Tyrosinkinase Ror2: Funktion, klinische Variabilität und Interaktionsnetzwerk

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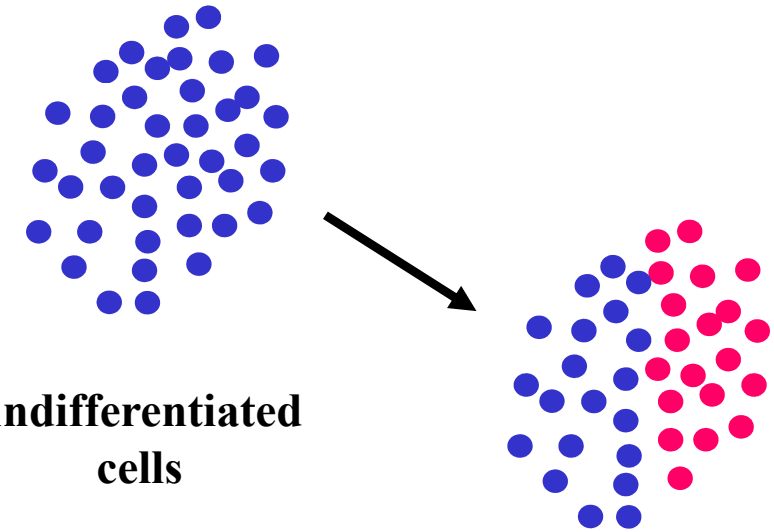
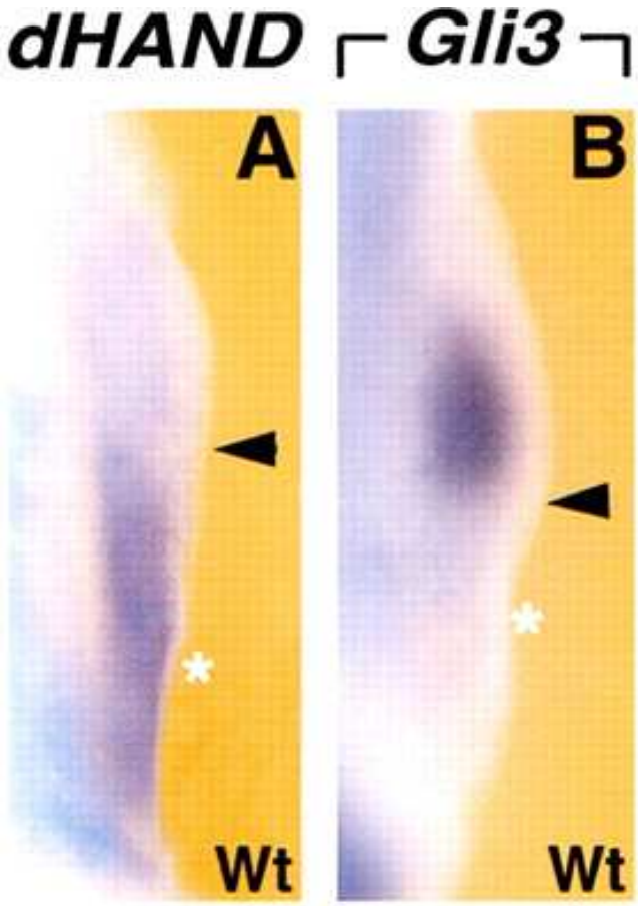
patterning, organogenesis, differentiation

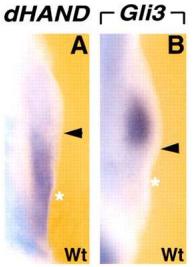


undifferentiated cells

patterning:
gene expression changes



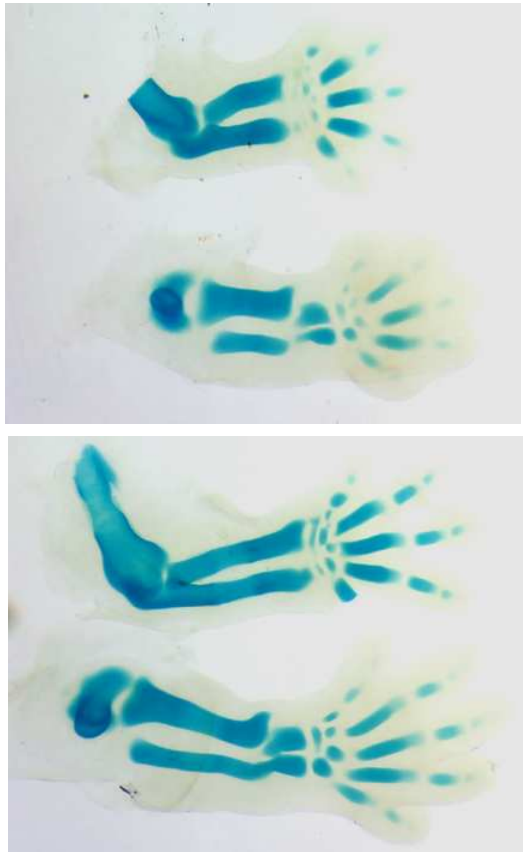
patterning, organogenesis, differentiation



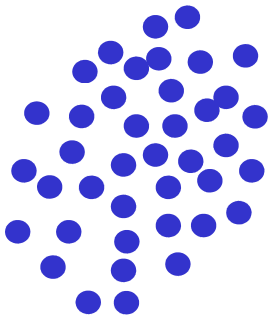
undifferentiated cells

patterning: gene expression changes

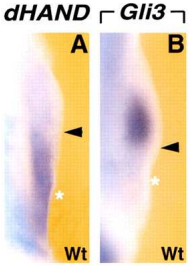
organogenesis: morphological shaping

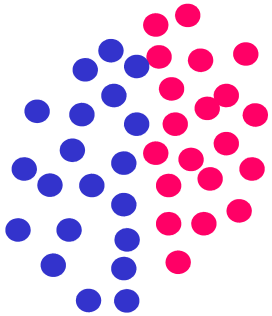


patterning, organogenesis, differentiation

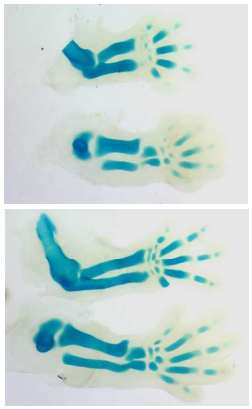


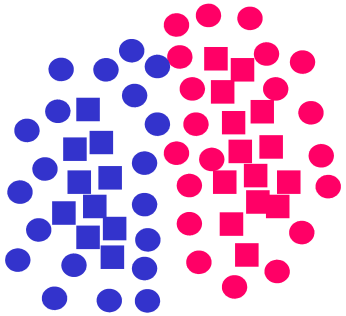
undifferentiated cells



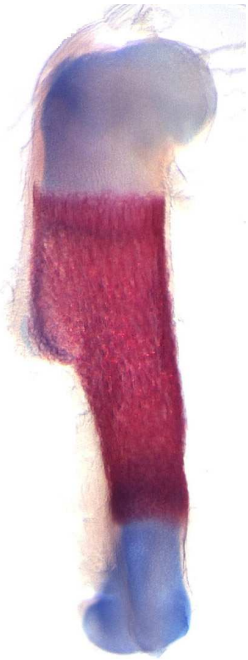


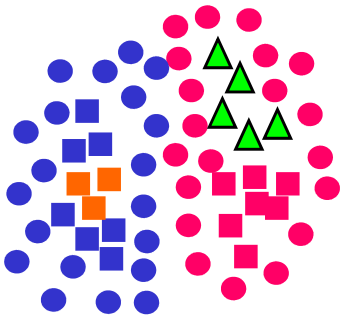
patterning:
gene expression changes





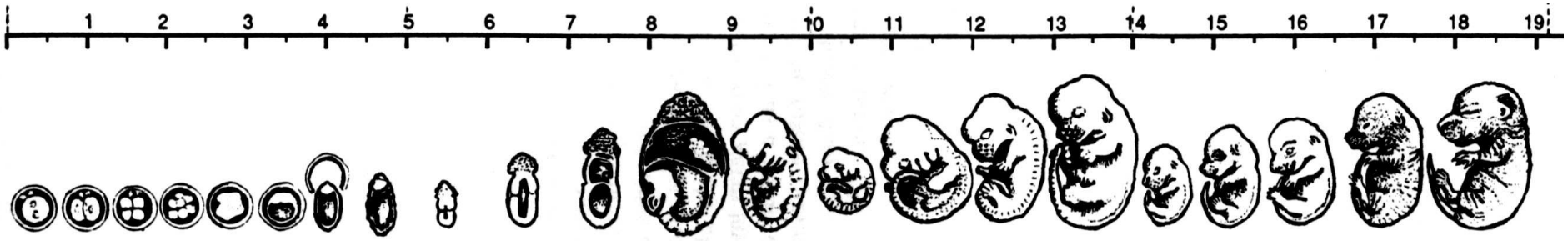
organogenesis:
morphological
shaping

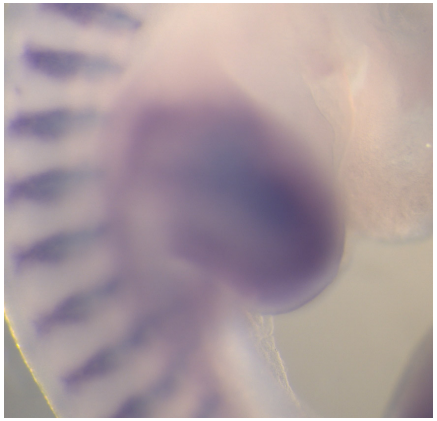


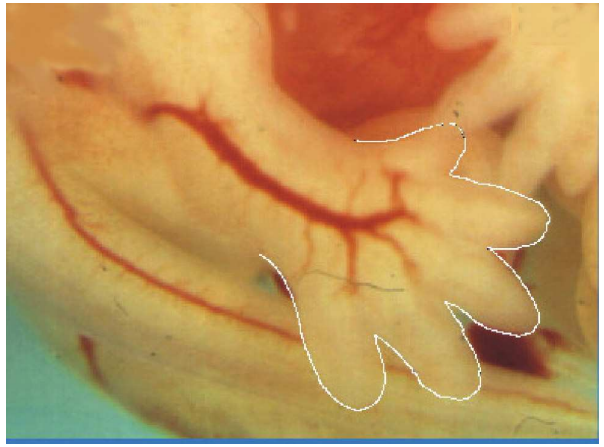


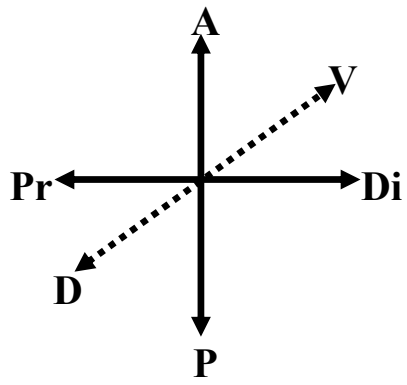
differentiation:
emergence of
new cell types
within the organ

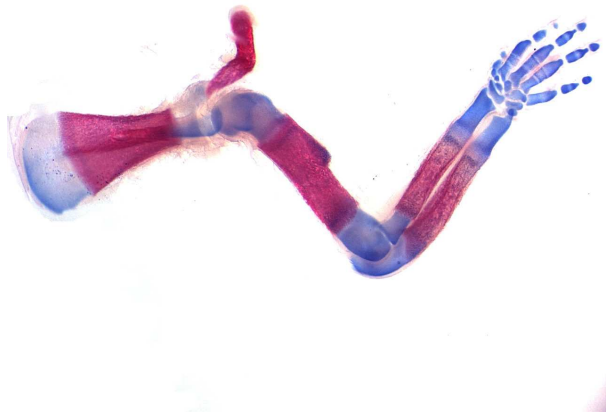
patterning, organogenesis, differentiation

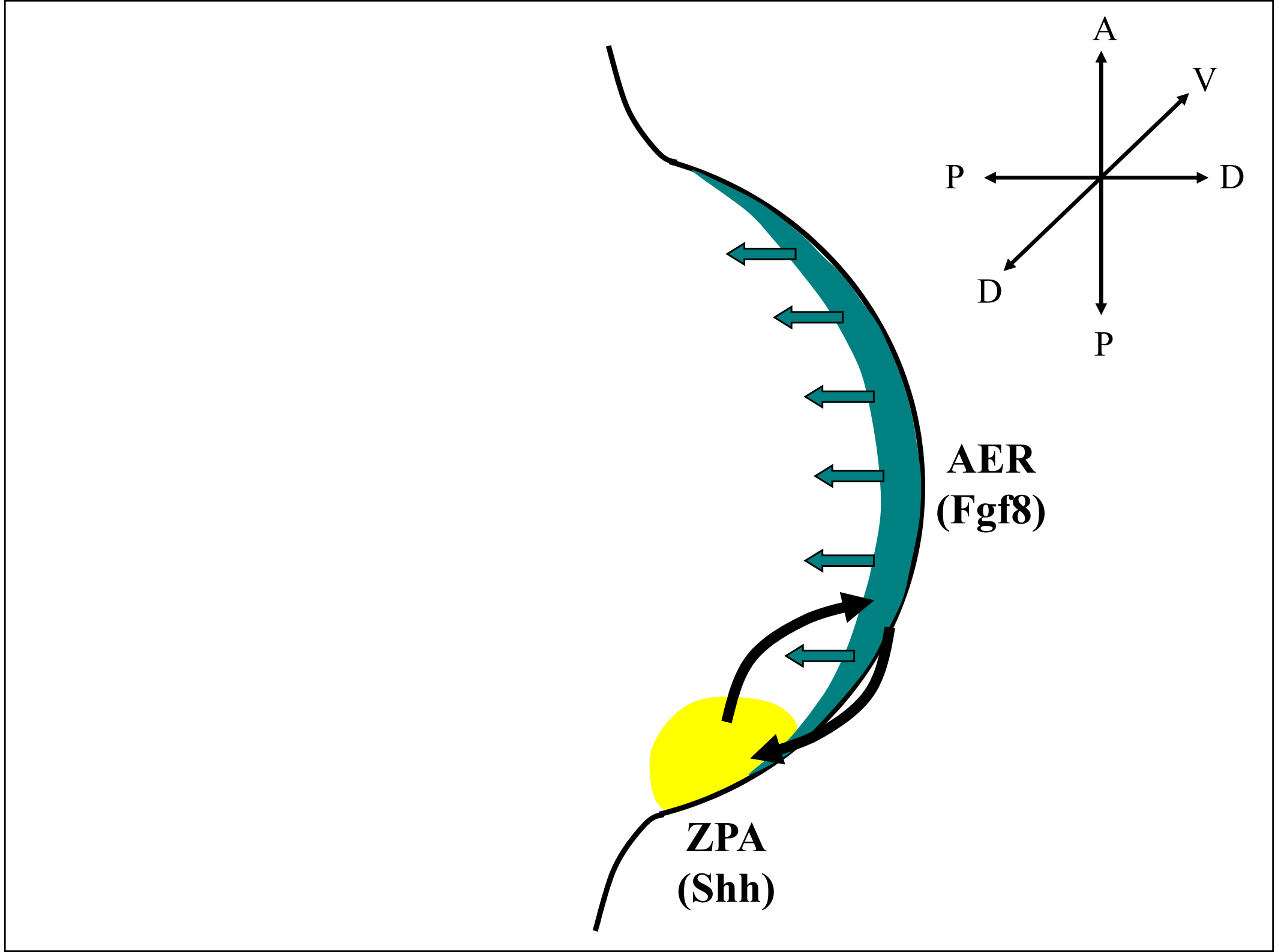


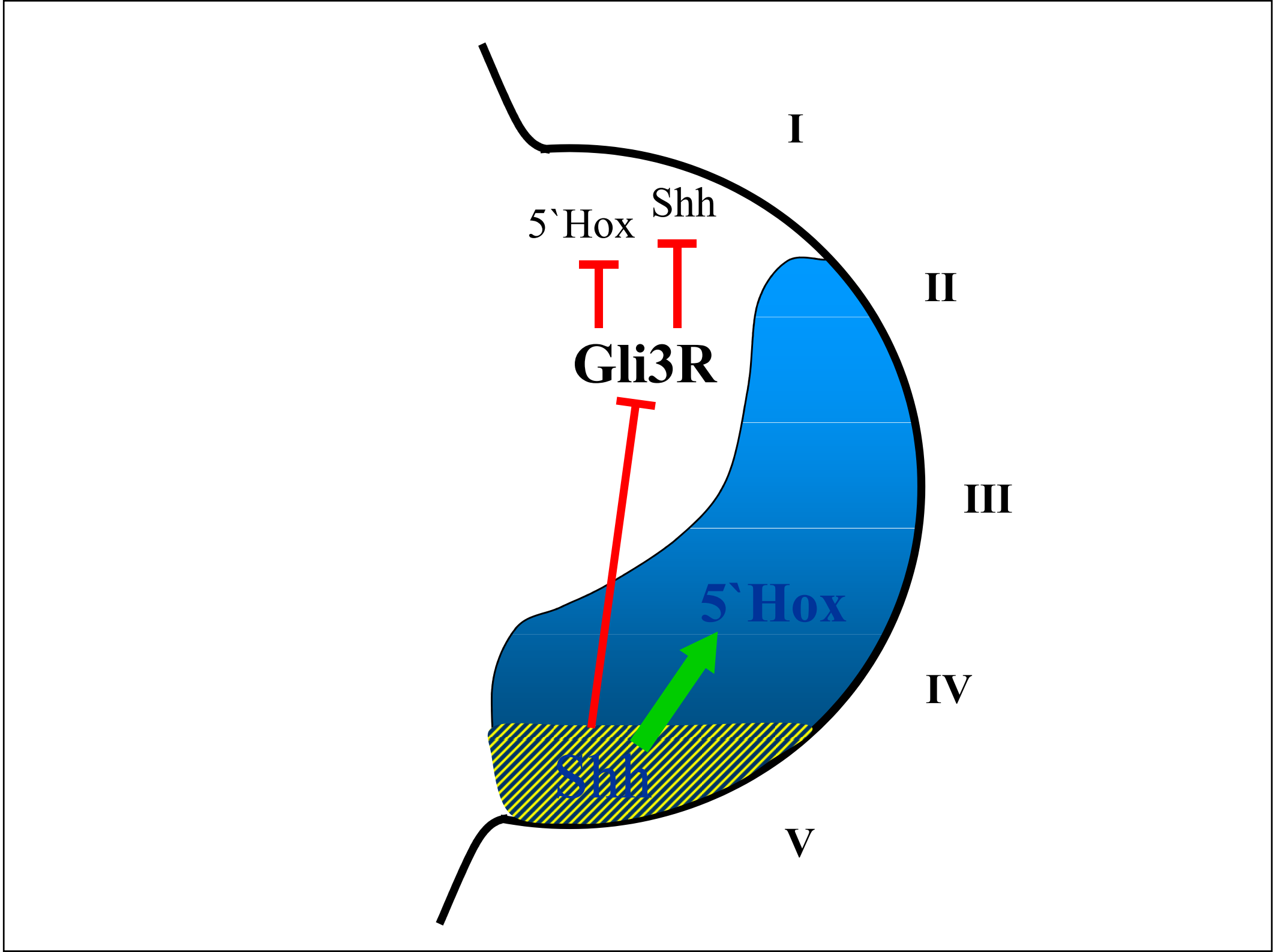


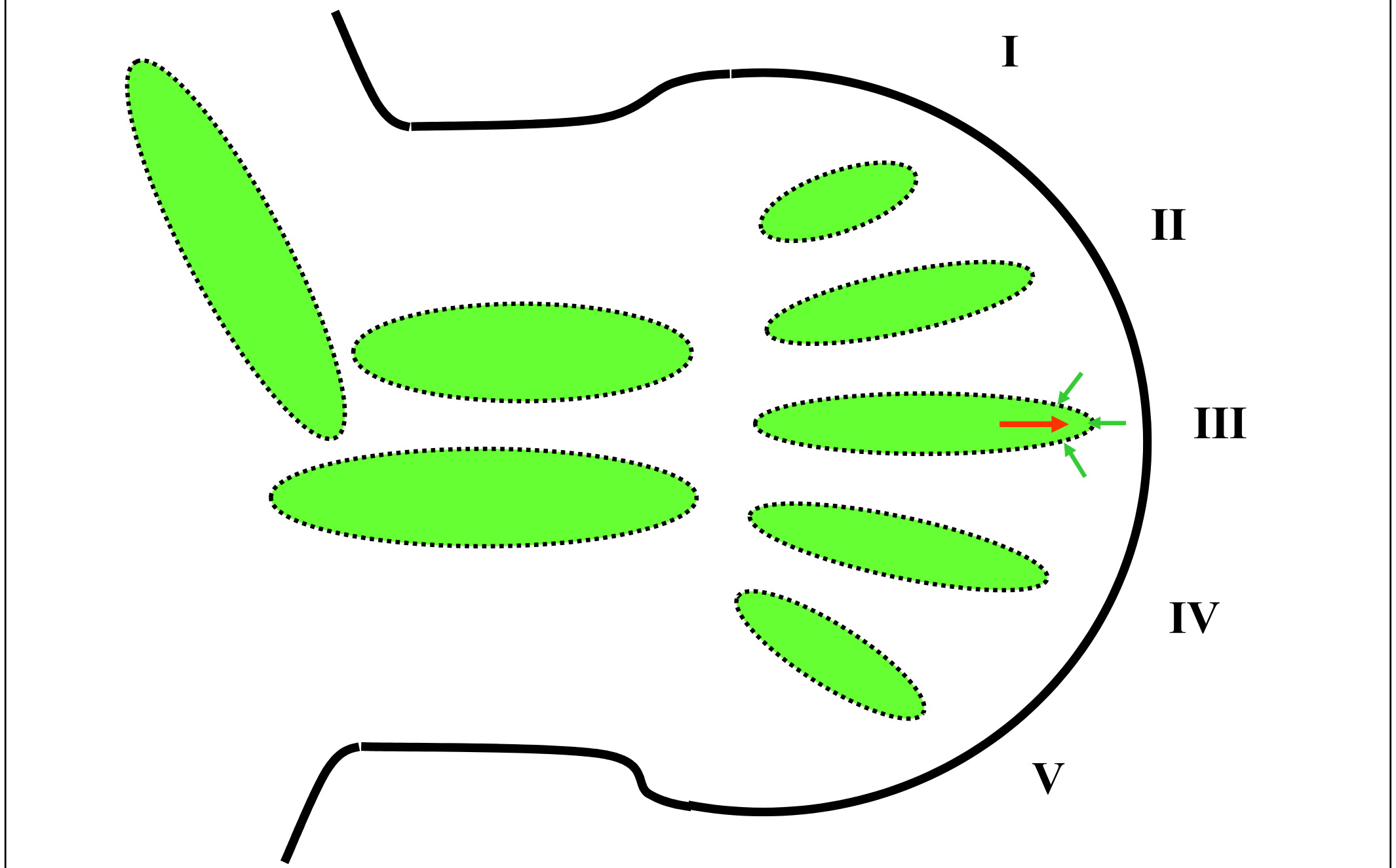


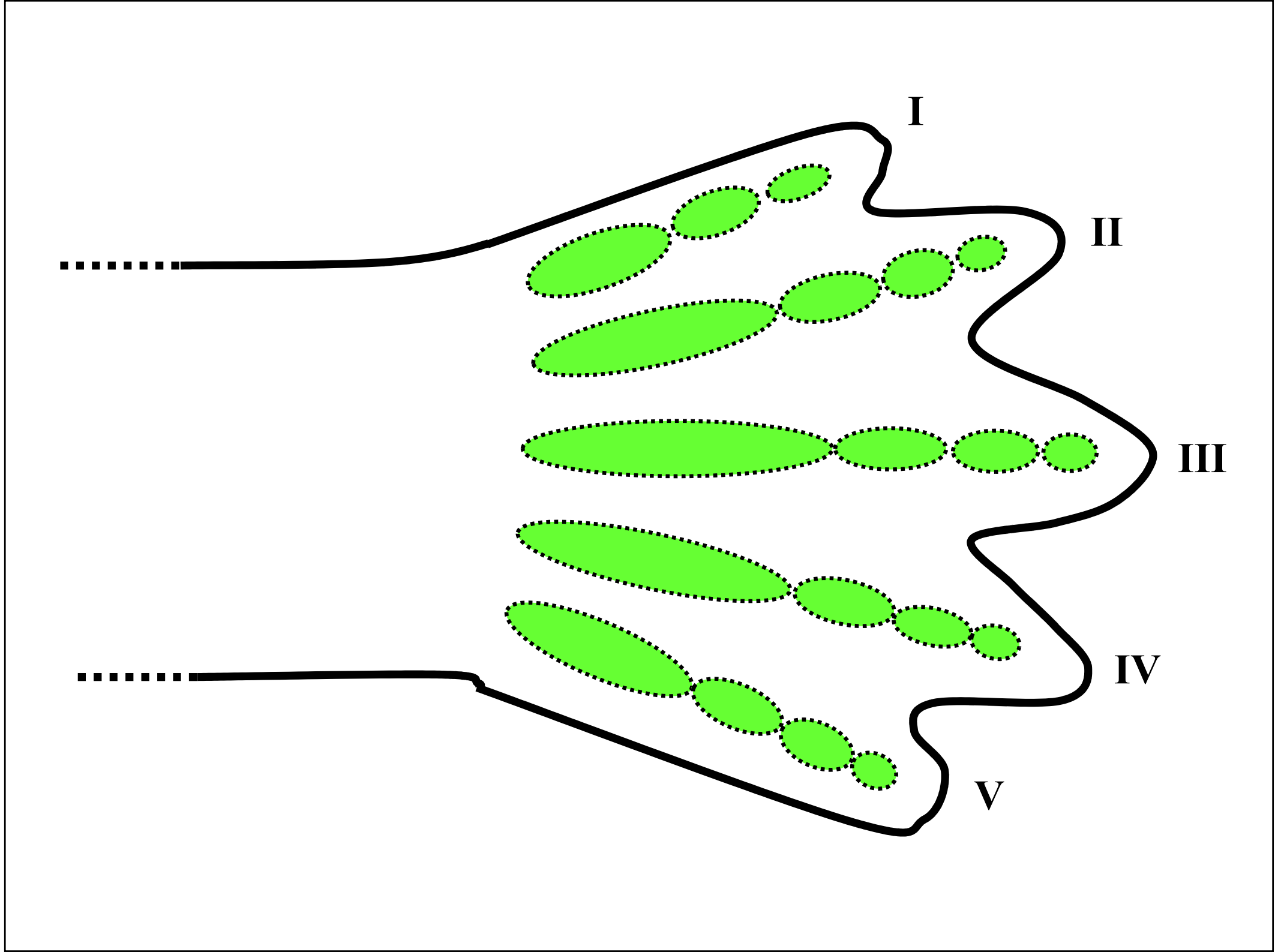




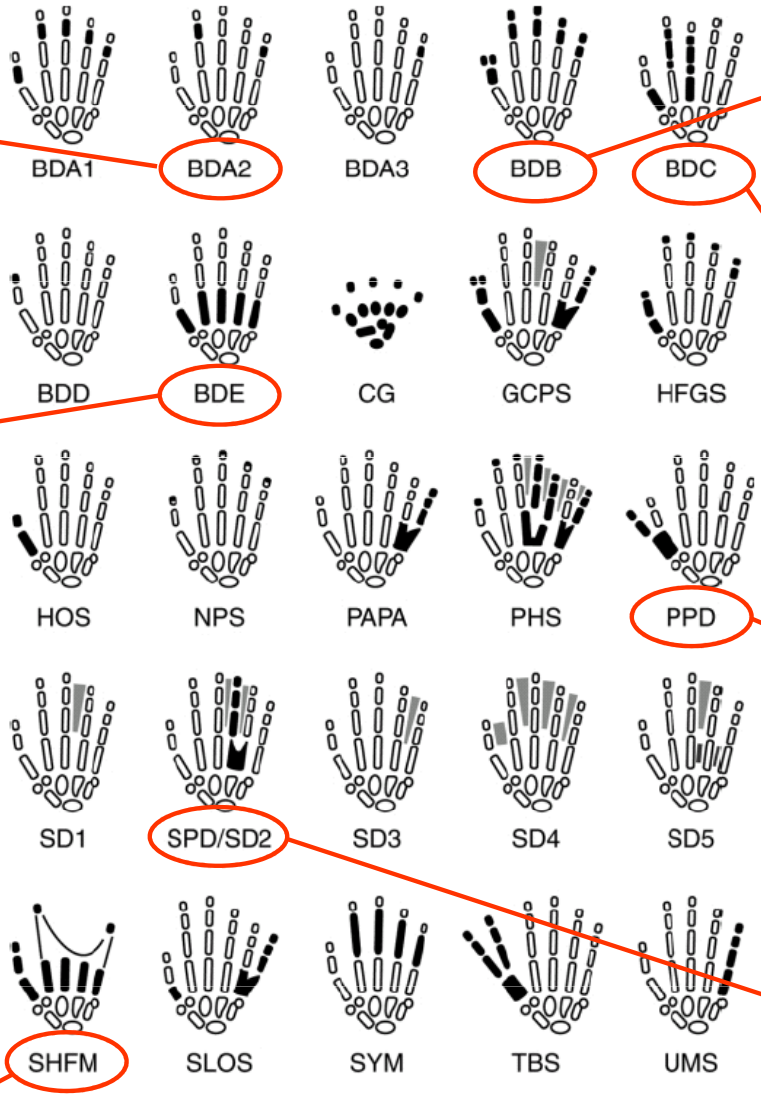

A
V
P
D
D
P
AER
(Fgf8)
ZPA
(Shh)

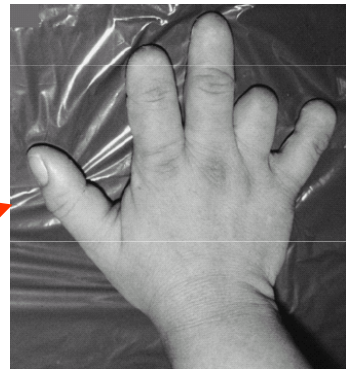

I
5`Hox
Shh
II
Gli3R
III
5`Hox
IV
Shh
V

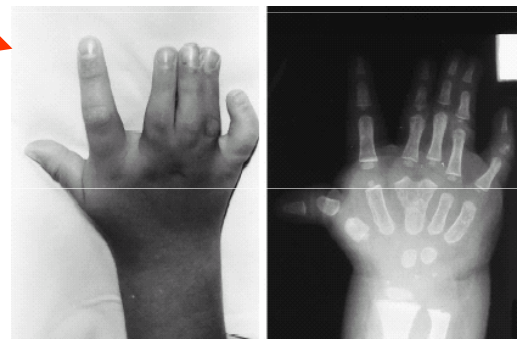

I
II
III
IV
V


I
II
III
IV
V

Hand malformations

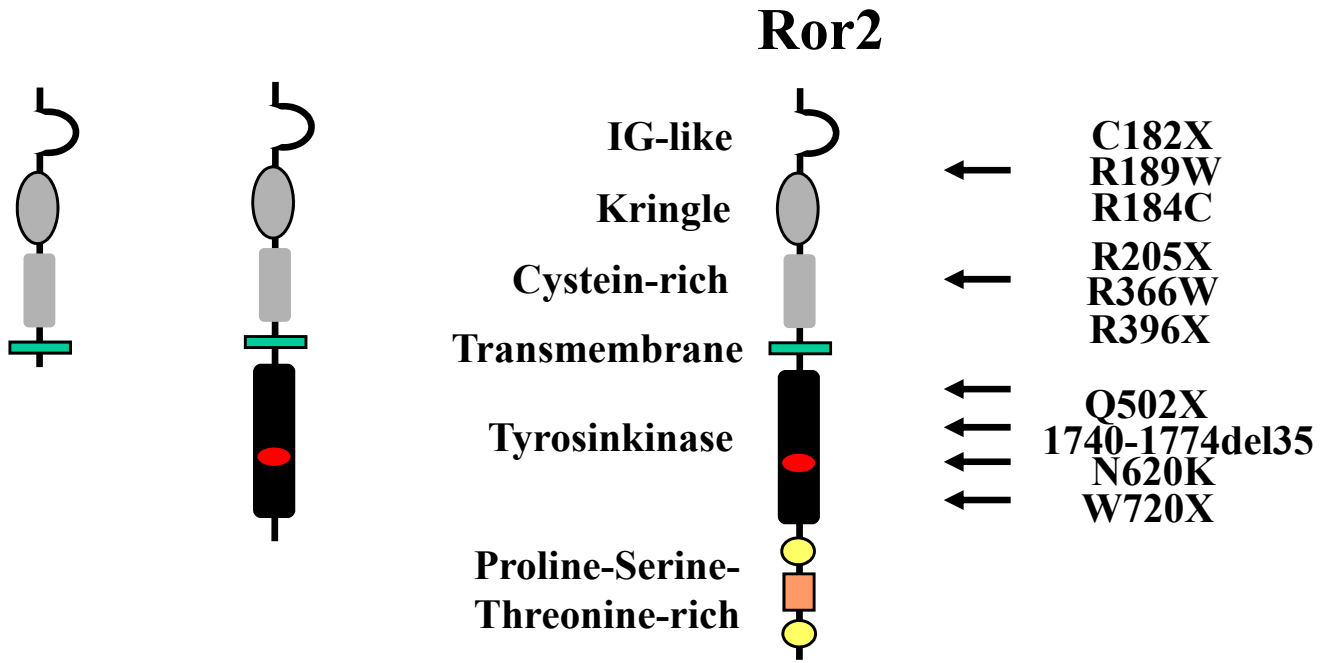






Mutations in Ror2 cause dominant Brachydactyly type B (BDB)

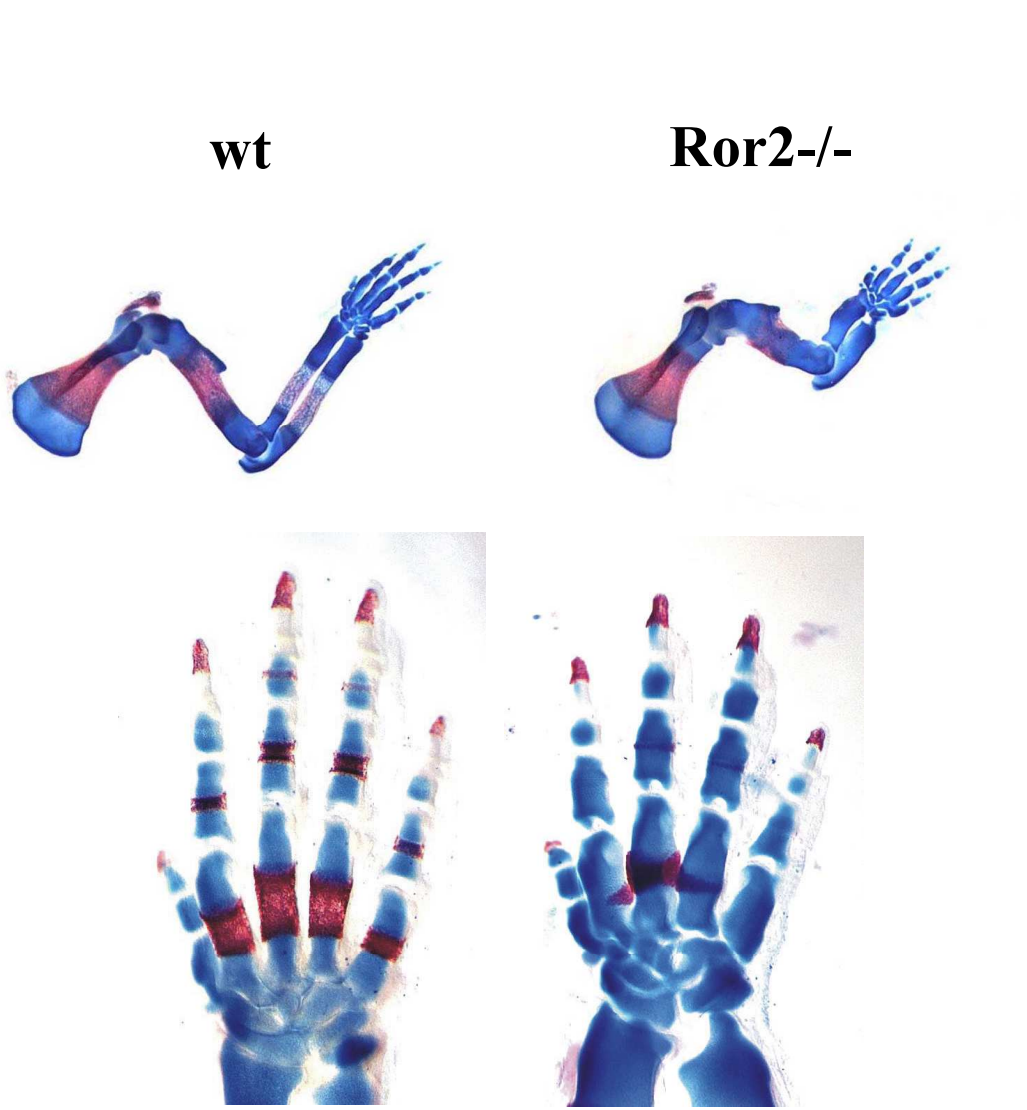
...and recessive Robinow syndrome (RRS)

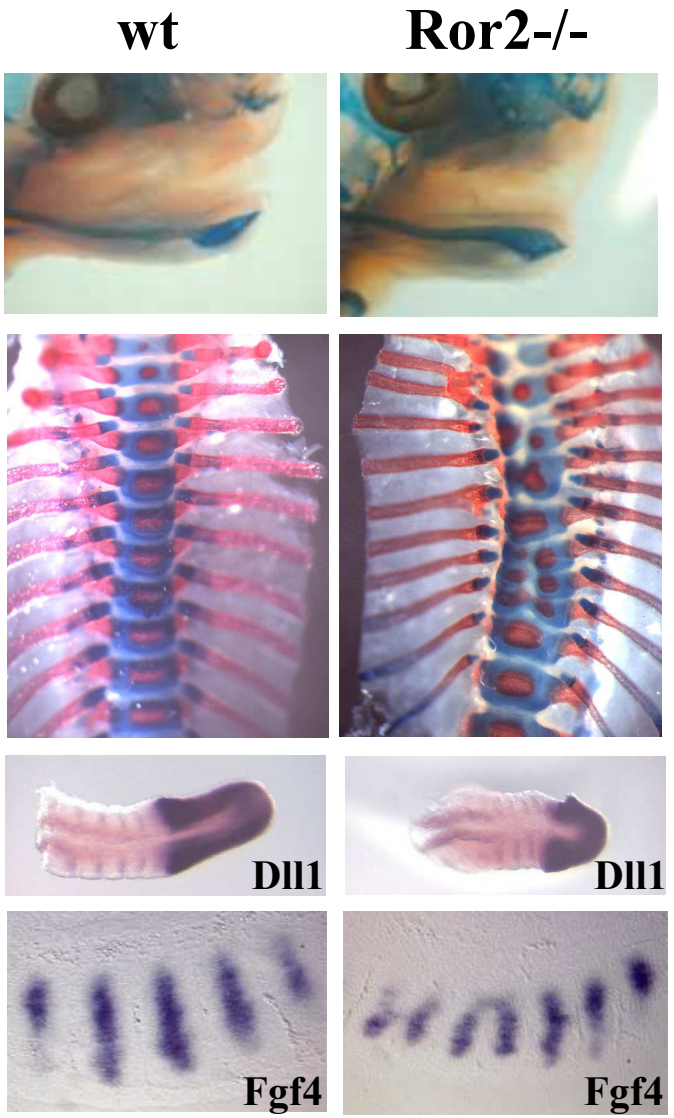


BDB

RRS

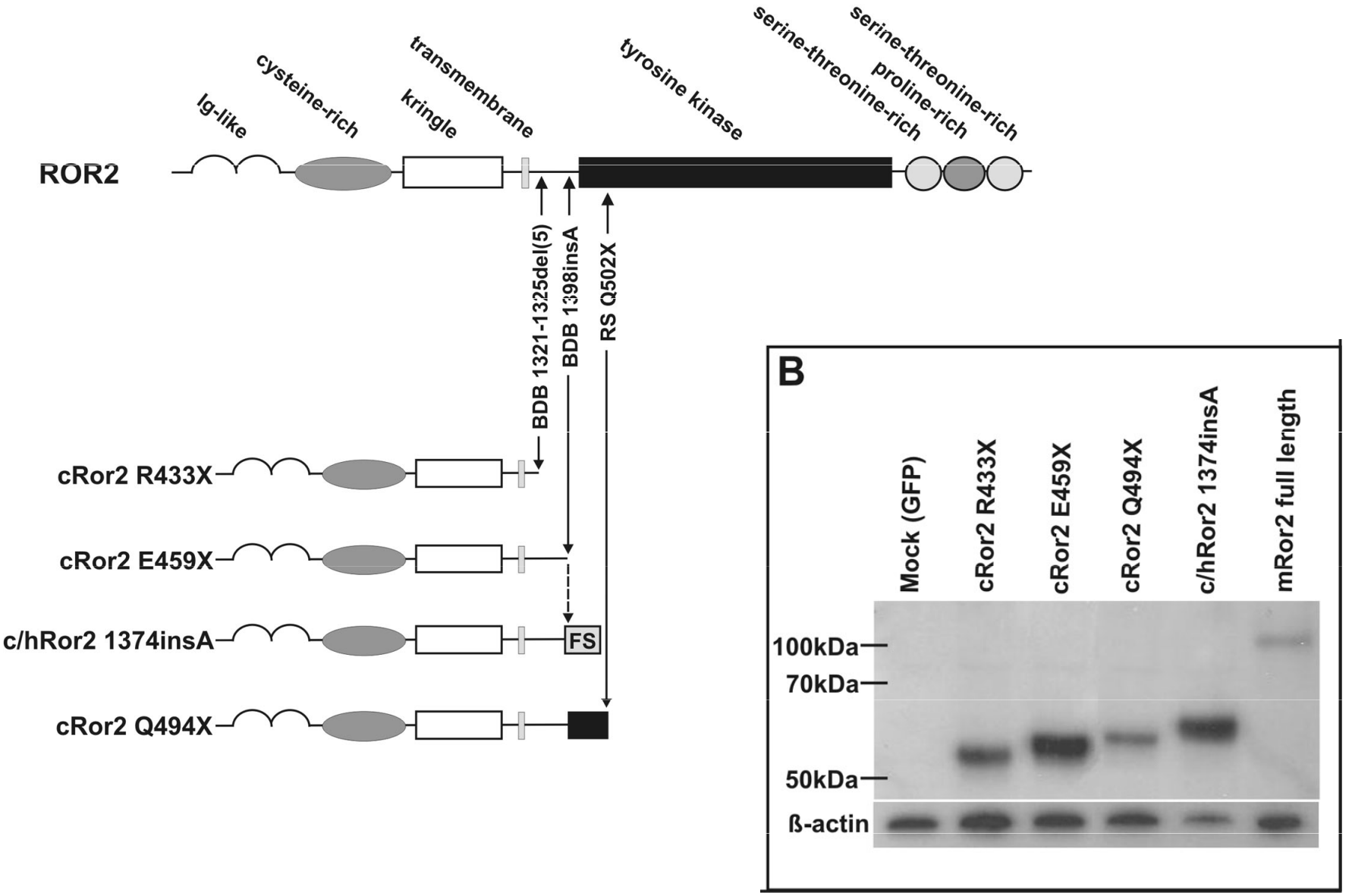
Ror2 Deficient Mice (delEx2)
as a Model for Recessive Robinow Syndrome



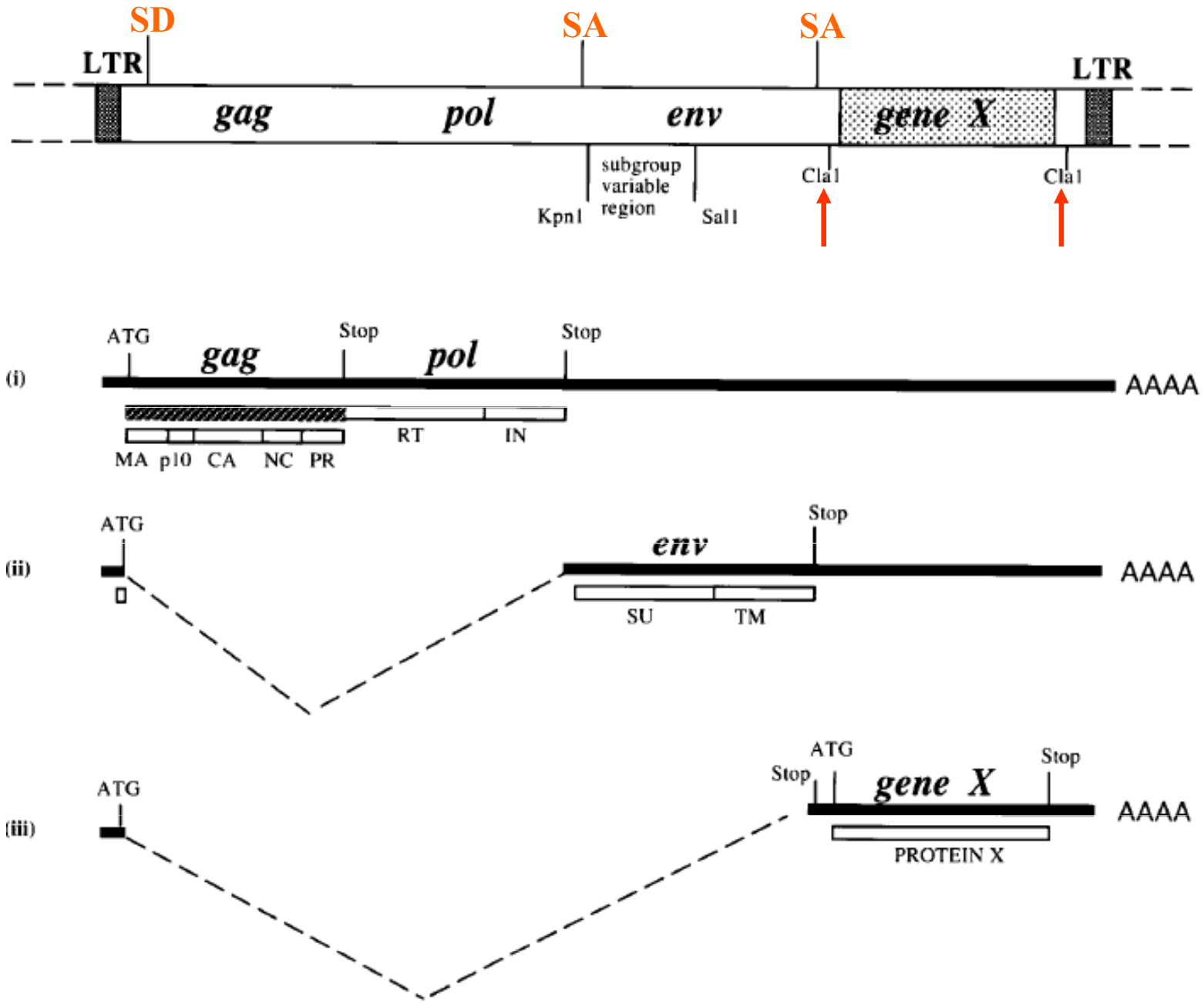


(Schwabe et al. Dev Dyn 2004)

Chicken Ror2 Constructs for Retroviral Overexpression

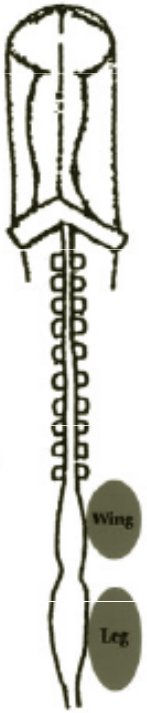


Retroviral Overexpression of Genes in the Chick Embryo

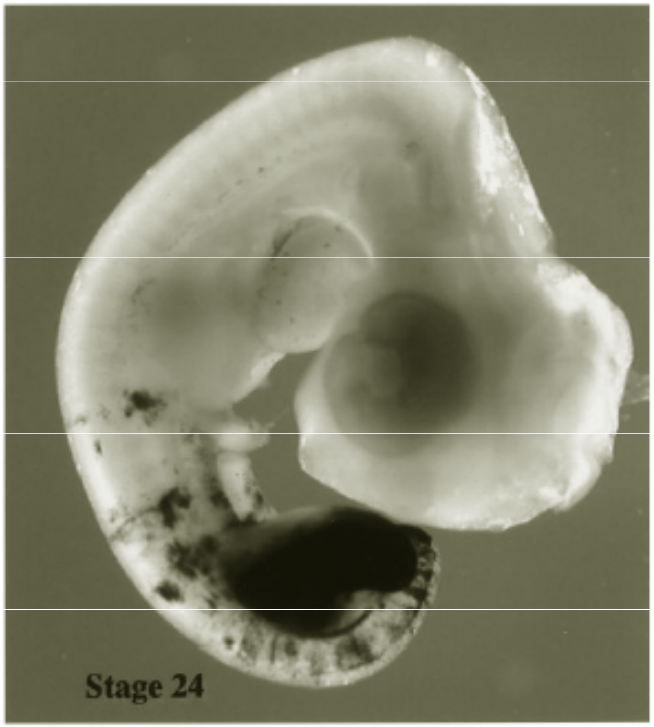


from Logan and Tabin, 1998

Injection into Limb Fields



Stage 10



Limitations of the RCAS system:

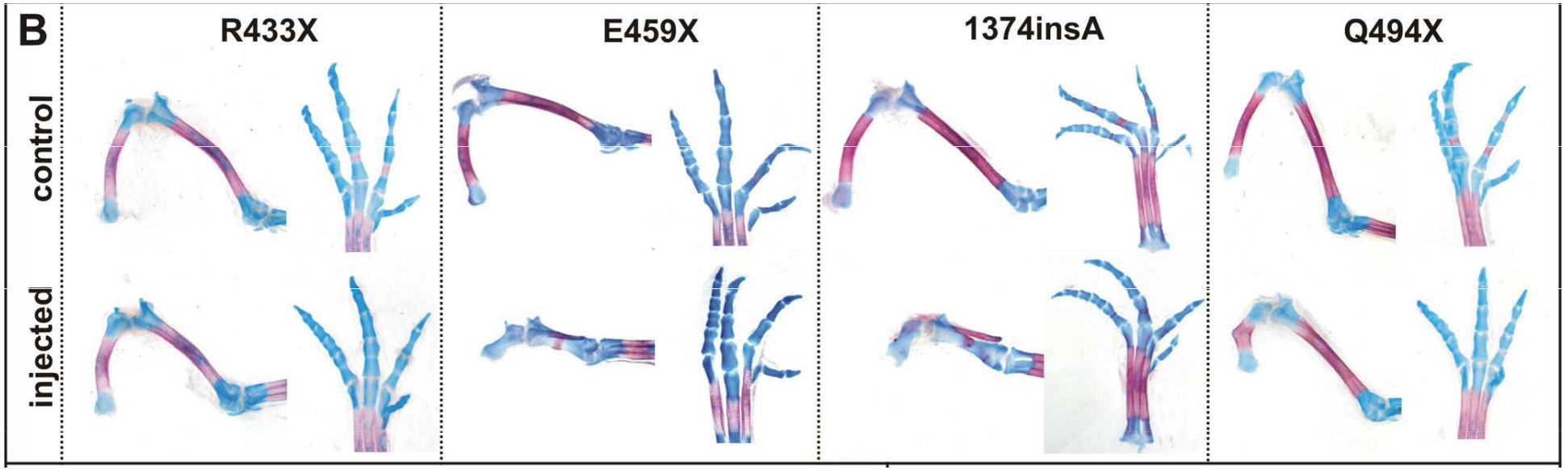
-maximum insert size ~2.4 kb

-RCAS infects any replicating cell → no cell-type specific overexpression

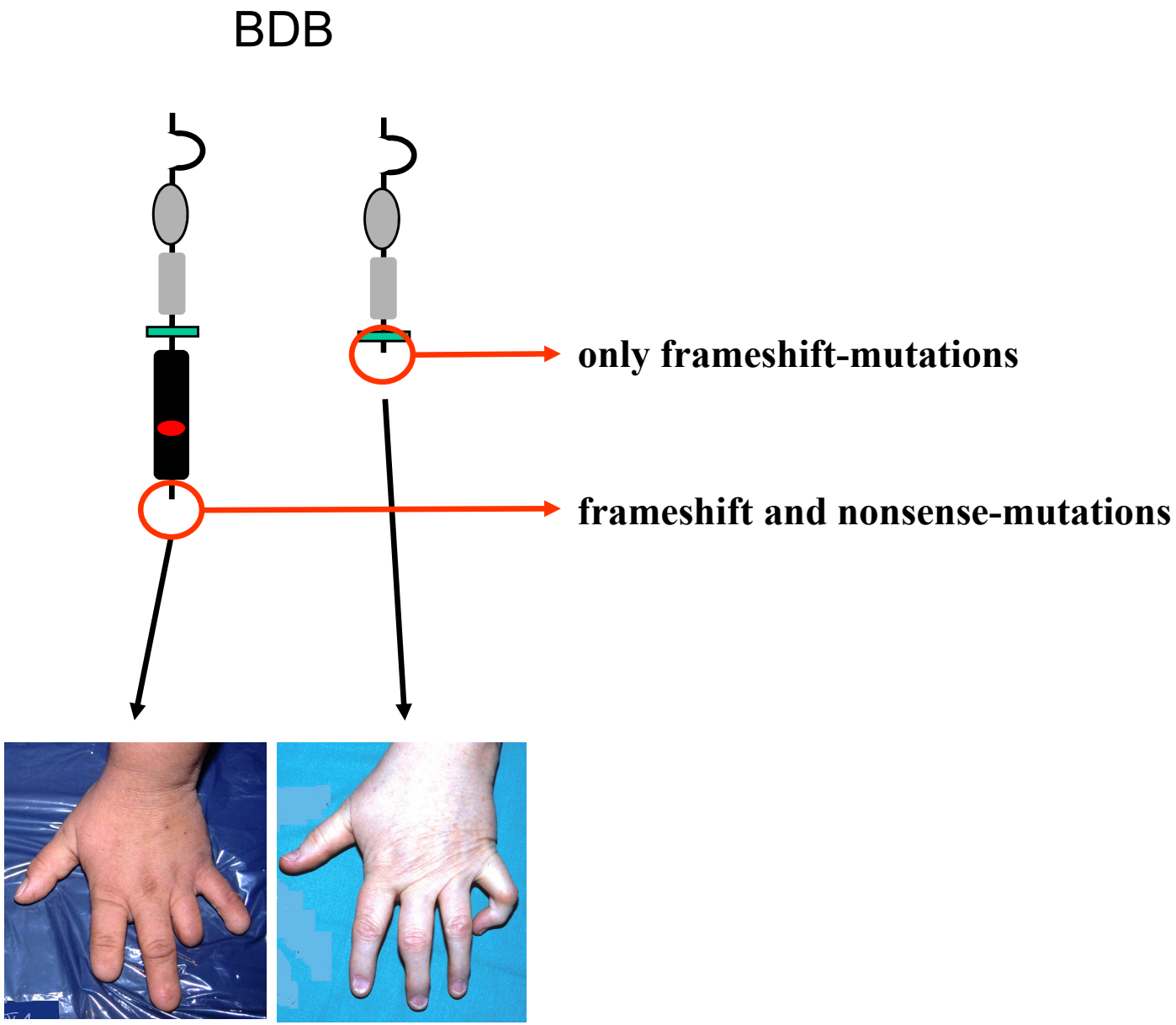
-variable efficiency of virus delivery, targeting of injection

from Logan and Tabin, 1998

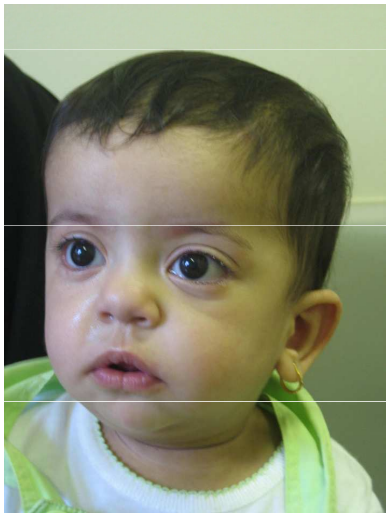
Overexpression of Ror2 Mutants in Chick Limb Field

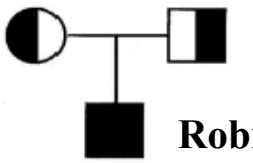


Genotype / Phenotype correlations: BDB



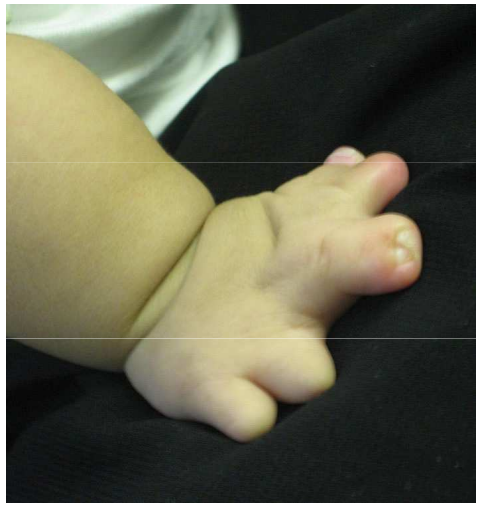
RRS Mutation C1324T → R442X





unaffected

Robinow syndrome
+ Brachydactyly



Mischphänotypen sind abhängig von Position und Art der Mutation

Dominant BDB

TM

1320 — **1321-1325del5 → FS**

1330

1340

1350

1360 — **1367insC → FS**

1370

1380 — **splice site → FS**

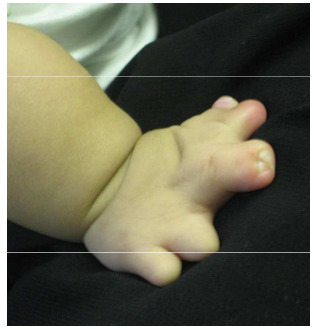
1390 — **1398insA → FS**

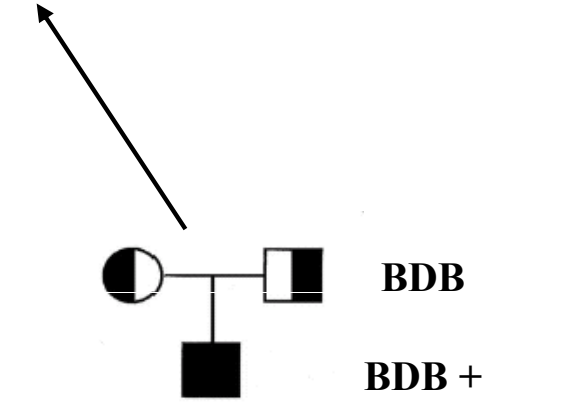
1400 — **1399insT → FS**

TK

Recessive Robinow syndrome
+Brachydaktyly (not dominant BDB!!)

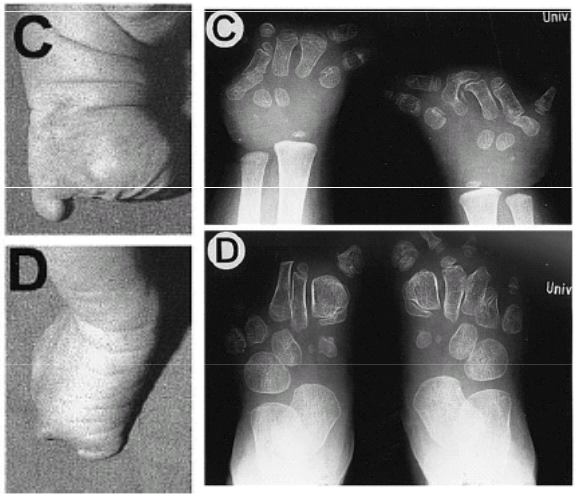
C1324T → Stop



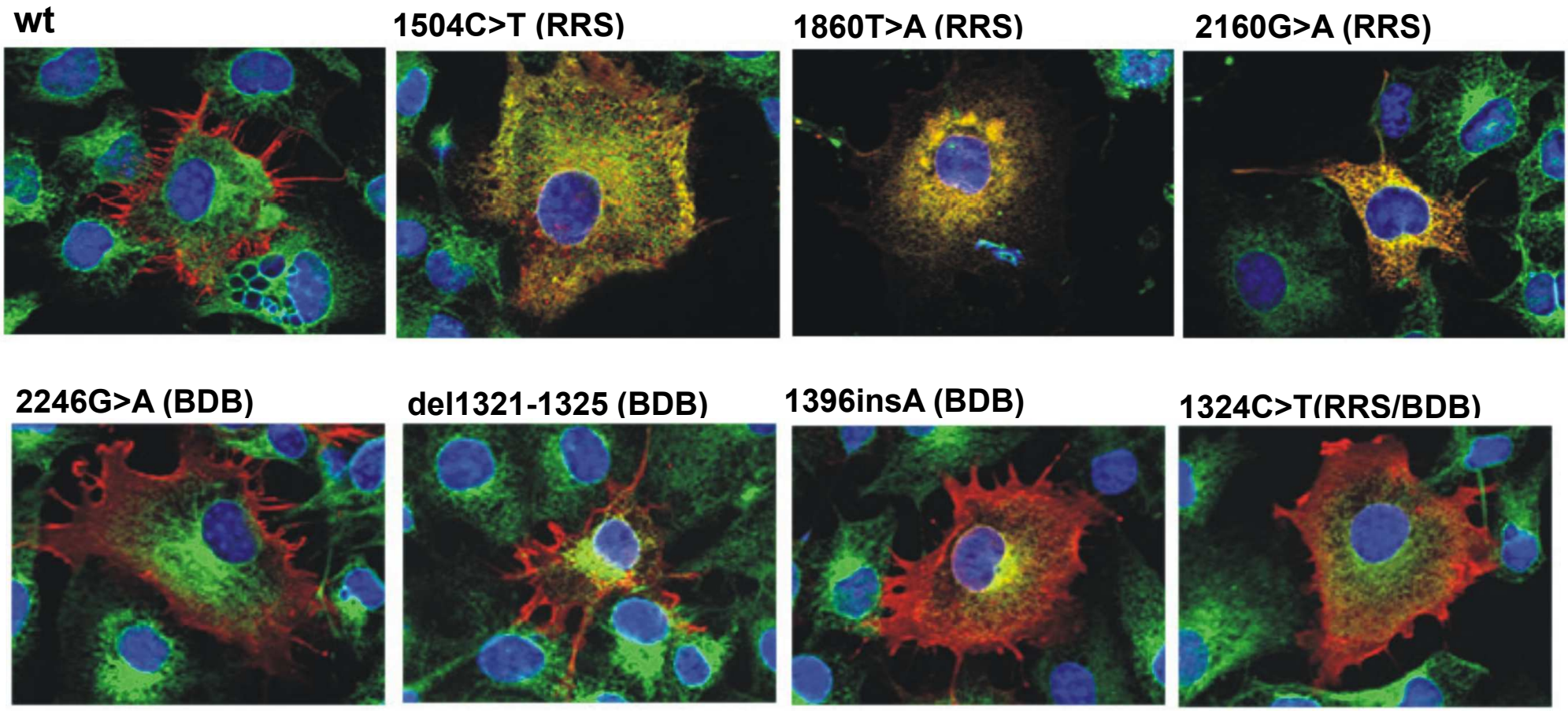


BDB

BDB +
Robinow features!



Intracellular localization of Ror2 wt and mutant protein



ROR2

BAP31

Difference BDB / RRS

TM

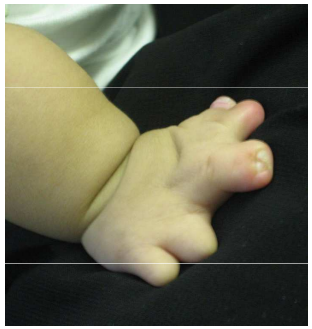
BDB

RRS

1320

1321-1325del5 → FS

C1324T → Stop



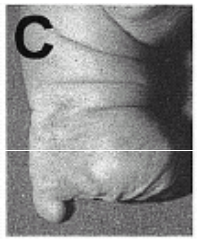
1330

1340

1350

1360

1367insC → FS



1370

1380

splice site → FS

1390

1398insA → FS

1400

1399insT → FS

TK

RRS

C1504T → Stop

membrane localization

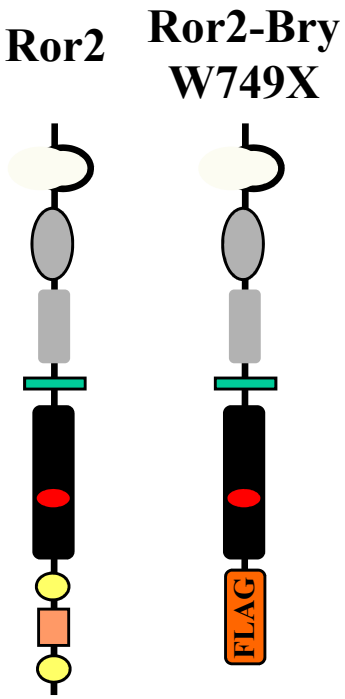
dominant-negative effect by truncated forms of Ror2

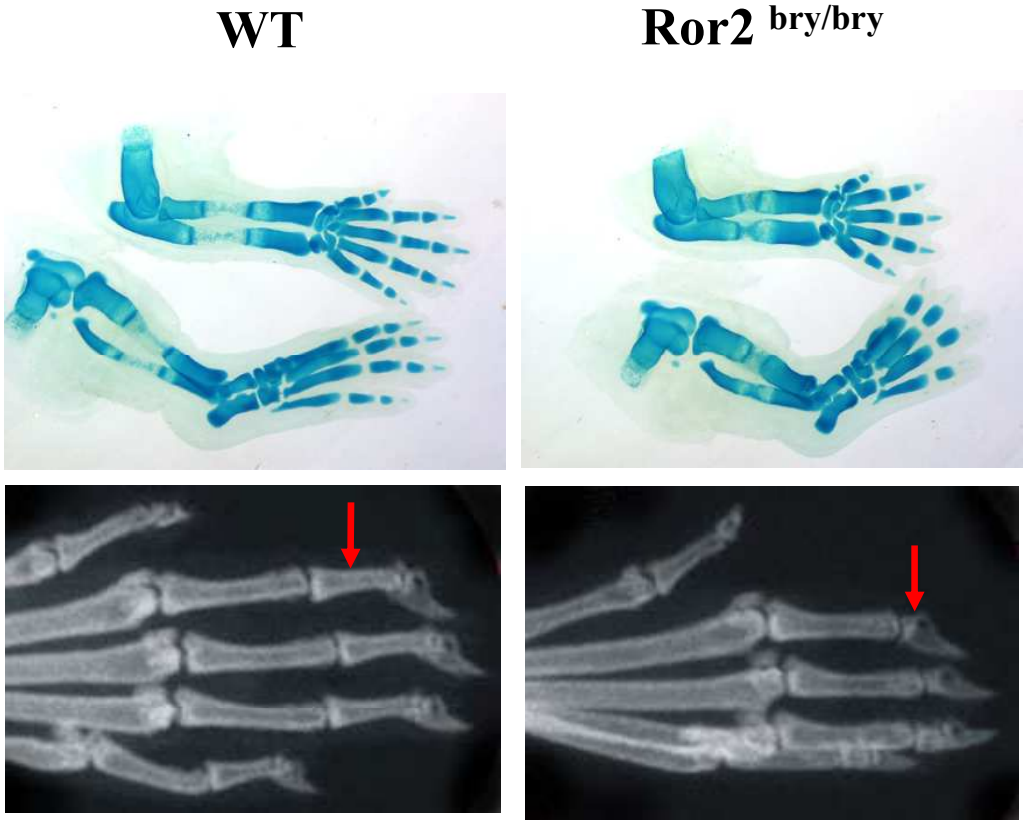
intracellular retention

loss-of-function probably unfolded protein response

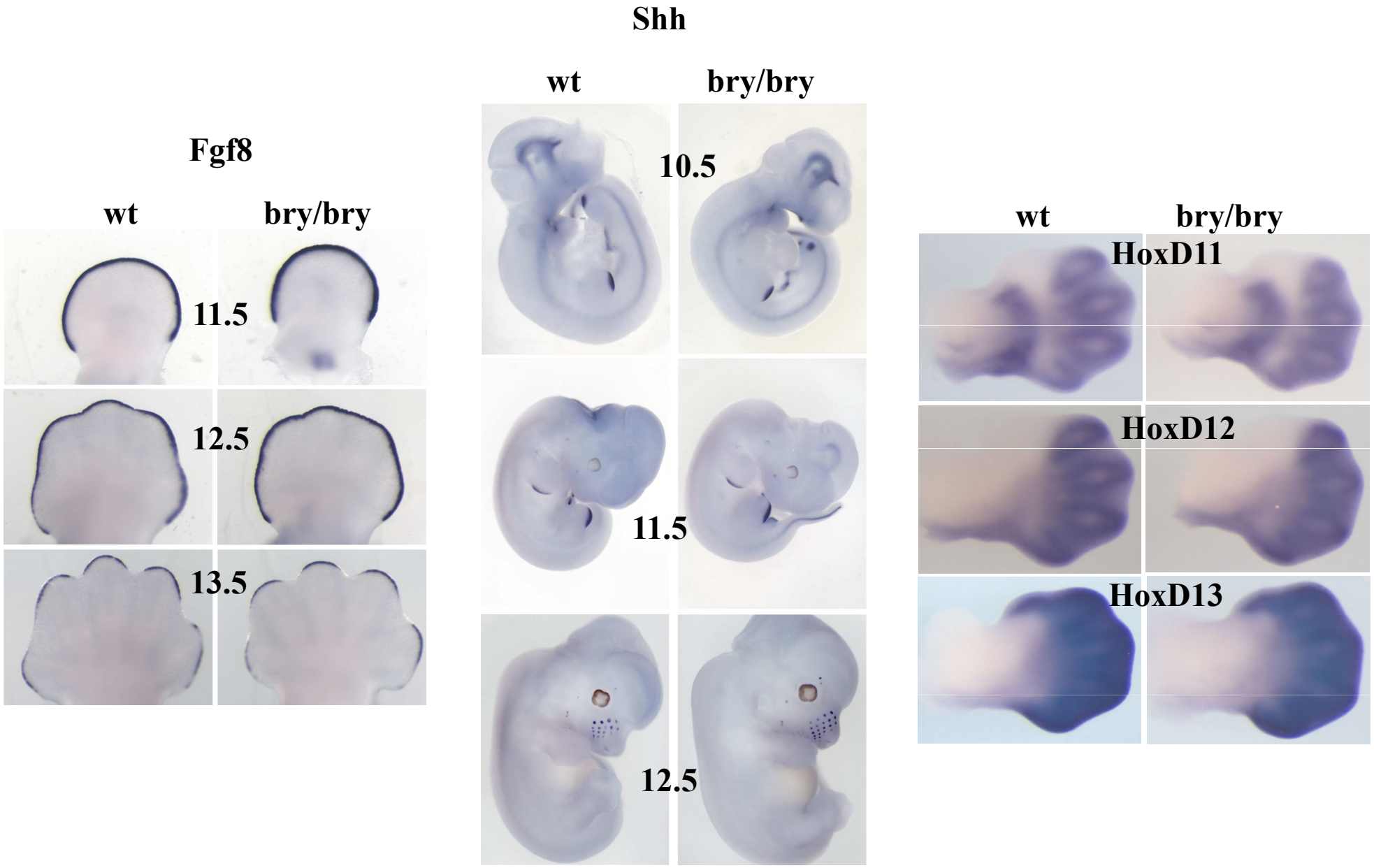
Die Ror2-Bry (W749X) Maus

Aris Economides / Regeneron Inc., Tarrytown, NY

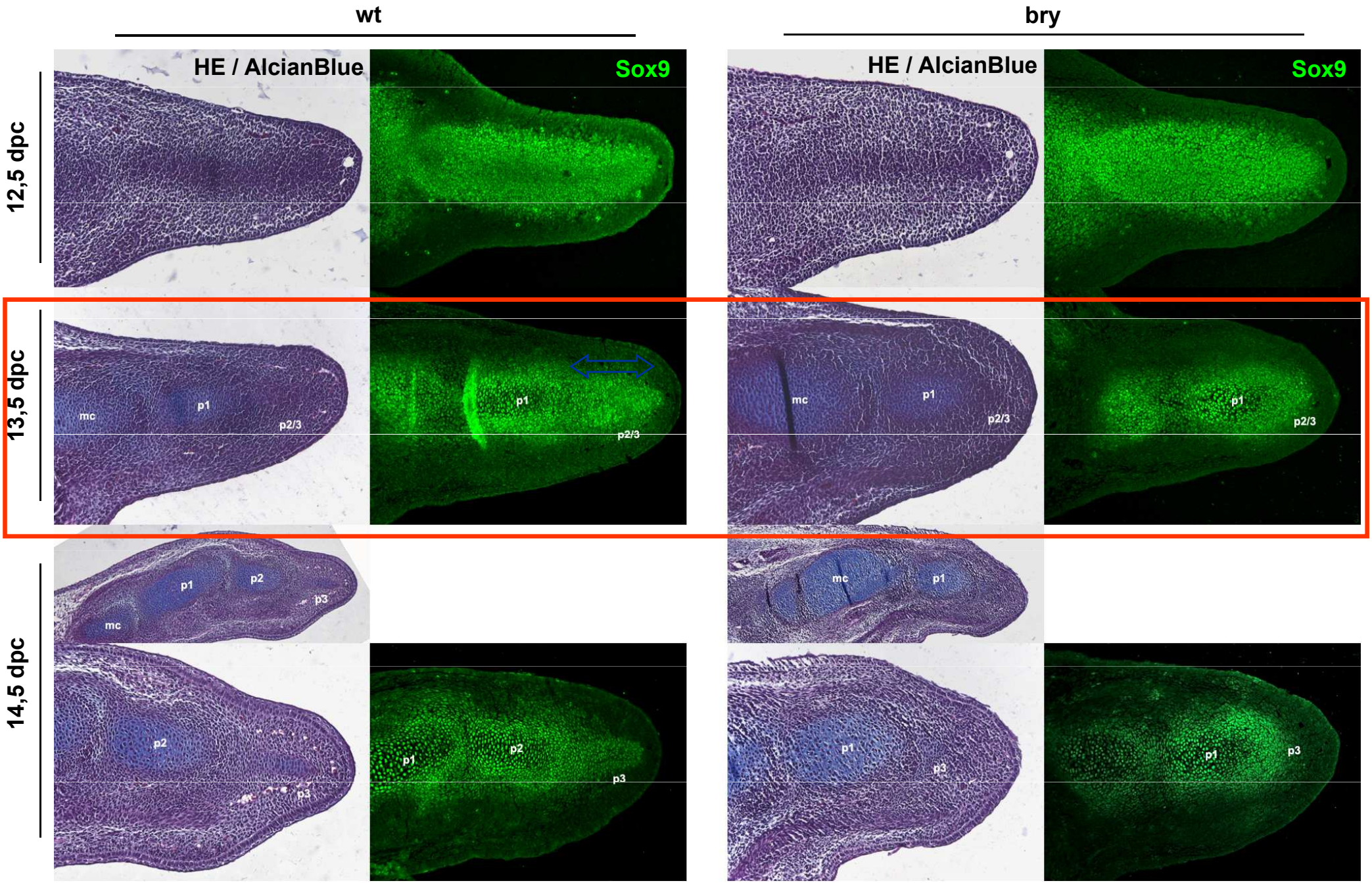




No early patterning defect in the Ror2-Bry mouse

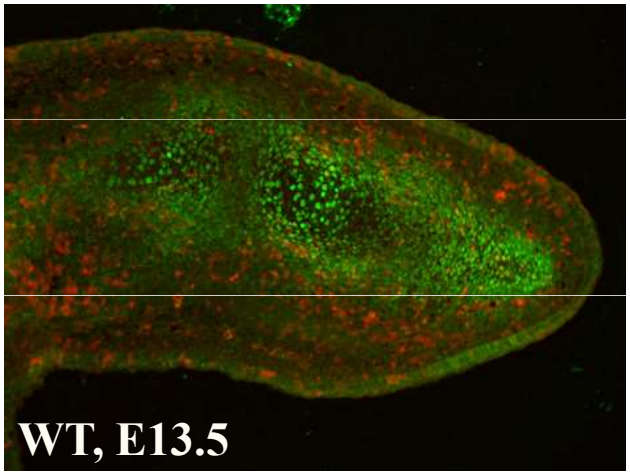


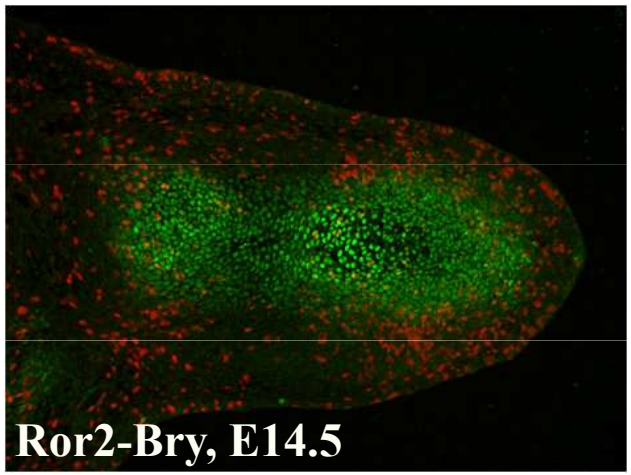
Phenotype part 1: Cartilage condensation in the Ror2-Bry mouse

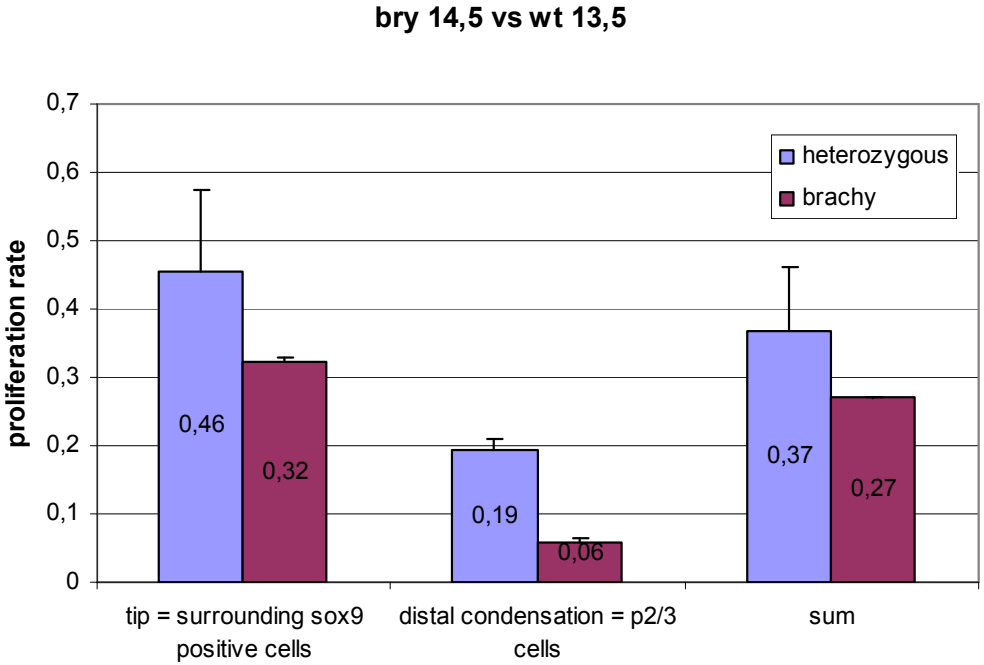


Cartilage condensation: cell recruitment

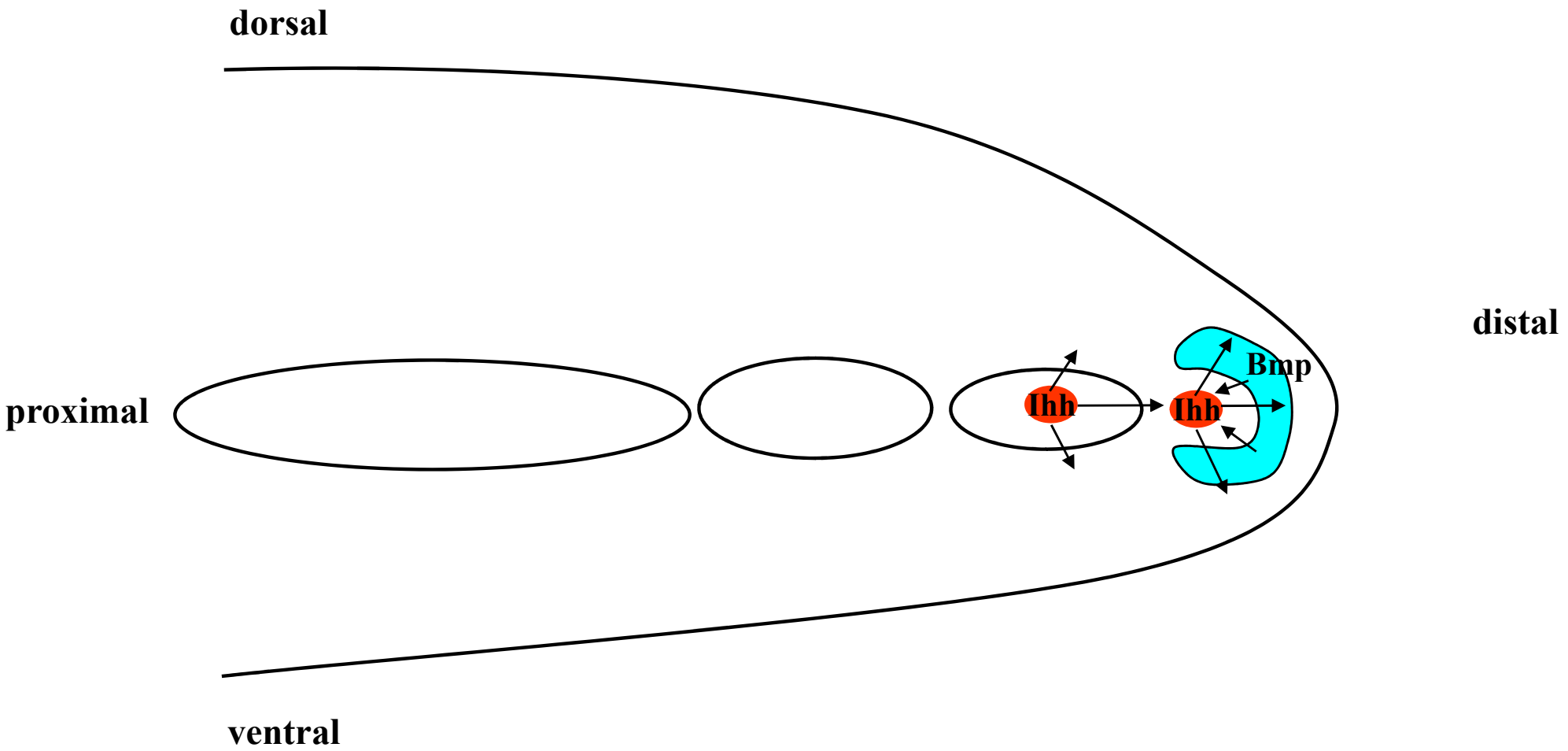
Pulse-Chase experiment: 1h BrdU labeling (Pulse), 10h unlabeled uridine (Chase)



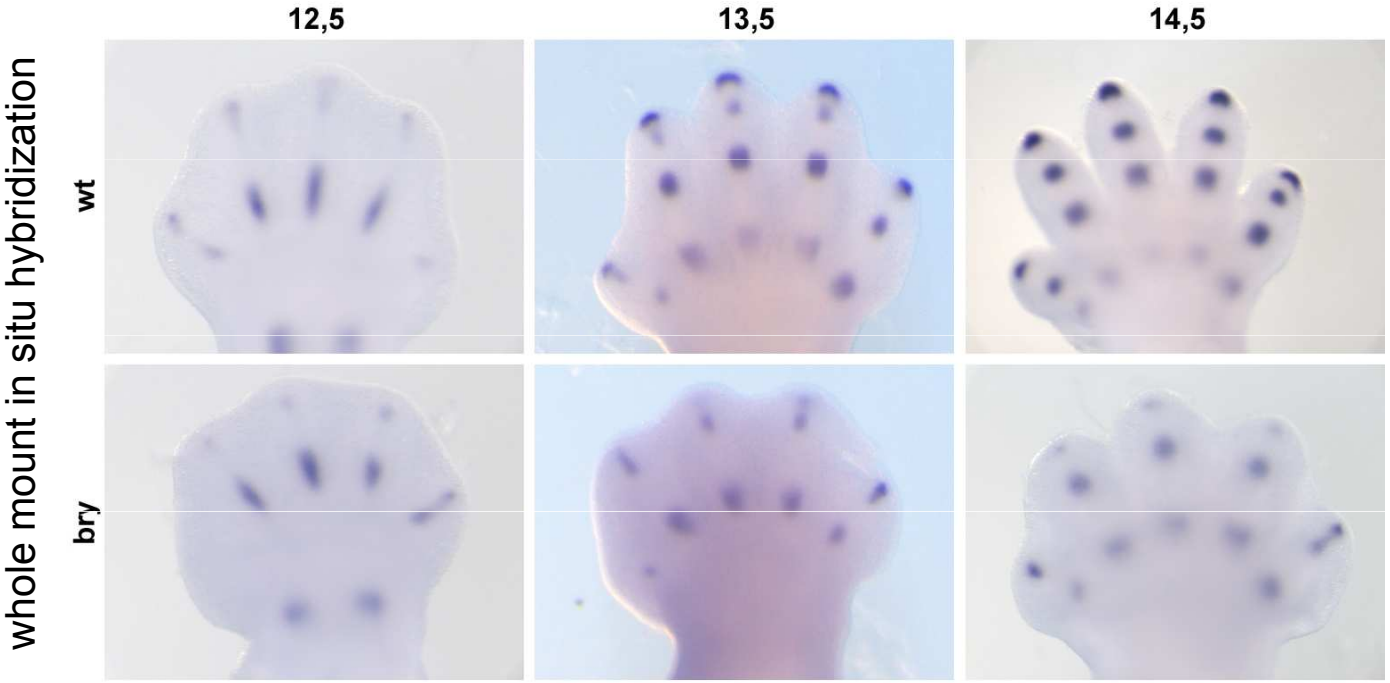


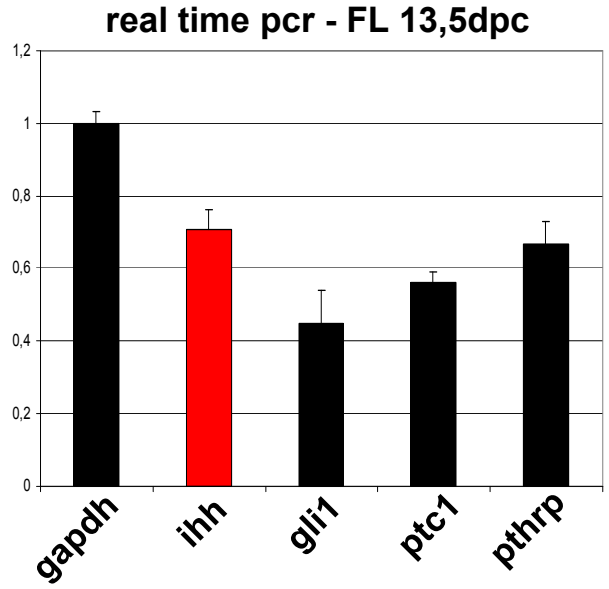


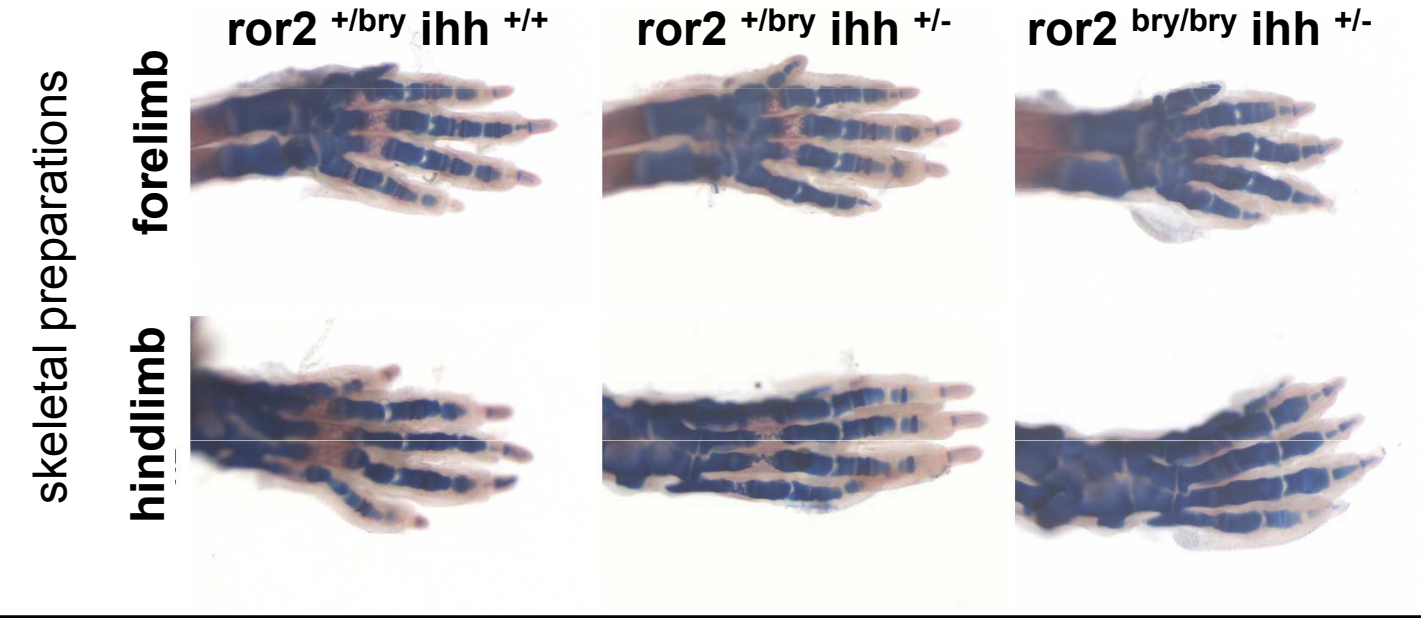
Pathways in phalangeal condensation



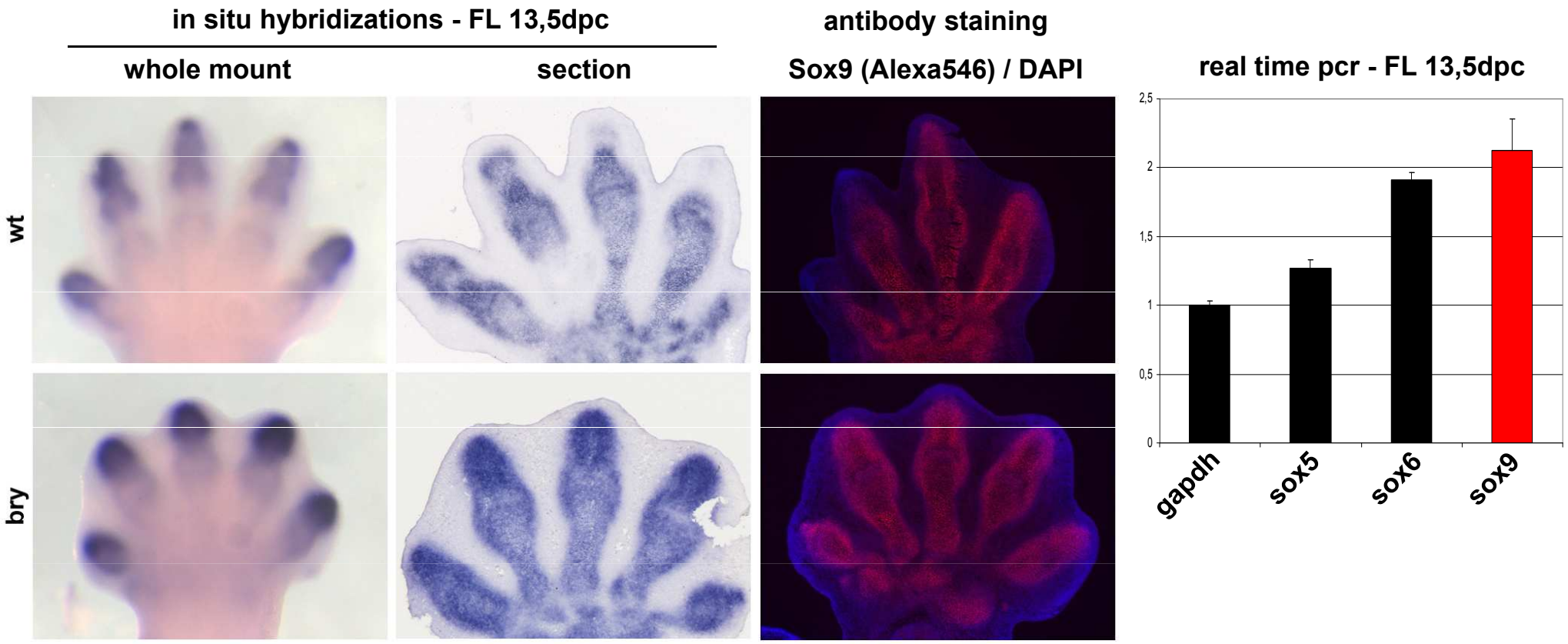
Disturbed Ihh signaling in the Ror2-Bry mouse







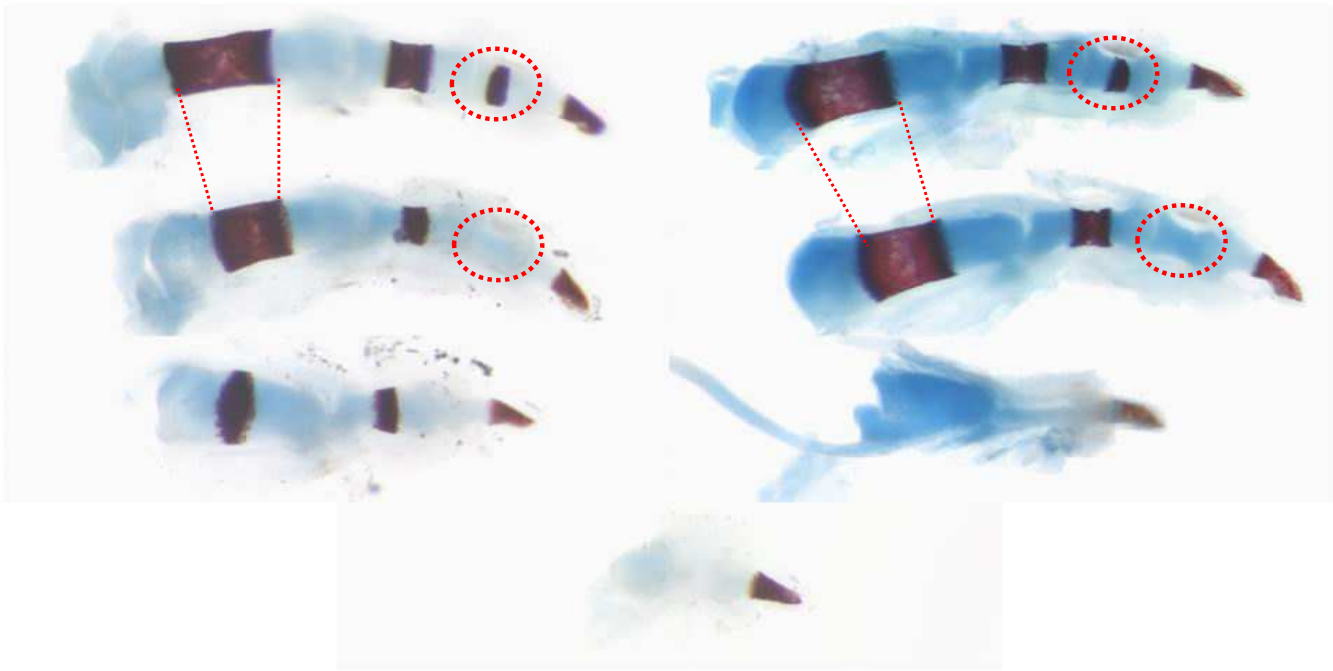
Deregulation of Sox9 in distal condensations



Bmp Signaling: Ror2-BDB and Gdf5 show genetic interaction

crossing ror2-brachy with gdf5-brachypodism mice

middle fingers of newborn mice



bry het / gdf5 wt

bry het / gdf5 het

bry hom / gdf5 het

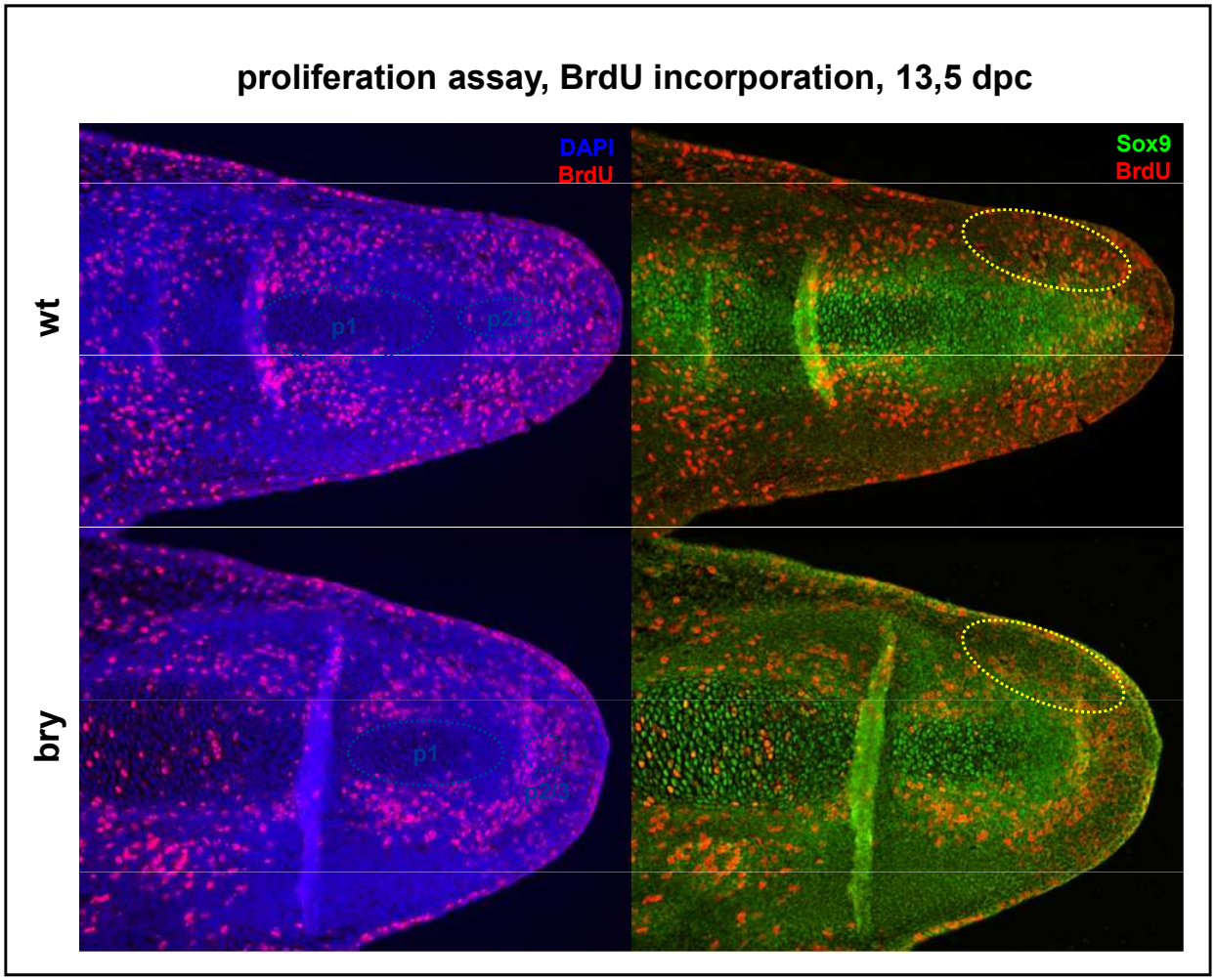
bry wt / gdf5 het

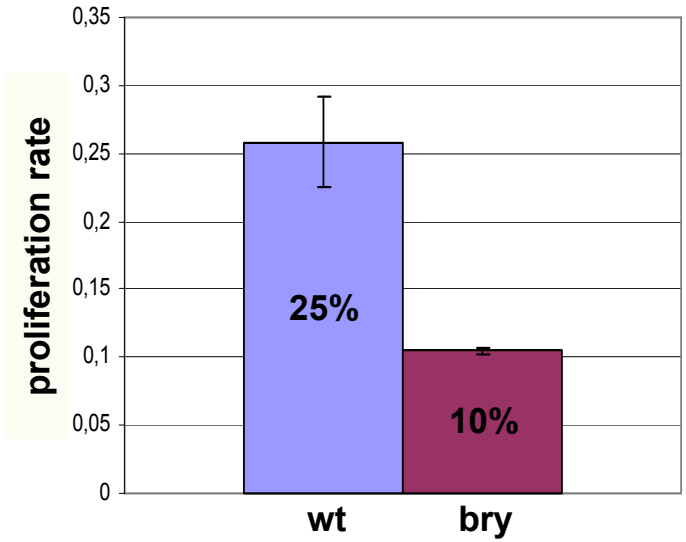
bry het / gdf5 het

bry het / gdf5 hom

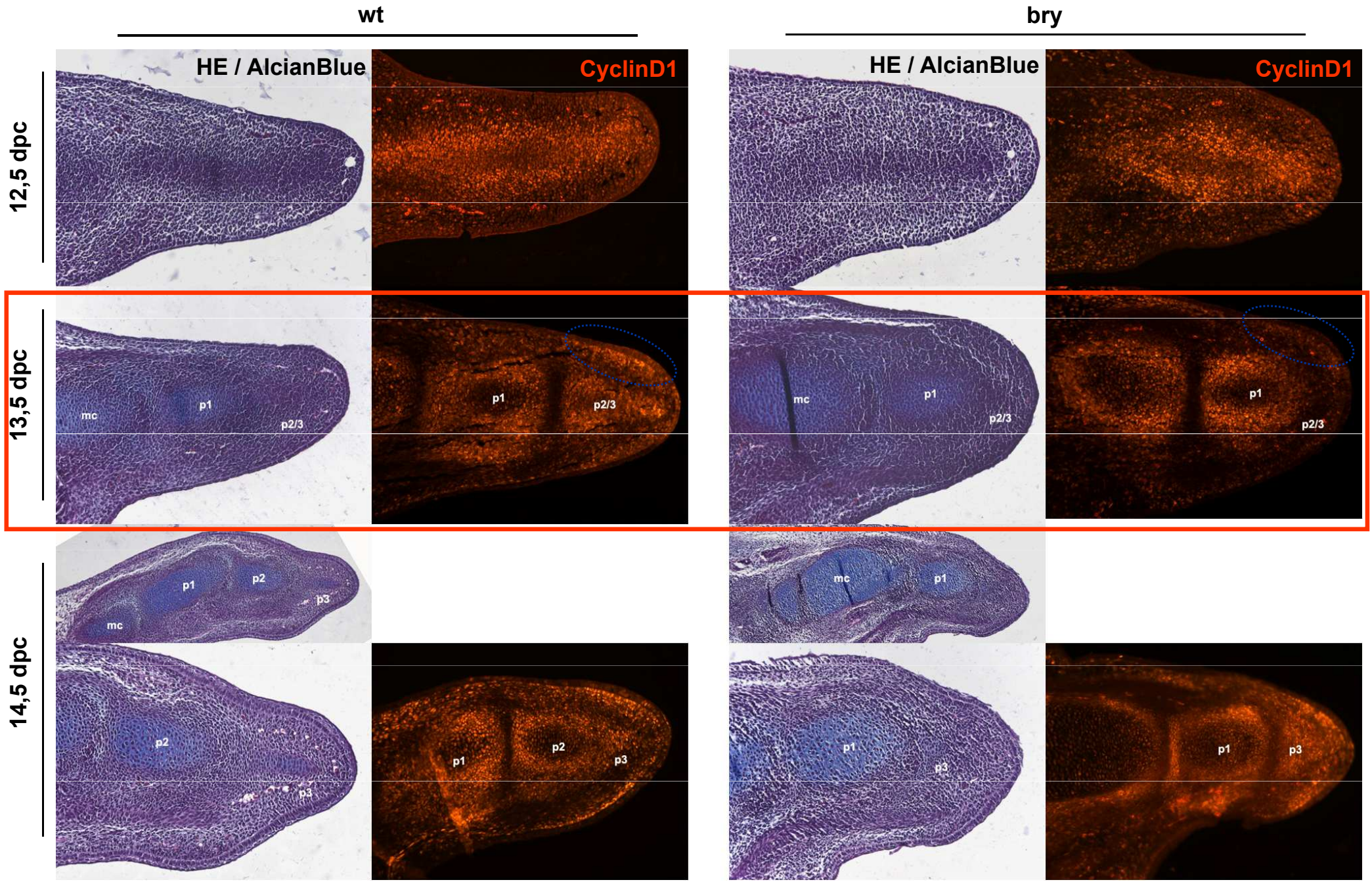
bry hom / gdf5 hom

Phenotype part 2: decreased proliferation in flanking mesenchyme

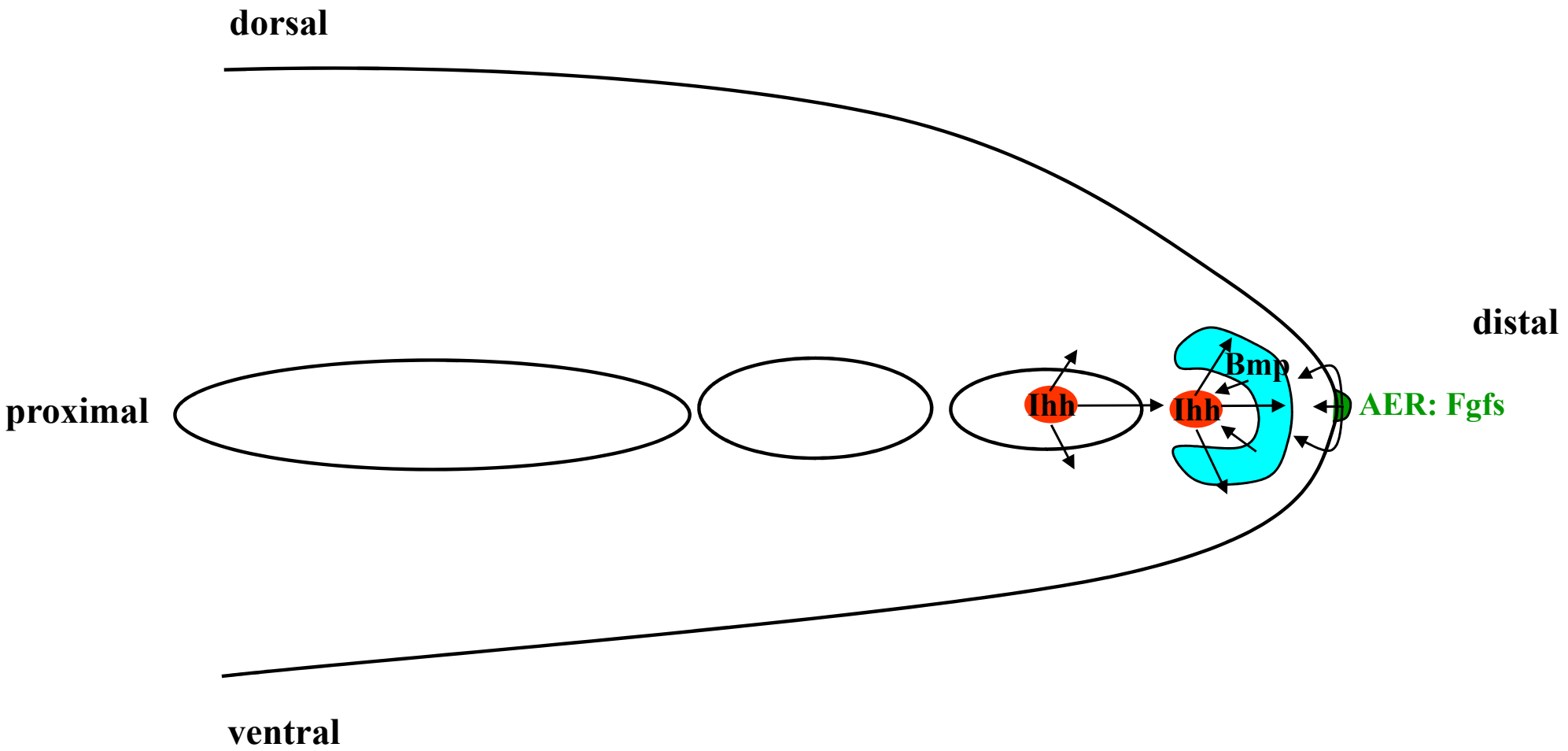




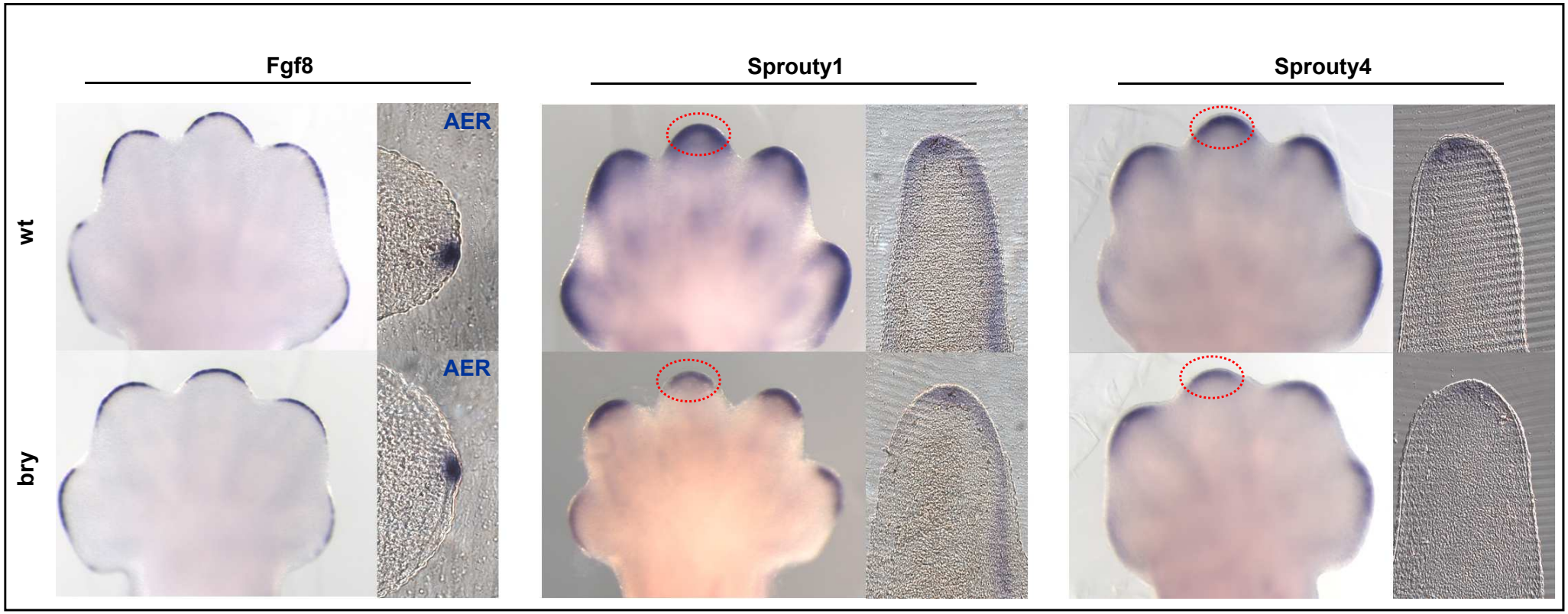
decreased proliferation due to decreased expression of CyclinD1



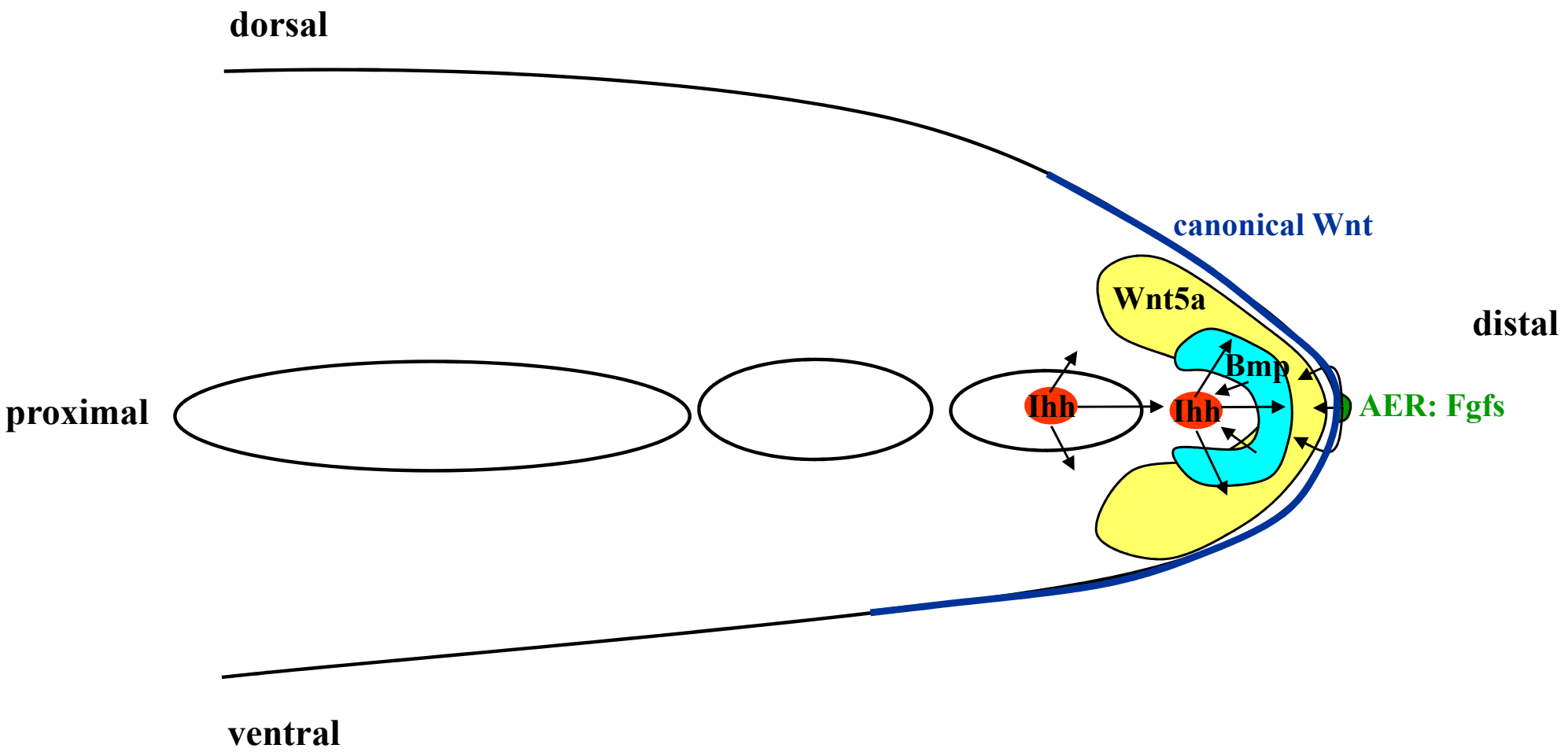
Pathways in phalangeal condensation



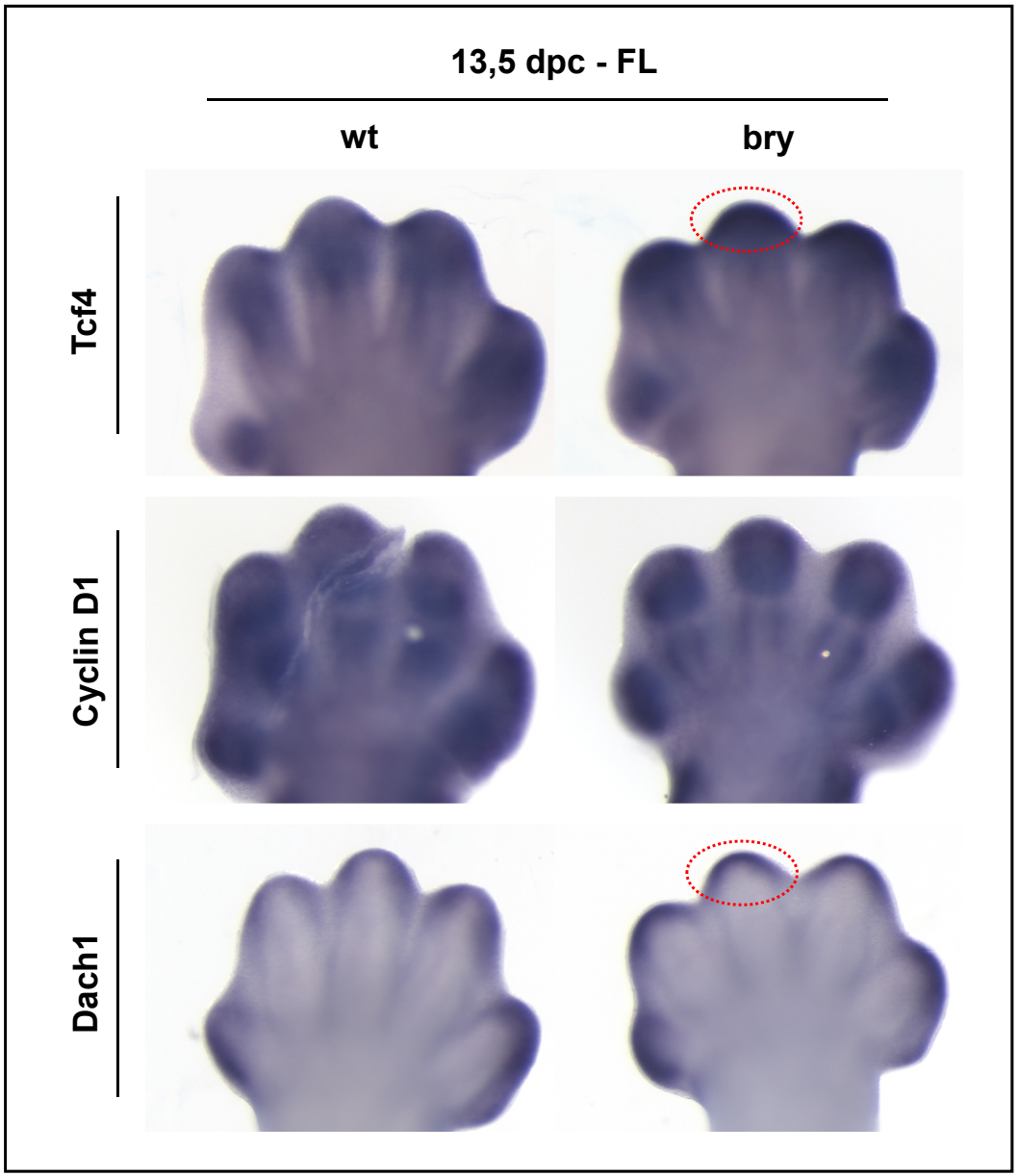
Reduced Fgf signalling in the Ror2-Bry mouse

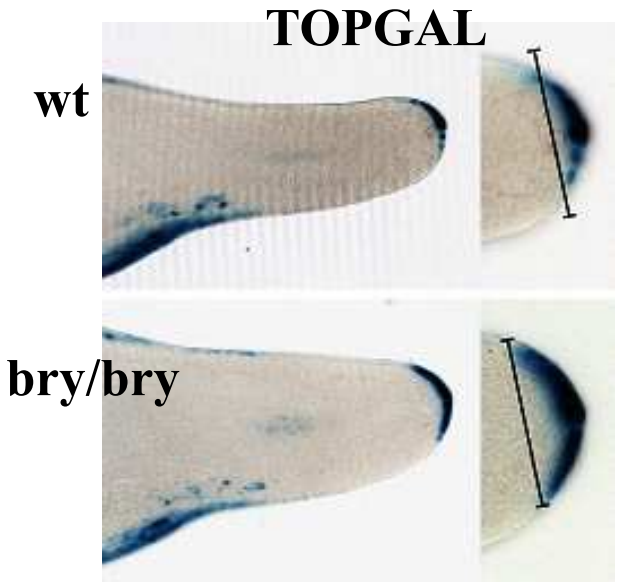


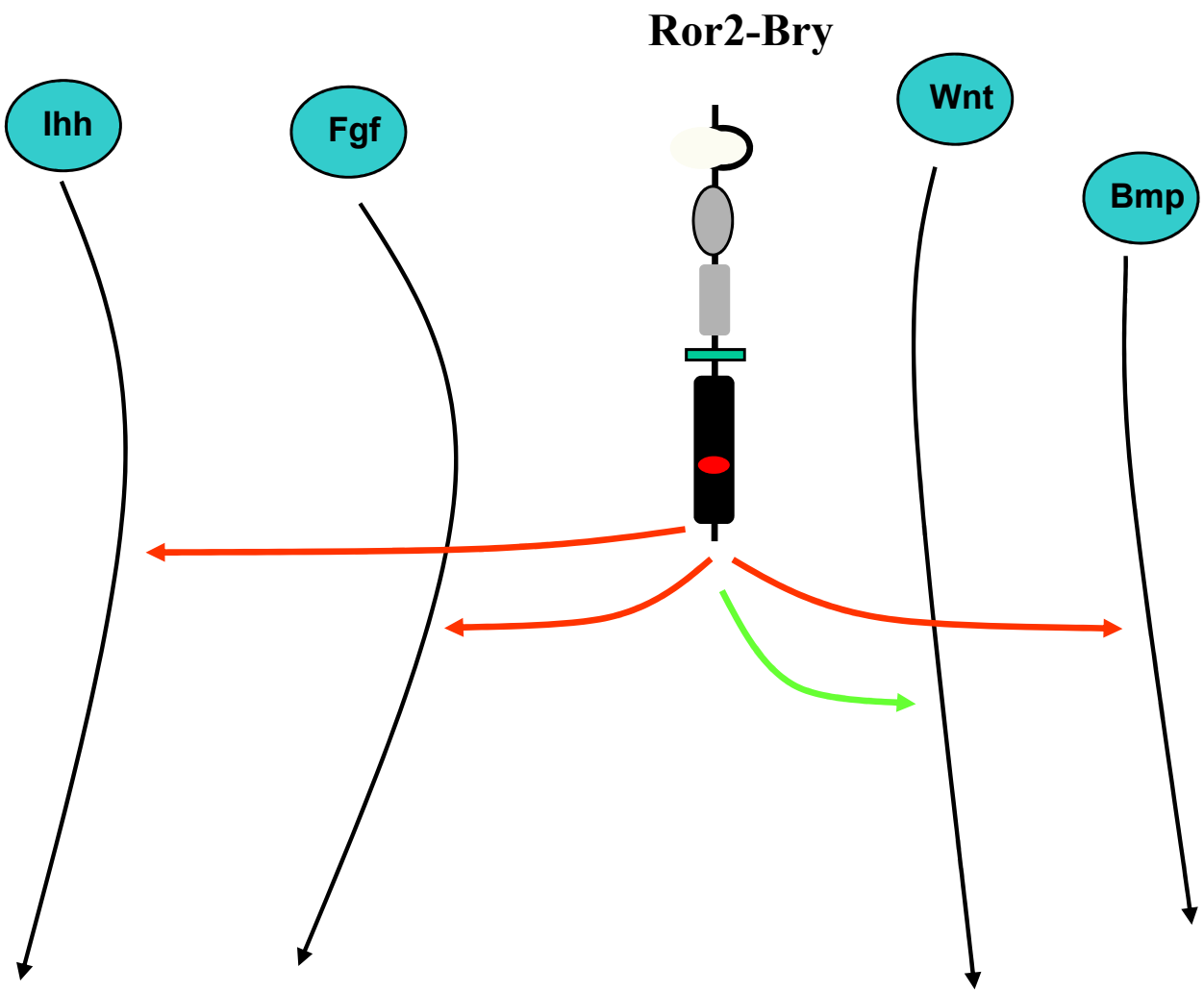
Pathways in phalangeal condensation



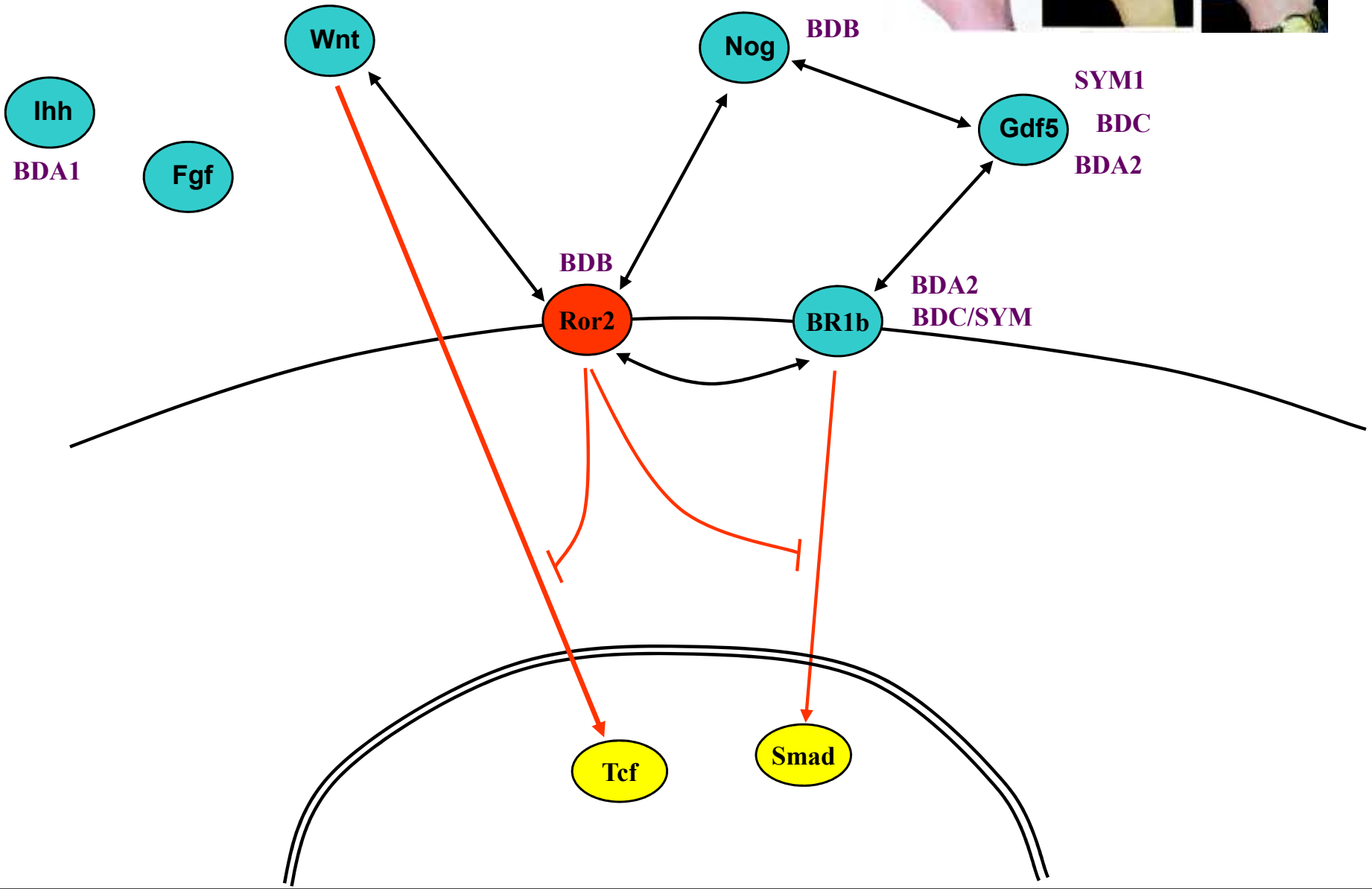
Upregulation of canonical Wnt signalling ??






Ror2-Bry
Ihh
Fgf
Wnt
Bmp

The brachydactylies: a syndrome family approach



Thank You

MPI Berlin:

Stefan Mundlos

Florian Witte
Wibke Schwarzer
Norbert Brieske
Britta Hoffmann
Kathrin Seidel

Brno University:

Vitezlav Briya

Karlsruhe University:

Alexandra Schambony

Regeneron Inc. NY:

Aris N. Economides
Regina Raz