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Gene Section
Review

DLX6 (distal-less homeobox 6)

Yorick Gitton, Giovanni Levi

Evolution des Regulations Endocriniennes, CNRS, UMR7221, Museum National d'Histoire Naturelle, Paris, France (YG, GL)

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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.

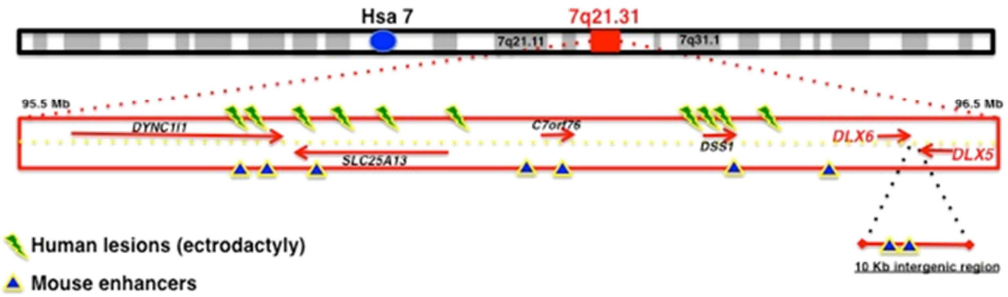

Figure 1. Genomic context of the human DLX5/DLX6 bigenic locus.

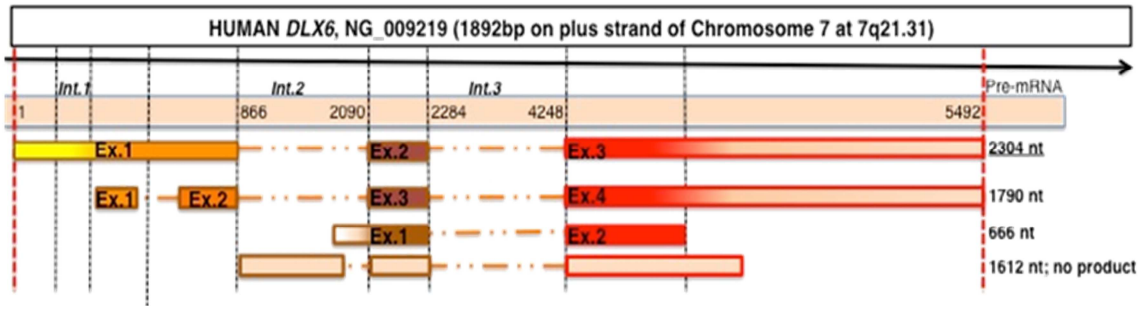

Figure 2. The four known human DLX6 transcripts.

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.

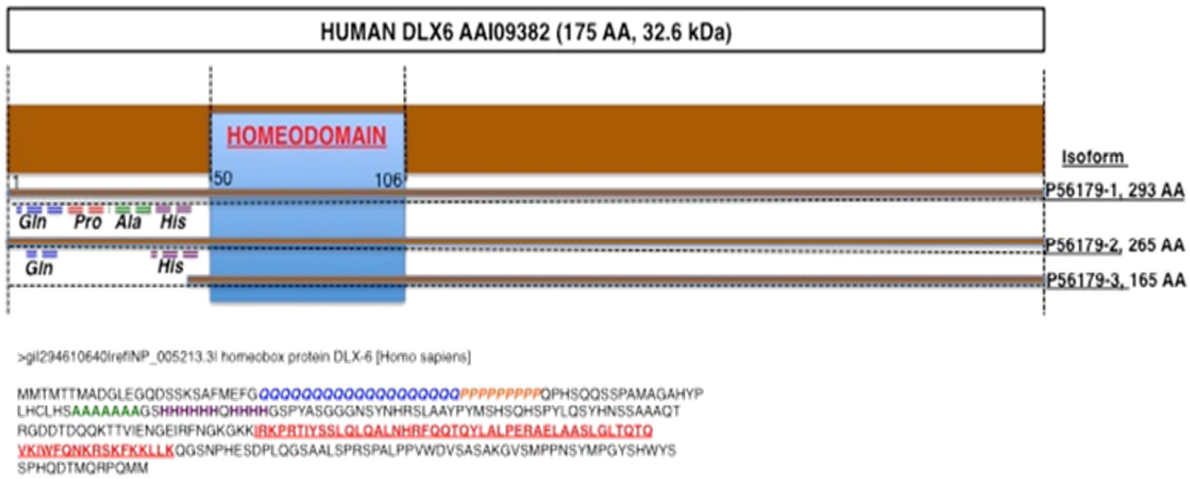

Figure 3. Structure of the three DLX6 protein isoforms. Sequence below belongs to the longest isoform. Note the N-terminal series of poly-residue stretches.

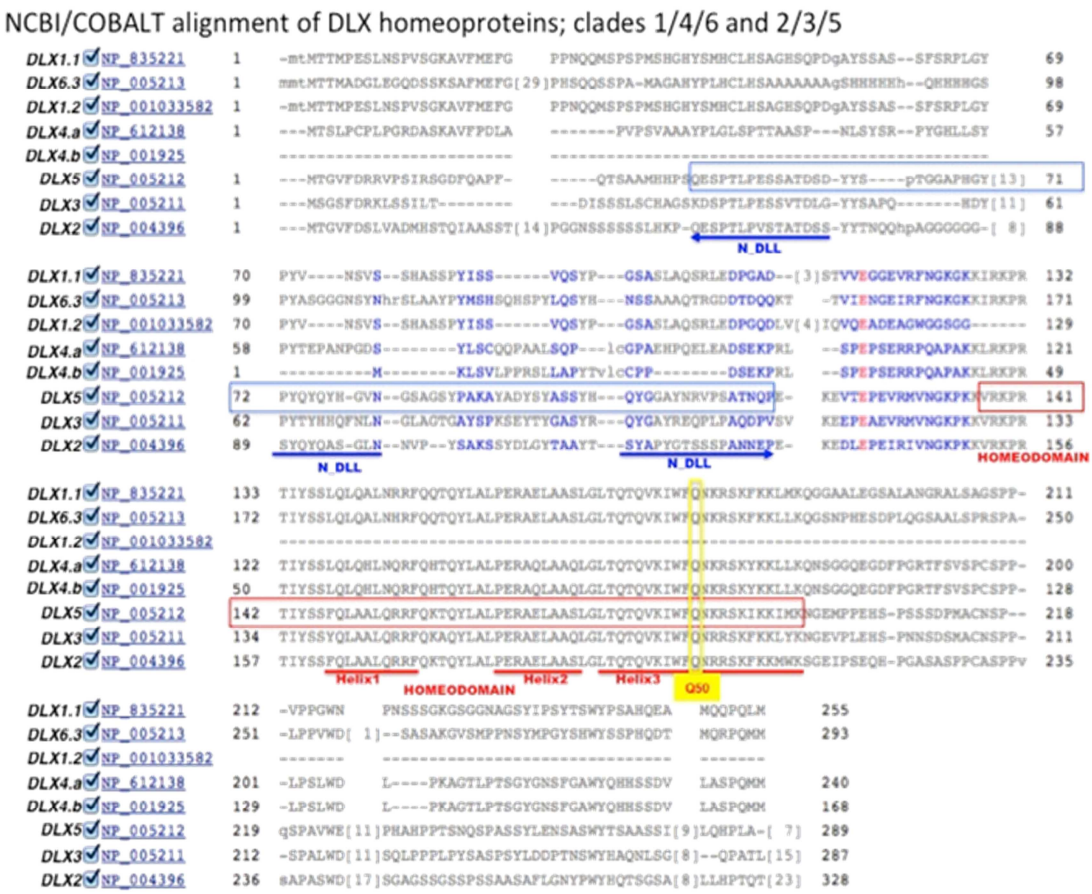

Figure 4. NCBI/COBALT alignment of DLX homeoproteins. Note the disposition according to the DLX 1/4/6 versus DLX 2/3/5 clades. Indicated by a yellow box is the ultraconserved Glutamine featured by most homeoproteins at position 50 of the homeodomain.

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 agressivity 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 functionaly 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/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., 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).

References

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

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

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

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

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

Charité J, McFadden DG, Merlo G, Levi G, Clouthier DE, Yanagisawa M, Richardson JA, Olson EN. Role of Dlx6 in regulation of an endothelin-1-dependent, dHAND branchial arch enhancer. Genes Dev. 2001 Nov 15;15(22):3039-49

Ferro P, dell'Eva R, Pfeffer U. Are there CAG repeat expansion-related disorders outside the central nervous system? Brain Res Bull. 2001 Oct-Nov 1;56(3-4):259-64

Pfeffer U, Ferro P, Pavia V, Trombino S, Dell'Eva R, Merlo G, Levi G. The coding region of the human DLX6 gene contains a polymorphic CAG/CCG repeat. Int J Oncol. 2001 Jun;18(6):1293-7

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

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

Feng J, Bi C, Clark BS, Mady R, Shah P, Kohtz JD. The Evf-2 noncoding RNA is transcribed from the Dlx-5/6 ultraconserved region and functions as a Dlx-2 transcriptional coactivator. Genes Dev. 2006 Jun 1;20(11):1470-84

Kraus P, Lufkin T. Dlx homeobox gene control of mammalian limb and craniofacial development. Am J Med Genet A. 2006 Jul 1;140(13):1366-74

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

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

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

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

Gitton Y, Heude E, Vieux-Rochas M, Benouaiche L, Fontaine A, Sato T, Kurihara Y, Kurihara H, Couly G, Levi G. Evolving maps in craniofacial development. Semin Cell Dev Biol. 2010 May;21(3):301-8

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

Napoletano M, Pennino D, Izzo G, de Maria S, Ottaviano R, Ricciardi M, Mancini R, Schiattarella A, Farina E, Metafora S, Cartenì 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

Vieux-Rochas M, Bouhali K, Baudry S, Fontaine A, Coen L, Levi G. Irreversible effects of retinoic acid pulse on Xenopus jaw morphogenesis: new insight into cranial neural crest specification. Birth Defects Res B Dev Reprod Toxicol. 2010 Dec;89(6):493-503

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

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, Cunniff 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

Berghoff EG, Clark MF, Chen S, Cajigas I, Leib DE, Kohtz JD. Evf2 (Dlx6as) lncRNA regulates ultraconserved enhancer methylation and the differential transcriptional control of adjacent genes. Development. 2013 Nov;140(21):4407-16

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, Turnpenny PD, Turner CL, Weedon MN, Ellard S. Next generation sequencing of chromosomal rearrangements in patients with split-hand/split-foot malformation provides evidence for DYNC1I1 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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