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To cite this version:

Yorick Gitton, Giovanni Levi. DLX5 (distal-less homeobox 5). Atlas of Genetics and Cytogenetics in Oncology and Haematology, 2014, 18 (11), pp.810-816. 10.4267/2042/54163 . hal-03092626

HAL Id: hal-03092626

https://hal.science/hal-03092626v1

Submitted on 2 Jan 2021

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Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL INIST-CNRS

Gene Section
Review

DLX5 (distal-less homeobox 5)

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Published in Atlas Database: March 2014

Online updated version : http://AtlasGeneticsOncology.org/Genes/DLX5ID44295ch7q21.html
DOI: 10.4267/2042/54163

This article is an update of :
Xu J, Testa JR. DLX5 (distal-less homeobox 5). Atlas Genet Cytogenet Oncol Haematol 2012;16(8):526-528.

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Abstract

DLX5 belongs to the six-member family of DLX genes characterized by a homeobox related to that found in the insect Distal-less (Dll) gene. 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) 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.

Identity

Other names: SHFM1D

HGNC (Hugo): DLX5

Location: 7q21.3

Local order: -DLX6-**DLX5**-ACN9-

DNA/RNA

Description

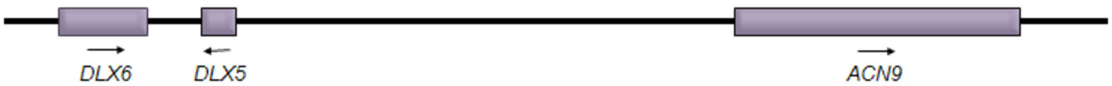
The DLX5 gene is composed of 3 exons spanning a genomic region of 4442 bp.

Genomic features

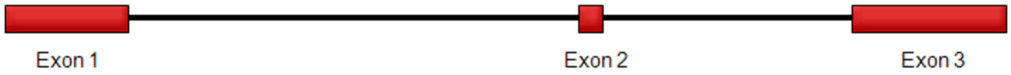
Mutations: Breakpoint analyses of genomic deletions and chromosomal rearrangements in the congenital split-hand/split-foot malformation (SHFM type 1D, OMIM #220600), have shown that positional effect and disrupted regulatory elements controlling DLX5/DLX6 activity are involved in the pathogenesis of this developmental disorder (see further "dysmorphologies").

In-depth sequencing of the candidate regions has shown that the expression of DLX6 depends upon the activity of conserved regulatory elements shared with DLX5, and located both within the DLX5/DLX6 intergenic territory and outside of the locus (Lango Allen et al., 2014).

Furthermore these enhancers have been identified in all examined species - including in mouse where transgenic analyses have allowed the functional characterization of their tissue-specificity.



Local order of DLX5 and flanking genes DLX6 and ACN9 is shown, with centromere at left and telomere (qter) at right. Arrows indicate transcriptional orientation of individual genes. DLX6 gene range: 96635290 - 96640352; DLX5 gene range: 96649702 - 96654143; ACN9 gene range: 96745905 - 96811075 (Hillier et al., 2003).



Exon 1: 1 - 563; exon 2: 2463 - 2647; exon 3: 3767 - 4442.

Moreover, recent analyses of genomic integrity in SHFM1D probands have unravelled two new intragenic, non-synonymous mutations within the open reading frame of DLX5.

Imprinting: The status of parental imprinting of the DLX5/DLX6 locus has recently gained strong interest as these genes have been considered to be putative methylation targets of the methyl-CpG binding protein-2 (MECP2), and thus might be indirectly involved in the aetiology of the Rett syndrome, a severe X-linked neurodevelopmental disorder afflicting girls with MECP2 mutation (see further "Rett syndrome").

Transcription

The DLX5 coding sequence consists of 870 bp from the start of the first codon to the stop codon (Simeone et al., 1994).

Pseudogene

None known.

Protein

Description

The DLX5 protein consists of 289 amino acids with a calculated molecular weight of 31,5 kDa.

The protein contains two motifs, one dubbed homeobox protein distal-less-like N terminal and a second known as a homeodomain.

Localisation

Nucleus.

Function

Transcription factor important in the control of bone formation in embryonic development (Hassan et al., 2004). Transcription from DLX5 yields three splice variants, which range from 1062 b to 1688 b (major isoform) due to alternative splicing sites throughout the precursor transcript. The shortest (Dlx5-002) is not processed. The other two share exon 1 which encodes an N-terminal DLL domain, and exon 2 which encodes a part of the homeodomain. The shorter transcript (DLX5-003) encodes a predicted 191 AA-long, 20.9 kDa isoform with both N-terminal DLL domain and a homeodomain.

It should be observed that in vitro 35S-primed expression from full-length murine Dlx5 yields only one isoform at 32 kDa (Zhang et al., 1997). The latter study provided evidence for an incompatibility between Dlx5 DNA binding to its target homeodomain-responsive element (TAATTA) and heterodimerization with its partner Msx factor.

It further showed that both events were mutually antagonistic, suggesting a regulatory role during Dlx/Msx-controlled morphogenetic processes such as branchial arch and limb formation. During bone formation, Dlx5 (pI 9.3) transactivation activity is enhanced through serine phosphorylation in the nucleus by p38 MAP-kinase upon BMP2 signaling (Ulsamer et al., 2008).

Dlx5 has further been shown to be subjected to threonine phosphorylation by PKA during BMP2-induced osteoblast differentiation, which increases Dlx5 nuclear levels by improving its stability (Han et al., 2011).

Homology

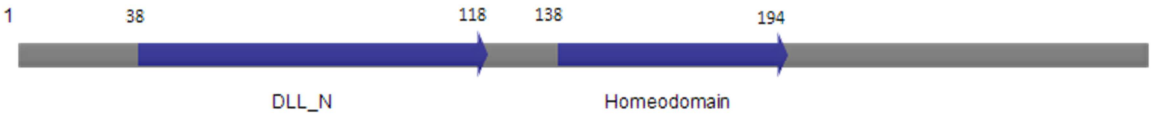
None reported to date.

Mutations

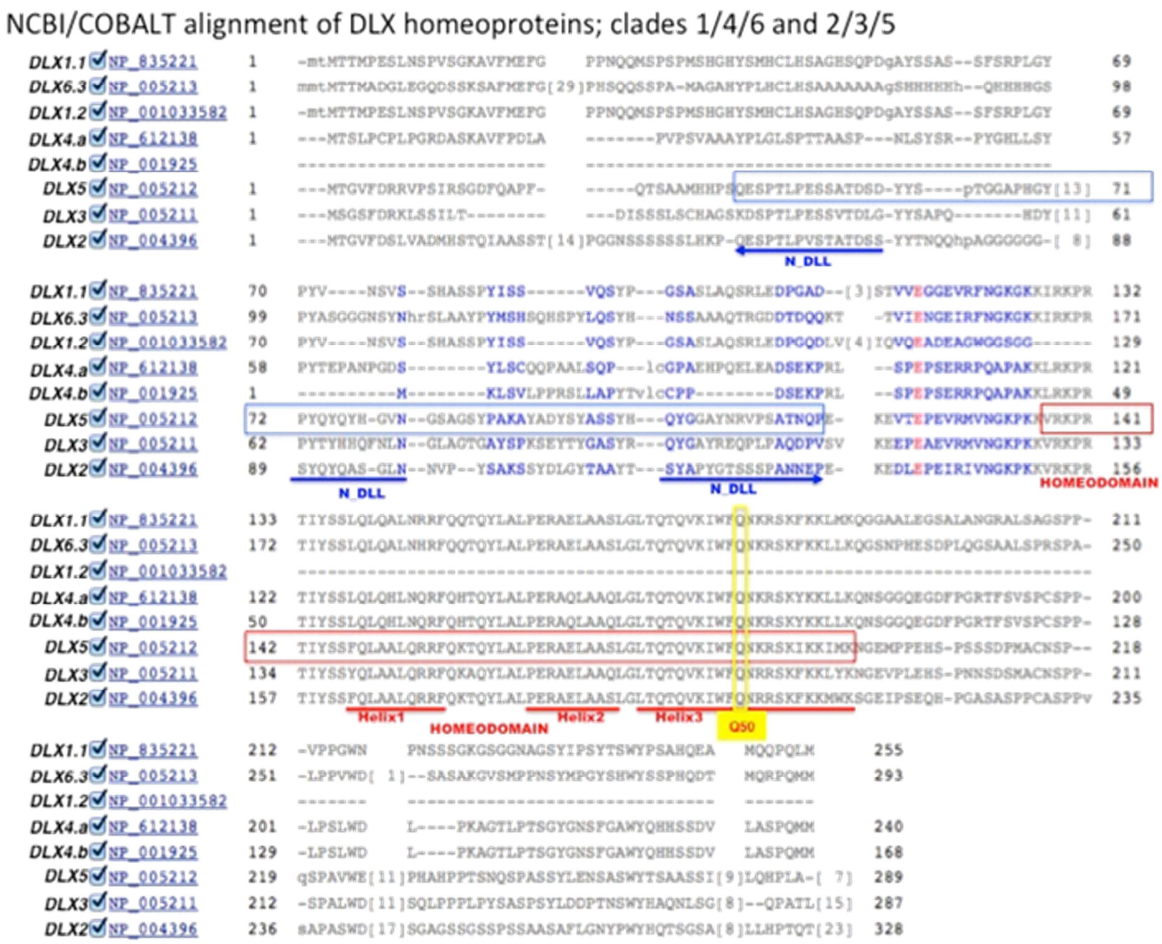
Germinal

A novel DLX5 mutation (c.A533C: p.Q178P) was identified in a family with autosomal recessive split hand and foot malformation (Shamseldin et al., 2012).

Recently, a second rare familial case of SHFM1 has been demonstrated to result, with highest probability, from intragenic missense mutations of a critical glutamine residue in the third helix of the DLX5 homeodomain - Q186H (Wang et al., 2014). The encoded mutant DLX5 has been demonstrated to fail at transactivating a bona fide MYC target.



DLL_N: homeobox protein distal-less-like N terminal; Homeodomain: homeobox DNA binding domain.



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.

Such an observation is not unexpected as this mutation affects Q50, the most conserved residue of all homeoproteins (see diagram above), which numerous biochemical studies have demonstrated to be responsible for the specificity of the DNA recognition at the TAATT homeo-element (for review, Galliot et al., 1999).

Somatic

A DLX5 mutation (c.C119G: p.S40C) was observed in an ovarian carcinoma (Cancer Genome Atlas Research Network, 2011).

Overexpression of DLX5 has been reported in several types of human malignancy including lung cancer (Kato et al., 2008; Xu and Testa, 2009), T-cell lymphoma (Tan et al., 2008), and ovarian cancer (Tan et al., 2010), etc.

Implicated in

Lung cancer

Note

The DLX5 gene was reported to be overexpressed in the great majority of human non-small cell lung cancers examined by Kato et al., 2008. Furthermore, immunohistochemical studies revealed that positive immunostaining for DLX5 correlated with tumor size and poorer prognosis.

A DLX5 transcript isoform has been shown to be strongly overexpressed in a large panel of primary lung cancer samples, providing a reliable prognosis marker (Kato et al., 2008). In this study, the detected isoform (1.8 kb on Northern blot using a probe spanning exon 3 and 3'UTR) was claimed to be found only in the placenta, among 23 normal adult tissues. It should be observed that other studies have reported numerous expression sites in adult human, including bone (osteoblasts and marrow), ear, tooth, fat and brain. With regards to function, down-regulation of DLX5 through RNA interference compromised the growth or survival of two lung cancer cell lines, suggesting that controling DLX5 expression levels might be clinically relevant (Kato et al., 2008).

Lymphoma

Note

DLX5 was found to be highly expressed in 3 of 7 (42%) patient-derived T-cell lymphomas compared with that observed in nonmalignant lymph node

samples (Tan et al., 2008). In addition, these investigators found repeated upregulation of Dlx5 in T-cell lymphomas from transgenic mice in which the Lck promoter was used to drive expression of a constitutively active form of Akt2 in the thymus. Dlx5 was overexpressed due to a novel chromosome inversion that placed the T-cell receptor beta (Tcrb) enhancer region near the Dlx5 locus.

Breast cancer

Note

Both DLX5 and DLX6 were found to be upregulated during metastasis formation after intravenous injection of MDA-MB-231 breast cancer cells. The in vitro treatment of MDA-MB-231 cells with endothelin 1, a peptide associated with breast cancer invasive phenotype, resulted in a switch from DLX2 to DLX5 expression. Mutually exclusive expression of DLX2 and DLX5 was found in both MDA-MB-231 cells and human breast cancer specimens. This evidence suggested that DLX genes are involved in human breast cancer progression, and that expression of DLX2 and DLX5 genes might serve as prognostic markers (Morini et al., 2010).

Astrocytoma

Note

Transcriptional profiling in search for prognosis markers has identified DLX5 as an upregulated candidate for high-grade astrocytomas (Phillips et al., 2006).

Various cancers

Note

DLX5 mRNA is abundantly expressed in many cancer cell lines derived from malignant tissues of breast, brain, lung, skin, and ovarian cancer patients, whereas expression of DLX5 was low or undetectable in tumor cells from patients with leukemia or with colorectal, prostate, and kidney cancers (Tan et al., 2010).

Dysmorphologies

Note

Split hand-foot malformation (SHFM) type 1 with sensory-neural hearing loss (SHFM1D; MIM:220600). This malformative syndrome affects hands and feet alike, resulting in moderate to severe median ray deficiency with syndactily. Among the described six non-syndromic SHFM loci, one spans the DLX5/DLX6 bigenic cluster (Scherer et al., 1994; Crackower et al., 1996). However, numerous reported mutations spare DLX5 or DLX6 open reading frames, suggesting it may rather be their common regulatory elements which is impacted (Robledo et al., 2002; Lo Iacono et al., 2008). However recently, one rare familial case of SHFM1 has been demonstrated to result, with highest probability, from an intragenic missense mutation of the DLX5 homeodomain (Q178P; Shamseldin et al., 2012). In the latter case, a causal link between defective DLX5/DLX6 expression and the pathogenic mechanism impairing limb development remains to be elucidated (Lango Allen et al., 2014).

On a further note, SHFM cases have often been reported to include hearing loss, a trait consistent with a developmental role demonstrated for Dlx5/Dlx6 during ear formation in mouse embryogenesis (Acampora et al., 1999; Merlo et al., 2002; Robledo and Lufkin, 2006; Chatterjee et al., 2010; Frenz et al., 2010). Moreover, both genes are major targets of two regulator genes whose deficiencies are responsible for a related pathogenic condition, the auriculo-condylar syndrome (ACS, Rieder et al., 2012; Brown et al., 2010).

Anorectal malformation associated with SHFM has been reported in a family with a missense mutation in the P63 gene, a known direct upstream regulator of DLX5/DLX6 during morphogenesis (Su et al., 2013). Whether DLX5/DLX6 expression is dysregulated in this condition, and whether this trait can be functionaly associated with the phenotype, remains to be elucidated.

Rett syndrome

Note

DLX5 and DLX6 (OMIM 600028) have been controversial candidates for neurodevelopmental defects progressively afflicting young girls suffering of Rett syndrome (OMIM 312750). This late onset disorder features fatal motor abnormalities, seizures, autism and mental retardation. While the genomic sequence of the DLX5/DXL6 locus remains unaffected in all reported cases, it is a direct target of the transcriptional regulator methyl-CpG-binding protein 2 (MeCP2), which has been strongly associated to this syndrome by linkage analysis (Horike et al., 2005). While still debated (Horike et al., 2005; Schüle et al., 2007; LaSalle, 2007; Miyano et al., 2008), initial MeCP2 deficiency is considered as causing defective neurogenesis through dysregulated expression of DLX5/DLX6, due to altered chromatin state at this target locus (Horike et al., 2005; Lilja et al., 2013). Mouse mutagenesis has substantiated this hypothesis by pinpointing GABA (γ-aminobutyric acid)-releasing neurons as a major cellular target expressing Dlx5 and Dlx6, whose deficiency impairs neurogenesis in MeCP2 null mutant (Chao et al., 2010).

Osteoporosis

Note

Mouse mutational studies have demonstrated a role for Dlx5 and Dlx6 as a major determinant of chondrogenesis and chondrocyte hypertrophy in the

endochondral skeleton, throughout embryogenesis and adulthood (Samee et al., 2007; Samee et al., 2008; Samee et al., 2009). These observations pave the way for a better understanding of human osteoporosis, in particular in patients with dysfunctional regulation of bone-remodeling hormonal levels (Prall et al., 2013).

Reproductive tract

Note

Dlx5 and Dlx6 are involved in the development and function of the reproductive tract. The dual mouse mutant for Dlx5 and Dlx6 displays abnormal urethra formation (Suzuki et al., 2007), reduced testicular steroidogenesis with feminization (Nishida et al., 2008), and early ovarian follicular depletion (Bouhali et al., 2011). A human mutation in a genomic region including DLX5 and DLX6 has been associated to a case of familial premature ovarian failure (Caburet et al., 2012).

Teratology

Note

With regards to pharmacologically-induced teratogenesis, dysregulation of DLX5/DLX6 gene expression has been demonstrated to be a major step during craniofacial embryopathy induced by two compounds:

i) retinoic acid, a vitamin A derivative found in the RoAccutane ® drug, which indirectly prevents the induction of DLX5/DLX6 in human (Lammer et al., 1985; Coberly et al., 1996) and in all animal models investigated (Vieux-Rochas et al., 2007), which share a wide range of jaw and ear malformations;

ii) the food contaminant ochratoxin A, a fungal toxin demonstrated to prevent Dlx5 activation in exposed mouse embryos, which later develop craniofacial malformations (Wei and Sulik, 1993; Napoletano et al., 2010). Although a causal link between Dlx5, Dlx6 and the toxin remains to be functionally demonstrated, this observation may account for teratogenesis observed in human embryos maternally exposed to the toxin (Hope and Hope, 2012; Thrasher et al., 2012).

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This article should be referenced as such:

Gitton Y, Levi G. DLX5 (distal-less homeobox 5). Atlas Genet Cytogenet Oncol Haematol. 2014; 18(11):810-816.