Overview of the Allen Human Brain Atlas
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Allen Brain Atlas: www.brain-map.org
Allen Human Brain Atlas

“All Genes – All Structures”
Classical histology and neuroanatomy

Genome-wide gene expression survey in whole brain

Referenced into 3D MR images

Cellular Resolution Data
Selected structures

Selected Gene Sets by Study
- Autism Study: 25 genes, autism vs. control, DLPFC
- Cortex Study: 1,000 genes, visual and temporal cortex
- Schizophrenia Study: 60 genes, SCZ vs. controls; DLPFC
- Subcortex Study: 65 genes, subcortical areas
- Neurotransmitter Survey: 176 genes, multiple cortical and 88 genes in subcortical areas

High resolution gene expression with histology
Data Generation and Analysis Pipeline

**TISSUE PROCESSING**
- Cut into slabs
- Section histology
- Block into 2x3 and section
- Anatomic sampling
- RNA processing

**DATA COLLECTION**
- Scanning DTI MRI
- Block face images
- Histology Nissl SMI-32
- Annotation
- ISH
- Microarray

**DATA INTEGRATION, STORAGE AND RETRIEVAL**
- Ontology
- LIMS

**INFORMATICS AND DATA ANALYSIS**
- Image preprocessing
- Microarray and ISH Data Processing
- Data normalization
- 3D Mapping and reconstruction

**ALLEN HUMAN BRAIN ATLAS**
Data Access • Visualization • Mining

**SEARCH FUNCTIONALITY**
- Gene
- Structure
- Neuroblast - correlation search

- Histology • Nissl, SMI-32, ISH, LCM
- Heat Maps, MRI, DTI,
- Raw Data Download

3D Brain Explorer
Whole Brain Microarray Survey

6 donors
- M, 24 yrs
- M, 39 yrs
- M, 57 yrs
- M, 31 yrs
- F, 49 yrs
- M, 55 yrs

Structural Ontology

58,692 probes

3702 samples
Microarray Data Search Service

Allows user to instantly search over the ~60,000 probes to find genes with specific expression patterns

**Differential Search**

Find genes which have higher expression in one set of structures (target) compared to another set of structures (contrast)

**Correlative Search**

Find genes that have a similar expression profile to a seed gene when compared over a user-specified anatomical domain
Differential Search
Correlative Search

Enter Gene Name, Gene Symbol, NCBI Accession Number or Entrez Gene ID:

Gene Search
Differential Search
Gene Classification

Show exact matches only

Structure:
- Grey Matter (GM)
- Telencephalon (Tel)
- Cerebral Cortex (Cx)
- Frontal Lobe (FL)
- middle frontal gyrus (MFG)
- middle frontal gyrus, Right (MFG)
- middle frontal gyrus, Right, superior bank of g

Gene Info:
Symbol: MET
Name: met proto-oncogene (hepatocyte growth factor receptor)
Probe: A_23_P16884
Expression - z-score: -0.430645, log2 Intensity: 3.76569
Related Data:
- Donor: H0351.2001, 24 yrs. M, Black or African American

Donor: H0351.1012
anterior orbital gyrus, Left (AOg)

Download this data

ALLEN INSTITUTE for BRAIN SCIENCE
Fueling Discovery
Tissue Acquisition and Processing

- Postmortem brains 18-68 years of age
- No known neuropsychiatric or neuropathological history
- MR Scan
  - In skull at UMD, out of skull at UCI
  - Approximately 1mm isotropic T1 and T2-weighted images
- Tissue frozen, slabbed at 0.5-1 cm, and shipped to Allen Institute
MR Registration

MNI152

Original T1

Registered

rigid

nonrigid
Tissue Sampling

- Slabs partitioned to fit on 2”x3” slides
- Tissue blocks sectioned at 25mm thickness, stained, and annotated
- Dissected samples analyzed on Agilent 8x60k microarrays

Macrodissection

LCM microdissection
Spatial Mapping Goal: Link Sample Sites to MR
Tissue Block to MR Registration

Landmarks placed on scans of Nissl-stained sections from the 2x3 blocks

Corresponding landmarks placed on the T1 MR image in MNI space
All Tissue Blocks Mapped to MR

Nissl slab image  x mapping  y mapping  MR target slice
3D Views

- FreeSurfer used for cortical parcellation, registration, surface inflation
- Sample centroids projected from MR voxels to surface vertices
- Inflated surface views available on the web and in the Brain Explorer application
Tutorial: Video Technical Tour

Overview of the Allen Human Brain Atlas

An orientation to the data and basic features.

Tutorial: Allen Human Brain Atlas
Allen Brain Atlas API
Characterization of transcriptional architecture


Initial dataset queries:

- Are expected patterns of expression observed? (benchmarking)
- Variance between individual brains?
- Variance between regions within a brain?
- What biological patterns are revealed by gene expression?
Structural Distribution of Dopaminergic Gene Expression Shows Expected Patterns

Dopamine Signaling Pathway Genes
Conservation of Gene Expression Across Two Brains

- 84% of genes expressed somewhere in the brain.
- Raw expression values are highly conserved between the first two brains characterized; high conservation with 3\textsuperscript{rd} brain
- Differential expression values between structures within a brain are also conserved.
Number of Differentially Expressed Genes Between Regions

Tabulation of the number of differentially expressed genes between structures (> 2.8-fold ratio)

- Among the most highly distinct profiles are striatum, globus pallidus and other specific subcortical regions.

- Neocortex and cerebellum have relatively low numbers of DEGs (relative homogeneity) except for postcentral gyrus, temporal pole and primary visual cortex.
Robust regional and subregional divisions

Top 5,000 varying genes

Hierarchical 2D clustering of samples (structures) and genes

Discrete subdivisions within each region: hippocampus, mesencephalon, pons and myelencephalon

Enrichment for GO gene classes
Cortical Transcriptome Recapitulates Spatial Topography

Brain 1 MRI-based neocortical spatial topography

Brain 1 Principal Component-derived neocortical genetic topography
Regional and cell types modules revealed by weighted gene co-expression network analysis
Characterization of transcriptional architecture

Initial dataset queries:

• Are expected patterns of expression observed?
  – Distribution of dopaminergic genes fits expected profile

• Variance between individual brains?
  – Highly conserved levels and differential expression patterns, perhaps suggesting a ‘brain blueprint’; but low n

• Variance between regions within brains?
  – Subcortical regions are highly distinct from each other and from cortex
  – Cortical and cerebellar regions are relatively homogenous

• What biological patterns are revealed by gene expression?
  – Cortical transcriptional relationships recapitulate spatial topography
  – Brain-wide variation reflects distributions of major cell classes (neurons, oligodendrocytes, astrocytes, microglia)
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Allen Institute for Brain Science

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