DLX2 (distal-less homeobox 2)

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Abstract

DLX2 belongs to the six-member family of DLX genes characterized by a homebox related to that found in the insect Distal-less (Dll) gene. It was the first human homologue to be discovered (Selski et al., 1993; McGuinness et al., 1996).

The six DLX genes are organized as three bigenic pairs with a tail-to-tail orientation (Zerucha et al., 2000) and located on chromosomes where HOX clusters are also found (DLX5/DLX6; 7q21.3, syntenic to the HOXA cluster), (DLX1/DLX2; 2q32 syntenic to the HOXD cluster; Simeone et al., 1994; Zerucha et al., 2000) and (DLX3/DLX4; 17q21.33 syntenic to the HOXB cluster).

During embryonic development DLX genes are involved in the control of appendage and craniofacial morphogenesis and in the differentiation of reproductive organs; in the adult they play a role in bone homeostasis and in the maintenance of tissue integrity (Kraus and Lufkin, 2006).

Identity

Other names: TES-1, TES1
HGNC (Hugo): DLX2
Location: 2q31.1
Local order
Reverse strand of human chromosome 2, from 172964167 to 172967628 - see Figure 1 below. DLX2 forms a bigenic cluster with DLX1 at 2q31.

DNA/RNA

Note

DLX2 is in an inverted convergent orientation from DLX1, with both exons 3 separated by 10.7 kb where two enhancers have been identified and functionally characterized (Zerucha et al., 2000; Sumiyama et al., 2002; Ghanem et al., 2003; Park et al., 2004).

Figure 1. Genomic context of the human DLX1/DLX2 bigenic locus.
While one regulatory element is enough and sufficient to drive proper and full expression of Dlx1/Dlx2 genes based upon mouse reporter assays, other, extragenic elements are involved in the dual regulation of Dlx1 and Dlx2. The imprinting status of the DLX1/DLX2 locus has received much less attention than that of their DLX5/DLX6 paralogs (see their respective cards). However, an epigenetic mechanism linking Dlx2 function with neural stem cell maintenance has been demonstrated in adult mice (Lim et al., 2009). Chromatin immunoprecipitation assays differentiating subventricular zone neural stem cells has shown that the Dlx2 locus is a direct bivalent target of the histone methyltransferase Mll1 (mixed-lineage leukemia 1). Whether such methylation process has a clinical relevance remains to be determined, as altered methylation of DLX2 has been observed in pathogenic conditions, including in primary cells from brain astrocytomas, where hypermethylation of DLX2 CpG island has been observed (Wu et al., 2010).

**Transcription**

Transcription from DLX2 yields two splice variants which share the first two exons, the homeodomain and the N-terminal DLL domain (see Figure 2). The major, mature isoform encodes a 328 AA long transcription factor (34.2 kDa and pI 9.25). Sense isoforms have not been reported for this gene.

**Protein**

**Description**

The major DLX2 isoform is a 328 AA helix-turn-helix homeodomain transcription factor (34.2 kDa and pI 9.5). The ultraconserved homeobox domain spans exons 1 and 2 at 153-211. A second N-terminal DNA binding domain, specific to the DLX2/3/5 clade within the distal-less family, is encoded by exon 1 at AA 51-132. Local composition biases include three poly-glycine and one poly-histidine stretches, and a phosphorylation target serine at 232 (see Figure 3 below).

**Expression**

DLX2 is a predominantly nuclear transcription factor, from the helix-turn-helix group. It transactivates target gene expression in heterodimeric association with other DLX and MSX transcription factors. Its consensus binding site is TTA(G/A)TTGA. Chromatin immunoprecipitation assays have shown that during mouse forebrain development, Dlx2 (along with Dlx1) specifically binds an intergenic enhancer within the Dlx5/Dlx6 locus (see their respective cards), and transactivates their expression (Zerucha et al., 2000; Zhou et al., 2004). Interestingly, regulation of the Dlx5/Dlx6 locus in the developing retina occurs through transactivation by Dlx2 but not Dlx1.
Figure 4. NCBI/COBALT alignment of DLX homeoproteins. Note the disposition according to the DLX 1/4/6 versus DLX 2/3/5 clades. Indicated by a yellow box is the ultraconserved glutamine featured by most homeoproteins at position 50 of the homeodomain.

**Function**

A particularity of Dlx2 is its ability to cooperate with a nuclear non-coding RNA (sense and single-stranded, 440 b), Evf-2, transcribed from the Dlx5/Dlx6 locus, to form a stable complex which binds and transactivates both Dlx5/6 intergenic enhancers (Feng et al., 2006).

While such an RNA/homeoprotein cooperativity has been demonstrated for other factors (Dubnau and Struhl, 1996), it has not been reported so far for other Dlx family members.

On the other hand, Dlx2 has been shown to autorepress its expression during mouse tooth formation when expressed alone, while autoactivating it when expressed in combination with PitX2 (Venugopalan et al., 2011).

This observation lends support to the notion that the transcriptional activity of DLX factors often depends upon cooperative binding with other homeproteins, including from the PTX and MSX families (Zhang et al., 1997; Vieux-Rochas et al., 2013).

**Homology**

With regards to other members of the DLX family, Dlx2 belongs to the DLX2/3/5 clade based on sequence homology (see Figure 4). It shares an N-terminal DLL-like domain specific to this clade. The homeodomain sequence remains close to the other DLX proteins.

**Implicated in**

**Breast tumors and their metastases to bone and lung tissues**

**Note**

Neoplastic processes often result from combinatorial activity of developmental genes (Abate-Shen, 2002). Dysregulated expression of homebox-containing genes of the distal-less family, arranged as three bigenic pairs in mammals (DLX1/2, DLX3/4 and DLX5/6; Kraus and Lufkin, 2006), has been reported to correlate with distinct oncogenic mechanisms.
DLX2 is expressed and necessary but insufficient to initiate metabolic stress-induced necrosis within several solid human high-grade tumors (Lee et al., 2011). DLX2 is strongly expressed in human primary breast tumors, its expression is associated with better prognosis and fewer relapses (Morini et al., 2010). In contrast, DLX2 expression is lost by breast tumor-derived metastatic cells found in lung or bone tissues - a poor prognosis marker (Morini et al., 2010). The combined downregulation of DLX2 and upregulation of DLX5 might thus prove a valuable prognostic marker.

DLX2 has been observed to be one of several homeogenes whose CpG islands were hypermethylated in luminal breast cancer cells, at 1 kb from the transcription start site (Kamalakaran et al., 2011). This status has been found to correlate significantly with higher expression level of DLX2, which lends support to the notion that DLX2 may serve as a candidate prognosis marker in breast cancer (Morini et al., 2010).

**Solid tumors involving other organs**

**Note**

Induction of DLX2 expression has been further reported in other solid tumors, including promoting advanced gastric adenocarcinoma (Tang et al., 2013), promoting growth from lung, prostate and glioma tumors, and correlates with melanoma malignancy (Yilmaz et al., 2011; Yan et al., 2013). It appears that at least one member of each DLX bigenic pair (DLX2, DLX5 and DLX4 : see Hara et al., 2007) is closely implicated with solid tumorigenicty.

**Acute lymphoblastic leukemia**

**Note**

Conversely, DLX2 expression is lost along with DLX3 and DLX4 in samples from patients afflicted by acute lymphoblastic leukemia with t(4;11)(q21;q23) chromosomal abnormality (Ferrari et al., 2003). In the same paper it is also shown that Dlx genes participate to the regulatory cascade initiated by acute lymphoblastic leukemia (ALL)-1, a recurring partner of translocations involving chromosome band 11q23 in human bipherotypic leukemias.

**Autism spectrum disorder**

**Note**

Autism has been recognized as a condition which may result from an imbalance between inhibitory and excitatory processes in the developing and mature brain. Dlx1 and Dlx2 control the specification, fate and metabolic function of a subset of neurons known to exert an inhibitory role in the brain. As part of a cascade of homeobox-containing genes controlling neuronal specification in the brain, the DLX1/2 locus has thus been examined for association with autism spectrum disorder. Extensive coverage of both coding and intergenic sequences among a large cohort of autistic probands has uncovered only a handful of non-synonymous variants - which nevertheless provides a strong set of functional candidates to assess whether disrupted DLX2 expression might play a role in autism (Hamilton et al., 2005). More recently, a large cohort study has pinpointed stronger candidate sites of polymorphism correlated with increased susceptibility to develop the neurologic condition (Liu et al., 2009) - however a direct functional impact remains to be evidenced. Interestingly, DLX2 was found to harbour trinucleotide repeats but as for its DLX6 paralog, family-based association analysis ruled out this polymorphism as a risk variant, in either autism or schizophrenia patients (Laroche et al., 2008).

**Dysmorphogenesis**

**Note**

Although mouse embryos invalidated for Dlx1 and/or Dlx2 display craniofacial abnormalities, a direct involvement of DLX1/DLX2 mutation in human malformations remains to be demonstrated. For instance, while synpolydactyly has been tightly linked to DLX2 (Sarfarazi et al., 1995), it is the lack of induction of its promoter by defective PITX2 which has been demonstrated to directly cause Axenfeld-Rieger syndrome (ARS, OMIM #180500) - an autosomal dominant condition featuring a wide range of tooth anomalies, maxillary hypoplasia, and eye malformation (Espinoza et al., 2002).

**References**


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