

## Gene Section

### Mini Review

# ID4 (inhibitor of DNA binding 4, dominant negative helix-loop-helix protein)

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## Identity

**HGNC (Hugo): ID4**

**Location: 6p22.3**

**Location (base pair): Starts at 19,945,596 and ends at 19,948,894 bp from pter.**

## DNA/RNA

### Description

The gene spans 3,3 kb on plus strand.

### Transcription

3 exons; mRNA 2,343 bp.

## Protein

### Description

161 amino acids; 16.6 KDa; contains a poly-Ala (from amino acid 39 to 48), a helix-loop-helix motif (65 to 105), and a poly-Pro (118 to 124).

### Expression

Expressed in various tissues.

### Function

ID4 is one of the members of the ID gene family: "Inhibitors of DNA binding". They are transcription factors which act as transcription inhibitory proteins. They are basic helix-loop-helix (bHLH) proteins which contain the bHLH dimerization domain, but lack the DNA binding domain. They are able to form heterodimers with other bHLH proteins, but inhibit the DNA binding, inactivating the process. Since bHLH

proteins act as trans-cription factors, ID genes are transcription repress-sors, modulating various functions. ID proteins play critical roles in early embryonic processes, growth, differentiation, senescence and apoptosis; they are also involved in angiogenesis. ID4 is expressed in the central nervous system. ID4 is required for G1-S transition and enhance proliferation in early cortical progenitors. On the other hand, ID4 enhances RB1 -mediated inhibition of proliferation of differentiating neurons, either by direct inter-action or through interaction with other molecules of the cell cycle machinery. Other ID genes are not redondant with ID4 during telencephalic develop-ment, supporting the idea that ID4 function is unique in this context (Yun et al., 2004). In immature neurons with high expression of ID proteins, heterodimers of bHLH-ID prevent DNA binding and expression of differentiation associated genes.

ID4 may play an important suppressive role in tumor progression, and its silencing by hyper-rmethylation favours tumorigenesis (see below).

## Implicated in

### ***B-cell acute lymphoblastic leukaemia (B-ALL) with t(6;14)(p22;q32) --> ID4 - IGH***

#### Note

ID4 was juxtaposed to the IGH enhancer, leading to ID4 overexpression. (Bellido et al., 2003; Russell et al., 2008).

#### Prognosis

Prognosis in this disease looks fair.

## Non Hodgkin lymphoma

### Note

ID4 promoter was found hypermethylated in follicular lymphomas, diffuse large B-cell lymphomas, as well as lymphoid cell lines (Hagiwara et al., 2007).

## Brain tumours

### Note

In oligodendroglial tumours and glioblastomas, ID4 is expressed in neoplastic astrocytes but not in neoplastic oligodendrocytes (Liang et al., 2005).

## Breast cancer

### Note

Hypermethylation of ID4 promoter and ID4 mRNA suppression was found in breast cancer cell lines as well as in primary breast cancers. In one study, it was a significant risk factor for nodal metastasis (Umetani et al., 2006). In another study, BRCA1, ER (estrogen receptor), and ID4 were found expressed in breast cancer specimens from patients with invasive carcinomas. Most of the patients who expressed BRCA1 also expressed ER, but were negative for ID4, and vice versa. BRCA1-ER and ID4 are linked in a negative correlation (Roldan et al., 2006). Id4 regulates BRCA1 expression and may be involved in hormone-dependent regulation of BRCA1 homeostasis (de Candia et al., 2004). ID4 is constitutively expressed in the normal human mammary epithelium but is suppressed in ER-.

Positive breast carcinomas and preneoplastic lesions. ER-negative carcinomas are Id4 positive (de Candia et al., 2006). These results support a possible role of Id4 as a tumor suppressor factor in the human breast and suggest that the expression of Id4 in the mammary ductal epithelium may be regulated by estrogen (de Candia et al., 2006).

## Bladder cancer

### Note

ID4 is part of the 6p22.3 amplicon frequently observed in advanced stage bladder cancer. ID4, as well as E2F3 and DEK, was overexpressed in bladder cancer cell lines. This overexpression was correlated with the copy number. However, ID4 expression was equivalent in fresh cancer tissues and normal urothelium (Wu et al., 2005).

## Gastric cancer

### Note

ID4 promoter is hypermethylated and showed a low level of expression in 30% of gastric adenocarcinomas and in most gastric cancer cell lines, while its expression was high in normal gastric mucosa. Furthermore, there was a significant association of ID4 promoter hypermethylation/ID4 down regulation and that of hMLH1 and microsatellite instability (Chan et al., 2003).

## Colorectal cancer

### Note

ID4 is silenced in colorectal cancer: Hyper-methylation was found in half of the primary colorectal cancer specimens tested (and in cell lines as well), in 3/4 of liver metastases of colorectal cancer specimens tested, but not in normal epitheliums nor in adenomas. Moreover, the methylation status was correlated with the histo-pathological grade, and hypermethylation of ID4 was identified as a significant independent risk factor of poor prognosis (Umetani et al., 2005).

## Rett syndrome

### Note

A significantly increased protein expression of ID genes was found in human brain tissue of Rett syndrome patients, compared to controls (Peddada et al., 2006). Rett syndrome is a X-linked neuro-developmental disorder resembling autism, and due to MECP2 (Xq28) mutations in most cases, more rarely due to mutations of CDKL5 (Xp22) or, much less convincingly, NTNG1 (1p13).

## References

- Andres-Barquin PJ, Hernandez MC, Israel MA. Injury selectively down-regulates the gene encoding for the Id4 transcription factor in primary cultures of forebrain astrocytes. *Neuroreport*. 1998 Dec 21;9(18):4075-80
- Andres-Barquin PJ, Hernandez MC, Israel MA. Id4 expression induces apoptosis in astrocytic cultures and is down-regulated by activation of the cAMP-dependent signal transduction pathway. *Exp Cell Res*. 1999 Mar 15;247(2):347-55
- Massari ME, Murre C. Helix-loop-helix proteins: regulators of transcription in eucaryotic organisms. *Mol Cell Biol*. 2000 Jan;20(2):429-40
- Beger C, Pierce LN, Kruger M, Marcusson EG, Robbins JM, Welch P, Welch PJ, Welte K, King MC, Barber JR, Wong-Staal F. Identification of Id4 as a regulator of BRCA1 expression by using a ribozyme-library-based inverse genomics approach. *Proc Natl Acad Sci U S A*. 2001 Jan 2;98(1):130-5
- Chaudhary J, Johnson J, Kim G, Skinner MK. Hormonal regulation and differential actions of the helix-loop-helix transcriptional inhibitors of differentiation (Id1, Id2, Id3, and Id4) in Sertoli cells. *Endocrinology*. 2001 May;142(5):1727-36
- Rivera R, Murre C. The regulation and function of the Id proteins in lymphocyte development. *Oncogene*. 2001 Dec 20;20(58):8308-16
- Bellido M, Aventin A, Lasa A, Estivill C, Carnicer MJ, Pons C, Matias-Guiu X, Bordes R, Baiget M, Sierra J, Nomdedeu JF. Id4 is deregulated by a t(6;14)(p22;q32) chromosomal translocation in a B-cell lineage acute lymphoblastic leukemia. *Haematologica*. 2003 Sep;88(9):994-1001
- Chan AS, Tsui WY, Chen X, Chu KM, Chan TL, Chan AS, Li R, So S, Yuen ST, Leung SY. Downregulation of ID4 by promoter hypermethylation in gastric adenocarcinoma. *Oncogene*. 2003 Oct 9;22(44):6946-53
- Shan L, Yu M, Qiu C, Snyderwine EG. Id4 regulates mammary epithelial cell growth and differentiation and is overexpressed in rat mammary gland carcinomas. *Am J Pathol*. 2003 Dec;163(6):2495-502

- de Candia P, Benera R, Solit DB. A role for Id proteins in mammary gland physiology and tumorigenesis. *Adv Cancer Res.* 2004;92:81-94
- Umetani N, Takeuchi H, Fujimoto A, Shinozaki M, Bilchik AJ, Hoon DS. Epigenetic inactivation of ID4 in colorectal carcinomas correlates with poor differentiation and unfavorable prognosis. *Clin Cancer Res.* 2004 Nov 15;10(22):7475-83
- Yun K, Mantani A, Garel S, Rubenstein J, Israel MA. Id4 regulates neural progenitor proliferation and differentiation in vivo. *Development.* 2004 Nov;131(21):5441-8
- Bedford L, Walker R, Kondo T, van Crüchten I, King ER, Sablitzky F. Id4 is required for the correct timing of neural differentiation. *Dev Biol.* 2005 Apr 15;280(2):386-95
- Liang Y, Bollen AW, Nicholas MK, Gupta N. Id4 and FABP7 are preferentially expressed in cells with astrocytic features in oligodendrogliomas and oligoastrocytomas. *BMC Clin Pathol.* 2005 Jul 15;5:6
- Umetani N, Mori T, Koyanagi K, Shinozaki M, Kim J, Giuliano AE, Hoon DS. Aberrant hypermethylation of ID4 gene promoter region increases risk of lymph node metastasis in T1 breast cancer. *Oncogene.* 2005 Jul 7;24(29):4721-7
- Wu Q, Hoffmann MJ, Hartmann FH, Schulz WA. Amplification and overexpression of the ID4 gene at 6p22.3 in bladder cancer. *Mol Cancer.* 2005 May 5;4(1):16
- Yu L, Liu C, Vandeusen J, Becknell B, Dai Z, Wu YZ, Raval A, Liu TH, Ding W, Mao C, Liu S, Smith LT, Lee S, Rassenti L, Marcucci G, Byrd J, Caligiuri MA, Plass C. Global assessment of promoter methylation in a mouse model of cancer identifies ID4 as a putative tumor-suppressor gene in human leukemia. *Nat Genet.* 2005 Mar;37(3):265-74
- de Candia P, Akram M, Benezra R, Brogi E. Id4 messenger RNA and estrogen receptor expression: inverse correlation in human normal breast epithelium and carcinoma. *Hum Pathol.* 2006 Aug;37(8):1032-41
- Peddada S, Yasui DH, LaSalle JM. Inhibitors of differentiation (ID1, ID2, ID3 and ID4) genes are neuronal targets of MeCP2 that are elevated in Rett syndrome. *Hum Mol Genet.* 2006 Jun 15;15(12):2003-14
- Roldán G, Delgado L, Musé IM. Tumoral expression of BRCA1, estrogen receptor alpha and ID4 protein in patients with sporadic breast cancer. *Cancer Biol Ther.* 2006 May;5(5):505-10
- Hagiwara K, Nagai H, Li Y, Ohashi H, Hotta T, Saito H. Frequent DNA methylation but not mutation of the ID4 gene in malignant lymphoma. *J Clin Exp Hematop.* 2007 Apr;47(1):15-8
- Russell LJ, Akasaka T, Majid A, Sugimoto KJ, Loraine Karran E, Nagel I, Harder L, Claviez A, Gesk S, Moorman AV, Ross F, Mazzullo H, Strefford JC, Siebert R, Dyer MJ, Harrison CJ. t(6;14)(p22;q32): a new recurrent IGH@ translocation involving ID4 in B-cell precursor acute lymphoblastic leukemia (BCP-ALL). *Blood.* 2008 Jan 1;111(1):387-91

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