

Gene Section

Short Communication

KLLN (killin, p53-regulated DNA replication inhibitor)

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Identity

Other names: CWS4, KILLIN

HGNC (Hugo): KLLN

Location: 10q23.31

DNA/RNA

Description

A single exon of 4277 bases.

Transcription

KLLN shares a transcription start site with PTEN and is transcribed from the minus strand.

Pseudogene

None.

Protein

Note

Calculated molecular weight: 19827 Da.

Description

178 amino acids, DNA binding domain amino acids 8-50.

Localisation

Nucleus.

Function

KLLN, a target gene of the tumor suppressor p53, is involved in cell cycle arrest and apoptosis (Cho and Liang, 2008). In breast cancer cell lines, KLLN

overexpression inhibits cellular proliferation and leads to cell cycle arrest and apoptosis while KLLN knockdown increases cellular proliferation (Wang et al., 2013b). KLLN can bind to DNA and act as a transcription factor; regulating the expression of genes including TP53, TP73, AR and CHK1 (Nizialek et al., 2013 ; Wang et al., 2013b).

Homology

None.

Mutations

Germinal

37% of Cowden syndrome patients who were PTEN mutation negative had KLLN promoter hypermethylation which was not seen in controls. Patients with KLLN promoter hypermethylation have an increased risk of breast and renal cancer compared to PTEN mutation positive patients. Methylation leads to a 250-fold decrease in KLLN expression (Bennett et al., 2010).

Germline KLLN promoter methylation has been observed in 56% of patients with apparently sporadic renal cell carcinoma (Bennett et al., 2011).

Germline KLLN mutations have been associated with apparently sporadic breast cancer. 3% of patients with sporadic breast cancer were found to have KLLN mutations while no mutations were observed in controls. Patients with KLLN mutations had a significant family history of breast cancer. These variants were found to dysregulate G2 cell cycle arrest possibly through dysregulated CHK1 expression (Nizialek et al., 2013).

1 mdrpgpgsar pgrtvhwgy rvevkvrrngr klqpsewagr gdlggfkrw kdtratvgtt
 61 frrrsrvslv gelskfppls dssggkssss fargalawcr qrnnpnscaa aetgartslp
 121 kercrgwrlg nwlhkhphpn tclrplacwl ppilterger vpklvpllac ypkskpkd

Amino acid sequence.

Somatic

Somatic KLLN promoter hypermethylation is seen in renal cell carcinoma (Bennett et al., 2011).

Somatic KLLN deletions were observed in 20% of breast carcinomas (Nizialek et al., 2013).

Implicated in

Cowden syndrome

Note

Cowden syndrome (CS) is an autosomal dominant syndrome and can be attributed to a PTEN mutation in 25% of cases and to KLLN promoter hypermethylation in 37% of PTEN mutation negative CS/CS-like cases. CS is characterized by benign hamartomas as well as malignancies including breast, thyroid, endometrial, and other cancers. Patients with KLLN epimutations are at increased risk for breast and renal cancer compared to patients with PTEN mutations (Bennett et al., 2010).

Breast cancer

Note

Germline KLLN mutations have been identified in 3% of patients with apparently sporadic breast cancer (Nizialek et al., 2013). KLLN is thought to be a low-penetrance breast cancer susceptibility gene. KLLN mutations were not associated with breast cancer in a cohort of high-risk Australian and New Zealand patients (Thompson et al., 2012).

Somatic deletions of the KLLN gene are observed in 20% of breast tumors. Patients with somatic KLLN deletions are more likely to have estrogen receptor and progesterone receptor negative tumors and tumors of a basal sub-type (Nizialek et al., 2013).

Loss of KLLN expression is seen in all subtypes of breast cancer and decreased KLLN in breast tumors is associated with increased tumor grade and with breast cancer metastasis (Wang et al., 2013a).

Renal cell carcinoma

Note

56% of patients with renal cell carcinoma were found to have germline KLLN promoter methylation of at least one of four CpG-rich regions housed in the genomic region between KLLN and PTEN. Somatic

KLLN promoter methylation was also seen in renal tumors, possibly increasing with more advanced stage of disease (Bennett et al., 2011).

Prostate cancer

Note

KLLN mRNA expression is significantly decreased in prostate tumors compared to normal prostate tissue. Immunohistochemistry staining of prostate tumors for KLLN expression shows decreased staining associated with high Gleason score (Wang et al., 2013b).

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