FHL2 (four and a half LIM domains 2)

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Identity

Other names: AAG11; DRAL; FHL-2; SLIM3
HGNC (Hugo): FHL2
Location: 2q12.2
Local order: 91kb telomeric to transforming growth factor, beta receptor associated protein 1 (TGFBRAP1).

DNA/RNA

Description

Human FHL2 gene spans around 80kb of genomic DNA on the chromosome 2q12-q14 in telomere-to-centromere orientation. FHL2 promoter contains putative transcription factor binding sites for SRF (serum response factor), NKX2-5, MEF-2, E2F and AP-1 (activator protein-1).

Transcription

Four transcript variants of FHL2 genes have been reported in Entrez Gene (NCBI). These alternative spliced transcripts are 1.55-1.91 kb in length, and differ in the 5′-UTR only.

Pseudogene

No pseudogenes for FHL2 are known.

Protein

Description

The open reading frame encodes a 279 amino acid protein with an estimated molecular weight of 32.2kDa. FHL2 protein constitutes four and a half

Chromosomal location of FHL2 gene (upper panel) and genomic organization of four FHL2 transcript variants.
N-terminal LIM domains. The four complete LIM domains extend from amino acid 40-92, 100-153, 162-217 and 220-275.

**Expression**

In human tissues, FHL2 expression is the most abundant in adult heart and ovary, and of low level in brain, lung, liver, kidney and intestine. FHL2 is initially identified as a downregulated gene in human rhabdomyosarcoma cells. However, elevated FHL2 expression is detected in other cancers, including hepatocellular carcinoma, glioblastoma, breast, prostate, ovarian, and gastrointestinal cancers.

**Localisation**

Cytoplasm and nucleus.

**Function**

At tissue level, FHL2 plays important roles in the development of cardiac circulatory system and placenta. It also induces osteoblast and myoblast differentiation. At cellular level, FHL2 participates in various processes, including cell survival, adhesion, motility, transcription and signal transduction. At molecular level, the LIM domains of FHL2 are double zinc finger motifs that physically interact with partner proteins to modulate RNA splicing, DNA replication and repair. It also functions as a transcriptional co-activator for androgen receptor, AP-1, CREB (cAMP response element binding protein), CREM (cAMP response element modulator), BRCA1 (breast cancer 1), WT-1 (Wilms' tumor), and NF-kB (nuclear factor-kB). Moreover, FHL2 is a transcriptional co-suppressor for ERK2 (extracellular signal regulated kinase 2), SRF and FOXO1 (forkhead box O1).

**Homology**

FHL2 belongs to the four-and-a-half-LIM-only protein family, which includes FHL1, FHL2, FHL3, FHL4 and FHL5 (ACT). Human FHL2 amino acid sequence is 48.2% identical with FHL1, 53.4% with FHL3, 48.4% with mouse FHL4, and 59.1% with FHL5. Orthologs of human FHL2 are found in macaque, mouse, rat, bovine, dog, chicken, frog, zebrafish, amphioxus, drosophila and C. elegans.

**Implicated in**

**Rhabdomyosarcoma**

Note
FHL2 expression is downregulated in rhabdomyosarcoma cells relative to normal myoblasts (Genini et al., 1997).

**Hepatocellular carcinoma**

Note
In 8 of 10 human liver tumors samples, FHL2 mRNA expression is higher than that in matched nontumor livers (Wei et al., 2003). In contrast, it is recently reported that FHL2 protein is down-regulated in liver tumors, as compared with matched nontumor liver tissues. In addition, FHL2 inhibits hepatoma cell growth in vitro and in nude mice (Ding et al., 2009).

**Ovarian cancer**

Note
FHL2 protein expression is upregulated in epithelial ovarian cancer, as compared with matched normal tissues (Gabriel et al., 2004).

**Breast cancer**

Note
FHL2 is overexpressed in human mammary carcinoma samples, compared with normal breast tissues. FHL2 induces the expression of cell cycle inhibitor p21Cip1/Waf1 in MDA-MB 231 breast cancer cells (Martin et al., 2007).

**Prognosis**

Patients with tumors expressing low amounts of FHL2 were characterized by a significantly better survival compared to those with high intratumoral FHL2 expression (Gabriel et al., 2006).

**Prostate cancer**

Note
FHL2 expression is downregulated by 2- to 4-fold in primary prostate cancer relatively to normal tissues for five pairs of samples (Kinoshita et al., 2005). Another study reports that FHL2 expression is increased in prostate adenocarcinoma cells when compared with benign epithelial cells. It might be the subcellular localization of FHL2 that governs the progression of prostate cancer (Muller et al., 2002). Androgen-induced FHL2 expression is mediated by SRF (Heemers et al., 2007).

**Prognosis**

Nuclear, but not cytoplasmic expression of FHL2 significantly correlate with the recurrence of prostate cancer (Kahl et al., 2006).

**Mutations**

**Somatic**

G142A missense mutation, corresponding to Gly48Ser within the first LIM domain, is identified in heterozygous state in a 49-years-old female dilated cardiomyopathy (DCM) patient. This mutation abrogates the binding of FHL2 with titin/connectin, and in turn impairs the abnormal recruitment of metabolic enzymes to cardiac sarcomere (Arimura et al., 2007).
**Gastrointestinal cancer**

**Note**
FHL2 expression is upregulated in gastric and colon cancer, compared with matched normal tissues. Suppression of FHL2 induces gastric and colon cell differentiation, and inhibits cell proliferation and expression of oncogenes (survivin, Cox-2, hTERT and c-jun) in vitro. Antisense FHL2 also inhibits tumorigenesis of colon cancer cells in xenograft nude mice model (Wang et al., 2007).

**Glioma**

**Note**
The mRNA level of FHL2 is elevated in both low (3 of 6) and high (11 of 13) grade glioma patient samples. FHL2 induces glioblastoma cell proliferation and migration in vitro, and promotes tumorigenesis in glioblastoma xenograft nude mice model. Overexpression of FHL2 decreases mRNA levels of p53 and its downstream proapoptotic genes, and enhances promoter activities of AP-1, human telomerase reverse transcriptase and survivin genes (Li et al., 2008).

**References**


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