

Gene Section

Mini Review

HDAC2 (histone deacetylase 2)

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Identity

Other names: EC 3.5.1.98; HD2; RPD3; YAF1

HGNC (Hugo): HDAC2

Location: 6q22.1

DNA/RNA

Description

The HDAC2 gene is composed of 14 exons that span 35.029 bp of genomic DNA.

Transcription

The length of the transcribed mRNA is about 6659 bp.

Pseudogene

No pseudogene has been described.

Protein

Description

There are two protein variants of 488 and 582 aa due to distinct pre-mRNA splicing events. The N-terminal tail of the protein contains the catalytic

domain that comprises most of the protein. The N-terminal domain also has a HDAC association domain (HAD) essential for homo- and heterodimerization. A coiled-coil domain essential for protein-protein interactions is present at the C-terminal tail. It also contains three phosphorylation sites at Ser394, Ser422 and Ser424, and two S-Nitrosylation sites at Cys262 and Cys274.

Expression

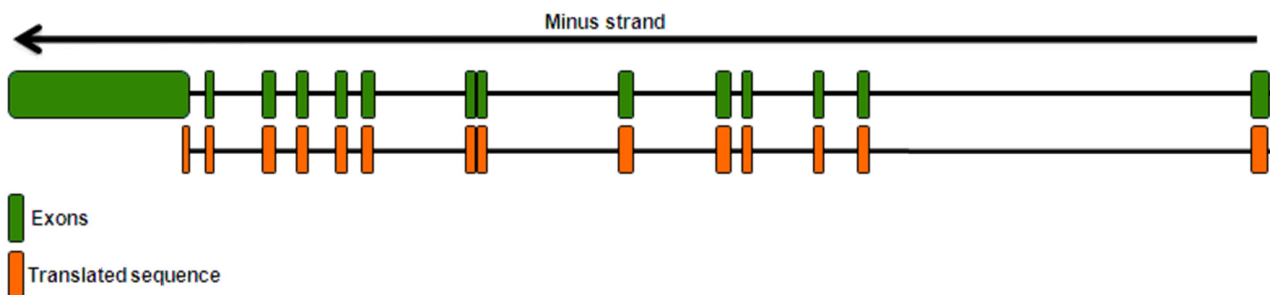
Widely expressed.

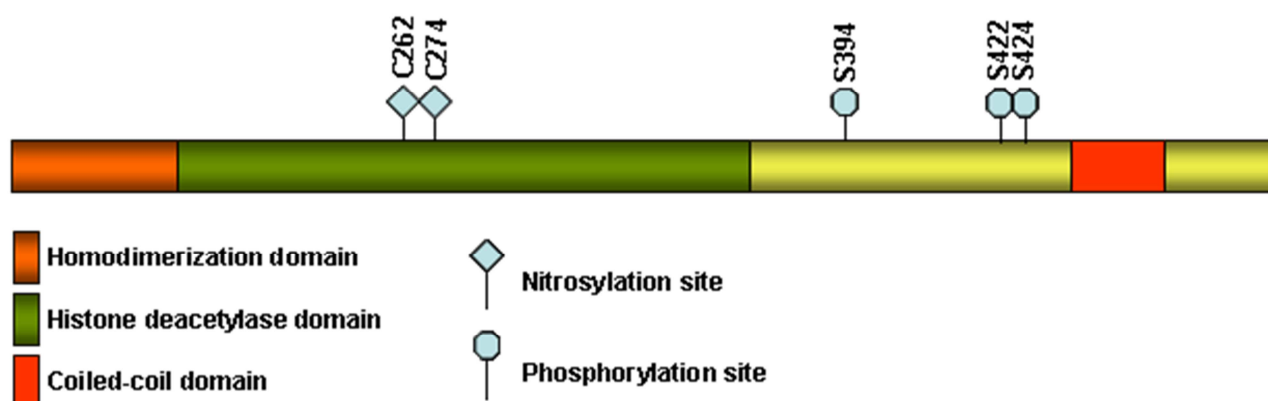
Localisation

Nucleus.

Function

HDAC2 belongs to class I histone deacetylases that also comprise HDAC1, HDAC3 and HDAC8. HDAC2 acts as a transcriptional repressor through the desacetylation of lysine residues present at the N-terminal tail of histone proteins (H2A, H2B, H3 and H4). HDAC2 heterodimerise with HDAC1, but the heterodimer cannot bind to DNA, so they have to be recruited by transcription factors such as YY1, SP1/SP3, the tumor suppressor genes p53 and BRCA1.





HDAC2 can also be tethered to DNA as a part of the multiprotein corepressor complexes CoREST, mSin3 and NuRD. These complexes are targeted to specific genomic sequences by interactions with sequence-specific transcription factors. For example, the HDAC2/HDAC1 containing Sin3-SAP corepressor complex is recruited by E2F family of transcription factors to repress transcription. HDAC2 containing complexes are also implicated in gene transcription-regulation mediated by nuclear receptors. These complexes also contain other epigenetic modifier genes, such as methyl-binding proteins (MeCp2), the DNA methyl transferases DNMT1, DNMT3A and DNMT3B, the histone methyl transferases SUVAR39H1 and G9a and histone demethylases (LSD1), providing another way by which HDAC2 regulates gene expression and chromatin remodelling. HDAC2 also regulates gene expression through the deacetylation of specific transcription factors that includes STAT3 and SMAD7.

HDAC2 is a key regulator of genes regulating cell cycle, apoptosis, cell adhesion and migration. Together with HDAC1, HDAC2 regulates the transcription of genes implicated in haematopoiesis, epithelial cell differentiation, heart development and neurogenesis. Montgomery et al. (2007) find that HDAC2 and HDAC1 double-null mice show an uncontrolled ventricular proliferation, while Trivedy and colleagues (2007) show the lack of cardiac hypertrophy in HDAC2 mutant mice. HDAC2 is also a key regulator of nervous system function acting as a repressor of synaptic plasticity genes that regulates learning and memory formation. HDAC2-deficient mouse have enhanced memory formation.

Homology

The histone deacetylase domain of HDAC2 is highly homologous to other class I HDACs (HDAC1, HDAC3 and HDAC8) showing the greater homology with HDAC1. This domain is also highly conserved between species (from yeast to human).

Mutations

Germinal

No germinal mutations have been found.

Somatic

HDAC2 is mutated in sporadic tumors with microsatellite instability and in tumors arising in individuals with hereditary non-polyposis colorectal carcinoma. This mutation consists in a deletion of a nine adenines repeat present in Exon1 that produce a truncated and inactive form of the protein. The expression of the mutant form of HDAC2 induces resistance to the proapoptotic and antiproliferative effects of HDAC inhibitors. The lack of HDAC2 expression and function produces the up-regulation of tumor-growth promoting genes.

Implicated in

Various cancer

Note

The deregulation of HDAC2 expression and activity has been linked to cancer development. HDAC2 is overexpressed in different tumor types including colon, gastric, cervical and prostate carcinoma. HDAC2 overexpression is implicated in cancer partly through its aberrant recruitment and consequent silencing of tumor suppressor genes. The repression of the tumor suppressor gene WAF1 is associated with histone hypoacetylation at the promoter region and can be reversed by the treatment with HDAC inhibitors.

Prognosis

HDAC2 expression is correlated with poor prognosis and advanced stage disease in colorectal, prostate and gastric carcinomas.

Colon cancer

Note

There are a number of studies showing HDAC2 overexpression in colon cancer. The increase of

HDAC2 expression has been found at the protein and mRNA level indicating that HDAC2 overexpression is due to transcriptional activation. These studies indicate that in this tumor type HDAC2 transcription is regulated by beta-catenin-TCF-myc signaling pathway that is deregulated in colon cancer. HDAC2 overexpression is correlated with poor prognosis and advanced stage disease in colorectal carcinoma. However, Ropero et al., found an inactivating mutation of HDAC2 in colon cancers with microsatellite instability.

Breast cancer

Note

Different studies show an important role of HDAC2 in breast cancer. HDAC2 Knockdown induces senescence in breast cancer cells. Moreover the loss of HDAC2 activity potentiates the apoptotic effect of tamoxifen in estrogen/progesterone positive breast cancer cells.

Prostate cancer

Note

Weichert et al., found that HDAC2 was strongly expressed in more than 70% of prostate cancer cases analyzed. The increase in HDAC2 expression was associated with enhanced tumor cell proliferation and poor prognosis in prostate cancer suggesting HDAC2 as a novel prognostic factor in this tumor type.

Chronic obstructive pulmonary disease (COPD)

Note

Reduced HDAC2 activity and expression is found in Chronic Obstructive Pulmonary Disease (COPD). The reduced activity of HDAC2 produces the upregulation of genes implicated in the inflammatory response and resistance to corticosteroids in COPD.

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