBN) carcinogenesis. Carcinogenesis. 2008 Apr;29(4):846-8

Barbe L, Lundberg E, Oksvold P, Stenius A, Lewin E, Björling E, Asplund A, Pontén F, Brismar H, Uhlén M, Andersson-Svahn H. Toward a confocal subcellular atlas of the human proteome. Mol Cell Proteomics. 2008 Mar;7(3):499-508

Onken MD, Worley LA, Harbour JW. A metastasis modifier locus on human chromosome 8p in uveal melanoma identified by integrative genomic analysis. Clin Cancer Res. 2008 Jun 15;14(12):3737-45

Chen L, Zhu Z, Sun X, Dong XY, Wei J, Gu F, Sun YL, Zhou J, Dong JT, Fu L. Down-regulation of tumor suppressor gene FEZ1/LZTS1 in breast carcinoma involves promoter methylation and associates with metastasis. Breast Cancer Res Treat. 2009 Aug;116(3):471-8

Califano D, Pignata S, Pisano C, Greggi S, Laurelli G, Losito NS, Ottaiano A, Gallipoli A, Pasquinelli R, De Simone V, Cirombella R, Fusco A, Chiappetta G. FEZ1/LZTS1 protein expression in ovarian cancer. J Cell Physiol. 2010 Feb;222(2):382-6

Kuo KT, Mao TL, Chen X, Feng Y, Nakayama K, Wang Y, Glas R, Ma MJ, Kurman RJ, Shih IeM, Wang TL. DNA copy numbers profiles in affinity-purified ovarian clear cell carcinoma. Clin Cancer Res. 2010 Apr 1;16(7):1997-2008

Wang XX, Zhu Z, Su D, Lei T, Wu X, Fan Y, Li X, Zhao J, Fu L, Dong JT, Fu L. Down-regulation of leucine zipper putative tumor suppressor 1 is associated with poor prognosis, increased cell motility and invasion, and epithelial-to-mesenchymal transition characteristics in human breast carcinoma. Hum Pathol. 2011 Oct;42(10):1410-9

This article should be referenced as such:

Vecchione A, Lavra L, Croce CM. LZTS1 (leucine zipper, putative tumor suppressor 1). Atlas Genet Cytogenet Oncol Haematol. 2012; 16(12):894-897.