PsychENCODE:

Using population-scale functional genomics to understand neuro-psychiatric disease

Mark Gerstein, Yale

Slides freely downloadable from Lectures.GersteinLab.org & “tweetable” (via @markgerstein). See last slide for more info.
Sample Sources: >2,500 brains

Cross-disorder: ASD, SCZ, BP, Neurodevelopmental, Neurotypical

Dorsolateral Prefrontal Cortex

Anterior Cingulate Cortex

Cerebellum

Striatum

Orbitofrontal Cortex

Temporlal Cortex

Amygdala

Anterior Cingulate Cortex

Benign Tissue

Neu -/Neu+ Sorted Cells

Single Cell

Limited Single Cell

Genome:
WGS, genotype

Epigenome:
ChIP-seq, ATAC-seq, HiC, ERRBS, Array Methylation, NOMESeq

Transcriptome:
RNA-seq, IncRNAseq,

Proteome:
MWP, LC-MS/MS

The PsychENCODE Consortium
A core issue addressed by PsychENCODE: Using functional genomics to reveal molecular mechanisms between genotype and phenotype in brain disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Heritability*</th>
<th>Molecular Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>81%</td>
<td>(C4A)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>70%</td>
<td>-</td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>58 - 79%</td>
<td>Apolipoprotein E (APOE), Tau</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30%</td>
<td>Renin–angiotensin–aldosterone</td>
</tr>
<tr>
<td>Heart disease</td>
<td>34-53%</td>
<td>Atherosclerosis, VCAM-1</td>
</tr>
<tr>
<td>Stroke</td>
<td>32%</td>
<td>Reactive oxygen species (ROS), Ischemia</td>
</tr>
<tr>
<td>Type-2 diabetes</td>
<td>26%</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>25-56%</td>
<td>BRCA, PTEN</td>
</tr>
</tbody>
</table>

Many psychiatric conditions are highly heritable
Schizophrenia: up to 80%
But we don’t understand basic molecular mechanisms underpinning this association
(in contrast to many other diseases such as cancer & heart disease)
Thus, interested in developing predictive models of psychiatric traits which:
Use observations at intermediate (molecular levels) levels to inform latent structure
Use the predictive features of these “molecular endo phenotypes” to begin to suggest actors involved in mechanism
2018 PsychENCODE “Rollout”

DEAN’S WORKSHOP
PsychENCODE: Functional Genomics of Human Brain Development and Neuropsychiatric Disorders

Friday, July 12, 2019
9:30 am – 3:00 pm
Jane Ellen Hope Building, H-110
315 Cedar St., New Haven

WELCOMING REMARKS, 9:30 - 9:40 AM
Robert Alpern, MD
Dean, Yale School of Medicine

INTRODUCTION TO THE PSYCHENCODE CONSORTIUM, 9:40 - 10:50 AM
Alexander Arguello, Ph.D.
2018 PsychENCODE “Rollout”
PsychENCODE: Using population-scale functional genomics to understand neuropsychiatric disease

- Construction of an **adult brain resource** with 1866 individuals, via data set fusion and uniform processing
- Using the changing proportions of cell types (via **single-cell deconvolution**) to account for expression variation across a population & disorders
- Large-scale processing defines ~79K PFC **enhancers & creates a comprehensive QTL** resource (~2.5M eQTLs + cQTLs & fQTLs)
- Connecting QTLs, enhancer activity relationships & Hi-C into a **brain regulatory network** & using this to link SCZ GWAS SNPs to genes
- Embedding the regulatory network in a **deep-learning model** to predict disease from genotype & transcriptome. Using this to suggest specific pathways & genes, as targets.
- **Other uses** for the resource: Highlighting aging related genes + consistently comparing the brain to other organs
Construction of an **adult brain resource** with 1866 individuals, via data set fusion and uniform processing

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Collecting functional genomic datasets for the adult brain from PsychENCODE, other large consortia & single cell studies.
Merging & Clustering Single Cell Data Sets

Single cell signatures, from:
- ~14K cells (Lake et al., '16 & '18)
- ~400 cells (Darmanis et al., PNAS, '15)
- ~18K cells (PsychENCODE)

Lake et al., 2018 data
PEC adult data
[Li et al. ('18), Science. Wang et al. ('18). Science]
Single-cell deconvolution

Step 1:

Supervised learning to estimate cell fractions

Individual and cross-population reconstruction accuracy via deconvolution

[Wang et al. (‘18) Science]
Different neuronal & glial cell fractions across disorders

Excitatory to Inhibitory imbalance at neuronal subtype level for ASD*

* Rubenstein et al., Model of autism: increased ratio of excitation/inhibition in key neural systems, Genes Brain Behav. 2003

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[Ex5] [In6] [Oligo]

[CTL] [SCZ] [BPD] [ASD]
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Developing a Reference Set of ~79K PFC Enhancers & Studying Their Population Variation

Consistent with ENCODE, active enhancers are identified as open chromatin regions enriched in H3K27ac and depleted in H3K4me3

We identified 79056 enhancers in the reference Brain

[Wang et al. (‘18) Science]
Developing a Reference Set of ~79K PFC Enhancers & Studying Their Population Variation

[Wang et al. (‘18) Science]
Quantitative Trait Loci (QTLs) associated with variation

Gene expression (eQTL)

Chromatin (cQTL)

Cell fraction QTLs (fQTLs)
Larger brain eQTL sets than previous studies, but strong overlap with them

[Wang et al. ('18) Science]
multi-QTLs from overlapping different types of QTLs: cQTL, fQTL, eQTL & isoQTL

<table>
<thead>
<tr>
<th></th>
<th>Numbers of QTLs</th>
<th>eGenes Enhancers</th>
<th>SNPs</th>
</tr>
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<tbody>
<tr>
<td>eQTL</td>
<td>2,542,908</td>
<td>32,944</td>
<td>1,341,182</td>
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<tr>
<td>isoQTL</td>
<td>2,628,259</td>
<td>19,790</td>
<td>1,052,939</td>
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<tr>
<td>cQTL*</td>
<td>8,464</td>
<td>8,484</td>
<td>7,983</td>
</tr>
<tr>
<td>fQTL</td>
<td>4,199</td>
<td>9</td>
<td>1,672</td>
</tr>
</tbody>
</table>

1391 SNPs (multi-QTLs) in at least three types among eQTLs, isoQTLs, cQTLs, fQTLs

[Wang et al. (‘18) Science]
Brain eQTLs and enhancers enriched with GWAS SNPs for brain disorders

Wang, et al., Science, 2018
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Hi-C

Gene

Enhancers
Topologically Associating Domain (TAD)
Potential Enhancer-Promoter (E-P) interaction in TAD

TF
Enhancer
Target gene

Transcription Factor Binding Sites (TFBSs)

Expression activity relationship

\[ C^* = \text{argmin}_C (||Y - XC||^2 + a||C||^2 + b||C||_{L1}) \]

TF expression (X) to predict target gene expression (Y) using Elastic net regression

QTLs

eQTL

Gene regulatory network inference from Hi-C, QTLs & Activity Correlations

[Wang et al. ('18) Science]
Imputed gene regulatory network for the human brain

- TAD (2,375)
- TF (674)
- Enh (79k)
- TG (20k)

Gene regulatory linkage

Activity
- TF to TG
- Enh to TG
- TF to Enh

Hi-C
- Interaction
- Enh to TG
- QTL

Inhibitory neuron
- Astrocyte
- Microglia

subnetworks targeting single cell marker genes

[Wang et al. ('18) Science]
Linking GWAS SNPs to disease genes using the regulatory network

321 high-confident SCZ genes

[Wang et al. (‘18) Science]
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Deep Structured Phenotype Network (DSPN)

Boltzmann machine

\[ y: \text{phenotypes} \]
\[ h: \text{hidden units (e.g., circuits)} \]
\[ x: \text{intermediate phenotypes (e.g., genes, enhancers)} \]
\[ z: \text{genotypes (e.g., SNPs)} \]
\[ W: \text{weights (e.g., regulatory network)} \]

Energy model:
\[
p(x, y, h|z) \propto \exp(-E(x, y, h|z))
\]

\[
E(x, y, h|z) = -z^T W_1 x - x^T W_2 x - x^T W_3 h - h^T W_4 h - h^T W_5 y - \text{Bias}
\]

[Wang et al. ('18) Science]
DSPN improves brain disease prediction by adding deep layers

**Table:**

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<tr>
<th>Method</th>
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<th>LR-transcriptome</th>
<th>cRBM</th>
<th>DSPN-imputation</th>
<th>DSPN-full</th>
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<td>73.6%</td>
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<tr>
<td>Bipolar Disorder</td>
<td>56.7%</td>
<td>63.3%</td>
<td>71.1%</td>
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<td>76.7%</td>
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<td>67.2%</td>
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**Accuracy = chance to correctly predict disease/health**

[Wang et al. ('18) Science]
DSPN improves brain disease prediction by adding deep layers

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[X 2.5]

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X 3.1
Accuracy = chance to correctly predict disease/health

[Wang et al. (‘18) Science]
• Start with a fully connected trained network
Multilevel Network Interpretation

- Start with a fully connected trained network
- Sparsify network using edges with largest absolute weights (+/-)

Actual network size: 5024/400/100/1 nodes

Weight ranks:
- ++
- +
- -
- --
Multilevel Network Interpretation

- Start with a fully connected trained network
- Sparsify network using edges with largest absolute weights (+/-)
- Extract ‘best positive paths’ to each prioritized module (e.g. a-a₁-a₂-SCZ) by summing weights and multiplying signs

Actual network size: 5024/400/100/1 nodes

[Wang et al. (‘18) Science]
DSPN discovers enriched pathways and linkages to genetic variation

Cross-disorder MOD/HOG enrichment ranking

<table>
<thead>
<tr>
<th>Ranking score</th>
<th>Functional categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 100 200</td>
<td>(<em>) RNA proc. (</em>) Synaptic (*) Metabolic</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Synaptic vesicle cycle</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Antigen proc. and presentation</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Proteasome</td>
</tr>
<tr>
<td></td>
<td>(*) mRNA processing</td>
</tr>
<tr>
<td></td>
<td>(#) Oxidative phosphorylation</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Retrograde endocannabinoid sig.</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Chemical synaptic transmission</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Peptidyl-lysine modification</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Endocytosis</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Ubiquitin mediated proteolysis</td>
</tr>
<tr>
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<td>(&gt;) Anterograde trans-synaptic sig.</td>
</tr>
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</tr>
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<td></td>
<td>(#) Phosphatidylinositol signaling</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Hippo signaling pathway</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Staph./ Epstein-Barr virus inf.</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Synaptic signaling</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Autophagy</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Dop./GABA/Glutamatergic synapse</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Calcium signaling</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Endocrine calcium reabsorption</td>
</tr>
<tr>
<td></td>
<td>(&gt;) RNA degradation / transport</td>
</tr>
<tr>
<td></td>
<td>(#) Ribosome</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Neuron projection morphogenesis</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Fc receptor signaling pathway</td>
</tr>
<tr>
<td></td>
<td>(&gt;) cGMP-PKG signaling pathway</td>
</tr>
<tr>
<td></td>
<td>(&gt;) mTOR signaling pathway</td>
</tr>
<tr>
<td></td>
<td>(&gt;) Cytokine-cytokine receptor int.</td>
</tr>
</tbody>
</table>

SCZ
- Synaptic vesicle cycle
- Glutamatergic synapse

BPD
- Synaptic vesicle cycle
- Glutamatergic synapse

ASD
- Synaptic vesicle cycle
- Glutamatergic synapse

[Wang et al. ('18) Science]
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Phase 1 PsychENCODE capstone resource: Layers of distributed information

Material in the 3 capstones:
- AC - Wang et al. ('18)
- DC - Li et al. ('18)
- NC - Gandal et al. ('18)
Cross tissue variation in Chromatin & Expression

Placing the Brain in context of all other Body Tissues

Transcriptome diversity increases in the non-coding portion of the brain genome while decreases in other tissues.
NRGN has variable expression over age and is in Synaptic vesicle cycle pathway is enriched in SCZ, BPD, ASD

NRGN is a gene associated with the Synaptic vesicle pathway and NGRN expression and methylation is correlated with Age
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“Adult Capstone” Team – 1 of 3 capstones

Daifeng Wang, Shuang Liu, Jonathan Warrell, Hyejung Won, Xu Shi, Fabio Navarro, Declan Clarke, Mengting Gu, Prashant Emani, Yucheng T. Yang, Min Xu, Michael Gandal, Shaoke Lou, Jing Zhang, Jonathan J. Park, Chengfei Yan, Suhn Kyong Rhie, Kasidet Manakongtreecheep, Holly Zhou, Aparna Nathan, Mette Peters, Eugenio Mattei, Dominic Fitzgerald, Tonya Brunetti, Jill Moore, Yan Jiang, Kiran Girdhar, Gabriel Hoffman, Selim Kalayci, Zeynep Hulya Gumus, Greg Crawford,

PsychENCODE Consortium,

Panos Roussos, Schahram Akbarian, Andrew E. Jaffe, Kevin White, Zhiping Weng, Renad Sestan, Daniel H. Geschwind, James A. Knowles

Dedicated to Pamela Sklar Resource.psychencode.org

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