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Gene Section
Review

LGI1 (leucine-rich, glioma inactivated protein 1 precursor)

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Identity

Hugo: LGI1
Other names: ADPEAF; EPT; Epitempin-1; ETL1; IB1099; uc001kjc.1
Location: 10q23.33
Local order: Plus strand orientation, between C10orf4 (protein isoform FRA10AC1-2) and TMEM20 (Transmembrane protein 20).

DNA/RNA

Note: LGI1 gene spans a 40,274 bp region of chromosome 10 (95,507,632 - 95,547,906).
NCBI assembly annotation:
NC_000010.9; NT_030059.12.
Alternate Celera assembly:
AC_000053.1; NW_924884.1.
LGI1 is considered a metastasis suppressor gene; it is also implicated in Autosomal Dominant Lateral Temporal Lobe Epilepsy (ADLTE).

Description

The LGI1 gene was isolated by positional cloning from a glioblastoma cell line (T98G) bearing a balanced translocation t(10;19)(q24;q13).
LGI1 gene comprises 8 exons. Exon 1 contains the 5'UTR (224 bp) and encodes the start methione. The size of exon 8 and the position of the stop codon are different in isoform 1 and 2. The 3'UTR consists of 356 bp in isoform 1 and of 386 bp in isoform 2.
A minimal promoter region is located immediately upstream of the TSS. Two Poly (A) sites are predicted by SVM from UCSC Genome Browser at the following positions: chr10:95547796-95547828 and chr10:95547881-95547919.
STS markers: IB1099; EST307318; RH51322; SHGC-155057.

Transcription

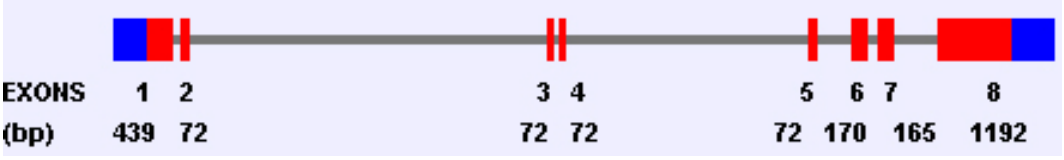
Isoform 1 mRNA is composed of 2290 bases.
Alternative splicing produces isoform 2 consisting of 1456 bases with a shorter exon 8 (425 bases).

Pseudogene

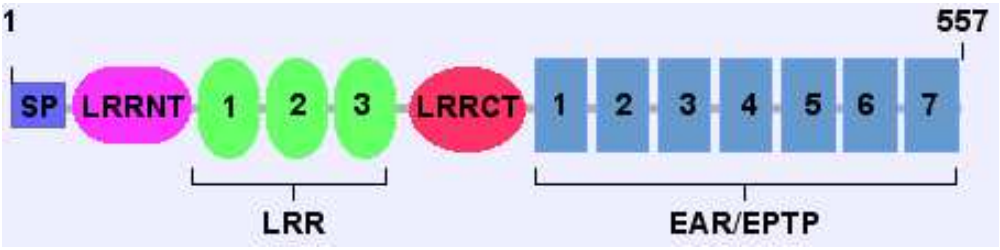
None.

Protein

Note: The unprocessed precursor of LGI1 comprises 557 Amino Acids with a Molecular weight of 63818 Da (isoform 1, UniProtKB/Swiss-Prot). Three potential N-linked glycosilation sites have been identified at AA positions: 192, 277 and 422.
Isoform 2 includes a sequence variation (AA: 280-291) and lacks the C-terminal AA stretch (292-557) yielding a protein length of 291 AA (Isoform ID: O95970-2).
Isoform 1 is potentially secreted.



Organization of LGI1 gene, depicting isoform 1 exons (1-8); exon size: (bp); red: translated region; blue: 5'UTR and 3'UTR.



Predicted domains of LGI1 protein (isoform 1): signal peptide (SP, AA: 1-34); N-terminal LRRNT (AA: 41-71); LRRs domains 1-3 (AA: 90-113, 114-137 and 138-161); C-terminal LRRCT (AA: 173-222). The C-terminal half includes the EAR/EPTP repeats 1-7 (AA: 224-267, 270-313, 316-364, 365-415, 418-462, 463-506, and 509-552).

Description

The N-terminal sequence of LGI1 precursor consists of a cleavable N-terminal signal peptide and of three leucine-rich repeats (LRRs) flanked by N-terminal and C-terminal cysteine-rich domains (LRRNT and LRRCT). The LRR domains are structurally similar to arcs and are generally involved in protein-protein interaction.

The C-terminal portion of LGI1 contains 7 repeats, termed Epilepsy Associated Repeats (EAR) or Epitempin (EPTP). The repeats potentially fold as beta-sheet and form a seven-bladed beta-propeller structure. Similar domains, identified in a number of proteins, probably represent protein interfaces. Isoform 2 lacks the six C-terminal EAR/EPTP domains.

Expression

LGI1 is highly expressed in neural tissue, particularly in specific brain regions comprising both neurons and glial cells; strong expression is also reported in some areas of the prostate, kidney, sebaceous glands, islets of Langerhans, endometrium, ovary and testis.

Expression is low or absent in the majority of glioma, glioblastoma, neuroblastoma, melanoma and breast cancer cell lines. The decrease of LGI1 expression correlates with the increasing grade of malignancy in astrocytic gliomas.

DNA microarray data substantiate high expression in brain, spinal cord, DRG, and in pituitary gland.

The expression profiles by SAGE and EST number support high expression in cerebellum and cerebrum, peripheral nerve, and also in B-lymphocytes, eye, lung, muscle, testis, and thymus; low or absent expression in neoplasia and tumors.

Localisation

Isoform 1 can be secreted, whereas a shorter isoform (which might correspond to isoform 2) is retained within the cell. Some mutants of LGI1 (isoform 1) linked to ADLTE, fail to be secreted and remain in the endoplasmic reticulum and Golgi.

Function

LGI1 is involved in the control of cell proliferation, cell migration and neurogenesis. Like other neuronal LRR proteins LGI1 may modulate synaptic function.

Re-expression in LGI1-null glioblastoma cells decreases cell proliferation through the inhibition of the ERK1/2 pathway and consequent down-regulation of matrix metalloproteinases. Increased expression in neuroblastoma cells reduces proliferation and triggers intrinsic apoptosis by inhibiting the PI3K/AKT pathway.

LGI1 forms membrane complexes with Kv1.1 potassium channels within the cell antagonizing the N-type inactivation by the Kvbeta1 subunit. It has been recognized as a ligand of the trans-membrane protein receptor ADAM22, which also causes seizure when mutated.

Homology

It belongs to a family comprising four highly homologous members denoted LGI1, LGI2, LGI3, and LGI4.

LRR repeats flanked by cysteine rich regions, are also part of adhesive proteins and receptors of the LRR superfamily. With respect to this domain LGI1 is particularly related to the Drosophila protein slit, involved in growth-cone guidance and neuronal migration; and to the portion of the mammalian Trk receptors involved in neurotrophin binding. These proteins are crucial for the development of the nervous system. A comparable role for LGI1 is consistent with its involvement in epilepsy and tumors.

The C-terminal seven-fold repeat shows the largest identity with the other members of the LGI protein family, and with a segment of the G protein coupled receptor MASS1/VLGR1, which carries mutations in a mouse model of audiogenic epilepsy.

Mutations

Note: The human LGI1 gene disclosed about 200 Single Nucleotide Polimorphism (SNP), NCBI Assembly Reference Cluster Report: rs1111820 - rs3083468.

Heterozygous point mutations are associated with ADLTE.

Large-scale homozygous mutations are linked to the development of brain malignancy.

Apparently the incidence of brain tumors is not increased in ADLTE.

Germinal

Several loss of function mutations (missense/nonsense, splicing, small deletions and insertions) have been reported in ADLTE patients.

Somatic

Complete loss of LGI1 expression is associated with malignant brain tumors. Rearrangement or deletion of the region 10q23-q26, following the complete loss of one copy of chromosome 10, frequently occurs in high-grade gliomas. Genetic abnormalities in this region, comprising tumor suppressor genes such as PTEN and DMBT next to the metastasis suppressor LGI1 gene, enhance the malignant progression. Even if rearrangements or mutations of LGI1 locus are absent in low-grade tumors LGI1 expression is often reduced, possibly due to epigenetic silencing.

Implicated in

Malignant brain tumors

Epilepsy with auditory features (ADLTE)

To be noted

Note: Consultation of "The Cancer Genome Anatomy Project" (CGAP) for breakpoints of region 10q24 associated with cancer yielded several balanced and unbalanced abnormalities, raising the possibility that interruption of LGI1 gene may be implicated in additional cancer pathologies.

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