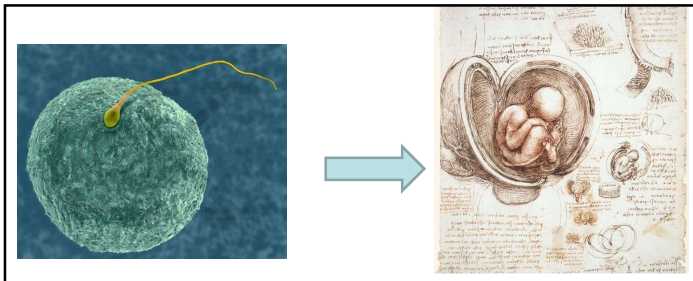
Developmental genetics and birth defects

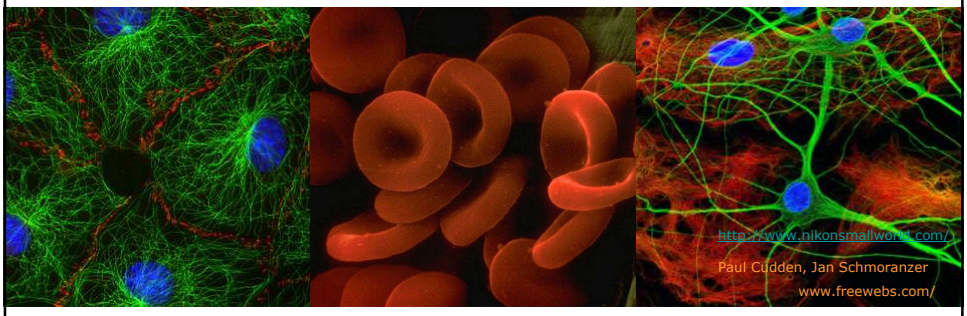
Regulators of Development

R. Rezsohazy

11.2.2022

Ontogenesis is a hereditary phenomenon



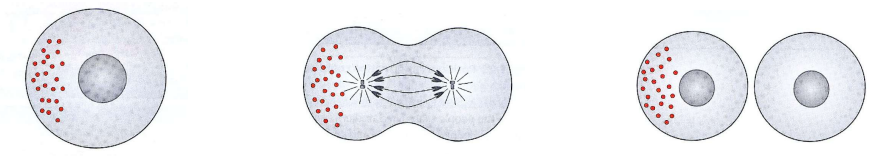


Genetic equivalence of cells ?

Differentiation of cell lineages → Shaping the embryo

Genetic equivalence of cells ?

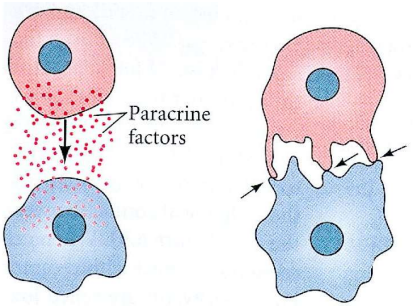
Differentiation of cell lineages → Shaping the embryo



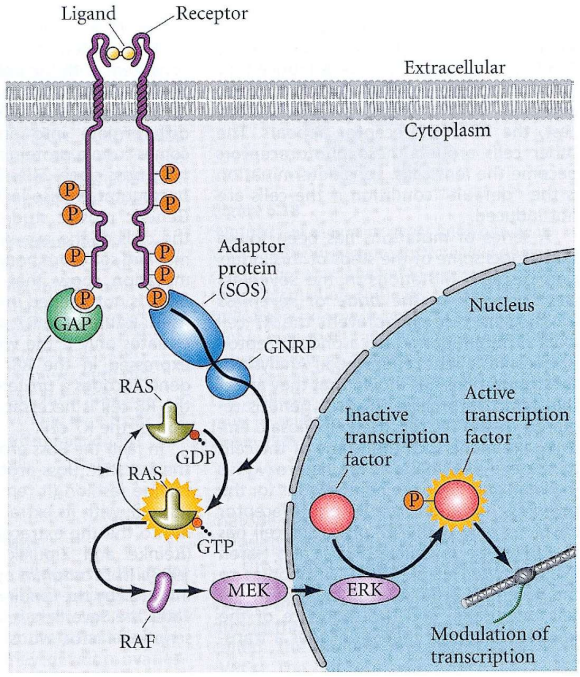
Symmetry breaking

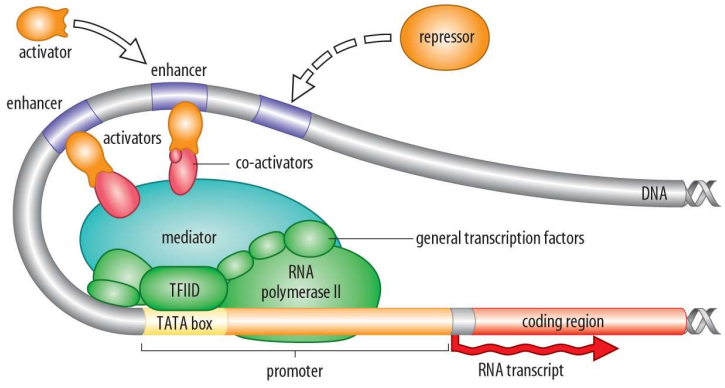
« epi »-genetic factors

« stuff » acting on genes



Signaling molecules





Gene regulators (transcription factors, etc…)

SCIENCE VOL 295 1 MARCH 2002

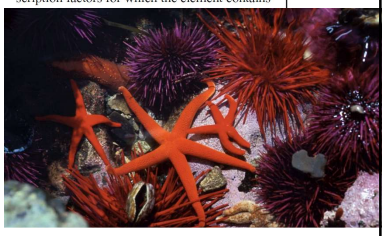
A Genomic Regulatory Network for Development

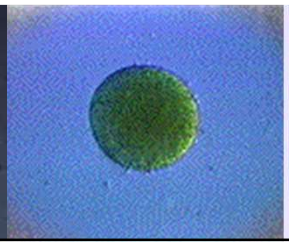
Eric H. Davidson,[1]* Jonathan P. Rast,[1] Paola Oliveri,[1] Andrew Ransick,[1] Cristina Calestani,[1] Chiou-Hwa Yuh,[1] Takuya Minokawa,[1] Gabriele Amore,[1] Veronica Hinman,[1] César Arenas-Mena,[1] Ochan Otim,[1] C. Titus Brown,[1] Carolina B. Livi,[1] Pei Yun Lee,[1] Roger Revilla,[1] Alistair G. 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]

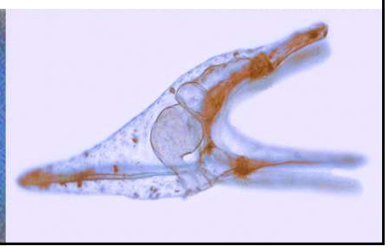
Development of the body plan is controlled by large networks of regulatory genes. A gene regulatory network that controls the specification of endoderm and mesoderm in the sea urchin embryo is summarized here. The network was derived from large-scale perturbation analyses, in combination with computational 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

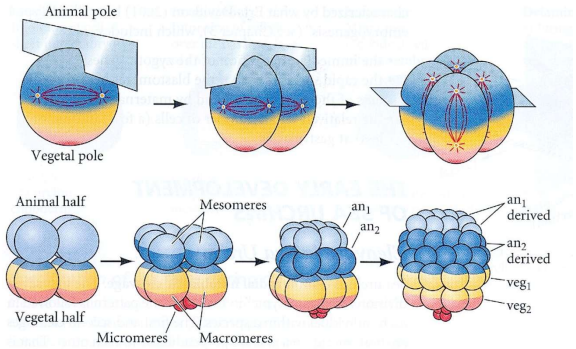
genes in the network; these inputs are the transcription factors for which the element contains



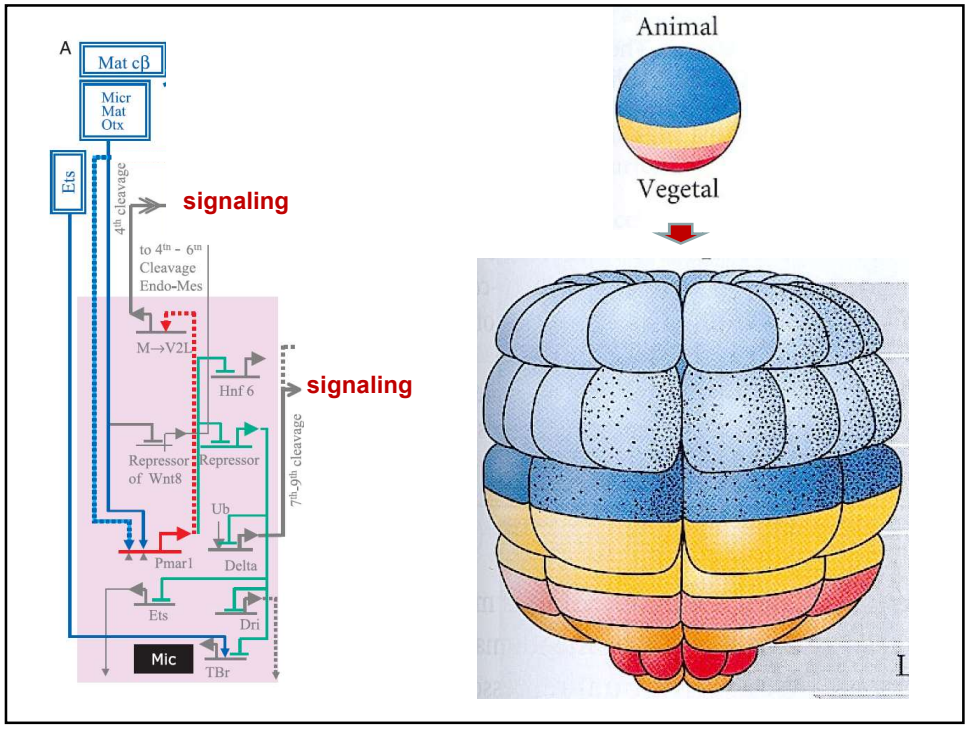




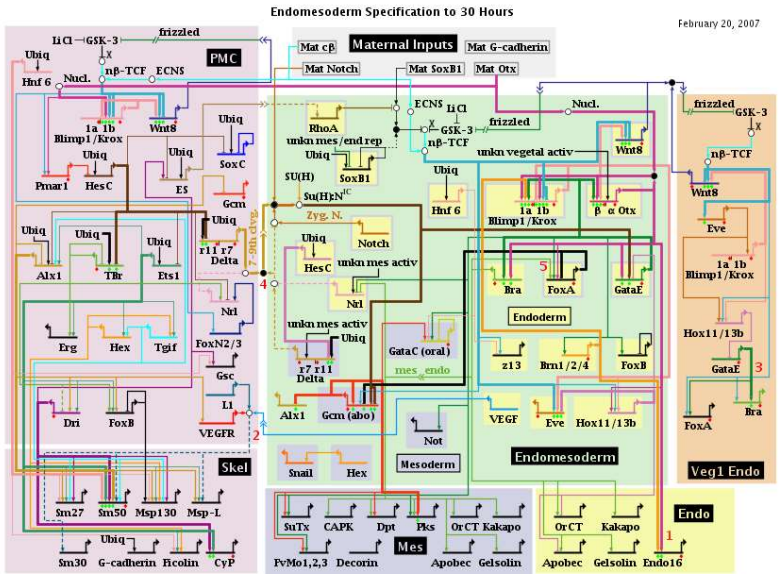
What is the first « symmetry breaking event » in development?



…Oogenesis !!!



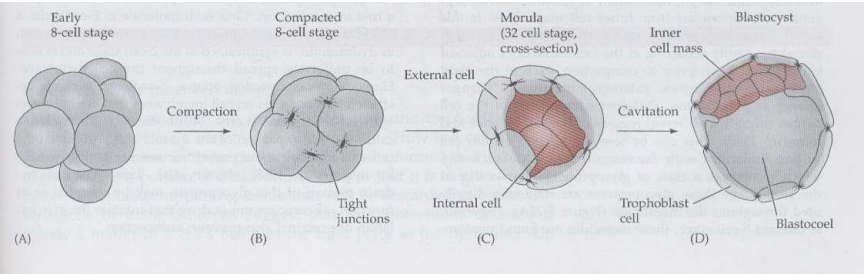
Next…: networks of cells and molecules in interaction



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

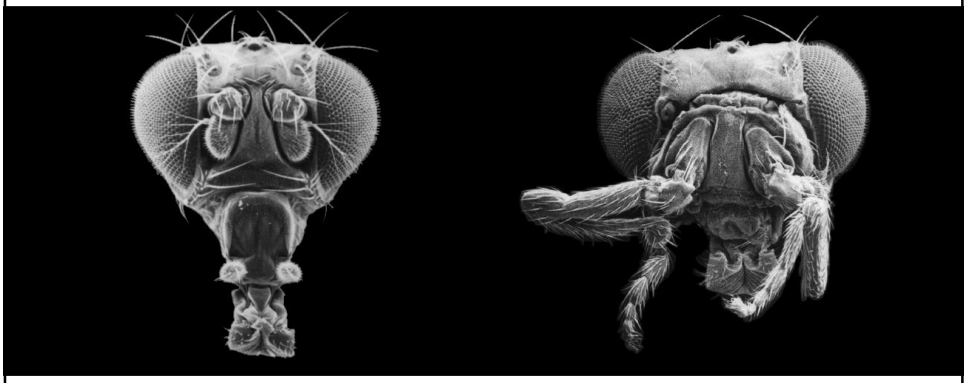
developmental programme

Signaling molecules

⇩

Gene regulators

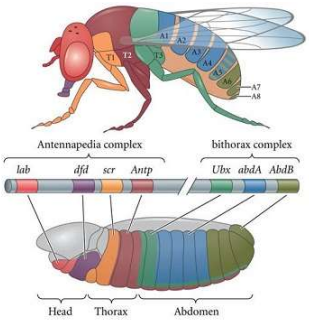
Patterning the embryo — *Hox* genes

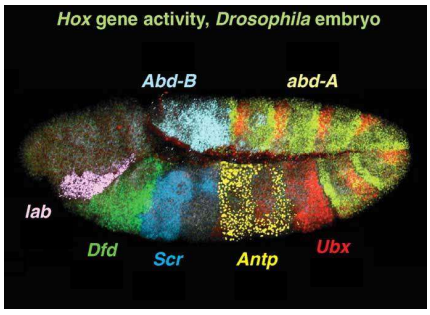


The Interactive Fly © Thomas B. Brody.

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

Specification of body segments

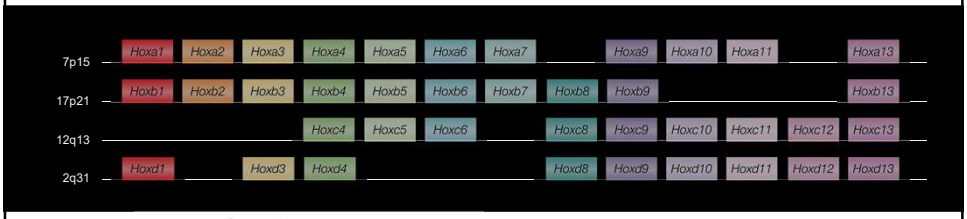


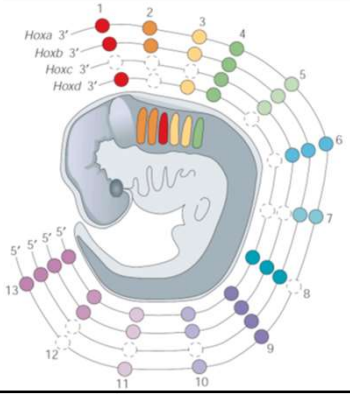


Gilbert, S, et al., *Developmental Biology*, 8th Ed, Sinauer, 2006

D. Lemons and W. Mc Ginnis, Science 2006

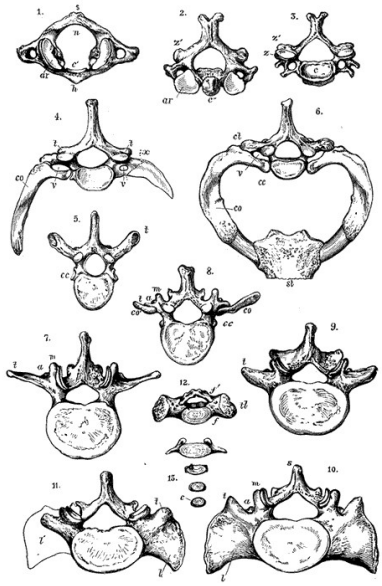
In mammals….

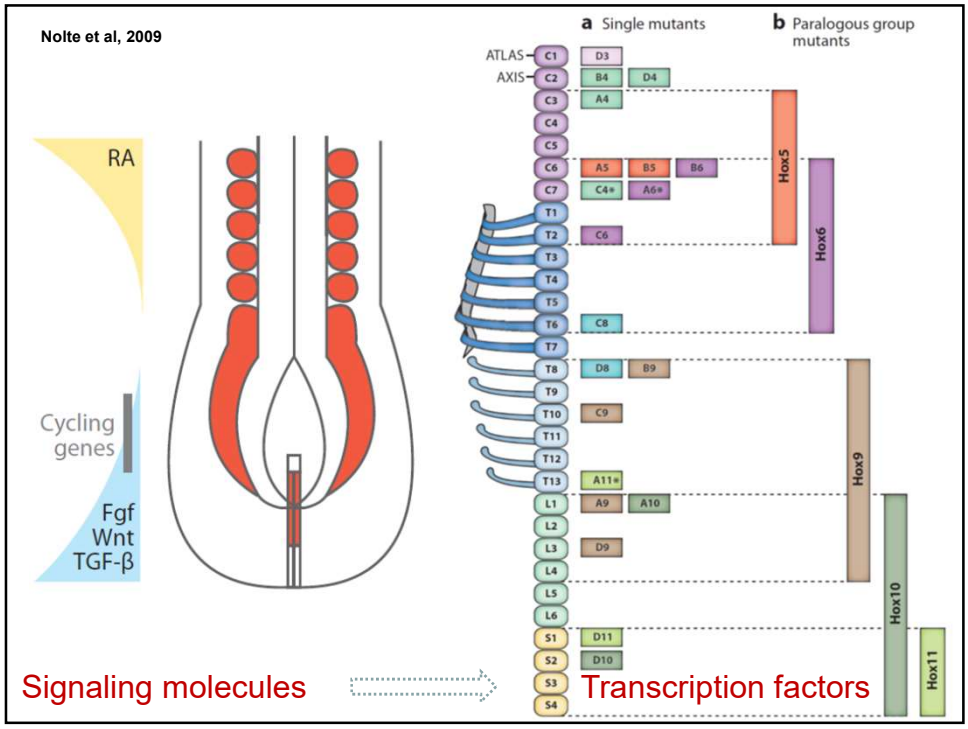


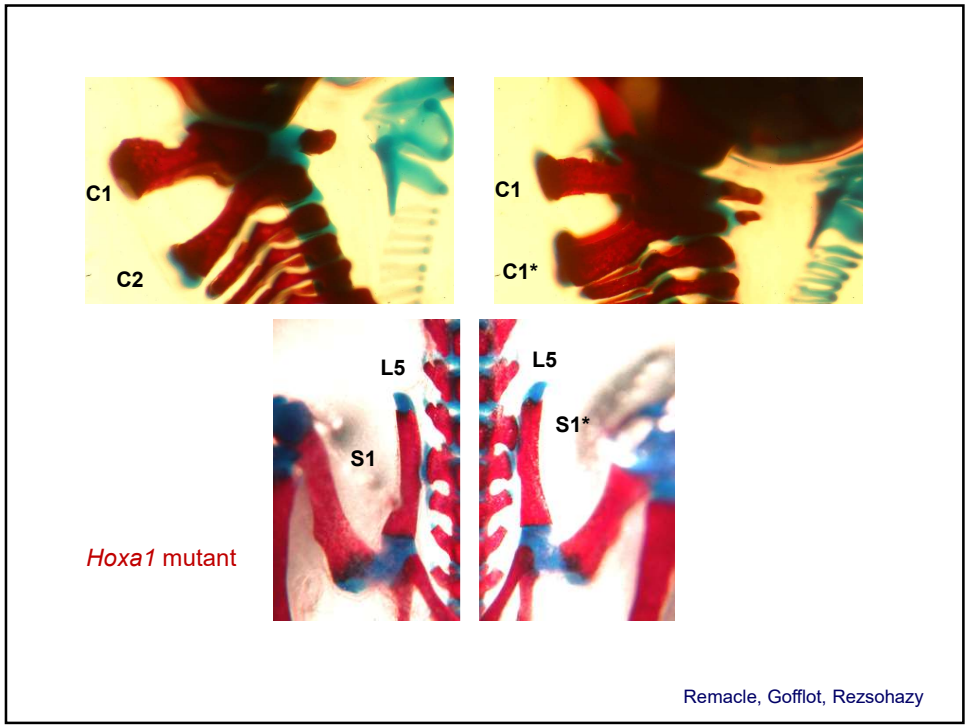


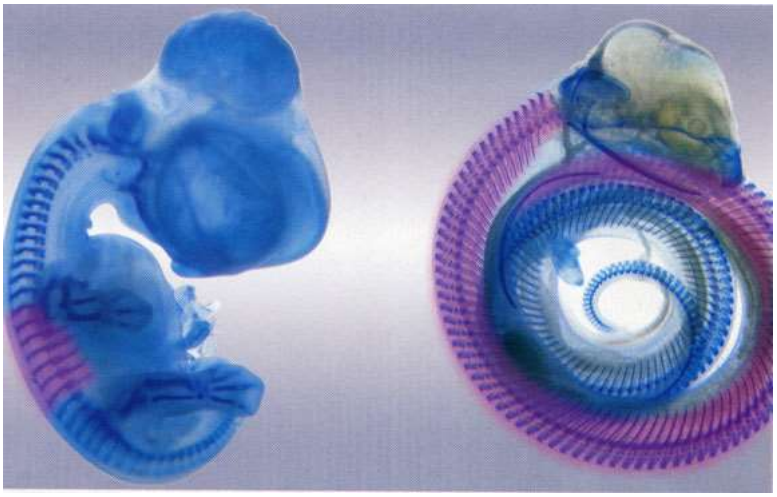
Santagati and Rijli, 2003

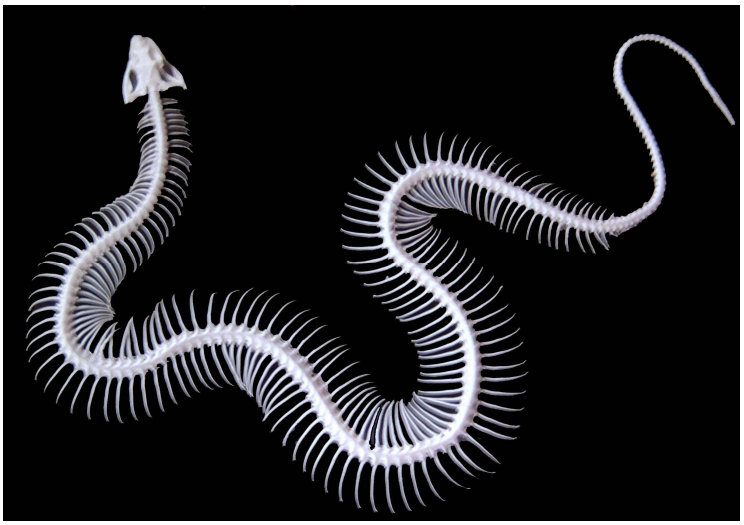
Vertebrae, ribs

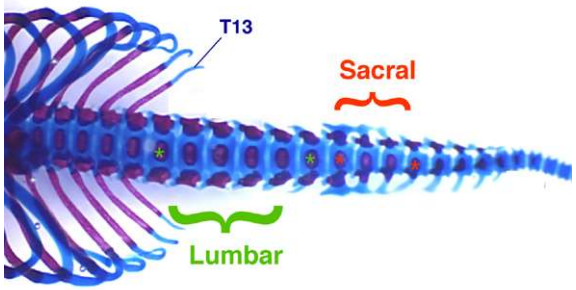


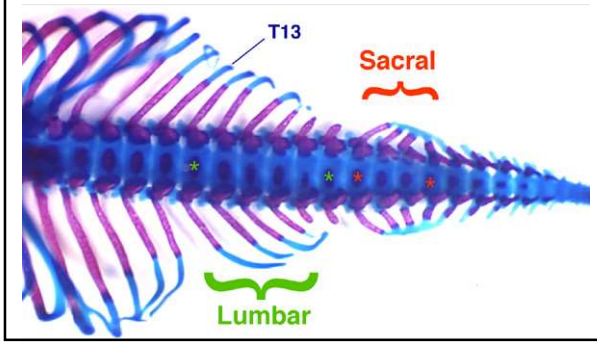

Nolte et al, 2009
a Single mutants
b Paralogous group mutants
RA
Cycling genes
Fgf
Wnt
TGF-β
ATLAS
AXIS
Hox5
Hox6
Hox9
Hox10
Hox11
Signaling molecules
Transcription factors


C1
C2
C1
C1*
L5
S1
L5
S1*
Hoxa1 mutant
Remacle, Gofflot, Rezsohazy

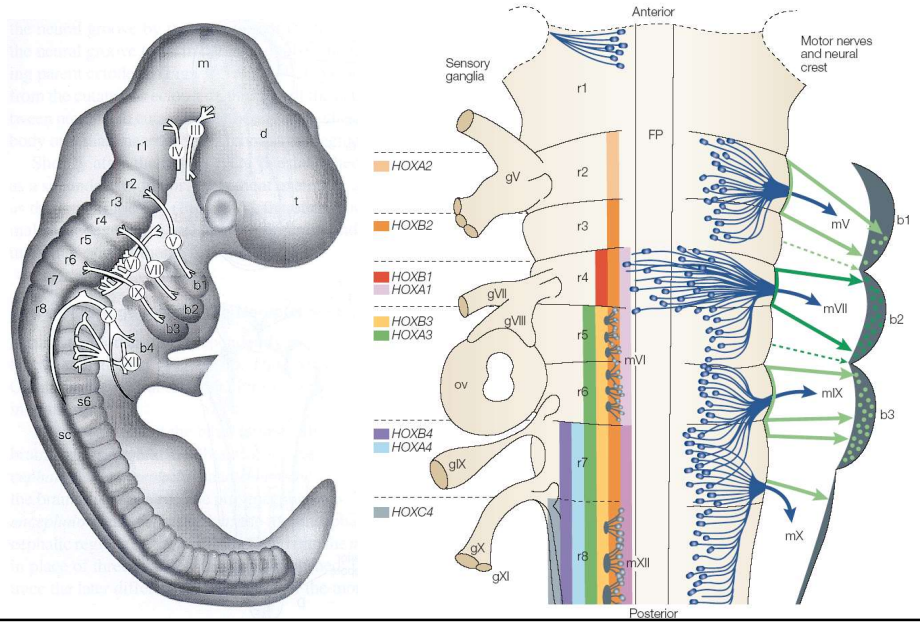




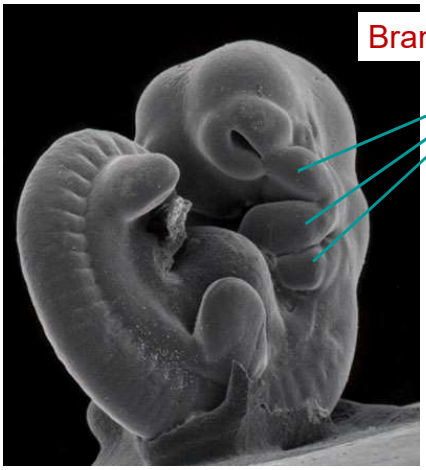


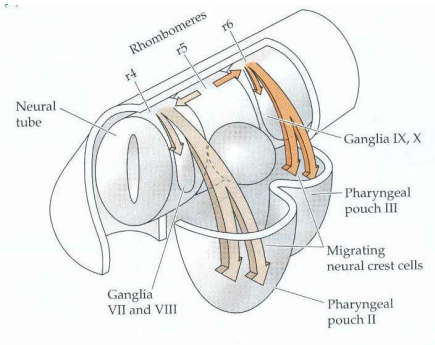


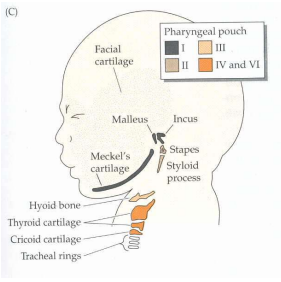
Hox genes and neural development



Branchial arches



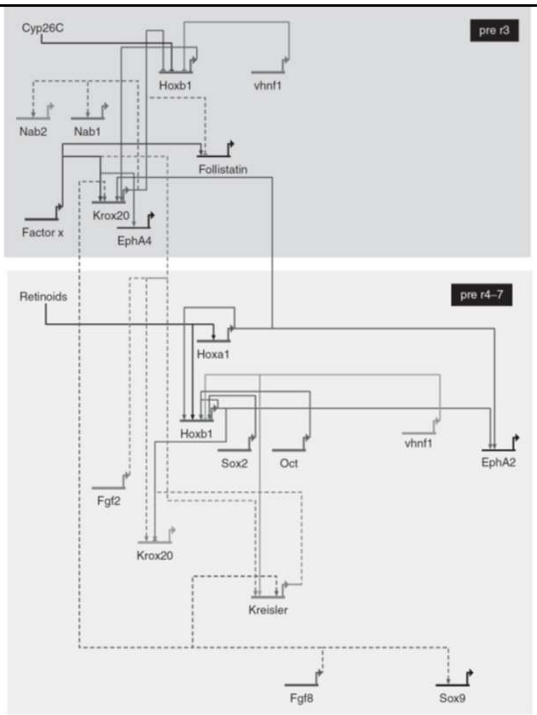




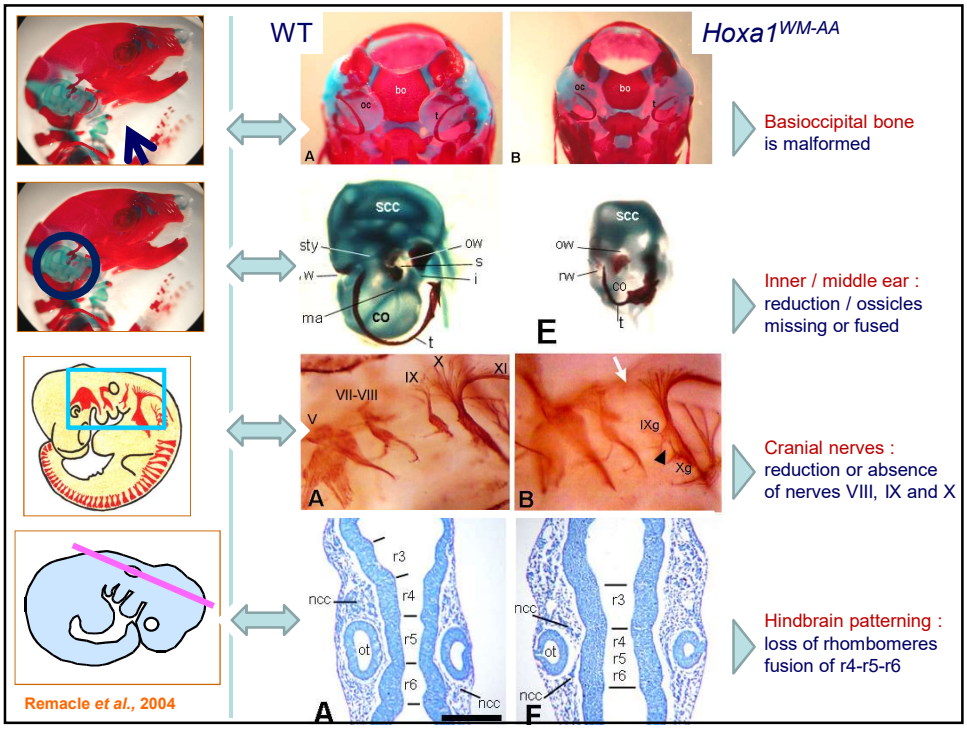
Signaling molecules

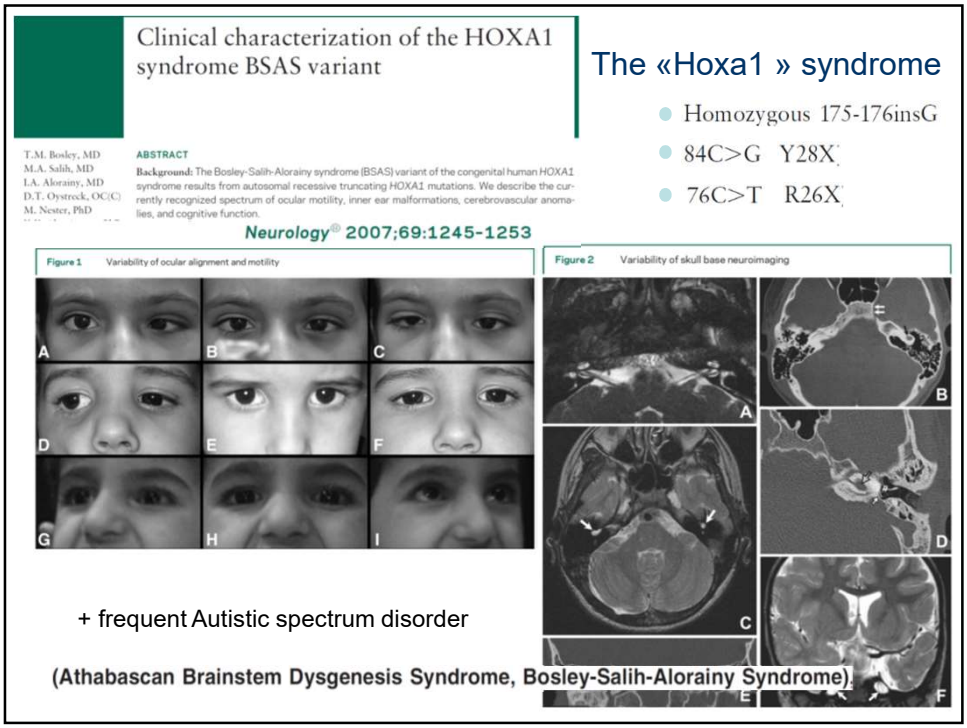
⇩

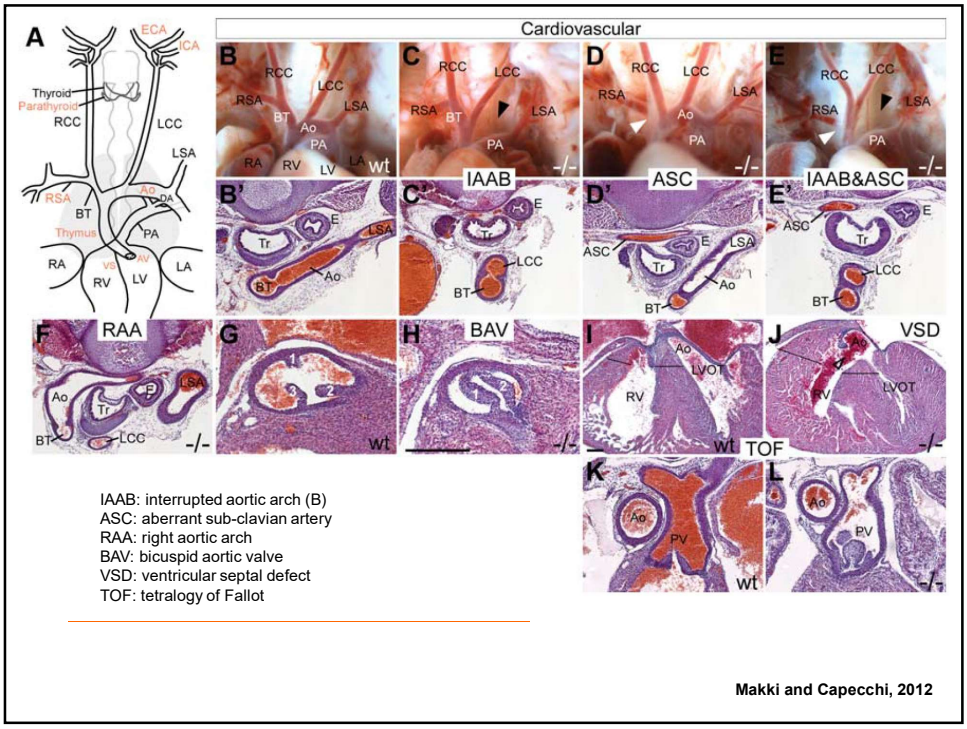
Transcription factors



Tumpel et al, 2009

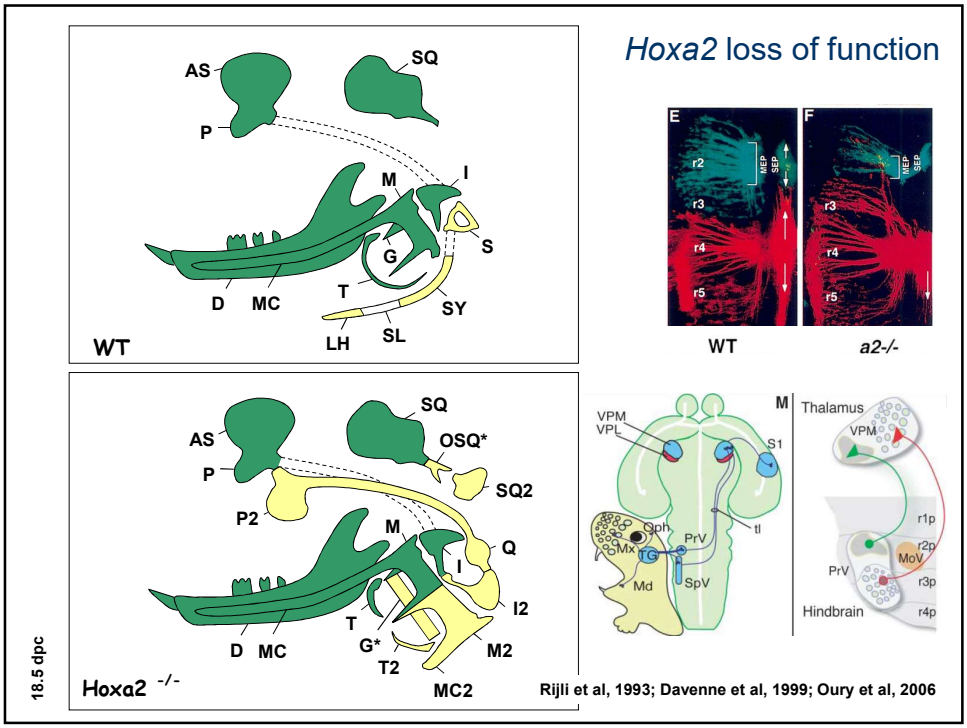

WT
Hoxa1WM-AA
Basioccipital bone is malformed
Inner / middle ear : reduction / ossicles missing or fused
Cranial nerves : reduction or absence of nerves VIII, IX and X
Hindbrain patterning : loss of rhombomeres fusion of r4-r5-r6
Remacle et al., 2004


Clinical characterization of the HOXA1 syndrome BSAS variant
The «Hoxa1 » syndrome
Homozygous 175-176insG
84C>G Y28X
76C>T R26X
Neurology® 2007;69:1245-1253
+ frequent Autistic spectrum disorder
(Athabascan Brainstem Dysgenesis Syndrome, Bosley-Salih-Alorainy Syndrome)

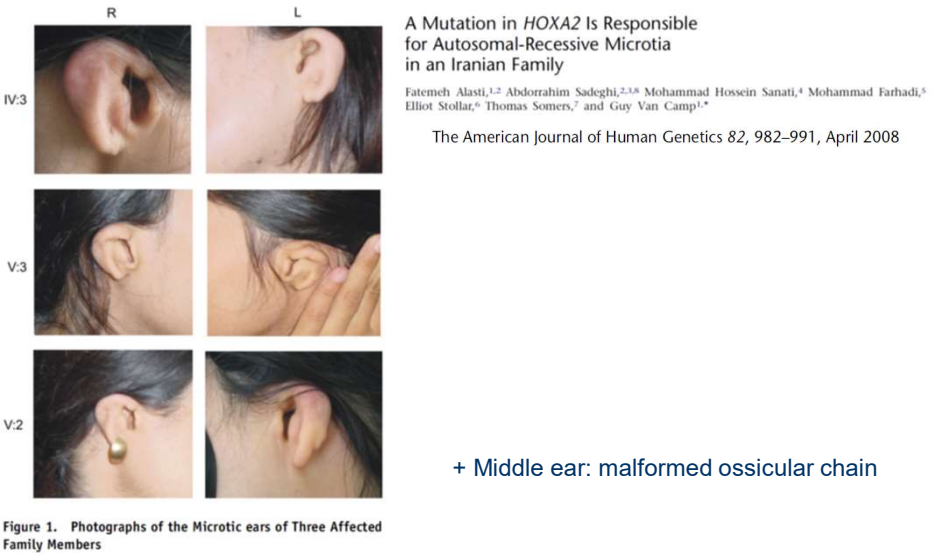


IAAB: interrupted aortic arch (B)
ASC: aberrant sub-clavian artery
RAA: right aortic arch
BAV: bicuspid aortic valve
VSD: ventricular septal defect
TOF: tetralogy of Fallot

Makki and Capecchi, 2012



Rijli et al, 1993; Davenne et al, 1999; Oury et al, 2006



A Mutation in *HOXA2* Is Responsible for Autosomal-Recessive Microtia in an Iranian Family

Fatemeh Alasti,[1,2] Abdorrahim Sadeghi,[2,3,8] Mohammad Hossein Sanati,[4] Mohammad Farhadi,[5] Elliot Stollar,[6] Thomas Somers,[7] and Guy Van Camp[1,*]

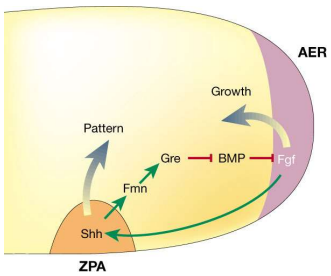
The American Journal of Human Genetics *82*, 982–991, April 2008

Figure 1. Photographs of the Microtic ears of Three Affected Family Members

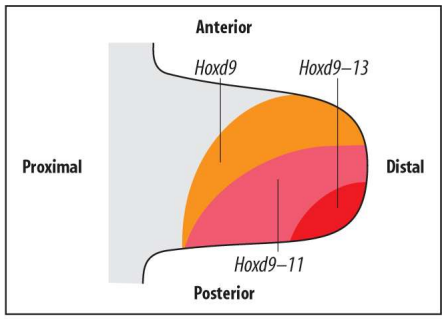
+ Middle ear: malformed ossicular chain

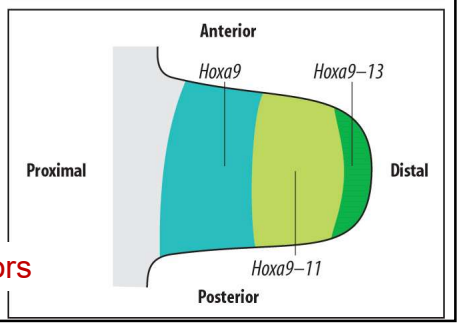
```
HOXA2 HUMAN  LELEKEFHFNKYLCRPRRVEIAALLDLTERQVKVWFQNRRMKHKR
HOXA2 MOUSE  LELEKEFHFNKYLCRPRRVEIAALLDLTERQVKVWFQNRRMKHKR
HOXA2 RAT    LELEKEFHFNKYLCRPRRVEIAALLDLTERQVKVWFQNRRMKHKR
HOXA2 CHICK  LELEKEFHFNKYLCRPRRVEIAALLDLTERQVKVWFQNRRMKHKR
                                          ▲ Q44K
```

Hox genes the limbs



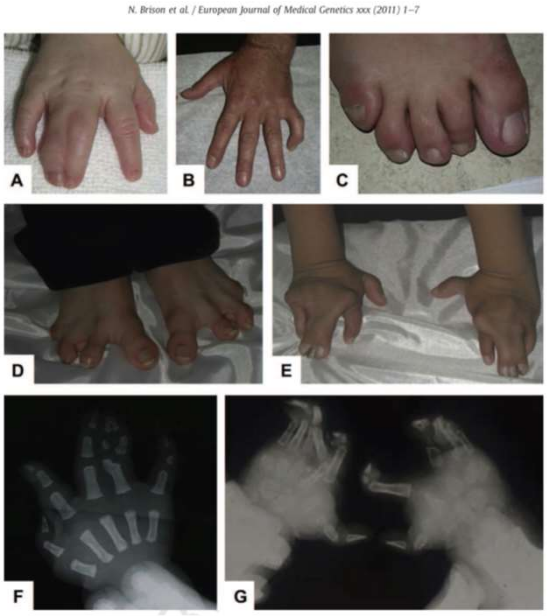
Signaling molecules





Transcription factors

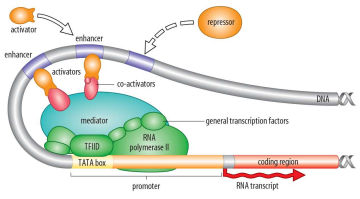
Synpolydactyly

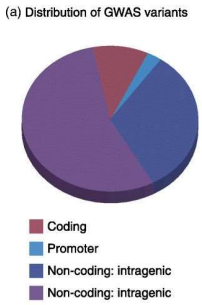


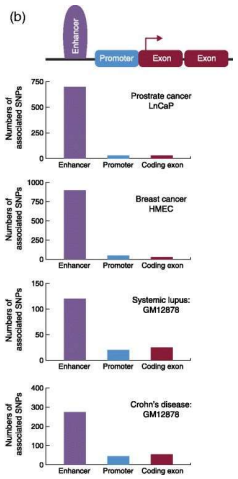
HOXD13

poly-alanine tract expansion

… regulatory mutations predominate

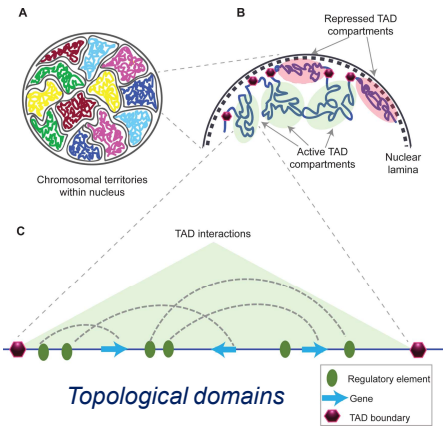




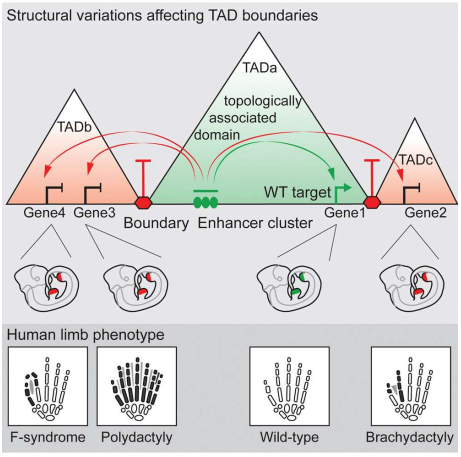


Most disease-related variations:

regulatory…



…and topological !



Hox genes:

Patterning the embryo → Vertebrae, ribs

Neural development

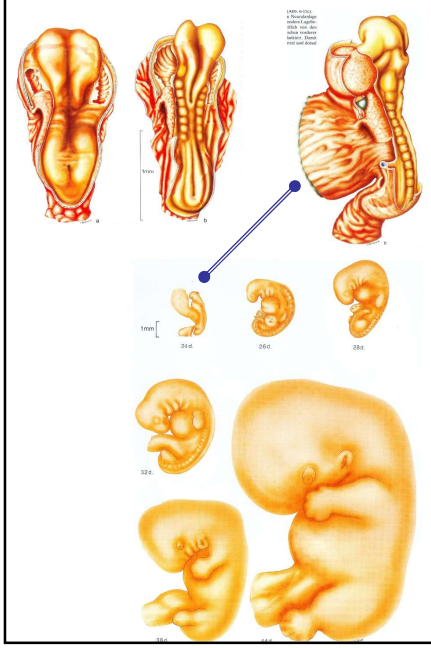
Neural crest

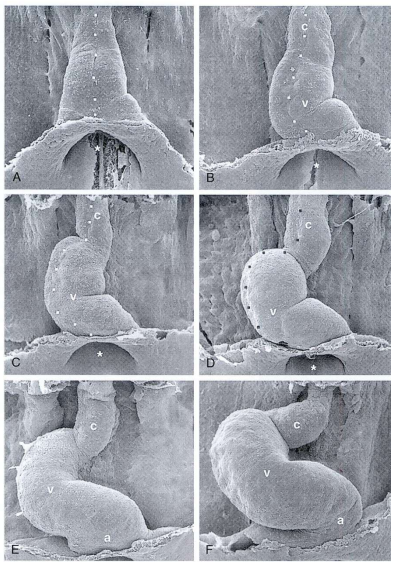
Branchial arches

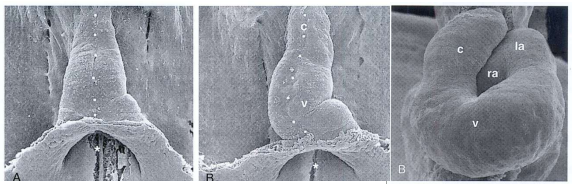
Limbs

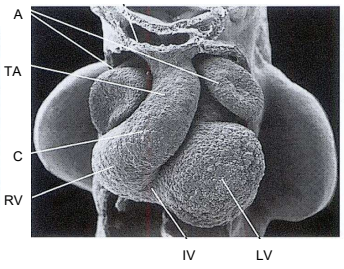
Organogenesis

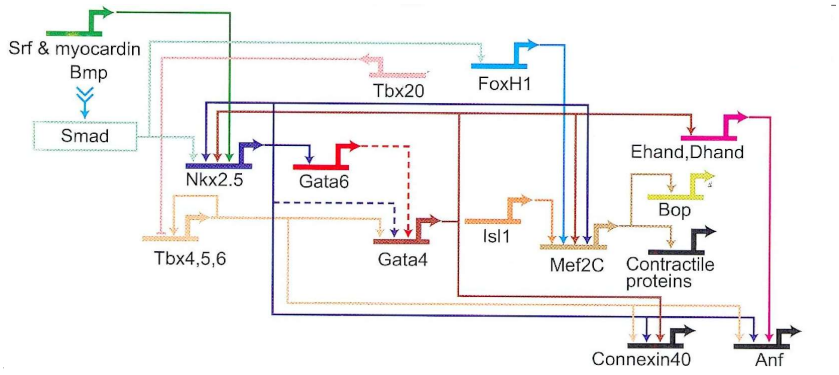
Heart development











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

Congenital Heart Disease

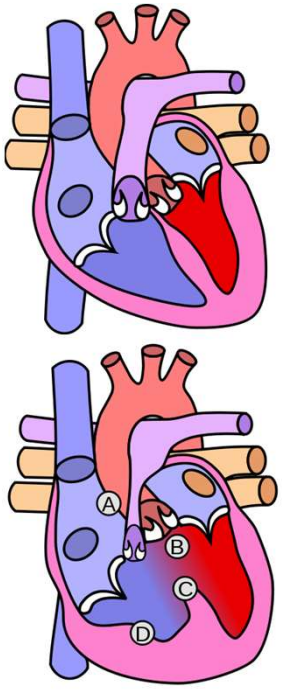
NKX2.5 Mutations in Patients With Congenital Heart Disease

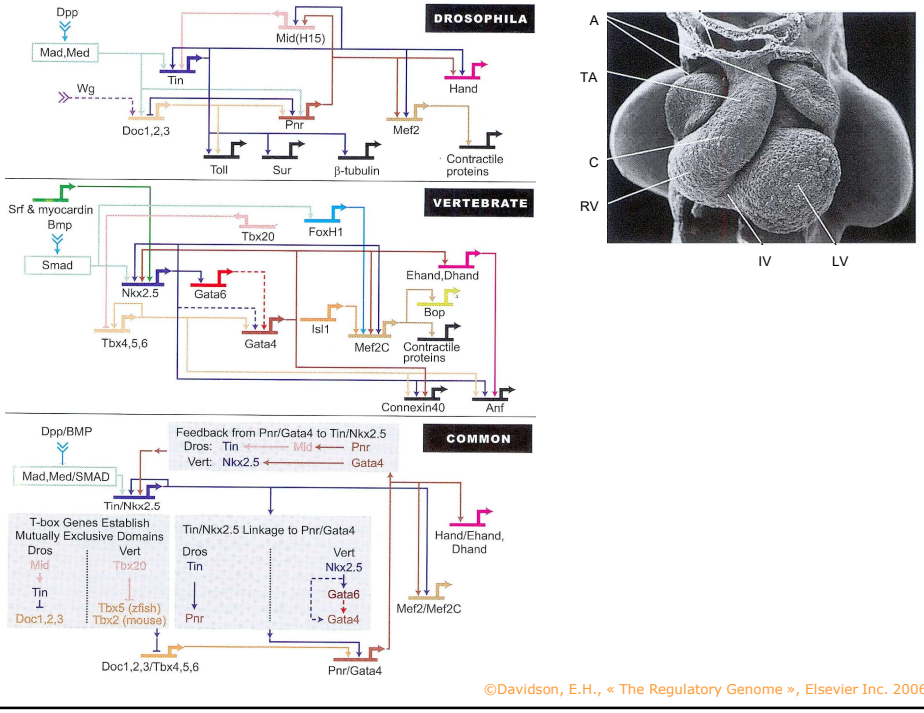
Doff B. McElhinney, MD,* Elizabeth Geiger, MS,* Joshua Blinder, BS,* D. Woodrow Benson, MD, PHD,† Elizabeth Goldmuntz, MD, FACC*

Philadelphia, Pennsylvania; and Cincinnati, Ohio

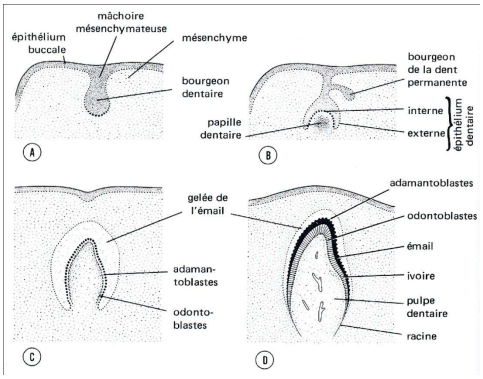
Cardiovascular Anomaly	# Patients Genotyped	# With Mutations
Secundum atrial septal defect	71	3 (4%)
Ebstein's malformation	7	0
Conotruncal anomalies		
Tetralogy of Fallot*	201	9 (4%)
D-transposition of the great arteries	86	0
Double-outlet right ventricle	31	1 (3%)
Interrupted aortic arch	23	1 (4%)
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%)

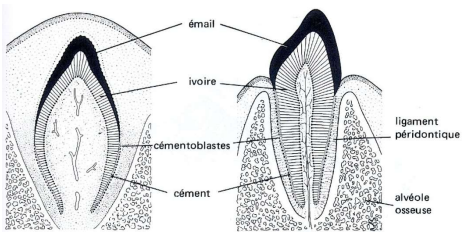
*Includes 134 consecutively recruited patients with tetralogy of Fallot described in the reports by Goldmuntz et al. (4) (n = 114) and Benson et al. (2) (n = 20) seven of whom had *NKX2.5* mutations.

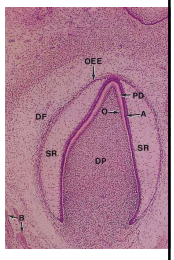


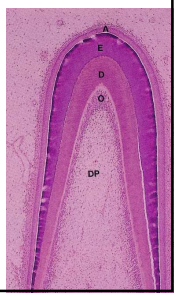


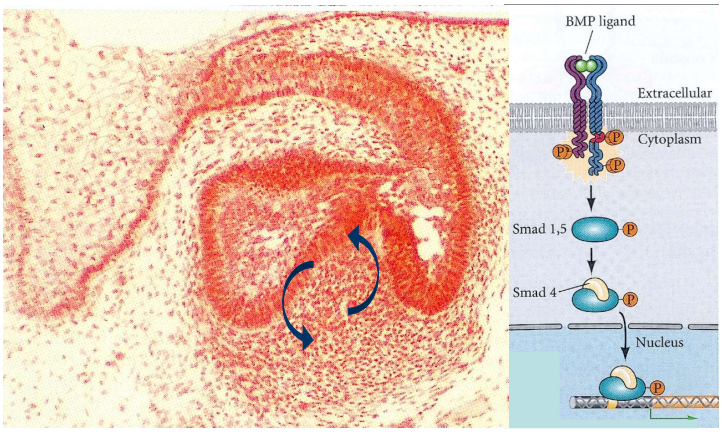
Teeth

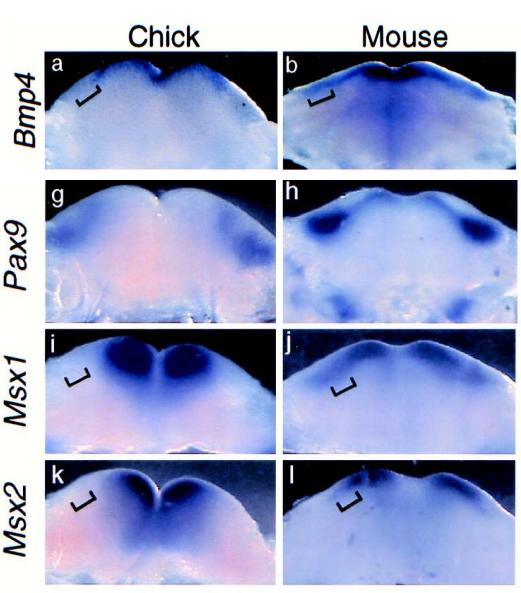


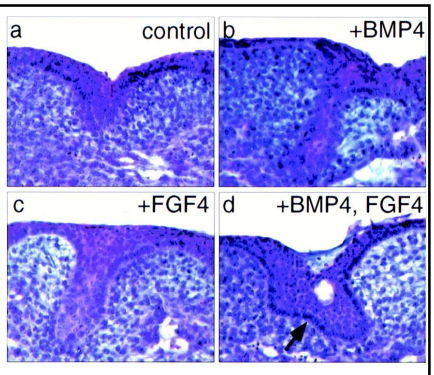








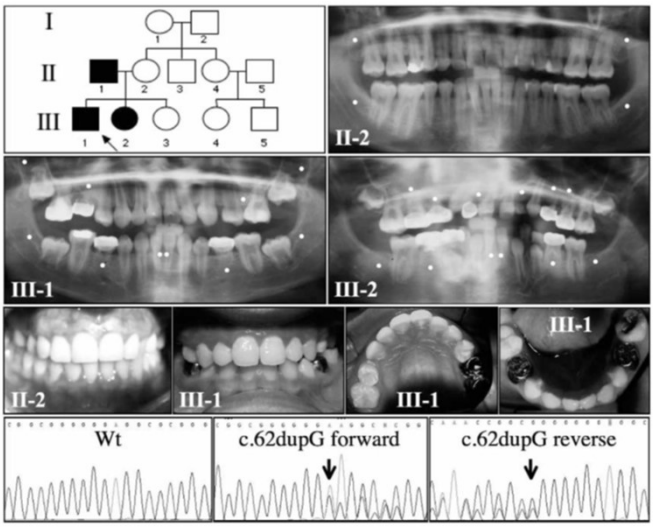




J Dent Res. 2006 March ; 85(3): 267–271.

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,*]

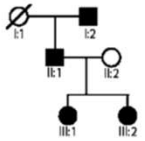


European Journal of Human Genetics (2006) 14, 403–409

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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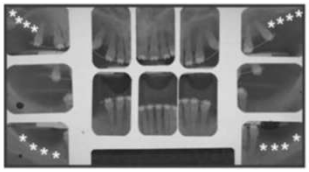

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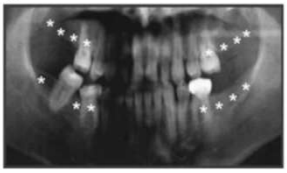
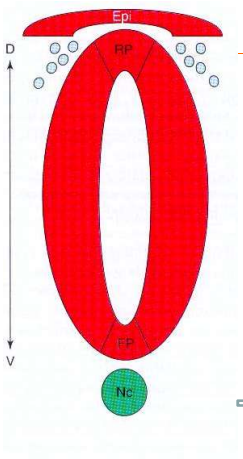
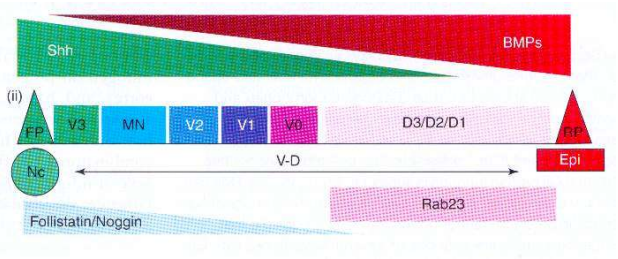


d

	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	*	*	*	*									*	*	*	*
	*		*	*									*	*	*	*

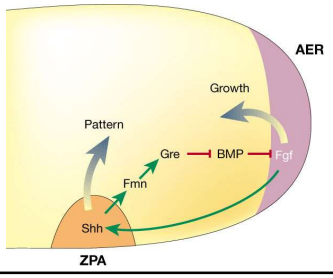
Hedgehog signalling





Neural tube

Limb bud



Hh Signalling Pathway

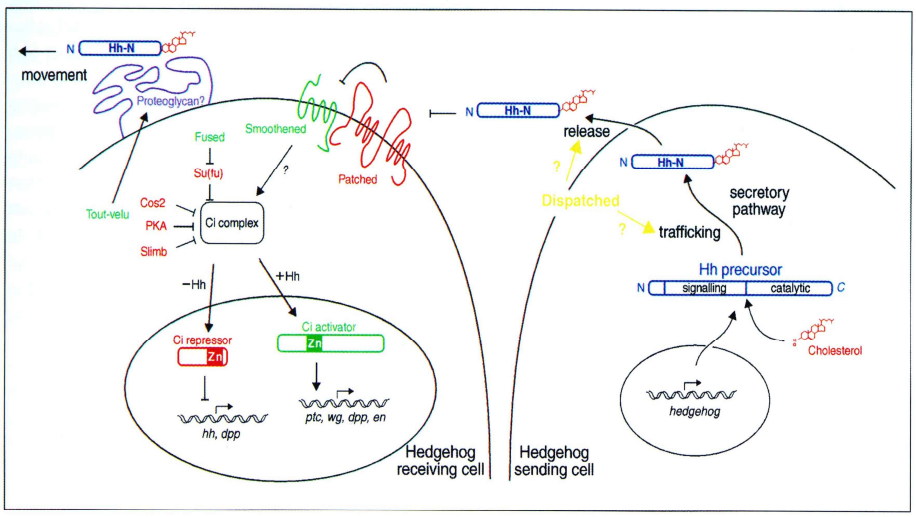
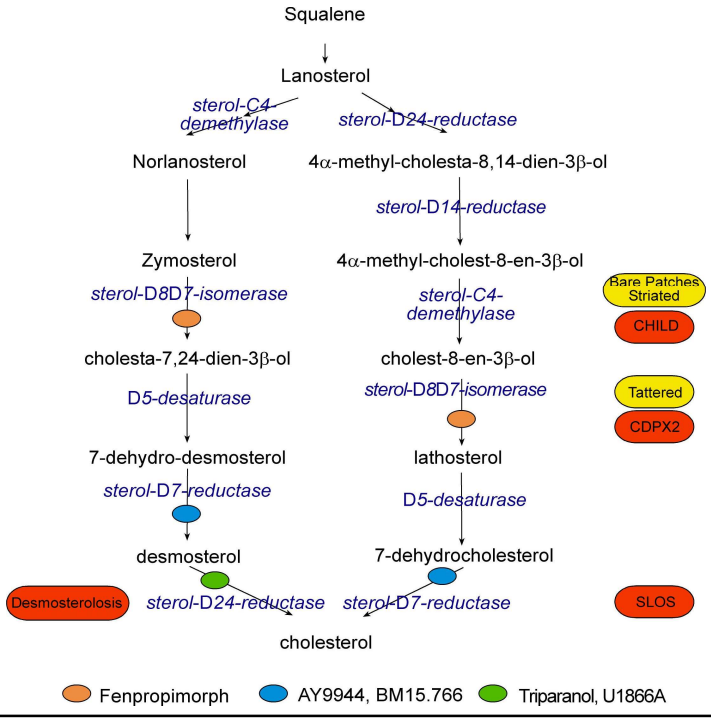


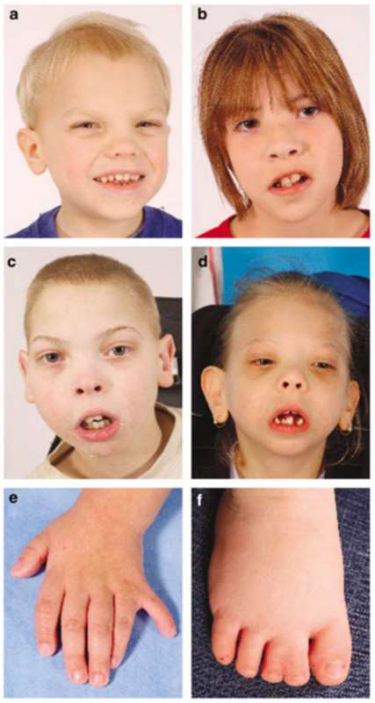
Figure 1. Schematic Representation of Hedgehog Signaling Pathway
Red components act negatively and blue components positively. See text for details.

McMahon, Cell, 2000

Sonic Hedgehog (Shh)

Chiang *et al.*, Nature 1996

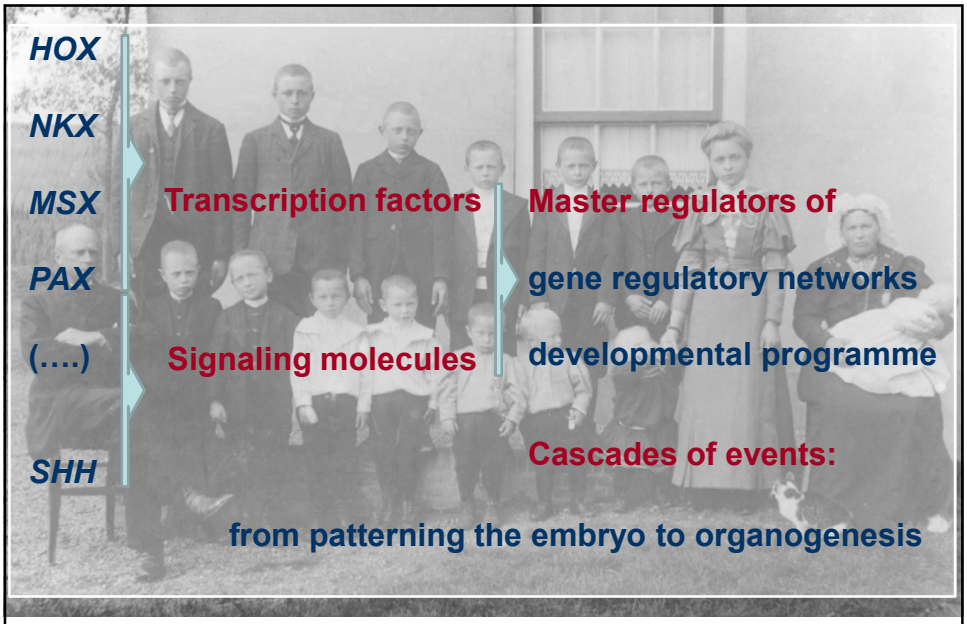




Smith–Lemli–Opitz syndrome: pathogenesis, diagnosis and management

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



Thanks for listening !!!