ALLEN INSTITUTE
for BRAIN SCIENCE
Fueling Discovery

ALLEN
BRAIN ATLAS
MOUSE BRAIN

AREA POSTREMA (AP)

Katie J. Glattfelder, Lydia L. Ng and John A. Morris

Introduction

This report contains a gene expression summary of the area postrema (AP), derived from the Allen Brain Atlas (ABA) in-situ hybridization (ISH) mouse data set. The structure's location and morphological characteristics in the mouse brain are described using the Nissl data found in the Allen Reference Atlas. Using an established algorithm, the expression values of the AP were compared to the values of the macro/parent-structure, in this case the medulla, for the purpose of extracting regionally specific gene expression data. The highest ranking ratios were then manually curated and verified. The 50 Select Genes were compiled for expression characterization. The experimental data for each gene may be accessed via the links provided; complementary sagittal data may also be accessed using the ABA. Correlation between gene expression in the AP and the rest of the brain, across all genes in the coronal dataset (~4300 genes), were derived computationally and are presented below. A gene ontology table (derived from DAVID Bioinformatics Resources 2007) is also included, highlighting possible functions of these 50 Select Genes.

To read more about how the 50 Select Genes list is derived, please refer to the Fine Structure Annotation white paper.

Allen Reference Atlas Coronal Levels: 127-131
Allen Reference Atlas Sagittal Levels: 19-21
Shown below is a plate from the Allen Reference Atlas, depicting the AP (level 128):
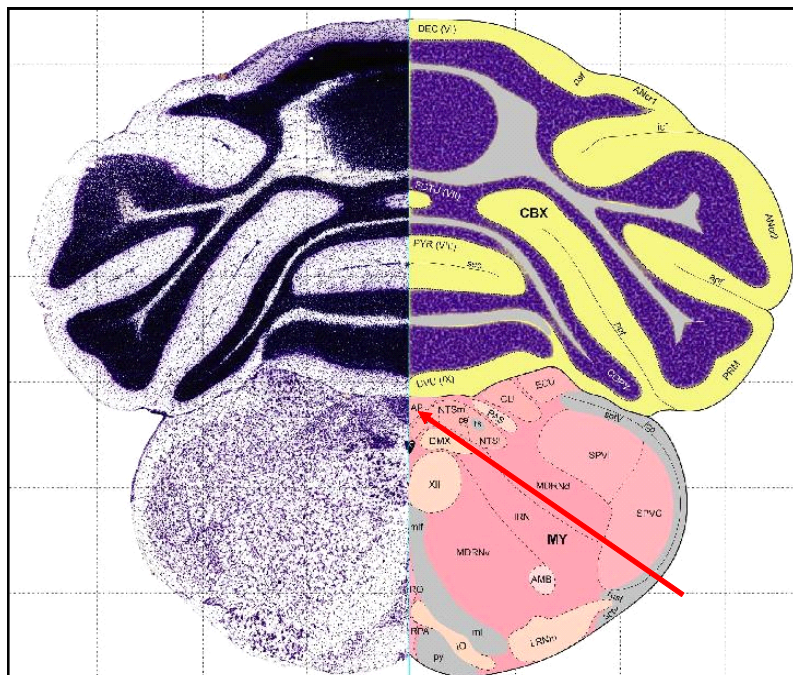
Description of Structure:

LOCATION and STRUCTURAL ANATOMY:

The hierarchical relationship within the brain is depicted below in the structure [legend](). The Allen Reference Atlas (based on Nissl-stained sections scanned at 10X) was the primary resource for the following descriptions.

For additional information please refer to the [Allen Reference Atlas white paper]().
[BrainInfo]() houses a search engine that allows searches for structure name aliases.

The area postrema (AP) is a compact substructure of the sensory-related medulla (MY-sen), located within the hindbrain. The AP straddles the midline in the dorsomedial region of the medulla, directly under the cerebellum, and forms the caudal wall of the fourth ventricle at the transition to the central canal (c). Laterally, the AP is bounded by the commissural portion of the nucleus of the solitary tract (NTSco), which has more diffuse, lighter cells that also extend to the ventral aspect of the posterior AP. In the coronal plane, the AP has an inverted triangular shape while in the sagittal plane the AP exhibits an elliptical or tear-drop shape. The small, dark staining, and uniformly packed cells of the AP make it readily apparent in both Nissl-stained and ISH data due to its location on the midline and the high density of its cells.

The appearance and location of the AP can be appreciated on the following two pages. Nissl-stained sections and Allen Reference Atlas plates reveal the cytoarchitecture and extent of the area postrema, and its location in relation to surrounding structures.

Atlas and Nissl:
Coronal:

Rostral

Caudal

Reference Atlas

Level 127 → Level 128 → Level 129 → Level 130
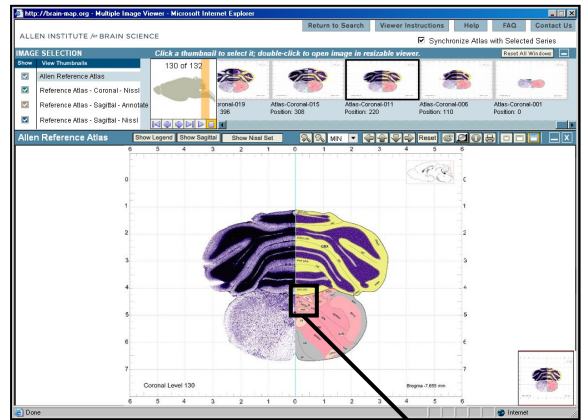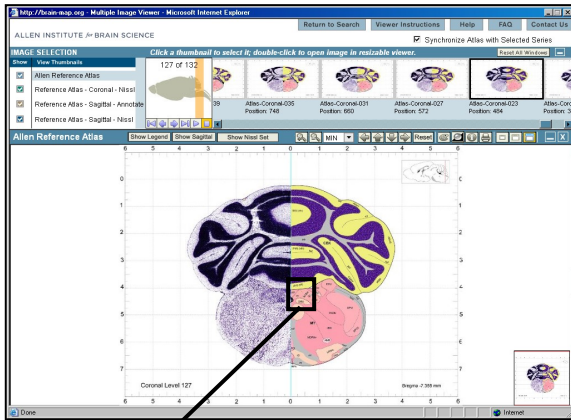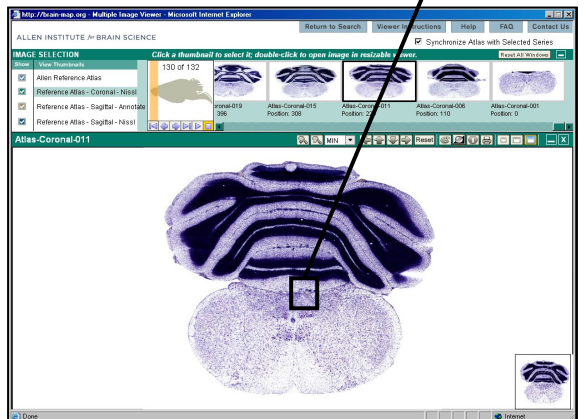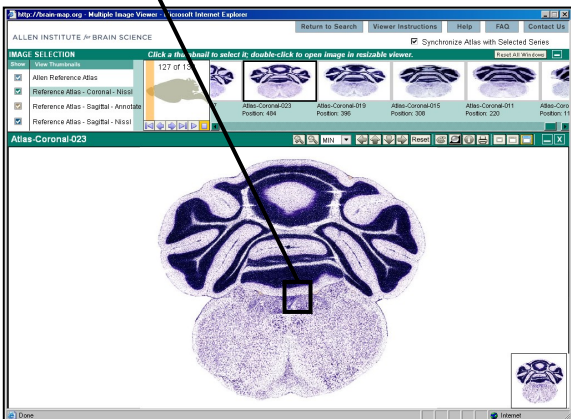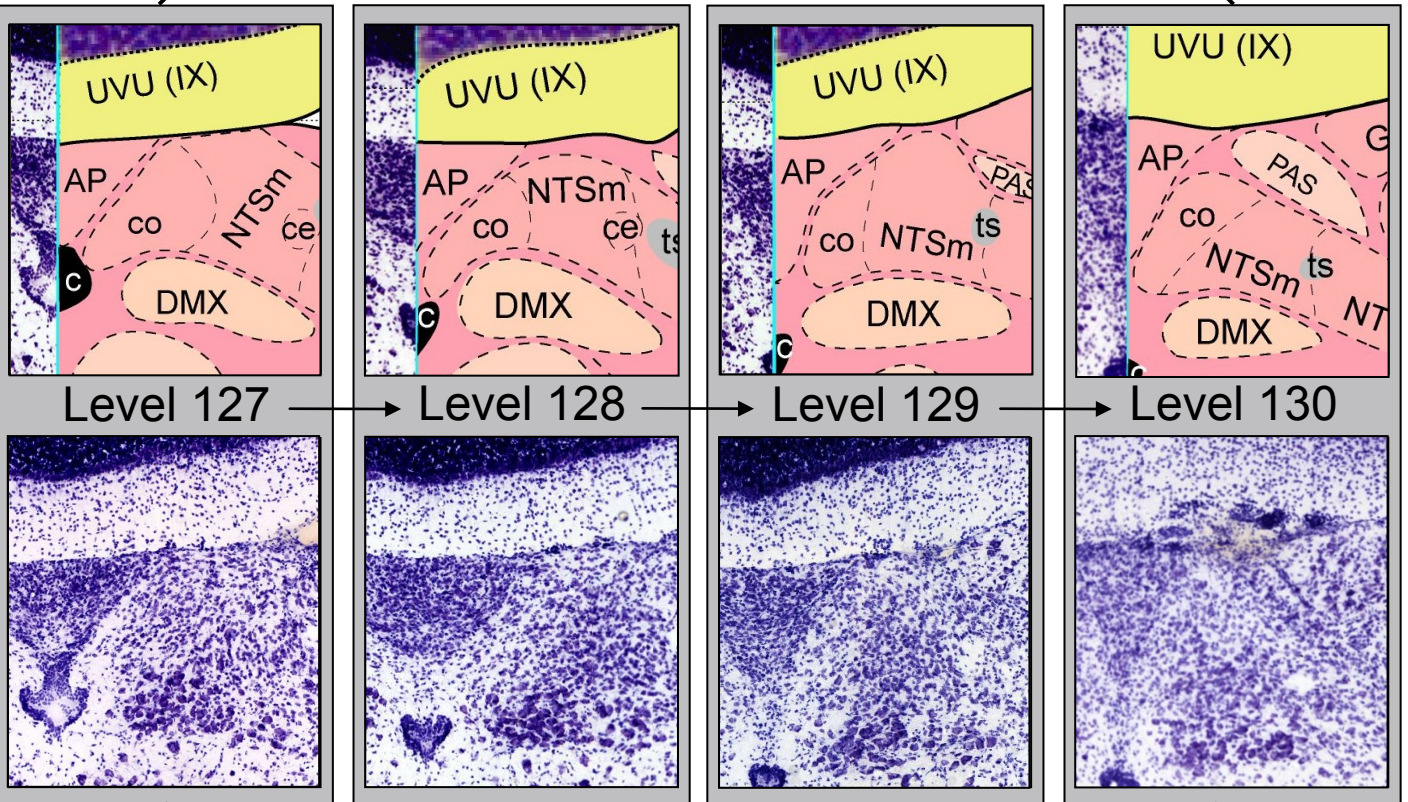
Nissl

Atlas and Nissl:
Sagittal:
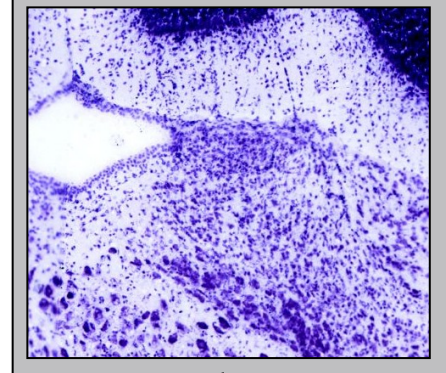
Lateral　　　　　　　　　　　　　　　**Medial**
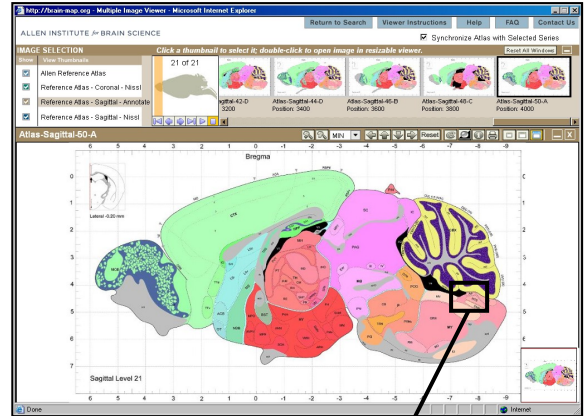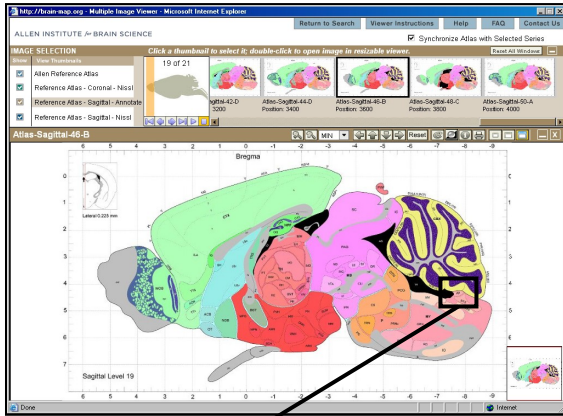
Reference Atlas
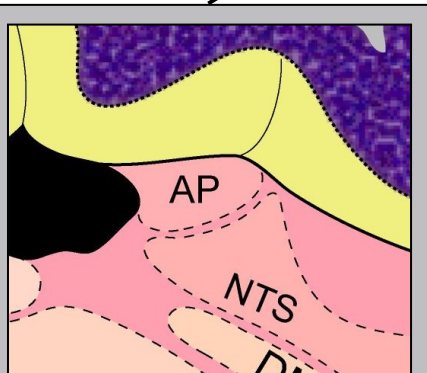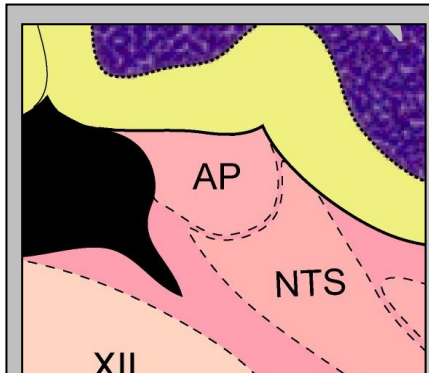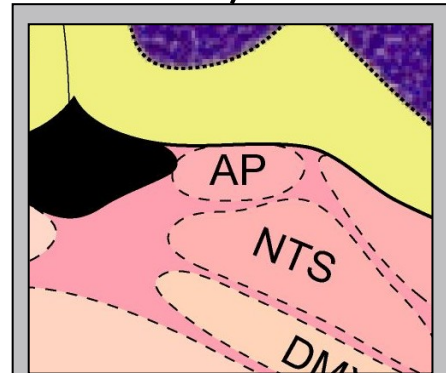
Level 19　→　Level 20　→　Level 21
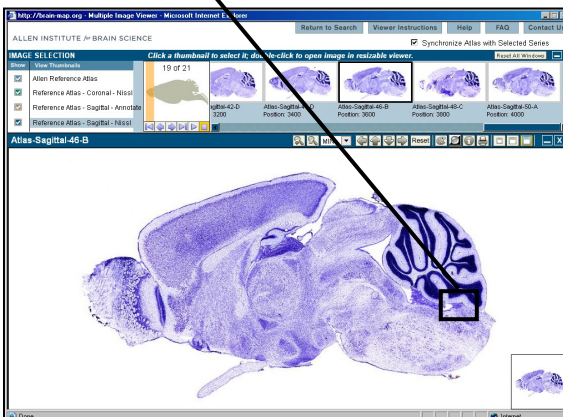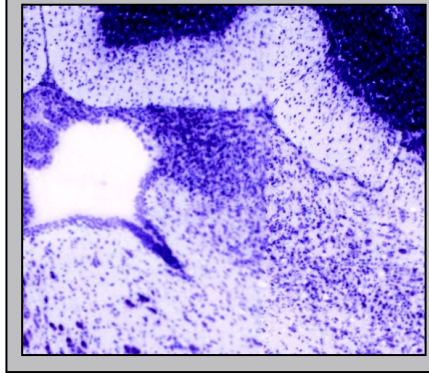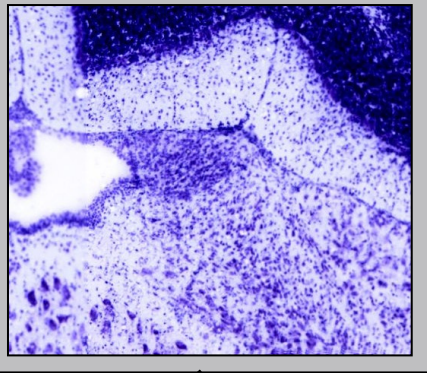
Nissl
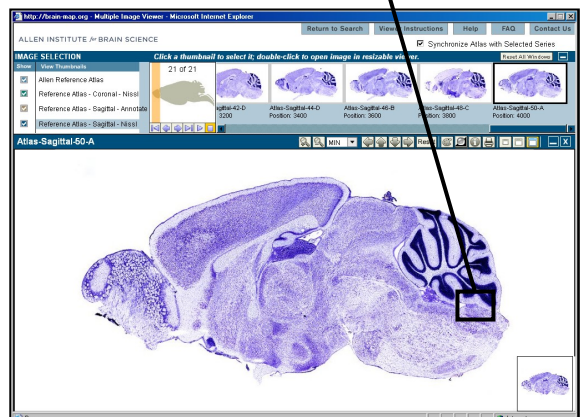
In-Situ Hybridization Expression Patterns of 50 Select Genes:

This survey of the 50 Select Genes showed a relatively narrow range of expression patterns in the AP. The majority of genes showed widespread expression across the entire nucleus, although the density of expression varied significantly from gene to gene, ranging from high (Wif1) to scattered (Nid1). In addition, some of the genes showed a subpopulation of cells: several genes expressed along the periphery of the AP while the internal cells remained either unexpressed or expressed at a lower density and/or intensity (Fabp7). In a few other genes the reverse was true with expression primarily within the interior of the AP and little expression along the periphery (Smoc2). Ependymal cells lining of the ventricles sometimes appear to show expression (e.g. Igfbp5) although further corroboration is necessary.

Cellular density expression key		Cellular intensity expression key	
None	No expression	No color	Very low intensity
Sparse	Very few cells expressing	Blue	Low intensity
Scattered	Less than 10% of cells expressing in scattered pattern	Green	Medium intensity
Medium	10-80% of cells expressing	Yellow	High intensity
High	Greater than 80% of cells expressing	Red	Very high intensity

To view heat map at brain-map.org, right click on an ISH image and select "Show Expression Analysis."

ISH DATA *The Allen Institute ISH images below were selected to highlight various expression patterns of the area postrema.*

ISH
Igfbp5

Coronal: High density expression in the AP, just below the molecular layer of the cerebellum.

Cerebellum | Central canal | Area Postrema
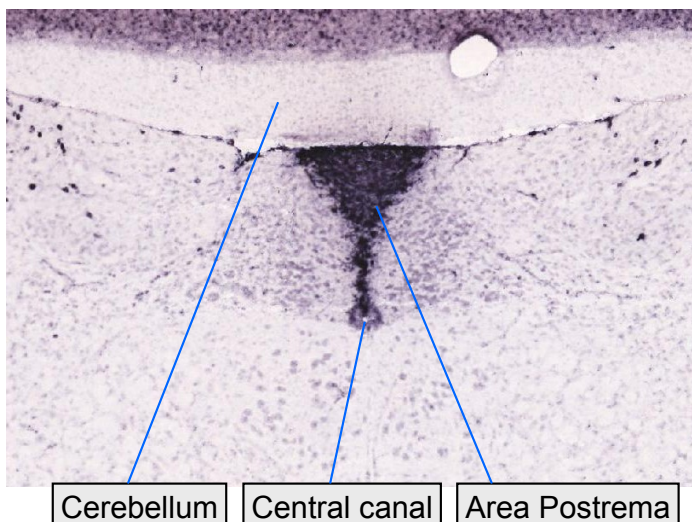
Heat map
Igfbp5

Coronal: The AP shows high density and very high intensity expression as shown by a heat map.

Cerebellum | Central canal | Area Postrema
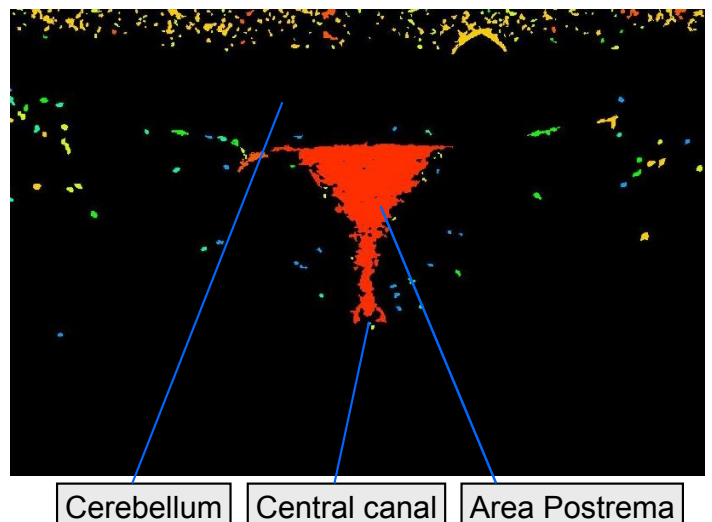
ISH
Igfbp5
Sagittal: The full rostrocaudal extent of the AP is shown.
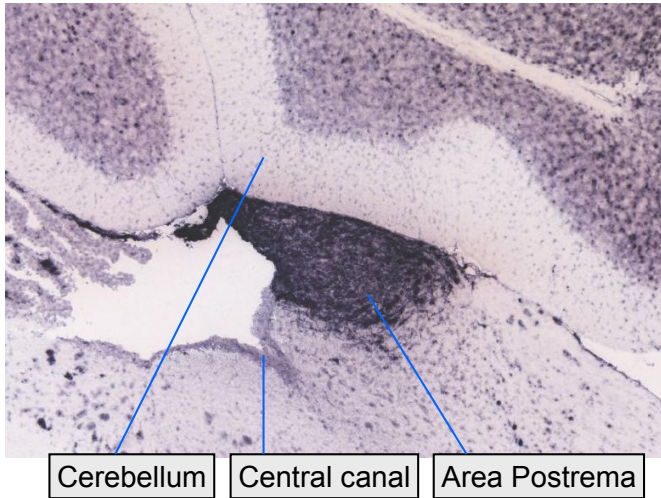

Cerebellum | Central canal | Area Postrema

Heat map
Igfbp5
Sagittal: Igfbp5 expression is presented as high density and very high intensity.

Cerebellum | Central canal | Area Postrema
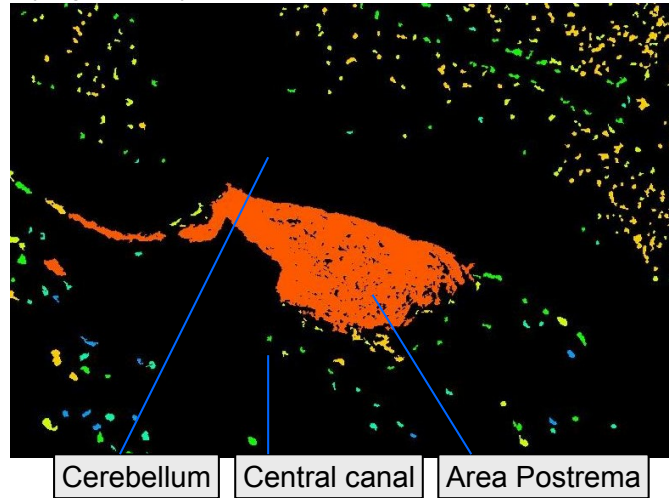
ISH
Nid1
Coronal: Small, interstitial cells in the AP.

Cerebellum | Central canal | Area Postrema
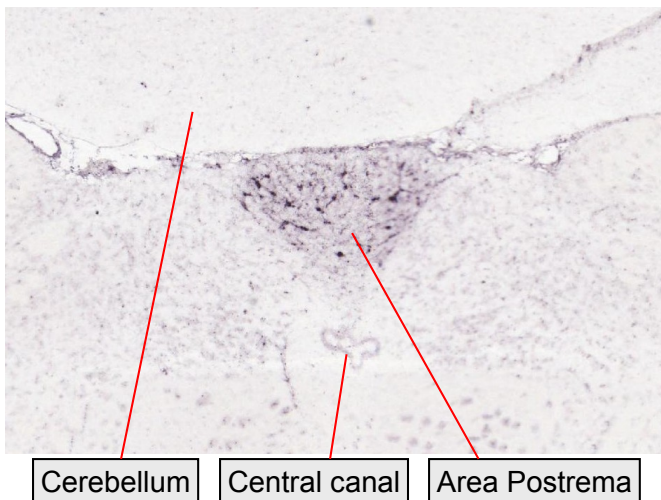
Heat map
Nid1
Coronal: The scattered density and high intensity can be seen in the section below.

Cerebellum | Central canal | Area Postrema
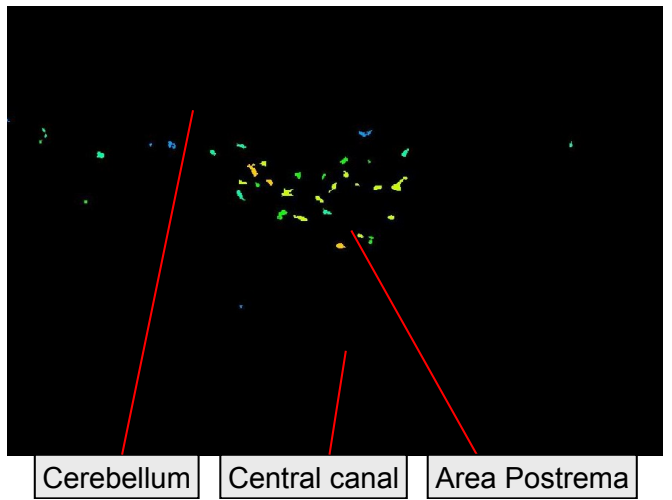
ISH
Nid1
Sagittal: Scattered expression throughout the AP.

Cerebellum | Area Postrema
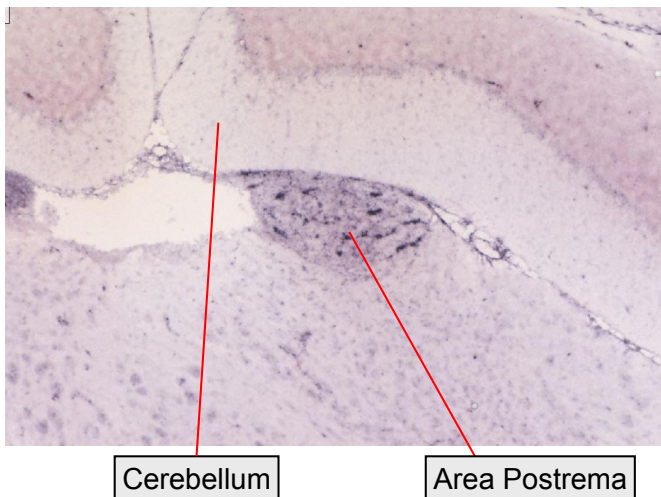
Heat map
Nid1
Sagittal: Nid1 expression, scattered density and high intensity.

Cerebellum | Area Postrema

6
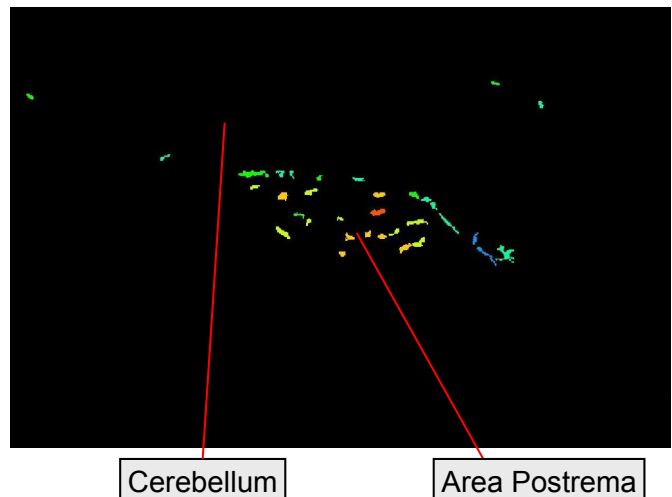
ISH
Fabp7
Coronal: Fabp7 shows a higher density of expression along the perimeter of the AP.
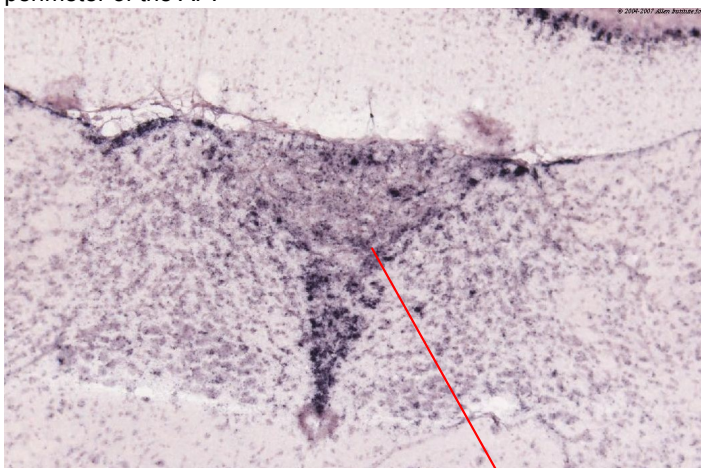
Area Postrema

Heat map
Fabp7
Coronal: Fabp7 shows medium density and high to very high intensity along the periphery
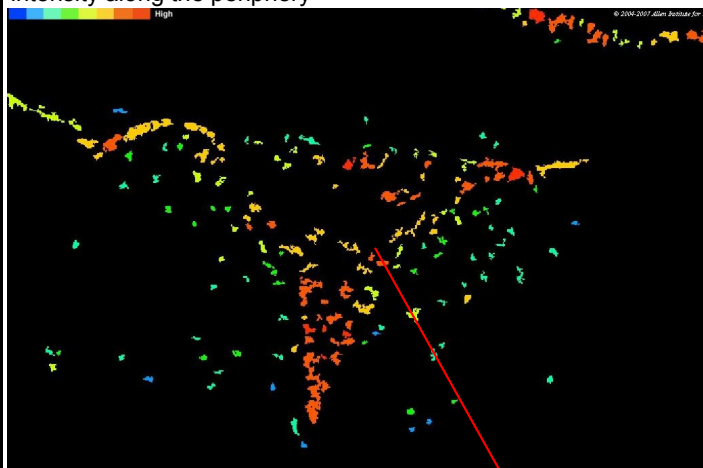
Area Postrema

ISH
Smoc2
Coronal: Smoc2 appears to show a lower density of expression along the perimeter of the AP than in the interior.
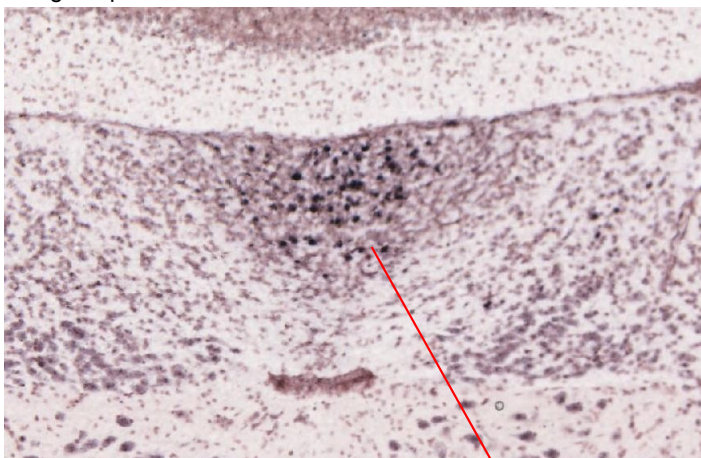
Area Postrema

Heat map
Smoc2
Coronal: Smoc2 appears to show sparse expression along the periphery of the AP with medium density in the interior region.

Area Postrema

50 SELECT GENES:

This gene list was generated by manual curation of an algorithmically derived list that compared gene expression values of area postrema to those of the medulla. Categories of expression are subjectively grouped by relative expression characteristics.

Curation of 50 Select Genes List: June 2007

General Expression Pattern

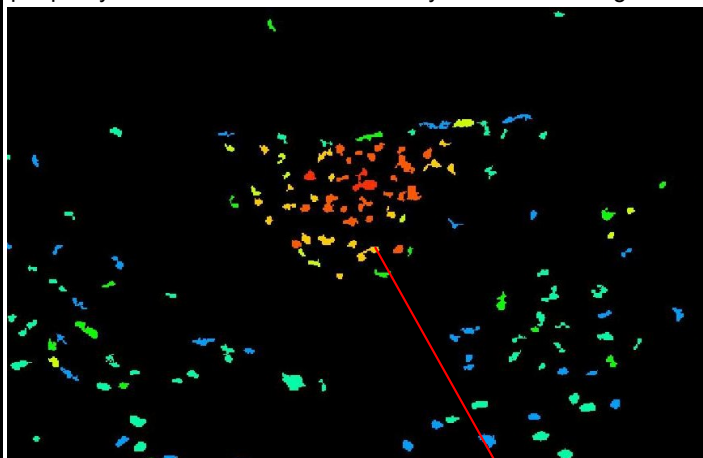| Number	Gene Symbol	Gene Name	Expression Pattern
1	Igfbp5	insulin-like growth factor binding protein 5	High density, very high intensity
2	Dap	death-associated protein	High density, very high intensity
3	Efnb2	ephrin B2	Medium density, high intensity
4	Dkk3	dickkopf homolog 3 (Xenopus laevis)	High density, high to very high intensity
5	Wif1	Wnt inhibitory factor 1	High density, very high intensity
6	Prokr2	prokineticin receptor 2	High density, very high intensity
7	Id4	inhibitor of DNA binding 4	High density, very high intensity
8	Fn1	fibronectin 1	High density, very high intensity
9	Cacng5	calcium channel, voltage-dependent, gamma subunit 5	High density, high to very high intensity
10	Casr	calcium-sensing receptor	Medium density, very high intensity
11	Ramp3	receptor (calcitonin) activity modifying protein 3	Medium density, very high intensity
12	C230071H18Rik	RIKEN cDNA C230071H18 gene	Medium density, medium to high intensity
13	Rfx4	regulatory factor X, 4 (influences HLA class II expression)	Medium density, medium to high intensity
14	A530088H08Rik	RIKEN cDNA A530088H08 gene	High density, very high intensity
15	Gdpd2	glycerophosphodiester phosphodiesterase domain containing 2	High density, high to very high intensity
16	Rarb	retinoic acid receptor, beta	High density, high intensity
17	B3gnt2	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 2	Medium density, medium to high intensity
18	Crym	crystallin, mu	Medium density, high to very high intensity
19	Pitpnm2	phosphatidylinositol transfer protein, membrane-associated 2	High density, high intensity
20	Agxt2l1	alanine-glyoxylate aminotransferase 2-like 1	High density, high to very high intensity
21	Slc20a2	solute carrier family 20, member 2	High density, very high intensity
22	Trp53i11	Trp53 inducible protein 11	High density, very high intensity
23	BC029169	cDNA sequence BC029169	High density, high intensity
24	Hoxa5	homeo box A5	Medium density, high intensity
25	Cd63	Cd63 antigen	Medium density, high intensity
26	Slc27a1	solute carrier family 27 (fatty acid transporter), member 1	High density, very high intensity
27	5730469M10Rik	RIKEN cDNA 5730469M10 gene	High density, high intensity
28	Sned1	sushi, nidogen and EGF-like domains 1	High density, very high intensity
29	Mgll	monoglyceride lipase	Medium density, high to very high intensity
30	Gpr139	G protein-coupled receptor 139	High density, high intensity
31	Accn4	amiloride-sensitive cation channel 4, pituitary	High density, high to very high intensity
32	Gemin4	gem (nuclear organelle) associated protein 4	Medium density, high intensity
33	Plxnd1	plexin D1	Medium density, medium to high intensity
34	Tacr3	tachykinin receptor 3	Medium density, medium intensity
35	Tgfbr2	transforming growth factor, beta receptor II	Scattered density, medium to high intensity
36	Gpr83	G protein-coupled receptor 83	Medium density, high intensity
37	Ghsr	growth hormone secretagogue receptor	High density, very high intensity
38	Nid1	nidogen 1	Scattered density, medium to high intensity
39	Prlhr	prolactin releasing hormone receptor	Scattered density, medium to high intensity
40	Calcr	calcitonin receptor	Scattered density, high intensity
41	Lzp-s	P lysozyme structural	Scattered density, high intensity

General Expression Pattern
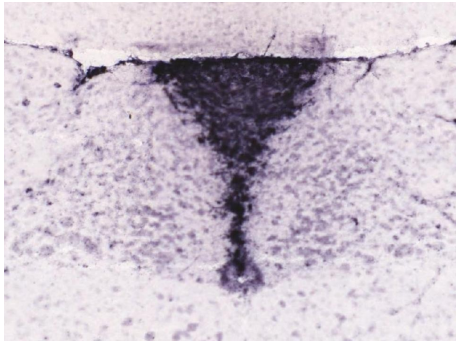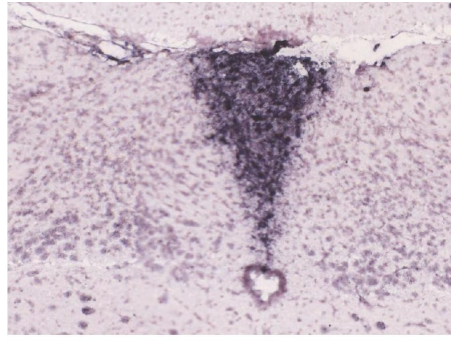
1.Igfbp5	2.Dap	3.Efnb2
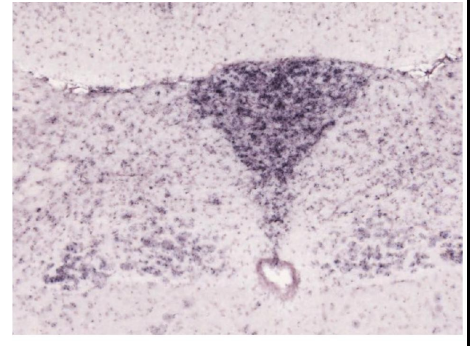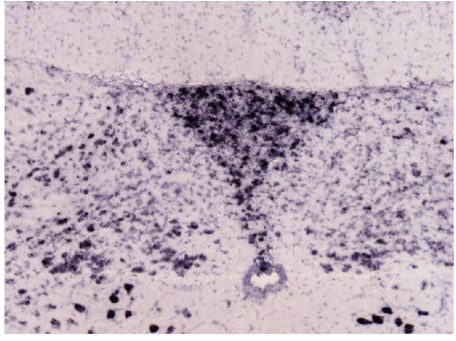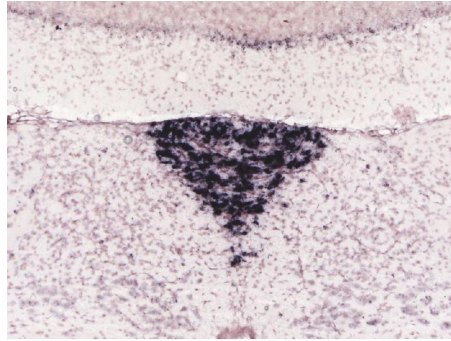
4.Dkk3	5.Wif1	6.Prokr2
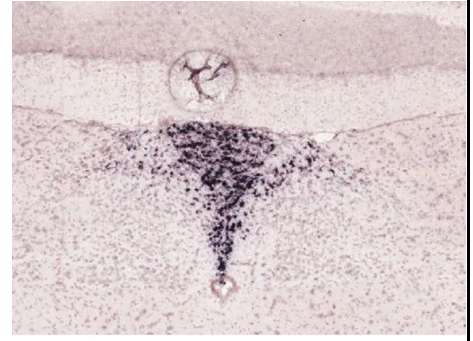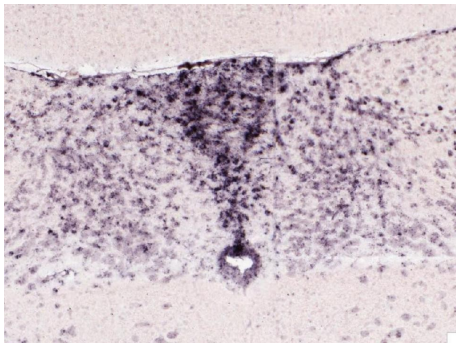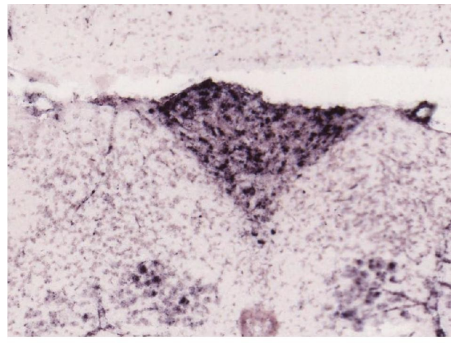
7.Id4	8.Fn1	9.Cacng5
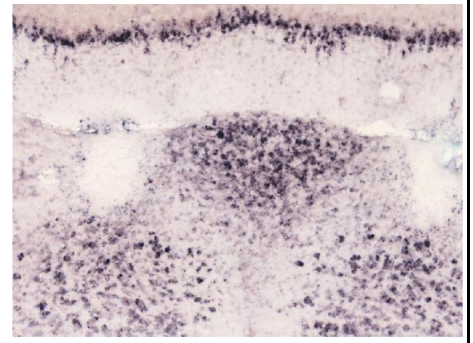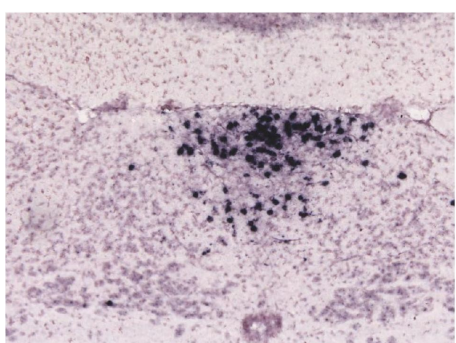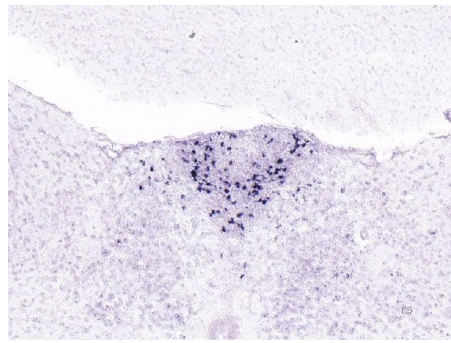
10.Casr	11.Ramp3	12.C230071H18Rik
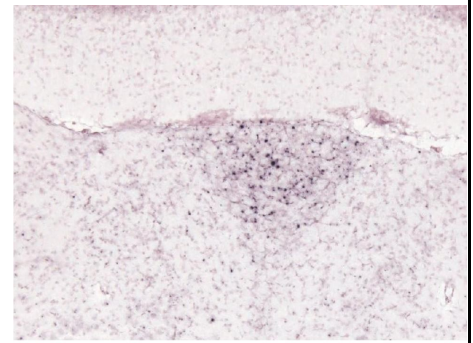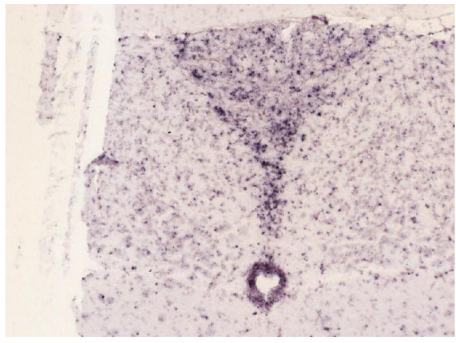
13.Rfx4	14.A530088H08Rik	15.Gdpd2
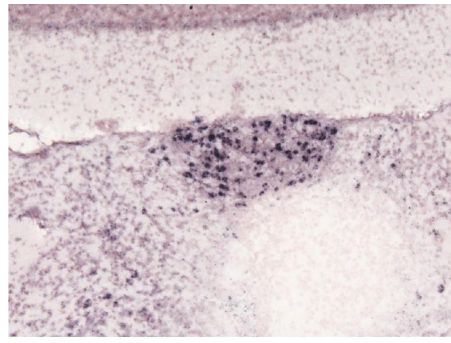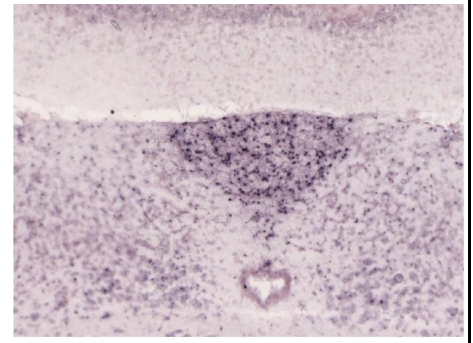
General Expression Pattern

16.Rarb
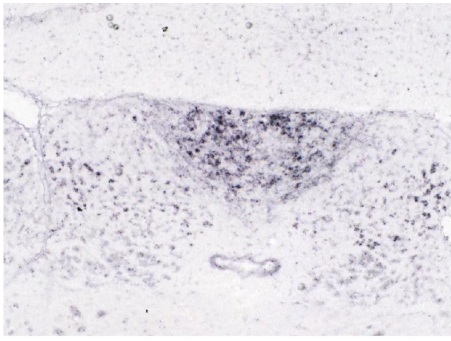
17.B3gnt2

18.Crym

19.Pitpnm2
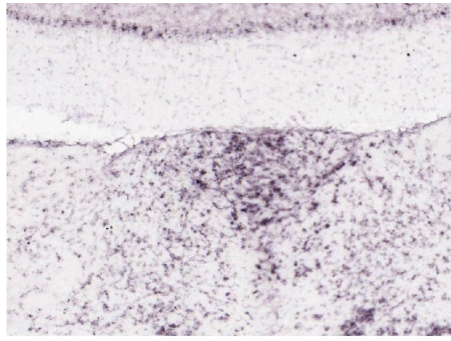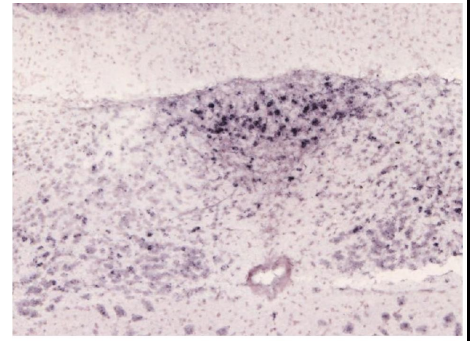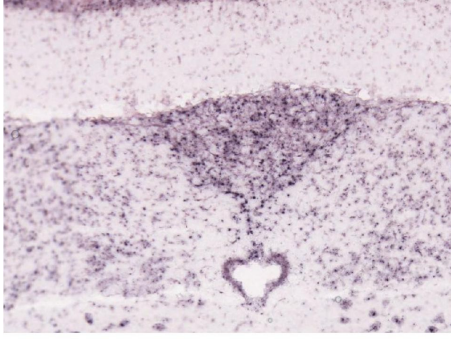
20.Agxt2l1
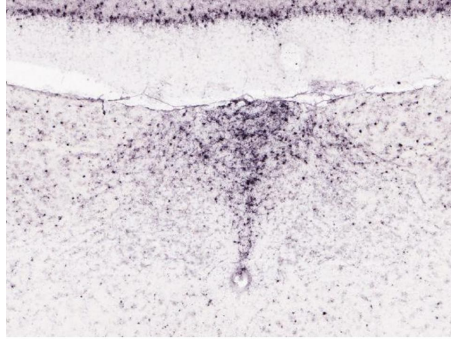
21.Slc20a2
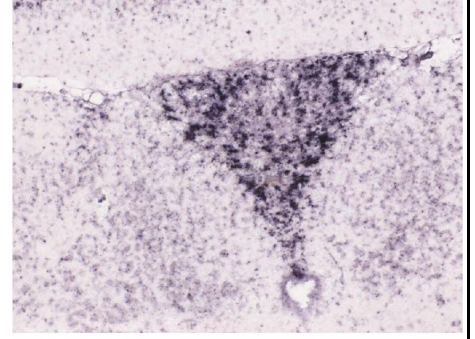
22.Trp53i11
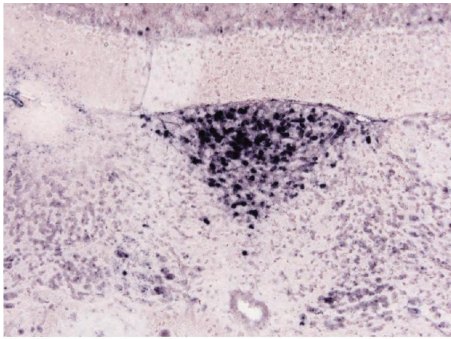
23.BC029169
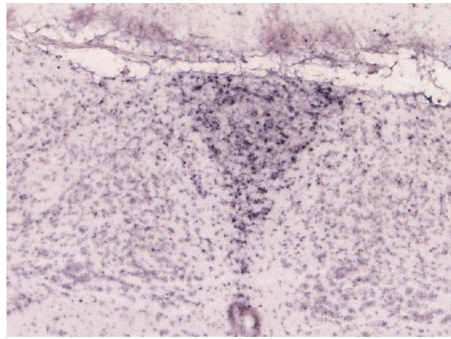
24.Hoxa5
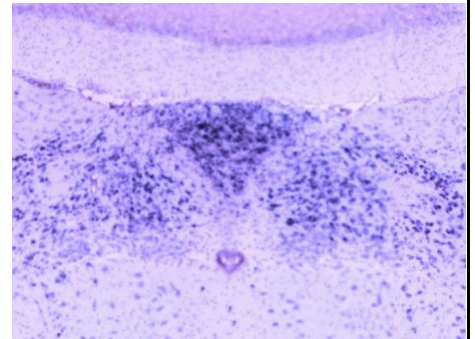
25.Cd63
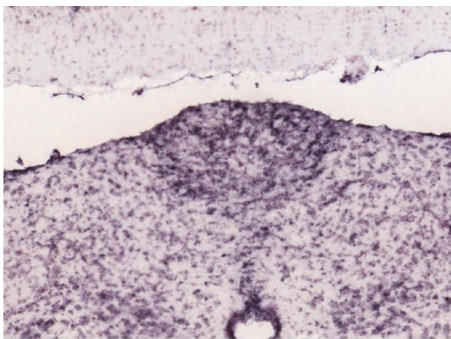
26.Slc27a1
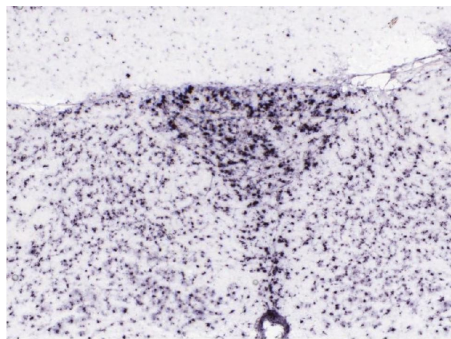
27.5730469M10Rik
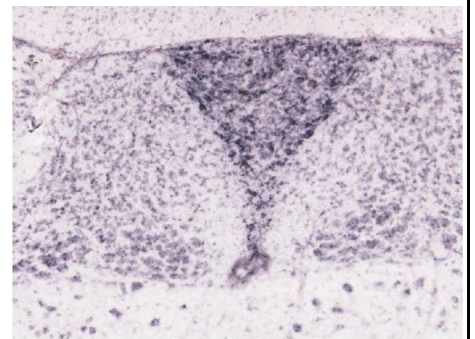
28.Sned1
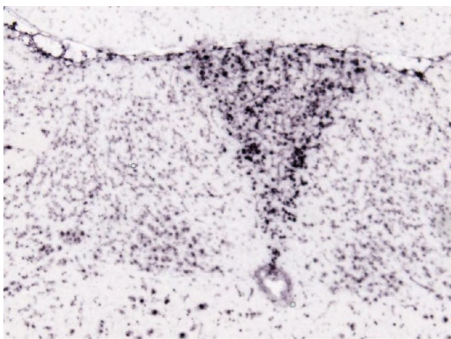
29.Mgll
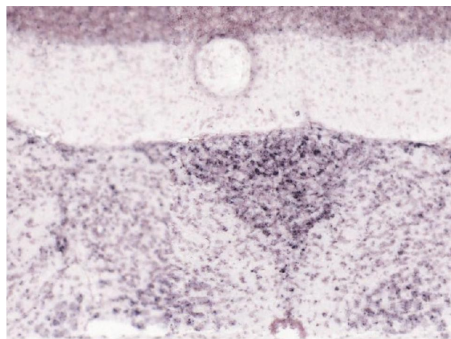
30.Gpr139
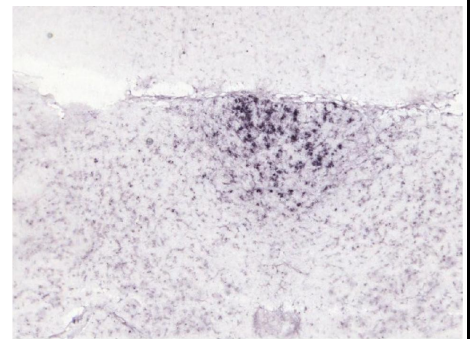
General Expression Pattern

31.Accn4
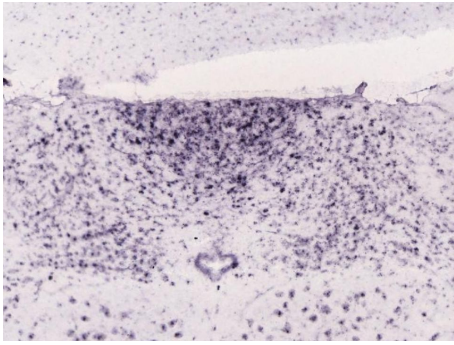
32.Gemin4
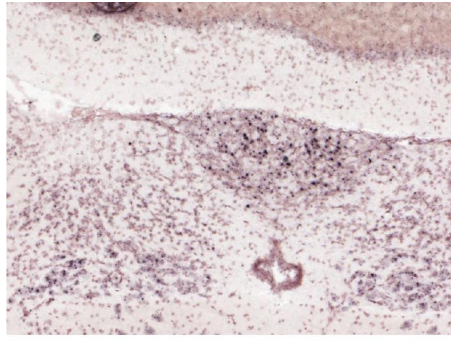
33.Plxnd1
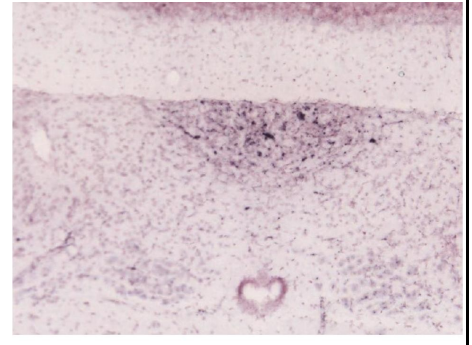
34.Tacr3
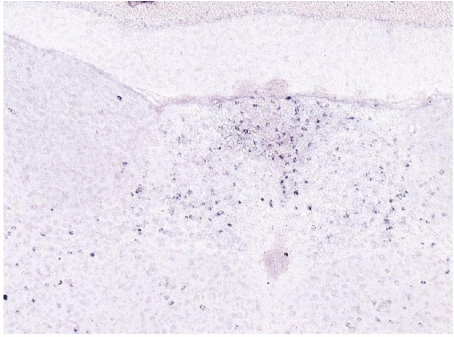
35.Tgfbr2
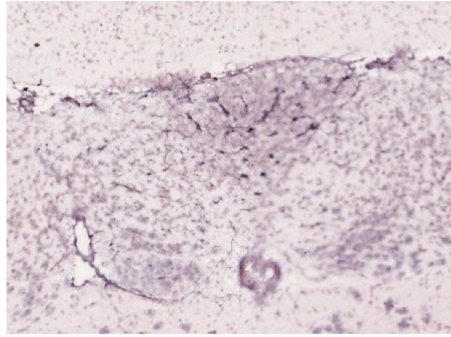
36.Gpr83
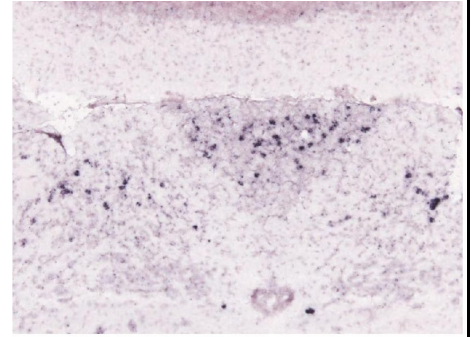
37.Ghsr
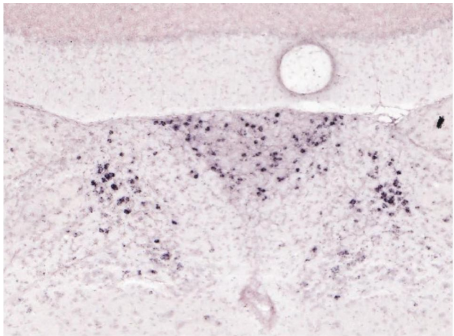
38.Nid1
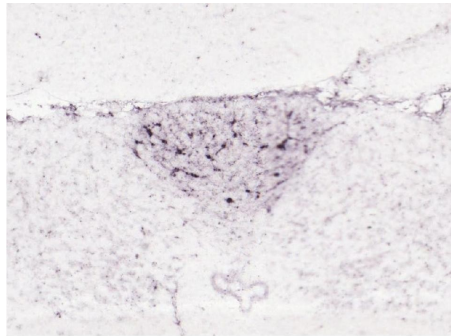
39.Prlhr
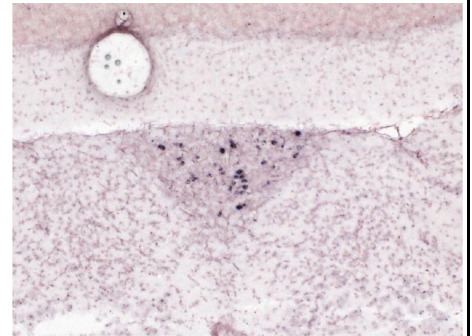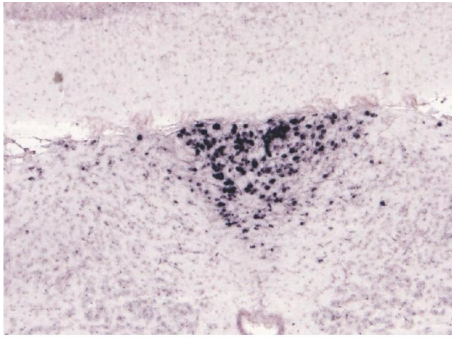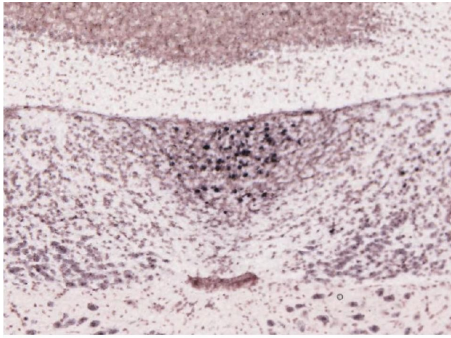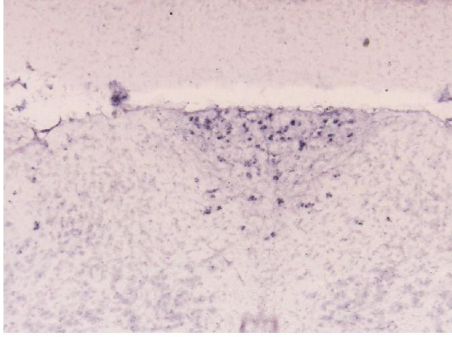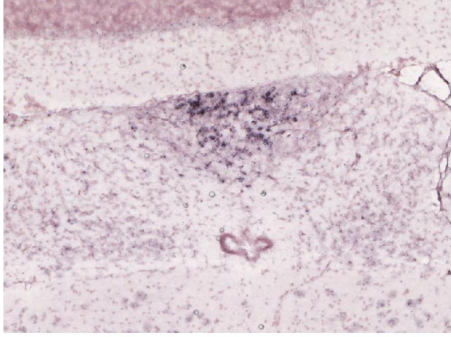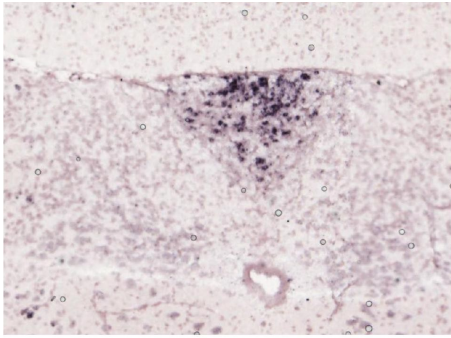
40.Calcr
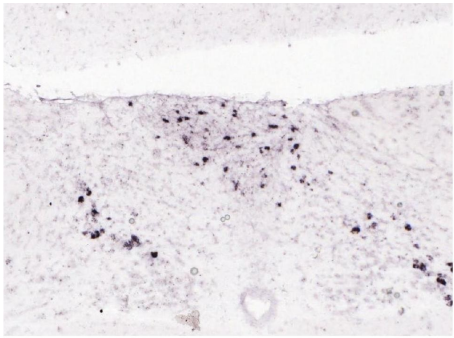
41.Lzp-s
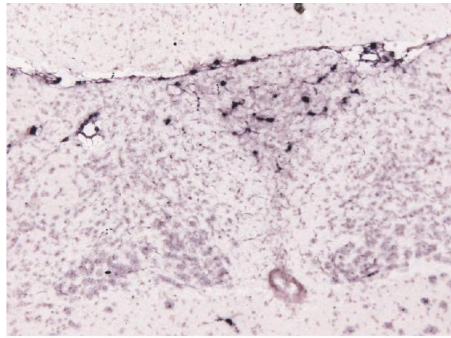
Internal Expression Pattern

Number	Gene Symbol	Gene Name	Expression Pattern
42	Ntrk1	neurotrophic tyrosine kinase, receptor, type 1	High density, very high intensity interior cells; scattered density, high intensity peripheral cells
43	Smoc2	SPARC related modular calcium binding 2	Medium density, very high intensity interior cells; scattered density, high intensity peripheral cells
44	Glp1r	glucagon-like peptide 1 receptor	Medium density, very high intensity interior cells; medium density, high intensity peripheral cells
45	Etv1	ets variant gene 1	Medium density, high intensity interior cells; sparse density, low intensity peripheral cells
46	A930001M12Rik	RIKEN cDNA A930001M12 gene	High density, high intensity interior cells; sparse density, low intensity peripheral cells

42.Ntrk1

43.Smoc2

44.Glp1r

45.Etv1

46.A930001M12Rik

Peripheral Expression Pattern			
Number	**Gene Symbol**	**Gene Name**	**Expression Pattern**
47	Edg1	endothelial differentiation sphingolipid G-protein-coupled receptor 1	Scattered density, medium intensity interior cells; high density, very high intensity peripheral cells
48	Fabp7	fatty acid binding protein 7, brain	Scattered density, high intensity interior cells; high density, very high intensity peripheral cells
49	Tgfb2	transforming growth factor, beta 2	Scattered density, medium intensity interior cells; medium density, high intensity peripheral cells
50	C230030N03Rik	RIKEN cDNA C230030N03 gene	Medium density, low to medium intensity interior cells; medium density, medium to high intensity peripheral cells

47.Edg1
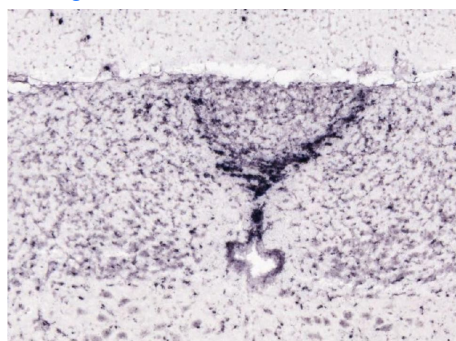
48.Fabp7
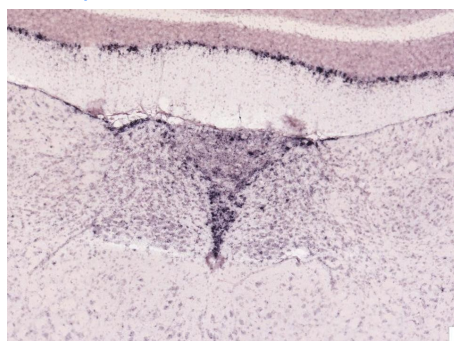
49.Tgfb2
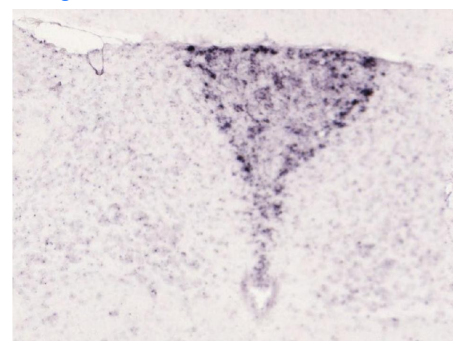
50.C230030N03Rik
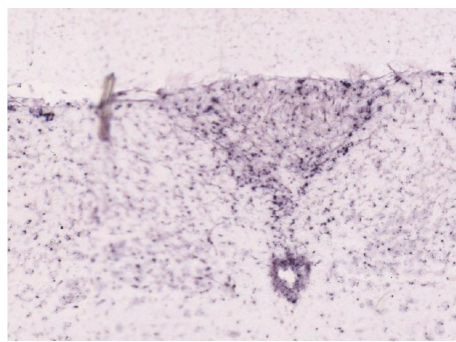
Correlated Expression:

The ABA coronal set contains the majority of genes of known scientific interest, as well as genes exhibiting marked or unique expression patterns. A correlation analysis of all available ABA coronal experiments (4376) was performed by comparing an expression value of the area postrema (AP) to expression values in other regions of the brain. Following image analysis, the data values for each experiment were mapped to a 3-D reference brain at 200µm^3 voxel resolution. Then, each voxel was assigned a single expression value based on the product of density and intensity of expression. Values from all 4376 experiments were computed, and the likelihood of co-expression between any two voxels or regions are reported as a Pearson's correlation coefficient.

For the purposes of determining correlated expression between the area postrema and other brain regions, expression values from all voxels within the area postrema were aggregated to form a single expression value. Two types of comparisons were then made. First, the aggregate expression values of the area postrema and those of other anatomically defined regions (~200 structures) were compared within the 3-D reference brain (structure vs. structure; table below). Second, a color map was then generated to display the correlation between the area postrema and each of the ~53,000 voxels of the reference volume (structure vs. voxel; correlation map on the following page).

STRUCTURE vs. STRUCTURE

The expression value of the AP was compared to expression values for all other defined atlas regions. Degree of correlation is displayed as a comparative fraction, with self-correlation = 1.000. Correlation between the AP and macro/parent-structures are presented, as well as correlation between the AP and the 25 highest ranking substructures. (The most highly correlated macro/parent-structures do not always contain the 25 top most correlated substructures). Columns match the Allen Reference Atlas palette.

Macro structure: *Rostral-> Caudal*

Macro structure	Correlation
OLF (Olfactory areas)	0.738206
STR (Striatum)	0.717063
PAL (Pallidum)	0.810784
CTX (Cerebral cortex)	0.708956
HY (Hypothalamus)	0.827481
TH (Thalamus)	0.752077
HIP (Hippocampal region)	0.704672
RHP (Restrohippocampal formation)	0.734412
MB (Midbrain)	0.813816
P (Pons)	0.78535
MY (Medulla)	0.799689
CB (Cerebellum)	0.716248

| Substructure	Correlation
Area postrema (AP)	1
Dorsal motor nucleus of the vagus nerve (DMX)	0.89496
Nucleus of the solitary tract (NTS)	0.873051
Dorsal column nuclei (DCN)	0.864949
Cuneate nucleus (CU)	0.864595
Parasolitary nucleus (PAS)	0.853472
Paraventricular hypothalamic nucleus (PVH)	0.837842
Periventricular region (PVR)	0.835768
Medial pretectal area (MPT)	0.835171
Pontine central gray (PCG)	0.833825
Dorsomedial nucleus of the hypothalamus (DMH)	0.825996
Midbrain raphe nuclei (RAmb)	0.824843
Lateral habenula (LH)	0.824149
Periaqueductal gray (PAG)	0.824113
Hypothalamic medial zone (MEZ)	0.823684
Median preoptic nucleus (MEPO)	0.82337
Olivary pretectal nucleus (OP)	0.820775
Superior colliculus, sensory related (SCs)	0.819915
Supragenual nucleus (SG)	0.819317
Periventricular zone (PVZ)	0.817248
Parabrachial nucleus (PB)	0.816901
Interpeduncular nucleus (IPN)	0.81412
Posterior hypothalamic nucleus (PH)	0.813803
Midbrain, behavioral state related (MBsta)	0.811624
Epithalamus (EPI)	0.811183

.81   1.0
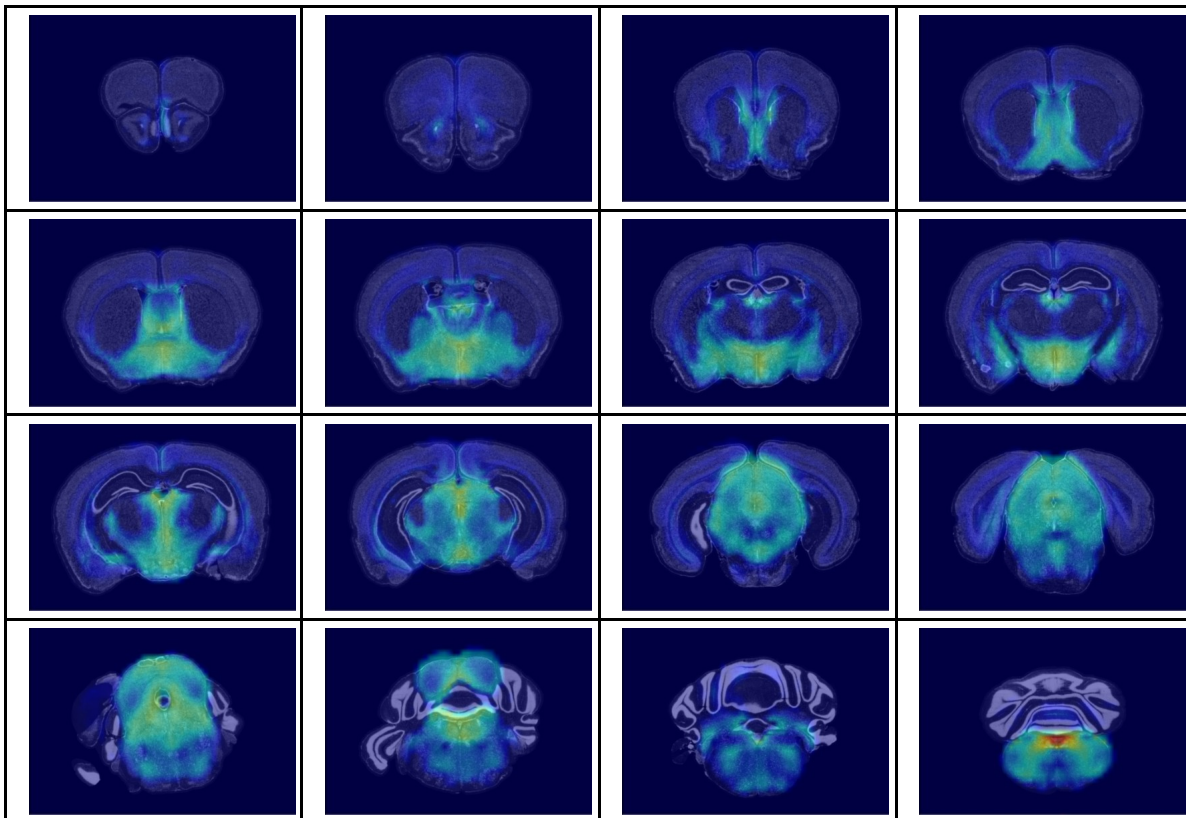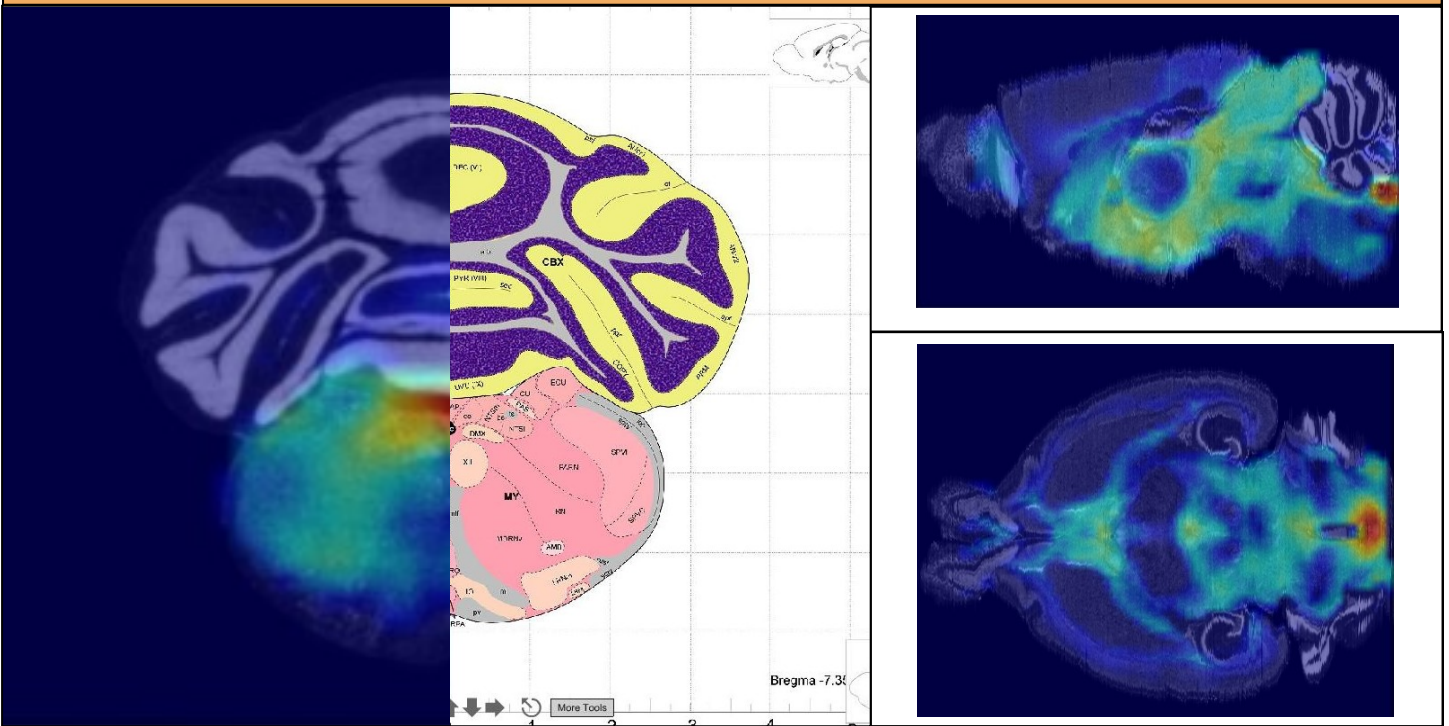
Gene Ontology (GO) Analysis:

GO TABLE: *Below is an ontological analysis of the 50 Select Genes, using [DAVID](#) Bioinformatics Resources.*

The functional terms that follow were returned using these constraints:

Category	Definition	Constraints
P-value	Probability that the term is over-represented in this 50 Select Genes list relative to the mouse genome	when p ≤ 0.05
Gene Count	The minimum number of genes that must fall into an onto-logical category to be considered a group	5 genes per term group
GO Level	The level of functional specificity for GO functional cate-gories: Molecular Function (mf), Biological Process (bp) and Cellular Components (cc)	Level GO_All
# of DAVID IDs	Number of unique DAVID gene IDs from user's input list	*49 DAVID gene IDs/* 50 input genes

Date of table completion: June 15th, 2007

GO Category	GO Term	Gene Count	% of Genes	p-value
GOTERM_CC_ALL	extracellular space	17	34.69%	3.19E-05
GOTERM_MF_ALL	peptide receptor activity	5	10.20%	1.16E-04
GOTERM_CC_ALL	extracellular region	17	34.69%	1.36E-04
GOTERM_MF_ALL	peptide binding	5	10.20%	2.91E-04
GOTERM_BP_ALL	development	15	30.61%	3.95E-04
GOTERM_BP_ALL	system development	8	16.33%	4.76E-04
GOTERM_MF_ALL	receptor activity	16	32.65%	0.00114106
GOTERM_BP_ALL	nervous system development	7	14.29%	0.001792063
GOTERM_MF_ALL	signal transducer activity	17	34.69%	0.003534057
GOTERM_BP_ALL	cell surface receptor linked signal transduction	15	30.61%	0.004982882
GOTERM_MF_ALL	transmembrane receptor activity	12	24.49%	0.006339499
GOTERM_BP_ALL	morphogenesis	8	16.33%	0.009324962
GOTERM_BP_ALL	organ development	8	16.33%	0.010680059
GOTERM_MF_ALL	G-protein coupled receptor activity	10	20.41%	0.014525386
GOTERM_CC_ALL	integral to membrane	21	42.86%	0.015631625
GOTERM_CC_ALL	intrinsic to membrane	21	42.86%	0.015978282
GOTERM_BP_ALL	G-protein coupled receptor protein signaling pathway	11	22.45%	0.035977527
GOTERM_BP_ALL	organ morphogenesis	5	10.20%	0.039380829
GOTERM_BP_ALL	positive regulation of cellular physiological process	5	10.20%	0.049000235

Glynn Dennis Jr., Brad T. Sherman, Douglas A. Hosack, Jun Yang, Michael W. Baseler, H. Clifford Lane, Richard A. Lempicki. "DAVID: Database for Annotation, Visualization, and Integrated Discovery." *Genome Biology.* 2003 **4**(5): P3.

alleninstitute.org

Area Postrema (AP) Summary:

Anatomy
- The AP is a small, midline structure positioned at the caudal wall of the fourth ventricle, ventral to the cerebellum.
- The cells within the AP appear small, evenly distributed, and densely packed.
- In Nissl-stained sections, the borders of the AP are easily distinguishable because of its location on the midline and the relatively high density of its cells.

Expression Patterns of the 50 Select Genes
- This survey showed a narrow range of expression patterns in the AP.
- Some genes appear to have a different density of expression along the periphery of the AP versus the interior.
- The border between the AP and the rest of the medulla could be sharply defined by gene expression, and agreed with the borders delineated in the Allen Reference Atlas.

Expression Correlation with AP
- Pallidum and hypothalamus correlated most highly with the AP.
- Cortex and hippocampus were the least correlated regions.
- Of the top ranking 25 sub-structures highly correlated with the AP, many reside in the midbrain and hypothalamus, although the epithalamus (medial and lateral habenulae) provides an interesting exception.

Please send comments or questions by email to !Annotation@alleninstitute.org. To further explore the gene expression data and analytical tools referred to in this report, please access the genome-wide data set at brain-map.org.

Other Tools:

NEUROBLAST:
Many of the 50 genes listed in this report can be used to explore the NeuroBlast tool. This unique mining tool works seamlessly from within brain-map.org to produce a list of genes that share similar expression patterns to any gene in the coronal data set. Search for and select any gene, then select one of several brain regions from the NeuroBlast drop-tab to explore a ranked list of similarly expressed genes for that region.
To learn more about this function, please refer to the NeuroBlast white paper.

BRAIN EXPLORER:
To compare gene expression levels across anatomical structures in 3-D detail, download the Brain Explorer desktop application. This program is used to view gene expression in 3-D view (coronal, sagittal, horizontal and everywhere in between) across all brain structures and allows for simultaneous viewing of multiple expression profiles.

The NeuroBlast spatial homology function and an anatomic search tool are also available from within Brain Explorer to allow the user to search for and visualize genes with similar expression patterns.

alleninstitute.org