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Gene Section
Short Communication

ID2 (inhibitor of DNA binding 2, dominant negative helix-loop-helix protein)

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Abstract

Review on ID2, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: GIG8, ID2A, ID2H, bHLHb26

HGNC (Hugo): ID2

Location: 2p25.1

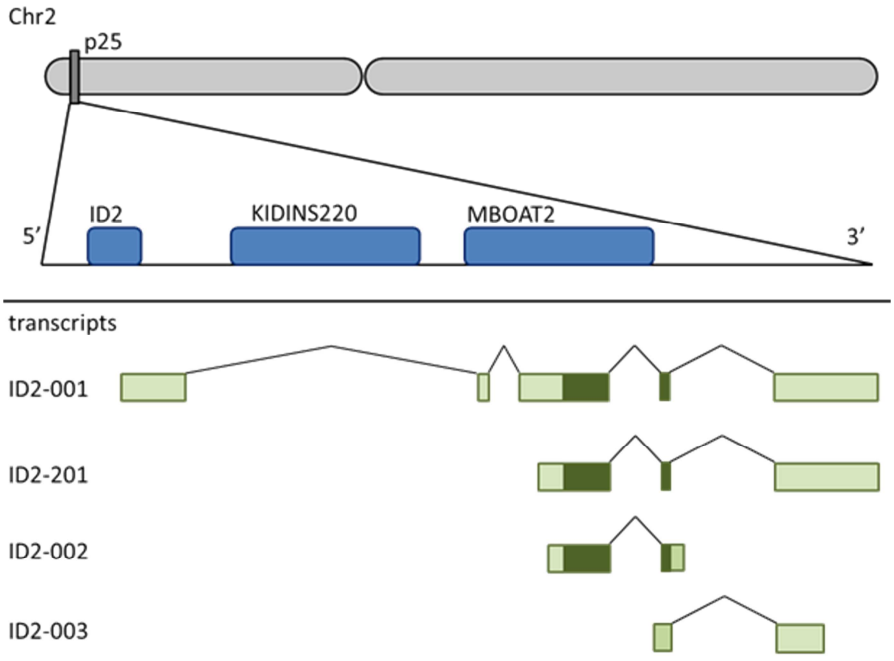
DNA/RNA

Description

The gene spans 5608 bp containing 5 exons of which 2 (exons 3 and 4) are protein-encoding.

Transcription

The ID2 gene has 4 transcripts, of which 3 can generate functional protein: ID2-001 (2041bp) contains all 5 exons, ID2-201 (1362 bp) contains 3 exons and ID2-002 contains 2 exons. ID2-003 (474 bp) contains a retained intron.



Pseudogene

A pseudogene of ID2 is located on chromosome 3.

Protein

Description

ID2 belongs to the helix-loop-helix (HLH) protein family. It is composed by 134 aa and belongs to a subgroup HLH family members (ID1, ID2, ID3, ID4) that lack a basic DNA-binding domain. ID proteins form heterodimers with class I basic HLH-group members such as MyoD (Langlands et al., 1997), NEDD9 (Law et al., 1999), and E2A gene products E12 and E47. ID2 has a main domain located on 38-79 aa responsible for the helix-loop-helix conformation. In addition, Id2 contains a 10 aa motif that is responsible for the nuclear export signaling.

Expression

Expression of ID2 is found in the brain, ovary, liver, lung, thyroid gland and prostate and several subsets of leukocytes. ID2 expression is especially high in Natural Killer (NK-) cells, but is also found in CD4+ T cells, CD8+ T cells, monocytes and precursor B cells.

Localisation

Nucleus.

Function

Although it does not bind directly to DNA, by binding basic helix-loop-helix transcription factors through its HLH motif, ID2 may control tissue-specific genes related to cell growth, proliferation and differentiation (Hara et al., 1994; Iavarone et al., 1994). ID2 functions in cell fate decisions in early leukocyte development. Specifically, ID2 is required for NK-cell, innate lymphoid and lymphoid tissue inducer cells (Boos et al., 2007; Moro et al., 2010; Yokota et al., 1999). Furthermore, ID2 functions in the development of several dendritic cell subsets: Langerhans cells, cutaneous dendritic cells and splenic CD8a+ dendritic cells (Hacker et al., 2003). Although ID2 seems redundant for T-cell development in thymus, ID2 promotes NKT-cell development (Verykokakis et al., 2013), and it is involved in effector differentiation (Masson et al., 2013), as well as γδT cell homeostasis (Zhang et al., 2014). Finally, ID2 inhibits progression of precursor-B-cell development (Hara et al., 1997; Jensen et al., 2013), as well as activation-induced deaminase expression during B-cell responses (Gonda et al., 2003), likely through inhibition of E47 (Sayegh et al., 2003).
Besides leukocytes, ID2 has been found to function in erythrocyte development (Ji et al., 2008), enterocyte precursor and lung epithelial cell differentiation in mice (Rawlins et al., 2009). Furthermore, female mice lacking ID2 show lactation defects (Mori et al., 2000), and male mice have impaired spermatogenesis (Sablitzky et al., 1998).

Homology

ID2 is highly conserved in vertebrates, including mammals, reptiles, and fish.

Mutations

Germinal

No germinal mutations have been reported.

Somatic

No somatic mutations have been reported.

Implicated in

Neuroblastoma

Note

ID2 functions as a key regulator in the phenotypic transition of neuroblastoma tumor cells (Chakrabarti et al., 2013). Anchorage-dependent (AD) neuroblastoma cells express much higher levels of ID2 than anchorage-independent (AI) cells. Moreover, knockdown of ID2 in AD cells induces an AI phenotype, whereas the opposite is seen upon forced expression of ID2 in AI cells. The function of ID2 in this process is at least in part via negative regulation of the TGFβ/Smad pathway.

Colon carcinoma

Note

ID2 expression is upregulated by enhanced beta-catenin signaling and subsequent beta-catenin /TCF mediated transcription.
The induction of ID2 expression increases anchorage-independent survival of these cells (Rockman et al., 2001).

Melanoma

Note

The transition of melanoma to a more aggressive malignancy is associated with the resistance to growth inhibition by TGF-β (Javelaud et al., 2008). In susceptible cells, TGF-β suppresses ID2 expression and allows $p15^{lnk4b}$ to induce a cell cycle arrest (Schlegel et al., 2009). Upon obtaining resistance to TGF-β, the tumor cells overexpress ID2 and remain in cycle.

Retinoblastoma

Note

ID2 is overexpressed due to transcriptional activation by oncoproteins of the Myc family in retinoblastoma, where it is thought to inhibit Retinoblastoma protein family members (Lasorella et al., 2000; Lasorella et al., 2005).

Hodgkin's lymphoma

Note

The majority of Hodgkin's lymphomas are derived from germinal center B cells. Still, Hodgkin-Reed/Sternberg (HRS) cells of classical Hodgkin's lymphoma have a very atypical phenotype.

This is the result of overexpression of ABF-1 and Id2, which inhibit the function of the B cell-determining transcription factor E2A (Mathas et al., 2006; Renne et al., 2006).

The mechanism resulting in ID2 overexpression, nor the impact of ID2 on cell cycle progression in HRS cells have been demonstrated experimentally yet (Cotta and Medeiros, 2008).

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