

## Gene Section

### Mini Review

# STK11 (serine/threonine kinase 11)

Bharati Bapat, Sheron Perera

Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Department of Lab Medicine and Pathobiology, University of Toronto, Canada

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## Identity

**Hugo:** STK11

**Other names:** LKB1; PJS (Peutz-Jeghers syndrome); EC 2.7.11.1; NY-REN-19 antigen

**Location:** 19p13.3

## DNA/RNA

### Description

10 Exons spanning 23 kb, the 10th exon occurs within the 3' untranslated region of the gene. The gene is transcribed in telomere to centromere direction.

### Transcription

The length of this transcript has not been reconciled. The curated human Vega transcript is the longest transcript reported to date (3,627 bp, Vega external transcript). The GeneBank sequence is the same but is shorter (3,286 bp) at the 3' end (NM\_000455.4). The exon/intron structures in GeneBank are given for 2

alternative assemblies (aligned with NT\_011255.14 and NW\_927173.1), of which the NT\_0112255.14 is consistent with the Vega annotation. Alternative transcripts although shown to occur, have not been well characterized.

## Protein

### Description

433 amino acids, 48.6 kDa; N-term with a nuclear localization domain and a putative cytoplasmic retention signal, a kinase domain, and a C-terminal CAAX box prenylation motif.

### Expression

Ubiquitous, especially high expression in the testis and fetal liver.

### Localisation

Found in both the nucleus and the cytoplasm. Localization is thought to be dependent on interaction with proteins such as BRG1, LIP1, STRAD, MO25.

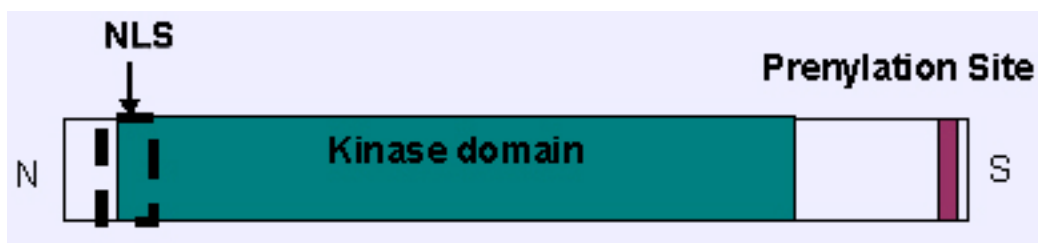


Diagram of STK11 protein (not drawn to scale). The kinase domain is depicted by the green box. The second box outlined by the dashed lines illustrates the location of the nuclear localization signal (NLS) and the purple box indicates the prenylation motif. This protein is believed to contain a putative cytoplasmic retention signal (not shown).

### Function

A serine/threonine protein kinase, recently classified as a part of the Ca<sup>2+</sup>/calmodulin kinase group of kinases.

STK11 was shown to associate and activate the pseudokinase, STRAD, resulting in the reorganization of non-polarized cells so they form asymmetrical apical and basal structures. Another mechanism by which this may occur is by the interaction of STK11 with the PAR1 family of serine/threonine kinases. AMPK is a protein kinase cascade that plays an important role in regulating energy homeostasis. The first report of an upstream regulator came when it was discovered that STK11, in complex with STRAD and the scaffolding protein MO25, can phosphorylate and activate AMPK. Subsequently, it was demonstrated that STK11 can phosphorylate the T-loop of 12 other AMPK related human kinases. In addition it has been implicated in a range of processes including, chromatin remodeling, cell cycle arrest, ras-induced cell transformation, p53 - mediated apoptosis and Wnt signaling.

### Homology

Orthologs found in several species and include: *Xenopus laevis* egg and embryonic kinase 1 (XEEK1), *Caenorhabditis elegans* partitioning defective gene 4 (PAR4), Mouse LKB1 and *Drosophila* LKB1.

## Mutations

### Germinal

Most mutations identified to date are in the catalytic domain of STK11, indicating that kinase activity is likely essential for its function as a tumor suppressor. Several types of mutations including insertions, deletions, nonsense, missense and splice site alterations have been identified to date. One family has been identified with complete germline deletion of this gene.

### Somatic

Many of the polyps that develop in Peutz-Jeghers syndrome (see below) show loss of heterozygosity and sometimes somatic mutations. Somatic mutations rarely occur in sporadic tumours, with the exception of adenocarcinoma of the lung. The inactivation of the LKB1 can also occur through promoter hypermethylation.

## Implicated in

### Peutz-Jeghers syndrome (PJS)

#### Disease

Autosomal dominant syndrome associated with mucocutaneous hyperpigmentation and benign intestinal polyps known as hamartomas. The relative incidence is estimated to vary from 1/29 000 to 1/120 000 births. Patients are at an increased risk of developing malignancies in epithelial tissues, for example it has been estimated that there is a about 84, about 213 and about 520 fold increased risk of

developing colon, gastric and small intestinal cancers respectively. PJS patients are also at an increased risk of developing cancers in the breast, lung, ovaries, uterus, cervix and testes.

### Hybrid/Mutated Gene

A majority (60-70%) of Peutz-Jeghers patients show germline mutations in STK11. Genetic locus heterogeneity may exist for this disease. A small percentage of families with no mutations in STK11/LKB1 have been identified, however no other candidate genes that predispose to Peutz-Jeghers syndrome have been identified to date.

### Oncogenesis

Patients inherit mutations in one allele, and the remaining allele is later inactivated generally by LOH or sometimes somatic mutation. This biallelic inactivation of STK11 leads to a loss of tumour suppressor activity, thereby promoting tumourigenesis.

### Lung adenocarcinoma

#### Disease

Adenocarcinoma is the most common non-small-cell lung cancer accounting for about 30-40% of all cases diagnosed to date. These tumors are thought to derive from epithelial cells that line the peripheral small airways and the heterogeneity of lung tumours is well documented. The outcome of non-small cell lung cancer is more difficult to predict, and about 50% of patients die from metastatic disease even after surgery of the primary tumour.

### Hybrid/Mutated Gene

As many as 33% of sporadic lesions analyzed display somatic mutations in STK11.

### Oncogenesis

Loss of protein function is seen in sporadic lung adenocarcinoma tumours.

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