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Supplementary Information for

Transcriptional Network Orchestrating Regional Patterning of Cortical Progenitors

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SUPPLEMENTARY TEXT

MATERIALS AND METHODS

Mice and genotyping

All procedures and animal care were approved and performed in accordance with National Institutes of Health and the University of California San Francisco Laboratoy Animal Research Center (LARC) guidelines. Mice strains that were used have been previously reported: *Pax6*^{Sey/Sey} (1), *Emx2*^{-/-} (2), *NR2F1*^{-/-} (3), *Emx1::Cre; NR2F1*^{-/-}; *NR2F2*^{fl/fl} (4, 5) and *Npas3*^{-/-} (6). All mice were genotyped as previously reported.

Method Details

Cortical expression analysis

The Developing Mouse Brain database of the Allen Brain Institute has generated *in situ hybridization* catalogs for hundreds of proteins in the mouse embryonic and postnatal brain. Three separate investigators annotated expression patterns of the TFs in the cortex at E11.5 by annotating both the density and the intensity of the *ISH* staining in the ventricular zone and the subventricular zone/mantle zone of the lateral ventral pallium (LVP), rostral dorsal pallium (RDP), caudal dorsal pallium (CDP) and medium pallium (MP). These annotations were then computationally mined to identify novel gradient patterns and/or regional expression.

<u>Histology</u>

Brains were fixed, cryopreserved and embedded as previously described (7). After cryostat-sectioning, brain sections were stained as described (8). In situ hybridization was performed as previously described (7). For details on how probes were generated, see ABA website.

Emx2 antibody production

A guinea-pig Emx2 antibody was generated by Genscript. It was raised against a peptide of the N-terminus of mouse Emx2 (aa 1-155) which specifically excluded the homeodomain of Emx2.

TF Chromatin Immunoprecipitation (ChIP)

Dissected cortices from embryos from multiple litters were dissociated and crosslinked at room temperature for 10 min in 1% formaldehvde (EMX2, LHX2) or 20 minutes in 1.5% formaldehvde (NR2F1, PAX6, PBX1) before being quenched for 5 mins in glycine (2.5mM) and washed gently with 1xPBS. Nuclei were extracted by lysing the fixed cells in a hypotonic buffer (50 mM Tris pH 7.5 / 0.5% NP40 / 0.25% Sodium Deoxycholate / 0.1% SDS / 150 mM NaCl). The crosslinked chromatin was sheared in dilution buffer (0.01% SDS, 1.1% Triton X- 100, 1.2mM EDTA, 16.7mM Tris-HCI, pH 8.1, 167mM NaCI) using a bioruptor (Diagenode) for either 18 rounds (for samples fixed in 1% PFA) or 40 rounds (1.5% PFA) (1 round = 30 s on/45 min off at high intensity) and incubated at 4°C overnight with 5 mg of antibody or either 20× blocking peptide or a control IgG which were used as negative controls as appropriate. Protein/antibody complexes were collected using Dynabeads (20 µL protein A + 20 µL protein G) before being washed in three wash buffers: low salt wash buffer (0.1% SDS, 1% Triton X-100, 2mM EDTA, 20mM Tris-HCl, pH 8.1, 150mM NaCl), high salt wash buffer (0.1% SDS, 1% Triton X-100, 2mM EDTA, 20mM Tris-HCI, pH 8.1, 500mM NaCI); and LiCI wash buffer (0.25M LiCI, 1% IGEPAL CA630, 1% deoxycholic acid (sodium salt), 1mM EDTA, 10mM Tris, pH 8.1and TE). Chromatin was eluted in Elution buffer (1%SDS, 10mM Codium bicarbonate buffer) at 65°C for 10 min. Eluted chromatin was reverse crosslinked overnight at 65°C with NaCl (500mM), then subsequently treated with RNase (10 µg/ 200 µl reaction, 15 min at 37°C) and Proteinase K (10 µg/ 200 µl reaction, 60 min at 55°C). DNA was then cleaned using a ChIP DNA Clean & Concentrator kit (Zymo Research). ChIP experiments were then validated by ChIP-gPCR using a 7900HT Fast Real-Time PCR System (Applied Biosystems) with SYBR Green gPCR SuperMix (Invitrogen, Cat. No. 11760-100).

ChIP-seq libraries were prepared using the Ovation Ultralow DR Multiplex System (NuGEN). Generated libraries were size selected using Blue Pippin (centered around 300 bp), QC tested on a Bioanalyzer

(Agilent) and sequenced as single-end 50 nucleotide reads on a HiSeq 4000 (Illumina) at the Center for Advanced Technology at UCSF (http://cat.ucsf.edu/).

ChIP-seq Computational Analysis

Clustering, base calling, and quality metrics were performed using standard Illumina software. Sequencing libraries were analyzed for overall quality and were filtered, and reads were mapped to the mouse genome (mm9) using Burrows-Wheeler Alignment (BWA) (9).

Pairwise Pearson Correlation

Pearson correlation between aligned read counts of pairs of TFs was determined using DeepTools (10) to show association between TFs and between different TF replicates.

Motif analysis

De novo motif discovery and enrichment was performed using HOMER version 4.9 (11) in the called peaks for each individual TF, using standard parameters, 300 bp up- and downstream of TF peaks. We compared the significant motifs discovered with the JASPAR (25) database. Motif enrichment was determined for all motifs present in the HOMER known motif database with p-value < 10^{-100} . We established the average motif coverage enrichment plot around 300 bp of peaks for each TF using custom R scripts.

Gene Ontology analysis

Gene Ontology analyses were conducted using the GREAT algorithm.

VISTA enhancer annotations

Relevant VISTA enhancers were annotated by at least two experts in the field. Their region of activity was ascertained on whole-mount embryos and where necessary, using sections. Gradients of activity were only defined when they were clear and when consensus was obtained between at least two observers.

Gradient modelling

We established the model associating TF binding, enhancer spatial activity gradients, and enhancer regional activity by determining the pairwise correlation of among the different factors. The TF binding combinations and other factors were intersected using custom R scripts, and the correlation matrix and plot with R ggcorrplot package. Only correlations with p < 0.01 was shown. Non-relevant associations were manually removed.

Histone mark ChIP

We used Cell Trace Yellow Cell Proliferation Kit (ThermoFisher, #C34567) or Cell Trace CFSE Cell Proliferation Kit (ThermoFisher, #C34554) to label the ventricular zone of Pax6 and Emx2 mutants and their control littermates at E12.5. FlashTag labeling was conducted by injecting 0.3 µl of 10 mM of a carboxyfluorescein succinimidyl ester (CellTrace Yellow or Cell Trace CFSE, ThermoFisher) bilaterally into the fourth ventricle of E12.5 embryos (12). Gentle manual pressure was then applied to the exterior of the embryonic head to promote even mixing of the dyes. After 20 minutes, the cortices were then dissected and papain-treated (Papain dissociation system, Worthington Biochemical Corporation) for 15-30 minutes at 37°C with rotation. After inhibiting the papain, dissociated cortical cells were resuspended in 4% FBS/1x-PBS and the singlet FTag-positive population was sorted using the BD FACS Aria III Cell Sorter at Helen Diller Cancer Building (UCSF). Approximately 200,000 cells were used for native ChIP as described in (13). Wild-type cells and mutant littermates were always injected, sorted and processed side by side using the same number of nuclei. Basically, nuclei were extracted from the sorted cells and digested for 8 mins with micrococcal nuclease (MNase, Sigma). Mono and di-nucleosomes were combined and used for ChIP of two epigenomic marks: H3 acetylated lysine 27 (H3K27ac, Abcam, ab472) and H3 trimethyl lysine-27 (H3K27me3, Active motif, 39157). After immunoprecipatation, DNA and libraries were prepared as for TF ChIP as described above.

ATAC-seq

ATAC-seq was performed on around 80,000 sorted nuclei. Basically, we fluorescently labeled the VZ of wild-type and mutant littermates using the FlashTag procedure as indicated above. After making nuclei,

the pellet was resuspended in 25uL of Tagment DNA buffer and 2uL of enzyme (Tagment DNA Enzyme, Nextera DNA Library Prep Kit, 15028211, Illumina). Tagmentation was performed at 37°C for 30 mins without shaking. Samples were then purified using MinElute columns (Qiagen), PCR-amplified for 8-10 cycles using the NEB Next High Fidelity 2x PCR Master Mix (NEB, 72 °C 5 min, 98 °C 30 s, (98 °C 10 s, 63 °C 30 s, 72 °C 60 s) per cycle, held at 72 °C). The generated amplified libraries were purified on Ampure XP Bead (Beckmann Coulter) and bioanalyzed. Sequencing was carried out on a HiSeq4000 (50 bp PE, Illumina).

PLAC-seq

PLAC-seq libraries for E12.5 cortex were prepared similar to the previously published protocol (14). 3 to 7 million cells were used for each library. If the cells appeared aggregated, they were dissociated with gentle MACS dissociator or dounce homogenizer. Each PLAC-seq library was prepared using DpnII as the restriction enzyme and Dynabeads M-280 sheep anti-rabbit IgG (Invitrogen #11203D) mixed with 5ug of H3K4me3 (04-745, Millipore) for the chromatin immunoprecipitation step. Finally, libraries were prepared with the Illumina Tru-seq adaptors and the final libraries were sent for paired-end sequencing on the HiSeq X Ten (150 bp reads).

PLAC-seq data analysis using the MAPS pipeline

We applied the MAPS pipeline (15) to detect statistically significant H3K4me3-centric long-range chromatin interactions from PLAC-seq data. We only analyzed intra-chromosomal interactions for autosomal chromosomes, and identified chromatin interactions at 10Kb bin resolution between 20Kb and 1Mb. We first mapped the raw paired-end reads (i.e. fastq file) to the mm10 reference genome using bwa mem. Next, we applied filtering steps to remove PCR duplicates, low quality reads (MAPQ <= 30) and chimeric reads (15). We then split the remaining mapped reads into short-range (distance between pair ends within 1Kb) and long-range reads (distance between pair ends between 1Kb and 1Mb). We used the short-range and long-range reads to measure protein immunoprecipitation (IP) efficiency and detect longrange chromatin interactions, respectively. In addition, we collected ChIP-seq peaks called by MACS2 from cortical cells. Among all 10Kb bin pairs, we only examined those 10Kb bin pairs in which at least one 10Kb bin overlapped with MACS2 ChIP-seq peaks, since these 10Kb bin pairs are enriched by H3K4me3 antibody during the PLAC-seg experiment (16). We fitted a positive Poisson regression model on all selected 10Kb bin pairs with more than one raw count, taking into consideration multiple bias factors including 1D genomic distance between two interacting bins, restriction enzyme cut site frequency, GC content, mappability score, and H3K4me3 antibody IP efficiency measured by the number of short-range reads in each bin. After modeling fitting, we obtained expected contact frequency, p-value and false discovery rate (FDR) for each 10Kb bin pairs. Finally, we defined a 10Kb bin pair as a statistically significant long-range chromatin interaction if the raw contact frequency >= 12, normalized contact frequency (defined as observed contact frequency/expected contact frequency) >= 2, and FDR < 0.01. We further merged adjacent significant chromatin interactions together, and defined those isolated significant chromatin interactions as singletons. We applied a more stringent FDR threshold (FDR < 0.0001) among those singletons to reduce potential false positives.

Enhancer-Gene maps (definitions and annotation strategy).

Associations were previously defined by correlation between the H3K27ac profile of putative enhancers and the total-RNA profile of annotated genes across embryonic development. Two different maps were used, based on a dataset of 29 (17) or 66 (18) samples representing time-courses considering up to 12 tissues and 7 time points. Given a list of genomic regions, a custom C++ script was used to annotate each one of these regions to the overlapping putative enhancers in these two maps (if any) and to associate them to the computationally inferred target gene.

Validated enhancers from the VISTA Enhancer Browser (derivation and annotation strategy)

Human and murine validated elements available on August 25, 2017 on the VISTA enhancer browser (http://enhancer.lbl.gov) (19). Human regions (hg19) were lifted to the mouse genome (mm10) using liftOver (20). This was run with default parameters except for *minmatch* that was set to 0.1 for mouse to human conversions and to 0.95 for mapping between mm9 and mm10. After that, the same script and strategy outlined in the previous paragraph were used to annotated a given list of genomic intervals to the regions in VISTA.

PLAC-seq data annotation

Using the same script and strategy outlined in the previous paragraphs, each end of the interaction was annotated to any overlapping: (1) VISTA element; (2) the putative target gene, as inferred separately from the two maps described in the previous paragraph; (3) TF-binding events, as inferred by ChIP-seq; in case of multiple overlapping peaks, the region was assigned the peaks with the highest enrichment score; (4) the closest gene on the linear genome, using the TSS of RefSeq genes as landmark. Coordinates of RefSeq genes were downloaded from the UCSC genome browser (19) on May 30, 2015. Merging of the resulting annotations was performed using the statistical computing environment R v3 (http://www.r-project.org).

Defining the interactome for loci in the Cortical Regionalization TF Network

We defined genomic loci based on the farthest PLAC-seq interaction between promoters and pREs for each loci. In cases in which this chromatin binding domain was restricted to only one side (upstream or downstream) of the gene body (i.e. *Bcl11a* or *Dmrt3*, Figure S5), we added a 100kb buffer on the other side of the TSS or 5'UTR.

Transgenic enhancer assays

Transgenic assays were performed according to published methods (21, 22) and the VISTA enhancer browser can be consulted here: <u>https://enhancer.lbl.gov</u>. A summary of the methodology can be found in Lindtner et al, 2019 (23).

Contact for Reagent and Resource Sharing

Further information and requests for resources should be directed to and will be addressed by the Lead Contacts, John L. R. Rubenstein (John.Rubenstein@ucsf.edu) and Alex S. Nord (asnord@ucdavis.edu).

Table S1: Key Resources Table

Reagent or Resource	Source	Identifier
Antibodies		
EMX2 (aa1-155)	This paper	N/A; Available from the authors
LHX2	S. Lomvardas	(24)
NR2F1	R&D Biosystems	PP-H8132-10
PAX6	Millipore	AB2237
PBX1	Santa Cruz	sc-888
H3K4me3	Millipore	04-745
H3K27me3	Millipore	Millipore Cat# 07-449; RRID: AB_310624
H3K27ac	Abcam	Cat# ab472
Anti-Digoxigenin-AP	Sigma-Aldrich	Cat# 11093274910
Goat anti-Rabbit IgG (H+L), Alexa Fluor 546	Thermo-Fisher	Cat# A-11035
Normal Rabbit IgG	Santa Cruz	sc-2027
Chemicals, Peptides and Rec	combinant Proteins	
DIG RNA labeling mix	Sigma-Aldrich	Cat# 11277073910
T7 RNA polymerase	Sigma-Aldrich	Cat# 10881767001
DNasel	Sigma-Aldrich	Cat# 10104159001
Sheep Serum	Sigma-Aldrich	Cat# S2263
Blocking reagent	Sigma-Aldrich	Cat# 11096176001
BM purple	Sigma-Aldrich	Cat# 11442074001
37% Formaldehyde	Ted Pella	Cat# 18508
Dynabeads Protein G	Thermo-Fisher	Cat# 10003D
Dynabeads Protein A	Thermo-Fisher	Cat# 10001D
RNase, DNase free	Sigma-Aldrich	Cat# 11119915001

Proteinase K	Sigma-Aldrich	Cat# 3115879001
PerfeCTa SYBR Green FastMix ROX	Quanta	Cat# 95073-012
MNase	Sigma-Aldrich	Cat# N3755-50UN
Thermo Scientific™ Shandon™ Aqua- Mount Slide Mounting Media	Fisher Scientific	Cat# 14-390-5
Complete EDTA-free Protease inhibitor	Sigma-Aldrich	Cat# 11873580001
Critical Commercial Assays		
ChIP DNA Clean and Concentrator	Zymo Research	D5205
Ovation Ultralow DR Multiplex System	Nugen	Cat# 0344-32
2% Agarose Gel Cassette Blue Pippin	Sage Science	Cat# BDF2010
High Sensitivity DNA Reagents	Agilent Technologies	Cat# 5067-4626
MinElute PCR Purification Kit	Qiagen	28004
Nextera DNA Library Prep Kit	Illumina	#FC-121-1030
Papain Dissociation System	Worthington	LK003153
NEBNext High Fidelity 2x PCR master mix	New England Biolabs	M0541L
Micrococcal Nuclease	New England Biolabs	M0247S
CellTrace™ Yellow Cell Proliferation Kit	ThermoFisher	C34567
CellTrace™ CFSE Cell Proliferation Kit	ThermoFisher	C34554
Experimental Models: Organi	sms/Strains	
Transgenic enhancer assay: FVB	Charles River	http://www.criver.com/
ChIP-seq: CD1	Charles River	http://www.criver.com/

Emx2-/-	JAX	MGI:2148858; (2)
Emx1::Cre; Nr2f1-/-, Nr2f2 ^{lox/lox}	Tang et al. 2012	(4, 5)
Nr2f1-/-	Zhou et al., 2001	(3)
Pax6 ^{-/-}	JAX	Stock #000391; (1)

A (Eastures of	Chiph	inding	Differe	ntial epig	enomic	marks i	n WT vs.	Mutant	DETTE
	pRE coordinates (mm9)	genomic locus	CIIFD	mung	P	ax6 muta	ant	N	r2f1 mut	ant	interaction
Pays Nr2f1/2		genenne recue	NR2F1	PAX6	27ac	27me3	ATAC	27ac	27me3	ATAC	interaction
i uno	Nr2f1 interactome										
	chr13:77535859-77537676	hs273 Enhancer	x		Same	2	Same			Same	x
	chr13:78031585-78032706	hs271 Enhancer	x	x	Loss		Same	Same		Same	x
Npas3 i	chr13:78033028-78033775		x	×	Loss		Same	Loss		Same	×
	chr13:78238631-78240287			×	Loss		Loss	Same		Same	x
$\langle \rangle$	chr13:78301285-78303743		x		Loss		Same	Same	Same	Same	x
	chr13:78318156-78320079	and the second se	x	x	Loss	Gain	Same	Loss	Loss	Same	x
	chr13:78336209-78338805	TSS		x	Loss	Same	Same	Loss	Loss	Loss	x
	chr13:78339478-78340485		x				Same		Loss	Same	x
1	chr13:78341891-78344303		x		Same		Same	Same	Loss	Same	x
Lmos	chr13:78565590-78568155			x	Loss		Same	Same		Same	x
	chr13:78583826-78587247	hs1550 Enhancer	x	x	Loss		Loss	Same		Same	x
D	chr13:78719884-78721593	hs1172 Enhancer	x	×			Same			Same	x
	Npas3 Interactome										
	chr12:54162201-54164479	mm1790 Enhancer			Loss		Same	Loss		Same	x
	chr12:54224810-54226545	A COLUMN TWO IS NOT THE OWNER.		x			Same			Same	
	chr12:54347665-54350320	TSS			Loss	l'	Same	Loss	1	Same	x
	chr12:54353494-54355559	Gene Body		x	Loss		Same	Loss		Same	x
	chr12:54391045-54394848	Gene Body	x		Loss		Same	Loss			x
	chr12:54548080-54550100	mm1789 Enhancer	x	x			Loss			Same	x
	chr12:54593760-54594932	Gene Body	x				Same			Same	x
	chr12:54723872-54727081	hs527 Enhancer	x	x	Loss	P	Loss	Same?		Same	x
	Lmo3 Interactome										
	chr6:138368197-138369679	mm1199 Enhancer		x	Loss		Loss	Loss			
	chr6:138372851-138374454	Gene Body	x	x			Same			Same	
	chr6:138375177-138376219	Gene Body		x			Loss			Same	
	chr6:138696588-138711025	hs1532 Enhancer	×	x		Loss	Loss		Same	Same	

Figure S1. Genetic circuitry controlling the patterning of the rostral latero-ventral pallium (LVP) (A) Schematic of transcriptional control of rostral LVP development.

(B) Depiction of the rostral LVP at E16.5. Piriform cortex ($Lmo3^+$ and $Npas3^+$) is pink. Endopiriform cortex and claustrum ($Nurr1^+$) are blue. Subplate is green.

(C) Table of regulatory elements (pREs) around the *Nr2f1, Npas3* and *Lmo3* loci, that may participate in rostral LVP patterning Shown are NR2F1 and PAX6 ChIP-seq peaks, differential epigenomic peaks in the *Nr2f1-^{-/-}* and *Pax6*^{-/-} and pRE/TSS interactions (see Figures 4, 6, 7).



<10 <33 <66 <100

Figure S2. Characterization of EMX2, LHX2, NR2F1, PAX6, and PBX1 combinatorial binding

(A) ISH cortical expression gradients of TFs used for ChIP at E11.5. *Lhx2* has a caudorostral (CR) gradient. *Emx2* has a CR and dorsoventral (DV) gradient. *Nr2f1* has a CR and ventrodorsal (VD) gradient. *Pax6* and *Pbx1* have a rostrocaudal (RC) and VD gradient.

(B) ChIP-qPCR on $Emx2^{+/+}$ (blue bars) and $Emx2^{-/-}$ (red bars) cortices at E15.5 shows significantly decreased enrichment of binding at genomic targets (enhancers around *Nfib*, *Dmrt3* and *Sp8*) in $Emx2^{-/-}$.

(C) Proximal (near promoter) vs. Distal binding for each TF ChIP-seq

(D) Heatmap showing pairwise Pearson Correlation for genome-wide coverage values for each TF ChIP-seq replicate.

(E) Enrichment of functional annotation terms (GO) for genomic loci showing combinatorial binding of 5 TFs by ChIP-seq.

(F) Relative motif enrichment for primary binding DNA motifs of EMX2, LHX2, NR2F1, PAX6 and PBX1 ChIP-seq across all pREs.

(G) Motif enrichment of all de novo motifs in pREs of the TF ChIPs.

(H) Counts of distance from TSS for loci showing combinatorial binding of 5TFs by ChIP-seq.

(I) Non-TF genes important in cortical development showing co-binding of 5TFs by ChIP-seq. Light green are genes with known functions during cortical development; Dark green are chromatin modifiers; Orange are TFs with expression in other brain regions.

(J) Analysis showing percentage of peaks with motif enrichment of primary binding motifs (described in Figure 4C) for each unique or combinatorial binding of TFs by ChIP-seq. Abbreviations: Hbox: homeobox.



Ventral

Figure S3. Using VISTA enhancers to model how combinatorial binding of EMX2, LHX2, NR2F1, PAX6, and PBX1 predicts cortical activity and graded expression in the developing pallial VZ.

(A) Plot showing how likely VISTA enhancer loci bound by the TFs are forebrain-active as opposed to active in other brain regions and elsewhere (heart as a surrogate). Main plot shows the frequency of occurrence, while the upper one depicts the comparison of mean number of enhancers hit by sampling, showing significant difference among different enhancer classes (p < 0.01).

(B) Examples of cortical VISTA enhancers with graded patterns of activity. The wholemounts and sections for each example are placed along the central grid according to their annotated gradient of activity in the developing pallium. hs1035 has a DV and RC gradient; hs798 has a DV and CR gradient; hs636 has a RC and VD gradient; and finally, hs1172 has a CR and VD gradient.

(C) Correlalogram showing the expansion of the modeling presented in Figure 4D showing the different combinations of TF binding and their predictions of gradients of activity (p < 0.01)



Figure S4. Epigenomic profiling of CRTFN genes (Cortical Regionalization TF Network) in the cortical VZ.

(A) Histology of Flash-Tag staining of the cortical VZ at E12.5; note that the Flash-Tag labeled VZ cells do not overlap with TBR2 immunostained SVZ progenitors.

(B) Example FACs plots showing data for Flash-Tag (CFSE) positive progenitor cells prepared from the E12.5 cortex. The histogram of FITC counts shows a bi-modal FITC negative population (VZ⁻) and a FITC positive population (VZ⁺). The dot plot depicting FSC vs. FITC shows the gating which was used to collect the FITC⁺ (VZ⁺) population. Black bar above VZ⁺ correspond to the cells collected for further analysis.

(C) Overview of epigenomic enrichment in pREs with differential combinatorial TF binding (0-5 TFs) for CRTFN TF gene loci. Number of pREs at each locus are in brackets (n=#pREs). Percentage of total pREs are indicated by a teal histogram bar. Percentage of pREs with the following epigenetic marks are indicated by the following colors: ATAC = yellow; H3K27ac = dark green; H3K27me3 = red. See Figure S4A which summarizes this data for each TF locus.

A					TF ChiP-	Seq		Ratio	VZ Ep	oigenomic I	larks
		PRES	Emx2	Lhx2	Nr2f1	Pax6	Pbx1	H3K27ac7 H3K27me3	H3K27ac	H3K27me3	ATAC
×	_					TFs with	Rostral to	Caudal Gra	dient		
Lmo1	*	45	20.0	17.8	13.3	15.6	4.4	0.1	8.9	68.9	31.1
Pou3f1		119	14.3	10.9	13.4	5.9	7.6	0.2	10.9	63.9	23.5
Zic1	0	39	23.1	20.5	15.4	20.5	2.6	0.3	12.8	46.2	38.5
Etv5		6	16.7	16.7	0.0	16.7	0.0	0.3	16.7	50.0	0.0
Tle1	0	39	42.5	42.5	27.5	35.0	15.0	0.5	12.5	27.5	32.5
Zic5	0	84	46.4	21.4	26.2	17.9	11.9	0.5	17.9	35.7	48.8
Nr2e1	0	48	34.0	16.0	44.0	20.0	2.0	0.7	26.0	36.0	44.0
Npas3		91	39.6	24.2	35.2	19.8	17.6	1.0	19.8	19.8	30.8
Pax6	*	73	35.6	23.3	26.0	28.8	9.6	1.1	26.0	24.7	39.7
Mycl1	*	25	8.0	0.0	24.0	0.0	4.0	1.1	40.0	36.0	36.0
Meis2		112	37.5	26.8	33.0	23.2	13.4	1.7	27.7	16.1	22.3
Pbx1		68	44.1	30.9	26.5	13.2	13.2	2.6	38.2	14.7	35.3
Pou3f3		70	37.1	25.7	41.4	27.1	14.3	2.9	37.1	12.9	31.4
Sox9		91	30.8	22.0	37.4	18.7	13.2	13.5	29.7	2.2	40.7
						TFs with	Caudal to	Rostral Gra	dient	1	
Sp8	+	89	22.6	14.3	14.3	10.7	7.1	0.1	7.1	69.0	28.6
Dmrt3	0	28	18.5	14.8	22.2	18.5	11.1	0.2	14.8	63.0	51.9
Nfatc4	0	19	5.3	5.3	26.3	0.0	0.0	0.3	15.8	47.4	52.6
Emx2	0	88	47.7	36.4	25.0	12.5	9.1	0.6	18.2	30.7	26.1
Nr2f1	0	72	36.1	26.4	43.1	22.2	13.9	0.6	22.2	37.5	31.9
Lef1	+	38	28.9	26.3	23.7	21.1	13.2	0.8	23.7	28.9	50.0
Tszh1		55	25.5	20.0	25.5	12.7	10.9	1.3	23.6	18.2	21.8
Fezf2	+	27	48.1	44.4	33.3	22.2	18.5	1.7	37.0	22.2	63.0
Nfix	+	55	18.2	7.3	40.0	7.3	1.8	2.0	40.0	20.0	80.0
Lhx2		107	21.5	19.6	25.2	10.3	11.2	3.2	50.5	15.9	43.9
Tcf4	+	70	34.8	20.3	26.1	20.3	8.7	3.4	39.1	11.6	18.8
Mycn		58	32.8	25.9	39.7	10.3	8.6	4.2	43.1	10.3	48.3
Dach1		60	43.3	45.0	18.3	20.0	11.7	4.5	15.0	3.3	18.3
NfiB	+	96	44.8	25.0	19.8	16.7	8.3	6.7	49.0	7.3	34.4
Bci11a	+	71	25.4	14.1	22.5	15.5	5.6	7.7	32.4	4.2	16.9
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Ascl1	*	62	29.0	11.3	24.2	21.0	1.6	0.3	12.9	37.1	19.4
Hes5	*	56	16.1	7.1	23.2	5.4	1.8	7.3	39.3	5.4	82.1
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Trim28	+	20	5.0	0.0	10.0	5.0	10.0	1.0	40.0	40.0	60.0
Plagi1	+	40	28.2	28.2	23.1	20.5	7.7	3.4	43.6	12.8	41.0
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Lmx1a		43	18.6	14.0	9.3	2.3	4.7	0.1	4.7	60.5	20.9
ld3		27	0.0	3.7	37.0	0.0	0.0	0.3	11.1	33.3	63.0



Ratio of H3K27ac/H3K27me3



* Ventral-Dorsal + Dorsal-Ventral O Medial Pallium

Figure S5. Epigenomic profiling of the cortical VZ shows a diminished H3K27ac/H3K27me3 ratio over pREs for MP TFs

(A) Table showing percentage enrichment of TF binding and epigenomic marks of pREs at each locus of the Cortical Regionalization TF Network. A H3K27ac/H3K27me3 ratio is calculated for each locus.

(B) Statistical analysis shows that the H3K27ac/H3K27me3 ratio is significantly lower for pREs in genomic loci of TFs with MP expression (red) compared to pREs for the non-MP TFs (purple) (p<0.05, unpaired two-tailed t-test).

(C) Plot of genomic features (TF binding, Epigenomic marks, H3K27ac, H3K27me3, ATAC) over VISTA enhancers that have pallial (dark green), subpallial (light green), non-telencephalic (yellow) and no activity (red) at E11.5.

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 TF ChIP Seq
 Differential epigenomic marks in WT vs. Mutant

 Pax6 mutant
 Emx2 mutant
 Nr2f1 mutant

 Ems2 Ux2 N2f1 Pax6 P9x1
 27Ac
 27mc3
 ATAC
 27Ac
 27mc3
 ATAC
 Plac-Seq Comp Genomic features chr39:5840000-6052600 chr39:592206-592667 chr39:592306-592667 chr39:5933064-5953876 chr39:5935064-5953876 chr39:5953064-5953876 chr39:5954313-15954154 chr39:59543465-59546274 chr39:5954345-59745620 chr39:5963471-59986542 chr39:60091231-6009543 chr39:60091231-6009543 chr39:60091631-69303387 1 2 3 4 5 6 7 8 9 10 11 12 Emx2 TSS Emx2 Gene Body hs1032 hs935 hs1221 * * * * * * x x Loss * * * * * * * * * * * * * * * Same Loss Same Same Same x Same Same Same * * * * * * * * × × Loss ×× Loss Loss Rab11fip2 mm449 ×× ×× Loss Loss Loss Loss Same Same Same Loss D19ertd737e TSS Ruler chr19 4D3 60100K 59500K 60200K 59700K 60300K 00K 3a2 50 60000K 60400K 60500K OOK Fam204a E330013P04Rik refGene 3a2 Emx2os Emx2™ Emx2™ ₩Pdzd8 2700089124Rid Rab11fip2 P hs935 mm448 [hs1032]] F VISTA enha Comp_Enc Comp_MO Emx2_1 hs1087 hs12361 mm449 [1221 hs15511 hs672 . 8 9 1112 10 Emx2_2 Lhx2_1 NR2F1_1 ~] NR2F1 2 NR2F1_3 Pax6_1 0_ Pax6_2 Pbx1_1 0 Pax6_WT1_27Ac 1. Pax6_WT2_27Ac 0 Pax6_WT3_27Ac 15 Pax6_Mut1_27Ac 150 14 . 0_-Pax6_Mut2_27Ac 150-Pax6_WT1_27me3 150 0 Pax6_WT2_27me3 ¹⁵⁰ Pax6_WT3_27me3 150 0 Pax6_Mut1_27me3 150 0 Pax6_Mut2_27me3160 Pax6_Mut2_27me3160 Pax6_Mut2_27me3160 Pax6_Mut2_27me3160 Pax6_Mut2_ATAC 500 Pax6_Mut2_ATAC 500 1 1 1 Emx2_Mut2_27Ac 150 - 0_3 mil. af. , he Emx2_WI1_27me3⁴⁰⁰ Emx2_WT1_27me3⁴⁰⁰ Emx2_WT2_27me3⁴⁰⁰ Emx2_Mu1_27me3⁴⁰⁰ . A . . Emx2_Mut2_27me3400 Emx2_Mut2_27me3⁰⁰ Emx2_WT1_ATAC ²⁰⁰ Emx2_WT2_ATAC ²⁰⁰ Emx2_Mut1_ATAC ²⁰⁰ 1 h Nr2f1_Mut1_27Ac 150 Nr2f1_Mut2_27Ac 150 -Nr2f1_Mut2_27Ac 100 0_ Nr2f1_WT1_27me3⁴⁰⁰ 4. 4 Nr2f1_WT2_27me3⁴⁰⁰ 0_ Nr2f1_Mut1_27me3²⁰⁰ .1 Nr2f1_Mut2_27me3⁴⁰⁰ 1 Nr2f1_Mut2_27me3⁴⁰⁰ 0_ Nr2f1_WT1_ATAC 150 0 Nr2f1_WT2_ATAC 150 0 Nr2f1_Mut1_ATAC 150 Nr2f1_Mut2_ATAC 150



		Motifs	TF ChIP Seq	Pax6 muta	Differen	ntial epige	nomic marks i Emx2 mutant	in WT vs.	Mutant	r2f1 mutar	nt	Plac	Compu	Genomic features
Etv5 d	chr16:22275000-22830000	Emx2 Nr2/1 Pax6 Pax6 P Pbx1	Emx2 Lhx2 Nr2f1 Pax6 I	Pbx1 27Ac 27me3	ATAC	27Ac	27me3	ATAC	27Ac	27me3	ATAC	1	tation	
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	R+c V	hs434 hs435
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	Differential epigenomic mark	ks in WT vs. Mutant
Motifs TF ChIP Seq Pax6 mutant Emer2 chr14:1300000-13320000 Fills fills 27Ac 27me3	Emx2 muta ATAC 27Ac 27me3	nt Nr2f1 mutant Plac Compu ATAC 27Ac 27me3 ATAC Genomic features
Image: https://www.image.org/action	Same Same Same Loss Gain Loss Loss Gain Same Loss Gain Loss Gain Gain Loss Loss	Since Same Same Same Nxl34 Same Same Nxl34 Nxl34 Same Same Same Nxl34 Same Same Same Nxl34
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	Motifs	TF ChIP Seq	Pa	Diff ix6 mutant	erential epigenom Emxi	ic marks in WT vs. 2 mutant	Mutant Nr2f1	mutant	Plac	Compu	Genomic features
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	Hollfs TF ChiP Seq	* D/V Differential epigeno Pax6 mutant Em	nic marks in WT vs. Mutant x2 mutant Nr2f1 mutant	hs1050
Lef1 chr3:130280000-131120000 1 chr3:130664999-130657081 2 chr3:130774287-130775523 3 chr3:13076473-13079557 4 chr3:130809043-130812870 5 chr3:131035570-131040367	Circle Particle Particle Envice Institution Particle	27Ac 27me3 ATAC 27Ac Loss Loss Same Same Same Same Same	27me3 ATAC 27Ac 27me3 Same Same Loss Same Same Same Gain Same Same Same	ATAC Same x hs1545 Same Same Lef1 Promoter Same Cyp2u1
Ruler chr3 130300K refGene Col25a Col25a EtropP EtropP	130400K 130500K 1 Ostof # 1 Rp134 Rp134 Rp134 Rp134 Rp134	нссэ 130600К 130700К	130800K 130800K Lef12 L	131000K → Sgms2→1+→ dadh+→→ Cyp2u→→→
VISTA Enhancers	hs1050	hs1545	2 3 4	5
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Motifs TF ChIP Seq Differential epigent Emi2 repti Past Past Past P Emi2 (mod Virtual) Emi2 (mod Virtu	omic marks in WT vs. Mutant Piac- m.z mutant Nr211 mutant Seq Lation Genomic features 27ms3 ATAC 27Ac 27me3 ATAC Genomic features Minick TSS
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4 chr1:	3:78238631-78240287	×				×	x		×		Loss		Loss	Loss		Loss	Same		Same		×	
5 chr1	3:78301285-78303743	x				x		×			Loss		Same	Same	Same	Same	Same	Same	Same		×	
6 chr1:	3:78318156-78320079	×				×		×	×		Loss	Gain	Same	Loss	Gain	Same	Loss	Loss	Same		×	
7 chr1:	3:78320294-78321148	×				×					Same	Gain	Same	Loss	Gain	Same	Same	Loss	Same		×	
8 chr1:	3:78333521-78334986	-									Loss	Same	Same	Loss	Gain	Same	Loss	Loss	Same		×	Nr2f1 Gene Body
9 chr1:	3:78336209-78338805	×				×			×		Loss	Same	Same	Loss	Gain	Same	Loss	Loss	Loss		×	Nr2f1 TSS
10 chr1:	3:78339478-78340485	×				×	x	×					Same		Gain	Loss		Loss	Same		- C.	
11 chr1:	3:78341891-78344303							×			Same		Same	Loss	Gain	Loss	Same	Loss	Same		×	
12 chr1:	3:78348092-78349649	×				×	x				Loss	Same	Loss	Loss	Gain	Same		Loss	Same		×	
13 chr1:	3:78565590-78568155	×				×	×		×		Loss		Same	Loss	Gain	Same	Same		Same	×	×	
14 chr1:	3:78583826-78587247					×		×	×		Loss		Loss	Loss	Gain	Same	Same		Same	×		hs1550
15 chr1:	3:78719884-78721593	×	×	×	×	×	×	×	×	x			Same	Loss	Gain	Same			Same	×	I I	hs1172
16 chr1:	3:78781101-78783086	x				x	x			x	Loss		Loss	Loss		Loss	Same		Same	x		

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		Emx2 HB	Nr2f1	Pax6 Hb	Pax6	P Pbx1	Emx2	Lhx2	Nr2f	1 Paxe	5 Pbx1	27Ac	27me3	ATAC	27Ac	27me3	ATAC	27Ac	27me3	ATAC	Seq	tation	
Pbx1	chr1:169860000-171370500			2000																		1	
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2	chr1:170175012-170176937						×		×		×	Loss		Same	Loss		Same	Loss		Same	×		Pbx1 Gene Body
3	chr1:170229514-170231269						L					Loss			Loss			Loss			×		hs1144
4	chr1:170257128-170258791						×	×				Same		Same	Same		Loss	Same		Same	×	I	hs203
5	chr1:170321692-170324410						×	x	×	x		Same		Loss	Loss		Loss	Loss			x	x	Pbx1 Gene Body
6	chr1:170340225-170341639						×							Loss			Same			Same		x	Pbx1 Gene Body
7	chr1:170360324-170363111						63		x		x	Loss		Same	Same		Same	Same		Same		x	Pbx1 TSS
8	chr1:170837816-170839853						×	×	×		×	Loss		Same	Loss		Loss	Same		Same	×		hs202

Ruler	αH2 β															
chr1	169900K	170000K	170100K	170200K	170300K	170400K	170500K	170600K	170700K	170800K	170900K	171000K	171100K	171200K	171300K	
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			Motifs		TF	F ChIP Seq		()	Pax6 muta	Different	ential epigenon Ema	nic marks in WT vs 2 mutant	Mutant	Nr2f1 muta	int	Plac-	Compu	Genomic features
Plagi1 chr10:12700000-13	3310000	Emix2 Nr2f1	Hb Pax6	P Pbx1 En	nx2 Lhx	2 Nr2f1 Pax	6 Pbx1	27Ac	27me3	ATAC	27Ac 2	27me3 ATAC	27Ac	27me3	ATAC	944	Cattorn	
1 chr10:12809880-12 2 chr10:12826983-12	2812996	×			x x	××	x	Loss		Same Same	Loss	Same Same	Same Same		Same Same		×	PlagI1 TSS PlagI1 Gene body
4 chr10:13043102-13 5 chr10:13135354-13	8045156 8136688	×××			x x	×		Loss		Same	Same	Same	Loss		Same	××	<u>^</u>	Phactr2 TSS
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refGene 1			Plag					Phactr2			***	•	((0			Fuc	a2911 1-	
а			Plag	(2+++) (2+++)				Phactr2					····	*****	•••••	H	Per	Adat2
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Ruler chr4 123600K 12370 refGene Rrago	0K 123800K 123900K 124000K	124100K 124200K	124300K 124400K 124500K Pou3f1# Mit/ >+ 0115
>•Mycbp		4933407E24Rik	Sf3a3 Yrdo Utp11 110065P20Rik Fil3 1110065P20Rik Gm12915 Maneat
VISTA Enhancers hs850 hs1139 hs1031 Comp Encode	1 bet560	2 3-7 hs1008 hs790 hs270 hs2088 hs1179 hs270 hs2088 hs1179	8 Inpp5b=+
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Pax6_Mu2_ATAC 00 Pax6_Mu3_ATAC 00 Emc_WT1_ZTAC 10 Emc_WT2_ZTAC			
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			Motifs TF Chi			Chip	Sea			Differential epigenomic marks in WT vs		s in WT vs.	Mutant			10000	Contractor (
				Toura					Citar	964			Pax6 mutan	t		Emx2 mutar	it		Nr2f1 mutan	t	Plac-	Compu	Genomic features
		Emx2 HB	Nr2f1	Pax6 Hb	Pax6 P	Pbx1	Emx2	Lhx2	Nr2f1	Pax6	Pbx1	27Ac	27me3	ATAC	27Ac	27me3	ATAC	27Ac	27me3	ATAC	Seq tation		
9 chr11:1117000	00-113500000			-														4					
chr11:1120583	52-112060480	x		×	×	×	x	х	х	×	x	Loss		Same	Same		Same	Loss		Same			
chr11:1122732	36-112274832	×					x	x	x			Loss		Same	Loss		Loss	Loss		Same		1 1	mm634
chr11:1126699	70-112674132						x	×	×			Loss		Same	Loss		Same	Loss				1 1	
chr11:1128380	32-112839034	x					x	x	×			Loss		Same	Same		Same	Loss		Same	×	x	
chr11:1128435	12-112845082	×		×			x	x	×	x		Same		Loss	Same		Same	Same		Same	×		
chr11:1128779	02-112879155						×	×	×			Same		Same	Loss		Same	Same		Same	×	×	mm636
chr11:1133000-	47-113301927			×			x		×			Same		Same	Loss		Same	Same		Same	1 C C	x	

refGene		110001		BC006965	26100350 31= 31=	017Rik 4732490	B19Rik Slc39a114 < < < < <	Sstr2 Sstr2
				1700012H	19Rik		Slc39a11	····
VISTA Enhancers	mm633	hs1489	mm634	mm1285 mm635	i mm	536 mm637	mm926 mm1	526
Comp_MO Emy2_1 10	٥٦		1 2	1	3 4	-5 6	11 1	7
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Pax6_WT2_27Ac 15	°]				hat water and a			
Pax6_WT3_27Ac 15	0]		line a man and a survey	to attack to be a set to a started	A July and a second	Level and an and an	مسرا سيعاد من حمد الم	and and an and the second
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Pax6_WT2_27me3 15	°]							
Pax6_WT3_27me3 15	°]							1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
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Pax6_WT1_ATAC 50	°]		1		1.1.1			
Pax6_Mut2_ATAC 50	0-			f f				
Pax6_Mut3_ATAC 50	0-		1	· · · · · · · · · · · · · · · · · · ·				
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Emx2_WT2_27Ac 25	۰ <u>۱</u>	an and all the shifts of the	Ann	he water all the second se	A characteristic and a characteristic and	Los Andread Strends	hat the material	and a static design of the second
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Nr211_VV11_27me3	o		****		•	<u></u>		
N/211_VV12_2/me3**	o				•			••••••••••••••••••••••••••••••••••••••
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		Motifs		Motifs					ChTO					Differe	intial epige	nomic mark	s in WT vs.	Mutant					24 250 55 FC	
				Piour	•				CHIP	ped		1	Pax6 mutar	t		Emx2 mutar	t	1	Nr2f1 mutar	t	Plac-	Compu	Genomic features	
		Emx2 HB	Nr2f1	Pax6 HD	Pax6 P	P Pbel	Ema2	Un/2	Nr2f1	Paxt	Pox1	27Ac	27me3	ATAC	27Ac	27me3	ATAC	27Ac	27me3	ATAC	bed	cation		
Sp8	chr12:119000000-120191051	-				-																		
1	chr12:119043999-119045761	×		х	×		×	×		×	×		Same	Loss		Same	Same		Same	Same	×		hs807	
2	chr12:119047456-119048848	×					x	x	×		x			Same			Loss			Same	x			
3	chr12:119266560-119267560	×						×					Same	Same		Loss			Same		×			
4	chr12:119639681-119646276												Loss			Loss			Same		×			
5	chr12:119767849-119769440	×		х	х		x		x			Loss		Loss	Loss		Same	Same		Same	x			
6	chr12:119888958-119890368			×			×		×	×	×			Loss			Gain			Same	×	×	hs1226	
7	chr12:119897620-119901100	×		×			x	×	×	x	x		Same	Loss		Same	Same		Same	Same	x			
8	chr12:119957232-119961000	×					×	×	×				Same	Same		Loss	Same		Same	Same				
9	chr12:120019929-120024242	×					×	×	×				Same	Same		Loss			Same					
10	chr12:120078064-120080117	×					x	×	×	×		Loss	Gain	Loss	Same	Same	Same	Same	Same	Same		×	hs844	
11	chr12:120084740-120088847						1.000					Loss	Gain	Same	Gain	Same	Same	Loss	Same	Same	-	x	Sp8 Gene body	

chr12)00K	119100K	119200K	119300K 1194	00K 119	500K 1	19600K	119700K	119800K 1	19900K	120000K	1201	JOK 12
refGene	Rapge	Cdca7P			Sp4 Sp4			D230030E09Rik				Abcb5	
		Chairment								hs114	18	mm844	
VISTA Enhancers Comp_Encode		hs807	hs294					Inst	23 hs701	hs1226	1 hs1007 hs	1019 hs2	.39
Comp_MO Emx2_1	00 7	1-2		3				4 1	5	6-7	8 9	10-11	1
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Pax6_WT3_27Ac	0_10	. <mark>Saukawa</mark> n				an mand we							
Pax6_Mut1_27Ac	0 50 -								L 				
Paxe_Mut2_2/Ac	0 50 T					madente							
Paxe_wr1_2/me3	0	-									ater a state a	And Mary	
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Pax6_WT1_ATAC 5	0_ 	b 1	All A Long Chillin .	lite all the state of the state	a shirt a state of	add, Bak, Stradie		heliterer. Bet. adastider	and and the second s	1 L	And a state of the A	dat	and the second second
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Pax6_Mut3_ATAC 5	00-					-							
Emx2_WT1_27Ac 1	507	And Andrews	· · · · · · · · · · · ·						h		he said a	an an addition	
Emx2_WT2_27Ac 2	507		de la calence e calence e	adata teathat at a	mark	and the state	of banks an	addeb to an An An An	and and a state of the state of			-	And a star star
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Emx2_WT1_27me34	00	4			1					ales a	ab	1. 186	
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Figure S6. CRTFN transcriptional network in Emx2^{-/-}, Nr2f1^{-/-} and Pax6^{-/-}

For each of the 38 TFs in the CRTFN, we show:

- ISH of TF gene in wild-type and mutant mice at E11.5.

- pallial VISTA enhancer wholemount (and sections if available) showing activity in the cortex at E11.5.

- Table with a comprehensive list of pREs that shows differential regulation in $Pax6^{-/-}$, $Emx2^{-/-}$ and $Nr2f1^{-/-}$ around the interactome of the relevant TF. Each pRE in this table is highlighted by a yellow column in the genome tracks below. The highlighted columns have orange numbers matched to the row number in this table.

- TF's genomic loci showing:

- 1. RefSeq genes around the TF gene (highlighted in purple).
- 2. Genomic position of VISTA enhancers with cortical activity (Green), activity in other regions (Blue) or no activity (Red) at E11.5.
- Computationally derived enhancer-gene associations based on correlation between the putative enhancer activity (using Encode data: Comp_Encode or data generate here: Comp_MO) and the expression level of the genes residing in the same topologicallyassociating domain.
- 4. TF ChIP binding for EMX2, LHX2, NR2F1, PAX6 and PBX1; replicates are shown.
- 5. Epigenomic marks in VZ of Wild-Type (Shaded in white) and *Pax6^{-/-}*, *Emx2^{-/-}* and *Nr2f1^{-/-}* littermates (shaded in grey). For each experiment, H3K27ac tracks are in blue, H3K27me3 tracks are in purple, and ATAC-seq tracks are in red. Replicates are shown.
- 6. pRE-promoter interactions derived from PLAC-seq are shown by arcs (magenta) using two statistical stringencies (5k and 10k).

pREs with differential epigenomic marks in any one mutant are highlighted in yellow columns. These columns are labelled by orange numbers that correspond to the rows in the table above.

#pREs for CRTFN

<u>Figure S7.</u> Bar plot showing proportion of pREs for CRTFN genomic loci that are sensitive (light green) or insensitive (dark green) to the effects of $Pax6^{-/-}$, $Emx2^{-/-}$ and $Nr2f1^{-/-}$.

DATASETS

DATASET S1: Annotation of TF expression in pallium at E11.5. Expression levels were assessed on a scale of 0-5 for density (D) and intensity (I) of ISH staining in subregions of the pallium: LVP, RDP, CDP, MP. When possible, VZ/SVZ and Mantle zone expression were assessed (blank means levels of staining in these regions could not be assessed).

DATASET S2: Genomic coordinates of CRTFN pRES annotated for TF ChIP-seq peaks (EMX2, LHX2, NR2F1, PAX6 and PBX1), histone ChIP-seq peaks (H3K27ac, H3K27me3) and ATAC-seq peaks. Each row is a pRE. Column A is the TF gene and column B-D is the interactome of a given TF gene. Column H is the size of the pRE. Numbers in column I are the number of TFs co-bound to a given pRE. Numbers in columns (J-Q) indicates how many replicates have a peak. Number of replicates for each ChIP-seq/ATAC-seq is indicated in parenthesis in the title of column. Column R annotates the presence of a VISTA enhancer.

DATASET S3: Classification of CRTFN VISTA enhancers as Pallial, Subpallial, Non-telencephalic and Inactive at E11.5. Table shows VISTA enhancer name, genomic coordinates, region of activity and VISTA annotation of other regions of activity, TF and histone ChIP-seq peaks. Table includes: enhancer name, genomic coordinates, size of enhancer, relevant region of activity of enhancer (P for Pallial, SP for Subpallial, N for Non-telencephalic and I for Inactive), other regions of activity of enhancer, TF ChIP-seq, WT histone marks (H3K27ac and H3K27me3) and ATAC-seq peaks. In rows, x indicates presence of that particular feature.

DATASET S4: Classification of gradients of activity in CRTFN VISTA enhancers. Table shows VISTA enhancer name, genomic coordinates, flanking genes, cortical gradient of activity (RC = rostrocaudal, CR = caudorostral, DV = dorsoventral, VD = ventrodorsal) and a detailed analysis of their subregional cortical expression of activity when sections were available (columns J-R). Number 1 in column indicates presence of that particular feature.

DATASET S5: PLAC-seq and computational pREs-promoter interactions in the interactome of CRTFN genes. Tab 1 maps the interactions derived from PLAC-seq in CRTFN interactomes using a 5k stringency. Computationally derived enhancer-gene associations are also indicated. This computational analysis is based on correlation between the putative enhancer activity (using Encode data: Comp_Encode or data generated here: Comp_MO) and the expression level of the genes residing in the same topologically-associating domain. Tab 2 is the same as Tab 1 with a stringency for PLAC-seq of 10k. Footnotes and abbreviations for Tab 1-2 is in Tab 3.

DATASET S6: Coordinates and activity annotations of newly tested VISTA enhancers. Each row is a newly tested VISTA enhancer and includes information about its coordinates, its activity overall, its cortical activity (column F), annotations of other regions of activity, annotations for presence of TF ChIP-seq, histone and ATAC ChIP-seq peaks, and pRE-promoter interactions. x and xx indicate presence of peaks in 1 or 2 replicates respectively.

DATASET S7: Coordinates and annotations (Gain, Loss, No Change) of pREs that show changes in histone marks and/or chromatin accessibility in *Pax6^{-/-}, Emx2^{-/-}* and *Nr2f1^{-/-}*. This table shows for each interactome: coordinates of sensitive pREs (column B); primary DNA binding motifs (column C-G); TF ChIP-Seq (column H-L); Gain, Loss and No Change in Histone marks and ATAC Seq in Pax6, Emx2 and Nr2f1 mutants (Columns M-U); Plac-Seq and computation pRE-promoter binding (Column V-W); Genomic features of a given pRE.

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