

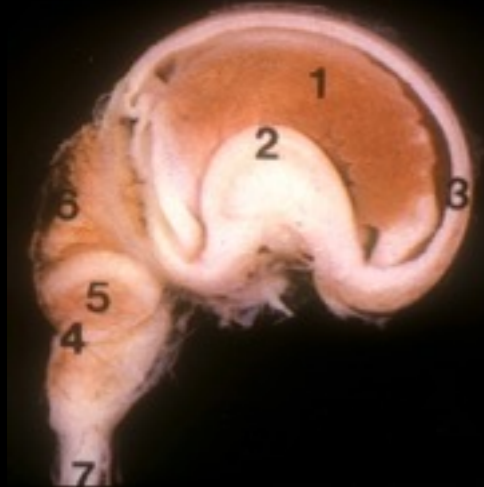
**Journée SoFFoet du 09 juin 2017 : Le
cerveau postérieur normal et pathologique**

Contrôle moléculaire du développement du cervelet.
Etude causale des anomalies fréquentes.





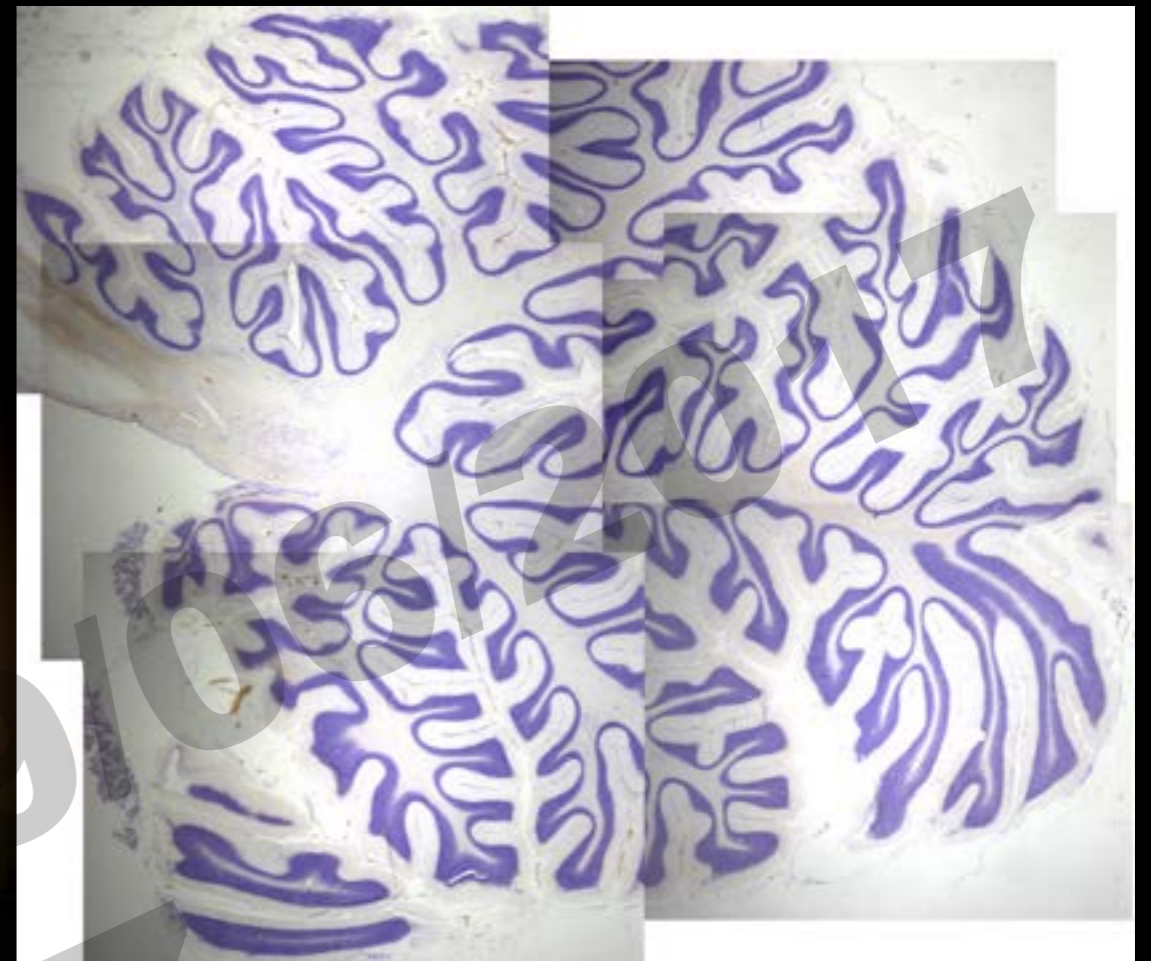
4 w



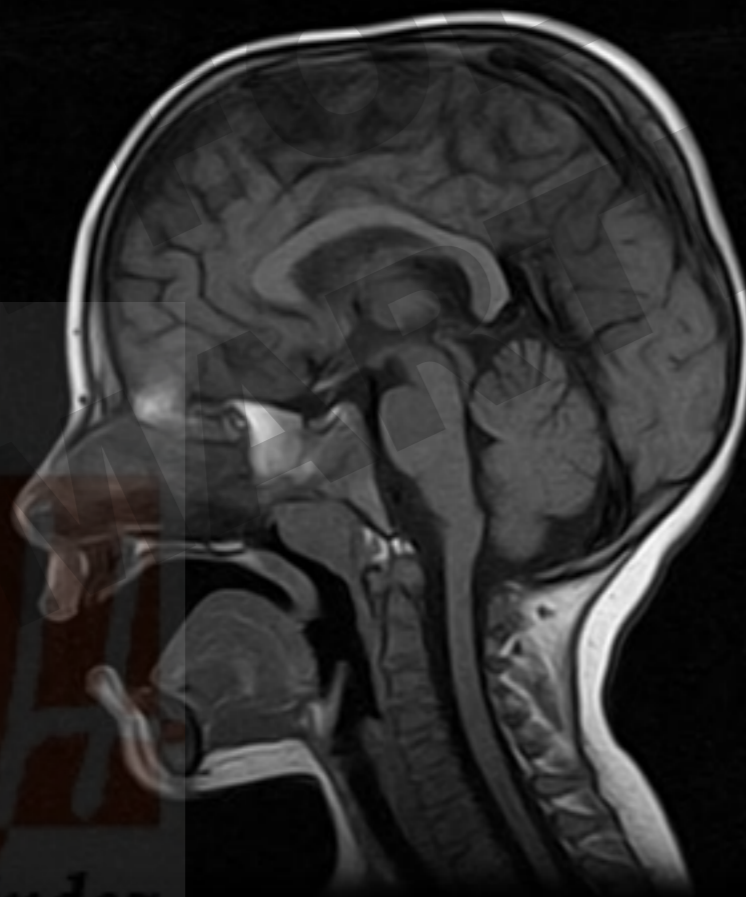
6 w



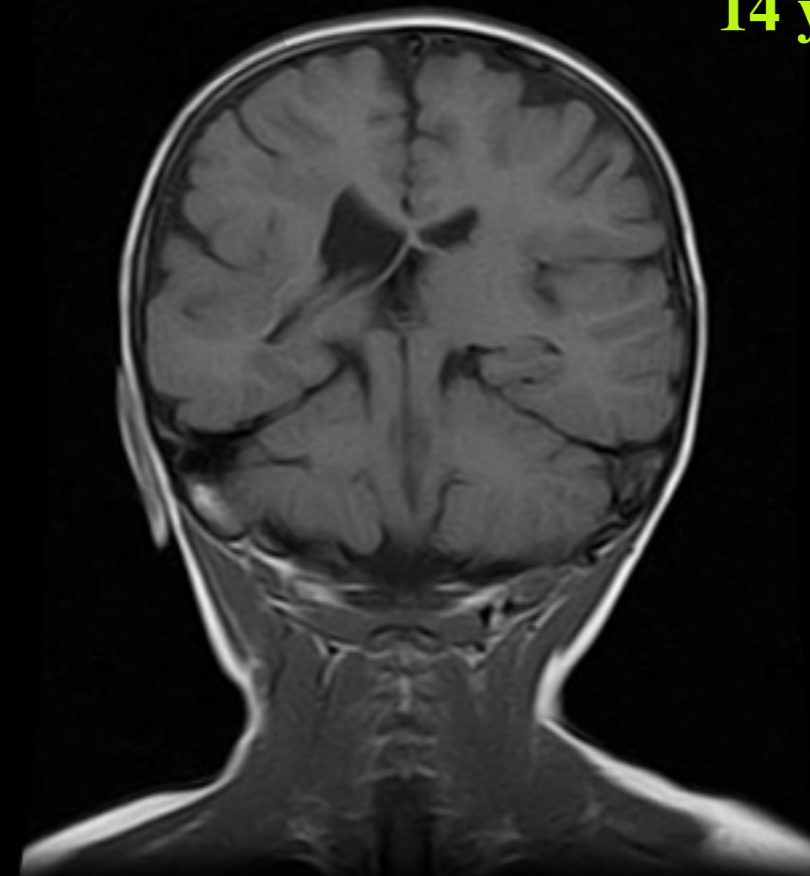
18 w

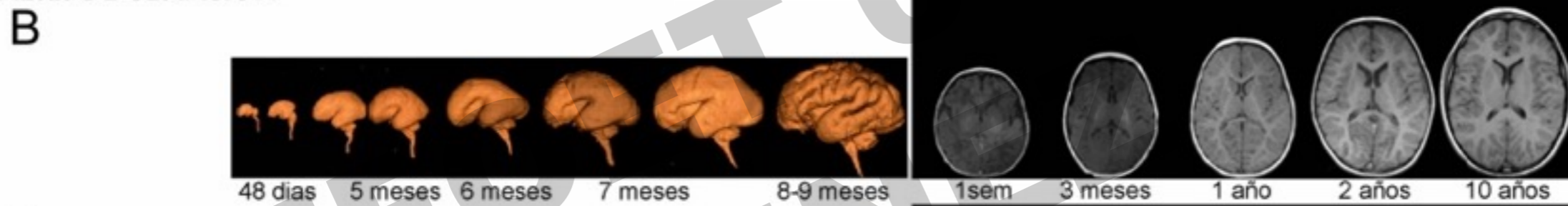
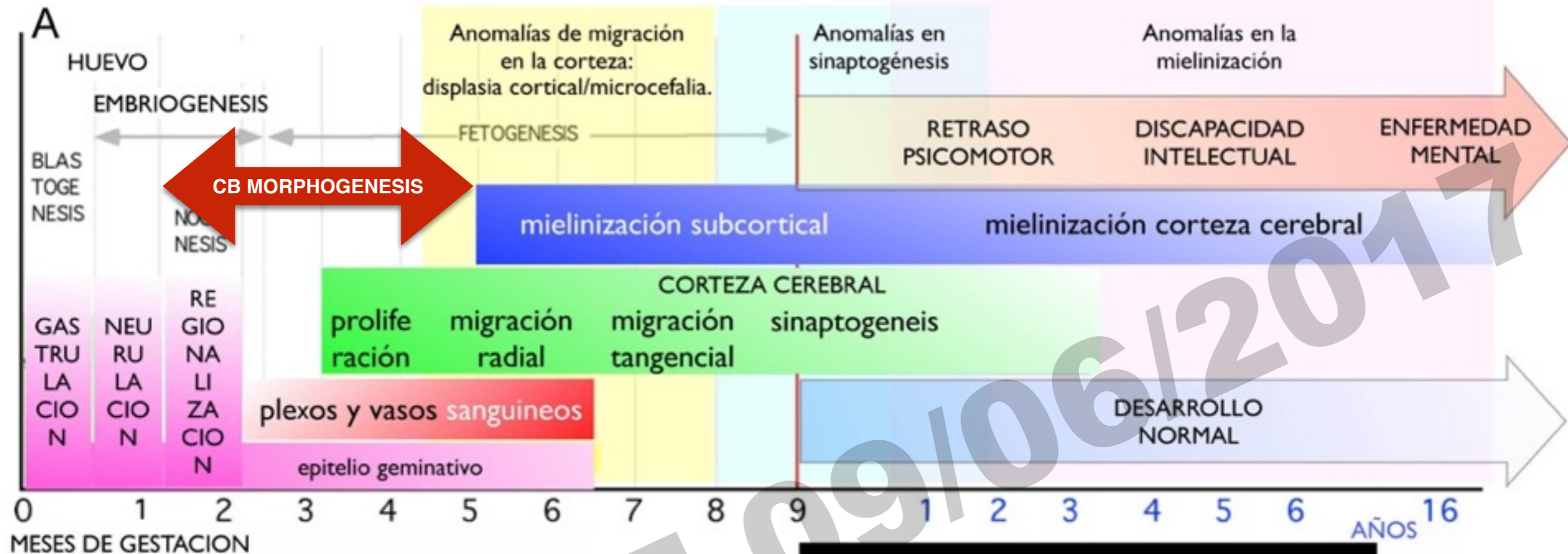


14 year old



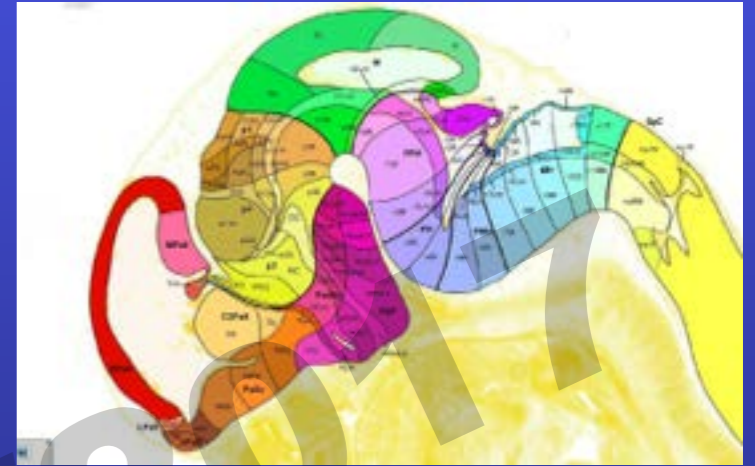
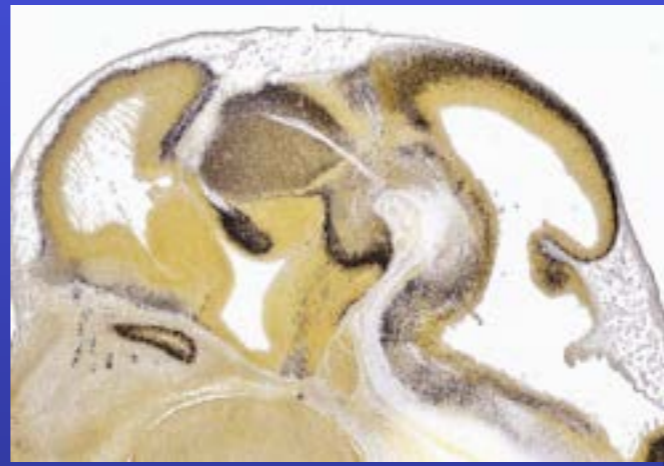
p3





Time program of main histogenetic processes of brain development

RÉGIONALISATION DU CERVEAU



La spécification moléculaire se réfère à des complexes processus de développement génétique et épigénétique conduisant à une sélection régionale des combinaisons de gènes (gènes régulateurs) qui sont transcrites dans des ensembles de cellules donnés.

L'expression restreinte spatialement des gènes régulateurs produit des combinaisons spécifiques de facteurs de transcription dans des domaines spatiaux distincts de l'embryon.

Le processus dynamique par lequel une telle spécification avance dans le cerveau primordium est connu sous le nom de **régionalisation ou de patterning neural**.

This BASIC PATTERN of vertebrate brains is regulated by conservative mechanisms of positional information.

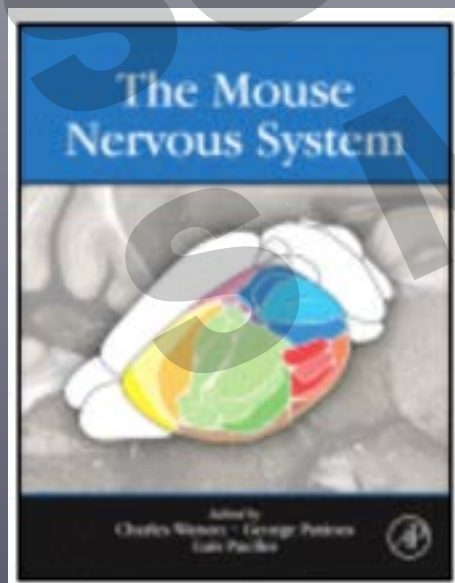
Positional information is coded by gradients of molecular signals

MORPHOGENETIC CODE

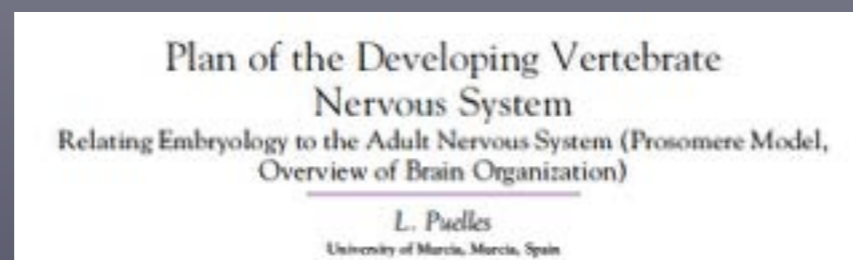
Signals from organizer centers → positional information → molecular regionalization (regulatory genes)

These signals are generated regions:

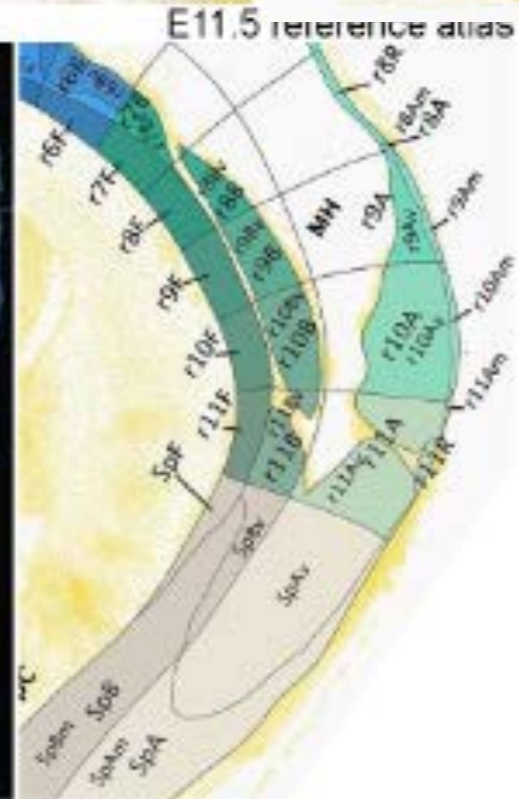
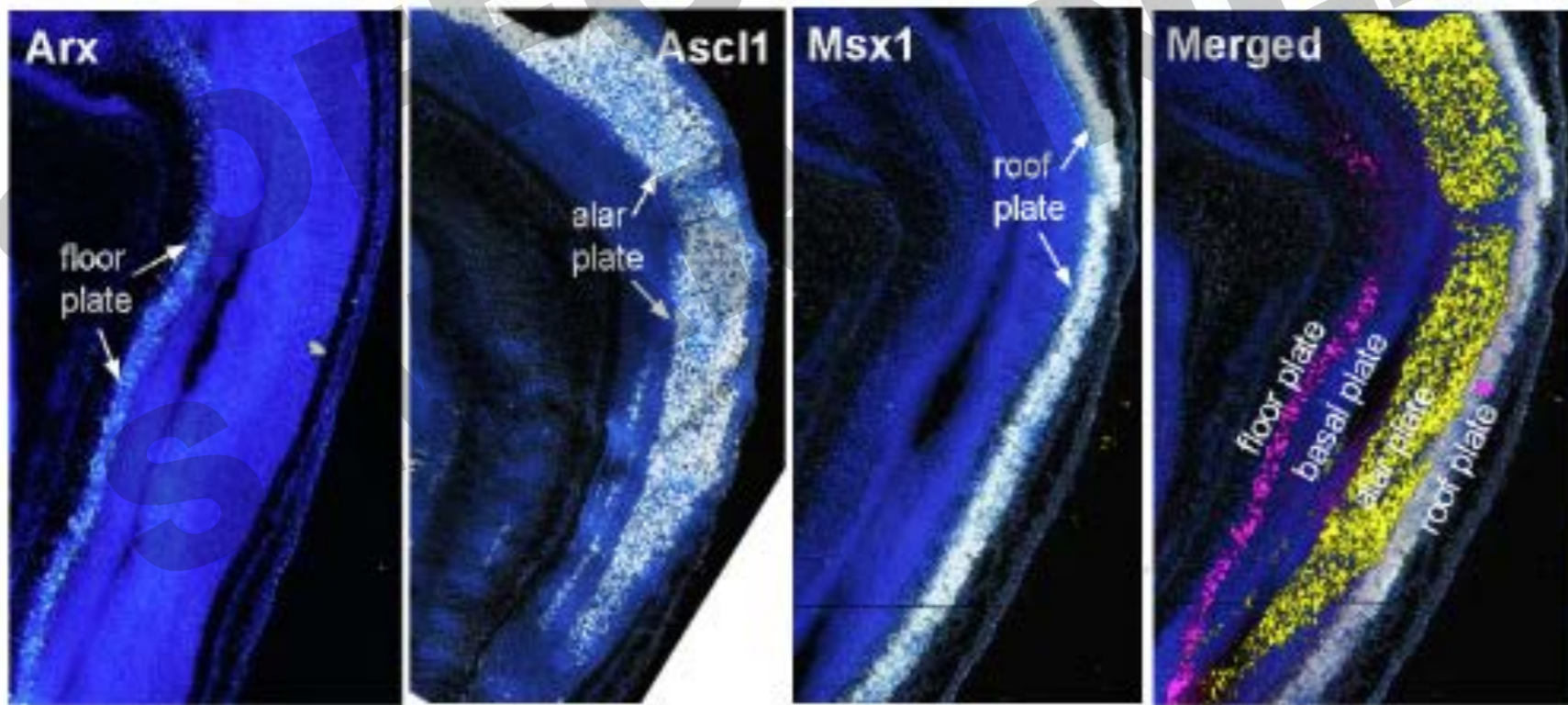
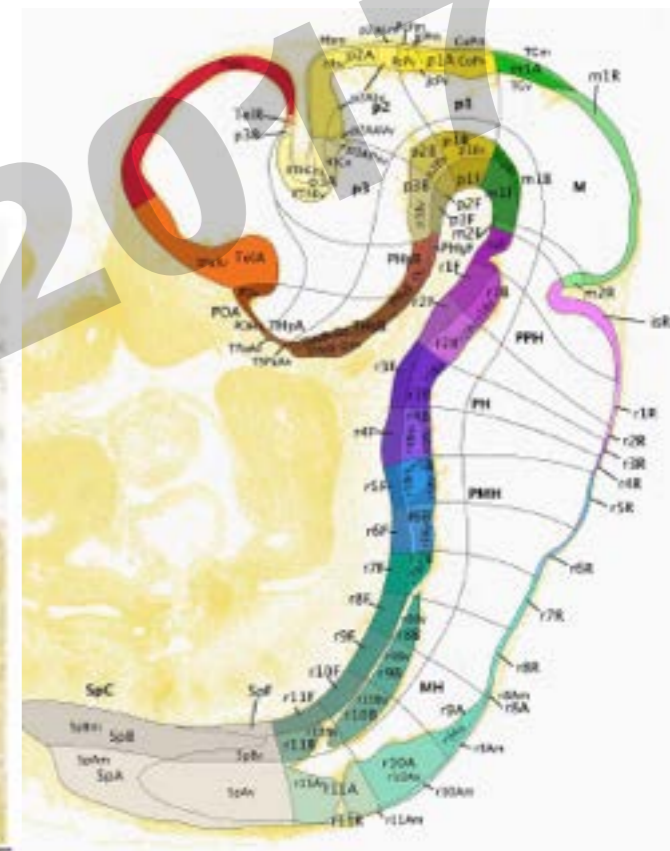
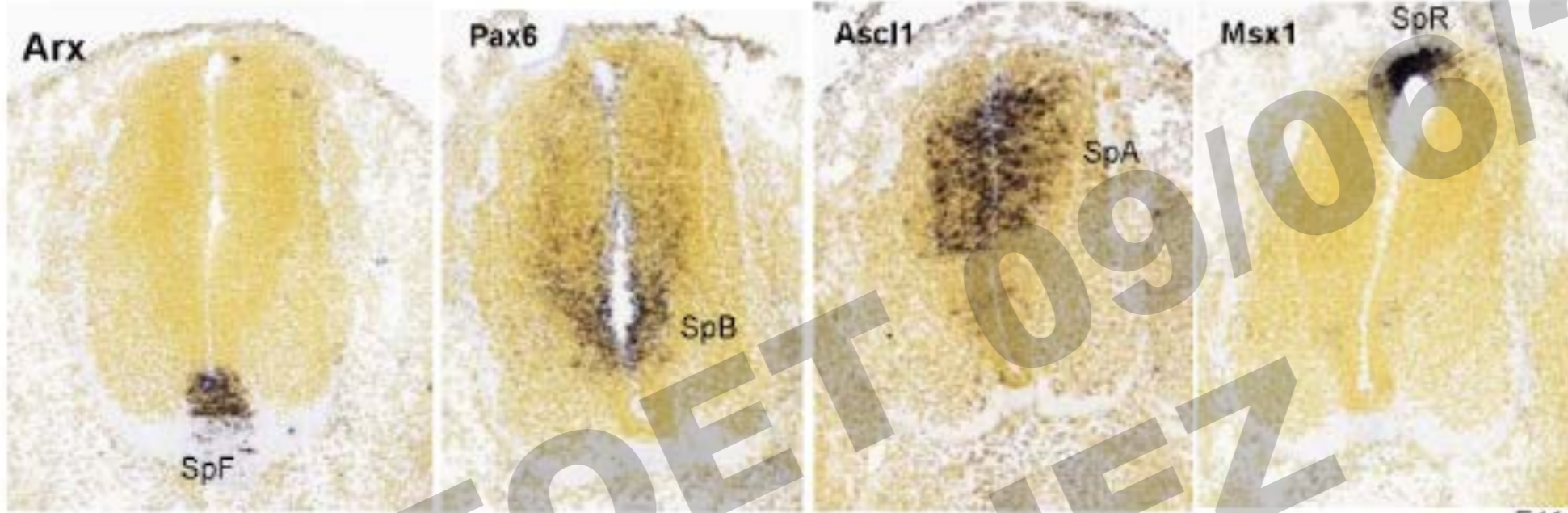
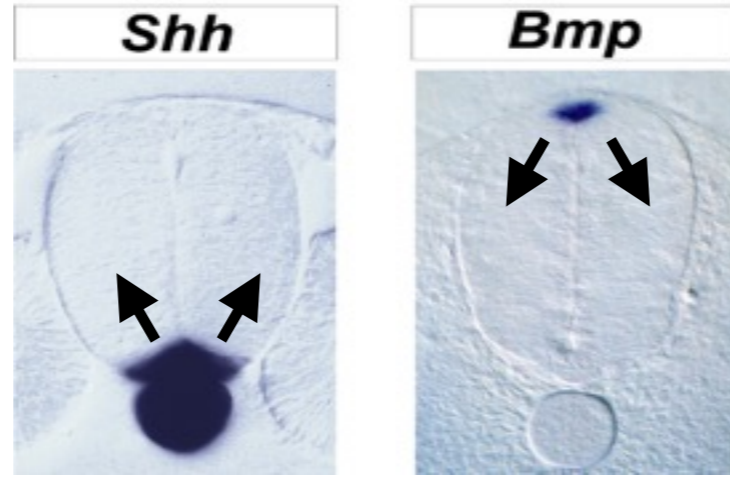
ORGANIZERS



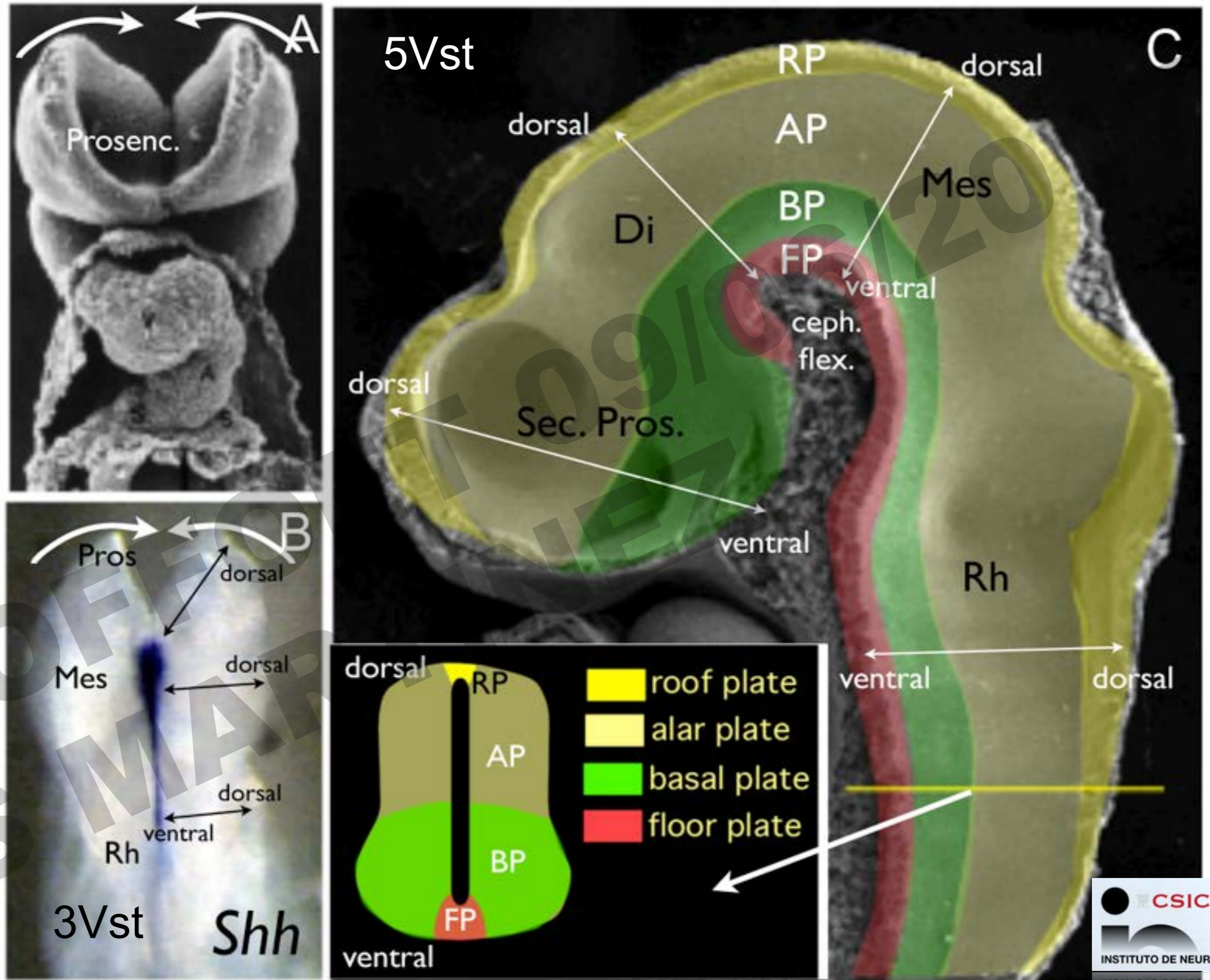
*Edited by: Charles Watson,
George Paxinos and Luis Puelles*
ISBN: 978-0-12-369497-3



V-D Patterning



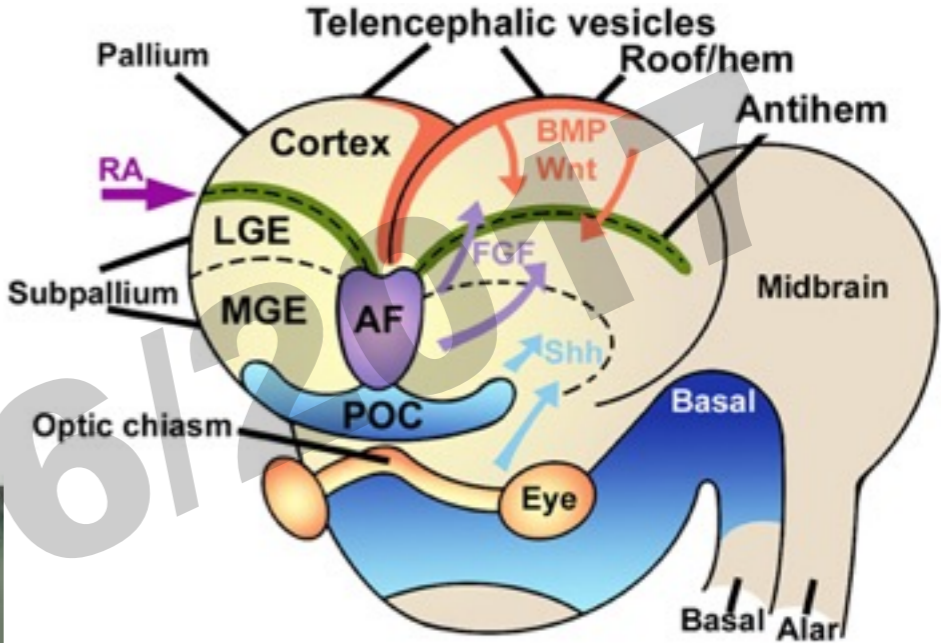
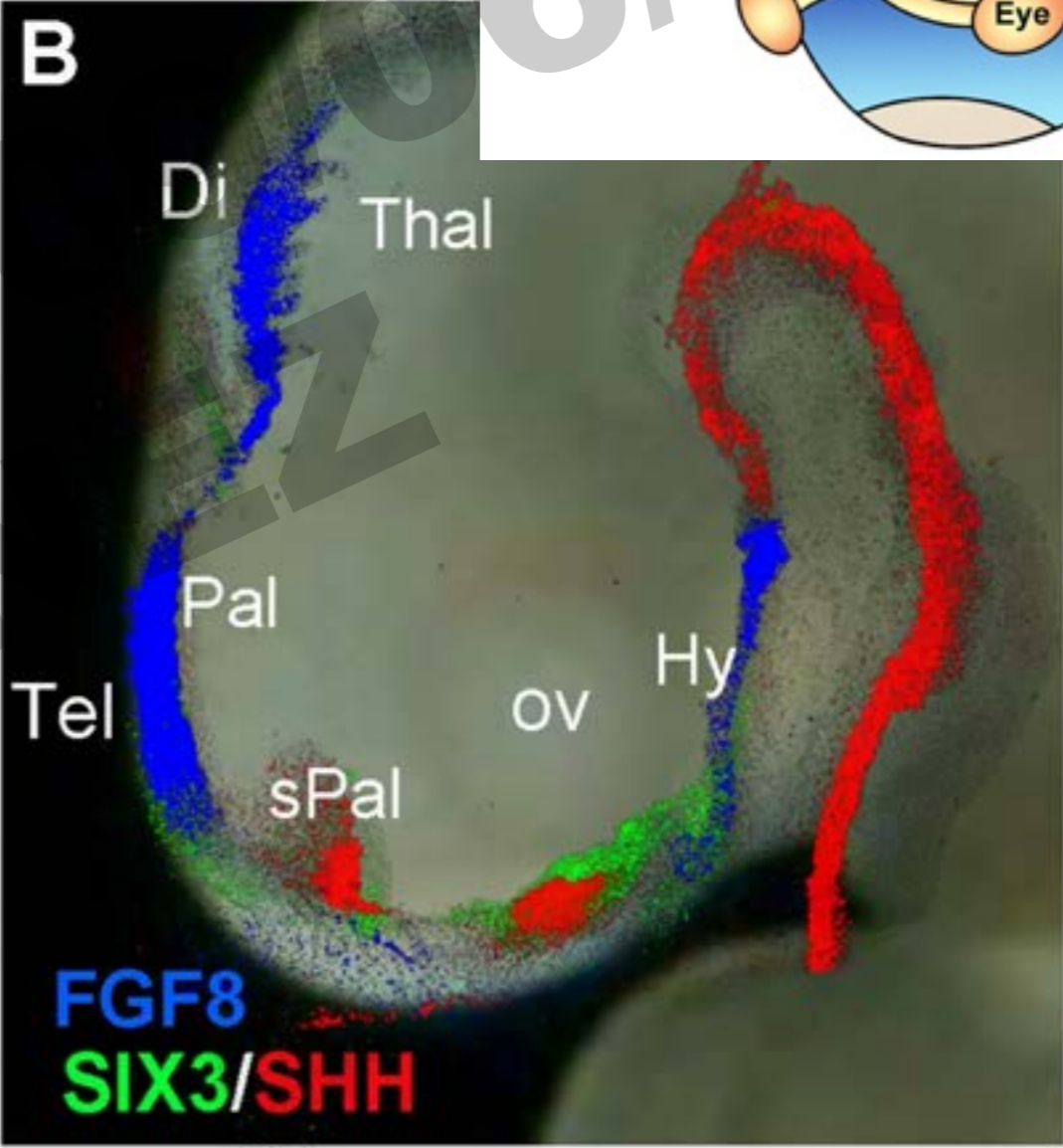
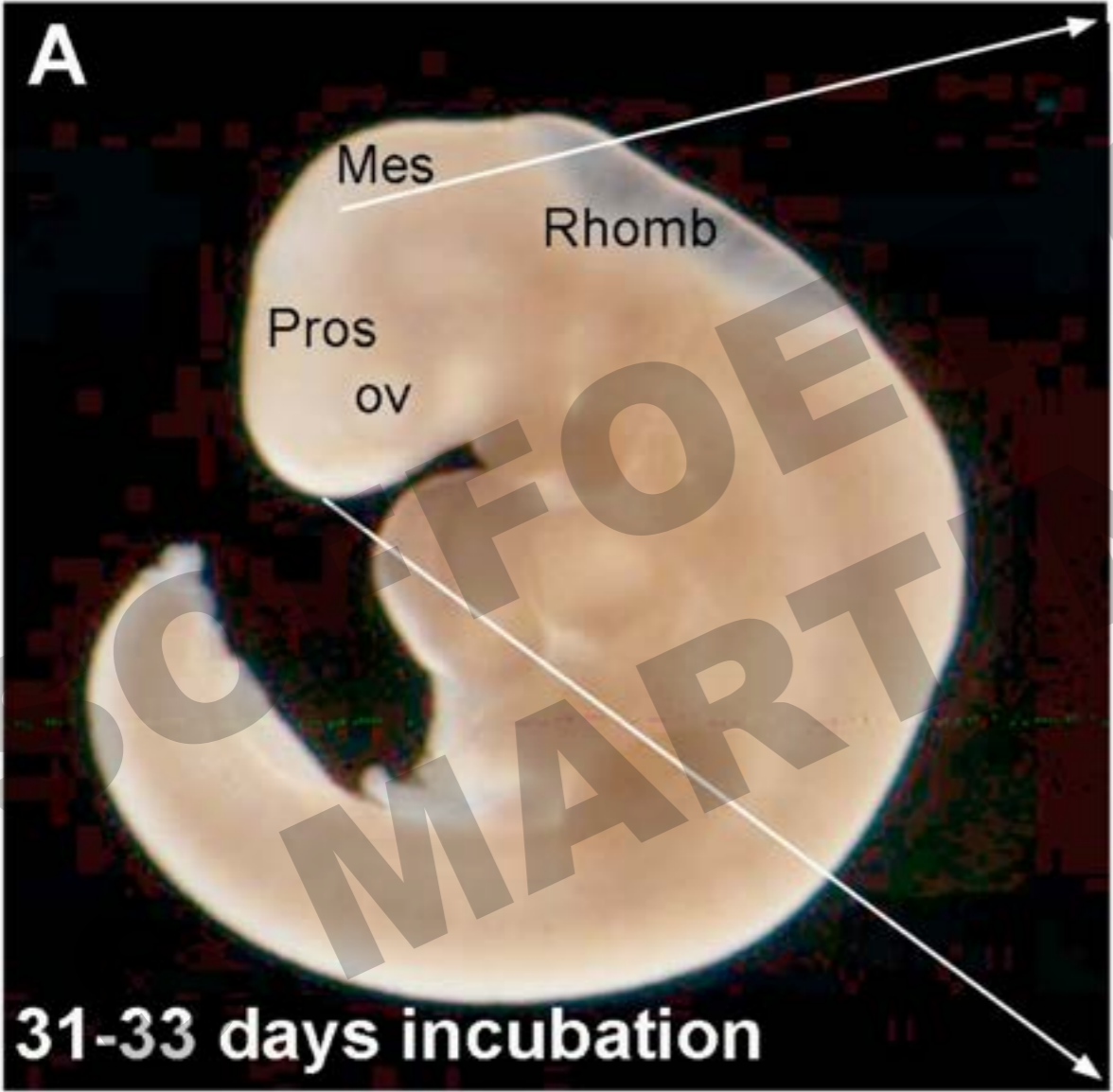
NEURULATION= V-D REGIONALIZATION



Genes regulating prosencephalon dev.

Copy number variants (mutations):
holoprosencephaly sequence

Figure 1



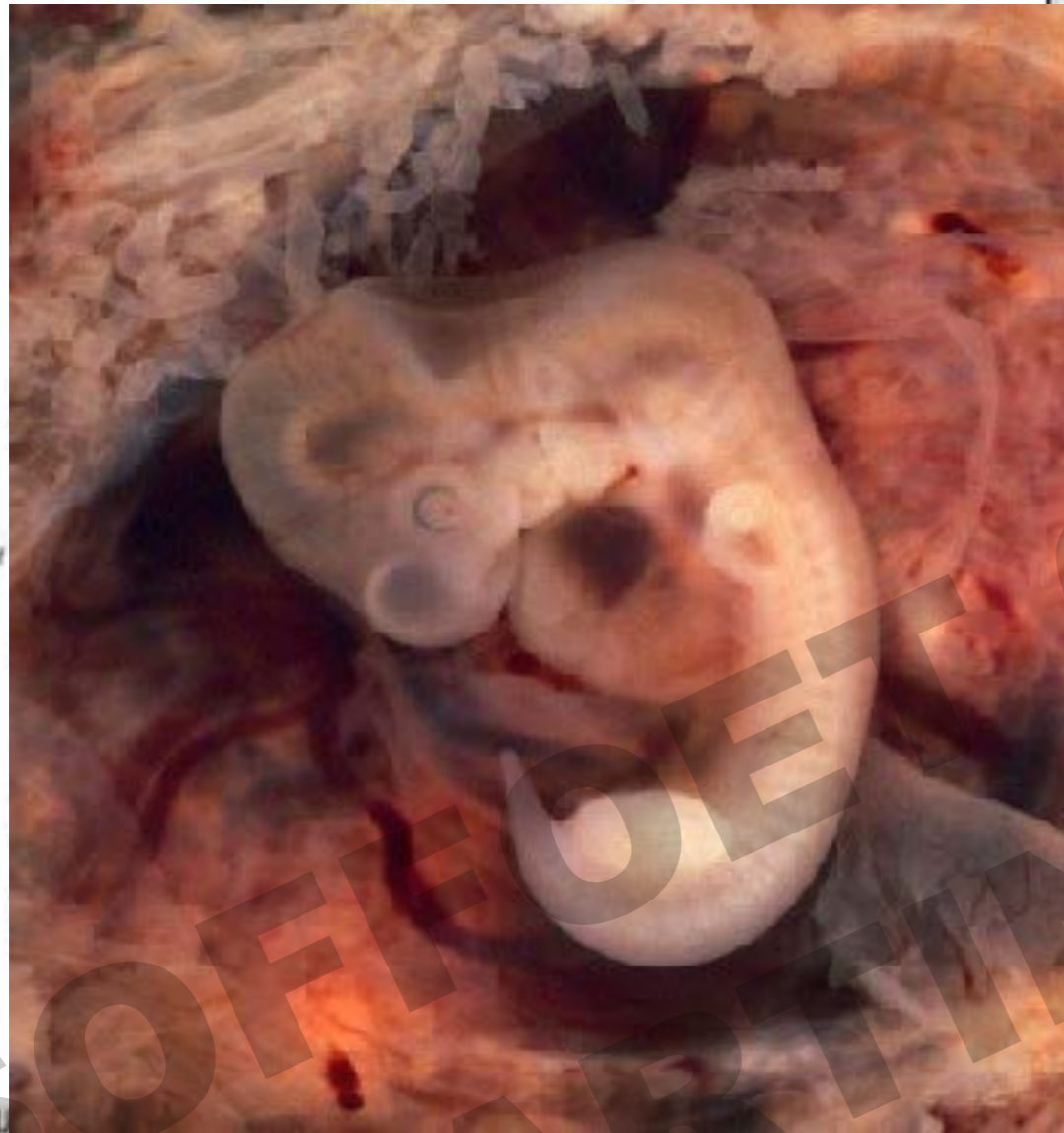
Specification of cell identity: rhombencephalic segments

Drosophila embryo

Head

Thorax

Abdomen

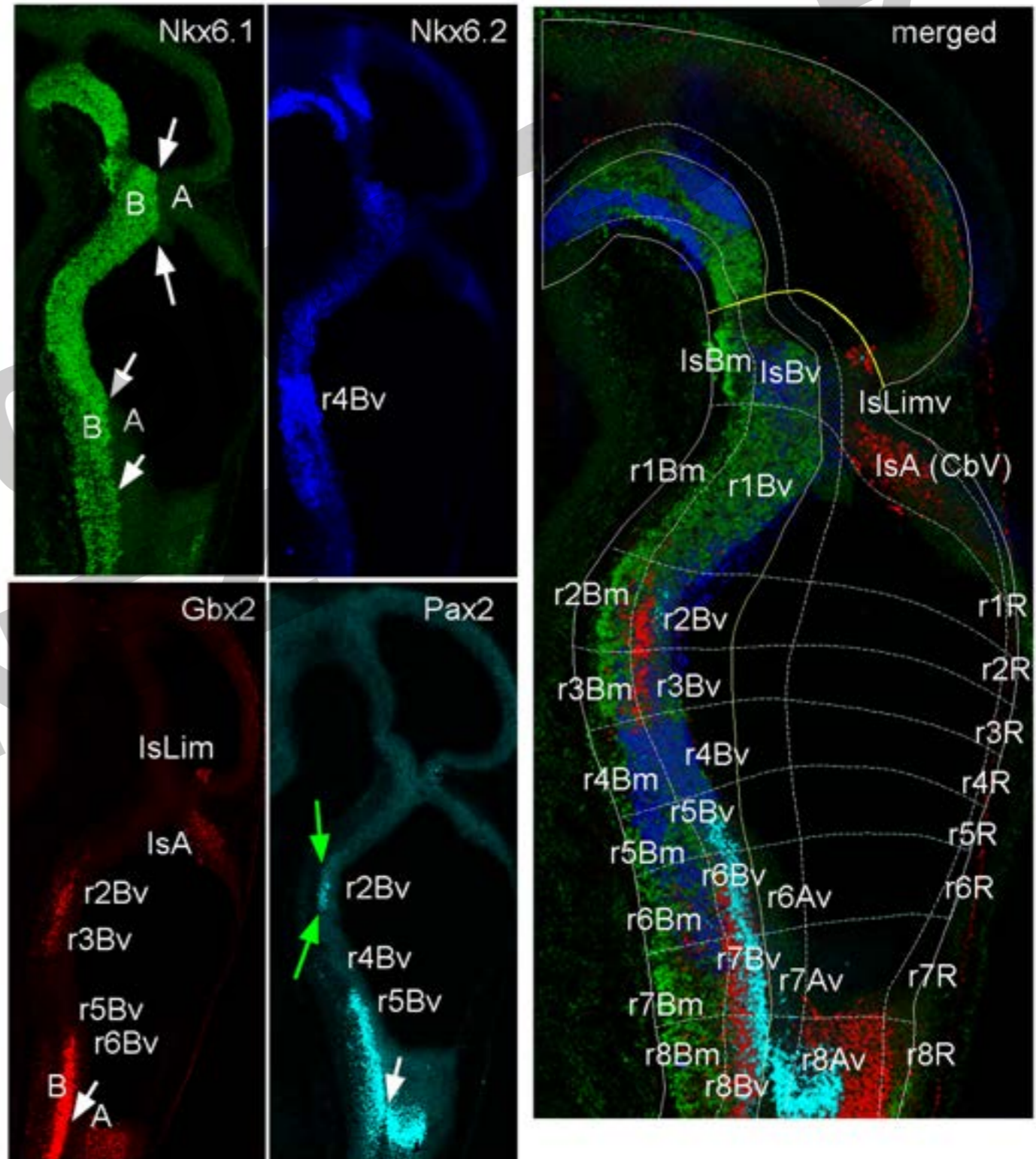


Drosophila
Hox C

Hypothetical
common ancestor

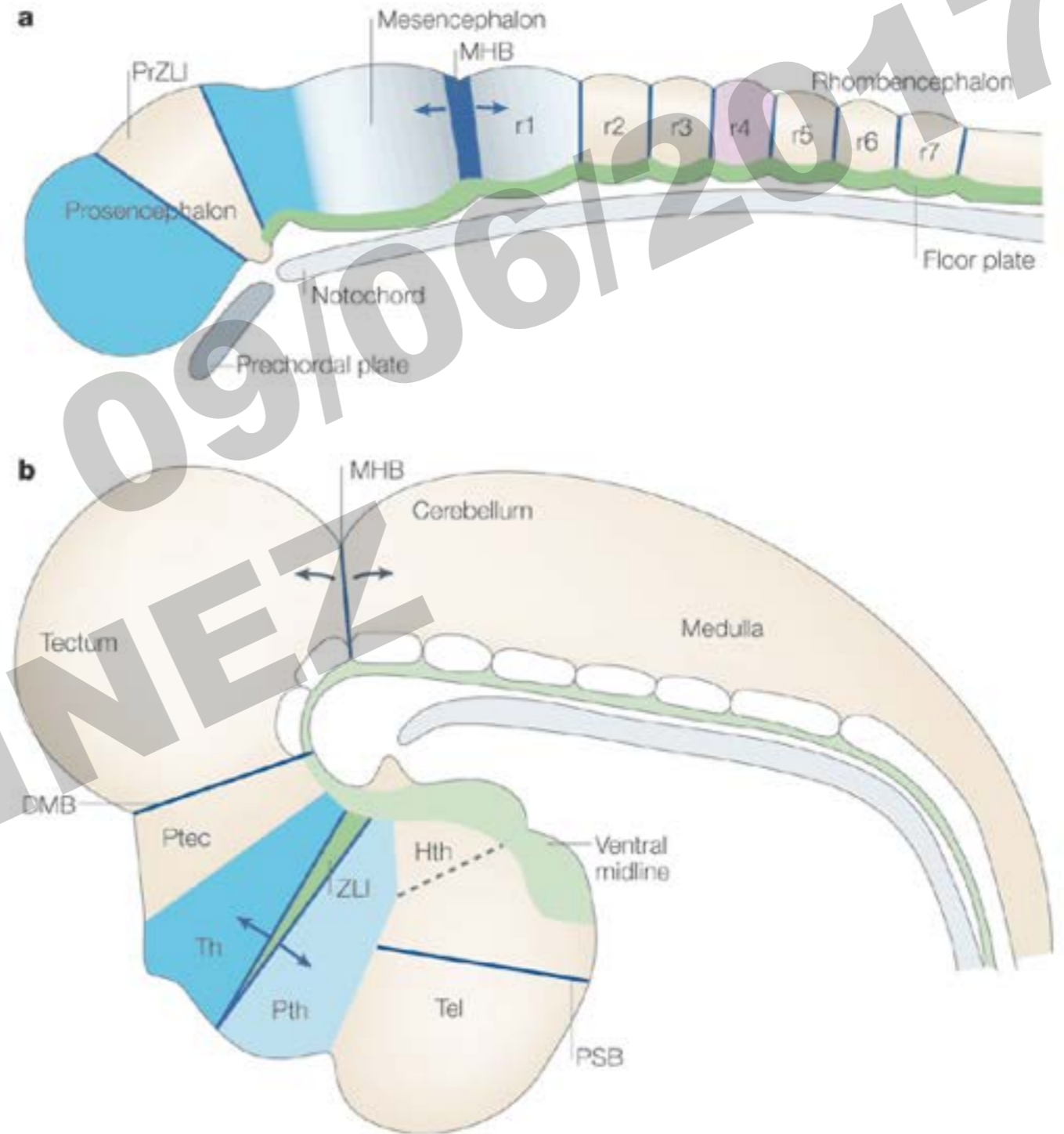
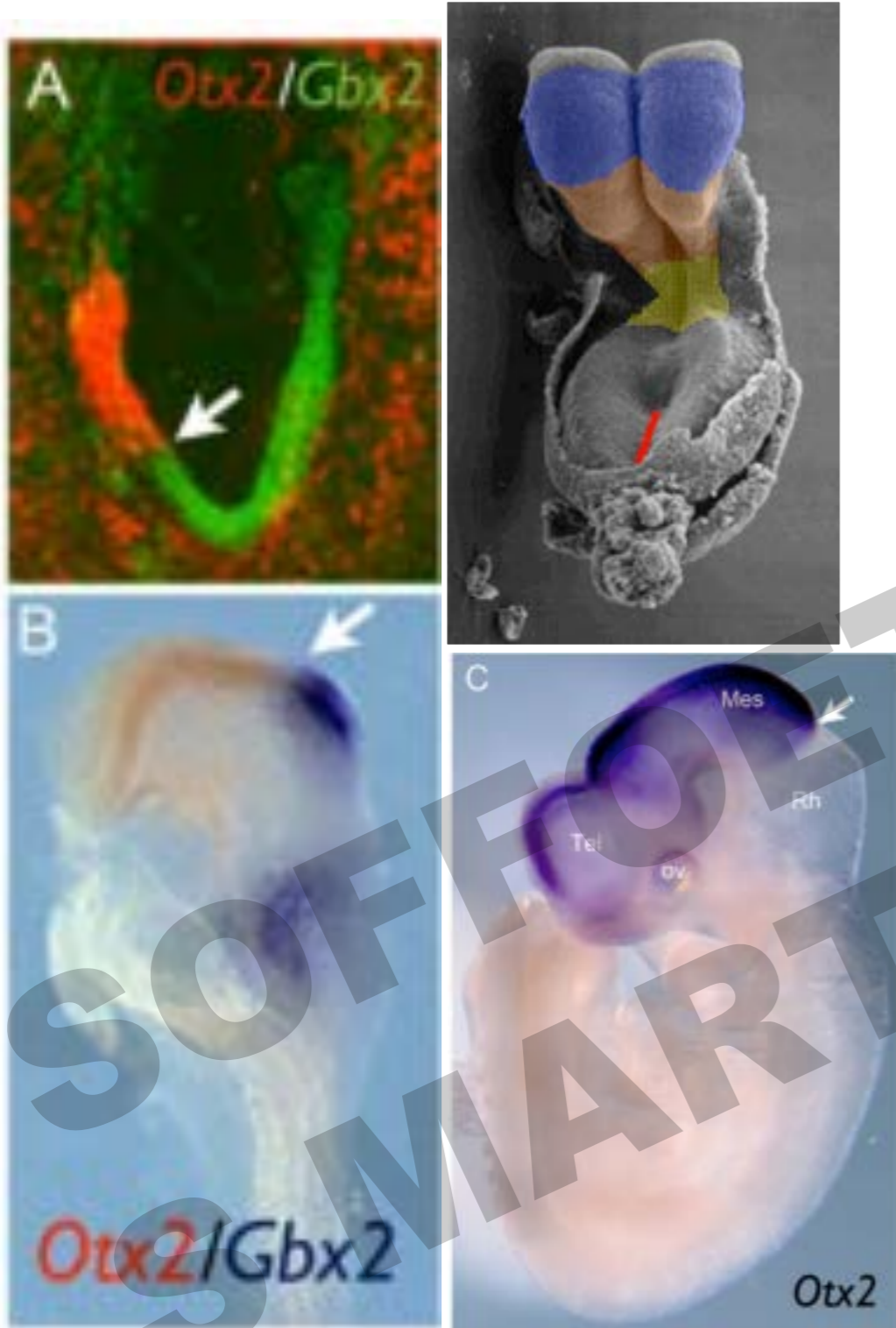
Amphioxus
Hox cluster

Mouse Hoxa
Mouse Hoxb
Mouse Hoxc
Mouse Hoxd

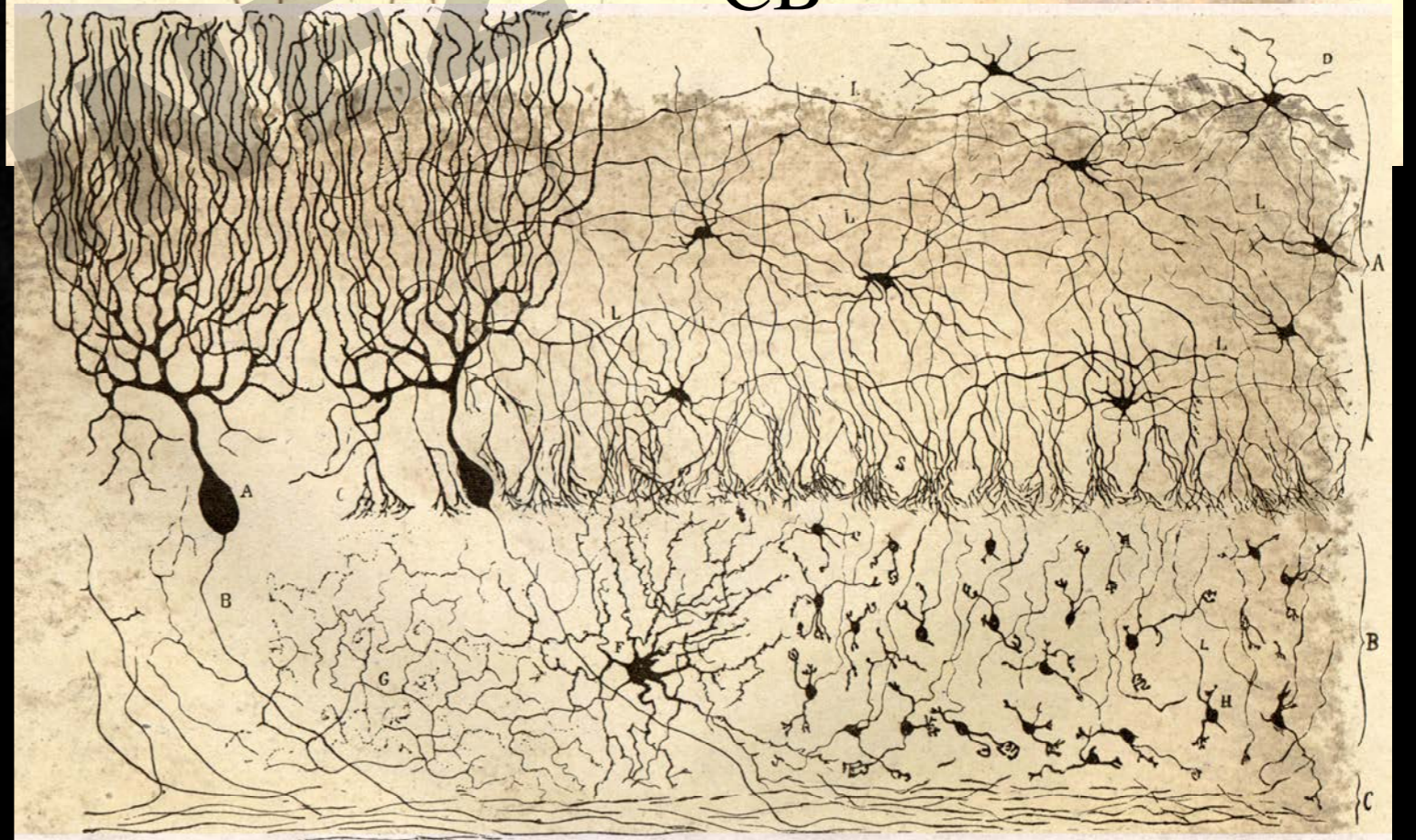
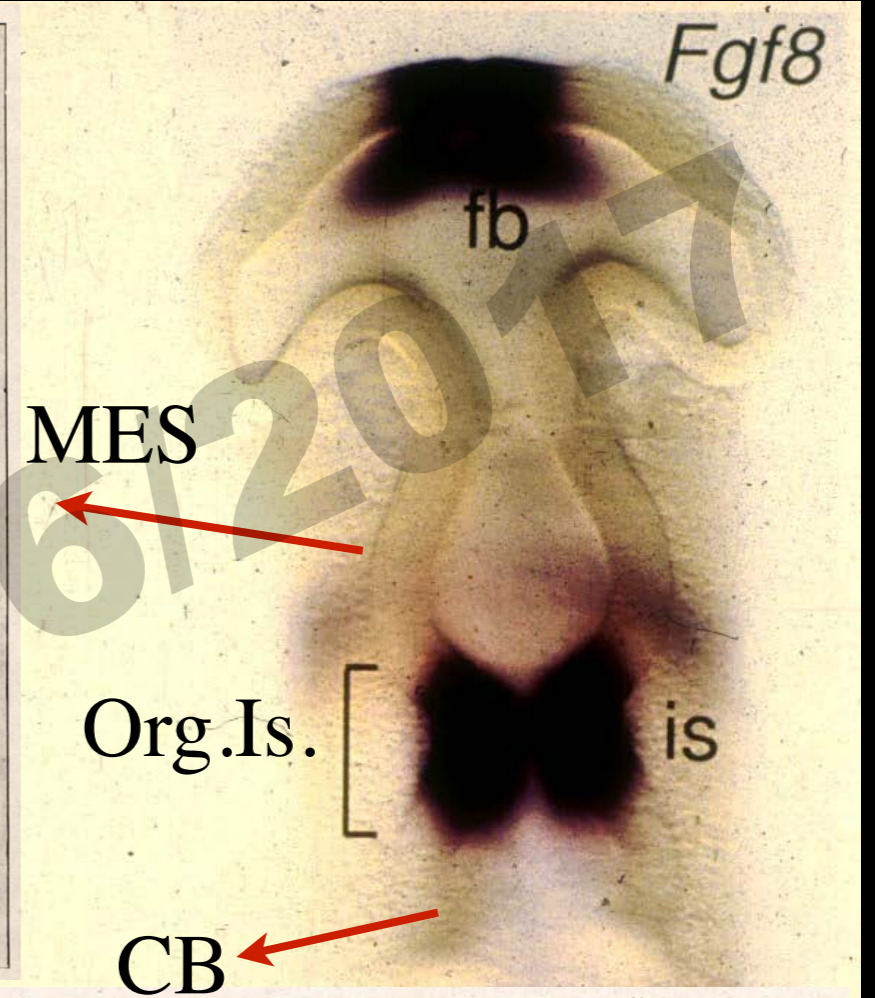
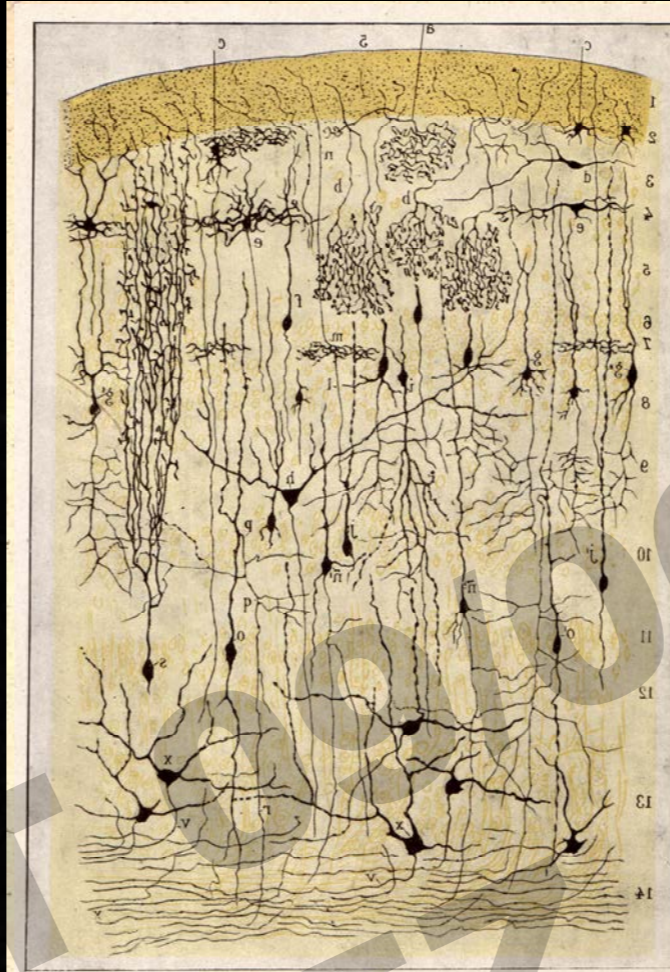
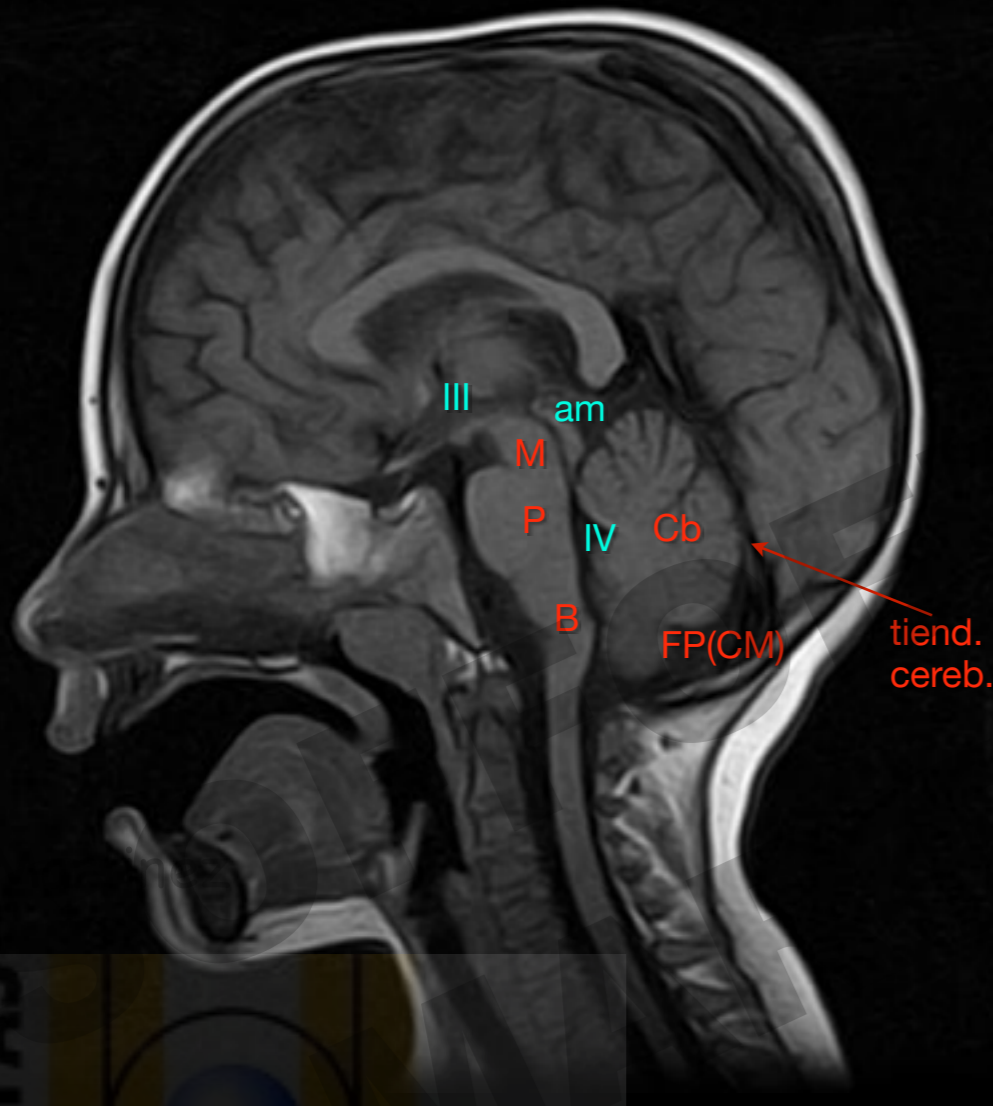


NEURULATION= A-P REGIONALIZATION

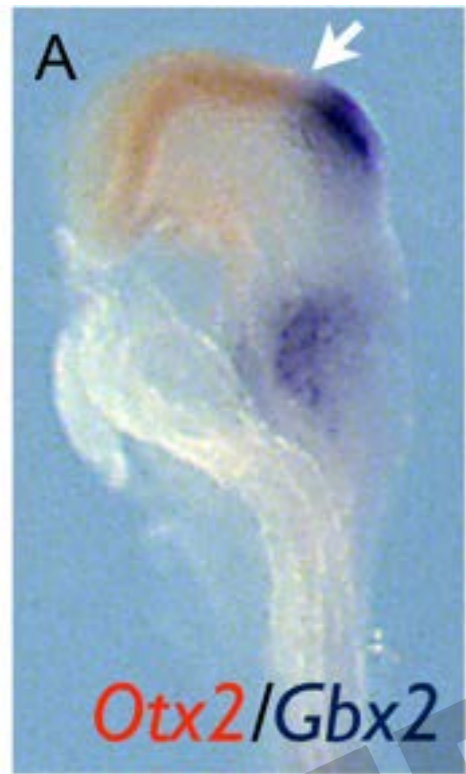
BRAIN SEGMENTATION



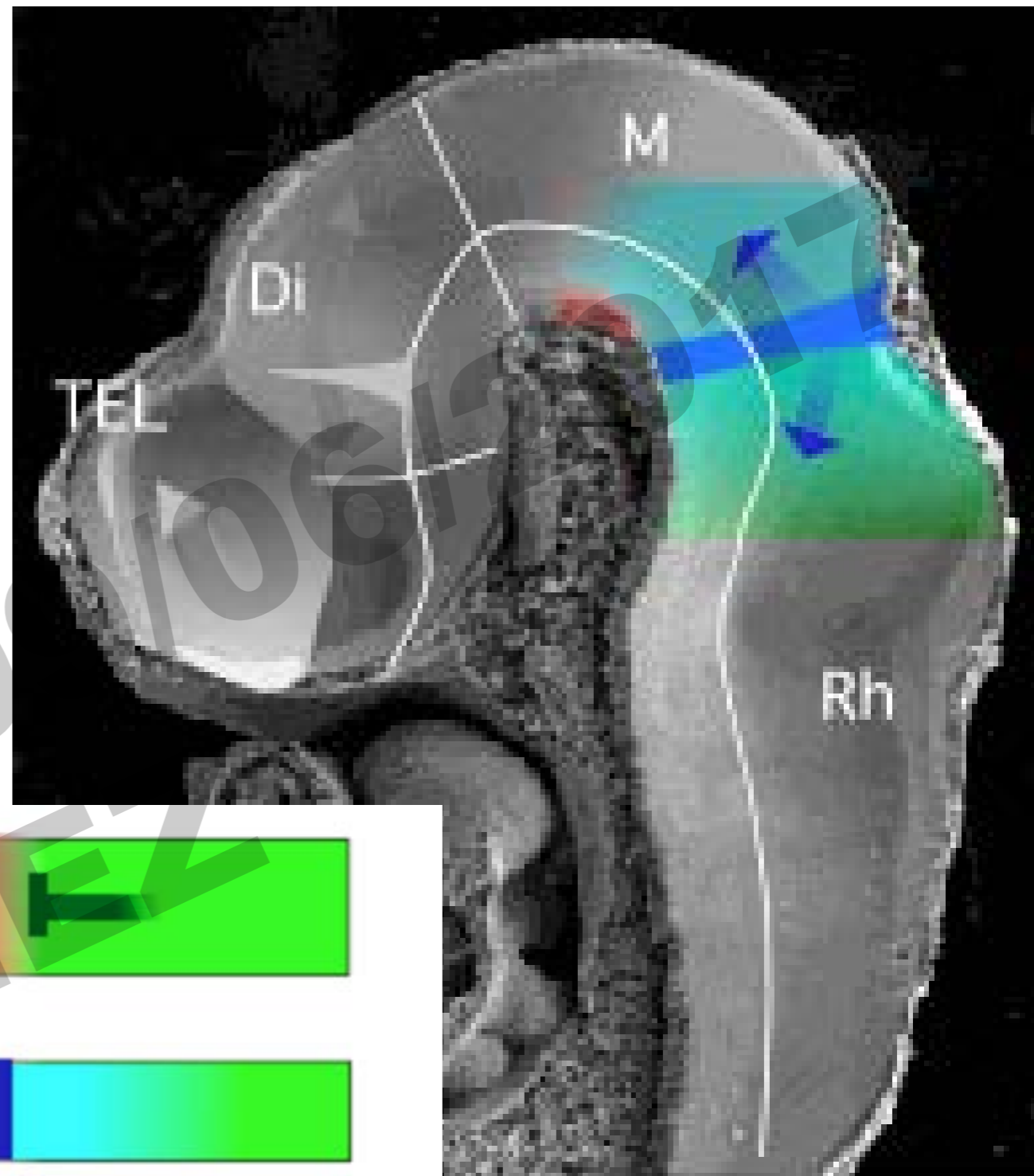
CEREBELLUM ET MESENCEPHALON



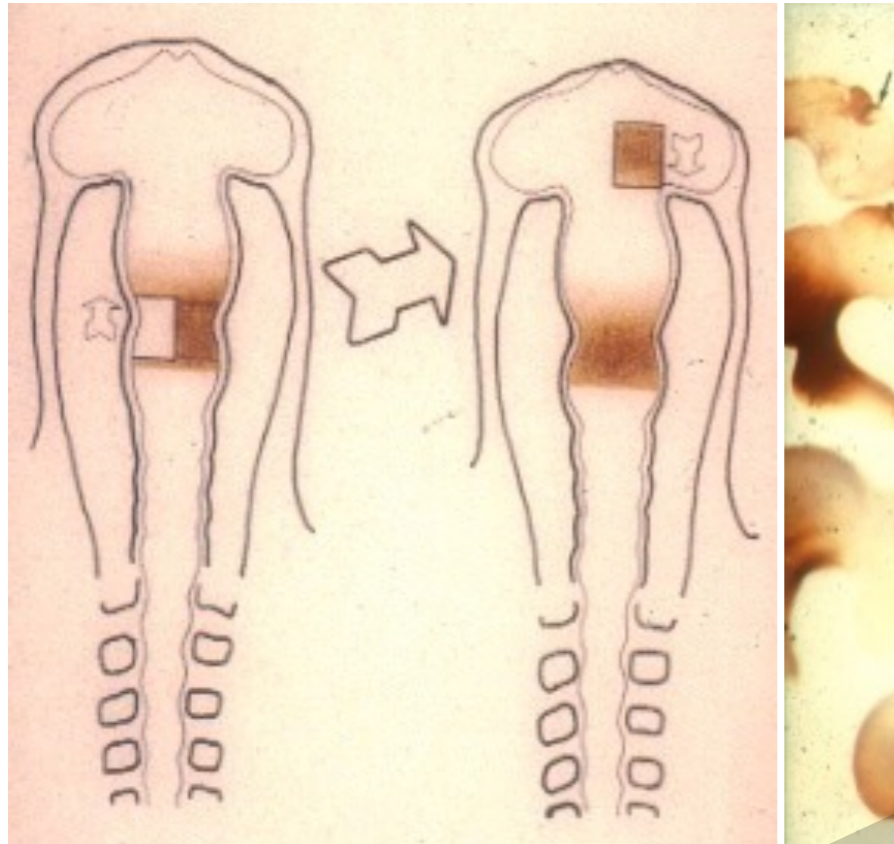
The IsO



Fgf8



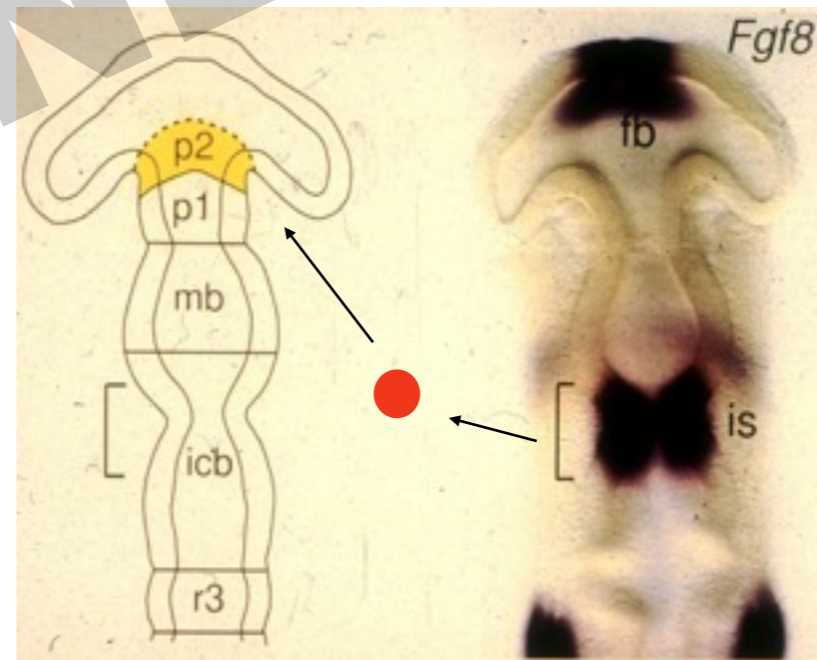
THE ISTHMIC ORGANIZER.



Martínez, S. ; Wassef, M. and Alvarado-Mallart, R.M.

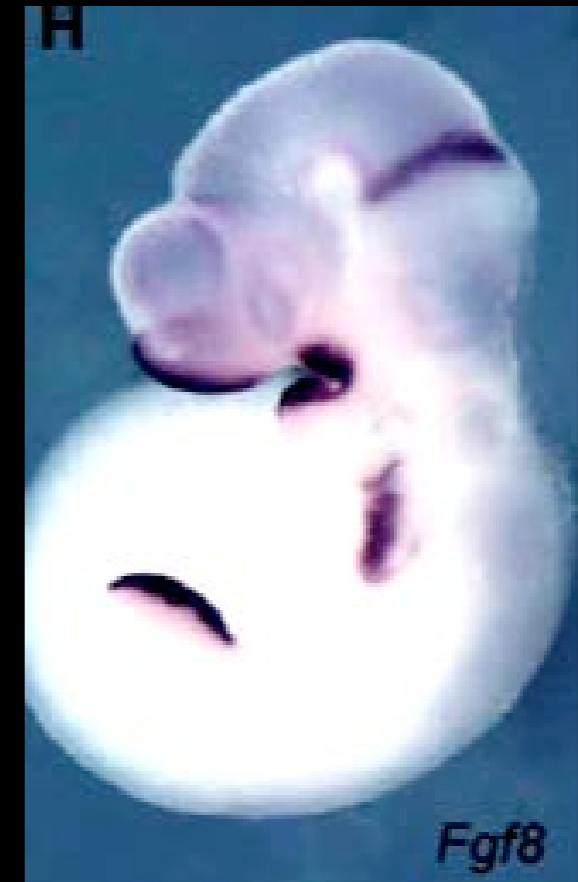
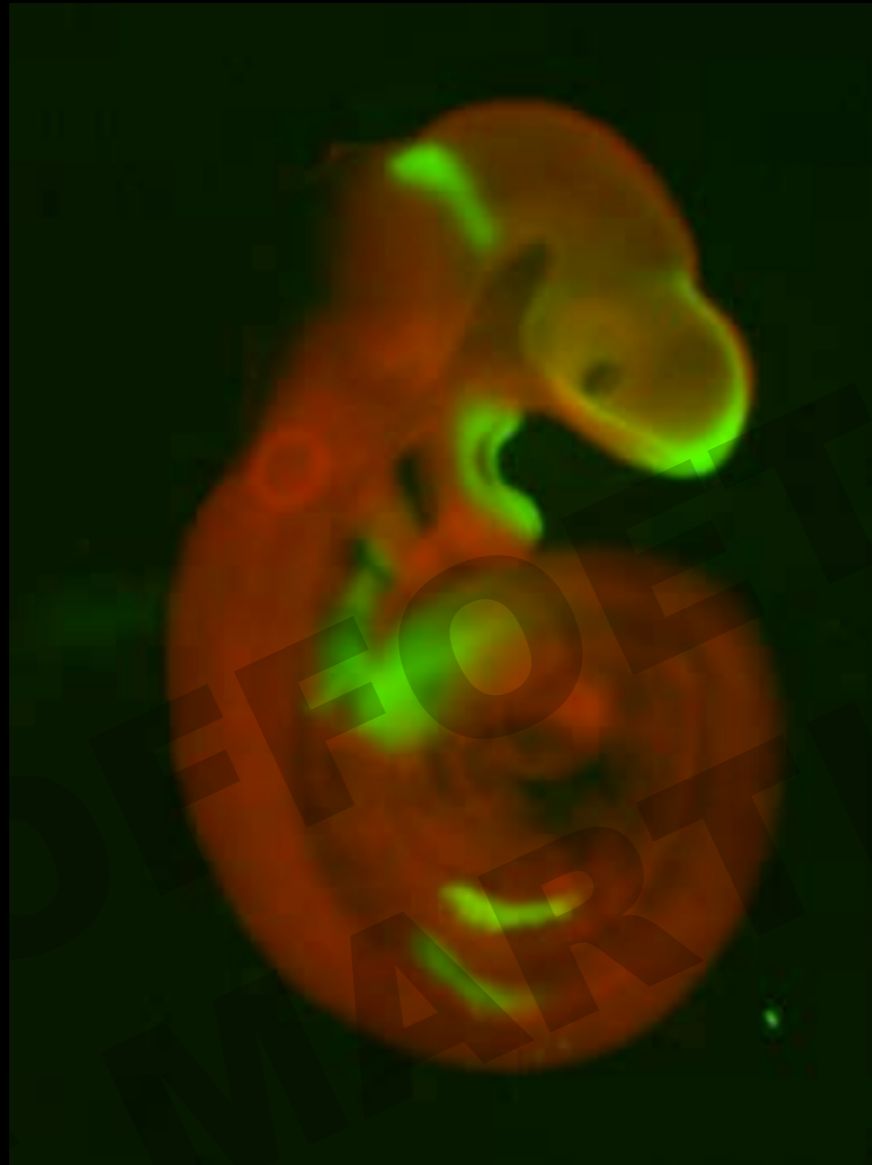
"Induction of a mesencephalic phenotype in the 2-day-old chick prosencephalon is preceded by the early expression of the homeobox gene En".
Neuron, 6, 971-981 (1991)

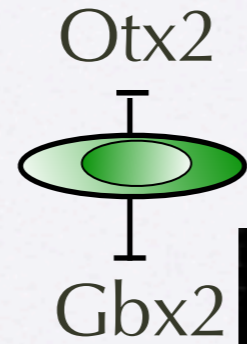
Fgf8: The signaling molecule



Fgf8. THE MANAGER OF BRAIN ORGANIZERS

Fgf8





Fgf8

En1/2

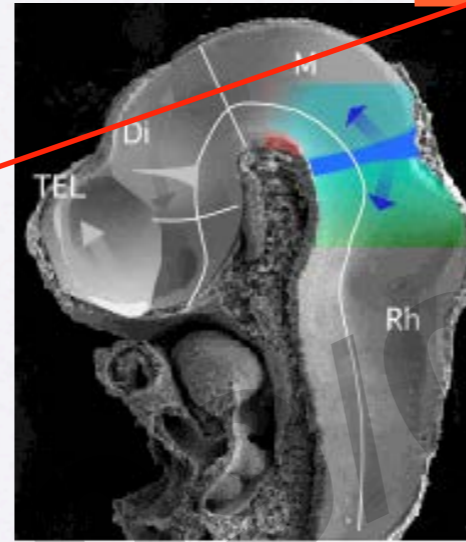
Wnt1

Pax2/5

GRN

Midbrain

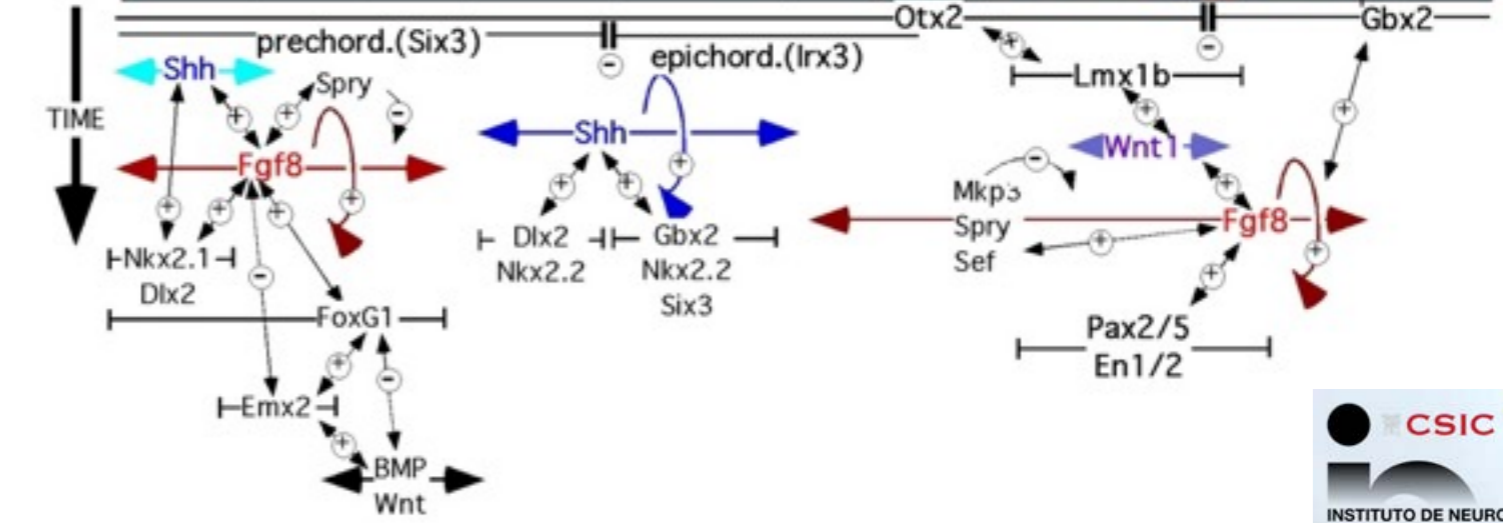
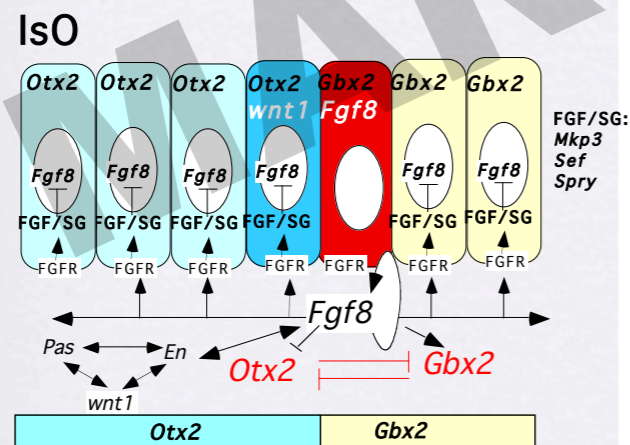
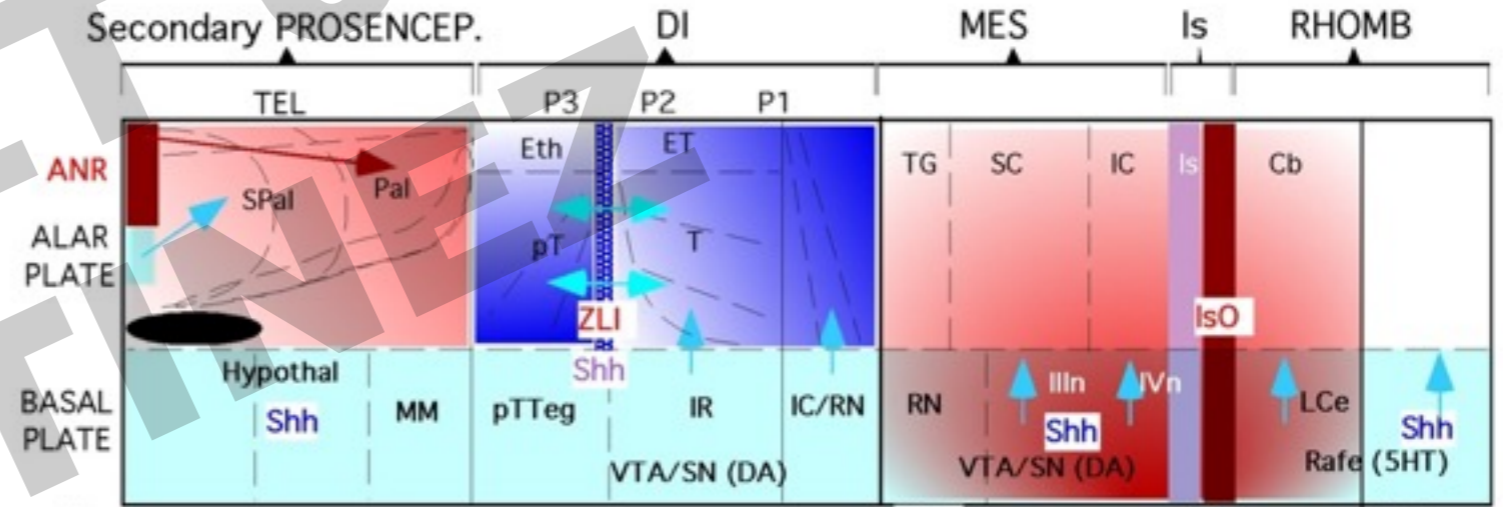
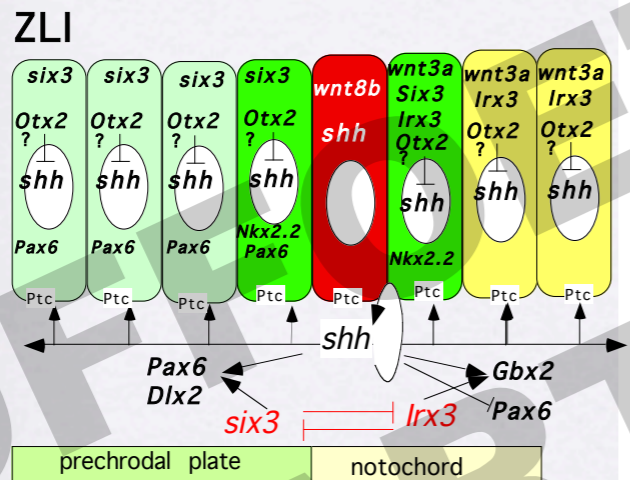
Cerebellum

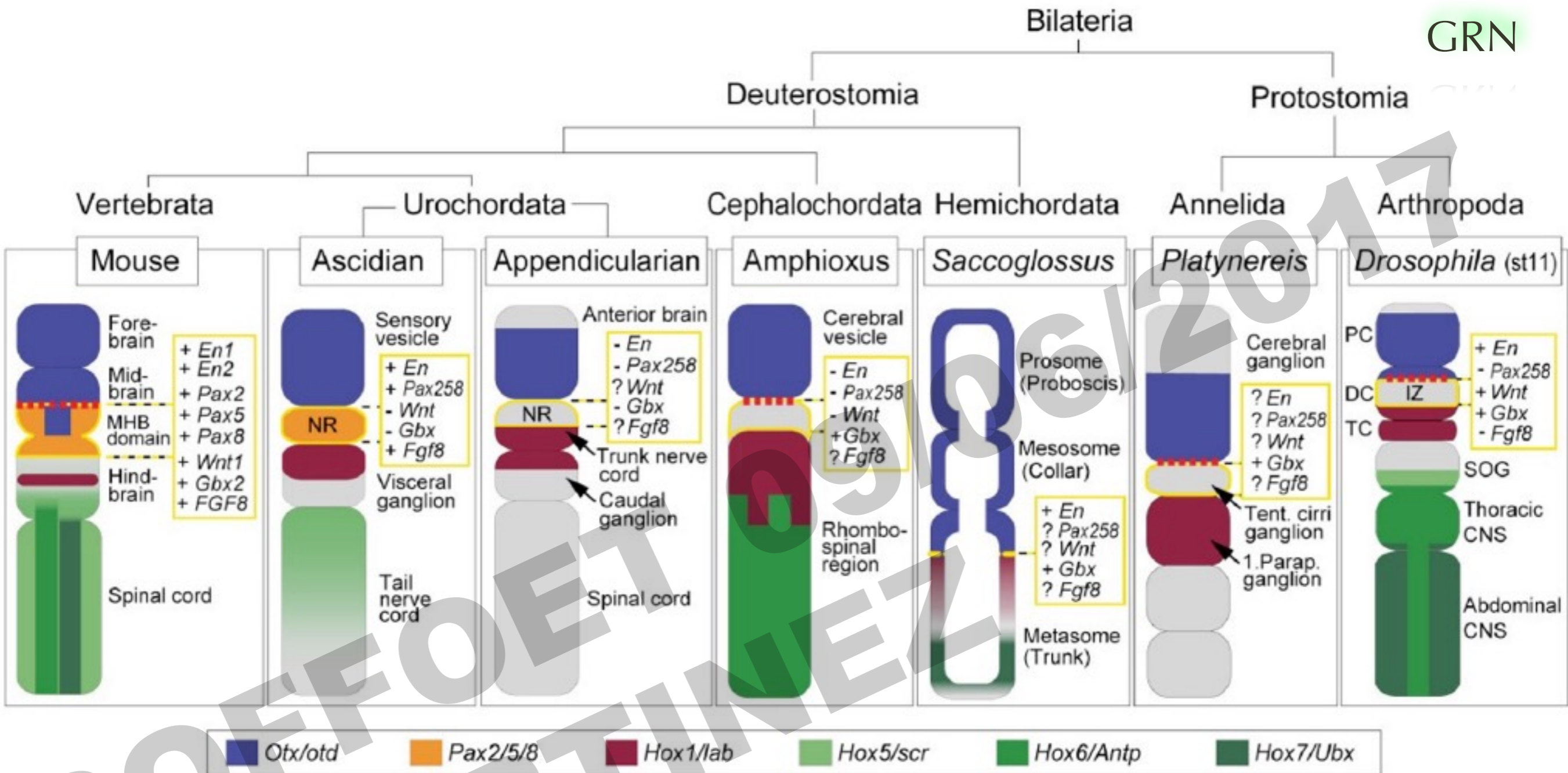


Is ORGANIZER 1999

En2 overexpression
polimorfisms
Autism Spectrum Dis

TEN YEARS LATTER....





Comparison of CNS regions and gene expression domains among chordates, hemichordates, annelids, and arthropods. Focus is on the anteroposterior regionalization of the anterior CNS, including the brain. The schemes reflect the situation in the CNS of the vertebrate mouse (at about embryonic day 10–12.5), the ascidians *Ciona* and *Halocynthia* [11, 13, 43, 44, 54], the appendicularian *Oikopleura* (at the late hatchling stage) [14], the amphioxus *Branchiostoma* (at the 10–13 somite stages) [15, 16, 45, 76], the hemichordate *Saccoglossus* (at the one gill slit stage) [48, 49], the polychaete annelid *Platynereis* (neuroectoderm at the metatrochophora stage) [46, 47], and the arthropod *Drosophila* (at stage 11, st11; this study). Expression of *Otx/otd*, *Pax2,5,8*, *Hox1/lab*, *Hox5/scr*, *Hox6/Antp*, and *Hox7/Ubx* genes is indicated according to the colour code. The dashed line in red indicates the interface between *Otx/otd* and *Gbx/unpg* expression domains. The expression of further genes within the gap (encircled in yellow) between the anterior *Otx/otd* and posterior *Hox1/lab* domains is noted: '+' indicates expression of the respective gene; '-' absence of expression; and '?' expression is not yet determined. The phylogenetic tree is based on [76]. For further details, see the text. IZ, intervening zone; MHB domain, midbrain/hindbrain boundary domain; NR, neck region; Parap., Parapodial; Tent., Tentacular.

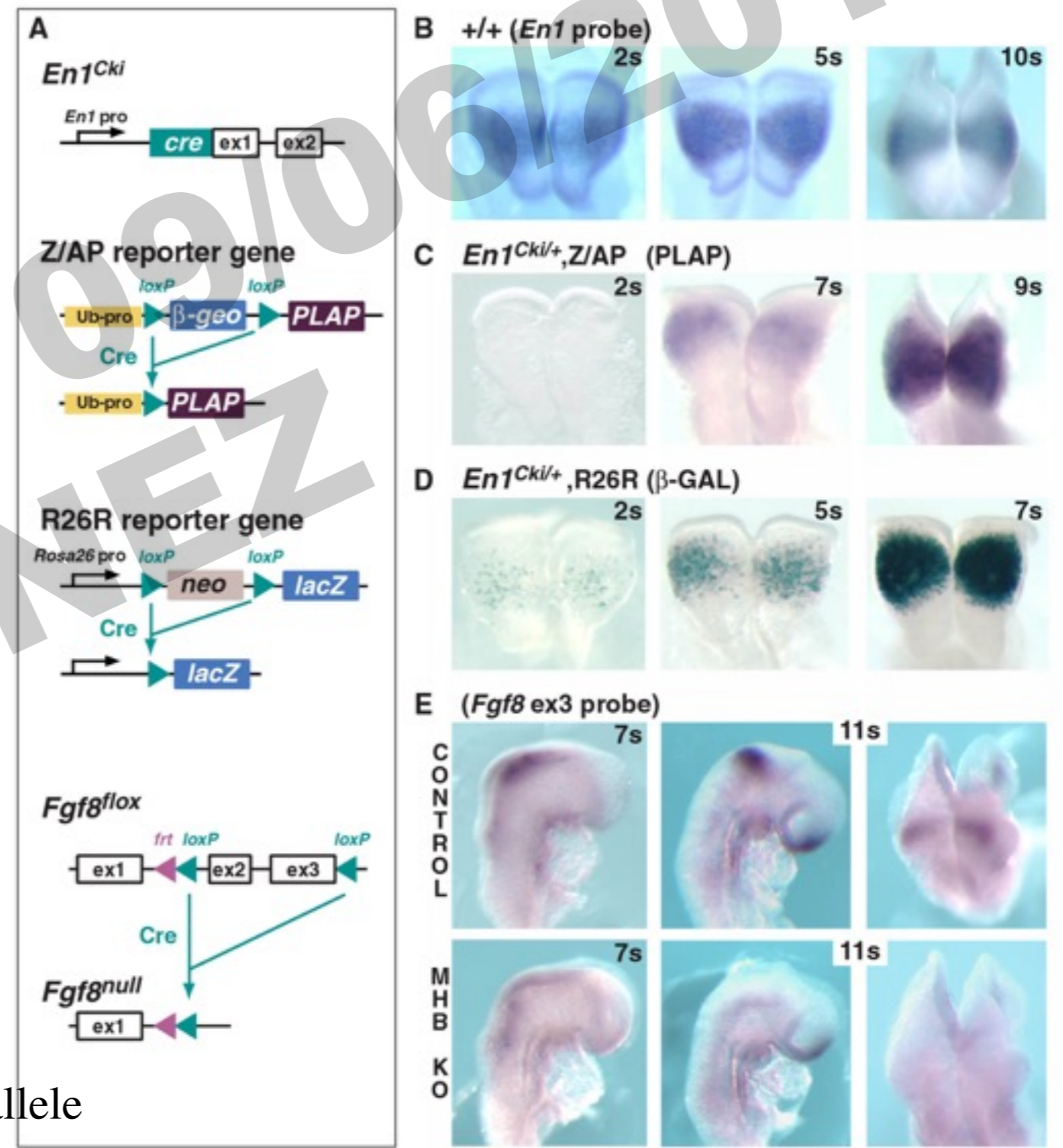
The isthmic organizer signal FGF8 is required for cell survival in the prospective midbrain and cerebellum

Candace L. Chi¹, Salvador Martinez², Wolfgang Wurst³, and Gail R. Martin¹

Fgf8 = Cb
→ Mes

cell proliferation
cell survival
graded information ?

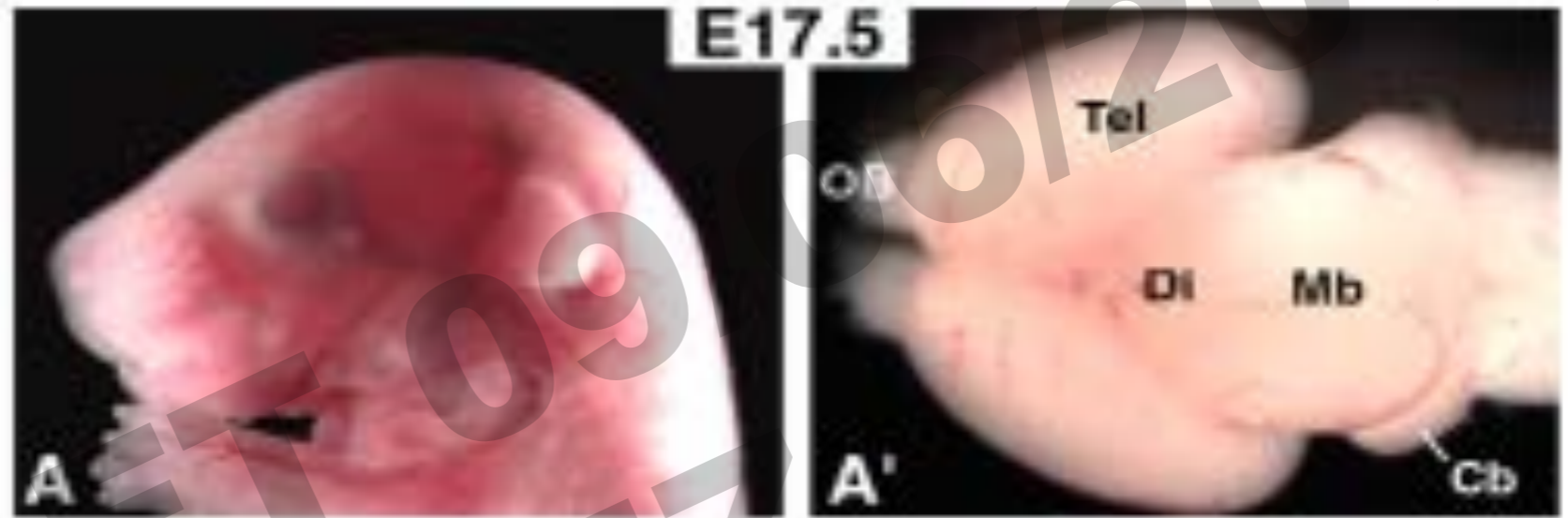
Figure 1



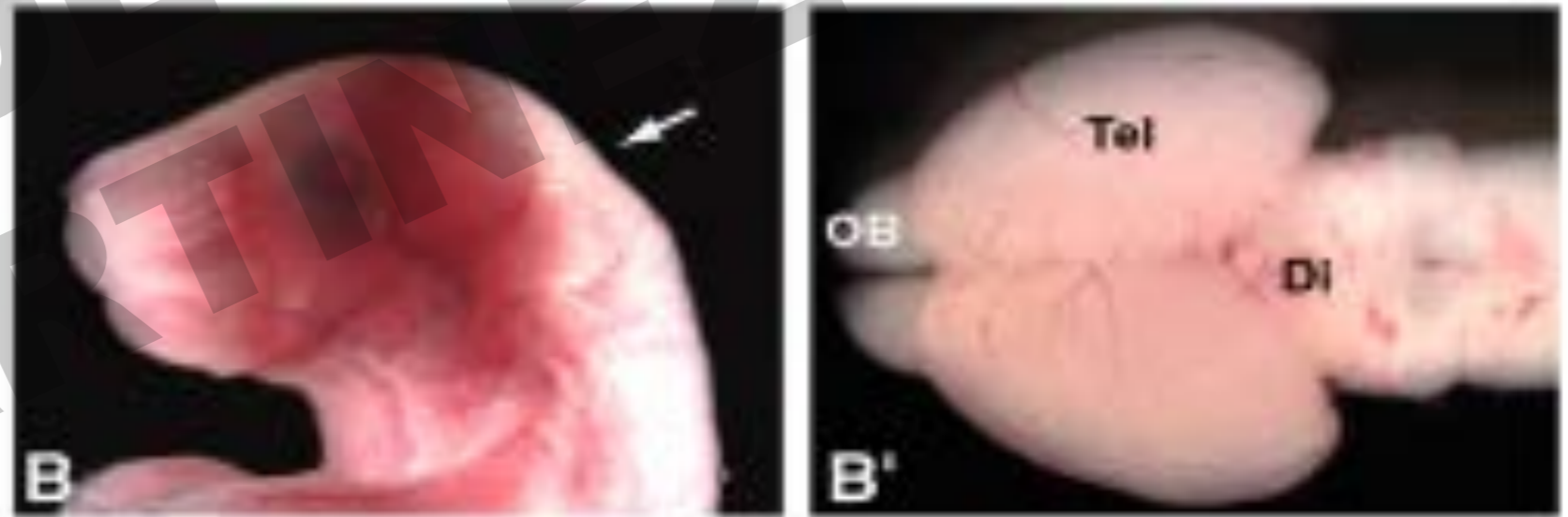
Cre-mediated recombination of *Fgf8^{lox}* deletes exons 2 and 3, creating the *Fgf8^{null}* allele

Figure 2

control

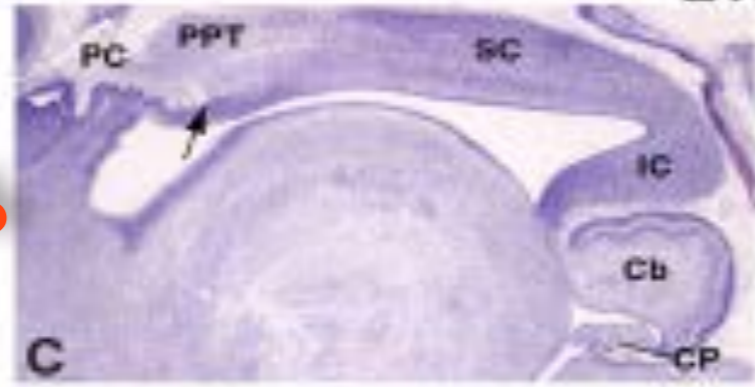


MHB KO

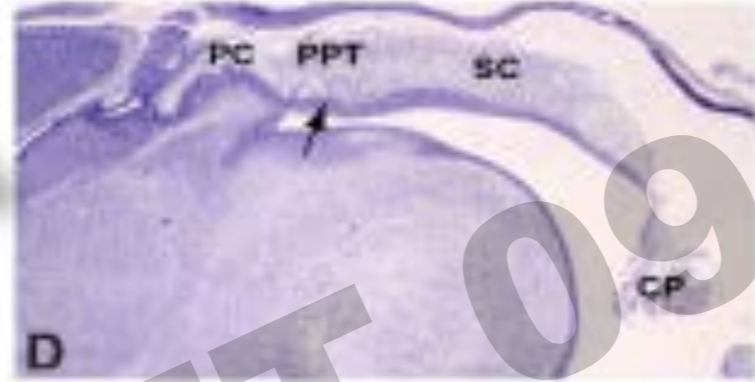


E17

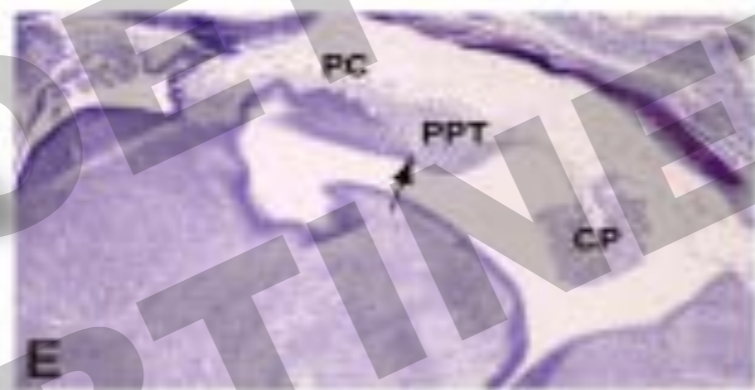
control
Fgf8



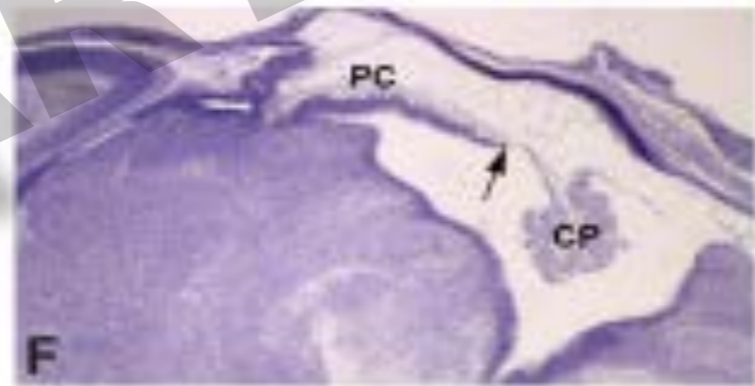
neo/neo
Fgf8 ↓



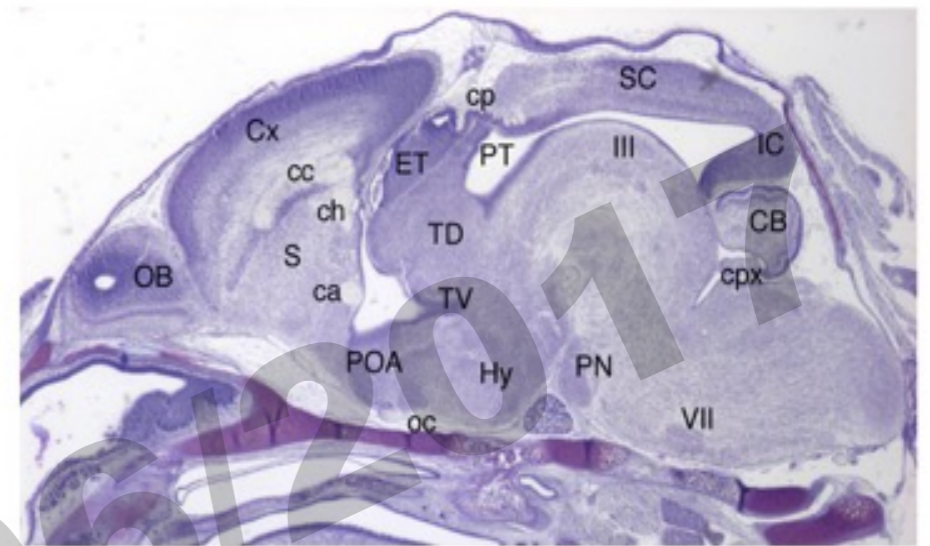
neo/null
Fgf8 ↓↓



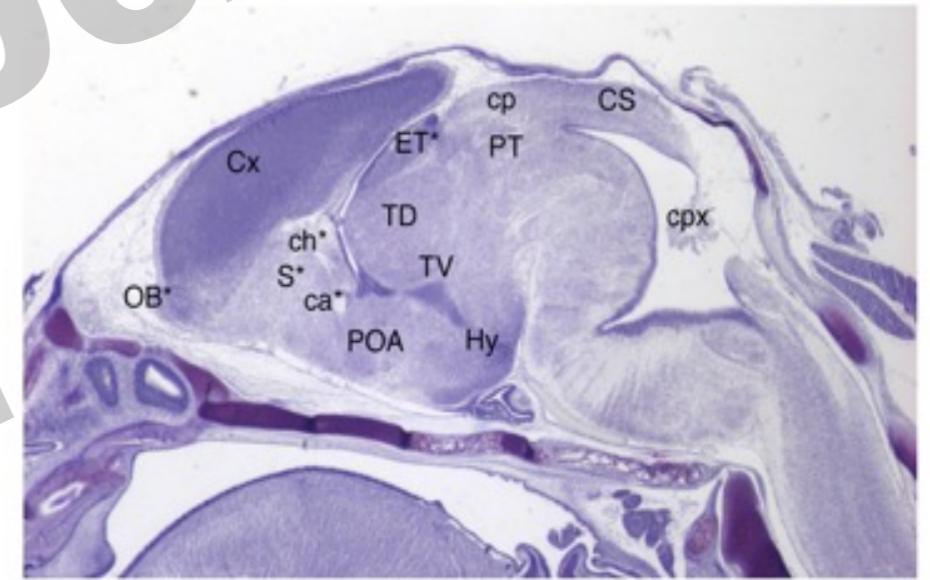
MHB KO
XXX



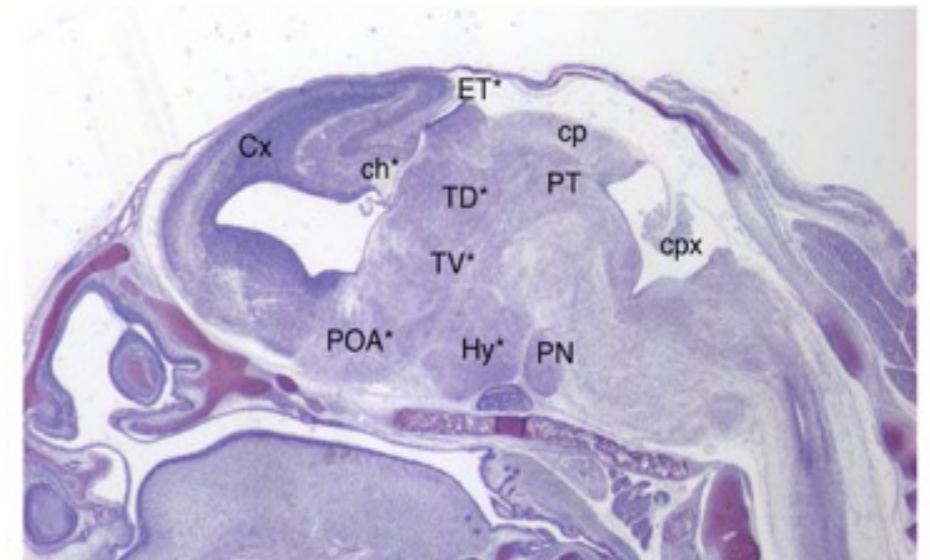
WT



neo/
neo



neo/
null



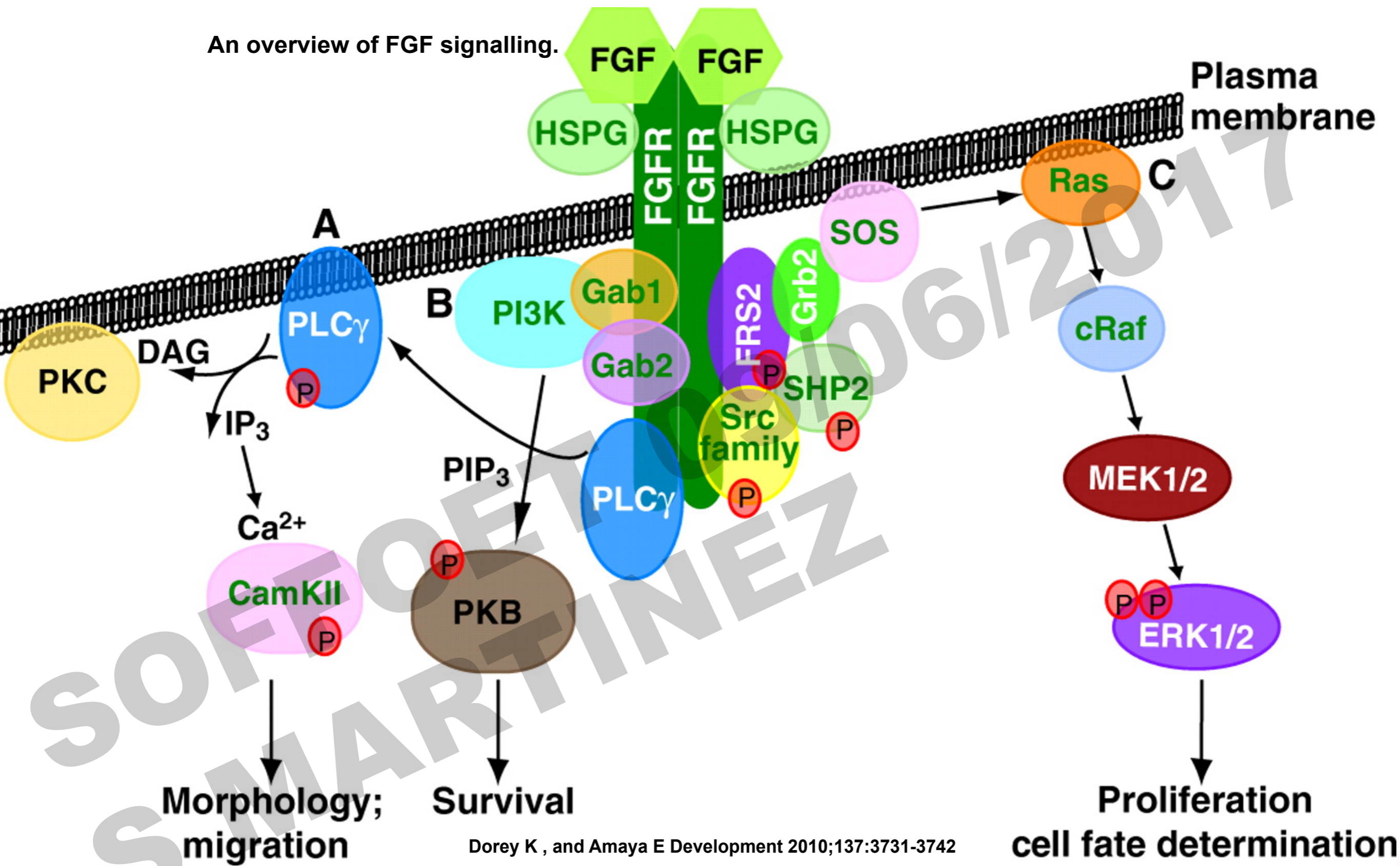
D-aSC-pSC -IC-Is-Cb

D-aSC-pSC-IC-Is-Cb

D-aSC-pSC-IC-Is-Cb

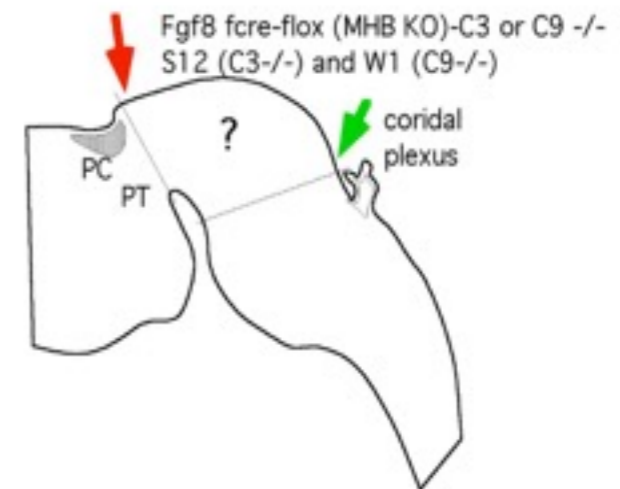
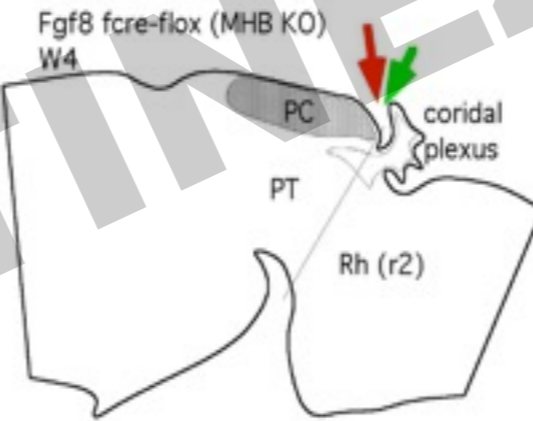
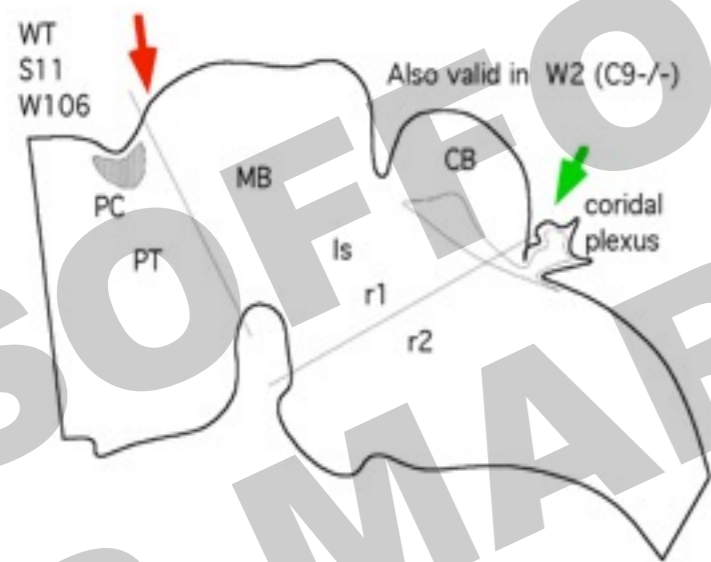
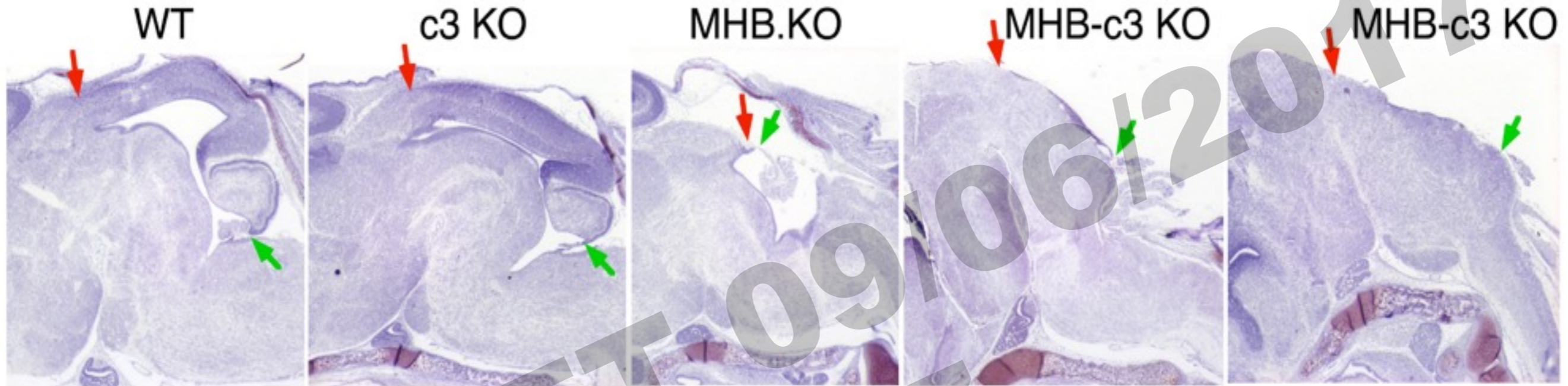
D-aSC-pSC-IC-Is-Cb

An overview of FGF signalling.



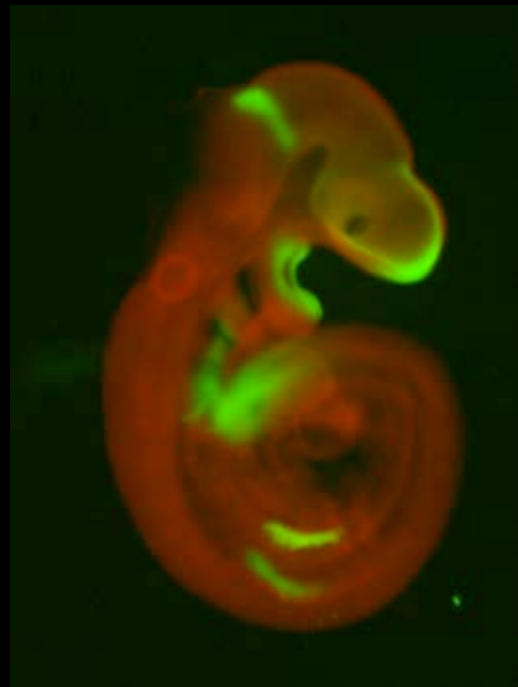
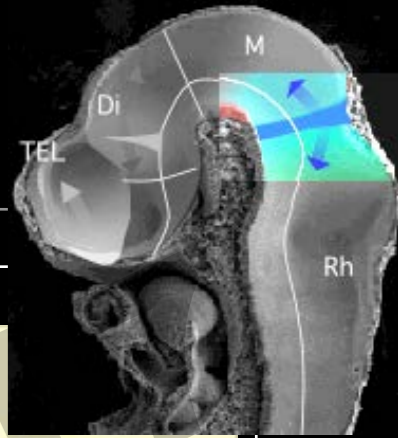
Dorey K, and Amaya E Development 2010;137:3731-3742

HAS FGF8 OTHER ROLE THAN CELL SURVIVAL?

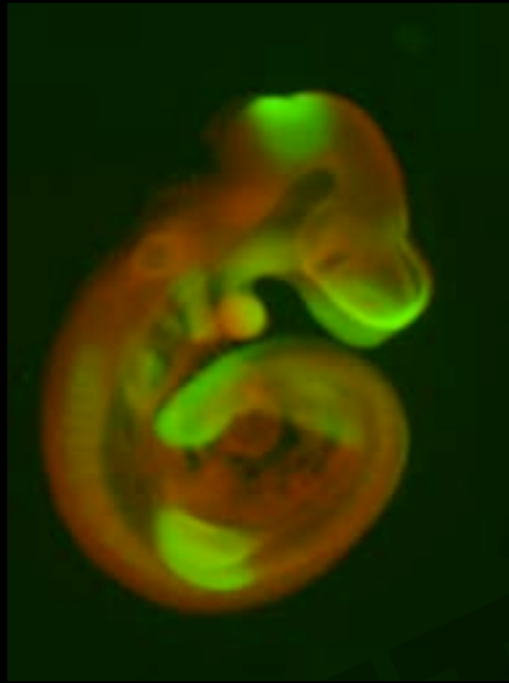


YES. Fgf8 has PATTERNING PROPERTIES.

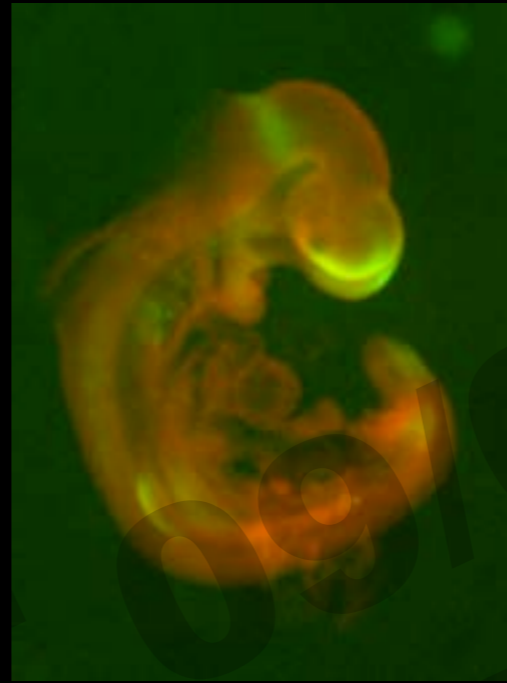
CONTROL OF Fgf8 ACTIVITY



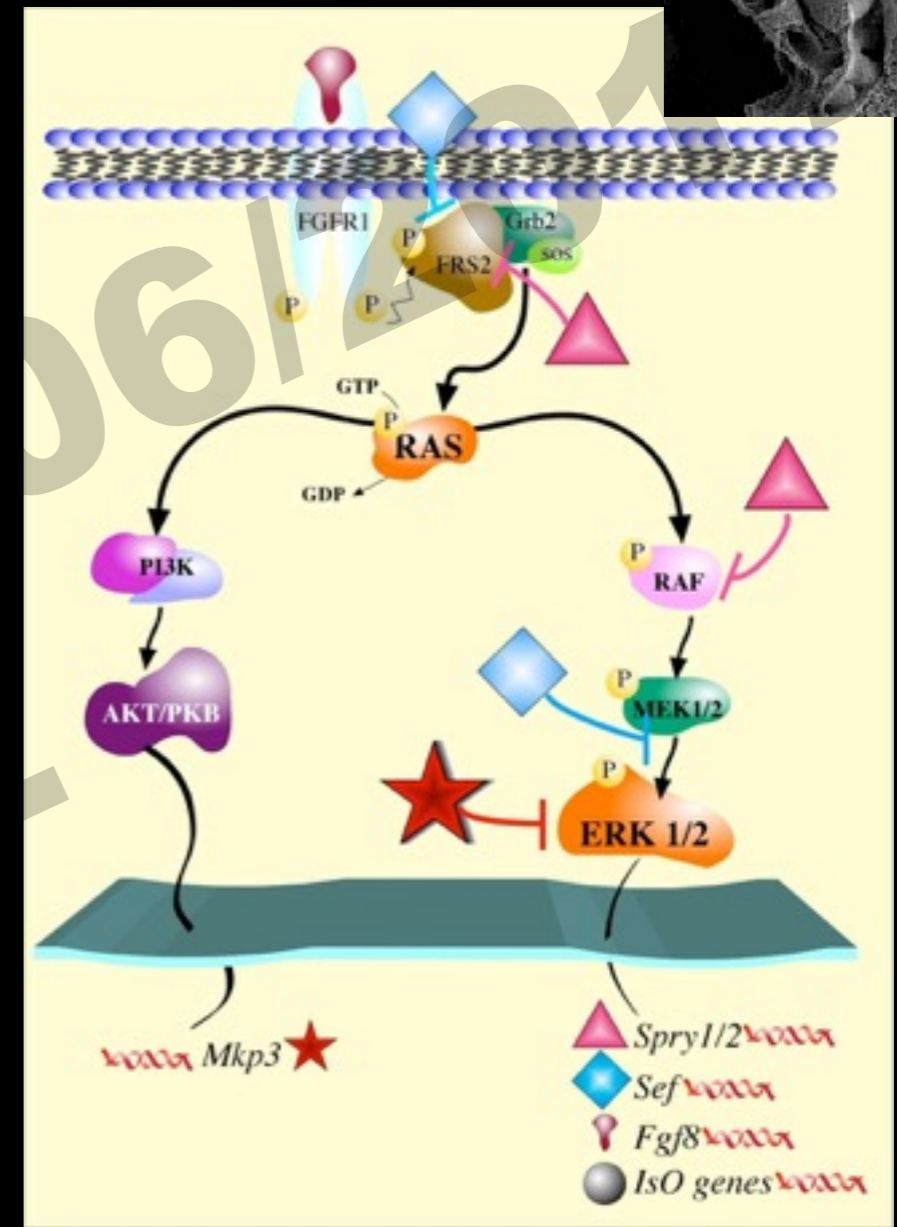
Fgf8



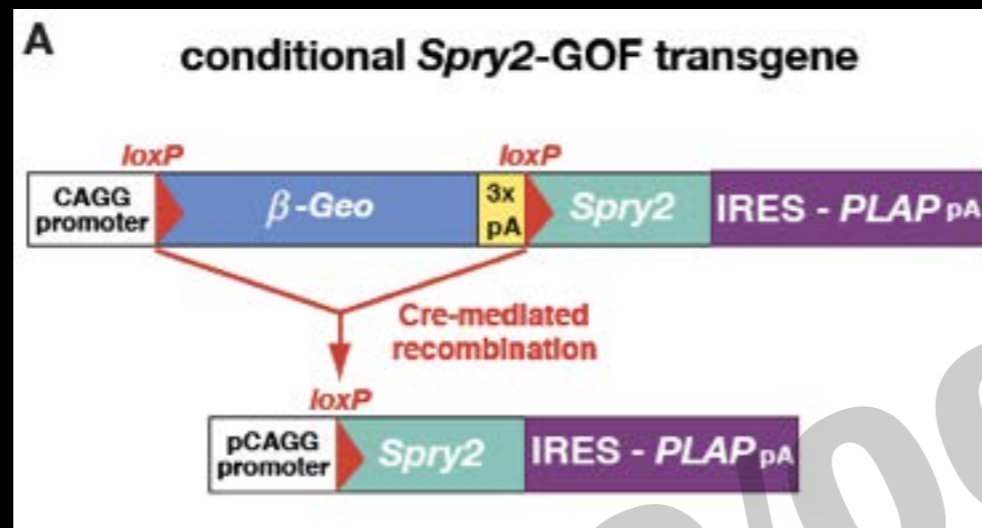
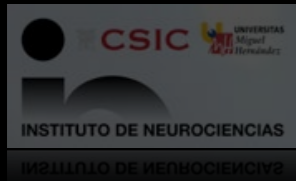
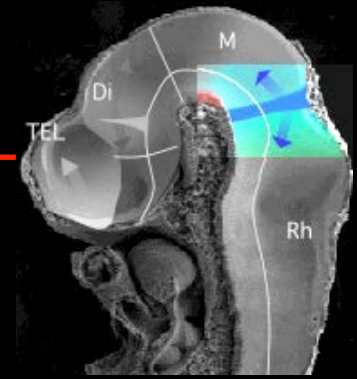
Spry2



*Mkp3/
Dusp6*



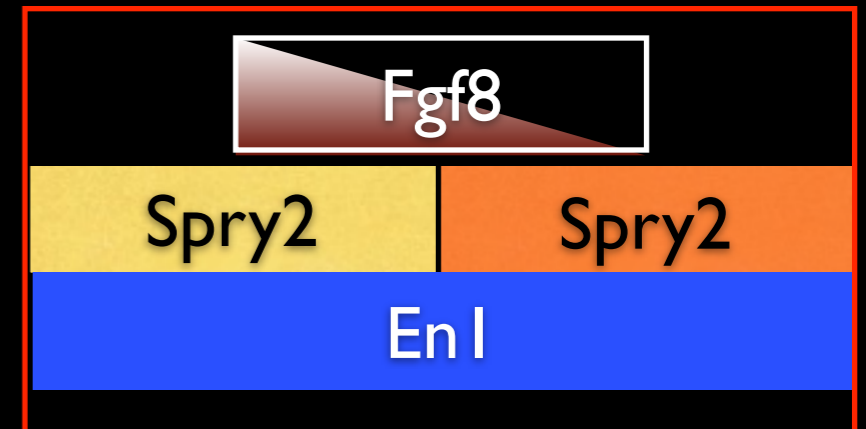
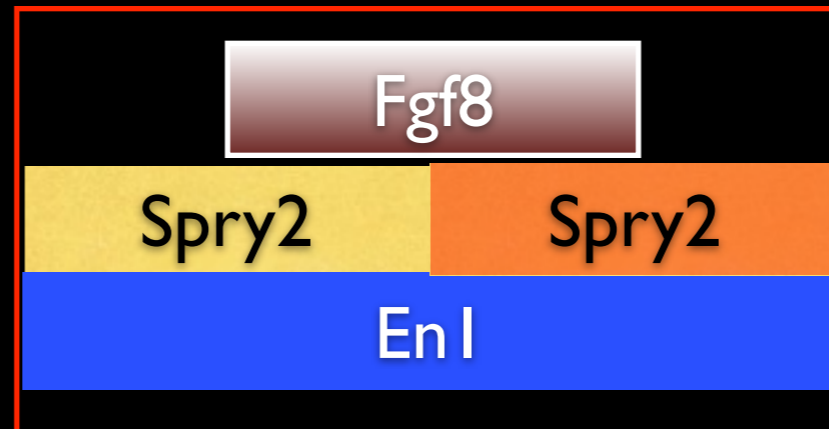
The isthmus region conditional mutation



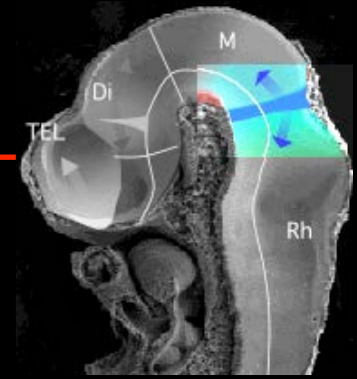
CONTROL

m/r1; S2 GOF

m/r1; S2 GOF; F8



The isthmus region conditional mutation



CONTROL

m/r1; S2 GOF

m/r1; S2 GOF; F8

Fgf8

Fgf8

Fgf8

Spry2

Spry2

Spry2

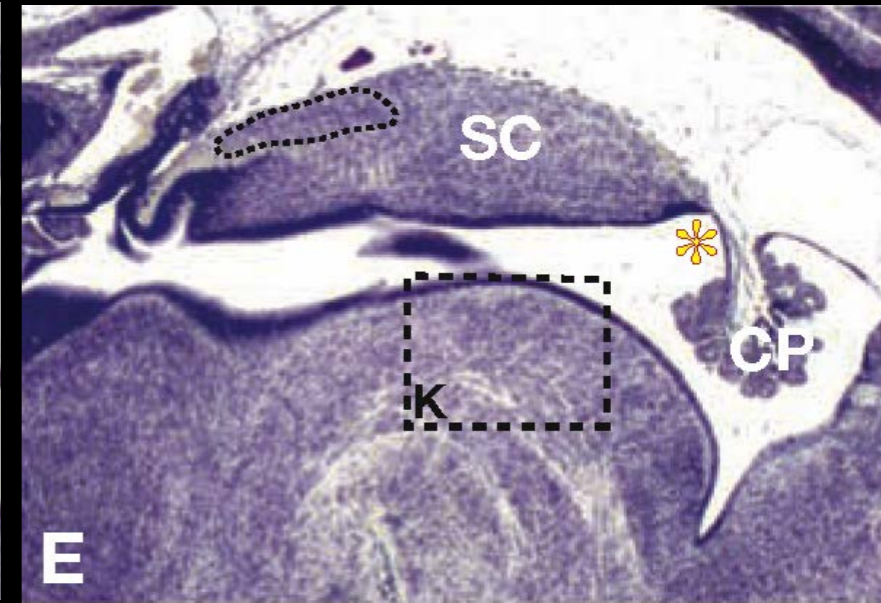
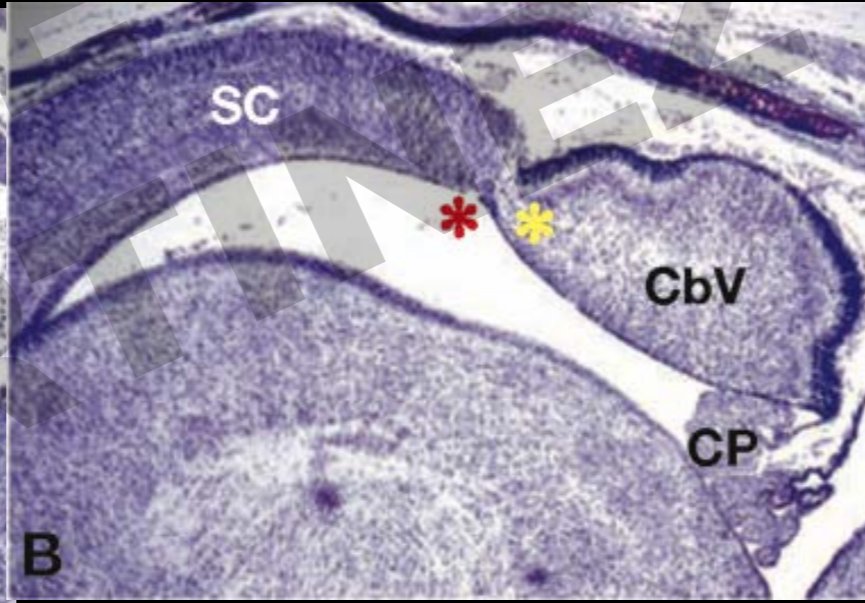
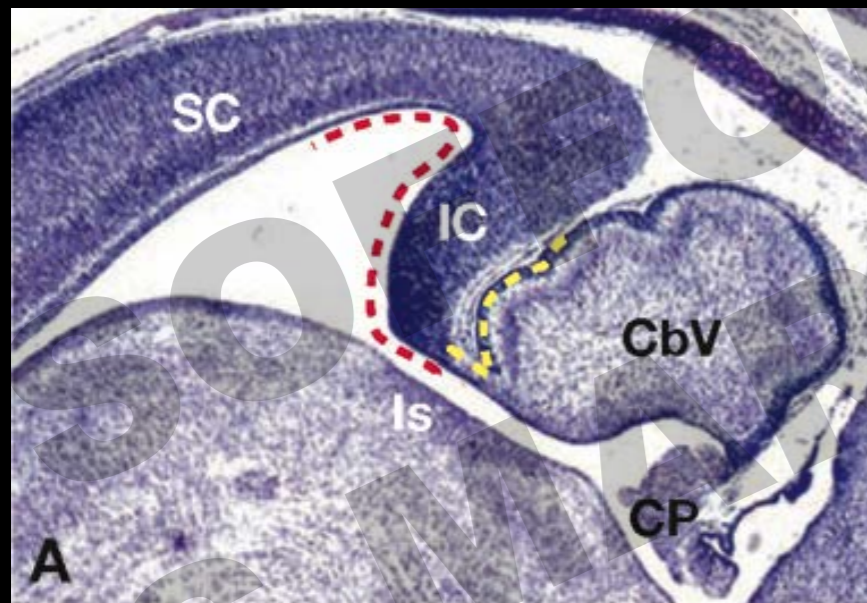
Spry2

Spry2

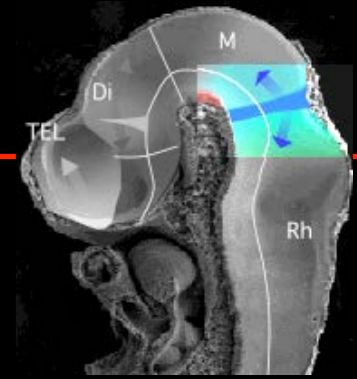
En1

En1

En1

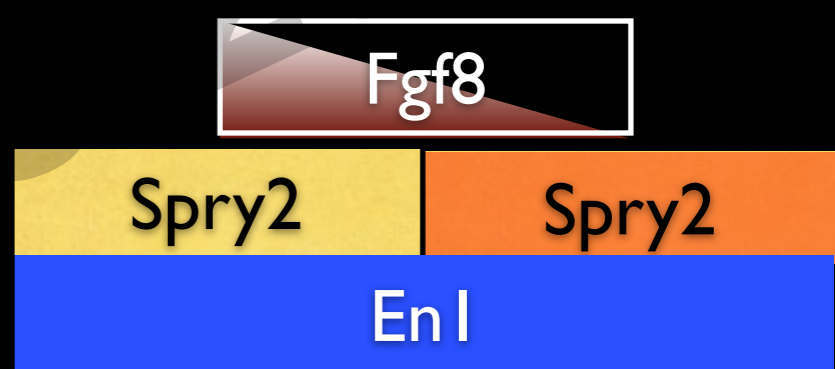


The isthmus region conditional mutation

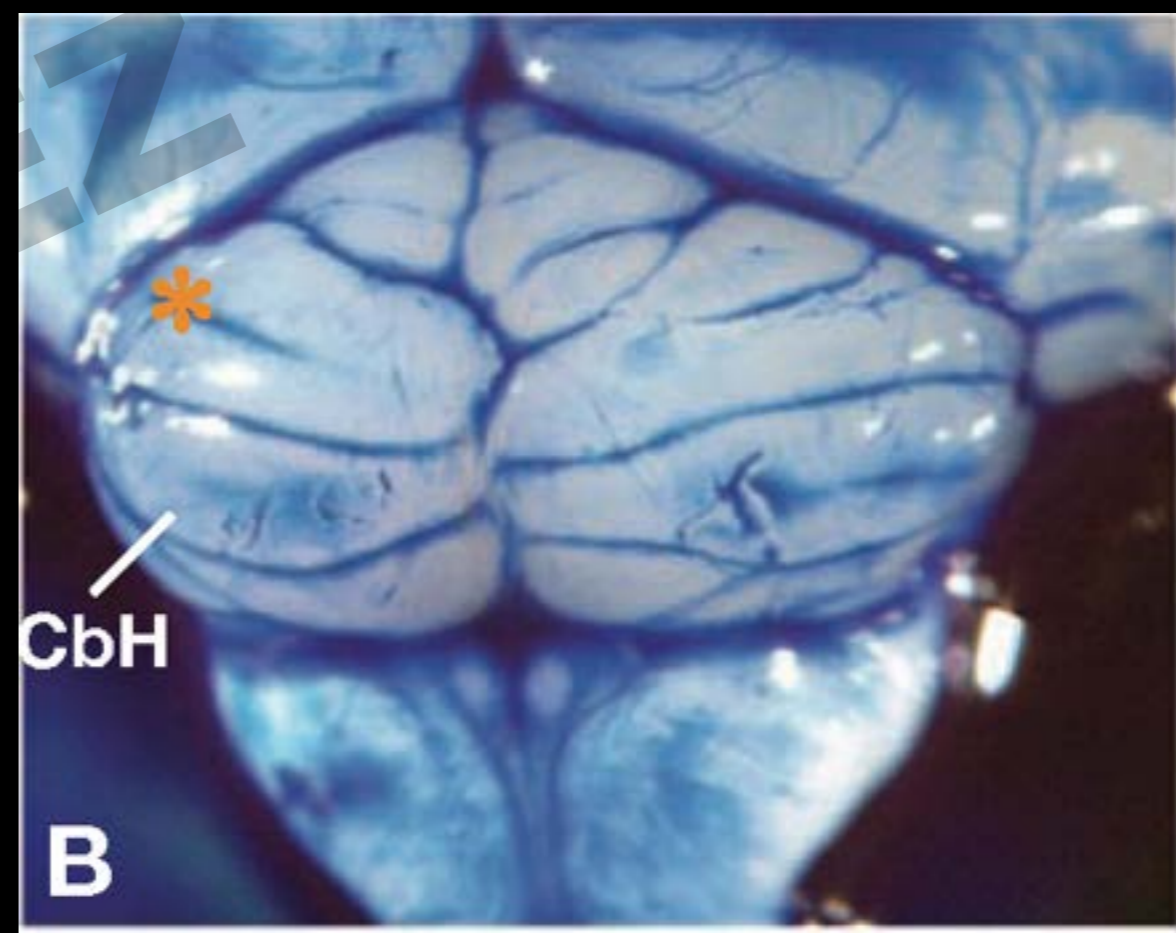
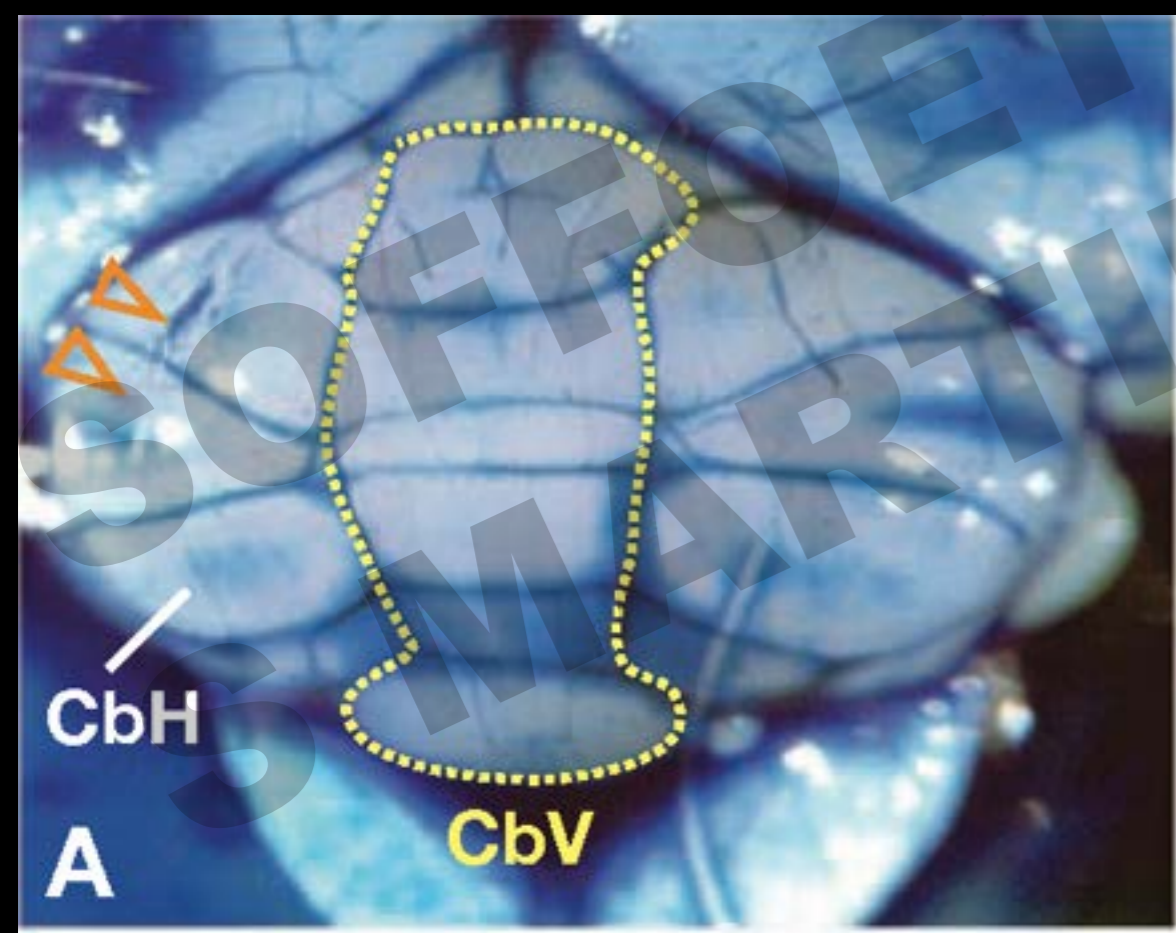


CONTROL

m/r1; S2 GOF; F8

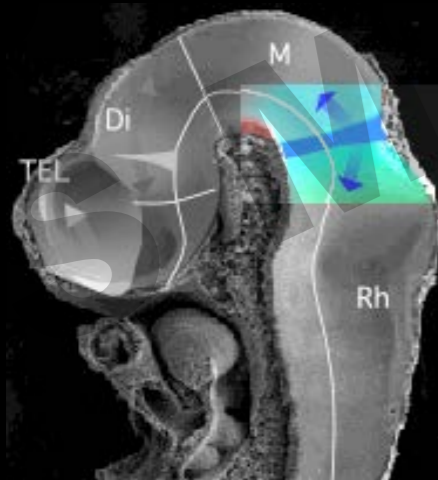
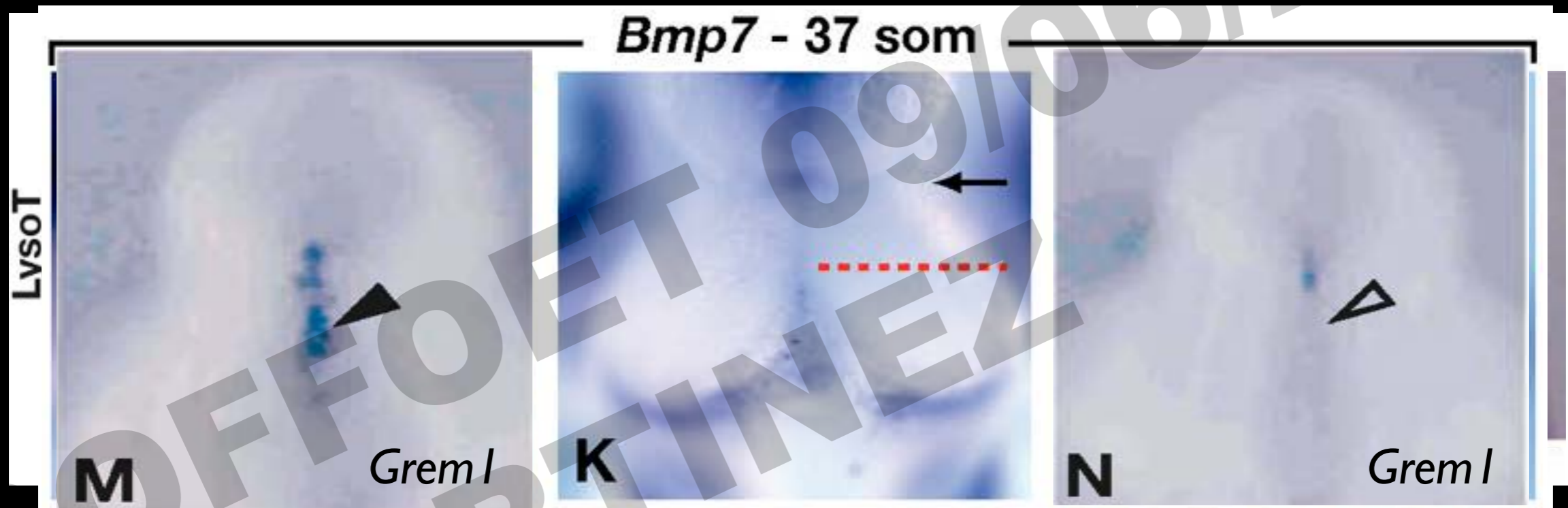


P21

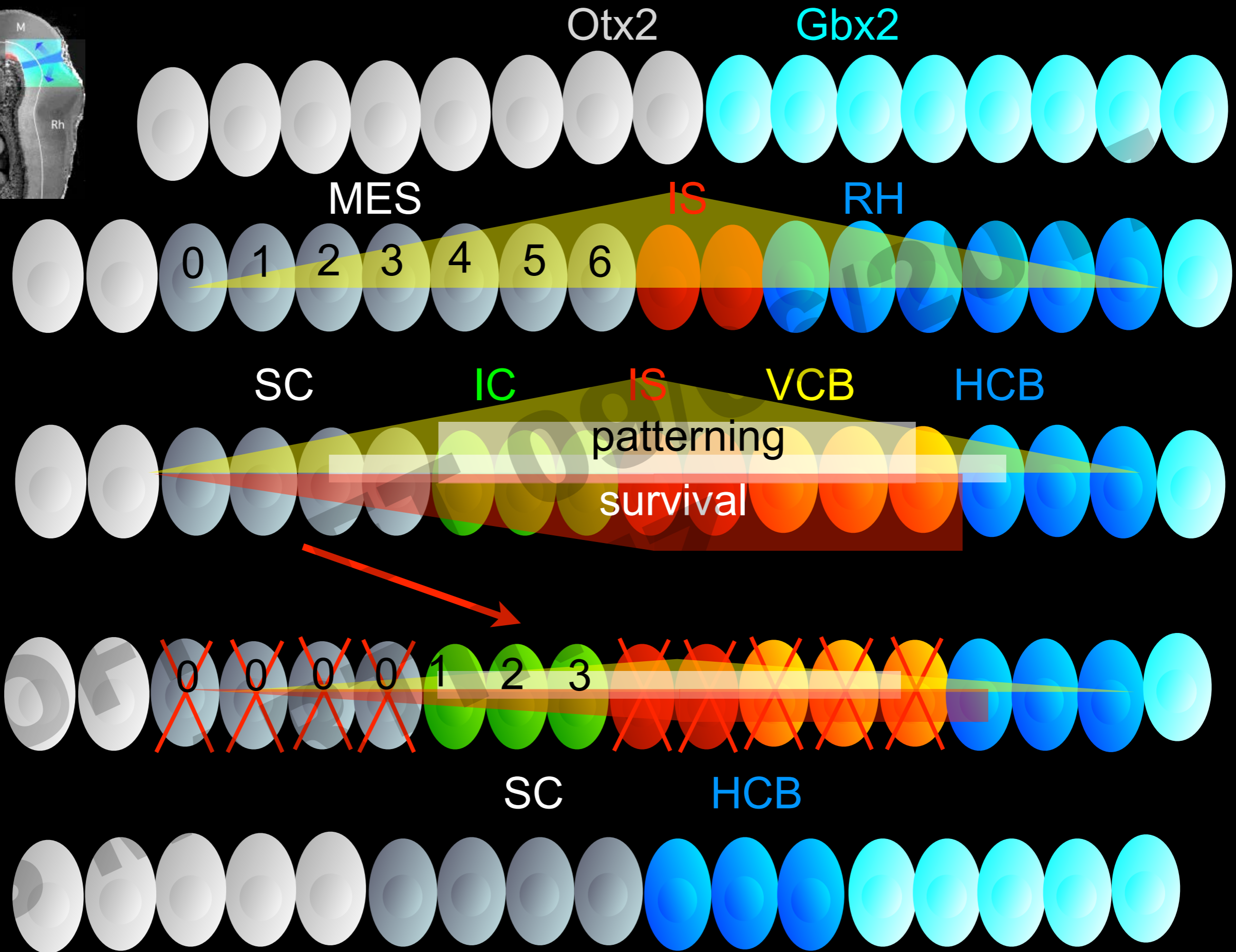
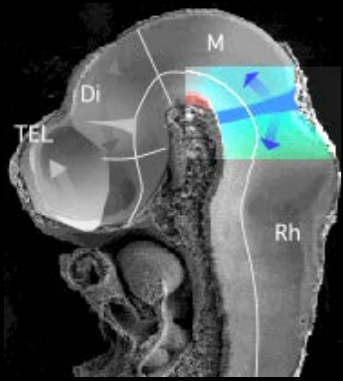


Lost of vermis suggests change in the fate of roof plate
vermis progenitors

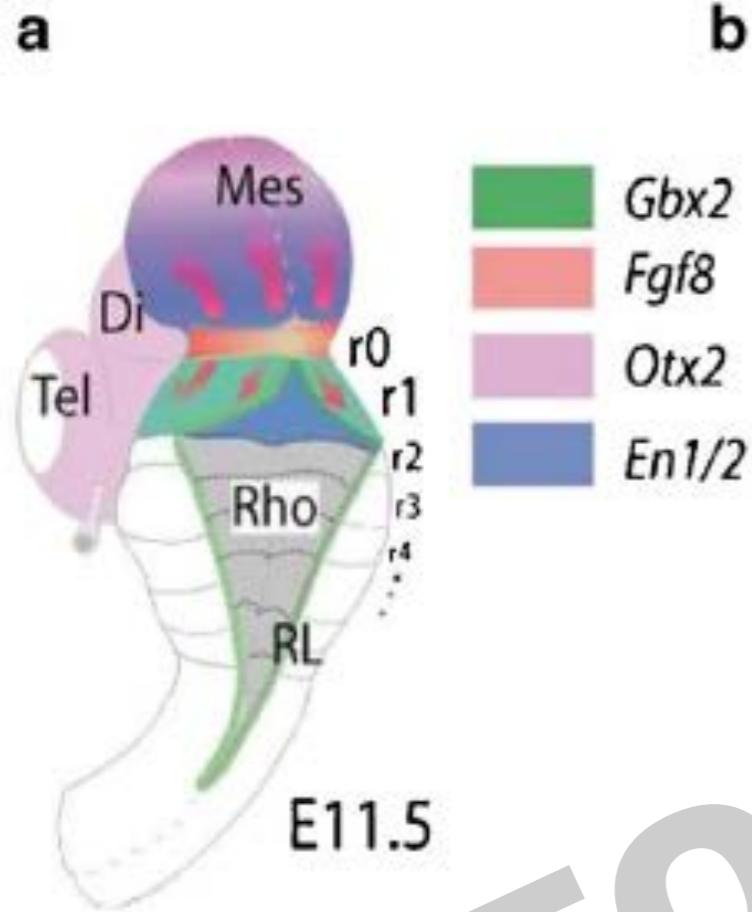
Lost of vermis does not depend of a cell death mechanism
phenomen



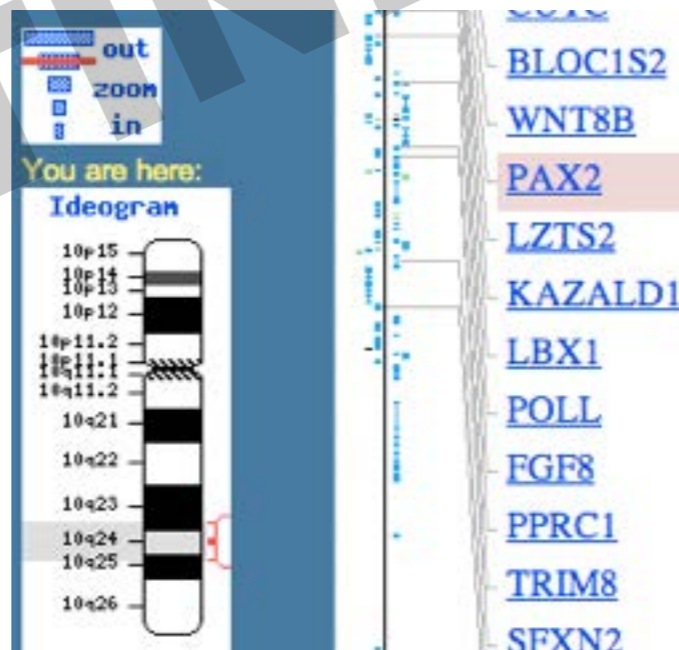
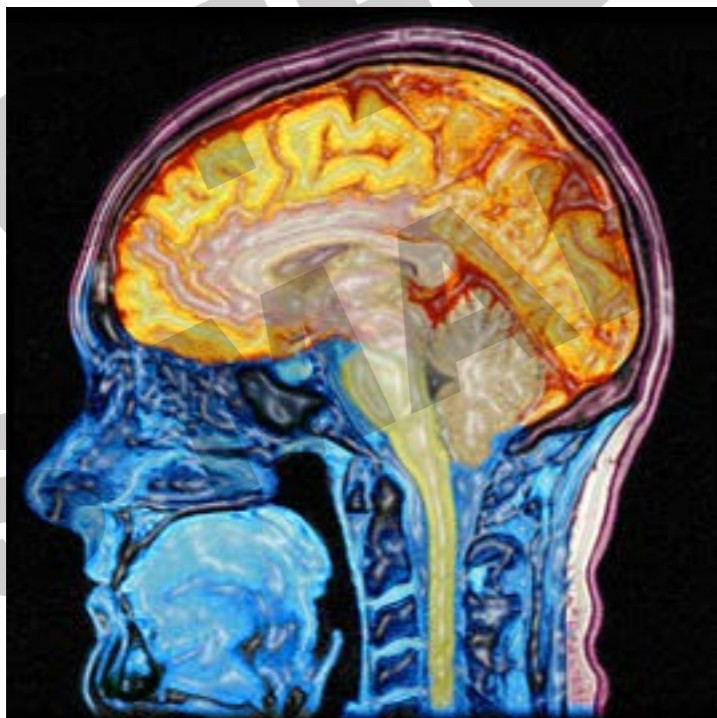
Basson*, Echevarria* et al., 2008



the cerebellum gene regulatory network



	Otx2	Gbx2	Wnt1	Lmx1b	En1	En2	Pax2	Fgf8	Mkp3	Spry1	Spry2	Sef
	H/TF	H/TF	M/EP	H/TF	H/TF	H/TF	H/TF	M/EP	E/Inh	E/Inh	E/Inh	E/Inh
Di	+++											
Mes	+++					+						+
Isth	+++		+++	+++	++	++			+	++	++	++
R ₁		+++		+	+++	+++	+++	+++	+++	+++	+++	+++
R ₂		+++			++	++	++		++	++	++	++
R ₃												

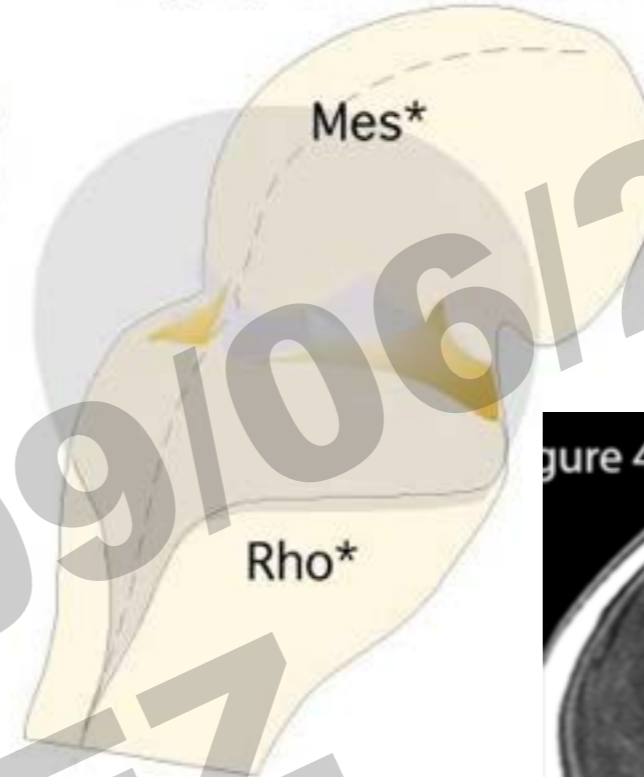
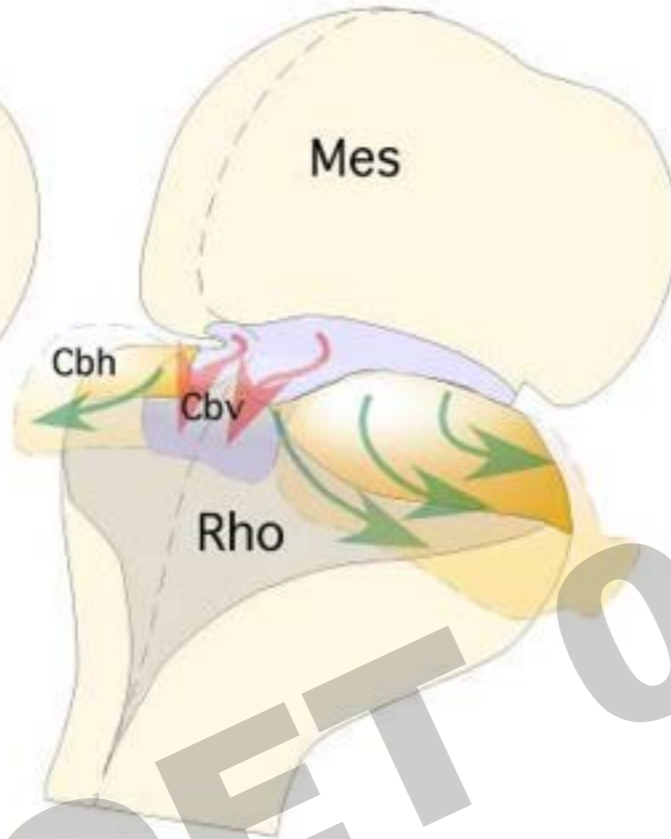
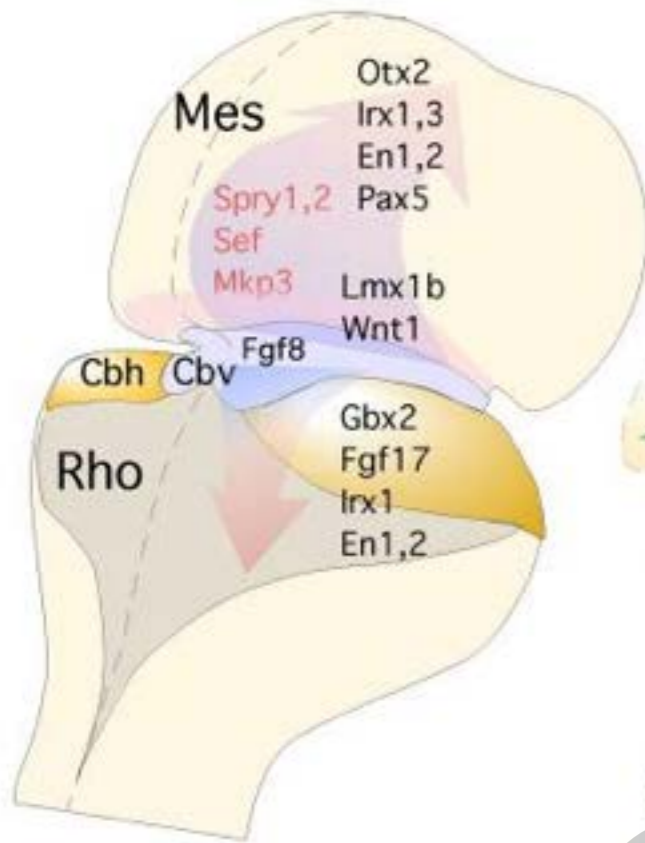


Spinocerebellar ataxia, infantile-onset, with sensory neuropathy
 Fgf8 and PAX2 (10q24):

A molecular regionalization

B morphogenetic movements

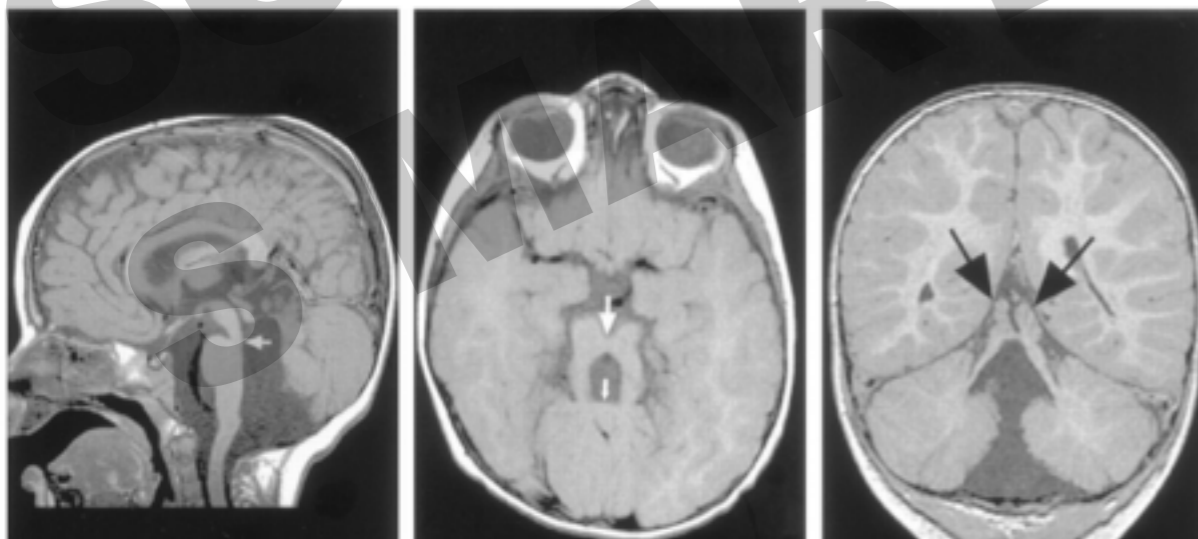
C patterning alterations
(Type I /A,B [Barkovich et al., 2009]):
cerebellar/pontine/mesencephalic
hypoplasia and posterior fossa disorders



Analysis and Classification of Cerebellar Malformations

Sandeep Patel and A. James Barkovich

American Journal of Neuroradiology August 2002, 23 (7) 1074-1087



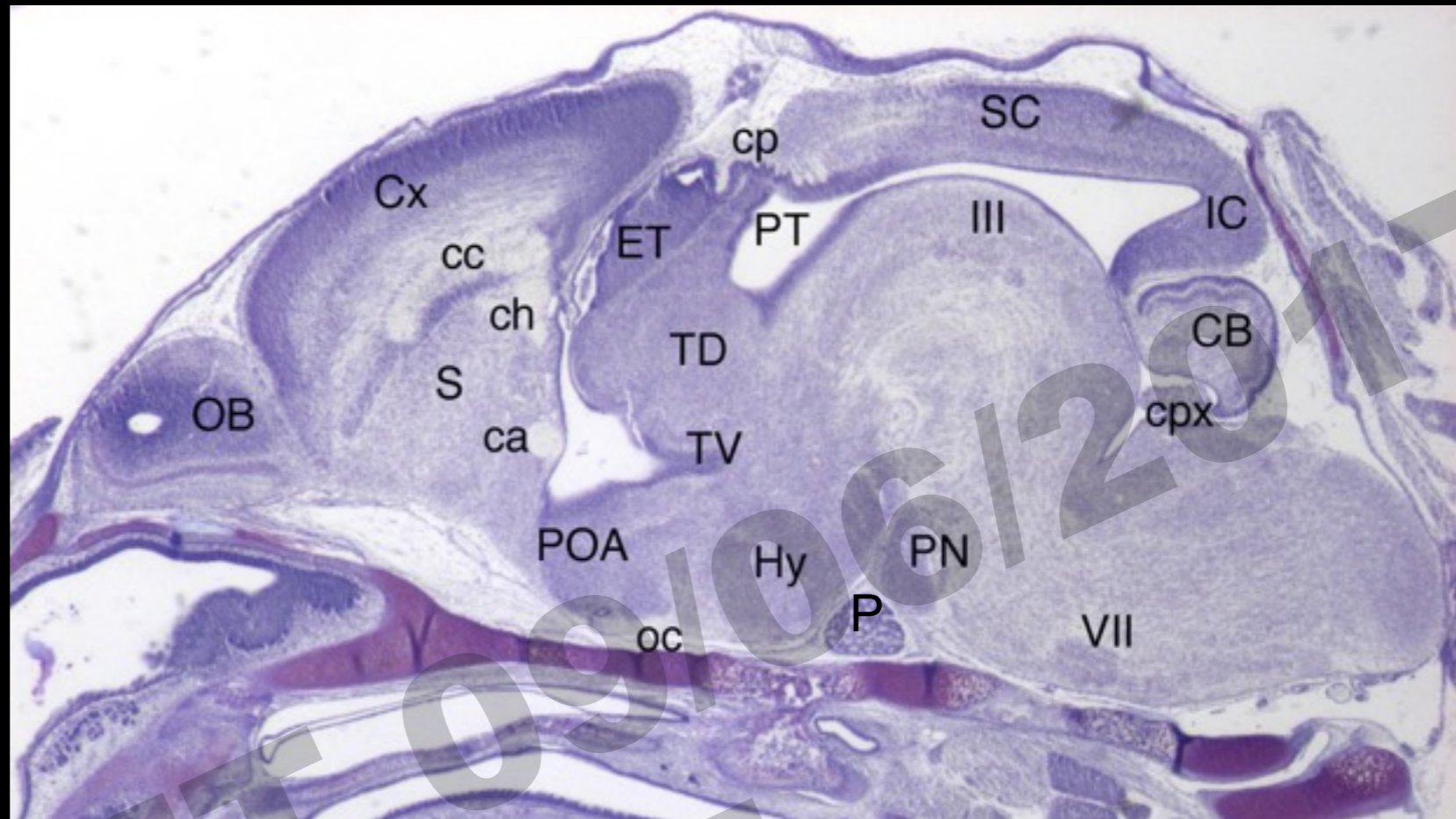
Molar tooth malformation in a 18-month-old patient with Joubert syndrome. A, Sagittal spin-echo (500/11) image shows a small, dysplastic cerebellar vermis. The folial pattern is abnormal. Note the narrow isthmus (junction of the mesencephalon and pons) (arrow). B, Axial spin-echo (500/15) image shows the very small vermis (small arrow), the broad, horizontal superior cerebellar peduncles, and the narrow isthmus (large arrow). C, Coronal spin-echo (500/11) image shows a midline cleft separating the two dysplastic areas of vermis (arrows).

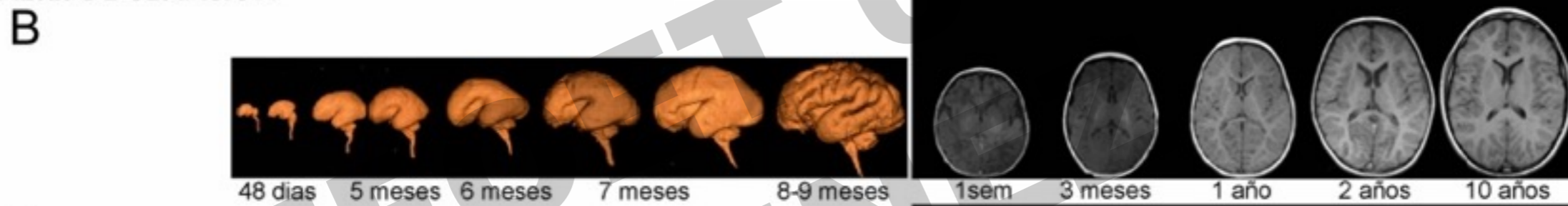
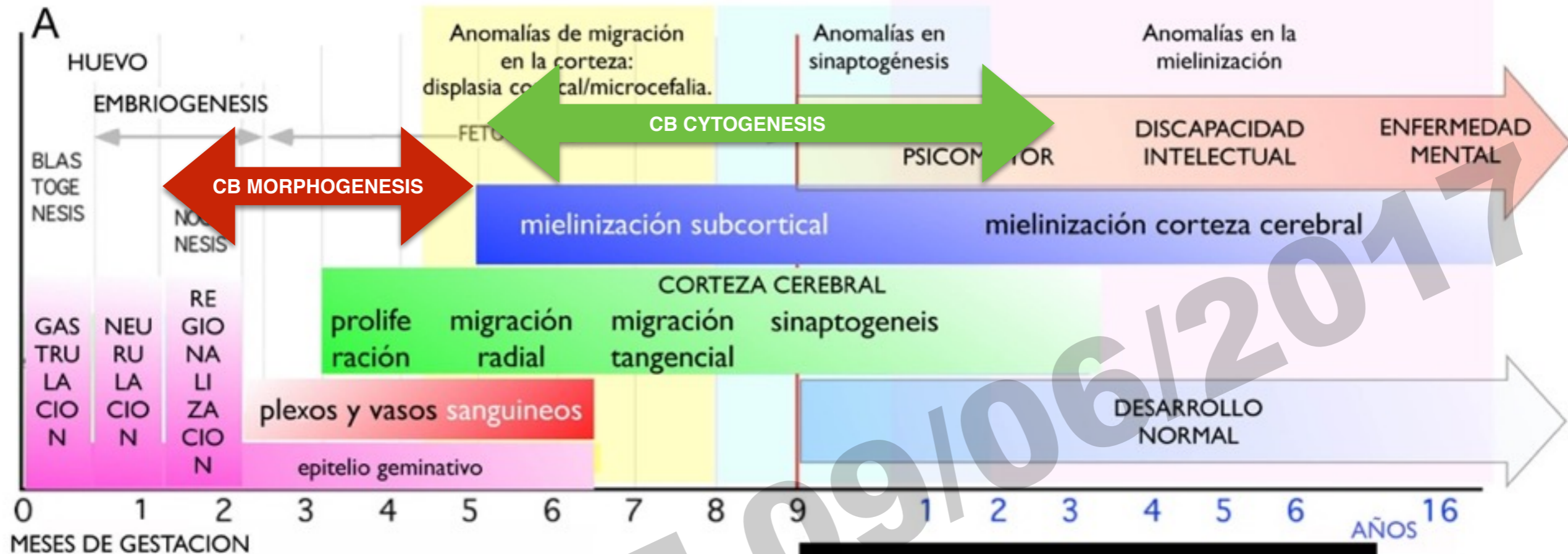
FGF8 gene is active both in the rostradorsal cerebral midline (in the region of the septum) and in the isthmic organizer (where the cerebellar anlage is induced)

The lack of decussation of these pathways being the primary anomaly and the associated dysplasia of the vermis, cerebellar nuclei, and brain stem nuclei being secondary. Whatever the cause, the vermis is clearly dysplastic (based on both pathologic and imaging criteria), and the dysplasia appears to be medial, and therefore, focal.



Otx2^{-/-}(*Otx1*)





Time program of main histogenetic processes of brain development

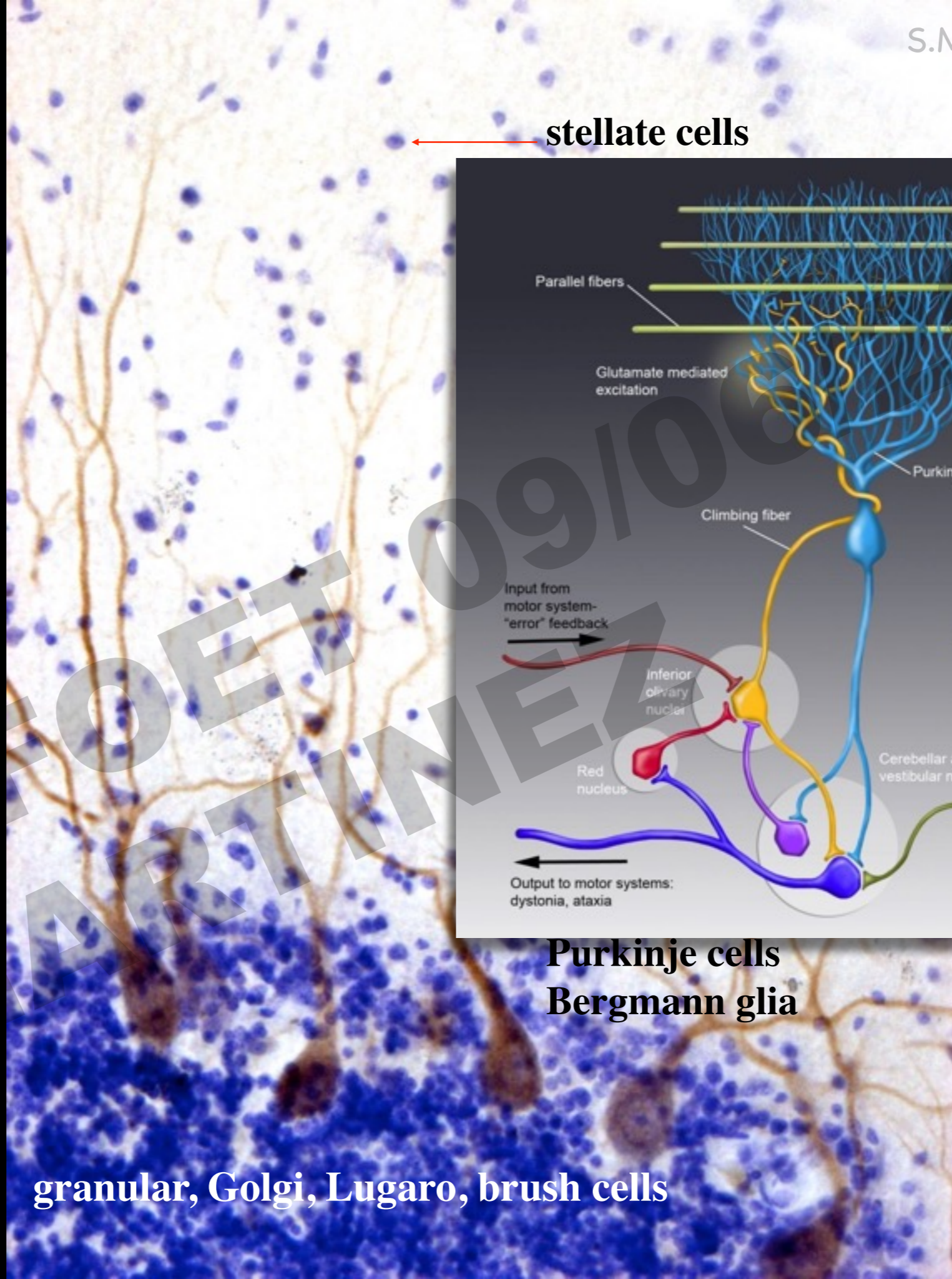
C
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PCL

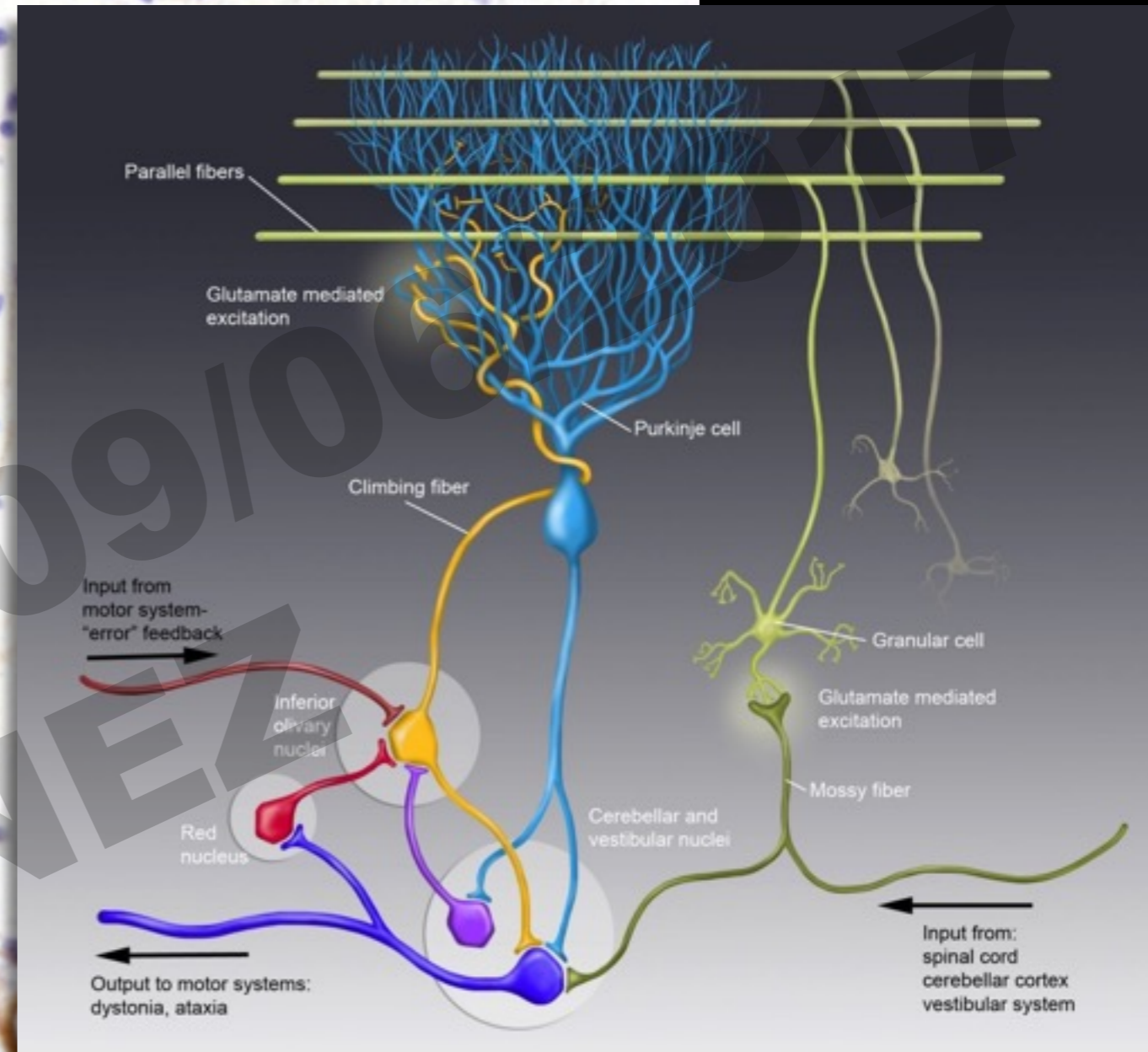
GL



S.M

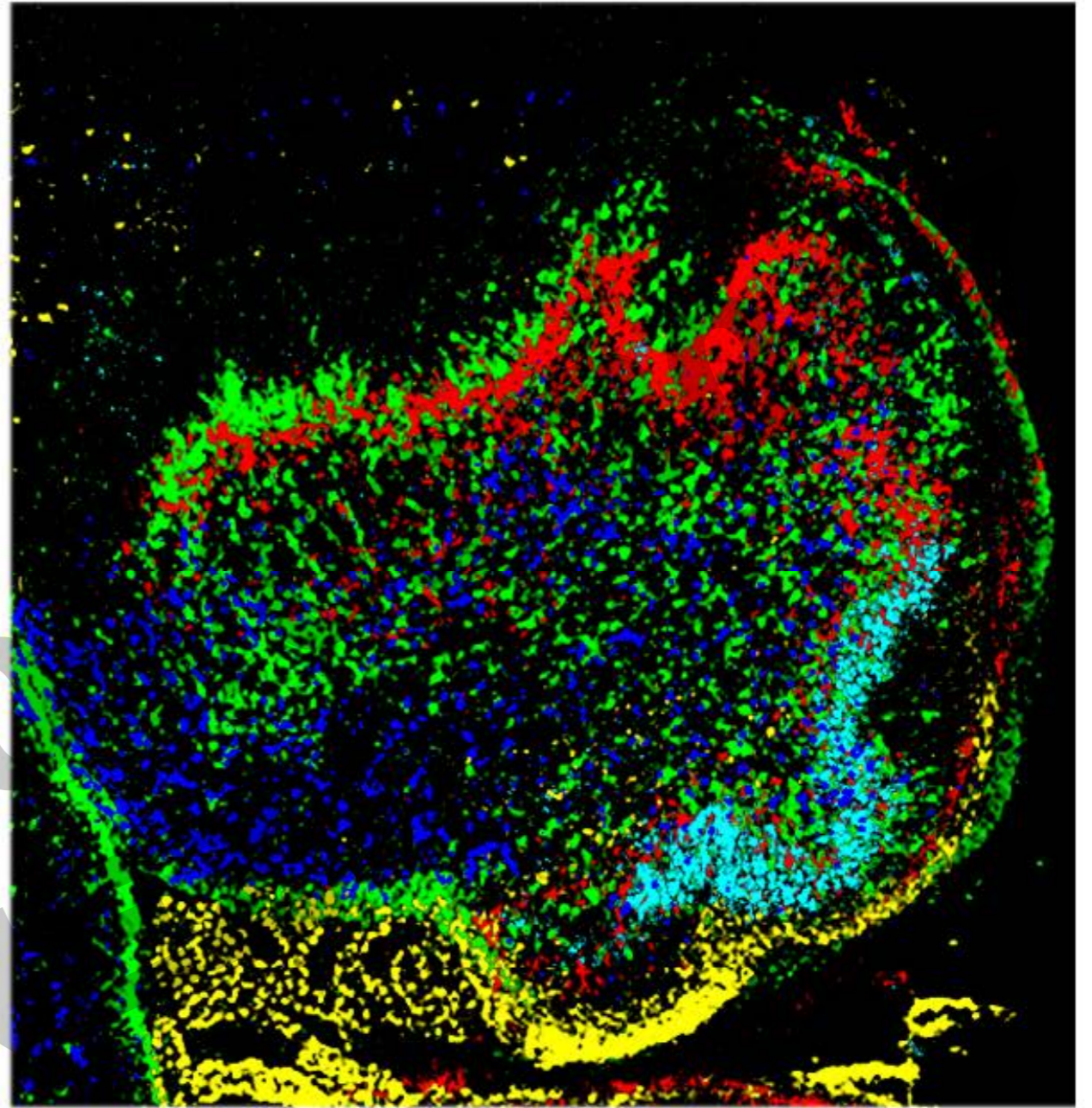
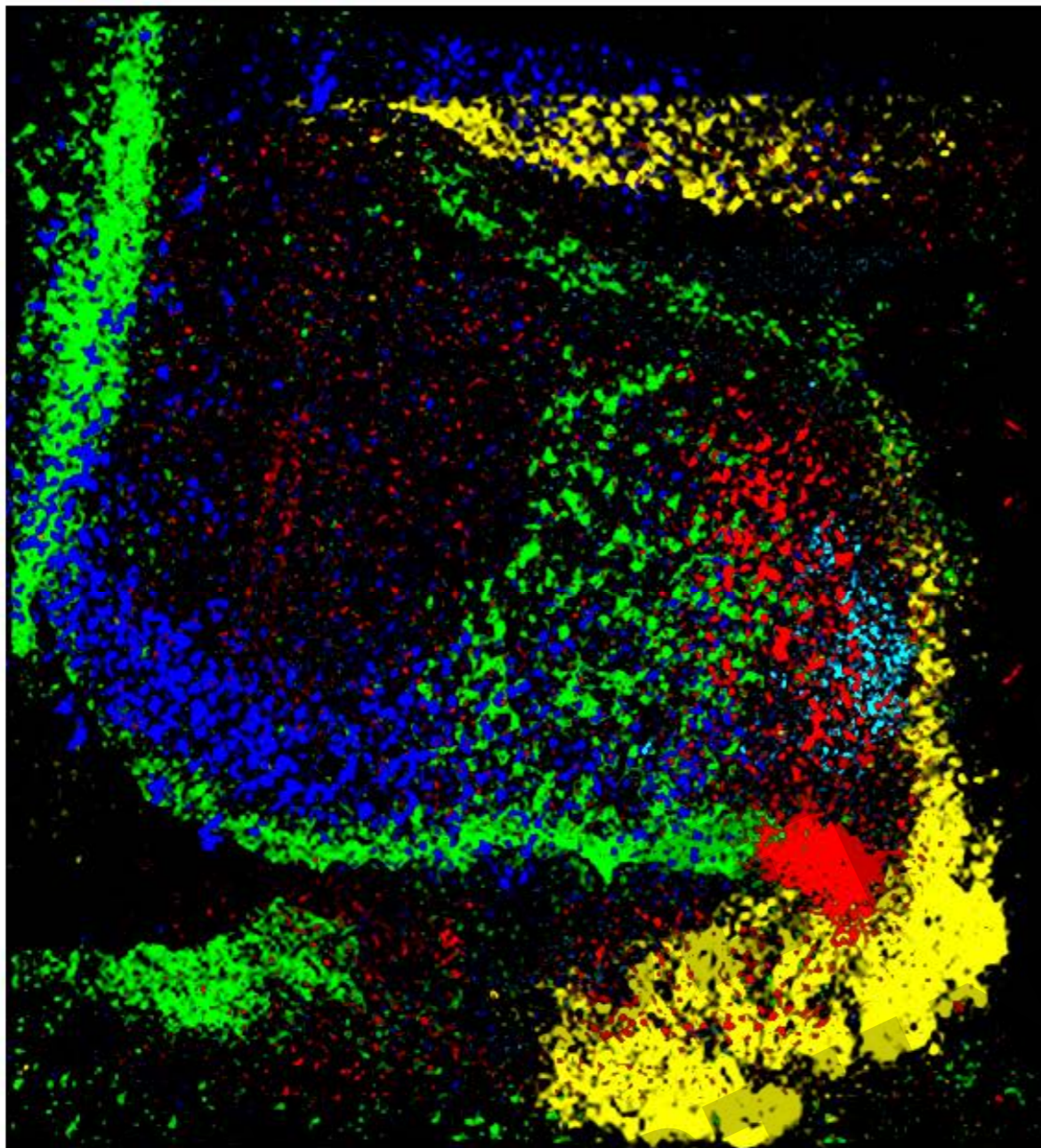


stellate cells

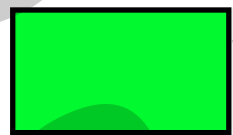


Purkinje cells
Bergmann glia

granular, Golgi, Lugaro, brush cells



E15.5



Slc1a3



Gad1



Otx2



Gdf10

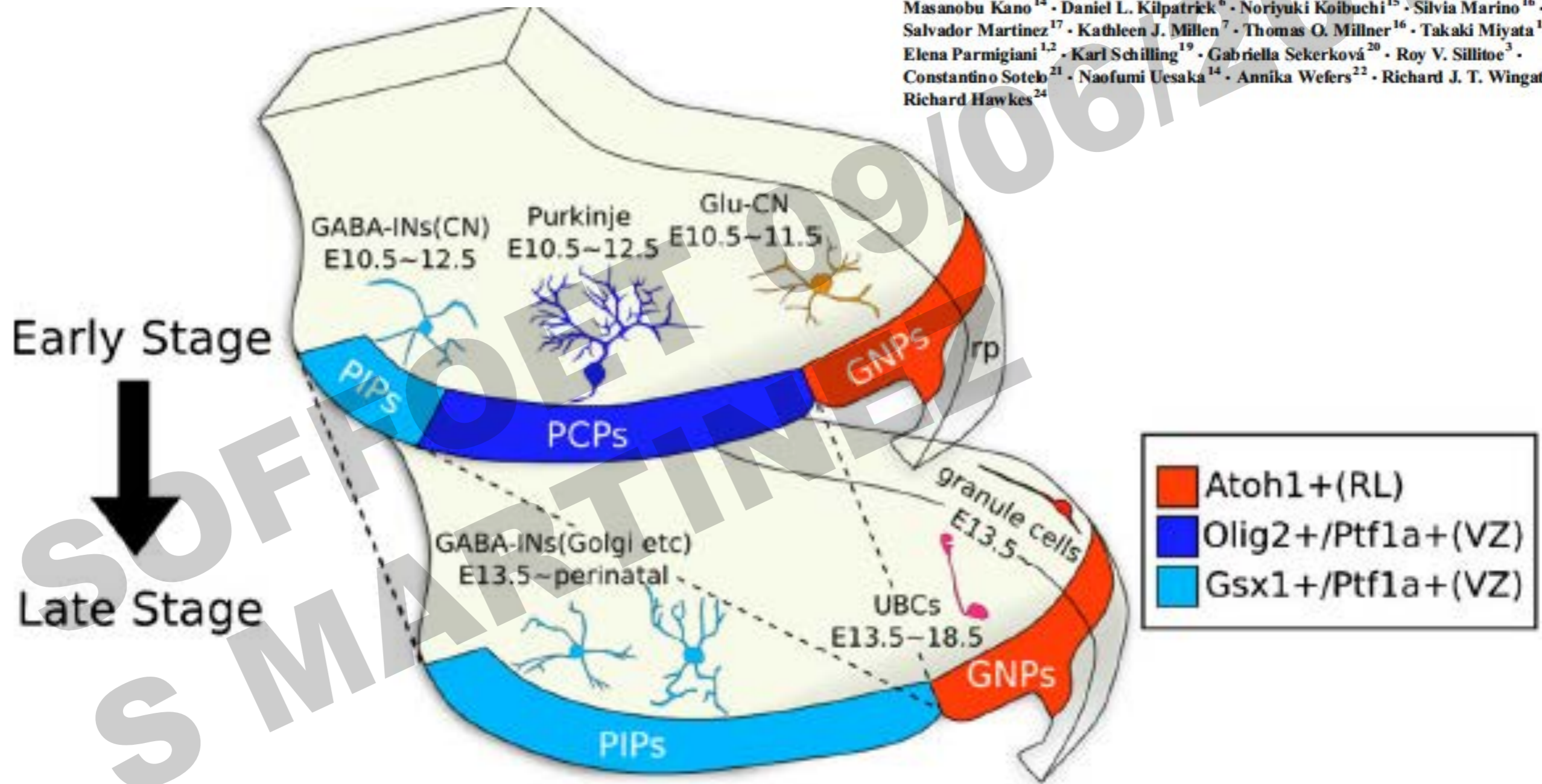
E18.5

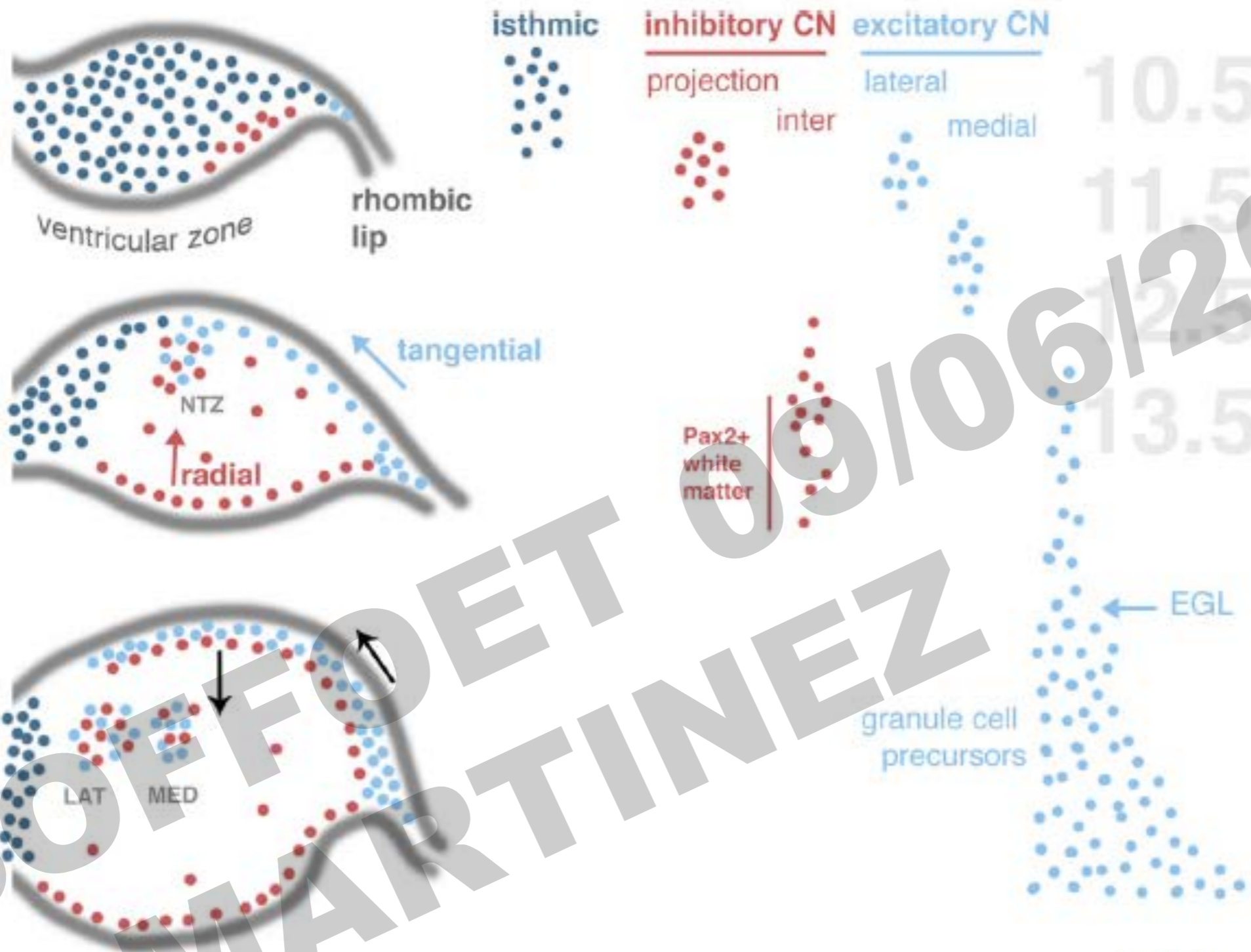


Slc1a6

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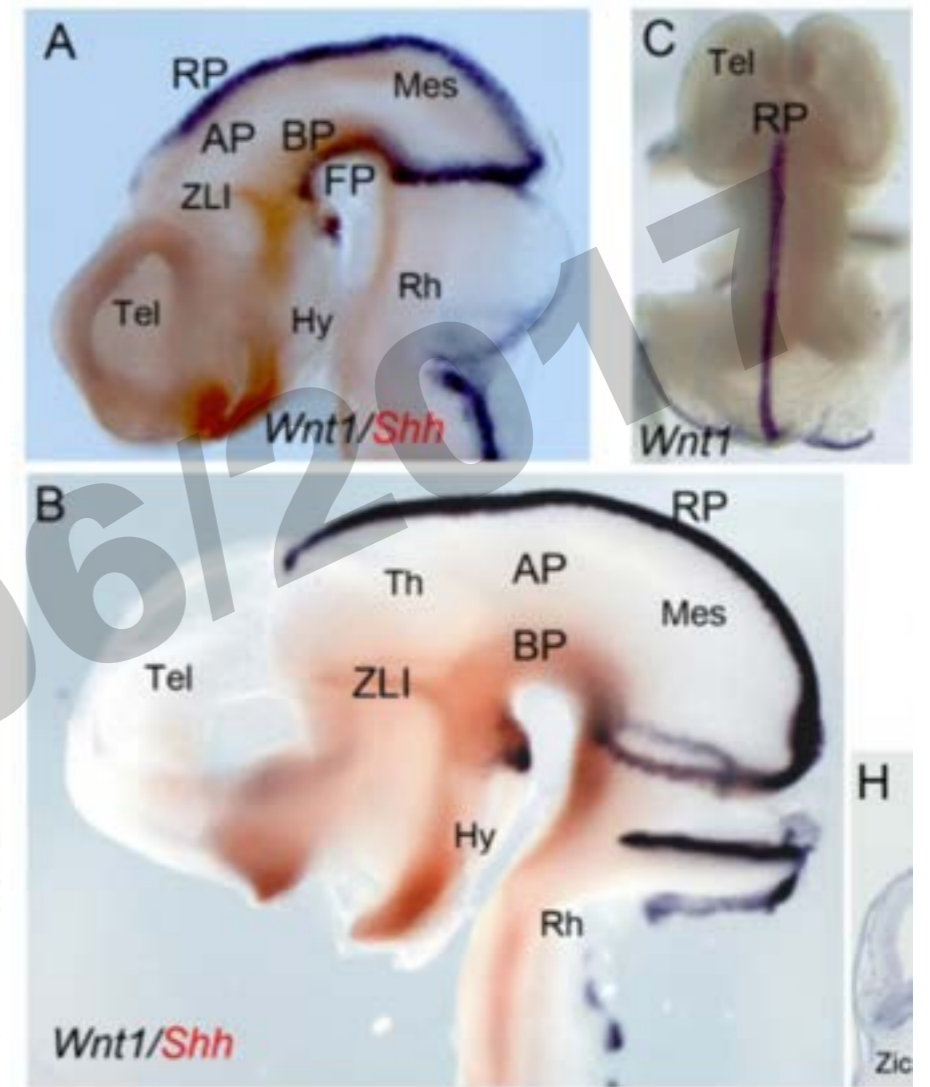
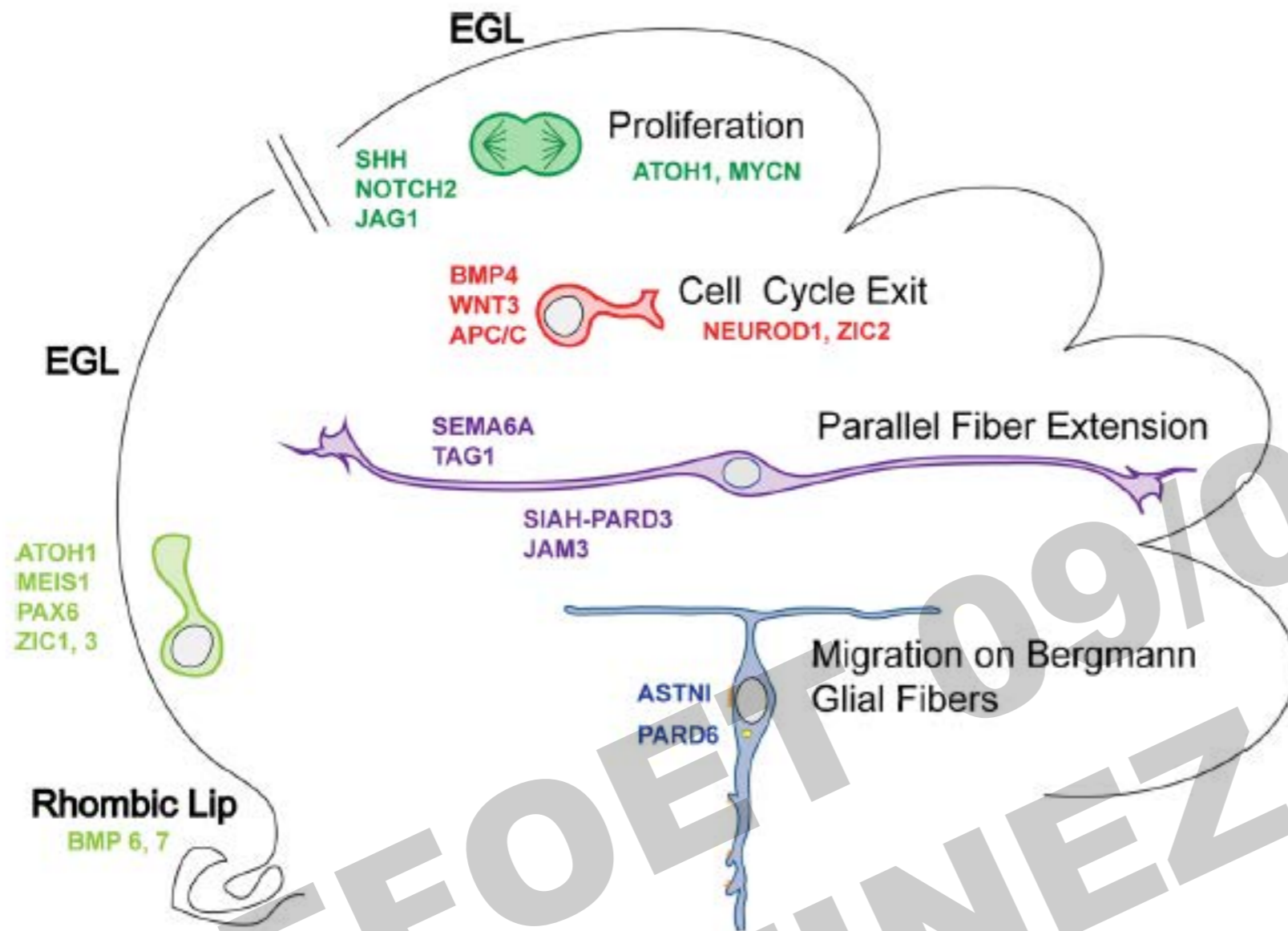


Cerebellum (2016) 15:789-828
 DOI 10.1007/s12311-015-0724-2

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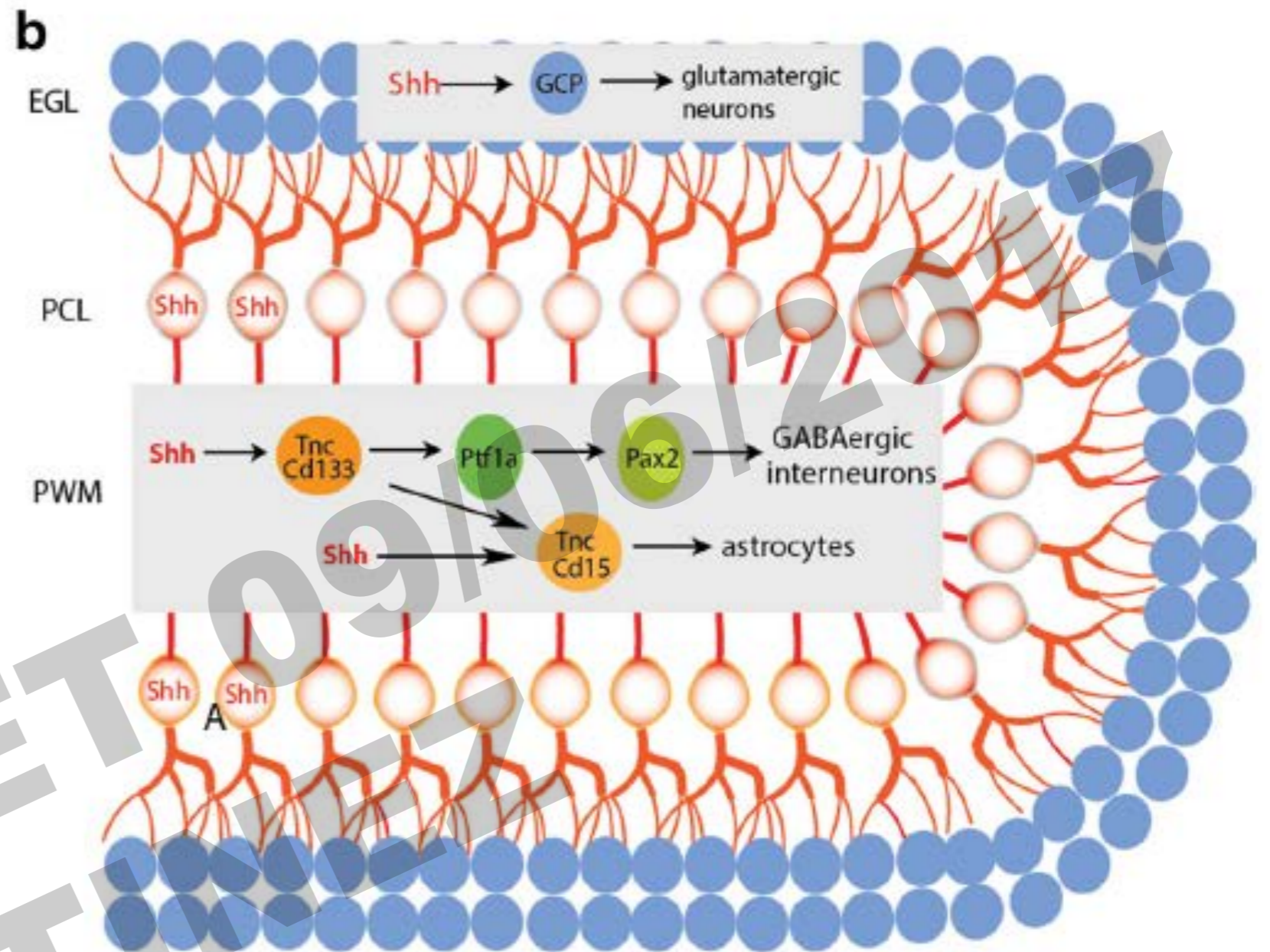
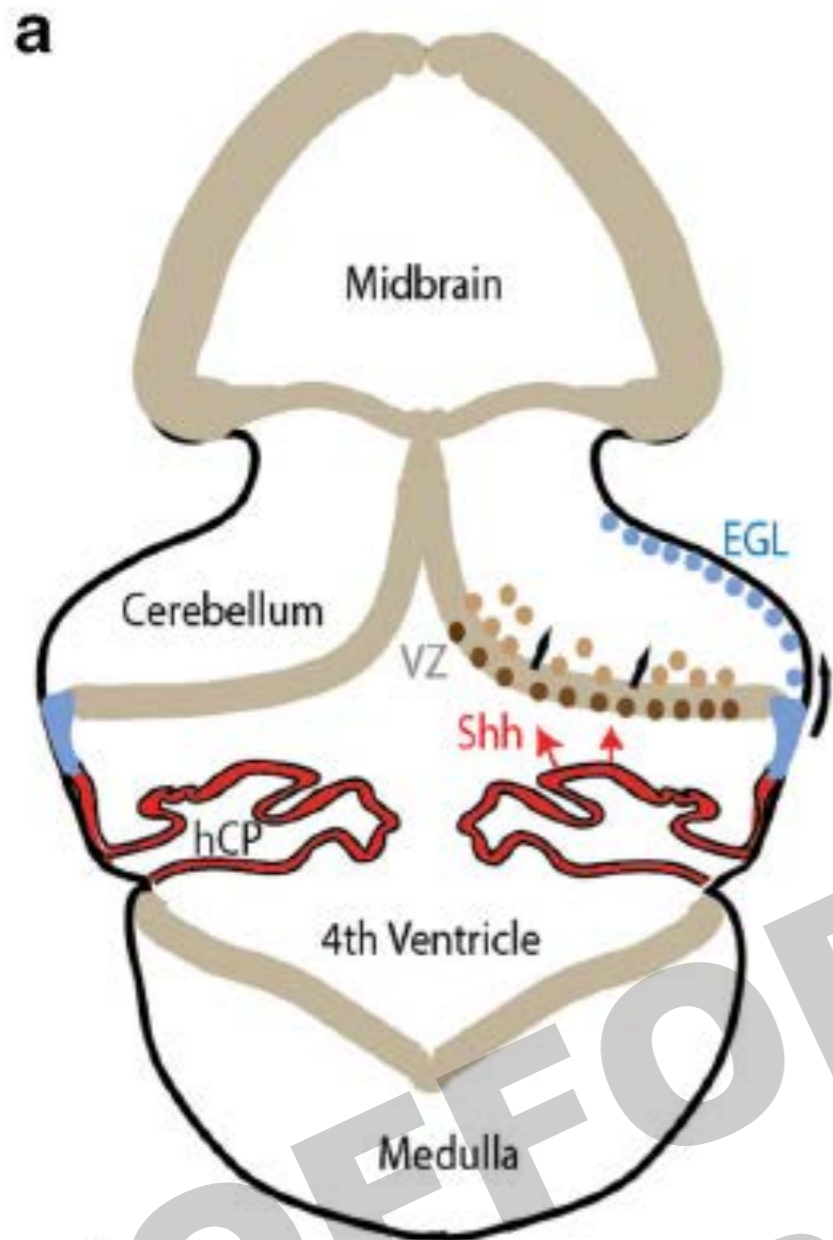


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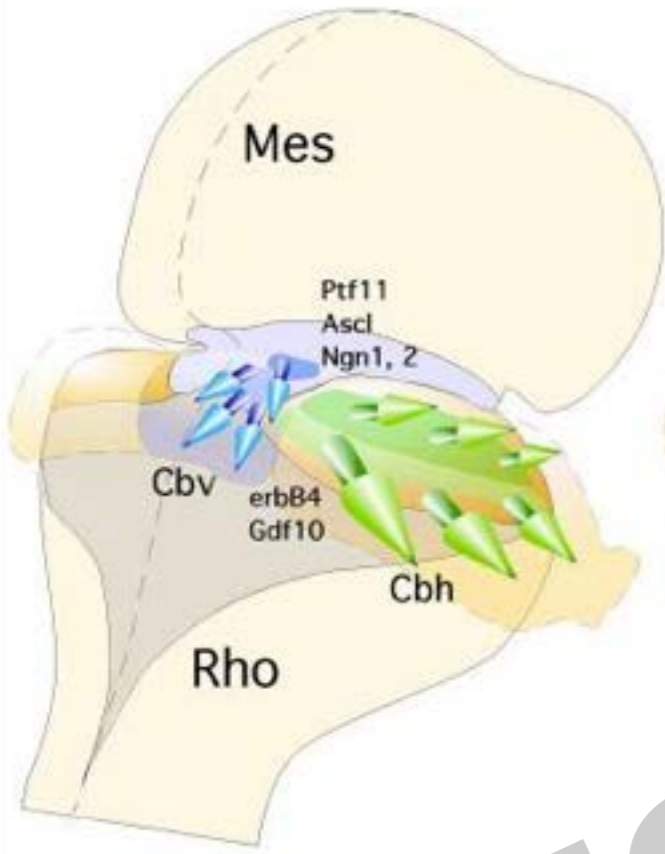
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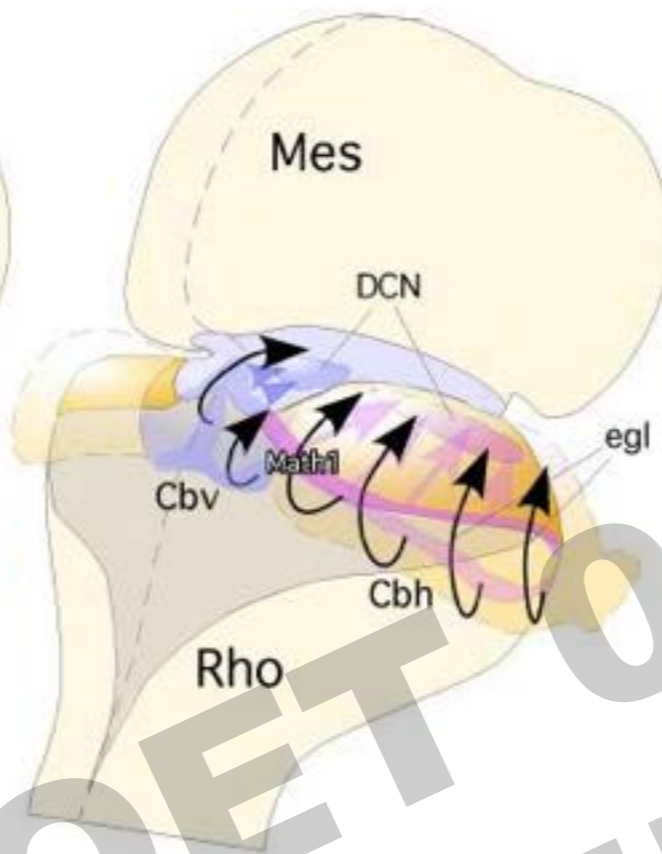
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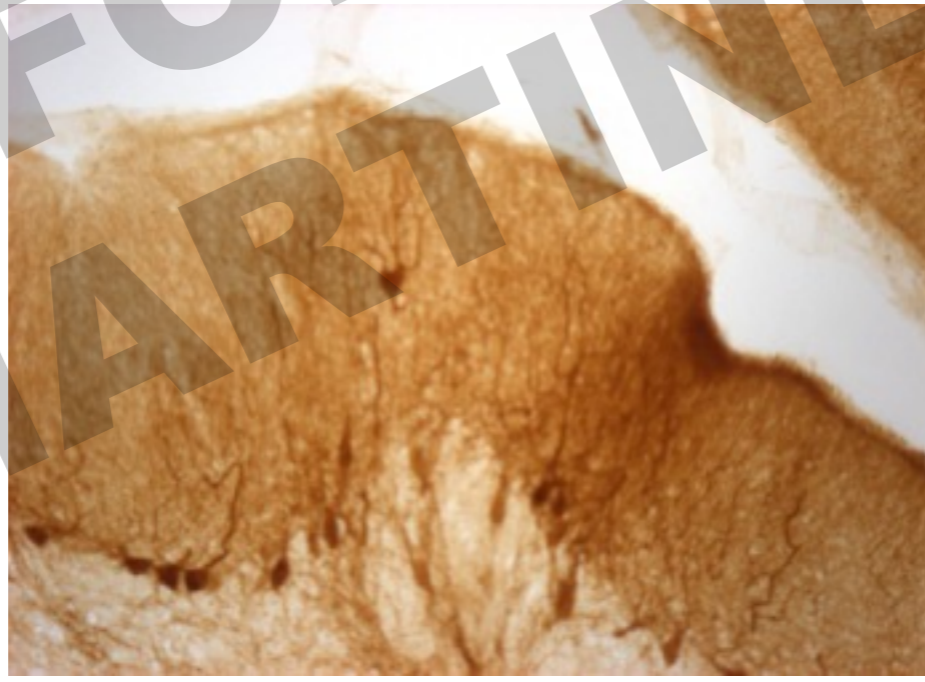
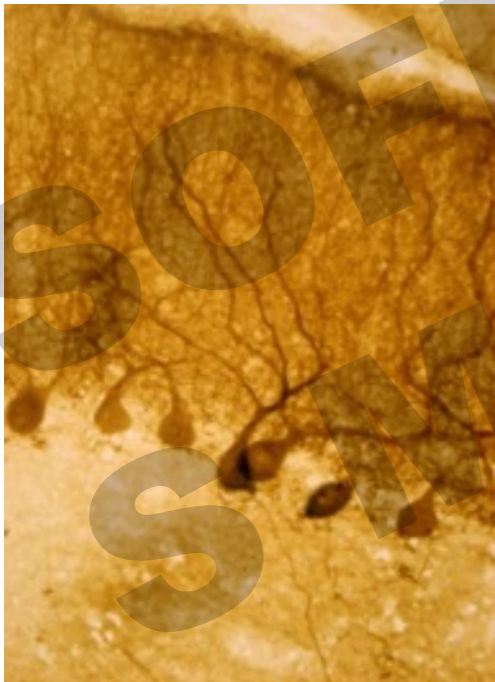
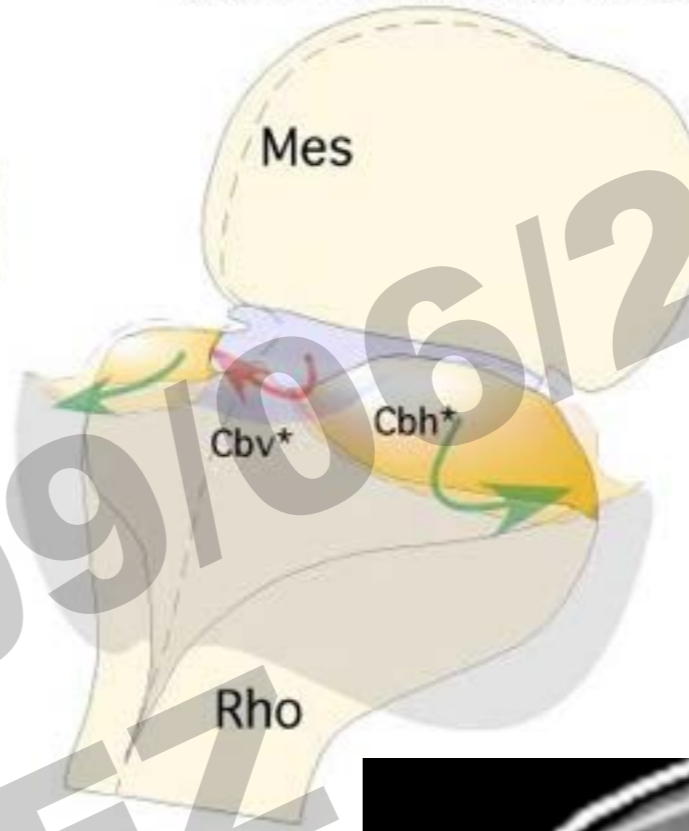
D radial migration
(GABAergic neurons)



E tangential migration
(Glutamatergic neurons)



F neuronal proliferation and migration alterations:
cerebellar dysgenesis:
(Type II [Barkovich et al., 2009])



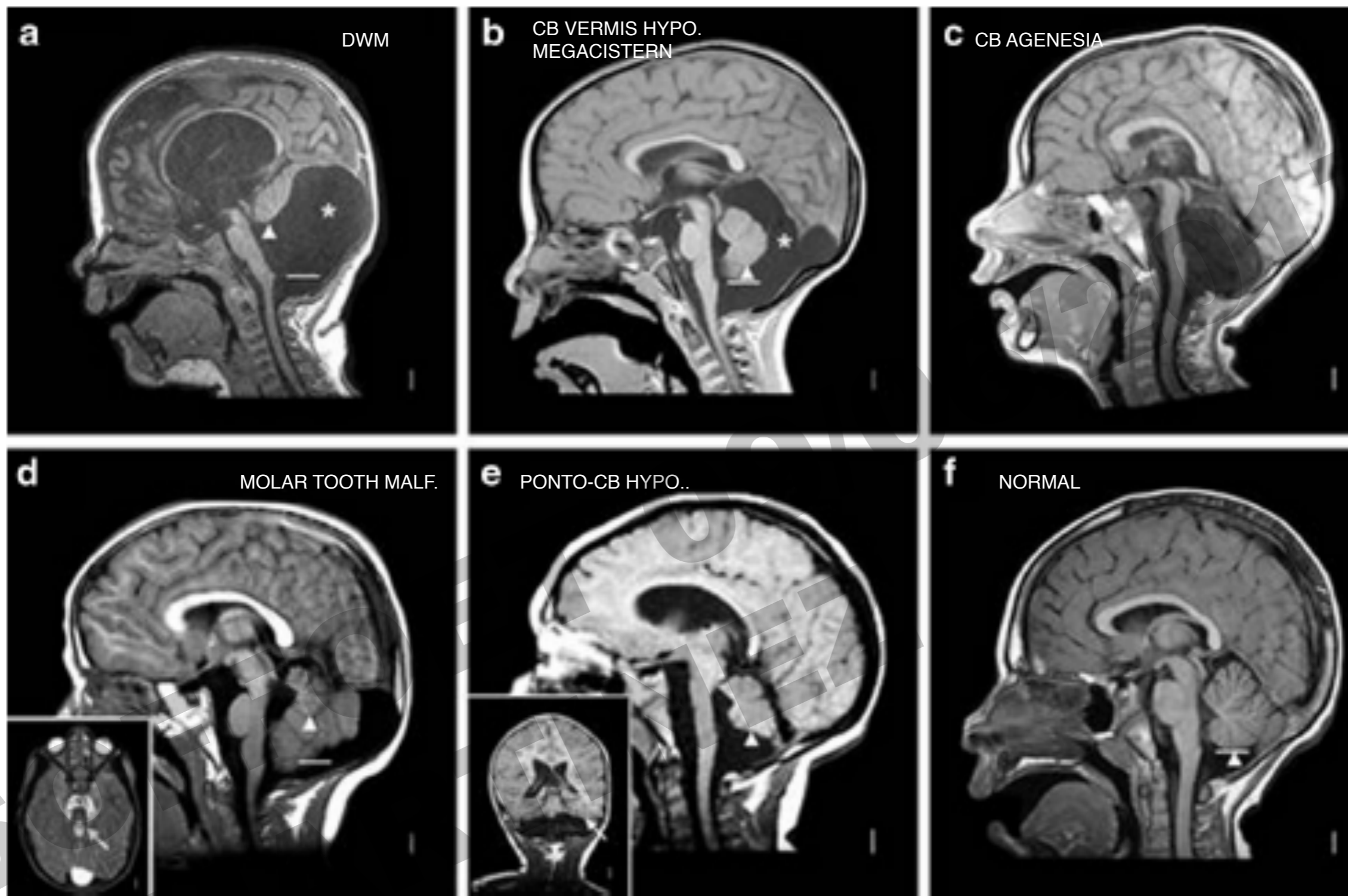


Fig. 14 Brain imaging in mid-hindbrain malformations. T1-weighted midline sagittal magnetic resonance images show the key features of classic DWM (a), cerebellar vermis hypoplasia with mega-cisterns magna (b), complete cerebellar agenesis (c), molar tooth malformation seen in JSRD (d), pontocerebellar hypoplasia (e), and normal (f). The *solid white lines* in most images mark the level of the obex, while the *arrowheads* point to the lower edge of the vermis (both landmarks are absent in c). The *asterisk* denotes an enlarged posterior fossa. In (a), the vermis is small and rotated far upwards, the fourth ventricle is enlarged into a cyst-like structure, and the posterior fossa is greatly enlarged causing an elevated

tentorium. In (b), the vermis is small but located in the anatomic position, but the posterior fossa is again greatly enlarged. A posterior extension of the cyst appears to scallop the inner table of the skull. In (c), the brainstem is thin without any landmarks other than the tectum, and no cerebellum is seen. In (d), the vermis is very small but located in the correct anatomic position, with portions of the cerebellar hemispheres seen beneath. The *inset* shows the associated “molar tooth” sign (*arrow*). In (e), the brainstem is thin but the obex can just be seen, and the vermis is moderately small. The even more “pancake-like” flattening of the hemispheres is shown in the *inset* (*arrow*)

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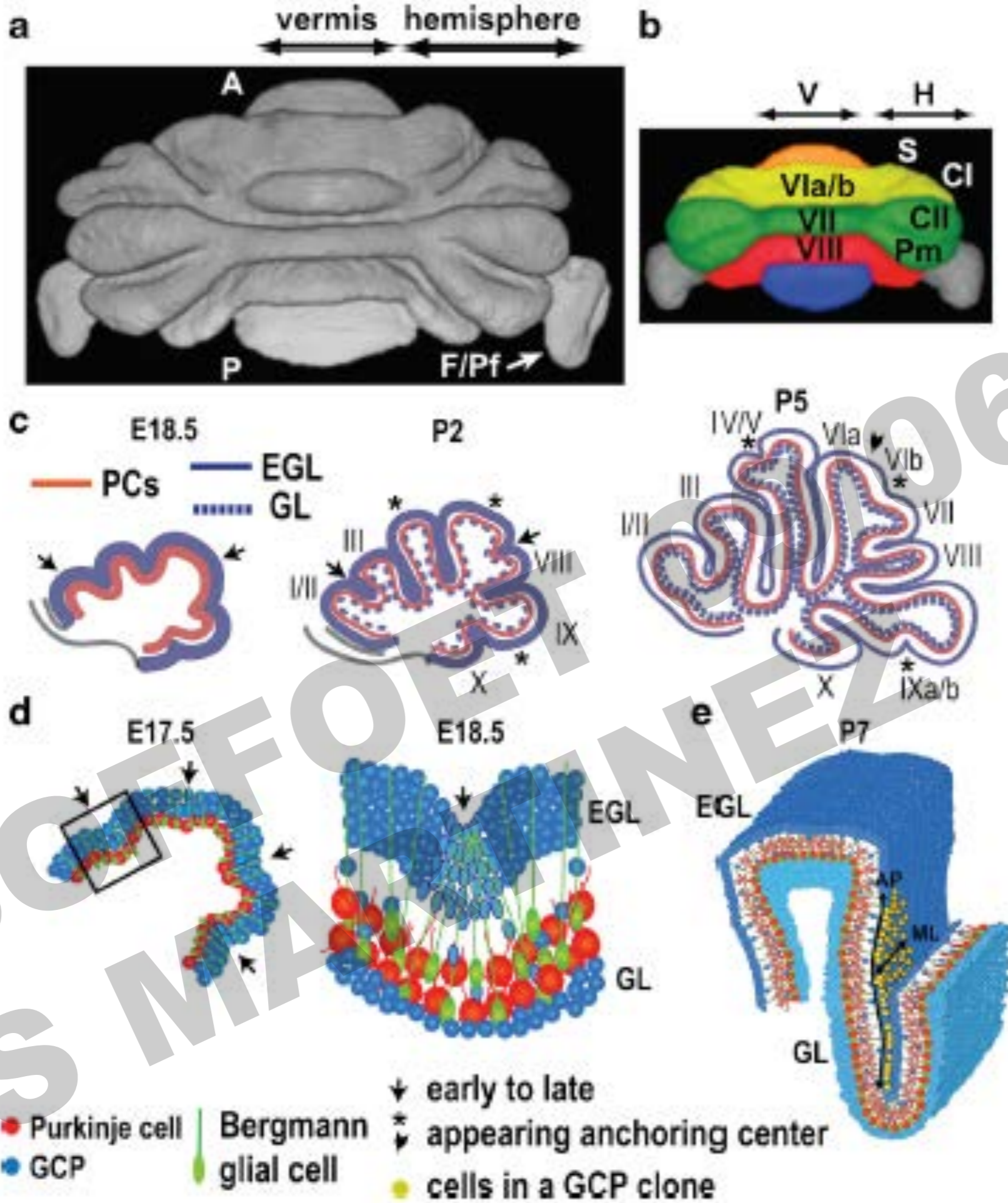
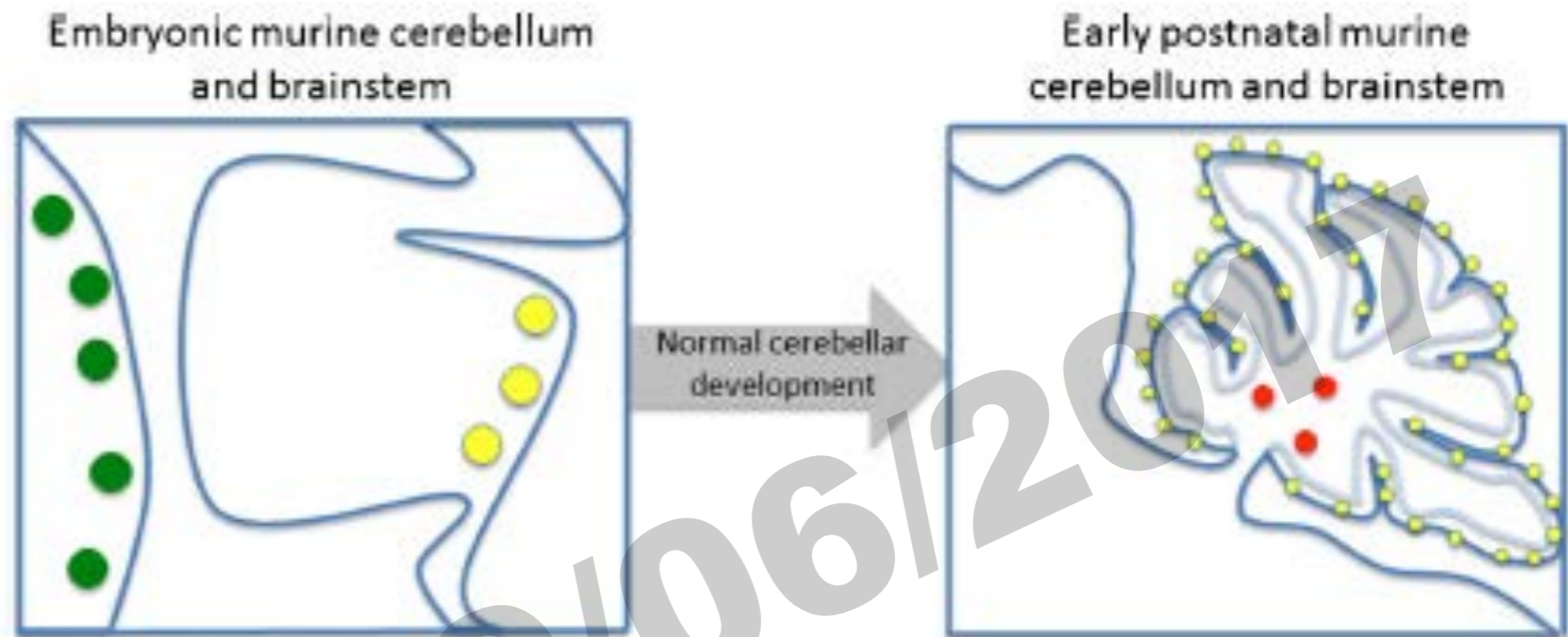





Fig. 16 Medulloblastoma subgroups and their cells of origin. The schematic shows the embryonic and early postnatal murine cerebellum and brainstem with the spatial and temporal locations of likely cells of origin of MB subgroups (*green dots* represent dorsal brainstem precursor cells, *yellow dots* represent GCPs, *red dots* represent cerebellar stem cells). The table shows the genetics, gene expression profile, predominant histology, and prognosis of the MB subgroups for each of these cells of origin



Cell of origin	Dorsal brainstem precursor 	Granule cell precursor 	Cerebellar stem cell 
Genetics	Monosomy 6, CTNNB1 mutation	PTCH, SMO and SUFU mutations, Gli2 and MYCN amplification	i17q, MYC amplification
Gene expression	WNT signaling	SHH signaling	MYC+++
Predominant Histology	Classic	Desmoplastic/nodular	Large cell/anaplastic
Prognosis	Very good	Intermediate	Poor

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