

The genetics of body axis formation

Genetics and Population Genetics



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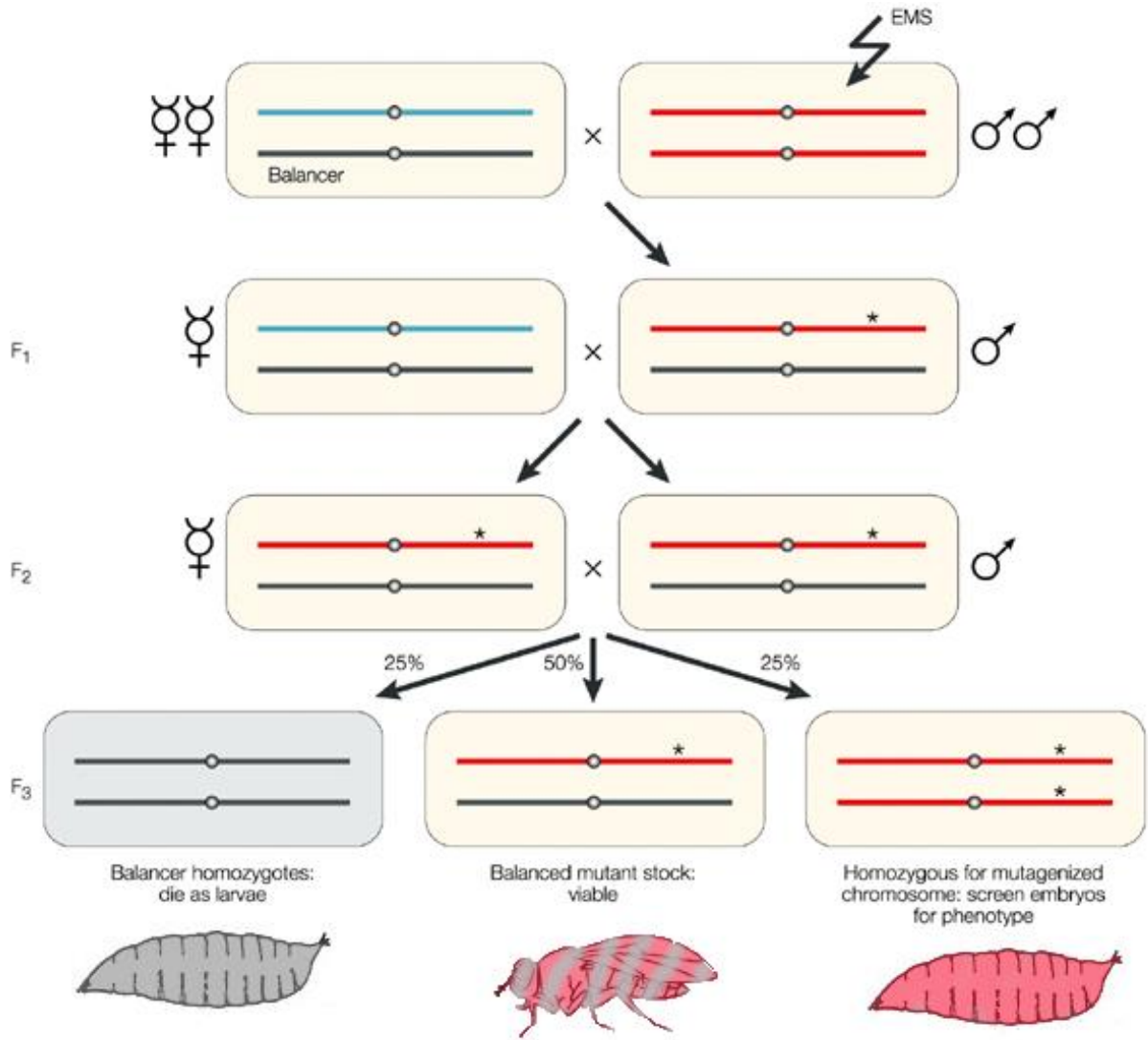
First genetic screen to study embryonic development: 1978-1980 Heidelberg



Christiane Nüsslein-Volhard

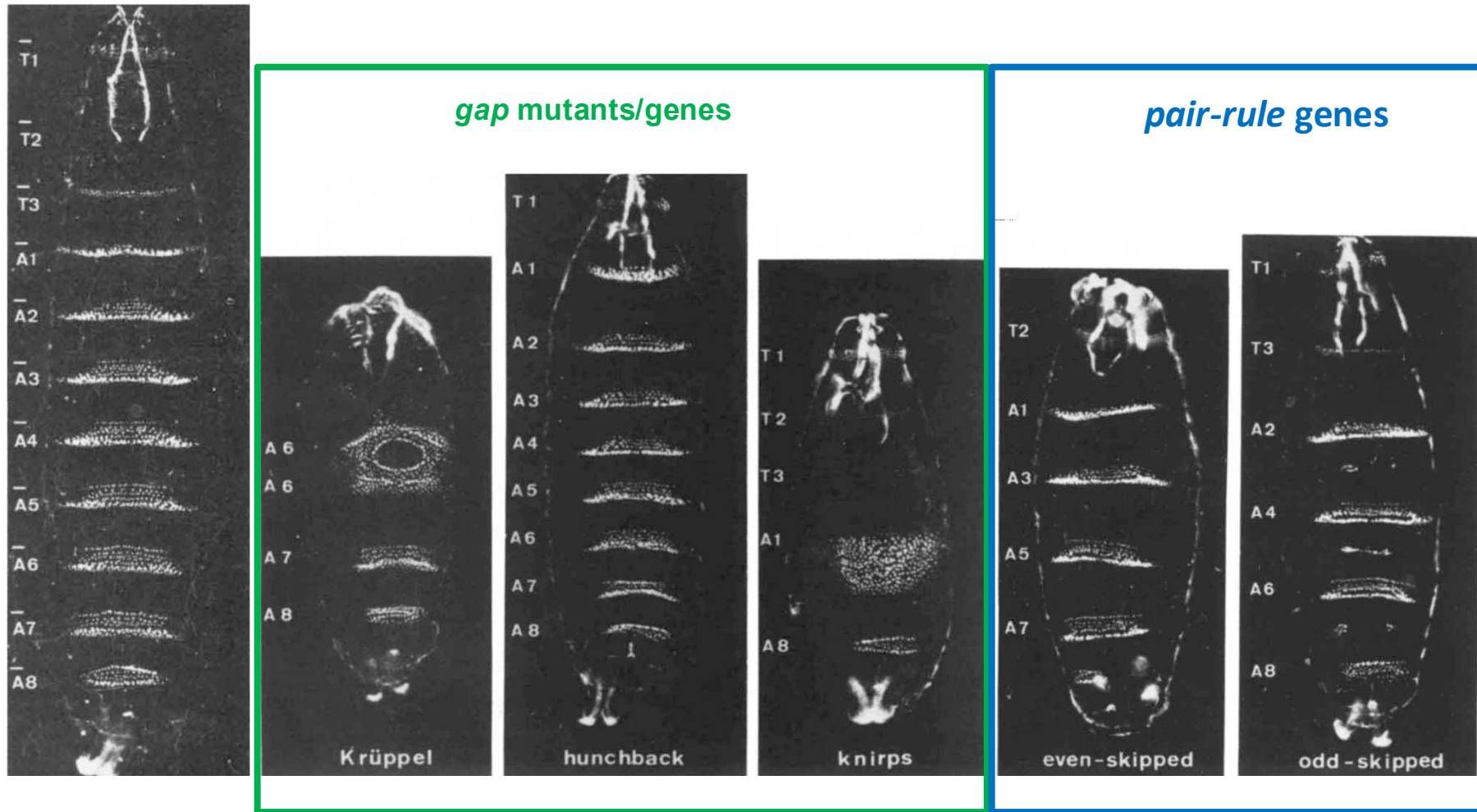


Eric Wieschaus





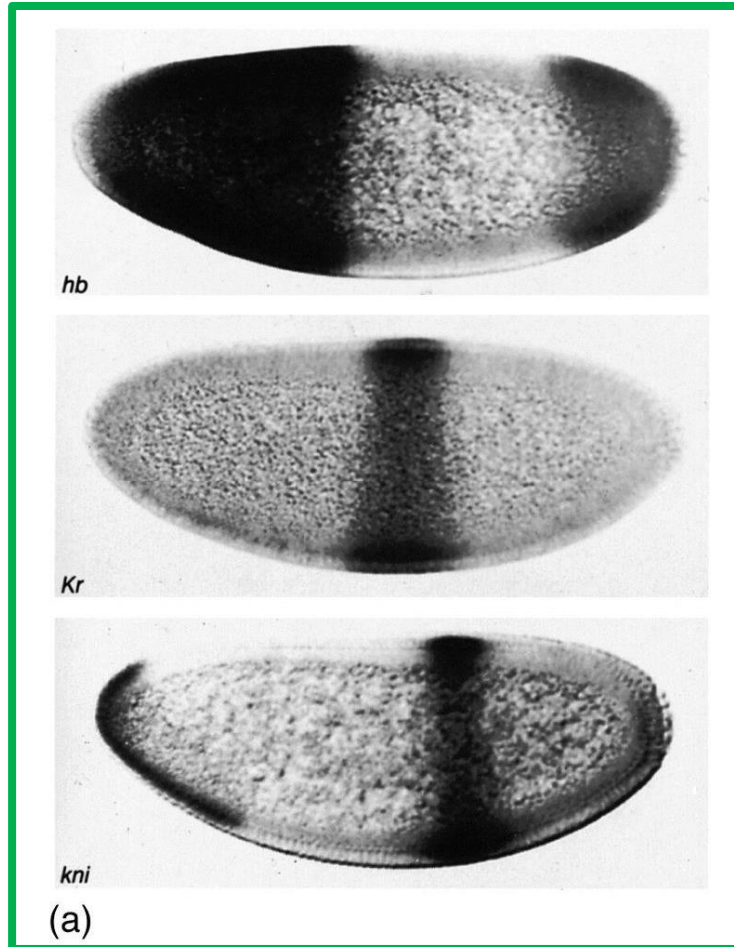
Zygotic genes involved in the formation of the antero-posterior (AP) axis



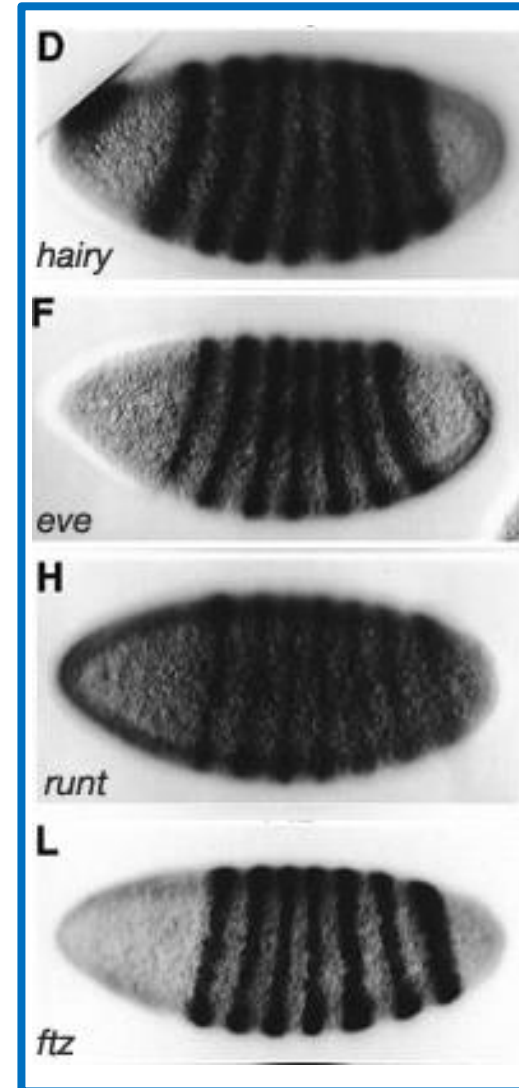


Zygotic genes involved in the formation of the antero-posterior (AP) axis

gap genes



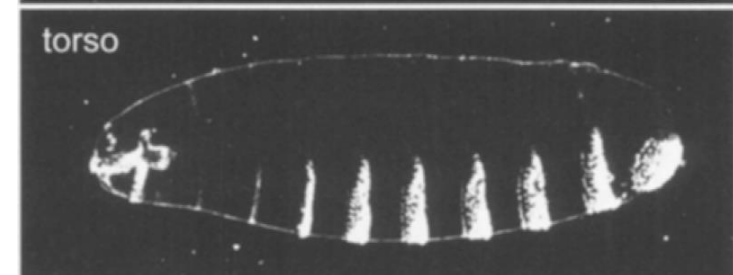
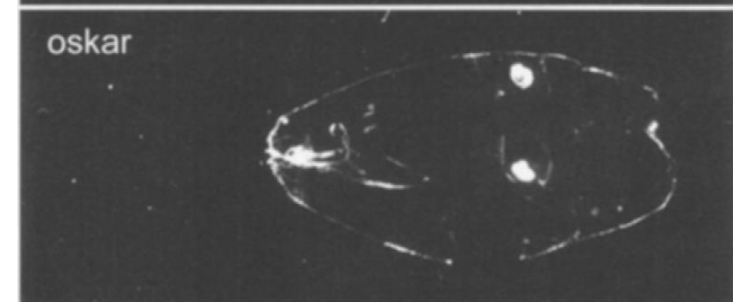
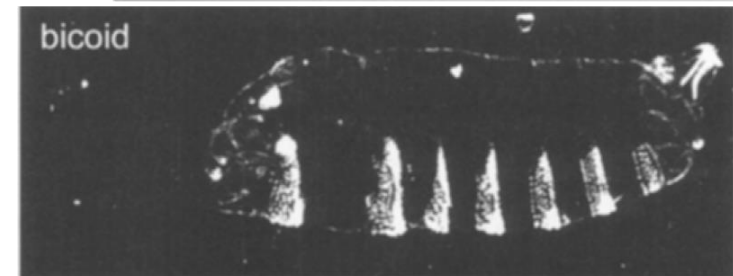
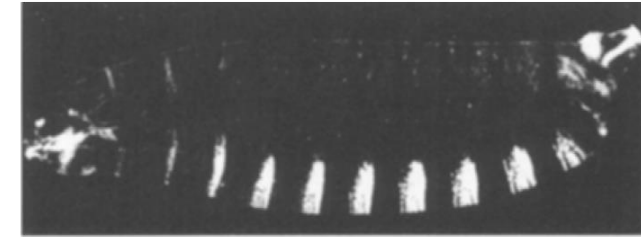
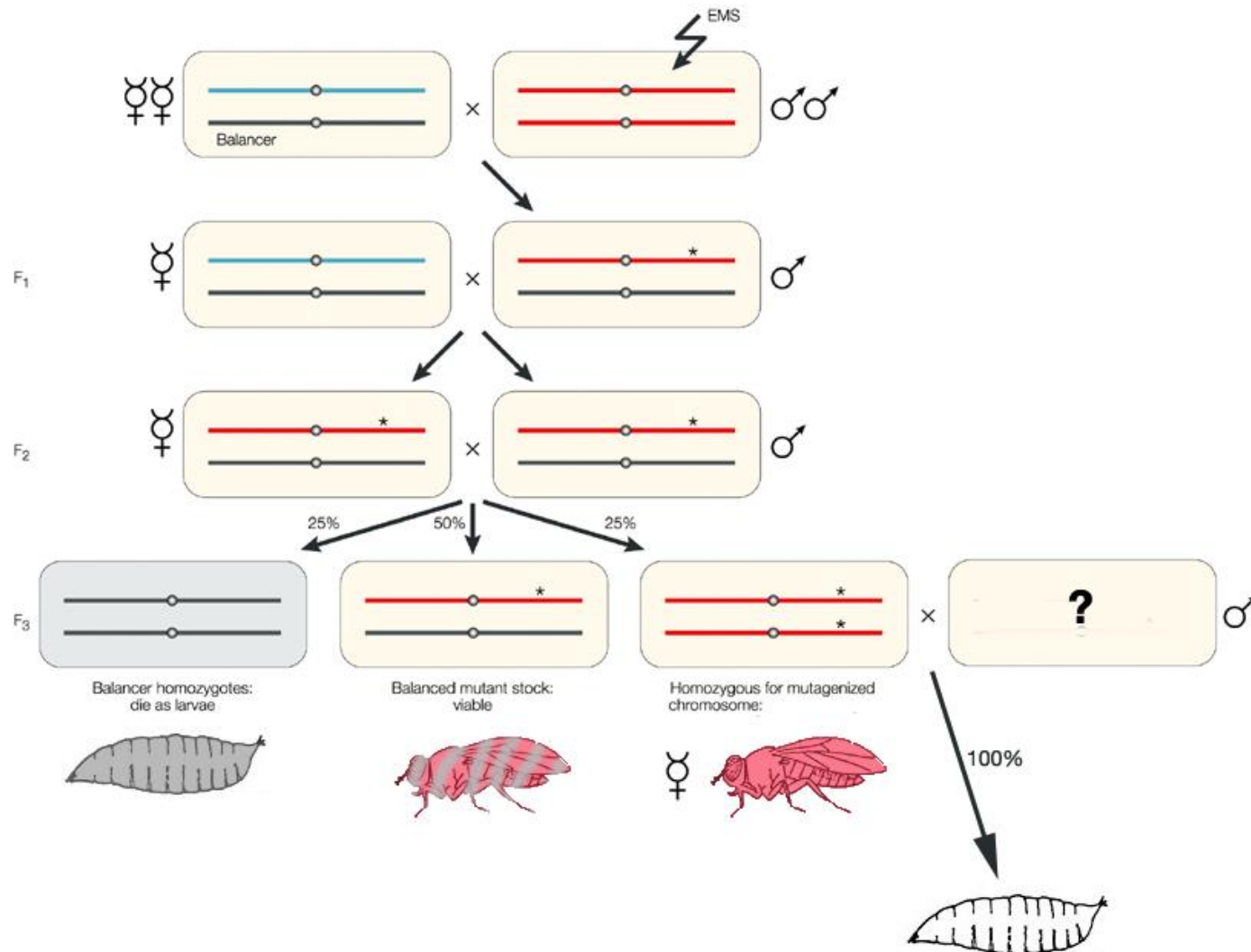
pair-rule genes



BUT: what regulates the expression of *gap* genes?



Looking for maternal mutants





Looking for maternal mutants

bicoid (bcd)

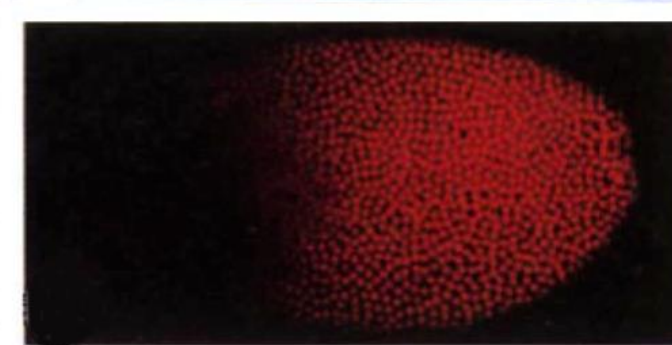
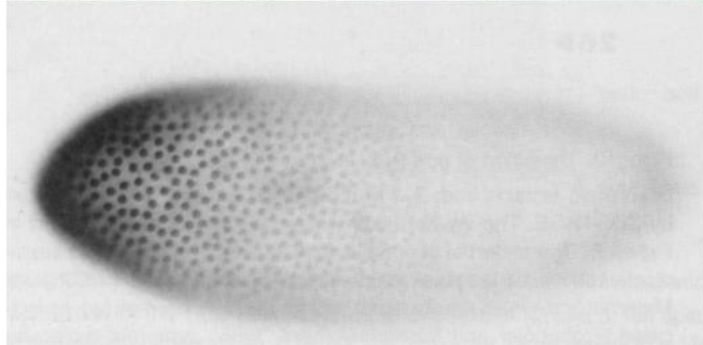
caudal (cad)

nanos (nos)

mRNA



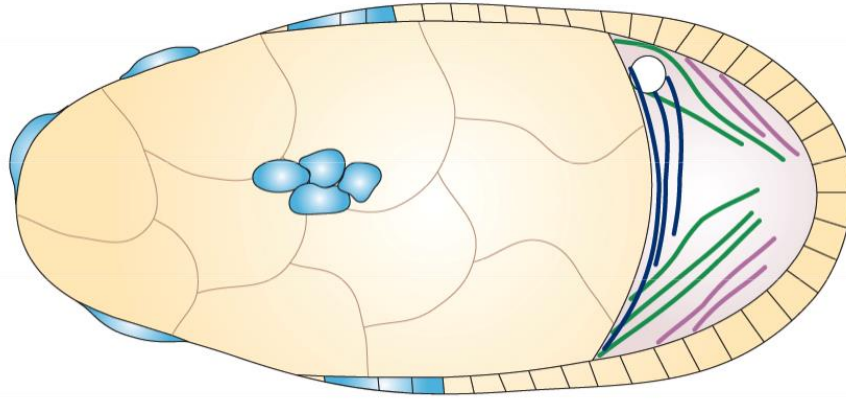
protein



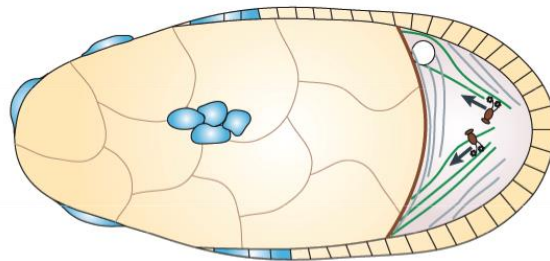


Localization of maternal mRNAs with the help of microtubules

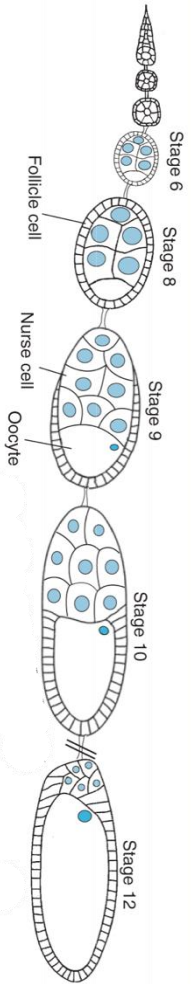
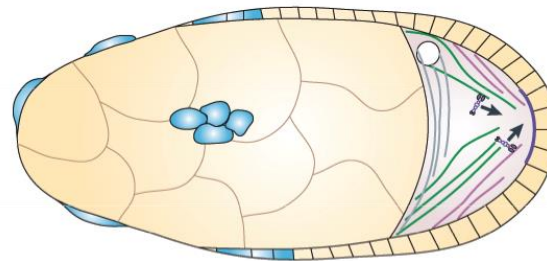
a Microtubule populations in the *Drosophila melanogaster* oocyte



c *bicoid* mRNA



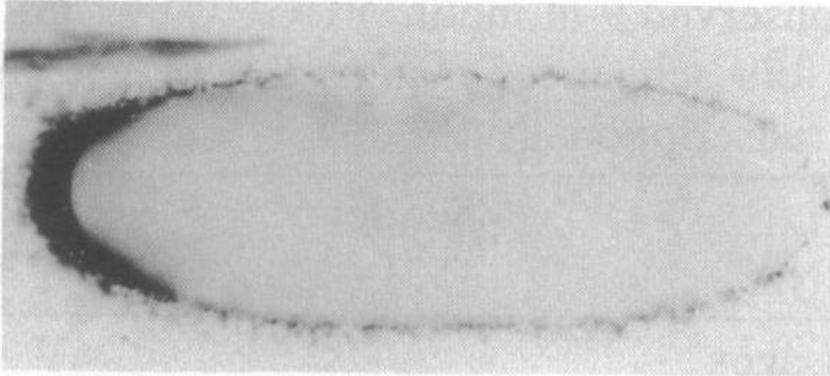
d *oskar* mRNA



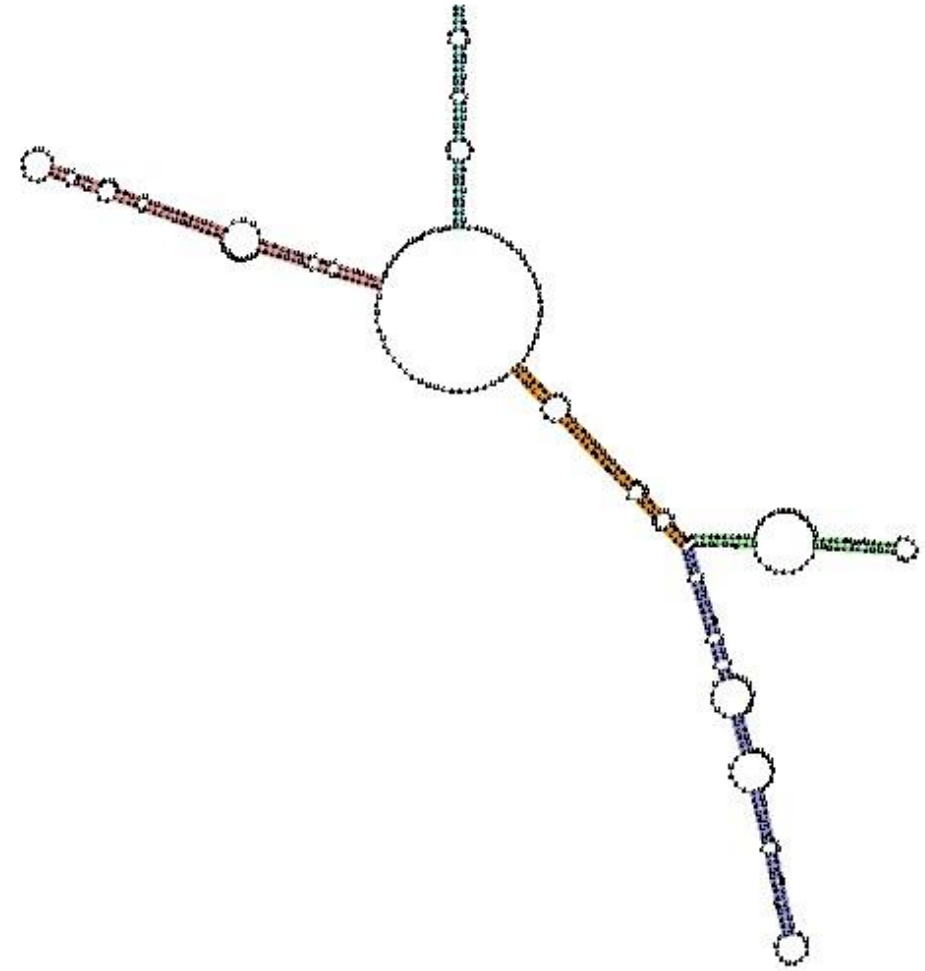
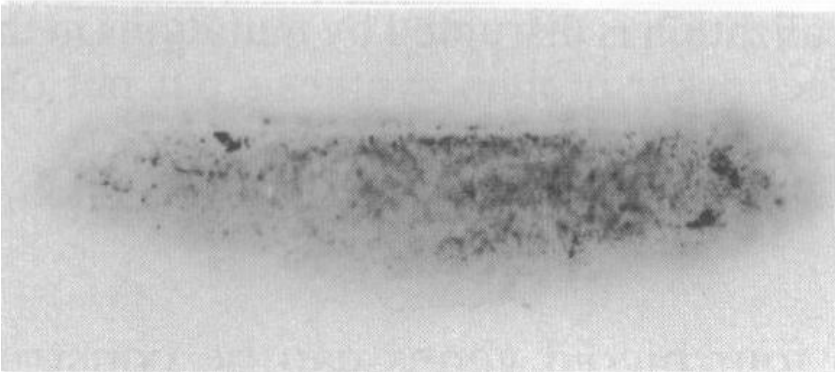


The 3'UTR of the *bcd* mRNA is involved in mRNA localisation

Wild type *bicoid* mRNA



No 3' UTR *bicoid* mRNA



Secondary structure of the *bicoid* mRNA 3' UTR

(Gottlieb et al., 1992 *PNAS*)



Looking for maternal mutants

bicoid (bcd)

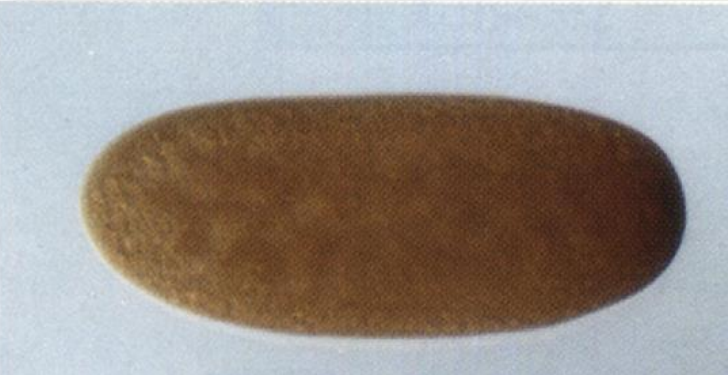
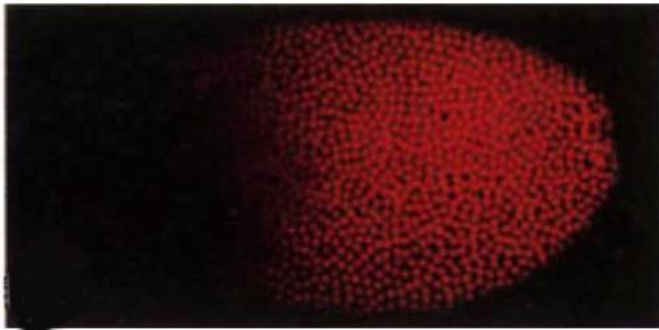
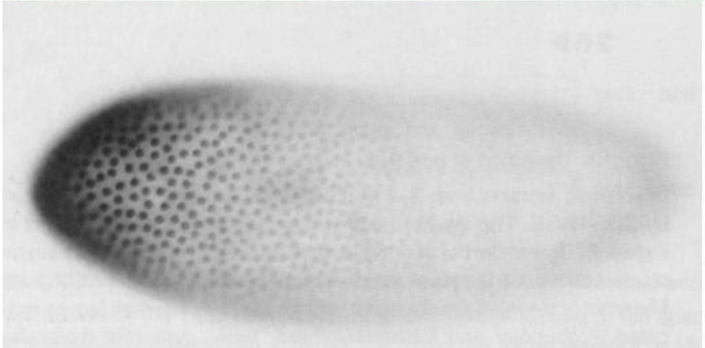
caudal (cad)

nanos (nos)

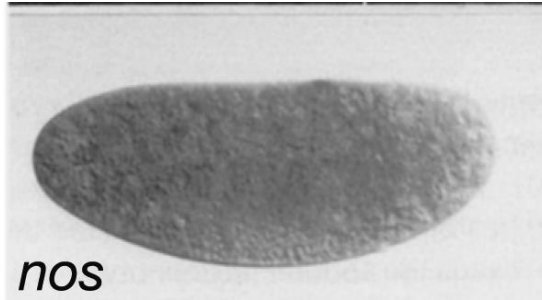
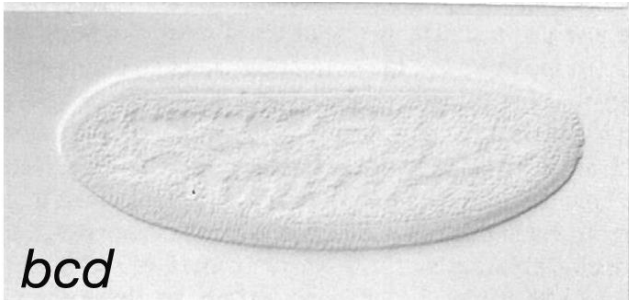
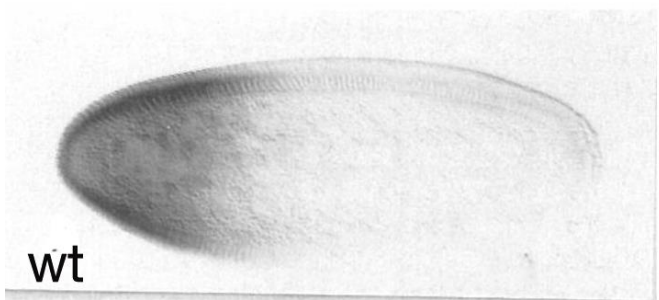
mRNA



protein



Bicoid and Nanos are the regulators of *hunchback*



wt

bcd

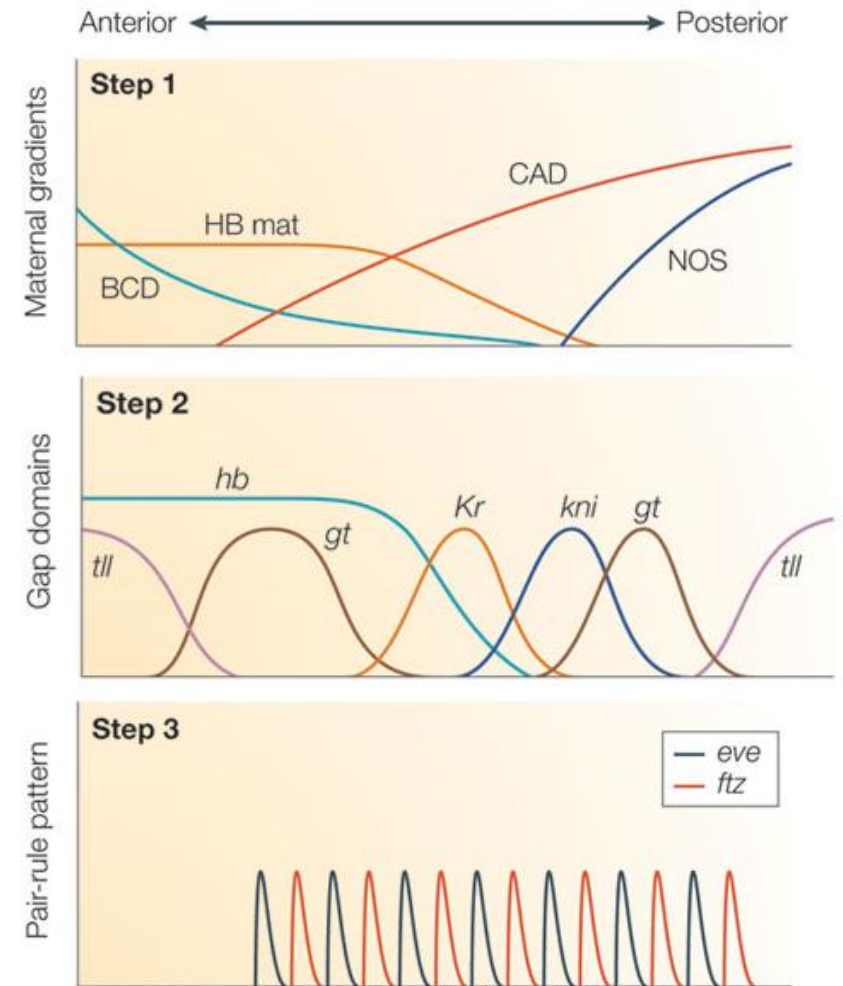
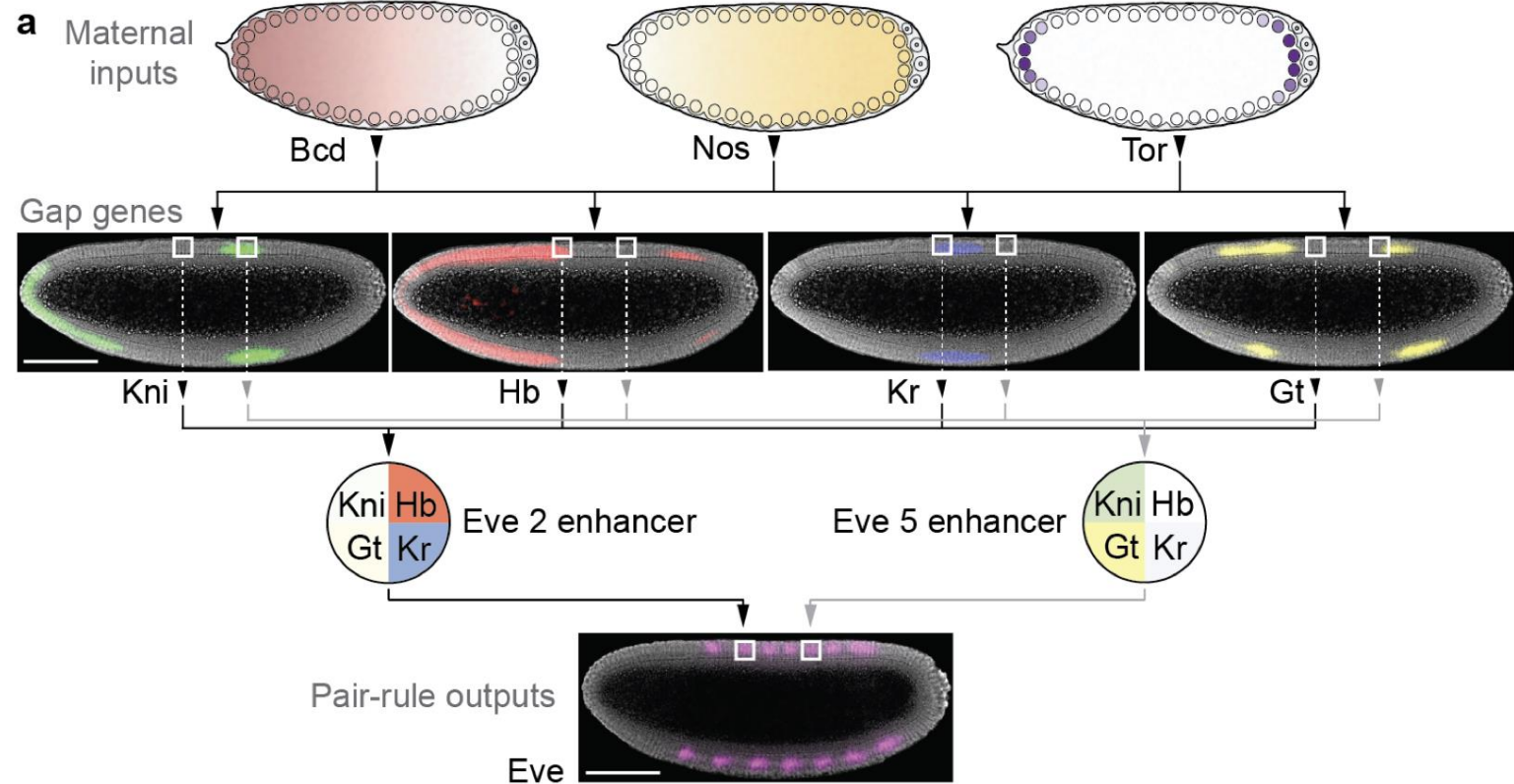
nos

hb mRNA

Hb protein



Segmentation networks in *Drosophila*

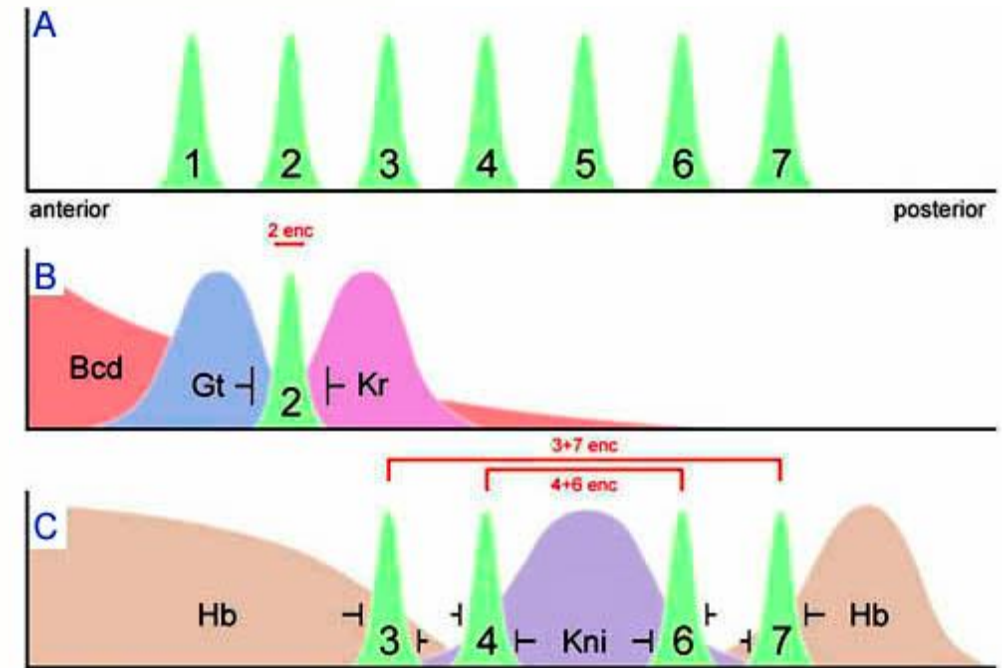
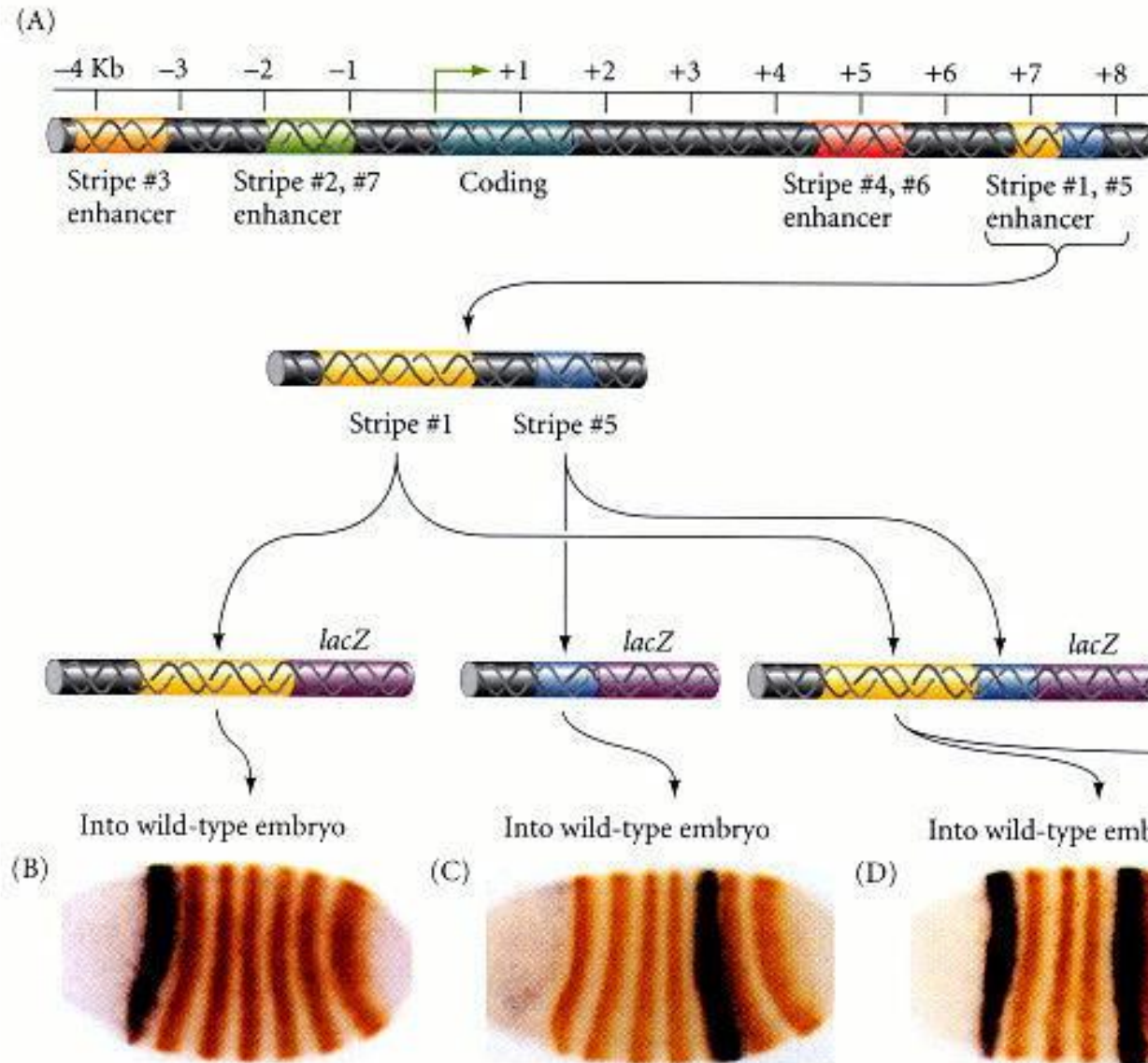


(Petkova et al., 2016 *arXiv*)

(Peel et al., 2005 *Nat Rev Gen*)



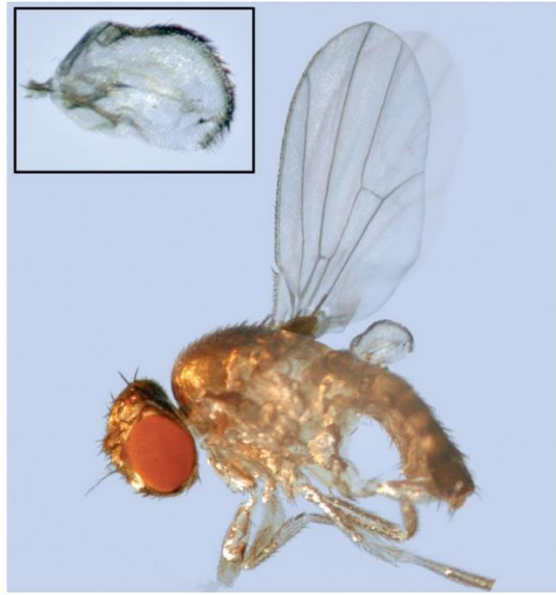
Segmentation in *Drosophila*: the regulation of the *even-skipped* (*eve*) gene



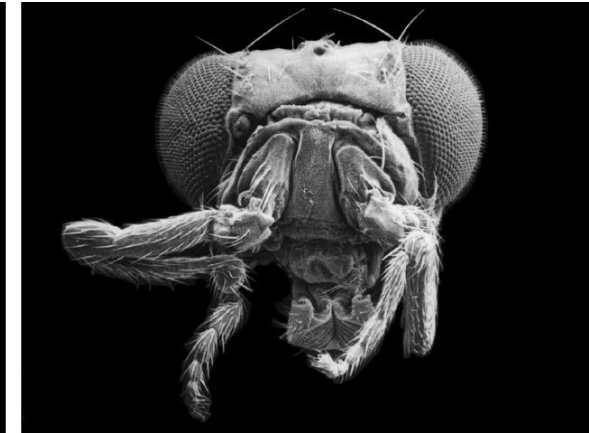
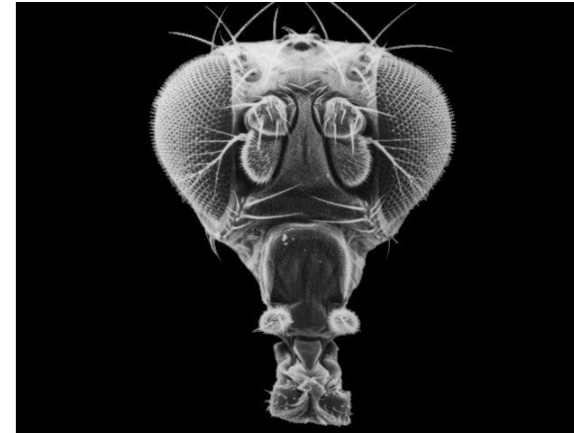
Segment identity: homeotic mutants



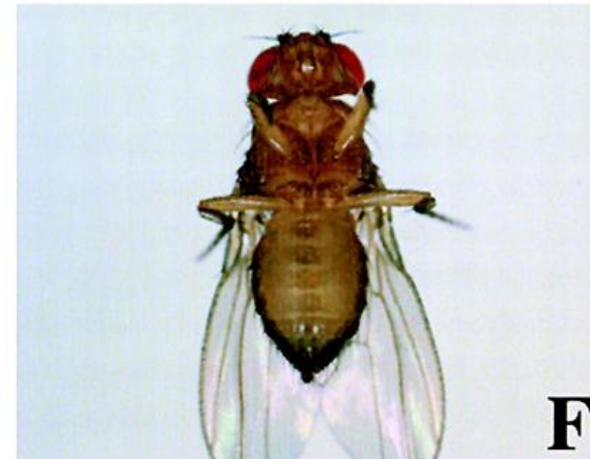
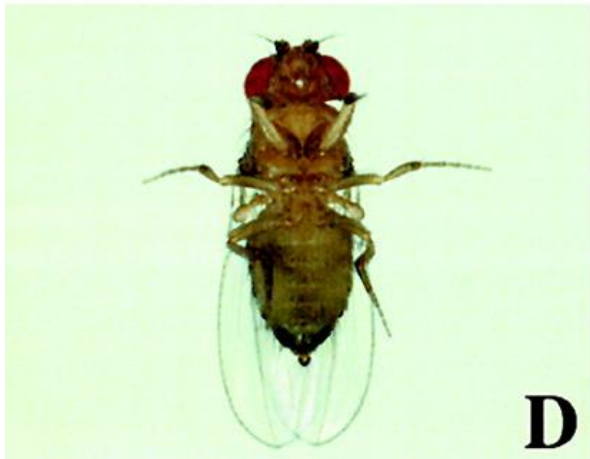
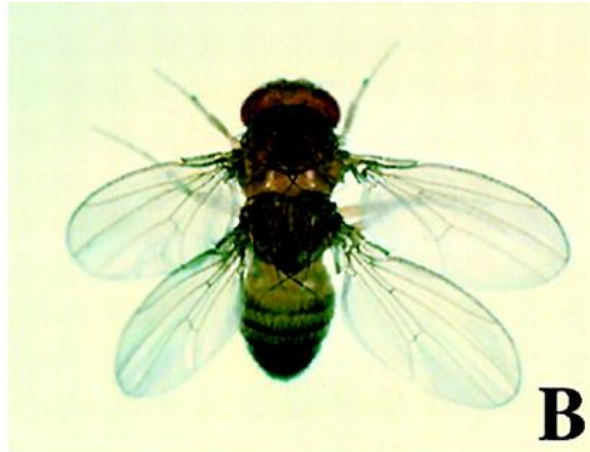
- the *bithorax* mutation



- the *antennapedia* mutation

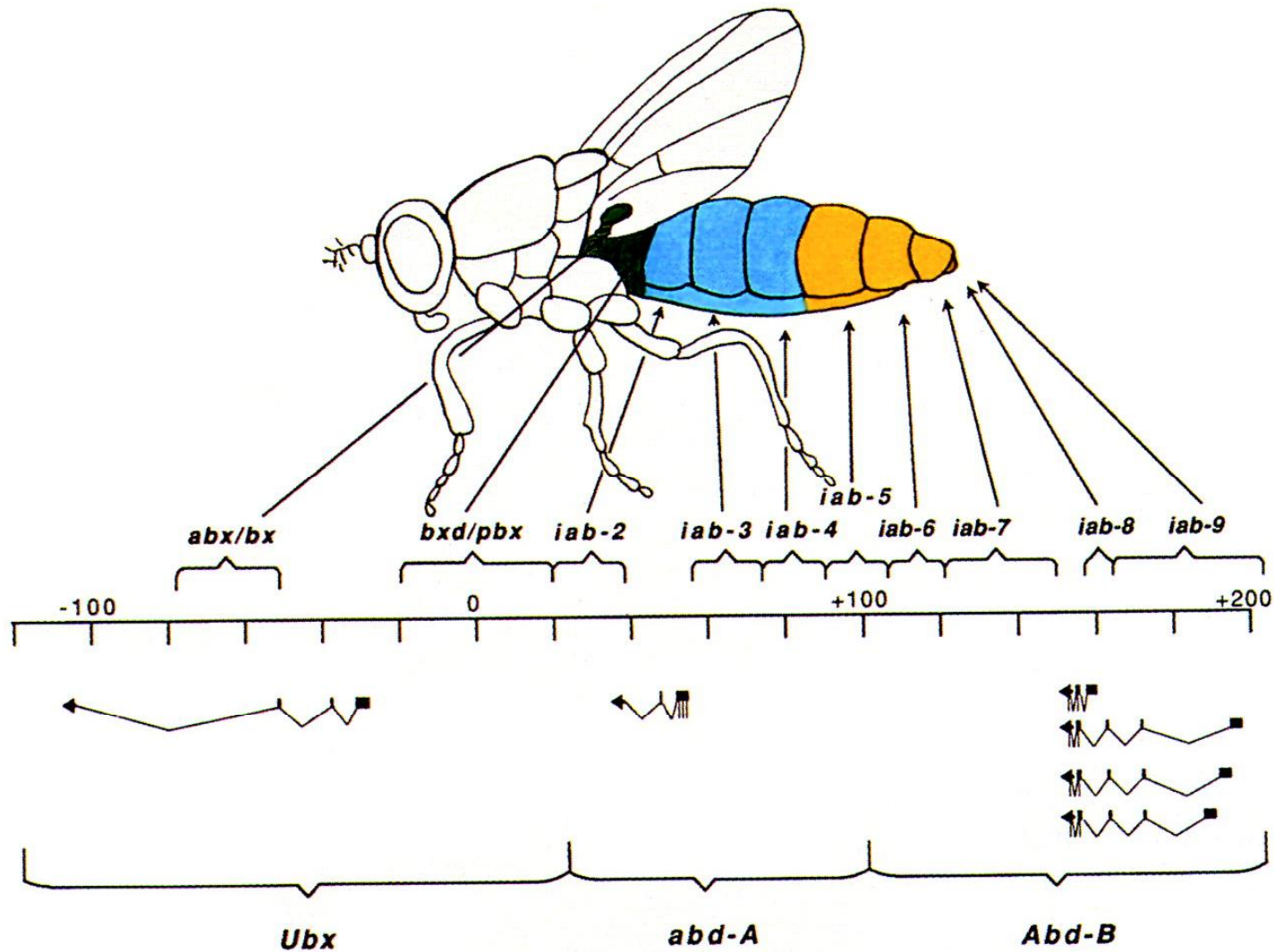


Segment identity: homeotic mutants





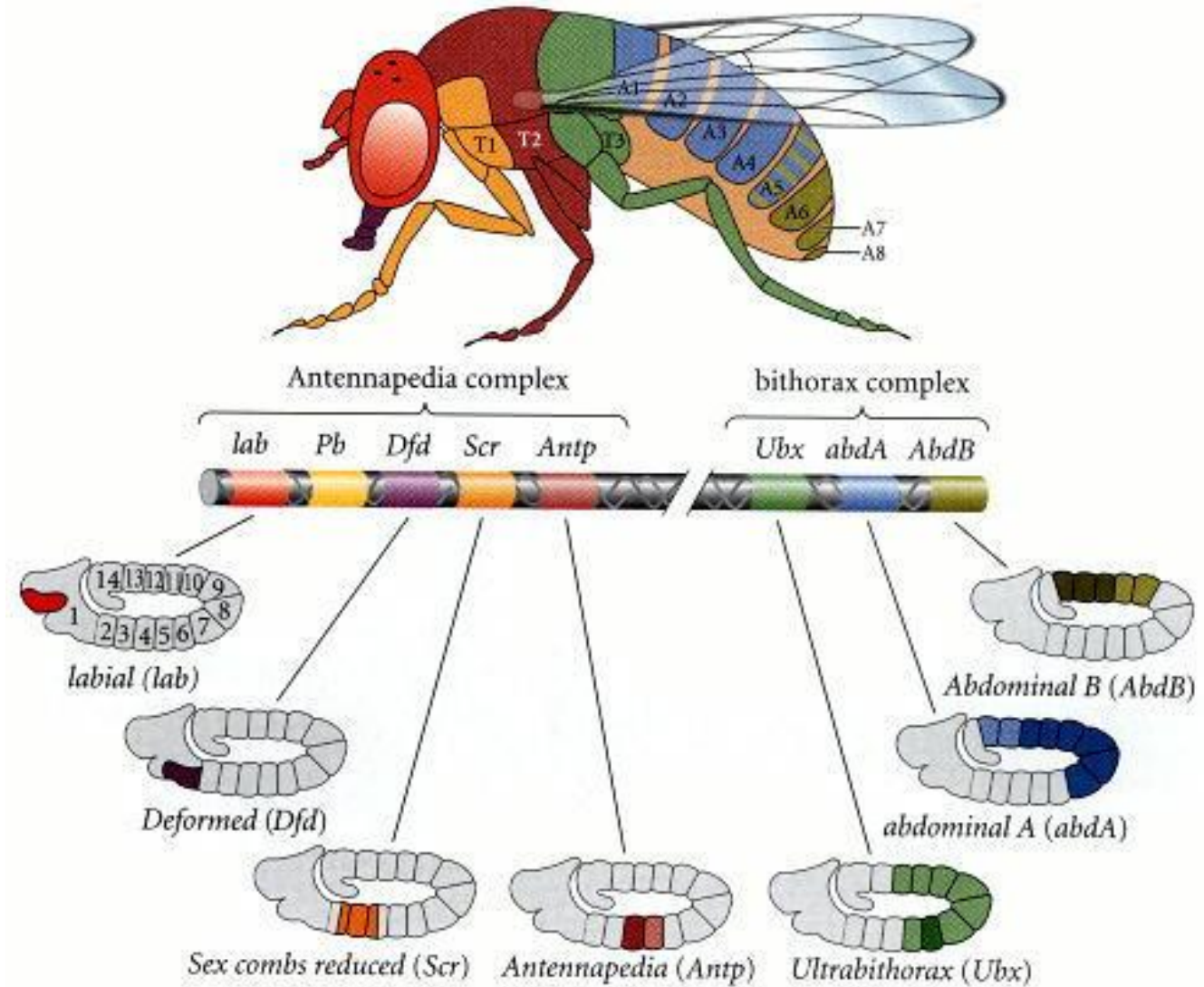
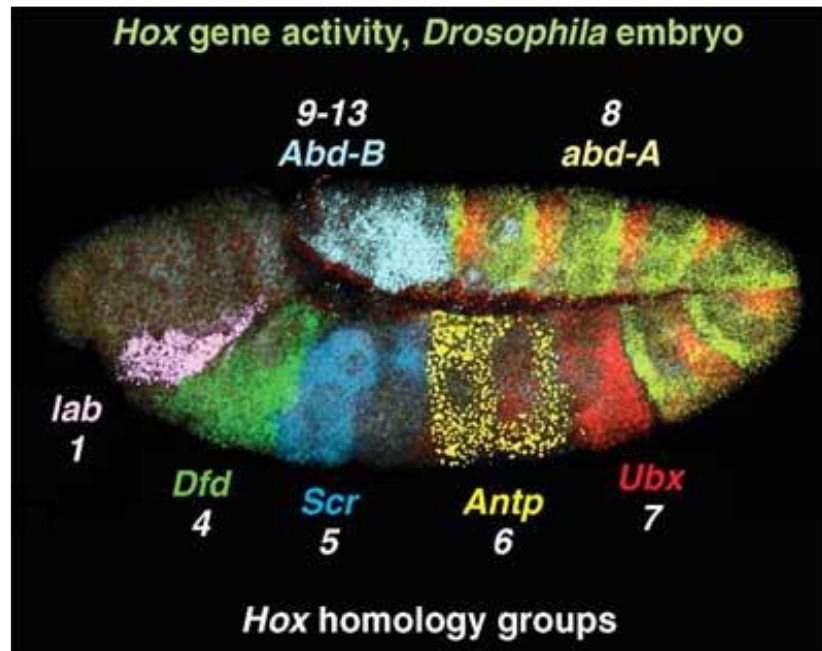
Segment identity: the *bithorax* complex



Edward B. Lewis

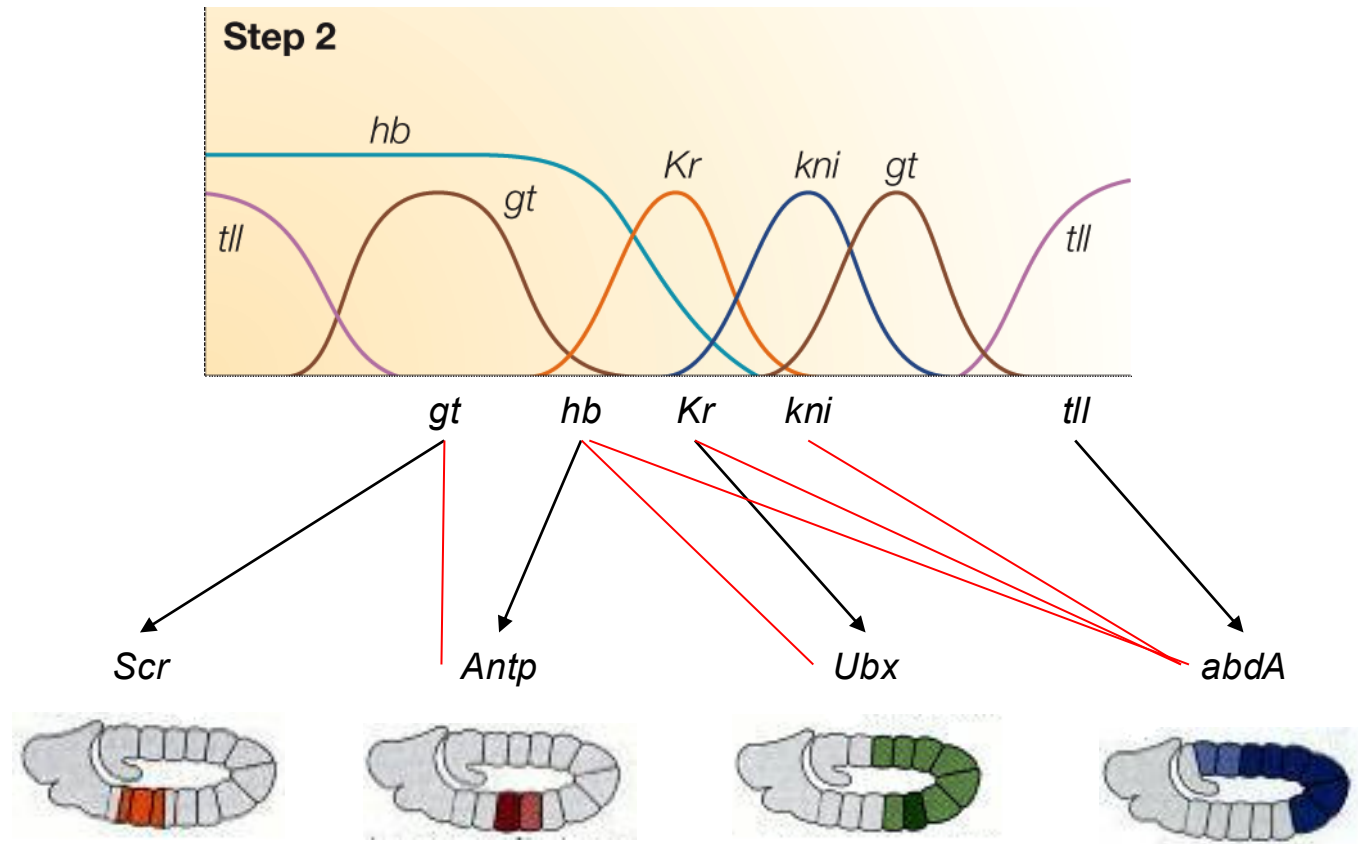


Segment identity: *Hox* genes



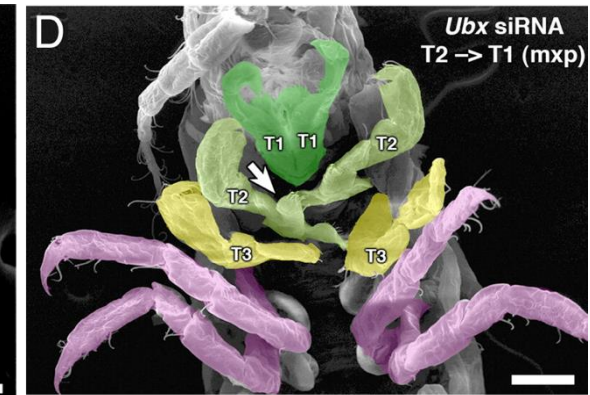
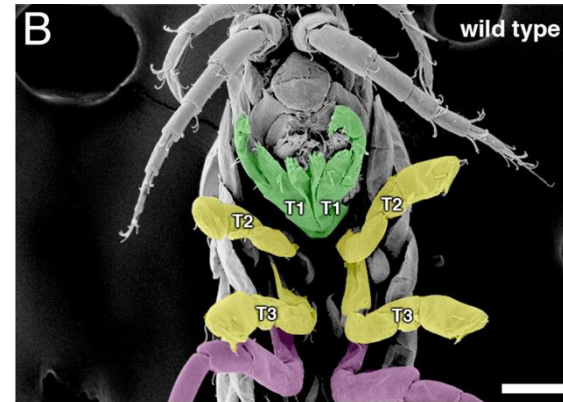
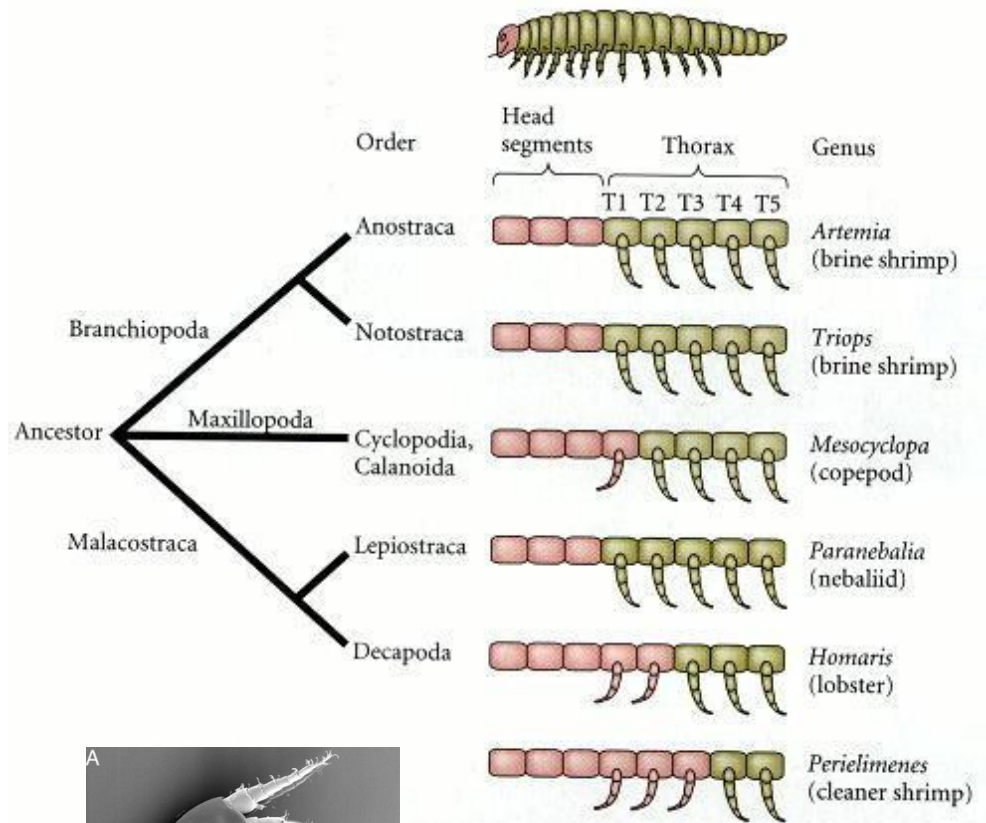


Hox genes are regulated by *gap* genes

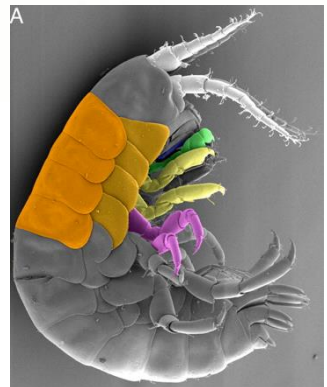




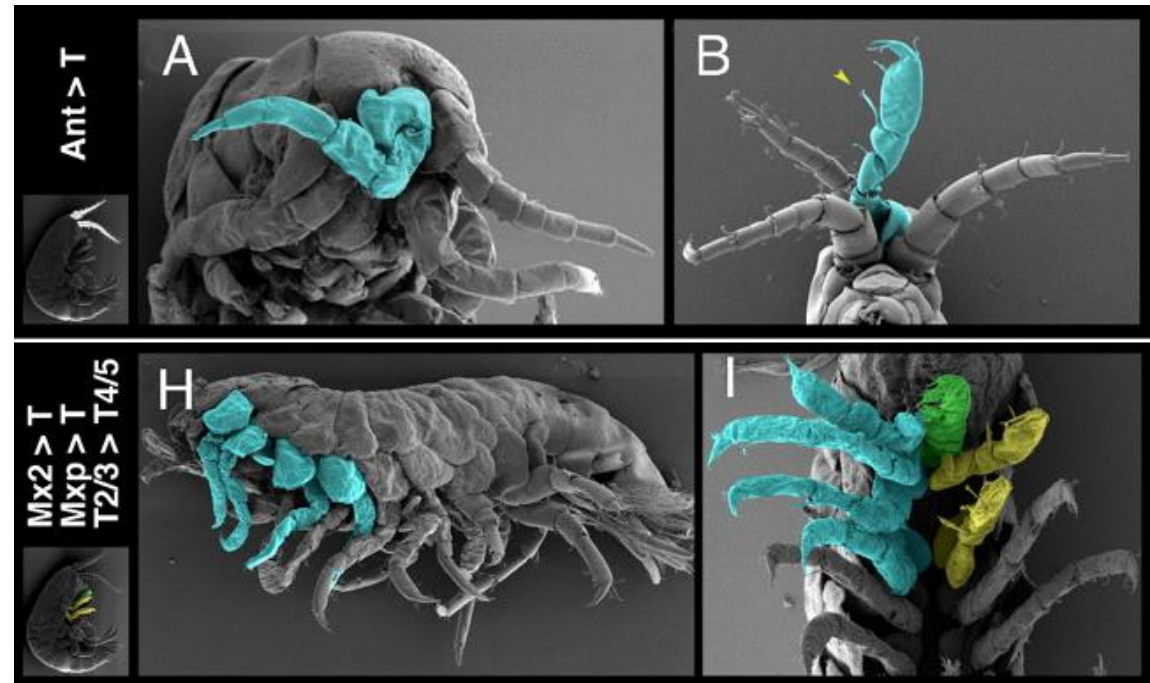
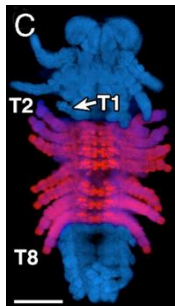
Hox genes (*Ubx*) and evolution of the arthropod bodyplan



(Liubicich et al., 2009 *PNAS*)

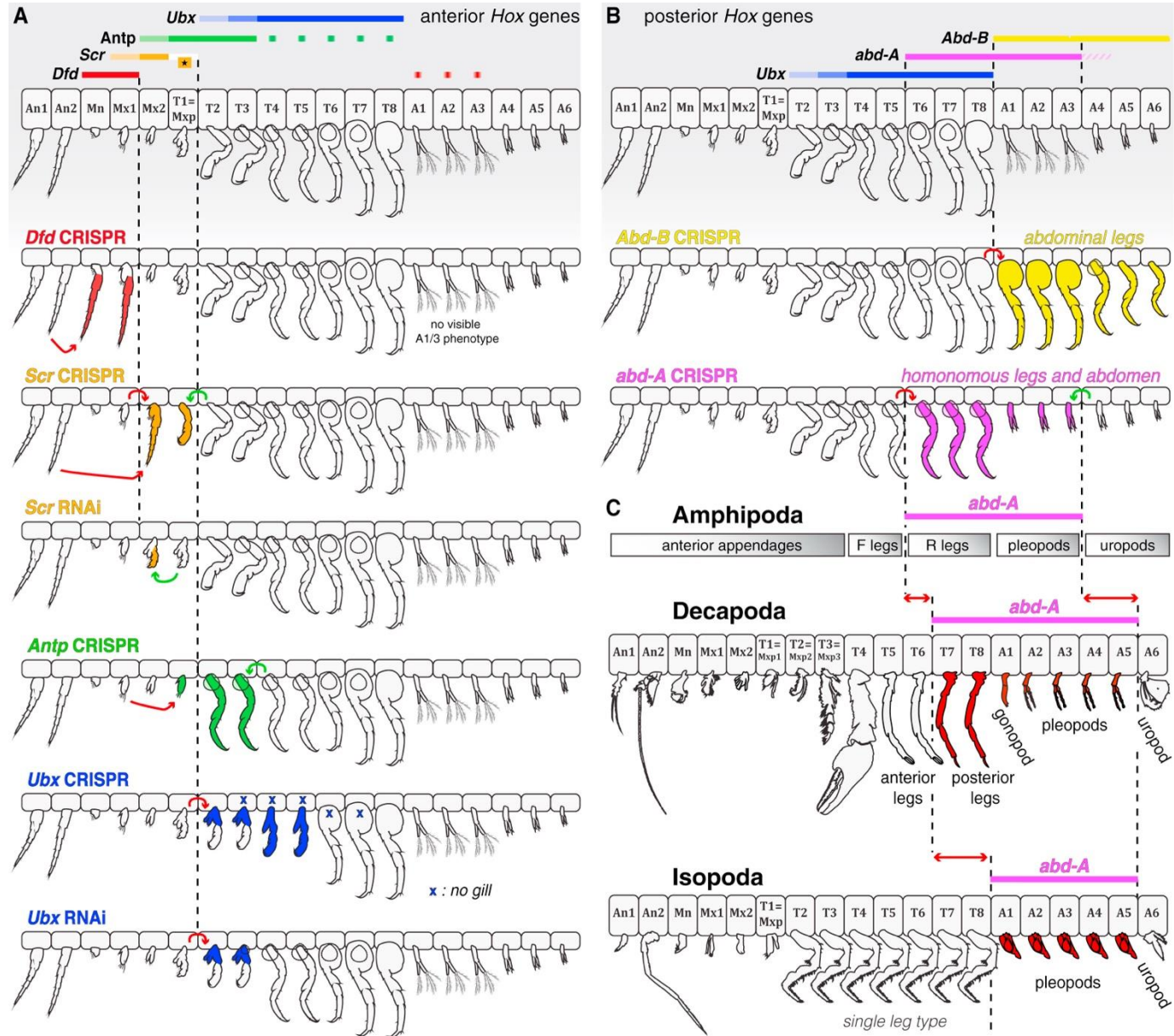
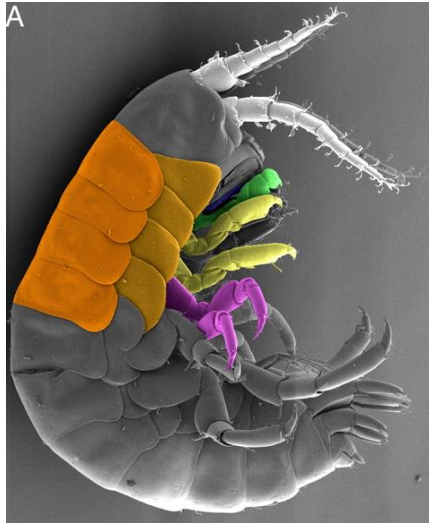


Parhyale hawaiensis



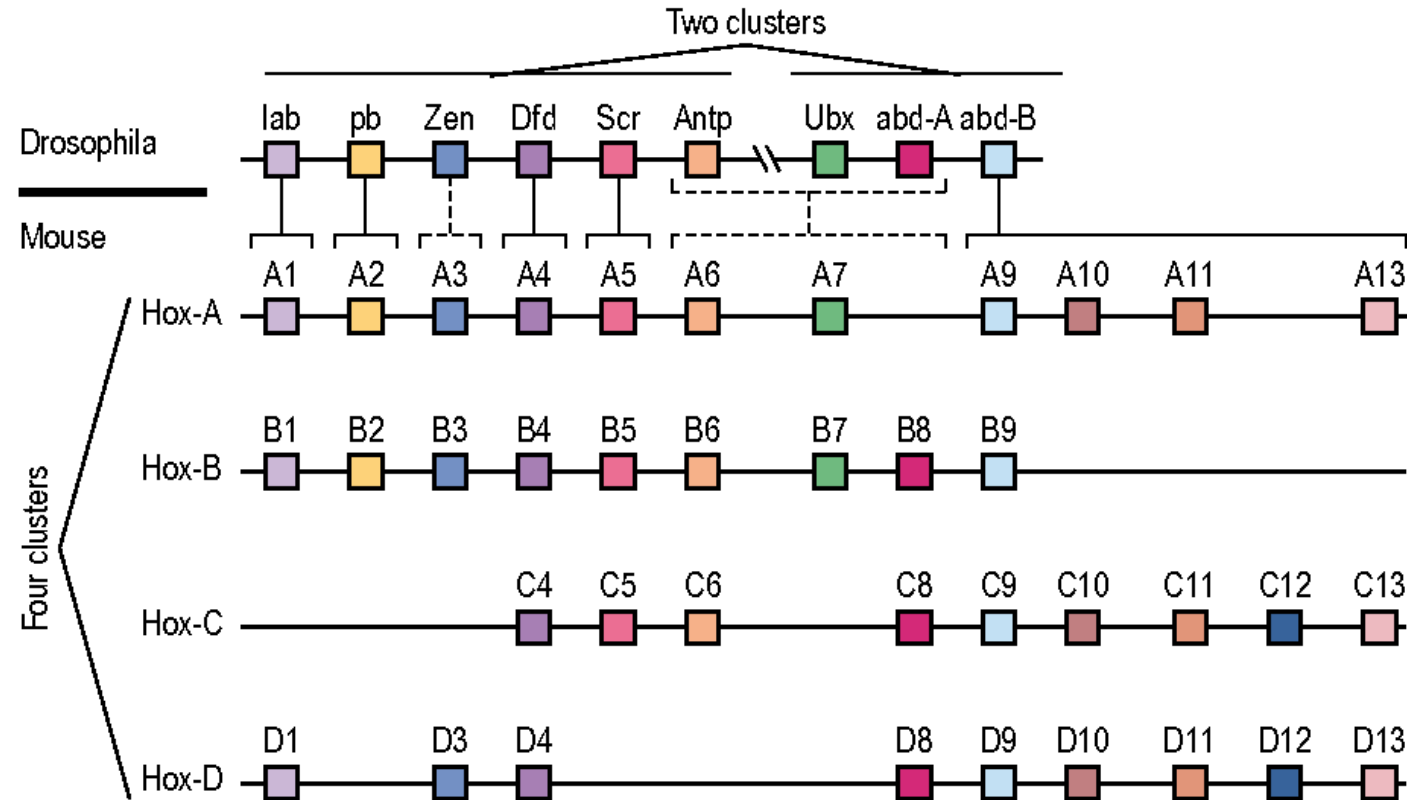
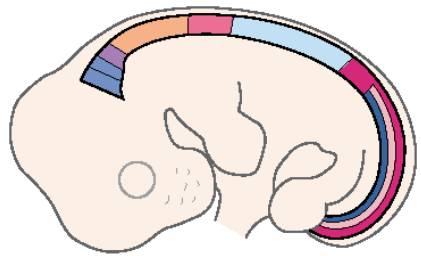
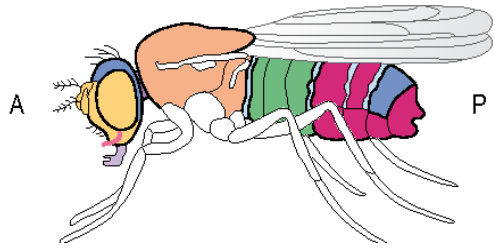
(Pavlopoulos et al., 2009 *PNAS*)

Hox genes and the evolution of the arthropod bodyplan: uropods



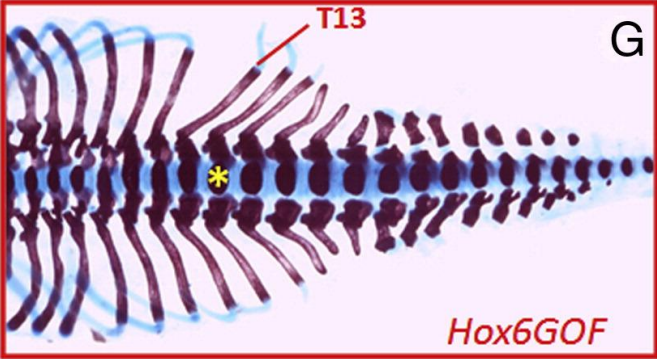
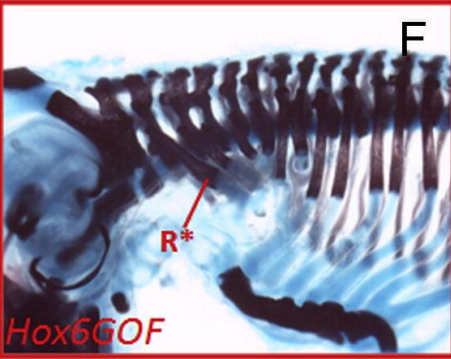
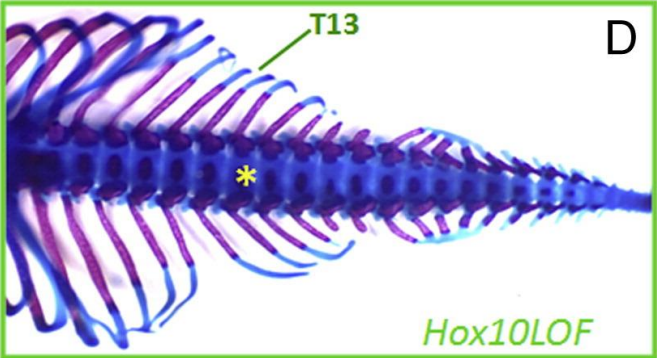
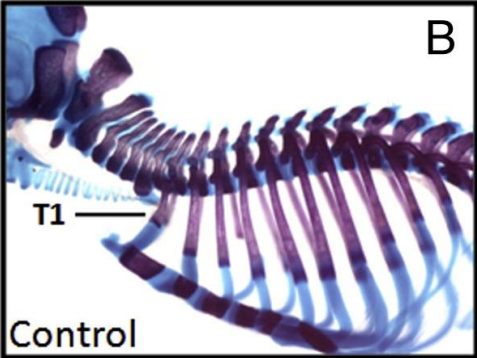
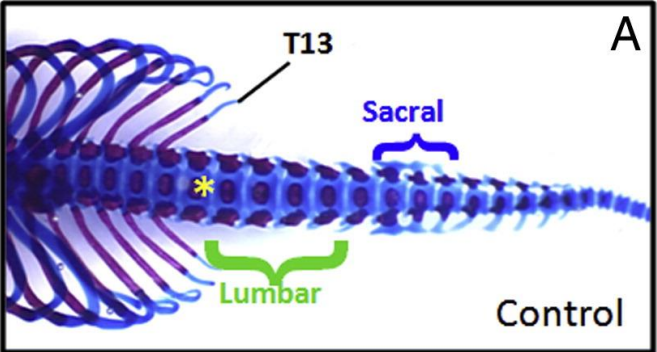
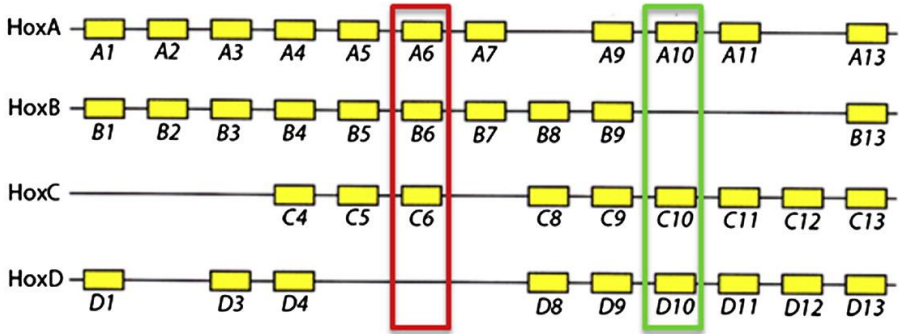
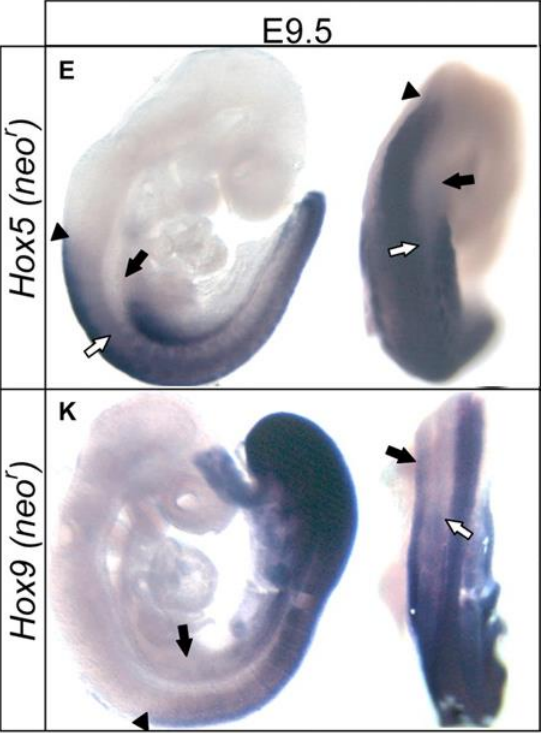


The *Hox* cluster is (almost) universal amongst animals





Homeotic mutants in vertebrates



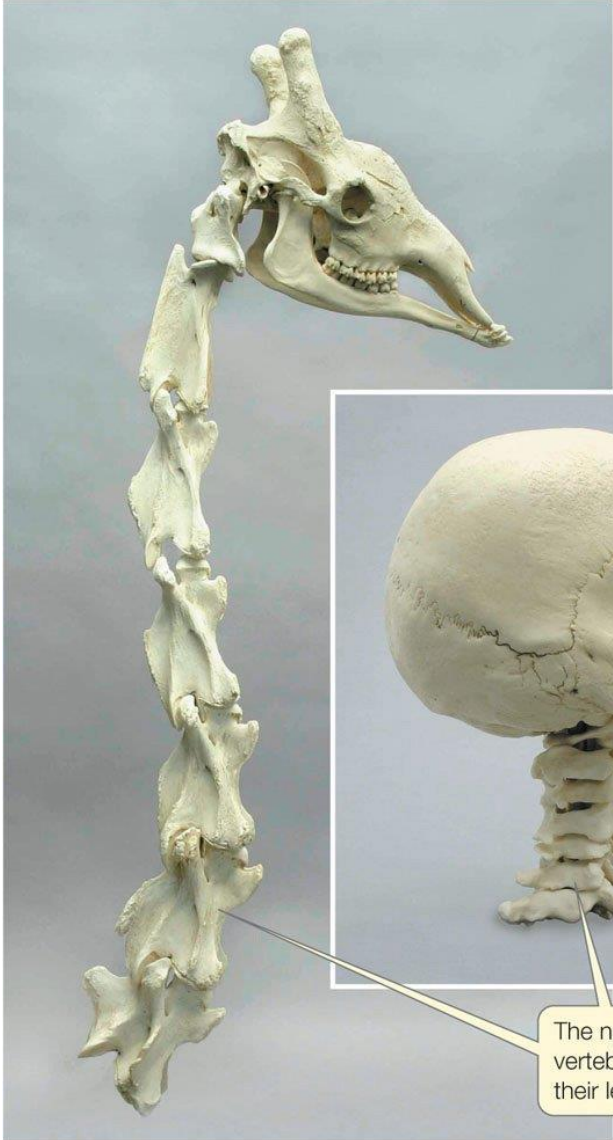
(McIntyre et al., 2007 *Development*)

(Mallo et al., 2010 *Dev Biol*)

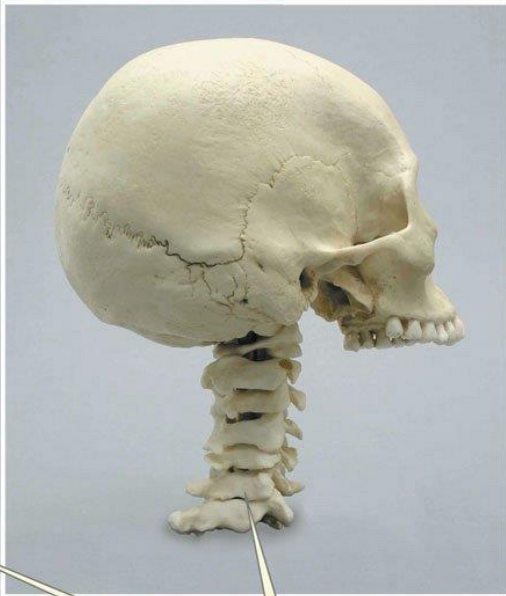


Homeotic mutants in vertebrates

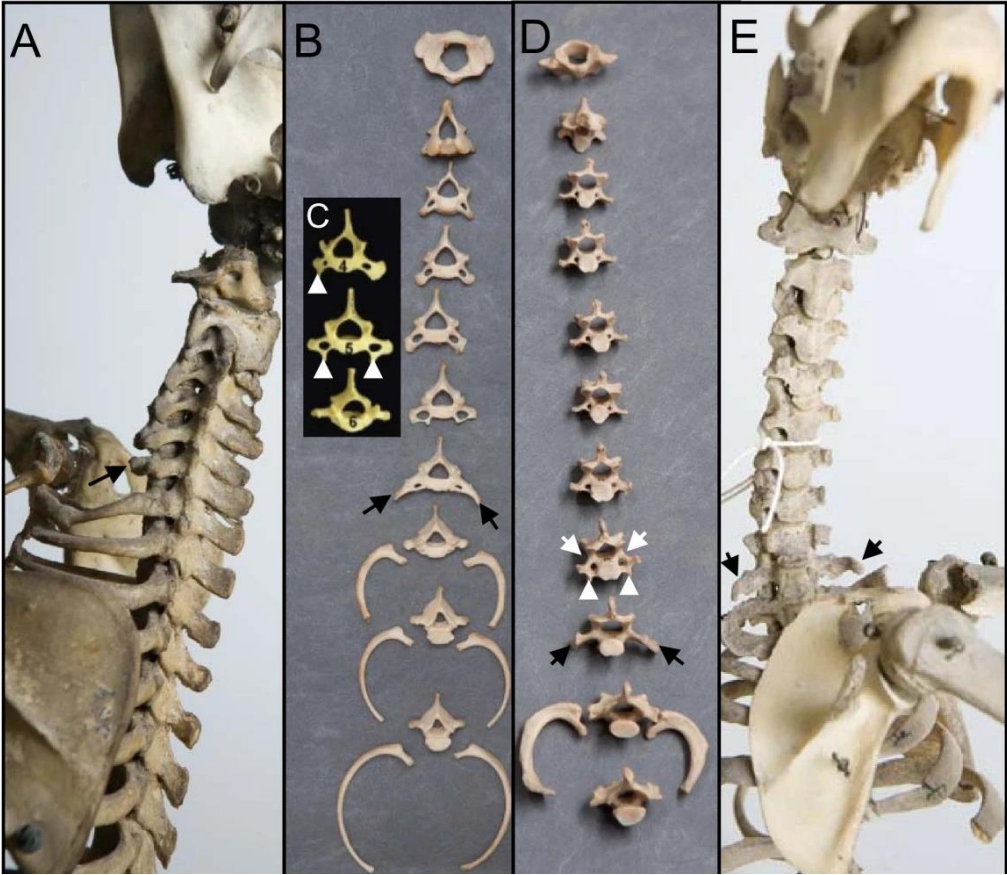
(A) Giraffe



(B) Human



The number of cervical vertebrae is the same, but their lengths are different.



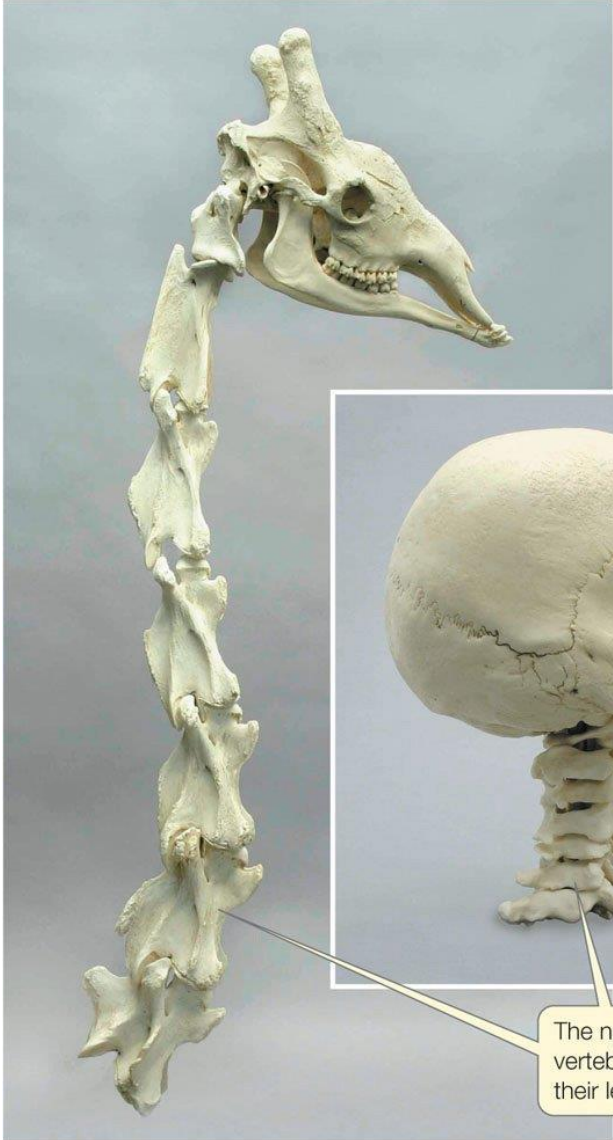
sloths

manatees

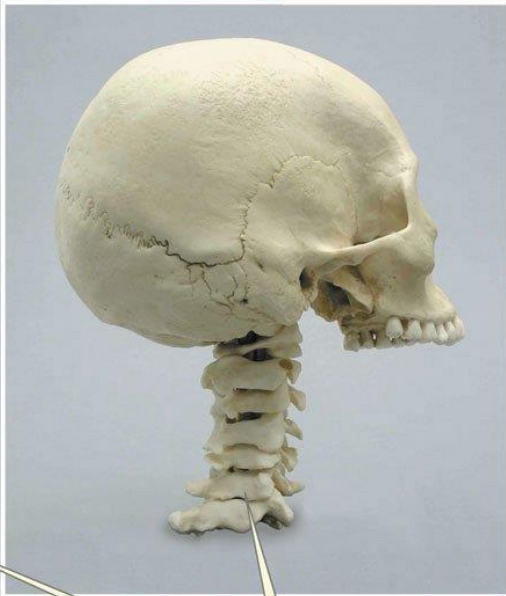


Homeotic mutants in vertebrates

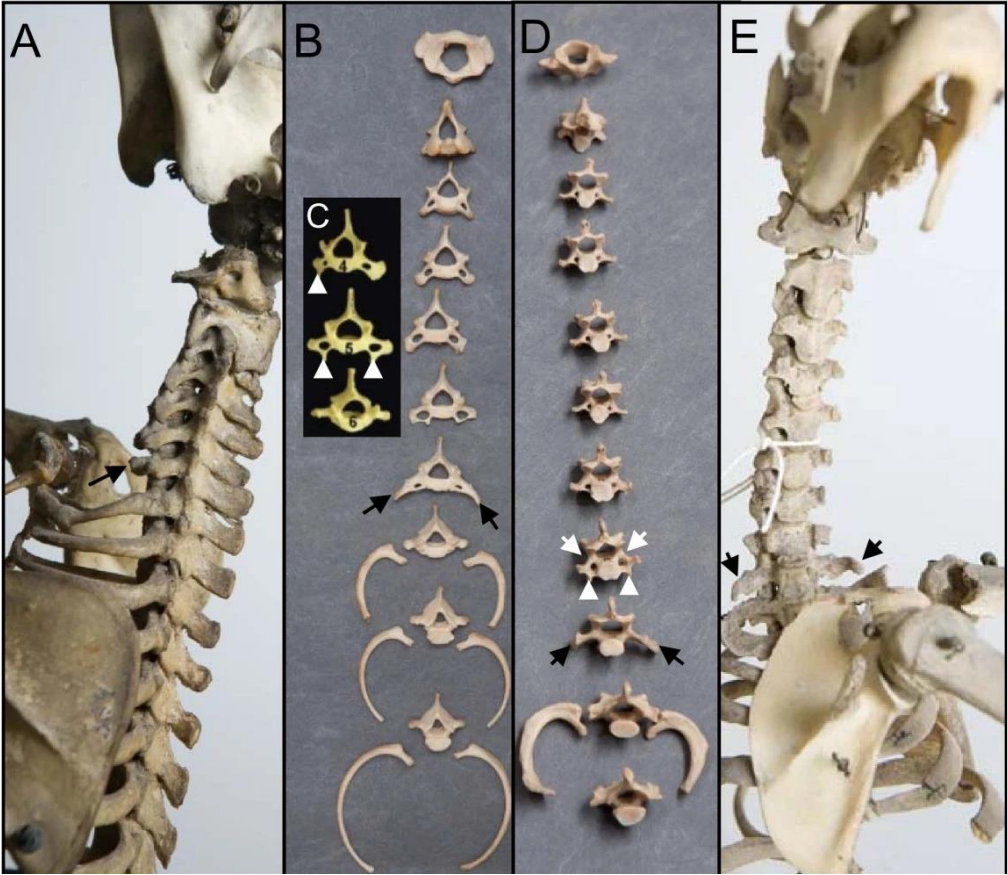
(A) Giraffe



(B) Human



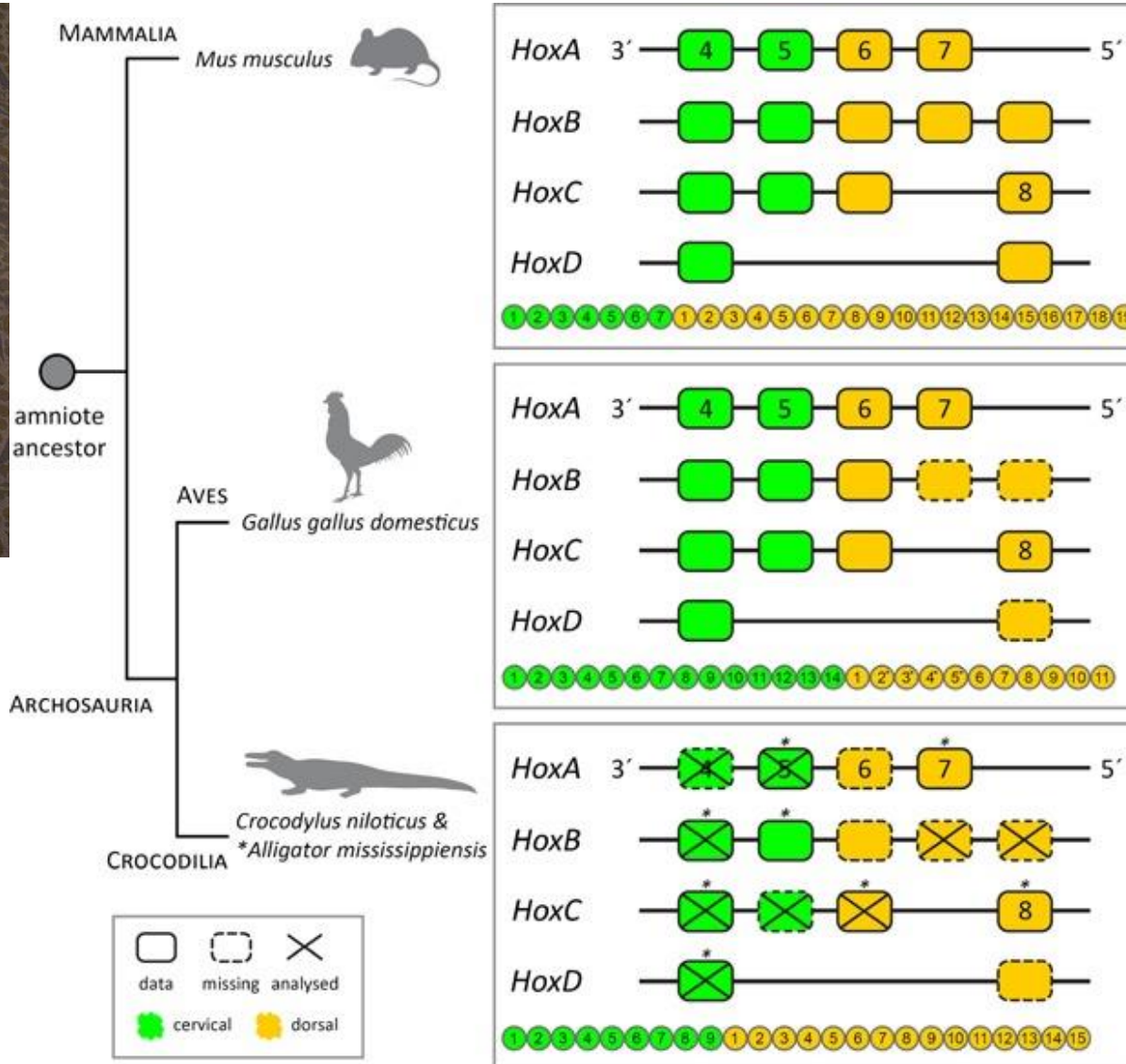
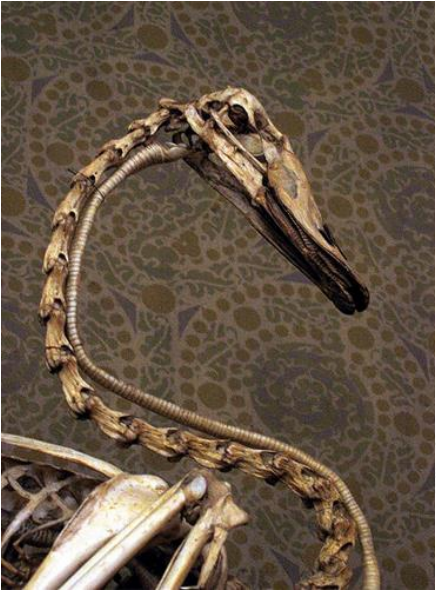
The number of cervical vertebrae is the same, but their lengths are different.



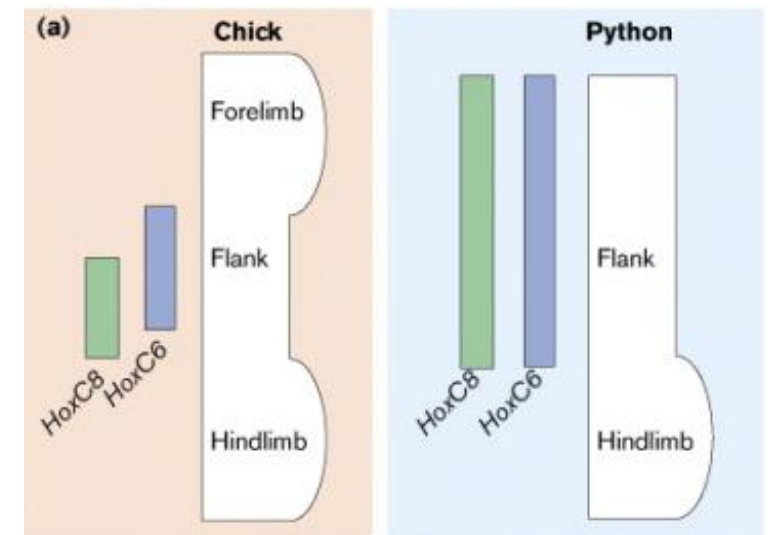
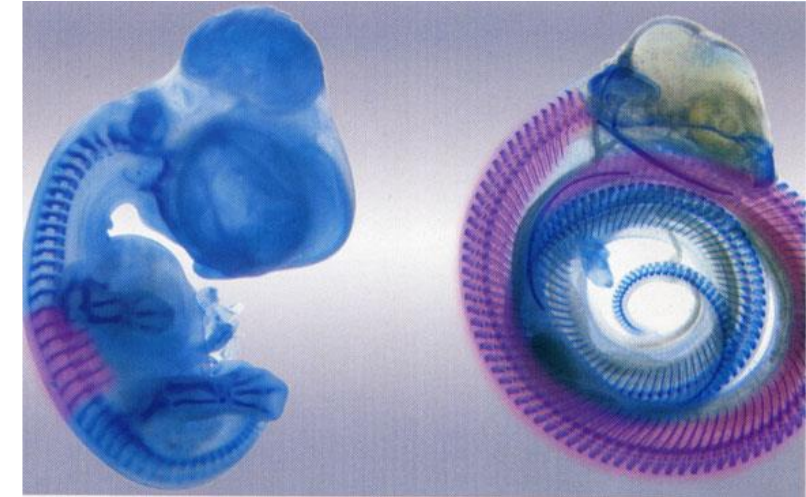
sloths

manatees

Hox genes and vertebrate evolution

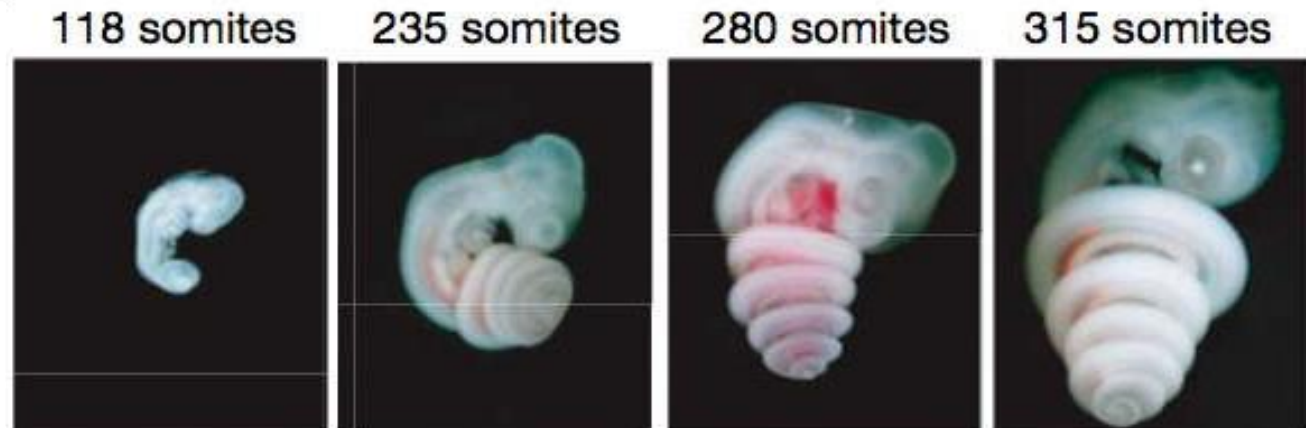
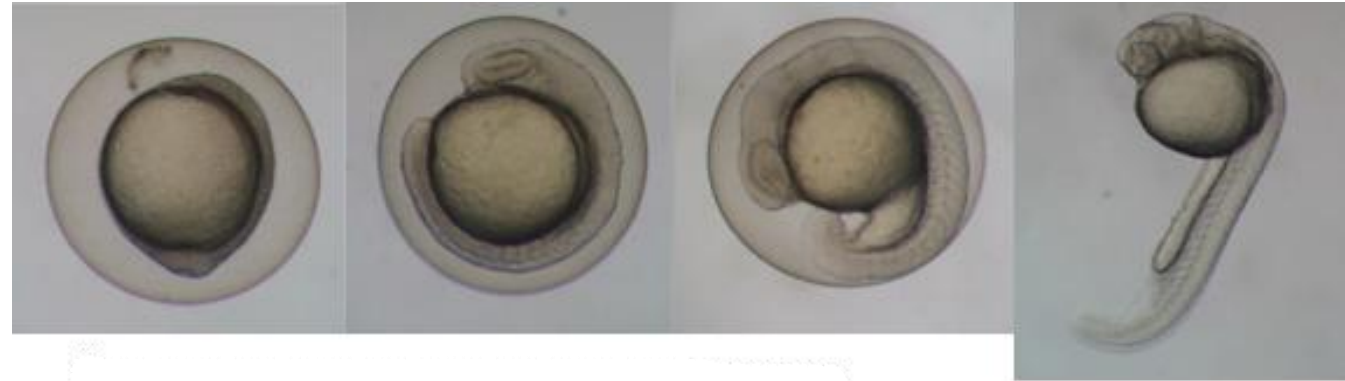
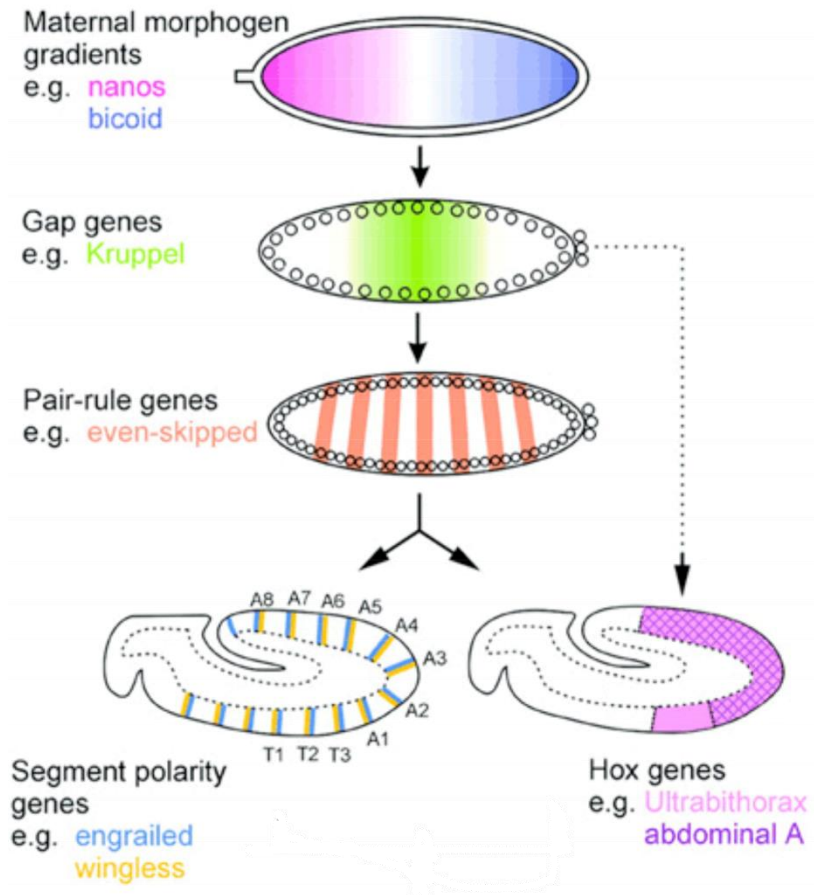


hoxc6 expression pattern





The AP axis formation in *Drosophila* and vertebrates is fundamentally different

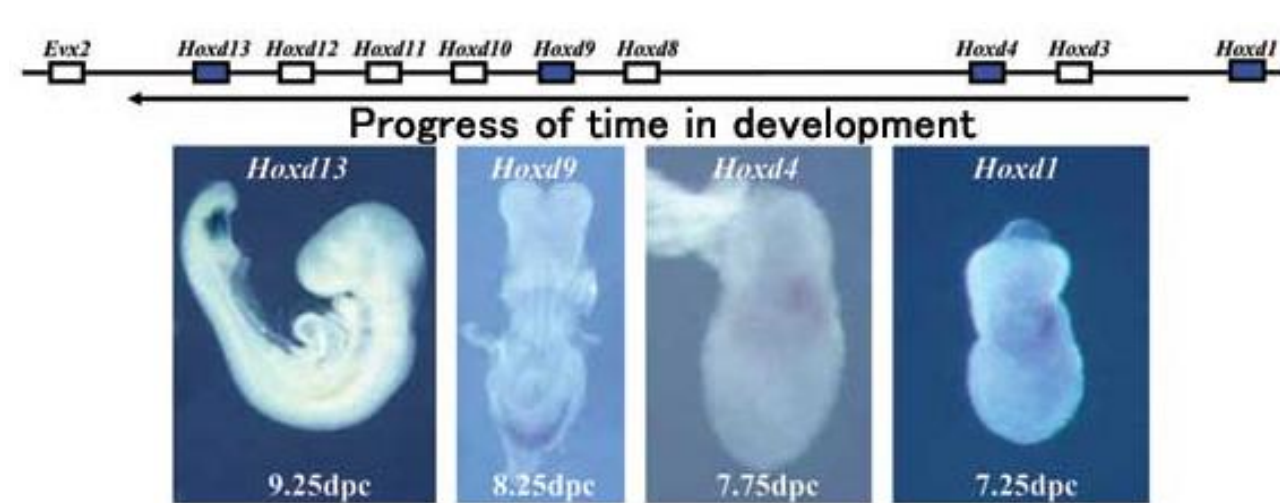


In a *Drosophila* embryo the primordia of all future segments are present from the very beginning (this is not general even for insects = “long germ insect”)

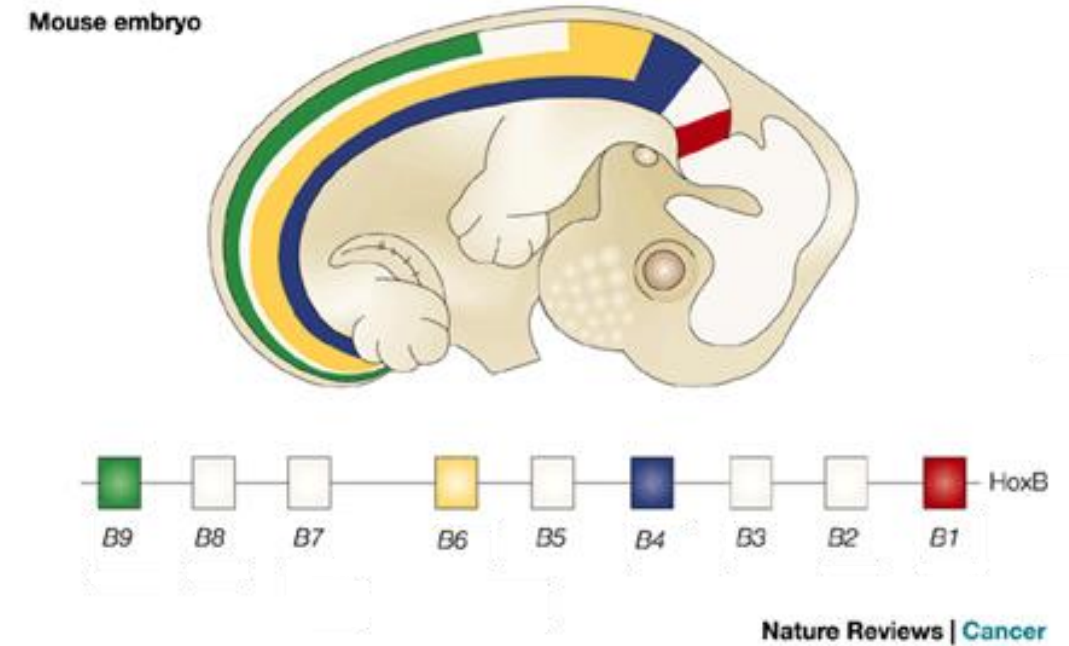
In vertebrates by the end of gastrulation only the anterior structures are specified and later segments arise from the growth zone of the embryonic tailbud.



Hox genes and colinearity



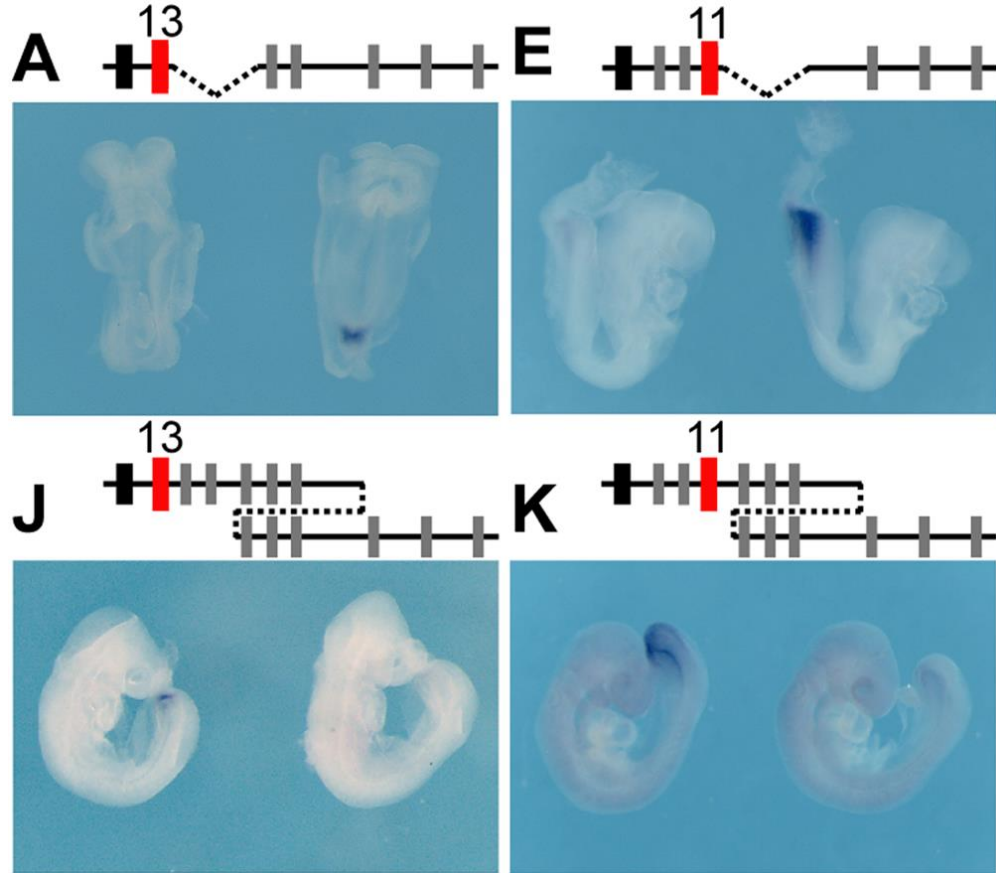
- **Temporal colinearity:** *Hox* genes that more 3' in the cluster are expressed earlier



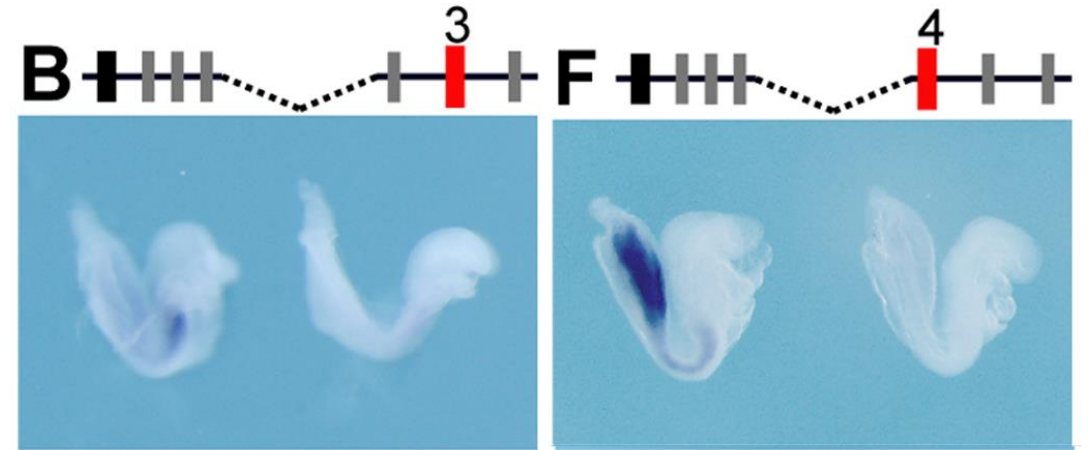
- **Spatial colinearity:** *Hox* genes that more 3' in the cluster are expressed more anteriorly



Temporal colinearity is dependent on the relative position to the telomeres and centromeres



The closer the telomere, the faster the activation of a given *Hox* gene can be observed.

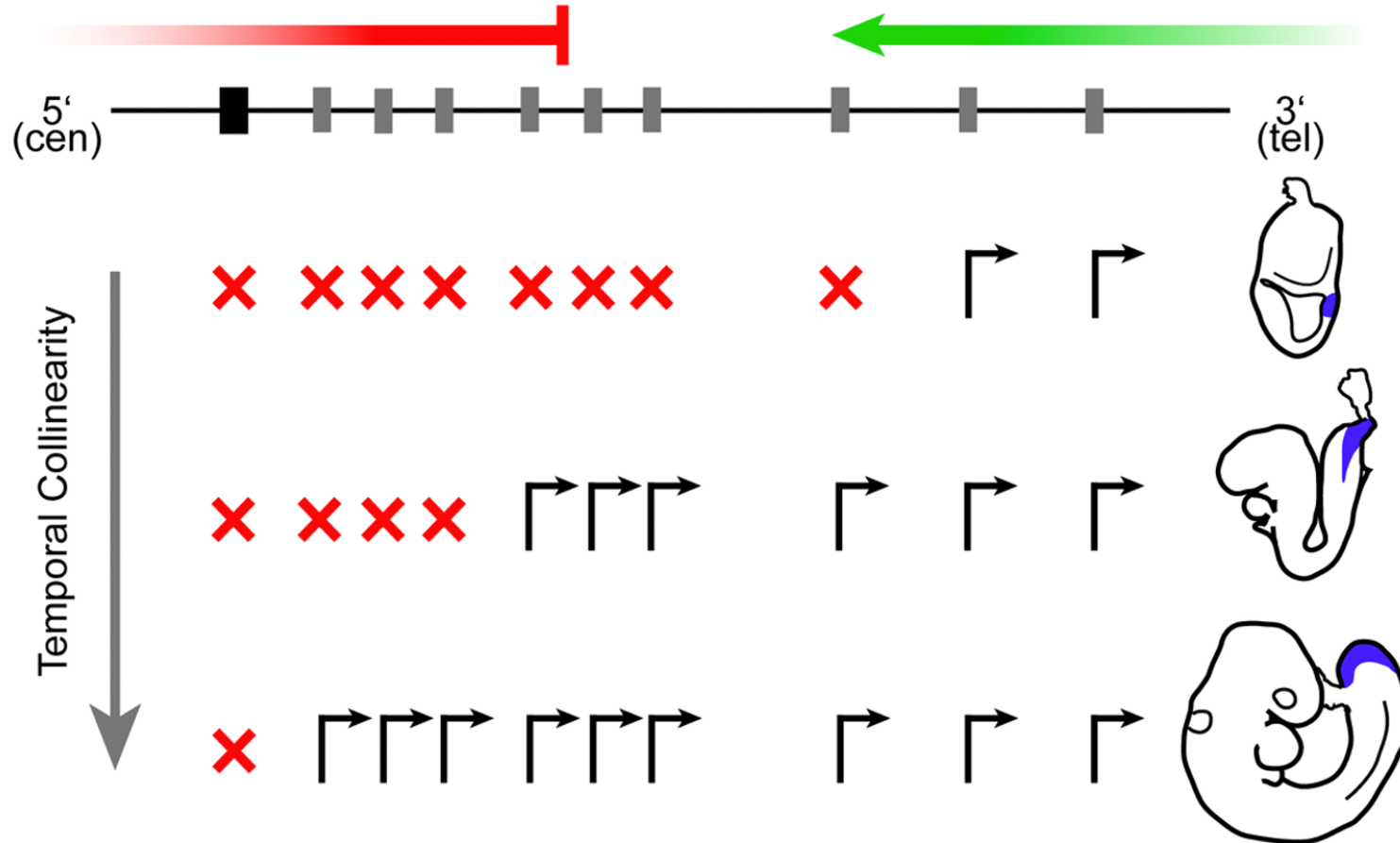


The proximity of the centromere inhibits *Hox* gene expression.



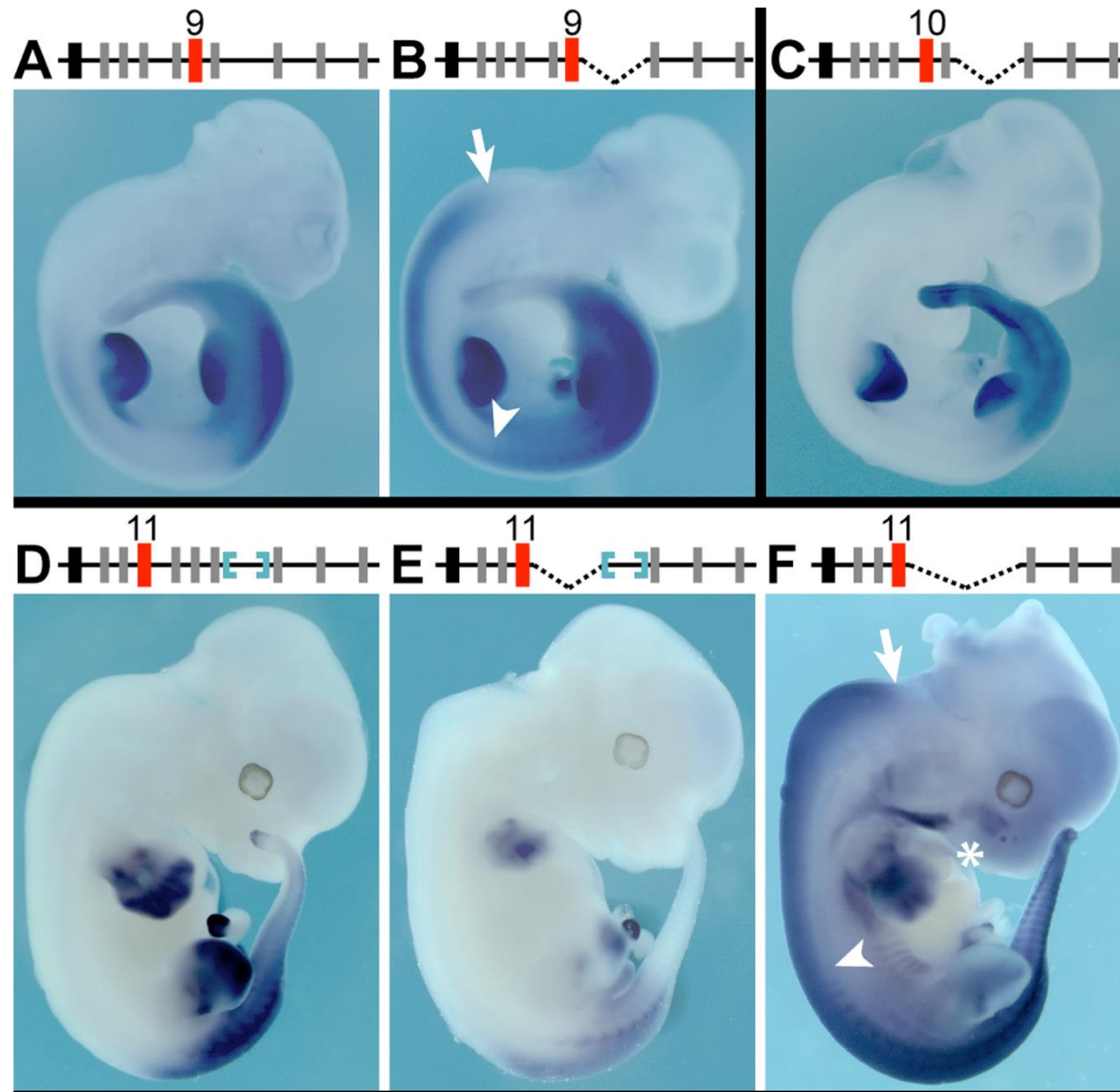
Temporal colinearity is dependent on the relative position to the telomeres and centromeres

Early Phase





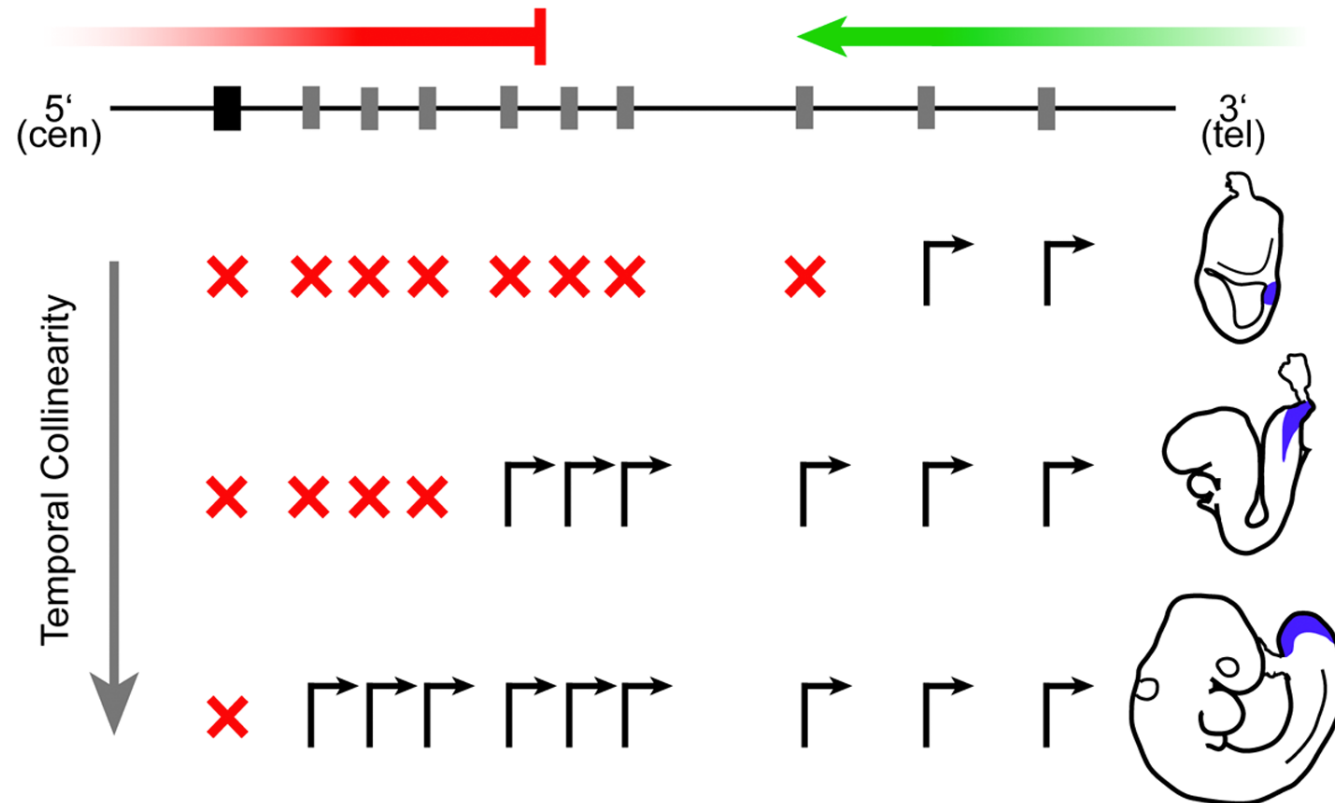
Spatial colinearity is dependent on local interactions



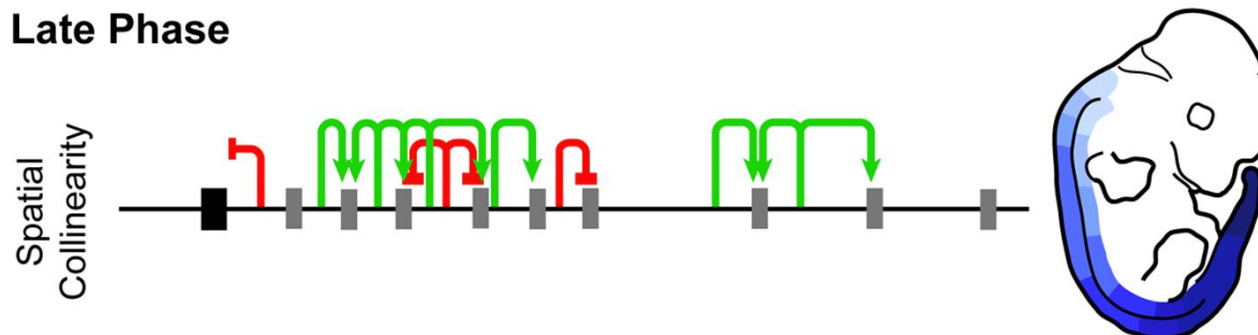


Spatial colinearity is dependent on local interactions

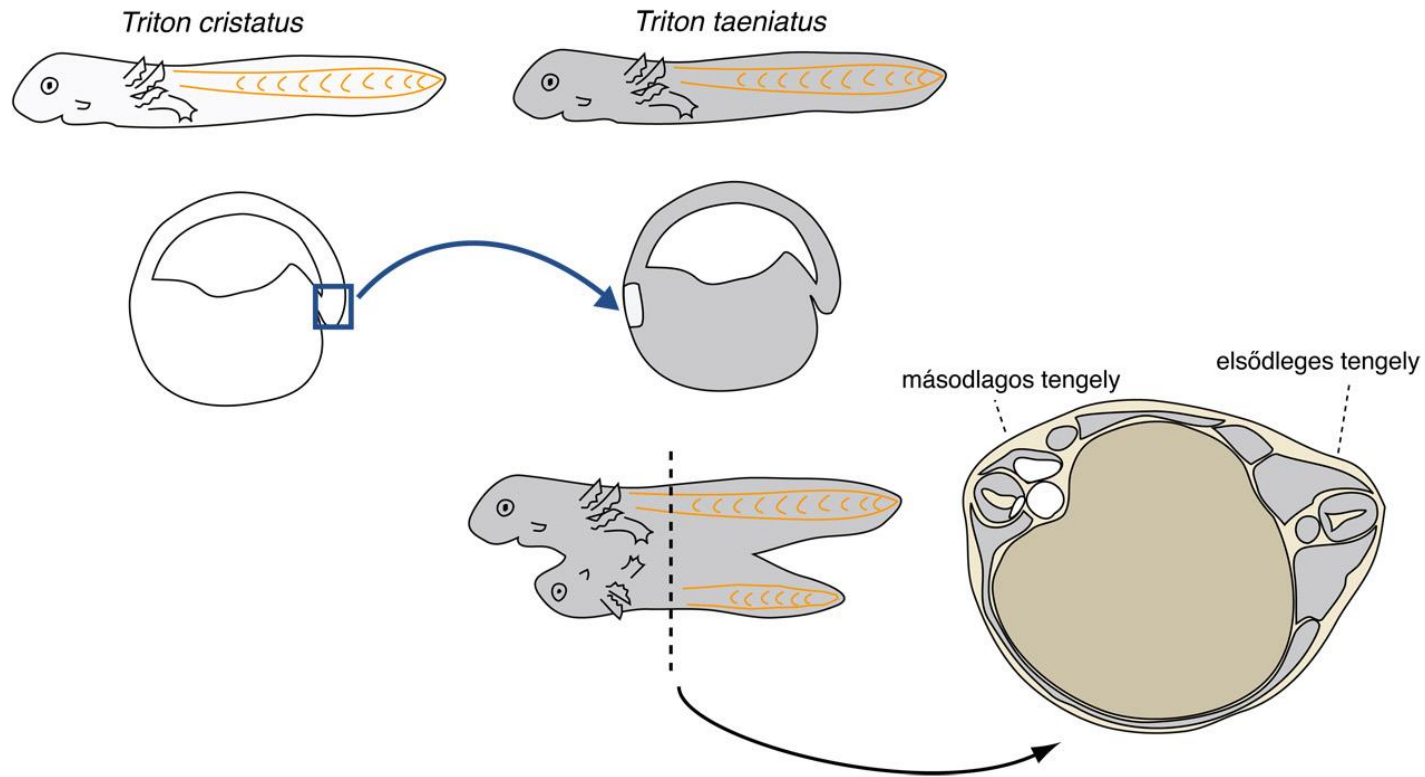
Early Phase



Late Phase



The Spemann-Mangold experiment and the discovery of the dorsal organizer (1924)



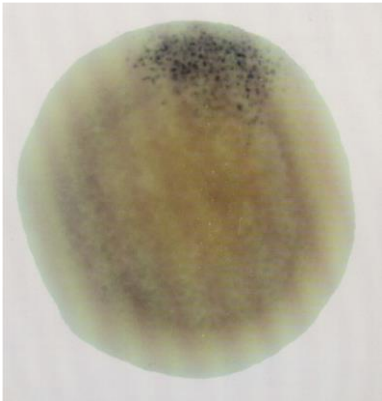
Hilde
Mangold
(née Pröschold)



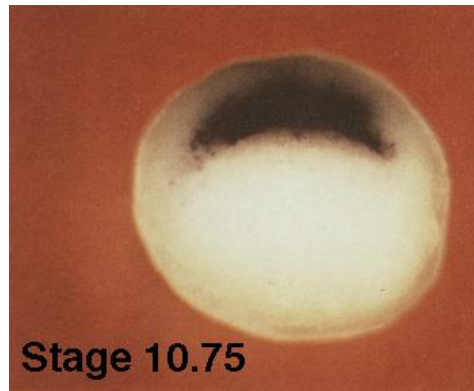
Hans
Spemann



The Spemann-Mangold organizer expresses BMP antagonists

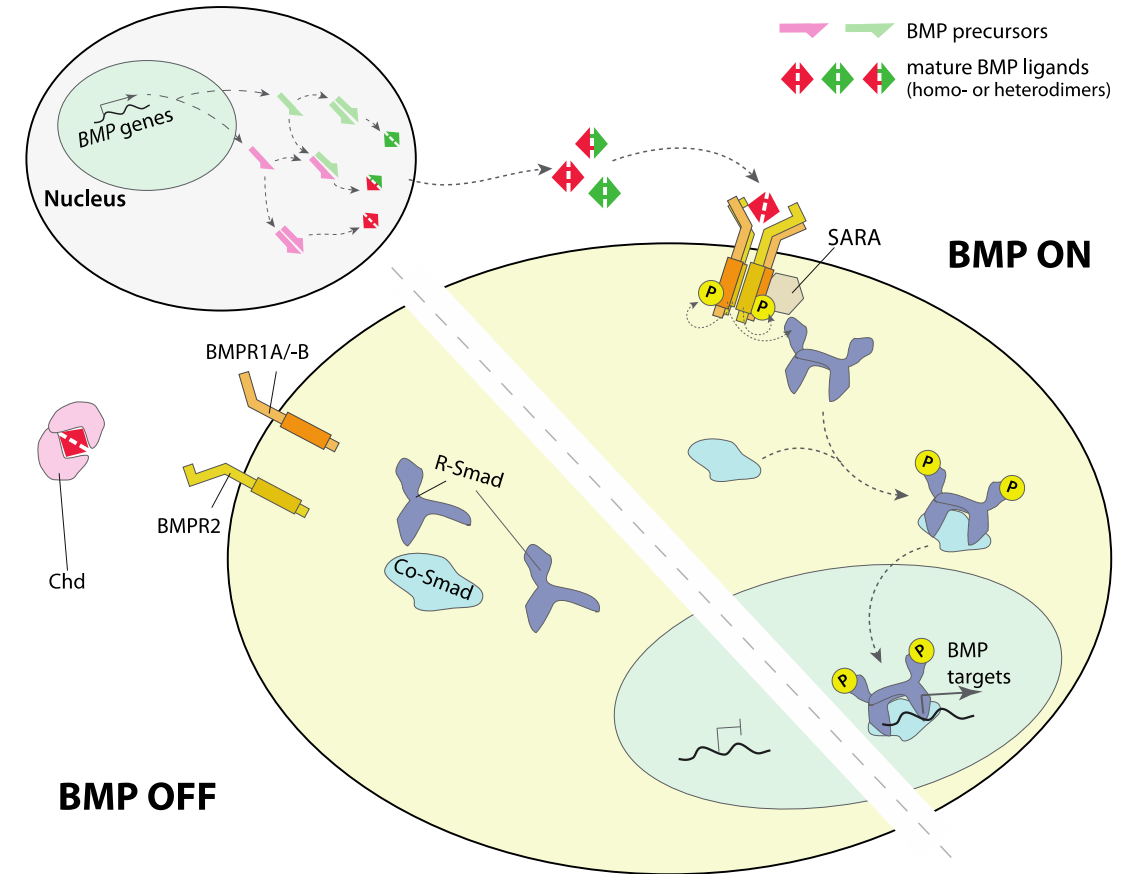


noggin
Smith and Harland (1992)



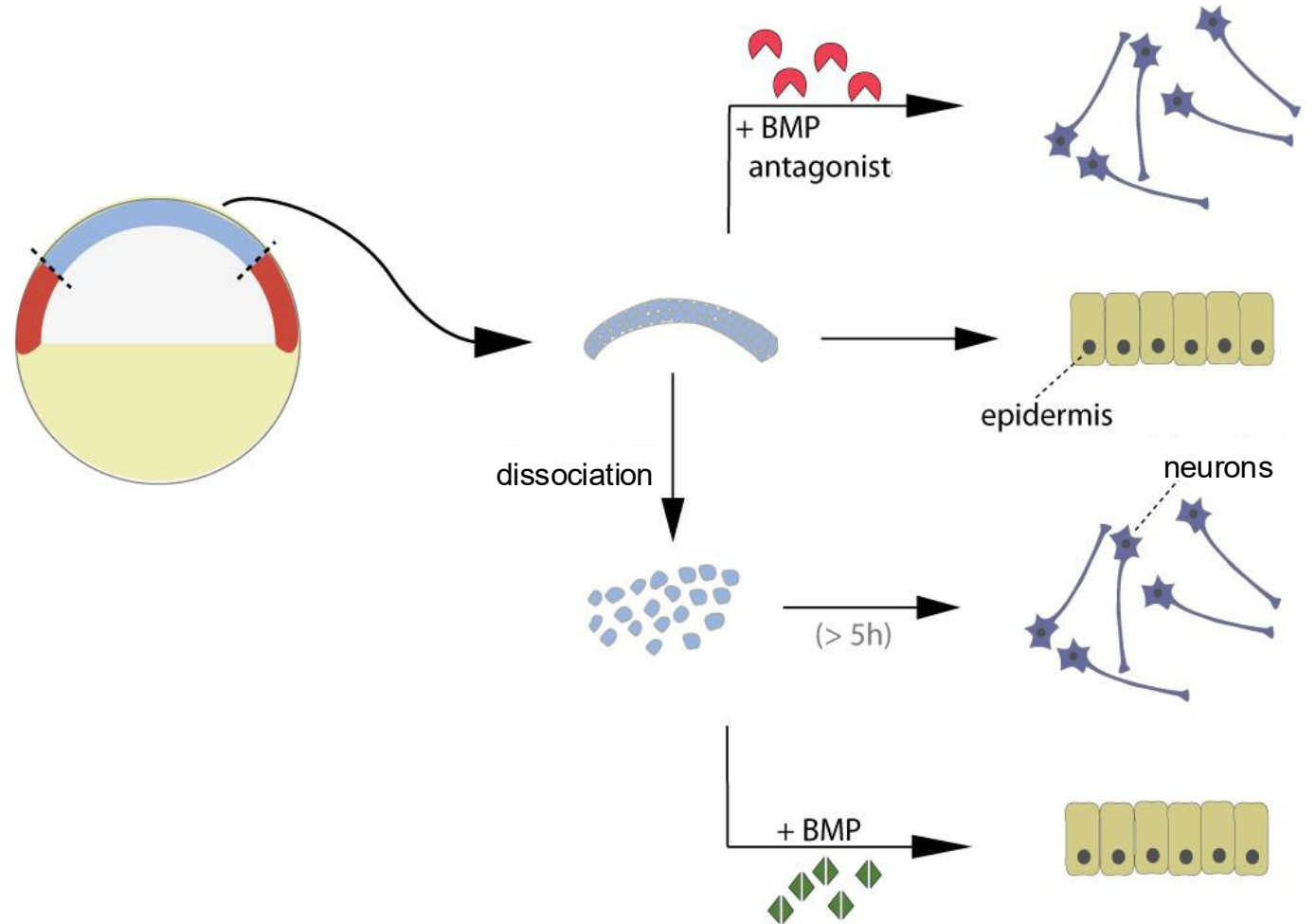
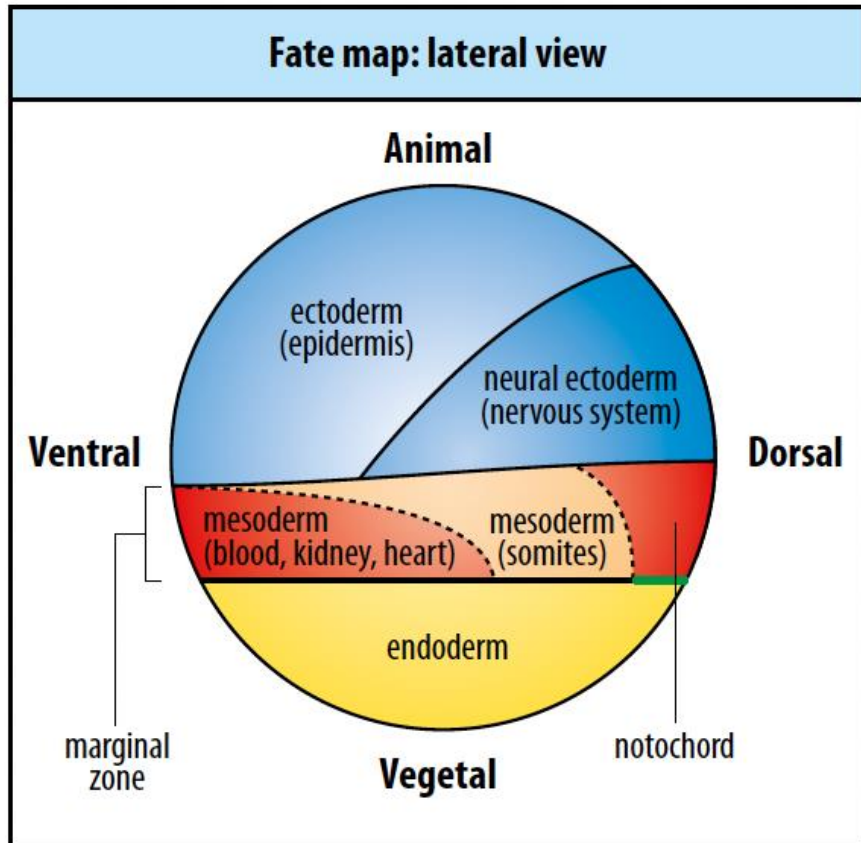
Stage 10.75

chordin - Sasai et al. (1994)





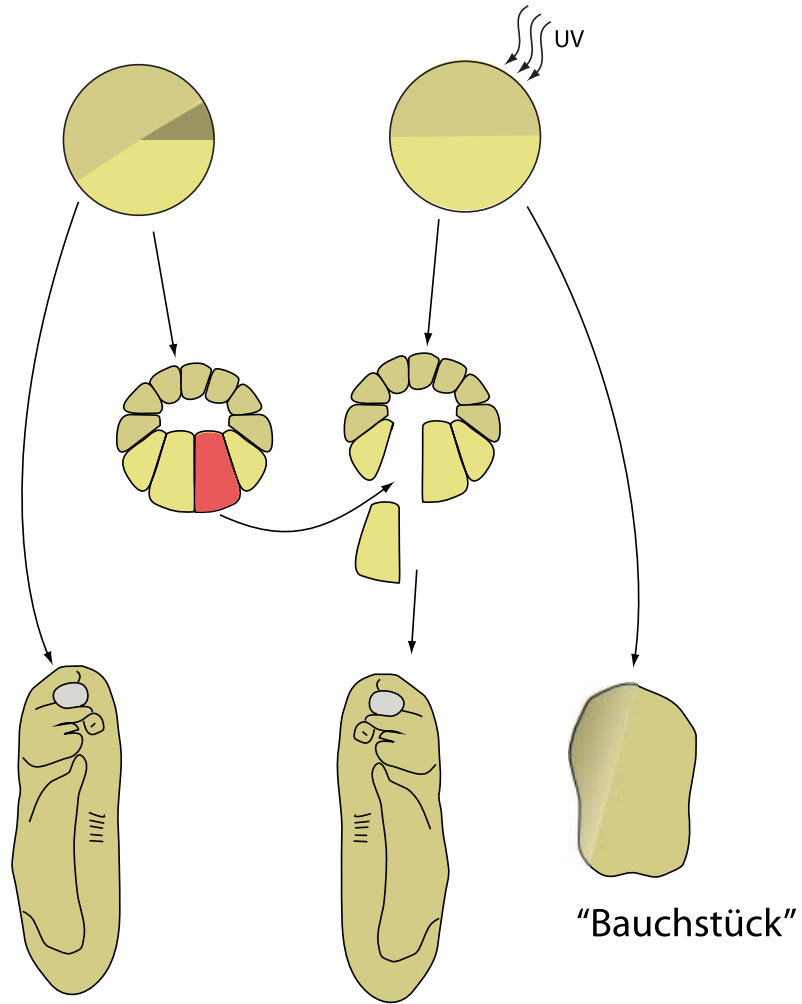
The role of BMPs in the specification of the future nervous system



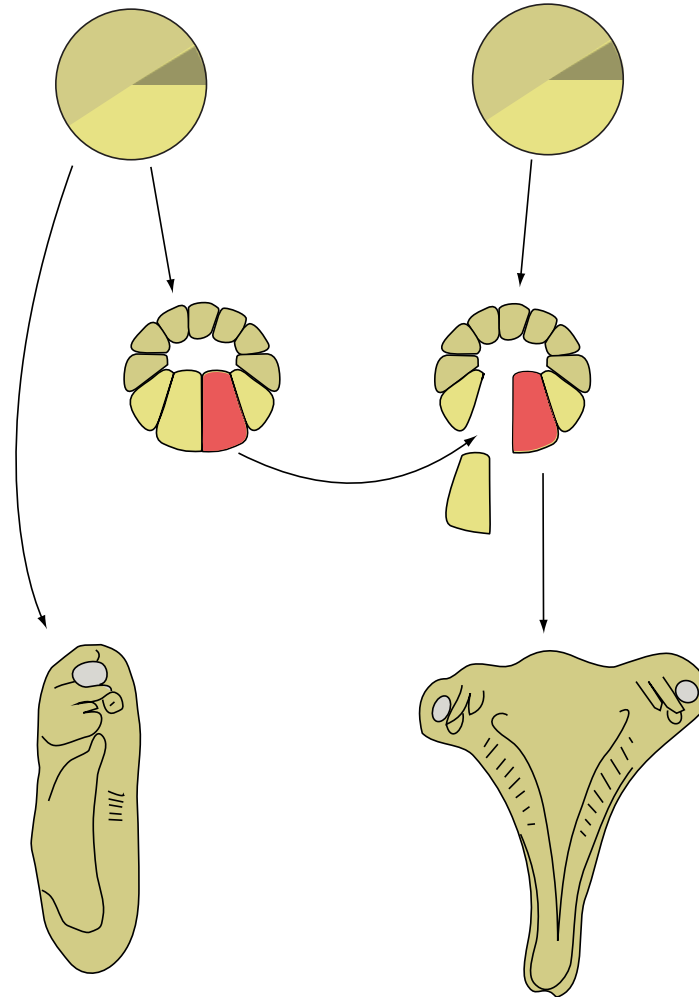


The Nieuwkoop centre and the origins of dorso-ventral (DV) polarity

A

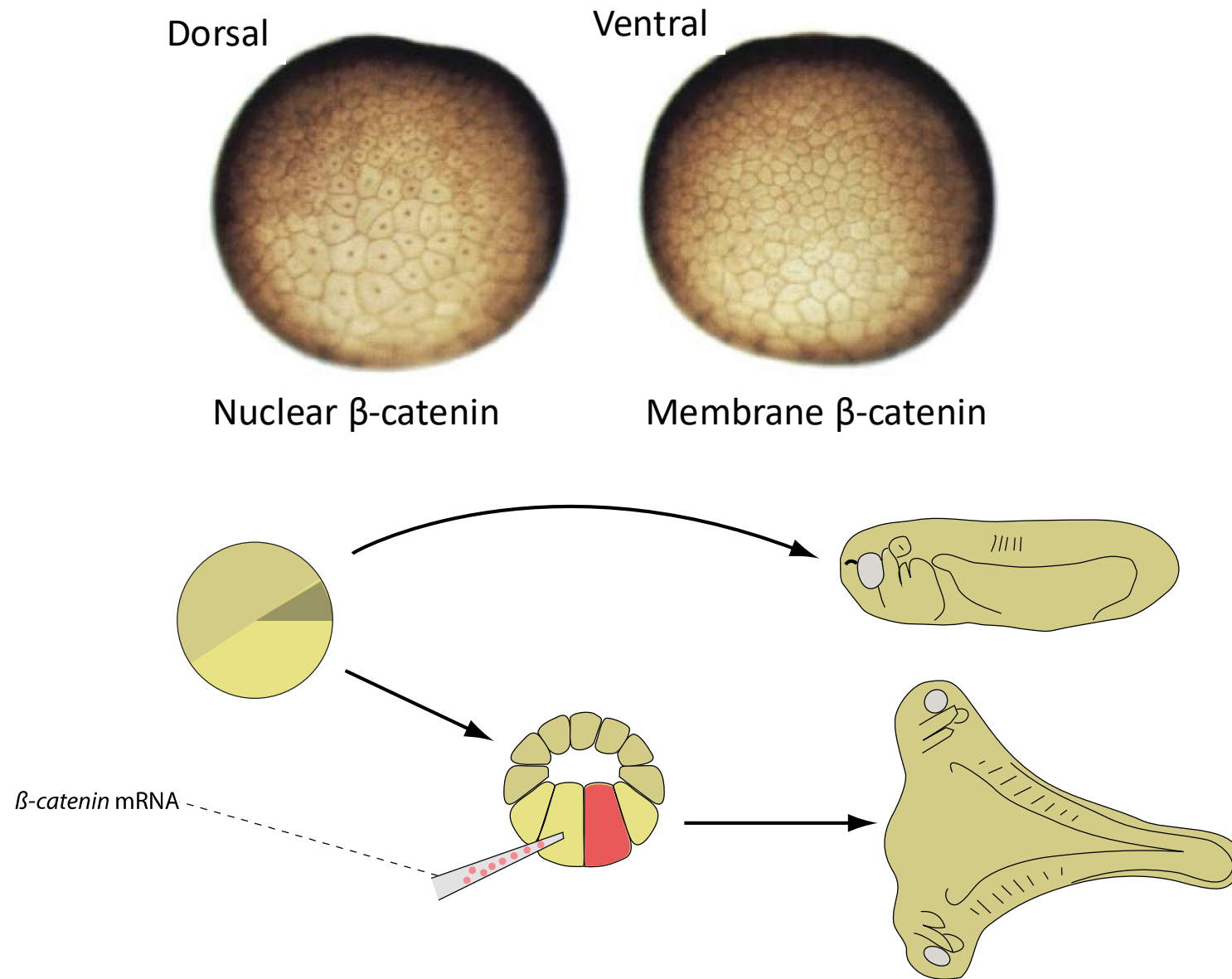


B





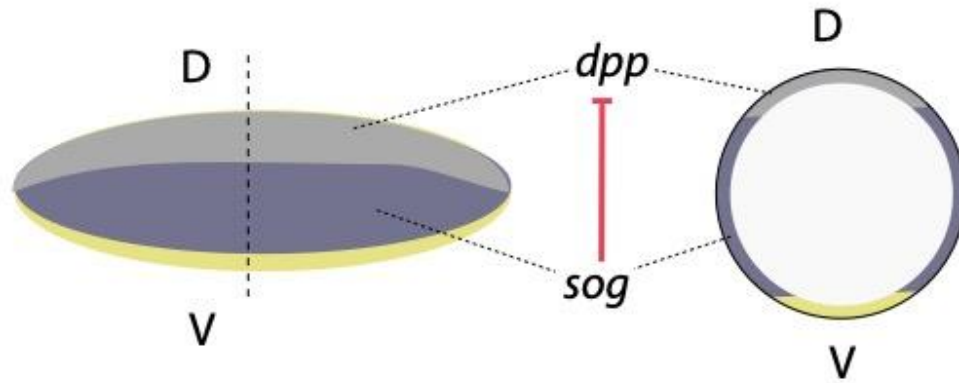
Ectopic induction of canonical Wnt-pathway mimics the organizer



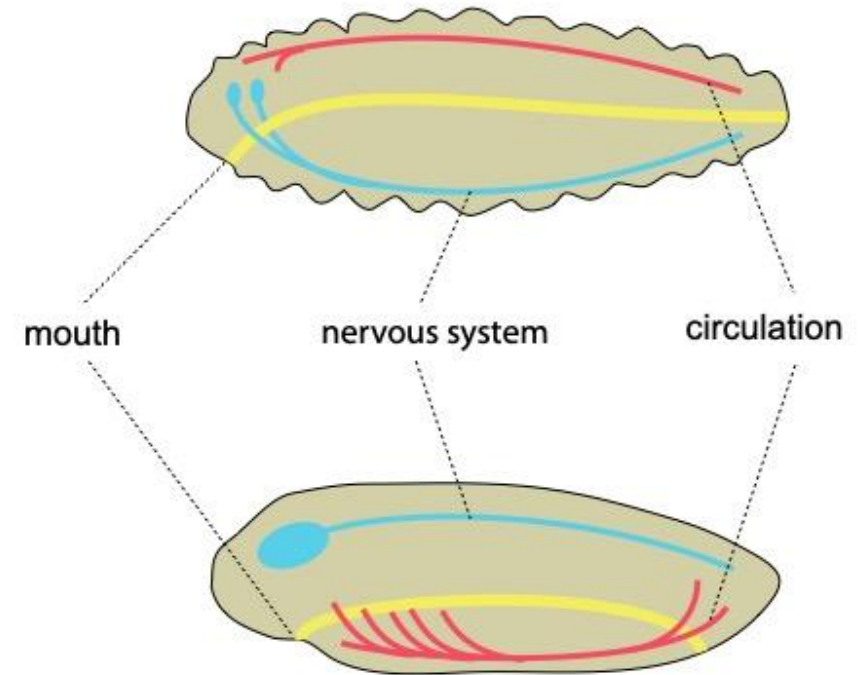
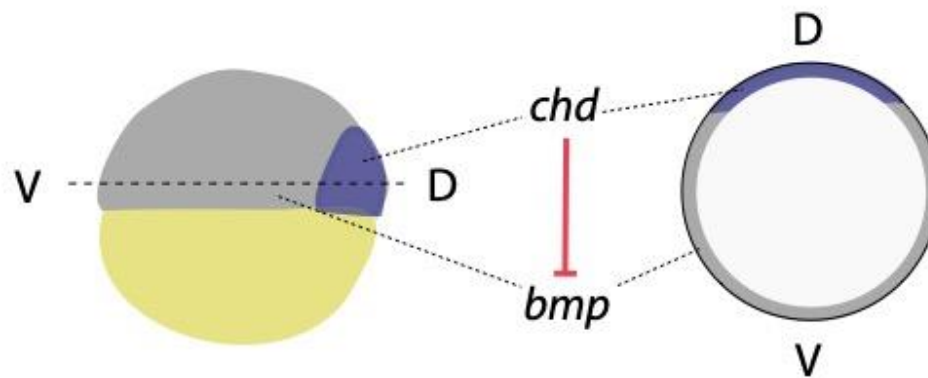


The urbilaterian origin of DV patterning mechanisms

A

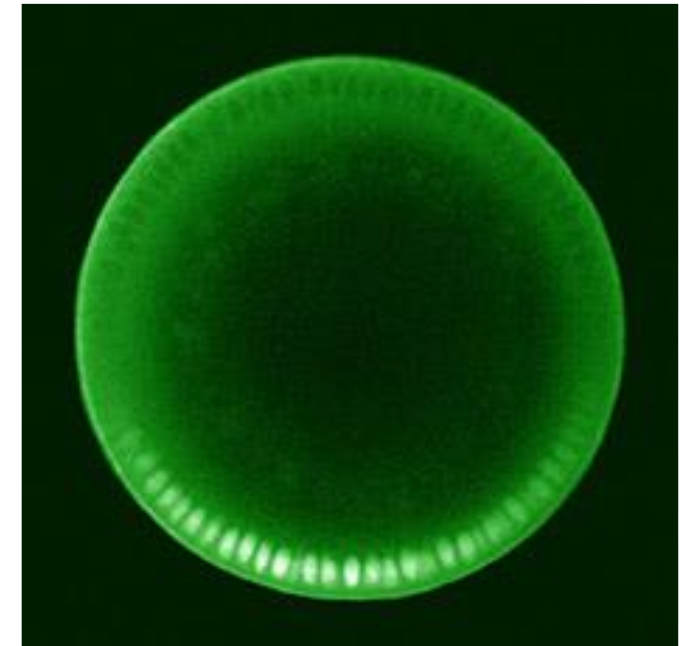
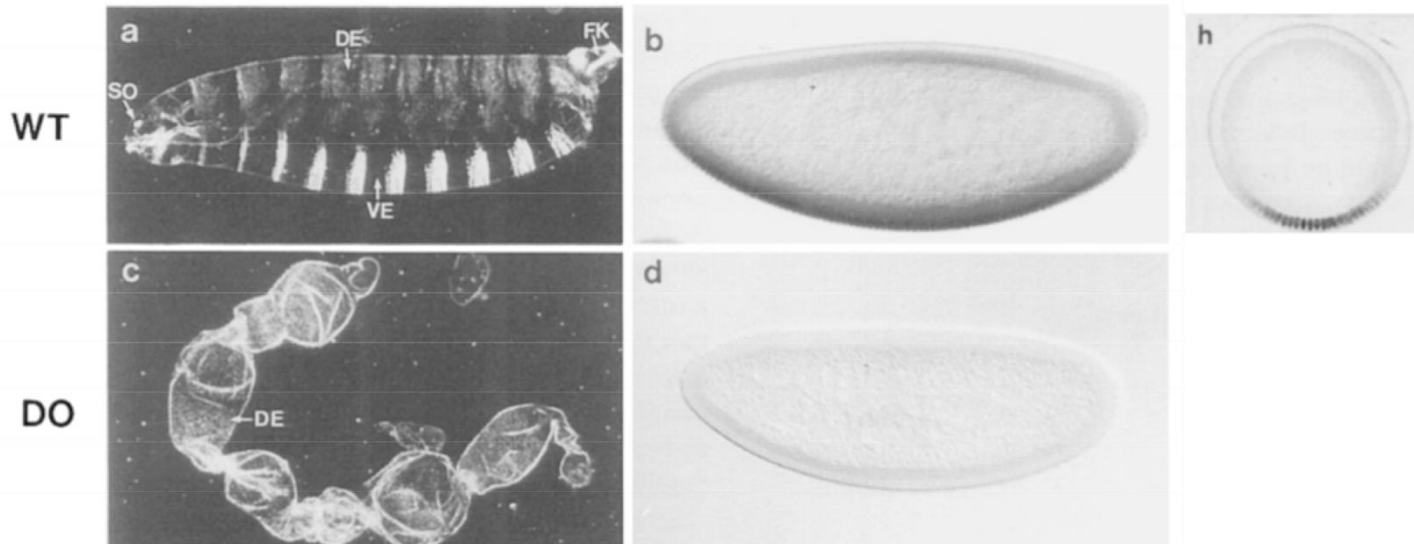
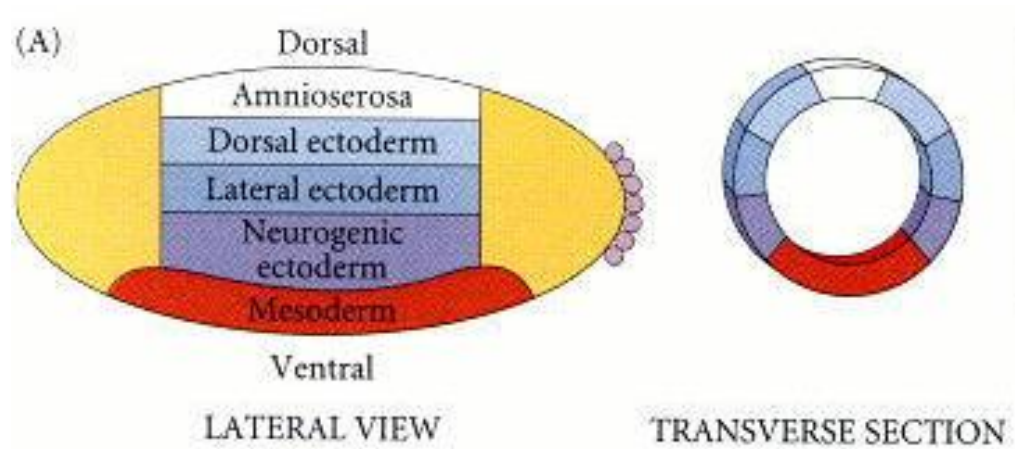


B





The urbilaterian origin of DV patterning mechanisms

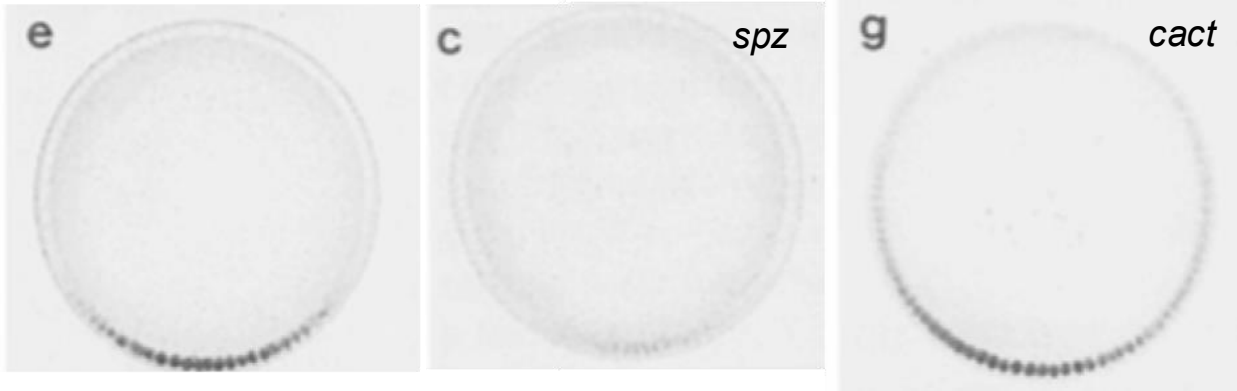


Dorsal is present in all cells, but it is nuclear only in the cells of the ventral side

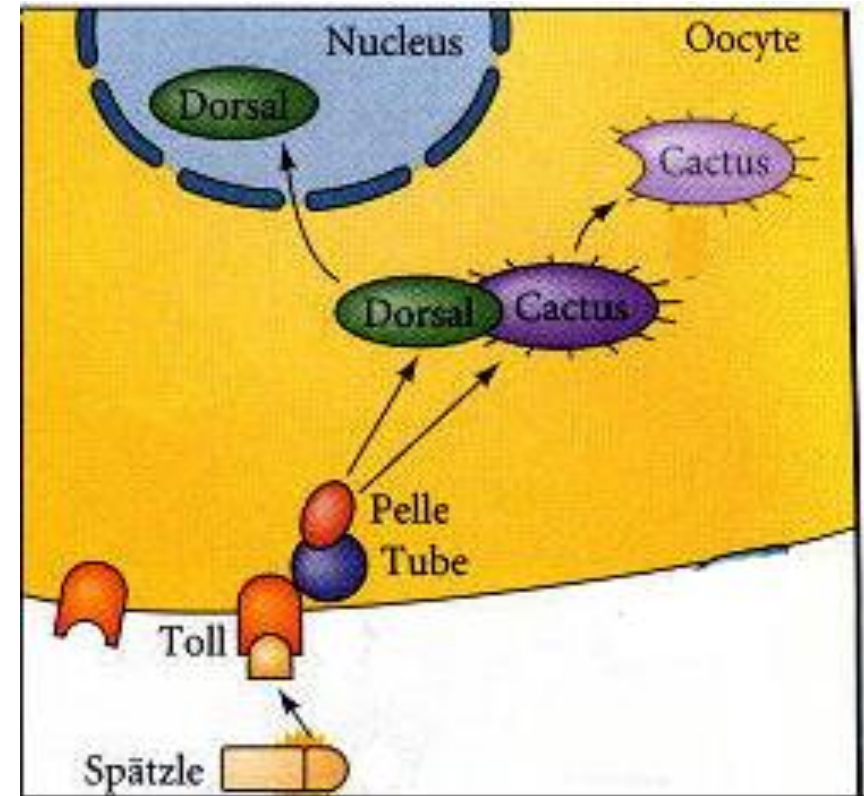


spätzle (spz) and *cactus (cact)* – regulators of *dorsal*

Localisation of Dorsal in DV mutants



(Roth et al., 1989 *Cell*)



- Dorsal and Cactus are the *Drosophila* orthologs of NF- κ B and IF- κ B
- Extracellular cleavage of Spätzle is necessary for its function
- => The follicular cells surrounding the oocytes also have an important role in DV axis formation!

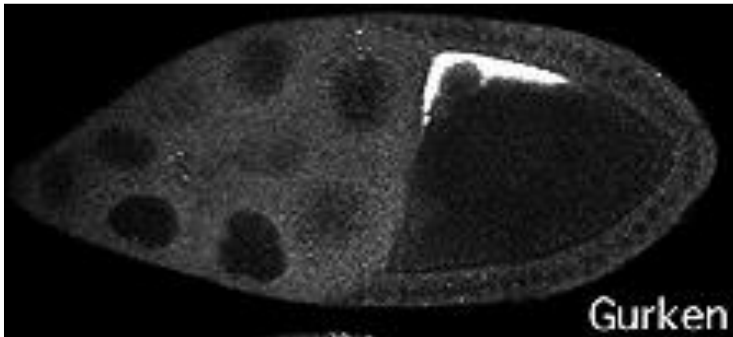


Maternal determination of the future dorsal side by *gurken*

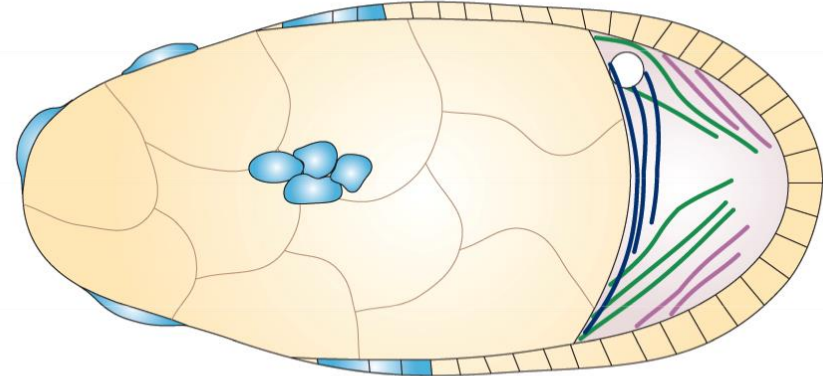
gurken mRNA



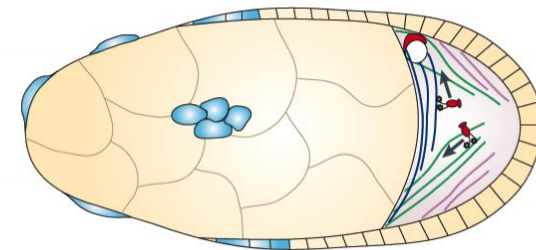
Gurken protein



a Microtubule populations in the *Drosophila melanogaster* oocyte



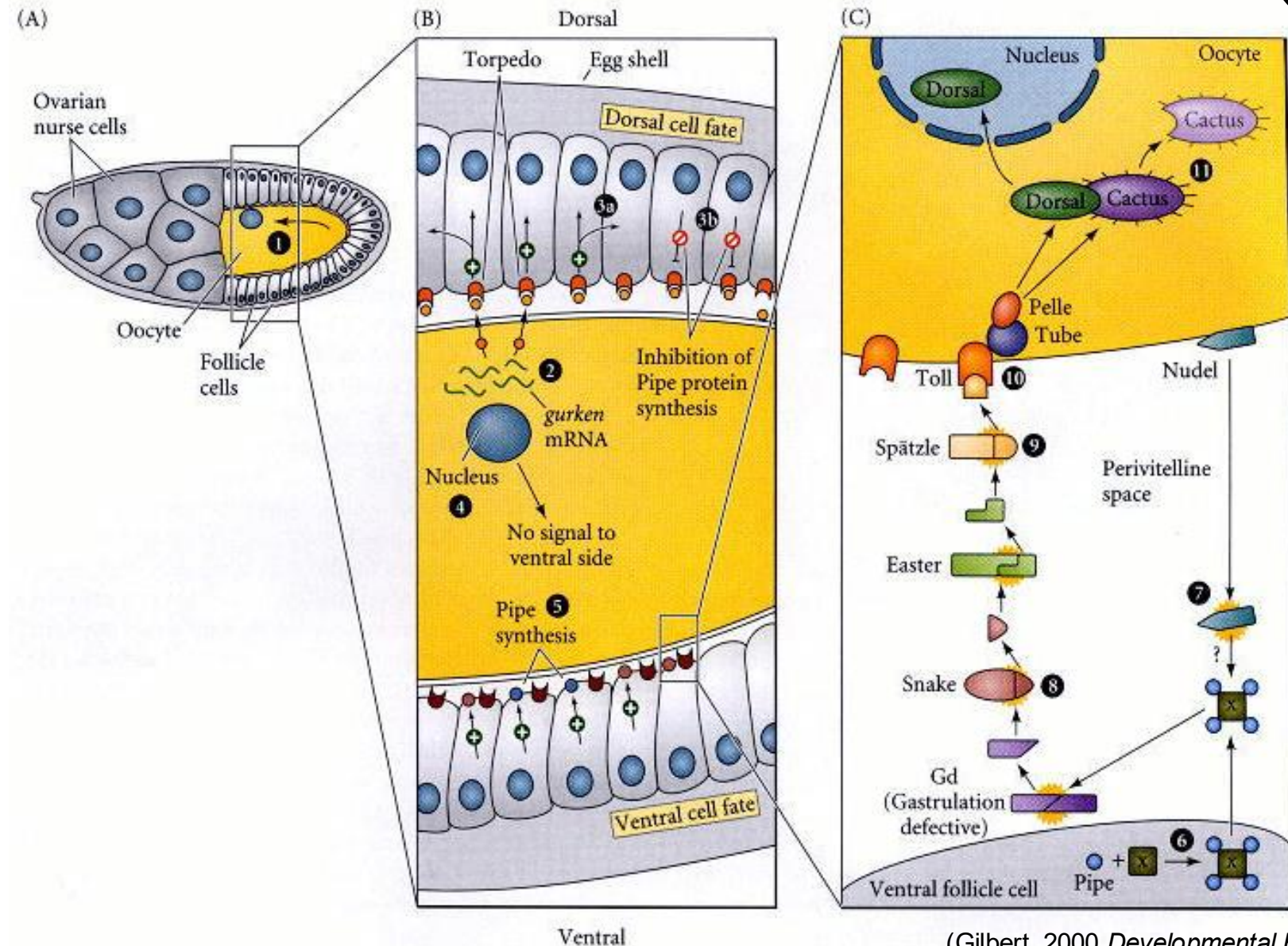
b *gurken* mRNA





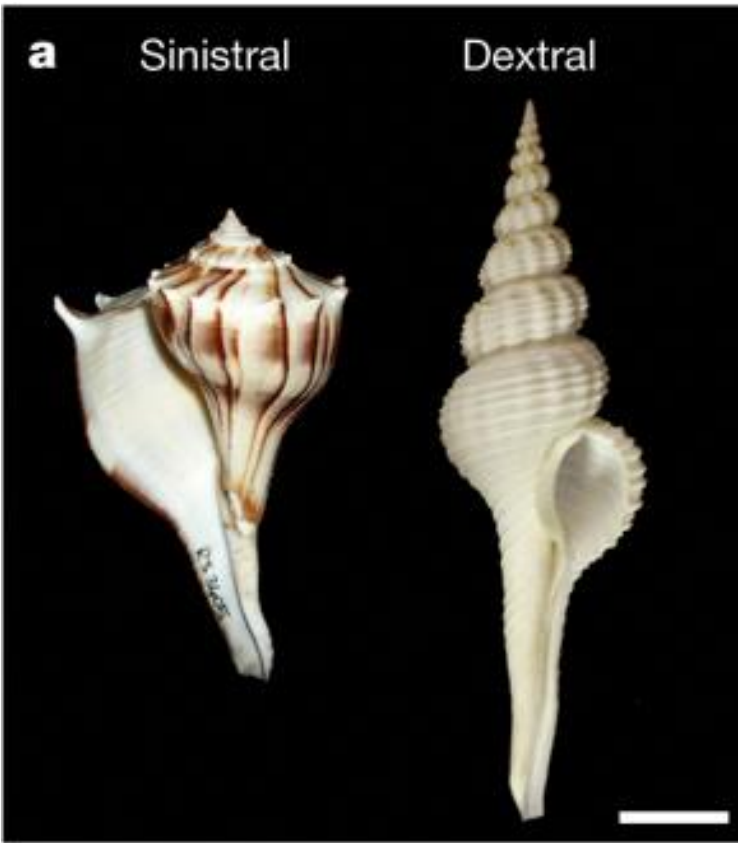
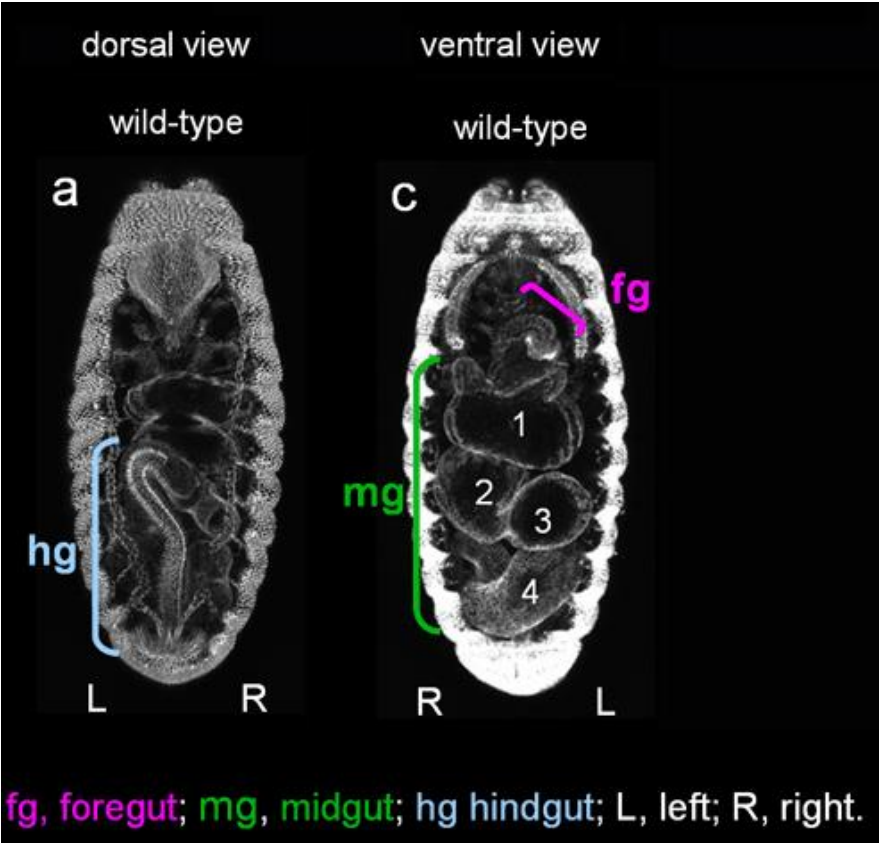
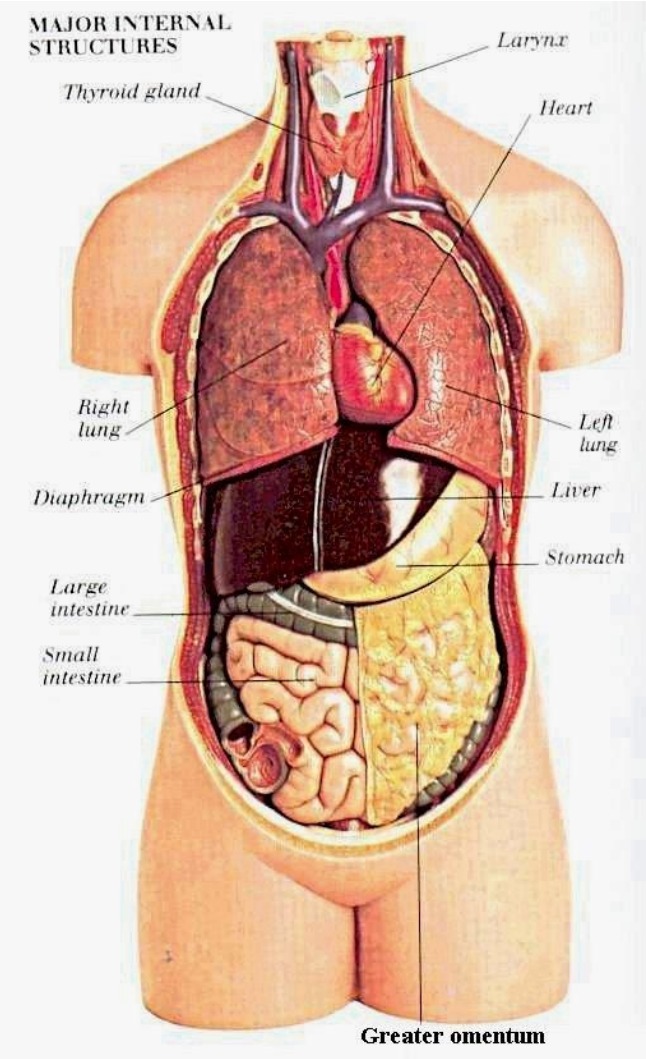
The genetics of *Drosophila* DV polarity

- 1 Oocyte nucleus travels to anterior dorsal side of oocyte. It synthesizes *gurken* mRNA which remains between the nucleus and the follicle cells.
- 2 *gurken* messages are translated. The Gurken protein is received by Torpedo proteins during mid-oogenesis.
- 3a Torpedo signal causes follicle cells to differentiate to a dorsal morphology.
- 3b Synthesis of Pipe protein is inhibited in dorsal follicle cells.
- 4 Gurken protein does not diffuse to ventral side.
- 5 Ventral follicle cells synthesize Pipe proteins.
- 6 In ventral follicle cells, Pipe completes the modification of unknown factor (x).
- 7 Nudel and factor (x) interact to split the Gastrulation-deficient (Gd) protein.
- 8 The activated Gd protein splits the Snake protein, and the activated Snake protein cleaves the Easter protein.
- 9 The activated Easter protein splits Spätzle; activated Spätzle binds to Toll receptor protein.
- 10 Toll activation activates Tube and Pelle, which phosphorylate the Cactus protein. Cactus is degraded, releasing it from Dorsal.
- 11 Dorsal protein enters the nucleus and ventralizes the cell.

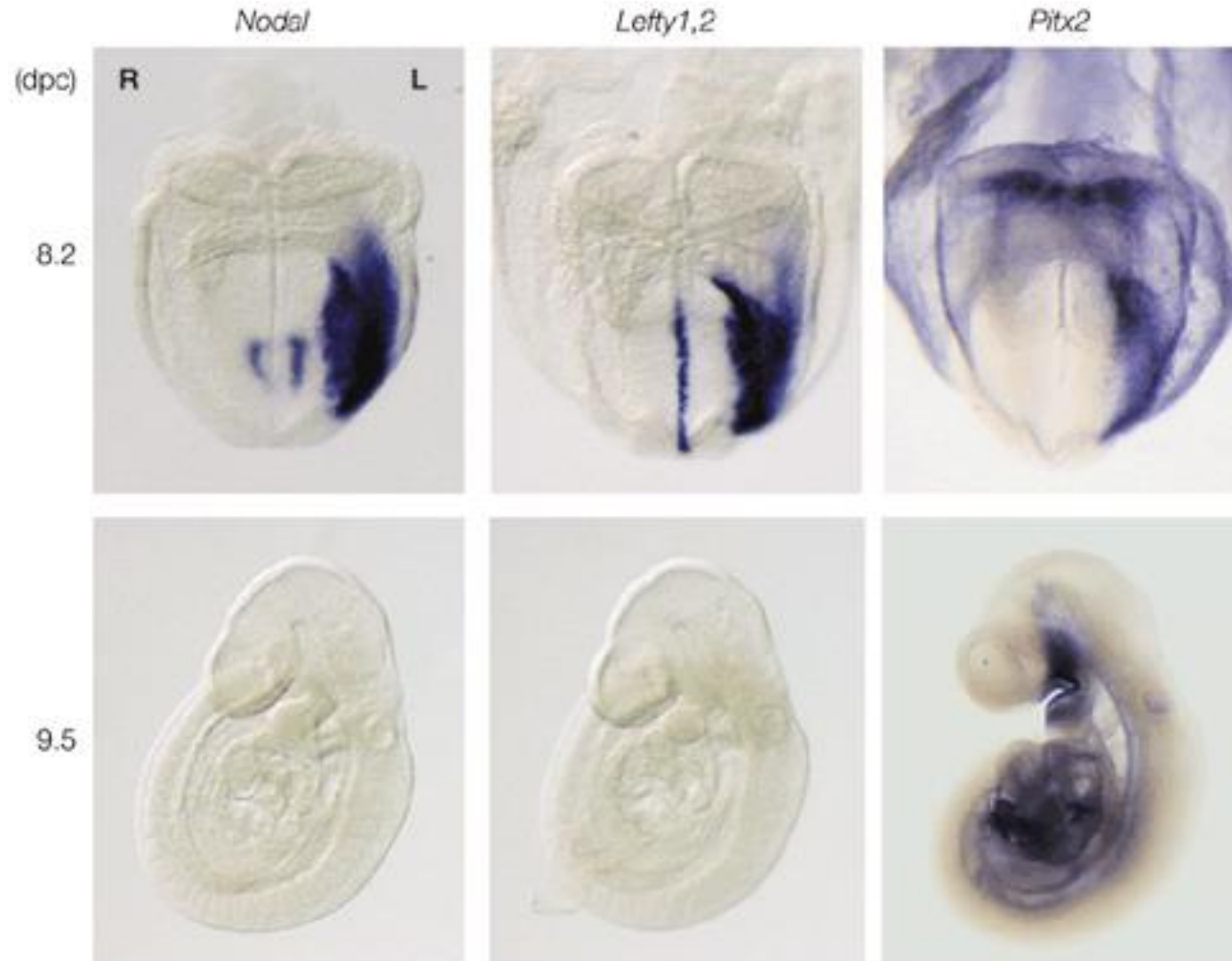




Laterality within animals

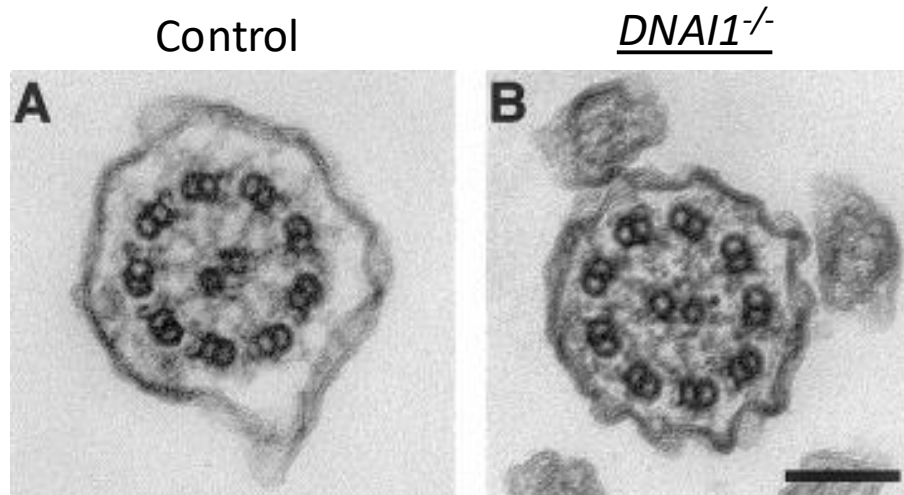


Left-right asymmetry in vertebrates correlates with transient asymmetric upregulation of Nodal signaling

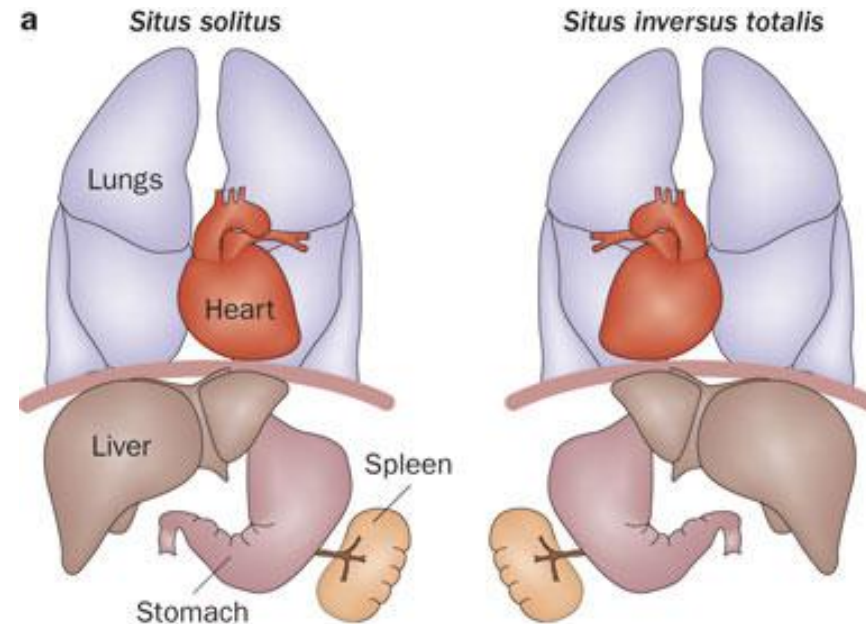




In mammals, cilia defects are associated with defects in laterality



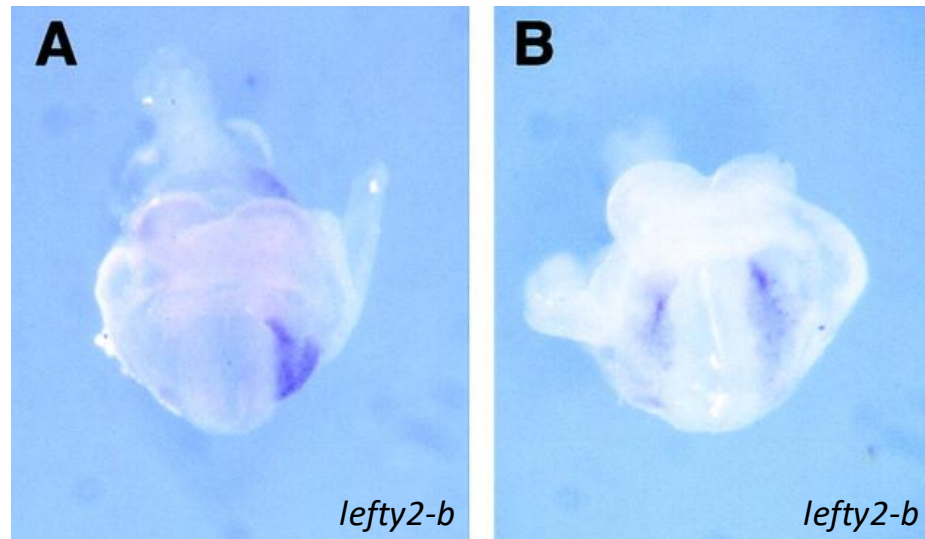
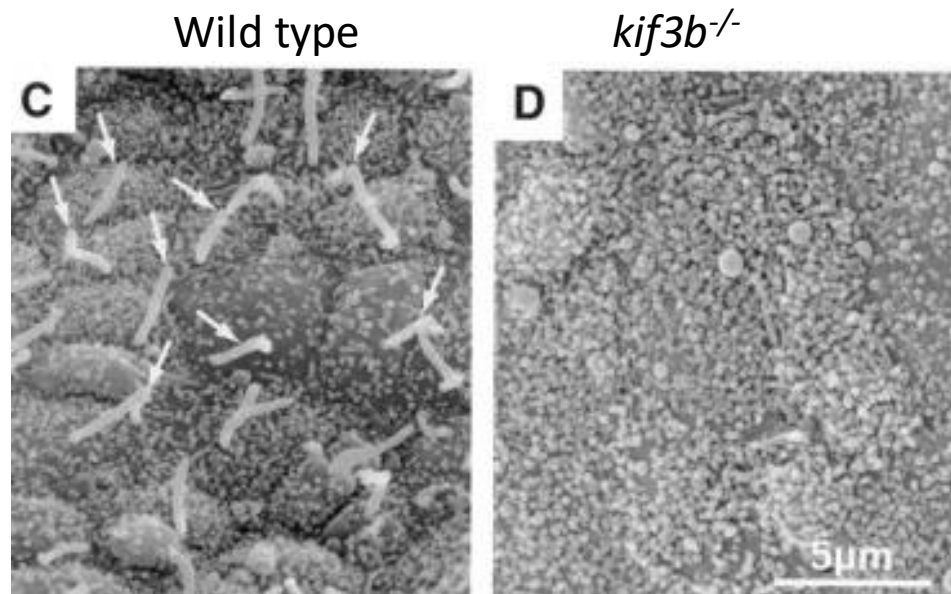
(outer dynein arms are shorter or missing)



(Guichard et al., 2001 *Am J Hum Gen*)



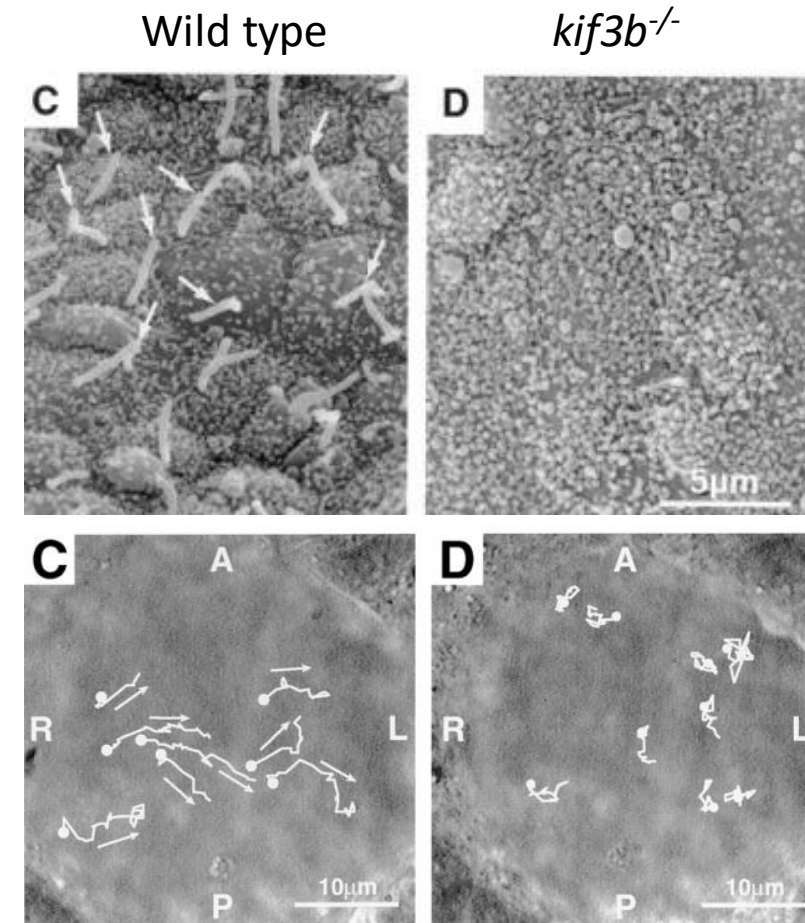
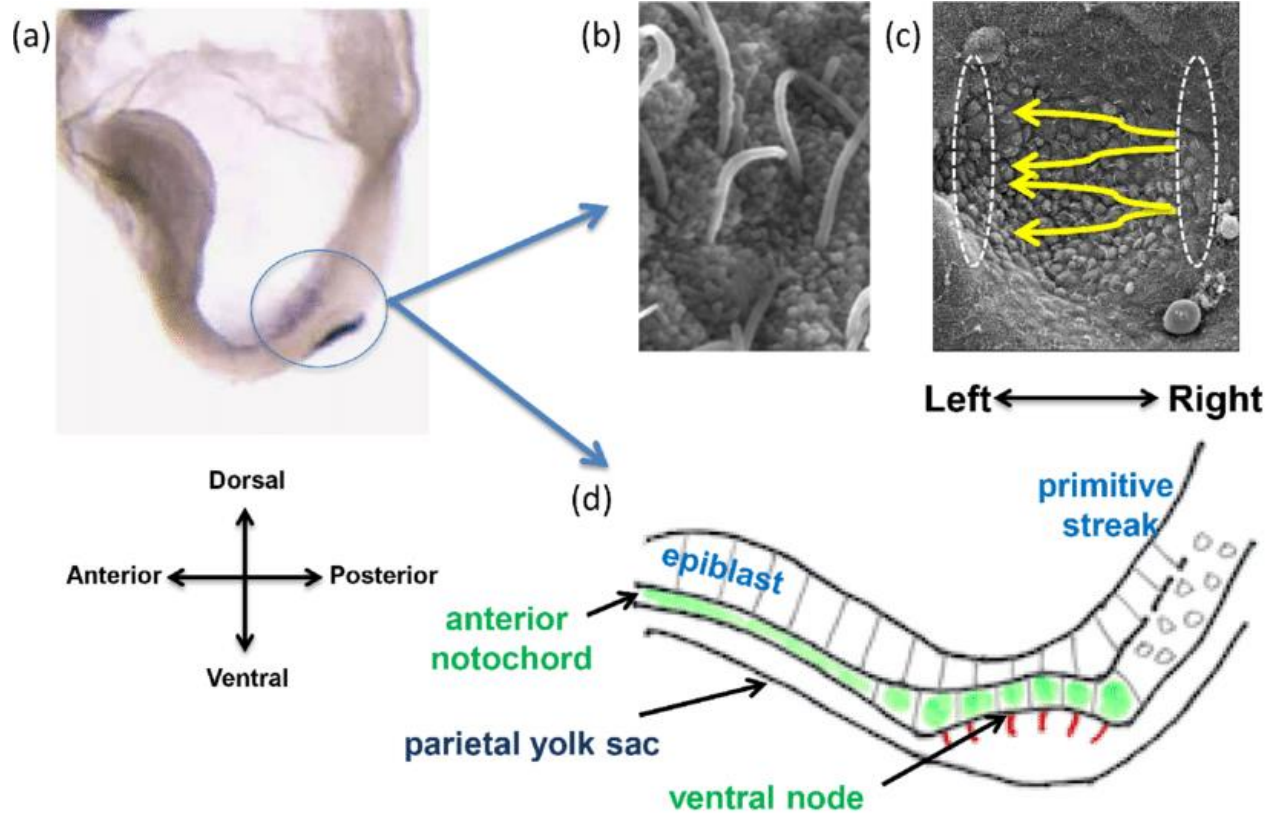
In mammals, cilia defects are associated with defects in laterality



(Nonaka et al., 1998 *Cell*)

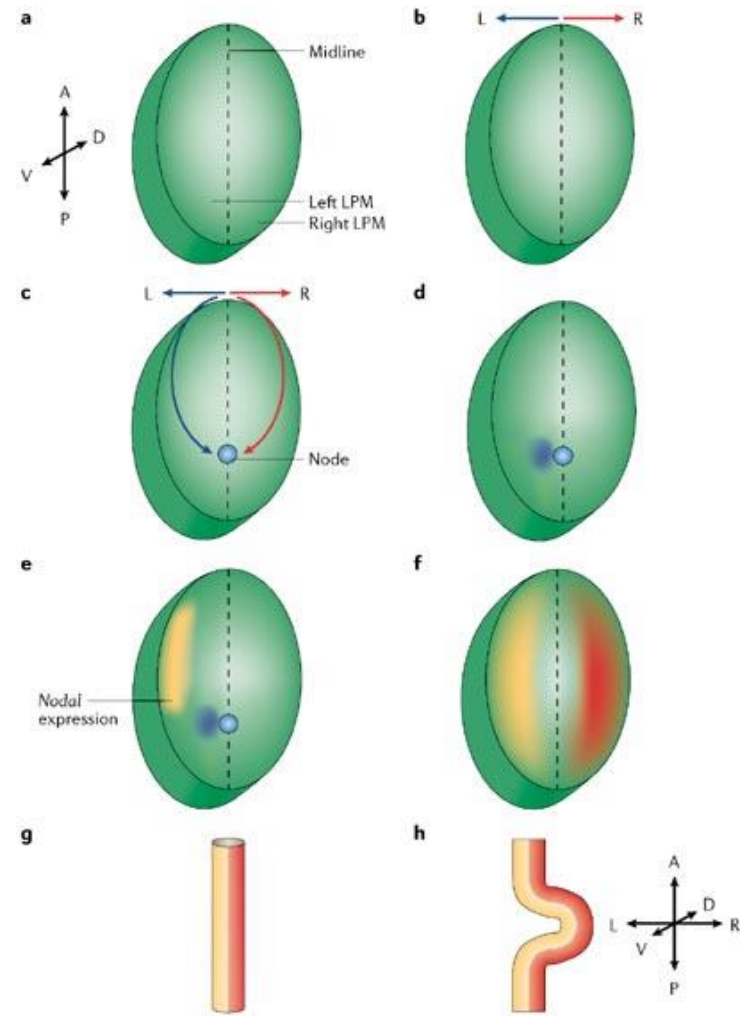
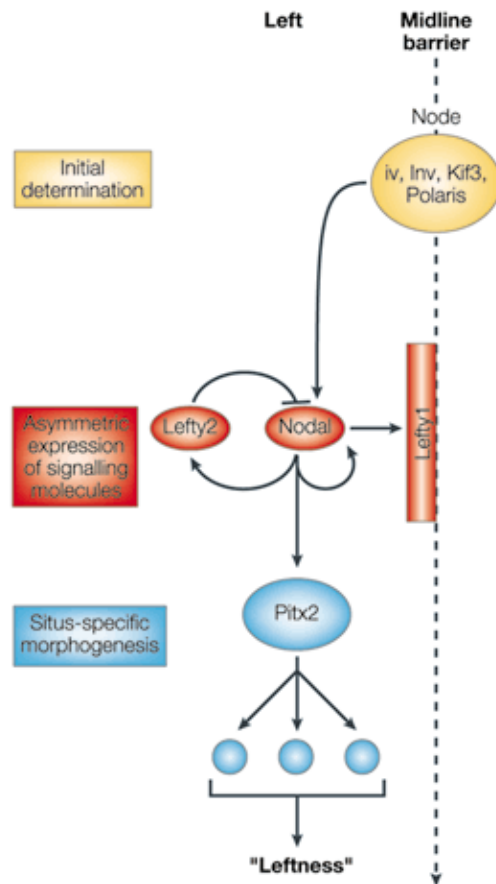


Cilia-driven fluid flow in the node has an important role in establishing LR asymmetry



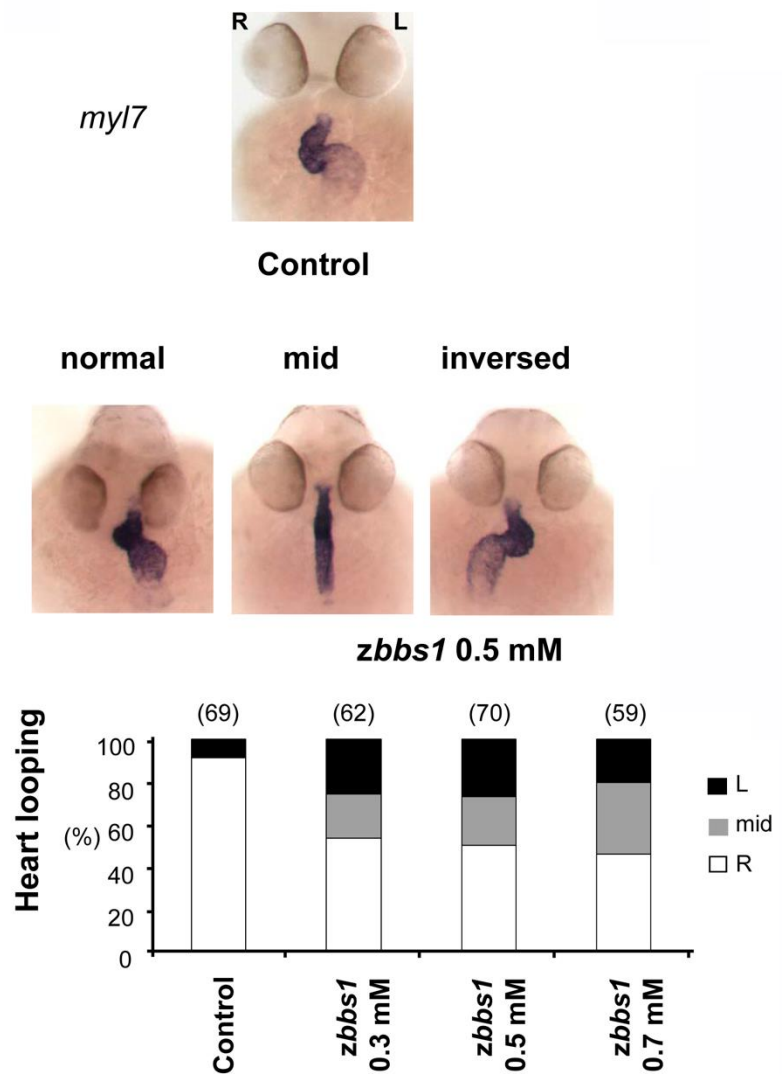


Generalized view of LR asymmetry establishment in vertebrates

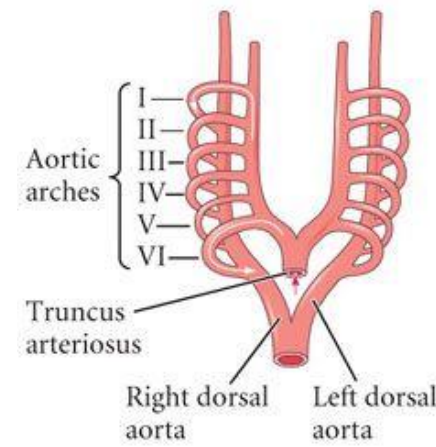




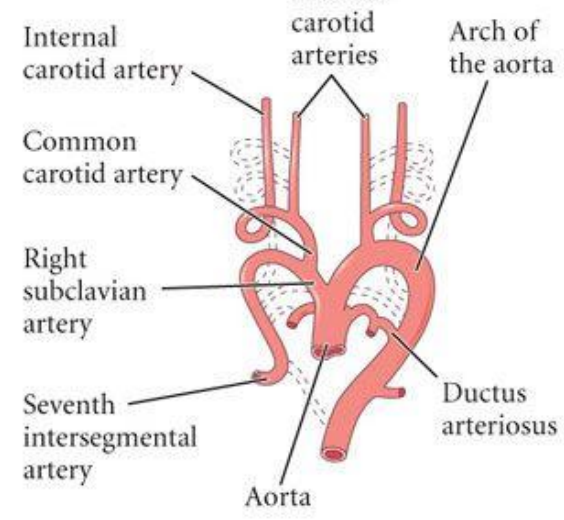
Laterality induces cardiac looping and asymmetric vessel regression



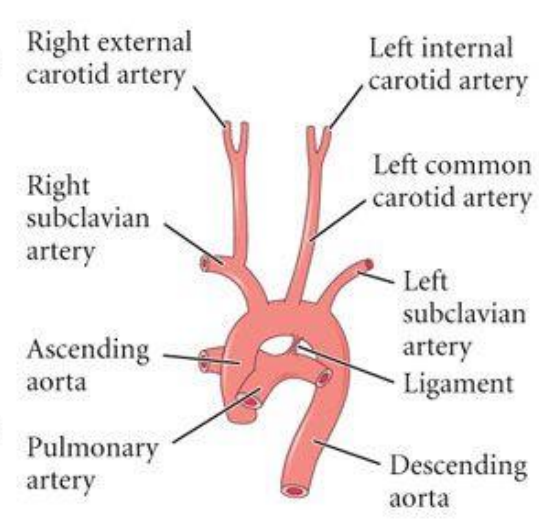
(A) Day 29



(B) Day 49



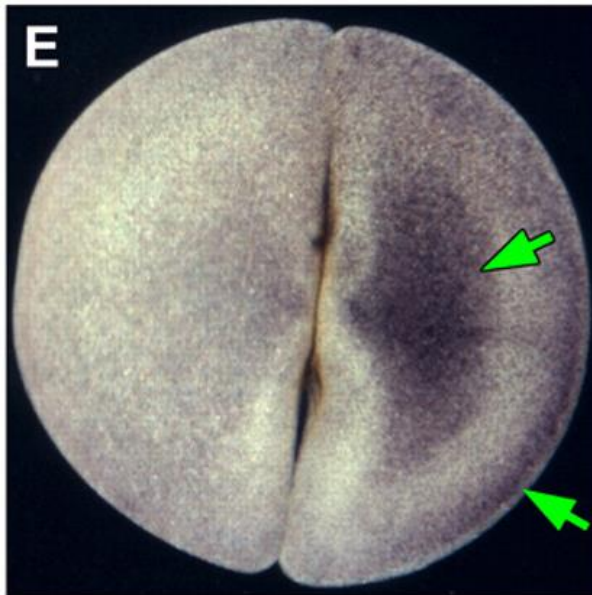
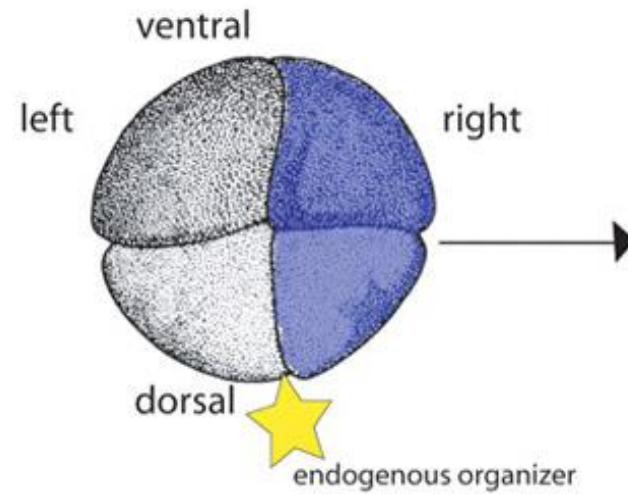
(C) Day 56



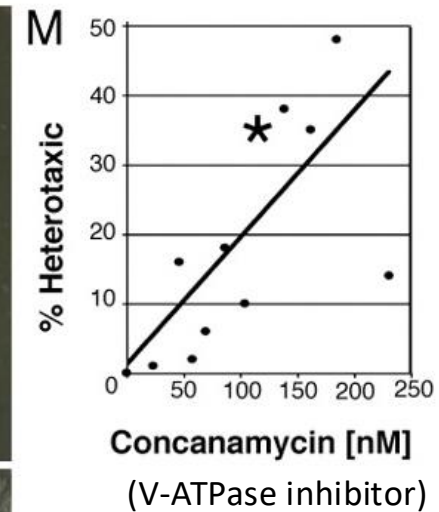
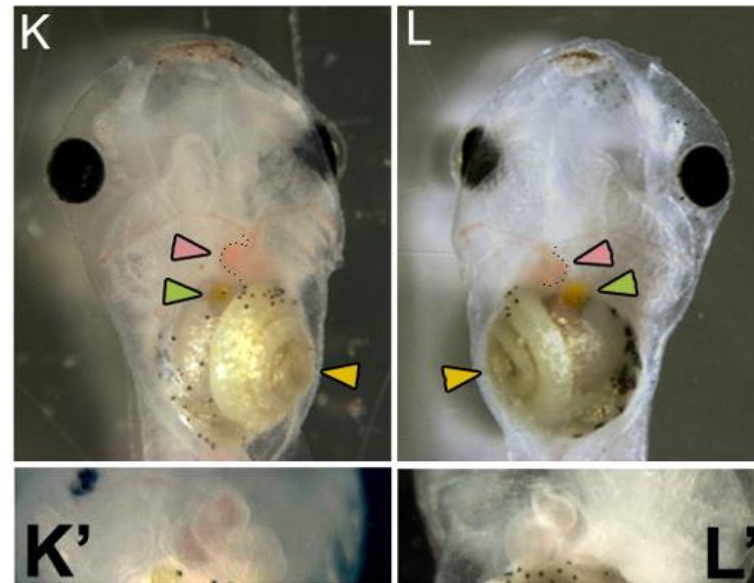
(*zbb1* – zebrafish Bardet-Biedl syndrome (BBS) gene)



Some inconvenient truths: in some animals, laterality is induced much earlier, though



H+V-ATPase subunit A



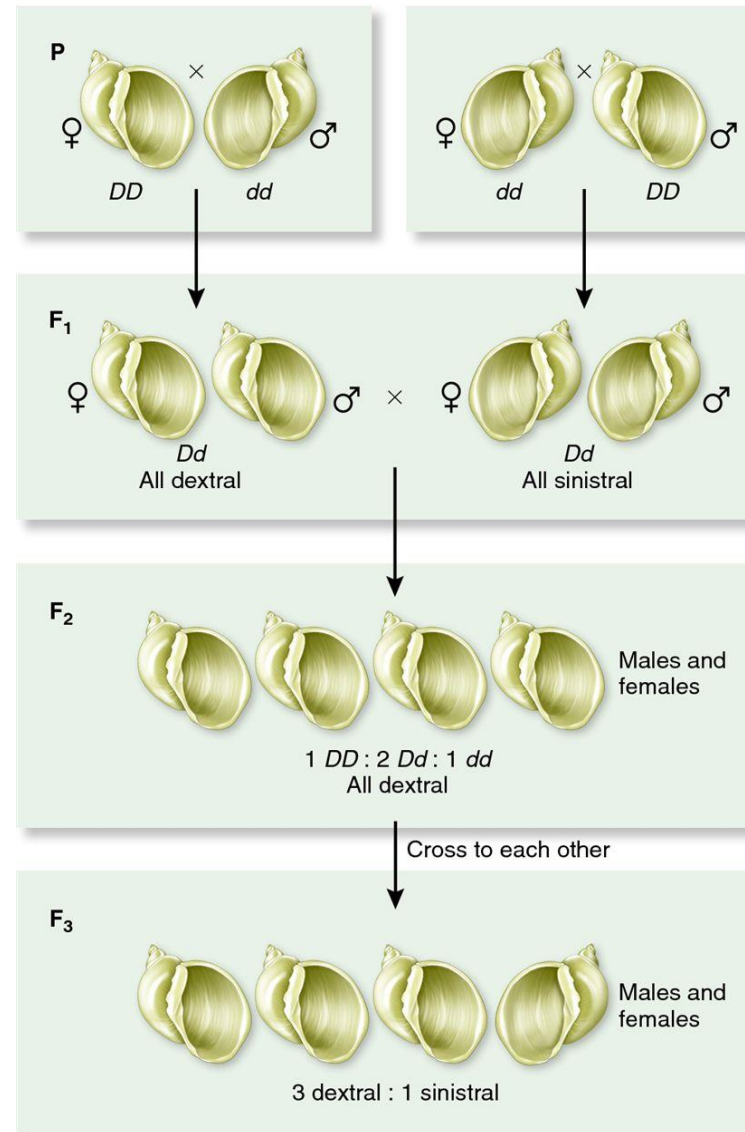


Vertebrate strategies to establish LR asymmetry during development

		EARLY DEVELOPMENT	GASTRULATION	NEURULA	Morphological markers
DEUTEROSTOMES	Vertebrates				
	Mouse		Nodal cilia	Nodal St. E7-8	
	Chicken	Ion transporters H^+/K^+ H^+/V depolarisation	Hensen's node	Nodal St. 3-4	
	Xenopus	Actin H^+/K^+ H^+/V H^+ efflux	Gastrocoel roof plate	Xnr-1 Late neurula	Heart looping
	Zebrafish	H^+/V	Kupffer's vesicle	Ndr-2 St. 12 somites	
	Sea Urchin	H^+/K^+	Cilia?	Nodal 24h embryo	Pluteus larva R L Adult rudiment



Chirality in snails is a genetically encoded (maternal) trait



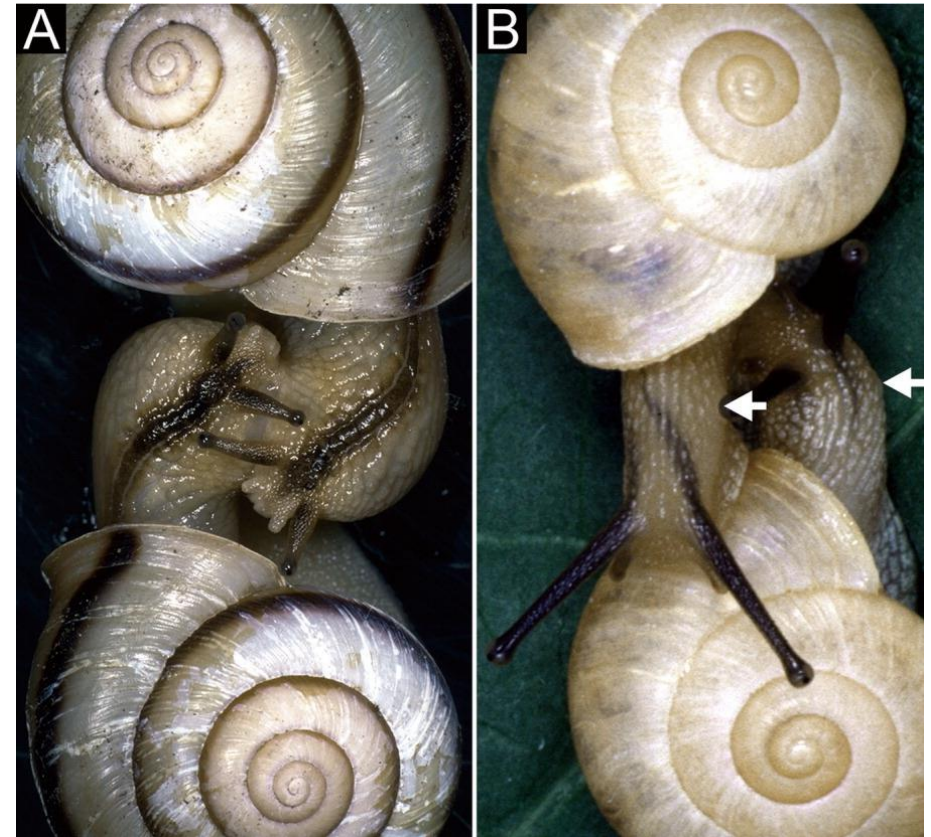


Chirality in snails – a matter of reproductive isolation

New Zealand launches campaign to find love for rare and lonely left-spiralling snail Ned

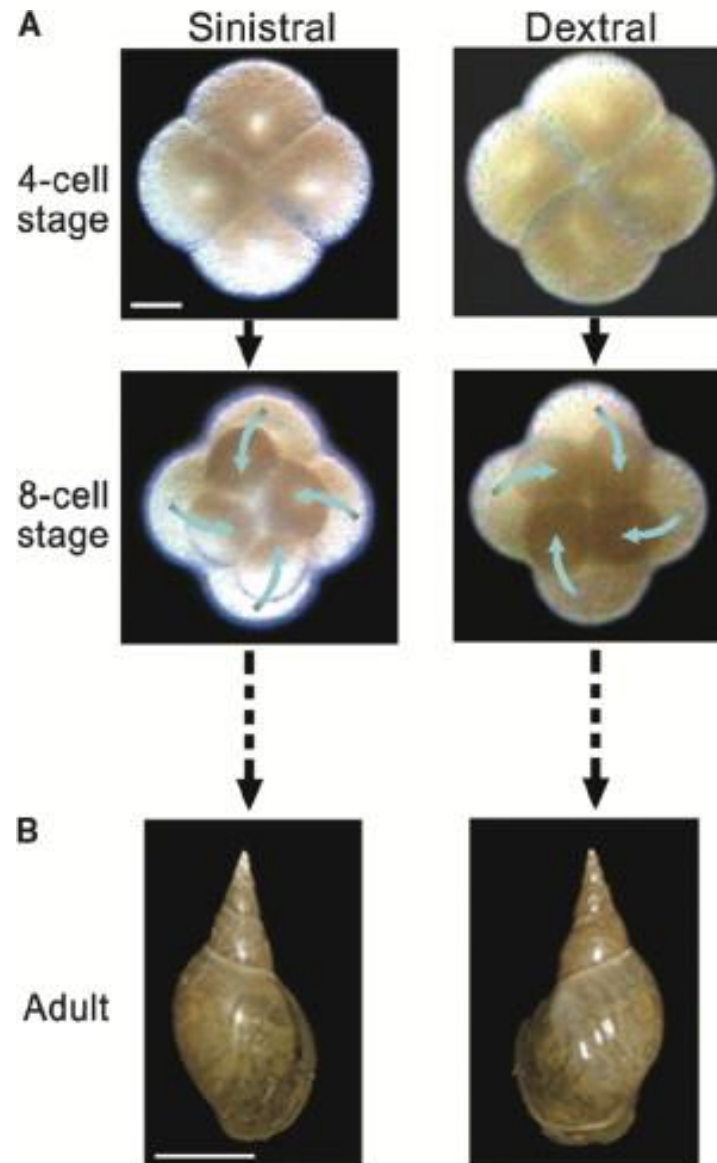


Reproductive mismatch between snails of opposite chirality



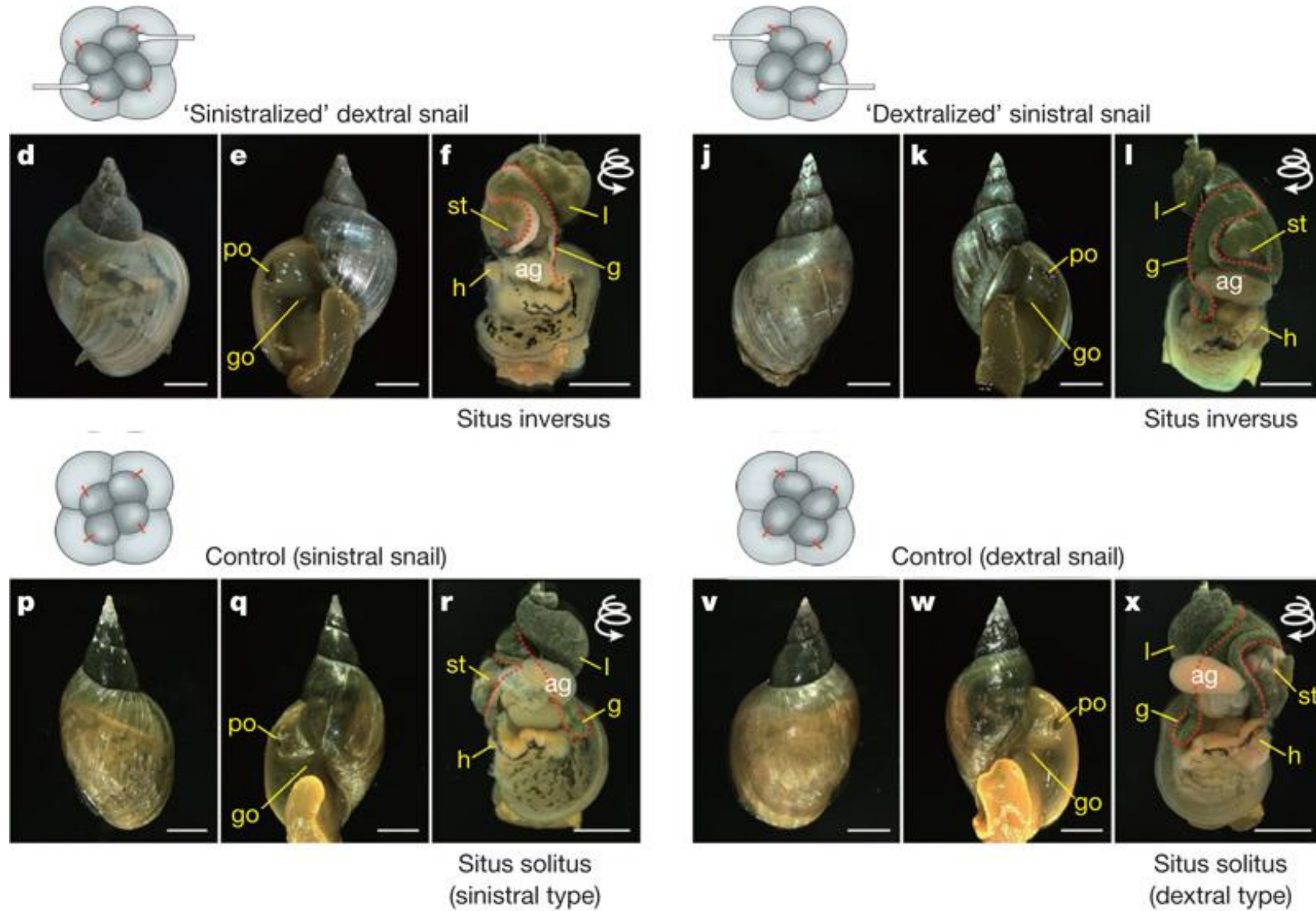


Body handedness in snails is determined by early cleavage planes



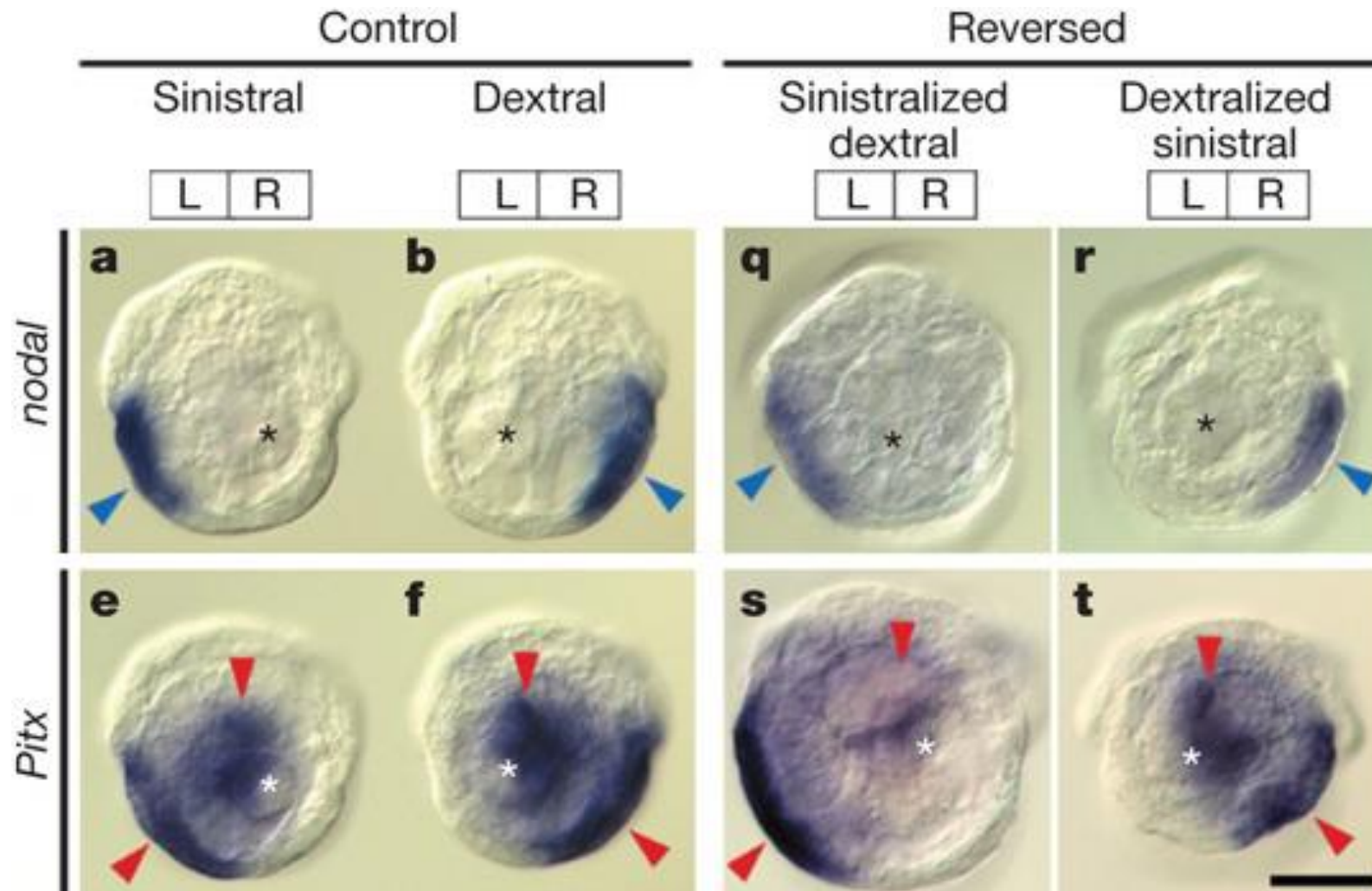


Body handedness in snails is determined by early cleavage planes



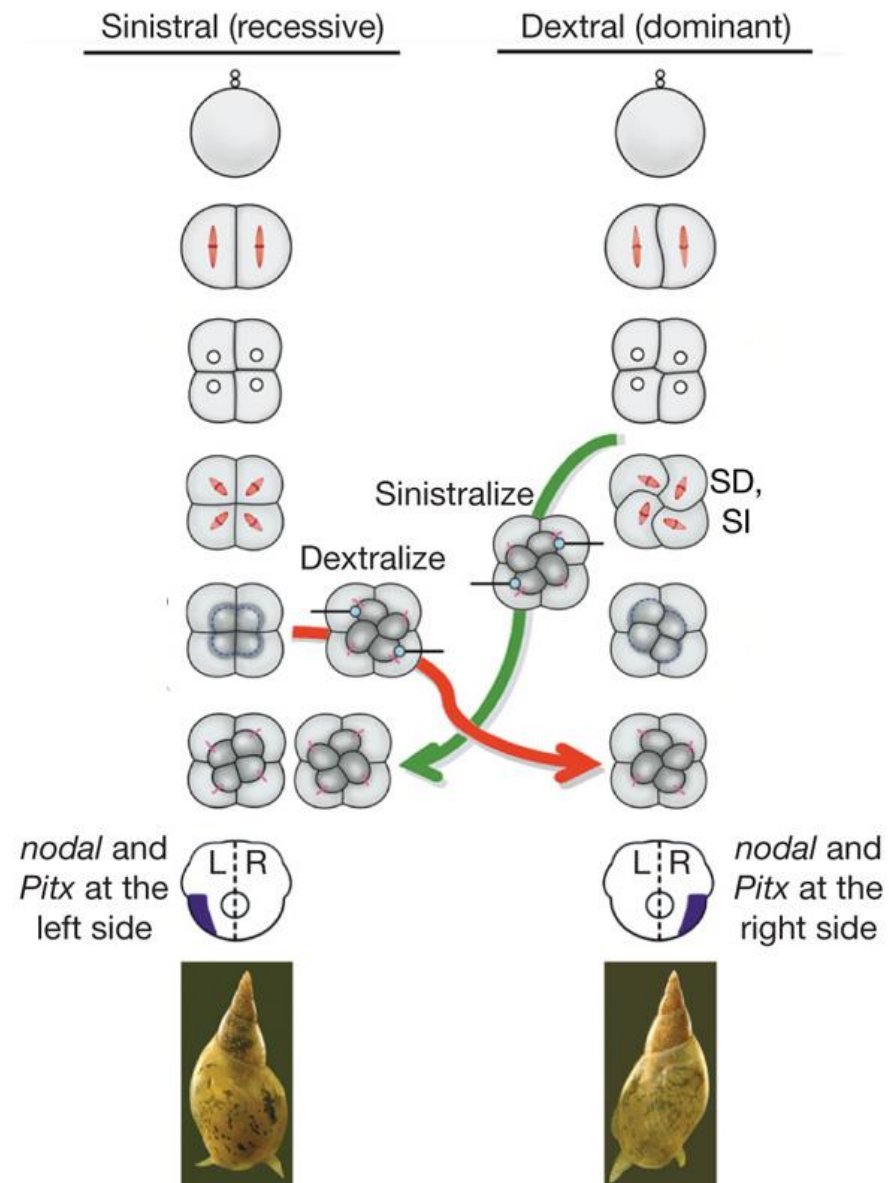


Lateralized expression of *nodal* and *Pitx* can be seen during gastrulation





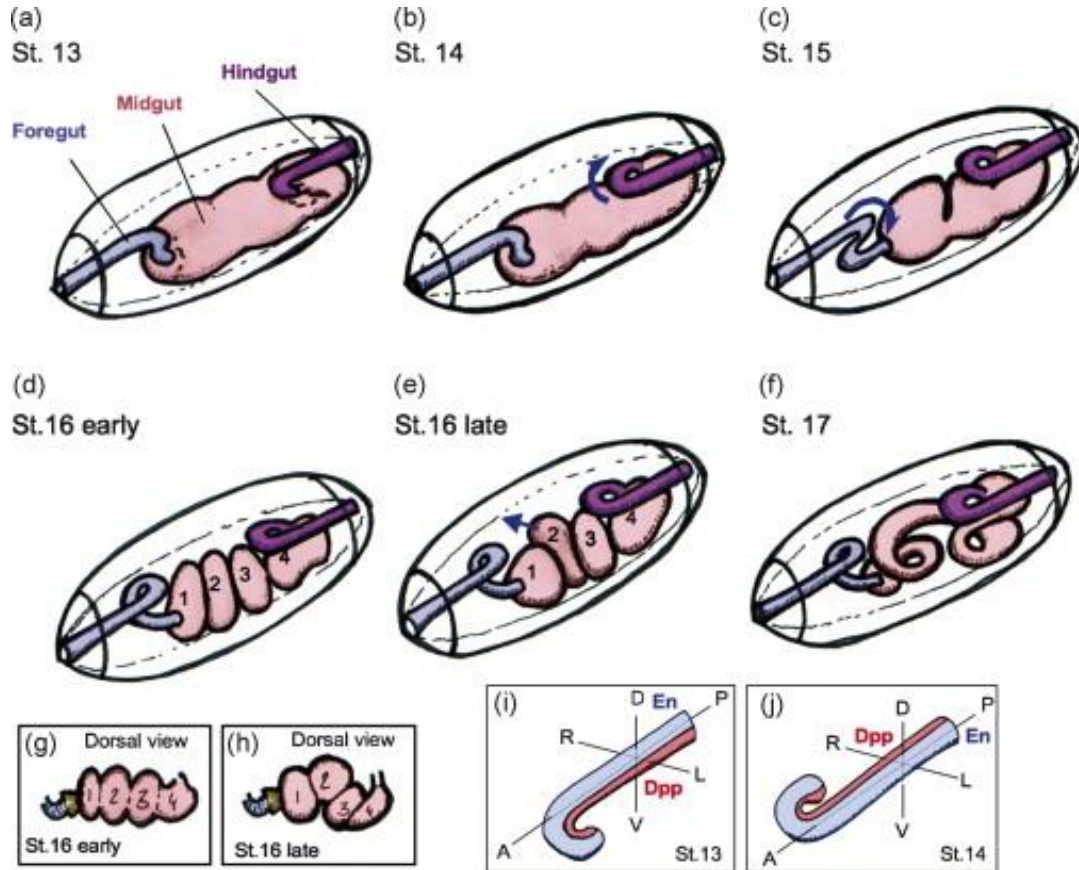
Determinants of chirality in snails



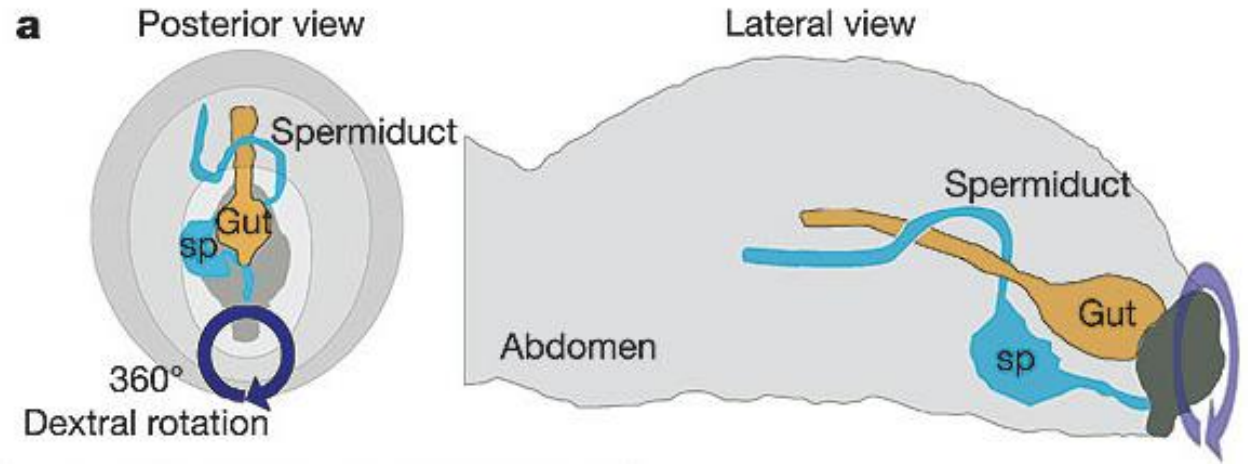


Left-right asymmetries during *Drosophila* development

Asymmetry during gut development

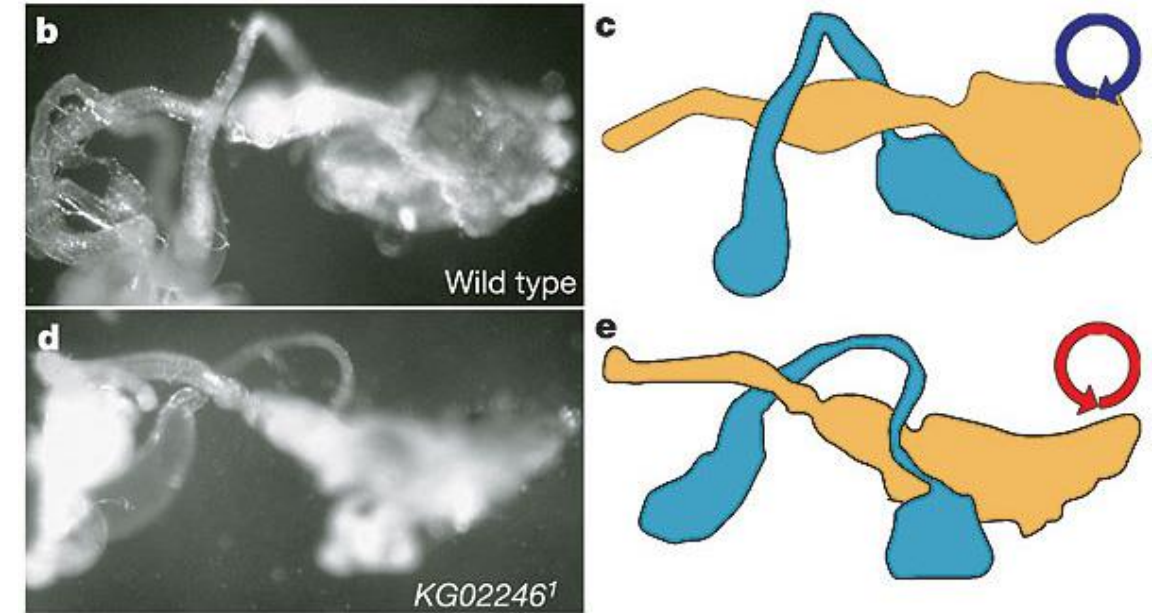
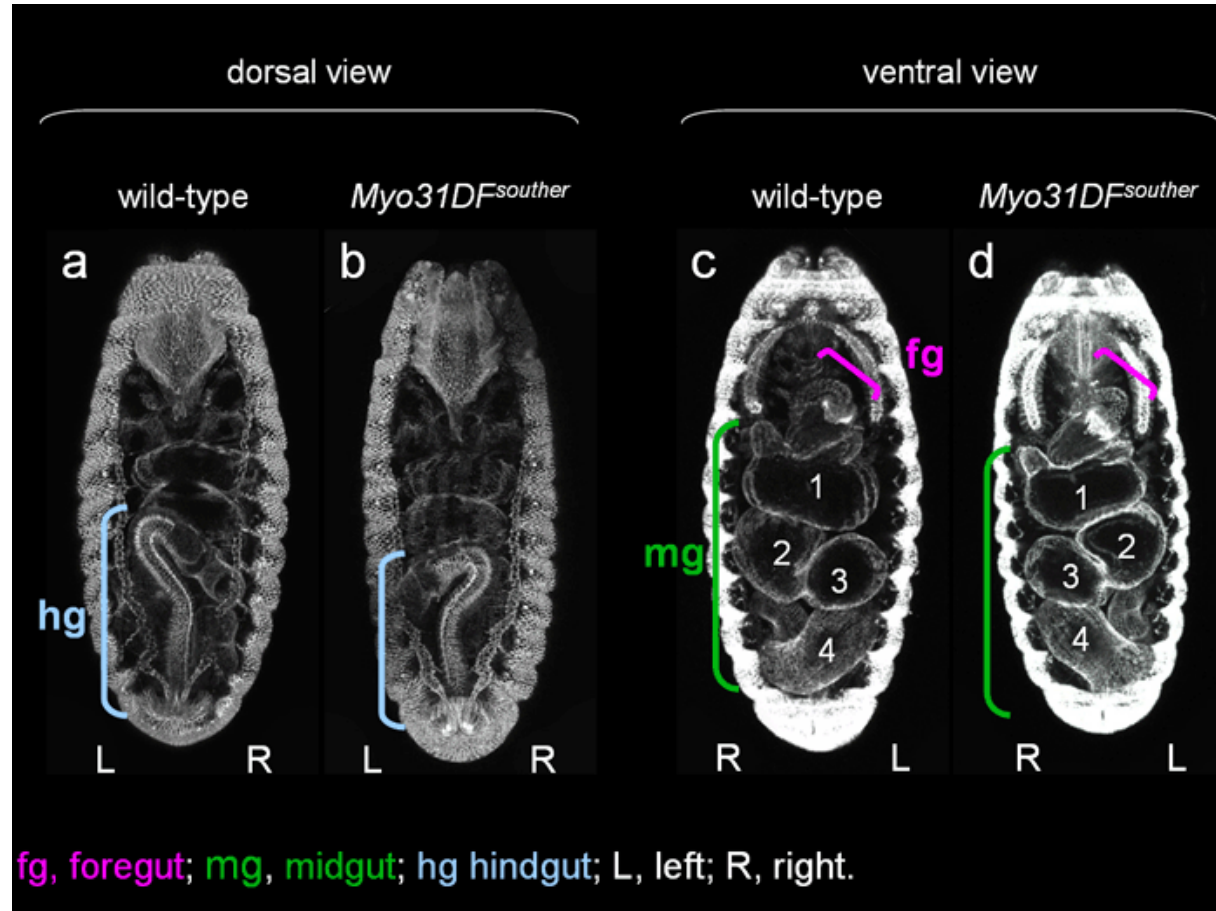


Asymmetry during male genitalia development





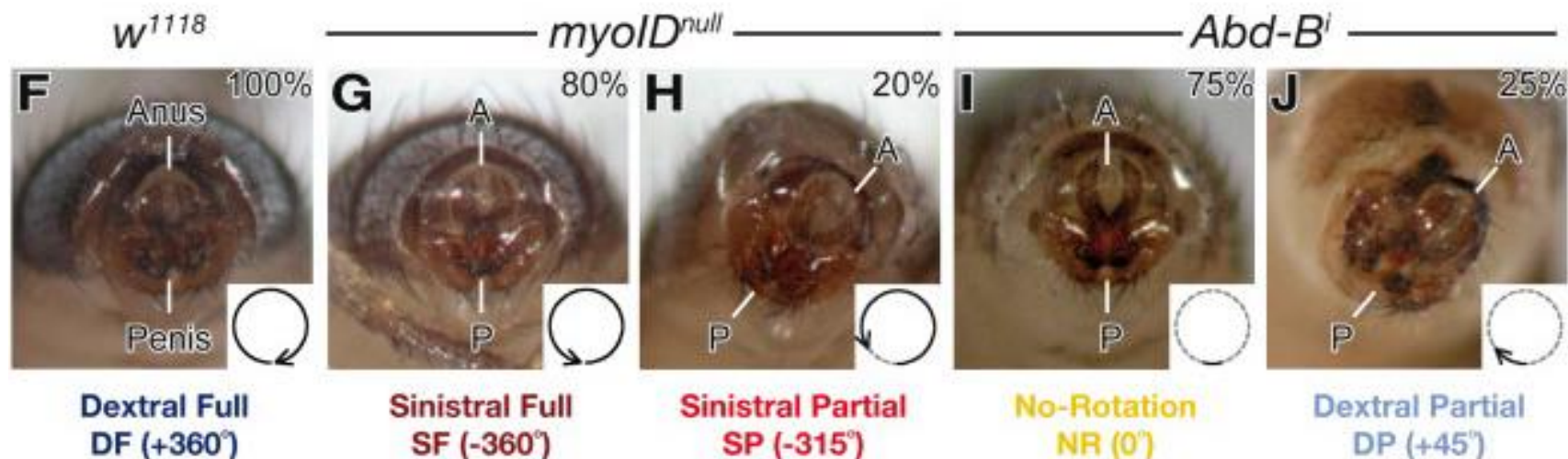
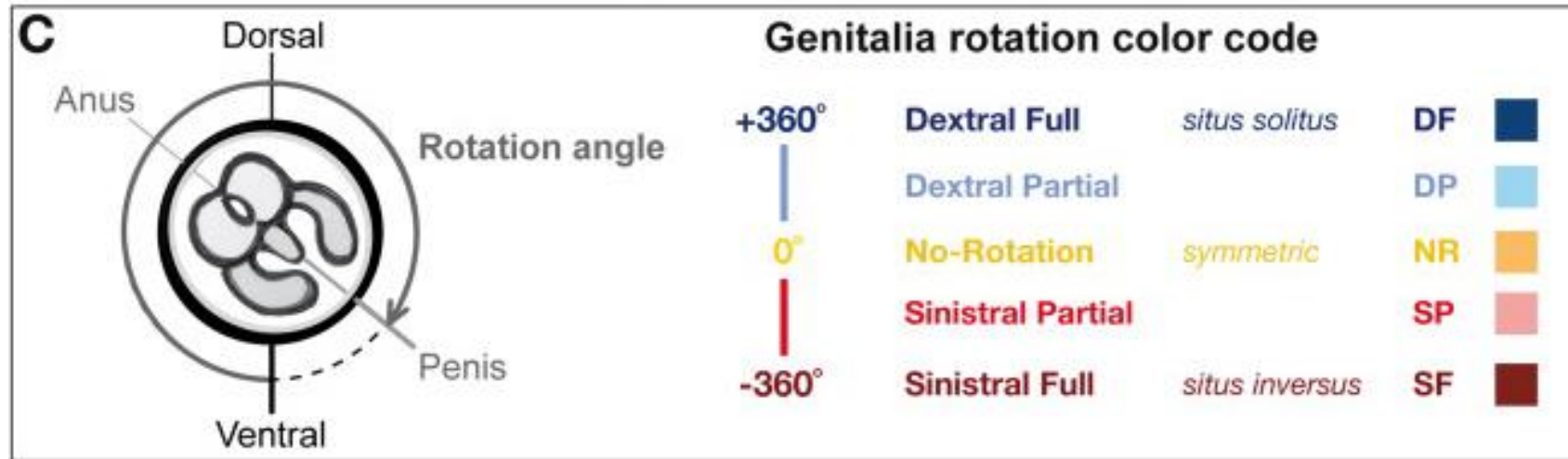
An unconventional myosin is responsible for gut and male genitalia rotation



(*KG02246* – *Myo31DF* mutant)



Only *Abd-B* mutations will completely abolish *Drosophila* laterality





Abd-B acts upstream of *MyoID* to control laterality

