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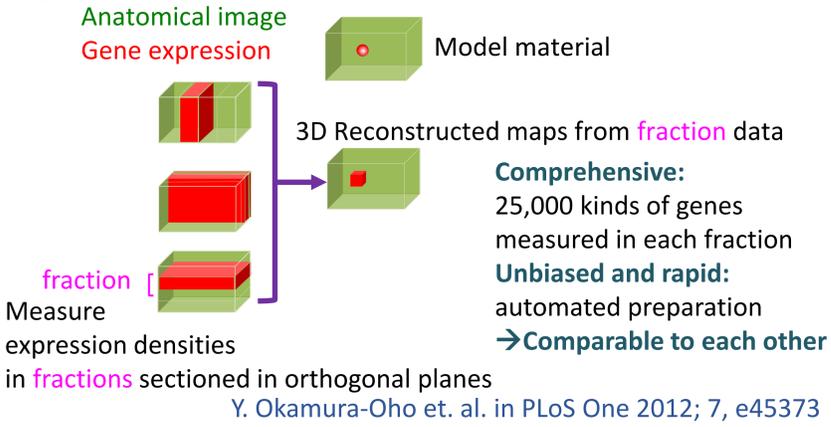
ABSTRACT: Detection of gene expression-anatomy association is crucial for understanding functions, in particular, of novel coding and non-coding genes. We have invented a framework for comprehensive gene expression density mapping on the whole three dimensional (3D) anatomical context, Transcriptome Tomography (PLoS One 2012; 7, e45373): here, the methodology is shown in Movie 1. Measured expression densities are usable directly for gene-by-gene correlation analysis of co-expression, and then we have developed a novel bioinformatics framework for comprehensively assessing co-expression patterns that are latent within expression maps. Co-expression search using almost all genes expressed in the adult mouse brain can be done on our website: ViBrism DB (<http://vibrism.neuroinf.jp/>) In this presentation we would focus on previously uncharacterized mouse-specific genes that were co-expressed with genes encoding transcription factors and related molecules. The combinatorial expression of these genes associated with a discrete cell lineage of developmental stages seems to occur in the adult brain and the previously uncharacterized non-coding genes were located in a co-expression network position linking the combinations. This linkage suggests characteristics of these genes that coordinate multiple gene groups and create mouse-specific designs of neurogenesis.

INTRODUCTION:

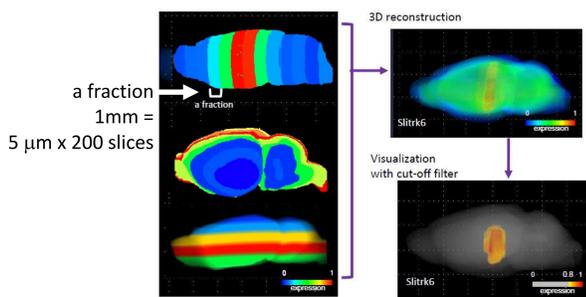
A. Transcriptome Tomography

Movie 1: Mapping Genes onto Brain Structures (rikenchannel) <https://www.youtube.com/watch?v=Td4rGRQIZuY>

1: a schema



2: 3D-reconstruction : an example gene map



1. 3 materials sectioned in each of orthogonal directions and transformed into a single coordinate (fraction template).
2. Expression densities measured with microarray are assigned to the voxel in the templates.
3. 3 expression densities in a voxel are averaged and the averaged value is visualized with pseudo-color codes.

B. ViBrism Database

<http://vibrism.neuroinf.jp/>

SET Search

1. Type a gene symbol and press "search"
2. Co-expressed genes show up
3. Press "gene ID" of interest
4. Press "open" to get 3D views

Target Gene Symbol	Target Gene ID	Target Probe ID	SET Gene Symbol	SET Gene ID	SET Probe ID	Pearson Correlation
Arx	NK_007492	A_52_P176405	Arx	AK051353	A_51_P425815	0.9658184
Arx	NK_007492	A_52_P176405	Kat5	NM_201531	A_52_P203316	0.98023565
Arx	NK_007492	A_52_P176405	Dlx1	NM_0210023	A_52_P464481	0.9791128
Arx	NK_007492	A_52_P176405	Kat4	NM_008422	A_51_P166740	0.97802060
Arx	NK_007492	A_52_P176405	Dmrt2	NM_122266	A_51_P110081	0.9784286
Arx	NK_007492	A_52_P176405	Dlx5	NM_081214	A_52_P112463	0.97632975
Arx	NK_007492	A_52_P176405	Kat4	NM_008422	A_52_P42426	0.97108100
Arx	NK_007492	A_52_P176405	Arx	AK051352	A_52_P380471	0.96967447
Arx	NK_007492	A_52_P176405	Dlx2	NM_011051	A_51_P480262	0.96911681
Arx	NK_007492	A_52_P176405	Pknox1	NM_122458	A_51_P311904	0.96763483
Arx	NK_007492	A_52_P176405	Kat5	NM_008119	A_51_P333914	0.96586760
Arx	NK_007492	A_52_P176405	Rarb1	BE85330	A_52_P444946	0.96392325
Arx	NK_007492	A_52_P176405	Gata2	NM_010266	A_52_P118006	0.95922375
Arx	NK_007492	A_52_P176405	Gata2	AK013350	A_51_P228869	0.95486172
Arx	NK_007492	A_52_P176405	Sox3b	BC038636	A_51_P184331	0.95354557
Arx	NK_007492	A_52_P176405	Kat5	NM_010861	A_52_P510330	0.95288947
Arx	NK_007492	A_52_P176405	Arx	AK051351	A_52_P511537	0.95182315

3D views of gene expression of interest

ANALYSIS:

Measured expression densities are usable directly for gene-by-gene correlation analysis of co-expression

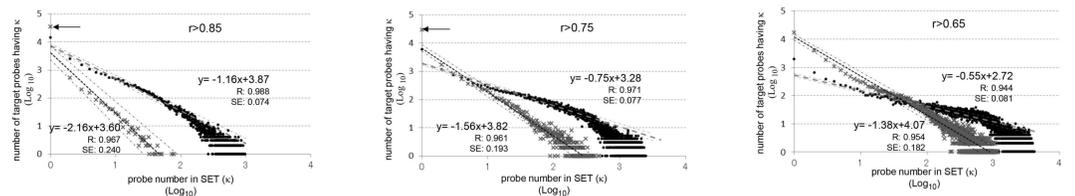
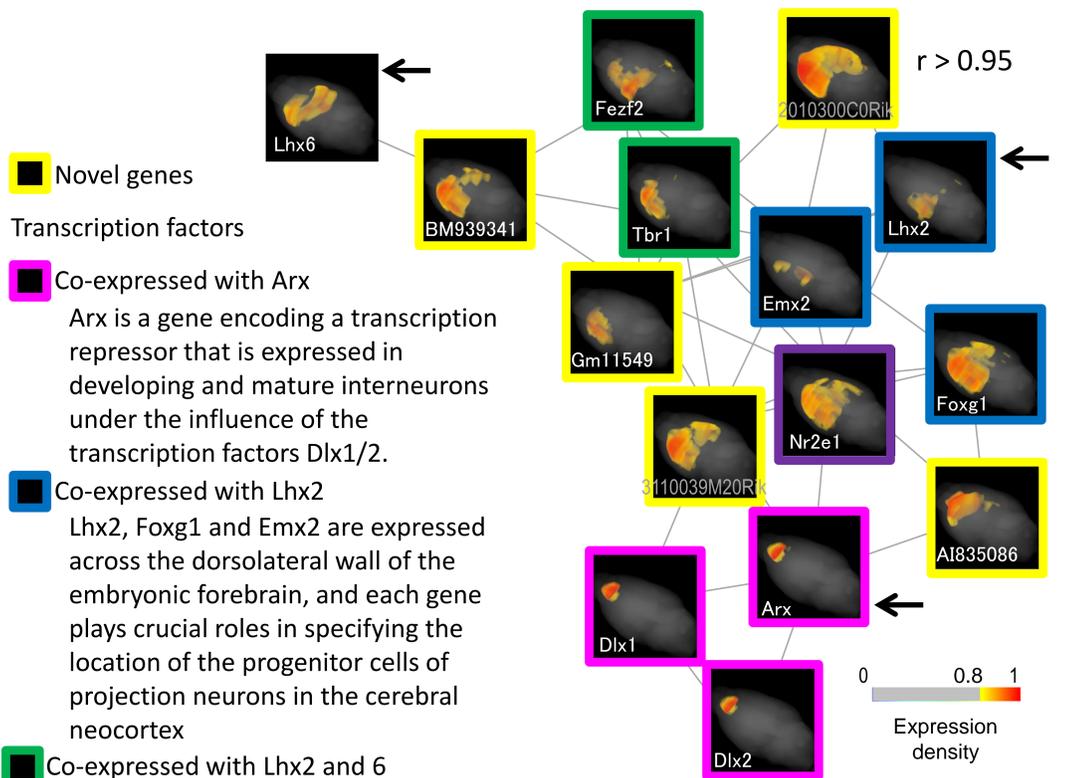


Figure 1. Distribution of the number of probes in SET (k) calculated in measured (Closed circles) and computationally randomized (gray cross marks) datasets. Distributions of k in all datasets follow a power law feature. However, with $r > 0.85$, k distributions in the two datasets are significantly distinguished throughout the range of $\text{Log}_{10} k > 0$ with a larger number of probes exhibiting k in the experimental dataset. The probes accompanied with $\text{Log}_{10} k > 2$ (co-expression hubs) are only present in the experimental dataset.



Lhx6 is a determinant of GABAergic interneurons in the CPU and parts of the cerebral cortex and a determinant of GABAergic projection pathway in subcortical regions of the ventral forebrain. Fezf2 is a gene encoding a zinc finger transcription factor, which can be used to experimentally generate glutamatergic projection neurons directly from GABAergic precursors in the CPU. Tbr1 is a T-box transcription factor, which restrains Fezf2 activity to the lower-layer neocortex, where glutamatergic projection neurons normally originate.

Nr2e1 controls the division of progenitor cells to generate subsets of neurons in the upper layer neocortex of the cerebrum: Lhx2 and Nr2e1 are known to cooperate in demarcating the eye field

Figure 2. Novel genes linking networks of co-expression hub genes. Genes for transcription factors, Arx, Lhx2 and Lhx6, are expression hub genes ($k > 100$ at $r > 0.85$, indicated with arrows) and novel genes, which are uniquely present in the mouse genome, are located in the linking position of the networks of the hub genes. The networks are composed of genes for functionally related transcription factors as mentioned above.

Conclusion: Network analysis suggests characteristics of the novel genes that link multiple gene groups and coordinate them to create mouse-specific designs of neurogenesis.

Y. Okamura-Oho et al; Provisionally included in Scientific Reports