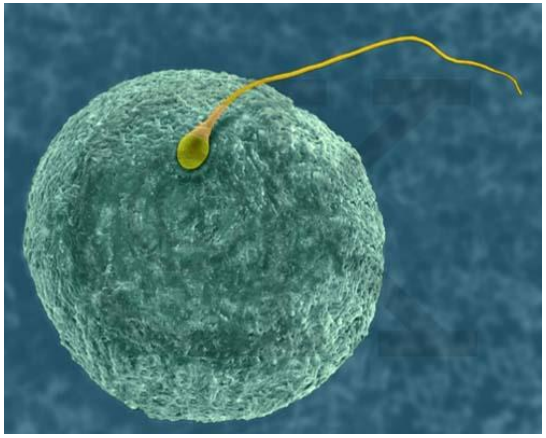
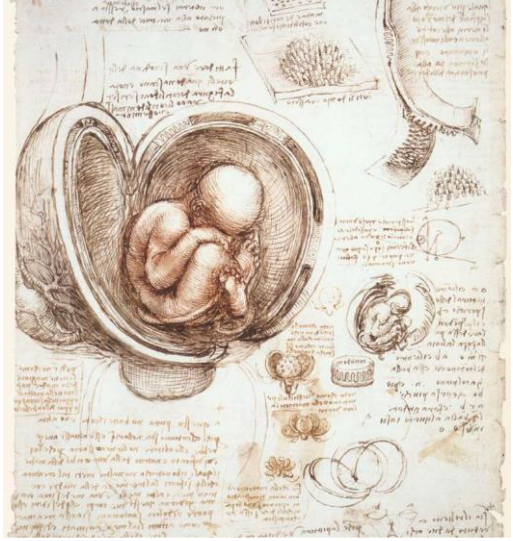
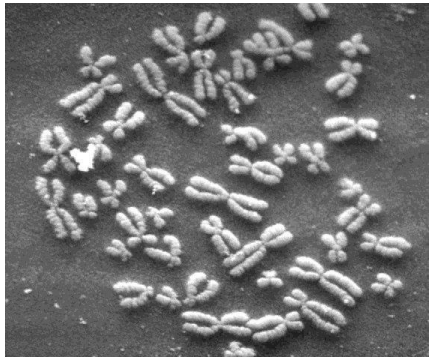
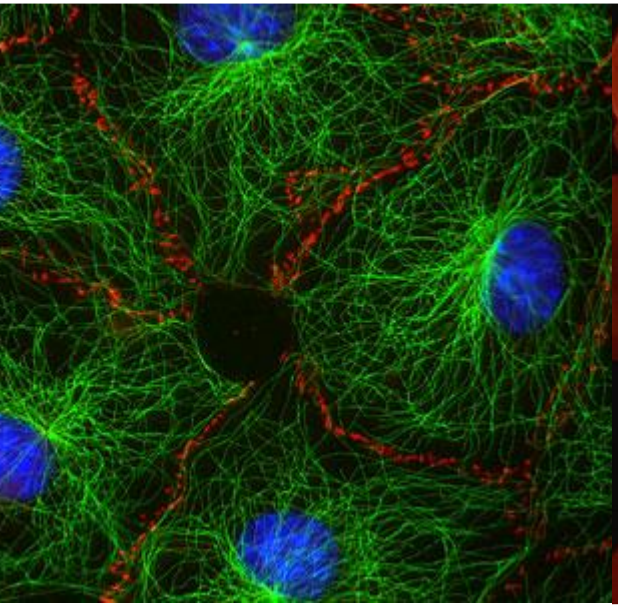
Regulators of Development

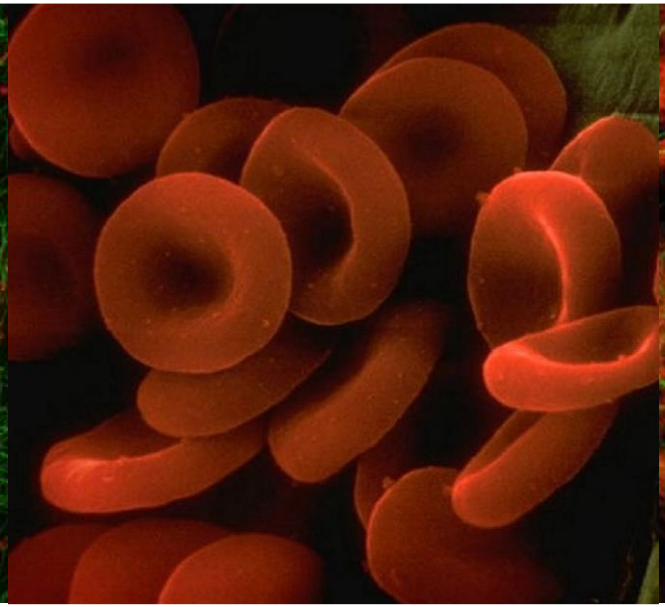
Ontogenesis is a hereditary phenomenon

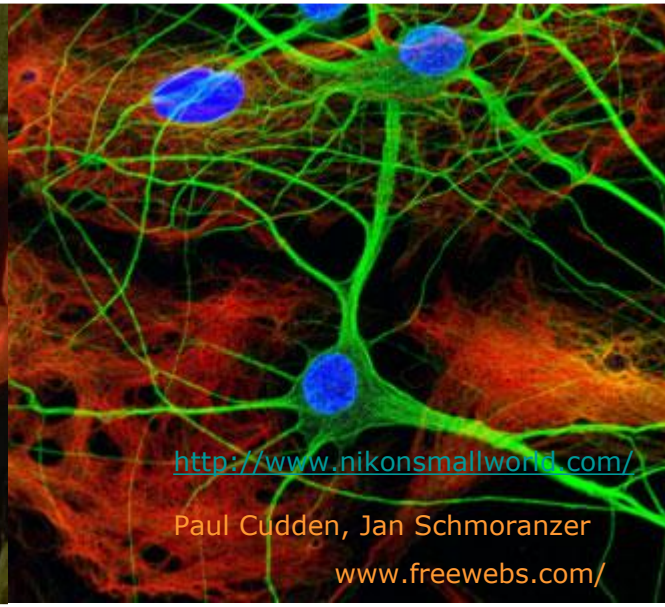










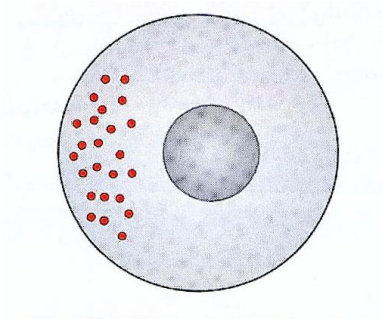


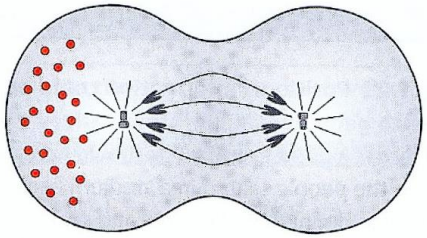
Genetic equivalence of cells ?

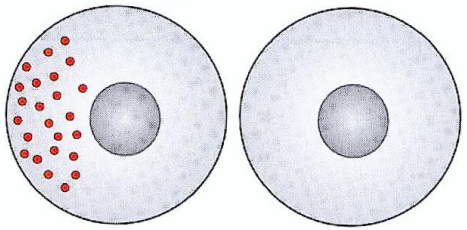
Differentiation of cell lineages → Shaping the embryo

Genetic equivalence of cells ?

Differentiation of cell lineages → Shaping the embryo



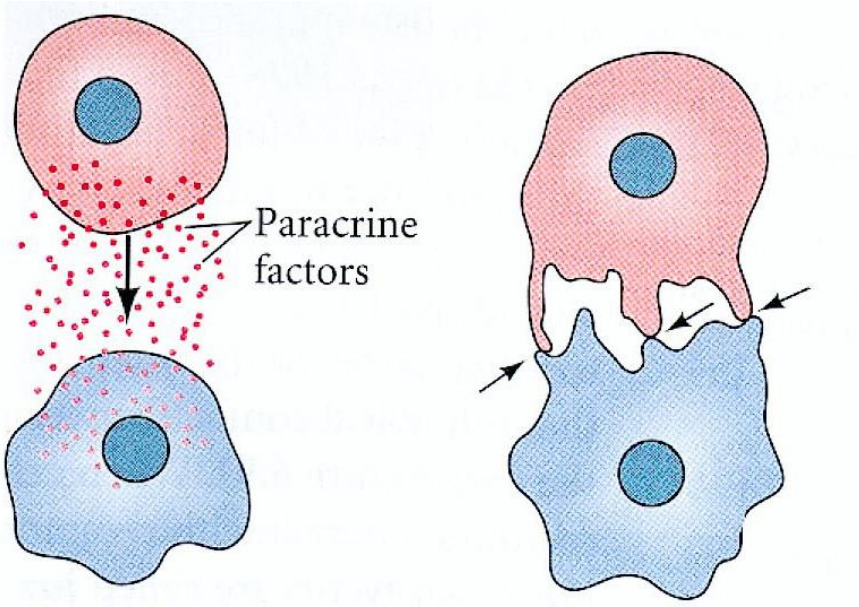




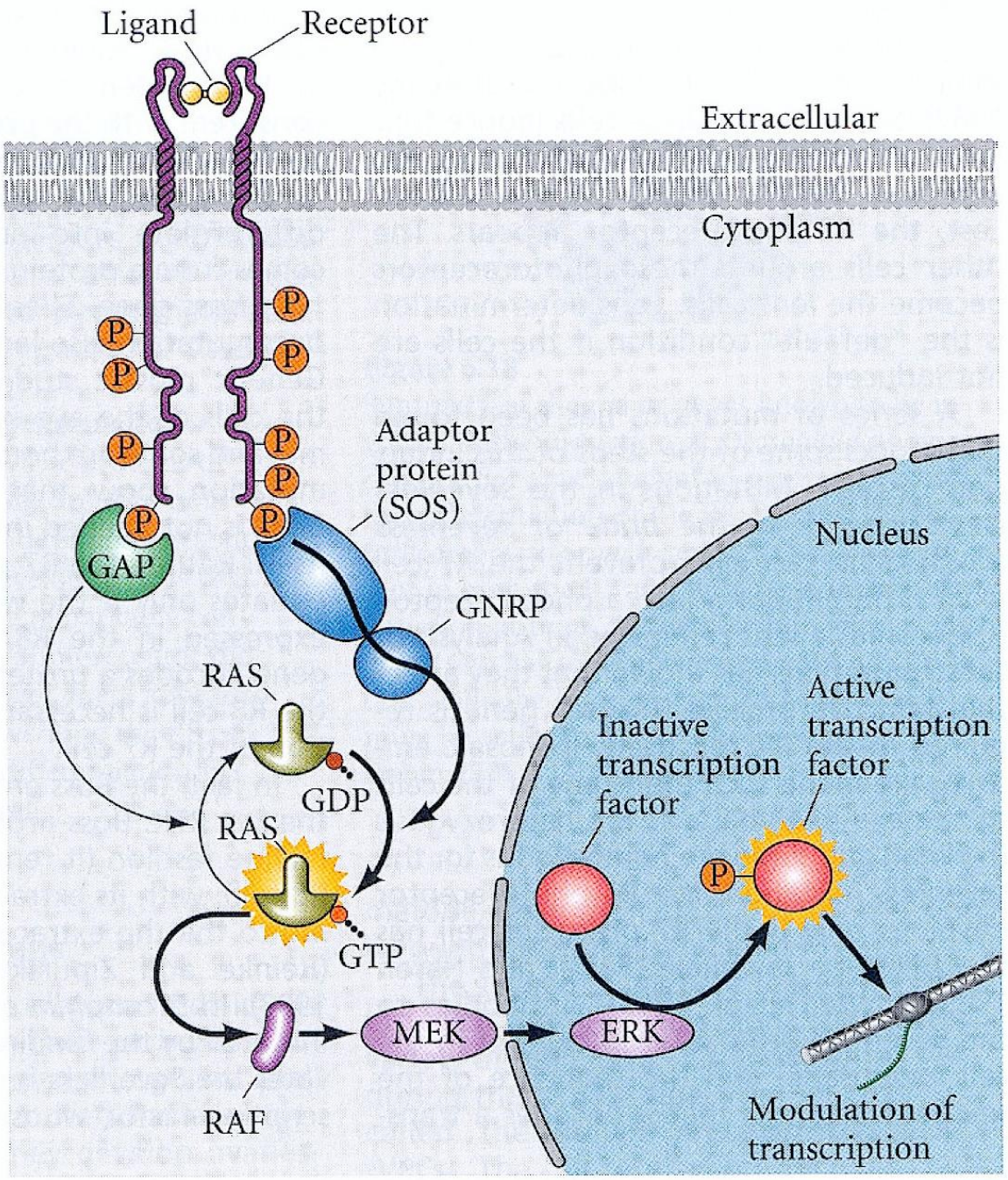
Symmetry breaking

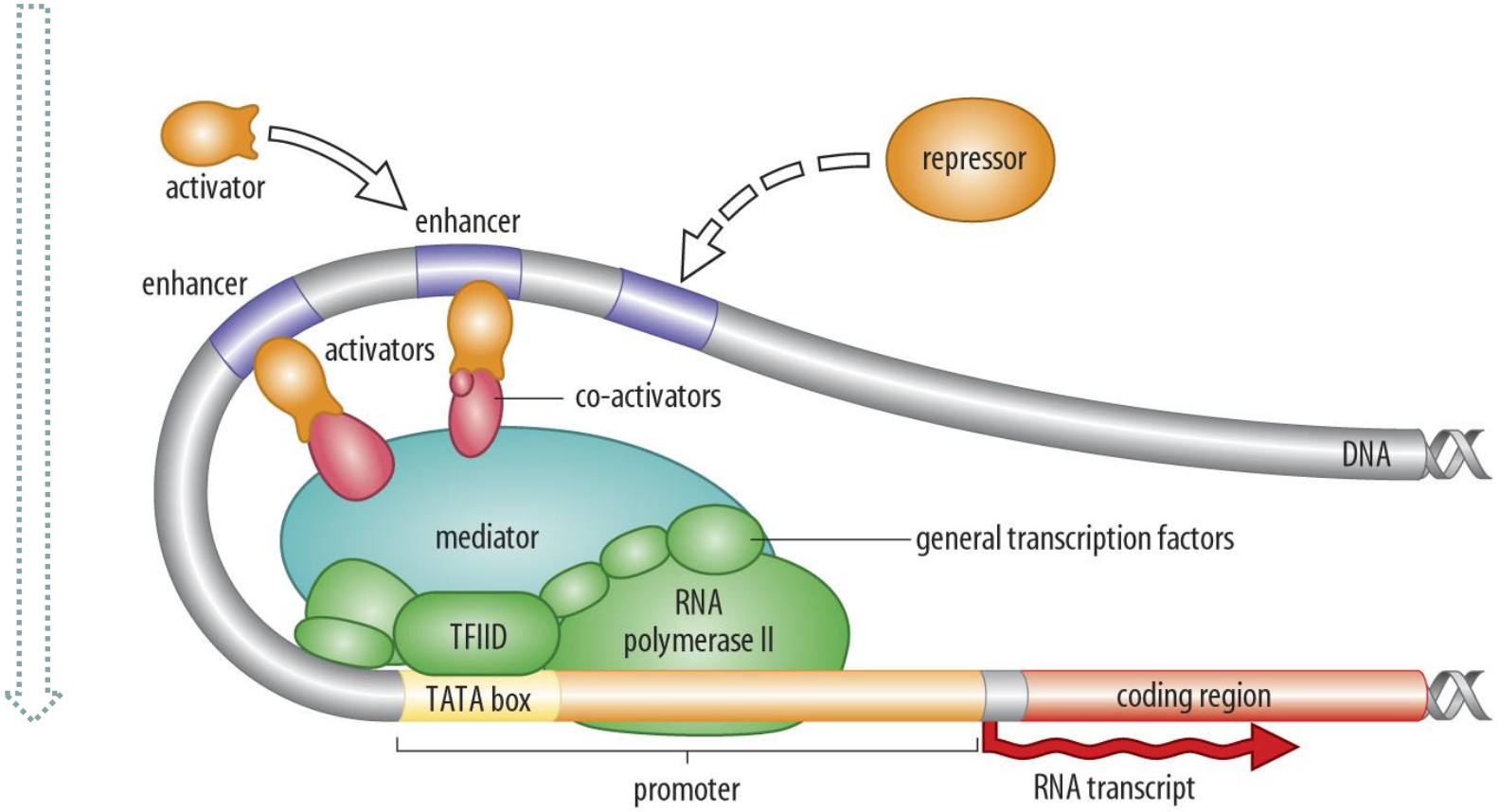
« epi »-genetic factors

« stuff » acting on genes



Signaling molecules





Gene regulators (transcription factors, etc…)

A Genomic Regulatory Network for Development

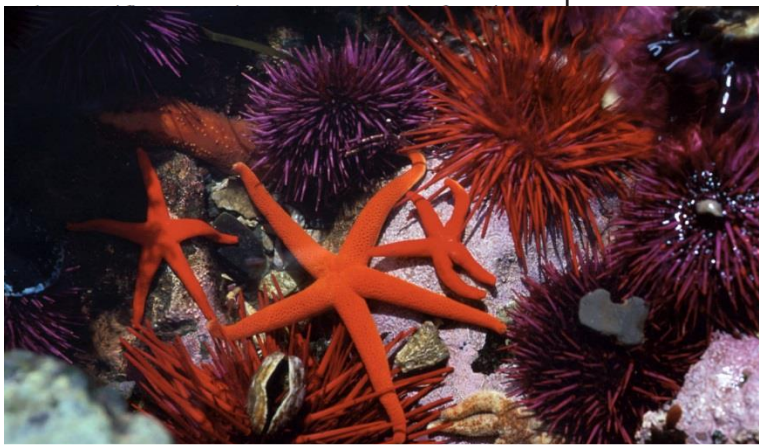
Eric H. Davidson,[1]* Jonathan P. Rast,[1] Paola Oliveri,[1] Andrew Ransick,[1] Cristina Calestani,[1] Chiou-Hwa Yuh,[1] Takuya Minokawa,[1] Gabriele Amore,[1] Veronica Hinman,[1] César Arenas-Mena,[1] Ochan Otim,[1] C. Titus Brown,[1] Carolina B. Livi,[1] Pei Yun Lee,[1] Roger Revilla,[1] Alistair G. Rust,[2]† Zheng jun Pan,[2]‡ Maria J. Schilstra,[2] Peter J. C. Clarke,[2] Maria I. Arnone,[3] Lee Rowen,[4] R. Andrew Cameron,[1] David R. McClay,[5] Leroy Hood,[4] Hamid Bolouri[2]

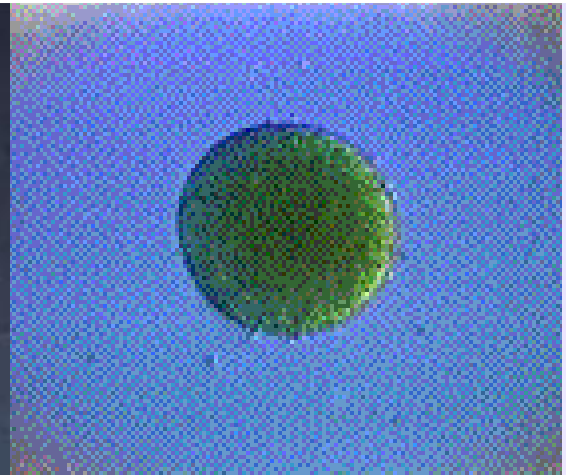
Development of the body plan is controlled by large networks of regulatory genes. A gene regulatory network that controls the specification of endoderm and mesoderm in the sea urchin embryo is summarized here. The network was derived from large-scale perturbation analyses, in combination with computational methodologies, genomic data, cis-regulatory analysis, and molecular embryology. The network contains over 40 genes at present, and each node can be directly verified at the DNA sequence level by cis-regulatory analysis. Its architecture reveals specific and general aspects of development, such as how given cells generate their ordained fates in the embryo and why the process moves inexorably forward in developmental time.

nechanism causing cats to beget cats and
o beget fish is hardwired in the genomic
, because the species specificity of the
plan is the cardinal heritable property. But

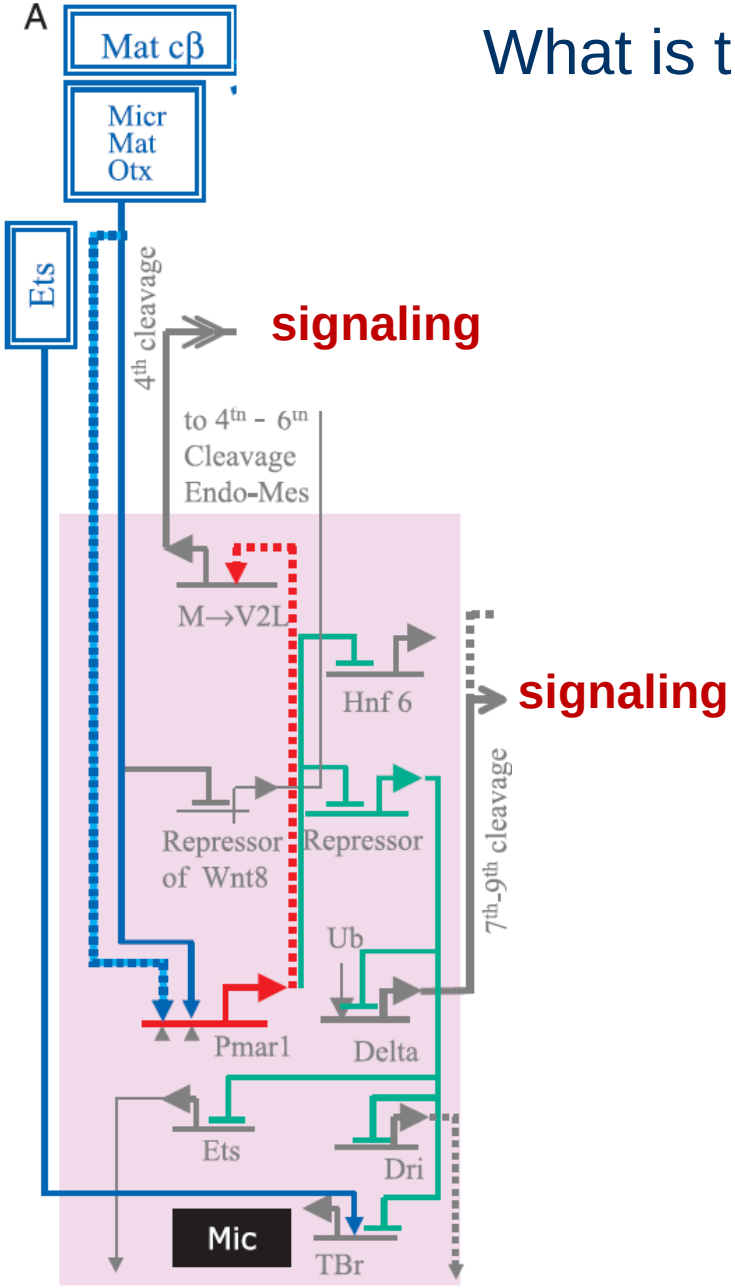
present tough challenges because they go through successive stages of pattern formation in order to generate complex morphologies, and their development is initiated from states that

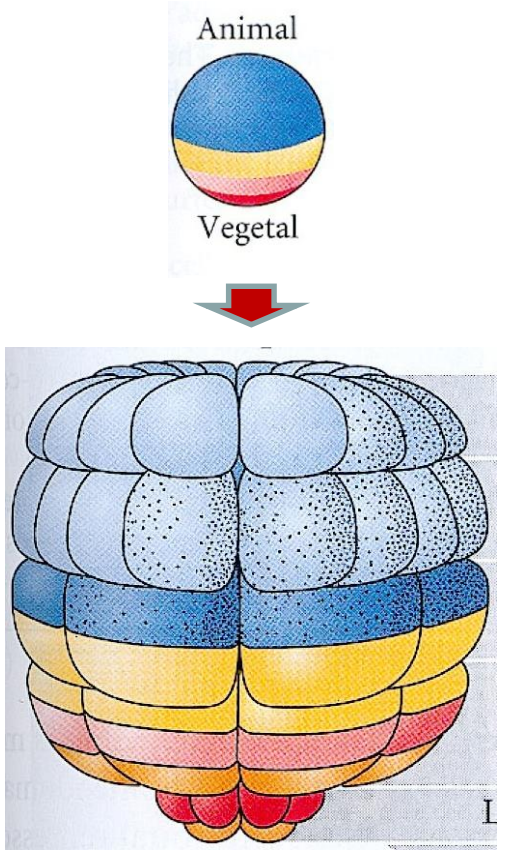
genes in the network; these inputs are the transcription factors for which the element contains





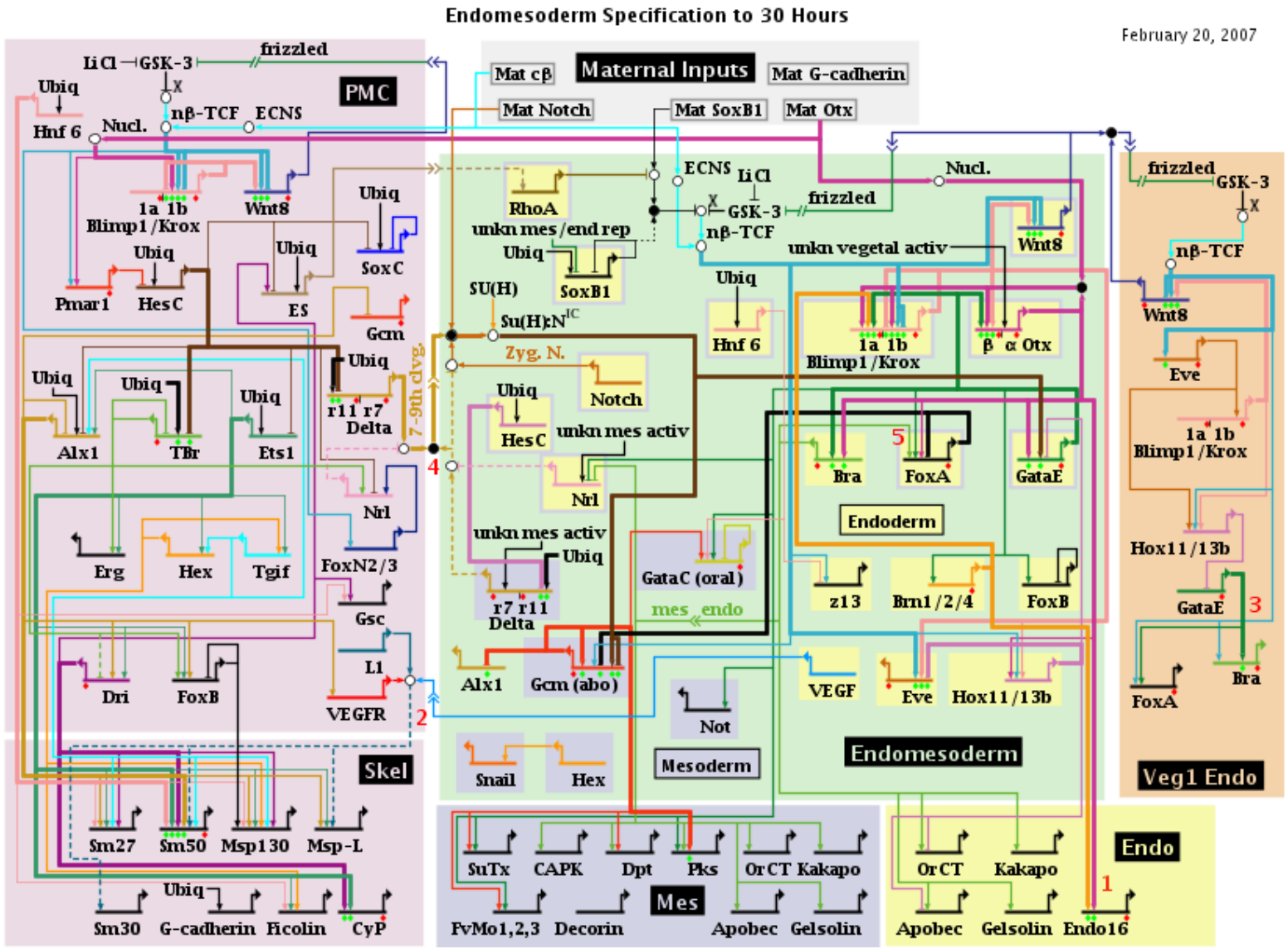
What is the first « symmetry breaking event » in development?





…Oogenesis !!!

Next…: networks of cells and molecules in interaction

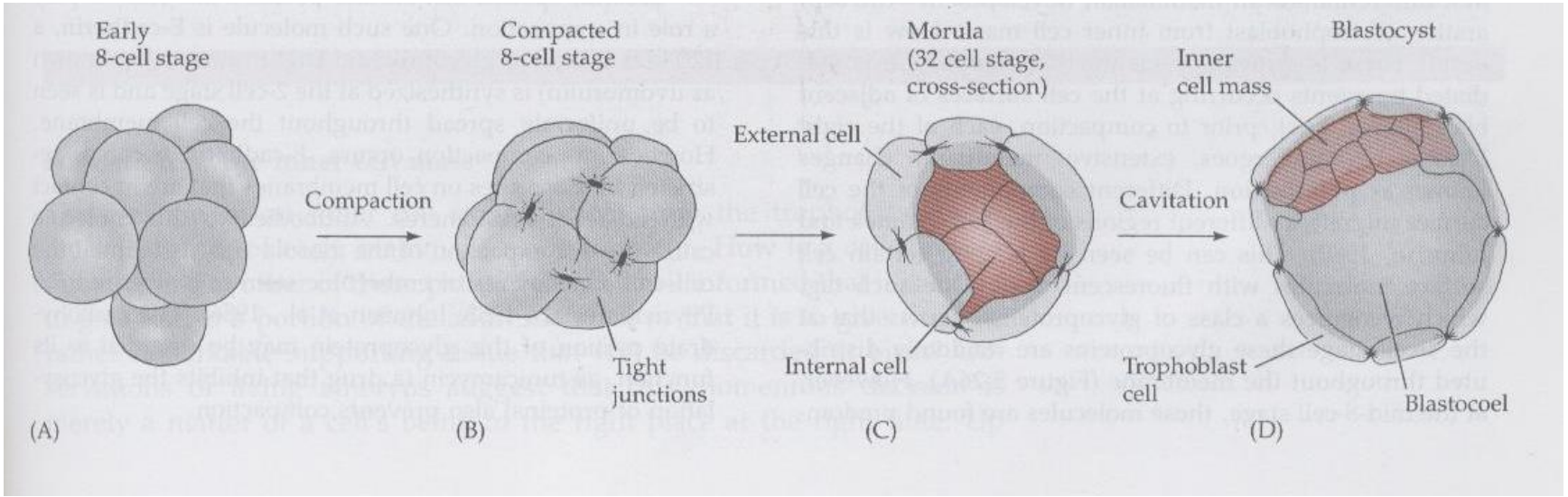


gene regulatory networks

developmental programme

What is the first « symmetry breaking event » in

human development?



Ontogenesis is a hereditary phenomenon

Genetic equivalence of cells

Differentiation of cell lineages ⇨ Shaping the embryo

From «symmetry breaking» to :

gene regulatory networks

developmental programme

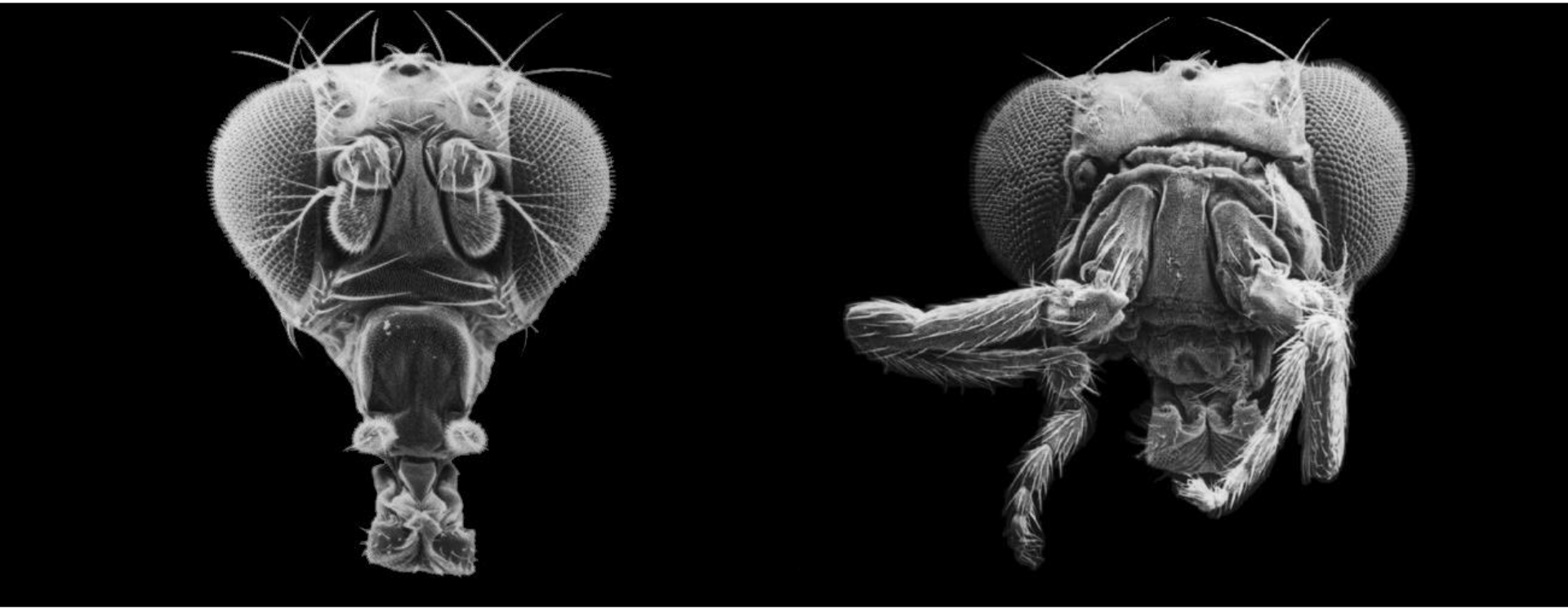
Signaling molecules

⇩

Gene regulators

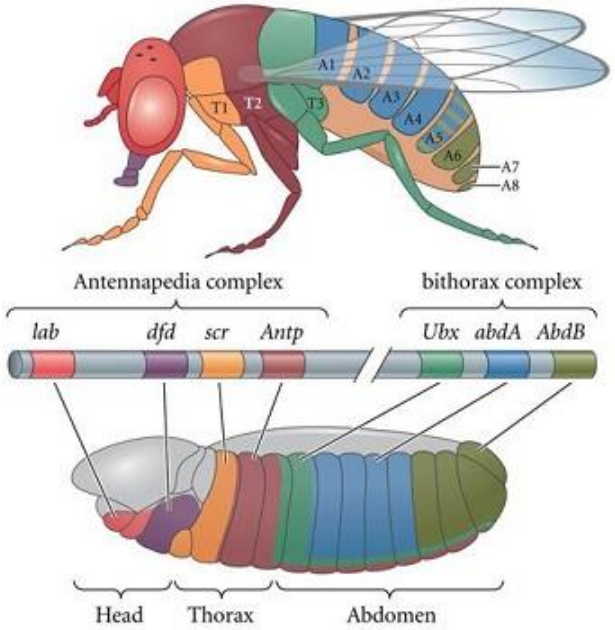
Patterning the embryo

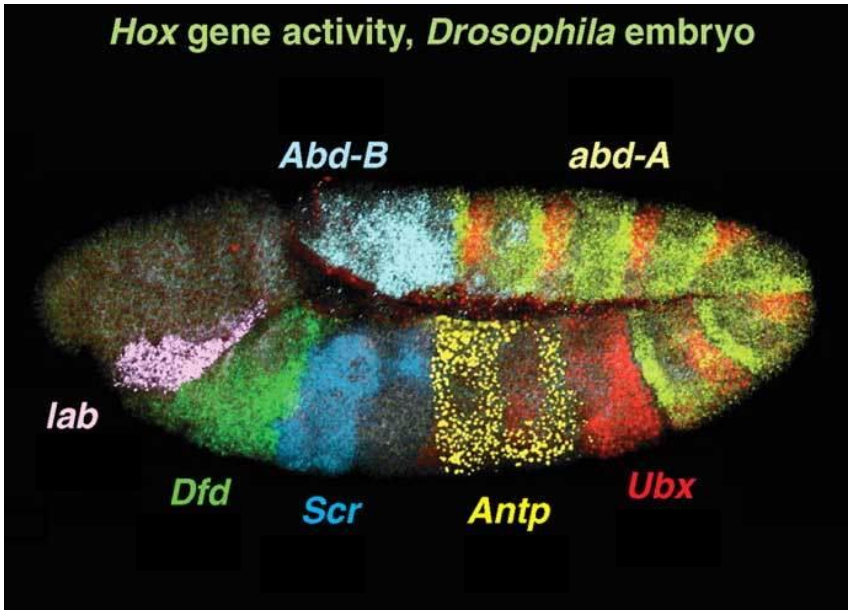
Hox genes



« **H**omeob**ox** » genes… *Hox* genes

Specification of body segments

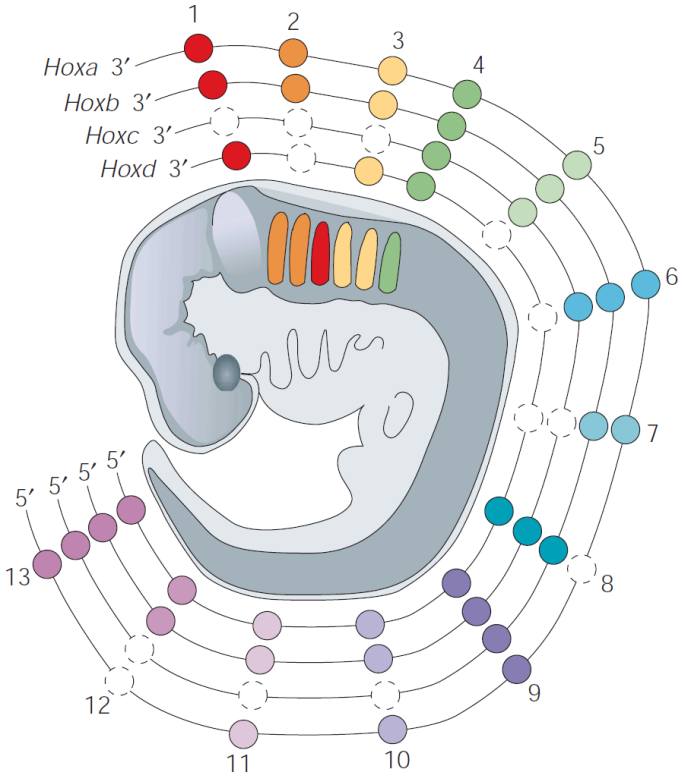




Gilbert, S, et al., *Developmental Biology*, *8th Ed,* Sinauer, 2006

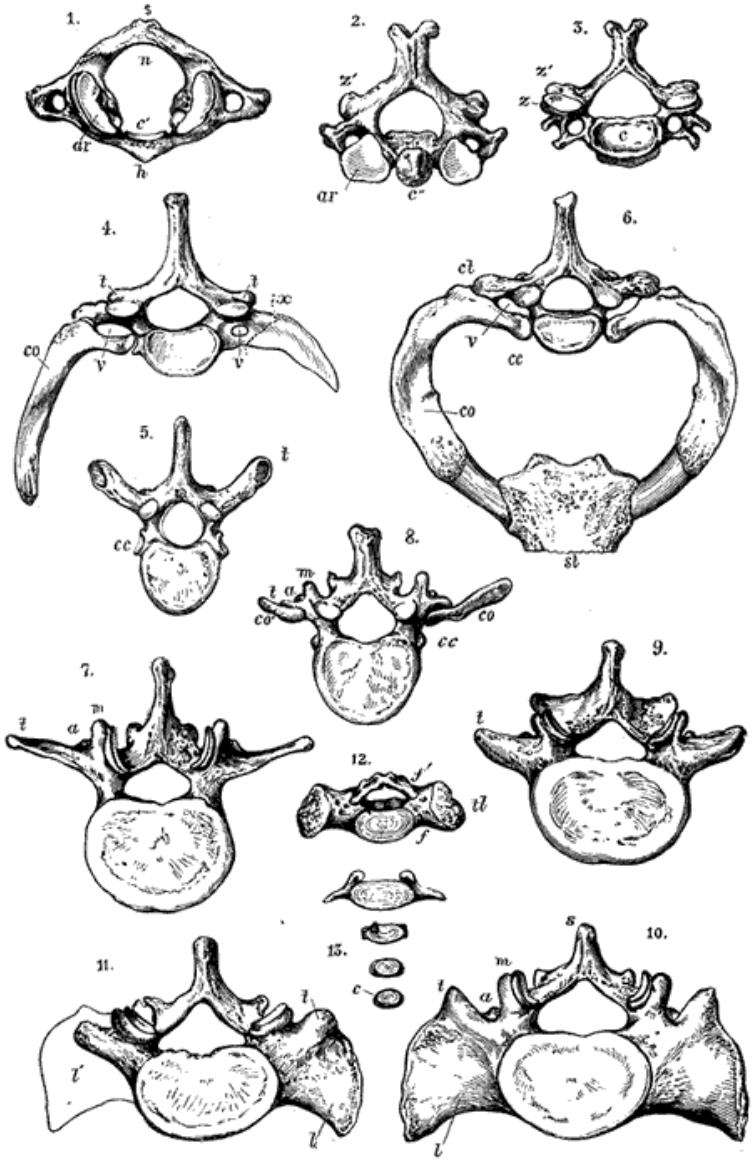
D. Lemons and W. Mc Ginnis, Science 2006

In mammals….

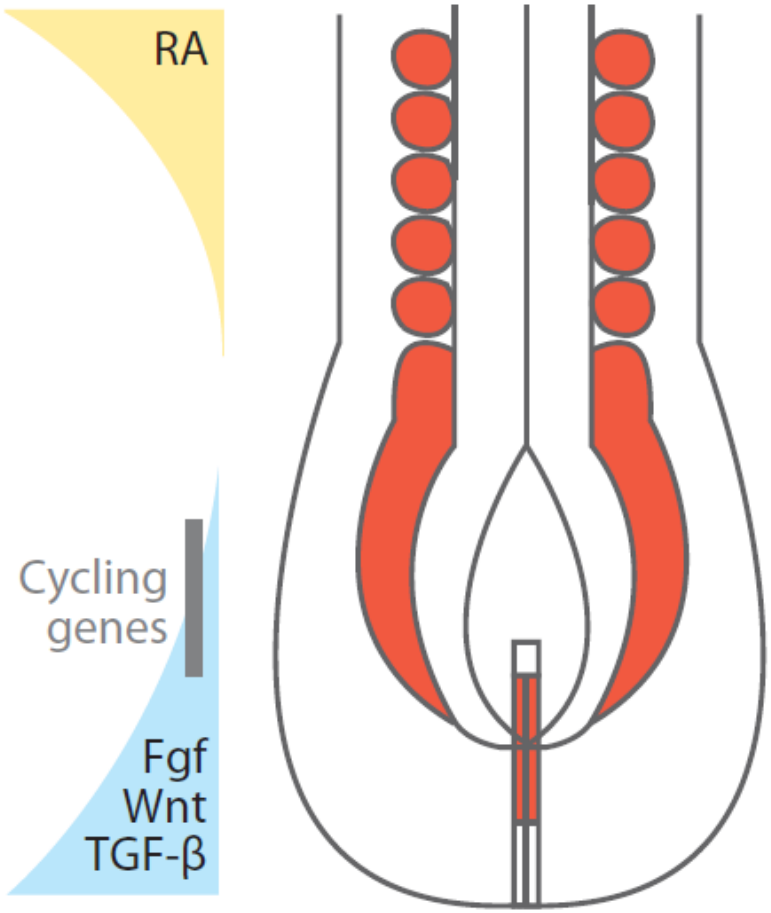


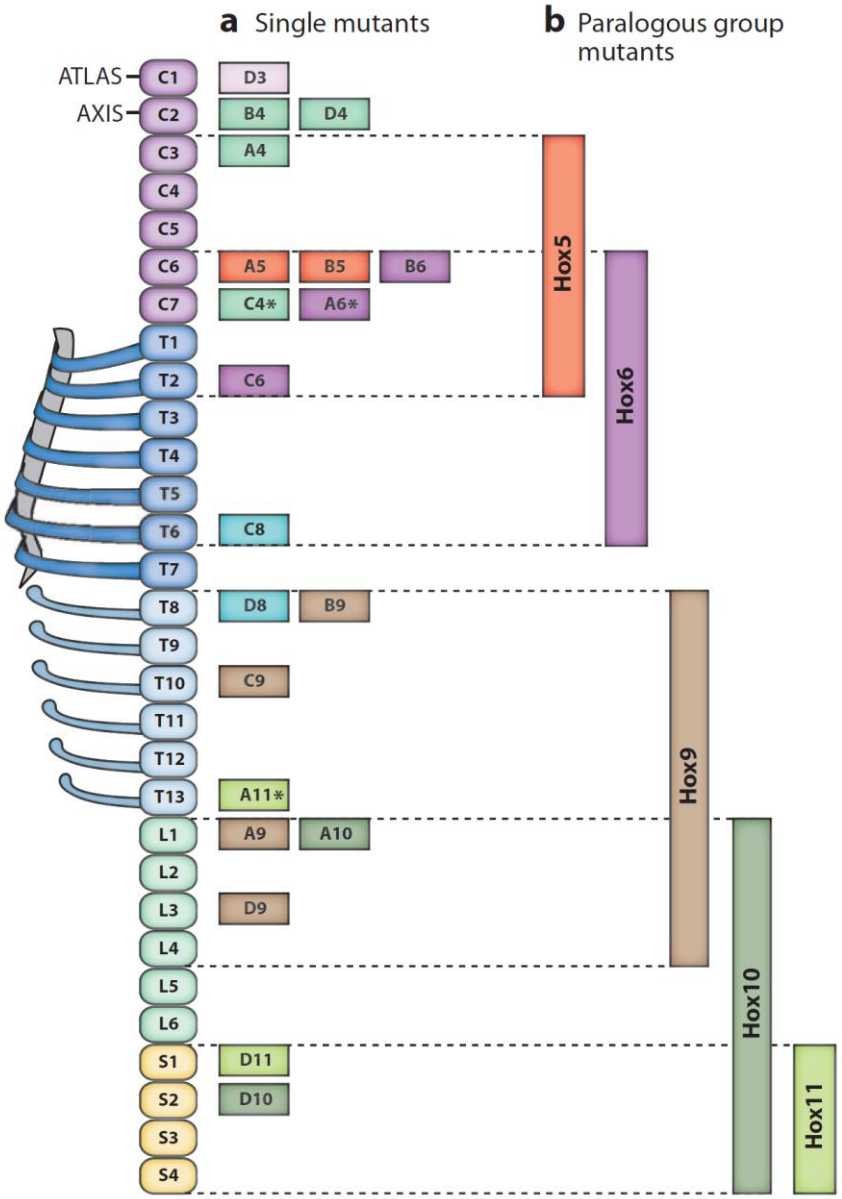
Santagati and Rijli, 2003

Vertebrae, ribs

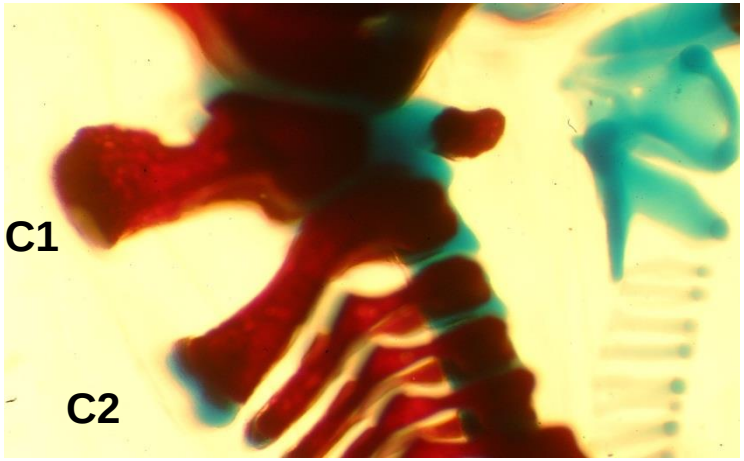


Nolte et al, 2009



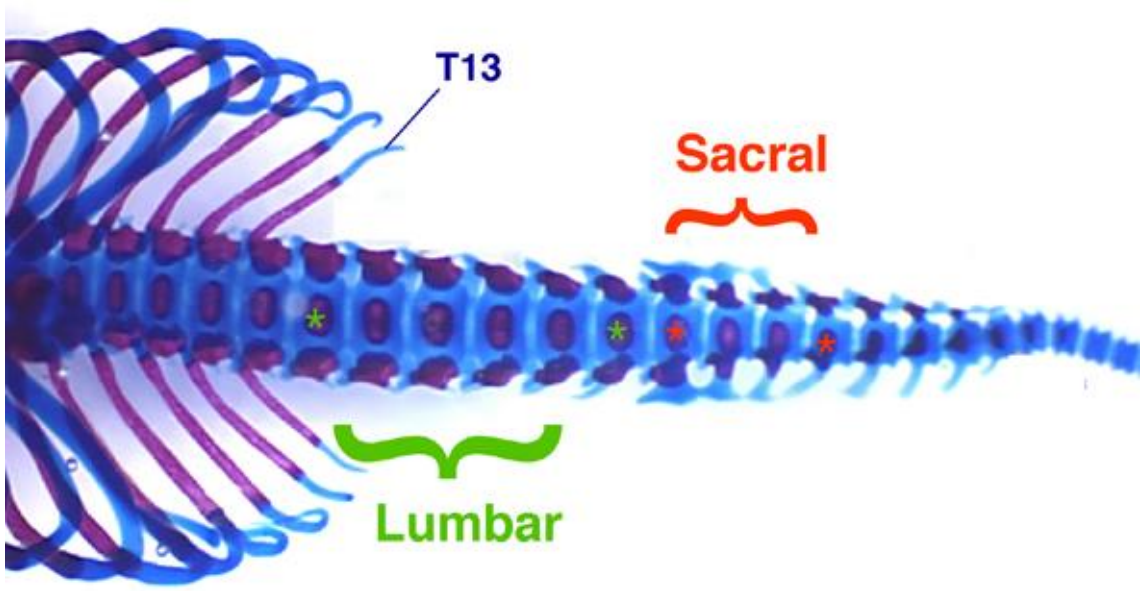


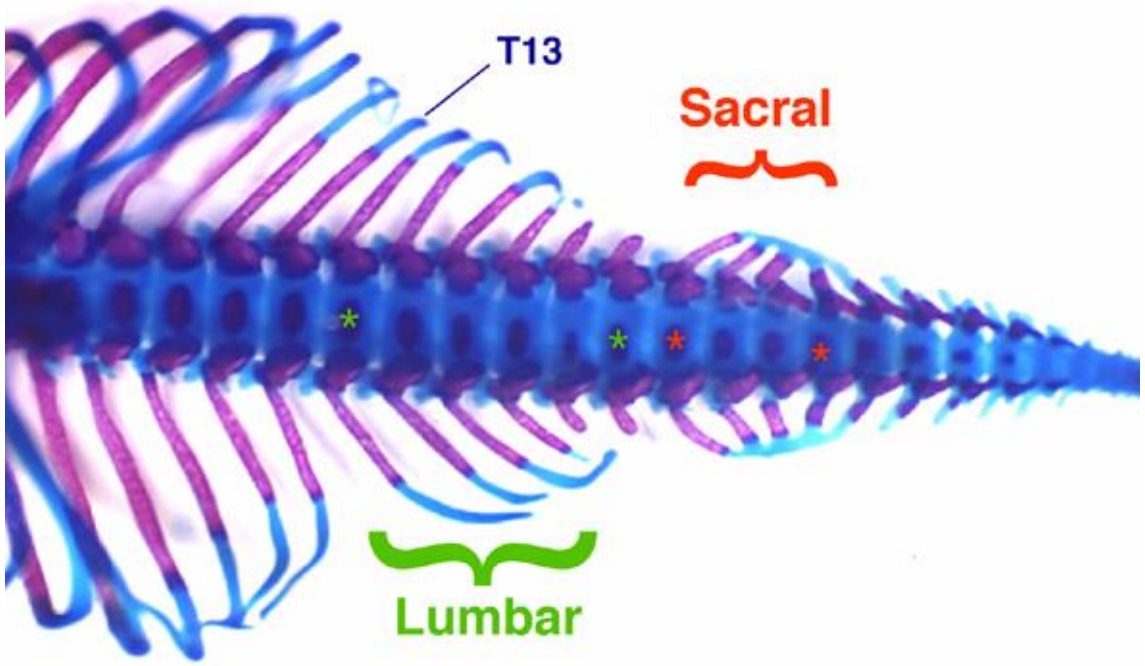
Signaling molecules → Transcription factors



Hoxa1$^{NA\text{-}KR}$ mutant

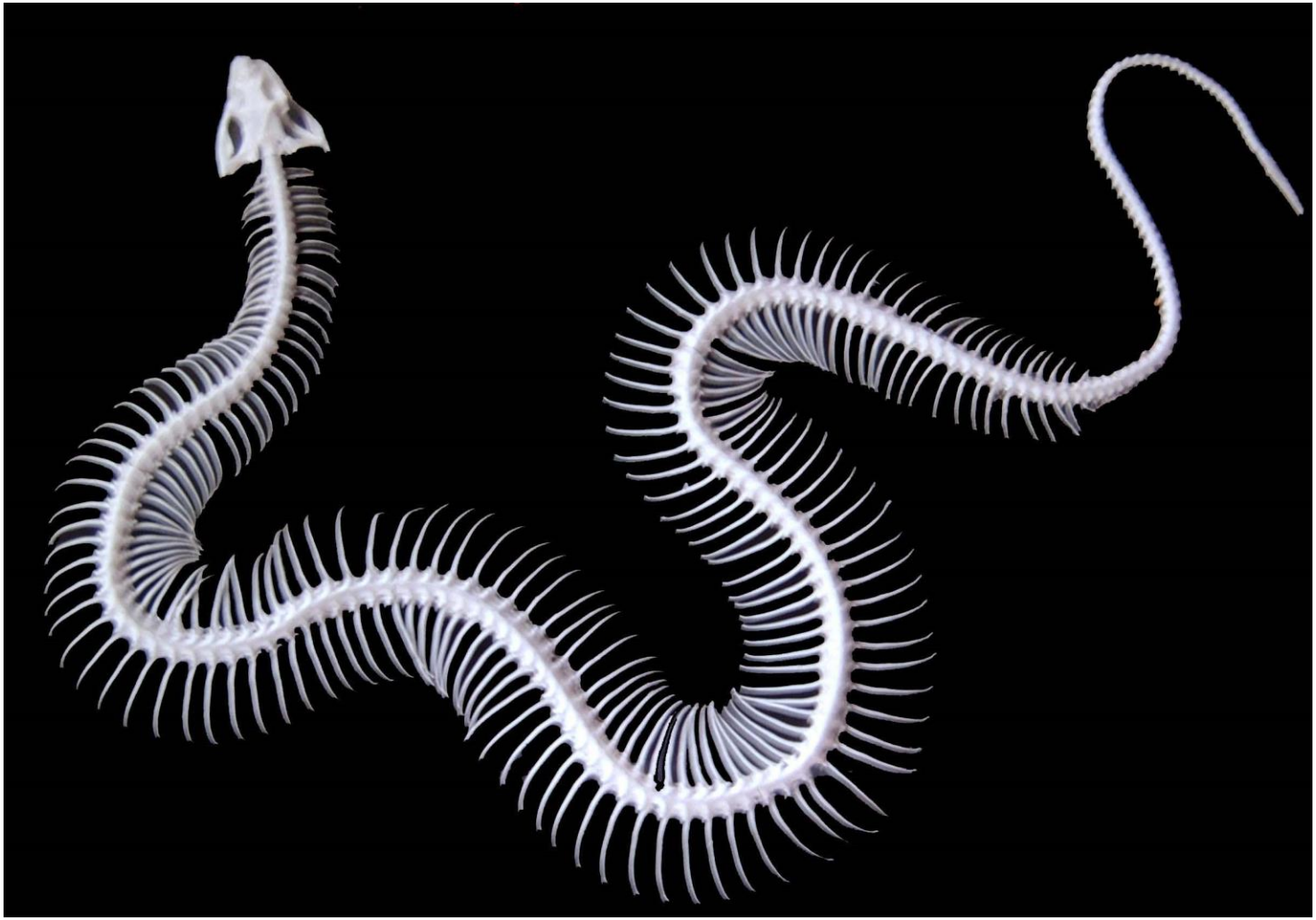
Remacle, Gofflot, Rezsohazy, *unpublished*

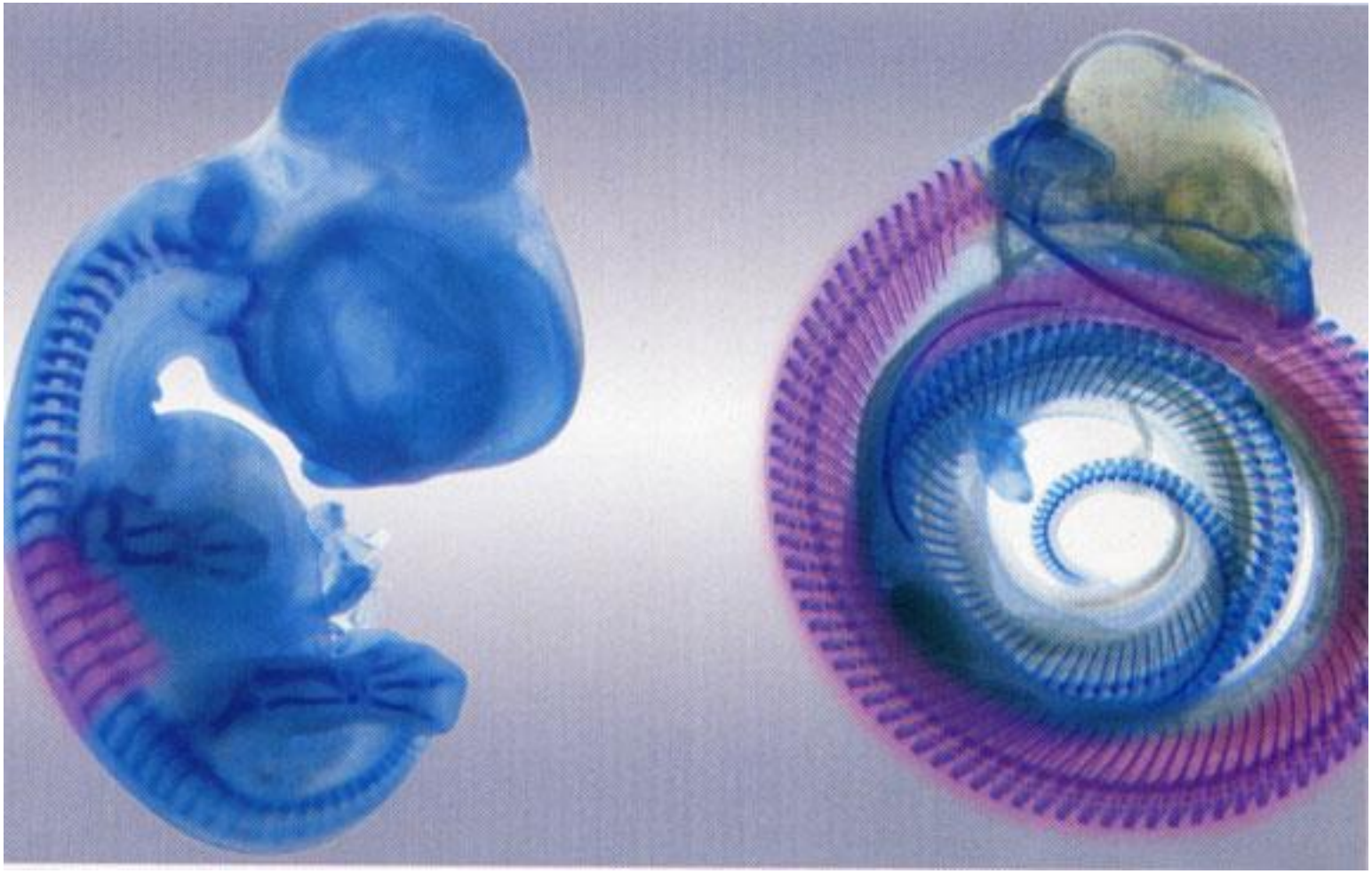




Hoxa10/c10/d10

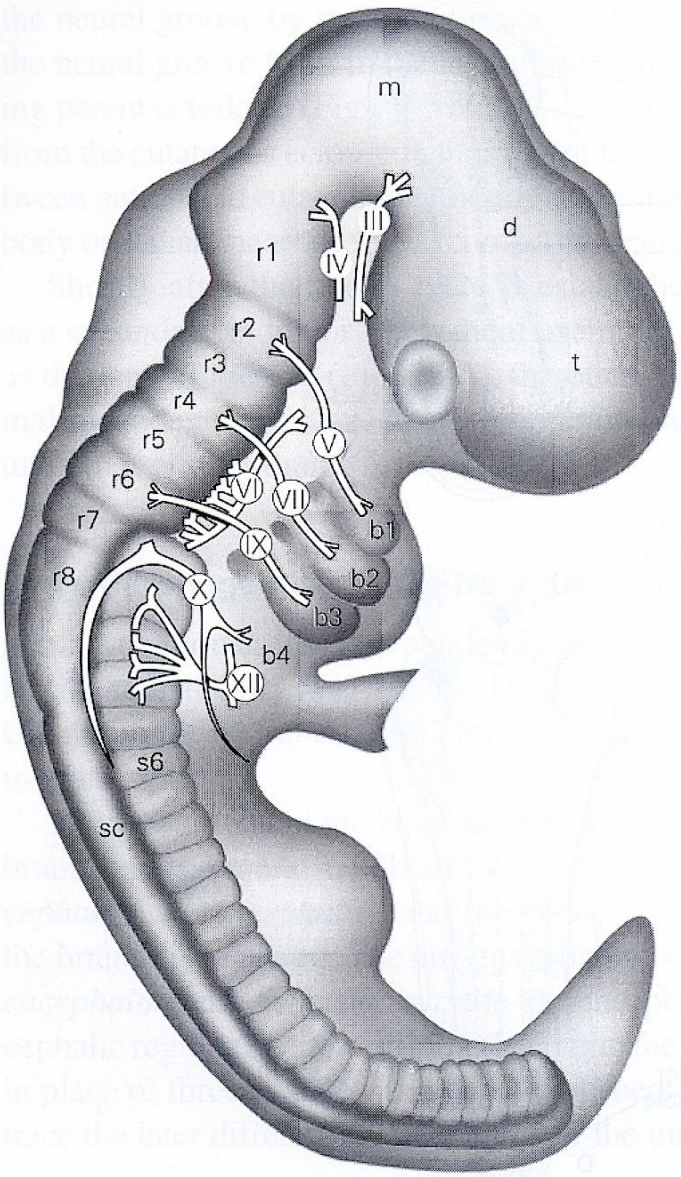
Knockout mutant

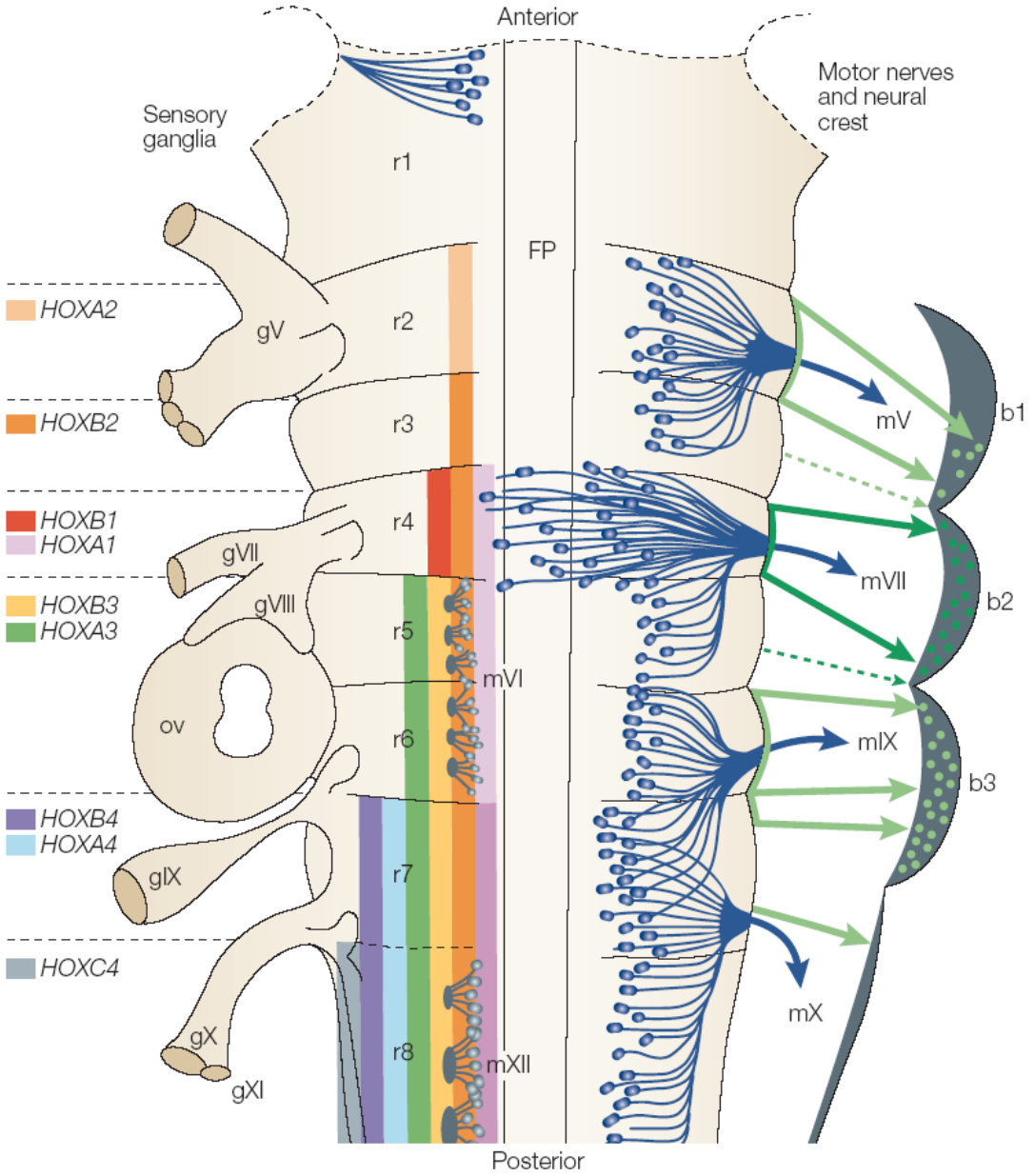




The « Evo-Devo » connection

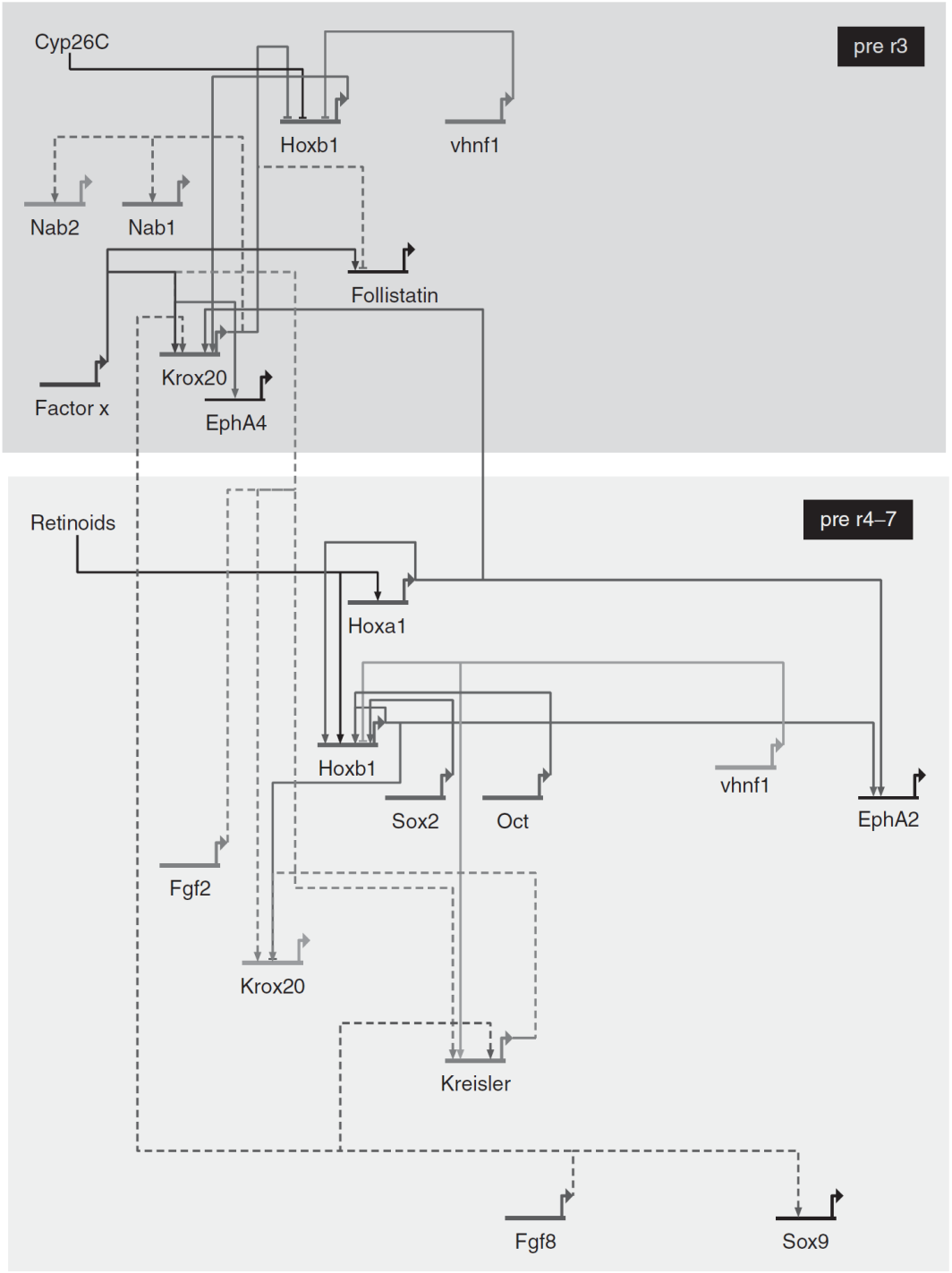
Hox genes and neural development





Signaling molecules

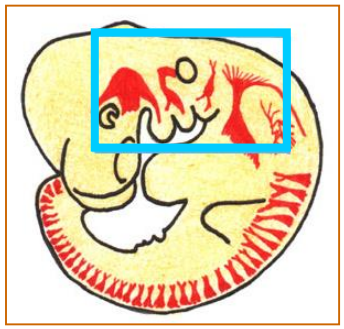
Transcription factors

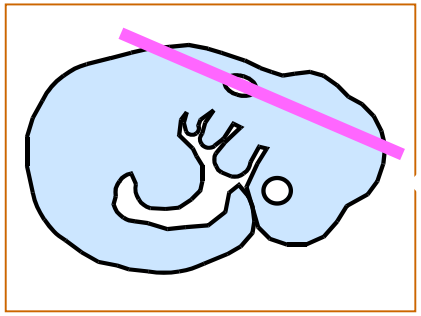


Tumpel et al, 2009

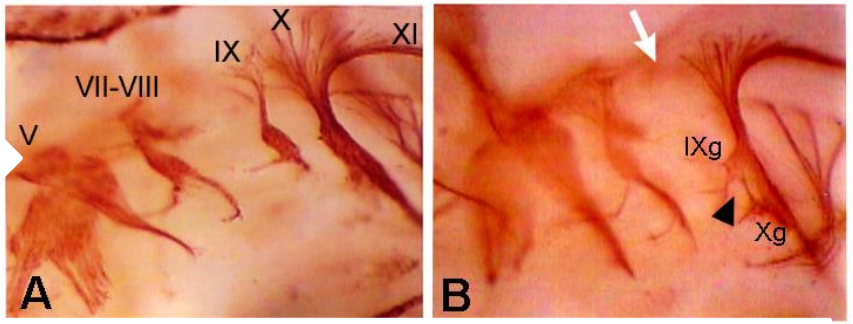
WT

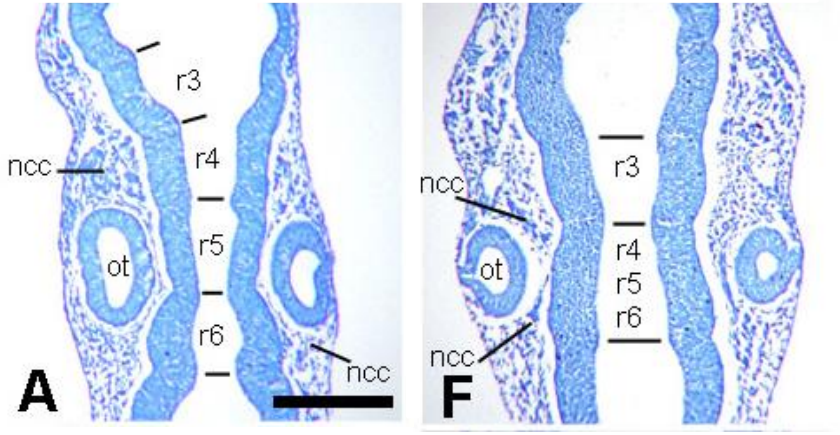
Hoxa1$^{WM\text{-}AA}$





Remacle *et al.*, 2004





Cranial nerves :
reduction or absence
of nerves VIII, IX and X

Hindbrain patterning :
loss of rhombomeres
fusion of r4-r5-r6

Clinical characterization of the HOXA1 syndrome BSAS variant

T.M. Bosley, MD
M.A. Salih, MD
I.A. Alorainy, MD
D.T. Oystreck, OC(C)
M. Nester, PhD

ABSTRACT

Background: The Bosley-Salih-Alorainy syndrome (BSAS) variant of the congenital human *HOXA1* syndrome results from autosomal recessive truncating *HOXA1* mutations. We describe the currently recognized spectrum of ocular motility, inner ear malformations, cerebrovascular anomalies, and cognitive function.

Neurology® 2007;69:1245-1253

The «HOXA1» syndrome

- Homozygous 175-176insG
- 84C>G Y28X
- 76C>T R26X

Figure 1 Variability of ocular alignment and motility

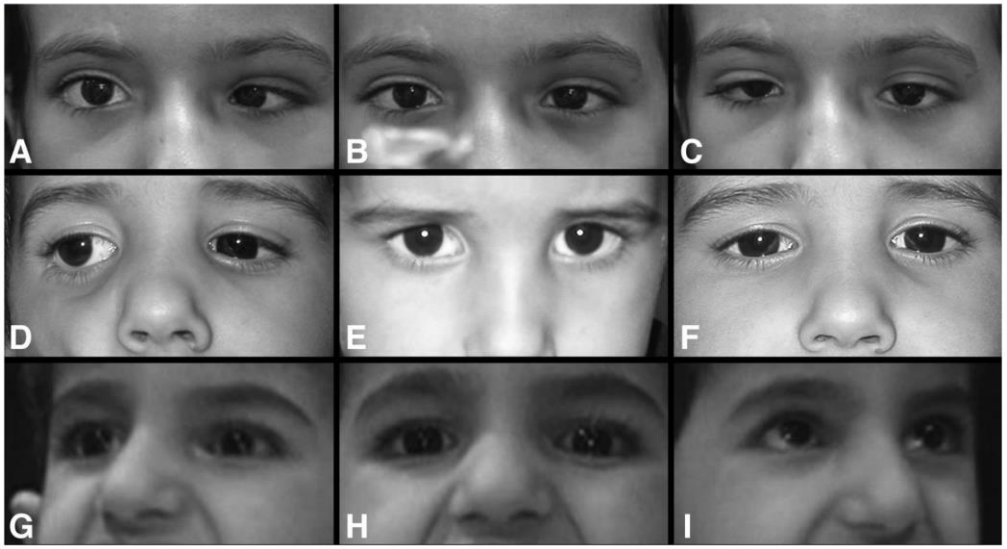
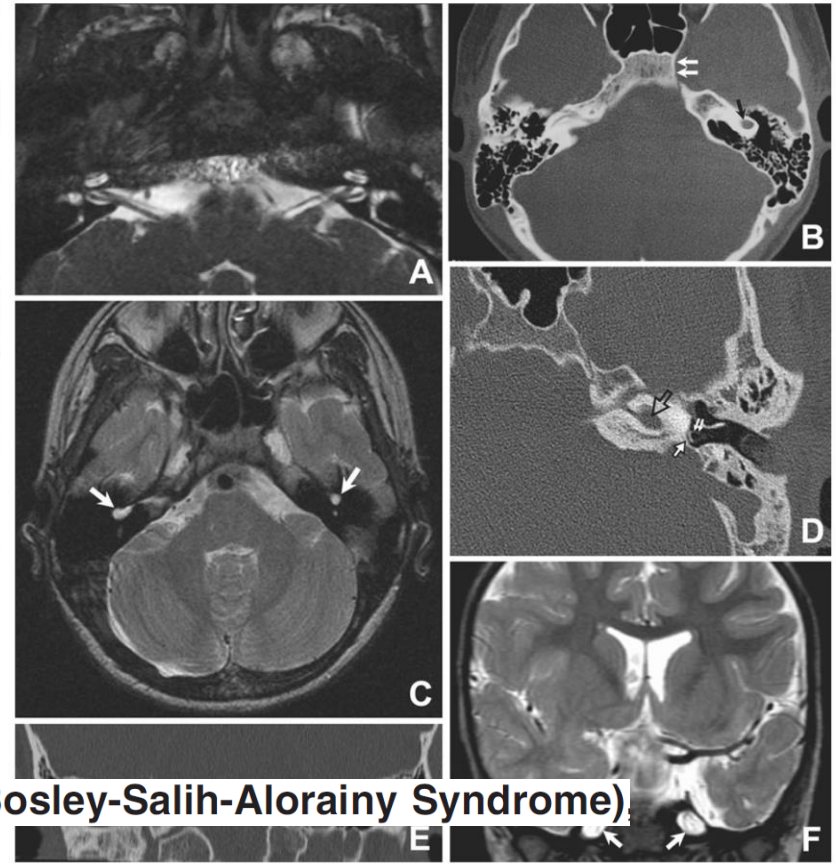


Figure 2 Variability of skull base neuroimaging

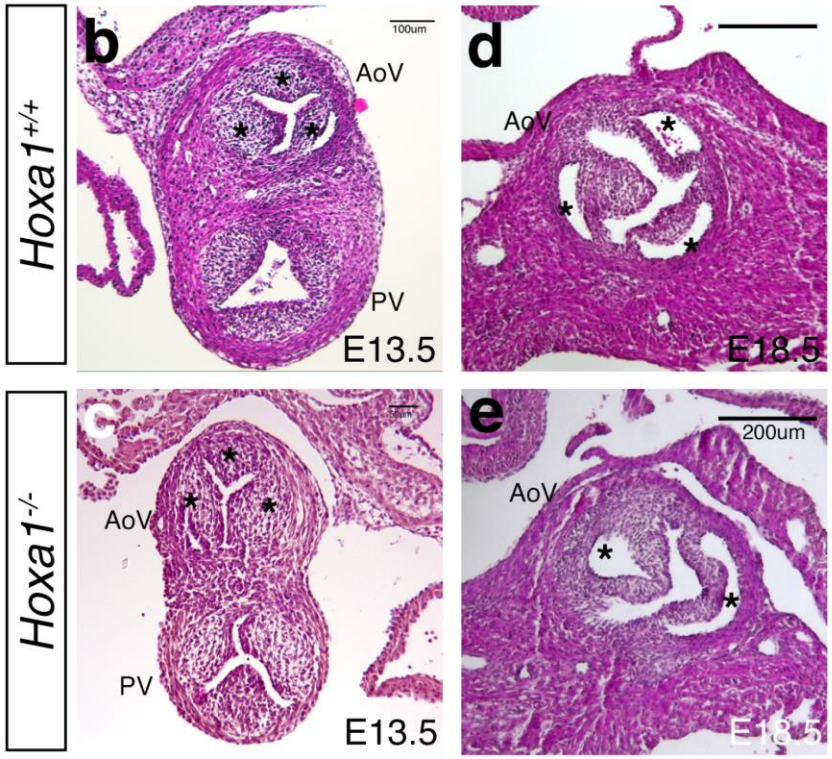


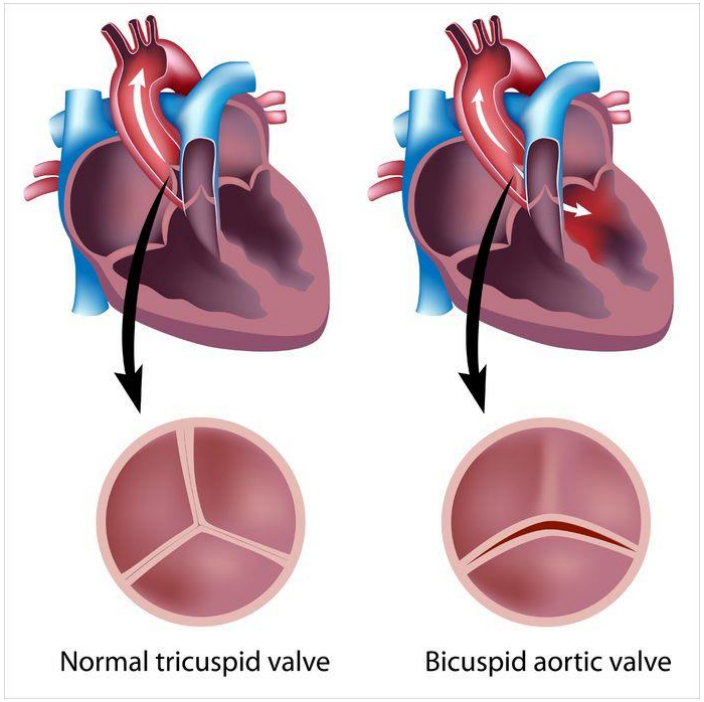
+ frequent Autistic spectrum disorder

(Athabascan Brainstem Dysgenesis Syndrome, Bosley-Salih-Alorainy Syndrome)

a

Genotype	Total mice at E18.5	Normal AoV	Abnormal AoV	AoV morphology
WT	10	10	0	-
Hoxa1$^{neo/neo}$	11	0	3	3 BAV (27%)





The *Hoxa1* KO mice display Bicuspid Aortic Valve (BAV)

Makki and Capecchi, 2012

Journal of the American College of Cardiology
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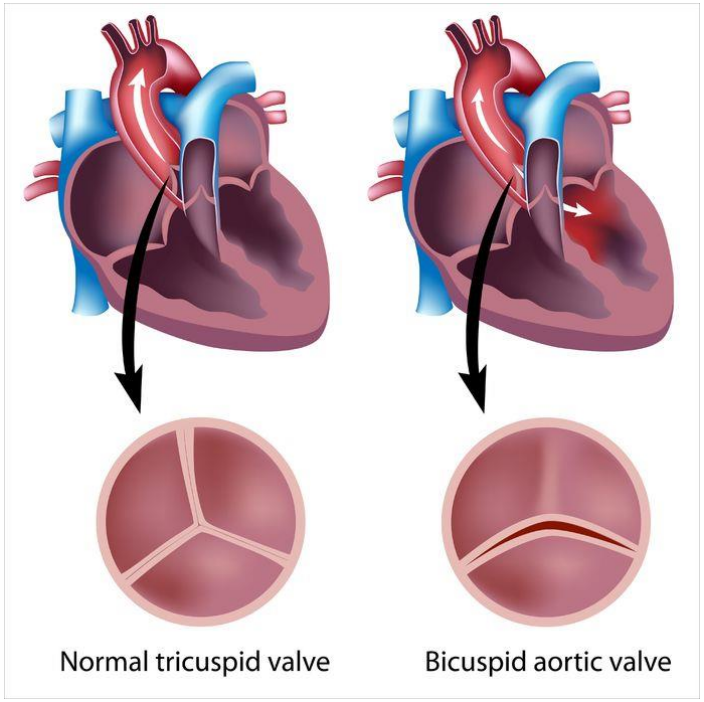
Published by Elsevier Inc.

Vol. 44, No. 1, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.03.050

Bicuspid Aortic Valve Is Heritable

Linda Cripe, MD,* Gregor Andelfinger, MD,* Lisa J. Martin, PhD,† Kerry Shooner, MS,*
D. Woodrow Benson, MD, PhD*

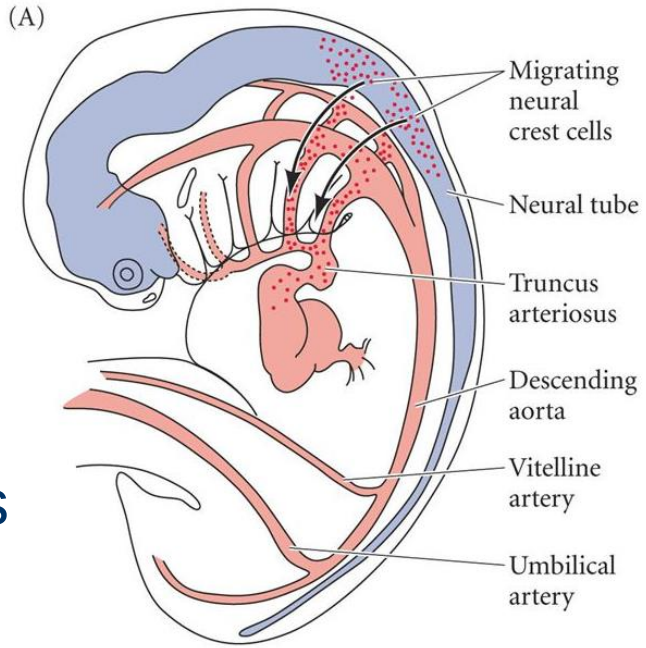
→ 89% of heritability.

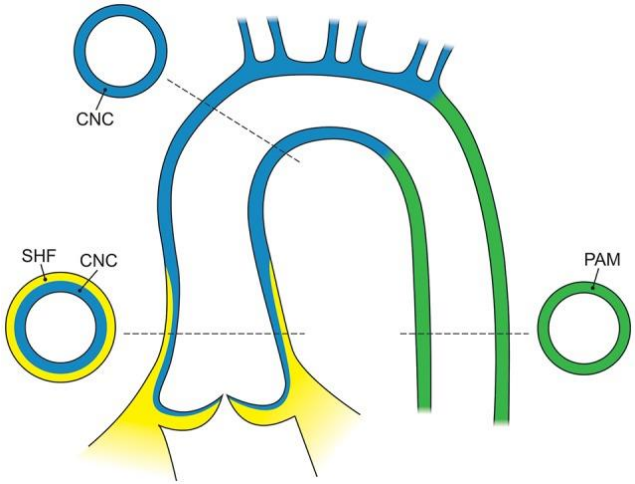


Bicuspid Aortic Valve: 2 ‰ for the girls and 7 ‰ for the boys.

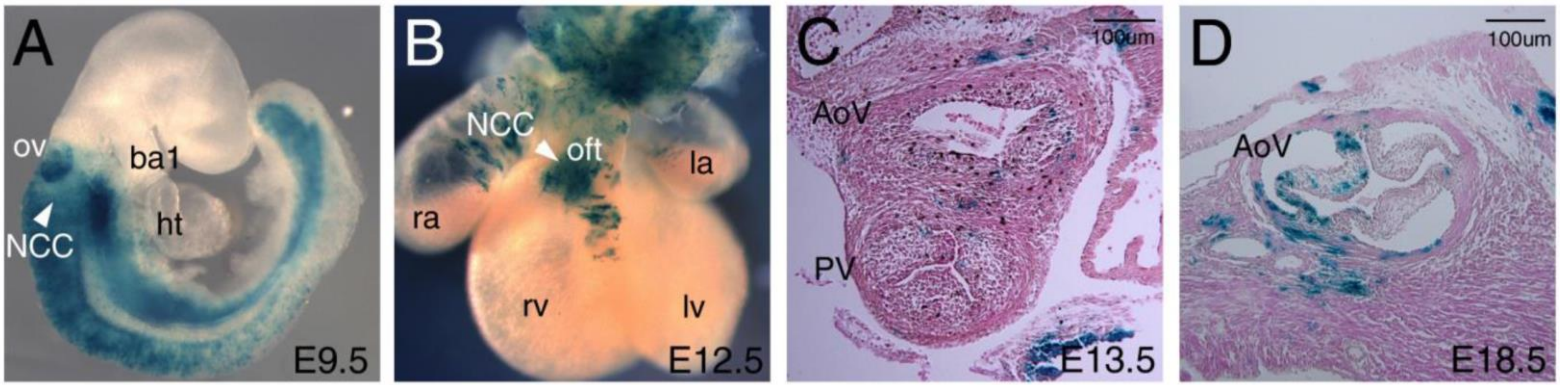
Most common cardiovascular malformation.

Neural crest cells





The *Hoxa1* cell lineage colonizes the developing heart



Gilbert, S, et al., *Developmental Biology*, *8th Ed,* Sinauer, 2006

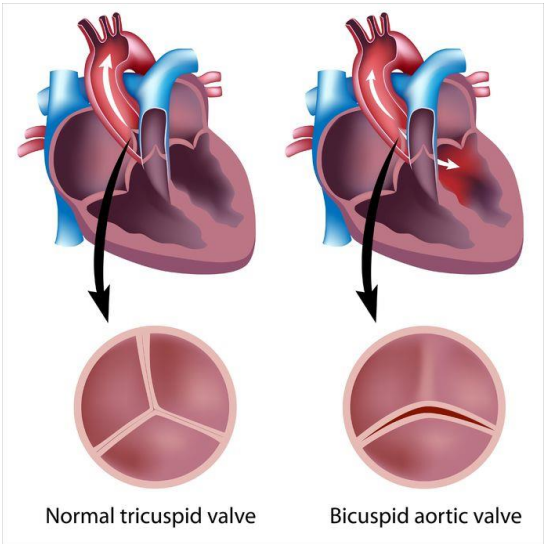
Pinard, A., PhD Thesis, 2016

Yassine et al., 2017

The HOXA1 protein

BAV patients

11 HisA — HHHHHHHHHHH
11 HisG — HHHHHHHHHRH
9 HisA — HHHHHHHHH
9 HisG — HHHHHHHRH
7 HisG — HHHHHRH



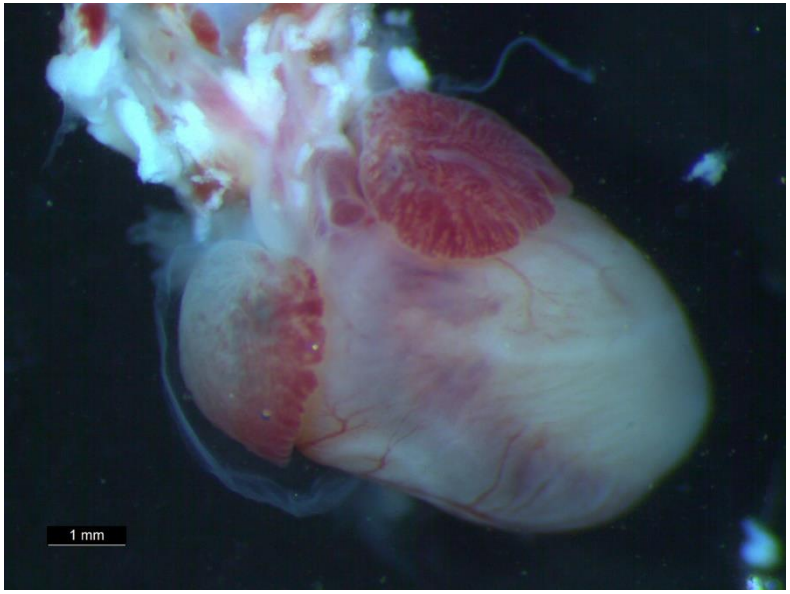
33 His tract variants / 338 patients (Gnomad: 0,000778)

Odelin et al., 2023

Marseille Medical Genetics

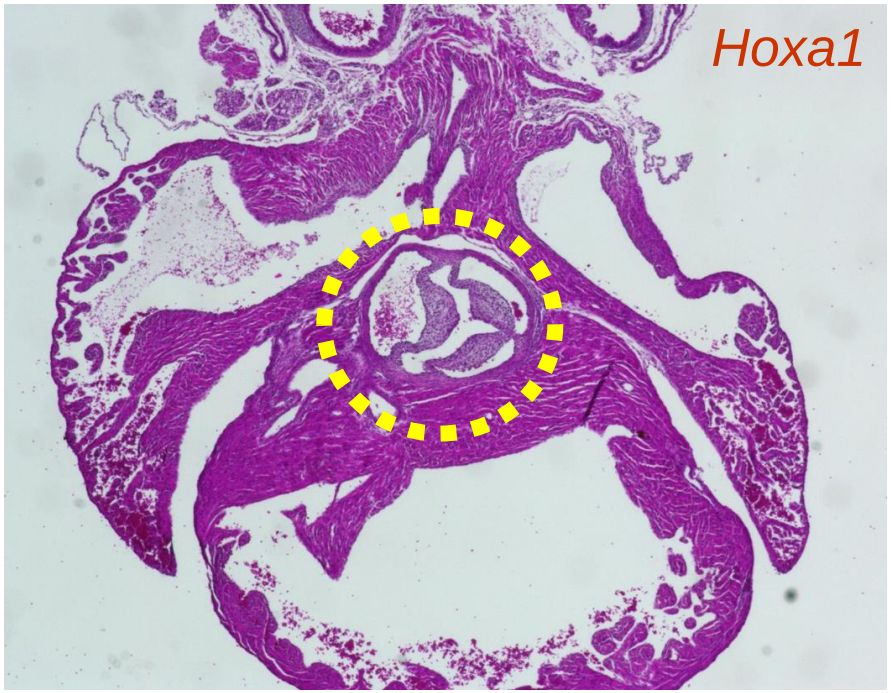
Hoxa1$^{8\text{-}His}$
Hoxa1$^{10\text{-}His}$
Hoxa1$^{12\text{-}His}$
Hoxa1$^{13\text{-}His}$

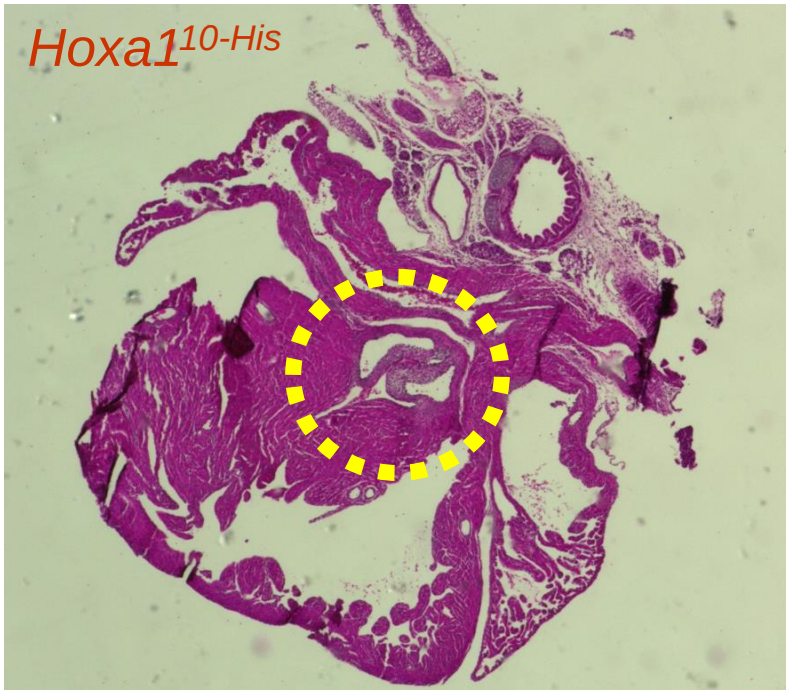
alleles



The His mutant versions of HOXA1

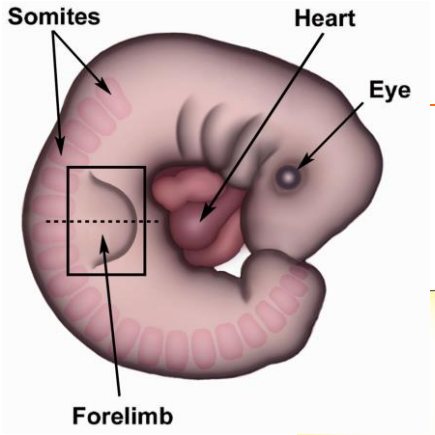
provoke valvular malformations *in vivo*

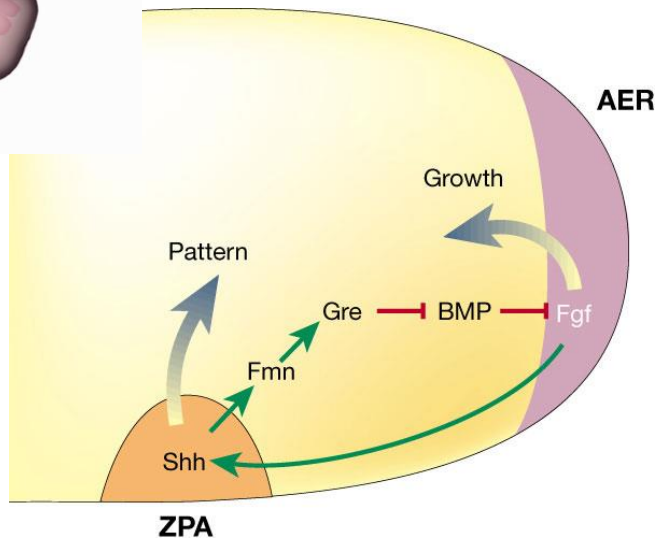


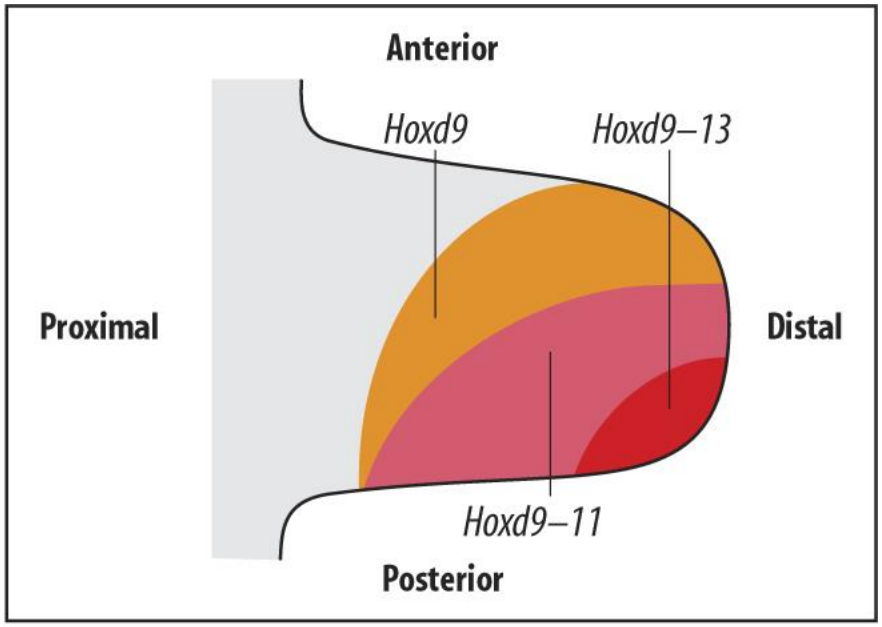


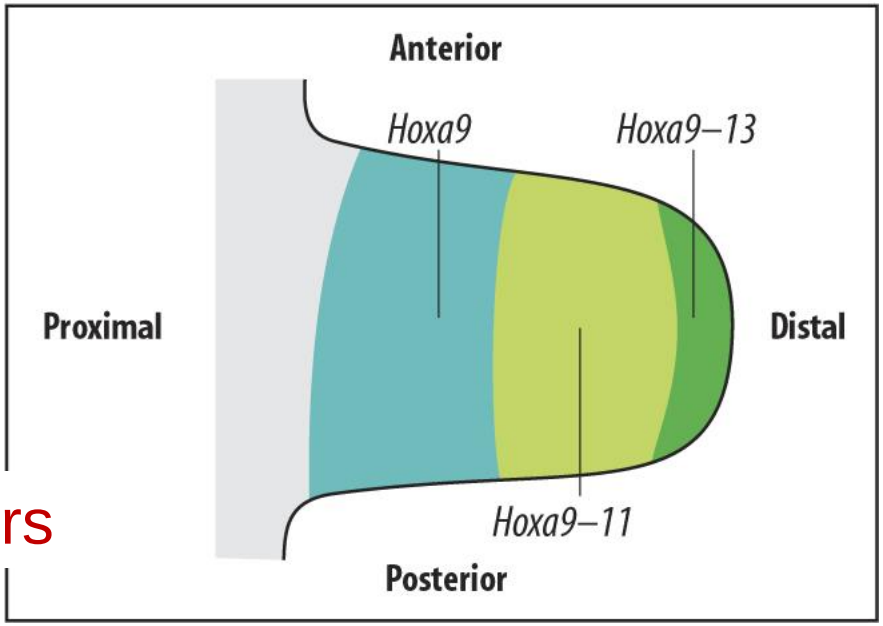
Odelin et al., 2023

Hox genes the limbs









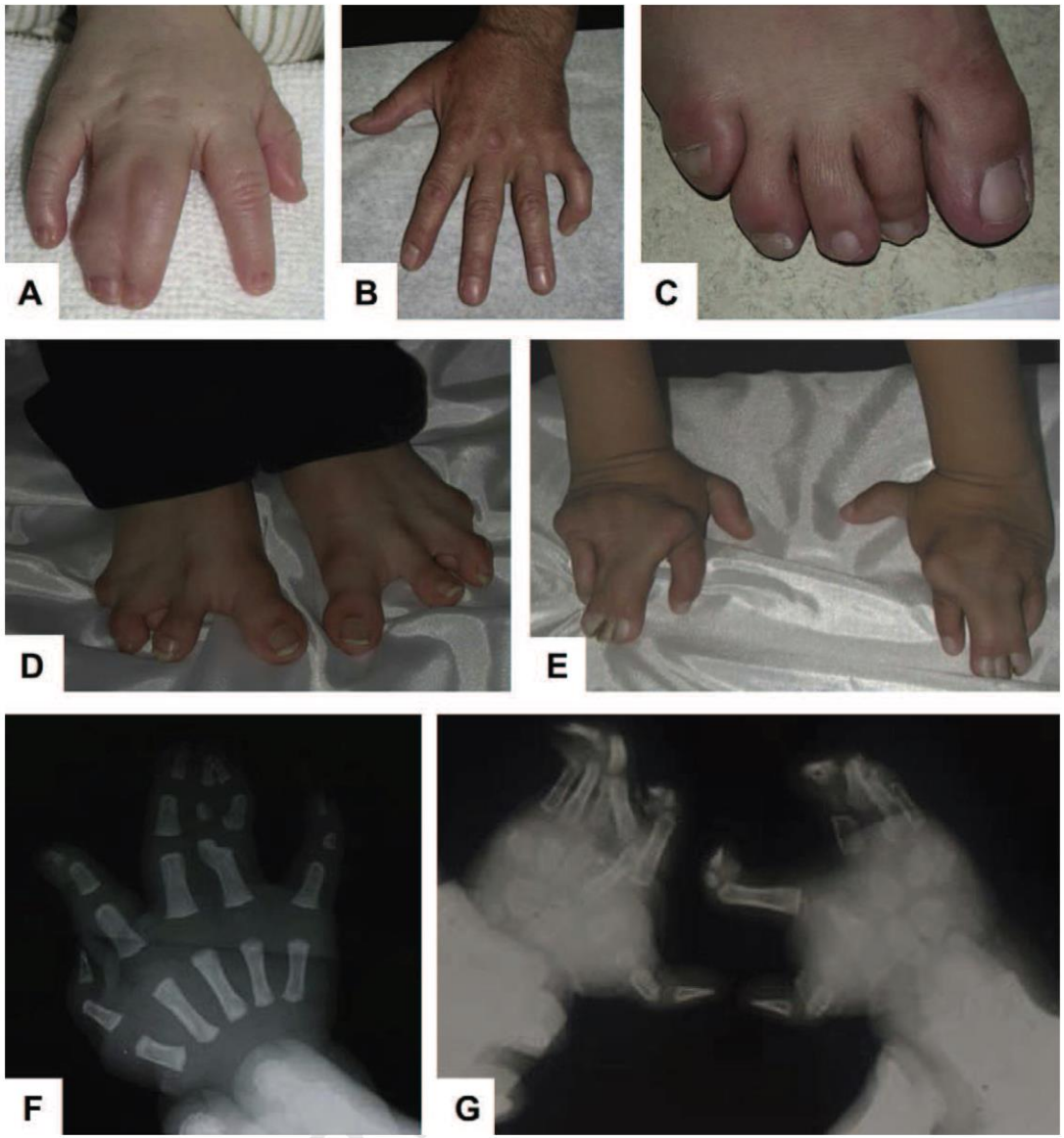
Signaling molecules

Transcription factors

Oberg, 2019

Synpolydactyly

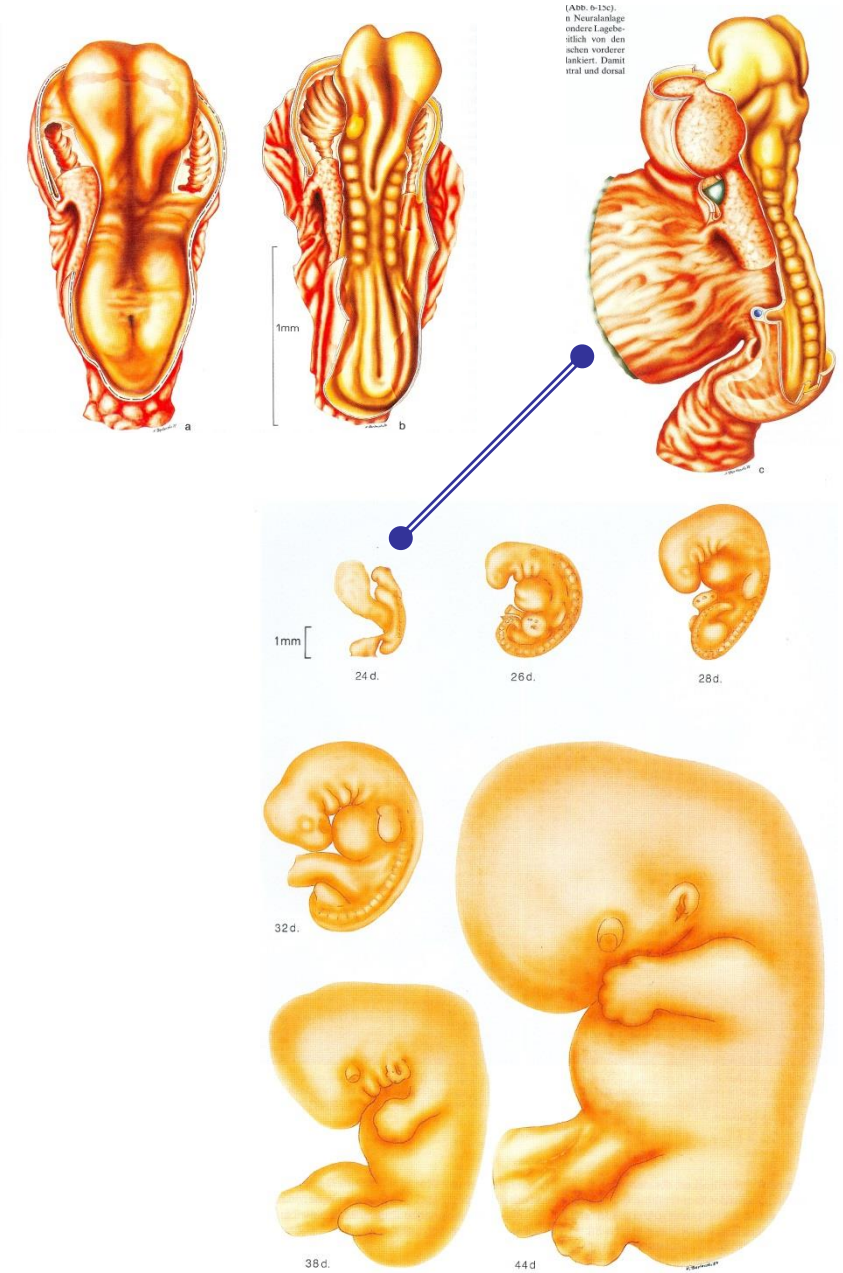
N. Brison et al. / European Journal of Medical Genetics xxx (2011) 1–7

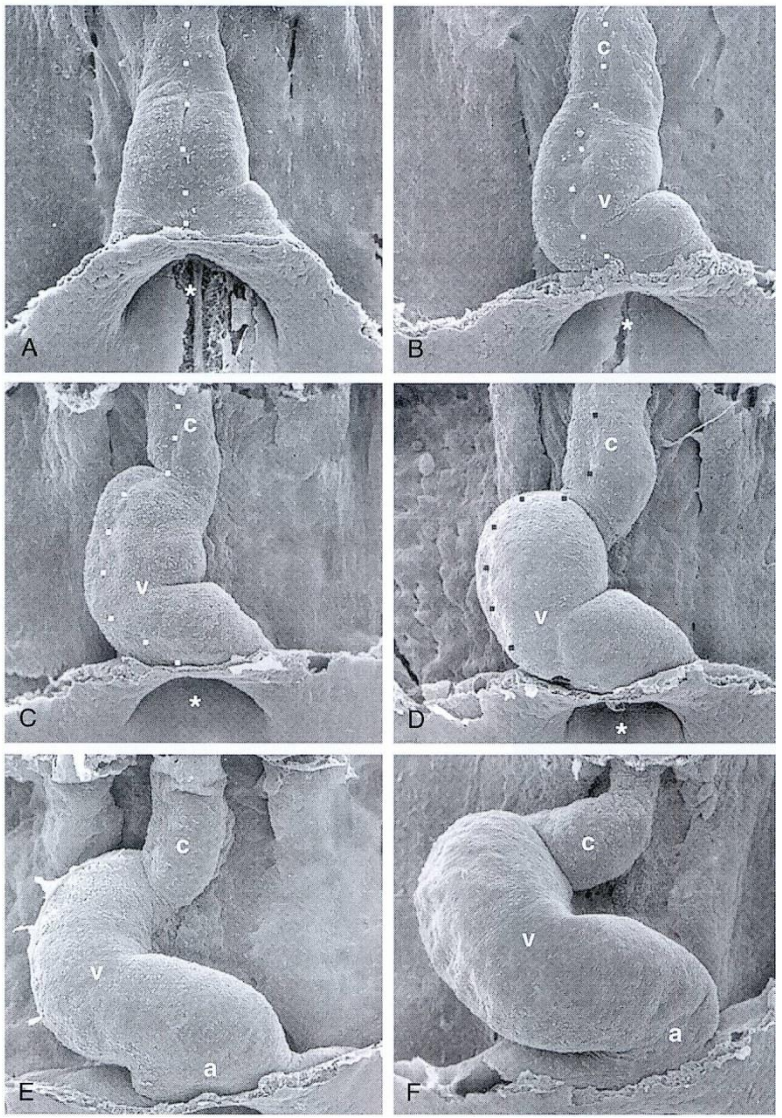


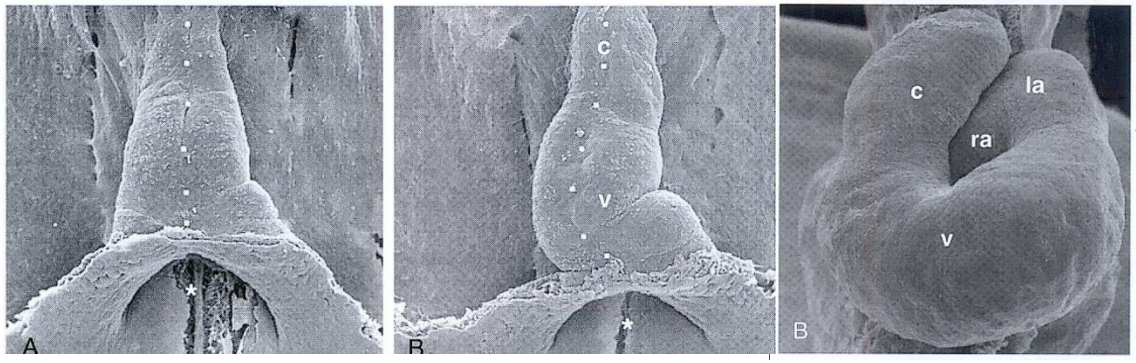
HOXD13

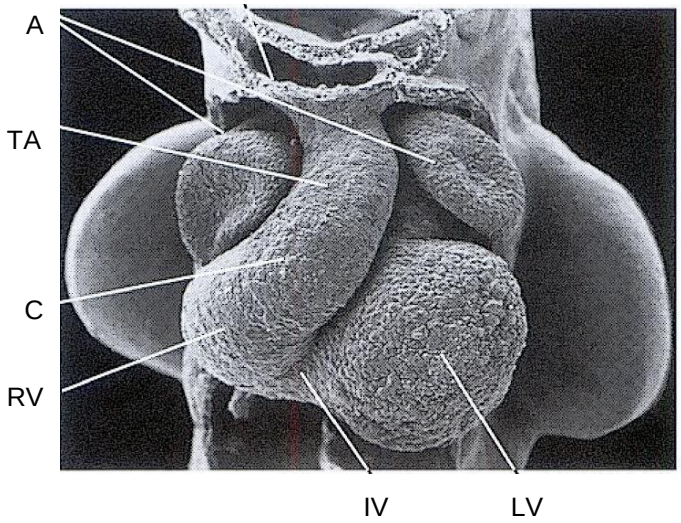
poly-alanine tract expansion

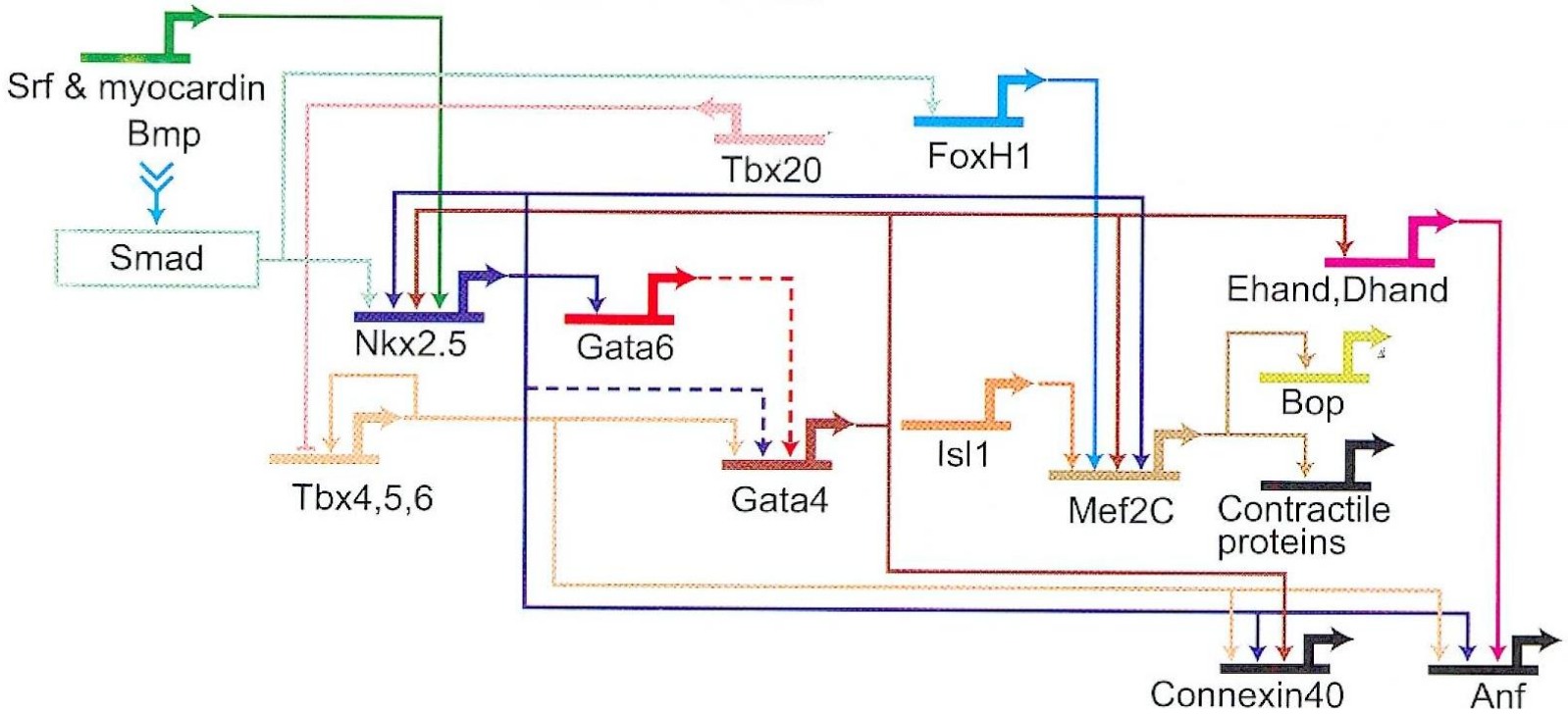
Heart development











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doi:10.1016/S0735-1097(03)01082-9

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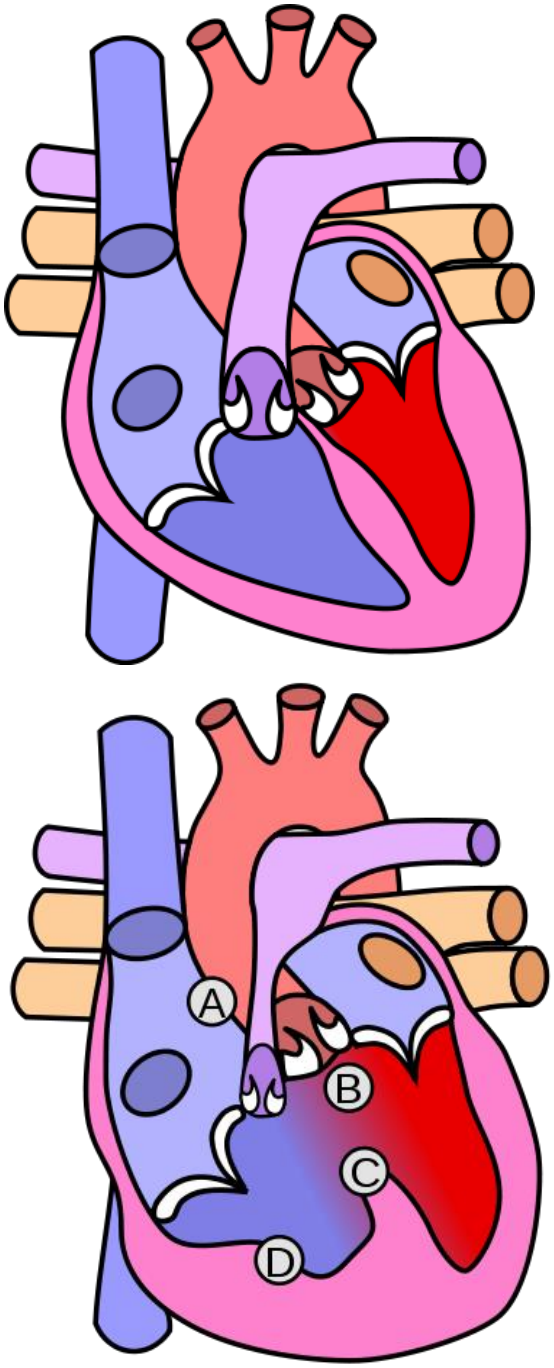
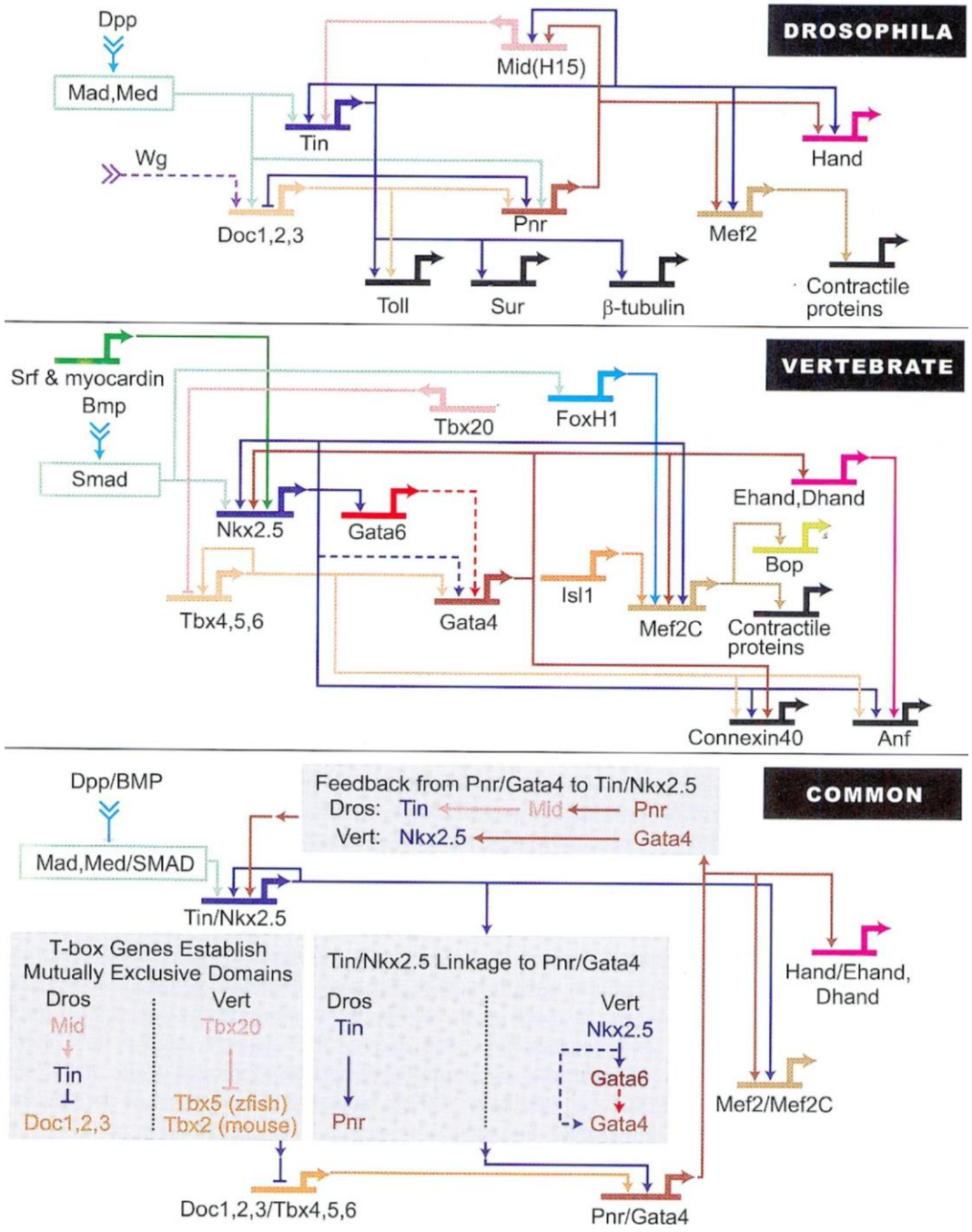
NKX2.5 Mutations in Patients With Congenital Heart Disease

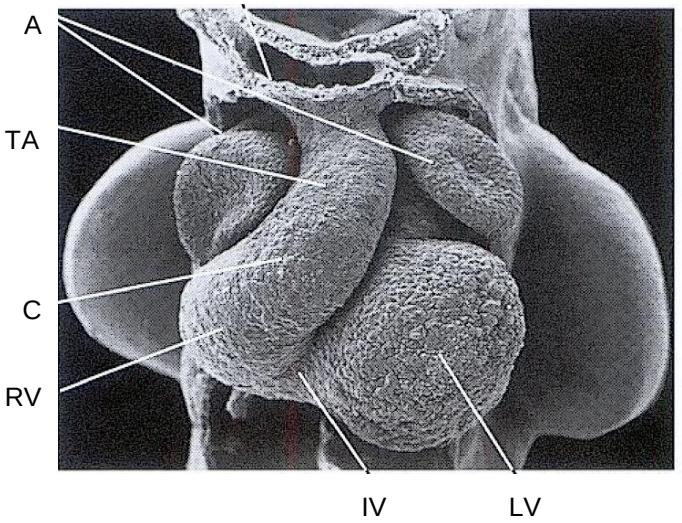
Doff B. McElhinney, MD,* Elizabeth Geiger, MS,* Joshua Blinder, BS,* D. Woodrow Benson, MD, PHD,† Elizabeth Goldmuntz, MD, FACC*
Philadelphia, Pennsylvania; and Cincinnati, Ohio

Cardiovascular Anomaly	# Patients Genotyped	# With Mutations
Secundum atrial septal defect	71	3 (4%)
Ebstein's malformation	7	0
Conotruncal anomalies		
Tetralogy of Fallot*	201	9 (4%)
D-transposition of the great arteries	86	0
Double-outlet right ventricle	31	1 (3%)
Interrupted aortic arch	23	1 (4%)
Truncus arteriosus	22	1 (4%)
L-transposition of the great arteries	7	1 (14%)
Subtotal (conotruncal anomalies)	370	13 (4%)
Left-sided lesions		
Hypoplastic left heart syndrome	80	1 (1%)
Coarctation of the aorta	59	1 (2%)
Valvar aortic stenosis	21	0
Subtotal (left-sided lesions)	160	2 (2%)
Total	608	18 (3%)

*Includes 134 consecutively recruited patients with tetralogy of Fallot described in the reports by Goldmuntz et al. (4) (n = 114) and Benson et al. (2) (n = 20) seven of whom had *NKX2.5* mutations.







The « Evo-Devo » connection

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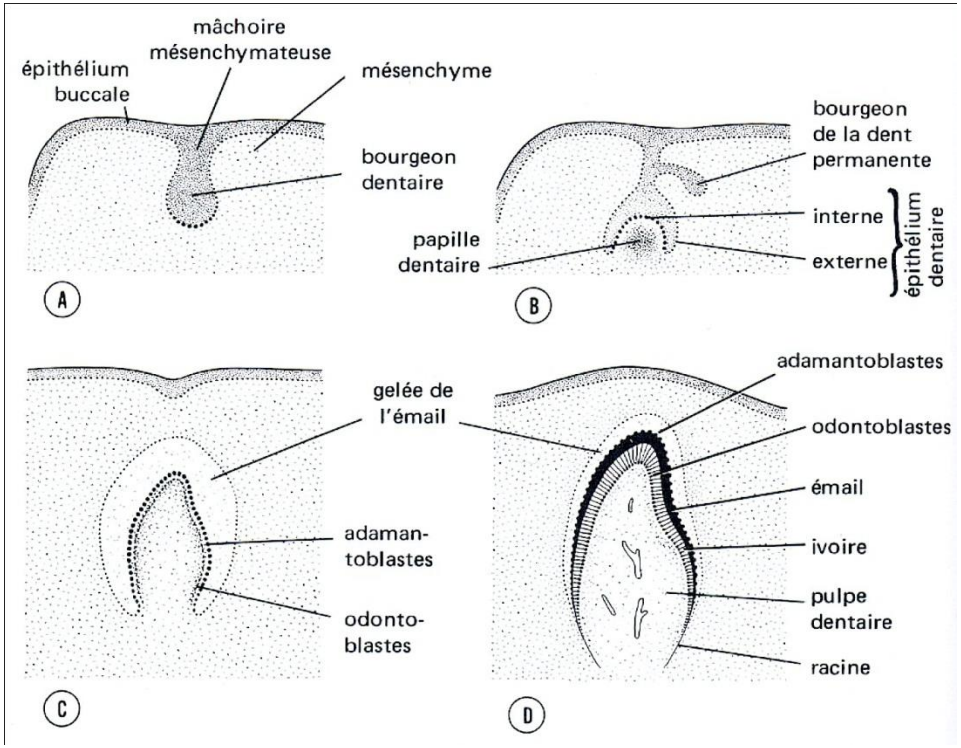
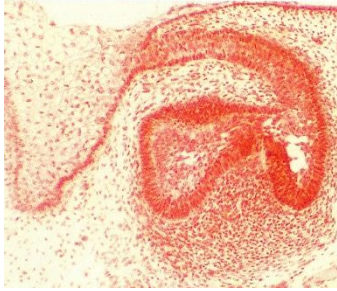
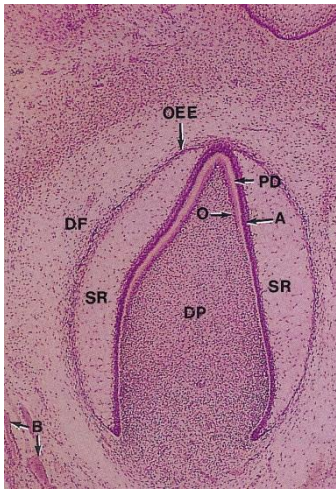
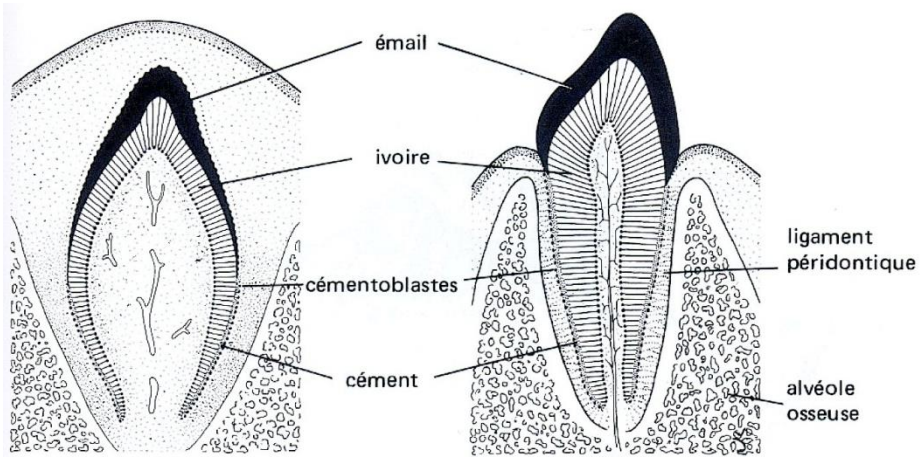
© Inra , centre de Tours

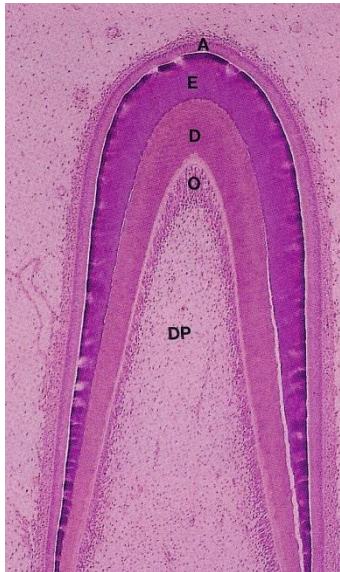
Teeth

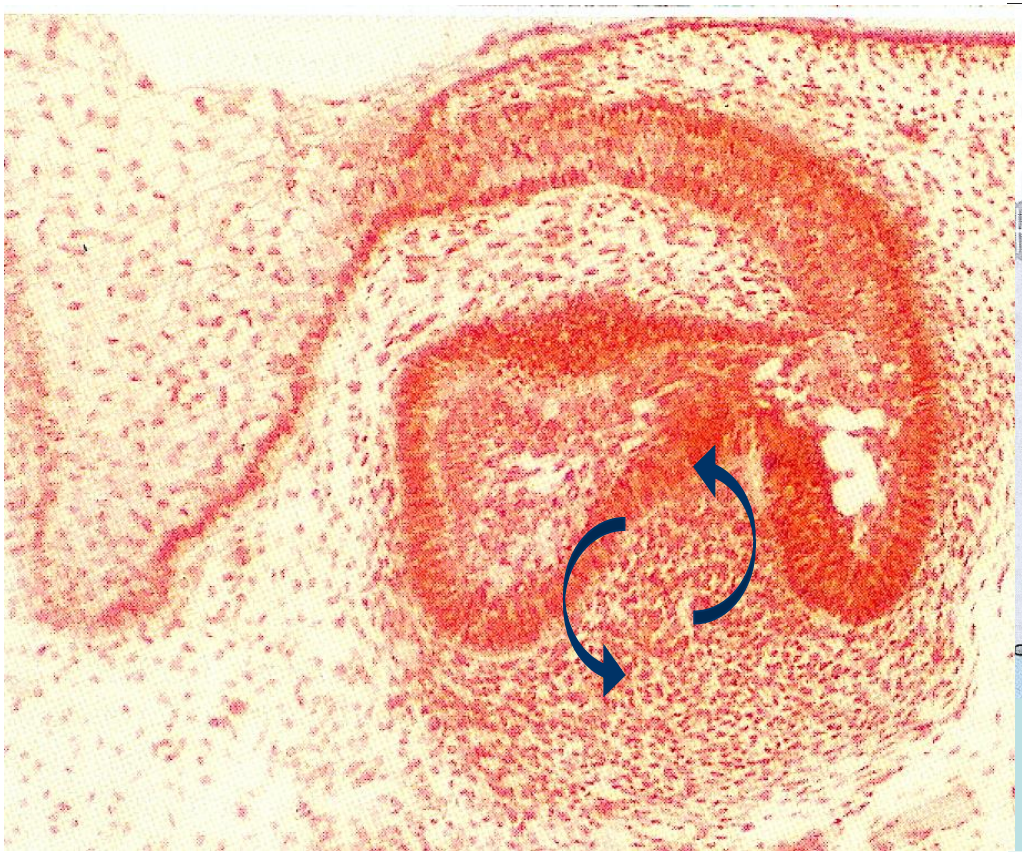


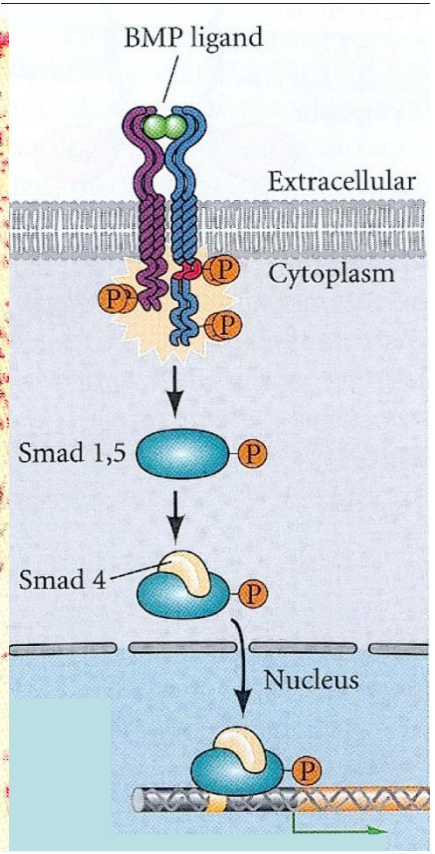


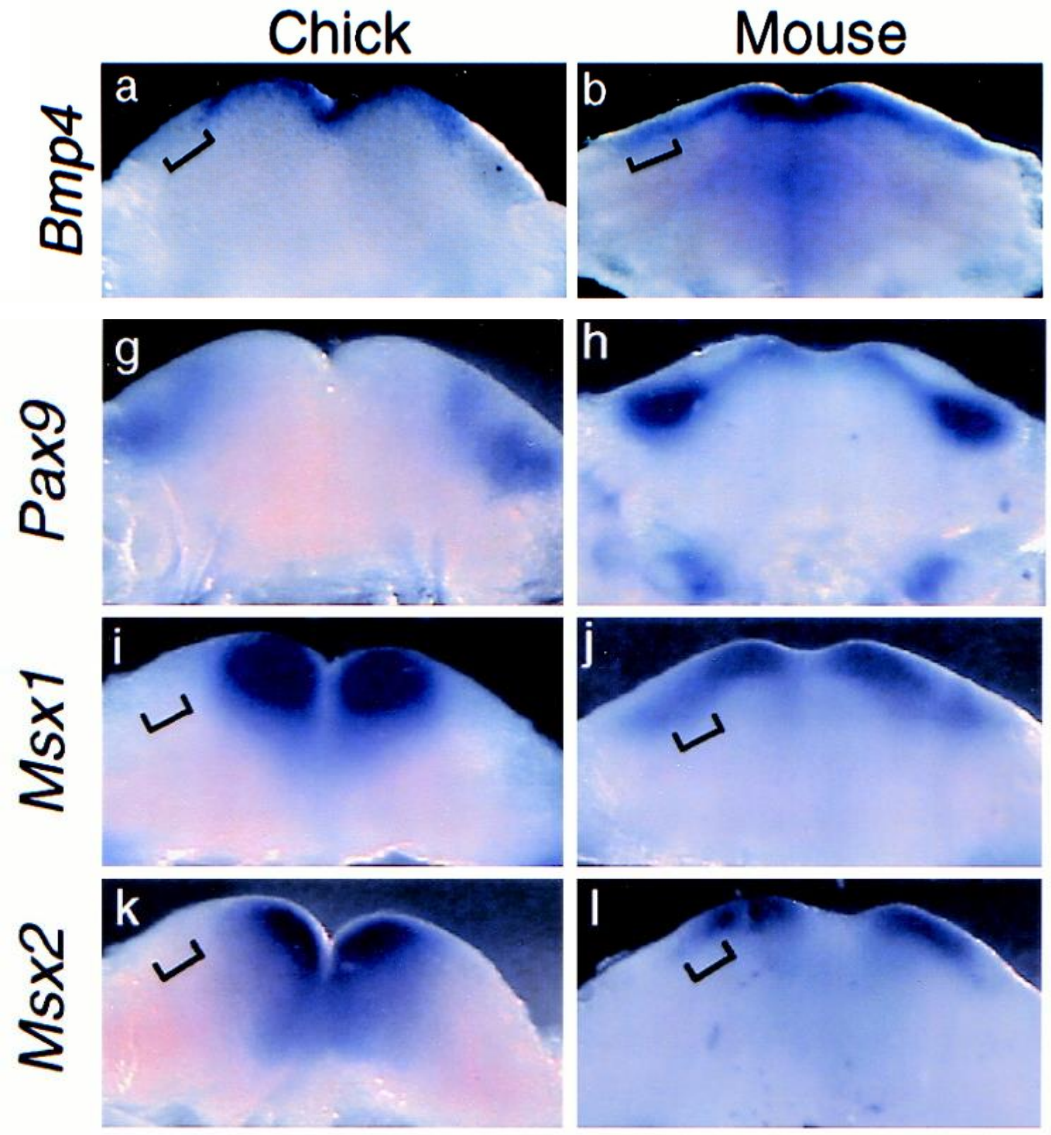


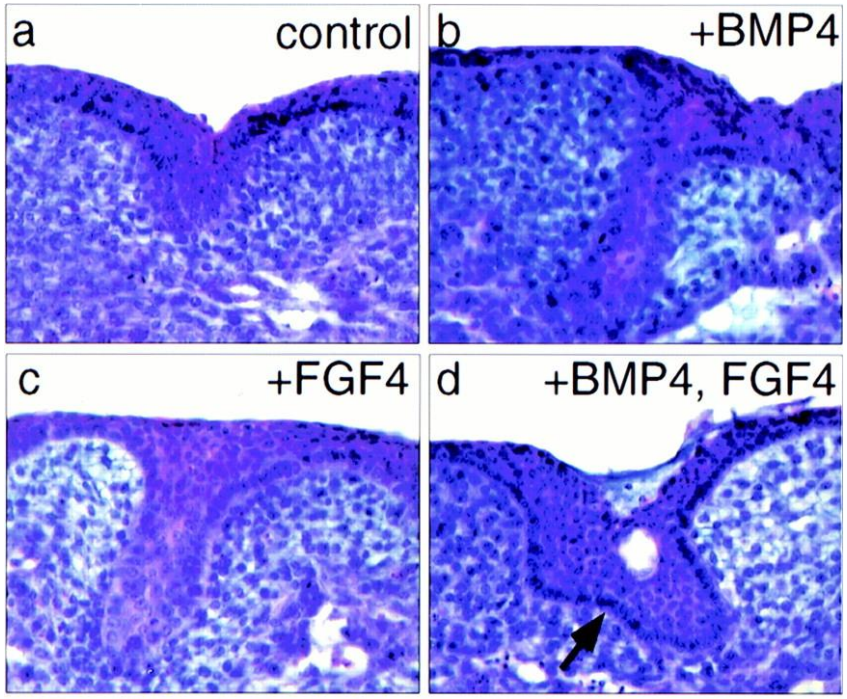










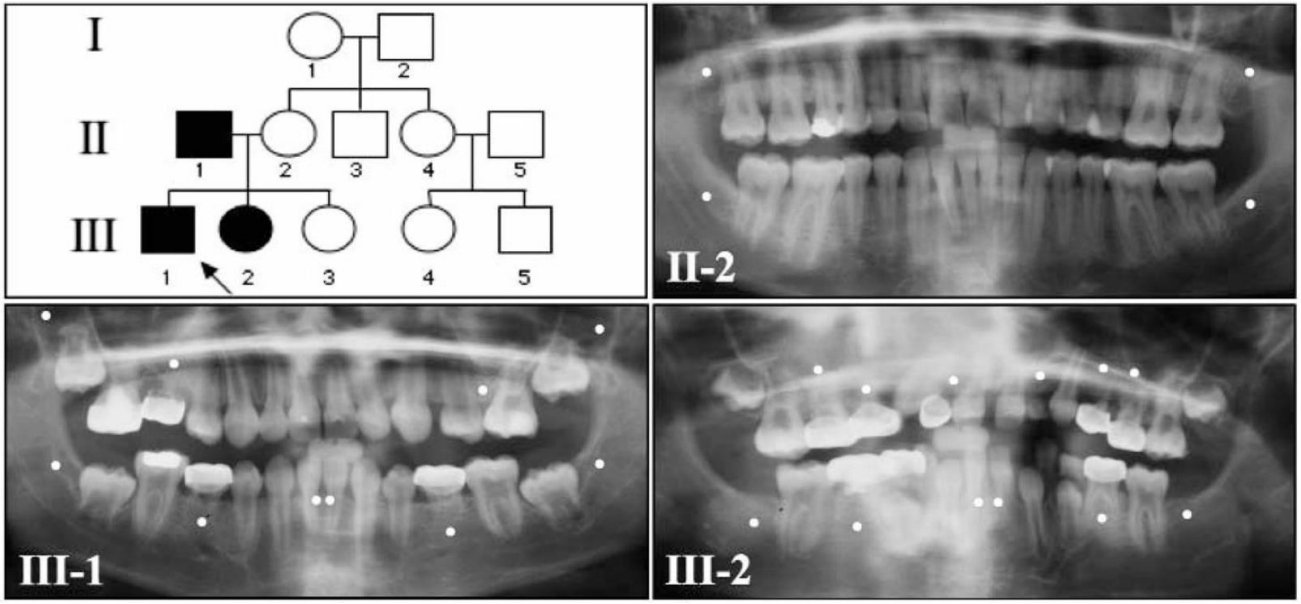


The « Evo-Devo » connection

J Dent Res. 2006 March ; 85(3): 267–271.

Novel *MSX1* Frameshift Causes Autosomal-dominant Oligodontia

J.-W. Kim[1,2], **J.P. Simmer**[1], **B.P.-J. Lin**[3], and **J.C.-C. Hu**[1,*]

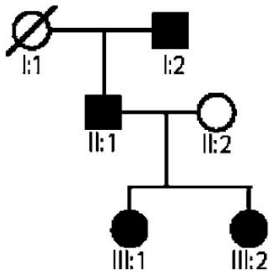


European Journal of Human Genetics (2006) 14, 403–409

Molecular characterization of a novel *PAX9* missense mutation causing posterior tooth agenesis

Hitesh Kapadia[1,2], Sylvia Frazier-Bowers[1,3], Takuya Ogawa[1] and Rena N D'Souza*[,1]

a



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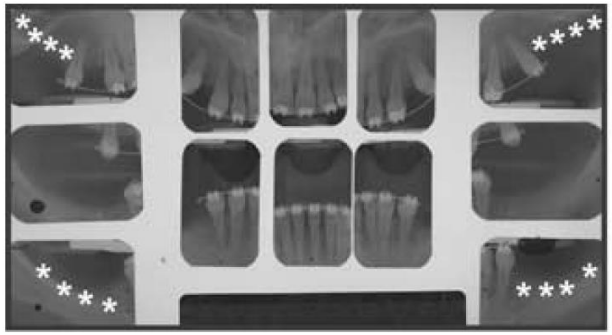

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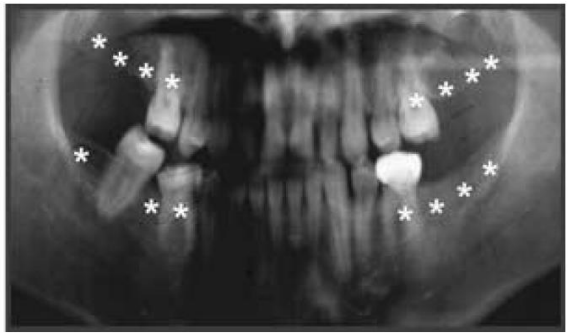
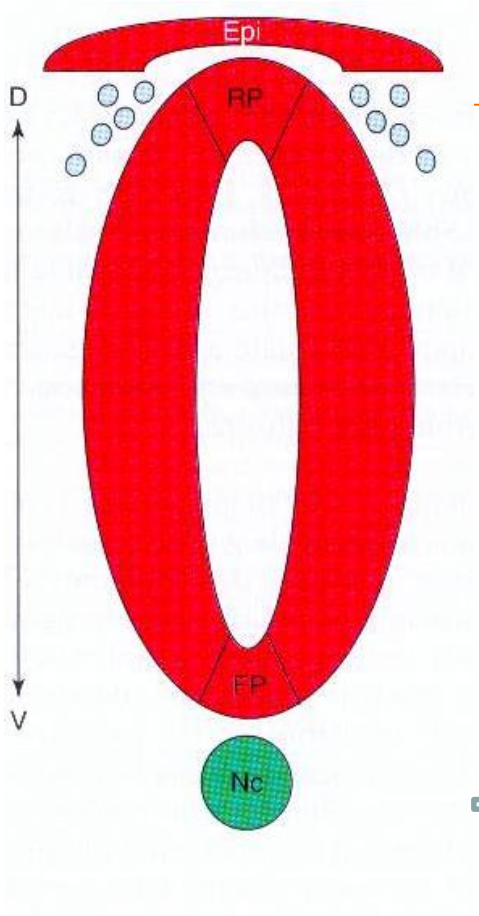
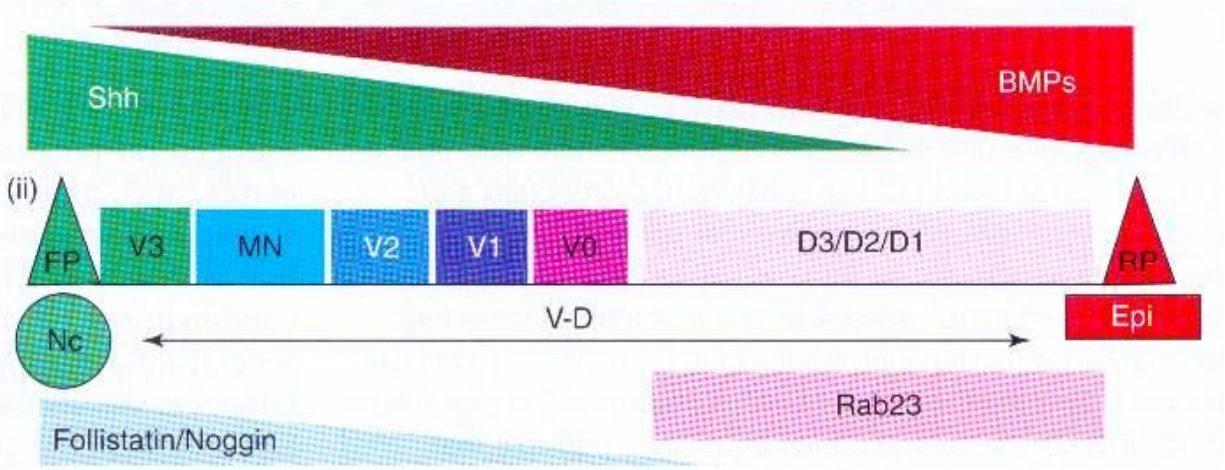


d

	Right								Left							
	M			P		C	I		I	C	P		M			
Maxilla	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8
Mandible	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8
III:1	*	*	*	*									*	*	*	*
	*	*	*	*									*	*	*	*
III:2	*	*	*	*									*	*	*	*
	*		*	*									*	*	*	*

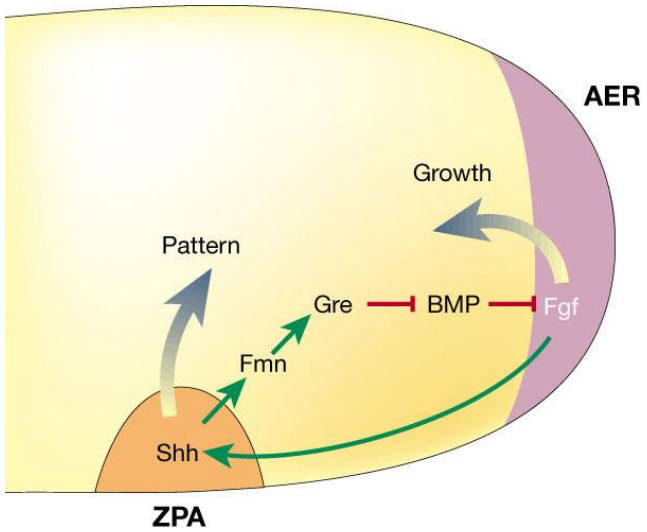
Hedgehog signalling





Neural tube

Limb bud



Hedgehog Signalling Pathway

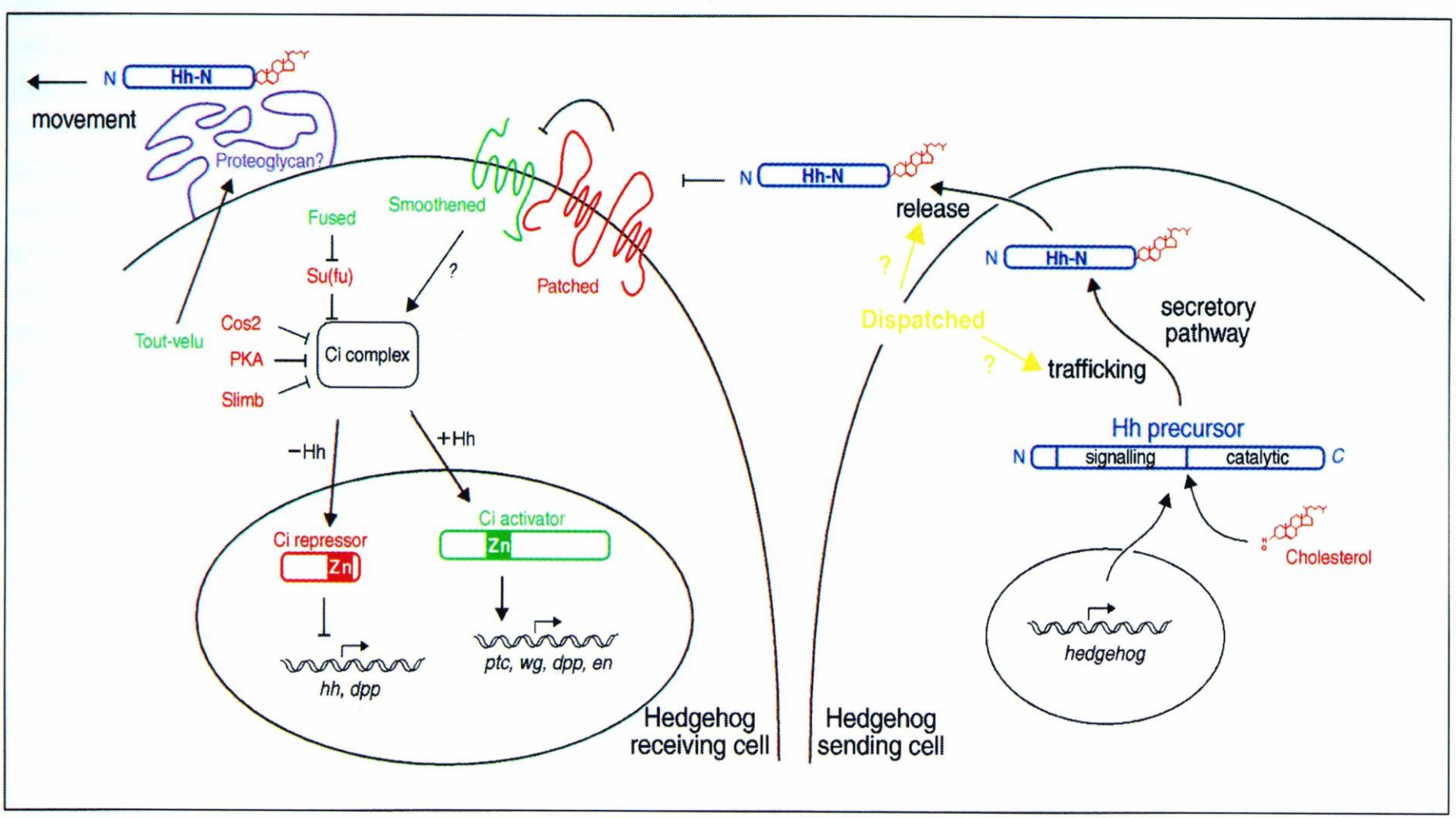
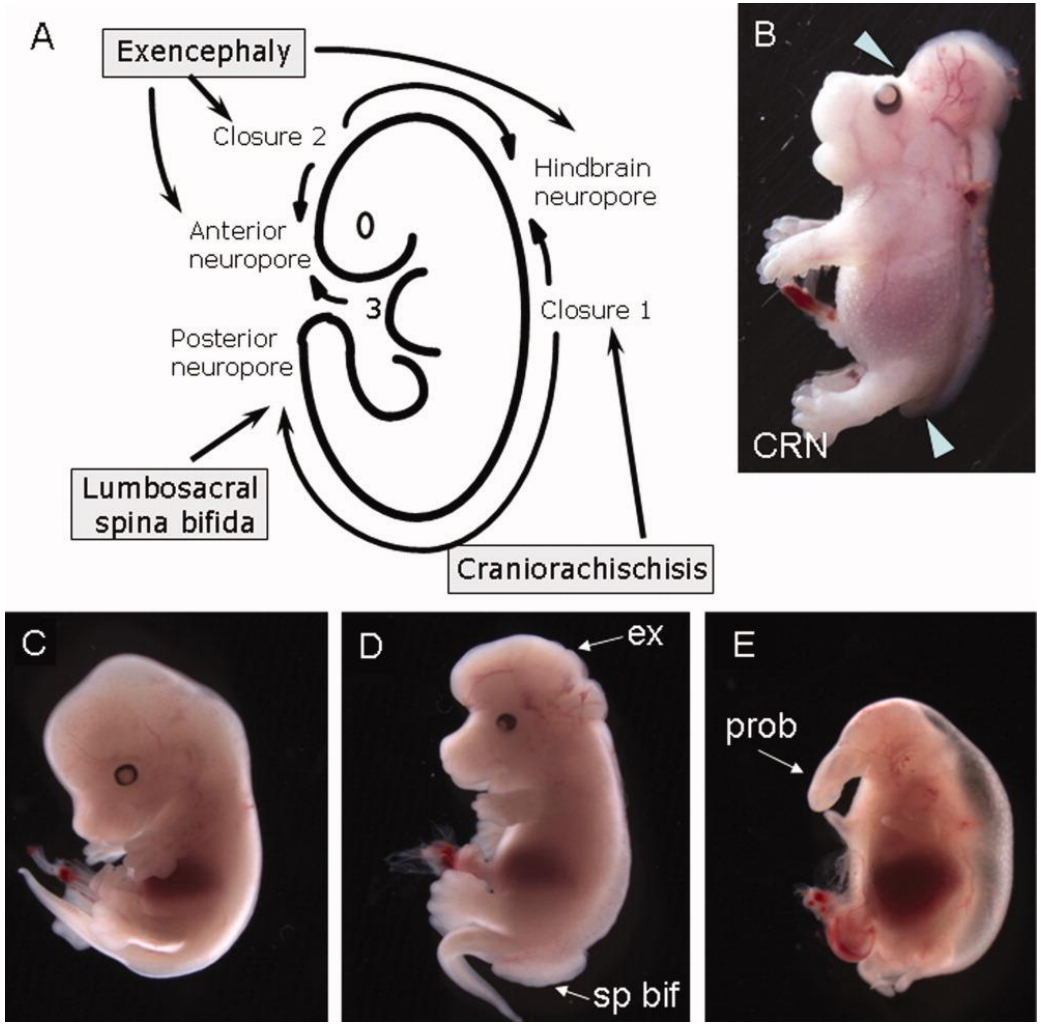


Figure 1. Schematic Representation of Hedgehog Signaling Pathway

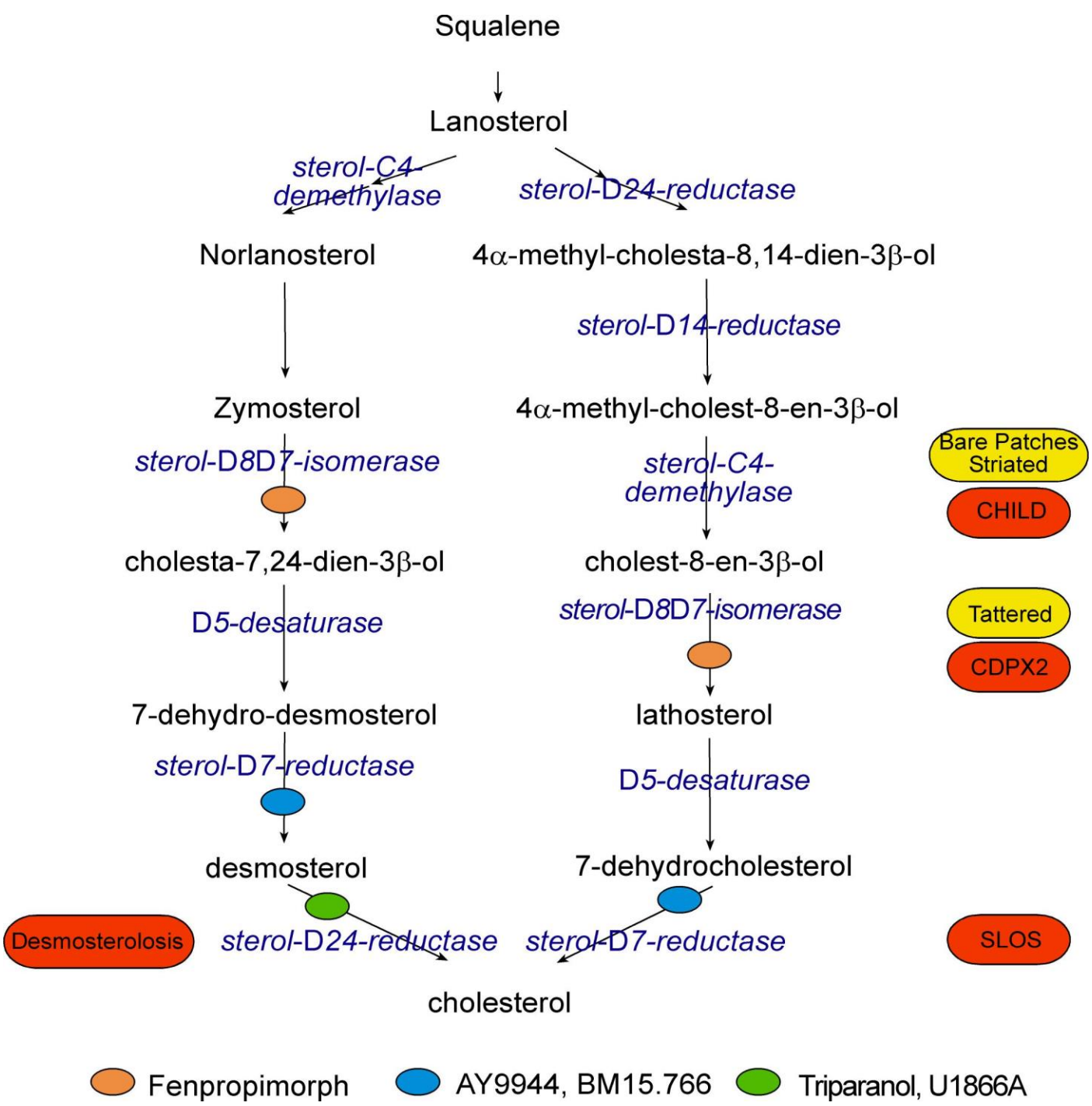
Red components act negatively and blue components positively. See text for details.

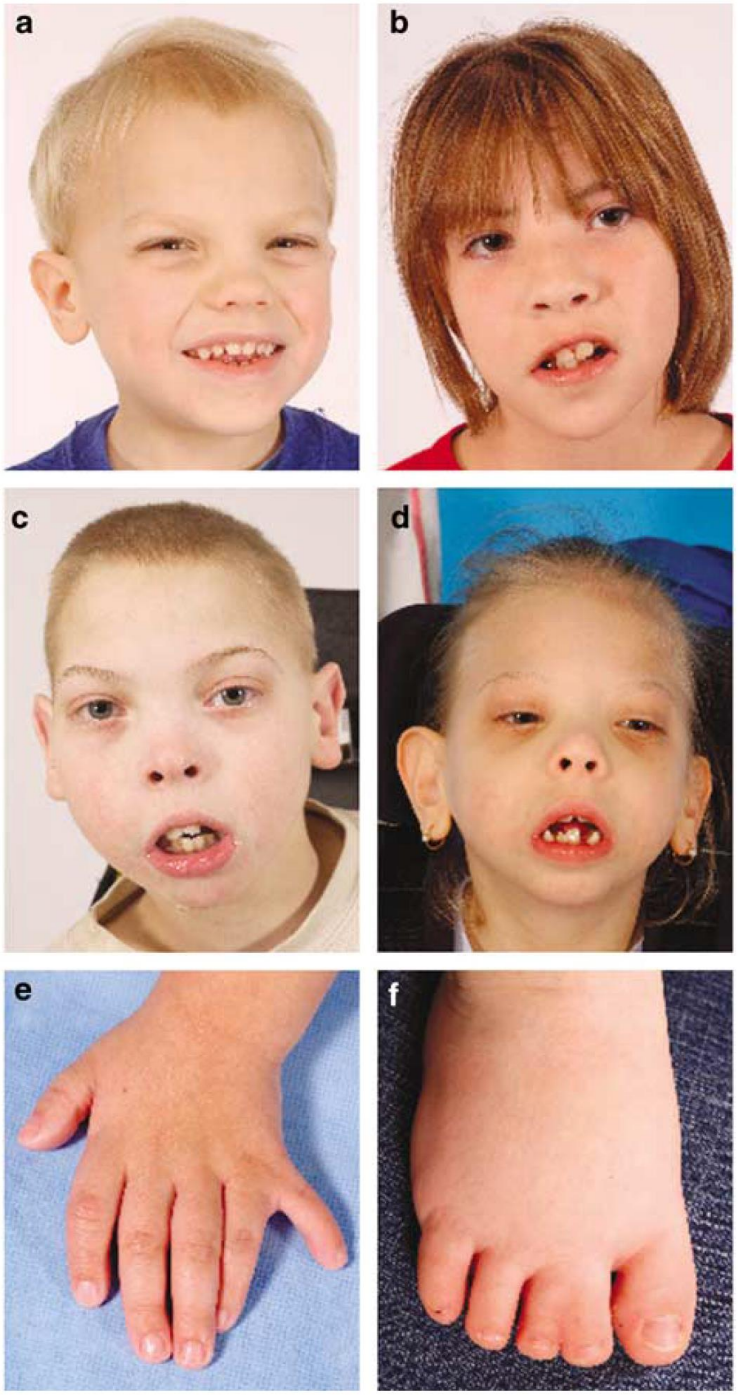
McMahon,2000

Sonic Hedgehog (Shh)



Murdoch and Copp, 2010


Squalene
Lanosterol
sterol-C4-demethylase
sterol-D24-reductase
Norlanosterol
4α-methyl-cholesta-8,14-dien-3β-ol
sterol-D14-reductase
Zymosterol
4α-methyl-cholest-8-en-3β-ol
sterol-D8D7-isomerase
sterol-C4-demethylase
Bare Patches Striated
CHILD
cholesta-7,24-dien-3β-ol
cholest-8-en-3β-ol
D5-desaturase
sterol-D8D7-isomerase
Tattered
CDPX2
7-dehydro-desmosterol
lathosterol
sterol-D7-reductase
D5-desaturase
desmosterol
7-dehydrocholesterol
Desmosterolosis
sterol-D24-reductase
sterol-D7-reductase
SLOS
cholesterol
Fenpropimorph
AY9944, BM15.766
Triparanol, U1866A

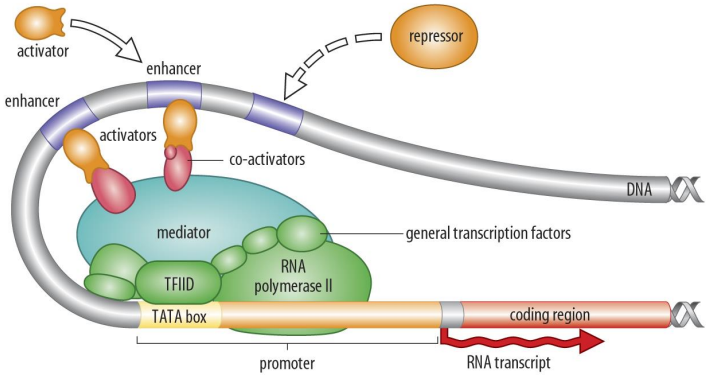


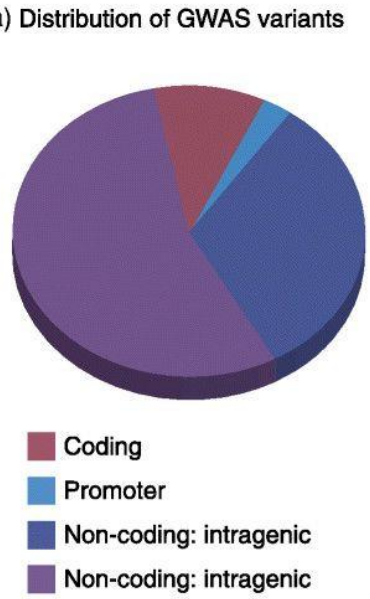
Smith–Lemli–Opitz syndrome: pathogenesis, diagnosis and management

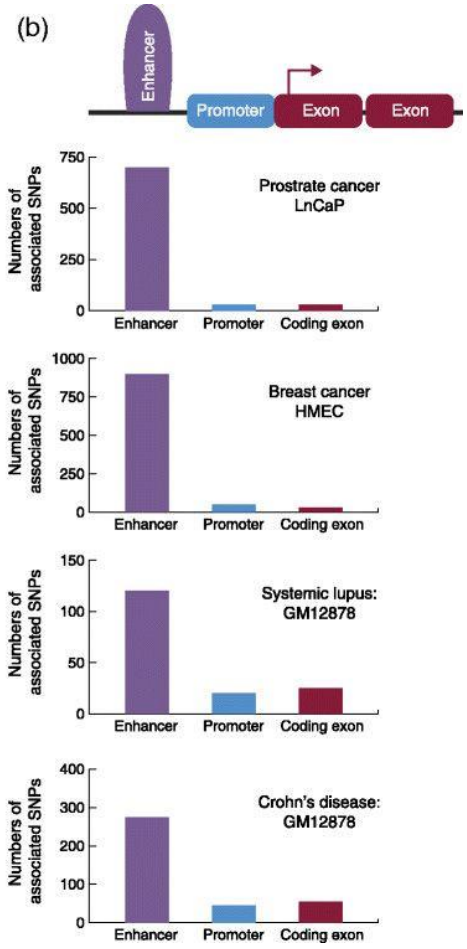
Smith–Lemli–Opitz syndrome (SLOS) is a malformation syndrome due to a deficiency of 7-dehydrocholesterol reductase (DHCR7). DHCR7 primarily catalyzes the reduction of 7-dehydrocholesterol (7DHC) to cholesterol. In SLOS, this results in decreased cholesterol and increased 7DHC levels, both during embryonic development and after birth. The malformations found in SLOS may result from decreased cholesterol, increased 7DHC or a combination of these two factors. This review discusses the clinical aspects and diagnosis of SLOS, therapeutic interventions and the current understanding of pathophysiological processes involved in SLOS.

European Journal of Human Genetics (2008) 16, 535–541

… regulatory mutations predominate

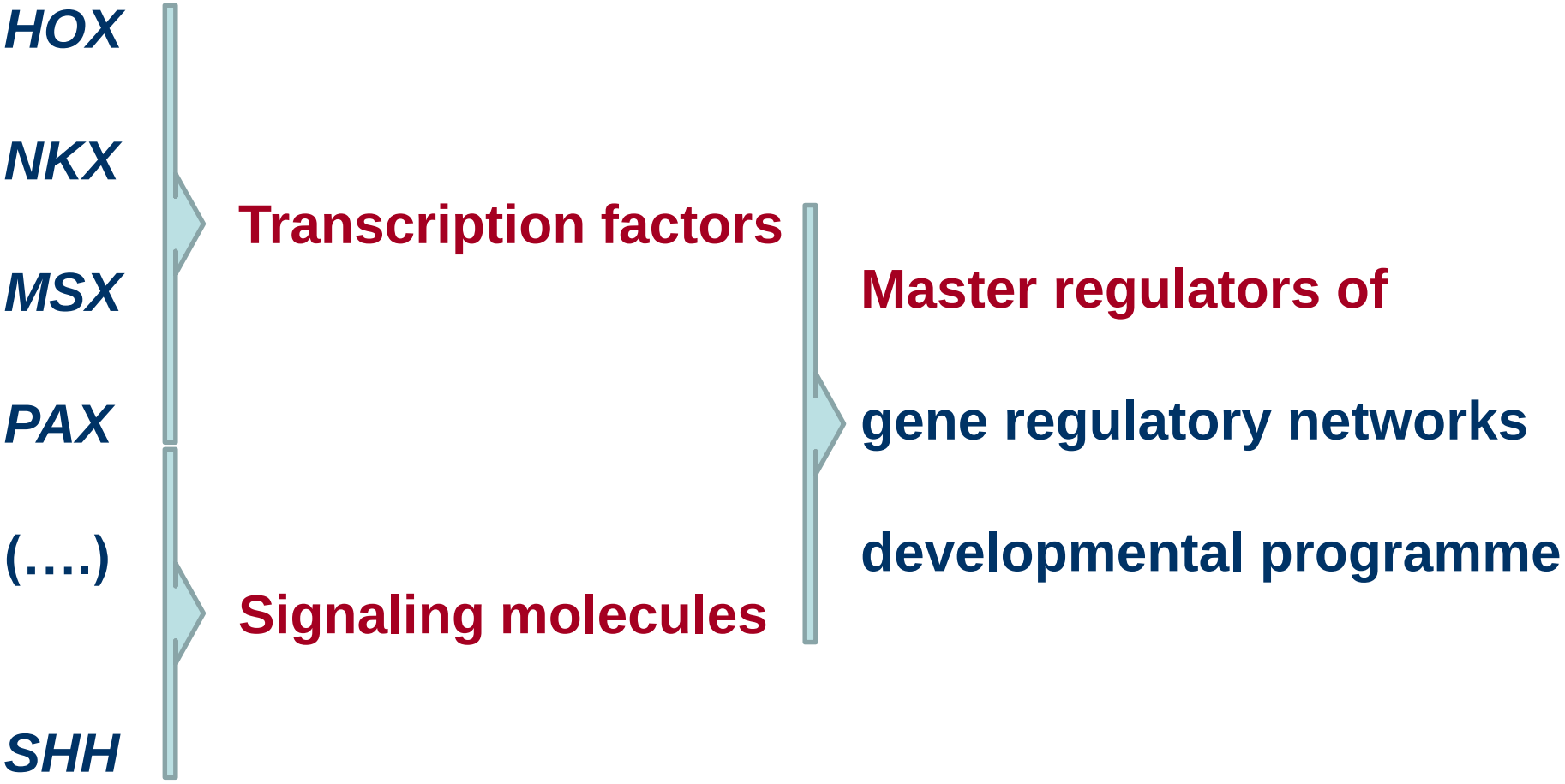






Most disease-related variations:

regulatory…



Cascades of events:

from patterning the embryo to organogenesis

Thanks for listening !!!