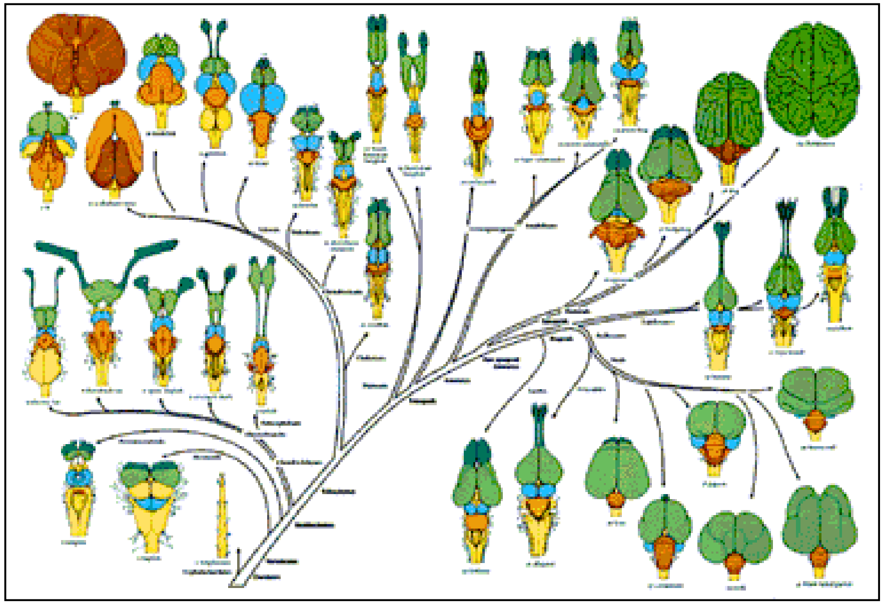
Development and Evolution of the Vertebrate Forebrain



From: Springer-Verlag Berlin Heidelberg (1998) R. Nieuwenhuys, H.J. ten Donkelaar, C. Nicholson. The Central Nervous System of Vertebrates.

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Master 2 Paris-Saclay
UE Neural stem cells and CNS development, Septembre 2024

Outline

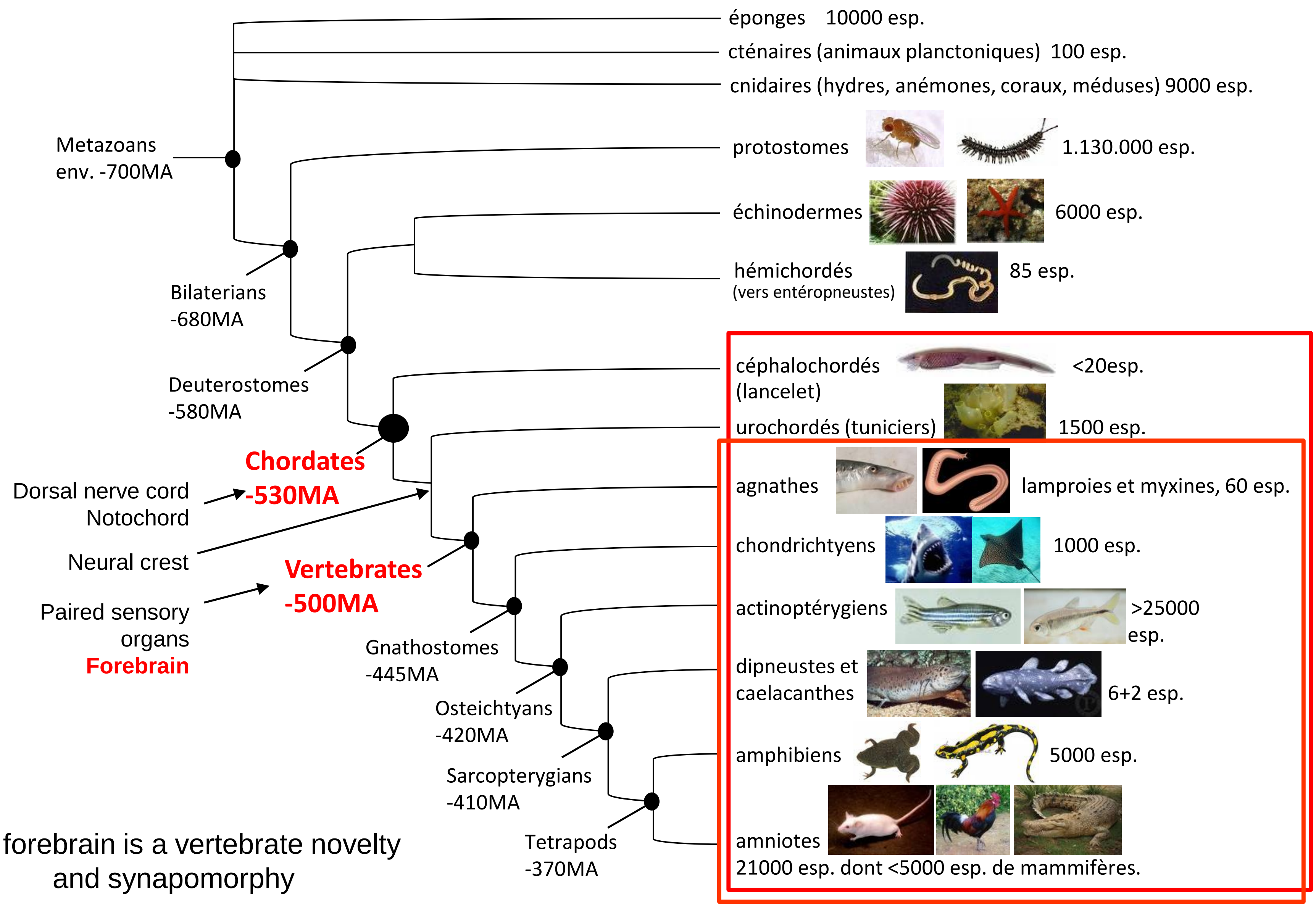
I- presentation of the forebrain

II- plan of organisation and morphogenesis of the vertebrate forebrain

III- macro-evolution: example of the lamprey and hagfish brains

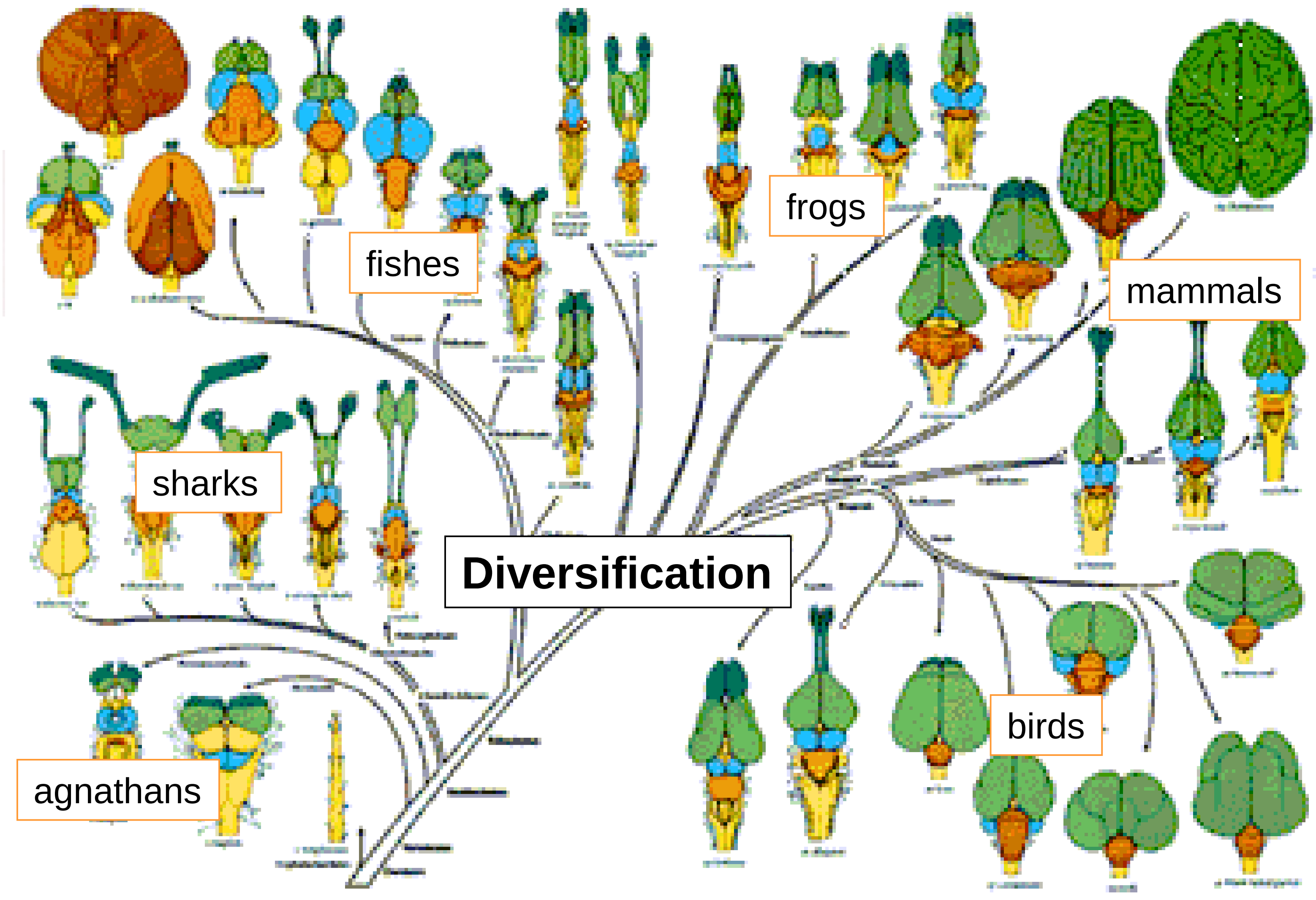
IV- micro-evolution: example of the cavefish brain

Metazoan phylogeny – Phylogenetic « tree-thinking »



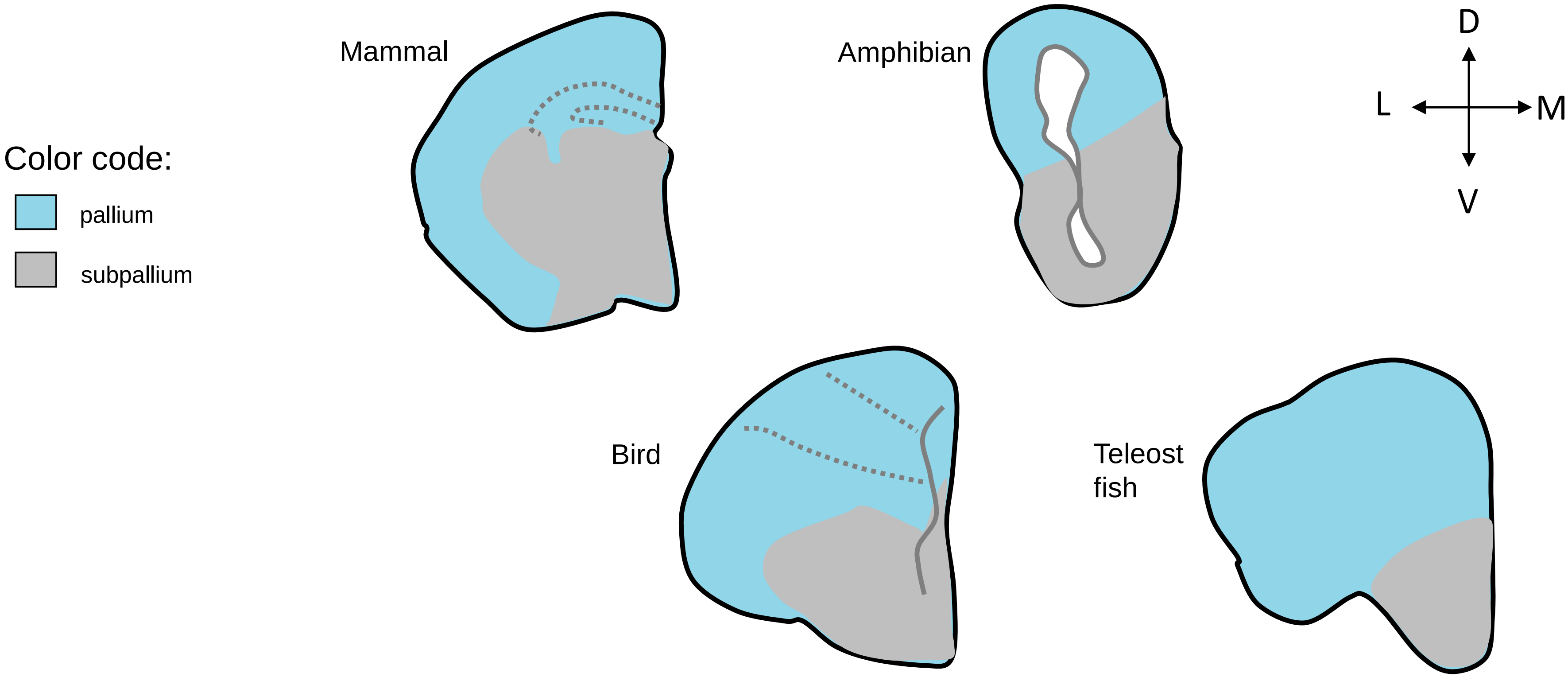
The forebrain is a vertebrate novelty and synapomorphy

Amazing diversity in forms, sizes, structures of the brains



Forebrain diversification – Notion of homology

Transverse sections, adult brains, telencephalon:



Shared caracters can be inherited from a common ancestor (=homology)
or can be independently-evolved (=homoplasy or convergence).

Homology
inheritance from a common ancestor
shared developmental origin
multitude and high degree of similarities
can be traced in the genome

≠

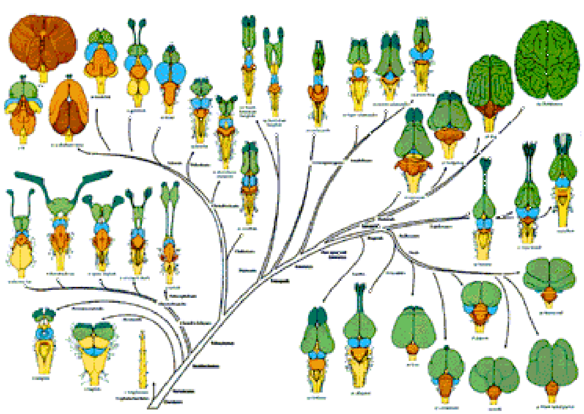
Homoplasy/convergence
similar caracters of independent origin
(ex: bat wing/bird wing)

Evo-Devo, principle

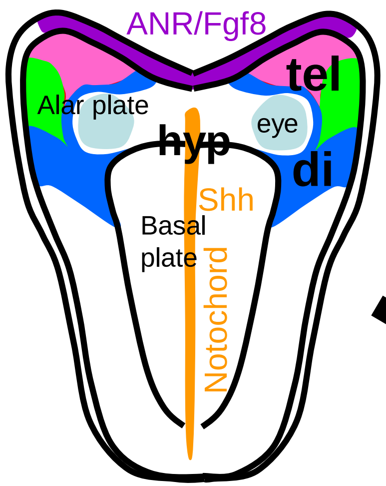
Evolutionary developmental biology (**evolution of development**, **Evo-Devo**) is a field of biology that compares the developmental processes of different organisms/species to determine the ancestral relationship between them, and to discover how developmental processes evolved.

It addresses the origin and evolution of embryonic development; how modifications of development and developmental processes lead to the production of novel features and to diversification of structures; and the developmental basis of homology and homoplasy.

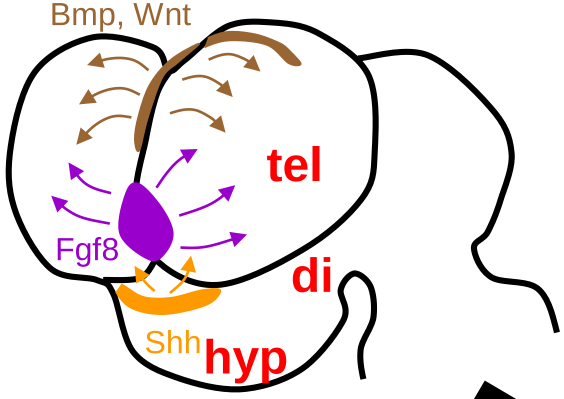
Evo-Devo is based on the idea that morphological differences observed between the adult brains of various species ***must*** originate from variations in the developmental processes.



Forebrain development



Neural plate stage
(end of gastrulation)



Neurulation
Morphogenesis
Field of organisation

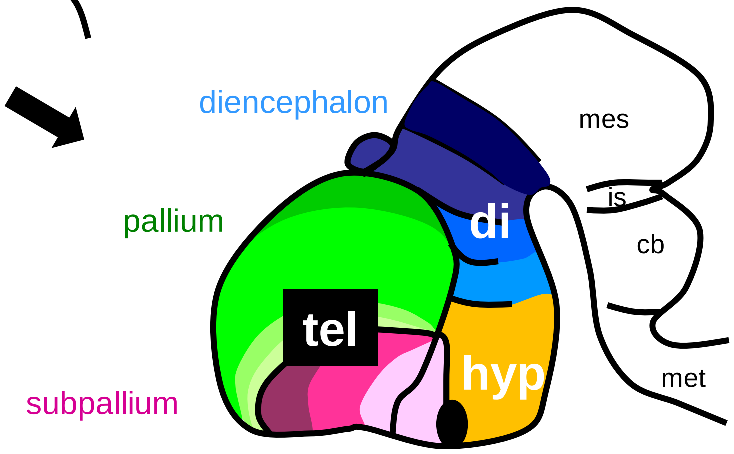
-secondary organiser centers

-morphogen signals

-regional identity

-neurogenesis

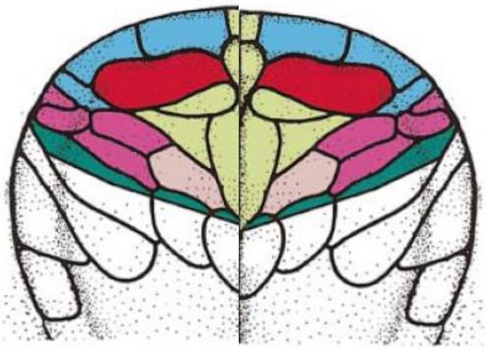
-combinatorial codes of transcription factors



Regionalised forebrain
Functional units

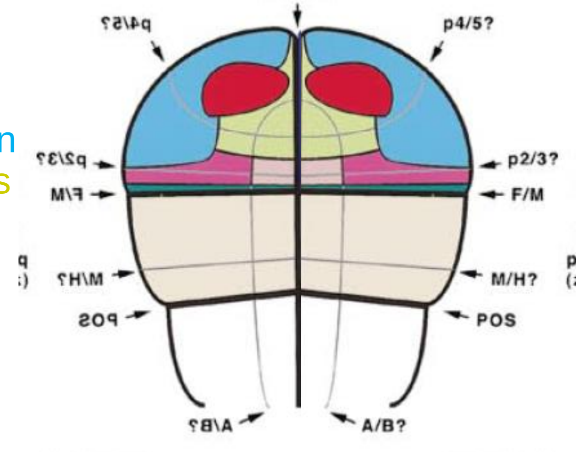
Compared « fate maps » of vertebrate neural plates

Xenopus
Eagleson and Harris, 1990

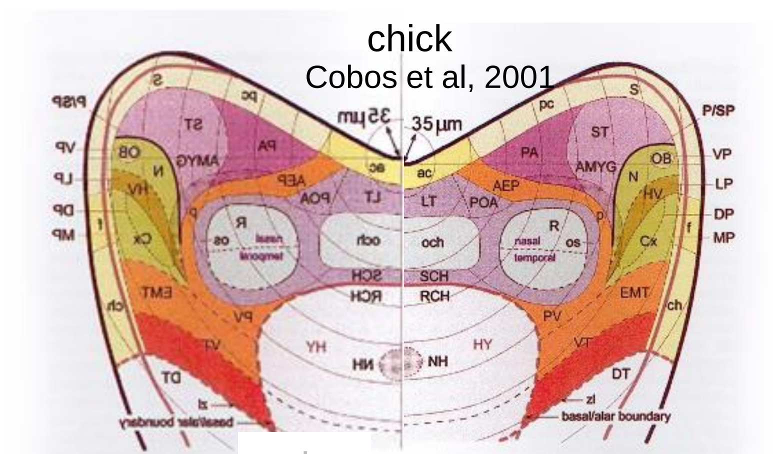


retina
telencephalon
hypothalamus
thalamus

mouse
Inoue et al, 2000

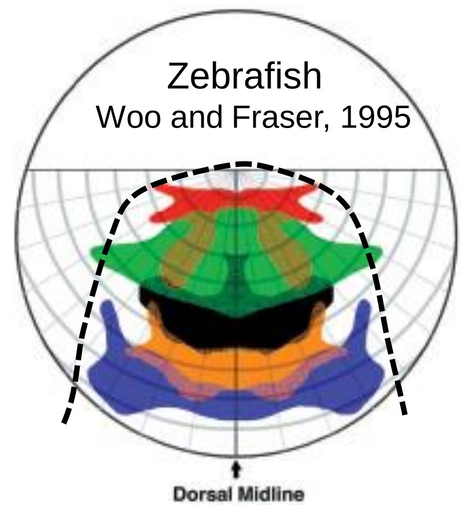


chick
Cobos et al, 2001



retina
telencephalon pallium
telencephalon subpallium
thalamus

Zebrafish
Woo and Fraser, 1995



retina
telencephalon
diencephalon

(vocabulary)	plaque du plancher (floor plate)	plaque basale (basal plate)	plaque alaire (alar plate)	plaque du toit (roof plate)	Sulcus limitans

Morphogenesis and regionalisation

neuroepithelium

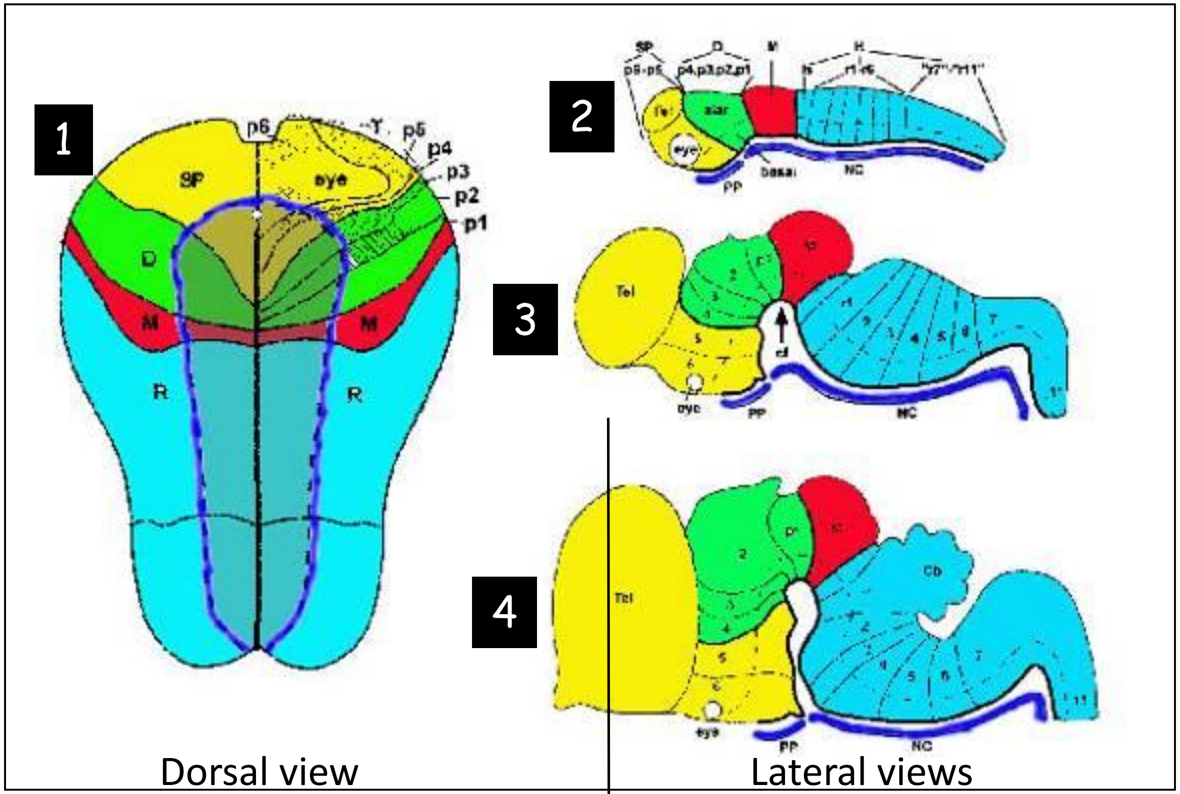
↓

morphogenesis (amniotes)

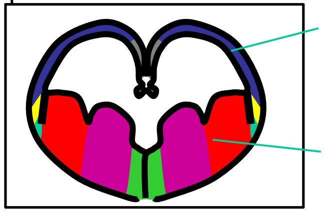
-neurulation
-evagination
(telencephalic vesicles, optic vesicles, olfactory bulbs, epiphysis)
-inwards growth (ganglionic eminences)
-flexure of the longitudinal axis

+ regionalisation
+ cell/neuronal differentiation
+ extensive migrations

mouse

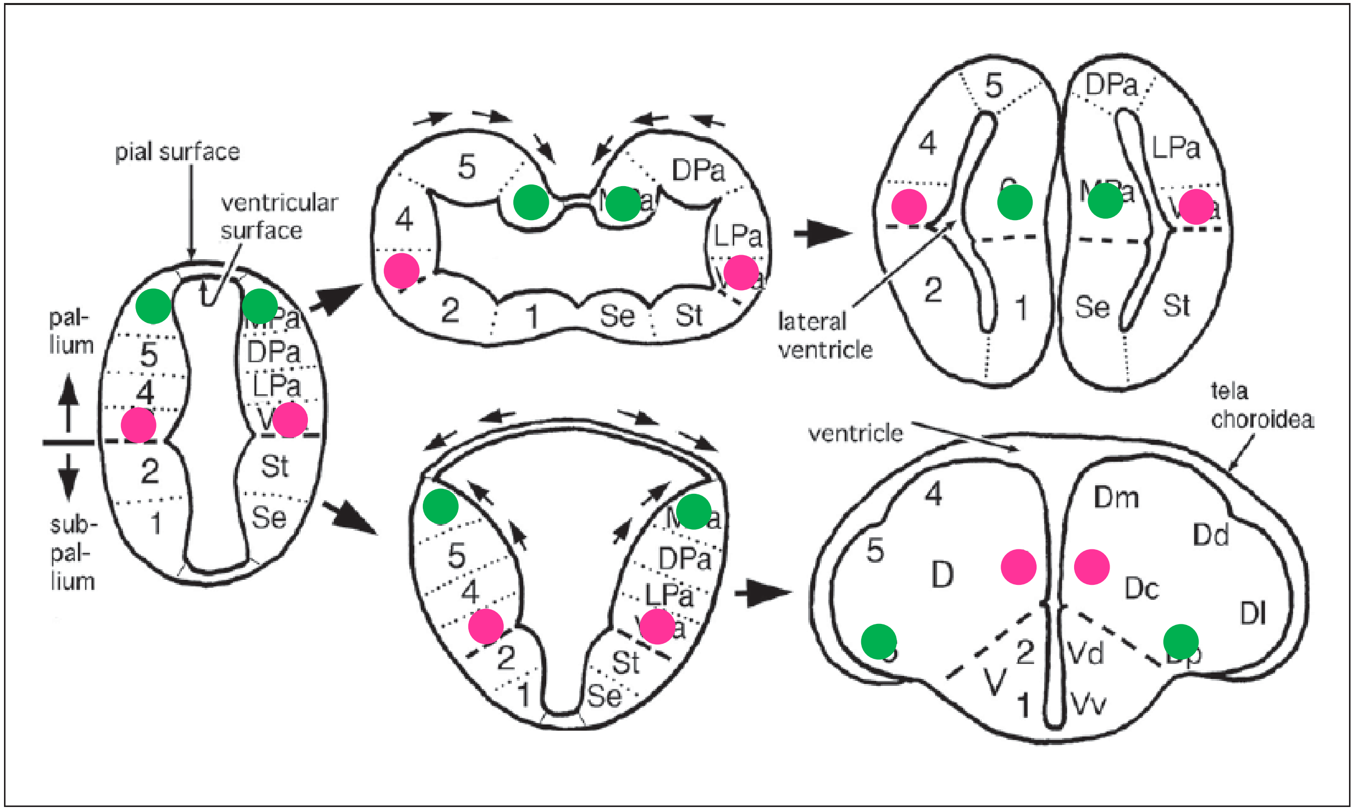


!! Massive deformations which notably complicate the compared anatomical analyses!!



Telencephalic morphogenesis: diversification of tissue movements

Example…



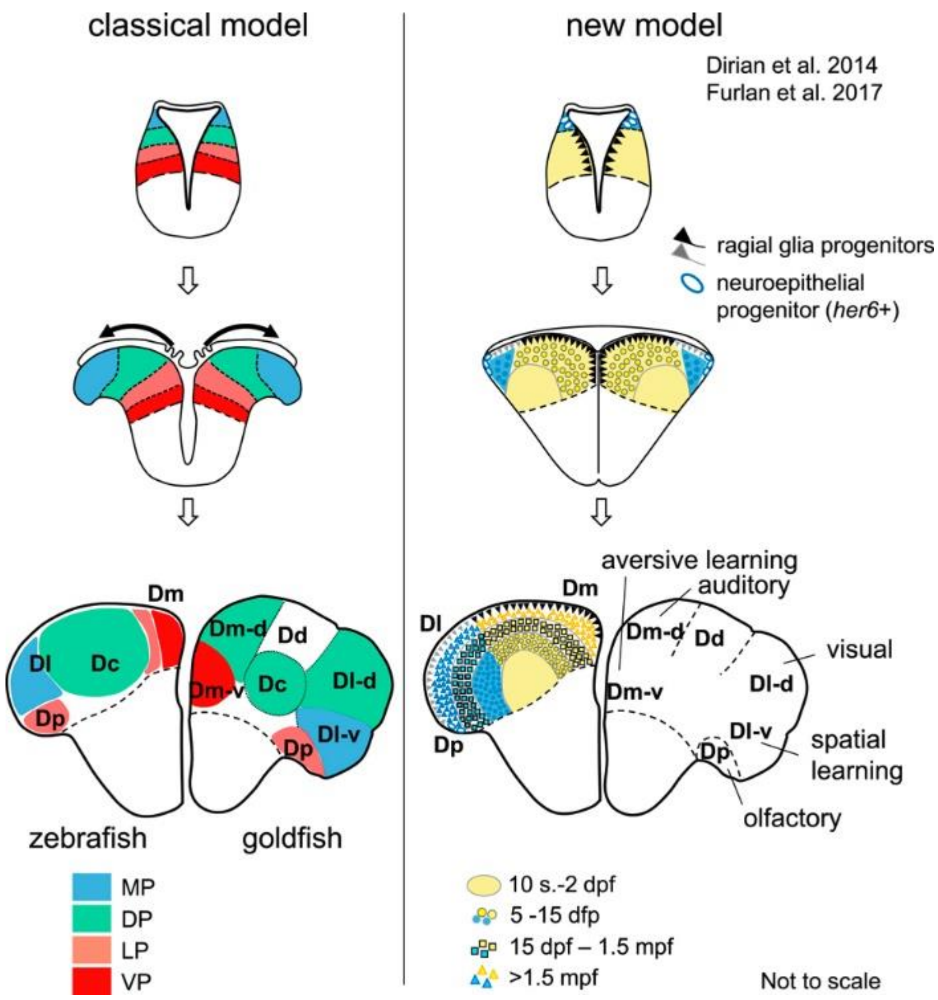
« Classical » evagination

Eversion in teleost fish

> Inverted topology of the pallium

Telencephalic morphogenesis: diversification of tissue movements

Example…with some further complications…



Yamamoto et al, BBE 2024

The construction of the teleost pallium is not simply a reversed version of the sarcopterygian pallium.

The teleost pallium does not develop by extension of the preexisting three or four embryonic subdivisions.

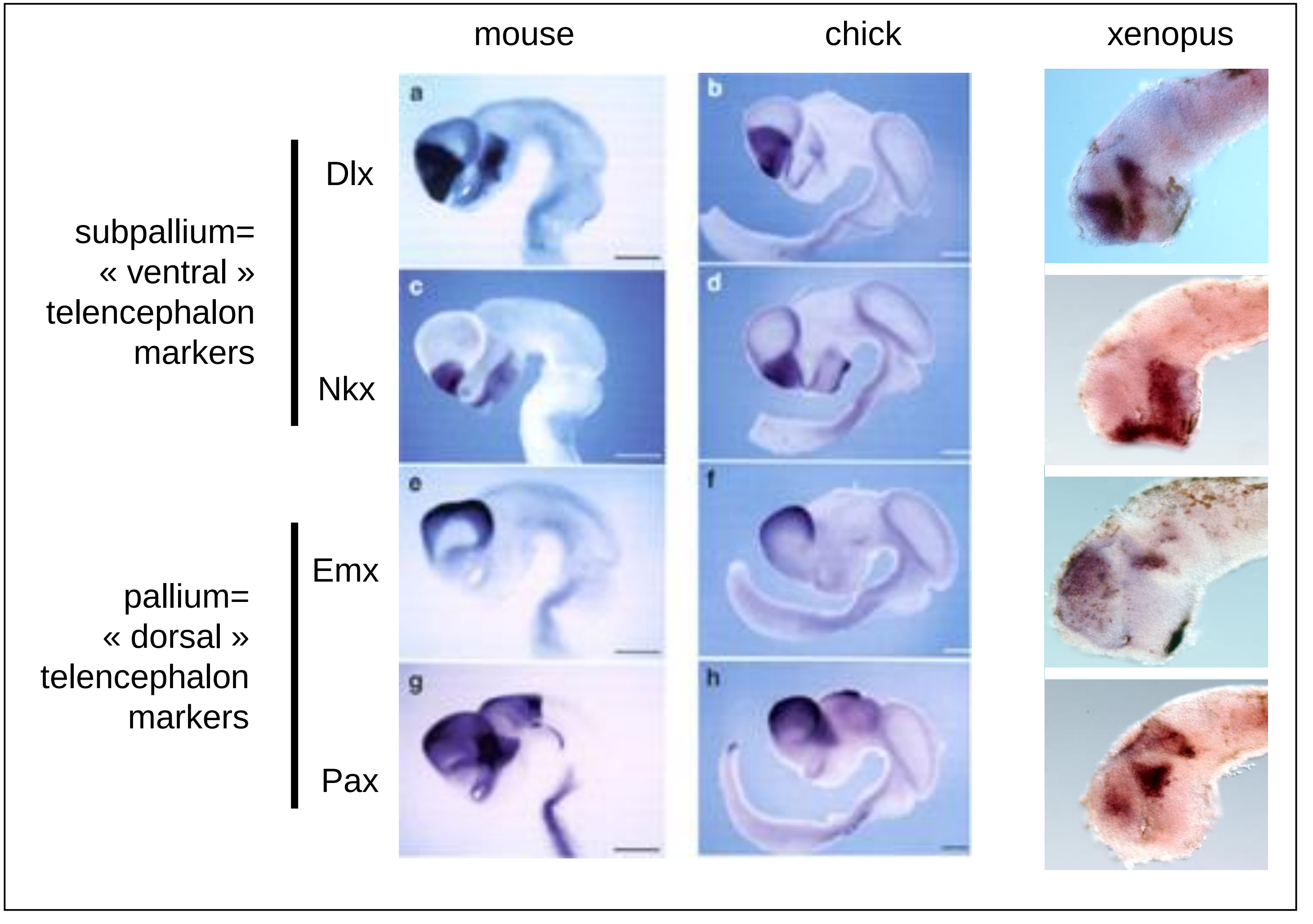
Newly born neurons are progressively “stacking-up” on top of the old ones.

All the lateral parts of the pallium containing Dl and Dp are derived from the *her6+* progenitors located at the dorsal tip of the neural tube until 2 dpf.

Hence, the teleost “MP” gives rise to neural populations not only playing a hippocampus-like role in spatial memory (ventral Dl), but also in visual sensory (dorsal Dl) and in olfactory sensory (part of Dp) processing. Thus, in teleosts, a simple “Dl = hippocampus = MP” framework is not supported by developmental data.

Therefore, the pallium is homologous as a field in vertebrates, but the pallial subdivisions are not homologous: they lack shared developmental origin.

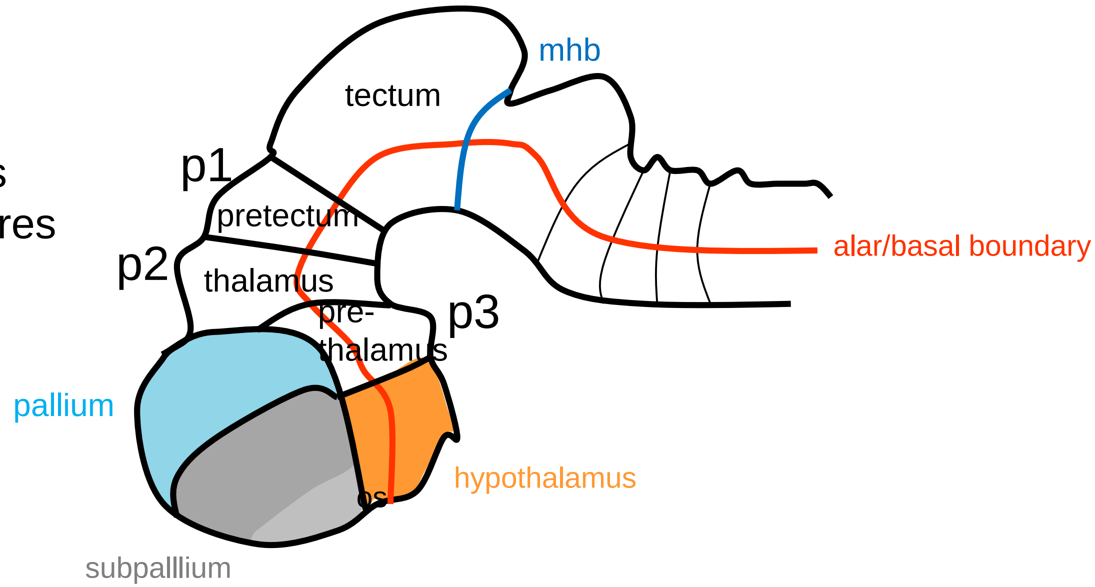
Regionalisation and genetic specification
The embryonic brain of vertebrates has a shared plan of organisation

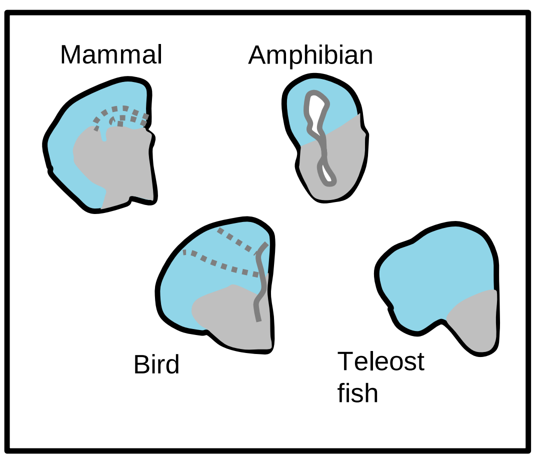


Conserved *Bauplan*. Shared genetic specification

Bauplan of the tetrapod brain

- telencephalic divisions
- diencephalic prosomeres

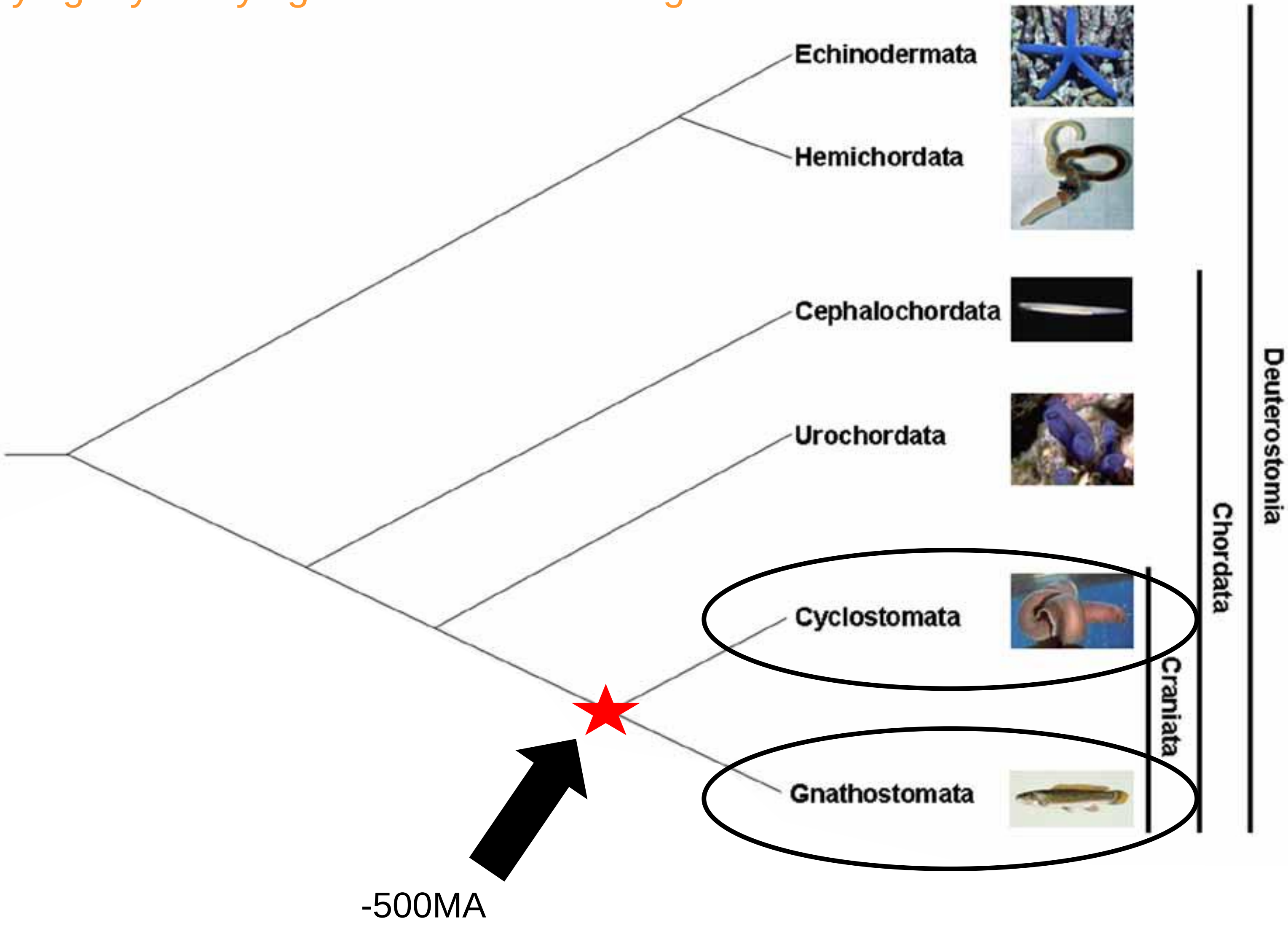




➢ A shared embryological origin AND genetic specification allows proposing the homology between pallial and subpallial regions of the brain in different vertebrates.

➢ Looking for the ancestral craniate brain ???

Phylogeny - Phylogenetic « tree-thinking »

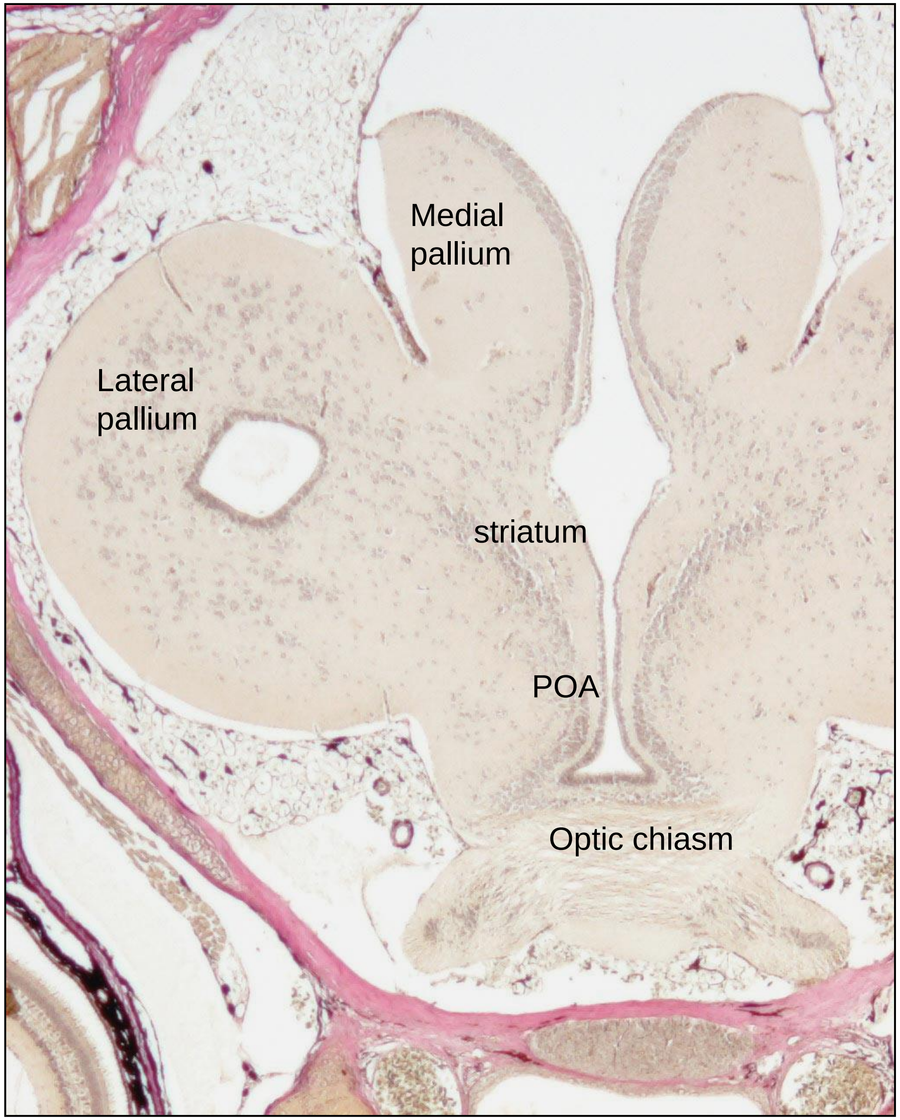


The lamprey, agnathan vertebrate, divergence ~500 MA : macro-evolutionary scale

No jaws,
No scales,
No paired fins,
No stomach

<u>They have</u>:
internal cartilage skeleton
complete braincase and rudimentary but true vertebrae
sucker surrounding the mouth, strenghtened by an annular cartilage
a brain including a forebrain

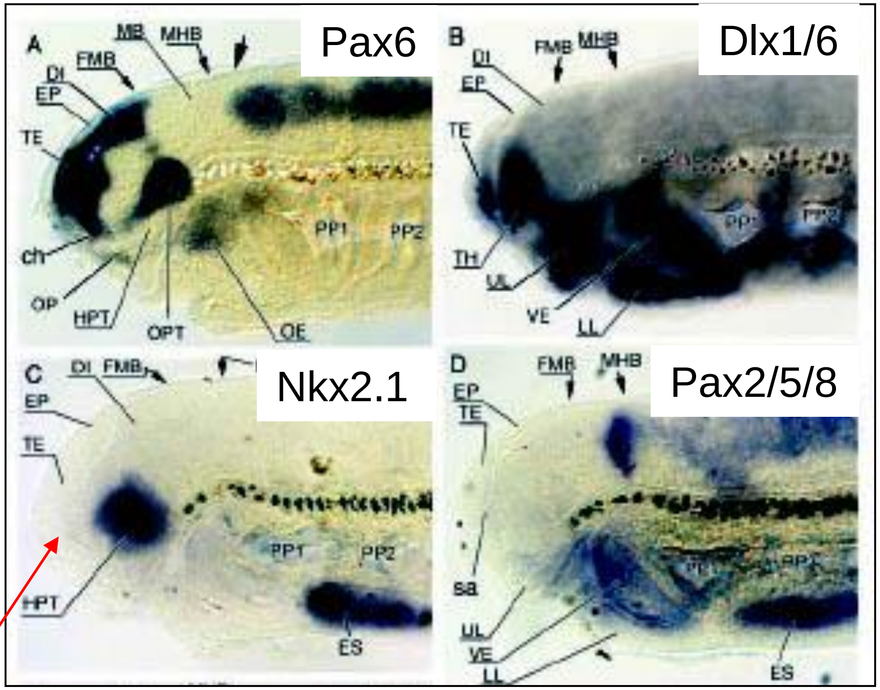
The lamprey adult brain



Transverse section / telencephalon adult *Lampetra*

- Poorly « migrated » brain, low cell density
- Partial evagination of the telencephalon
- No pallidum in the subpallium

Genetic specification of the forebrain subdivisions in embryonic lamprey



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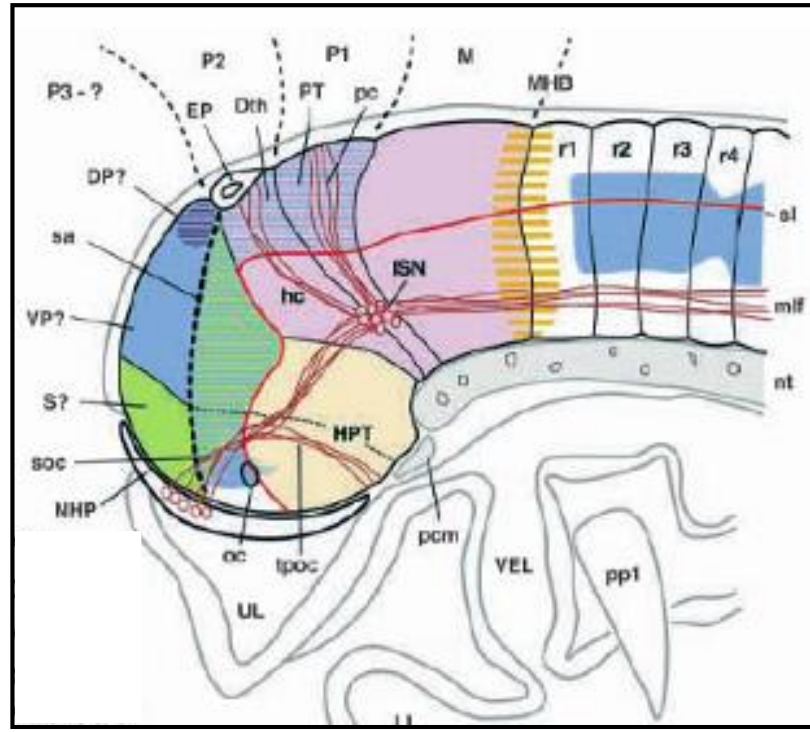

Murakami et al, Development 2001

- prosomeric organisation of the diencephalon
- two pallial subdivisions
- no Nkx2.1 in the subpallium, only one subpallial division

Phenocopy of the lamprey case in Nkx2.1$^{-/-}$ mouse ?

Loss of *Nkx2.1* homeobox gene function results in a ventral to dorsal molecular respecification within the basal telencephalon: evidence for a transformation of the pallidum into the striatum

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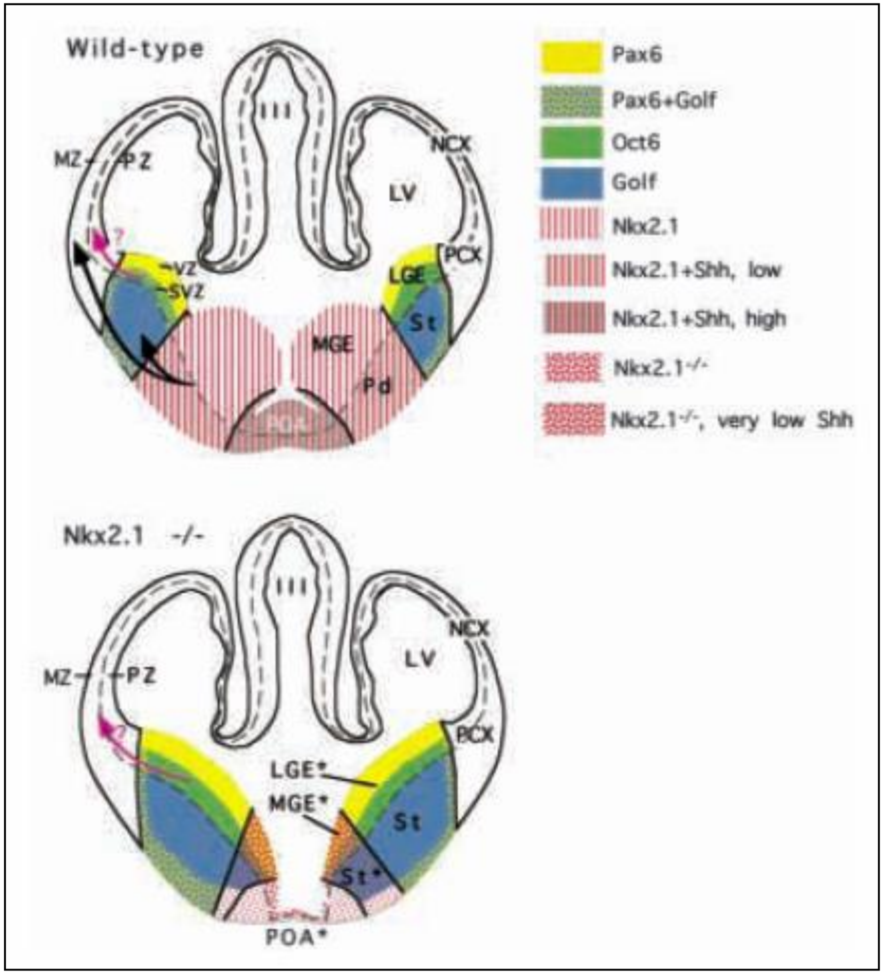
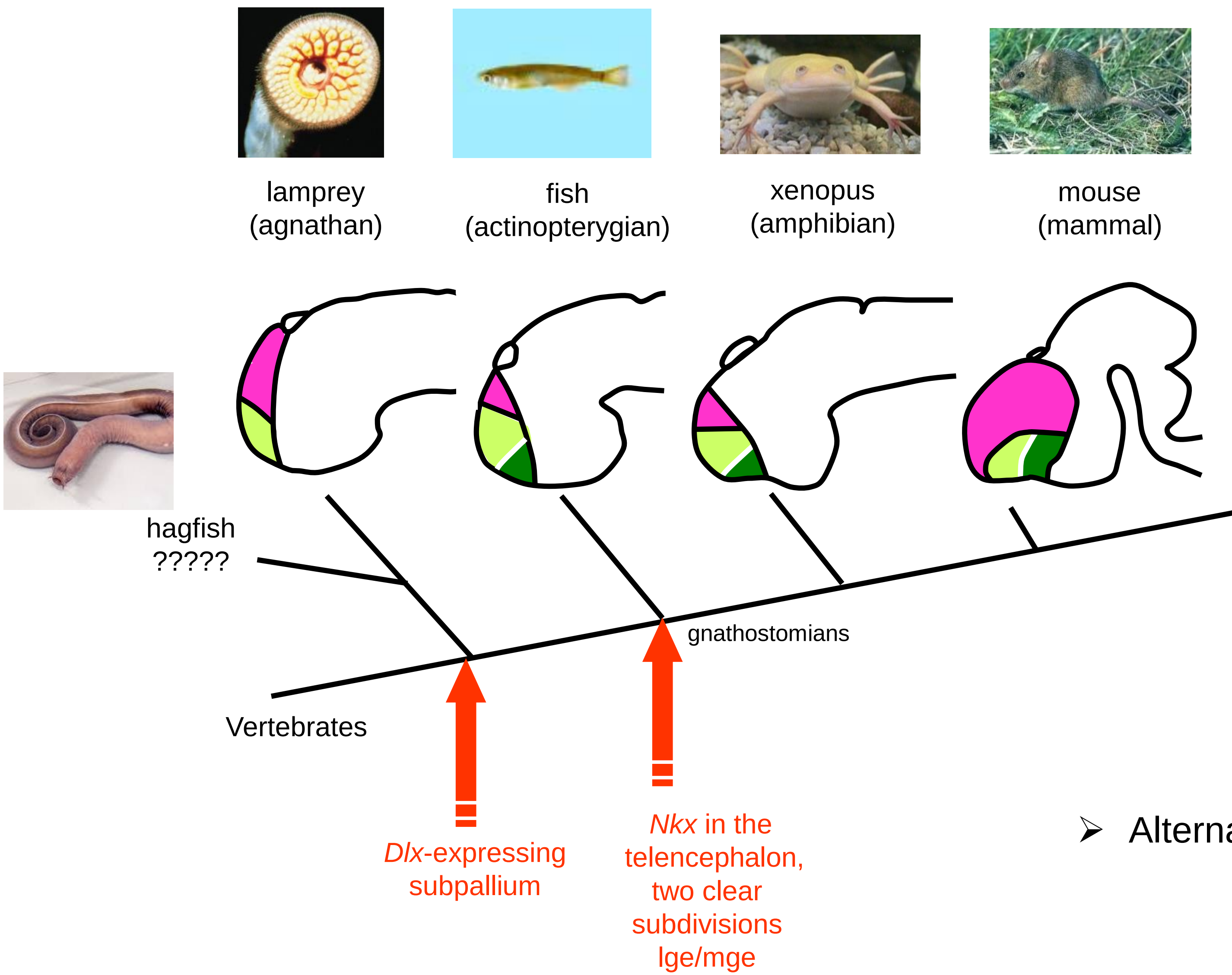


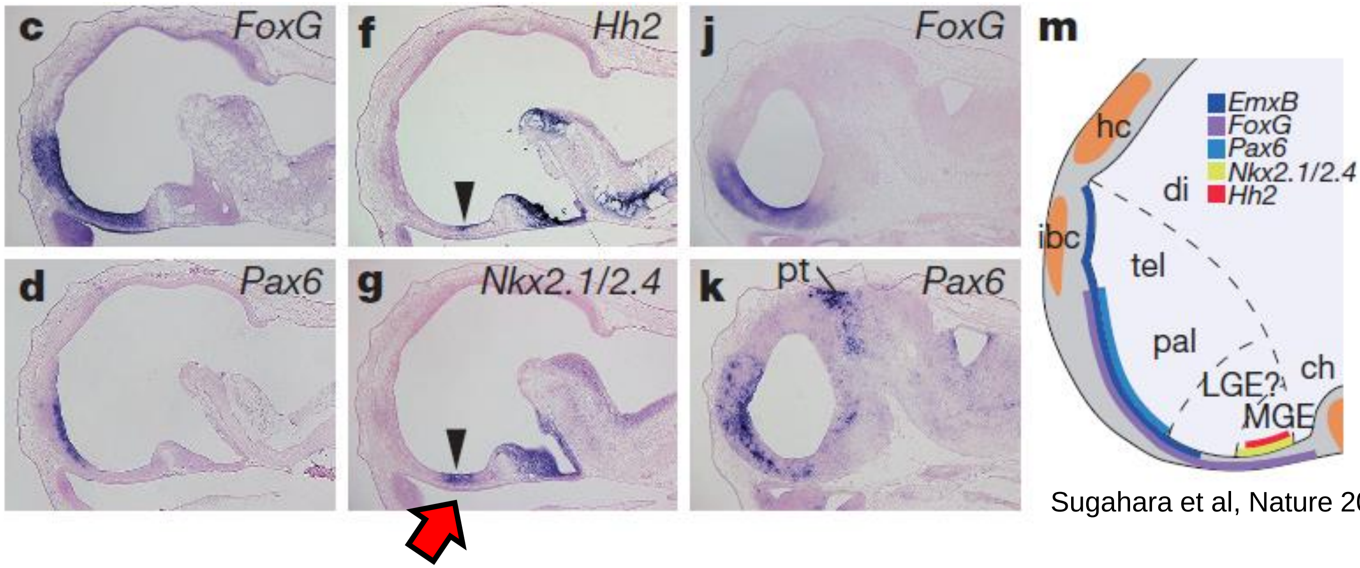
Evolutionary scenario ?



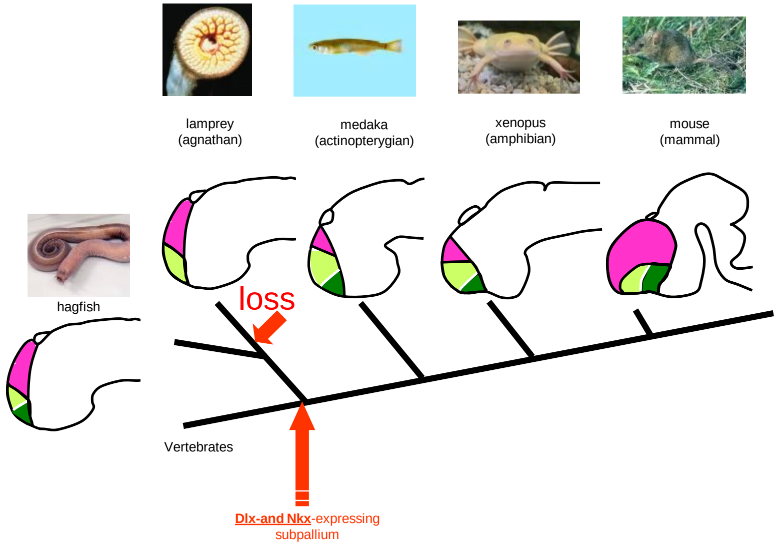
- Alternative hypothesis?

Genetic specification of the forebrain subdivisions in embryonic hagfish

Eptatretus burgeri



Sugahara et al, Nature 2016

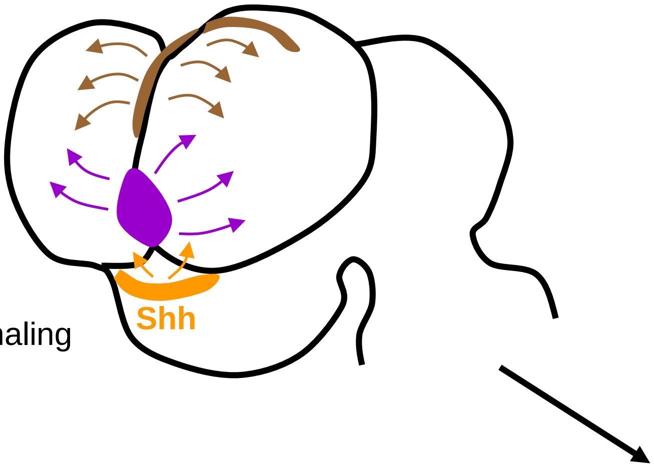


- Importance of phylogenetic sampling
- Evolution can proceed by loss

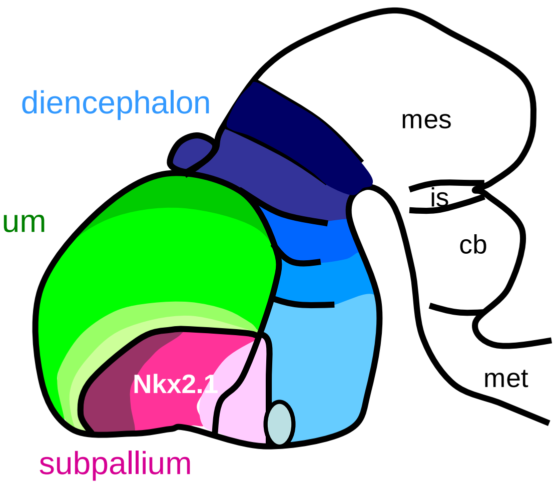
➢ Origin of these patterning variations?

Secondary organiser centers :
a role for the emergence of brain diversification and novelties?

Morphogen signaling

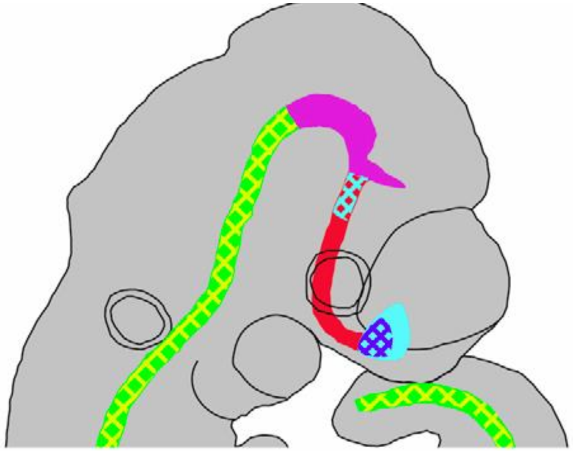


Regionalised brain

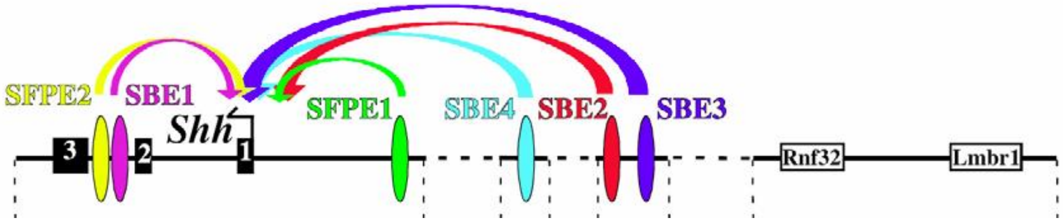


? Loss of nkx2.1 induction by Shh in lampreys ? Evolution at regulatory level?

Role of *cis*-regulatory sequences in evolution ? Example of Shh



Jeong et al, Development 2005

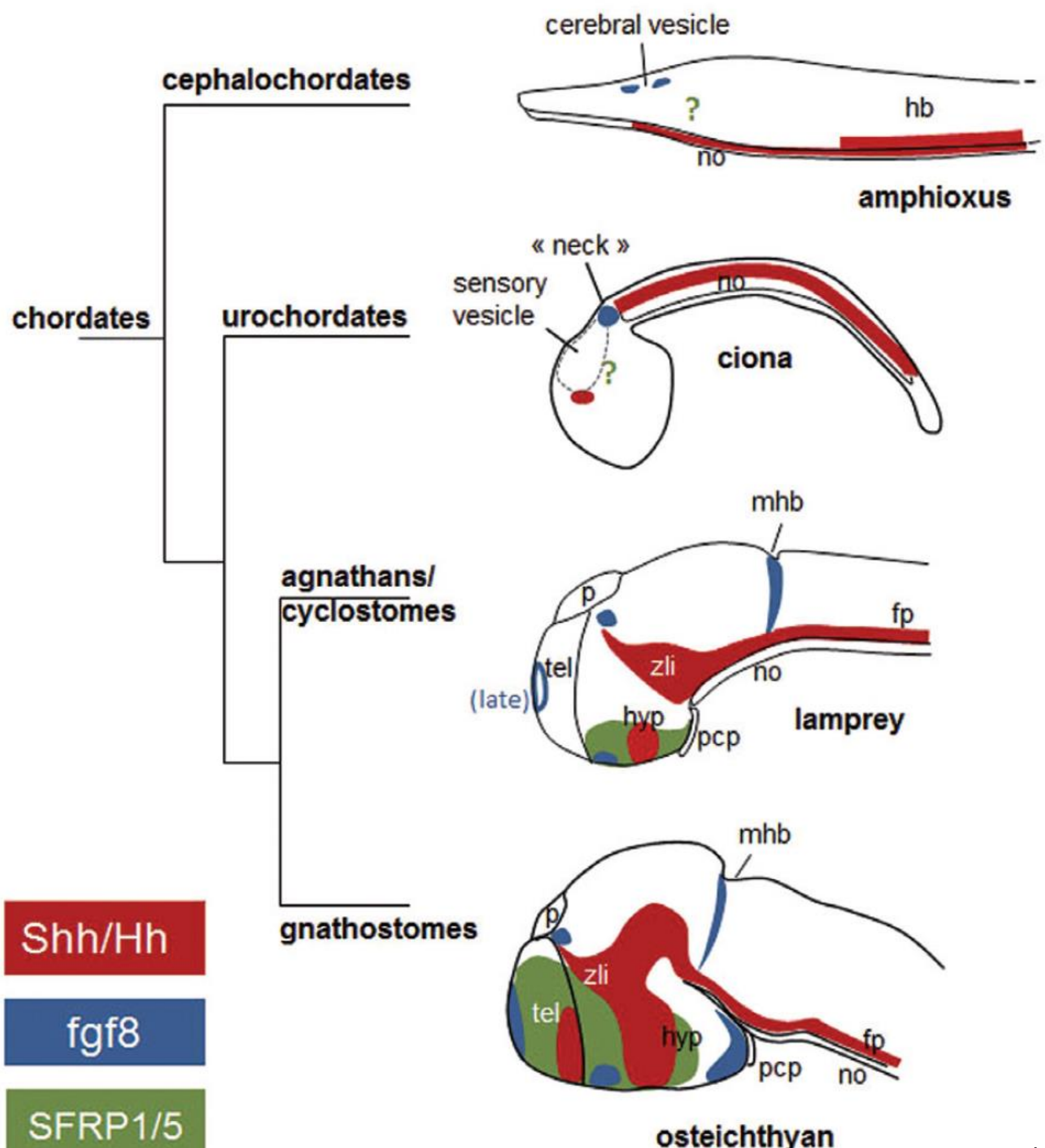


Modular structure of CNEs,
« Evolvable » system

The **modular nature of cis-regulatory elements and pleiotropy of gene products** allows for selective spatio-temporal changes of expression patterns and morphological changes
(Sean Carroll)

Carroll, Cell 2008

Evolution of signaling centers and emergence of the vertebrate telencephalon

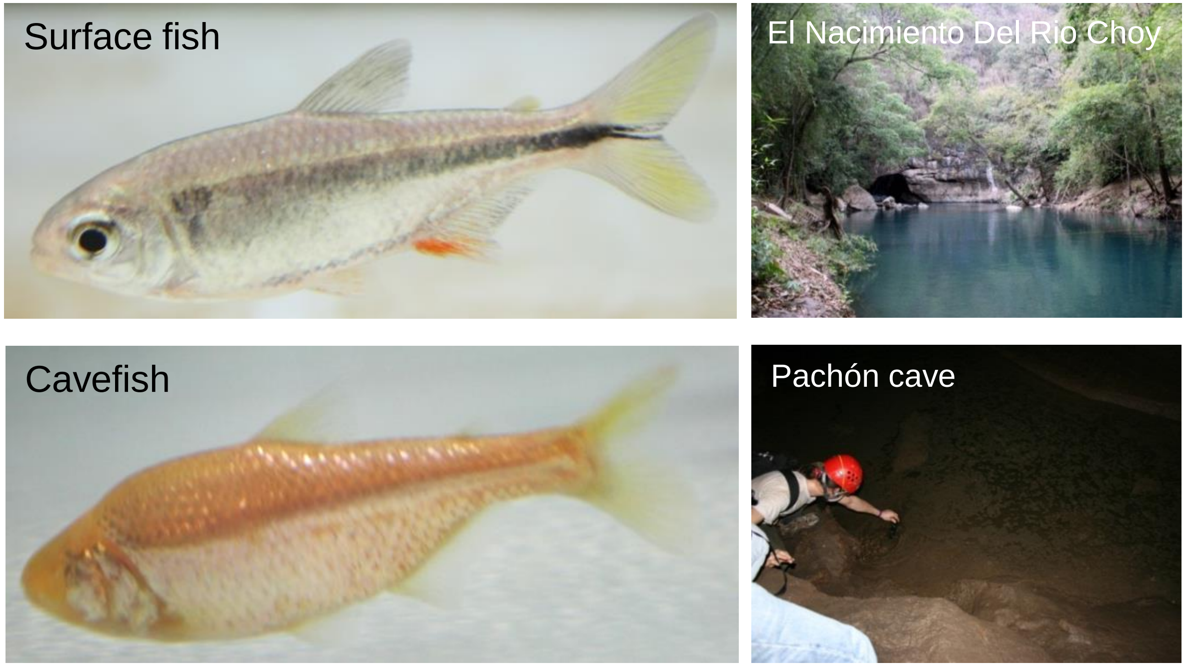


Anteriorisation/ aquisition of novel expression domains for key morphogen signaling molecules

Rétaux et al,
Advances in Evolutionary Developmental Biology, 2013

Micro-Evo-devo of the brain : the case of the blind cavefish

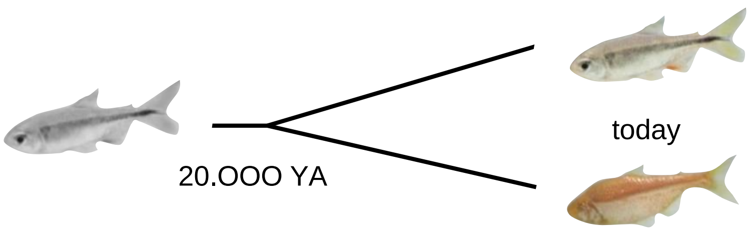
Astyanax mexicanus



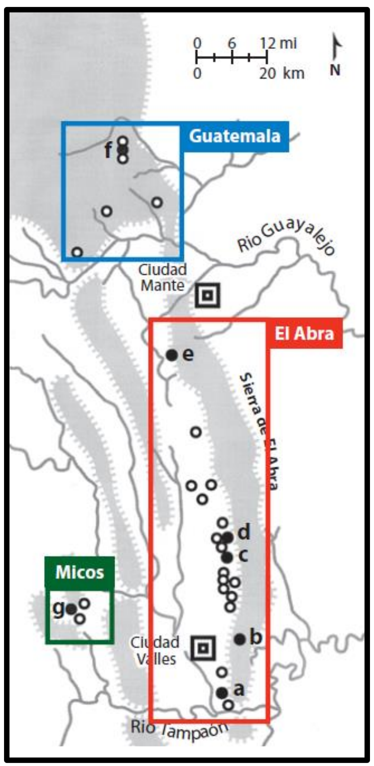
One species, ~20.000 years of evolution in cave environment

- cavefish have adapted to permanent darkness and irregular/low food supply
- they have undergone both gains and losses at the morphological, physiological, and behavioral levels

Astyanax mexicanus cavefish: evolutionary history



-cavefish have evolved from surface fish-« like » ancestors



(From Jeffery, 2009)

- many caves with cavefish, all blind and depigmented

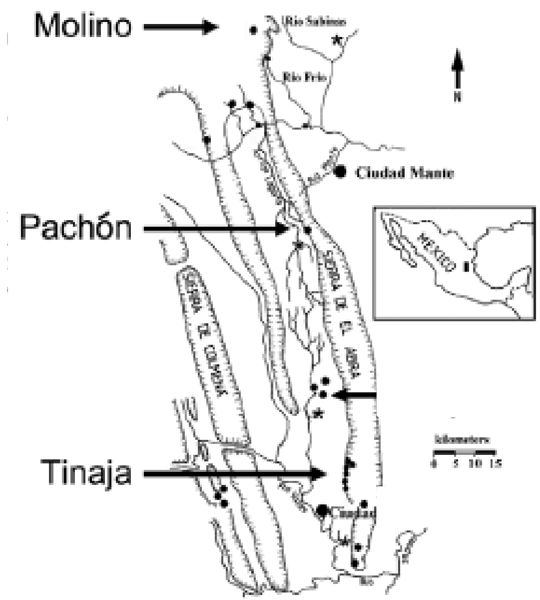
- 2 independent colonisation events

- parallel /convergent evolution

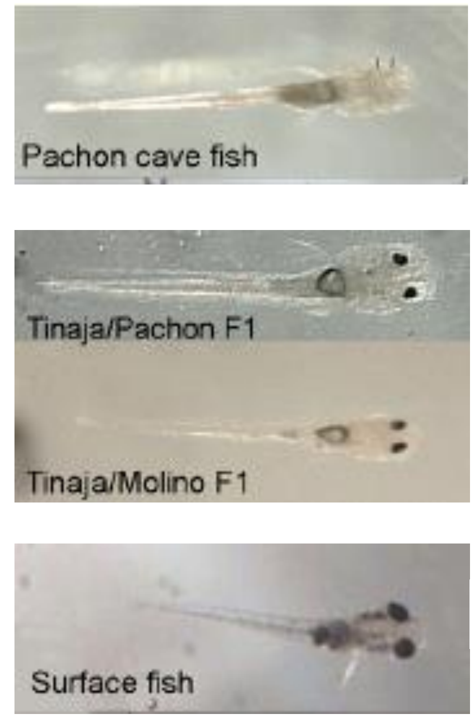
Mechanisms underlying eye loss: genetics

Restoring sight in blind cavefish

Richard Borowsky



Complementation crosses:



0% can see

8% see

39% see

100% see

- Case of convergent evolution
- Independent events (at least in part)

Developmental mechanisms underlying eye loss

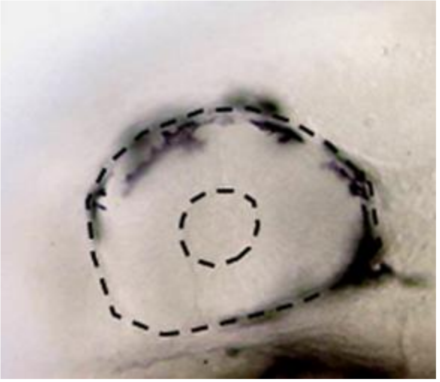



Comparative development during the first 24 hours: cavefish first develop eyes

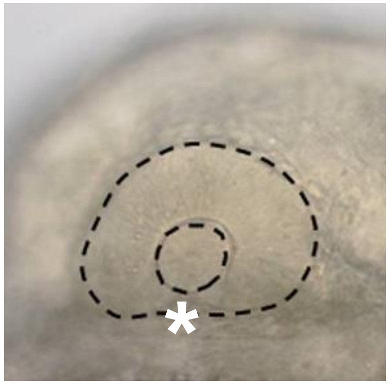
Cavefish eyes suffer coloboma

Surface fish eye

24hpf

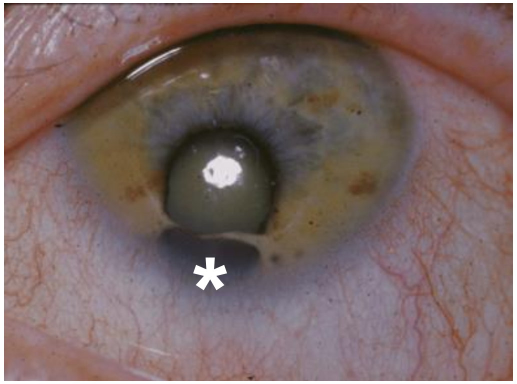


Cavefish coloboma



Small & malformed

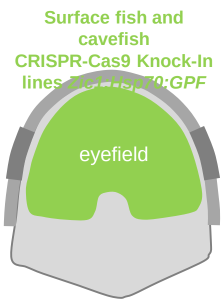
Human coloboma



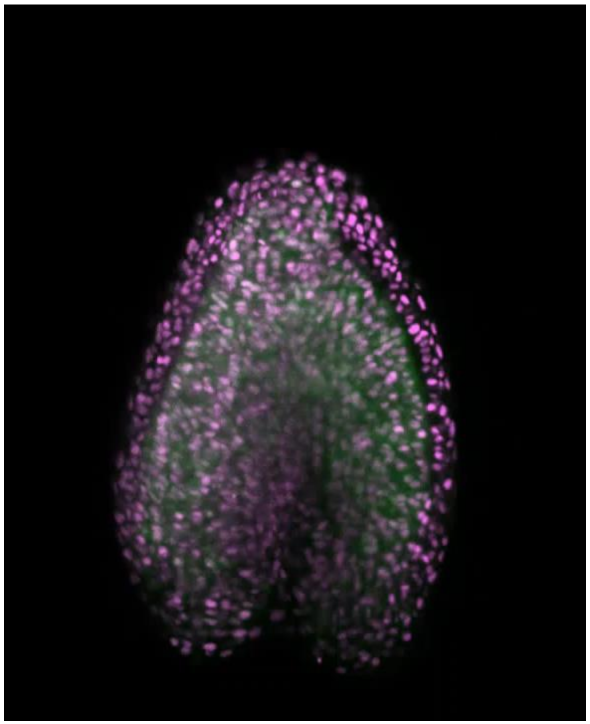
Incidence ~1/100.000

- What is the developmental origin of this morphogenetic defect?

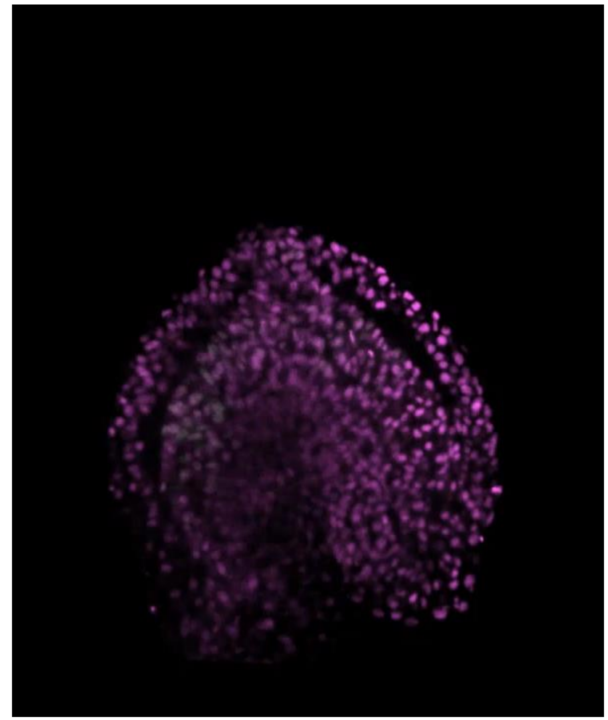
Comparing eye morphogenesis through live imaging



surface fish



cavefish

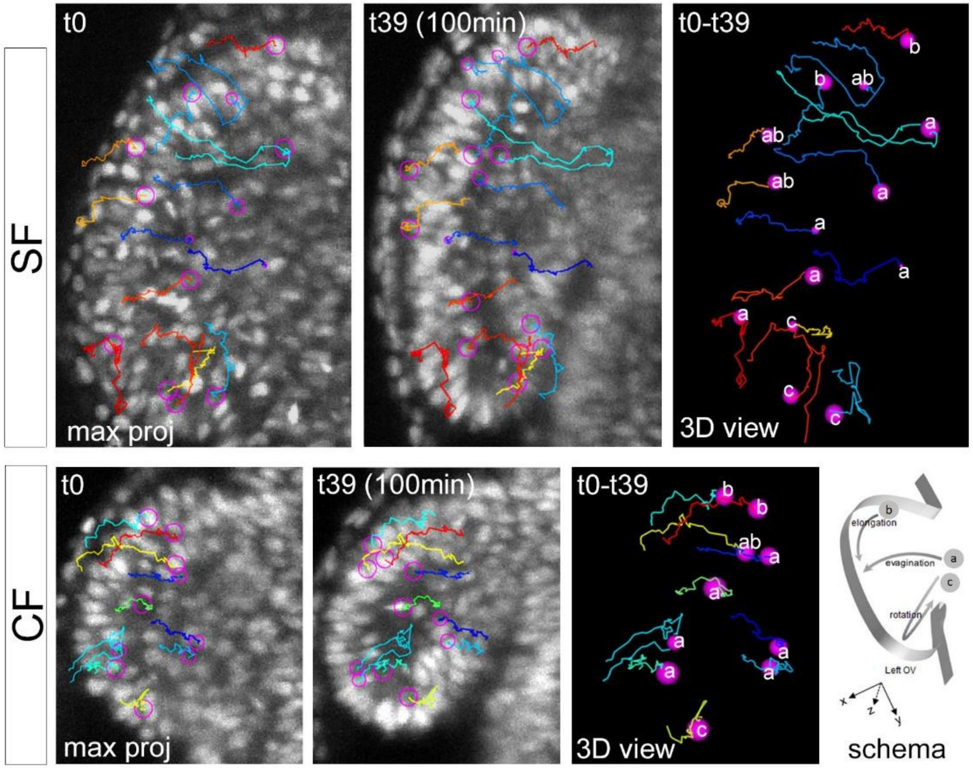


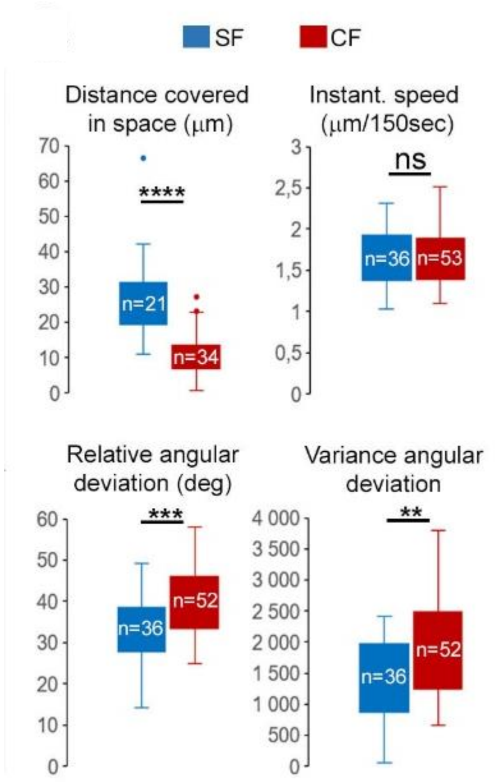
Light-sheet microscopy, live imaging from 10 to 36hpf
Zic1:Hsp70:GPF + H2B-mCherry mRNA injection

- Defective morphogenetic movements

Devos et al, Biology Open 2021

Improper cell behaviors during morphogenesis



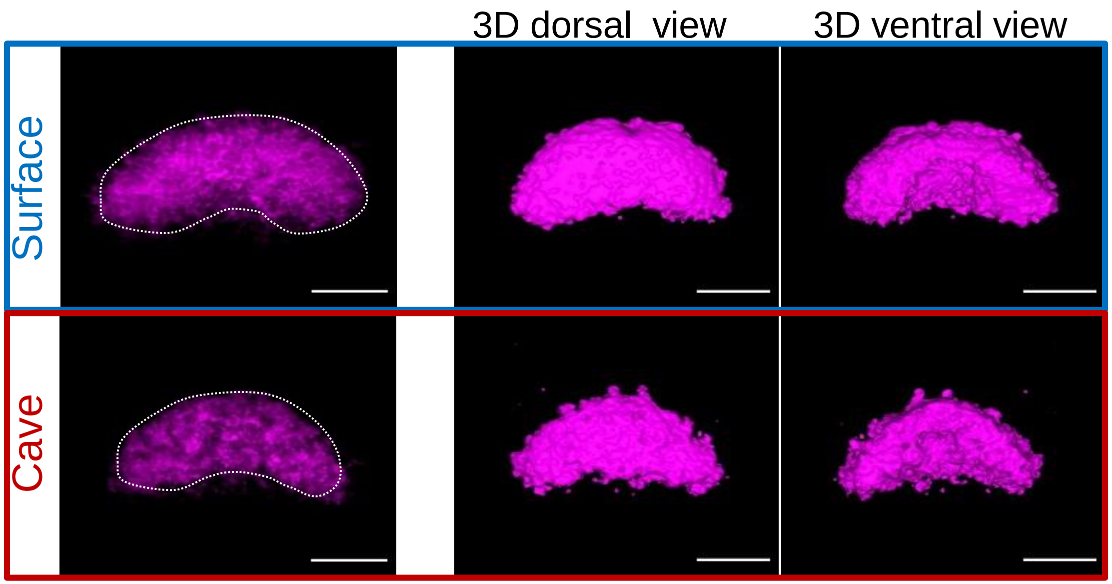


- Cavefish optic cells adopt aberrant trajectories

Evo-Devo and specification of the eyefield, *rx3*

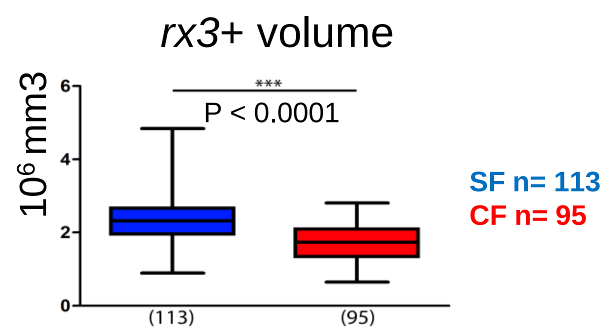
The rx3 transcription factor confers eye/retina identity in the neural plate in all vertebrates

rx3
10hpf



RNA-seq

	Log2 (FC)	P value
Rx3	**-1.8567**	**8.16E-19**

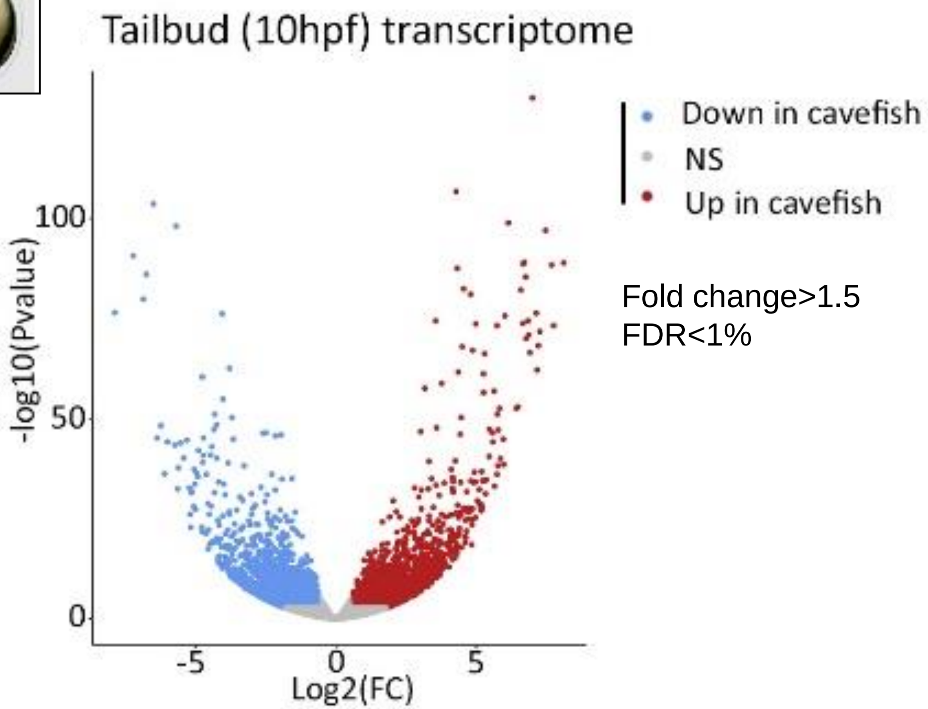


(1) rx3 is expressed at **low level**
> Identity problem?

(2) rx3+ eyefield is 25% **smaller**
> Size problem?

Agnès et al, Development 2022

Comparative transcriptomics

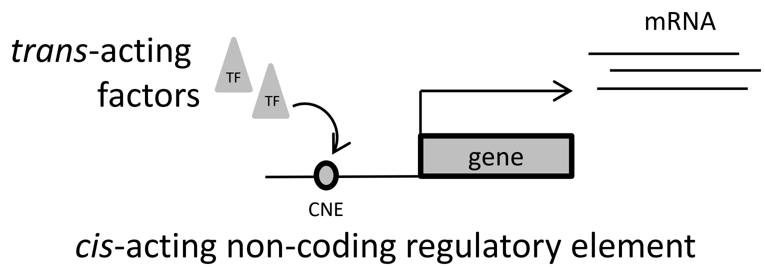


Fold change>1.5
FDR<1%

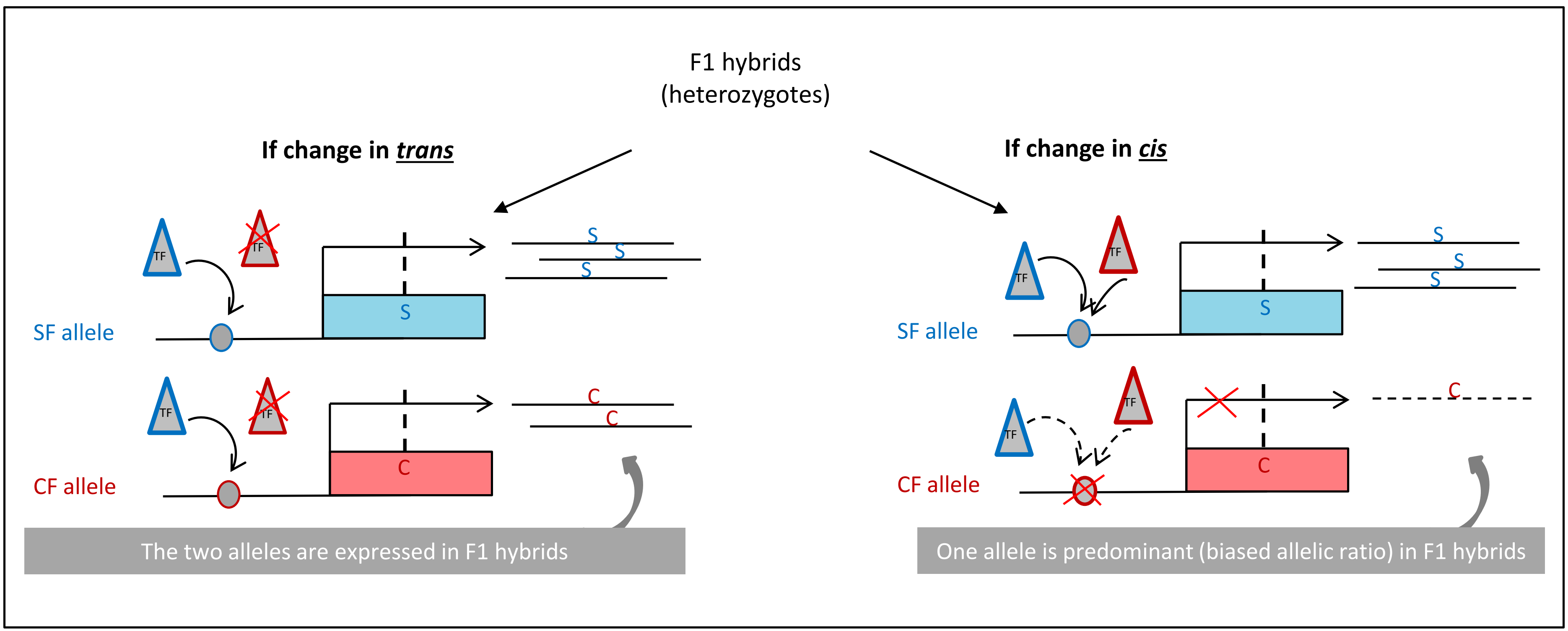
- ~19% of the transcriptome is differentially expressed (4483 transcripts)
- Is it due to *cis*- or *trans*- regulatory divergences?

Leclercq et al, Development 2024

cis- versus *trans*- regulatory changes in cavefish?

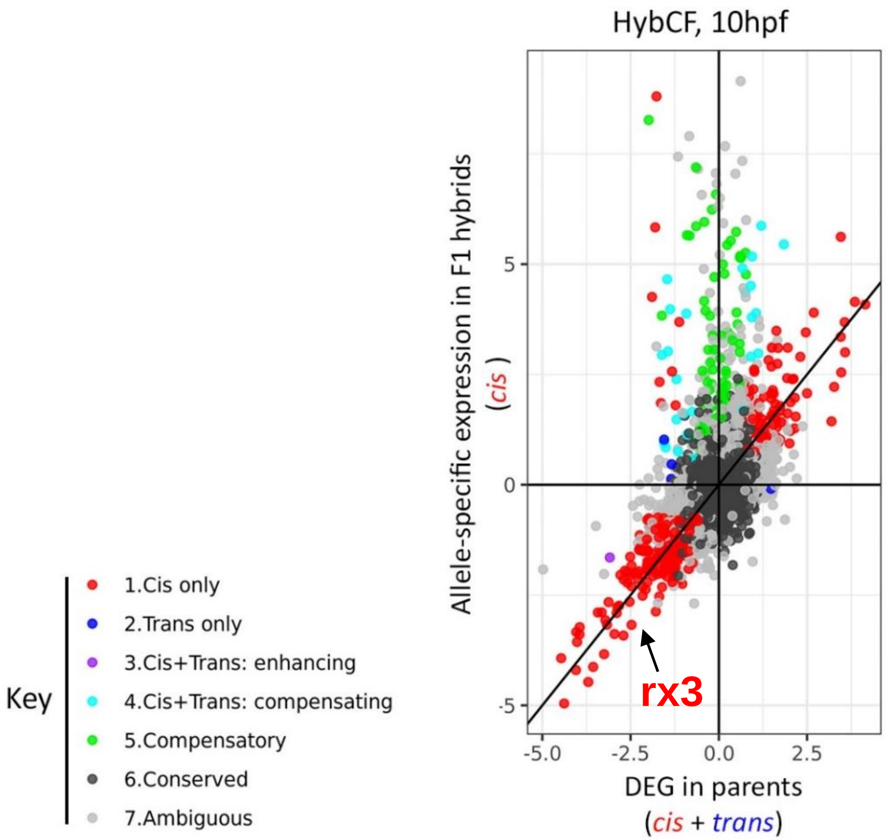


The F1 hybrid test:



NB: fixed polymorphisms are used to recognize transcripts of surface or cave origin in the F1 transcriptome

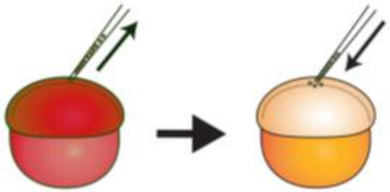
Gene expression regulation in cavefish embryos



Leclercq et al, Development 2024

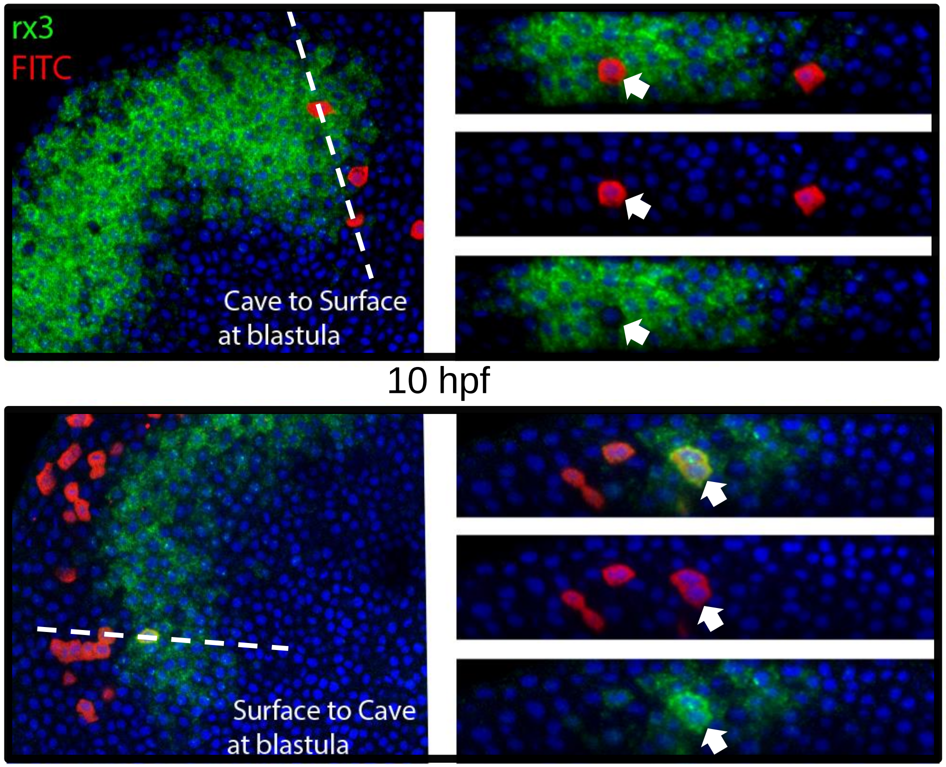
- *Cis*-regulatory changes have a major contribution to evolution of developmental gene expression in cavefish
- A *cis*-regulatory element has changed in the cavefish *rx3* gene and is involved in the developmental evolution of the cavefish eye

Mechanism for control of cellular *rx3* expression level

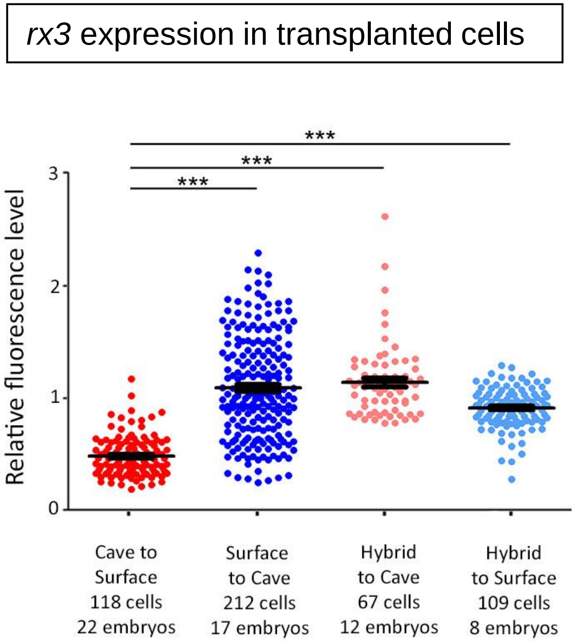


Intermorph cell-transplantation at matching stages

Cave to Surface



Surface to Cave

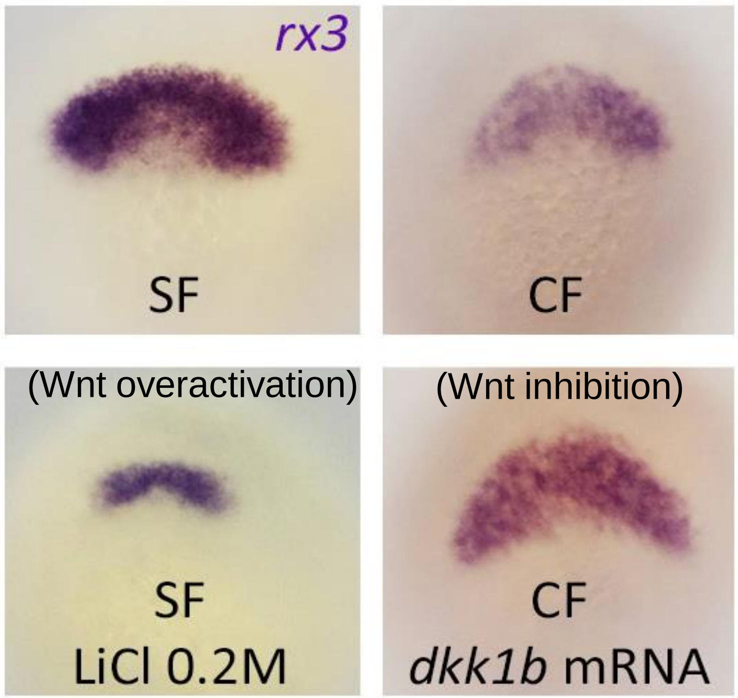


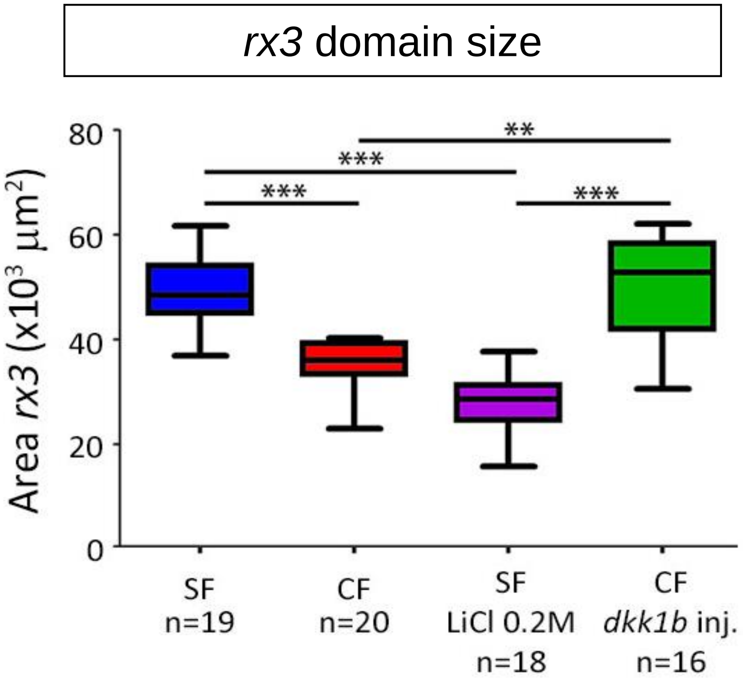
The regulation of cellular *rx3* expression level has evolved in *cis* and is cell-autonomously regulated

Mechanism for control of *rx3* expression domain size

Wildtype :

Manipulation of the Wnt pathway :



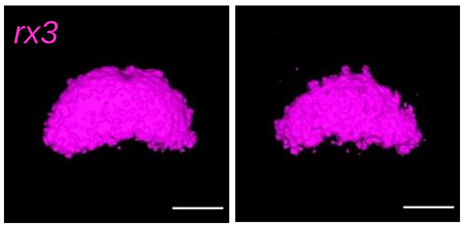


rx3 domain size depends on non-autonomous Wnt signaling mechanisms

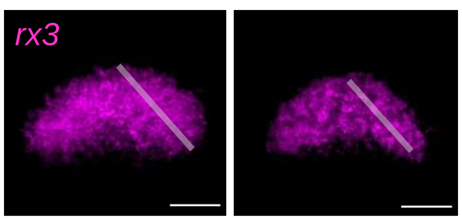
rx3 regulation : uncoupling the control of eye size and optic fate specification

Surface fish   Cavefish

10hpf



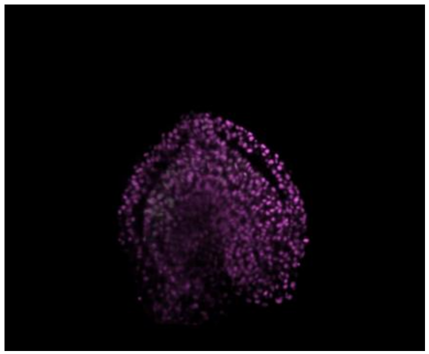
eyefield size



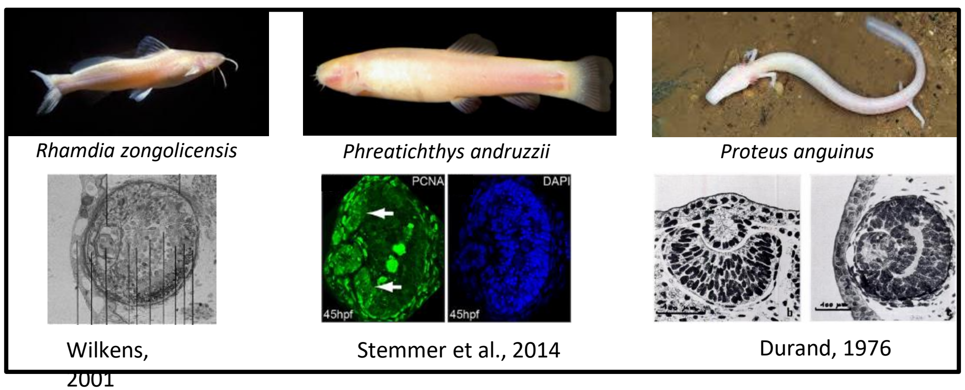
expression level

Mechanism	Outcome
Change in non-autonomous cell-cell signaling	Change in eye size
Change in *cis*-regulation, cell-autonomous	Change in optic cells specification and behaviors

Why do cavefish first develop eyes???
A developmental constraint to morphological evolution



- The coordonated cell movements of eye morphogenesis must proceed for the rest of the forebrain to be properly formed.



- Forming eyes is absolutely required for a vertebrate embryo
- There are shapes and anatomies that developmental processes cannot produce

Conclusions - Summary

A conserved plan of organization for the vertebrate brain

> Morphogenetic variations in sizes and shapes (examples)

An important role for signaling centers in brain evolution

> Both for emergence of novelties and for diversification (examples)

An important role for changes in *cis*-regulatory sequences

> Modularity of enhancers and spatio-temporal control of gene expression (examples)