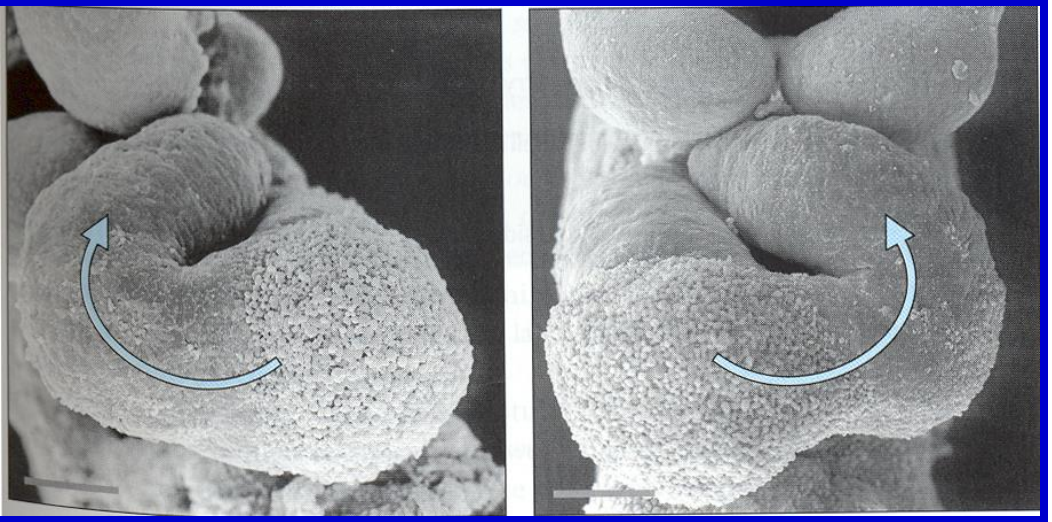
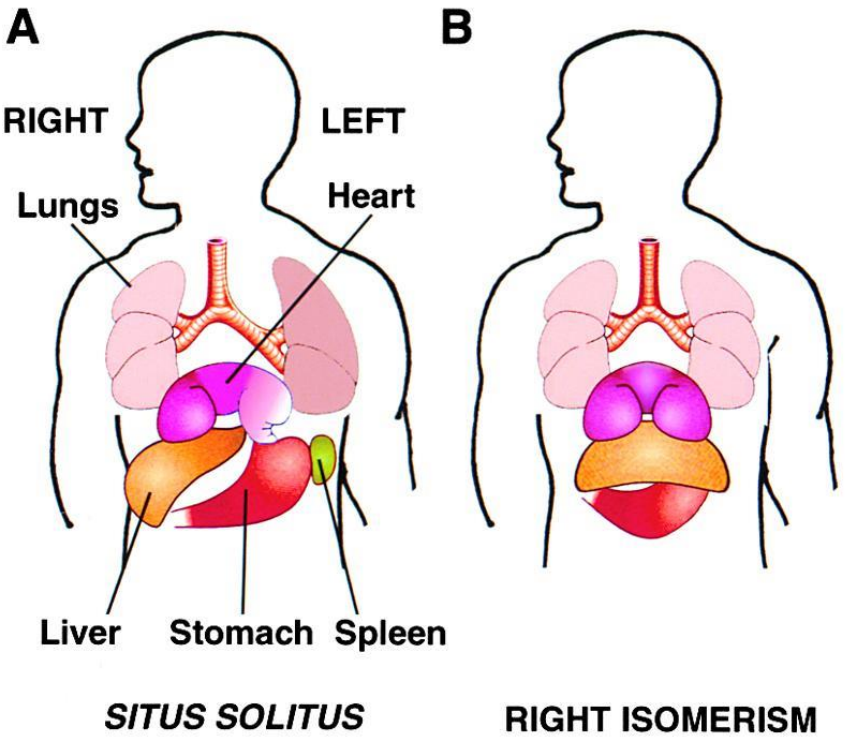
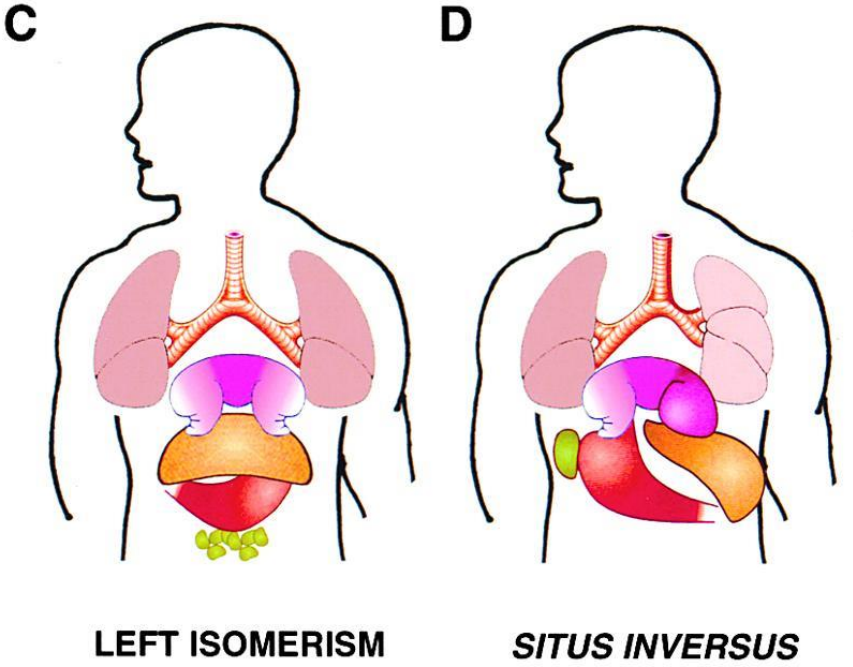
Cell Dynamics:

Signals for the Left-Right Asymmetric Development

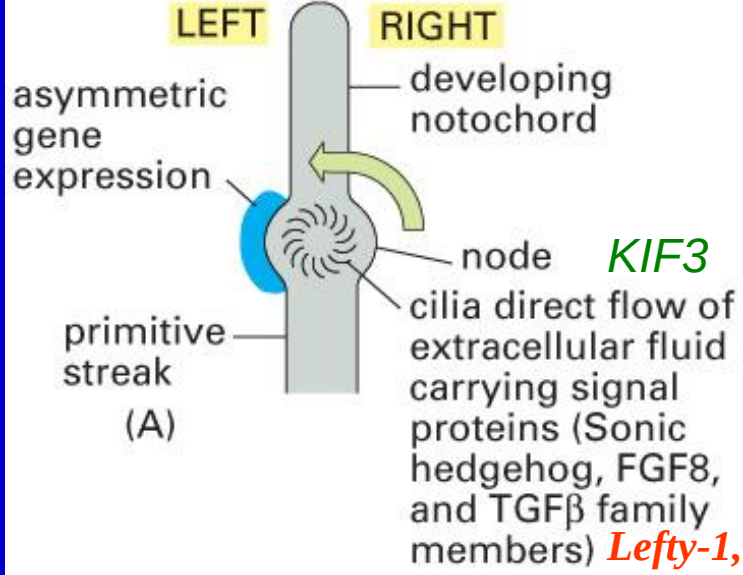






Left-Right Asymmetry of the Body Derives from Molecular Asymmetry in the Early Embryo

Sonic hedgehog, FGF8, homeobox gene Pitx2, and TGF-beta superfamily members



KIF3

Lefty-1, Lefty-2, Nodal, etc.

Nodal expression pattern

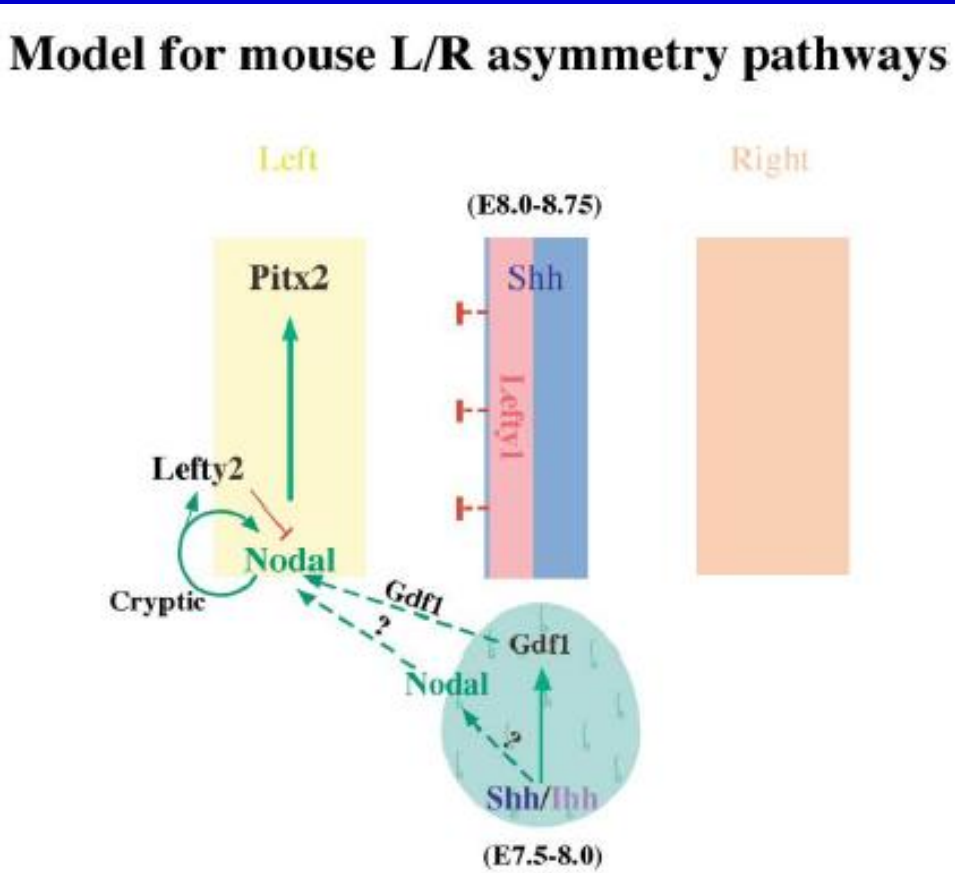
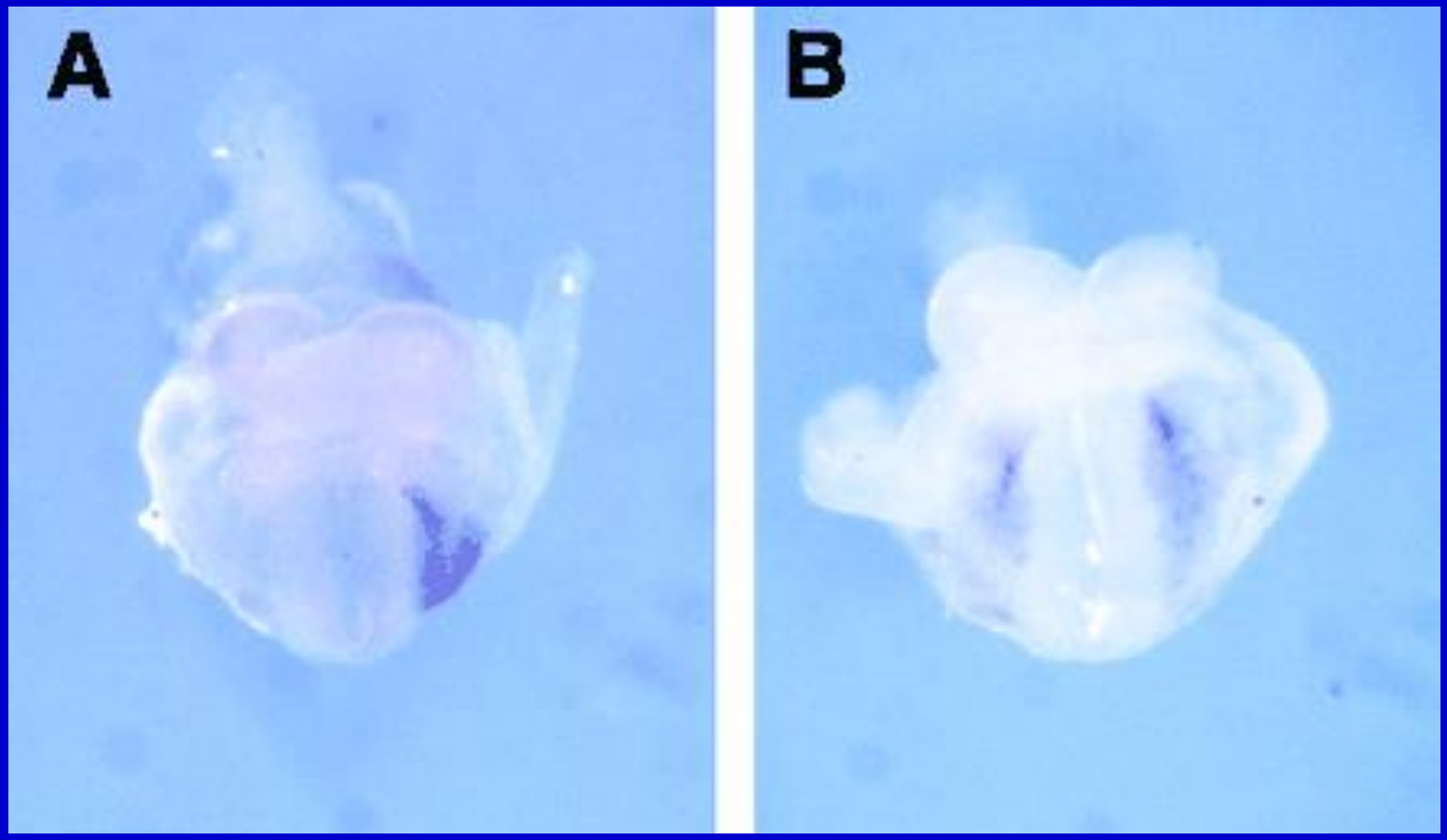


Figure 21–82. Molecular Biology of the Cell, 4th Edition.

Altered *lefty-2* Expression in *kif3B*$^{-/-}$ Embryos

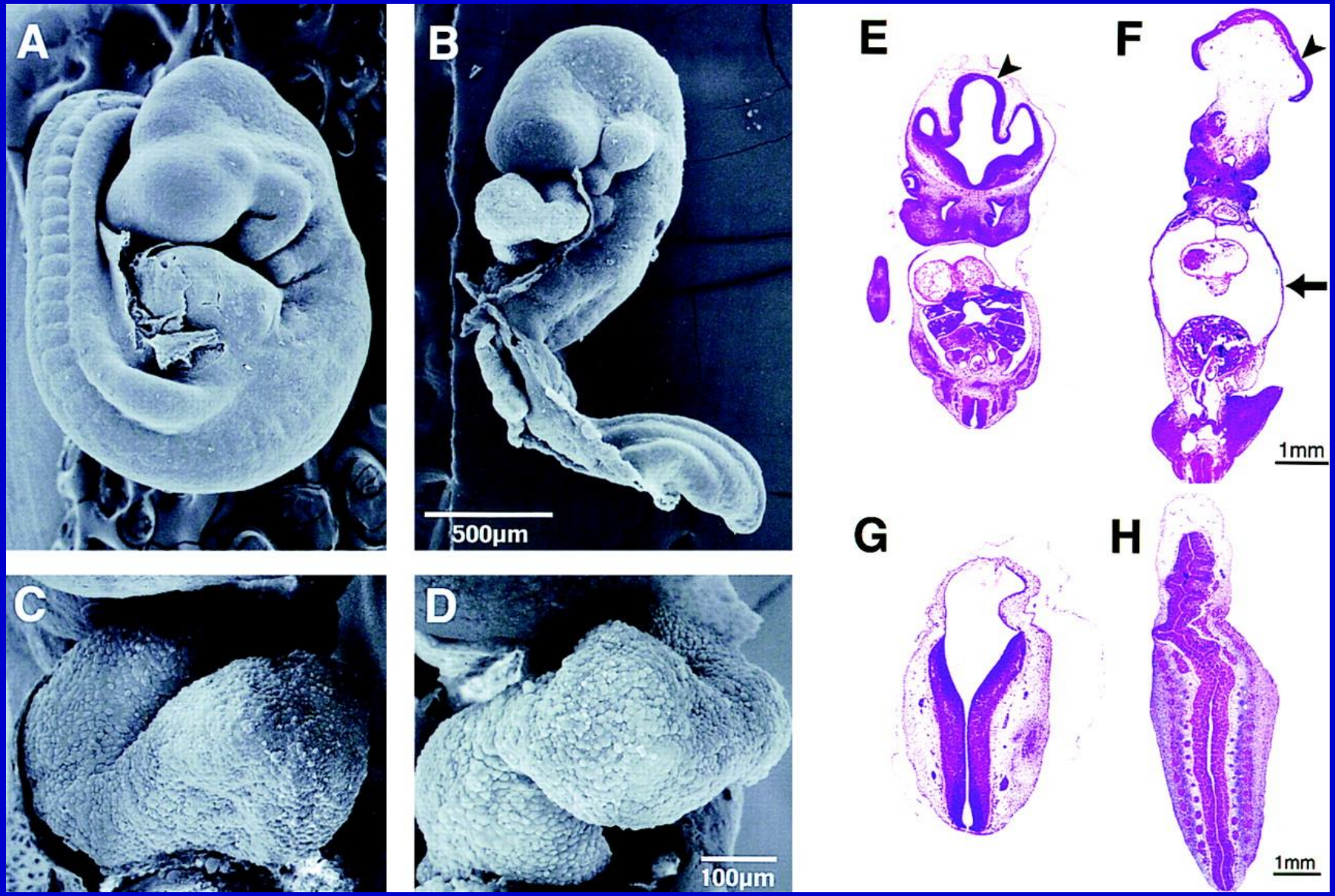
S. Nonaka, Y. Tanaka, Y. Okada, S. Takeda, A. Harada, Y. Kanai, M. Kido, and ***N. Hirokawa****. Randomization of left-right asymmetry due to loss of nodal cilia generating leftward flow of extraembryonic fluid in mice lacking KIF3B motor protein.* **Cell 95(6): 829-37. 1998**.



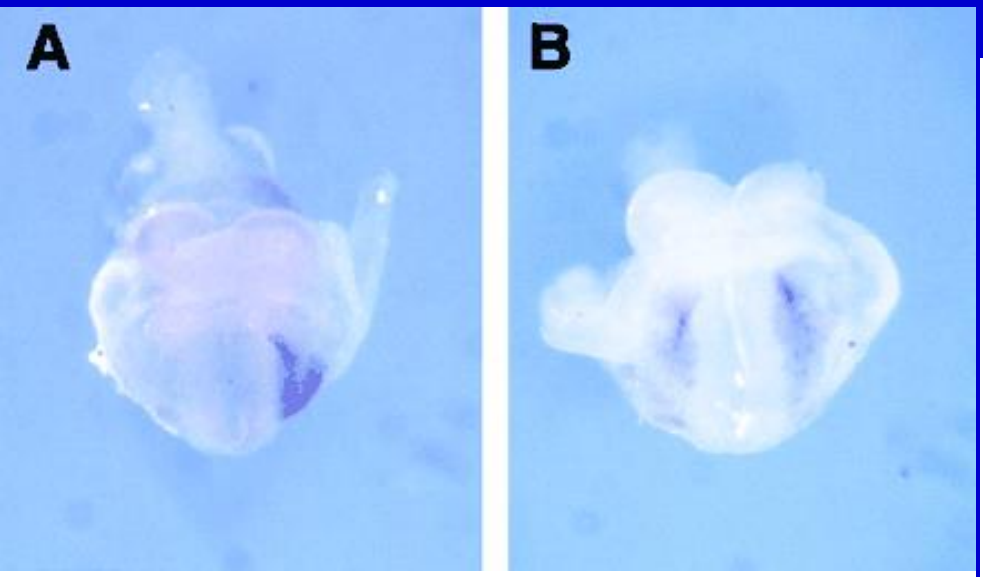
A wild-type embryo at 8.0 dpc expressing *lefty-2* only in the left lateral plate mesoderm

A littermate null mutant embryo with bilateral expression. Some *kif3B*$^{-/-}$ embryos gave no detectable signals

Morphological Abnormalities in *kif3B*$^{-/-}$ Embryos



Nodal Flow Models for L-R Asymmetry Specification



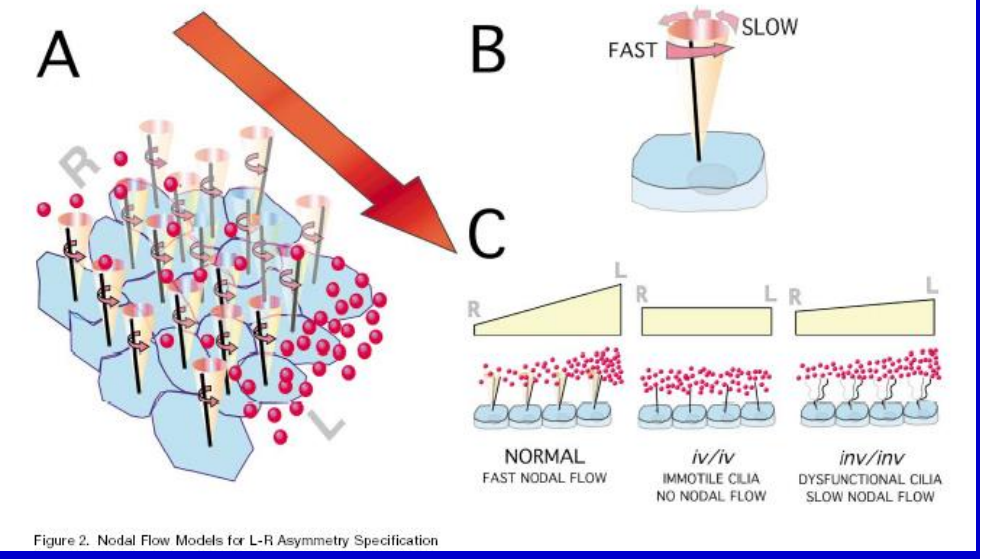


Figure 2. Nodal Flow Models for L-R Asymmetry Specification

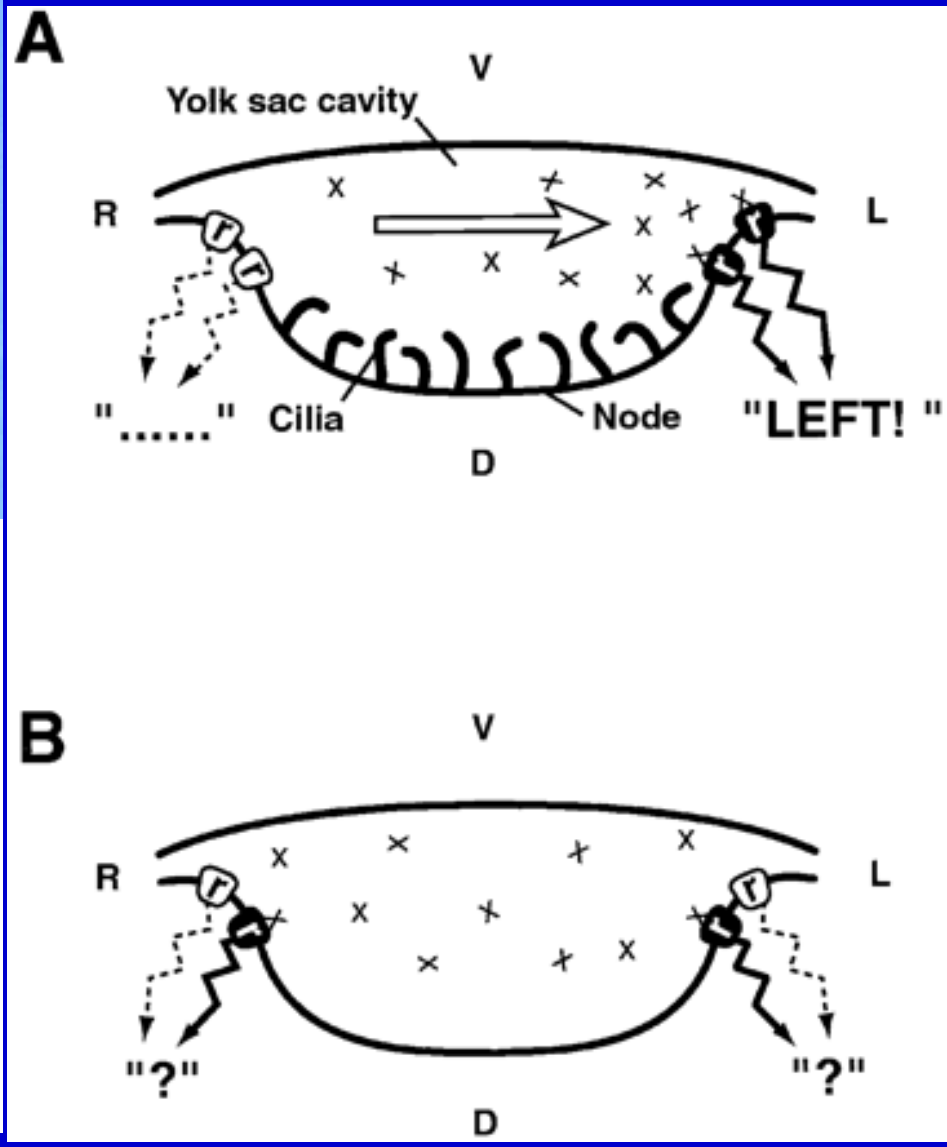


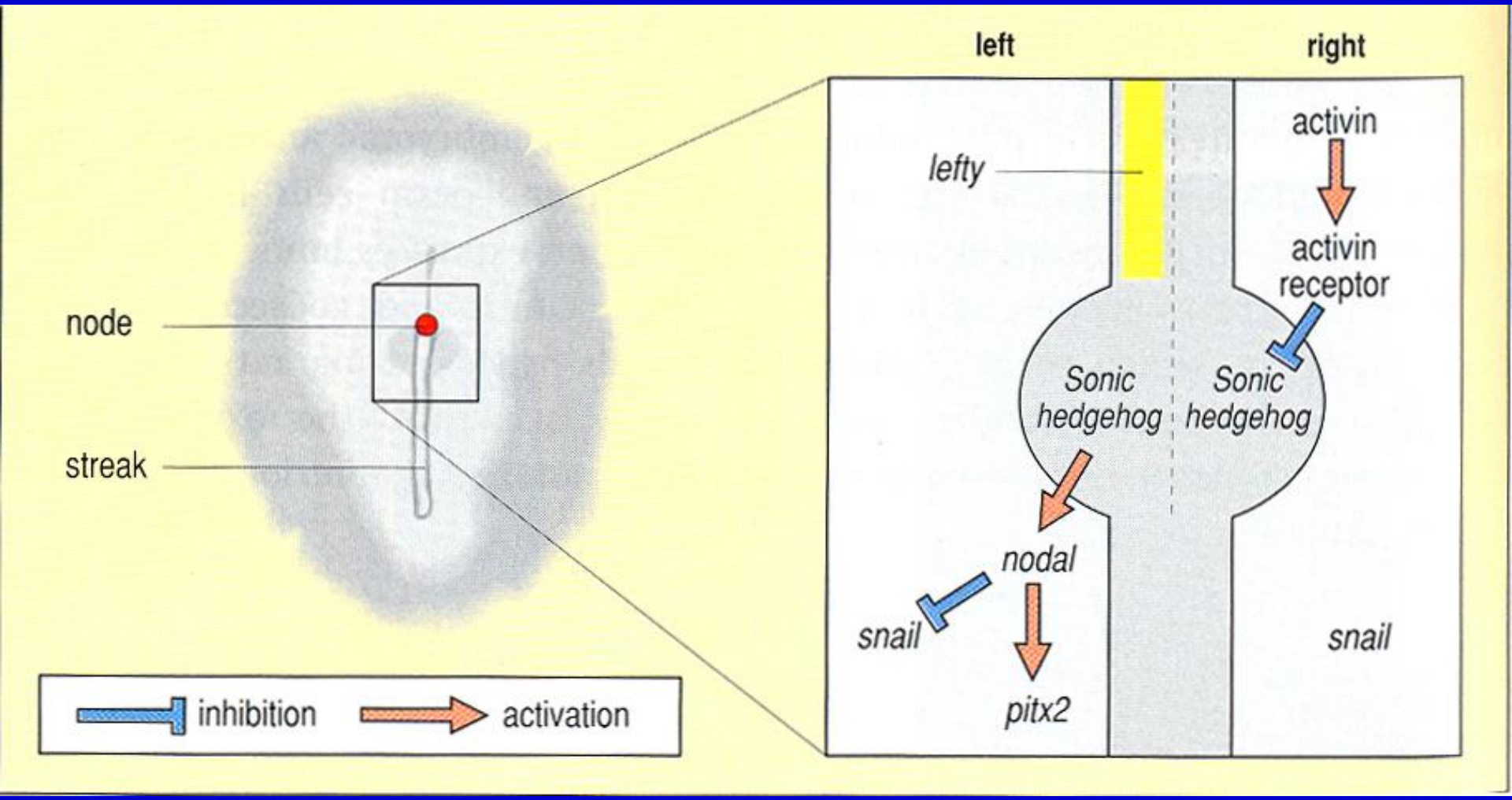
TABLE 21–1 Some Signal Proteins That Are Used Over and Over Again as Inducers in Animal Development

SIGNALING PATHWAY	LIGAND FAMILY	RECEPTOR FAMILY	EXTRACELLULAR INHIBITORS/MODULATORS
Receptor tyrosine kinase (RTK)	EGF	EGF receptors	Argos
	FGF (Branchless)	FGF receptors (Breathless)	
	ephrins	Eph receptors	
TGFβ superfamily	TGFβ	TGFβ receptors	chordin (Sog), noggin
	BMP (Dpp)	BMP receptors	
	Nodal		
Wnt	Wnt (Wingless)	Frizzled	Dickkopf, Cerberus
Hedgehog	Hedgehog	Patched, Smoothened	
Notch	Delta	Notch	Fringe

Only a few representatives of each class of proteins are listed—mainly those mentioned in this chapter. Names peculiar to *Drosophila* are shown in parentheses. Many of the listed components have several homologs distinguished by numbers (FGF1, FGF2, etc.) or by forenames (Sonic hedgehog, Lunatic fringe). For further details, see Chapter 15.

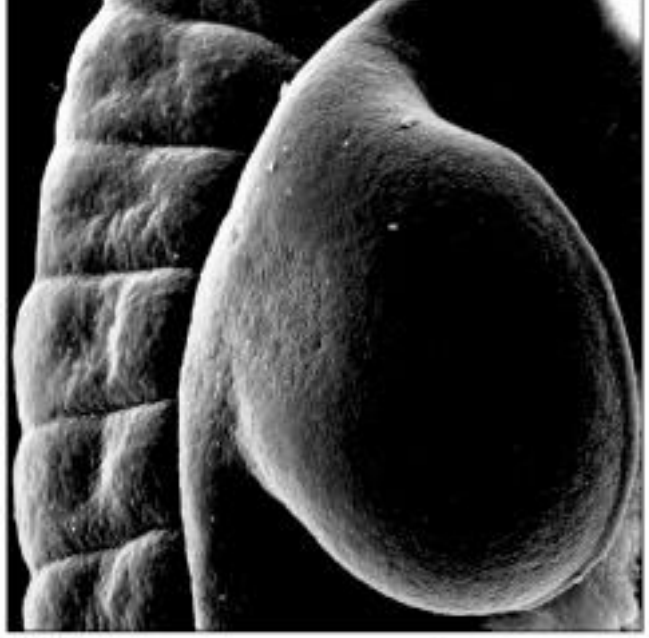
Shh: Sonic Hedgehog
Ihh: Indian Hedgehog
Ptc: Patched (receptor for *Sonic Hedgehog)*
Smo: Smoothened (receptor for *Sonic Hedgehog)*

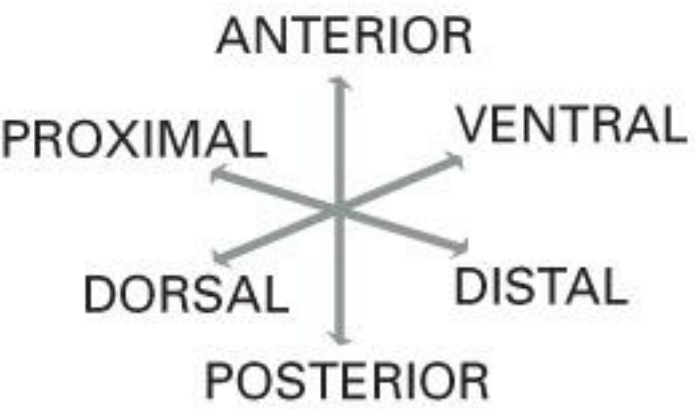
Pathways determining left-right asymmetry in the chick embryo



Molecules that control patterning in a vertebrate limb bud

Sonic hedgehog





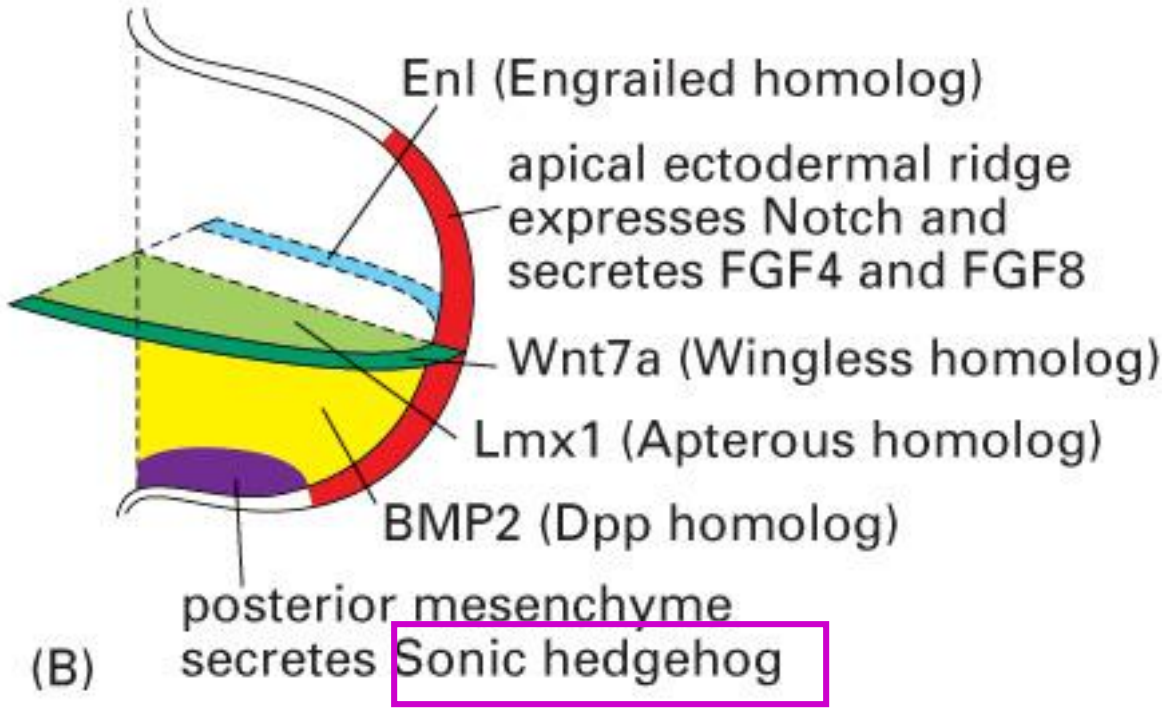
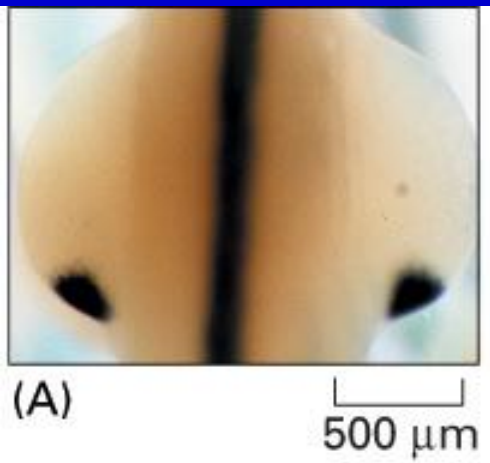


Figure 21–56. Molecular Biology of the Cell, 4th Edition.

Sonic Hedgehog as a morphogen in chick limb development



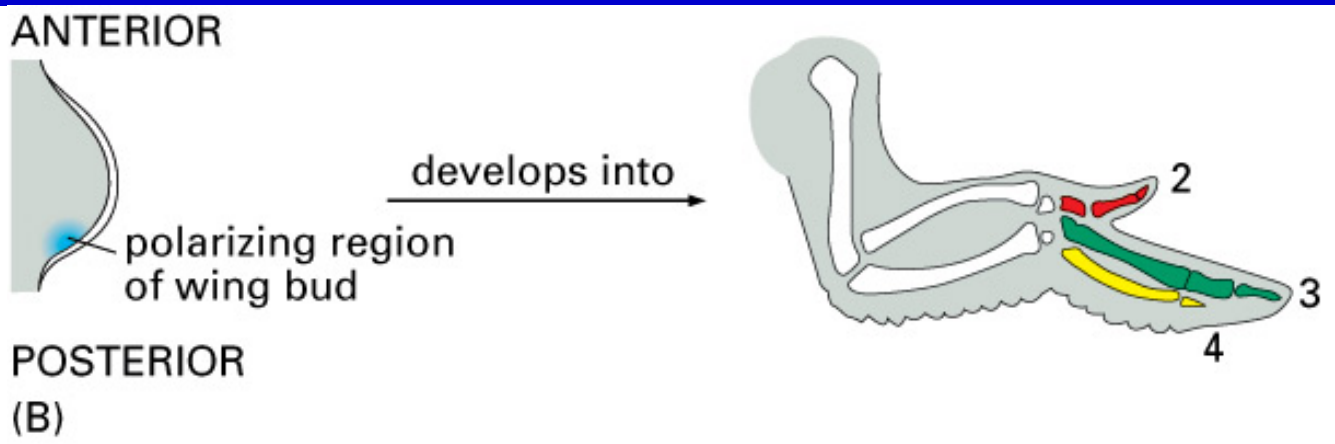


Figure 21–13 part 1 of 2. Molec

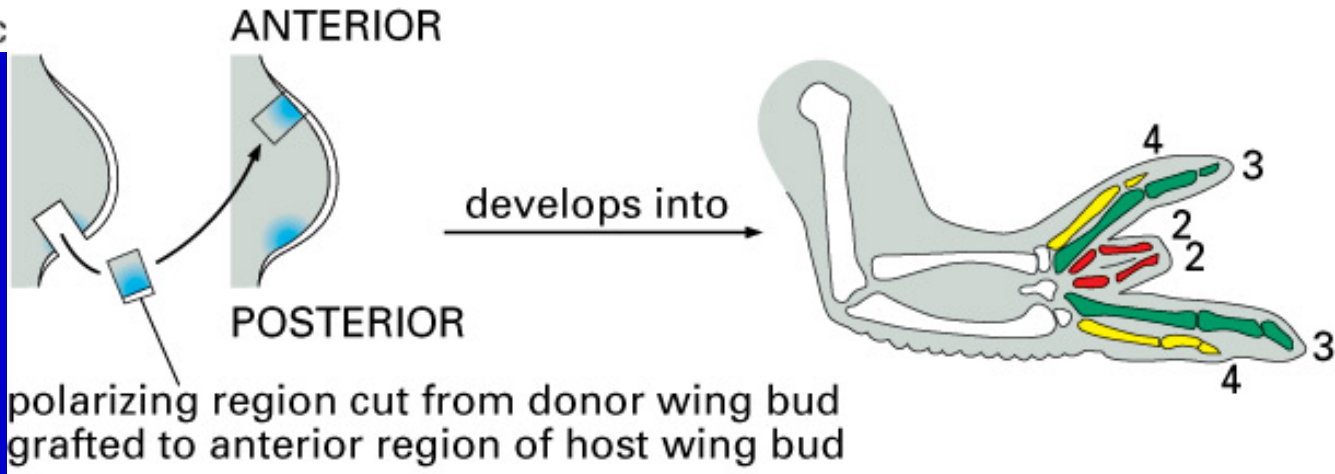
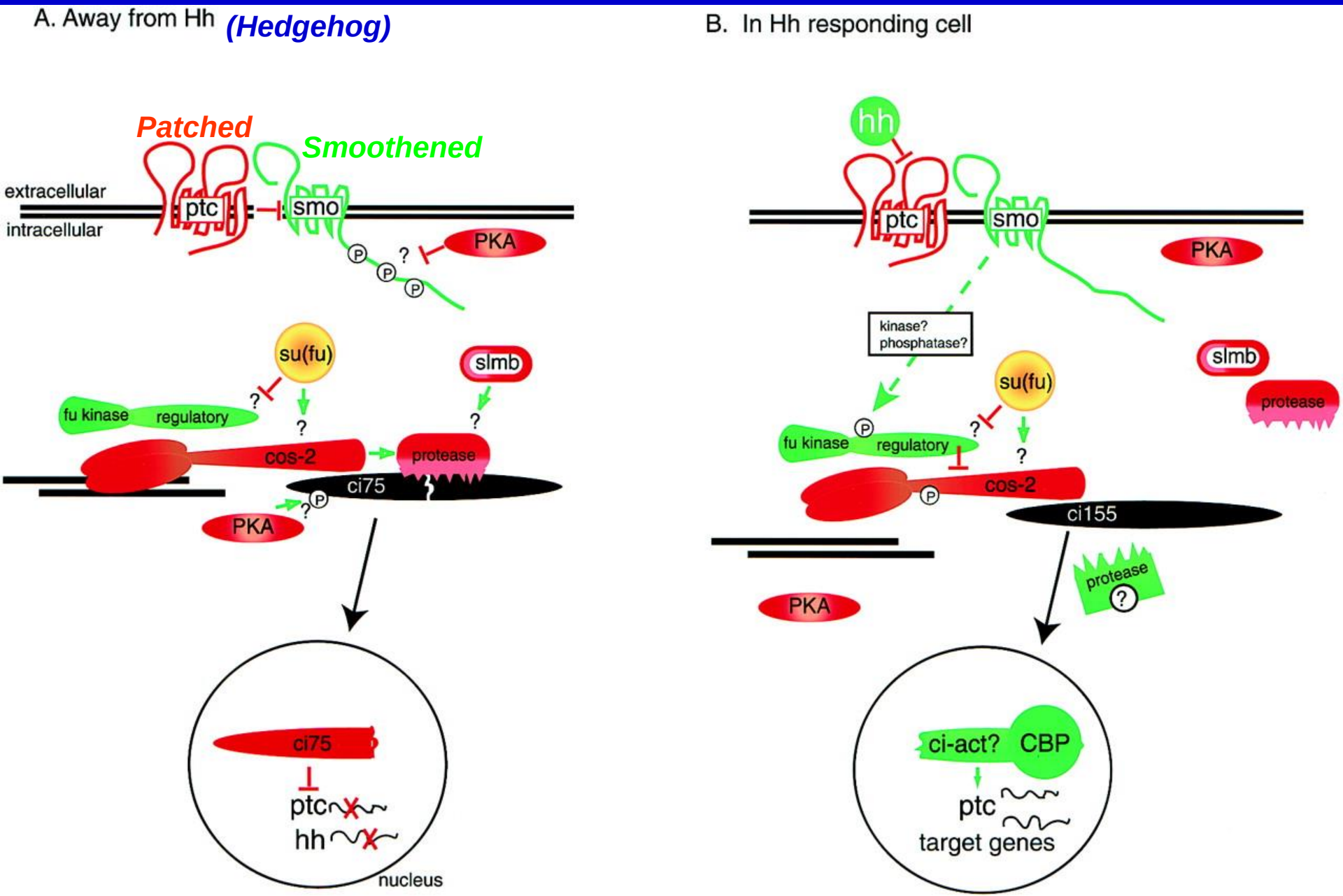


Figure 21–13 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

The *Hedgehog–Patched* Signaling Pathway

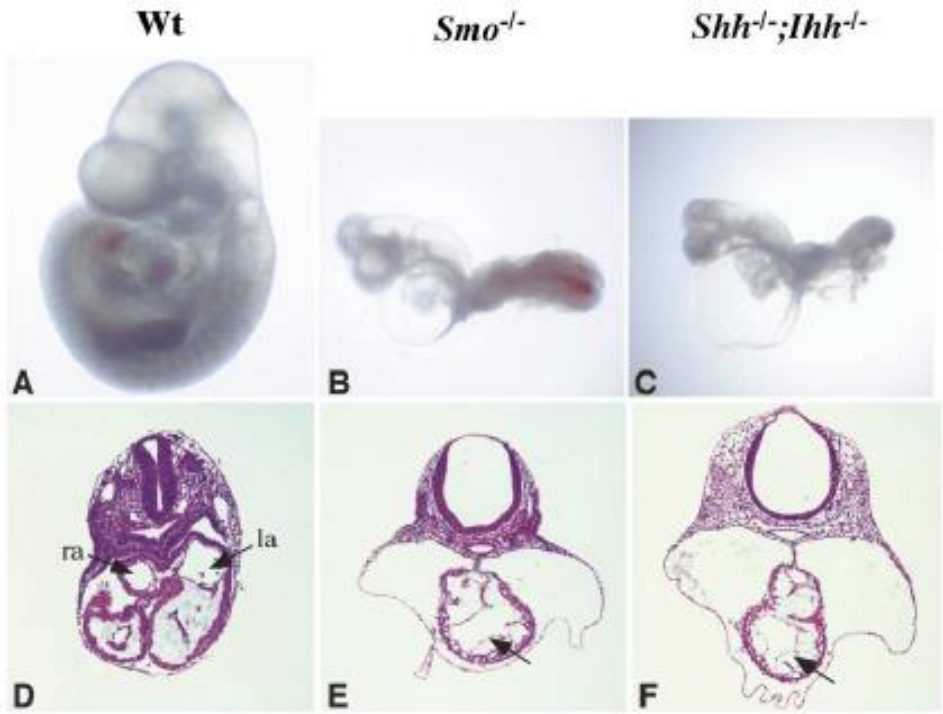
Neuron, Vol. 21, 1243–1257, 1998 **Hedgehog and Patched in Neural Development and Disease**

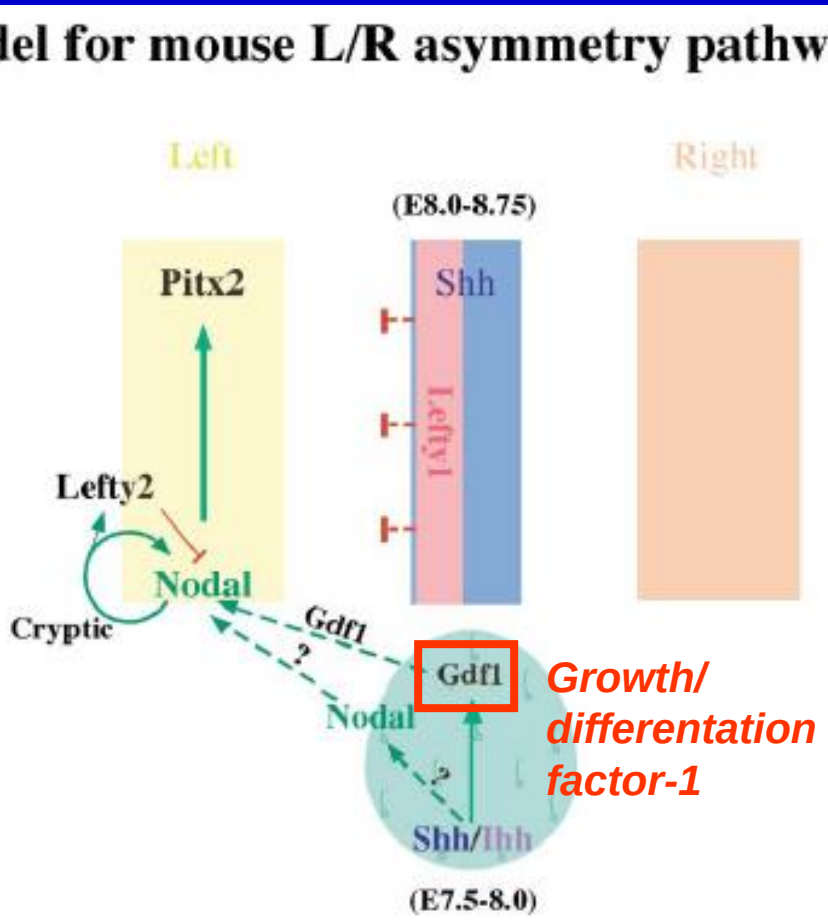


Cell, Vol. 105, 781–792, June 15, 2001, Copyright ©2001 by Cell Press

Smoothened Mutants Reveal Redundant Roles for Shh and Ihh Signaling Including Regulation of L/R Asymmetry by the Mouse Node

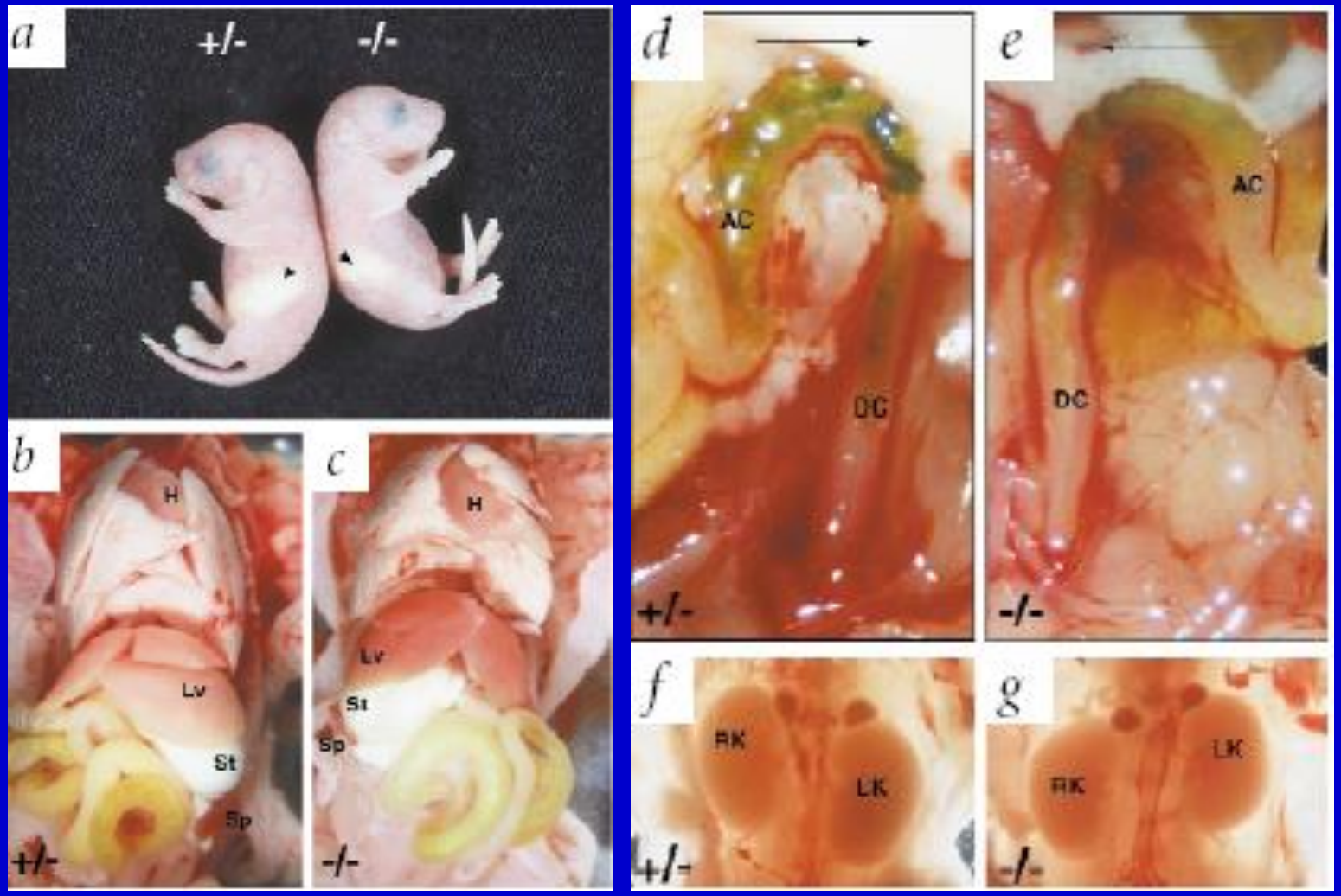
Smo: Smoothened (receptor for *Sonic Hedgehog)*
Shh: Sonic Hedgehog
Ihh: Indian Hedgehog





Regulation of left-right patterning in mice by growth/differentiation factor-1

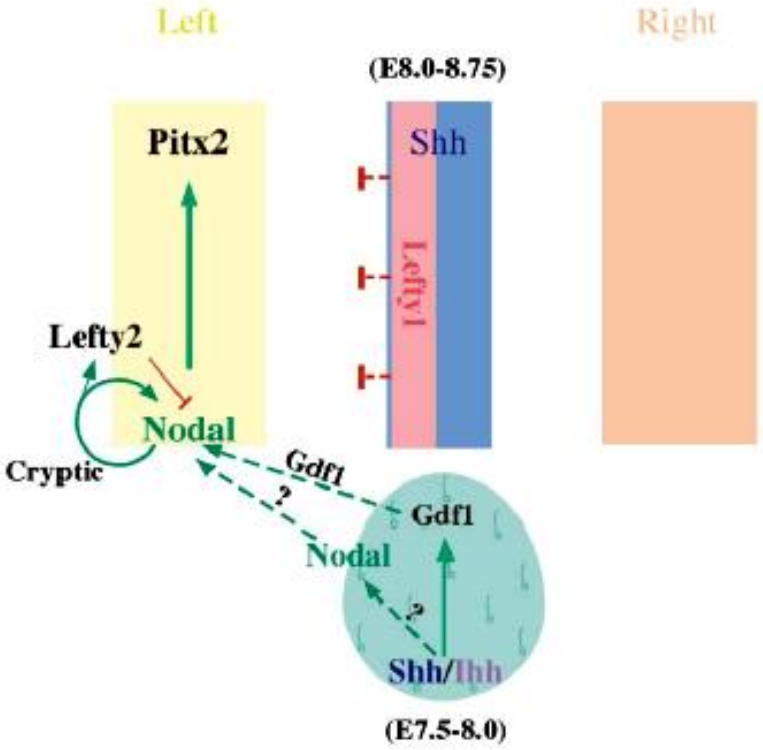
Nature Genet. (2000) Vol. 24:262-5

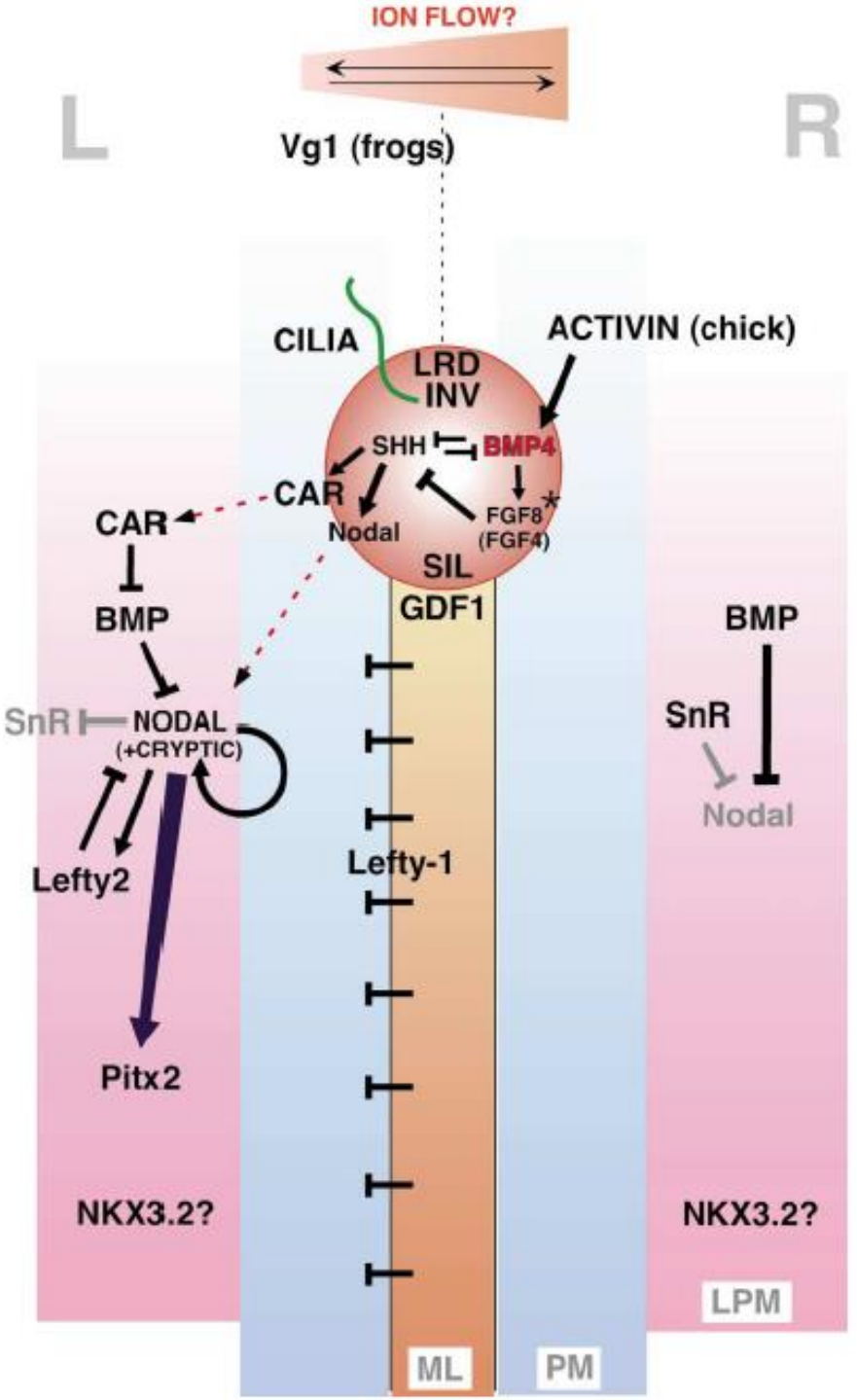


TGF-beta superfamily members

Lefty-1, Lefty-2,
Nodal, *BMP2, and BMP4*

Model for mouse L/R asymmetry pathways





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	FGF (Branchless)	FGF receptors (Breathless)	
	ephrins	Eph receptors	
TGFβ superfamily	TGFβ	TGFβ receptors	chordin (Sog), noggin
	BMP (Dpp)	BMP receptors	
	Nodal		
Wnt	Wnt (Wingless)	Frizzled	Dickkopf, Cerberus
Hedgehog	Hedgehog	Patched, Smoothened	
Notch	Delta	Notch	Fringe

Only a few representatives of each class of proteins are listed—mainly those mentioned in this chapter. Names peculiar to *Drosophila* are shown in parentheses. Many of the listed components have several homologs distinguished by numbers (FGF1, FGF2, etc.) or by forenames (Sonic hedgehog, Lunatic fringe). For further details, see Chapter 15.

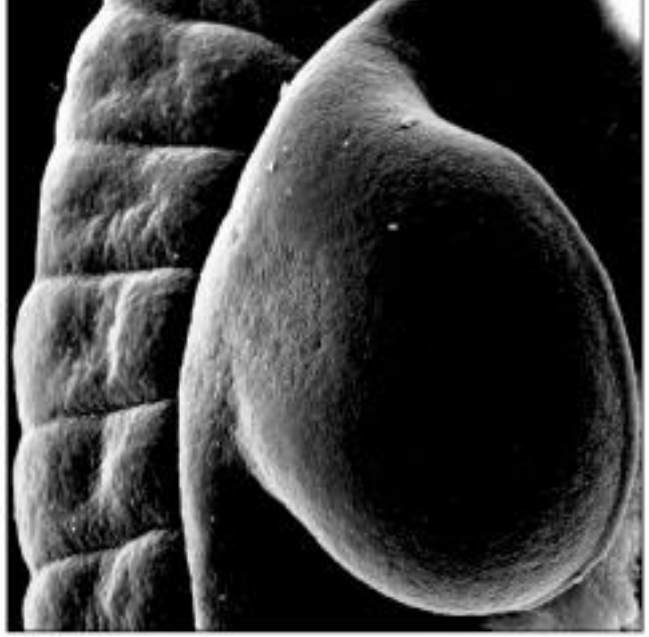
TGF-beta superfamily members:

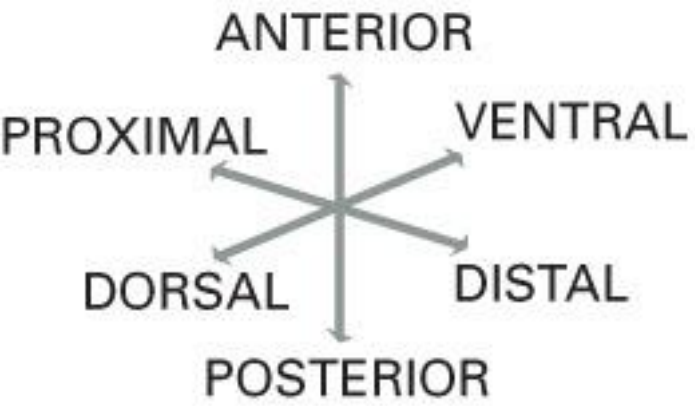
BMP: bone morphogenetic proteins (BMP2, BMP4)

Lefty-1, Lefty-2, and Nodal

Molecules that control patterning in a vertebrate limb bud

TGF-beta superfamily members: BMP





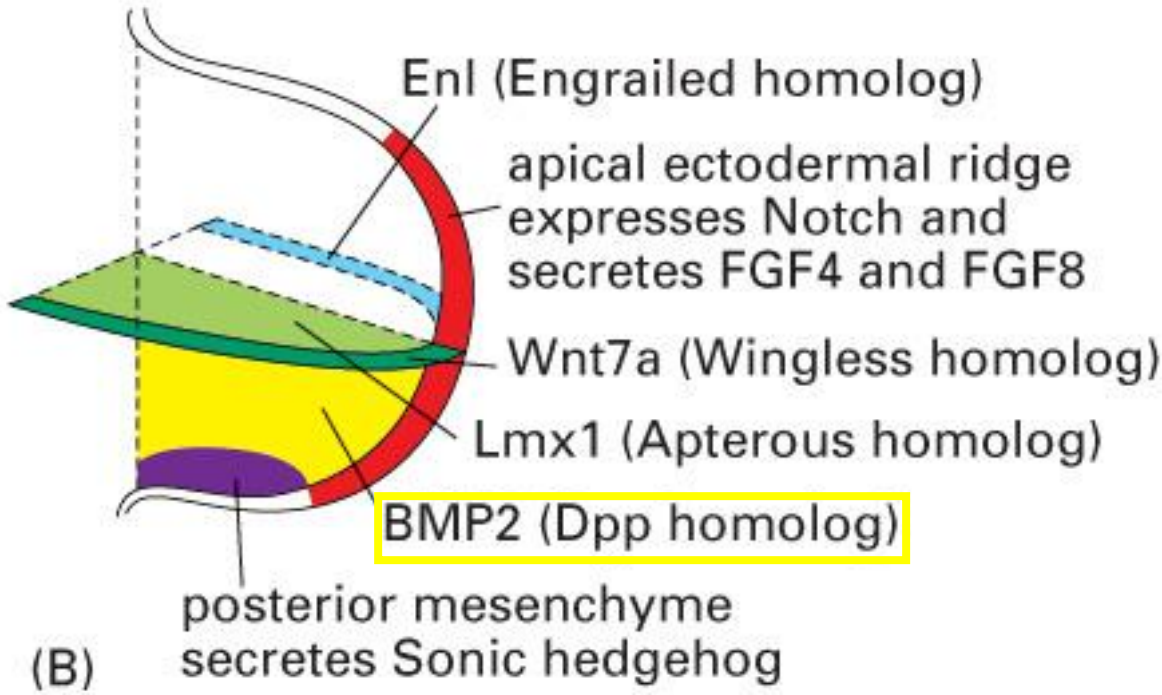
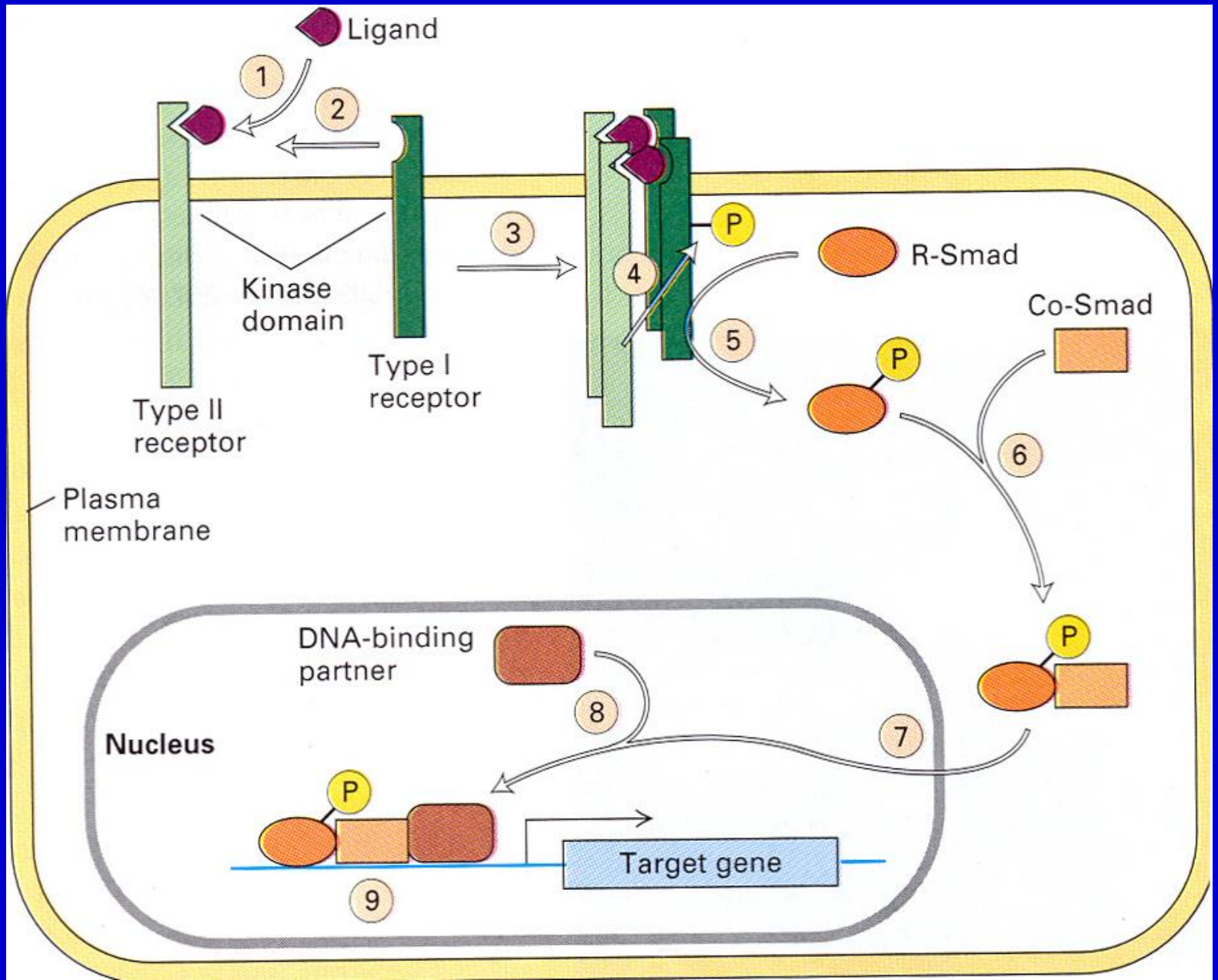
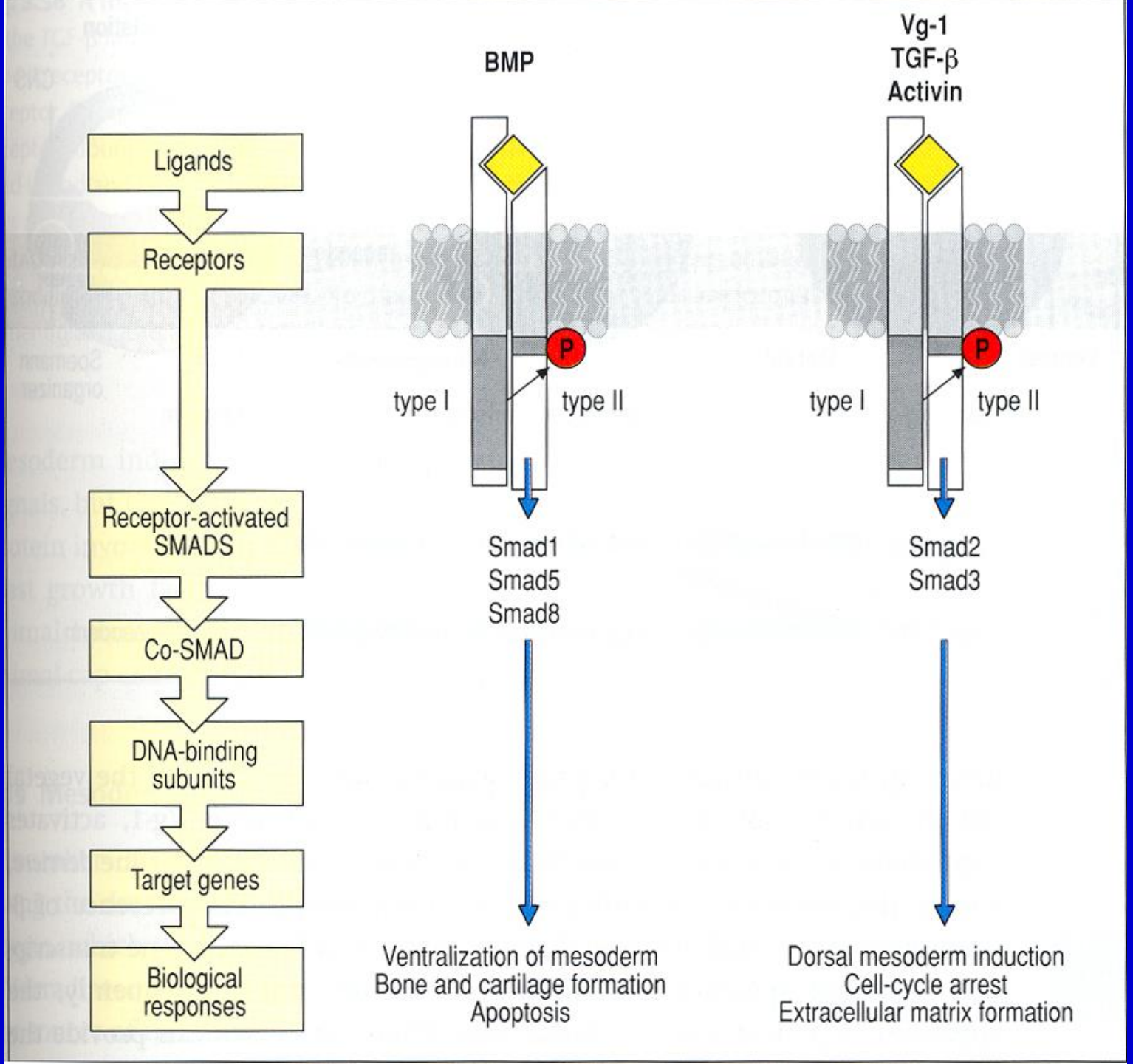


Figure 21–56. Molecular Biology of the Cell, 4th Edition.

TGF-beta signaling pathway

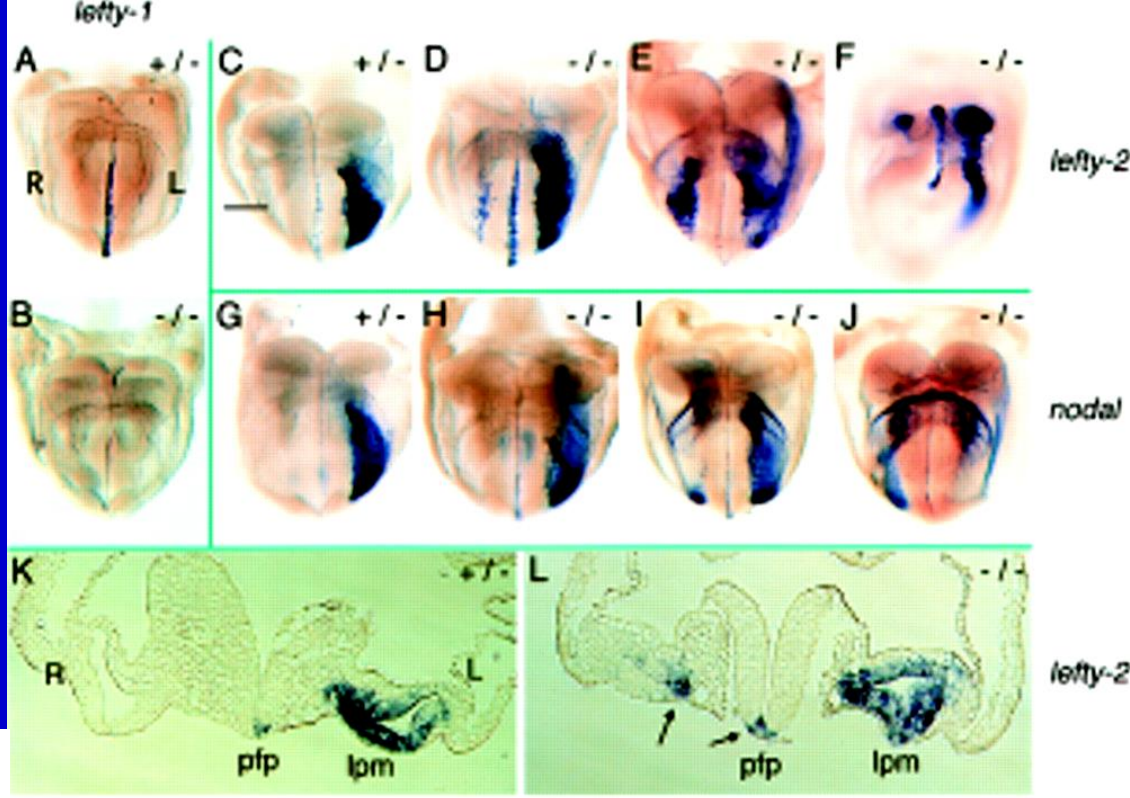



Ligands
Receptors
Receptor-activated SMADS
Co-SMAD
DNA-binding subunits
Target genes
Biological responses
BMP
type I
type II
P
Smad1
Smad5
Smad8
Ventralization of mesoderm
Bone and cartilage formation
Apoptosis
Vg-1
TGF-β
Activin
type I
type II
P
Smad2
Smad3
Dorsal mesoderm induction
Cell-cycle arrest
Extracellular matrix formation

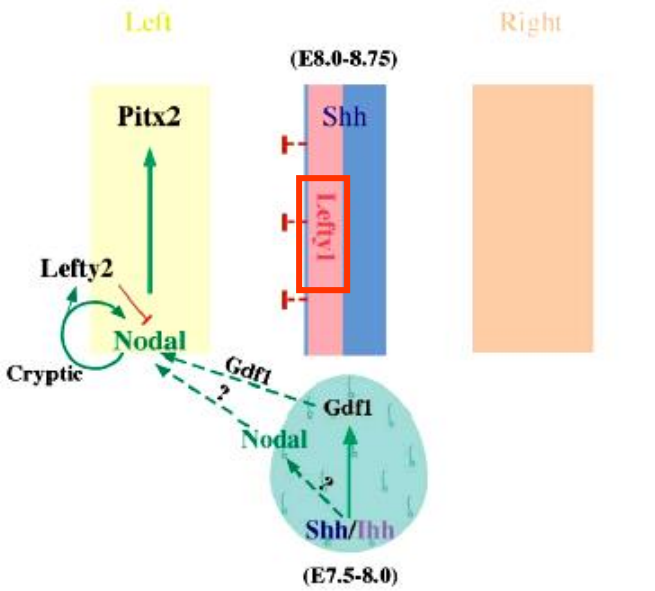
lefty-1 Is Required for Left-Right Determination as a Regulator of *lefty-2* and *nodal*

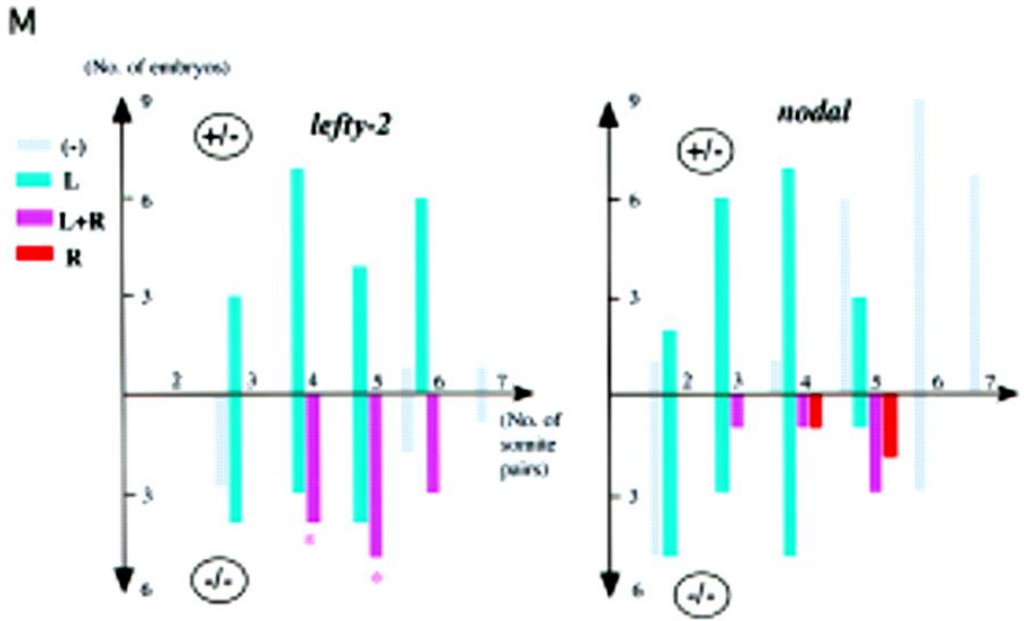
Cell, Vol. 94, 287–297, 1998

Bilateral Expression of *lefty-2* and *nodal* in *lefty-1* -/- Mutant Embryos



Model for mouse L/R asymmetry pathways





Development 129, 3431-3440 (2002)
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DEV2851

BMP signaling positively regulates Nodal expression during left right specification in the chick embryo

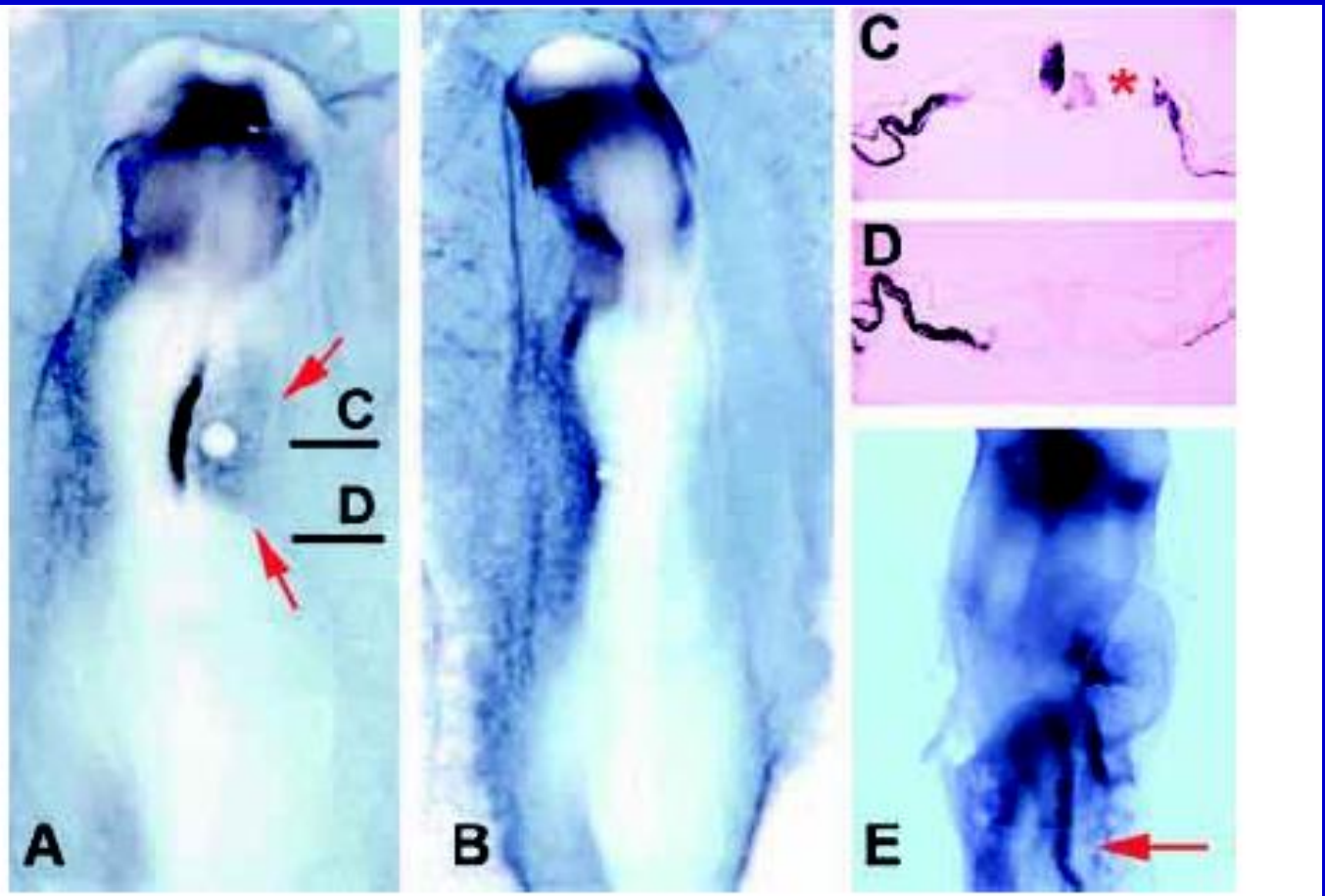

Fig. 2. BMPs positively regulates *Pitx2* expression. (A) Ectopic *Pitx2*

Development 129, 3421-3429 (2002)
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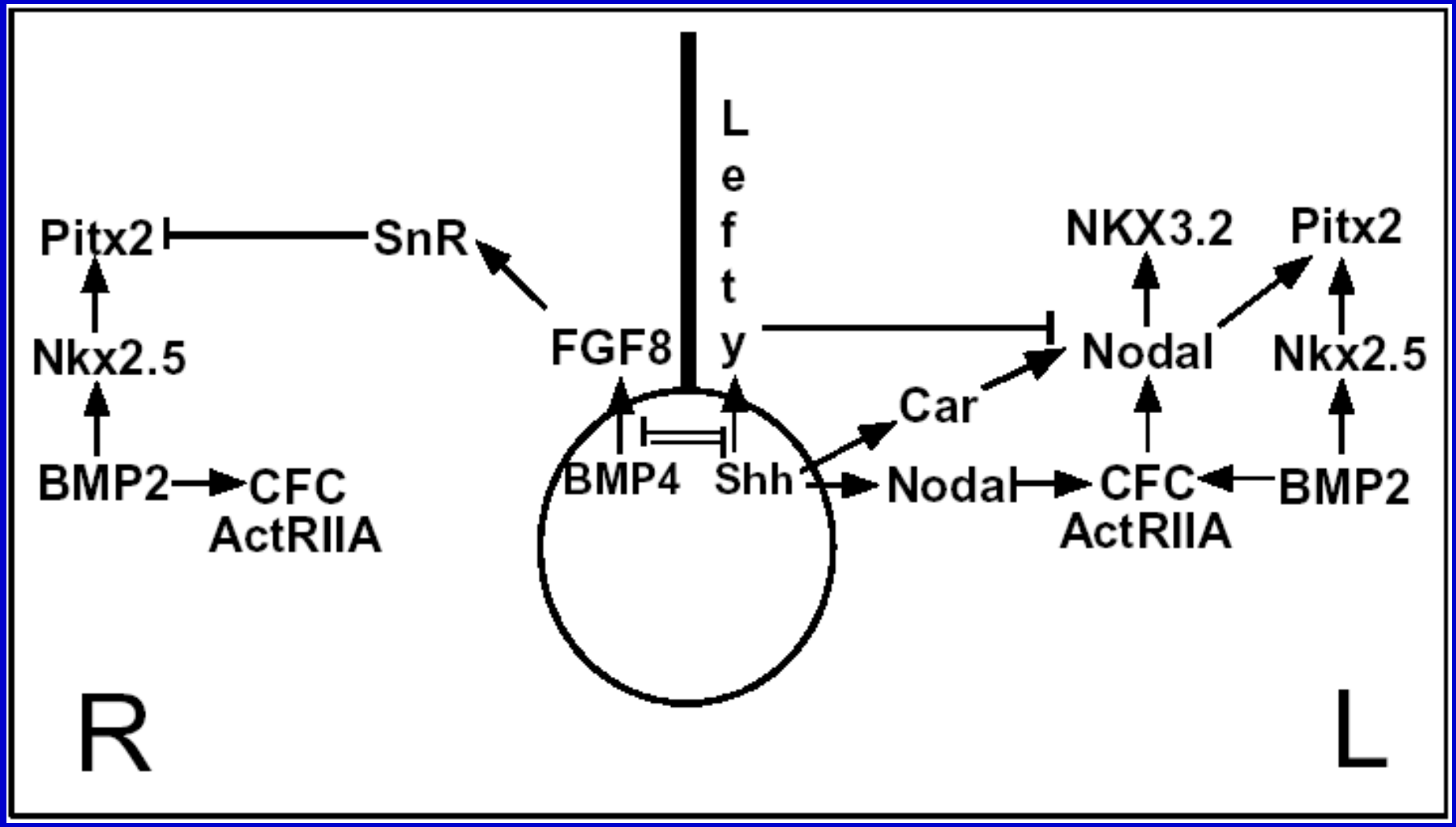
DEV2852

BMP2 is a positive regulator of Nodal signaling during left-right axis formation in the chicken embryo



Molecular Cell, Vol. 7, 789–799, April, 2001, Copyright ©2001 by Cell Press

BMP4 Plays a Key Role in Left–Right Patterning in Chick Embryos by Maintaining Sonic Hedgehog Asymmetry

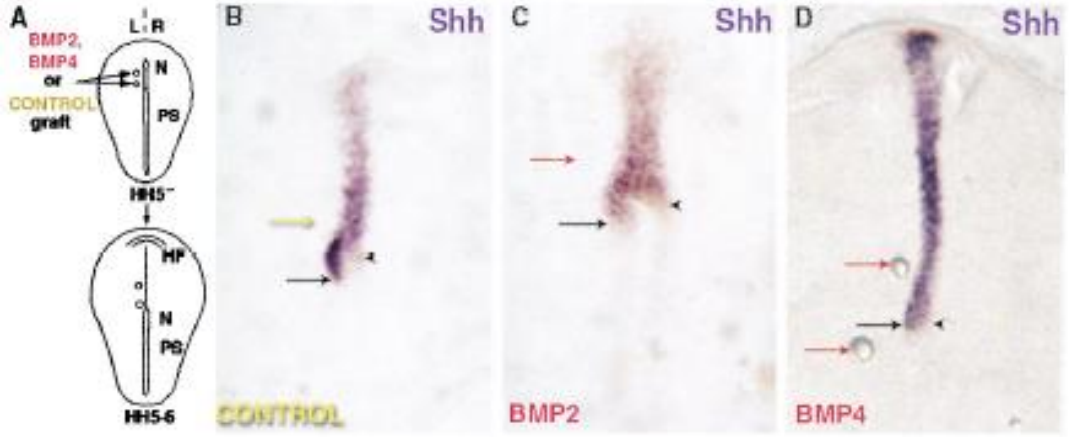
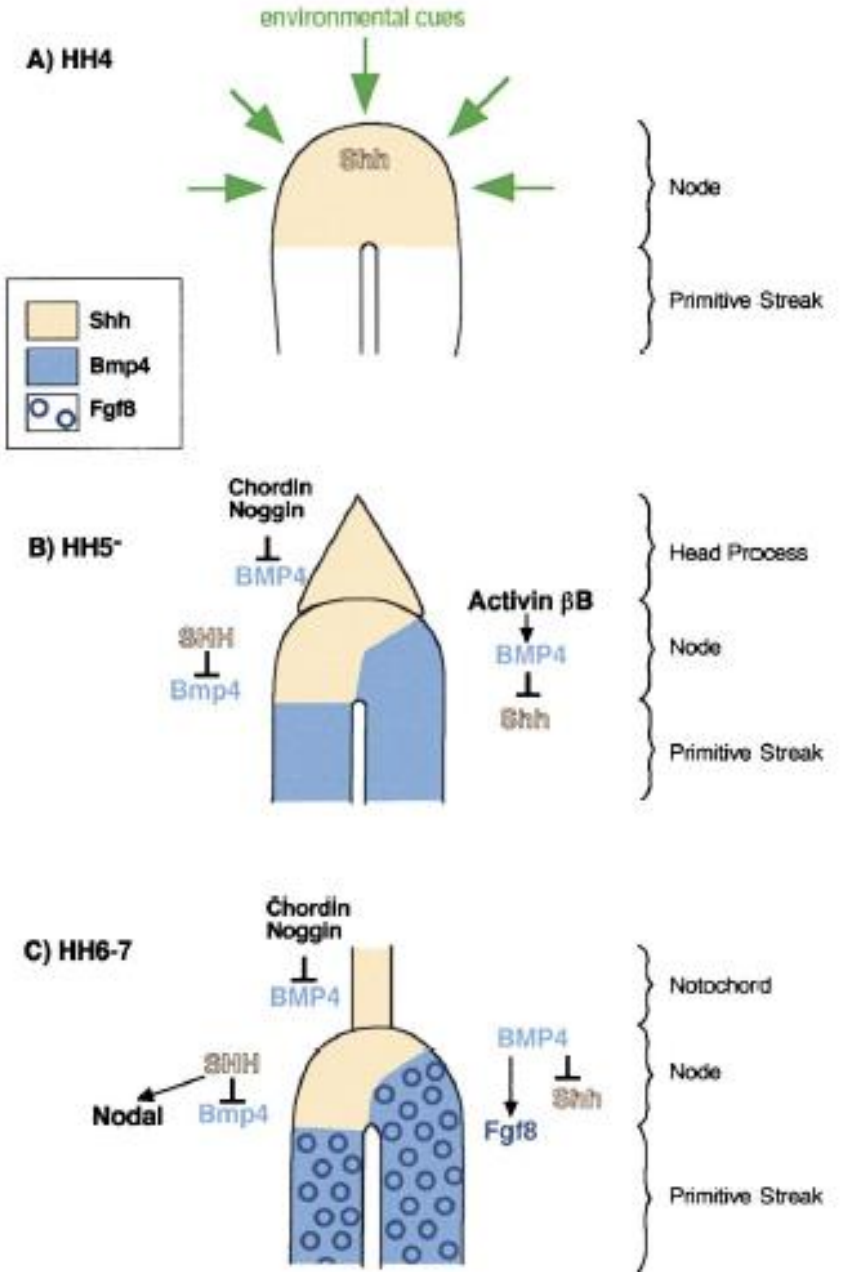


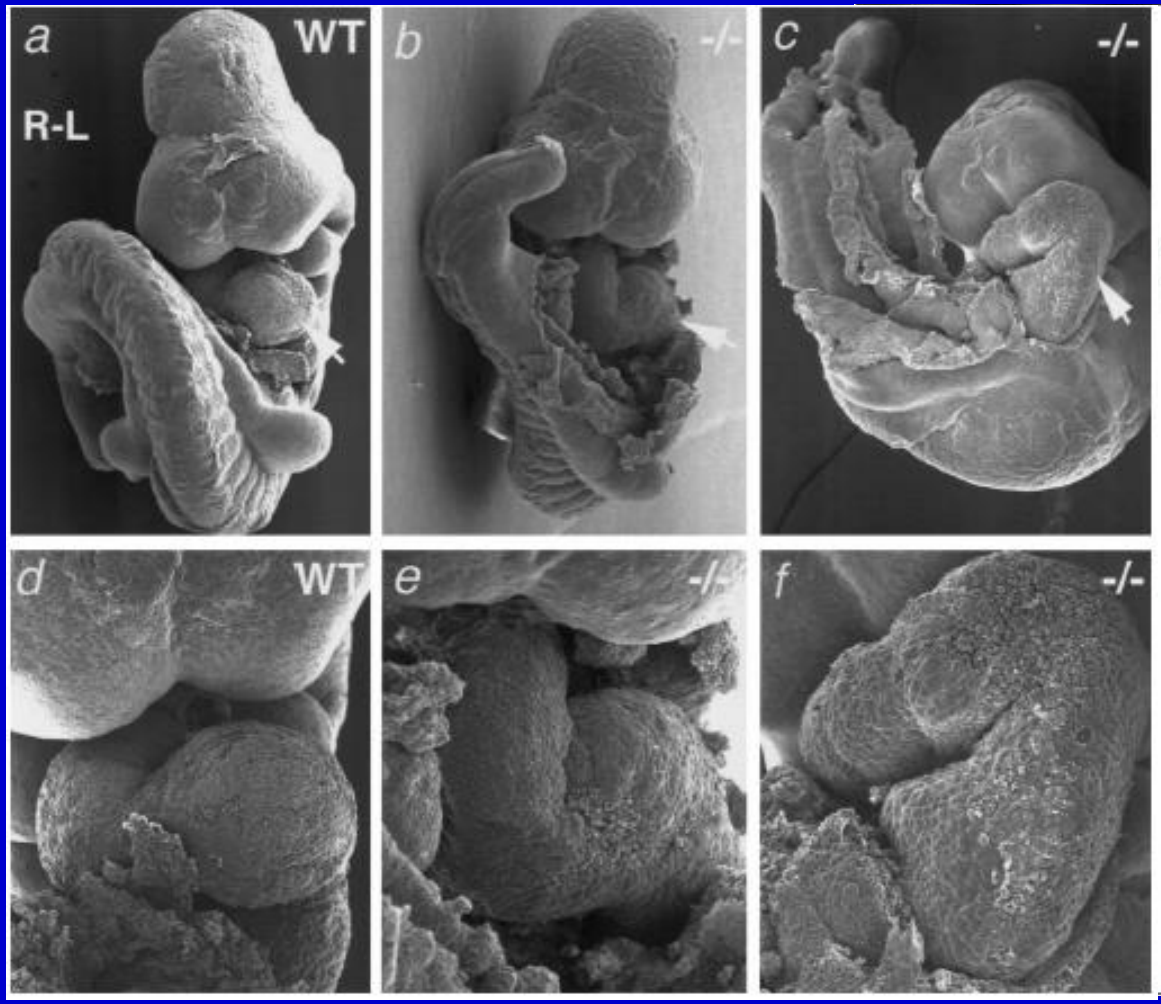
Figure 3. *Shh* Expression in the Node Is Controlled by *Bmp4*

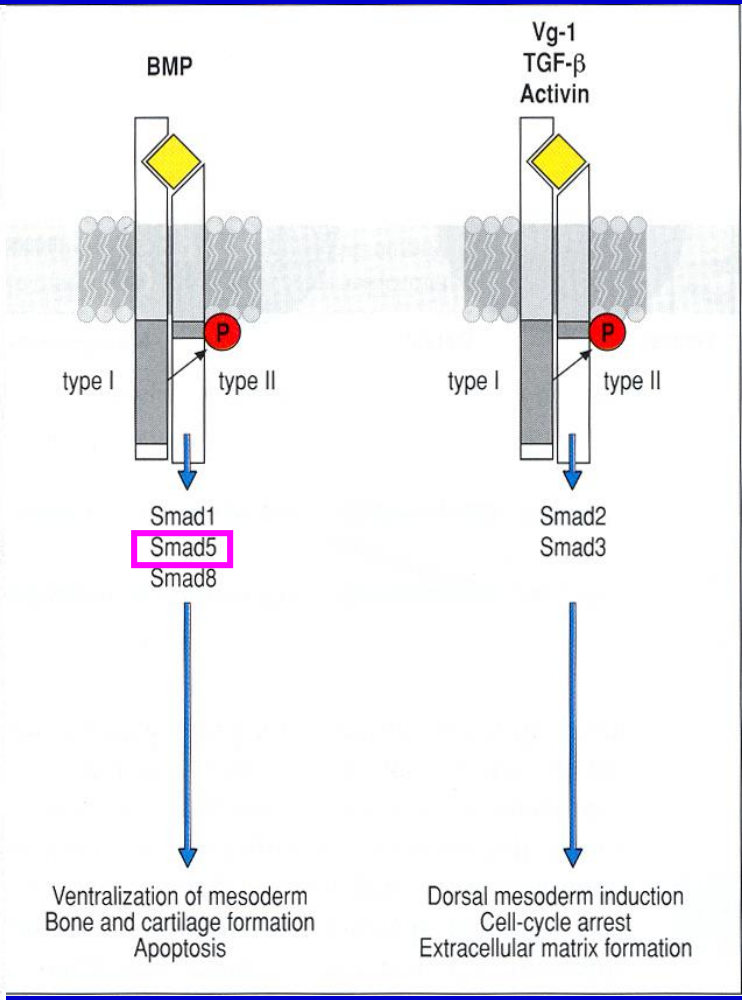
(A–D) The effect of exogenous BMPs on *Shh* gene expression was tested by implanting either control, BMP2, or BMP4 sources on the left side of the node ([A]).



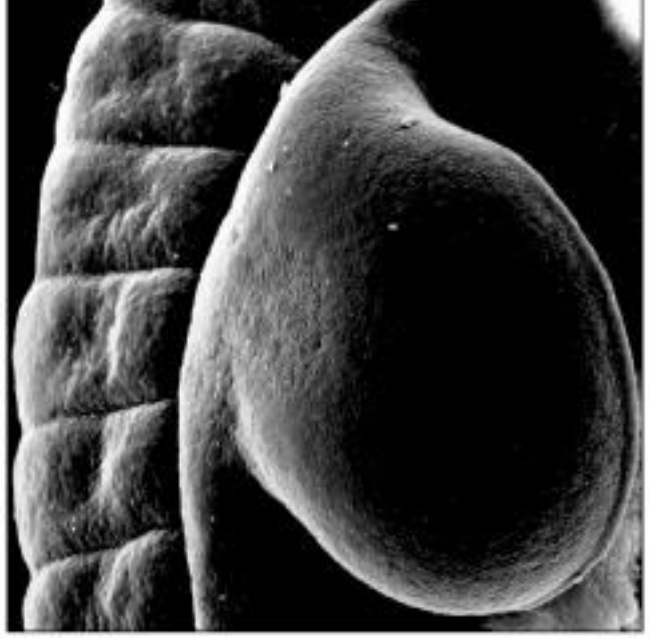
Developmental Biology 219, 71–78 (2000)
doi:10.1006/dbio.1999.9594, available online at http://www.idealibrary.com on IDEAL®

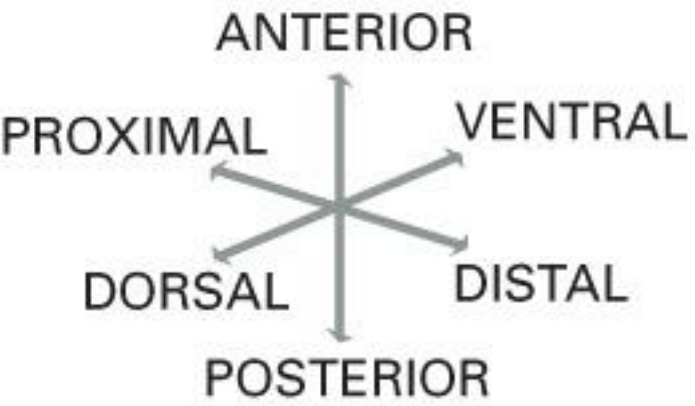
Smad5 Is Essential for Left–Right Asymmetry in Mice





Molecules that control patterning in a vertebrate limb bud: **FGF8**





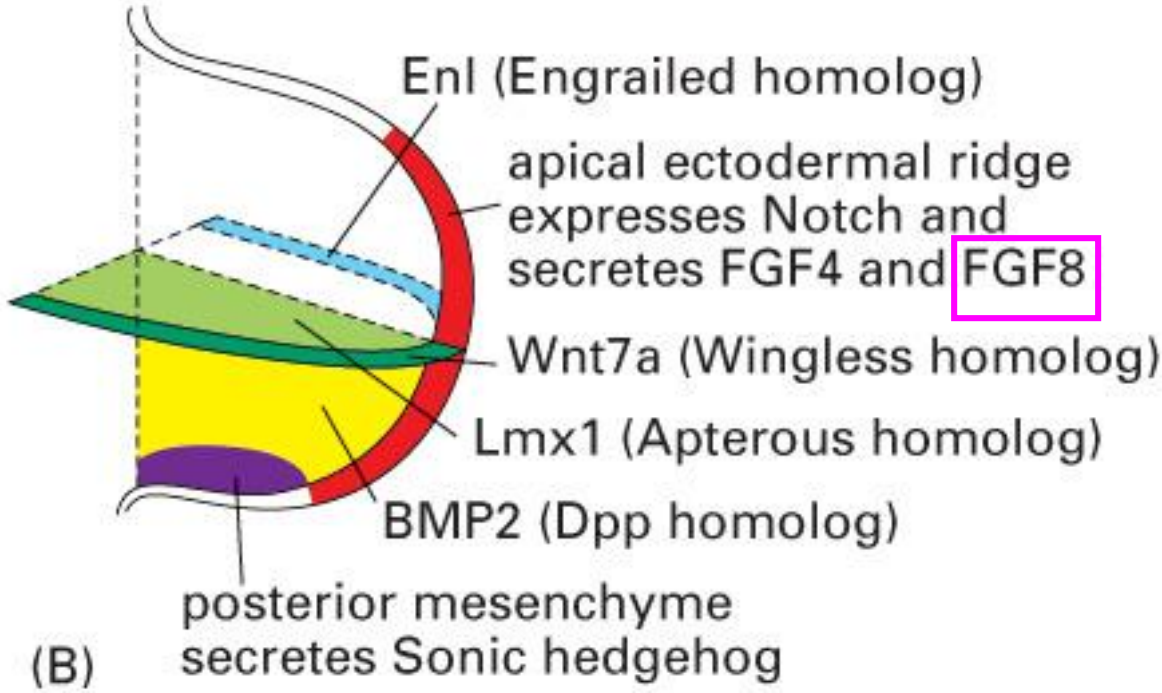
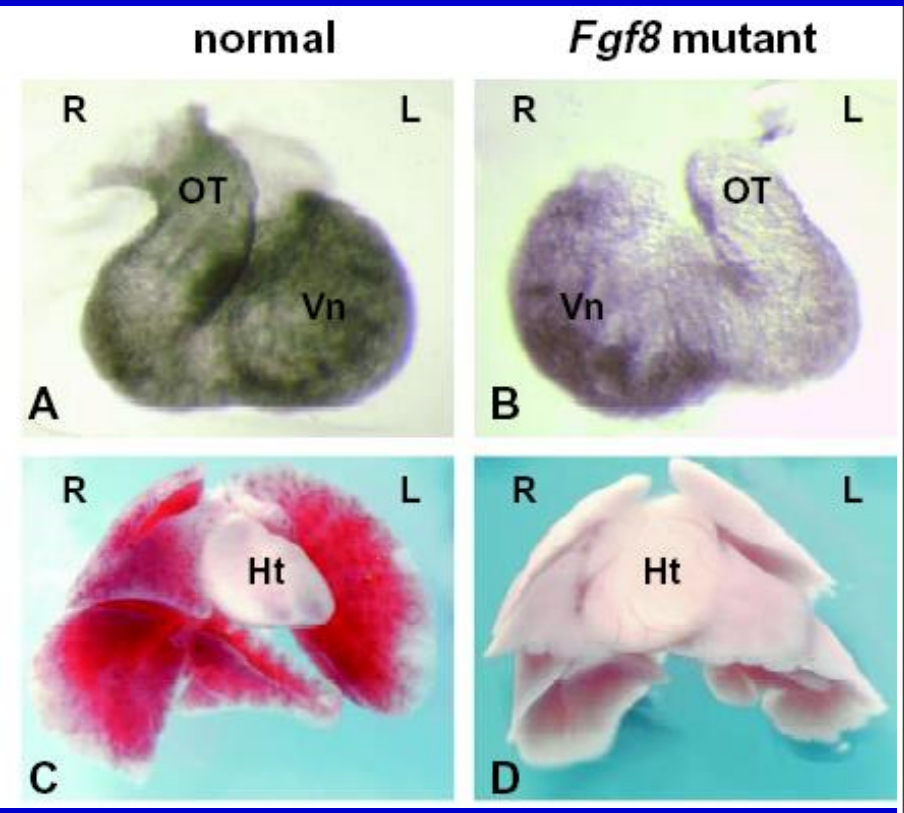
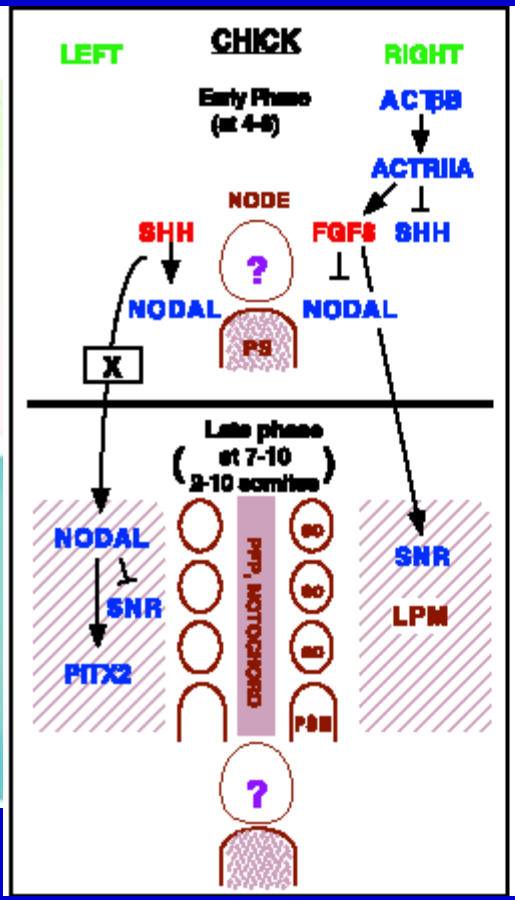


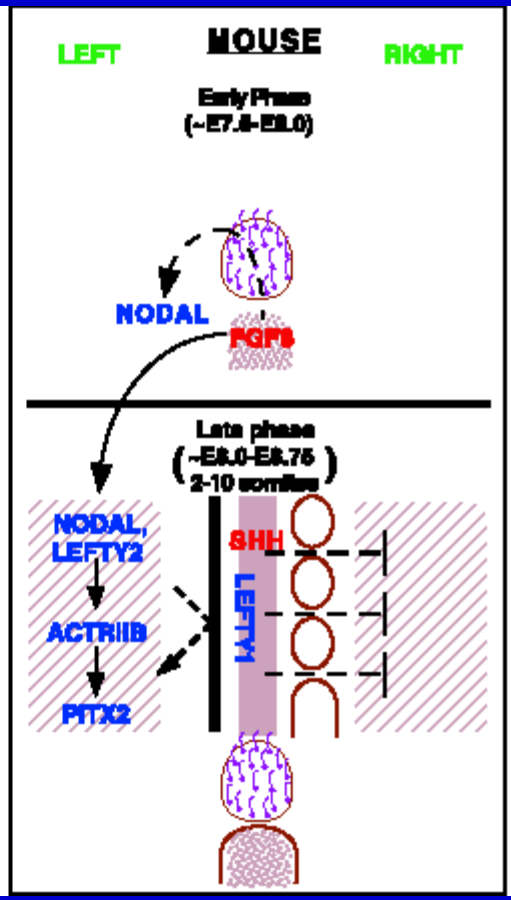
Figure 21–56. Molecular Biology of the Cell, 4th Edition.

Differences in Left-Right Axis Pathways in Mouse and Chick: Functions of FGF8 and SHH

Science (1999) 285:403-406

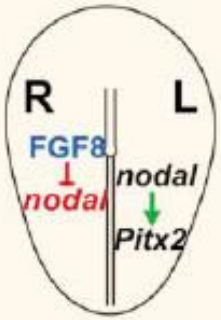
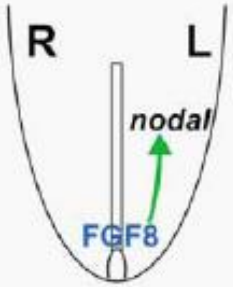
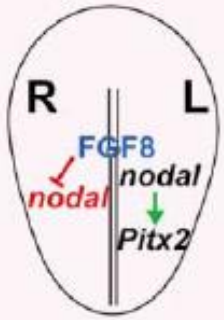






Current Biology, Vol. 12, 1807–1816, October 29, 2002, ©2002 Elsevier Science Ltd. All rights reserved. PII S0960-9822(02)01222-8

FGF8 Acts as a Right Determinant during Establishment of the Left-Right Axis in the Rabbit

	chick	mouse	rabbit
	bird blastodisc	mammal egg cylinder	mammal blastodisc
			
FGF8:			
expression	asymmetric	symmetric	symmetric
left bead	⊥ *nodal/Pitx2*	wt *nodal/Pitx2*	⊥ *nodal/Pitx2*
right bead	wt *nodal/Pitx2*	↑ *nodal/Pitx2*	wt *nodal/Pitx2*
loss-of-function	induction of: *nodal* *Pitx2*	randomized: heart looping *nodal, Pitx2* right lung isomerism	induction of: *nodal* *Pitx2*
L/R function	**right**	**left**	**right**

Development 126, 1225-1234 (1999)
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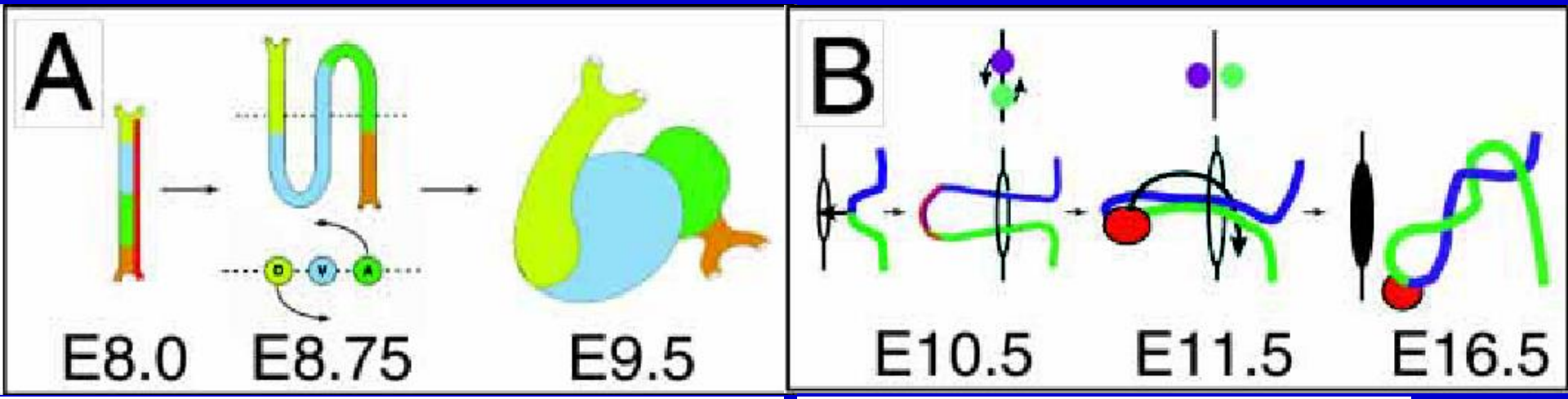
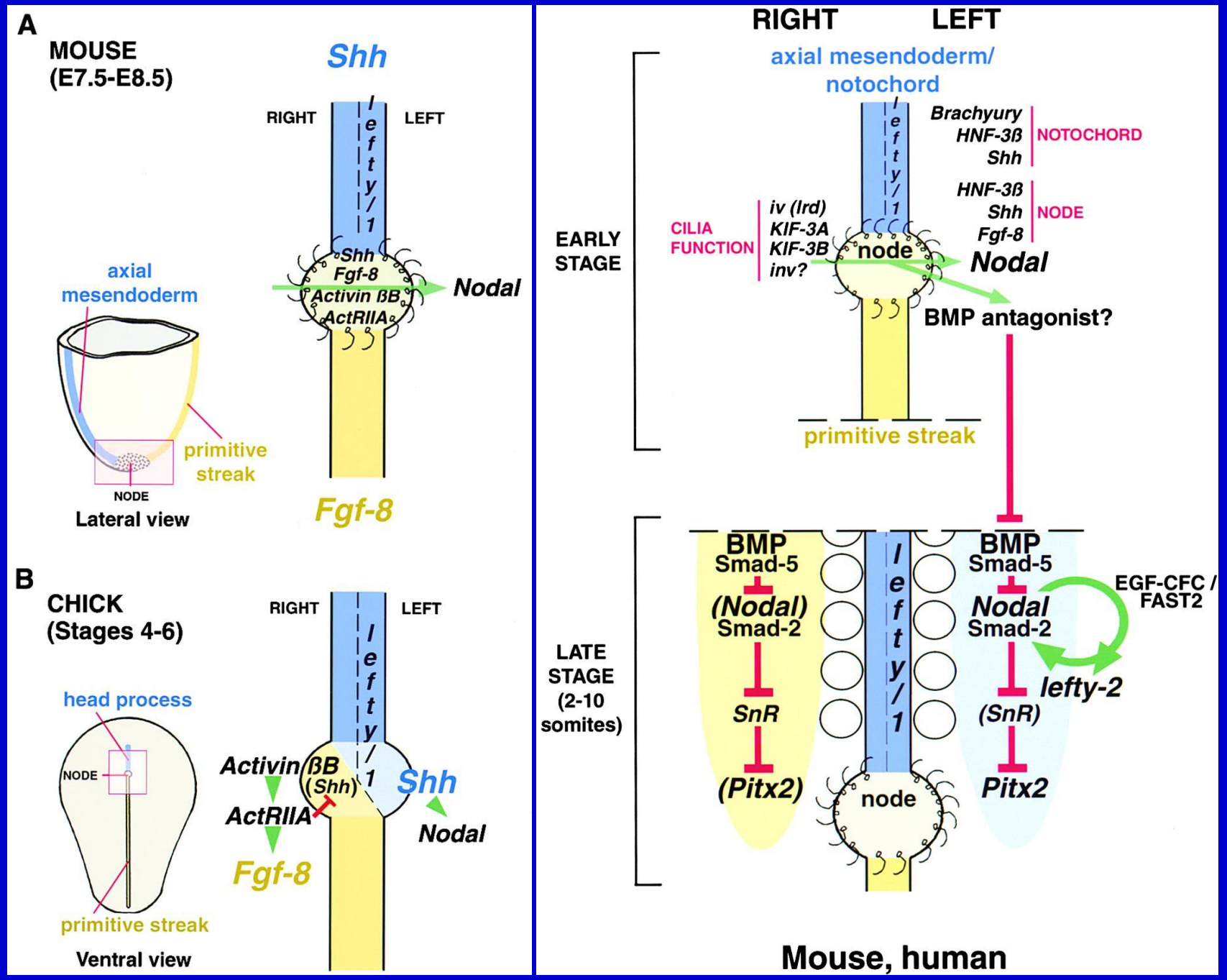
DEV2373

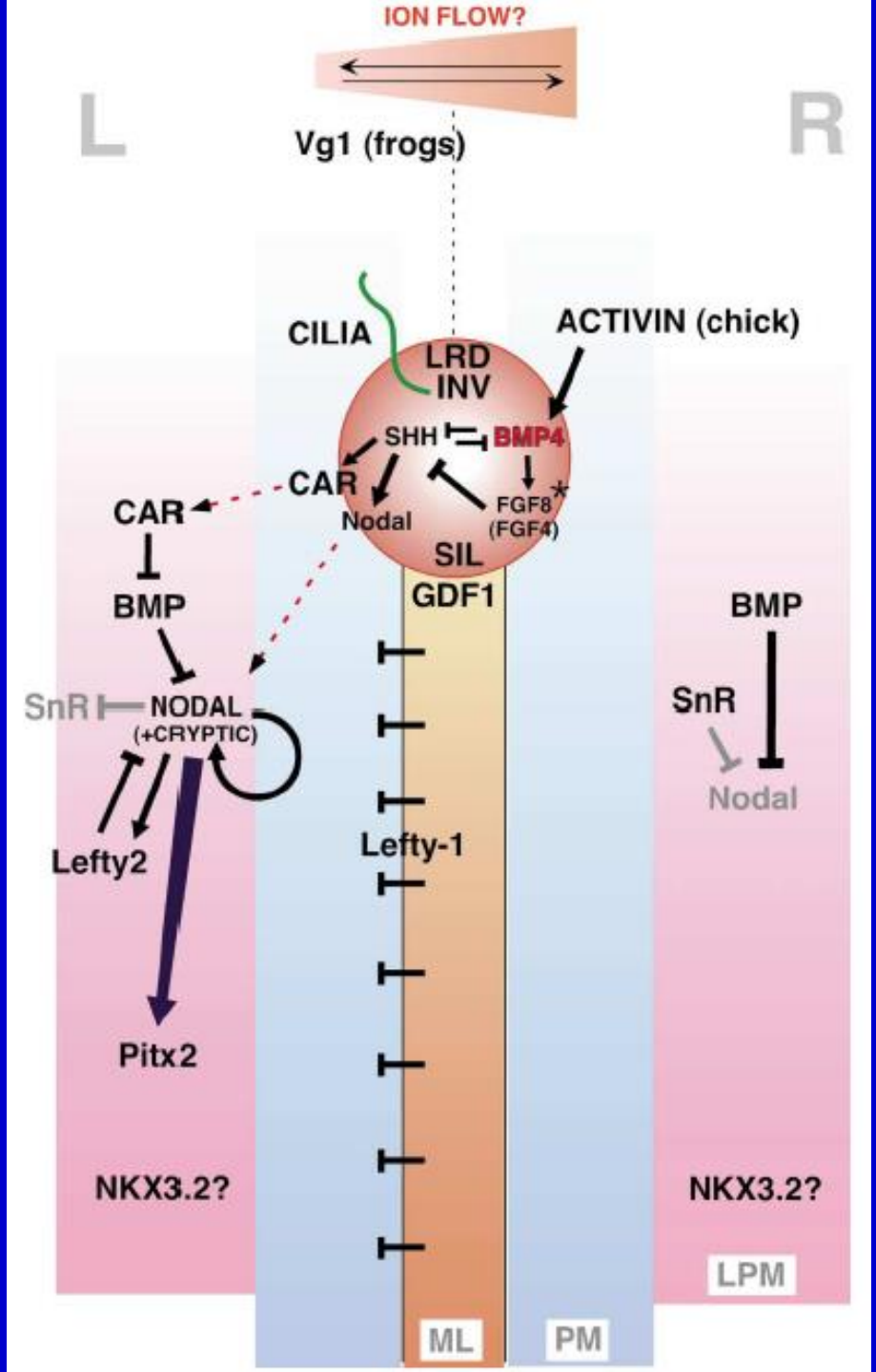
The homeobox gene *Pitx2:* mediator of asymmetric left-right signaling in vertebrate heart and gut looping

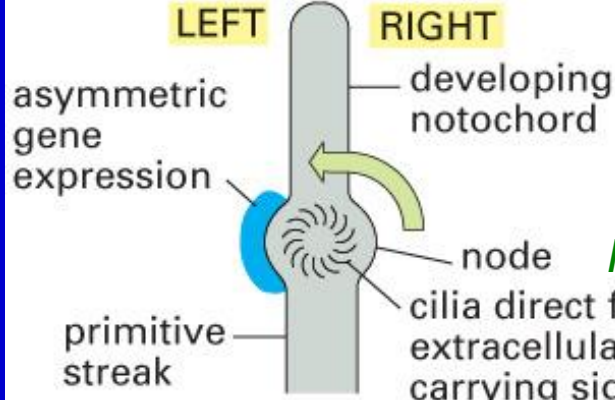


(A) Heart looping. Two phases can be distinguished. First, the linear tube adopts S-shape. Outflow tract (yellow) and atrium (green) then move such that the outflow tract lies in front (ventral) and the atrium at the back (dorsal) of the ventricle, which is illustrated by arrows in the cross section taken at the level of the broken line. Inflow tract: orange; ventricle: blue. Left-sided expression of *Pitx2* in the linear heart is indicated in red.

(B) Midgut. Looping occurs while it is located outside of the body in the so-called physiological umbilical hernia. The loop undergoes a 90° counterclockwise bend such that the two limbs lie next to each other. The future caecum becomes visible just distal to the apex of the midgut loop as a conical bud. When the physiological hernia retracts into the peritoneal cavity the caecum moves about 180° counterclockwise across the small intestine to complete the turning of the midgut. Small intestine: purple; large intestine: green. *Pitx2* expression is


A
MOUSE
(E7.5-E8.5)
Shh
RIGHT
LEFT
lefty/1
Shh
Fgf-8
Activin ßB
ActRIIA
Nodal
axial
mesendoderm
primitive
streak
NODE
Lateral view
Fgf-8
B
CHICK
(Stages 4-6)
RIGHT
LEFT
lefty/1
head process
NODE
Activin ßB
(Shh)
Shh
ActRIIA
Nodal
Fgf-8
primitive streak
Ventral view
RIGHT
LEFT
axial mesendoderm/
notochord
lefty/1
Brachyury
HNF-3ß
Shh
NOTOCHORD
HNF-3ß
Shh
Fgf-8
NODE
CILIA
FUNCTION
iv (lrd)
KIF-3A
KIF-3B
inv?
EARLY
STAGE
node
Nodal
BMP antagonist?
primitive streak
BMP
Smad-5
(Nodal)
Smad-2
SnR
(Pitx2)
lefty/1
node
BMP
Smad-5
Nodal
Smad-2
(SnR)
Pitx2
EGF-CFC /
FAST2
lefty-2
LATE
STAGE
(2-10
somites)
Mouse, human





KIF3

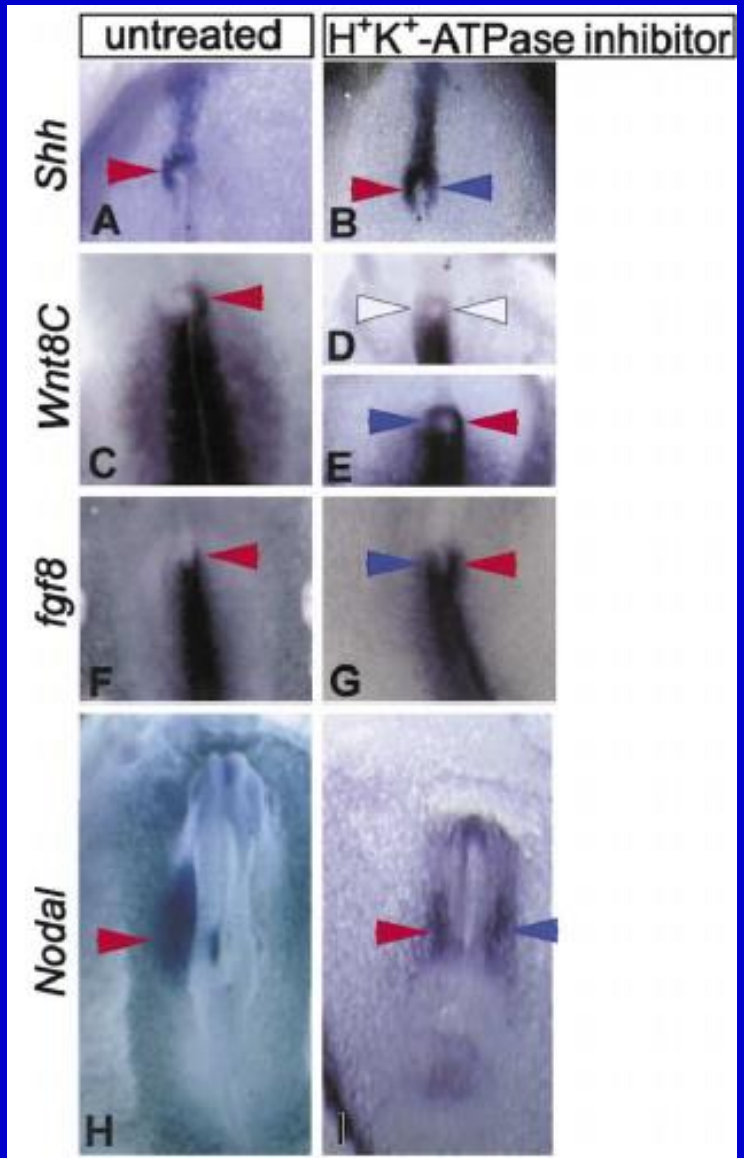
cilia direct flow of extracellular fluid carrying signal proteins (Sonic hedgehog, FGF8, and TGFβ family members) ***Lefty-1, Lefty-2, Nodal, BMP, etc.***

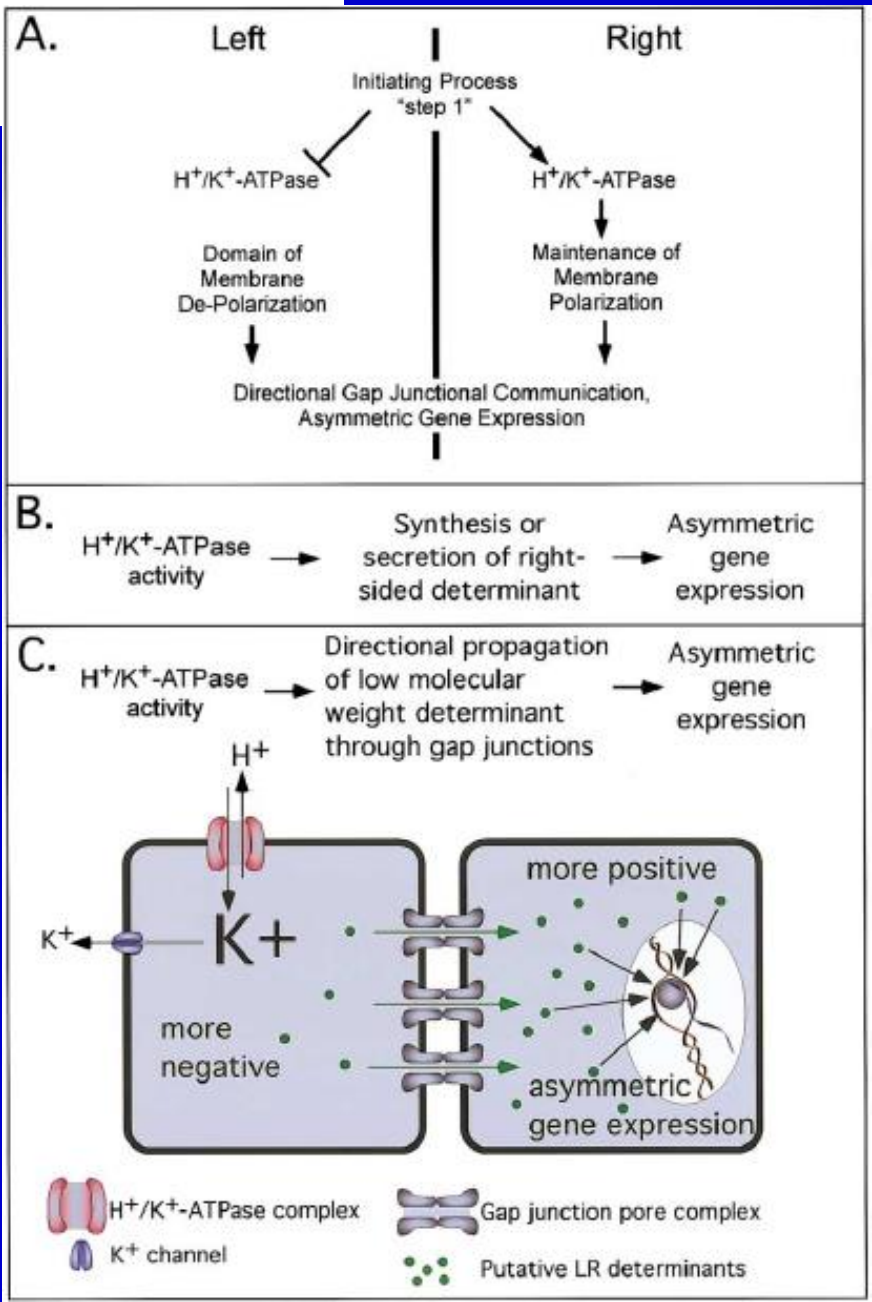
Nodal expression pattern

Figure 21–82. Molecular Biology of the Cell, 4th Edition.

Cell, Vol. 111, 77–89, October 4, 2002, Copyright ©2002 by Cell Press

Asymmetries in H^+/K^+-ATPase and Cell Membrane Potentials Comprise a Very Early Step in Left-Right Patterning





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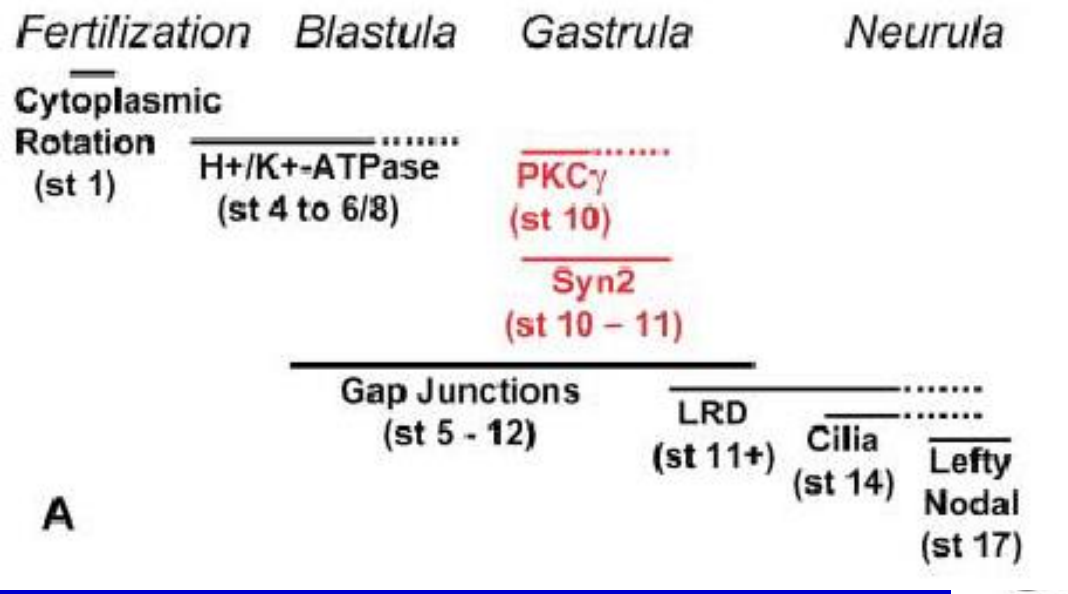
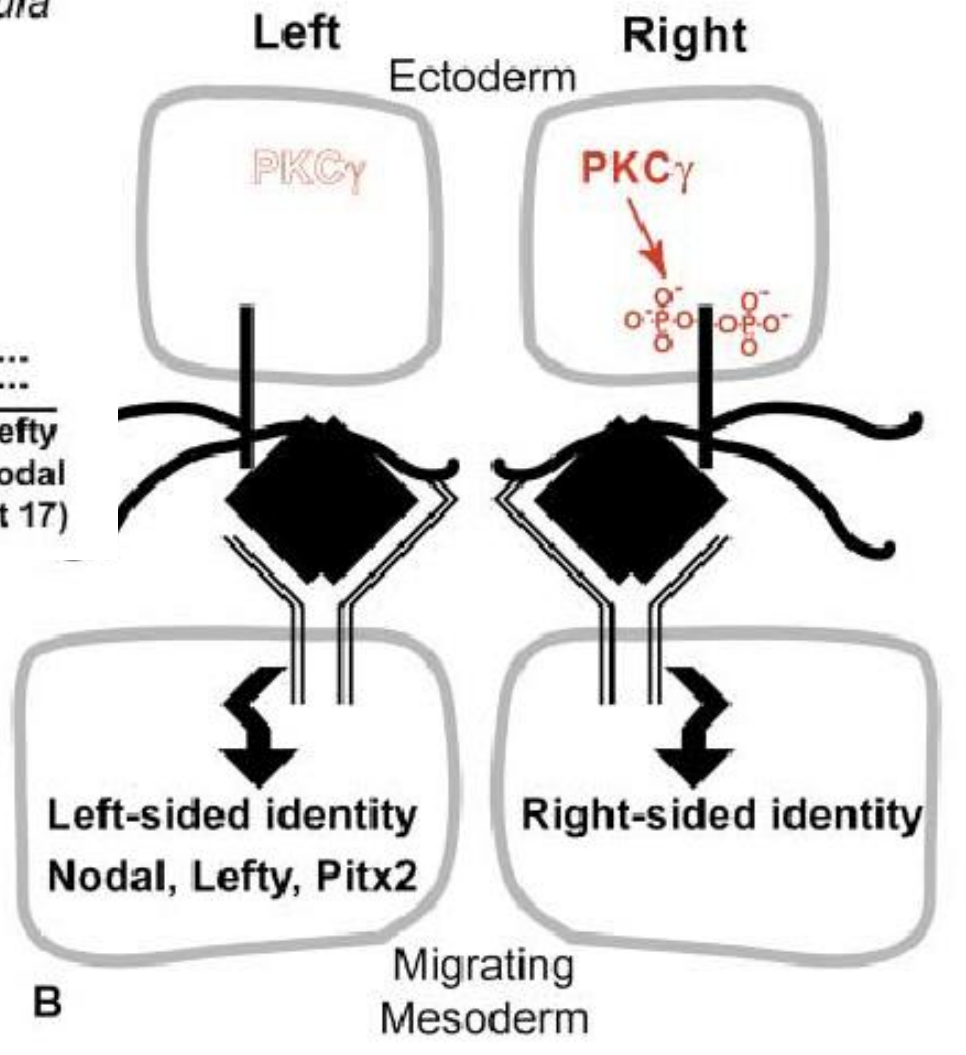
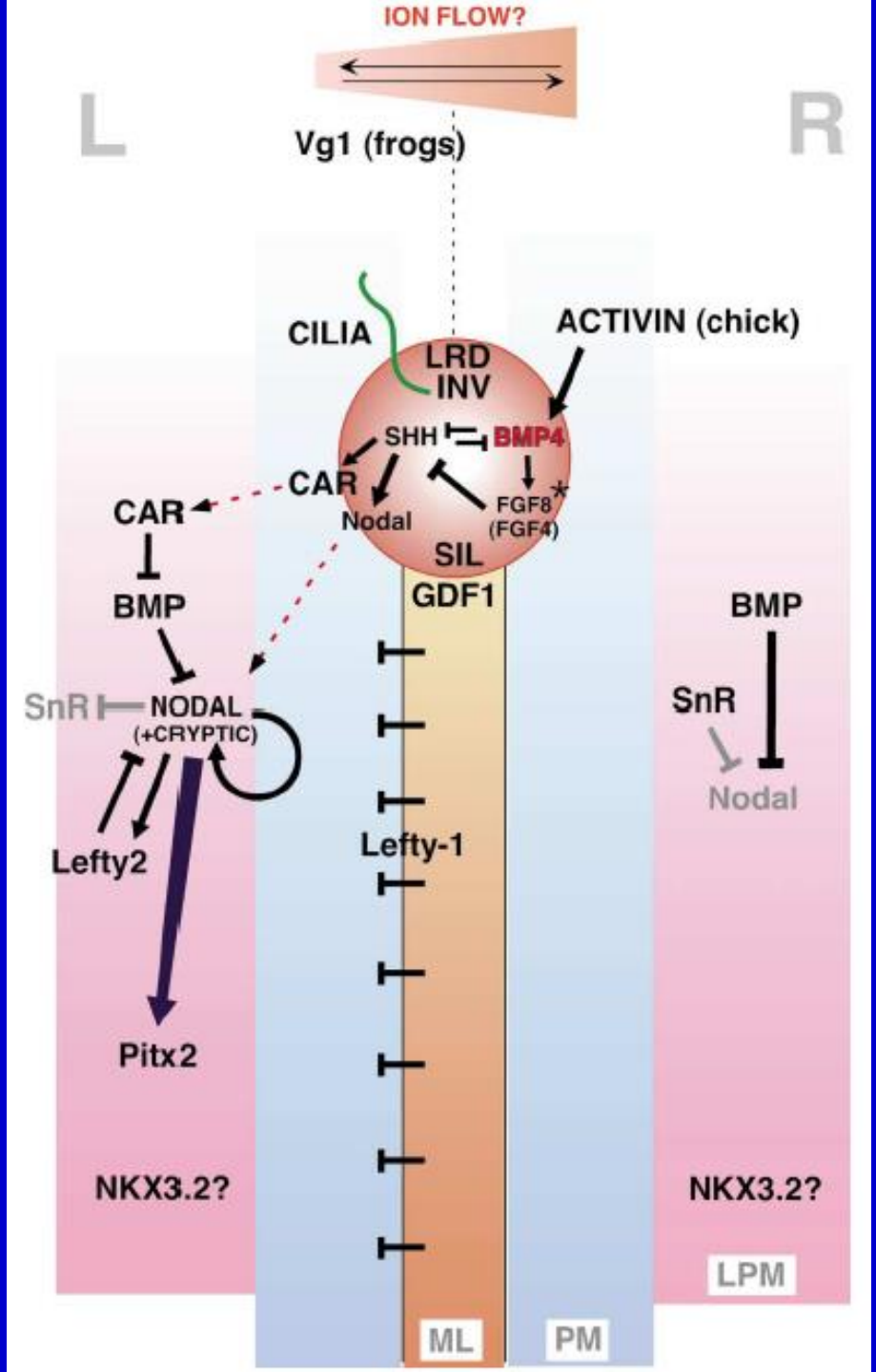
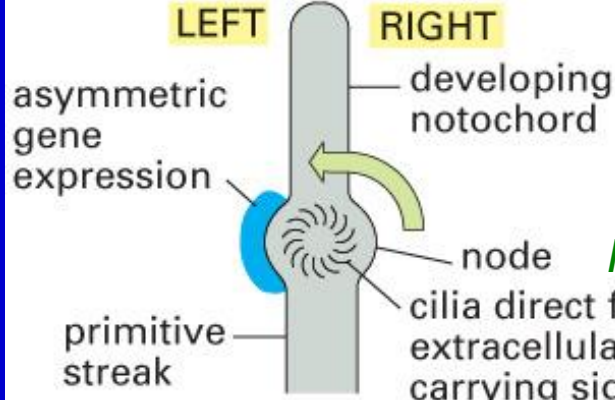
PKCγ Regulates Syndecan-2 Inside-Out Signaling during *Xenopus* Left-Right Development









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Summary

- Cytoskeletal protein KIF3 in nodal cilia
- Sonic hedgehog and its receptor Smoothened
- Growth/differentiation factor-1
- **TGF-beta superfamily members**
- **Lefty-1, Lefty-2, Nodal,** BMP2, BMP4, and Smad5
- FGF8
- Homeobox gene Pitx2