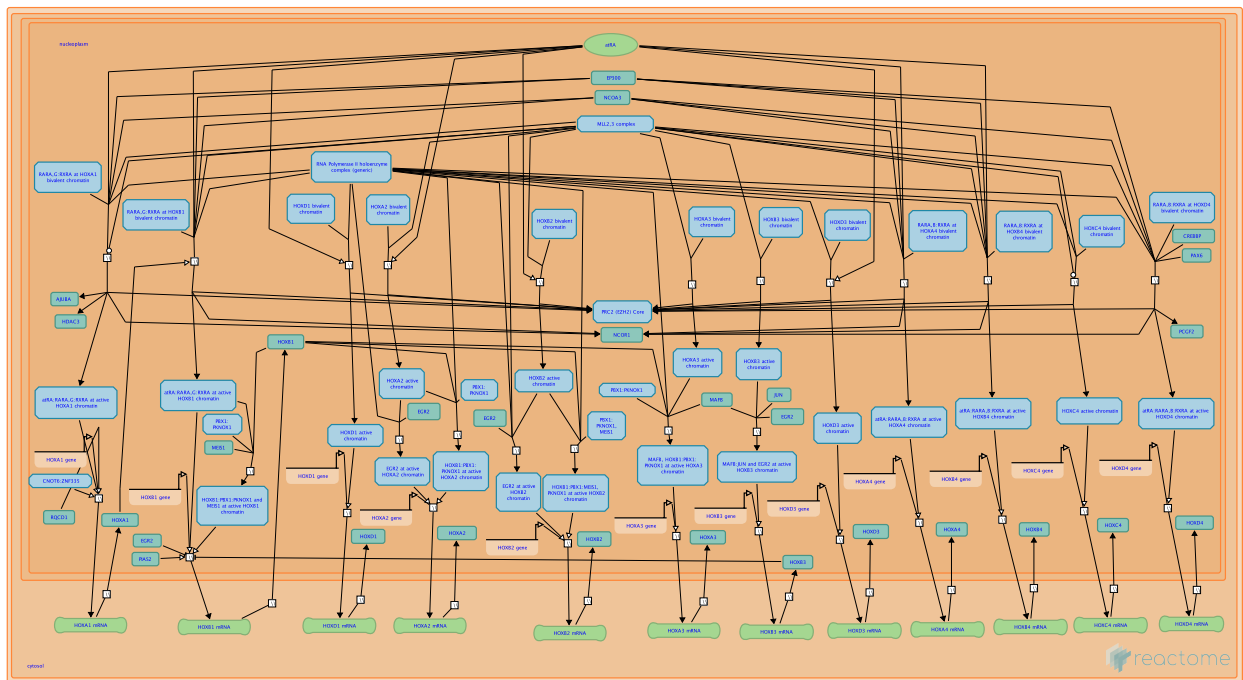


Activation of anterior HOX genes in hind-brain development during early embryogenesis



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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

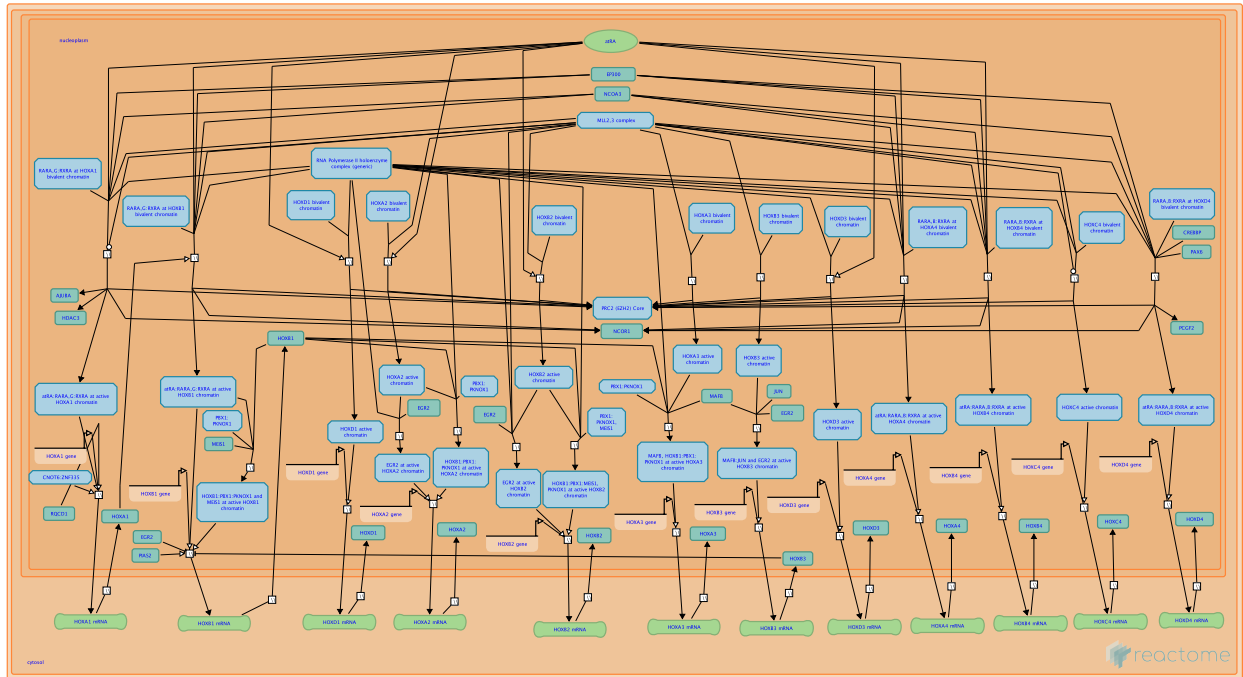
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Reactome database release: 77

This document contains 1 pathway and 43 reactions ([see Table of Contents](#))

Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617472



In mammals, anterior Hox genes may be defined as paralog groups 1 to 4 (Natale et al. 2011), which are involved in development of the hindbrain through sequential expression in the rhombomeres, transient segments of the neural tube that form during development of the hindbrain (reviewed in Alexander et al. 2009, Soshnikova and Duboule 2009, Tumpel et al. 2009, Mallo et al. 2010, Andrey and Duboule 2014). Hox gene activation during mammalian development has been most thoroughly studied in mouse embryos and the results have been extended to human development by in vitro experiments with human embryonal carcinoma cells and human embryonic stem cells.

Expression of a typical anterior Hox gene has an anterior boundary located at the junction between two rhombomeres and continues caudally to regulate segmentation and segmental fate in ectoderm, mesoderm, and endoderm. Anterior boundaries of expression of successive Hox paralog groups are generally separated from each other by 2 rhombomeres. For example, HOXB2 is expressed in rhombomere 3 (r3) and caudally while HOXB3 is expressed in r5 and caudally. Exceptions exist, however, as HOXA1, HOXA2, and HOXB1 do not follow the rule and HOXD1 and HOXC4 are not expressed in rhombomeres. Hox genes within a Hox cluster are expressed colinearly: the gene at the 3' end of the cluster is expressed earliest, and hence most anteriorly, then genes 5' are activated sequentially in the same order as they occur in the cluster.

Activation of expression occurs epigenetically by loss of polycomb repressive complexes and change of bivalent chromatin to active chromatin through, in part, the actions of trithorax family proteins (reviewed in Soshnikova and Duboule 2009). Hox gene expression initiates in the posterior primitive streak that will contribute to extraembryonic mesoderm. Expression then extends anteriorly into the cells that will become the embryo, where expression is first observed in presumptive lateral plate mesoderm and is transmitted to both paraxial mesoderm and neuroectoderm formed by gastrulation along the primitive streak (reviewed in Deschamps et al. 1999, Casaca et al. 2014).

Prior to establishment of the rhombomeres, expression of HOXA1 and HOXB1 is initiated near the future site of r3 and caudally by a gradient of retinoic acid (RA). (Mechanisms of retinoic acid signaling are re-

viewed in Cunningham and Duester 2015.) The RA is generated by the ALDH1A2 (RALDH2) enzyme located in somites flanking the caudal hindbrain and degraded by CYP26 enzymes expressed initially in anterior neural ectoderm of the early gastrula and then throughout most of the hindbrain (reviewed in White and Schilling 2008). HOXA1 with PBX1,2 and MEIS2 directly activate transcription of ALDH1A2 to maintain retinoic acid synthesis in the somitic mesoderm (Vitobello et al. 2011). Differentiation of embryonal carcinoma cells and embryonic stem cells in response to retinoic acid is used to model the process of differentiation in vitro (reviewed in Soprano et al. 2007, Gudas et al. 2013).

HOXA1 appears to set the anterior limit of HOXB1 expression (Barrow et al. 2000). HOXB1 initiates expression of EGR2 (KROX20) in presumptive r3. EGR2 then activates HOXA2 expression in r3 and r5 while HOXB1, together with PBX1 and MEIS:PKNOX1 (MEIS:PREP), activates expression of HOXA2 in r4 and caudal rhombomeres. AP-2 transcription factors maintain expression of HOXA2 in neural crest cells (Maconochie et al. 1999). HOXB1 also activates expression of HOXB2 in r3 and caudal rhombomeres. EGR2 negatively regulates HOXB1 so that by the time rhombomeres appear, HOXB1 is restricted to r4 and HOXA1 is no longer detectable (Barrow et al. 2000). EGR2 and MAFB (Kreisler) then activate HOXA3 and HOXB3 in r5 and caudal rhombomeres. Retinoic acid activates HOXA4, HOXB4, and HOXD4 in r7, the final rhombomere. HOX proteins, in turn, activate expression of genes in combination with other factors, notably members of the TALE family of transcription factors (PBX, PREP, and MEIS, reviewed in Schulte and Frank 2014, Rezsóhazy et al. 2015). HOX proteins also participate in non-transcriptional interactions (reviewed in Rezsóhazy 2014). In zebrafish, *Xenopus*, and chicken factors such as Meis3, Fgf3, Fgf8, and vHNF regulate anterior hox genes (reviewed in Schulte and Frank 2014), however less is known about the roles of homologous factors in mammals.

Mutations in HOXA1 in humans have been observed to cause developmental abnormalities located mostly in the head and neck region (Tischfield et al. 2005, Bosley et al. 2008). A missense mutation in HOXA2 causes microtia, hearing impairment, and partially cleft palate (Alasti et al. 2008). A missense mutation in HOXB1 causes a similar phenotype to the *Hoxb1* null mutation in mice: bilateral facial palsy, hearing loss, and strabismus (improper alignment of the eyes) (Webb et al. 2012).

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Editions

2014-08-08	Authored, Edited	May, B.
2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsóhazy, R.

Retinoic acid activates HOXA1 chromatin ↗

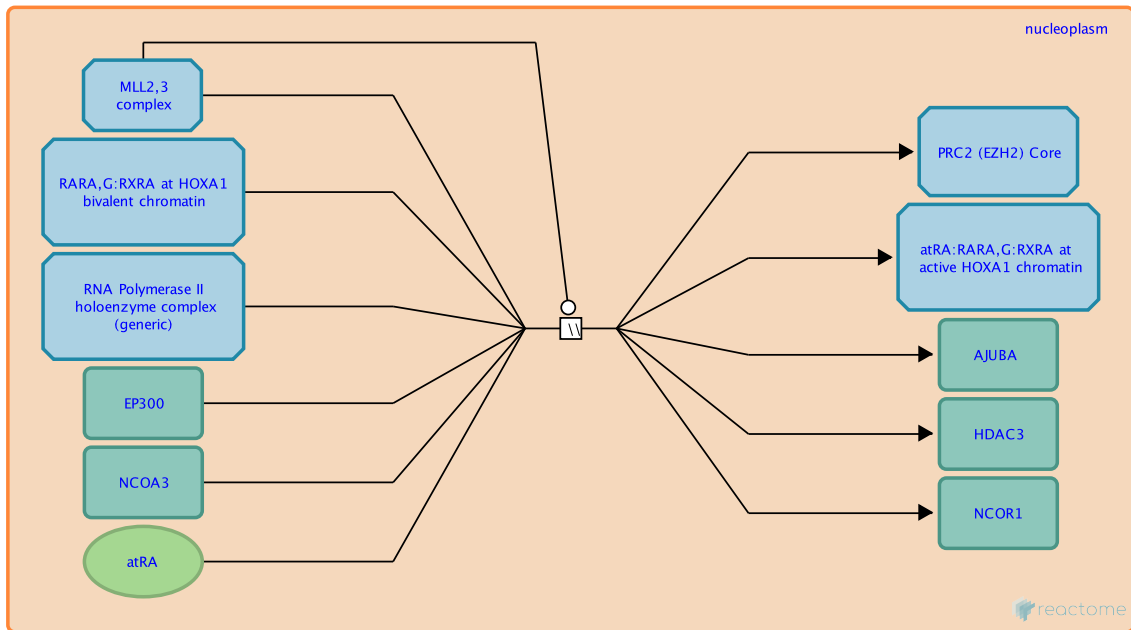
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617431

Type: omitted

Compartments: nucleoplasm

Inferred from: Retinoic acid activates Hoxa1 chromatin (Mus musculus)



As inferred from mouse embryos and cell lines, retinoic acid binds the RARA or RARG receptor in a RAR:RXR dimer bound to the 3' region of HOXA1. Ligand binding by retinoic acid receptors causes dismissal of corepressors such as NCOR1 (Klein et al. 2000), recruitment of coactivators such as NCOA3, and alteration of chromatin at the HOXA1 gene to an active conformation. Similar activation of HOXA1 is also observed in vitro in human breast cancer cells (Chariot et al. 1995). In mouse and *Xenopus* *Hoxa1* acts in a feedback loop to maintain retinoic acid synthesis by directly binding and activating the promoter of the *Raldh2* gene.

In addition to recruiting transcription coactivators, retinoic acid also appears to affect histone modifications and DNA methylation. In human embryonal carcinoma cells, KDM6A (UTX) binds the HOXA1 gene upon retinoic acid treatment and demethylates trimethylated lysine-27 of histone H3 (H3K27me3) (Lee et al. 2007). Reduced H3K27me3 is also observed at HOXA1 in lung fibroblasts (Lan et al. 2007). Experiments with mouse embryos lacking *Kdm6a* and *Kdm6b* indicate other factors also participate in demethylation of H3K27me3 (Shpargel et al. 2014). Polycomb repressive complex 2 (PRC2), which binds H3K27me3, is also lost during activation by retinoic acid (inferred from mouse cells and also observed in human embryonal carcinoma cells, Lee et al. 2007, Sessa et al. 2007). KDM6A forms complexes with the histone methyltransferases KMT2C,D (MLL2,3) (Lee et al. 2007) which may participate in methylating histone H3 at lysine-4 (H3K4me3), an activating chromatin modification. At the 3' end of the HOXA cluster 5-methylcytosine in CG-rich regions is converted to 5-hydroxymethylcytosine by TET2 during retinoic acid induced differentiation of embryonal carcinoma cells (Bocker et al. 2012). During retinoic acid activation of HOXA genes in human monocytic leukemia cells the HOXA cluster is unfolded and its chromosomal domain is repositioned within the nucleus (Rousseau et al. 2014). Similar large-scale rearrangements may occur during embryogenesis.

In mouse embryos, expression of *Hoxa1* occurs in the neural tube, adjacent mesenchyme, paraxial mesoderm, somites, and gut epithelium from rhombomere 4 to the caudal-most region of the embryo. (Rhombomeres are transiently formed segments in the neural tube that will eventually form the hind-brain.)

Followed by: [HOXA1 gene is transcribed](#)

Literature references

Chariot, A., Moreau, L., Senterre, G., Sobel, ME., Castronovo, V. (1995). Retinoic acid induces three newly cloned HOXA1 transcripts in MCF7 breast cancer cells. *Biochem. Biophys. Res. Commun.*, 215, 713-20. [↗](#)

Lan, F., Bayliss, PE., Rinn, JL., Whetstone, JR., Wang, JK., Chen, S. et al. (2007). A histone H3 lysine 27 demethylase regulates animal posterior development. *Nature*, 449, 689-94. [↗](#)

Lee, MG., Villa, R., Trojer, P., Norman, J., Yan, KP., Reinberg, D. et al. (2007). Demethylation of H3K27 regulates polycomb recruitment and H2A ubiquitination. *Science*, 318, 447-50. [↗](#)

Sessa, L., Breiling, A., Lavorgna, G., Silvestri, L., Casari, G., Orlando, V. (2007). Noncoding RNA synthesis and loss of Polycomb group repression accompanies the colinear activation of the human HOXA cluster. *RNA*, 13, 223-39. [↗](#)

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HOXA1 gene is transcribed [↗](#)

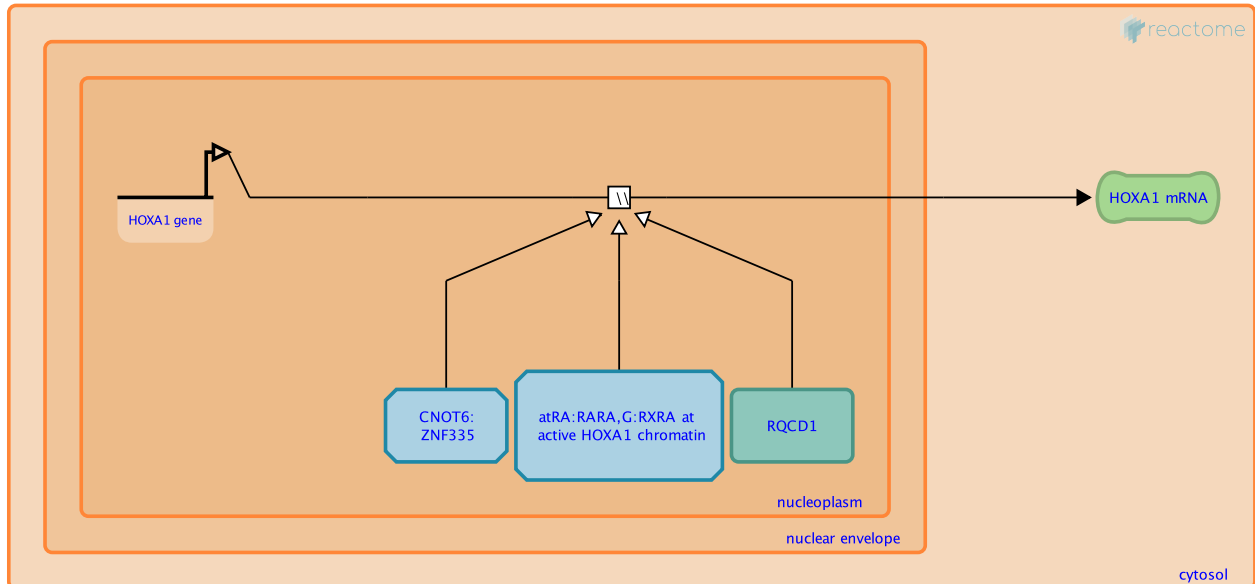
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617471

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: [Hoxa1 gene is transcribed \(Mus musculus\)](#)



After activation by retinoic acid, the HOXA1 gene is transcribed to yield mRNA (inferred from mouse embryos, also demonstrated in human cancer cells, Chariot et al. 1995, Xu et al. 2014). The mRNA is a target of the microRNAs miR-10a in megakaryocytes (Garzon et al. 2006), miR210 in tumors (Huang et al. 2009), let-7c in non-small cell lung cancer cells (Zhan et al. 2013), miR-99 in epithelial cells (Chen et al. 2013), and miR-100 in tumor cells (Chen et al. 2014), however it is unknown if these play a role in embryogenesis. Opposite strand intergenic transcripts are also observed in adult tissues and placenta (Sessa et al. 2007).

In mouse embryos, expression of Hoxa1 occurs in the neural tube, adjacent mesenchyme, paraxial mesoderm, somites, and gut epithelium from rhombomere 4 to the caudal-most region of the embryo. (Rhombomeres are transiently formed segments in the neural tube that will eventually form the hindbrain.)

Preceded by: [Retinoic acid activates HOXA1 chromatin](#)

Followed by: [HOXA1 mRNA is translated](#)

Literature references

- Chen, D., Chen, Z., Jin, Y., Dragas, D., Zhang, L., Adjei, BS. et al. (2013). MicroRNA-99 family members suppress Homeobox A1 expression in epithelial cells. *PLoS ONE*, 8, e80625. [↗](#)
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Chariot, A., Moreau, L., Senterre, G., Sobel, ME., Castronovo, V. (1995). Retinoic acid induces three newly cloned HOXA1 transcripts in MCF7 breast cancer cells. *Biochem. Biophys. Res. Commun.*, 215, 713-20. [↗](#)

Sessa, L., Breiling, A., Lavorgna, G., Silvestri, L., Casari, G., Orlando, V. (2007). Noncoding RNA synthesis and loss of Polycomb group repression accompanies the colinear activation of the human HOXA cluster. *RNA*, 13, 223-39. [↗](#)

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HOXA1 mRNA is translated [↗](#)

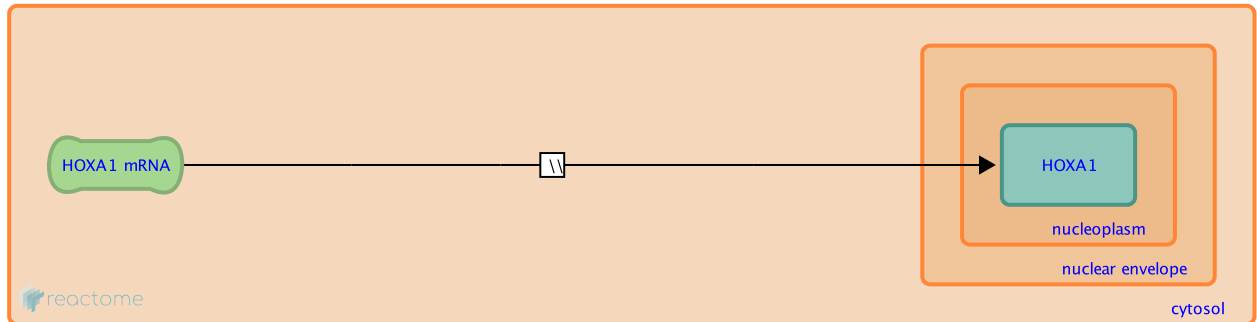
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-5617458

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxa1 mRNA is translated \(Mus musculus\)](#)



The HOXA1 mRNA is translated to yield HOXA1 protein (Chen et al. 2013, Chen et al. 2014). MicroRNAs miR-10a (Garzon et al. 2006), let-7c (Zhan et al. 2013), miR-99 (Chen et al. 2013) and miR-100 (Chen et al. 2014) negatively regulate translation in adult cells, however their roles in embryonic cells are unknown.

Preceded by: [HOXA1 gene is transcribed](#)

Literature references

- Garzon, R., Pichiorri, F., Palumbo, T., Iuliano, R., Cimmino, A., Aqeilan, RI. et al. (2006). MicroRNA fingerprints during human megakaryocytopoiesis. *Proc. Natl. Acad. Sci. U.S.A.*, 103, 5078-83. [↗](#)
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Retinoic acid activates HOXB1 chromatin ↗

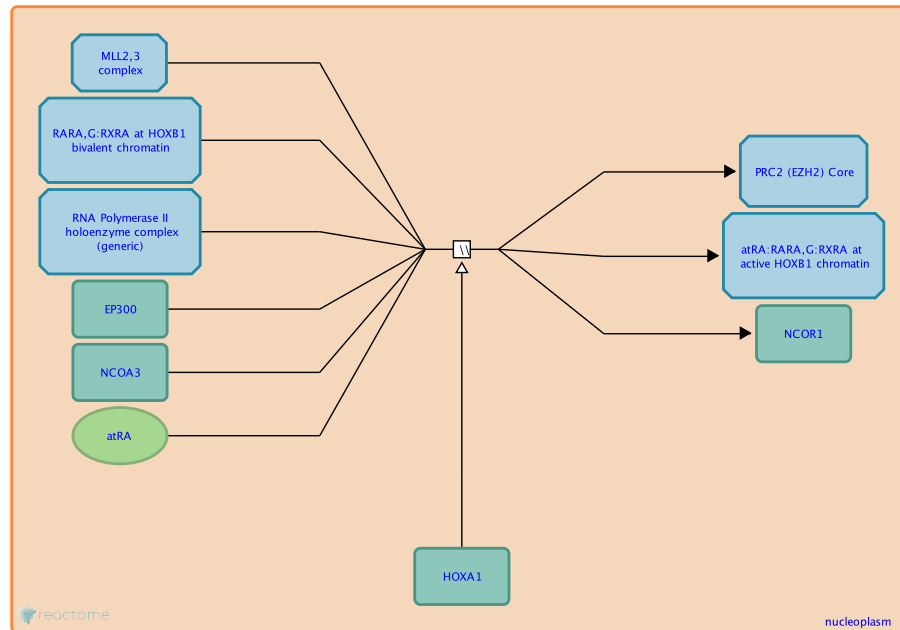
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617452

Type: omitted

Compartments: nucleoplasm

Inferred from: Retinoic acid activates Hoxb1 chromatin (Mus musculus)



As inferred from mouse embryos and cell lines, retinoic acid binds receptors (RARA or RARG) at retinoic acid response elements (RAREs) located 3' to the HOXB1 gene, causing recruitment of coactivators such as NCOA3 and alteration of chromatin at the HOXB1 gene to an active conformation. Similar activation of the HOXB cluster by retinoic acid is observed in human embryonal carcinoma cells (Simeone et al. 1990). In human carcinoma cells and primary fibroblasts, KDM6A (UTX) binds the HOXB1 gene upon retinoic acid treatment (Agger et al. 2007, Lee et al. 2007) and may demethylate trimethylated lysine-27 of histone H3 (H3K27me3). Reduced H3K27me3 is also observed at HOXB1 in lung fibroblasts (Lan et al. 2007). Other demethylases may be redundant with KDM6A. Polycomb repressive complex 2 (PRC2), which binds H3K27me3, is also lost during activation (Lee et al. 2007). KDM6A forms complexes with the histone methyltransferase KMT2C,D (MLL2,3) which may participate in methylating histone H3 at lysine-4 (H3K4me3), an activating chromatin modification (Lee et al. 2007). After activation by retinoic acid HOXB1 maintains its own expression by binding elements in its own promoter and activating expression (Di Rocco et al. 1997).

In mouse embryos, Hoxb1 is expressed in mesoderm and neurectoderm of primitive streak stage embryos and then becomes restricted to rhombomeres of the hindbrain. Before rhombomere formation Hoxb1 is initially expressed in the region that becomes r3-7. After rhombomere formation Hoxb1 becomes restricted to r4 and is also observed in caudal mesoderm. Hoxb1 activates expression of Egr2 (Krox20), a transcription factor that subsequently activates Hoxa2, Hoxb2, and Hoxb3 and represses Hoxb1.

Followed by: HOXB1 maintains activation of HOXB1 chromatin, HOXB1 gene is transcribed

Literature references

Agger, K., Cloos, PA., Christensen, J., Pasini, D., Rose, S., Rappsilber, J. et al. (2007). UTX and JMJD3 are histone H3K27 demethylases involved in HOX gene regulation and development. *Nature*, 449, 731-4. [↗](#)

Lan, F., Bayliss, PE., Rinn, JL., Whetstine, JR., Wang, JK., Chen, S. et al. (2007). A histone H3 lysine 27 demethylase regulates animal posterior development. *Nature*, 449, 689-94. [↗](#)

Lee, MG., Villa, R., Trojer, P., Norman, J., Yan, KP., Reinberg, D. et al. (2007). Demethylation of H3K27 regulates polycomb recruitment and H2A ubiquitination. *Science*, 318, 447-50. [↗](#)

Di Rocco, G., Mavilio, F., Zappavigna, V. (1997). Functional dissection of a transcriptionally active, target-specific Hox-Pbx complex. *EMBO J.*, 16, 3644-54. [↗](#)

Simeone, A., Acampora, D., Arcioni, L., Andrews, PW., Boncinelli, E., Mavilio, F. (1990). Sequential activation of HOX2 homeobox genes by retinoic acid in human embryonal carcinoma cells. *Nature*, 346, 763-6. [↗](#)

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HOXB1 maintains activation of HOXB1 chromatin [↗](#)

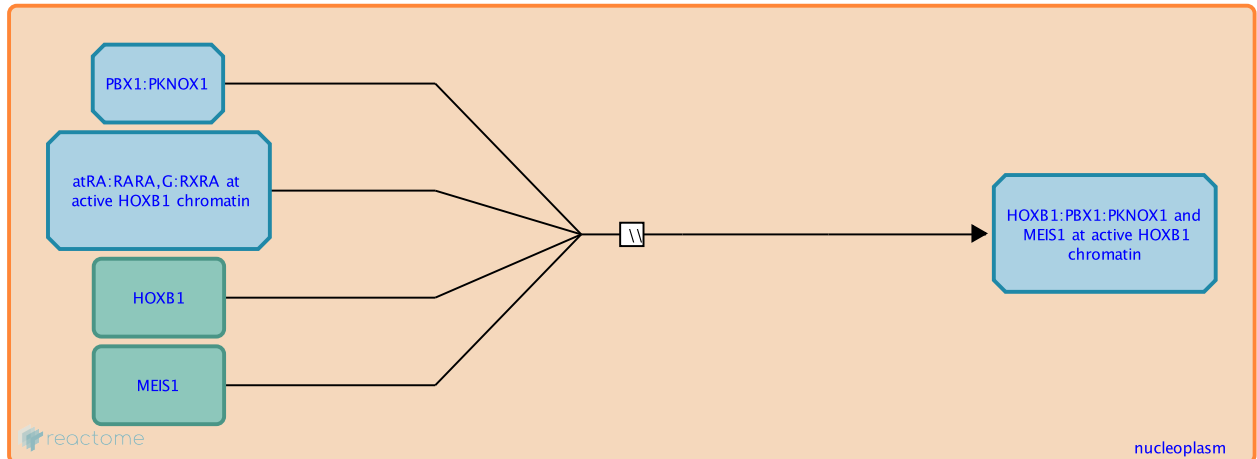
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-5693644

Type: omitted

Compartments: nucleoplasm

Inferred from: [Hoxb1 maintains activation of Hoxb1 chromatin \(Mus musculus\)](#)



As inferred from mouse embryos and embryonal carcinoma cells, HOXB1 binds with the PBX1:PKNOX1 (PBX1:PREP1) heterodimer (Berthelsen et al. 1998) and MEIS1 at the promoter of the HOXB1 gene to maintain expression after initial activation of HOXB1 by retinoic acid signaling. Binding of SOX:OCT heterodimers to the mouse HOXB1 promoter also appear to positively regulate HOXB1 transcription.

Preceded by: [Retinoic acid activates HOXB1 chromatin](#)

Literature references

Berthelsen, J., Zappavigna, V., Ferretti, E., Mavilio, F., Blasi, F. (1998). The novel homeoprotein Prep1 modulates Pbx-Hox protein cooperativity. *EMBO J.*, 17, 1434-45. [↗](#)

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2014-08-08	Authored	May, B.
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HOXB1 gene is transcribed ↗

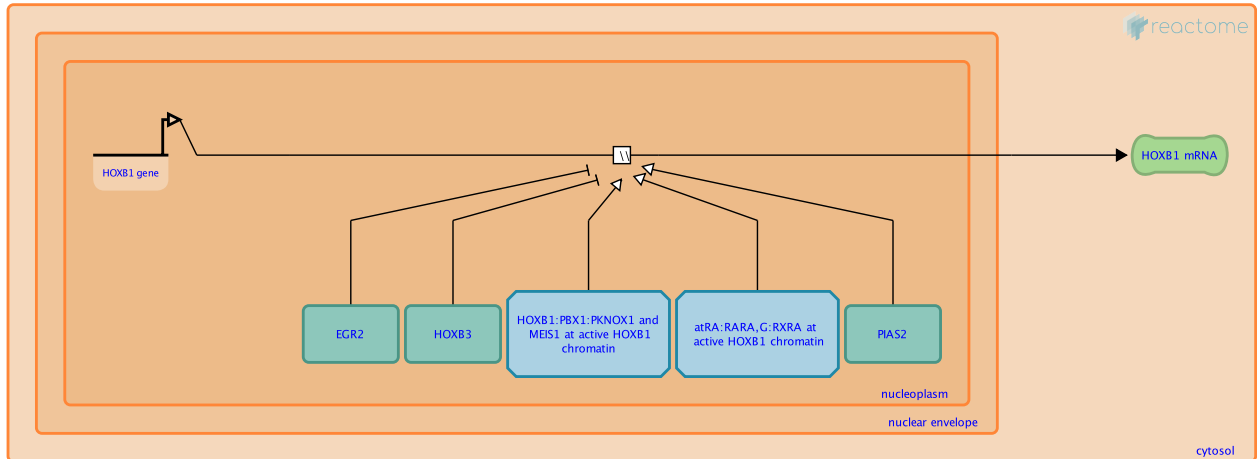
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-5617454

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: [Hoxb1 gene is transcribed \(Mus musculus\)](#)



After activation by retinoic acid, the HOXB1 gene is transcribed to yield mRNA (in embryos in Giampaolo et al. 1989, in human embryonal carcinoma cells in Simeone et al. 1990, Ogura and Evans 1995).

In mouse embryos, Hoxb1 is expressed in mesoderm and neurectoderm of primitive streak stage embryos and then becomes restricted to rhombomeres of the hindbrain. Before rhombomere formation Hoxb1 is initially expressed in the region that becomes r3-7. After rhombomere formation Hoxb1 becomes restricted to r4 and is also observed in caudal mesoderm.

Preceded by: [Retinoic acid activates HOXB1 chromatin](#)

Followed by: [HOXB1 mRNA is translated](#)

Literature references

- Ogura, T., Evans, RM. (1995). A retinoic acid-triggered cascade of HOXB1 gene activation. *Proc. Natl. Acad. Sci. U.S.A.*, 92, 387-91. ↗
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- Giampaolo, A., Acampora, D., Zappavigna, V., Pannese, M., D'Esposito, M., Carè, A. et al. (1989). Differential expression of human HOX-2 genes along the anterior-posterior axis in embryonic central nervous system. *Differentiation*, 40, 191-7. ↗

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2014-08-08	Authored, Edited	May, B.
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HOXB1 mRNA is translated ↗

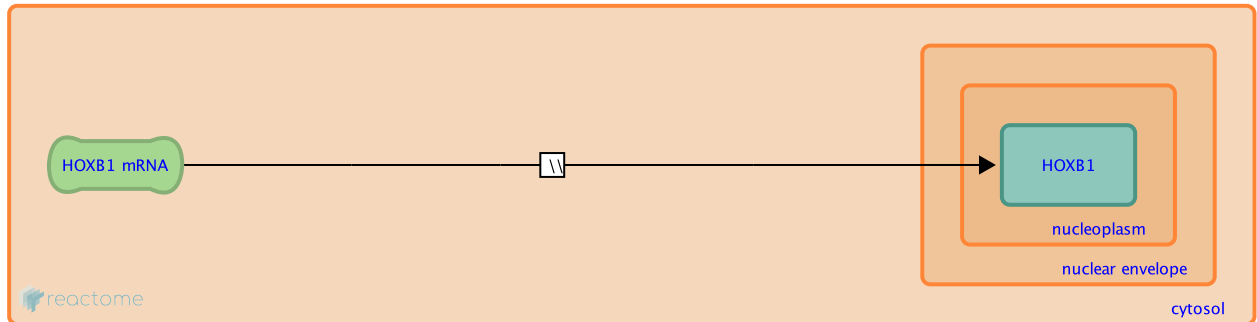
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617457

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: Hoxb1 mRNA is translated (Mus musculus)



The HOXB1 mRNA is translated to yield HOXB1 protein. The HOXB1 mRNA is a target of miR-10a (Weiss et al. 2009) and miR-196 (Yekta et al. 2008).

Preceded by: HOXB1 gene is transcribed

Followed by: HOXB1 activates HOXB2 expression, MAFB (KREISLER) and HOXB1:PBX1:PKNOX1 (HOXB1:PBX1:PREP1) activate HOXA3 expression, HOXB1 activates HOXA2 expression

Literature references

Weiss, FU., Marques, IJ., Woltering, JM., Vlecken, DH., Aghdassi, A., Partecke, LI. et al. (2009). Retinoic acid receptor antagonists inhibit miR-10a expression and block metastatic behavior of pancreatic cancer. *Gastroenterology*, 137, 2136-45.e1-7. ↗

Yekta, S., Tabin, CJ., Bartel, DP. (2008). MicroRNAs in the Hox network: an apparent link to posterior prevalence. *Nat. Rev. Genet.*, 9, 789-96. ↗

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HOXD1 chromatin is activated ↗

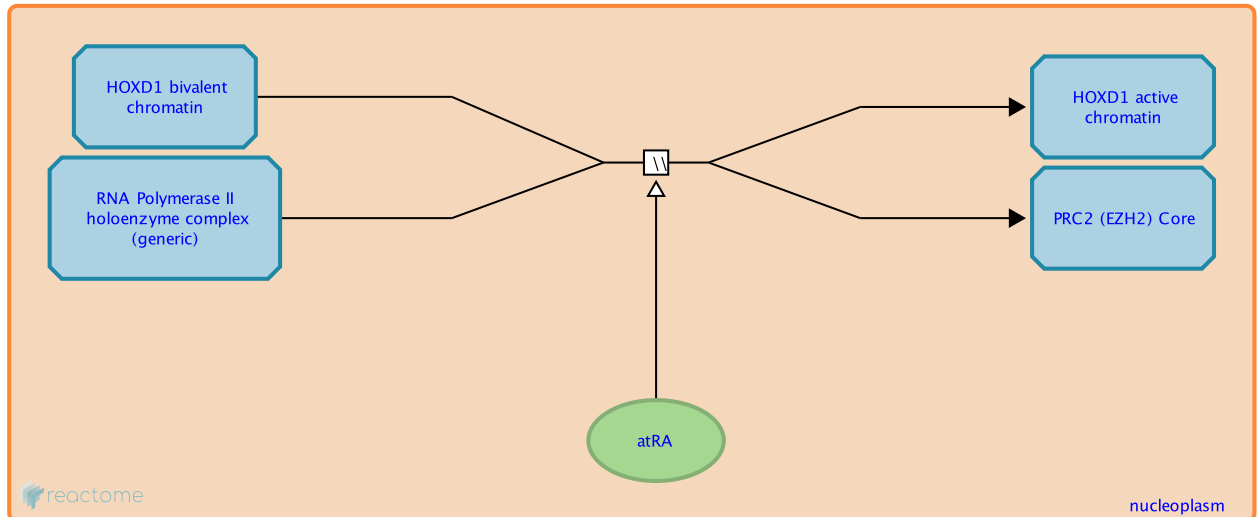
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617445

Type: omitted

Compartments: nucleoplasm

Inferred from: Hoxd1 chromatin is activated (Mus musculus)



As inferred from the Hoxd1 homolog in mouse embryos, HOXD1 is not expressed in hindbrain. In mouse, expression of Hoxd1 begins at E8.5 in caudal lateral mesoderm. At E9.5 to E11.5 Hoxd1 expression is observed in prosomeres p2 and p3 of the diencephalon, dermatomes, urogenital tubercle, and tail bud. Expression is inducible by retinoic acid in neuroblastoma cells, however it is unknown if the induction is direct or indirect (Manohar et al. 1996, Zha et al. 2012). Nerve Growth Factor induces Hoxd1 expression in nociceptors of mouse embryos. As inferred from human posterior HOXD genes in primary human fibroblasts (Lan et al. 2007), other anterior HOX genes, and mouse Hoxd1, the activation of HOXD1 chromatin may be associated with loss of methylation at lysine-27 of histone H3 (H3K27me3) loss of polycomb repressive complex 2 (PRC2), gain of histone acetylation, and gain of methylation at histone H3K4. Like other Hox gene clusters, the HoxD cluster in mouse changes position relative to other loci in the nucleus during activation.

Followed by: HOXD1 gene is transcribed

Literature references

- Zha, Y., Ding, E., Yang, L., Mao, L., Wang, X., McCarthy, BA. et al. (2012). Functional dissection of HOXD cluster genes in regulation of neuroblastoma cell proliferation and differentiation. *PLoS ONE*, 7, e40728. ↗
- Manohar, CF., Salwen, HR., Furtado, MR., Cohn, SL. (1996). Up-regulation of HOXC6, HOXD1, and HOXD8 homeobox gene expression in human neuroblastoma cells following chemical induction of differentiation. *Tumour Biol.*, 17, 34-47. ↗
- Lan, F., Bayliss, PE., Rinn, JL., Whetstine, JR., Wang, JK., Chen, S. et al. (2007). A histone H3 lysine 27 demethylase regulates animal posterior development. *Nature*, 449, 689-94. ↗

Editions

2014-08-01	Edited	May, B.
2014-08-08	Authored	May, B.
2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsöházy, R.

HOXD1 gene is transcribed [↗](#)

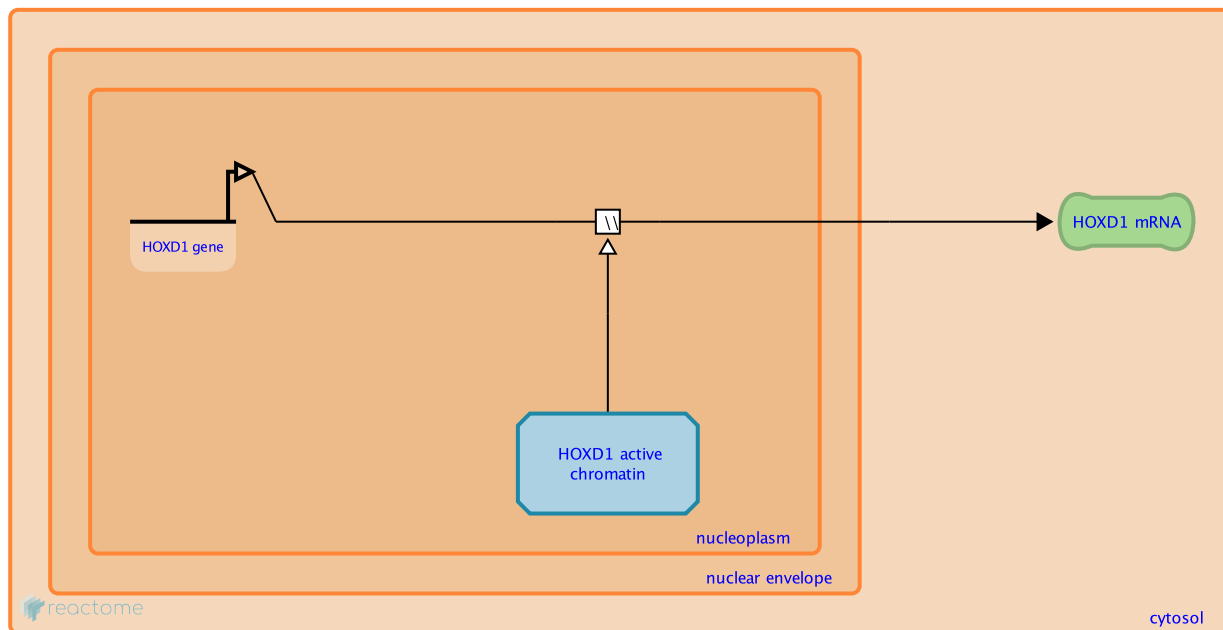
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617462

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: [Hoxd1 gene is transcribed \(Mus musculus\)](#)



The HOXD1 gene is transcribed to yield mRNA (Manohar et al. 1996, Zha et al. 2012). The Hoxd1 homologue in mouse is expressed in caudal lateral mesoderm, prosomeres p2 and p3, dermatomes, urogenital tract, gut endoderm, and tail bud.

Preceded by: [HOXD1 chromatin is activated](#)

Followed by: [HOXD1 mRNA is translated](#)

Literature references

Zha, Y., Ding, E., Yang, L., Mao, L., Wang, X., McCarthy, BA. et al. (2012). Functional dissection of HOXD cluster genes in regulation of neuroblastoma cell proliferation and differentiation. *PLoS ONE*, 7, e40728. [↗](#)

Manohar, CF., Salwen, HR., Furtado, MR., Cohn, SL. (1996). Up-regulation of HOXC6, HOXD1, and HOXD8 homeobox gene expression in human neuroblastoma cells following chemical induction of differentiation. *Tumour Biol.*, 17, 34-47. [↗](#)

Editions

2014-08-08	Authored, Edited	May, B.
2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsohazy, R.

HOXD1 mRNA is translated ↗

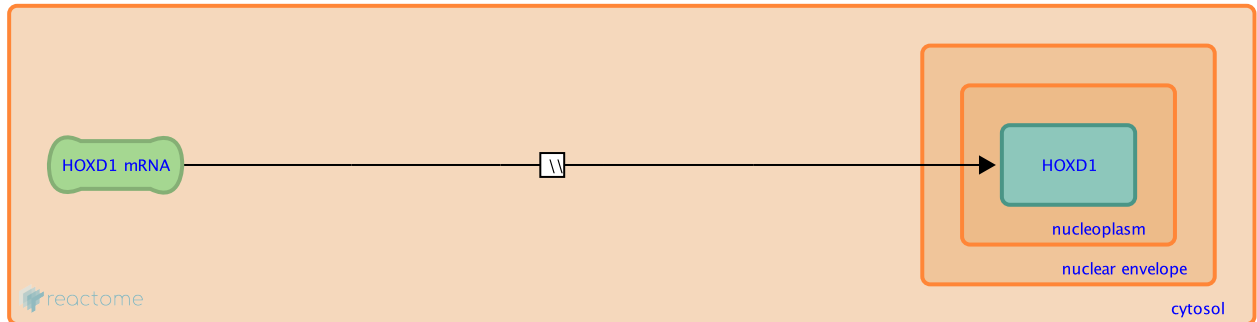
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617446

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxd1 mRNA is translated \(Mus musculus\)](#)



The HOXD1 mRNA is translated to yield HOXD1 protein.

Preceded by: [HOXD1 gene is transcribed](#)

Editions

2014-08-08	Authored, Edited	May, B.
2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsohazy, R.

HOXA2 chromatin is activated ↗

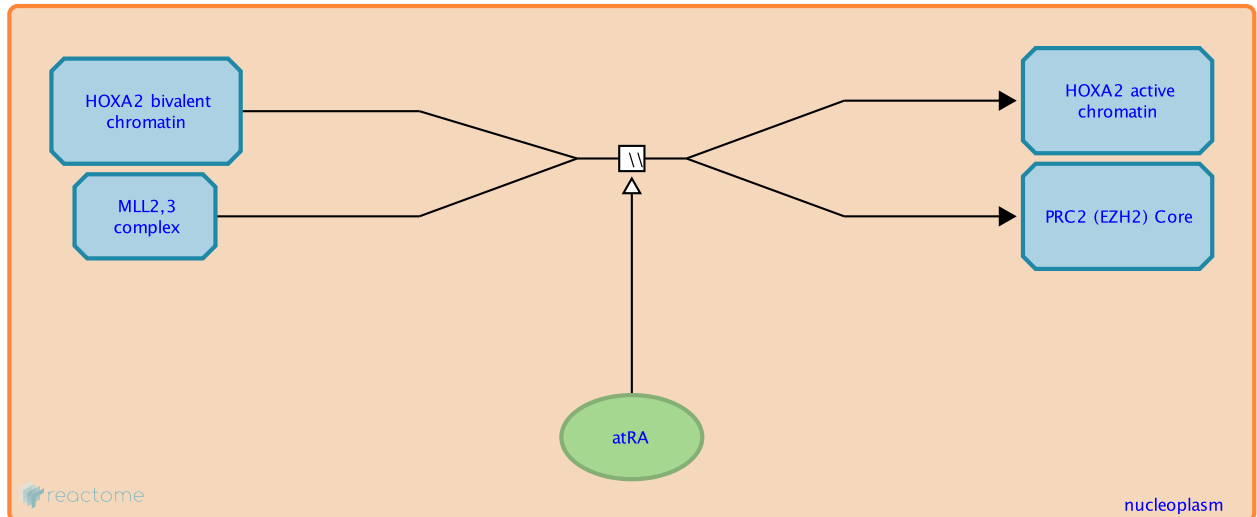
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-6810139

Type: omitted

Compartments: nucleoplasm

Inferred from: [Hoxa2 chromatin is activated \(Mus musculus\)](#)



In human cell lines and tissues activation of HOXA2 chromatin by retinoic acid occurs through loss of methylation at lysine-27 of histone H3 (H3K27), dissociation of polycomb repressive complexes, and gain of methylation at H3K4 (Lee et al. 2007 Supplementary, Sakamoto et al. 2007, Sessa et al. 2007). The change in chromatin may be produced by euchromatin spreading from distant 3' retinoic acid response elements. DNA methylation and MBD1 also appear to play a role in maintaining repression at HOXA2 in HeLa cells (Sakamoto et al. 2007). The histone demethylase KDM6A binds HOXA2 (Lee et al. 2007 Supplementary) and may participate in removing H3K27 methylation. KDM6A associates with histone methyltransferases KMT2C,D (MLL2,3) which may participate in methylating H3K4 in embryonal carcinoma cells (Lee et al. 2007, also observed at other HOXA genes in Lan et al. 2007). The conformation of the entire HOXA cluster in the nucleus changes during differentiation of a myeloid leukemia cell line and the conformation changes correlate with gene activity, H3K27me_{2,3} occurrence, and proximity to CTCF binding sites (Rousseau et al. 2014, see also Lonfat and Duboule 2015).

Followed by: [EGR2 \(KROX20\) activates HOXA2 expression](#), [HOXB1 activates HOXA2 expression](#)

Literature references

- Sessa, L., Breiling, A., Lavorgna, G., Silvestri, L., Casari, G., Orlando, V. (2007). Noncoding RNA synthesis and loss of Polycomb group repression accompanies the colinear activation of the human HOXA cluster. *RNA*, 13, 223-39. ↗
- Lee, MG., Villa, R., Trojer, P., Norman, J., Yan, KP., Reinberg, D. et al. (2007). Demethylation of H3K27 regulates polycomb recruitment and H2A ubiquitination. *Science*, 318, 447-50. ↗
- Sakamoto, Y., Watanabe, S., Ichimura, T., Kawasuji, M., Koseki, H., Baba, H. et al. (2007). Overlapping roles of the methylated DNA-binding protein MBD1 and polycomb group proteins in transcriptional repression of HOXA genes and heterochromatin foci formation. *J. Biol. Chem.*, 282, 16391-400. ↗
- Rousseau, M., Crutchley, JL., Miura, H., Suderman, M., Blanchette, M., Dostie, J. (2014). Hox in motion: tracking HoxA cluster conformation during differentiation. *Nucleic Acids Res.*, 42, 1524-40. ↗

Lonfat, N., Duboule, D. (2015). Structure, function and evolution of topologically associating domains (TADs) at HOX loci. *FEBS Lett.*, 589, 2869-76. [↗](#)

Editions

2014-08-08	Authored	May, B.
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2015-11-08	Edited	May, B.
2015-11-15	Authored	Rezsohazy, R.

EGR2 (KROX20) activates HOXA2 expression ↗

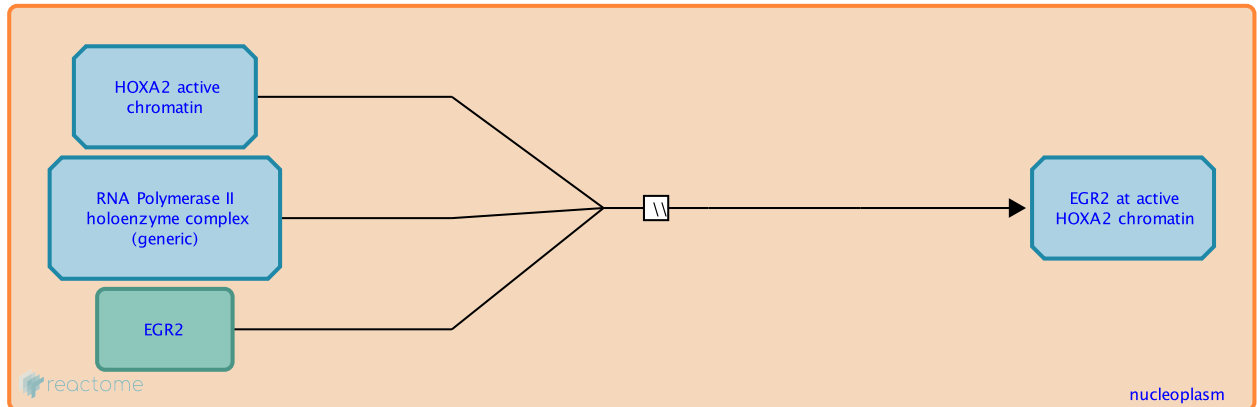
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-5617484

Type: omitted

Compartments: nucleoplasm

Inferred from: [Egr2 activates Hoxa2 chromatin \(Mus musculus\)](#)



As inferred from mouse embryos, HOXA2 expression is directly driven by EGR2 (KROX20) in rhombomeres 3 and 5 (r3, r5) of the hindbrain and by HOXB1 in r4. EGR2 binds sites in the 5' region of the HOXA2 gene. HOXB1 sets up the correct EGR2 expression domain in r3 and thereby indirectly regulates HOXA2 in this region. (HOXA2 is the only HOX gene active in r2. An unknown activator, possibly a transcription factor of the SOX family, may be involved in expression in r2.)

Preceded by: [HOXA2 chromatin is activated](#)

Followed by: [HOXA2 gene is transcribed](#)

Editions

2014-08-08	Authored	May, B.
2014-08-09	Edited	May, B.
2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsohazy, R.

HOXB1 activates HOXA2 expression ↗

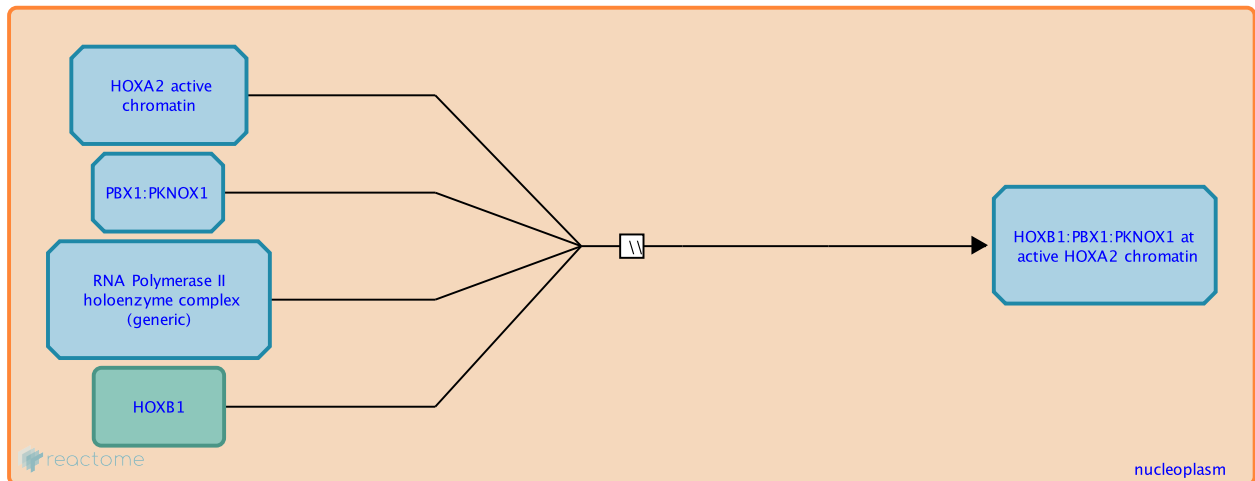
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5621010

Type: omitted

Compartments: nucleoplasm

Inferred from: Hoxb1 activates Hoxa2 expression (Mus musculus)



As inferred from mouse homologs, HOXA2 expression is driven by HOXB1 in rhombomere 4 (r4) and EGR2 (KROX20) in r3 and r5. HOXB1 together with PBX and PREP/MEIS cofactors bind an element in the intron of HOXA2. (HOXA2 is the only HOX gene active in r2. An unknown activator, possibly a transcription factor of the SOX family, may be involved in expression in r2.)

Preceded by: HOXB1 mRNA is translated, HOXA2 chromatin is activated

Followed by: HOXA2 gene is transcribed

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2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsohazy, R.

HOXA2 gene is transcribed [↗](#)

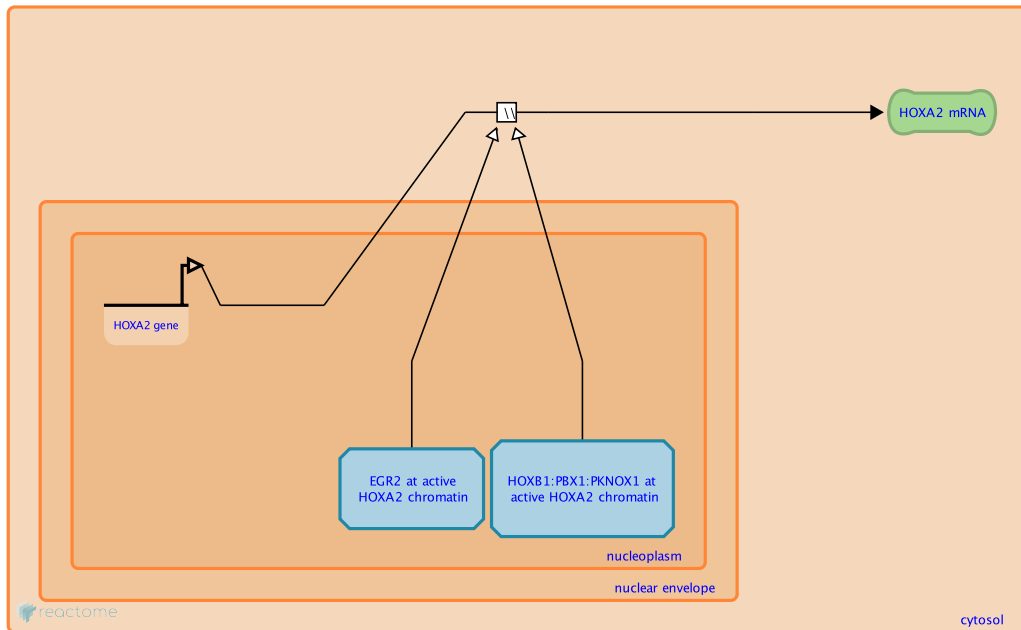
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617483

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxa2 gene is transcribed \(Mus musculus\)](#)



The HOXA2 is transcribed to yield mRNA (in carcinoma cells, Yates et al. 2010). In mouse embryos Hoxa2 mRNA is observed in rhombomere 2 and caudally through posterior hindbrain, spinal cord, larynx, lungs, vertebrae, sternum, and intestine. Hoxa2 mRNA is a target of microRNA miR-3960 in differentiating mouse osteoblasts.

Preceded by: [EGR2 \(KROX20\) activates HOXA2 expression](#), [HOXB1 activates HOXA2 expression](#)

Followed by: [HOXA2 mRNA is translated](#)

Literature references

Yates, JA., Menon, T., Thompson, BA., Bochar, DA. (2010). Regulation of HOXA2 gene expression by the ATP-dependent chromatin remodeling enzyme CHD8. *FEBS Lett.*, 584, 689-93. [↗](#)

Editions

2014-08-08	Authored	May, B.
2014-08-09	Edited	May, B.
2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsohazy, R.

HOXA2 mRNA is translated ↗

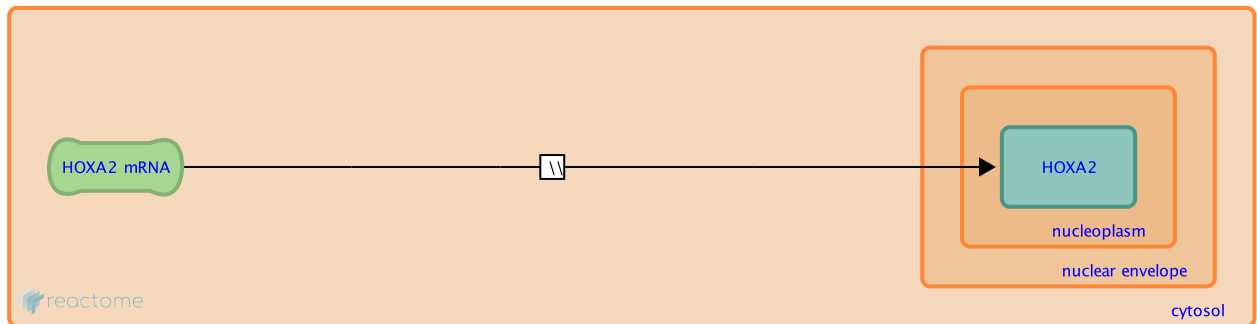
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-5617479

Type: omitted

Compartments: cytosol

Inferred from: [Hoxa2 mRNA is translated \(Mus musculus\)](#)



HOXA2 mRNA is translated to yield HOXA2 protein. The microRNA miR-3960 represses translation of HOXA2 (inferred from mouse).

Preceded by: [HOXA2 gene is transcribed](#)

Editions

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2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsohazy, R.

HOXB2 chromatin is activated ↗

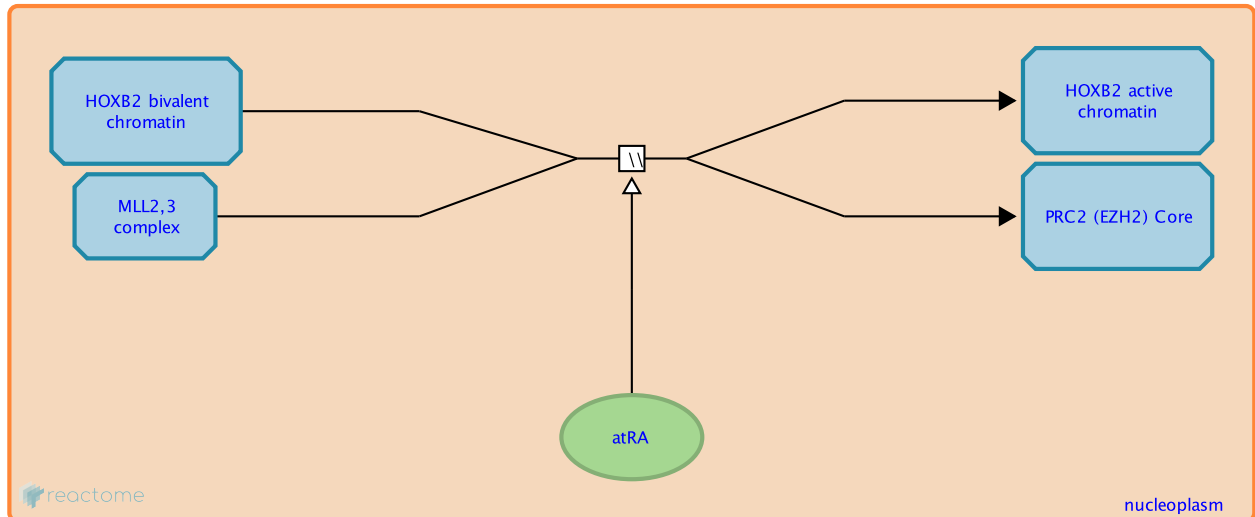
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-6810159

Type: omitted

Compartments: nucleoplasm

Inferred from: Hoxb2 chromatin is activated (Mus musculus)



During activation of HOXB1 by retinoic acid in human embryonal carcinoma cells, methylation at lysine-27 of histone H3 (H3K27me3) is lost and methylation at lysine-4 (H3K4me3) is gained (Lan et al. 2007, Lee et al. 2007). The histone demethylase KDM6A (UTX) binds HOXB2 chromatin and may demethylate H3K27me3 (Lee et al. 2007). Other factors may also participate in demethylation. Loss of H3K27me3 is associated with loss of polycomb repressive complex 2 (PRC2) (Lan et al. 2007, Lee et al. 2007). KDM6A forms complexes with the histone methyltransferases KMT2C,D (MLL2,3) which may participate in methylating H3K4 (Lee et al. 2007). The activation of HOXB1 chromatin may be produced by euchromatin spreading from distant 3' retinoic acid response elements.

Followed by: EGR2 (KROX20) activates HOXB2 expression, HOXB1 activates HOXB2 expression

Literature references

- Lan, F., Bayliss, PE., Rinn, JL., Whetstine, JR., Wang, JK., Chen, S. et al. (2007). A histone H3 lysine 27 demethylase regulates animal posterior development. *Nature*, 449, 689-94. ↗
- Lee, MG., Villa, R., Trojer, P., Norman, J., Yan, KP., Reinberg, D. et al. (2007). Demethylation of H3K27 regulates polycomb recruitment and H2A ubiquitination. *Science*, 318, 447-50. ↗

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2014-08-08	Authored	May, B.
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2015-11-15	Authored	Rezsohazy, R.

EGR2 (KROX20) activates HOXB2 expression ↗

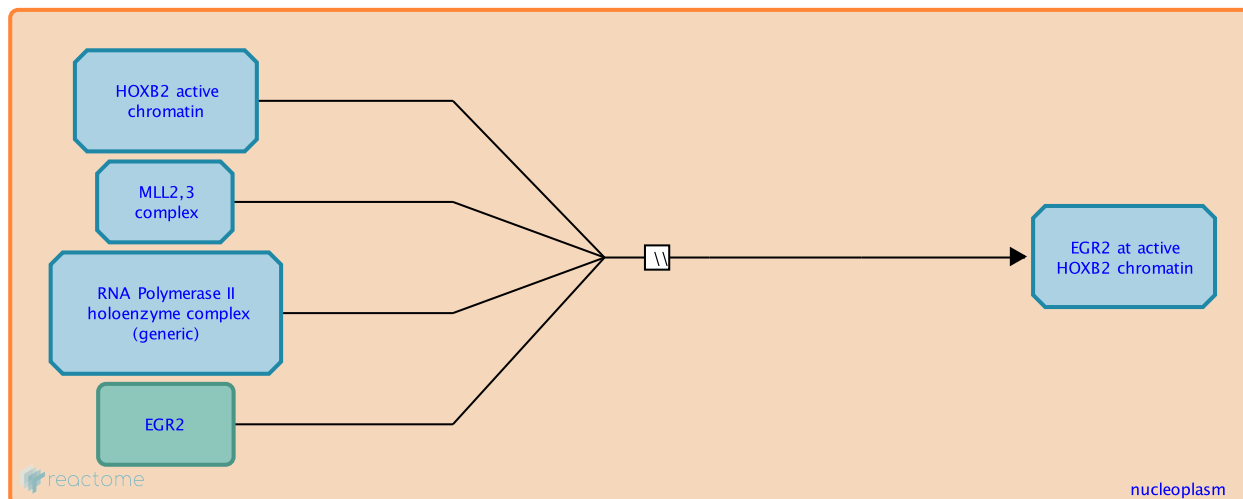
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-5617492

Type: omitted

Compartments: nucleoplasm

Inferred from: [Egr2 \(Krox20\) activates Hoxb2 expression \(Mus musculus\)](#)



As inferred from mouse embryos, EGR2 (KROX20) binds three sites in the 5' region of the HOXB2 gene and activates expression in rhombomere 3 (r3) and r5. HOXB1 activates HOXB2 in r4 and expression is also observed in r6 and r7.

Preceded by: [HOXB2 chromatin is activated](#)

Followed by: [HOXB2 gene is transcribed](#)

Editions

2014-08-08	Authored	May, B.
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2015-11-15	Authored	Rezsohazy, R.

HOXB1 activates HOXB2 expression ↗

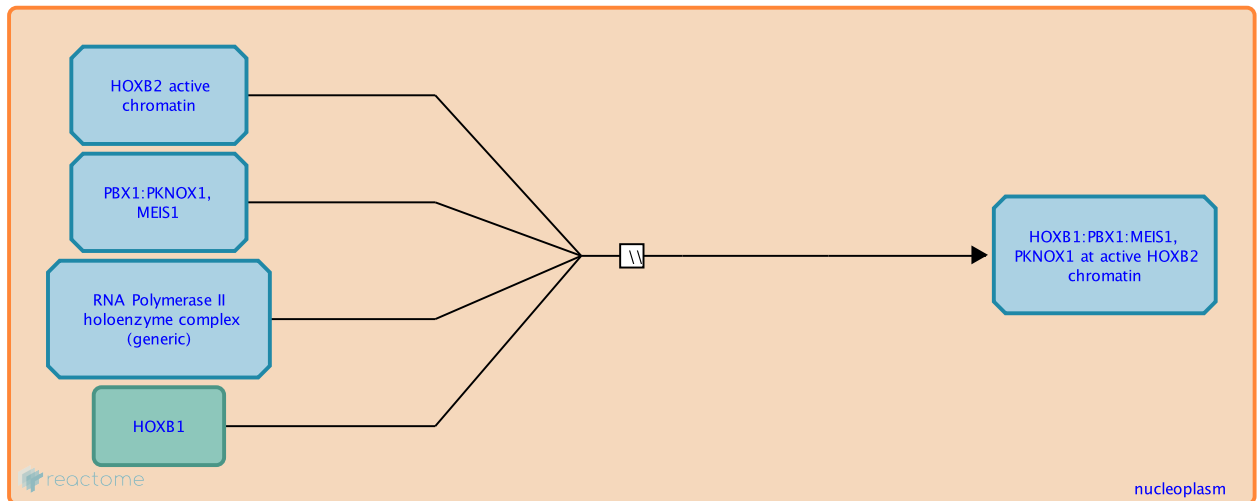
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5621002

Type: omitted

Compartments: nucleoplasm

Inferred from: Hoxb1 activates Hoxb2 expression (Mus musculus)



As inferred from mouse embryos, HOXB1 in a trimeric complex with PBX1 and MEIS1 or PKNOX1 (PREP1) binds an enhancer located 5' to the HOXB2 gene and activates expression of HOXB2 in rhombomere 4 (r4). EGR2 (KROX20) activates HOXB2 in r3 and r5 and expression is also observed in r6 and r7.

Preceded by: HOXB1 mRNA is translated, HOXB2 chromatin is activated

Editions

2014-08-08	Authored	May, B.
2014-08-09	Edited	May, B.
2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsohazy, R.

HOXB2 gene is transcribed [↗](#)

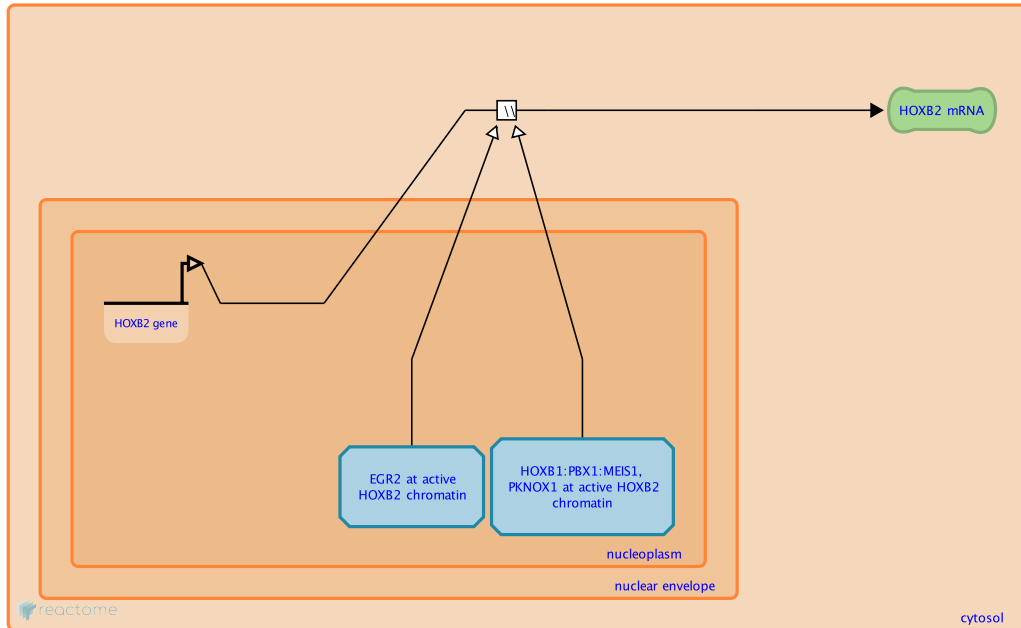
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617486

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxb2 gene is transcribed \(Mus musculus\)](#)



The HOXB2 gene is transcribed to yield mRNA (in embryos in Giampaolo et al. 1989, in carcinoma cells in Simeone et al. 1990). In mouse embryos Hoxb2 mRNA is observed in rhombomere 3 and caudally in the neural tube and mesoderm derivatives such as lung.

Preceded by: [EGR2 \(KROX20\) activates HOXB2 expression](#)

Followed by: [HOXB2 mRNA is translated](#)

Literature references

Giampaolo, A., Acampora, D., Zappavigna, V., Pannese, M., D'Esposito, M., Carè, A. et al. (1989). Differential expression of human HOX-2 genes along the anterior-posterior axis in embryonic central nervous system. *Differentiation*, 40, 191-7. [↗](#)

Simeone, A., Acampora, D., Arcioni, L., Andrews, PW., Boncinelli, E., Mavilio, F. (1990). Sequential activation of HOX2 homeobox genes by retinoic acid in human embryonal carcinoma cells. *Nature*, 346, 763-6. [↗](#)

Editions

2014-08-08	Authored	May, B.
2014-08-09	Edited	May, B.
2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsohazy, R.

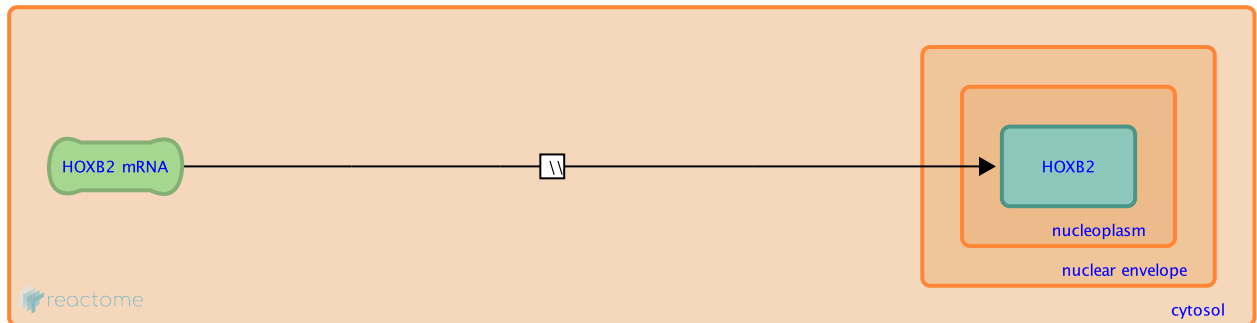
HOXB2 mRNA is translated [↗](#)

Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-5617485

Type: omitted

Compartments: cytosol



The HOXB2 mRNA is translated to yield HOXB2 protein (Sengupta et al. 1994, Segara et al. 2005, Zhai et al. 2005).

Preceded by: [HOXB2 gene is transcribed](#)

Literature references

Zhai, J., Lin, H., Cañete-Soler, R., Schlaepfer, WW. (2005). HoxB2 binds mutant SOD1 and is altered in transgenic model of ALS. *Hum. Mol. Genet.*, 14, 2629-40. [↗](#)

Sengupta, PK., Lavelle, DE., DeSimone, J. (1994). The 87-kD A gamma-globin enhancer-binding protein is a product of the HOXB2(HOX2H) locus. *Blood*, 83, 1420-7. [↗](#)

Segara, D., Biankin, AV., Kench, JG., Langusch, CC., Dawson, AC., Skalicky, DA. et al. (2005). Expression of HOXB2, a retinoic acid signaling target in pancreatic cancer and pancreatic intraepithelial neoplasia. *Clin. Cancer Res.*, 11, 3587-96. [↗](#)

Editions

2014-08-08	Authored	May, B.
2014-08-09	Edited	May, B.
2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsohazy, R.

HOXA3 chromatin is activated ↗

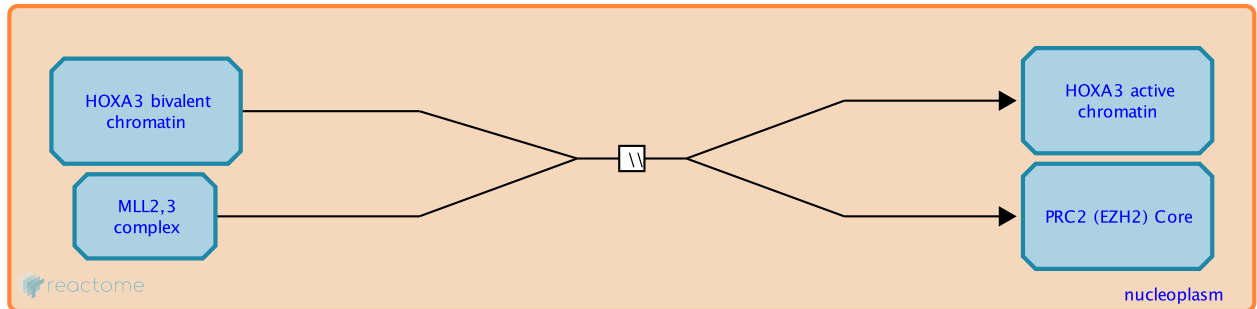
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-6810161

Type: omitted

Compartments: nucleoplasm

Inferred from: [Hoxa3 chromatin is activated \(Mus musculus\)](#)



In human fibroblasts (Lan et al. 2007) and human embryonic carcinoma cells (Lee et al. 2007, Sessa et al. 2007) treated with retinoic acid HOXA3 chromatin is activated by loss of methylation at lysine-27 of histone H3 (H3K27me3) and gain of H3K4me3. KDM6A (UTX) binds near HOXA3 (Lan et al. 2007, Lee et al. 2007) but does not appear to participate in the loss of H3K27me3. KDM6A forms complexes with the histone methyltransferases KMT2C,D (MLL2,3) which may participate in methylating H3K4 (Lee et al. 2007). Polycomb repressive complex 2 (PRC2), which binds H3K27me3, is also lost during activation of HOXA3 (Lan et al. 2007, Lee et al. 2007, Sessa et al. 2007). The change in chromatin at HOXA3 may result from euchromatin spreading from distant 3' retinoic acid response elements. The chromosomal conformation of the entire HOXA cluster changes during activation (Rousseau et al. 2014).

Followed by: [MAFB \(KREISLER\) and HOXB1:PBX1:PKNOX1 \(HOXB1:PBX1:PREP1\) activate HOXA3 expression](#)

Literature references

- Lan, F., Bayliss, PE., Rinn, JL., Whetstine, JR., Wang, JK., Chen, S. et al. (2007). A histone H3 lysine 27 demethylase regulates animal posterior development. *Nature*, 449, 689-94. ↗
- Lee, MG., Villa, R., Trojer, P., Norman, J., Yan, KP., Reinberg, D. et al. (2007). Demethylation of H3K27 regulates polycomb recruitment and H2A ubiquitination. *Science*, 318, 447-50. ↗
- Sessa, L., Breiling, A., Lavorgna, G., Silvestri, L., Casari, G., Orlando, V. (2007). Noncoding RNA synthesis and loss of Polycomb group repression accompanies the colinear activation of the human HOXA cluster. *RNA*, 13, 223-39. ↗
- Rousseau, M., Crutchley, JL., Miura, H., Suderman, M., Blanchette, M., Dostie, J. (2014). Hox in motion: tracking HoxA cluster conformation during differentiation. *Nucleic Acids Res.*, 42, 1524-40. ↗
- Xu, M., Zhao, GN., Lv, X., Liu, G., Wang, LY., Hao, DL. et al. (2014). CTCF Controls HOXA Cluster Silencing and Mediates PRC2-Repressive Higher-Order Chromatin Structure in NT2/D1 Cells. *Mol. Cell. Biol.*, 34, 3867-79. ↗

Editions

2014-08-08	Authored	May, B.
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2015-11-15	Authored	Rezsohazy, R.

MAFB (KREISLER) and HOXB1:PBX1:PKNOX1 (HOXB1:PBX1:PREP1) activate HOXA3 expression ↗

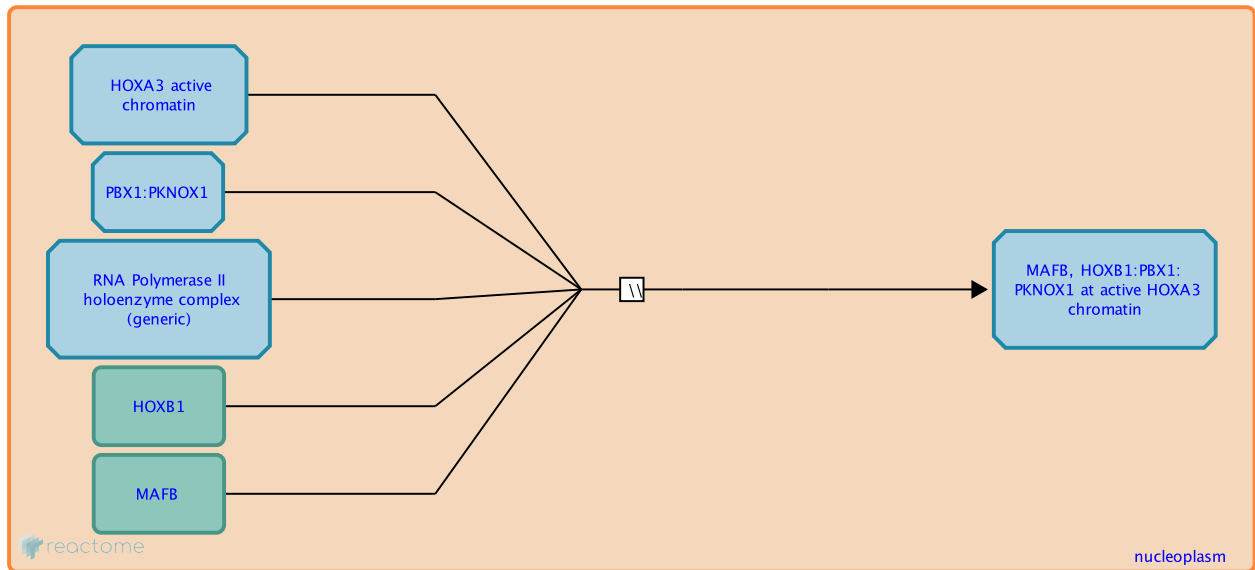
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617641

Type: omitted

Compartments: nucleoplasm

Inferred from: Mafb and Hoxb1:Pbx1:Pknox1 (Hoxb1:Pbx1:Prep1) activate Hoxa3 expression (Mus musculus)



As inferred from mouse embryos, the transcription factor MAFB (KREISLER, KMRL) initially activates the HOXA3 gene in rhombomere 5 (r5) and r6. Weaker expression is also observed in r7. HOXA3 autoregulates by binding and activating its own promoter.

Preceded by: HOXB1 mRNA is translated, HOXA3 chromatin is activated

Followed by: HOXA3 gene is transcribed

Editions

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2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsóhazy, R.

HOXA3 gene is transcribed [↗](#)

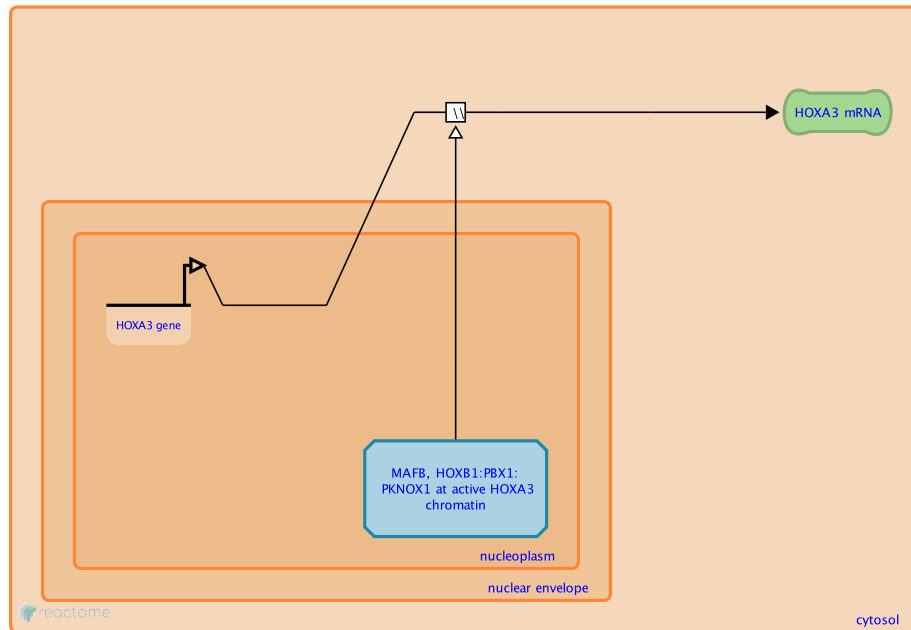
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617676

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxa3 gene is transcribed \(Mus musculus\)](#)



The HOXA3 gene is transcribed to yield mRNA (Han et al. 2007). In mouse embryos Hoxa3 mRNA is observed in rhombomere 5 and caudally through the central nervous system, ectoderm, and somitic mesoderm. HOXA3 mRNA is a target of the microRNA miR-10a (Han et al. 2007).

Preceded by: [MAFB \(KREISLER\) and HOXB1:PBX1:PKNOX1 \(HOXB1:PBX1:PREP1\) activate HOXA3 expression](#)

Followed by: [HOXA3 mRNA is translated](#)

Literature references

Han, L., Witmer, PD., Casey, E., Valle, D., Sukumar, S. (2007). DNA methylation regulates MicroRNA expression. *Cancer Biol. Ther.*, 6, 1284-8. [↗](#)

Editions

2014-08-08	Authored	May, B.
2014-08-12	Edited	May, B.
2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsohazy, R.

HOXA3 mRNA is translated ↗

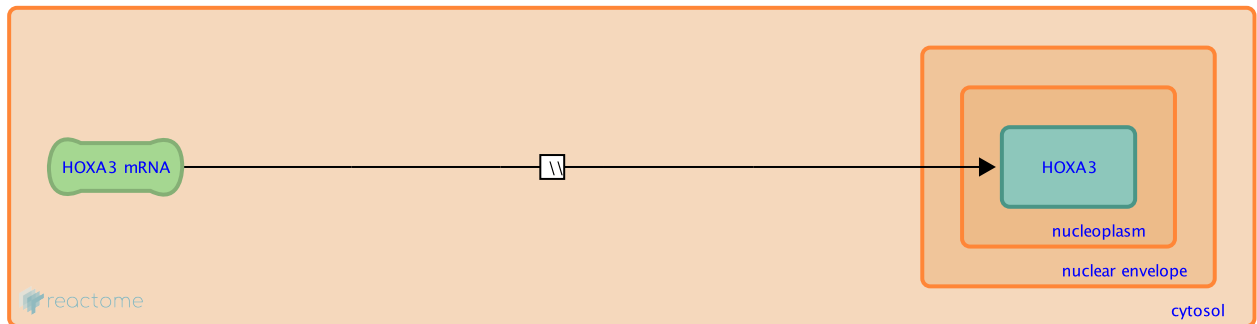
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617643

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxa3 mRNA is translated \(Mus musculus\)](#)



HOXA3 mRNA is translated to yield HOXA3 protein.

Preceded by: [HOXA3 gene is transcribed](#)

Editions

2014-02-22	Edited	May, B.
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2015-11-15	Authored	Rezsohazy, R.

HOXB3 chromatin is activated ↗

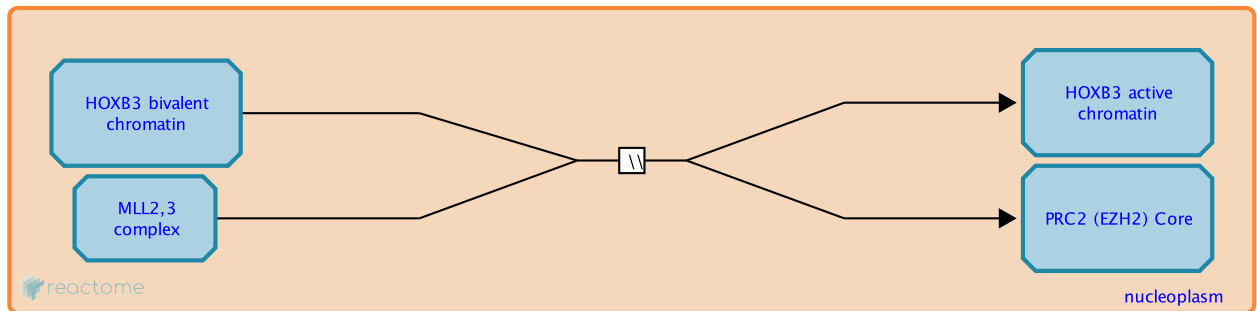
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-6810158

Type: omitted

Compartments: nucleoplasm

Inferred from: [Hoxb3 chromatin is activated \(Mus musculus\)](#)



During activation of HOXB3 by retinoic acid in fibroblasts (Lan et al. 2007) and embryonal carcinoma cells (Lee et al. 2007) chromatin at HOXB3 loses methylation at lysine-27 of histone H3 (H3K27me3), loses PRC2, and gains methylation at H3K4. The demethylase KDM6A (UTX) binds HOXB3 chromatin during activation (Lan et al. 2007, Lee et al. 2007) and may participate in demethylating H3K27me3. KDM6A forms complexes with the histone methyltransferases KMT2C,D (MLL2,3) which may participate in methylating H3K4 (Lee et al. 2007)

Literature references

Lan, F., Bayliss, PE., Rinn, JL., Whetstine, JR., Wang, JK., Chen, S. et al. (2007). A histone H3 lysine 27 demethylase regulates animal posterior development. *Nature*, 449, 689-94. ↗

Lee, MG., Villa, R., Trojer, P., Norman, J., Yan, KP., Reinberg, D. et al. (2007). Demethylation of H3K27 regulates polycomb recruitment and H2A ubiquitination. *Science*, 318, 447-50. ↗

Editions

2014-08-08	Authored	May, B.
2015-05-13	Reviewed	Blasi, F.
2015-11-15	Edited	May, B.
2015-11-15	Authored	Rezsohazy, R.

MAFB:JUN and EGR2 activate HOXB3 expression ↗

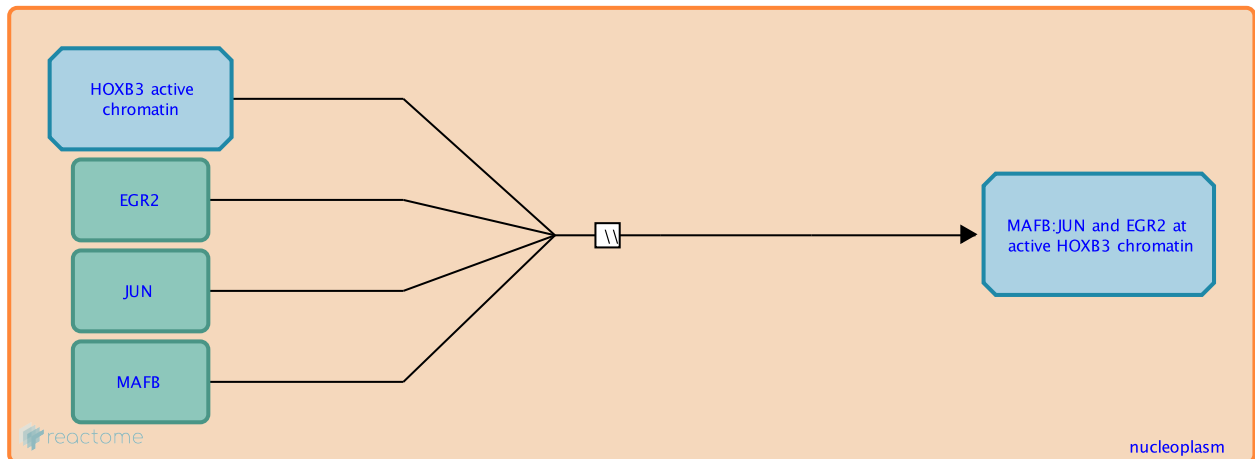
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617661

Type: omitted

Compartments: nucleoplasm

Inferred from: Mafb:Jun and Egr2 activate Hoxb3 expression (Mus musculus)



As inferred from mouse embryos, the MAFB:JUN (KREISLER:JUN) heterodimer binds the rhombomere 5 (r5) enhancer located 5' to the P1 promoter of the HOXB3 gene and activates expression in r5. EGR2 (KROX20) also binds the r5 enhancer is required to activate the HOXB3 gene in r5. After initial activation HOXB3 is hypothesized to maintain its own expression. HOXB3 is expressed most strongly in r5 and more weakly in caudal rhombomeres r6 and r7.

Followed by: [HOXB3 gene is transcribed](#)

Editions

2014-08-08	Authored	May, B.
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2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsöházy, R.

HOXB3 gene is transcribed [↗](#)

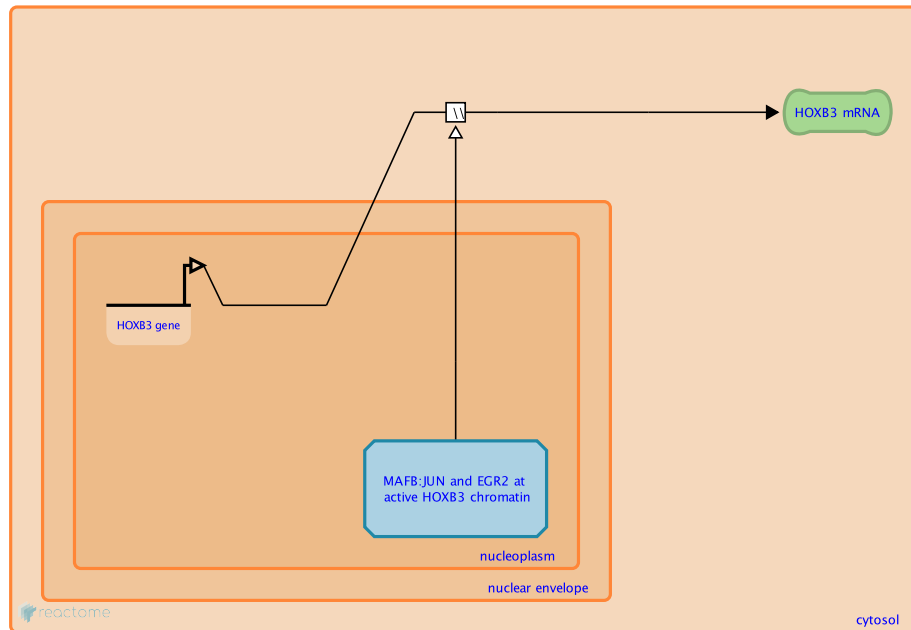
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-5617672

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxb3 gene is transcribed \(Mus musculus\)](#)



The HOXB3 gene is transcribed to yield mRNA (in embryos in Giampaolo et al. 1989, in carcinoma cells in Simeone et al. 1990). The HOXB3 mRNA is a target of the microRNAs miR-7 and miR-218 in breast cancer cells (Li et al. 2012) and miR-10A (Weiss et al. 2009). In mouse embryos Hoxb3 mRNA is observed strongly in rhombomere 5 and more weakly in rhombomeres 6 and 7 of the hindbrain. Hoxb3 mRNA is also observed in mesodermal derivatives including lung, stomach, pancreas, and metanephros, and in neural crest derivatives.

Preceded by: [MAFB:JUN and EGR2 activate HOXB3 expression](#)

Followed by: [HOXB3 mRNA is translated](#)

Literature references

- Li, Q., Zhu, F., Chen, P. (2012). miR-7 and miR-218 epigenetically control tumor suppressor genes RASSF1A and Claudin-6 by targeting HoxB3 in breast cancer. *Biochem. Biophys. Res. Commun.*, 424, 28-33. [↗](#)
- Giampaolo, A., Acampora, D., Zappavigna, V., Pannese, M., D'Esposito, M., Carè, A. et al. (1989). Differential expression of human HOX-2 genes along the anterior-posterior axis in embryonic central nervous system. *Differentiation*, 40, 191-7. [↗](#)
- Simeone, A., Acampora, D., Arcioni, L., Andrews, PW., Boncinelli, E., Mavilio, F. (1990). Sequential activation of HOX2 homeobox genes by retinoic acid in human embryonal carcinoma cells. *Nature*, 346, 763-6. [↗](#)
- Weiss, FU., Marques, IJ., Woltering, JM., Vlecken, DH., Aghdassi, A., Partecke, LI. et al. (2009). Retinoic acid receptor antagonists inhibit miR-10a expression and block metastatic behavior of pancreatic cancer. *Gastroenterology*, 137, 2136-45.e1-7. [↗](#)

Editions

2014-08-08	Authored	May, B.
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2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsöházy, R.

HOXB3 mRNA is translated ↗

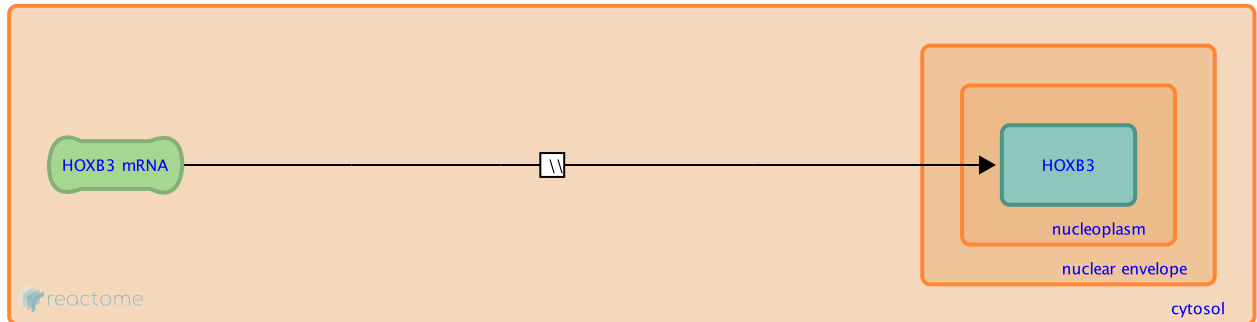
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-5617668

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxb3 mRNA is translated \(Mus musculus\)](#)



HOXB3 mRNA is translated to yield HOXB3 protein (Palakurthy et al. 2009, Li et al. 2012, Chen et al. 2013). Translation is repressed by the microRNAs miR-7 and miR-218 (Li et al. 2012) and miR-10A (Weiss et al. 2009).

Preceded by: [HOXB3 gene is transcribed](#)

Literature references

- Li, Q., Zhu, F., Chen, P. (2012). miR-7 and miR-218 epigenetically control tumor suppressor genes RASSF1A and Claudin-6 by targeting HoxB3 in breast cancer. *Biochem. Biophys. Res. Commun.*, 424, 28-33. ↗
- Chen, J., Zhu, S., Jiang, N., Shang, Z., Quan, C., Niu, Y. (2013). HoxB3 promotes prostate cancer cell progression by transactivating CDCA3. *Cancer Lett.*, 330, 217-24. ↗
- Palakurthy, RK., Wajapeyee, N., Santra, MK., Gazin, C., Lin, L., Gobeil, S. et al. (2009). Epigenetic silencing of the RASSF1A tumor suppressor gene through HOXB3-mediated induction of DNMT3B expression. *Mol. Cell*, 36, 219-30. ↗
- Weiss, FU., Marques, IJ., Woltering, JM., Vlecken, DH., Aghdassi, A., Partecke, LI. et al. (2009). Retinoic acid receptor antagonists inhibit miR-10a expression and block metastatic behavior of pancreatic cancer. *Gastroenterology*, 137, 2136-45.e1-7. ↗

Editions

2014-08-08	Authored	May, B.
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2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsohazy, R.

HOXD3 chromatin is activated ↗

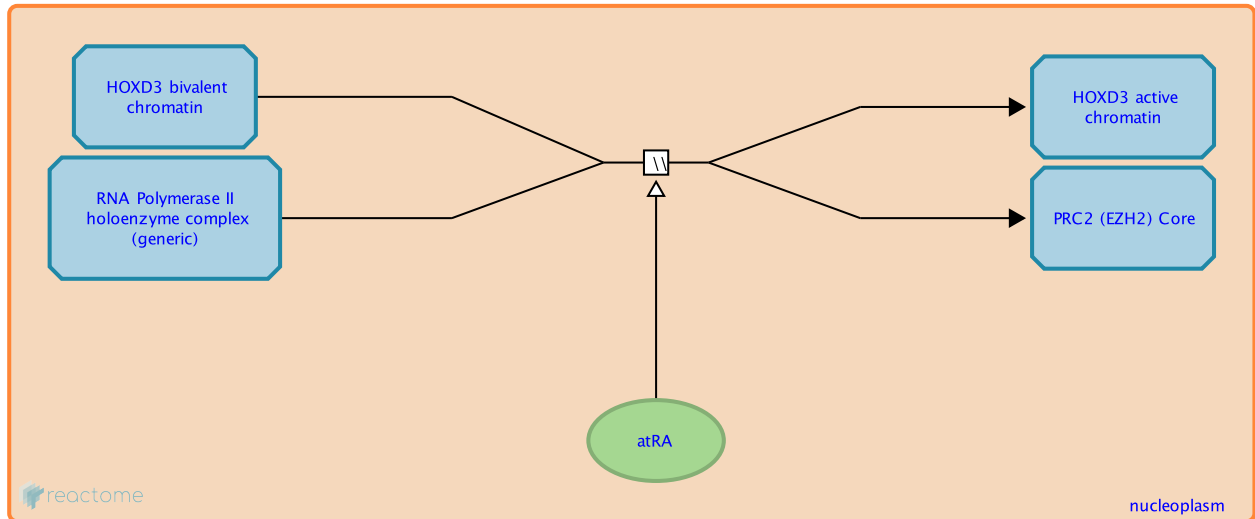
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617650

Type: omitted

Compartments: nucleoplasm

Inferred from: [Hoxd3 chromatin is activated \(Mus musculus\)](#)



Retinoic acid induces expression of HOXD3 in neuroblastoma cells (Zha et al. 2012) and mouse embryos but it is unknown if the effect is direct or indirect. In mouse embryos the retinoid receptor Rarb is not responsible for the inducibility. As inferred from mouse embryos HOXD3 is expressed in rhombomeres 5, 6, and 7 (r5-7). As inferred from mouse Hoxd3, activation of HOXD3 chromatin is associated with loss of methylation at lysine-27 of histone H3 (H3K27), loss of PRC2, and gain of methylation at H3K4.

Followed by: [HOXD3 gene is transcribed](#)

Literature references

Zha, Y., Ding, E., Yang, L., Mao, L., Wang, X., McCarthy, BA. et al. (2012). Functional dissection of HOXD cluster genes in regulation of neuroblastoma cell proliferation and differentiation. *PLoS ONE*, 7, e40728. ↗

Editions

2014-08-08	Authored	May, B.
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2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsohazy, R.

HOXD3 gene is transcribed [↗](#)

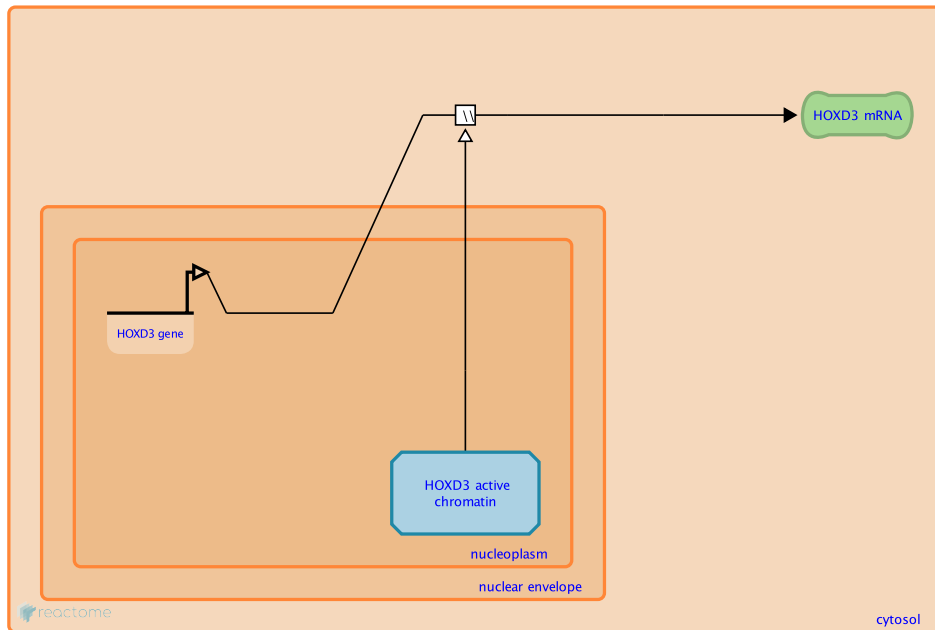
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-5617642

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxd3 gene is transcribed \(Mus musculus\)](#)



The HOXD3 gene is transcribed to yield mRNA (Zha et al. 2012). In mouse embryos Hoxd3 mRNA is observed in the neural tube with an anterior boundary at the junction of rhombomeres 4-5 and in the dorsal root ganglia, first cervical vertebra, thyroid gland, kidney tubules, esophagus, stomach, and intestines.

Preceded by: [HOXD3 chromatin is activated](#)

Followed by: [HOXD3 mRNA is translated](#)

Literature references

Zha, Y., Ding, E., Yang, L., Mao, L., Wang, X., McCarthy, BA. et al. (2012). Functional dissection of HOXD cluster genes in regulation of neuroblastoma cell proliferation and differentiation. *PLoS ONE*, 7, e40728. [↗](#)

Editions

2014-08-08	Authored	May, B.
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HOXD3 mRNA is translated ↗

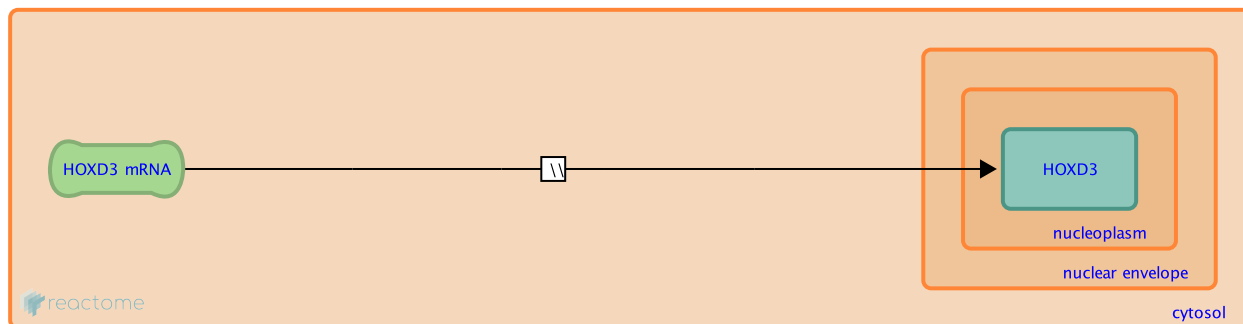
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-5617652

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxd3 mRNA is translated \(Mus musculus\)](#)



HOXD3 mRNA is translated to yield HOXD3 protein (Zha et al. 2012).

Preceded by: [HOXD3 gene is transcribed](#)

Literature references

Zha, Y., Ding, E., Yang, L., Mao, L., Wang, X., McCarthy, BA. et al. (2012). Functional dissection of HOXD cluster genes in regulation of neuroblastoma cell proliferation and differentiation. *PLoS ONE*, 7, e40728. ↗

Editions

2014-08-08	Authored	May, B.
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2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsohazy, R.

Retinoic acid activates HOXA4 chromatin ↗

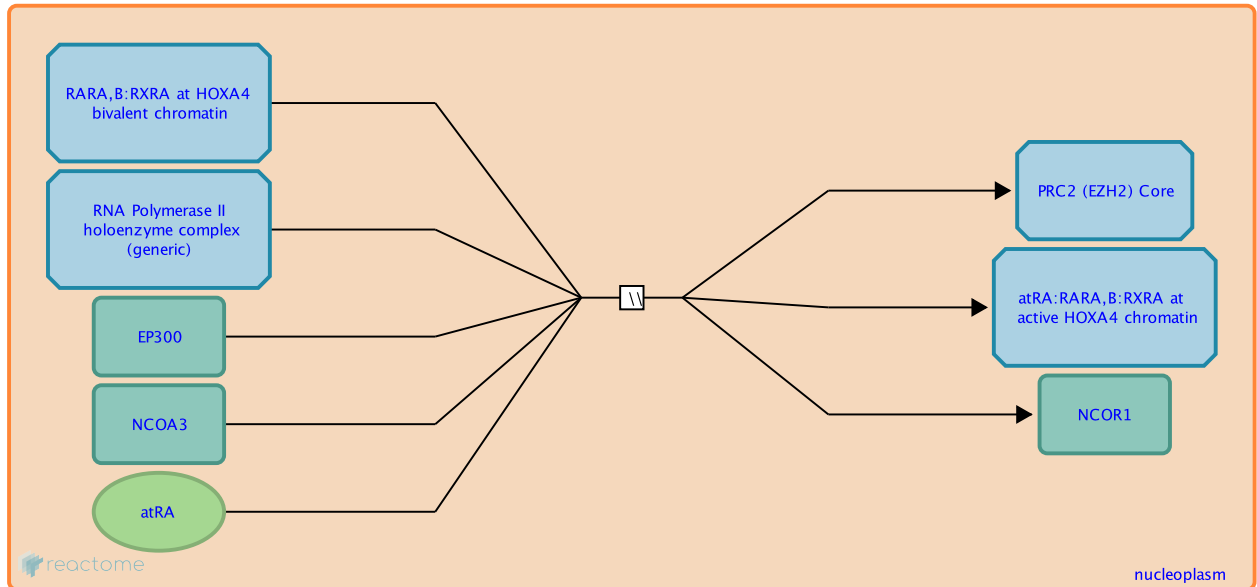
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617862

Type: omitted

Compartments: nucleoplasm

Inferred from: Retinoic acid activates Hoxa4 chromatin (Mus musculus)



As inferred from mouse embryos, retinoic acid initially activates expression of the HOXA4 gene in rhombomere 7 (r7) by binding RARB or RARA in dimeric RAR:RXR complexes located at retinoic acid response elements (RAREs) in the 5' flanking region of the HOXA4 promoter (also observed in human teratocarcinoma cells in Doerksen et al. 1996, Sessa et al. 2007), correlating dissociation of corepressors and recruitment of coactivators. In mouse embryos Hoxa4 itself maintains later expression in an autoregulatory loop.

In human fibroblasts (Lan et al. 2007) and teratocarcinoma cells (Sessa et al 2007) activation of HOXA4 chromatin is accompanied by loss of methylation at lysine-27 of histone H3 (H3K27me3) and gain of H3K4me3. The polycomb repressive complex 2 (PRC2), which binds H3K27me3, is also reduced at active HOXA4 chromatin (Lan et al. 2007, Sessa et al. 2007).

Followed by: HOXA4 gene is transcribed

Literature references

- Doerksen, LF., Bhattacharya, A., Kannan, P., Pratt, D., Tainsky, MA. (1996). Functional interaction between a RARE and an AP-2 binding site in the regulation of the human HOX A4 gene promoter. *Nucleic Acids Res.*, 24, 2849-56. ↗
- Lan, F., Bayliss, PE., Rinn, JL., Whetstine, JR., Wang, JK., Chen, S. et al. (2007). A histone H3 lysine 27 demethylase regulates animal posterior development. *Nature*, 449, 689-94. ↗
- Sessa, L., Breiling, A., Lavorgna, G., Silvestri, L., Casari, G., Orlando, V. (2007). Noncoding RNA synthesis and loss of Polycomb group repression accompanies the colinear activation of the human HOXA cluster. *RNA*, 13, 223-39. ↗
- Rousseau, M., Crutchley, JL., Miura, H., Suderman, M., Blanchette, M., Dostie, J. (2014). Hox in motion: tracking HoxA cluster conformation during differentiation. *Nucleic Acids Res.*, 42, 1524-40. ↗

Xu, M., Zhao, GN., Lv, X., Liu, G., Wang, LY., Hao, DL. et al. (2014). CTCF Controls HOXA Cluster Silencing and Mediates PRC2-Repressive Higher-Order Chromatin Structure in NT2/D1 Cells. *Mol. Cell. Biol.*, 34, 3867-79. [↗](#)

Editions

2014-08-08	Authored	May, B.
2014-08-13	Edited	May, B.
2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsohazy, R.

HOXA4 gene is transcribed [↗](#)

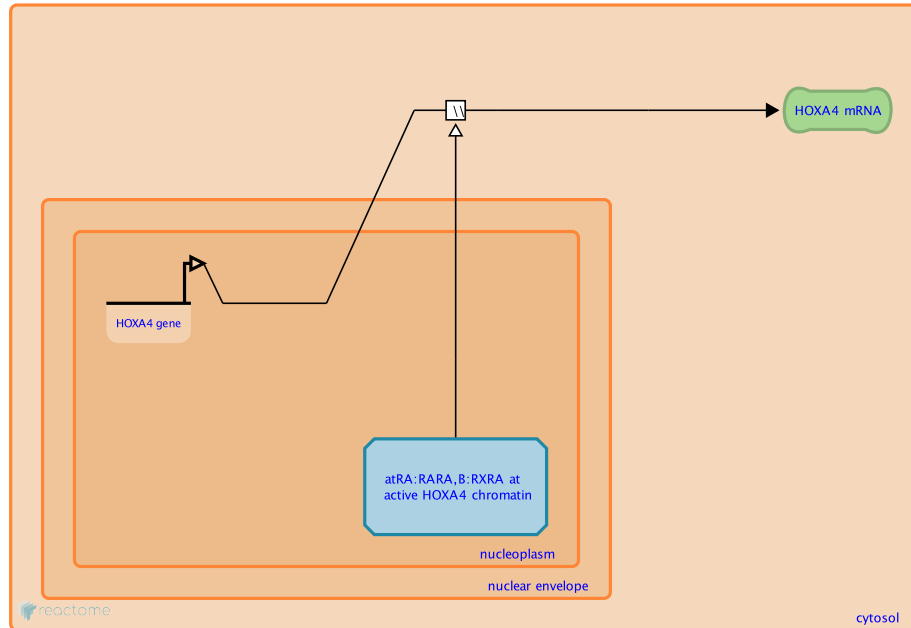
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617877

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxa4 gene is transcribed \(Mus musculus\)](#)



The HOXA4 gene is transcribed to yield mRNA (Doerksen et al. 1996). In mouse cells, microRNAs miR-196a-2, miR-196b, and miRNA miR-222 target Hoxa4 mRNA untranslated regions. In mouse embryos Hoxa4 mRNA is observed in rhombomere 7, mesoderm (including somites, lung, and kidney), rostral-dorsal stomach, rostral prececal gut, and large intestine.

Preceded by: [Retinoic acid activates HOXA4 chromatin](#)

Followed by: [HOXA4 mRNA is translated](#)

Literature references

Doerksen, LF., Bhattacharya, A., Kannan, P., Pratt, D., Tainsky, MA. (1996). Functional interaction between a RARE and an AP-2 binding site in the regulation of the human HOX A4 gene promoter. *Nucleic Acids Res.*, 24, 2849-56. [↗](#)

Editions

2014-08-08	Authored	May, B.
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2015-11-15	Authored	Rezsohazy, R.

HOXA4 mRNA is translated ↗

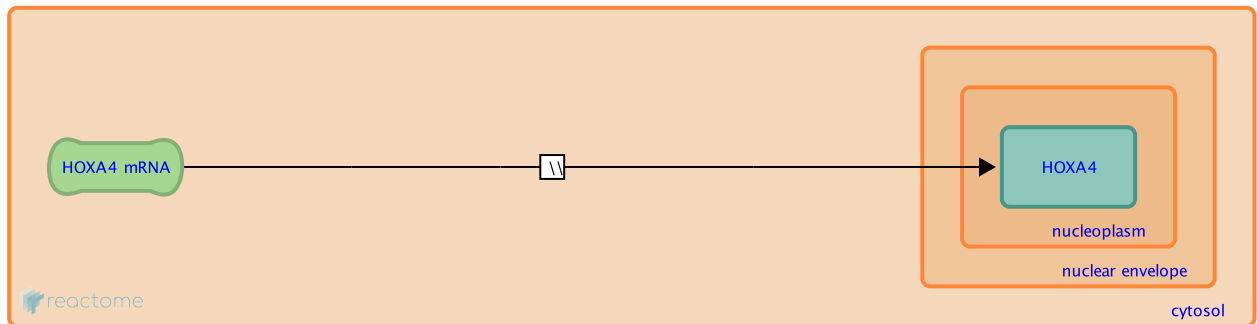
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617879

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxa4 mRNA is translated \(Mus musculus\)](#)



The HOXA4 mRNA is translated to yield HOXA4 protein. In mouse cells the microRNAs miR-196a-2, miR-196b, and miR-222 repress expression of Hoxa4.

Preceded by: [HOXA4 gene is transcribed](#)

Editions

2014-08-08	Authored	May, B.
2014-08-13	Edited	May, B.
2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsohazy, R.

Retinoic acid activates HOXB4 chromatin ↗

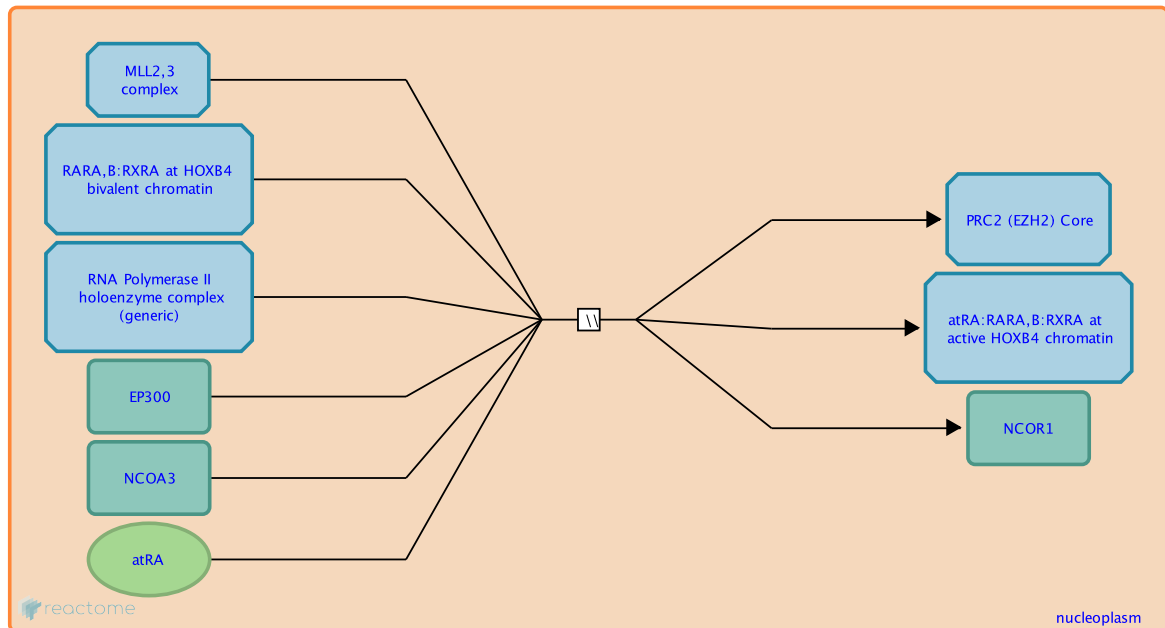
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617859

Type: omitted

Compartments: nucleoplasm

Inferred from: Retinoic acid activates Hoxb4 chromatin (Mus musculus)



As inferred from mouse embryos, retinoic acid activates the HOXB4 gene in rhombomere 7 (r7) by binding retinoic acid receptor RARB (Folberg et al. 1999) and perhaps RARA in RAR:RXR dimers bound to retinoic acid response elements (RAREs) located in the 3' flanking region of the HOXB4 gene, causing dissociation of corepressors and recruitment of coactivators. HOXB4 maintains its own expression by binding and activating its own promoter.

In human fibroblasts activation of chromatin at the HOXB4 gene accompanied by loss of methylation of lysine-27 at histone H3 (H3K27me3, Lan et al. 2007). Based on observations from mouse embryonic stem cells, Polycomb repressive complex 2 (PRC2), which binds H3K27me3, is anticipated to be lost while methylation of H3K4 is gained, possibly through the action of the histone demethylase KDM6A (UTX) which, in human fibroblasts, binds HOXB4 (Lan et al. 2007). Other factors may be involved in demethylating H3K27me3. KDM6A can form complexes containing the histone methyltransferases KMT2C,D (MLL2,3) which may participate in methylating H3K4 (Lee et al. 2007).

Followed by: HOXB4 gene is transcribed

Literature references

- Lan, F., Bayliss, PE., Rinn, JL., Whetstine, JR., Wang, JK., Chen, S. et al. (2007). A histone H3 lysine 27 demethylase regulates animal posterior development. *Nature*, 449, 689-94. ↗
- Lee, MG., Villa, R., Trojer, P., Norman, J., Yan, KP., Reinberg, D. et al. (2007). Demethylation of H3K27 regulates polycomb recruitment and H2A ubiquitination. *Science*, 318, 447-50. ↗

Editions

2014-08-08	Authored	May, B.
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2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsóhazy, R.

HOXB4 gene is transcribed [↗](#)

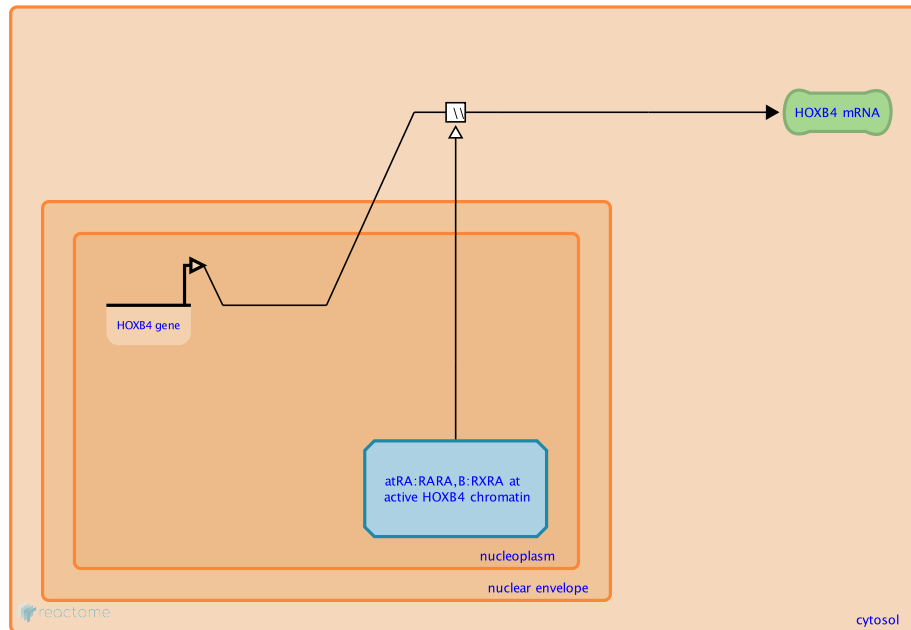
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-5617867

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxb4 gene is transcribed \(Mus musculus\)](#)



The HOXB4 gene is transcribed to yield mRNA (in embryos in Giampaolo et al. 1989, in carcinoma cells in Simeone et al. 1990). The microRNA miR-23a binds the 3' untranslated region of HOXB4 mRNA (Koller et al 2013). In mouse embryos Hoxb4 mRNA is observed in rhombomere 7, paraxial mesoderm of somite 7, and caudally.

Preceded by: [Retinoic acid activates HOXB4 chromatin](#)

Followed by: [HOXB4 mRNA is translated](#)

Literature references

Koller, K., Das, S., Leuschner, I., Korbilius, M., Hoefler, G., Guertl, B. (2013). Identification of the transcription factor HOXB4 as a novel target of miR-23a. *Genes Chromosomes Cancer*, 52, 709-15. [↗](#)

Giampaolo, A., Acampora, D., Zappavigna, V., Pannese, M., D'Esposito, M., Carè, A. et al. (1989). Differential expression of human HOX-2 genes along the anterior-posterior axis in embryonic central nervous system. *Differentiation*, 40, 191-7. [↗](#)

Simeone, A., Acampora, D., Arcioni, L., Andrews, PW., Boncinelli, E., Mavilio, F. (1990). Sequential activation of HOX2 homeobox genes by retinoic acid in human embryonic carcinoma cells. *Nature*, 346, 763-6. [↗](#)

Editions

2014-08-08	Authored	May, B.
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2015-11-15	Authored	Rezsohazy, R.

HOXB4 mRNA is translated [↗](#)

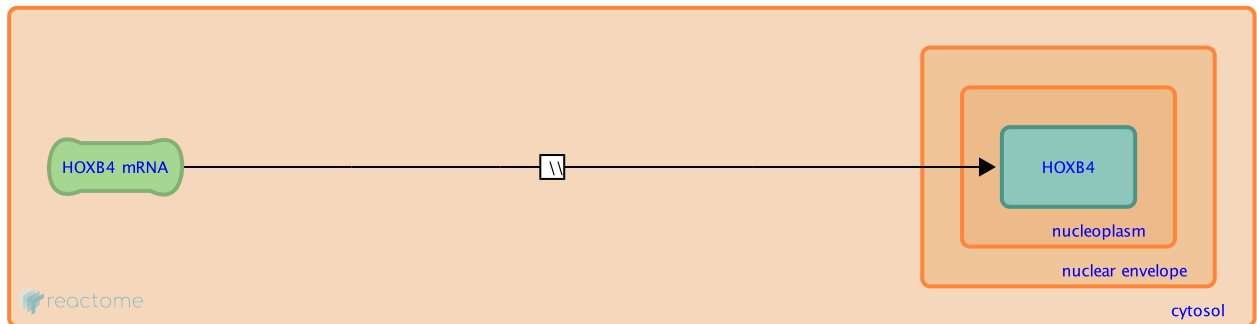
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-5617881

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxb4 mRNA is translated \(Mus musculus\)](#)



HOXB4 mRNA is translated to yield HOXB4 protein. Protein expression is repressed by miR-23a (Koller et al. 2013).

Preceded by: [HOXB4 gene is transcribed](#)

Literature references

Koller, K., Das, S., Leuschner, I., Korbilius, M., Hoefler, G., Guertl, B. (2013). Identification of the transcription factor HOXB4 as a novel target of miR-23a. *Genes Chromosomes Cancer*, 52, 709-15. [↗](#)

Editions

2014-08-08	Authored	May, B.
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2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsohazy, R.

HOXC4 chromatin is activated ↗

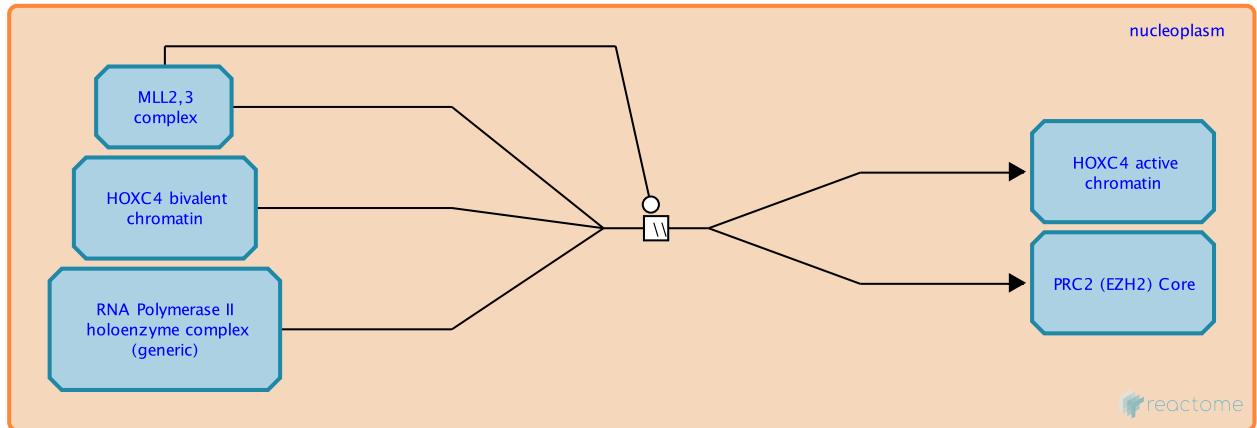
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-5617887

Type: omitted

Compartments: nucleoplasm

Inferred from: [Hoxc4 chromatin is activated \(Mus musculus\)](#)



As inferred from mouse embryos, HOXC4 is expressed at E12.5 caudal to rhombomere 7 (r7) and at the level of prevertebrae 4-5 and caudally. In carcinoma cells treated with retinoic acid (Lee et al. 2007) and primary fibroblasts (Lan et al. 2007) chromatin at HOXC4 loses methylation at lysine-27 of histone H3 (H3K27me3), loses polycomb repressive complex 2 (PRC2), and gains methylation at lysine-4 of histone H3 (H3K4me3). In embryonal carcinoma cells KDM6A (UTX) binds HOXC4 and participates in demethylating H3K27 at HOXC4 (Lee et al. 2007)

Followed by: [HOXC4 gene is transcribed](#)

Literature references

Lan, F., Bayliss, PE., Rinn, JL., Whetstine, JR., Wang, JK., Chen, S. et al. (2007). A histone H3 lysine 27 demethylase regulates animal posterior development. *Nature*, 449, 689-94. ↗

Lee, MG., Villa, R., Trojer, P., Norman, J., Yan, KP., Reinberg, D. et al. (2007). Demethylation of H3K27 regulates polycomb recruitment and H2A ubiquitination. *Science*, 318, 447-50. ↗

Editions

2014-08-08	Authored	May, B.
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2015-11-15	Authored	Rezsohazy, R.

HOXC4 gene is transcribed ↗

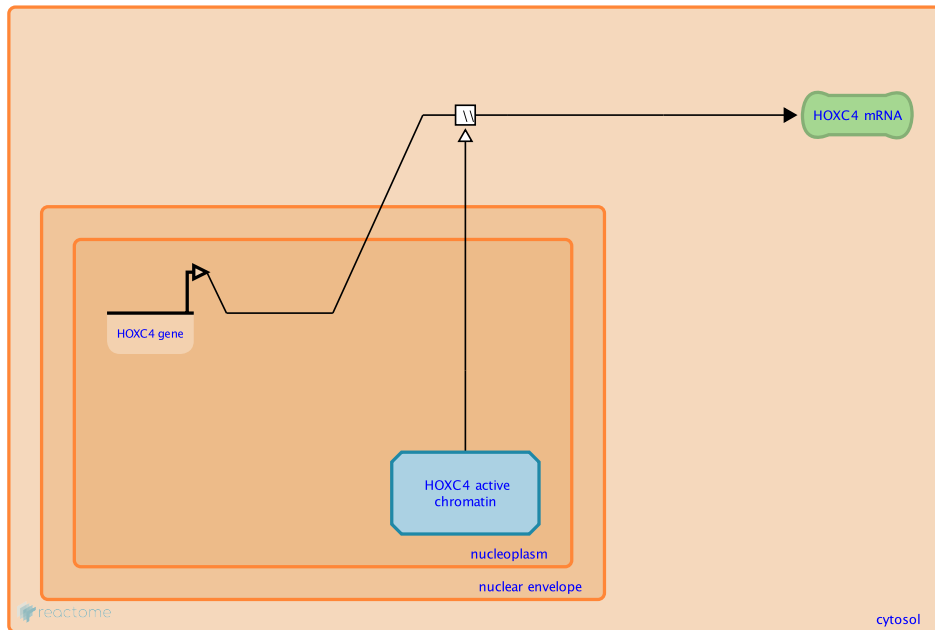
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617866

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxc4 gene is transcribed \(Mus musculus\)](#)



The HOXC4 gene is transcribed to yield mRNA. In mouse embryos Hoxc4 mRNA is observed caudal to rhombomere 7 in spinal column, prevertebrae, esophagus, metanephric kidney, lung, and trachea.

Preceded by: [HOXC4 chromatin is activated](#)

Followed by: [HOXC4 mRNA is translated](#)

Editions

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2015-05-13	Reviewed	Blasi, F.
2015-11-15	Authored	Rezsohazy, R.

HOXC4 mRNA is translated [↗](#)

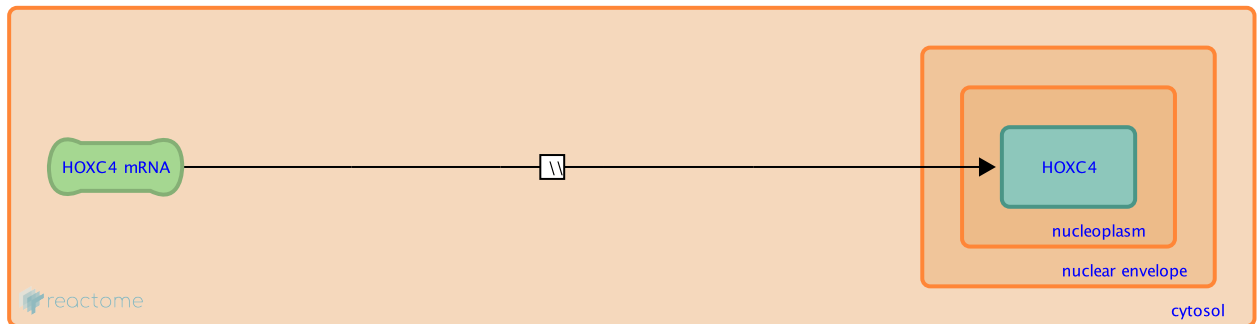
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-5617855

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxc4 mRNA is translated \(Mus musculus\)](#)



HOXC4 mRNA is translated to yield HOXC4 protein.

Preceded by: [HOXC4 gene is transcribed](#)

Editions

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Retinoic acid activates HOXD4 chromatin ↗

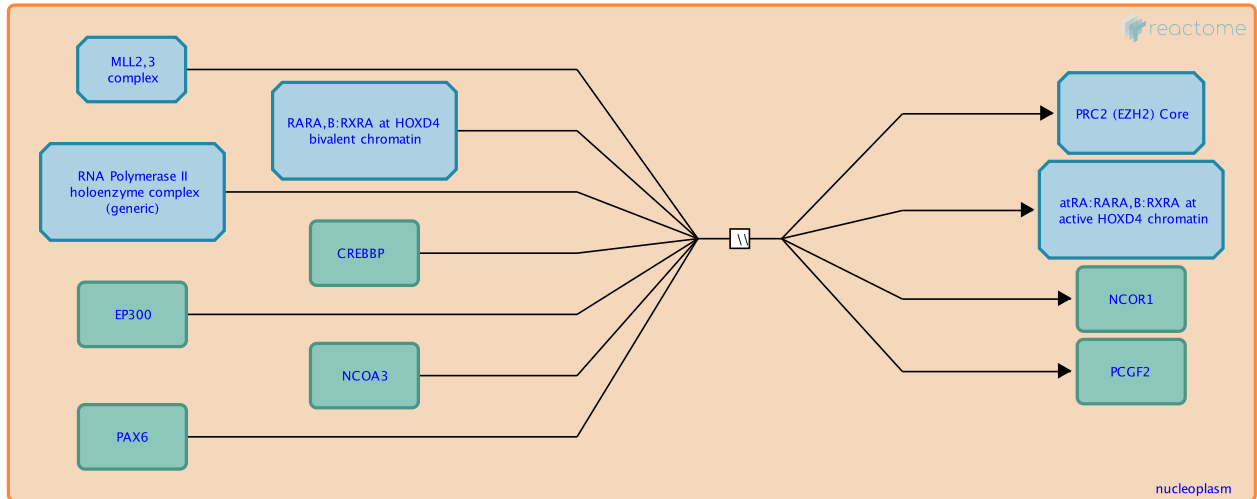
Location: Activation of anterior HOX genes in hindbrain development during early embryogenesis

Stable identifier: R-HSA-5617896

Type: omitted

Compartments: nucleoplasm

Inferred from: Retinoic acid activates Hoxd4 chromatin (Mus musculus)



As inferred from mouse embryos, retinoic acid activates the HOXD4 gene in rhombomere 7 (r7) by binding RARB or RARA in RAR:RXR receptor dimers bound to a retinoic acid response element (RAREs) in the 5' flanking region of the gene. Ligand binding by retinoic acid receptors causes dismissal of corepressors such as NCOR1 and recruitment of coactivators such as NCOA3 (Klein et al. 2000). The response of HOXD4 to retinoic acid is also observed in human embryonal carcinoma cells (Moroni et al. 1993, Morrison et al. 1996, Morrison et al. 1997). PAX6 binds near the RARE and is required for maximal activation.

In human fibroblasts chromatin at HOXA genes is activated by loss of methylation at lysine-27 (H3K27me3), loss of Polycomb repressive complex 2 (PRC2), and gain of H3K4me3 (Lan et al. 2007). Similar changes occur at Hoxd4 in mouse embryos. The histone demethylase KDM6A (UTX) binds the HOXD4 gene in human lung fibroblasts and may participate in demethylating H3K27me3 (Lan et al. 2007). Other factors may also be involved in demethylation. KDM6A associates with the histone methyltransferases KMT2C,D (MLL2,3) which may participate in methylating H3K4 (Lee et al. 2007). As inferred from mouse homologs, PCGF2 (MEL18) dissociates from Hoxd4 during activation. After activation by retinoic acid, HOXD4 maintains its own expression by binding and activating its own promoter.

Followed by: HOXD4 gene is transcribed

Literature references

- Morrison, A., Moroni, MC., Ariza-McNaughton, L., Krumlauf, R., Mavilio, F. (1996). In vitro and transgenic analysis of a human HOXD4 retinoid-responsive enhancer. *Development*, 122, 1895-907. ↗
- Moroni, MC., Viganó, MA., Mavilio, F. (1993). Regulation of the human HOXD4 gene by retinoids. *Mech. Dev.*, 44, 139-54. ↗
- Morrison, A., Ariza-McNaughton, L., Gould, A., Featherstone, M., Krumlauf, R. (1997). HOXD4 and regulation of the group 4 paralog genes. *Development*, 124, 3135-46. ↗
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Zha, Y., Ding, E., Yang, L., Mao, L., Wang, X., McCarthy, BA. et al. (2012). Functional dissection of HOXD cluster genes in regulation of neuroblastoma cell proliferation and differentiation. *PLoS ONE*, 7, e40728. [↗](#)

Editions

2014-08-08	Authored	May, B.
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2015-11-15	Authored	Rezsohazy, R.

HOXD4 gene is transcribed [↗](#)

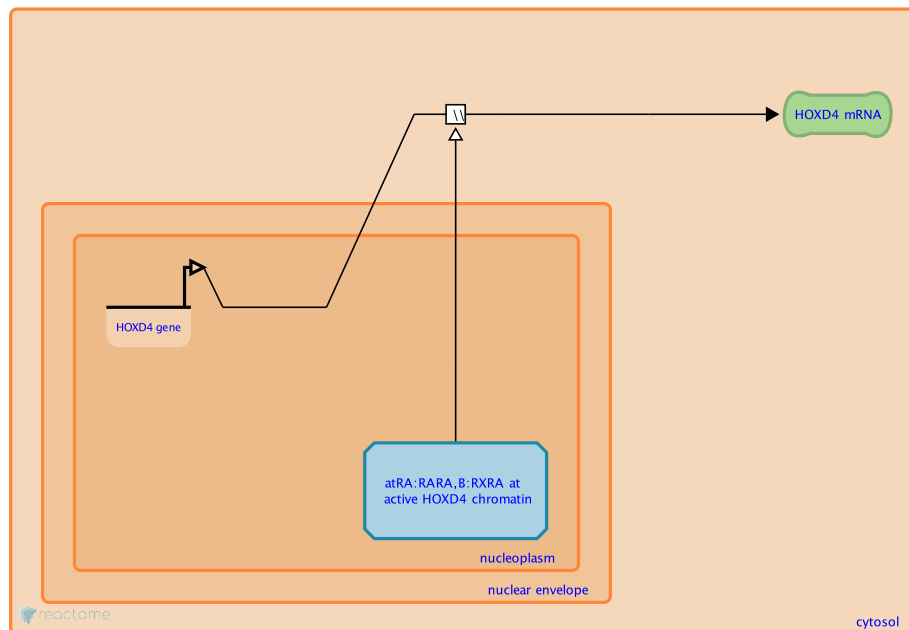
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-5617874

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxd4 gene is transcribed \(Mus musculus\)](#)



The HOXD4 gene is transcribed to yield mRNA (Moroni et al. 1993, Morrison et al. 1996, Morrison et al. 1997). In mouse embryos Hoxd4 mRNA is observed in rhombomere 7 and caudally in spinal cord and prevertebrae. The HOXD4 promoter region is a target of the microRNA miR-10a, which causes repression of transcription (Tan et al. 2009).

Preceded by: [Retinoic acid activates HOXD4 chromatin](#)

Followed by: [HOXD4 mRNA is translated](#)

Literature references

Morrison, A., Moroni, MC., Ariza-McNaughton, L., Krumlauf, R., Mavilio, F. (1996). In vitro and transgenic analysis of a human HOXD4 retinoid-responsive enhancer. *Development*, 122, 1895-907. [↗](#)

Moroni, MC., Viganó, MA., Mavilio, F. (1993). Regulation of the human HOXD4 gene by retinoids. *Mech. Dev.*, 44, 139-54. [↗](#)

Morrison, A., Ariza-McNaughton, L., Gould, A., Featherstone, M., Krumlauf, R. (1997). HOXD4 and regulation of the group 4 paralog genes. *Development*, 124, 3135-46. [↗](#)

Tan, Y., Zhang, B., Wu, T., Skogerbø, G., Zhu, X., Guo, X. et al. (2009). Transcriptional inhibition of Hoxd4 expression by miRNA-10a in human breast cancer cells. *BMC Mol. Biol.*, 10, 12. [↗](#)

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HOXD4 mRNA is translated ↗

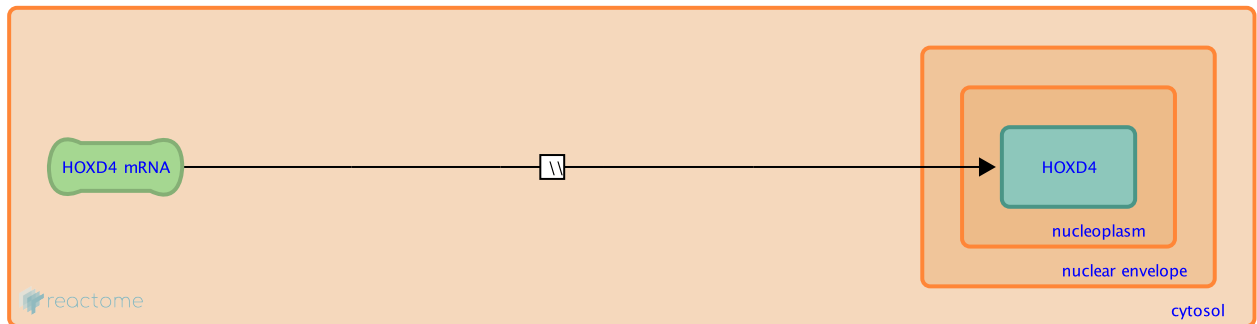
Location: [Activation of anterior HOX genes in hindbrain development during early embryogenesis](#)

Stable identifier: R-HSA-5617864

Type: omitted

Compartments: cytosol, nucleoplasm

Inferred from: [Hoxd4 mRNA is translated \(Mus musculus\)](#)



HOXD4 mRNA is translated to yield HOXD4 protein (Zappavigna et al. 1991).

Preceded by: [HOXD4 gene is transcribed](#)

Literature references

Zappavigna, V., Renucci, A., Izpisúa-Belmonte, J.C., Urier, G., Peschle, C., Duboule, D. (1991). HOX4 genes encode transcription factors with potential auto- and cross-regulatory capacities. *EMBO J.*, 10, 4177-87. ↗

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