CITED4 (Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 4)

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Identity
Other names: MRG2; MRG-2
HGNC (Hugo): CITED4
Location: 1p34.2

DNA/RNA
Description
DNA sequence is located at chromosome 1p.

Transcription
Transcription consists of a single exon without alternative splicing. mRNA: NM_133467.

Protein
Note
CITED4 protein is 184 amino acid long with a molecular weight of 18569 Da.

Description
CITED4 has a characteristic CITED domain motif conserved in all CITED peptides located at the carboxyl-terminal domain that binds with p300/CBP.

Expression
In all tissues with special intensity in heart, liver, pancreas and skeletal muscle.

Localisation
CITED4 has nuclear and cytoplasmatic location. In most cells it has a nuclear localization, but in others it was localized in nucleus and cytoplasm.

Function
Binds CBP and tumor suppressor protein EP300 by carboxy terminus domain (residues 138-184). Therefore it may be implicated in gene transcription. As other genes of the family, CITED4 physically interacts with transcription factor AP-2.
Coding and flanking regions of CITED4.

Fox et al. (2002) showed that CITED4 blocks the binding of hypoxia-inducible factor 1alpha to p300 in their experiments made in vitro and inhibits hypoxia-inducible factor-1alpha transactivation and hypoxia-mediated reporter gene activation. That is the reason why they concluded that CITED4 might be an inhibitor of hypoxia-inducible factor 1alpha.

**Homology**

CITED4 has 2 paralogues (CITED1 and CITED2) in humans. All of them belong to CITED family, found only in jawed vertebrates to date (Braganca et al., 2002).

**Mutations**

*Note*

No mutations has been reported yet, but a total of 16 polymorphisms with unknown consequences has been founded by Tews et al. (2007) and Torres-Martin et al. (2008).

**Implicated in**

**Oligodendroglioma**

*Note*

CITED4 promoter is methylated in oligodendrogliomas, especially in those with 1p/19q deletions. This hypermethylation is responsible of lower levels of CITED4 mRNA expression, suggesting a way by which CITED4 is almost silenced by both hypermethylation and chromosomal deletion (Tews et al., 2007).

**Prognosis**

CITED4 hypermethylation in oligodendroglioma patients is similar to prognosis associated to 1p/19q deletions. Thus, CITED4 hypermethylation might be an alternative or even a confirmation of 1p/19q testing.

**Breast cancer**

*Note*

Cytoplasmatic translocation and loss of nuclear expression has been associated with breast cancer by Fox et al. (2002). This loss may allow p300/CBP to interact with hypoxia-inducible factor 1a and oncogenes to enhance their transcriptional activity leading to an aggressive tumor phenotype (Fox et al., 2004).

**Prognosis**

CITED4 is located in the nucleus in normal tissue, but in breast tumors is present both nuclear and cytoplasmatic location. This characteristic might be used as prognosis factor of this kind of tumors.

**References**


Fox SB, Bragança J, Turley H, Campo L, Han C, Gatter KC, Bhattacharya S, Harris AL. CITED4 inhibits hypoxia-activated transcription in cancer cells, and its cytoplasmatic location in breast cancer is associated with elevated expression of tumor cell hypoxia-inducible factor 1alpha. Cancer Res. 2004 Sep 1;64(17):6075-81


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