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## Gene Section

### Review

# DLX5 (distal-less homeobox 5)

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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

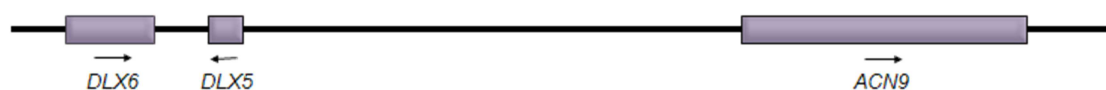
The DLX5 gene is composed of 3 exons spanning a genomic region of 4442 bp.

### Genomic features

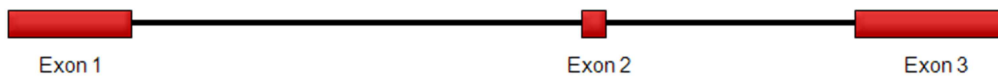
**Mutations:** Breakpoint analyses of genomic deletions and chromosomal rearrangements in the congenital split-hand/split-foot malformation (SHFM type 1D, OMIM #220600), have shown that positional effect and disrupted regulatory elements controlling DLX5/DLX6 activity are involved in the pathogenesis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

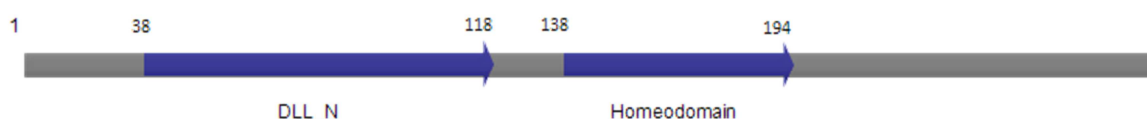
None reported to date.

## 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; clades 1/4/6 and 2/3/5

DLX1.1	NP_835221	1	-mtMTMPESLNSFVSGKAVFMEFG	FPNQMSPPMSHGYSMHCLHSAGHSQPDgAYSSAS--SFSRPLGY	69
DLX6.3	NP_005213	1	mtMTTMADGLEGGSSKSAFMEFG[29]	PNSQQSSPA--MAGAHYPLHCLHSAAAAAAAgSHHHEHh--QHEHNGS	98
DLX1.2	NP_001033582	1	-mtMTMPESLNSFVSGKAVFMEFG	FPNQMSPPMSHGYSMHCLHSAGHSQPDgAYSSAS--SFSRPLGY	69
DLX4.a	NP_612138	1	---MTSLPCPLPGRDASKAVFDLA	---PVPVAAAAYPLGLSPTTAASF---NLSYSR--PYGHLISY	57
DLX4.b	NP_001925		-----	-----	
DLX5	NP_005212	1	---MTGVFDRRVPSIRSGDFQAPF-	----QTSAAMHHPQESPTLPESSTATDSD--YYS---pTGAPHGY[13]	71
DLX3	NP_005211	1	---MSGSFDRKLSILT-----	---DISSLSCHAGSKDSPTLPESSVTDLG--YYSAPQ-----HDY[11]	61
DLX2	NP_004396	1	---MTGVFDSLVDHMSTQIAASST[14]	PGGNSSSSSLHKP--QESPTLPVSTATDSS--YTTNQhpaGGGGG-[8]	88
				N DLL	
DLX1.1	NP_835221	70	PVY---NSVS--SHASSFYISS-----VQSYF--GSASLAQSRLEDPGAD--[3]	STVVEGGEVRFNGKGIKIRKPR	132
DLX6.3	NP_005213	99	PYASGGGNSYhSLAAYFYMSHQHSYLYQSYH---NSSAAAQTRGDDTDQQKT	-TVIENGEIRFNGKGIKIRKPR	171
DLX1.2	NP_001033582	70	PVY---NSVS--SHASSFYISS-----VQSYF--GSASLAQSRLEDPGQDLV[4]	IQVQEADEAGWGGGG-----	129
DLX4.a	NP_612138	58	PYTEPANFGDS-----YLSGQPPAALSQP---lcGPAEHPQLEADSEKPRL	--SPESERRPQAPAKKLRKPR	121
DLX4.b	NP_001925	1	-----M-----KLSVLPFRSLLAPYTVlcCFP-----DSEKPRL	--SPESERRPQAPAKKLRKPR	49
DLX5	NP_005212	72	PYQYQYH-GVN--GSAGSYPAKAYADYSYASSYH---QYGGAYNRVPSATNQHE	KEVTEPEVKMVMNGKPKVVRKPR	141
DLX3	NP_005211	62	PYTYHHQFNLN--GLACTGAYSPKSEYTYGASYSR---QYGAYREQPLFAQDFVSV	KEEPEAEVVMVNGKPKVVRKPR	133
DLX2	NP_004396	89	SYOYQAS-GLN--NVF--YSAKSYDLYGTYAATT---SYAPYGTSSSPANNEPE-	KEDLEPEIRIVNGKPKVVRKPR	156
			N DLL	HOMEODOMAIN	
DLX1.1	NP_835221	133	TIYSSQLQALNRRFQQTQYLALPERAEAAASLGLTQTQVKIWFQKRSKFKKLMKQGGAALEGSALANGRALSGSPF-		211
DLX6.3	NP_005213	172	TIYSSQLQALNRRFQQTQYLALPERAEAAASLGLTQTQVKIWFQKRSKFKKLLKQGSNPHESDPLQGSAALESFSPA-		250
DLX1.2	NP_001033582		-----		
DLX4.a	NP_612138	122	TIYSSLOLQHLNORFQHTOYLALPERAAQAAQLGLTQTOVKIWFQKRSKFKKLLKQNSGGQEGDFPGRITFSVSPCSPF-		200
DLX4.b	NP_001925	50	TIYSSLOLQHLNORFQHTOYLALPERAAQAAQLGLTQTOVKIWFQKRSKFKKLLKQNSGGQEGDFPGRITFSVSPCSPF-		128
DLX5	NP_005212	142	TIYSSYQALQRRFQKQYLYALPERAEAAASLGLTQTQVKIWFQKRSKFKKIMKNGEMPFENS-FSSSDPMACNSP-		218
DLX3	NP_005211	134	TIYSSYQALQRRFQKQYLYALPERAEAAQGLTQTQVKIWFQKRSKFKKLYKNGEVPLEHS-PNNSDSMACNSP-		211
DLX2	NP_004396	157	TIYSSYQALQRRFQKQYLYALPERAEAAASLGLTQTQVKIWFQKRSKFKKMKKSGEIPSEQH-PGASAFPCASFPV		235
			Helix1 HOMEODOMAIN Helix2 Helix3 Q50		
DLX1.1	NP_835221	212	-VPPGWN PNSSSGKSGSGNAGSYI PSYTSWYPSARQEA MQQPQLM	255	
DLX6.3	NP_005213	251	-LPPVWD[1]--SASAKGVSMFPNSYMPGYSHWYSSPHQDT MQRPQMK	293	
DLX1.2	NP_001033582		-----		
DLX4.a	NP_612138	201	-LPSLWD L---PKAGTLPTS GYGNSFGAMYQHSSDV LASPQMM	240	
DLX4.b	NP_001925	129	-LPSLWD L---PKAGTLPTS GYGNSFGAMYQHSSDV LASPQMM	168	
DLX5	NP_005212	219	qSPAVWE[11]PHAHPPTSNQSPASSYLENSASWYSAASSI[9]LQHPLA-[7]	289	
DLX3	NP_005211	212	-SPALWD[11]SQLPPLFYSASPSYLDOPNSWYHAQLNSG[8]--QPATL[15]	287	
DLX2	NP_004396	236	SPASWD[17]SGAGSSGSSPSSAASFLGNYPWYHQTSGSA[8]LLHPTQT[23]	328	

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 controlling 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 syndactyly. 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 functionally 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/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., 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).

## References

- Lammer EJ, Chen DT, Hoar RM, Agnish ND, Benke PJ, Braun JT, Curry CJ, Fernhoff PM, Grix AW Jr, Lott IT. Retinoic acid embryopathy. *N Engl J Med.* 1985 Oct 3;313(14):837-41
- Wei X, Sulik KK. Pathogenesis of craniofacial and body wall malformations induced by ochratoxin A in mice. *Am J Med Genet.* 1993 Nov 1;47(6):862-71
- Scherer SW, Poorkaj P, Massa H, Soder S, Allen T, Nunes M, Geshuri D, Wong E, Belloni E, Little S. Physical mapping of the split hand/split foot locus on chromosome 7 and implication in syndromic ectrodactyly. *Hum Mol Genet.* 1994 Aug;3(8):1345-54
- Simeone A, Acampora D, Pannese M, D'Esposito M, Stornaiuolo A, Gulisano M, Mallamaci A, Kastury K, Druck T, Huebner K. Cloning and characterization of two members of the vertebrate Dlx gene family. *Proc Natl Acad Sci U S A.* 1994 Mar 15;91(6):2250-4
- Coberly S, Lammer E, Alashari M. Retinoic acid embryopathy: case report and review of literature. *Pediatr Pathol Lab Med.* 1996 Sep-Oct;16(5):823-36
- Crackower MA, Scherer SW, Rommens JM, Hui CC, Poorkaj P, Soder S, Cobben JM, Hudgins L, Evans JP, Tsui LC. Characterization of the split hand/split foot malformation locus SHFM1 at 7q21.3-q22.1 and analysis of a candidate gene for its expression during limb development. *Hum Mol Genet.* 1996 May;5(5):571-9
- Zhang H, Hu G, Wang H, Scivolino P, Iler N, Shen MM, Abate-Shen C. Heterodimerization of Msx and Dlx homeoproteins results in functional antagonism. *Mol Cell Biol.* 1997 May;17(5):2920-32
- Galliot B, de Vargas C, Miller D. Evolution of homeobox genes: Q50 Paired-like genes founded the Paired class. *Dev Genes Evol.* 1999 Mar;209(3):186-97
- Acampora D, Merlo GR, Paleari L, Zerega B, Postiglione MP, Mantero S, Bober E, Barbieri O, Simeone A, Levi G. Craniofacial, vestibular and bone defects in mice lacking the Distal-less-related gene Dlx5. *Development.* 1999 Sep;126(17):3795-809
- Zerucha T, Stühmer T, Hatch G, Park BK, Long Q, Yu G, Gambarotta A, Schultz JR, Rubenstein JL, Ekker M. A highly conserved enhancer in the Dlx5/Dlx6 intergenic region is the site of cross-regulatory interactions between Dlx genes in the embryonic forebrain. *J Neurosci.* 2000 Jan 15;20(2):709-21
- Abate-Shen C. Deregulated homeobox gene expression in cancer: cause or consequence? *Nat Rev Cancer.* 2002 Oct;2(10):777-85
- Merlo GR, Paleari L, Mantero S, Zerega B, Adamska M, Rinkwitz S, Bober E, Levi G. The Dlx5 homeobox gene is essential for vestibular morphogenesis in the mouse embryo through a BMP4-mediated pathway. *Dev Biol.* 2002 Aug 1;248(1):157-69
- Robledo RF, Rajan L, Li X, Lufkin T. The Dlx5 and Dlx6 homeobox genes are essential for craniofacial, axial, and appendicular skeletal development. *Genes Dev.* 2002 May 1;16(9):1089-101
- Hillier LW, Fulton RS, Fulton LA, Graves TA, Pepin KH, Wagner-McPherson C, Layman D, Maas J, Jaeger S, Walker R, Wylie K, Sekhon M, Becker MC, O'Laughlin MD, Schaller ME, Fewell GA, Delehaunty KD, Miner TL, Nash WE, Cordes M, Du H, Sun H, Edwards J, Bradshaw-Cordum H, Ali J, Andrews S, Isak A, Vanbrunt A, Nguyen C, Du F, Lamar B, Courtney L, Kalicki J, Ozersky P, Bielicki L, Scott K, Holmes A, Harkins R, Harris A, Strong CM, Hou S, Tomlinson C, Dauphin-Kohlberg S, Kozlowicz-Reilly A, Leonard S, Rohlfing T, Rock SM, Tin-Wollam AM, Abbott A, Minx P, Maupin R, Strowmatt C, Latreille P, Miller N, Johnson D, Murray J, Woessner JP, Wendl MC, Yang SP, Schultz BR, Wallis JW, Spieth J, Bieri TA, Nelson JO, Berkowicz N, Wohldmann PE, Cook LL, Hickenbotham MT, Eldred J, Williams D, Bedell JA, Mardis ER, Clifton SW, Chissoe SL, Marra MA, Raymond C, Haugen E, Gillett W, Zhou Y, James R, Phelps K, Iadonoto S, Bubb K, Simms E, Levy R, Clendenning J, Kaul R, Kent WJ, Furey TS, Baertsch RA, Brent MR, Keibler E, Flicek P, Bork P, Suyama M, Bailey JA, Portnoy ME, Torrents D, Chinwalla AT, Gish WR, Eddy SR, McPherson JD, Olson MV, Eichler EE, Green ED, Waterston RH, Wilson RK. The

- DNA sequence of human chromosome 7. *Nature*. 2003 Jul 10;424(6945):157-64
- Hassan MQ, Javed A, Morasso MI, Karlin J, Montecino M, van Wijnen AJ, Stein GS, Stein JL, Lian JB. Dlx3 transcriptional regulation of osteoblast differentiation: temporal recruitment of Msx2, Dlx3, and Dlx5 homeodomain proteins to chromatin of the osteocalcin gene. *Mol Cell Biol*. 2004 Oct;24(20):9248-61
- Horike S, Cai S, Miyano M, Cheng JF, Kohwi-Shigematsu T. Loss of silent-chromatin looping and impaired imprinting of DLX5 in Rett syndrome. *Nat Genet*. 2005 Jan;37(1):31-40
- Phillips HS, Kharbanda S, Chen R, Forrest WF, Soriano RH, Wu TD, Misra A, Nigro JM, Colman H, Soroceanu L, Williams PM, Modrusan Z, Feuerstein BG, Aldape K. Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. *Cancer Cell*. 2006 Mar;9(3):157-73
- Robledo RF, Lufkin T. Dlx5 and Dlx6 homeobox genes are required for specification of the mammalian vestibular apparatus. *Genesis*. 2006 Sep;44(9):425-37
- LaSalle JM. The Odyssey of MeCP2 and parental imprinting. *Epigenetics*. 2007 Jan-Mar;2(1):5-10
- Samee N, de Vernejoul MC, Levi G. Role of DLX regulatory proteins in osteogenesis and chondrogenesis. *Crit Rev Eukaryot Gene Expr*. 2007;17(3):173-86
- Schüle B, Li HH, Fisch-Kohl C, Purmann C, Francke U. DLX5 and DLX6 expression is biallelic and not modulated by MeCP2 deficiency. *Am J Hum Genet*. 2007 Sep;81(3):492-506
- Vieux-Rochas M, Coen L, Sato T, Kurihara Y, Gitton Y, Barbieri O, Le Blay K, Merlo G, Ekker M, Kurihara H, Janvier P, Levi G. Molecular dynamics of retinoic acid-induced craniofacial malformations: implications for the origin of gnathostome jaws. *PLoS One*. 2007 Jun 6;2(6):e510
- Kato T, Sato N, Takano A, Miyamoto M, Nishimura H, Tsuchiya E, Kondo S, Nakamura Y, Daigo Y. Activation of placenta-specific transcription factor distal-less homeobox 5 predicts clinical outcome in primary lung cancer patients. *Clin Cancer Res*. 2008 Apr 15;14(8):2363-70
- Lo Iacono N, Mantero S, Chiarelli A, Garcia E, Mills AA, Morasso MI, Costanzo A, Levi G, Guerrini L, Merlo GR. Regulation of Dlx5 and Dlx6 gene expression by p63 is involved in EEC and SHFM congenital limb defects. *Development*. 2008 Apr;135(7):1377-88
- Miyano M, Horike S, Cai S, Oshimura M, Kohwi-Shigematsu T. DLX5 expression is monoallelic and Dlx5 is up-regulated in the Mecp2-null frontal cortex. *J Cell Mol Med*. 2008 Aug;12(4):1188-91
- Nishida H, Miyagawa S, Vieux-Rochas M, Morini M, Ogino Y, Suzuki K, Nakagata N, Choi HS, Levi G, Yamada G. Positive regulation of steroidogenic acute regulatory protein gene expression through the interaction between Dlx and GATA-4 for testicular steroidogenesis. *Endocrinology*. 2008 May;149(5):2090-7
- Samee N, Geoffroy V, Marty C, Schiltz C, Vieux-Rochas M, Levi G, de Vernejoul MC. Dlx5, a positive regulator of osteoblastogenesis, is essential for osteoblast-osteoclast coupling. *Am J Pathol*. 2008 Sep;173(3):773-80
- Suzuki K, Haraguchi R, Ogata T, Barbieri O, Alegria O, Vieux-Rochas M, Nakagata N, Ito M, Mills AA, Kurita T, Levi G, Yamada G. Abnormal urethra formation in mouse models of split-hand/split-foot malformation type 1 and type 4. *Eur J Hum Genet*. 2008 Jan;16(1):36-44
- Tan Y, Timakhov RA, Rao M, Altomare DA, Xu J, Liu Z, Gao Q, Jhanwar SC, Di Cristofano A, Wiest DL, Knepper JE, Testa JR. A novel recurrent chromosomal inversion implicates the homeobox gene Dlx5 in T-cell lymphomas from Lck-Akt2 transgenic mice. *Cancer Res*. 2008 Mar 1;68(5):1296-302
- Ulsamer A, Ortuño MJ, Ruiz S, Susperregui AR, Osses N, Rosa JL, Ventura F. BMP-2 induces Osterix expression through up-regulation of Dlx5 and its phosphorylation by p38. *J Biol Chem*. 2008 Feb 15;283(7):3816-26
- Samee N, Geoffroy V, Marty C, Schiltz C, Vieux-Rochas M, Clément-Lacroix P, Belleville C, Levi G, de Vernejoul MC. Increased bone resorption and osteopenia in Dlx5 heterozygous mice. *J Cell Biochem*. 2009 Aug 1;107(5):865-72
- Xu J, Testa JR. DLX5 (distal-less homeobox 5) promotes tumor cell proliferation by transcriptionally regulating MYC. *J Biol Chem*. 2009 Jul 31;284(31):20593-601
- Morini M, Astigiano S, Gitton Y, Emionite L, Mirisola V, Levi G, Barbieri O. Mutually exclusive expression of DLX2 and DLX5/6 is associated with the metastatic potential of the human breast cancer cell line MDA-MB-231. *BMC Cancer*. 2010 Nov 25;10:649
- Brown KK, Reiss JA, Crow K, Ferguson HL, Kelly C, Fritsch B, Morton CC. Deletion of an enhancer near DLX5 and DLX6 in a family with hearing loss, craniofacial defects, and an inv(7)(q21.3q35). *Hum Genet*. 2010 Jan;127(1):19-31
- Chao HT, Chen H, Samaco RC, Xue M, Chahrour M, Yoo J, Neul JL, Gong S, Lu HC, Heintz N, Ekker M, Rubenstein JL, Noebels JL, Rosenmund C, Zoghbi HY. Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes. *Nature*. 2010 Nov 11;468(7321):263-9
- Chatterjee S, Kraus P, Lufkin T. A symphony of inner ear developmental control genes. *BMC Genet*. 2010 Jul 16;11:68
- Frenz DA, Liu W, Cvekl A, Xie Q, Wassef L, Quadro L, Niederreither K, Maconochie M, Shanske A. Retinoid signaling in inner ear development: A "Goldilocks" phenomenon. *Am J Med Genet A*. 2010 Dec;152A(12):2947-61
- Napoletano M, Pennino D, Izzo G, de Maria S, Ottaviano R, Ricciardi M, Mancini R, Schiattarella A, Farina E, Metafora S, Carteni M, Ritieni A, Minucci S, Morelli F. Ochratoxin A induces craniofacial malformation in mice acting on Dlx5 gene expression. *Front Biosci (Elite Ed)*. 2010 Jan 1;2:133-42
- Tan Y, Cheung M, Pei J, Menges CW, Godwin AK, Testa JR. Upregulation of DLX5 promotes ovarian cancer cell proliferation by enhancing IRS-2-AKT signaling. *Cancer Res*. 2010 Nov 15;70(22):9197-206
- Bouhali K, Dipietromaria A, Fontaine A, Caburet S, Barbieri O, Bellessort B, Fellous M, Veitia RA, Levi G. Allelic reduction of Dlx5 and Dlx6 results in early follicular depletion: a new mouse model of primary ovarian insufficiency. *Hum Mol Genet*. 2011 Jul 1;20(13):2642-50
- . Integrated genomic analyses of ovarian carcinoma. *Nature*. 2011 Jun 29;474(7353):609-15
- Han Y, Jin YH, Yum J, Jeong HM, Choi JK, Yeo CY, Lee KY. Protein kinase A phosphorylates and regulates the

osteogenic activity of Dlx5. *Biochem Biophys Res Commun.* 2011 Apr 15;407(3):461-5

Caburet S, Zavadakova P, Ben-Neriah Z, Bouhali K, Dipietromaria A, Charon C, Besse C, Laissue P, Chalifa-Caspi V, Christin-Maitre S, Vaiman D, Levi G, Veitia RA, Fellous M. Genome-wide linkage in a highly consanguineous pedigree reveals two novel loci on chromosome 7 for non-syndromic familial Premature Ovarian Failure. *PLoS One.* 2012;7(3):e33412

Hope JH, Hope BE. A review of the diagnosis and treatment of Ochratoxin A inhalational exposure associated with human illness and kidney disease including focal segmental glomerulosclerosis. *J Environ Public Health.* 2012;2012:835059

Rieder MJ, Green GE, Park SS, Stamper BD, Gordon CT, Johnson JM, Cuniff CM, Smith JD, Emery SB, Lyonnet S, Amiel J, Holder M, Heggie AA, Bamshad MJ, Nickerson DA, Cox TC, Hing AV, Horst JA, Cunningham ML. A human homeotic transformation resulting from mutations in *PLCB4* and *GNAI3* causes auriculocondylar syndrome. *Am J Hum Genet.* 2012 May 4;90(5):907-14

Shamseldin HE, Faden MA, Alashram W, Alkuraya FS. Identification of a novel *DLX5* mutation in a family with autosomal recessive split hand and foot malformation. *J Med Genet.* 2012 Jan;49(1):16-20

Thrasher JD, Gray MR, Kilburn KH, Dennis DP, Yu A. A water-damaged home and health of occupants: a case study. *J Environ Public Health.* 2012;2012:312836

Lilja T, Wallenborg K, Björkman K, Albåge M, Eriksson M,

Lagercrantz H, Rohdin M, Hermanson O. Novel alterations in the epigenetic signature of MeCP2-targeted promoters in lymphocytes of Rett syndrome patients. *Epigenetics.* 2013 Mar;8(3):246-51

Prall WC, Haasters F, Heggebö J, Polzer H, Schwarz C, Gassner C, Grote S, Anz D, Jäger M, Mutschler W, Schieker M. Mesenchymal stem cells from osteoporotic patients feature impaired signal transduction but sustained osteoinduction in response to BMP-2 stimulation. *Biochem Biophys Res Commun.* 2013 Nov 1;440(4):617-22

Su P, Yuan Y, Huang Y, Wang W, Zhang Z. Anorectal malformation associated with a mutation in the *P63* gene in a family with split hand-foot malformation. *Int J Colorectal Dis.* 2013 Dec;28(12):1621-7

Lango Allen H, Caswell R, Xie W, Xu X, Wragg C, Turpenny PD, Turner CL, Weedon MN, Ellard S. Next generation sequencing of chromosomal rearrangements in patients with split-hand/split-foot malformation provides evidence for *DYNC111* exonic enhancers of *DLX5/6* expression in humans. *J Med Genet.* 2014 Apr;51(4):264-7

Wang X, Xin Q, Li L, Li J, Zhang C, Qiu R, Qian C, Zhao H, Liu Y, Shan S, Dang J, Bian X, Shao C, Gong Y, Liu Q. Exome sequencing reveals a heterozygous *DLX5* mutation in a Chinese family with autosomal-dominant split-hand/foot malformation. *Eur J Hum Genet.* 2014 Feb 5;

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