LIMK1 (LIM domain kinase 1)

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Identity

Other names: EC 2.7.11.1; LIMK; LIMK-1
HGNC (Hugo): LIMK1
Location: 7q11.23
Local order: ELN, LIMK1, EIF4H, LAT2.

LIMK1 gene is located at chromosome 7 on the long arm (q11.23).

DNA/RNA

Description

The gene starts at 73136092 bp from pter and ends at 73174790 bp from pter. Its size is 38699 bases and its orientation lie in the plus strand. The 5' promoter region (1.5 kb) contains putative sites for transcriptional regulation including Sp1, MZF1, AP1 and NF-E2. No consensus TATA box is evident.

Transcription

The transcript contains 16 exons spanning a length of 3.332 kb. The mRNA contains a short 5'UTR but a long 3' end UTR. Two LIM domains, LIM1 and LIM2 are encoded by the exons 2-4. A single PDZ domain is encoded by the exons 2-6. A C-terminal domain is encoded by exons 8-16.

Pseudogene

None identified.

Protein

Description

The LIMK1 protein is composed of 647 amino acids. It belongs to a unique family of LIM domain containing dual specificity (serine threonine and tyrosine) protein kinase. LIMK1 also has a PDZ domain in the middle of the gene and a kinase domain at the C-terminal end. A stretch of basic amino acids resembling nuclear localisation signal is present in the kinase domain and two nuclear export signal sequences containing hydrophobic residues are present in the PDZ domain.
LIMK1 consists of specific domains, nuclear localisation signal (NLS) and nuclear exit signals (NES).

**Expression**

LIMK1 exhibits tissue specific expression. It is predominantly expressed in brain but to a moderate extent in the heart and skeletal muscle. The least amount of LIMK1 expression was noted in the liver. LIMK1 is also expressed in lesser amounts in various human epithelial cell lines and haematopoetic cell lines.

**Localisation**

LIMK1 is primarily localized in the cytoplasm but also transported to the nucleus. In the cytoplasm, LIMK1 is colocalized with microtubules, and actin at the focal adhesion, stress fiber and at the lamellipodia. In the mitotic cells, LIMK1 is localized to the centrosomes until early telophase and to the cleavage furrow during late telophase.

**Function**

LIMK1 regulates organization of actin cytoskeleton through inactivating phosphorylation of the actin depolymerizing family (ADF) protein cofilin. LIMK1 phosphorylates cofilin at Serine, which inhibits actin depolymerization and results in accumulation of F actin. LIMK1 also regulates microtubule stability and assembly through phosphorylation of p25/TPPP (tubulin polymerization protein), which destabilizes microtubules. Activated LIMK1 associates with gamma-tubulin at the centrosome during mitotic phases. LIMK1 is a multifunctional protein and is involved in regulation of cell motility, cell cycle, cytokinesis and cellular morphology. LIMK1 also regulates neurite growth, synaptic stability, growth cone motility, axon formation through modulation of Golgi dynamics and neuronal differentiation.

**Homology**

LIMK1 has 50% identity overall and 70% identity in the kinase domain with another family member LIMK2. Although both proteins phosphorylate cofilin and regulate actin cytoskeleton reorganization current studies showed that LIMK2 has also different cellular function.

**Mutations**

**Germinal**

Hemizygous deletion of LIMK1 along with Elastin gene in a 1.5 MB deletion has been noted in patients with Williams-Beuren syndrome. Patients with Williams Syndrome exhibit impaired visuospatial constructive cognition possibly because of loss of LIMK1 gene.

SNP: A single nucleotide polymorphism of LIMK1 in a haplotype spanning Elastin gene has been linked to susceptibility of intracranial aneurysm (IA).

**Implicated in**

**Prostate cancer**

**Disease**

Prostate cancer is the most prevalent malignancy second to lung cancer in men in the western world. Although slow growing, a subpopulation of prostate cancer patients develops highly invasive metastatic disease that is nonresponsive to anti-androgen therapy and is usually fatal.

**Prognosis**

The gold standard for diagnosis of prostate cancer are the Gleason scores and the serum PSA level. PSA level is also used for prognostic purposes. LIMK1 expression may have prognostic value for identification of metastatic progression as overexpression of LIMK1 has been noted in metastatic prostate cancer cells.

**Cytogenetics**

Through cytogenetics method such as CGH and FISH analysis chromosomal gain in 7q11.2 region or entire chromosome 7 including 7q11.23 locus has been reported in some prostate cancer cases.

**Oncogenesis**

LIMK1 is overexpressed in prostate cancer cells and tissues compared to benign prostatic hyperplasia. Because LIMK1 plays an important role in mitosis, microtubule dynamics and cytokinesis altered expression of LIMK1 may cause mitotic defects. Aberrant expression of LIMK1 is also involved in induction of invasion in prostate cancer cells.

**Breast cancer**

**Disease**

Breast cancer is one of the major cancers affecting women in the western world after skin cancer and second leading cause of cancer death in women. About 20% of breast cancers are familial and about 10% of breast cancer is because of inheritance of a mutated gene. Although the cure rate has been increased because of the improved diagnostic approaches and
early detection, the metastatic disease actually has been increased since 1990.

**Prognosis**
Overexpression of Her2/neu oncogene product is considered to be associated with worse prognosis. LIMK1 expression may have a prognostic value for metastatic breast cancer as overexpression of LIMK1 has been noted in metastatic breast cancer cells.

**Cytogenetics**
CGH analysis indicated a gain in chromosome 7 in majority of the infiltrating ductal carcinoma cases. Some of the chromosomal gains include the region encompassing Elastin and LIMK1 loci.

**Oncogenesis**
Overexpression of LIMK1 has been shown to increase invasion and metastasis in animals. LIMK1 also involved in regulation of EGFR turnover through endocytic pathway in invasive breast cancer cells, which may have implication in development of an agressive disease.

**Melanoma**
**Disease**
Malignant melanoma is an agressive type of skin cancer, which often metastatise leading to death. The progression of melanoma is unpredictable and sometimes show refractoriness to available chemotherapy.

**Cytogenetics**
Chromosomal analysis using tiling array and CGH showed a gain in chromosome 7 in melanoma cells. Increased expression of LIMK1 in melanoma cells (Skmel 28) harboring a break at 7q11.2 has also been reported.

**Williams-beuren syndrome (WBS)**
**Disease**
WBS is a genetic disorder with autosomal dominant inheritance. WBS is caused by microdeletion at 7q11.23 region with a phenotype of connective tissue abnormalities, growth and psychomotor retardation, muscular hypotonia, loss of visuospatial cognition and behavioural abnormalities.

**Prognosis**
The presence of supravalvular aortic stenosis, pulmonary stenosis, developmental retardation and characteristic facial features in children between 18 to 30 months.

**Cytogenetics**
Chromosome analyses showed a deletion at the LIMK1 locus at 7q11.23 caused by a distal recombination event at the common telomeric breakpoint.

**Alzheimer disease (AD)**
**Disease**
Dystrophic neurites are found to be associated with Alzheimer's pathology. Altered structures of axons and dendrites, deposition of amyloid plaques leading to neurofibrillary tangle formation in AD pathology are responsible for dementia and cognitive disorder in Alzheimer's patients.

**Prognosis**
Deposition of fibrillar amyloid beta in the brain is one of the events towards developing Alzheimer Disease. LIMK1 has been shown to be involved in amyloid beta-induced neuronal degeneration. Immunofluorescence analysis showed an increased number of phosphorylated LIMK1 positive neurons in the areas of brain with AD pathology. Inhibition of cofilin phosphorylation prevented neuronal degeneration, which supports the involvement of LIMK1 in AD.

**Intracranial Aneurysm**
**Disease**
Intracranial aneurysm is the localized dilation of the blood vessel which could be fatal upon rupture causing hemorrhage in the subarachnoid space. It occurs more frequently in adults than children and in women than men. Risk factors include family history of aneurysm and inherited disorders including polycystic kidney disease.

**Cytogenetics**
Genome wide linkage studies indicated a significant association between SNP in LIMK1 promoter sequence at 7q11.2 locus and incidence of IA in Japanese and Korean patients. The SNP in the promoter sequence of LIMK1 [C(-187)T] introduced an additional transcription factor (AP2) binding site, which leads to a reduced transcription of LIMK1 mRNA.

**References**


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