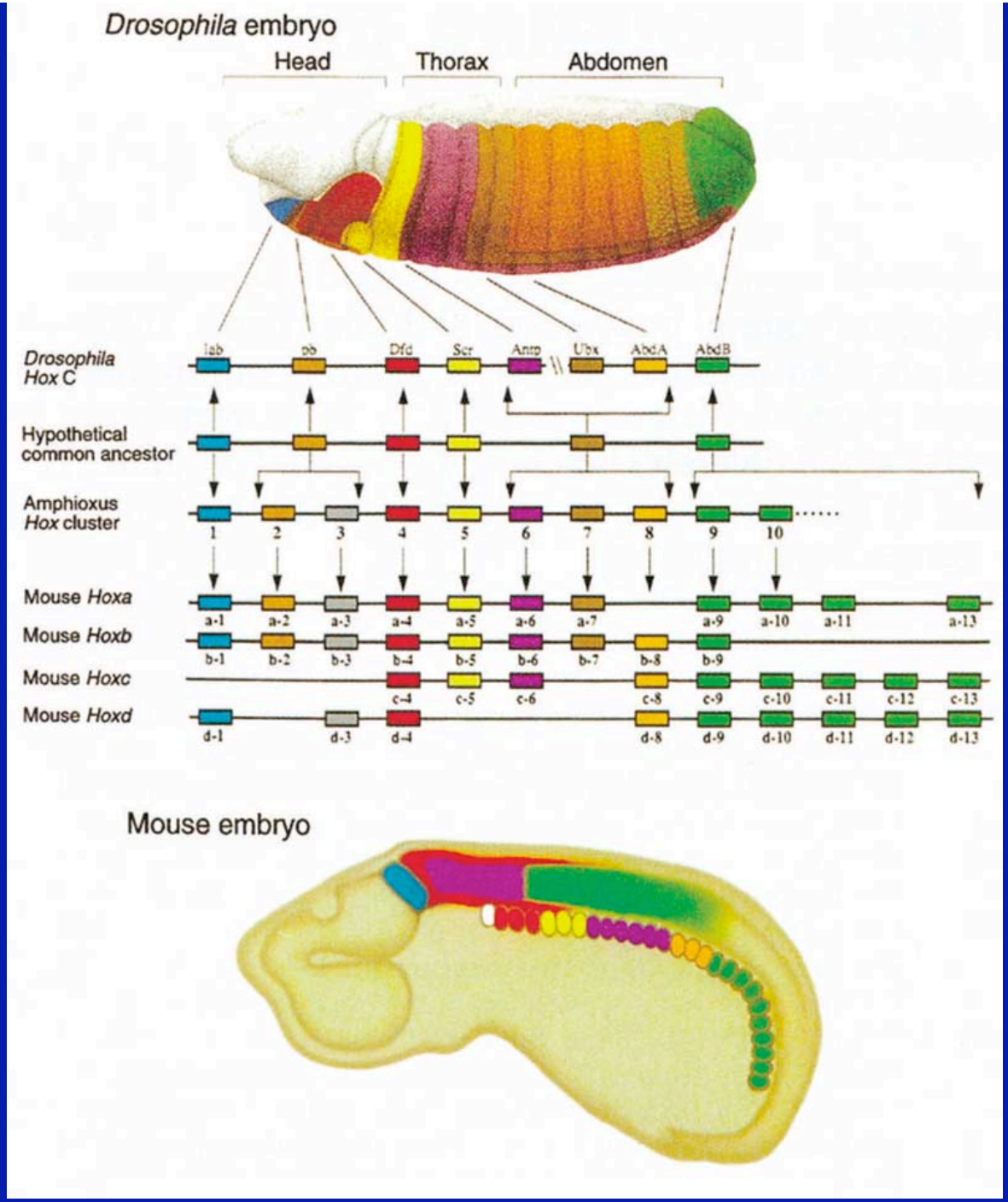
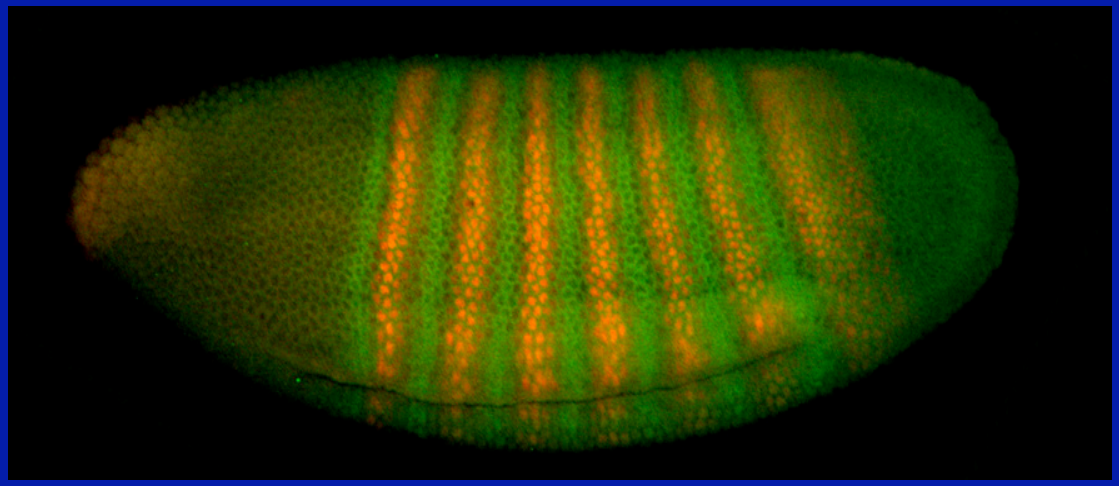
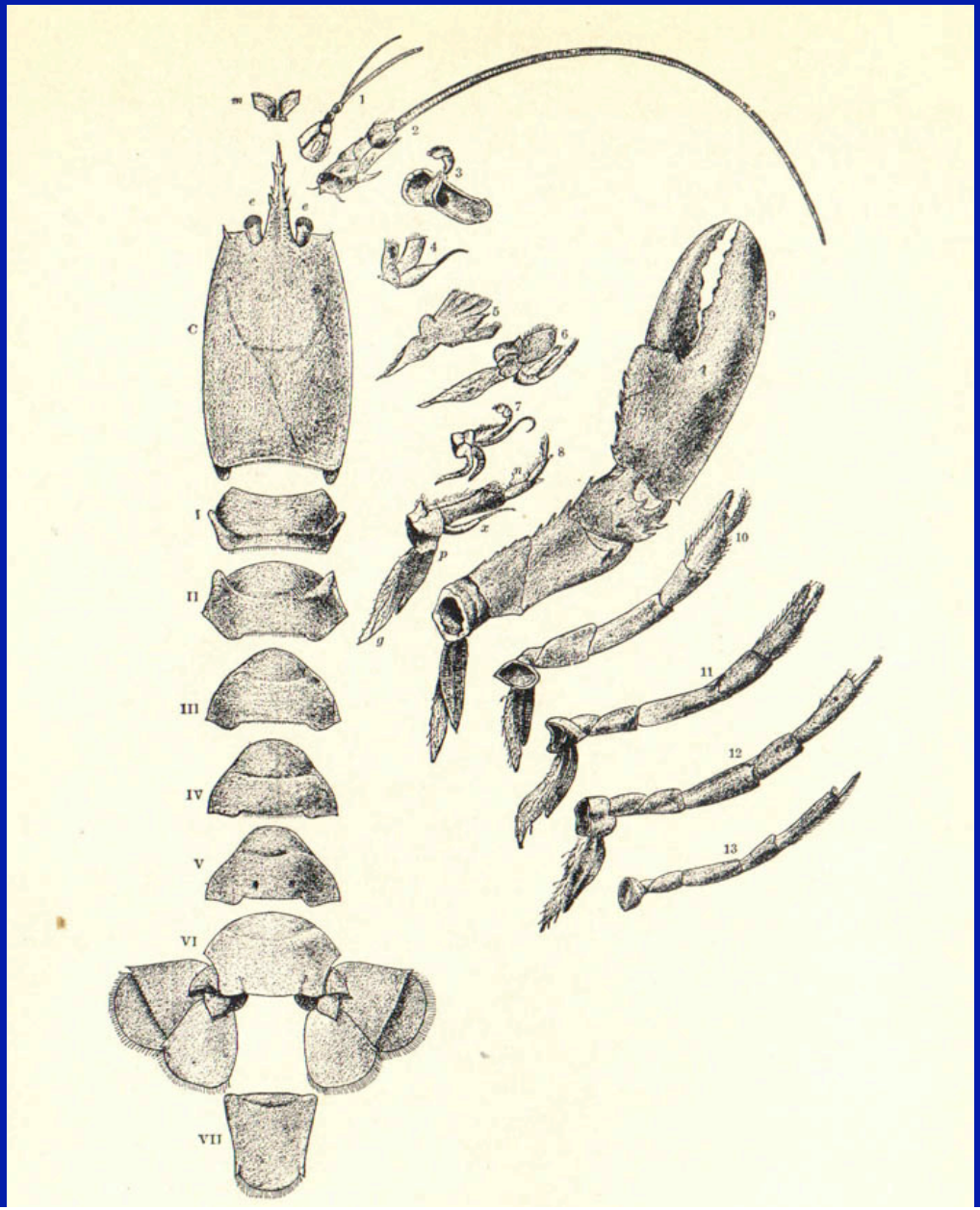
Hox genes

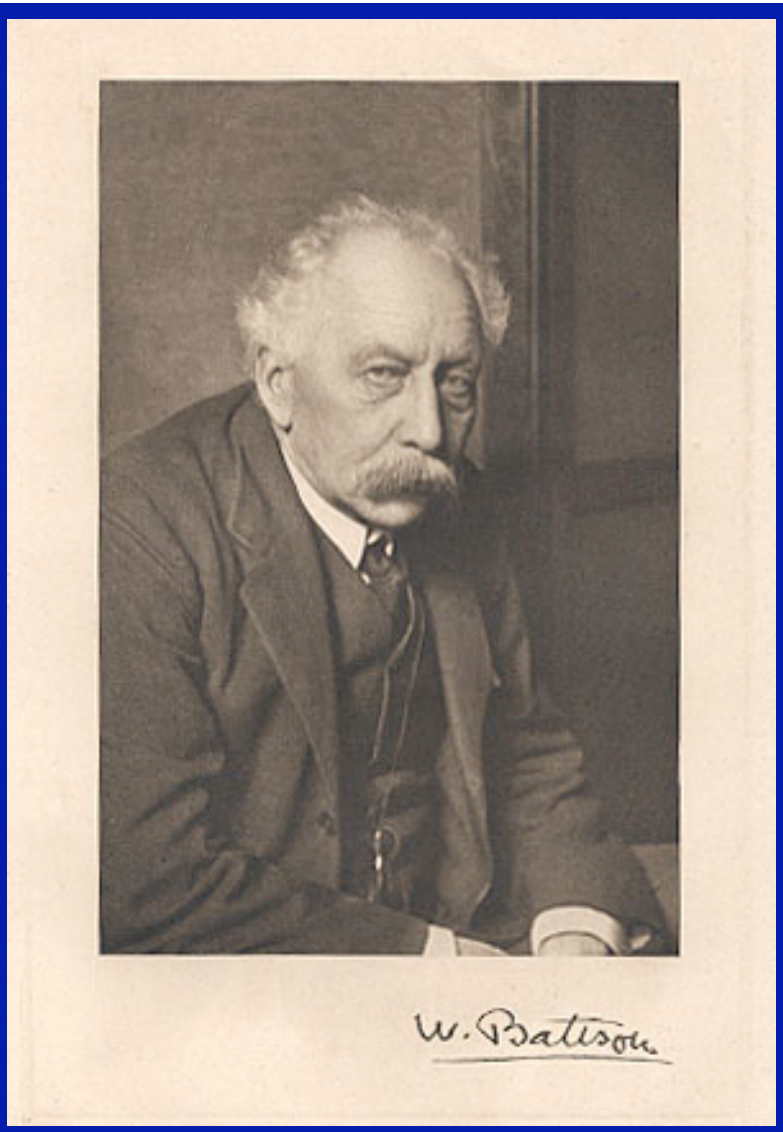

Drosophila embryo
Head
Thorax
Abdomen
Drosophila *Hox C*
lab
pb
Dfd
Scr
Antp
Ubx
AbdA
AbdB
Hypothetical common ancestor
Amphioxus *Hox* cluster
1 2 3 4 5 6 7 8 9 10
Mouse *Hoxa*
a-1 a-2 a-3 a-4 a-5 a-6 a-7 a-9 a-10 a-11 a-13
Mouse *Hoxb*
b-1 b-2 b-3 b-4 b-5 b-6 b-7 b-8 b-9
Mouse *Hoxc*
c-4 c-5 c-6 c-8 c-9 c-10 c-11 c-12 c-13
Mouse *Hoxd*
d-1 d-3 d-4 d-8 d-9 d-10 d-11 d-12 d-13
Mouse embryo

Segmentation



Serial Homology





William Bateson 1861-1926

MATERIALS

FOR THE

STUDY OF VARIATION

TREATED WITH ESPECIAL REGARD TO

DISCONTINUITY

IN THE

ORIGIN OF SPECIES.

BY

WILLIAM BATESON, M.A.

FELLOW OF ST JOHN'S COLLEGE, CAMBRIDGE

London:

MACMILLAN AND CO.

AND NEW YORK.

1894

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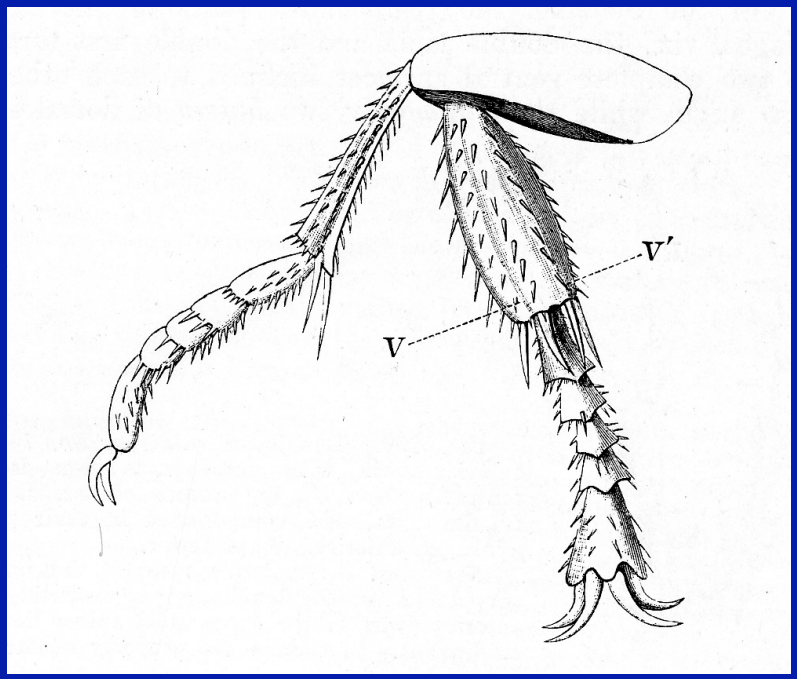
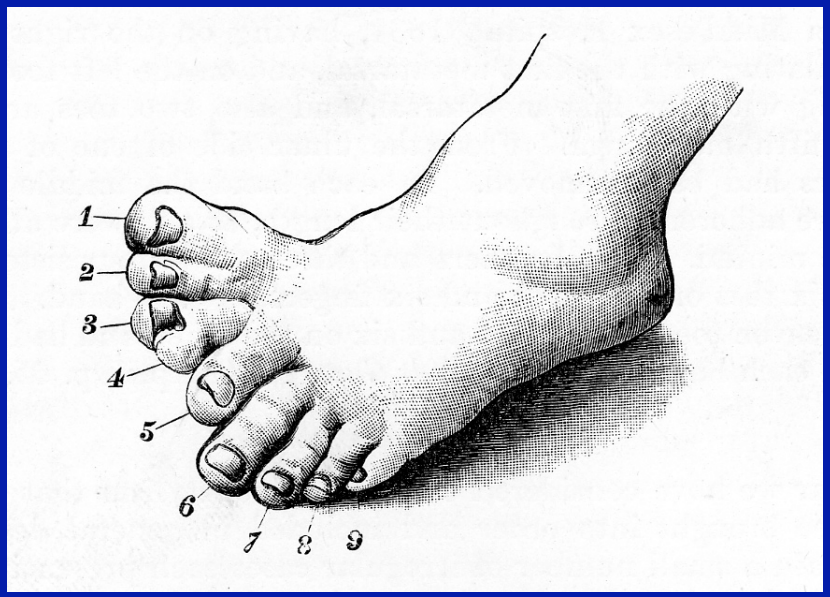
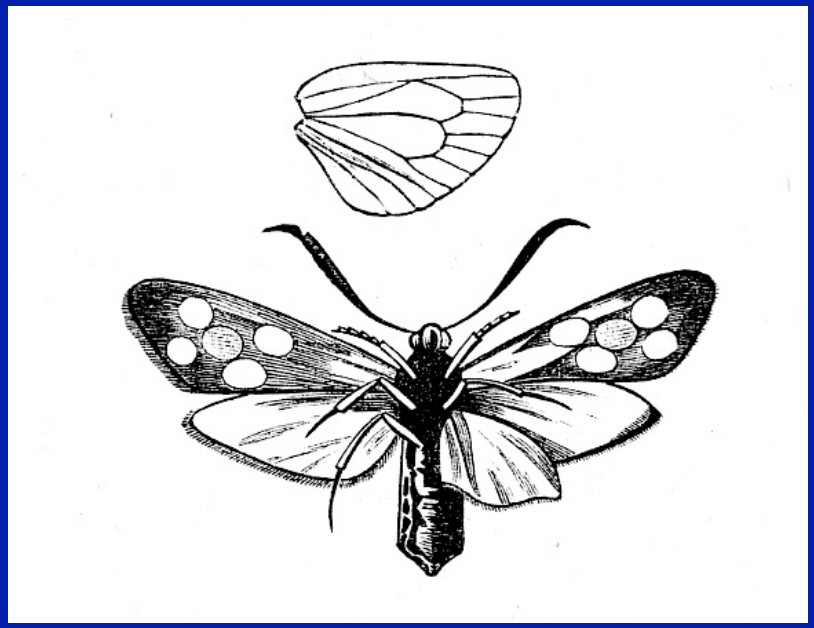
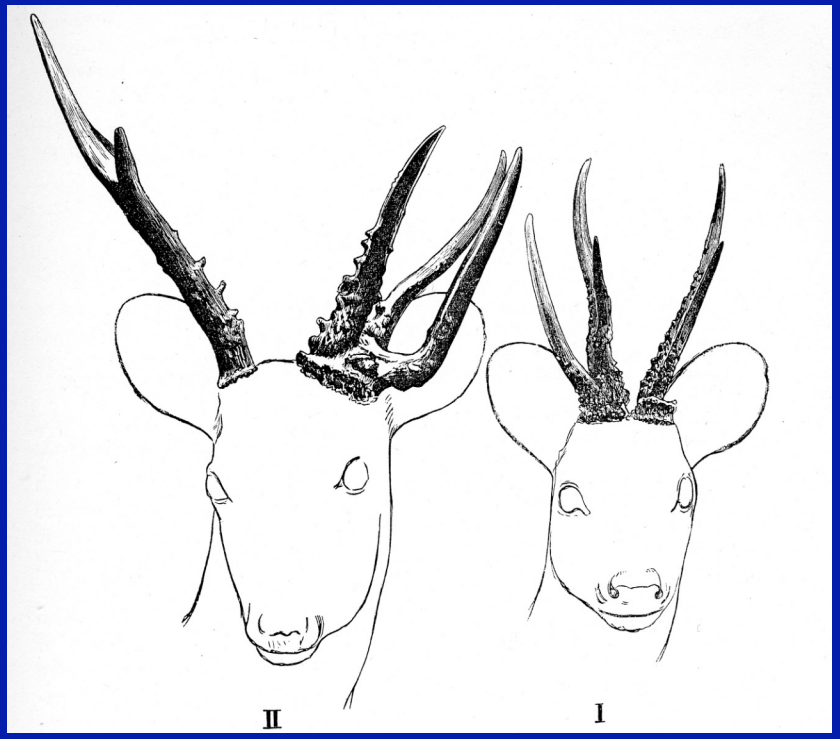
Homeosis: a variation in which 'something has been changed into the likeness of something else"

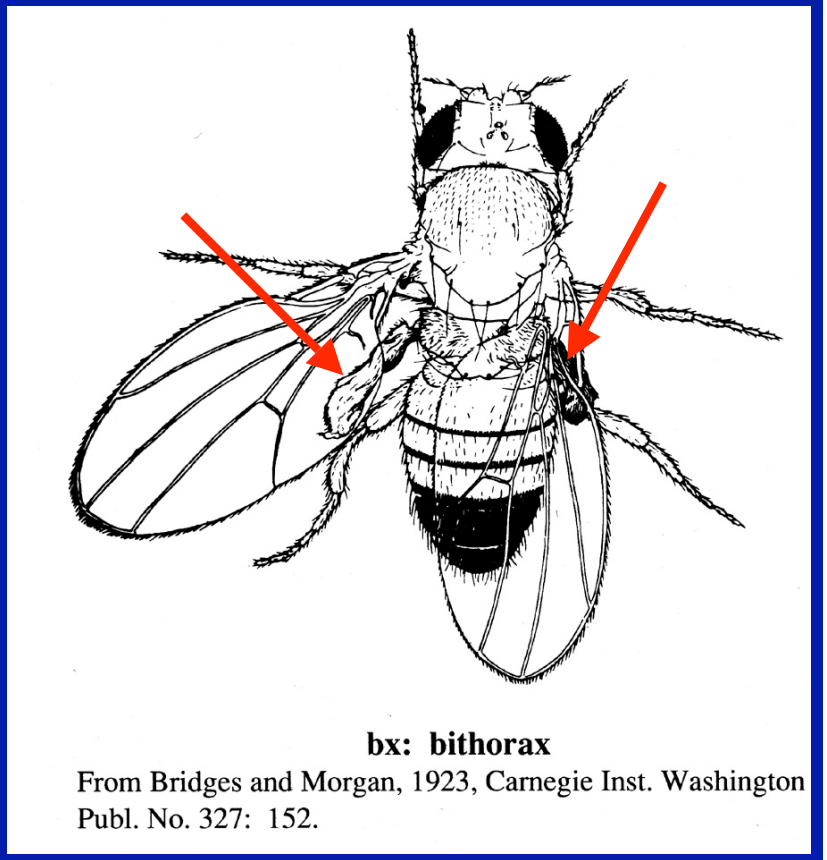

V'
V


1
2
3
4
5
6
7
8
9




II
I

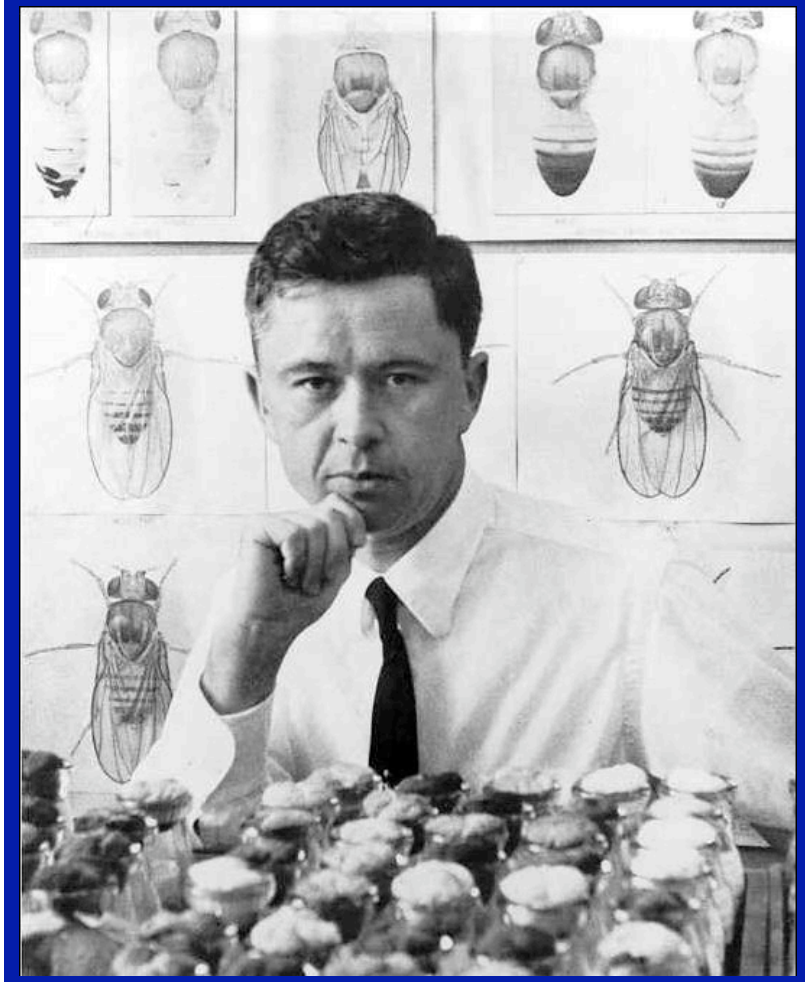
Calvin Bridges at Columbia



bx: bithorax

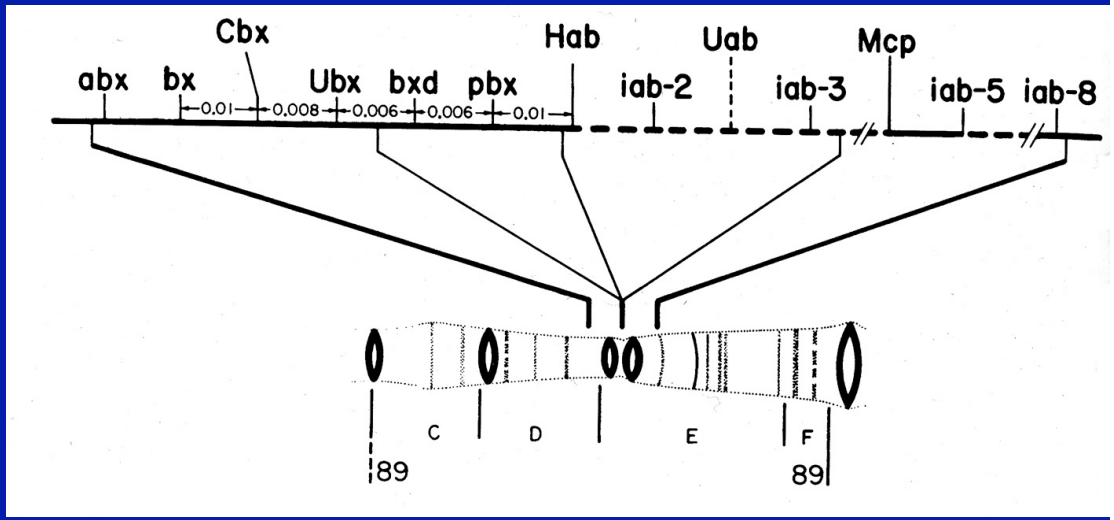
From Bridges and Morgan, 1923, Carnegie Inst. Washington Publ. No. 327: 152.

bithorax 1923

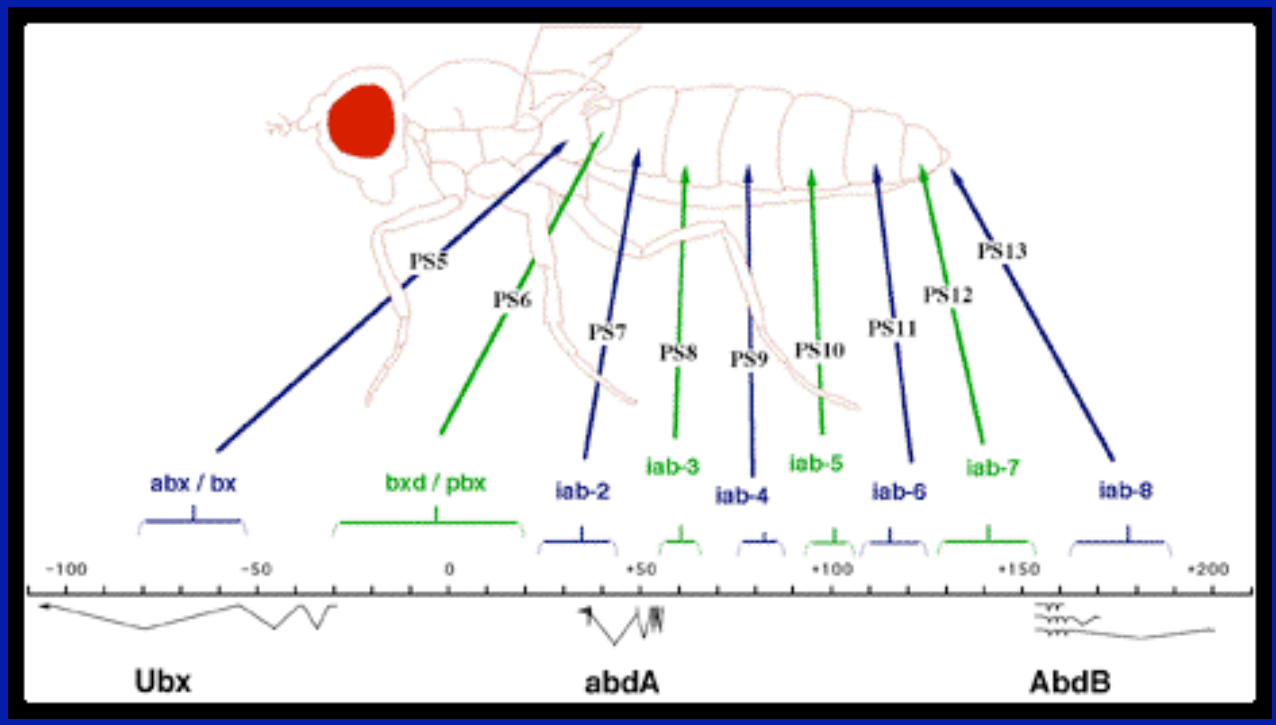


Ed Lewis, c. 1950

bx, pbx/Ubx



Genetic map of Bithorax complex

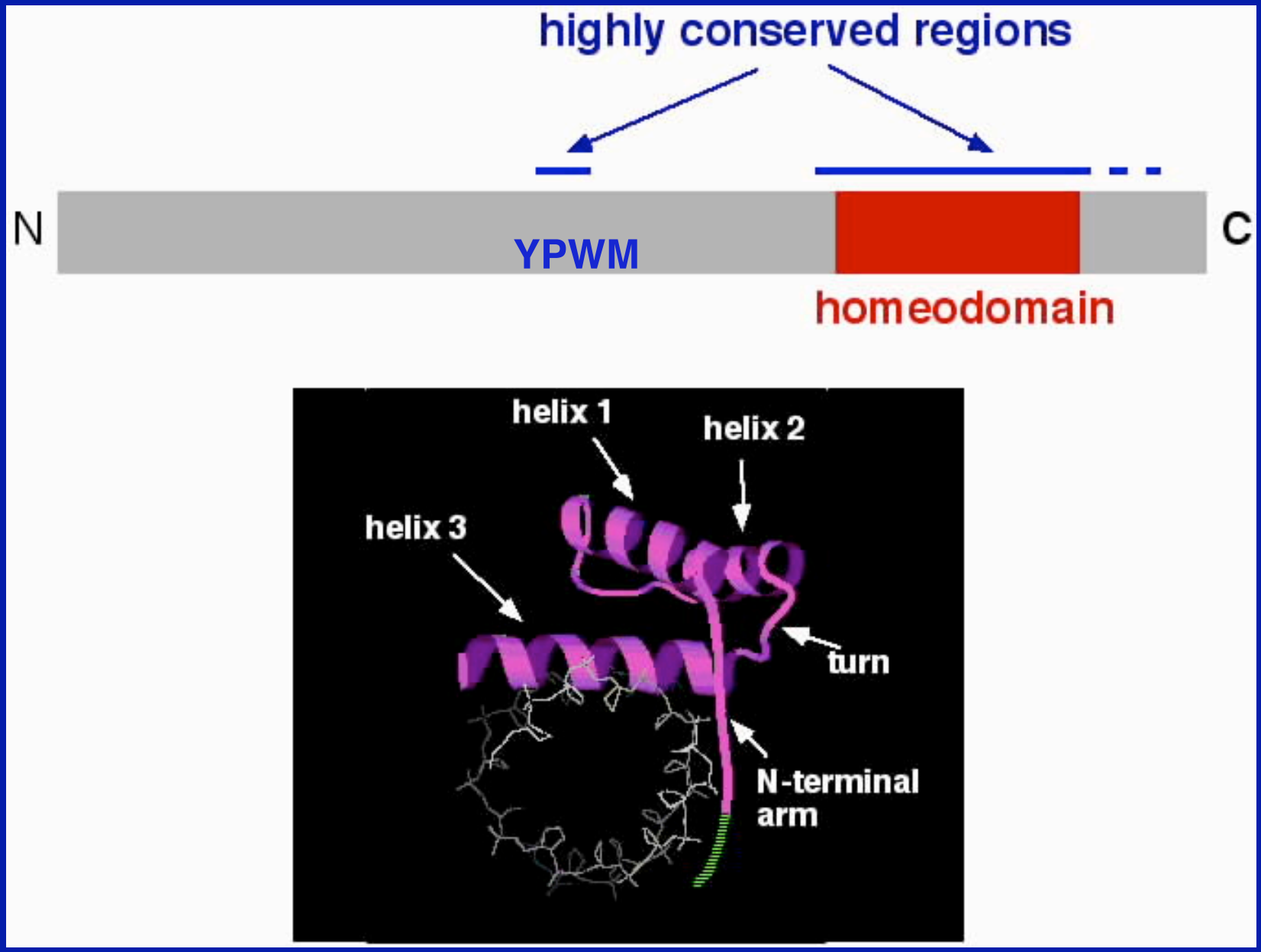


Cloning of Bx-C and molecular map
~1983

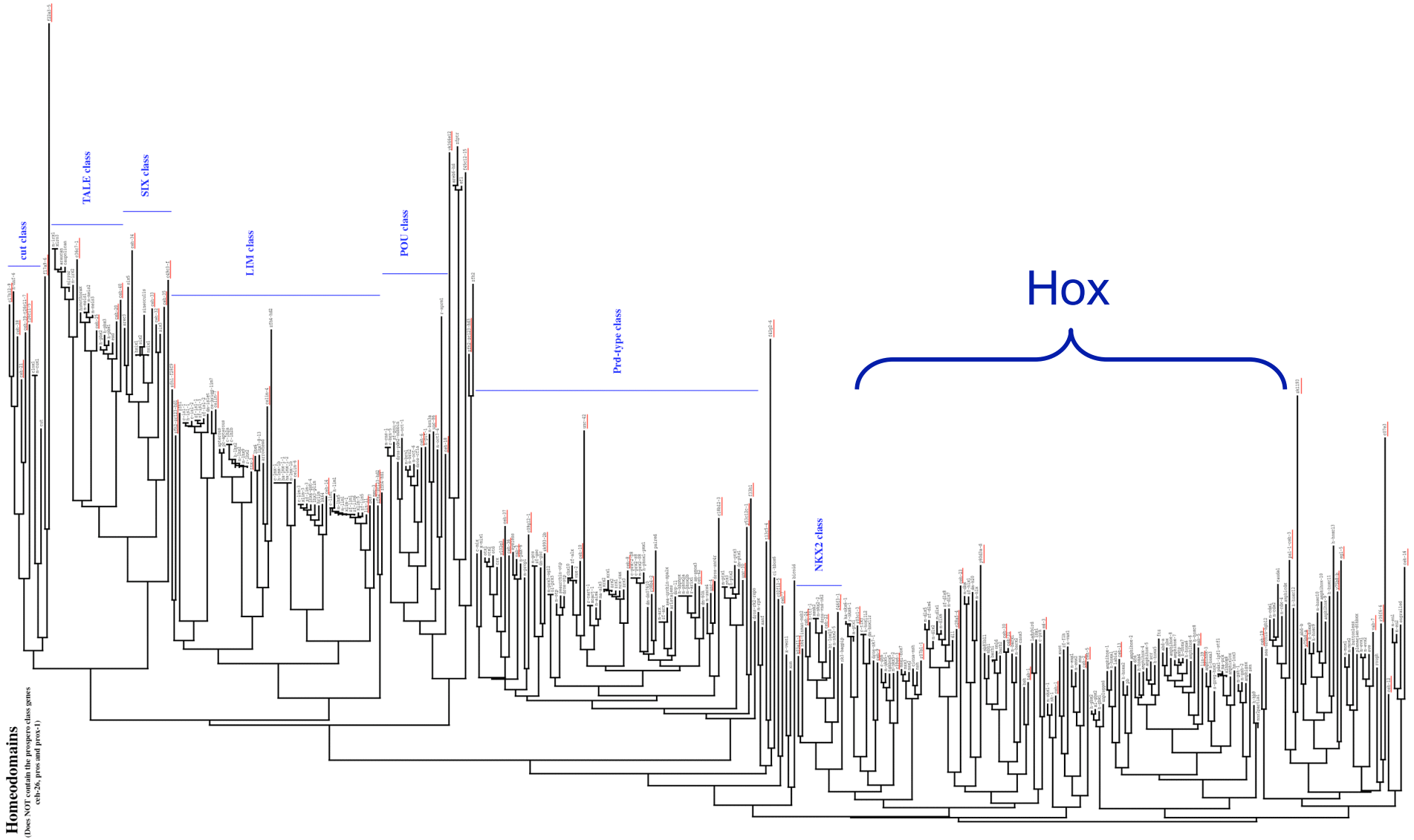
Discovery of homeobox, 1984

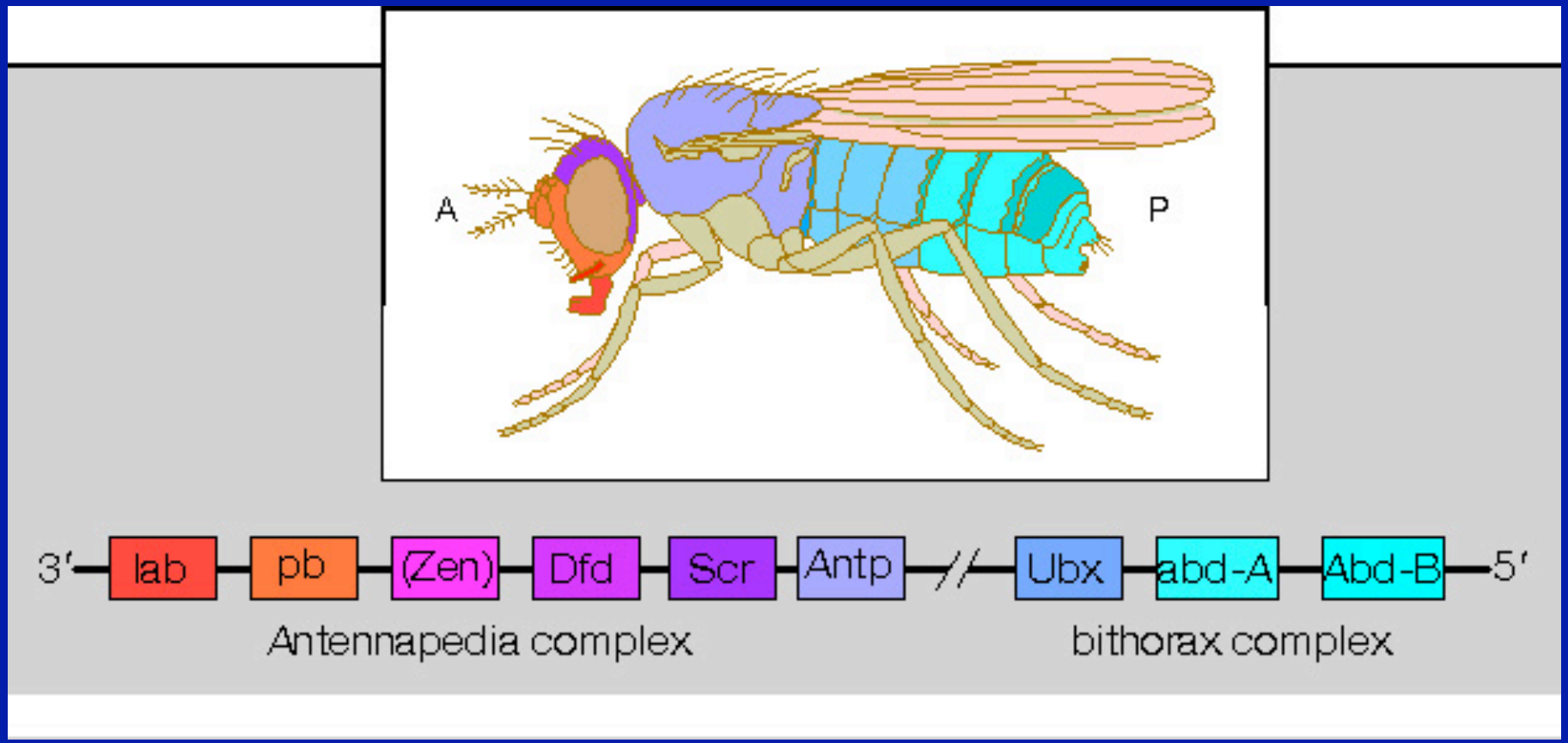
Homeodomain bound to DNA

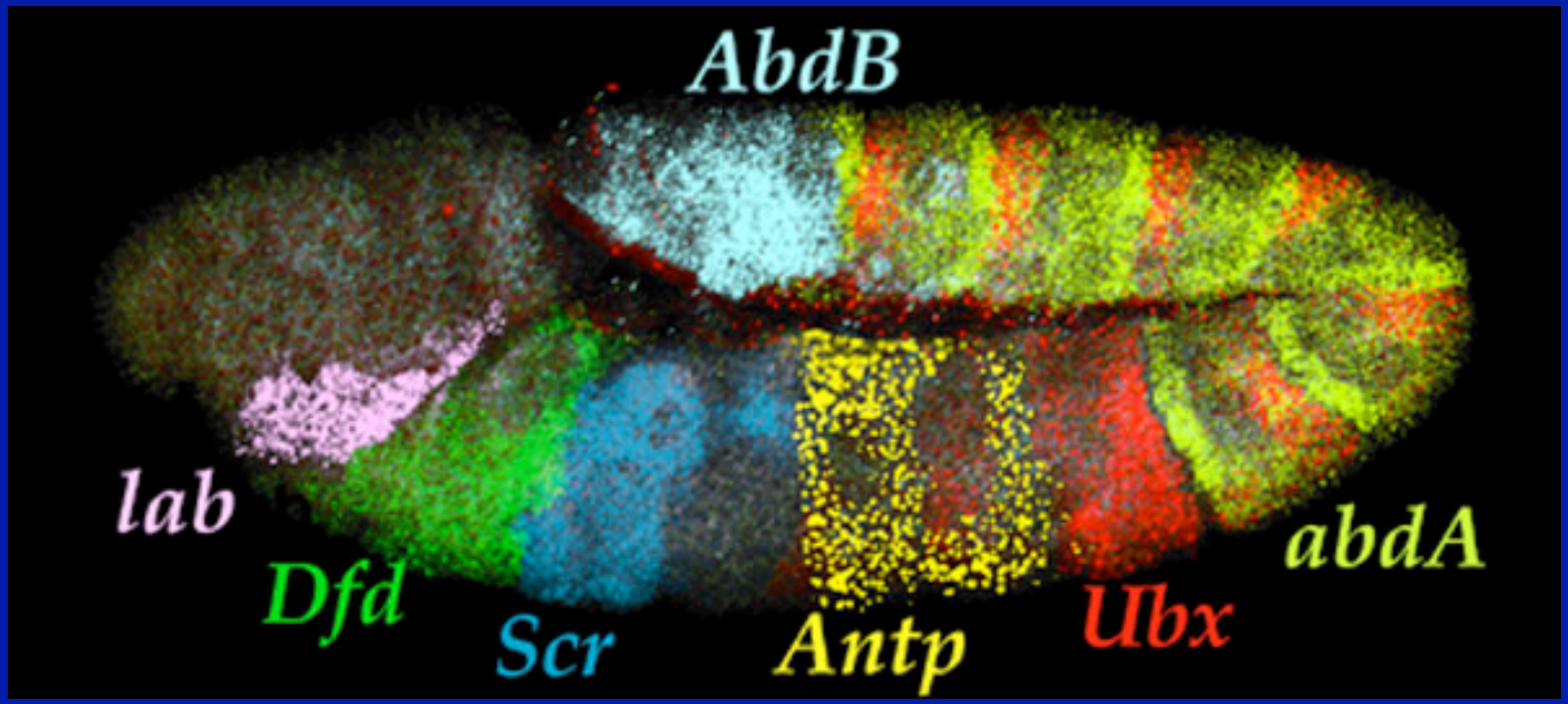
Hox proteins are homeodomain-containing transcription factors



Homeodomains are everywhere

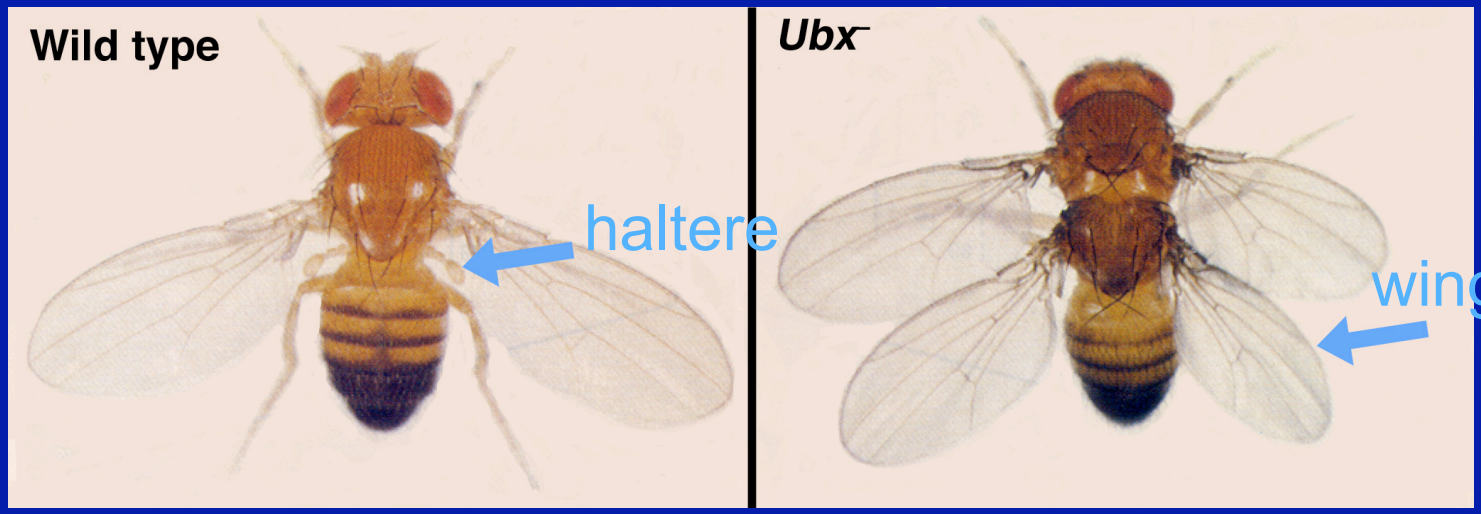


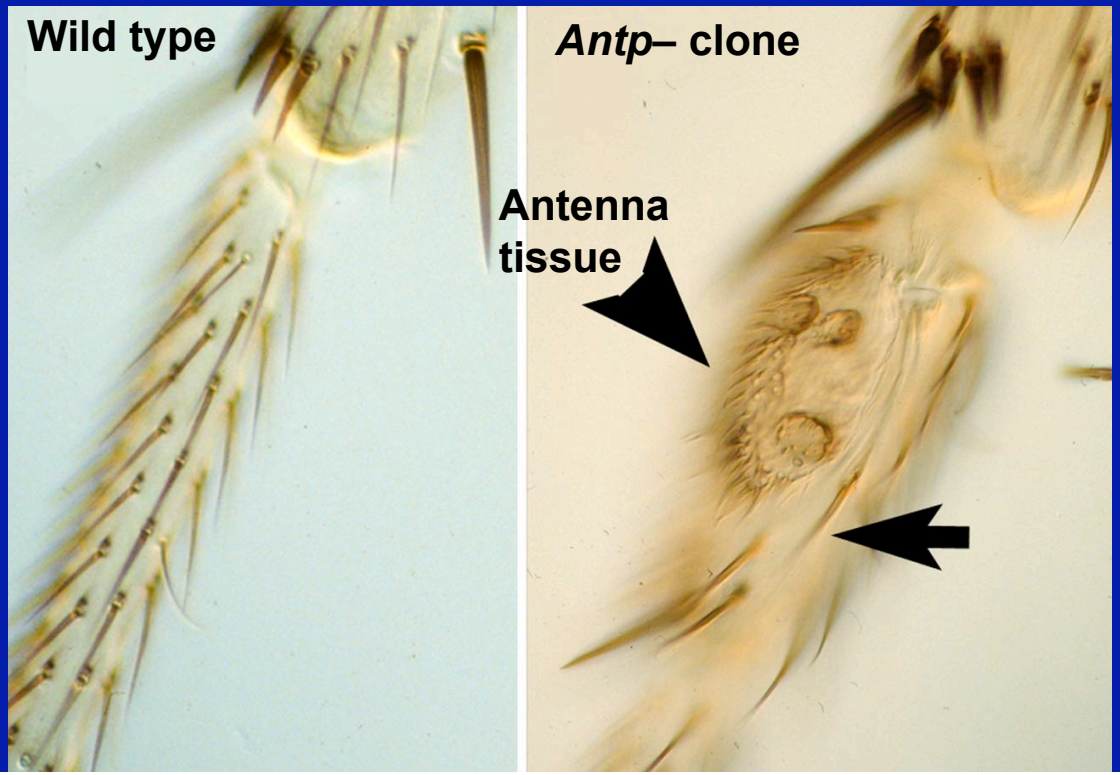

A
P
3′
lab
pb
(Zen)
Dfd
Scr
Antp
//
Ubx
abd-A
Abd-B
5′
Antennapedia complex
bithorax complex

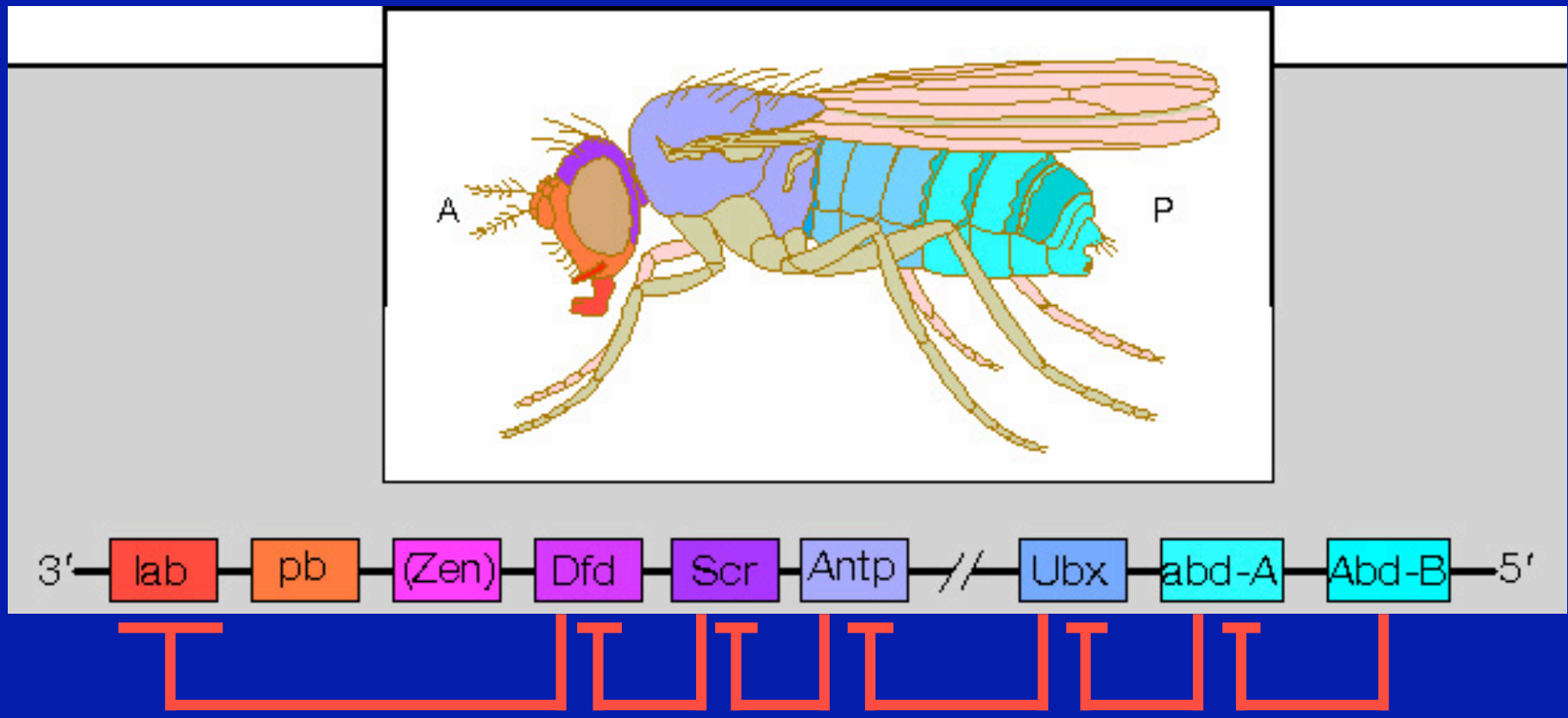


Kosman… McGinnis and Bier

Hox loss-of-function produces posterior to anterior transformations

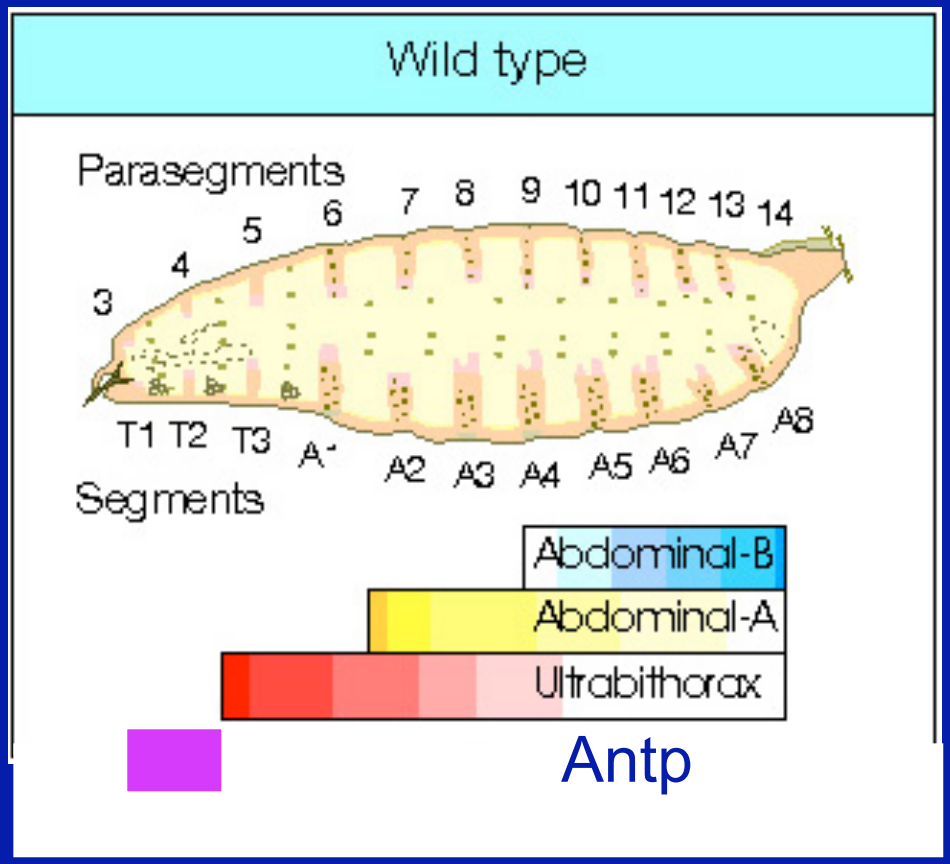


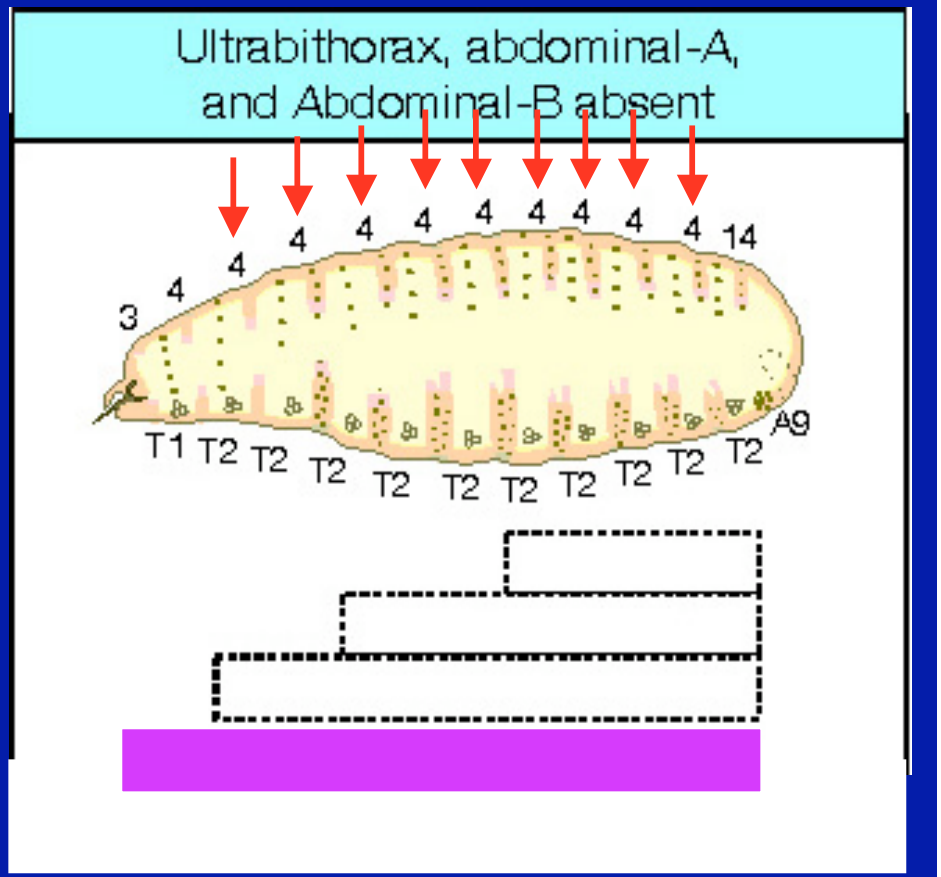



A
P
3′
lab
pb
(Zen)
Dfd
Scr
Antp
//
Ubx
abd-A
Abd-B
5′

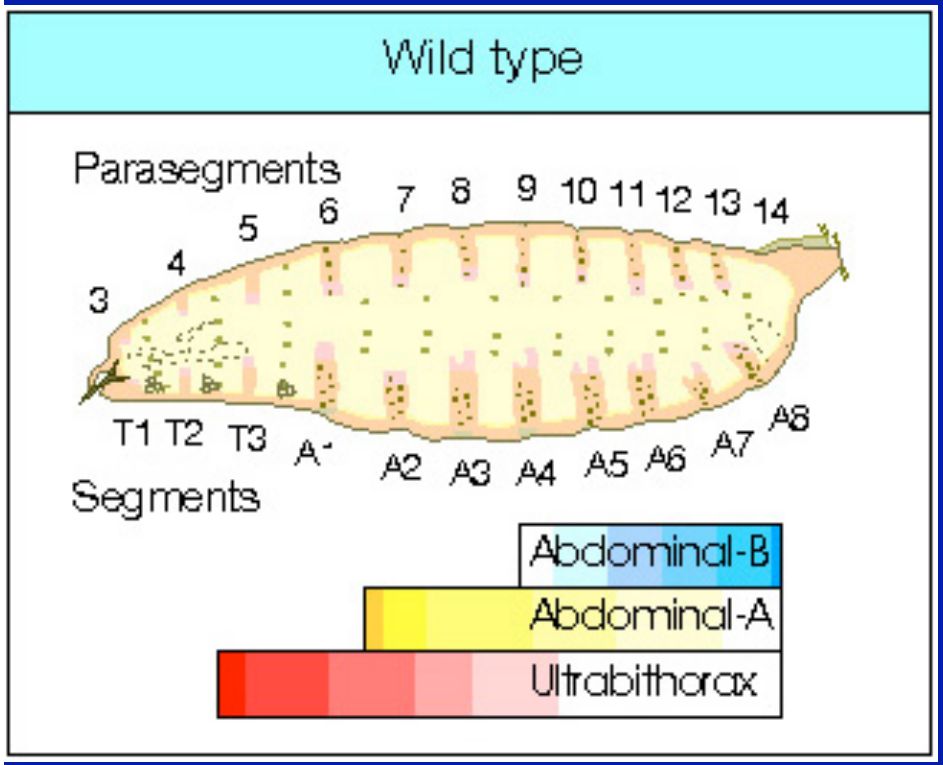
Segmentation is easily observed in the larva

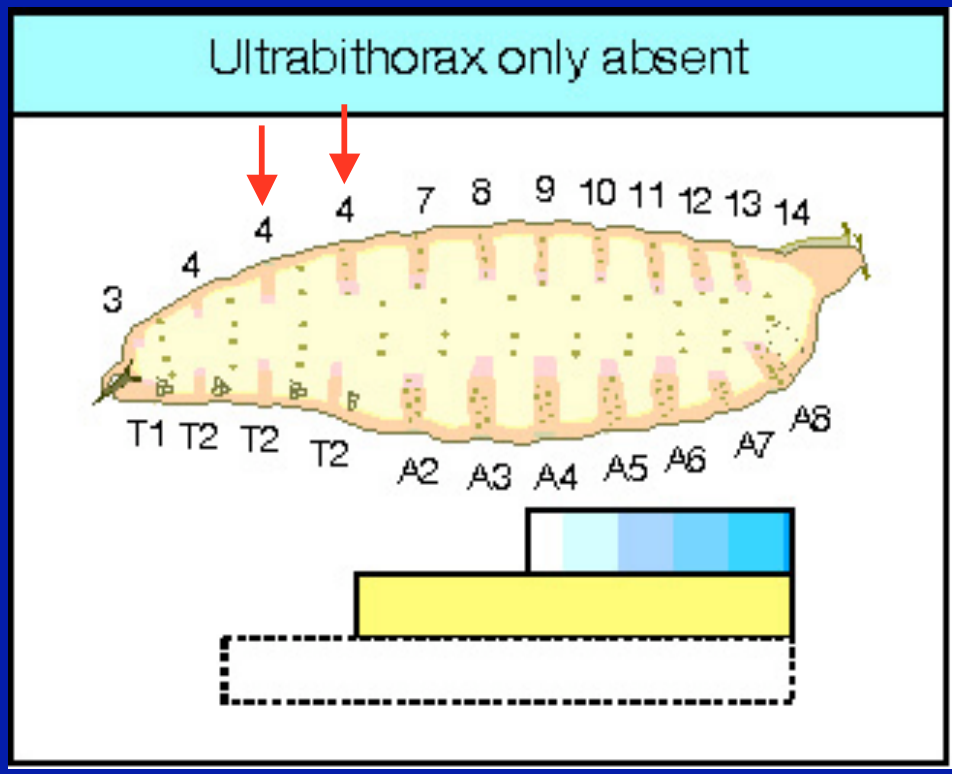
Posterior-to-anterior transformations of segment identity in Hox loss-of-function mutants: *Ubx- abdA- AbdB-*



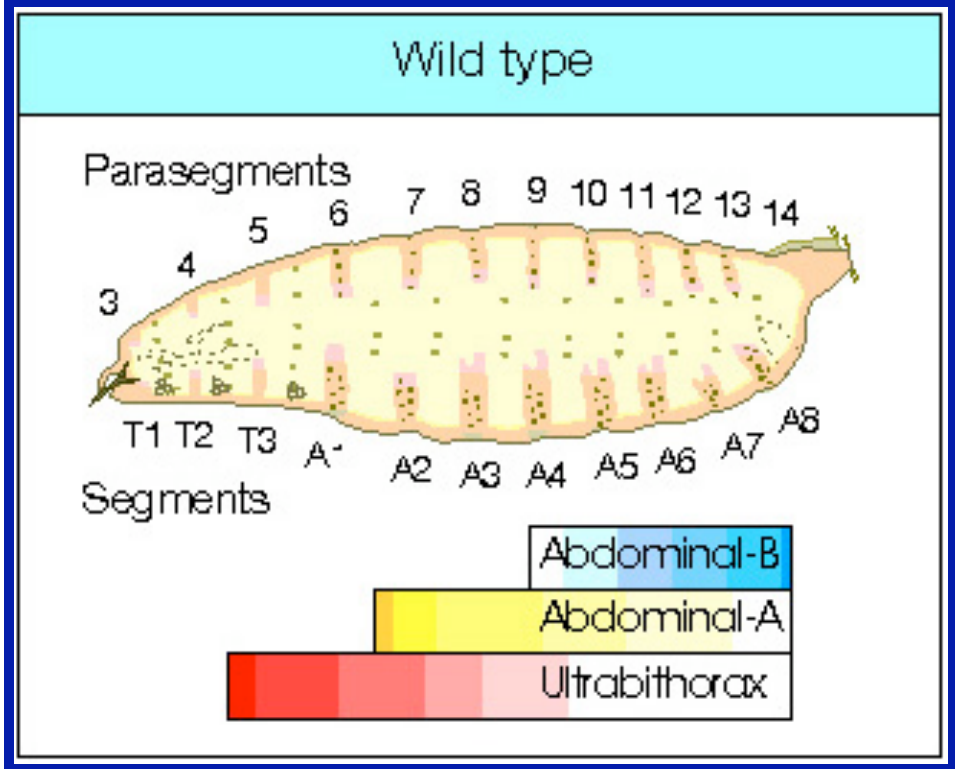


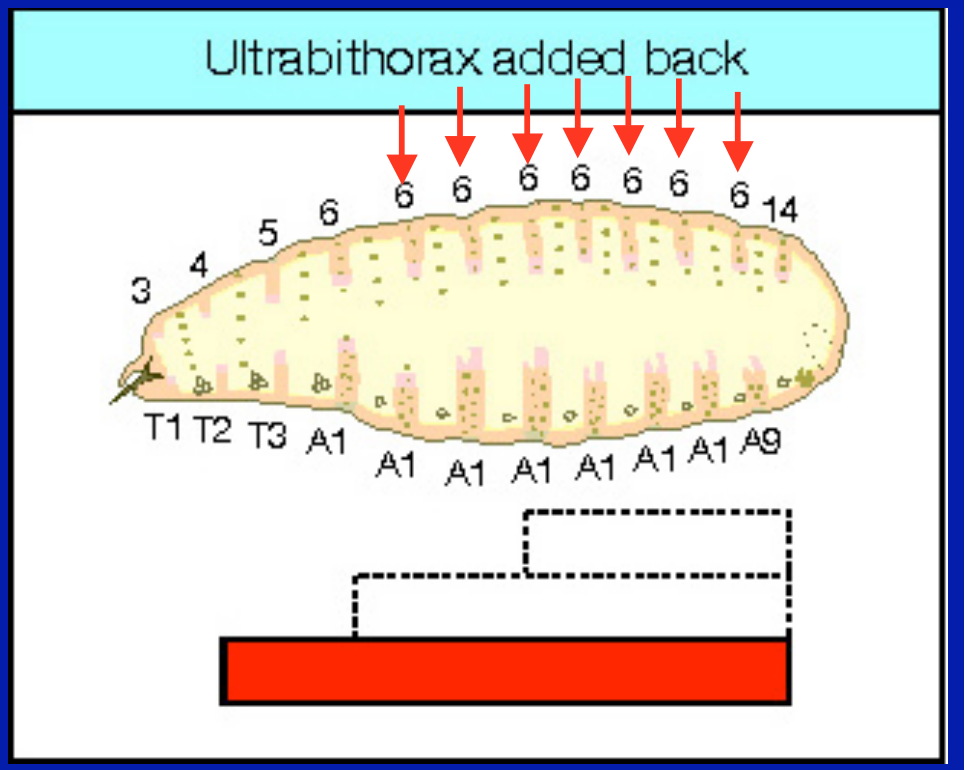
Posterior-to-anterior transformations of segment identity in Hox loss-of-function mutants: *Ubx-*



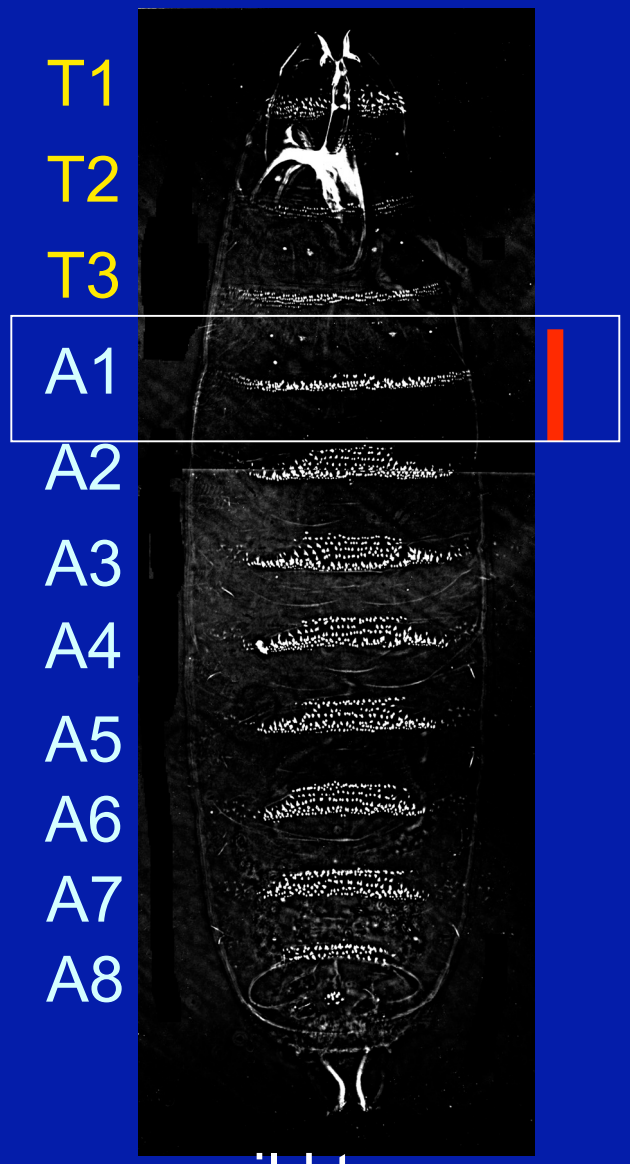


Posterior-to-anterior transformations of segment identity in Hox loss-of-function mutants: *abdA- AbdB-*

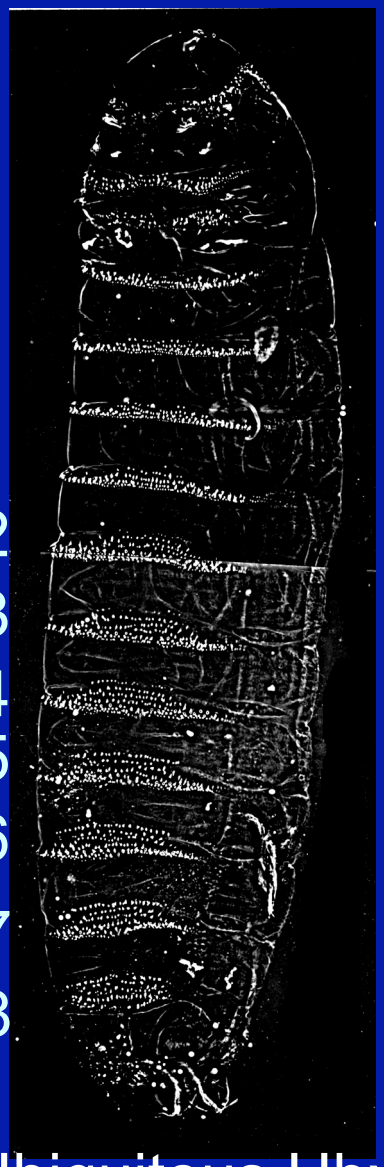




Hox gain-of-function produce anterior to posterior transformations within the constraints of ‘posterior prevalence’



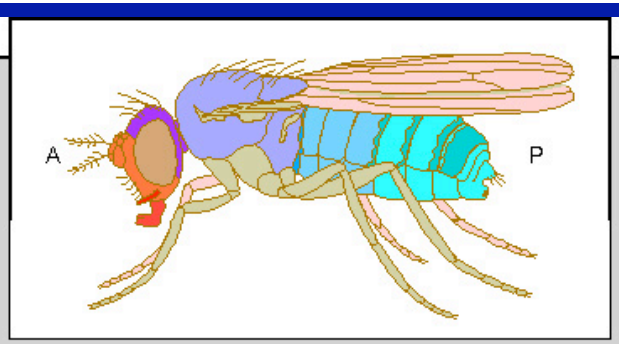
wild type



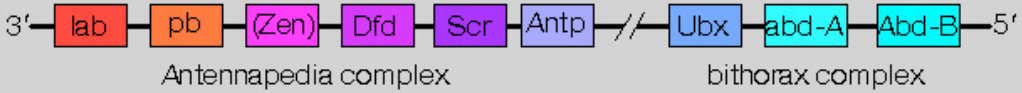
Ubiquitous Ubx

These segments are transformed to ‘A1’ identity

These segments are not affected

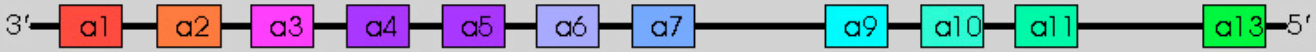


Drosophila

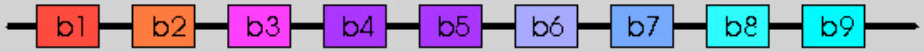


Mouse

Hoxa, chromosome 6

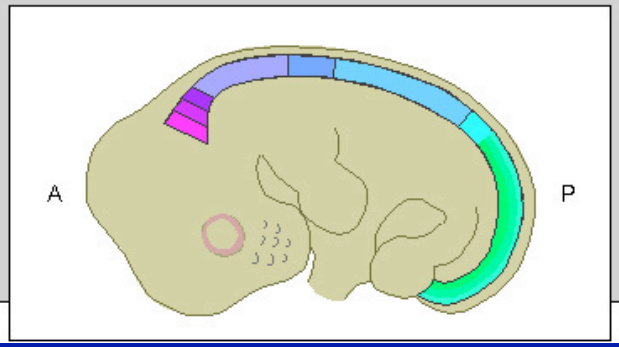


Hoxb, chromosome 11



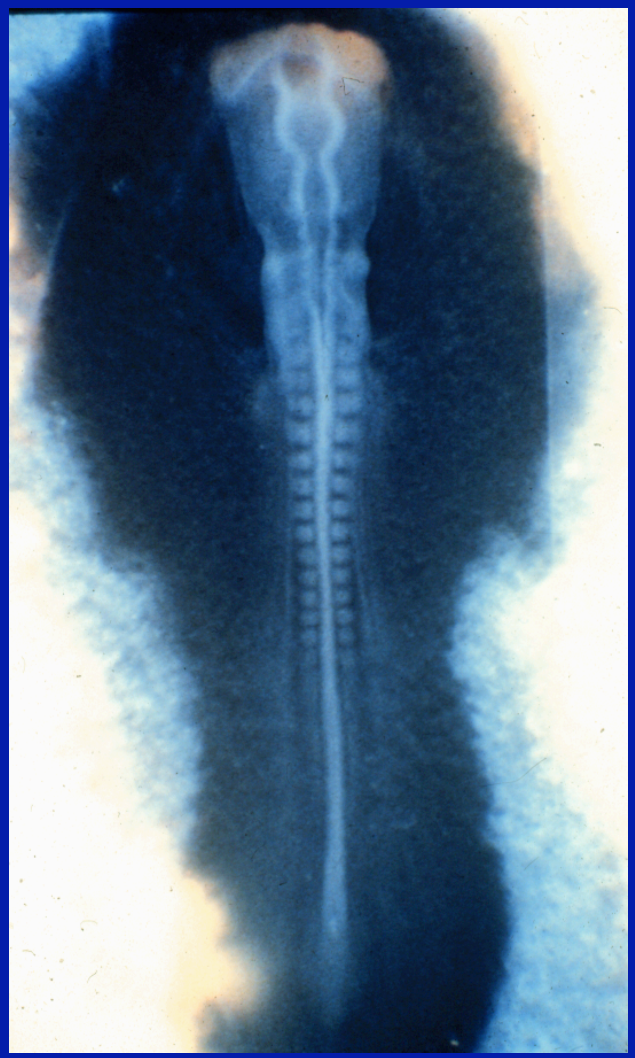
Hoxc, chromosome 15

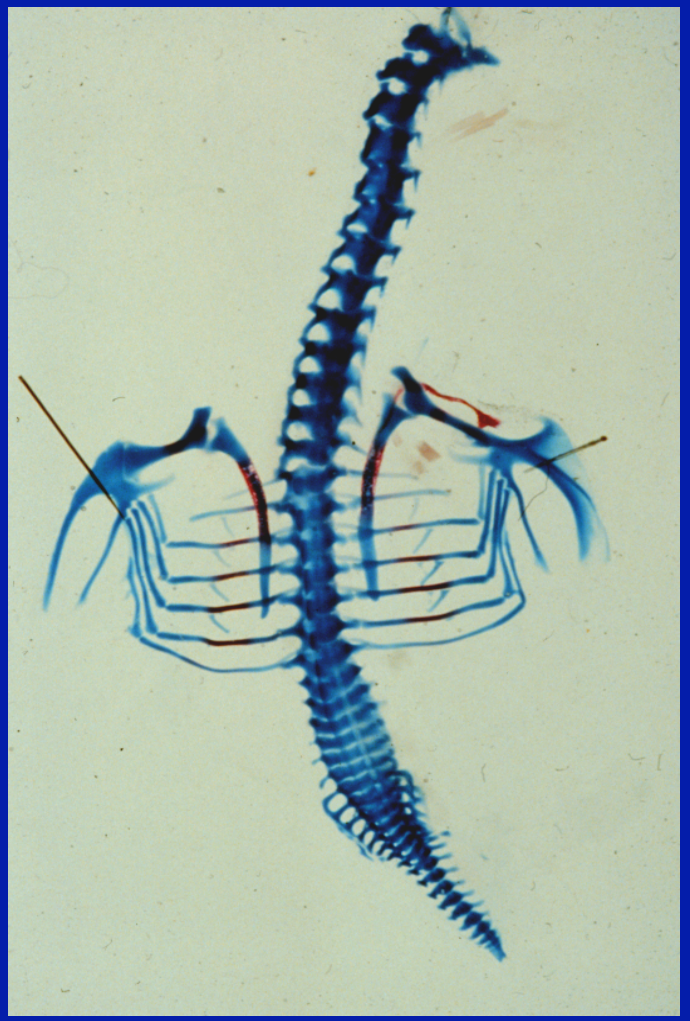
Hoxd, chromosome 2



Segmentation

Regionalization

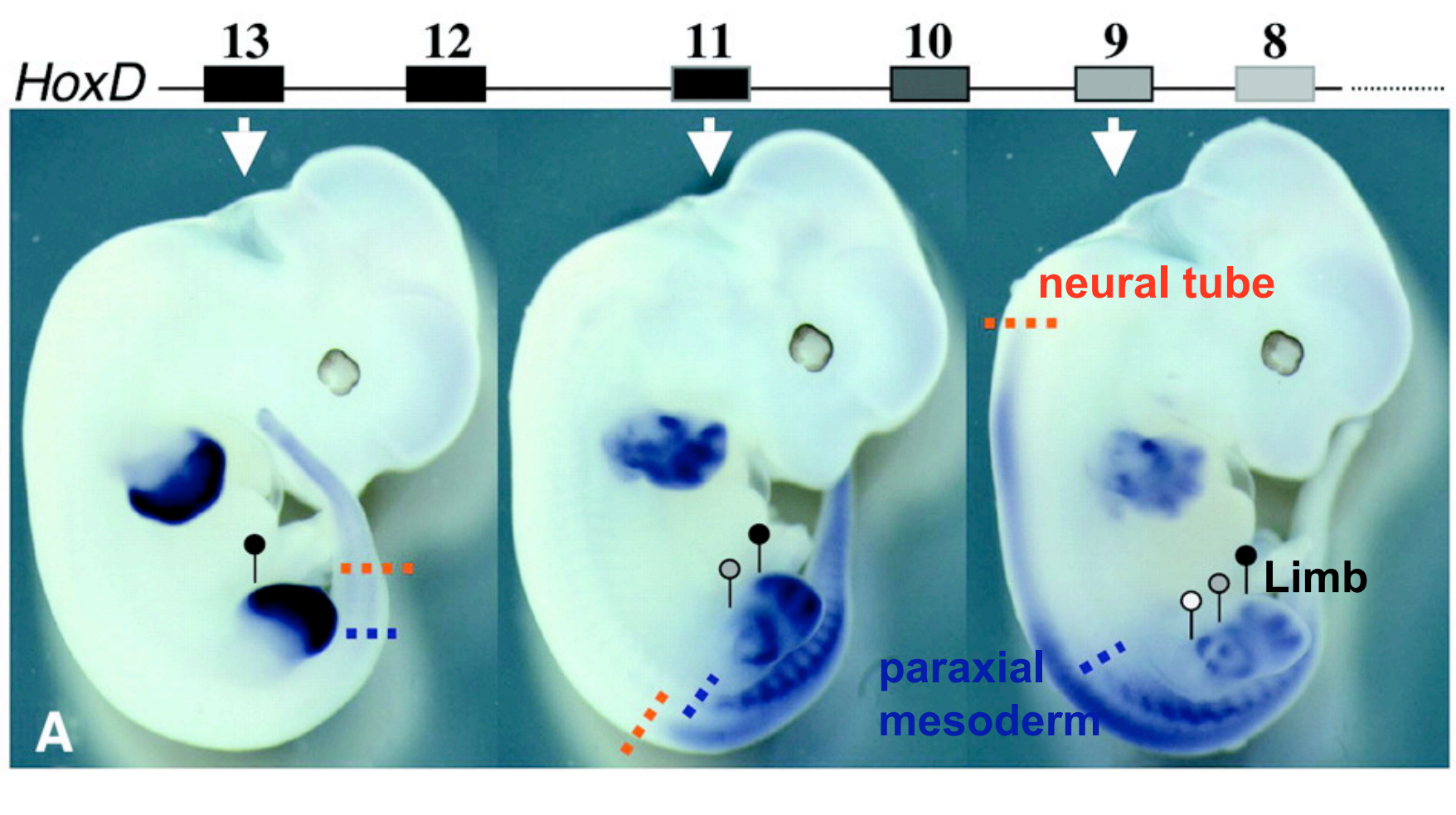


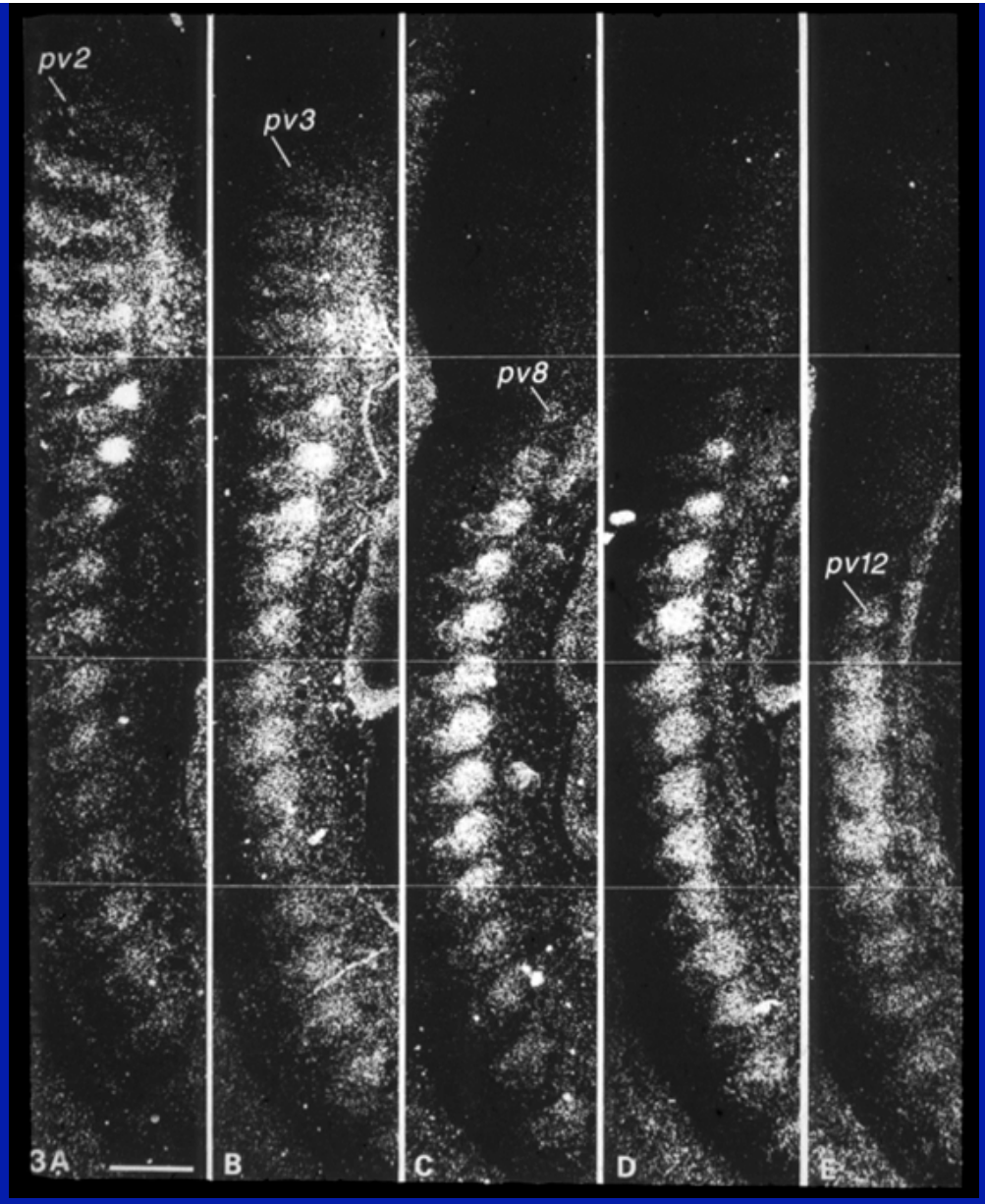


Segmentation Clock

Hox genes

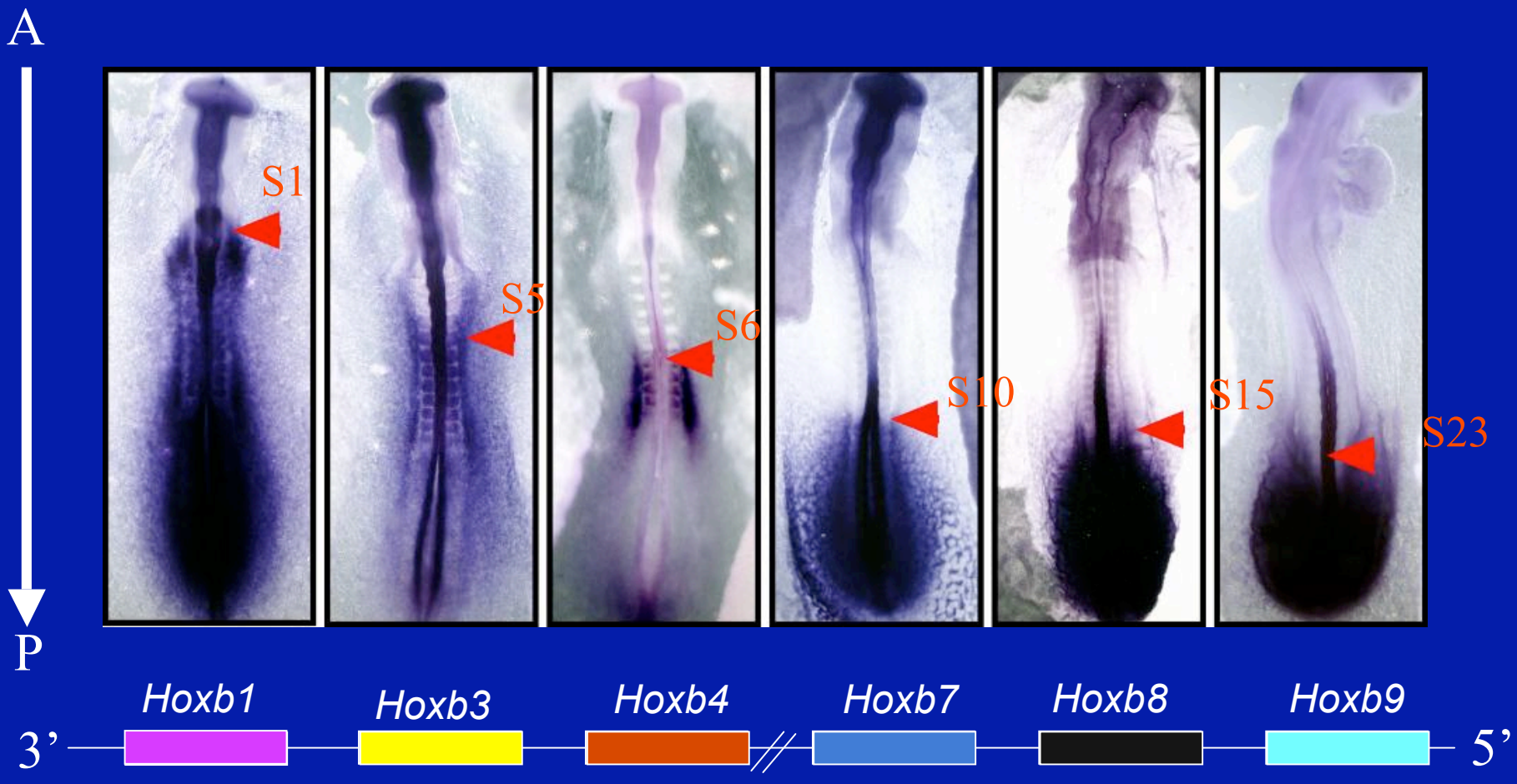
Spatial colinearity is observed in the vertebrate Hox genes



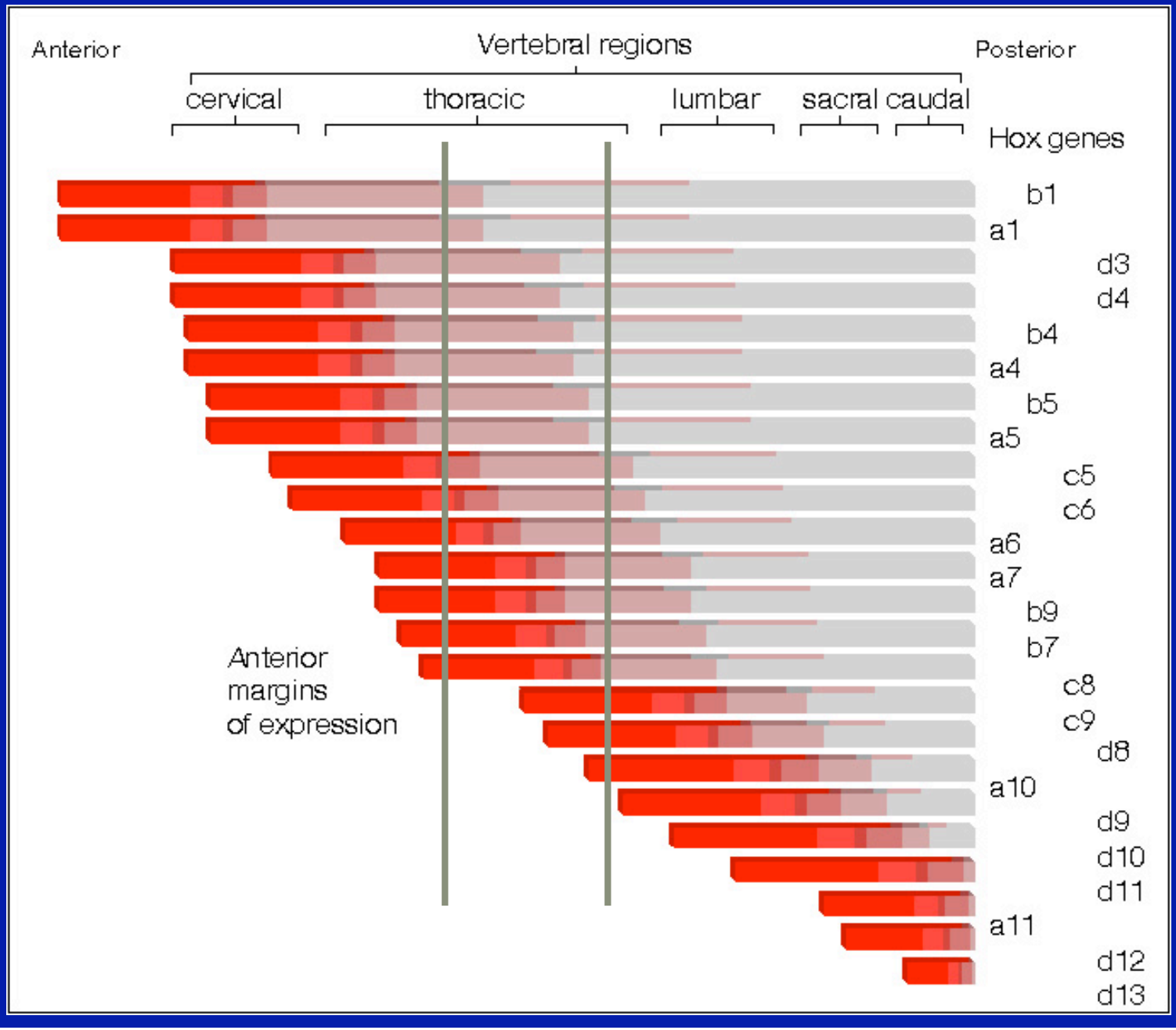


As in flies, vertebrate Hox genes are expressed in over-lapping anterior-posterior domains during embryogenesis

Regionalisation of *Hox* expression along the paraxial mesoderm



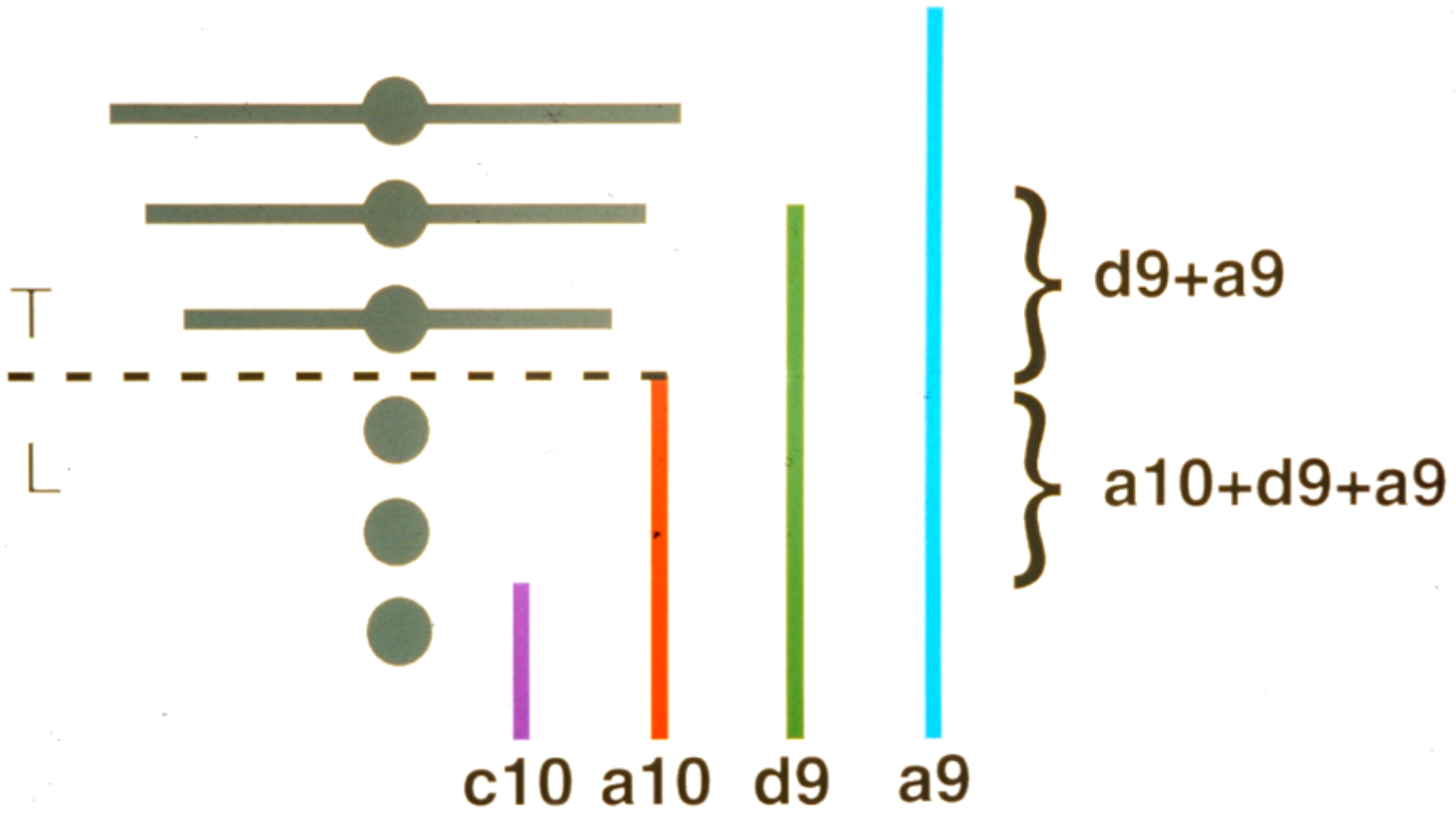
Is there a ‘Hox code’?

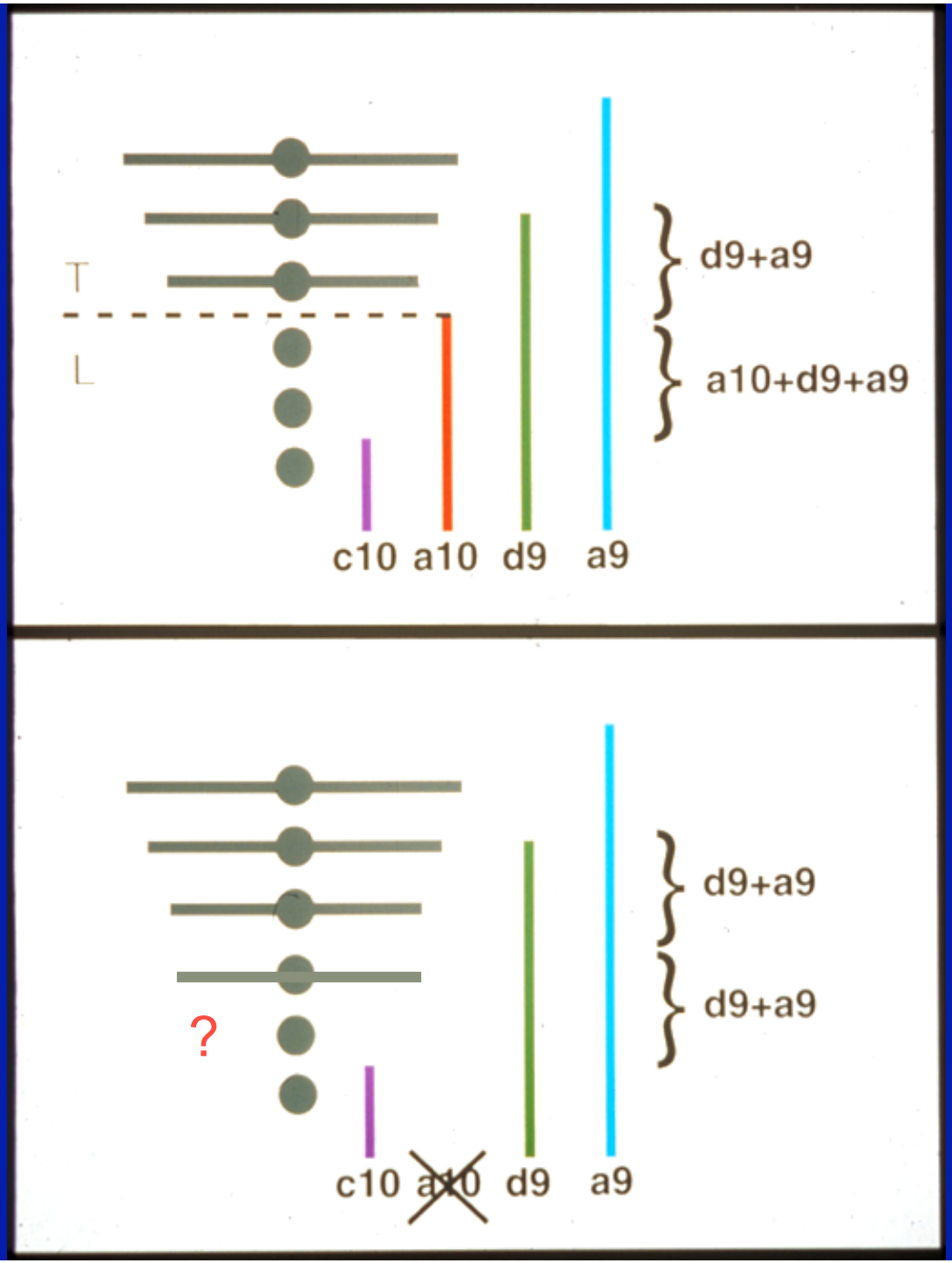


Different Hox genes correlate with different vertebral morphologies

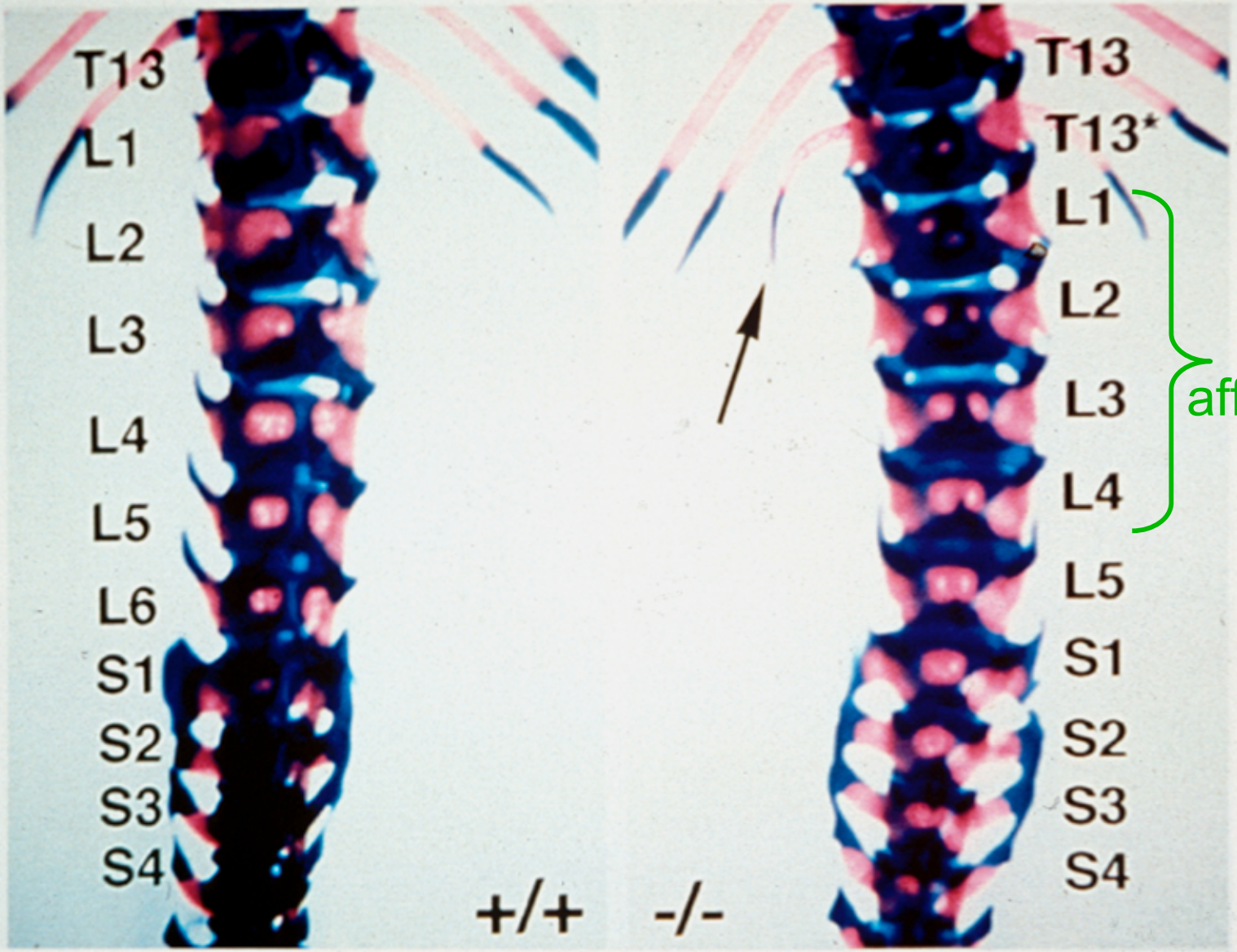
HOX CODE ASSIGNEMENT TO VERTEBRAL COLUMN

Gene	Atlas	Axis	C 3	C 4	C 5	C 6	C 7	T 1	T 2
Hox-1.6	+	+	+	+	+	+	+	+	+
Hox-1.5	+	+	+	+	+	+	+	+	+
Hox-2.6	+	+	+	+	+	+	+	+	+
Hox-4.2	+	+	+	+	+	+	+	+	+
Hox-1.4		+	+	+	+	+	+	+	+
Hox-2.1			+	+	+	+	+	+	+
Hox-1.3			+	+	+	+	+	+	+
Hox-2.5						+	+	+	+
Hox-3.4						+	+	+	+
Hox-3.3							+	+	+
Hox-1.2								+	+


T
L
c10
a10
d9
a9
d9+a9
a10+d9+a9



Predicted changes in a Hoxa10 mutant

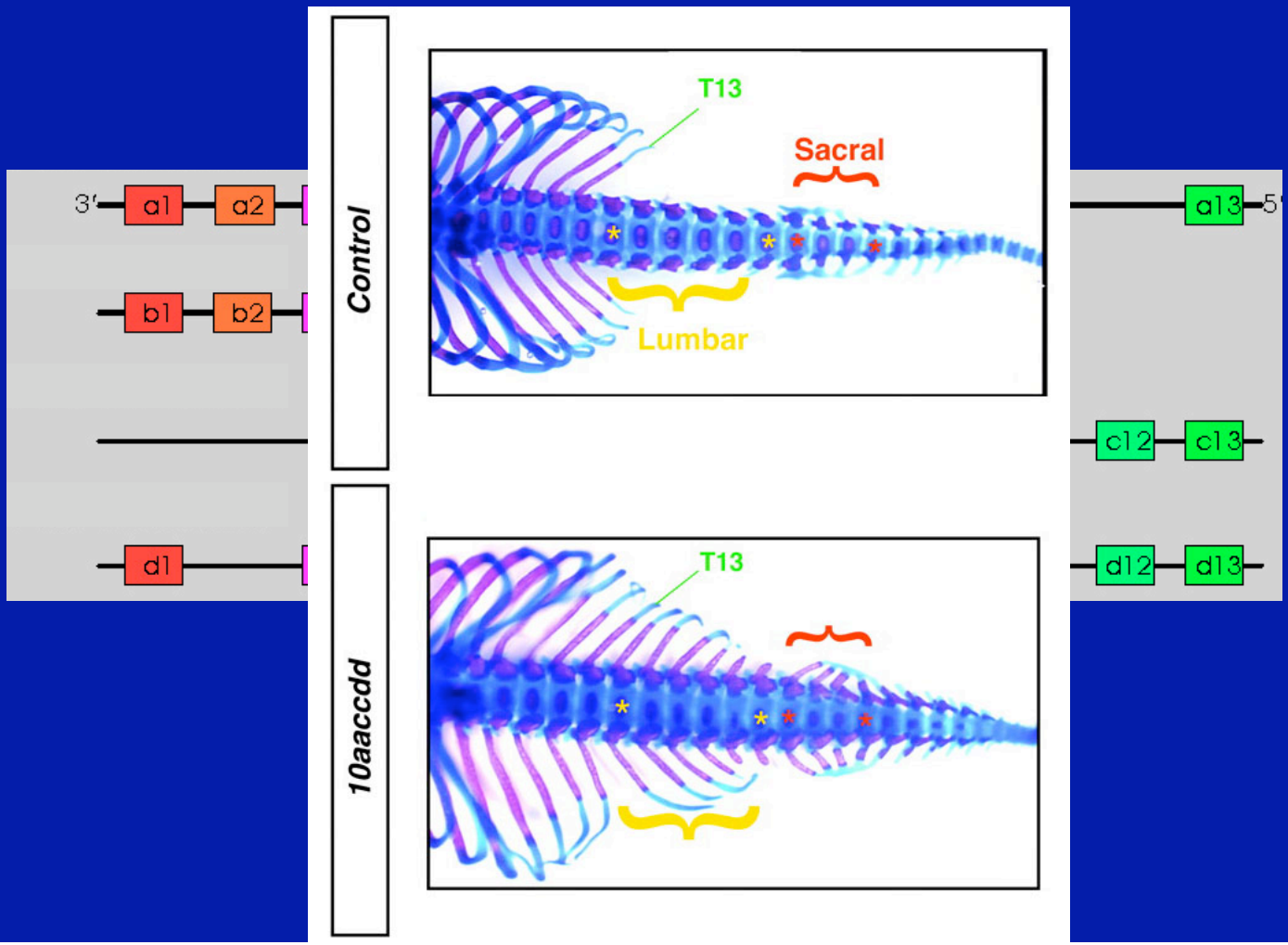


Hoxa-10 Mutant Phenotype

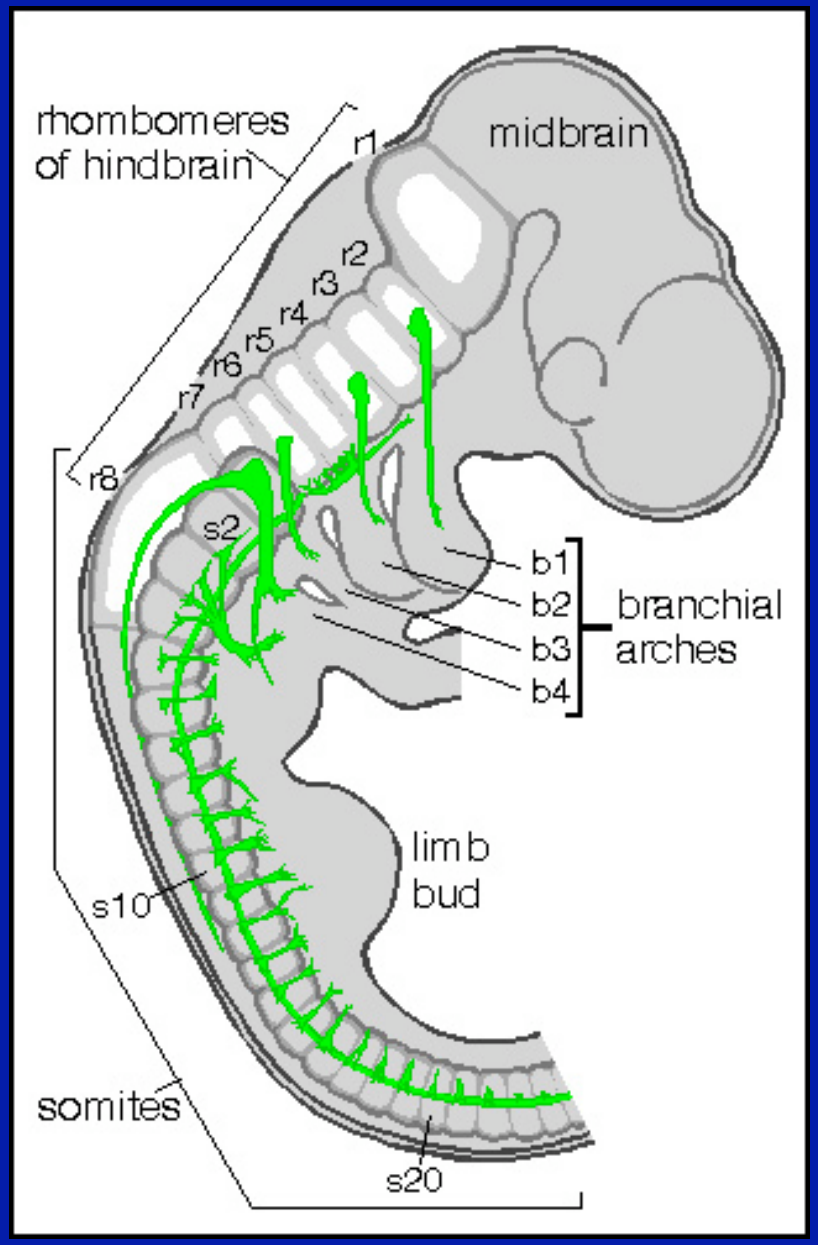
This analysis has been complicated by genetic redundancy—the expression and function of two or more similar *Hox* genes in overlapping domains.

Paralogs are expressed in similar domains, and substitute for each other.

When all *Hox10* paralogs are mutated, no lumbar vertebrae form, and instead, ribs project from all posterior vertebrae.

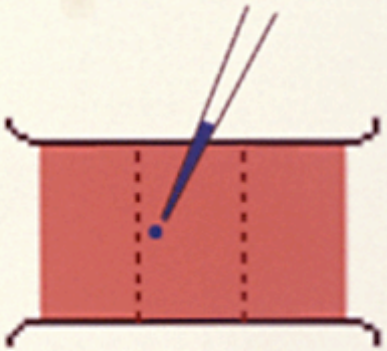


Transient segmentation of the hindbrain

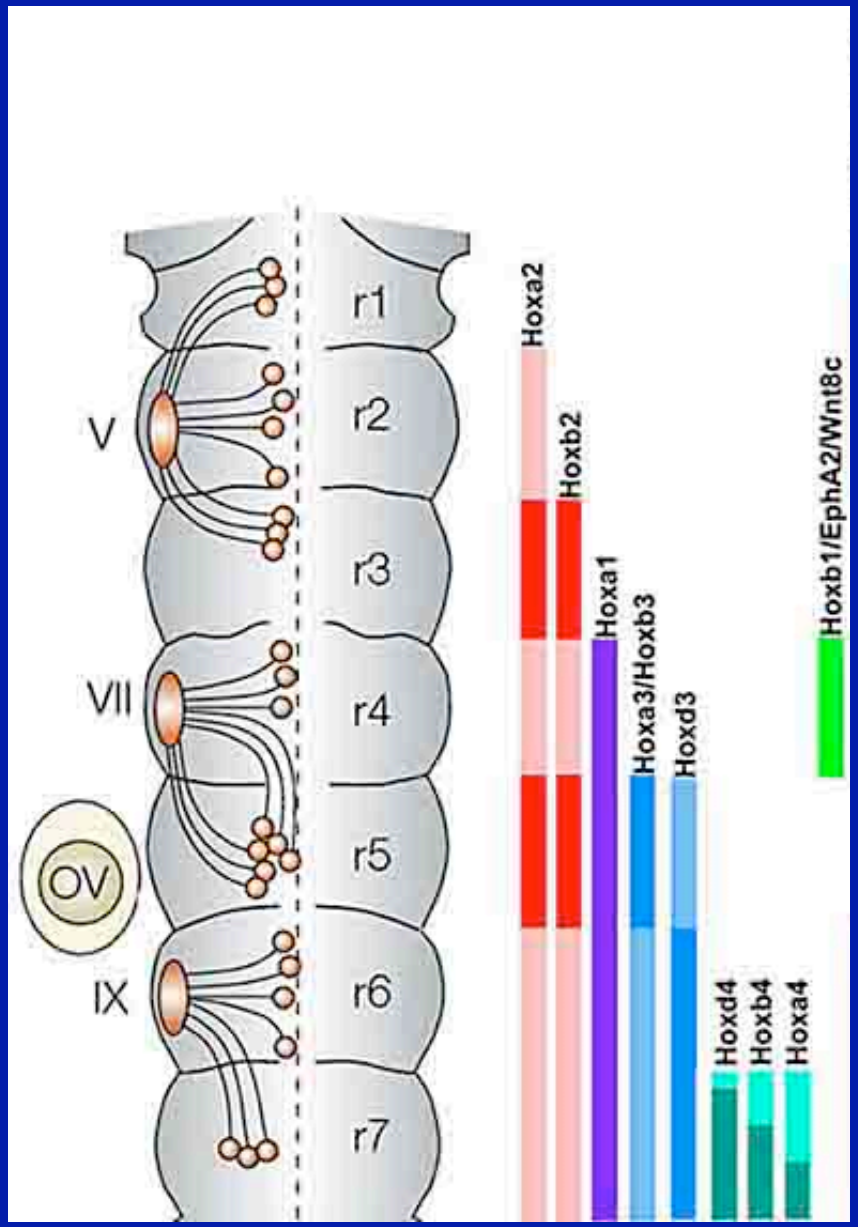

rhombomeres
of hindbrain
r1
midbrain
r2
r3
r4
r5
r6
r7
r8
s2
b1
b2
b3
b4
branchial
arches
limb
bud
s10
somites
s20

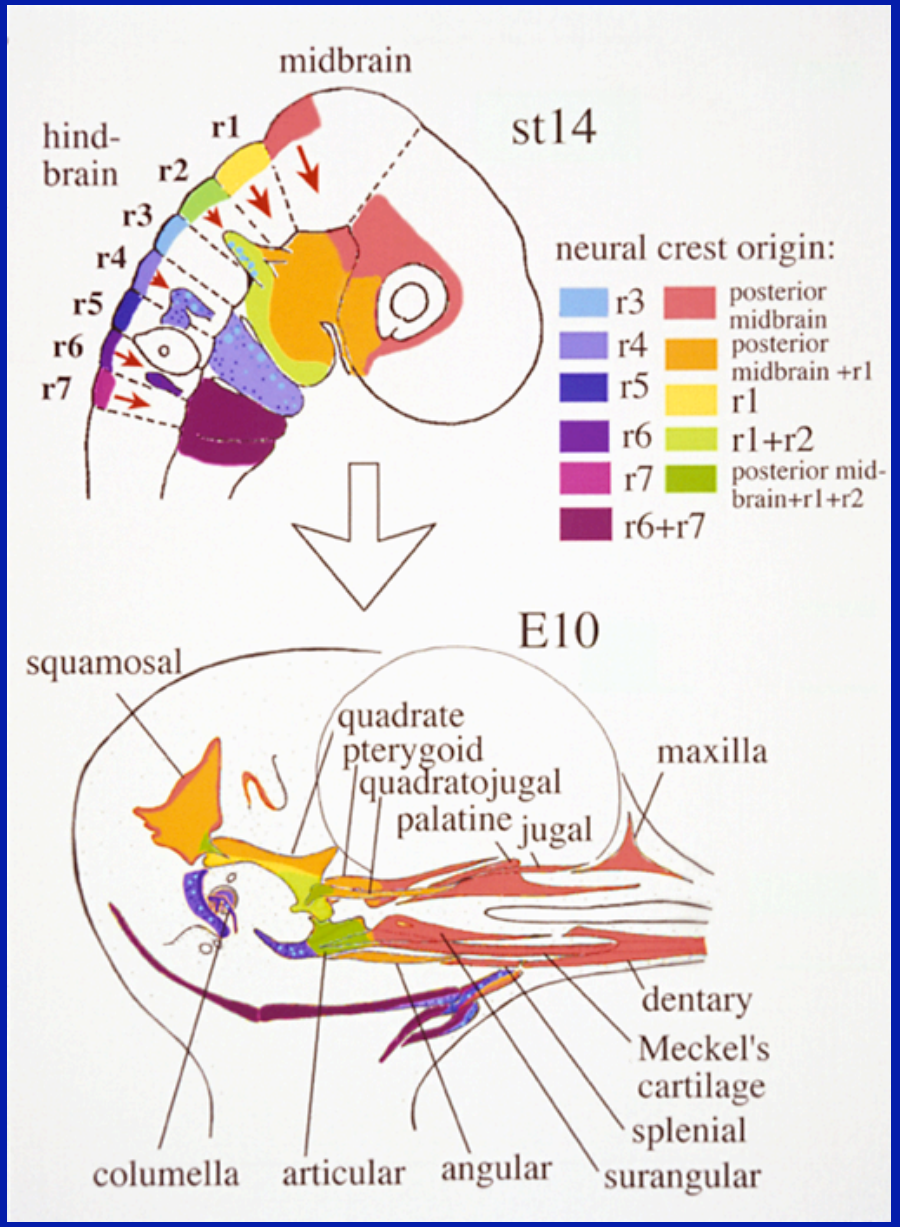
Rhombomeres are developmental "compartments" ie cell populations with distinct fates, which do not mix

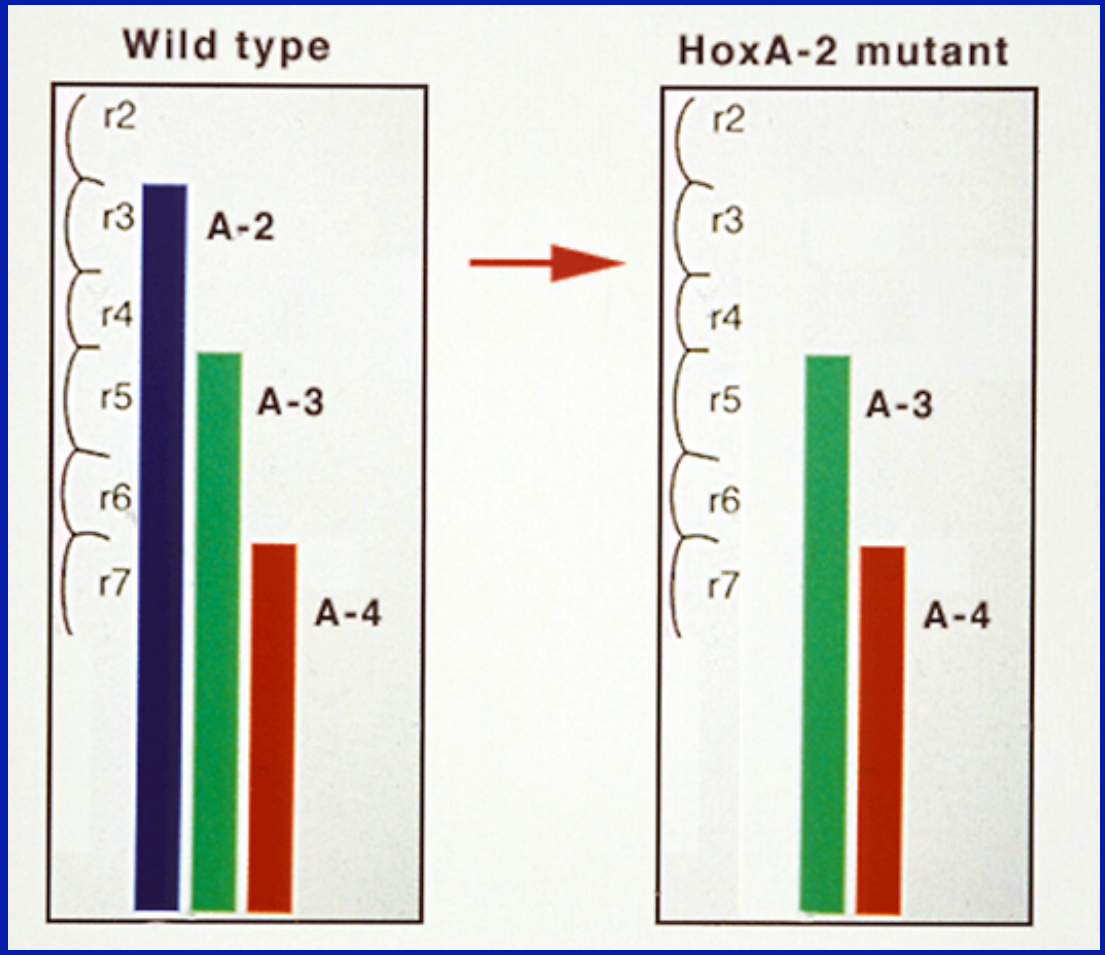
Mark a cell prior to morphpological formation of teh Rhombomeres



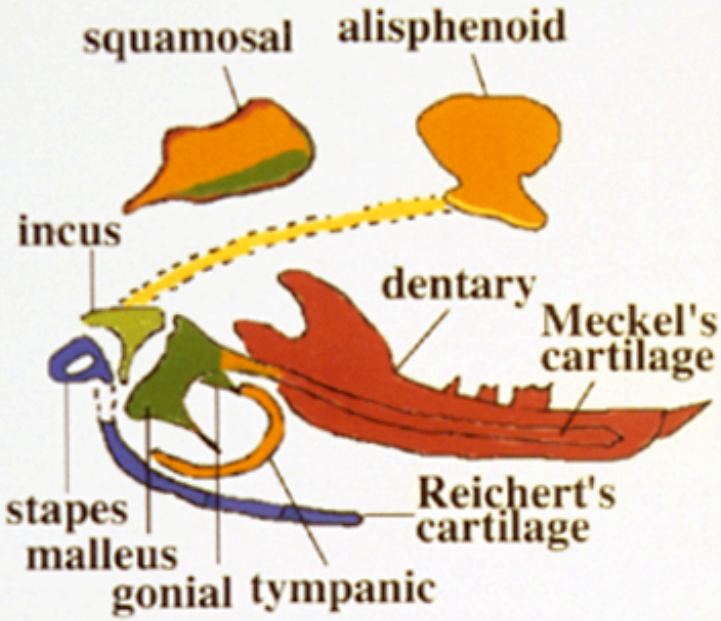
Resultant clone does not cross Rhombomere boundaries


r1
r2
r3
r4
r5
r6
r7
V
VII
IX
OV
Hoxa2
Hoxb2
Hoxa1
Hoxa3/Hoxb3
Hoxd3
Hoxd4
Hoxb4
Hoxa4
Hoxb1/EphA2/Wnt8c

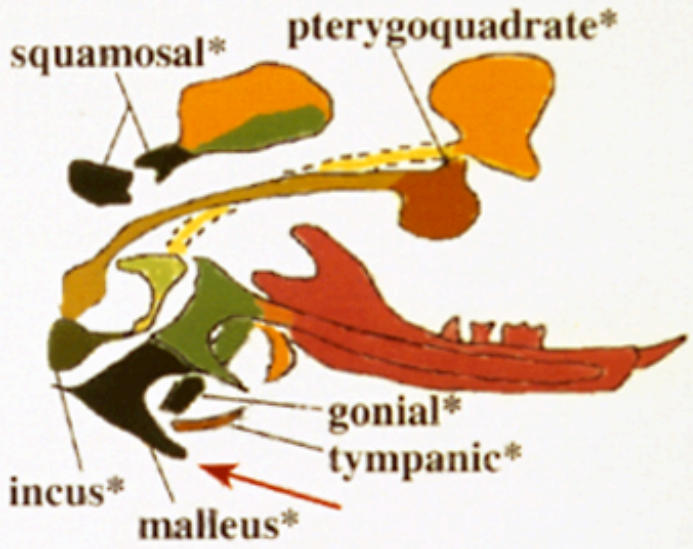

midbrain
hind-
brain
r1
r2
r3
r4
r5
r6
r7
st14
neural crest origin:
r3
r4
r5
r6
r7
r6+r7
posterior midbrain
posterior midbrain +r1
r1
r1+r2
posterior mid-brain+r1+r2
E10
squamosal
quadrate
pterygoid
quadratojugal
palatine
jugal
maxilla
dentary
Meckel's cartilage
splenial
surangular
columella
articular
angular


Wild type
r2
r3
r4
r5
r6
r7
A-2
A-3
A-4
HoxA-2 mutant
r2
r3
r4
r5
r6
r7
A-3
A-4

Hoxa-2 mutation results in duplication of first arch stuctures in the location of second arch derivatives



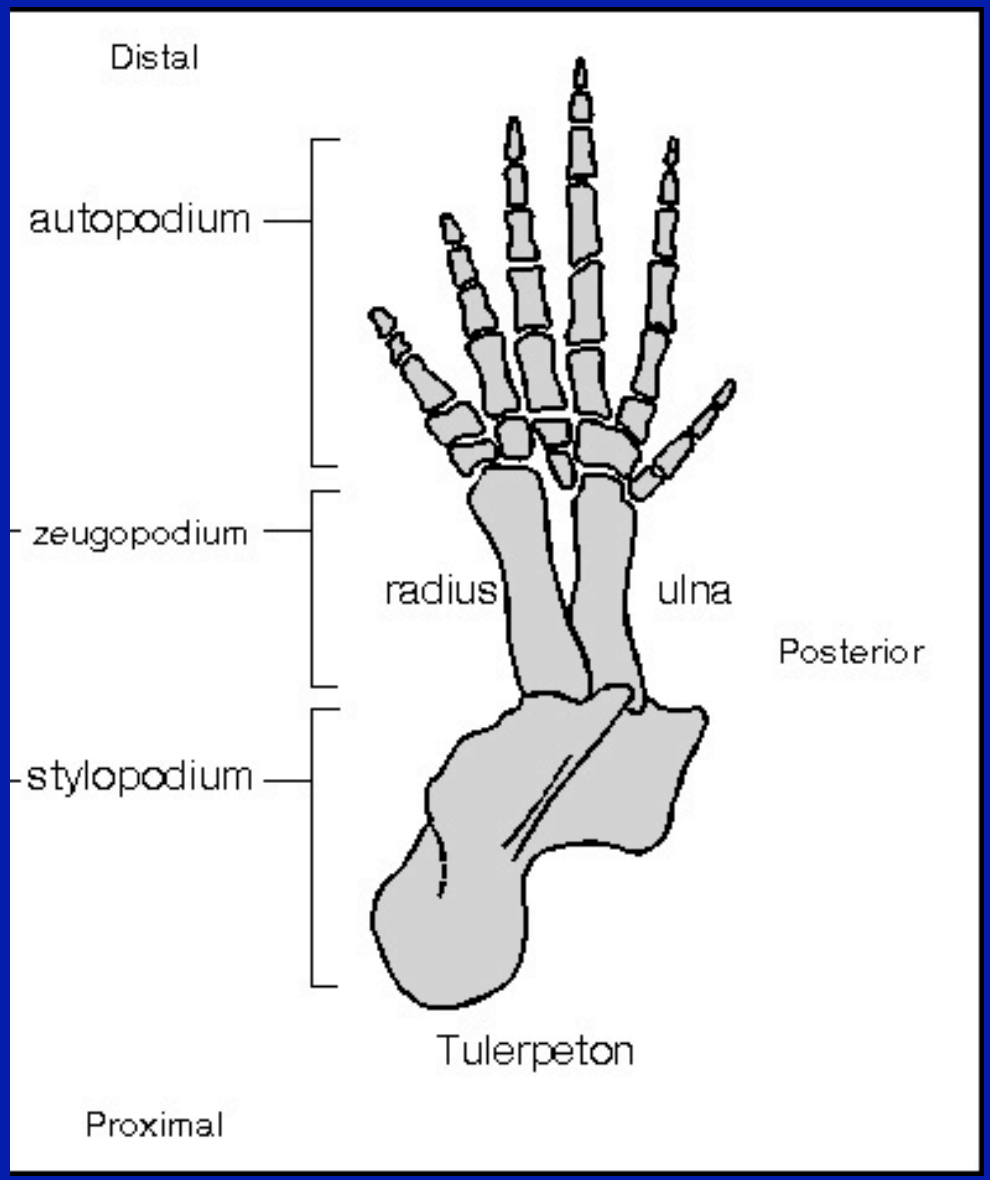
wt mouse



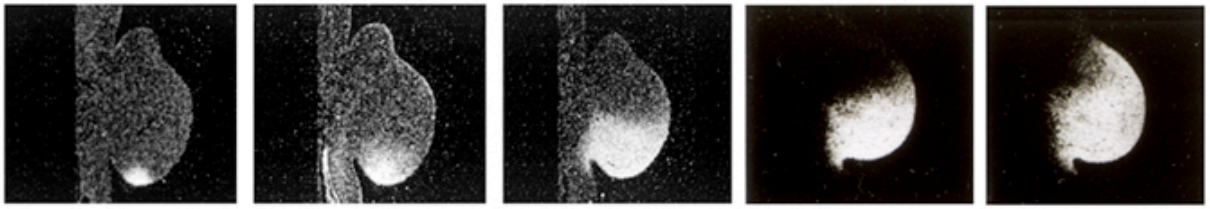
Hoxa-2$^{-/-}$ mouse

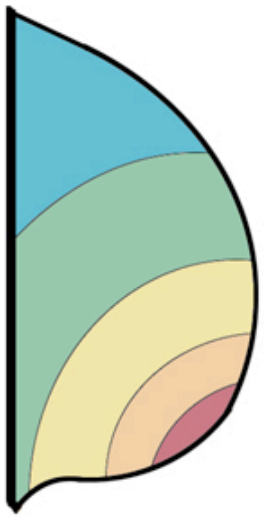
crest origin:

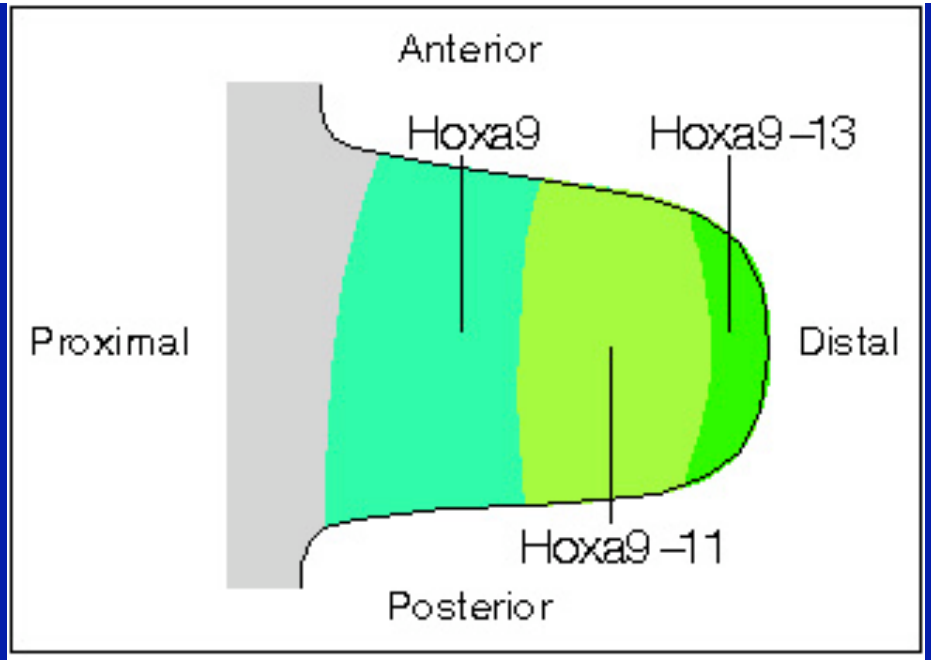
- posterior midbrain
- posterior midbrain +r1
- r1
- r1+r2
- post. mid-brain +r1+r2
- r3
- r4
- r5

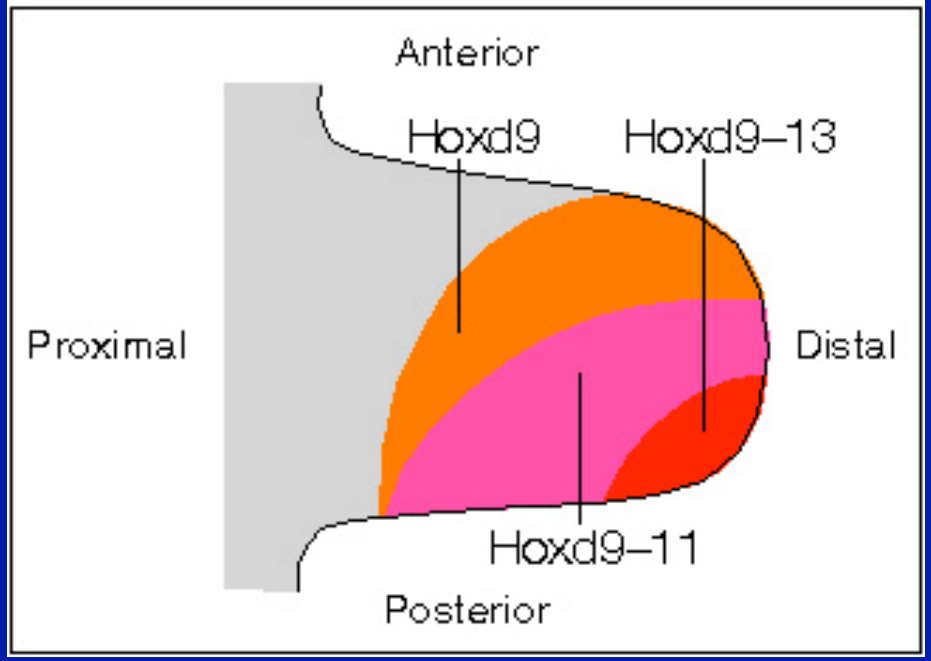

Distal
autopodium
zeugopodium
stylopodium
radius
ulna
Posterior
Tulerpeton
Proximal

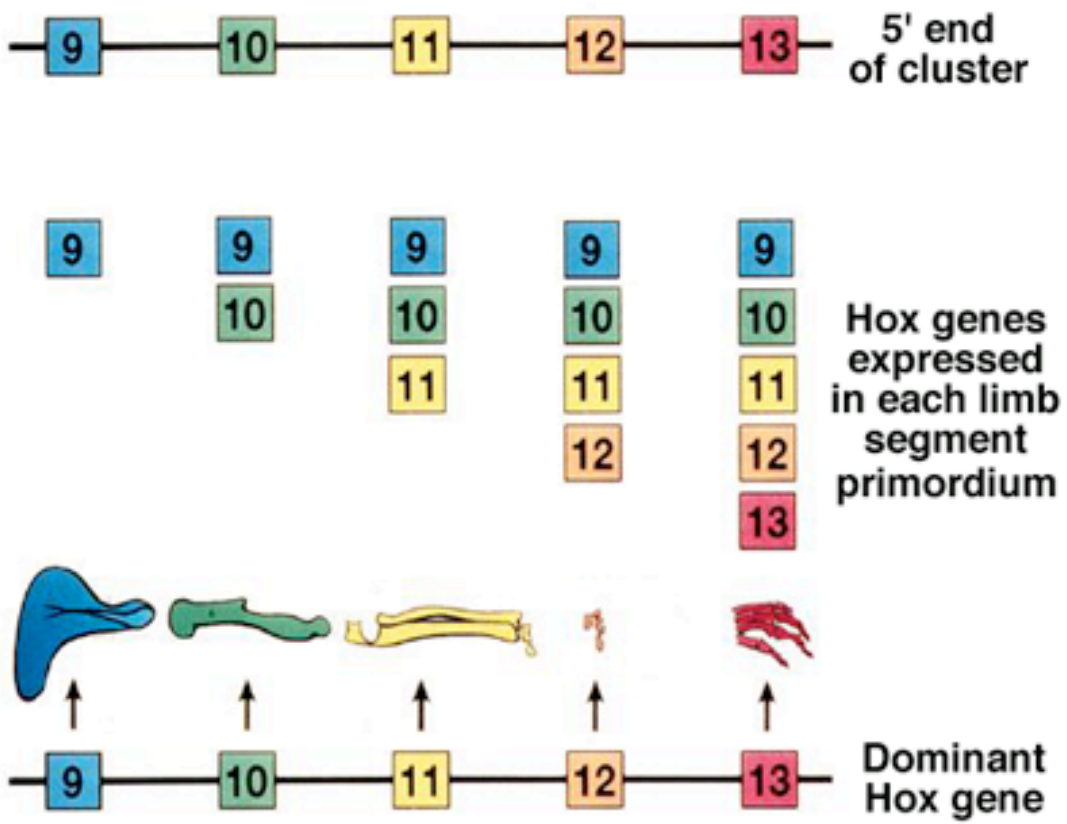
Nesting of Hoxd genes in the early limb bud



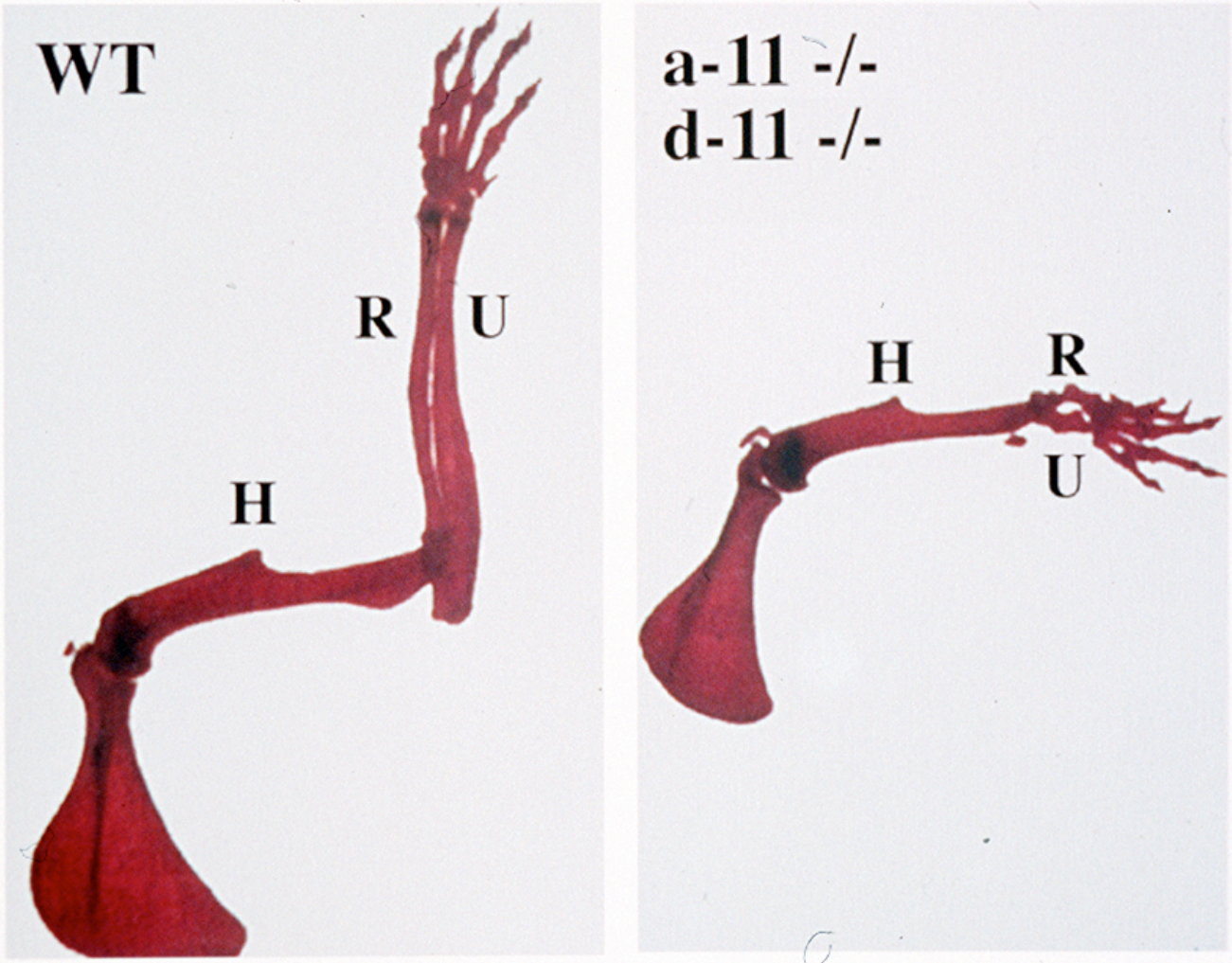



Anterior
Hoxa9
Hoxa9–13
Proximal
Distal
Hoxa9–11
Posterior


Anterior
Hoxd9
Hoxd9–13
Proximal
Distal
Hoxd9–11
Posterior

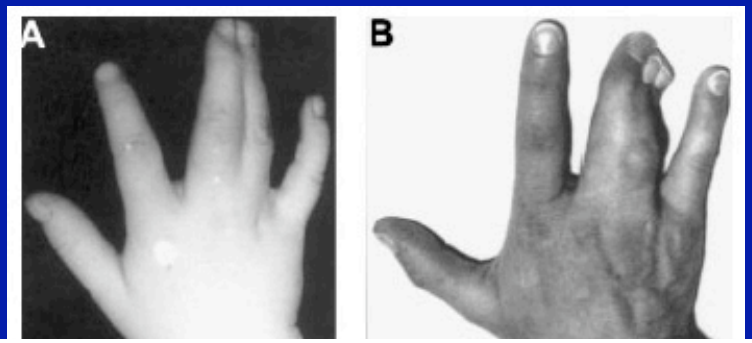

9
10
11
12
13
5' end
of cluster
9
9
10
9
10
11
9
10
11
12
9
10
11
12
13
Hox genes
expressed
in each limb
segment
primordium
9
10
11
12
13
Dominant
Hox gene

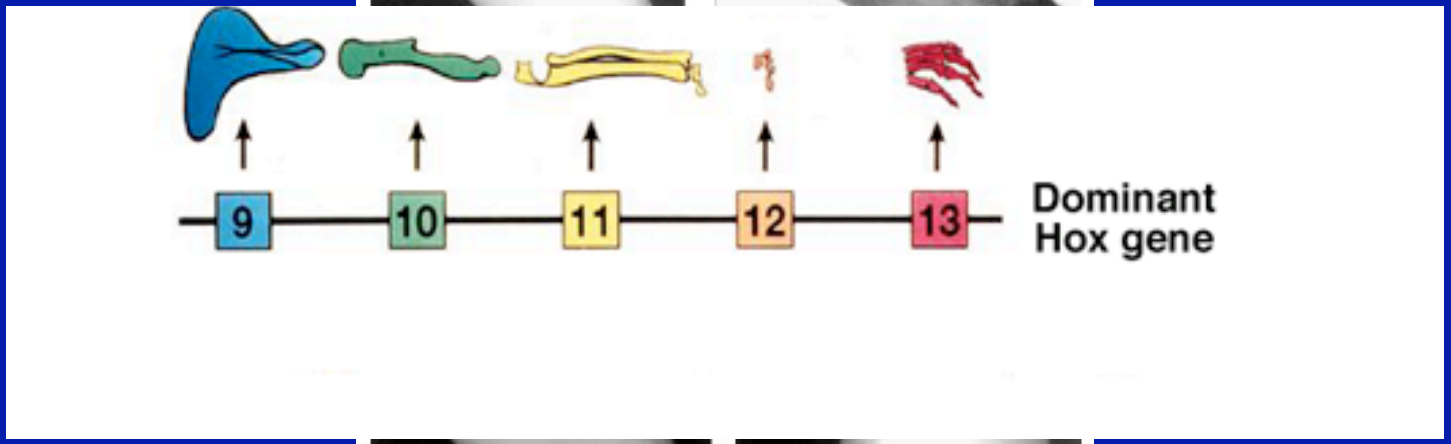
Without Hox-11 function the Radius and Ulna are rudimentary

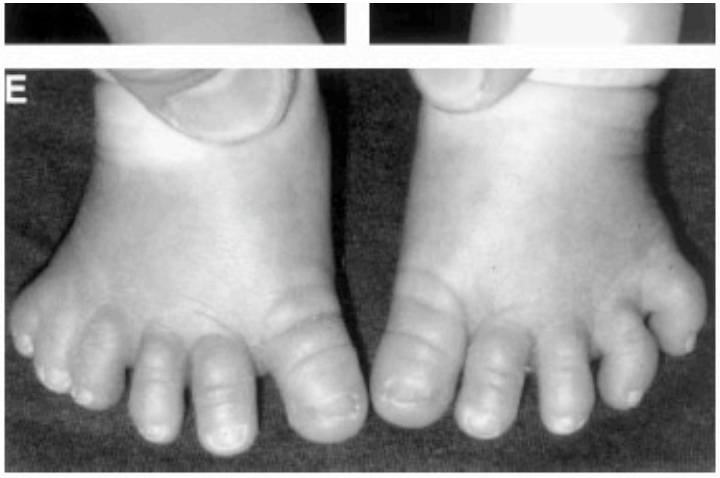


A. P. Davis and M. Capecchi

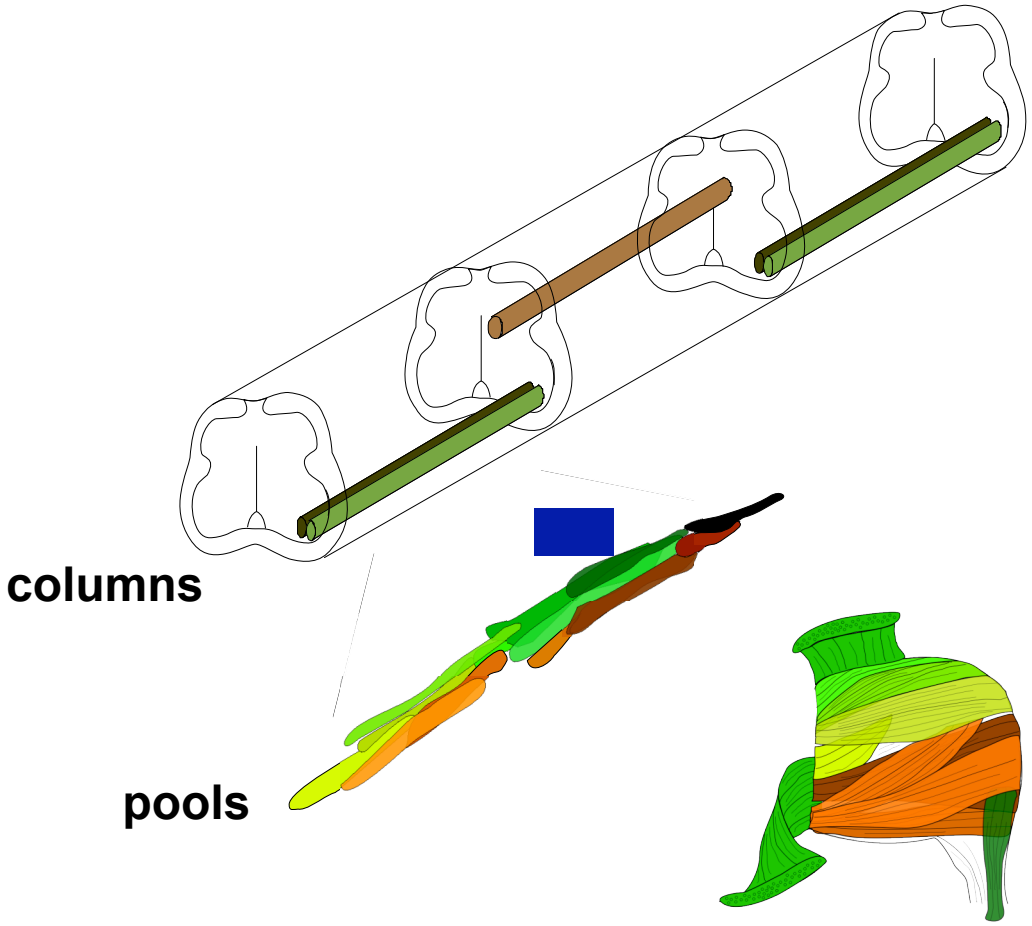
Synpolydactyly can be caused by alanine repeat expansions in Hox D13



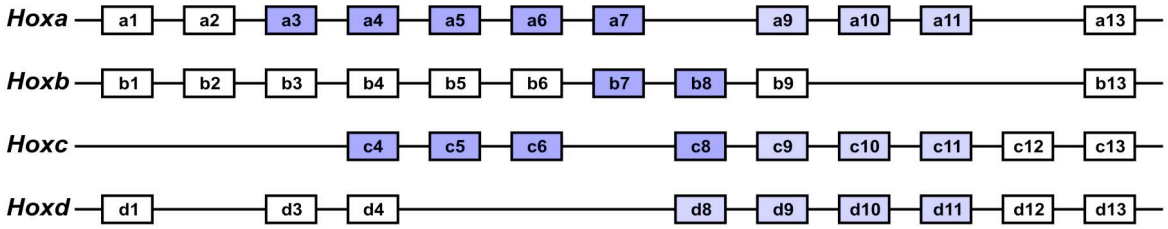


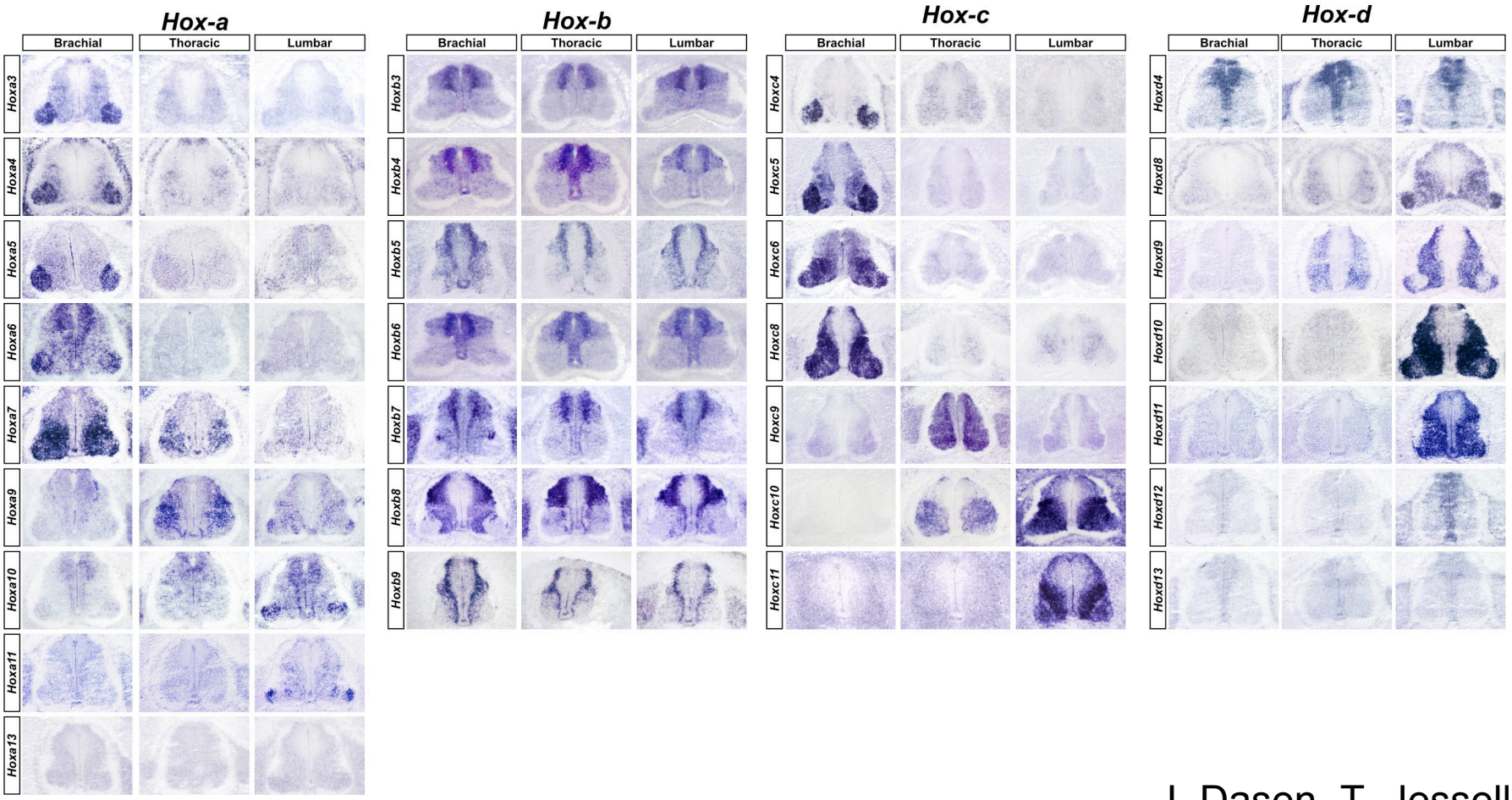


Motor neuron organization in the spinal cord



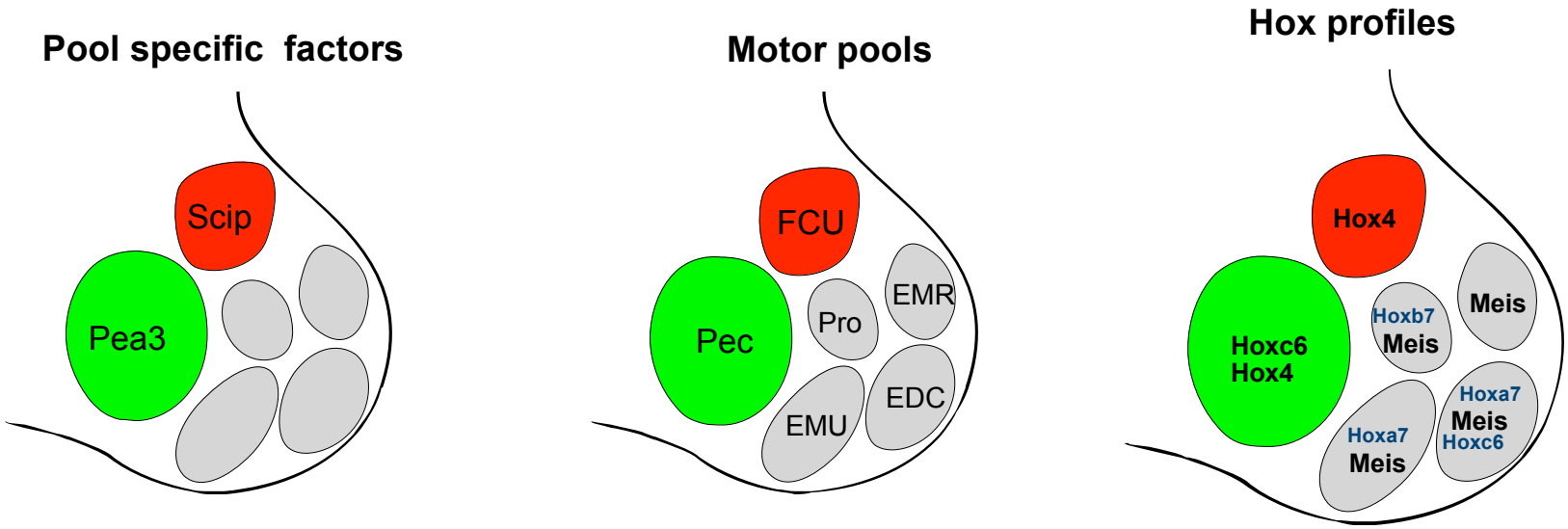
Expression of *Hox* genes by motor neurons



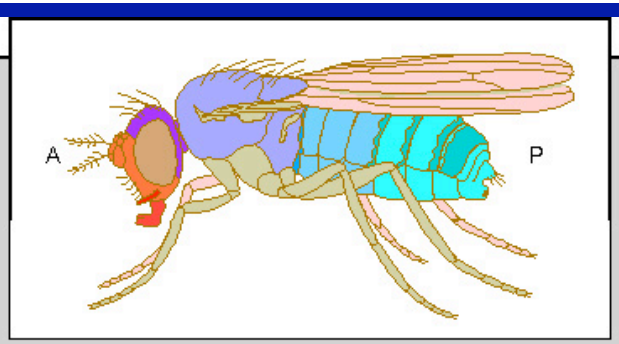


J. Dasen, T. Jessell

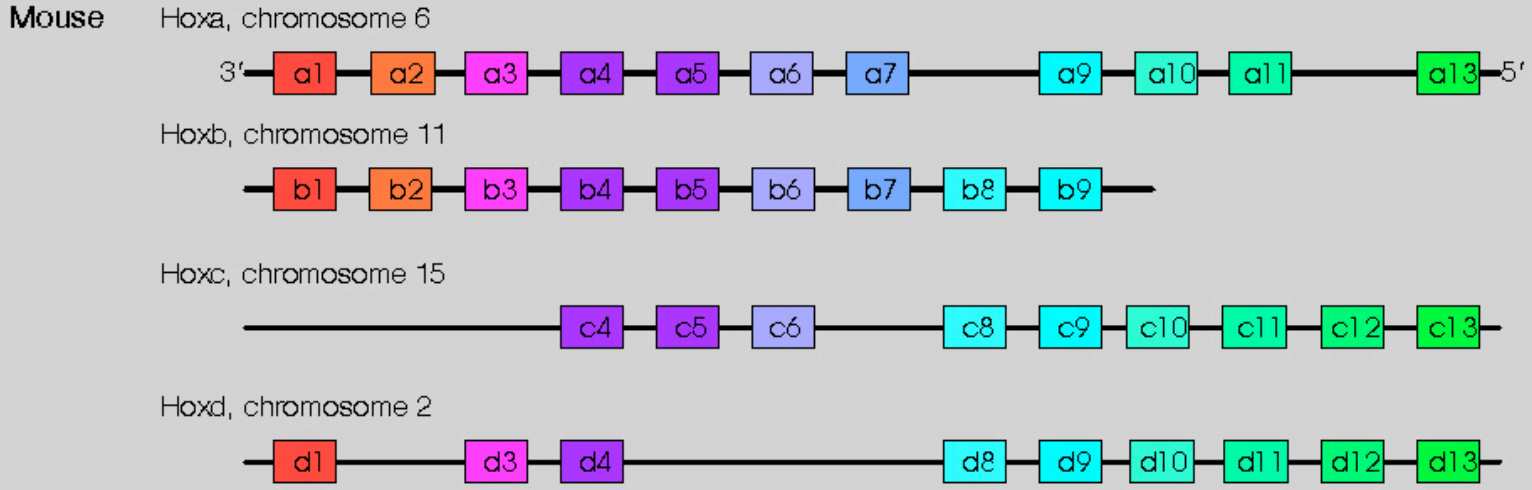
Hox proteins define the intrasegmental diversity of motor pools

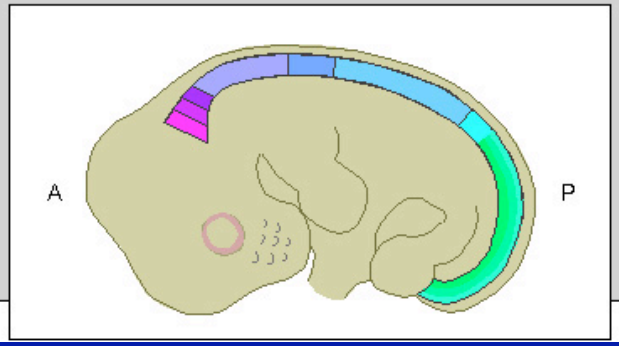


J. Dasen, T. Jessell

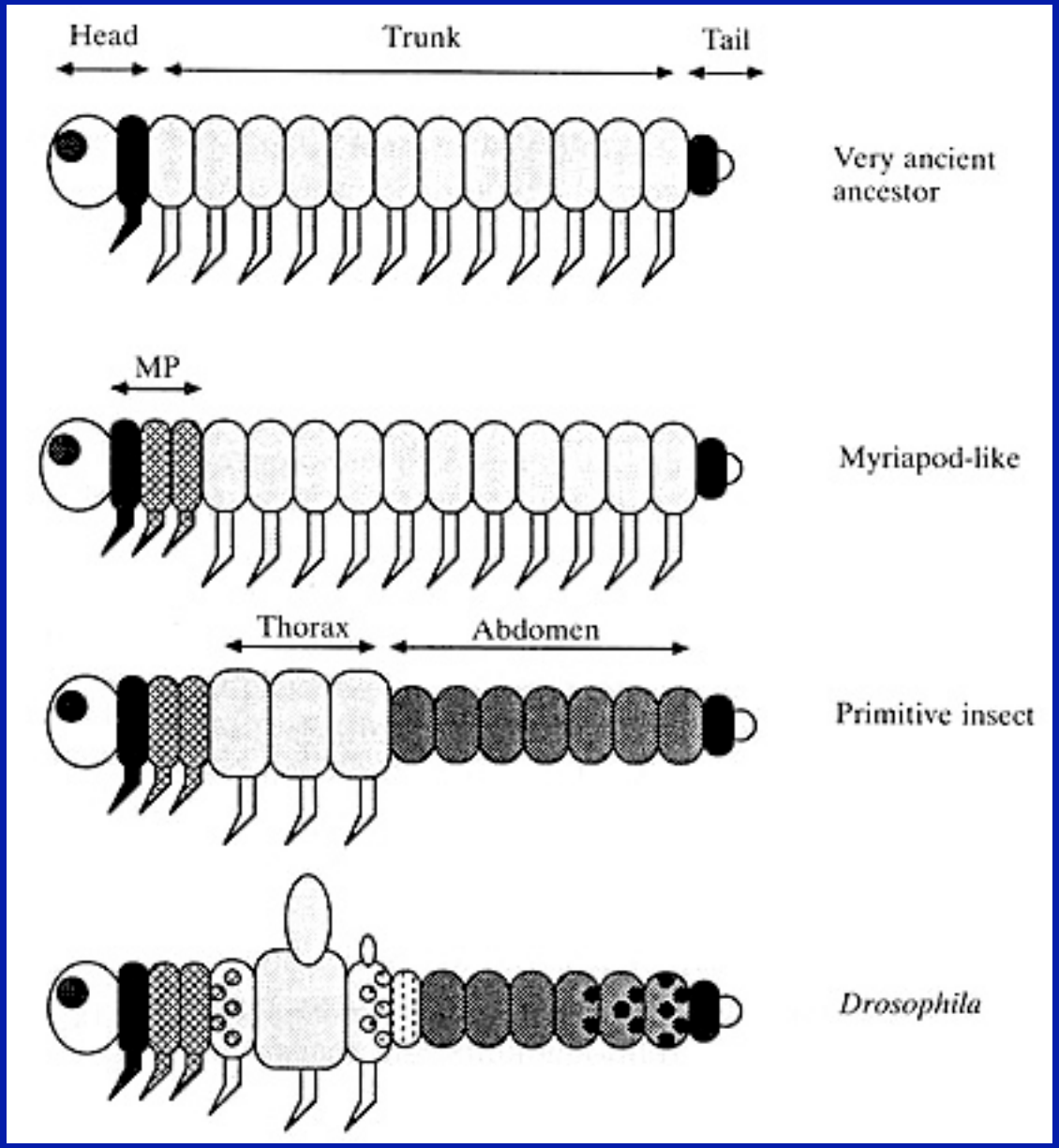


What can evolutionary comparisons tell about Hox function?





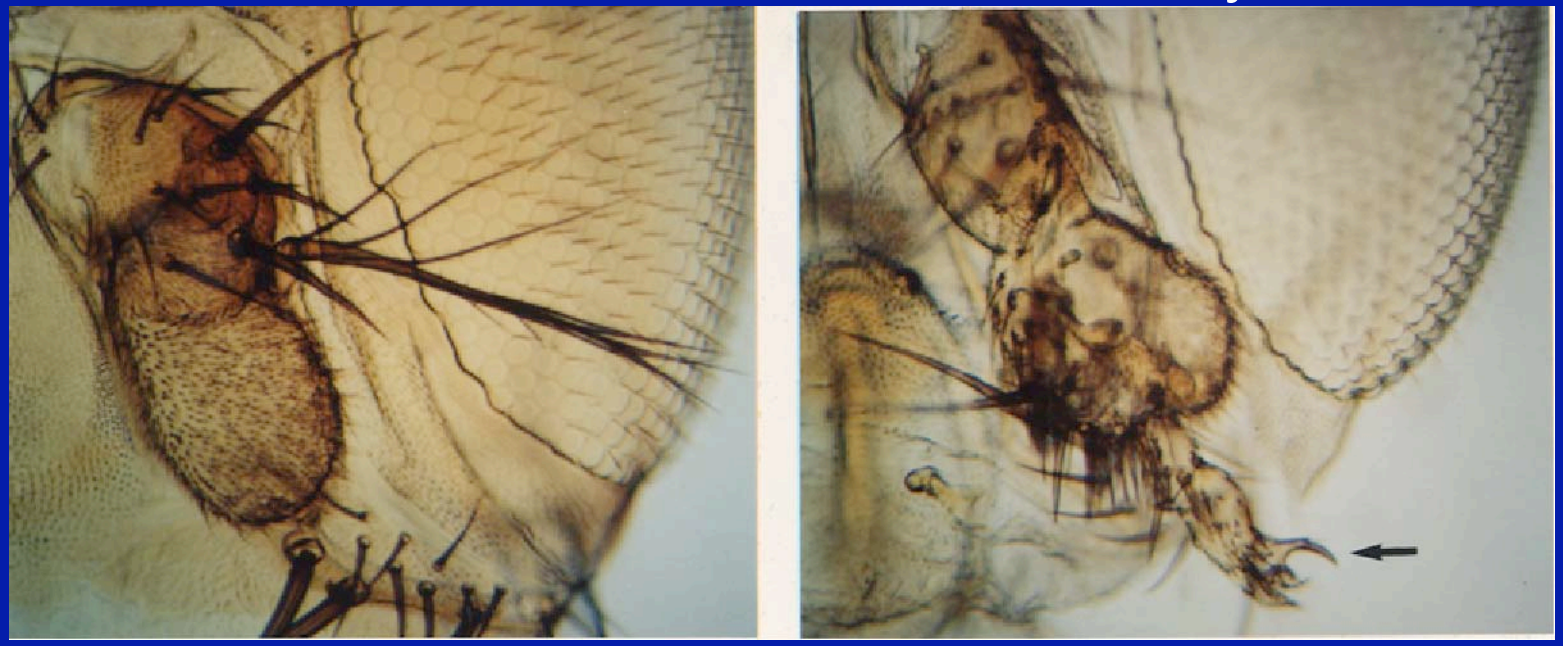
Hox genes and the evolution of AP diversity



Human Hox genes work in the fly to make fly structures

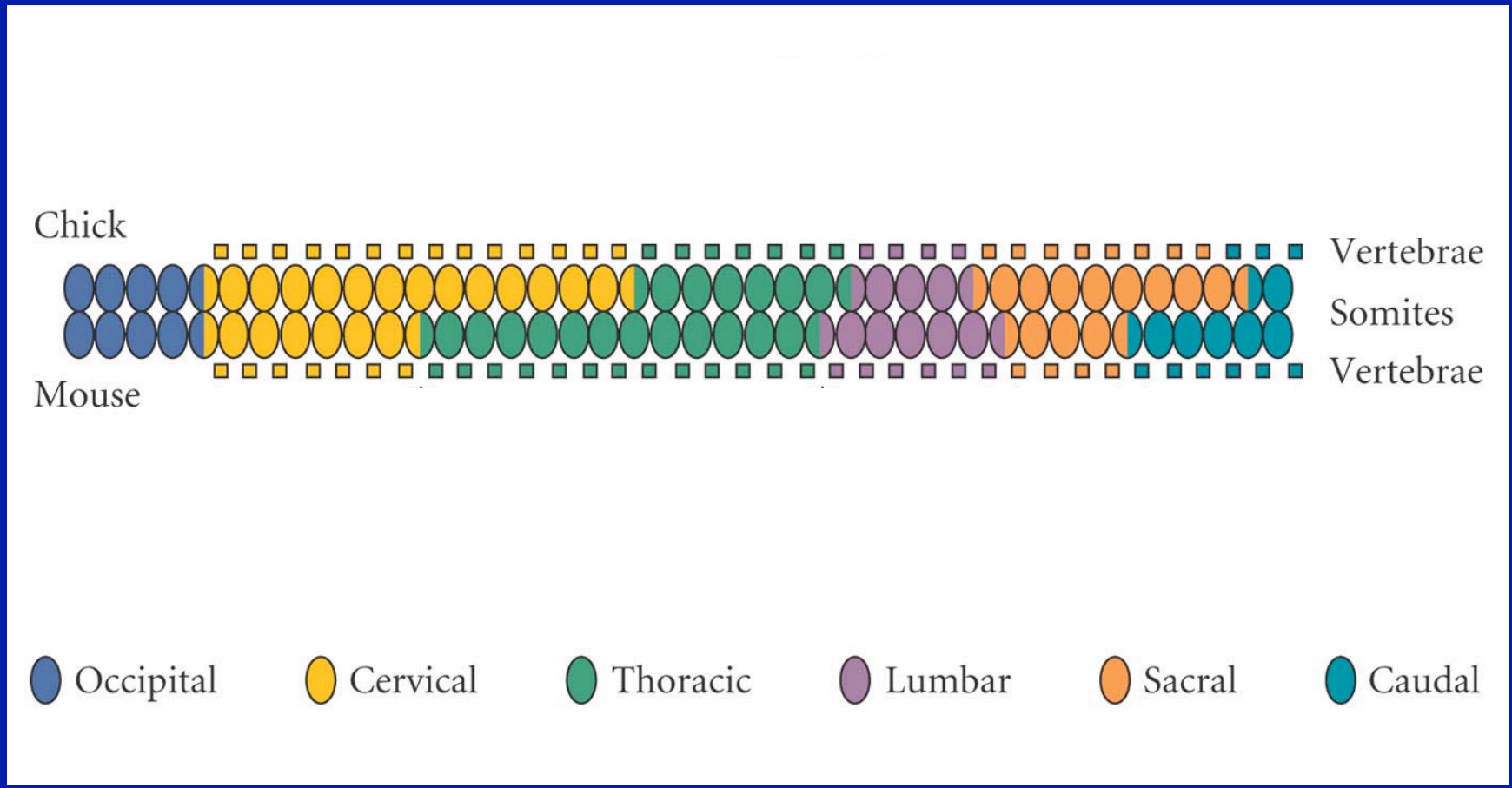
Wild type fly antenna

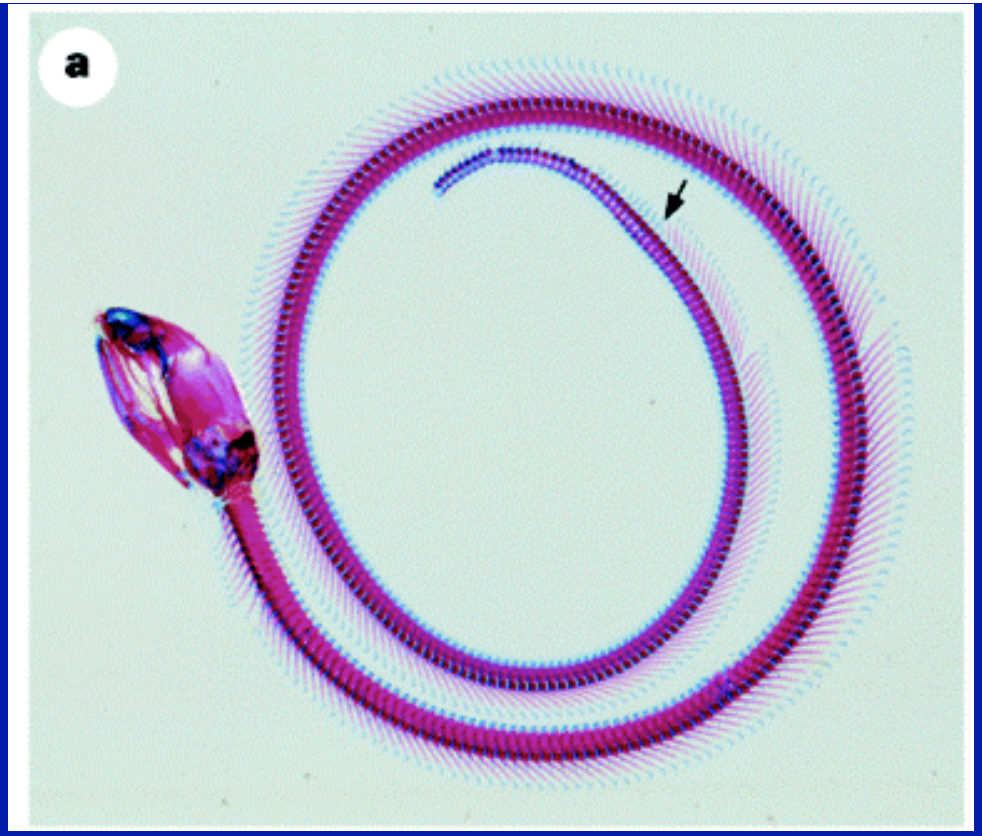
Antenna to leg transformation induced by HoxB6



W. McGinnis, L. Pick

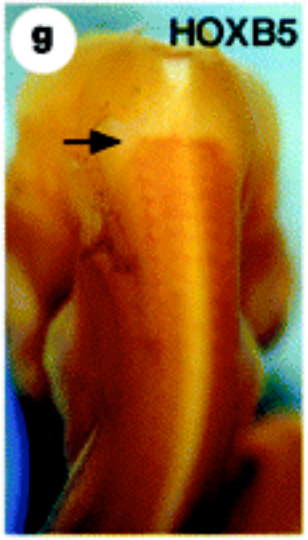
Mouse and Chick Vertebral Pattern along the Anterior-Posterior Axis

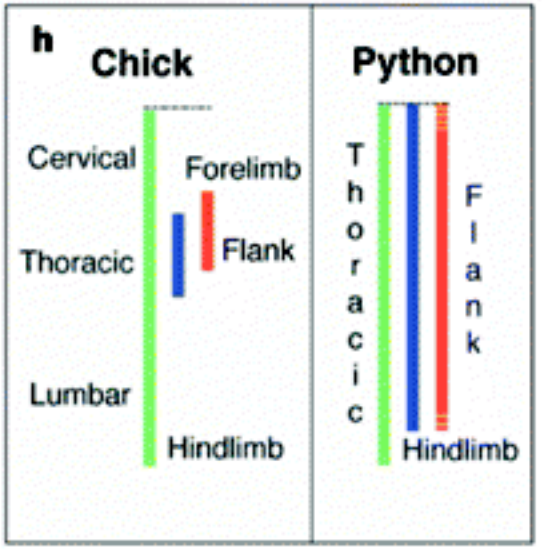



a

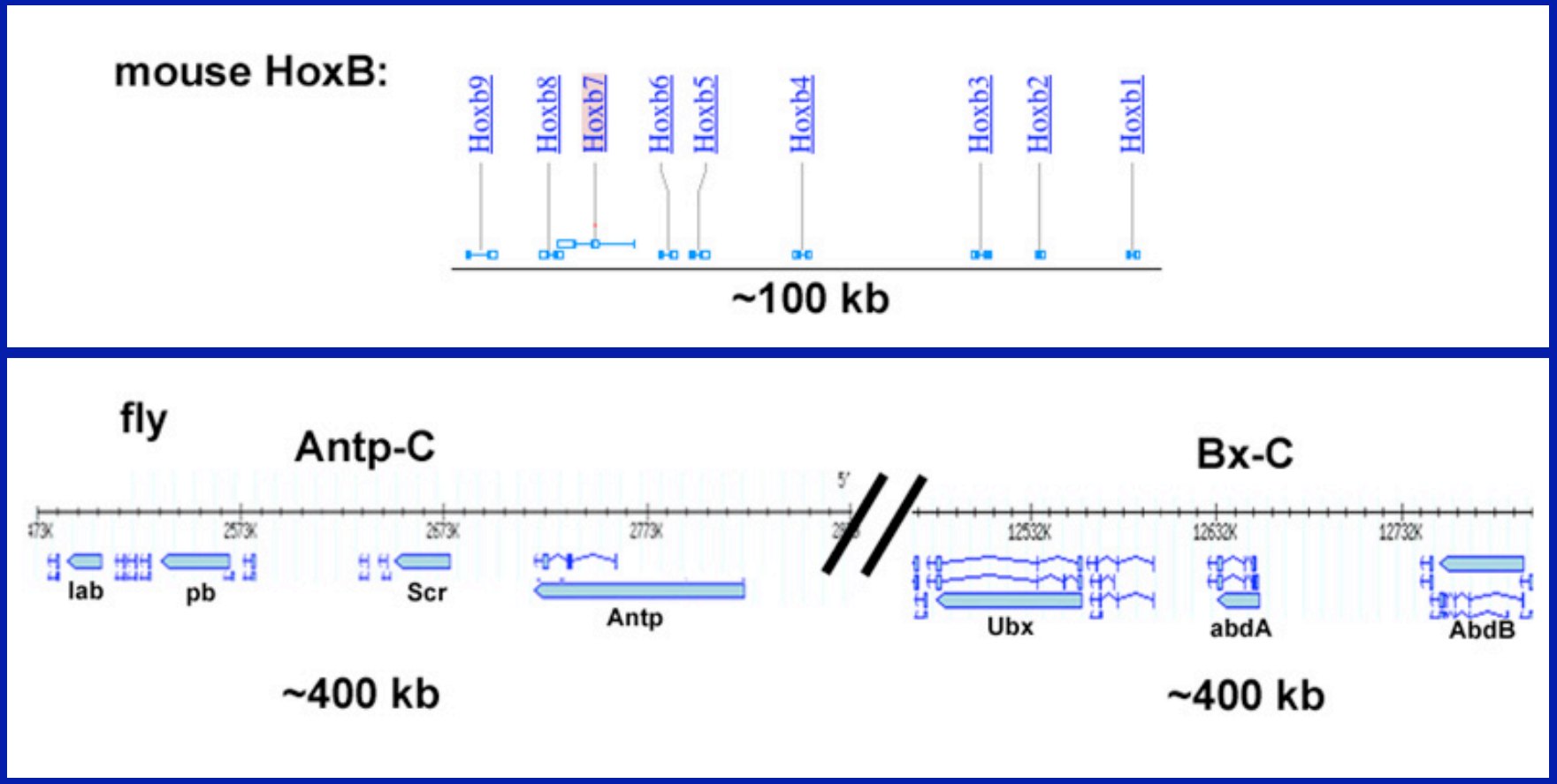

e
HOXC6


f
N
P
L
HOXB5

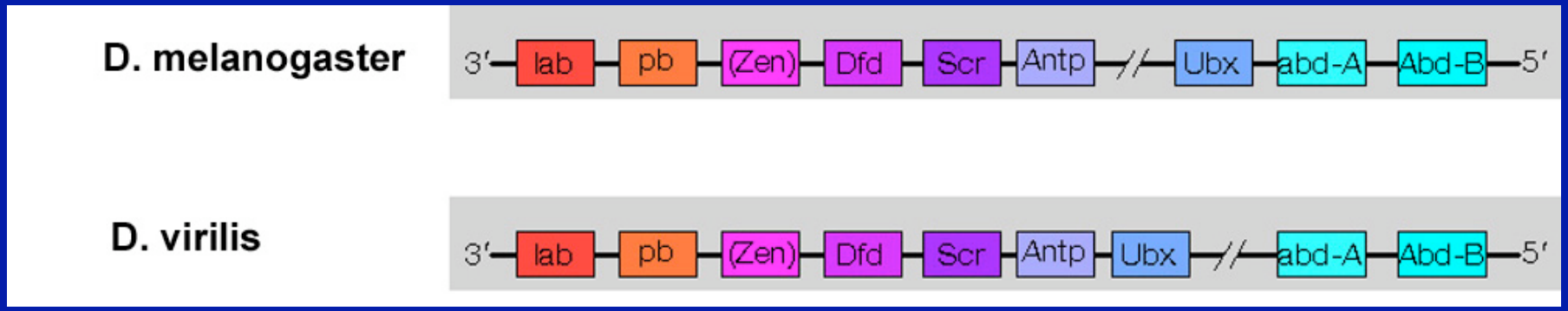

g
HOXB5


h
Chick
Cervical
Thoracic
Lumbar
Forelimb
Flank
Hindlimb
Python
Thoracic
Flank
Hindlimb

Differences between fly Hox and vertebrate Hox

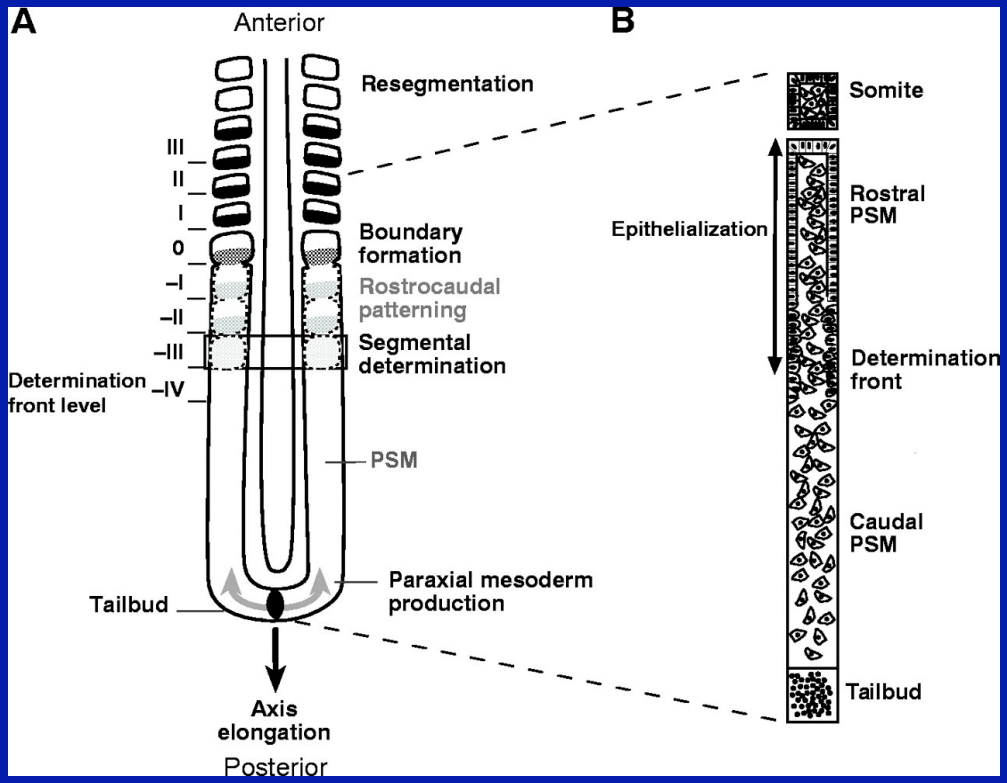


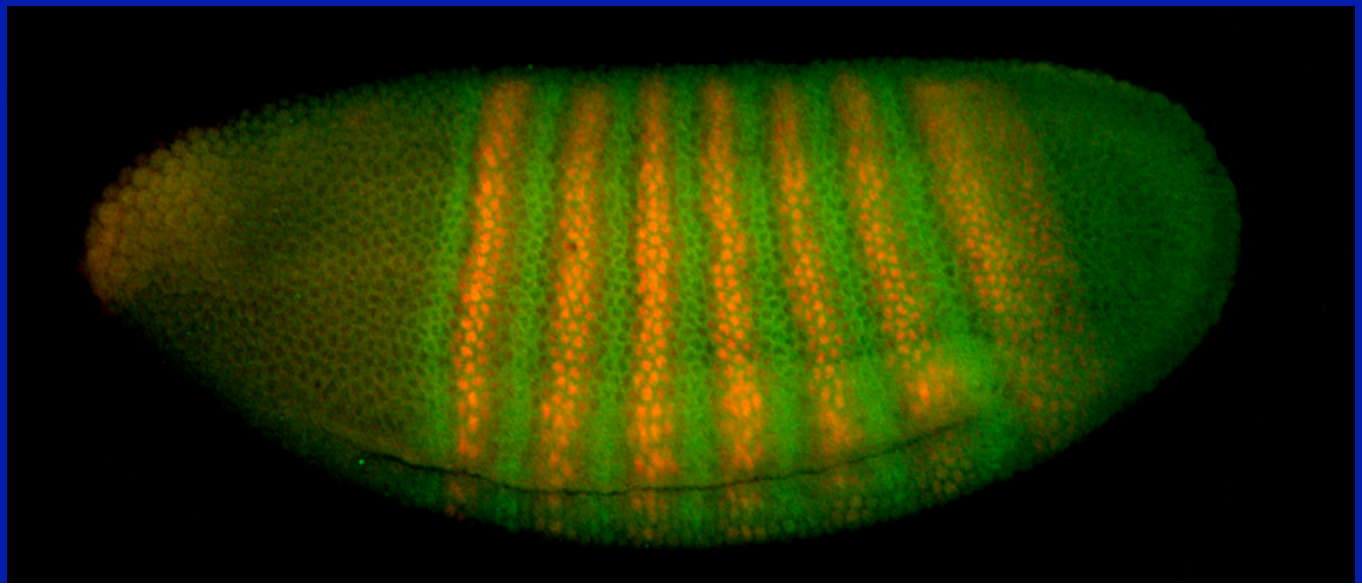
Differences between fly Hox and fly Hox



Conclusion: although still in clusters, the invertebrate complexes are ‘falling apart’, whereas the vertebrate clusters have retained their integrity, probably because of the way their expression is regulated.

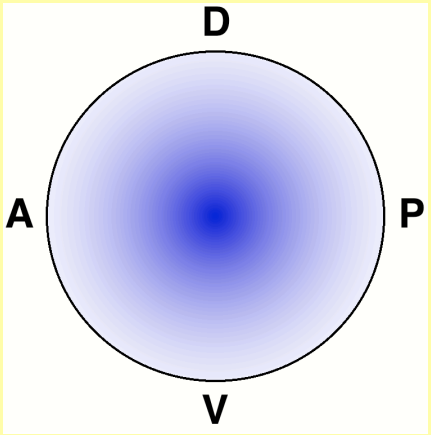
Big differences in vertebrate and fly segmentation mechanisms





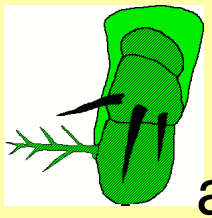
Segmentation is easily observed in the larva

Dpp
Wg
Hh



Prepattern

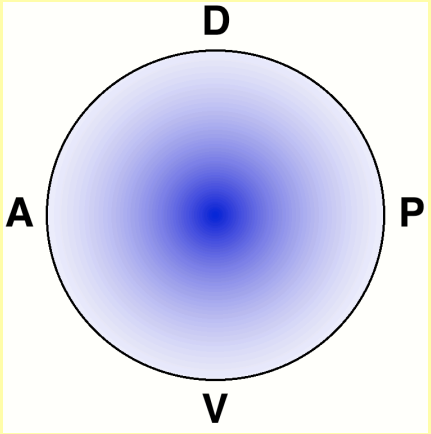
hth, Dll



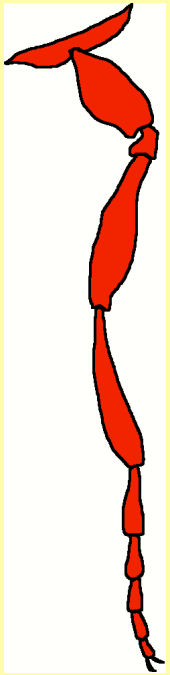
antenna

Selector genes

Dpp
Wg
Hh

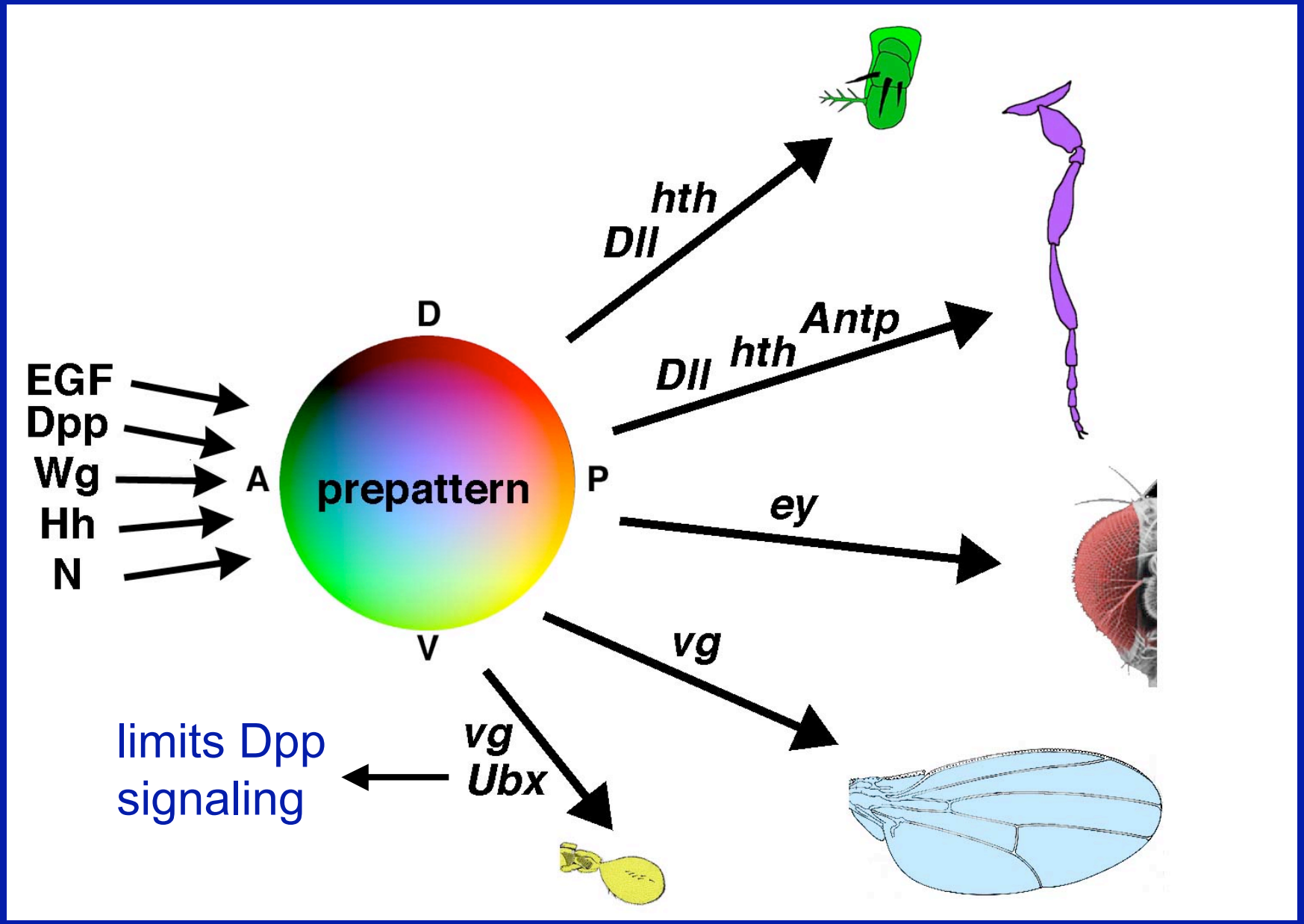


hth, Dll, Antp



leg

Selector genes interpret positional information



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