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► **To cite this version:**

Yorick Gitton, Giovanni Levi. DLX6 (distal-less homeobox 6). Atlas of Genetics and Cytogenetics in Oncology and Haematology, 2014, 10.4267/2042/54164 . hal-03092625

**HAL Id: hal-03092625**

**<https://hal.science/hal-03092625>**

Submitted on 2 Jan 2021

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## Gene Section

### Review

# DLX6 (distal-less homeobox 6)

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Published in Atlas Database: March 2014

Online updated version : <http://AtlasGeneticsOncology.org/Genes/DLX6ID52195ch7q21.html>  
DOI: 10.4267/2042/54164

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## Abstract

DLX6 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) 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

**HGNC (Hugo):** DLX6

**Location:** 7q21.3

### Local order

Forward strand of human chromosome 7, from 96634860 to 96640352 - see Figure 1 below. DLX6 forms a bigenic cluster with DLX5 at 7q21.31.

## DNA/RNA

### Description

In contrast to DLX5, no intragenic mutations have been found for DLX6. It is considered that disruption of distant regulatory elements is most usually responsible for DLX5/DLX6-related disorders in human. 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 (see Figure 1; 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.

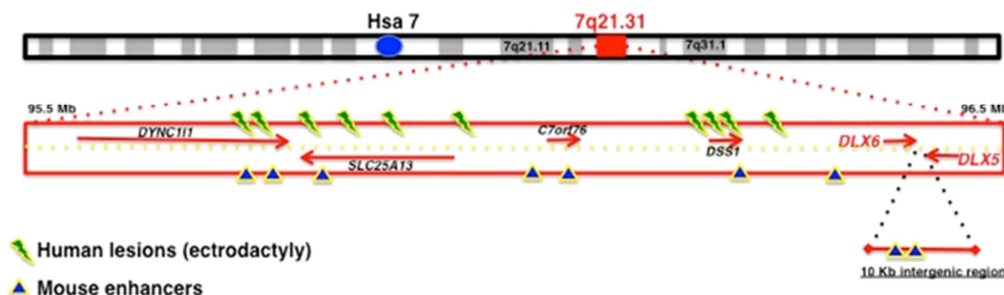


Figure 1. Genomic context of the human DLX5/DLX6 bigenic locus.

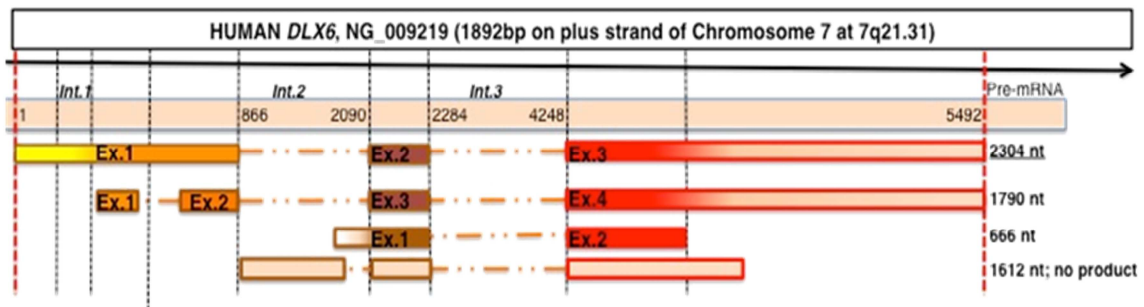


Figure 2. The four known human DLX6 transcripts.

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

Transcription from DLX6 yields four splice variants, one transcript being untranslated (see Figure 2). The three coding ones range from 666 b to 2304 b (major isoform) due to alternative splicing sites throughout the precursor transcript. Furthermore, two antisense non-coding transcripts have been characterized - one of which, Evf2 (Dlx6as/Dlx6os1; HNGC#37151), has been demonstrated to regulate transactivation from an intergenic enhancer of Dlx5/Dlx6 (Feng et al., 2006; Berghoff et al., 2013).

DLX6 sequence analysis of one sporadic SHFM patient (Ferro et al., 2001) has led to the discovery of a longer transcript endowing the N-terminus of DLX6 with an unusual dual poly-glutamine/poly-

proline stretch, 11-20 CAG/CCG repeat long, which has been found to be conserved in mouse (Pfeffer et al., 2001; see further "trinucleotide repeats"). The functional consequences of these expansions upon DLX6 activity remain to be determined.

## Protein

### Description

DLX6 is a 175 AA helix-turn-helix homeodomain transcription factor (19.7 kDa and pI 9.9). The homeodomain spans AA 49-108 across exons 2 and 3 (see Figure 3).

### Function

During mouse craniofacial morphogenesis, Dlx6 acts as transactivator of the helix-loop-helix dHand gene through a regulatory element, [ATTA/TAAT], which does not bind other Dlx factors. Noticeably, this binding is a specifically endothelin-1 signaling-dependent mechanism. Thus, despite sharing regulatory elements and subsequent expression patterns with Dlx5, the Dlx6 factor appears to be competent to exert selective roles depending upon specific cellular signalling contexts.

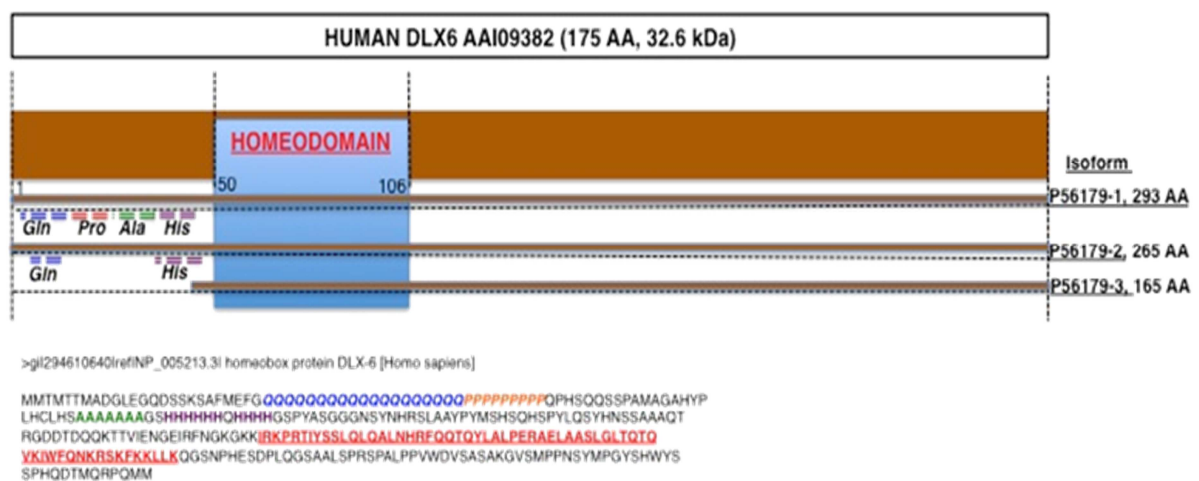


Figure 3. Structure of the three DLX6 protein isoforms. Sequence below belongs to the longest isoform. Note the N-terminal series of poly-residue stretches.

## NCBI/COBALT alignment of DLX homeoproteins; clades 1/4/6 and 2/3/5

DLX1.1	NP_835221	1	-mtMTTPESLNSPVSGKAVFMEFG	FPNQMSFSPMSHGYSMHCLESAGESQPDqAYSSAS--SFSRPLGY	69	
DLX6.3	NP_005213	1	mtMTTMADGLEQDSSKSAFMEFG[29]	PHSQSSPA--MAGAHYPLHCLHSAIAAAAAAqSHRHHh--QHRRHGS	98	
DLX1.2	NP_001033582	1	-mtMTTPESLNSPVSGKAVFMEFG	FPNQMSFSPMSHGYSMHCLESAGESQPDqAYSSAS--SFSRPLGY	69	
DLX4.a	NP_612138	1	---MTSLPCLPGRDASKAVFPDLA	-----FVPSVAAAYPLGLSPPTAASF---NLSYSR--FYGHLLSY	57	
DLX4.b	NP_001925		-----	-----		
DLX5	NP_005212	1	---HTGVFDRRVPFIRSGDFQAFP--	-----QTSAAAHHPFQESPTLPESATDSD--YYS---pTQGAfHGY[13]	71	
DLX3	NP_005211	1	---MSGGFDRKLSILT-----	---DISSLSCHAGSKDPTLPESSTVDLG--YYSAPQ-----HDY[11]	61	
DLX2	NP_004396	1	---MTGVFDSLVDHMSTQIAASST[14]	PGGNSSSSSLKHP--QESPTLPVSTATDSS--YTTNQHpaAGGGGGG-[8]	88	
				N DLL		
DLX1.1	NP_835221	70	FYV---NSVS--SHASSPYISS-----VQSYF--GSASLAQSRLEDPGAD--[3]	STVVEGGVEFRNGKGGKIRKPR	132	
DLX6.3	NP_005213	99	FYASGGGNSYNhrSLAAYPYMHSQHSPLYQSYH--NSSAAQTRGDDTQOKT	-TVIENGEIRFNGKGGKIRKPR	171	
DLX1.2	NP_001033582	70	FYV---NSVS--SHASSPYISS-----VQSYF--GSASLAQSRLEDPGQDLV[4]	IQVQFADEAGWGGGG-----	129	
DLX4.a	NP_612138	58	FYTEFANPGDS-----YLSCQPAALSQP--lcGPAEHPQELADSEKPRL	--SPEPSERRPQAPAKKLRKPR	121	
DLX4.b	NP_001925	1	-----M-----KLSVLFPRSLAPITVlcCFP-----DSEKPRL	--SPEPSERRPQAPAKKLRKPR	49	
DLX5	NP_005212	72	FYQYQYH-GVN--GSAGSYPAKAYADSYASSYH--QYGGAYNRVPSATNQPE-	KEVTFPEVRMVNGKPKVVRKPR	141	
DLX3	NP_005211	62	FYTYHHQFNLN--GLAGTGAYSPKSEYTYGASYSR--QYGAYREQPLPAQDPVSV	KEEPEAEVRMVNGKPKVVRKPR	133	
DLX2	NP_004396	89	SYOYQAS--GLN--NVP--YSAKSYDLGYTAAYT--SYAPYGTSSSPANPEP-	KEDLEPEIRIVNGKPKVVRKPR	156	
			N DLL	N DLL	HOMEODOMAIN	
DLX1.1	NP_835221	133	TIYSSLQLQALNRRFQQTQYLALPERAEAAASLGLTQTVKIFWFKRKSFKFKLMKQGGAALEG	SALANGRLSAGSFP--	211	
DLX6.3	NP_005213	172	TIYSSLQLQALNRRFQQTQYLALPERAEAAASLGLTQTVKIFWFKRKSFKFKLLKQGSNPH	ESDPLQGSAAALSPPSPA--	250	
DLX1.2	NP_001033582		-----	-----		
DLX4.a	NP_612138	122	TIYSSLQLQHLNORFQHTQYLALPERAAALAAQLGLTQTVKIFWFKRKSFKFKLLKQNSGG	QEGDFPGRTRFSVSPCSFP--	200	
DLX4.b	NP_001925	50	TIYSSLQLQHLNORFQHTQYLALPERAAALAAQLGLTQTVKIFWFKRKSFKFKLLKQNSGG	QEGDFPGRTRFSVSPCSFP--	128	
DLX5	NP_005212	142	TIYSSFLAALQRRFQKTQYLALPERAEAAASLGLTQTVKIFWFKRKSFKFKLMKQGGAA	LEGMPFPHS--PSSSDPKNACNSP--	218	
DLX3	NP_005211	134	TIYSSFLAALQRRFQKAQYLALPERAEAAALAAQLGLTQTVKIFWFKRKSFKFKLYKNGE	VPLEHS--PNSSDSNACNSP--	211	
DLX2	NP_004396	157	TIYSSFLAALQRRFQKTQYLALPERAEAAASLGLTQTVKIFWFKRKSFKFKMKSGEIPSE	QEP--PGASASFPFCAFPV	235	
			Helix1	Helix2	Helix3	
			HOMEODOMAIN	Q50		
DLX1.1	NP_835221	212	-VPPGWN	PNSSSGKSGGNAGSYIPLYTSWYPSARQEA	MQQPQLM	255
DLX6.3	NP_005213	251	-LPPVWD[1]	--SASAKGVSMPPNSYHMGYSHWYSSPHQDT	NQRPQMM	293
DLX1.2	NP_001033582		-----	-----		
DLX4.a	NP_612138	201	-LPSLWD	L----PKAGTLPTSQYGNISFGAWYQHSSSDV	LASPQMM	240
DLX4.b	NP_001925	129	-LPSLWD	L----PKAGTLPTSQYGNISFGAWYQHSSSDV	LASPQMM	168
DLX5	NP_005212	219	qSPAVWE[11]	PHAHPPTSNQGSPASSYLENSASWYTSAASSI[9]	LQHPLA-[7]	289
DLX3	NP_005211	212	-SPALWD[11]	SQLPPLPYASPSYLDQPTNSWYHAQNLGG[8]	--QPATL[15]	287
DLX2	NP_004396	236	APASWD[17]	SGAGSSGSSPSSAASAFIGNYPWYHQTSGSA[8]	LLHPTQT[23]	328

**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.

As other DLX factors, DLX6 modulates target genes expression through a domain which is distinct from the DNA-binding homeodomain, and in association within transactivating complexes which include MSX.

Composition biases in DLX6 include one poly-Gly and one-His stretches (see Figure 3).

Of note, DLX6 encodes for one long isoform endowed with a contiguous series of residue stretches including glutamine, proline, alanine and histidine (see Figure 3).

### Homology

With regards to other members of the DLX family, DLX6 belongs to the DLX1/4/6 clade based on sequence homology (see Figure 4). It shares a lack of N-terminal DLL-like domain specific to the other clade constituted by DLX2/3/5. The homeodomain remains close to all other DLX proteins.

## Implicated in

### Lung cancers

#### Note

Neoplastic processes often result from

combinatorial activity of developmental genes (Abate-Shen, 2002).

Dysregulated expression of homeobox-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.

DLX6 along with DLX5 is a direct MYC oncogene inducer, responsible for neoplastic initiation in many cancers, including lymphoma and lung cancers (Xu and Testa, 2009).

### Breast cancers and their bone metastases

#### Note

DLX6, together with DLX5, is upregulated in lung and bone metastatic cells derived from primary breast tumors in human - a pattern associated with tumour aggressivity and thus, poor prognosis and increased relapses (Morini et al., 2010). Transcriptional profiling in search for prognosis markers has identified DLX6 as an upregulated candidate for high-grade astrocytomas (Phillips et al., 2006).

## Dysmorphologies

### Note

DLX6 is often regarded as a functional substitute of DLX5 and autonomous regulation as been seldom observed; one rare such situation being the Endothelin-1→Endothelin-Ra→Dlx6→Hand2 signalling cascade which specifies lower jaw identity in the mouse embryo (Charité et al., 2001). As such, malformations described for DLX5 are commonly regarded as involving DLX6. In most mouse mutant models, severe phenotypes result from dual invalidation of Dlx5 and Dlx6. Malformative processes implying DLX6 will thus be simultaneously described on the DLX5 gene card.

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). 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, two rare familial cases of SHFM1 have been demonstrated to result, with highest probability, from intragenic missense mutations of two critical glutamine residues in the third helix of the DLX5 homeodomain (Q178P reported in Shamseldin et al., 2012; and Q186H characterized in Wang et al., 2014). In the first case, a causal link between defective DLX5/DLX6 expression and the pathogenic mechanism impairing limb development remains to be elucidated. In the second case, the mutated DLX5 has been demonstrated to fail at transactivating its bona fide MYC target. Such an observation is not unexpected as the mutation affects Q50, the most conserved residue of all homeoproteins (see diagram), 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).

Other pathogenetic processes: 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).

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 functionally associated with the phenotype, remains to be elucidated.

## Trinucleotide repeats

### Note

The first DLX6 exon harbours a trinucleotide repeat region of 11 to 20 CAG triplets in normal, heterozygous subjects. This CAG repeat is highly polymorphic (Pfeffer et al., 2001). While no obvious phenotype was associated with this newly discovered polymorphism in the investigated cohort, such repeat length variations are critical determinants of colon carcinogenesis and neurodegenerative disorder when occurring in the androgen receptor and huntingtin genes, respectively.

## Rett syndrome

### Note

DLX6 and DLX5 (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/DLX6 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 ( $\gamma$ -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., 2008), 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 prevents the induction of Dlx5/Dlx6 in all animal models investigated (Vieux-Rochas et al., 2007; Vieux-Rochas et al., 2010); this discovery has given strong insight into the aetiology of teratologic impact of fetal exposure to RoAccutane medication in man.

Analyses of retinoic acid-induced embryopathy in mouse neurulas have demonstrated that retinoic acid exposure prevents proper induction of both Dlx5 and Dlx6 by endothelin-1 signalling.

This disruption has been found to be finely tuned during a surprisingly short timeframe spanning a critical period of neurulation.

This exposure creates a functional invalidation of Dlx5/Dlx6-controlled cranio-facial morphogenesis (reviewed in Gitton et al., 2010);

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. DLX6 (distal-less homeobox 6). *Atlas Genet Cytogenet Oncol Haematol*. 2014; 18(11):817-823.

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