**PsychENCODE Consortium Workshop 7/7/17:**

* Epigenomic silencing of variant impacts GWAS?
* Morning session:
  + Nenad Sestan: developmental shortfalls in info, pre-brith; perinatal period essential; transcriptional neocortical differences in early development but grow closer with further development; cerebellum on the other hand becomes very dfferent during perinatal period;
  + Flora Vaccarino: ChIP and RNA-seq as a function of iPSCs terminal differentiation (TD): even late iPSC development orgaoids is not the same as mature organs; go all the way up to TD80 to detect upper layer neurons;
  + Dalila Pinto: lncRNAs by short-read and IsoSeq (full length isoforms); improvement using capture of lncRNAs; combination with proteomics?
  + Kiran Girdhar: Cell-type-specific ChIP-seq: two histone marks for neuronal and non-neuronal and two brain regions; genome coverage for H3K27ac slightly different for Neu vs non-Neu; linear mixed model for variance due to different variables; contribution of subject and cell-type to variance; difference in functional enrichments assoc. with Neu (signaling) vs non-Neu (immune);
  + Gregory Crawford: ATAC-seq on SCZ and controls; accessibility in enhancers?; open chromatin + sequence conservation better indicator of SCZ heritability?; but very few differential chromatin and cQTLs between cases and controls
  + Feinan Wu’s questions: H3K27me3 data? Multiple-testing FDR? P-val Cutoff for Broad peaks?
  + Mike Gandal: Polygenicity – convergent impact of multiple risk variants; modules of differential regulation in ASD; expand to other diseases; correlation bet SCZ and ASD transcriptomes, as well as SCZ and bipolar, and ASD and bipolar; different cell-type modules of DEX; ASD affected by Microglial, Astrocyte and synaptic dysfunction, but SCZ not much by microglial
  + Chunyu Liu: Using networks to find GWAS signals; CNV-lncRNA – mRNA networks; microRNA-mRNA networks TF impact on miRNA; network edge orienting (NEO);
  + Mark: discussion on interpretation of RCA
  + Andrew Jaffe: WGBS Methylation profiles; CpG vs non-CpG methylation; cell-type-specific
  + Alexey Kozlenkov: GLU and GABA neuronal nuclei; ChIP-seq data and Inputs; Cell-type-specific expression patterns; Enhancers show more DEX peaks for both GABA and GLU than TSSs; hydroxymethylation
* Single-cell discussion:
  + Nenad Sestan: difficulties of studying human brains, especially in developmental stages, only early fetal and adult, not much in between;
  + Flora: more is not better; so far only classifications of cell types are available, but lots of noise; What are the important questions to be answered? Whole-genome amplificiation: introduces noise and errors, only mRNA; extract single-cells from cell fractions? This would be useful.
  + Kevin White: data are dirty but illuminating; questions of normalization and interpretation; immune infiltration: methods to deconvolute cell types
  + Mark: started to deconvolute data using single-cell data; format differences make things difficult; need common methods;
  + Andrea: Human cell atlas; cross-platform and data set analysis; question for Jim: depth in dropSeq, value of each type of data sets?
  + Jim Knowles: need as few as 1000 reads to extract differences in cell types, so fairly easy; but disease vs non-disease is difficult; 10x genomics is better; need methods that use frozen samples; nuclear membrane is more robust to freezing/thawing cycle than cell membrane; epigenetic info is still in very early stages; get all information on same nuclei; need large amount of technological development;
  + Flora: Single-nuclei DNA or RNA should be feasible, but problem is with amplification; lots of ribosomal RNA, but can be purified using other techniques;
  + Nenad: sorting of cells into wells is best method, but very expensive
  + Andrea: three barriers: cost, technical issues, access to tissues
  + Chunyu: nuclei rather than cell;
  + Nenad: reiterating the development gap in tissue availability, as this may be important for disease
  + Flora: iPSCs may help with that issue
  + Nenad: difficulties with iPSCs, as many in vivo aspects cannot be captured; there are non-intrinsic aspects
  + Geetha: in vivo vs in vitro validation
  + Nenad: human vs. primate validation; helps to determine issues with ante- vs post-mortem issues
  + Andrew Jaffe: data-collection biases in single-cell data that mess with deconvolution;
  + Dalila: expand to other brain regions besides cortex?
  + Nenad: push for an atlas? Money is an issue
  + Geetha: PEC phase 2 to address more brain regions
  + Stella: which regions?
  + Nenad: need large concerted effort…
  + Andrea: in grants, specify why bulk or why single-cell and not the other. It will apper in the review process. NIH willing to pay more
* Afternoon sessions:
  + Suhn Rhie: CNON study (SCZ associated with deficits in olfactory perception); ChIP, HiC, Nucleosome Occupancy Methylome (NOMe-Seq)
  + Peter Zanfi: BipSeq RNA sequencing of the limbic system in BD; testing SNPs and DEX in BD vs controls;
  + Mette: PEC private collaboration space -> CapstoneProjects, can download queried subsets based, say, on type of disorder; separate clinical files with Individuals;
  + Eugenio: SCREEN tutorial; registry of candidate regulatory elements cREs; define representative DHSs, then filter and classify using other histone markers; 9 different states in 5 groups
* Breakout group for Capstone 4:
  + Andrew Jaffe:
    - eQTL: gene, exon, expressed regions, transcripts, splice junctions
    - extracting info through splice junctions
    - how would large data set improve? Improve access to low allele frequency variants; haplotypes, use pre-existing linear regression algorithms

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**Psychiatric Genomics in the Era of Team Science:**

1. Steven Hyman: SCZ occurs on a spectrum, that includes normalcy; polygenicity of SCZ, proposed by Gottesman and Shields 1967 (?)
2. Mark Daly: Genetic risk architecture; high heritability of psychiatric disorders; “Reproductive patterns in psychotic patients”
3. Benjamin Neale: Most heritability in noncoding variation; importance of assessment of FDR
4. Michael O’Donovan: Cross-disorder studies in PGC; PGC: Nature neuroscience 2015 Psychiatric Genome-wide association studies implicate neuronal…; Complement component 4, overlapping functions of genes and proteins (?); Stratification of SCZ and BD; Allardyce et al in BioRxiv “Spectrum of risk”
5. Buxbaum: Autism Sequencing Consortium; Chromatin modelling important for ASD, such as H3K4 methylation; TADA – data integration, CNVs, rare variants
6. Jeremy Willsey: BrainSpan data to study spatial and temporal genetic convergence; Willsey et al Cell 2013; State and Levitt Nat. Neurosci 2011
7. David Goldstein: ORION scores to identify regions intolerant to mutations; collapsing analyses: eg, gene-level collective analyses of variants, or exon- or regional-level
8. Stephen Sanders: Noncoding genome in ASD; no significant variants in any particular category based on allele frequency or coding vs non-coding; negative result; something about non-coding indels?
9. Peter Zandi: Bipolar Sequencing Consortium
10. Matthew State: gene Discovery in Tourette Disorder
11. Dan Stein: Gene Discovery in Xhosa; SCZ in African population; Ethical considerations: Consent in low literacy populations, Community advisors, Genetic explanations and their relationship with stigmatization
12. Mary-Claire King: Genetics of Xhosa; Enrichment of rare variants in African populations
13. Raquel Gur: 22q11.2 deletion syndrome; because 25-30% develop SCZ, this is a good system for studying the manner in which a single structural change, a deletion (~3Mb?) on chr 22, increases risk of SCZ
14. John Constantino: African-American ASD, higher coincidence of Intellectual Disabilites (ID); model of polygenic risk prediction breaks down in going from EUR to AFR, necessitating population-specific models
15. Panagiotis Roussos: Cell-type (neuronal vs non-neuronal) and regional differences in epigenomic markers; Differences between regions are observed mainly in neuronal cells
16. Dan Geschwind: HiC molecular networks; Molecular convergence of ASD risk genes; Parikshak, Gandal, Geschwind Nat Rev Gen 2015; Parikshak Cell 2013; Wang et al 2015 Neuron 88, 1- 8
17. Mike Gandal: Systems-level understanding of molecular hierarchies; gene expression modules; “Transcriptomic Severity” log2(Fold change) relative to SCZ, ASD greatest, BD similar to SCZ; Neuronal modules down-regulated, glial modules up-regulated; Neuronal module enriched for CNVs, rare and common variants
18. Flora Vaccarino: Somatic mosaicism; single cell – errors in whole genome amplification create noise; accumulation of SNVs in progenitor cells (5.0 SNVs per day?); Reconstruction of pre-gastrulation mutational tree
19. Chris Walsh: Mosaicism in disease brains: eg hemimegaloencephaly and certain dysplasias; present in small percentage of cells but still possibly lethal; Mosaic mutations make a significant contribution to ASD “Contribution of Mosaic variants to Autism Spectral Disorder” PLoS Genetics; Occur in some familiar and some new genes; correlation with de novo germline mutations
20. Steve McCarroll: Single-cell expression approaches; hundreds of specialized cell types revealed by Drop-seq; droplets to isolate large numbers of cells; bar-coded beads to extract cellular DNA; cerebral organoids have cellular components of sensory nervous system; Obesity GWAS – 100s of brain genes implicated; concentration of genetic influences on obesity in a single neuronal cell type (papers on Drop-seq by Masocko and others)
21. Elise Robinson: Deconstructing neuropsychiatric disorders; separation of ASD and ID impacts difficulty of acquiring phenotypic data such as IQ, behavioural data, etc.
22. Linda Brzustowicz: NIMH repository; both primary (eg processing of subject samples) and secondary (biosample bank) studies; analytical tool such as genotyping, sequencing, expression; phenotypic data available
23. Mette Peters: DREAM challenges, mPOWER sensor data

Follow-up papers:

* Gottesman and Shields 1967 (?)
* “Reproductive patterns in psychotic patients”
* PGC: Nature neuroscience 2015 Psychiatric Genome-wide association studies implicate neuronal…
* Allardyce et al in BioRxiv “Spectrum of risk”
* Willsey et al Cell 2013
* State and Levitt Nat. Neurosci 2011
* Parikshak, Gandal, Geschwind Nat Rev Gen 2015
* Parikshak Cell 2013
* Wang et al 2015 Neuron 88, 1- 8
* “Contribution of Mosaic variants to Autism Spectral Disorder” PLoS Genetics

Follow-up topics and questions:

* DSM
* Somatic mosaicism
* Mads Ha… Danish blood spot testing over extended periods of time
* Power of risk factors
* Tranche
* How does one connect GWAS studies with causal effects? Cross-disorder impacts of the same variants to confirm? Combination with RNA-seq to establish functional impact of individual variants in coding regions or non-coding transcribed regions? Cannot separate out impacts of LD though
* Nonsense vs missense?
* Molecular convergence
* Pleiotropy
* Are neuronal and non-neuronal cells post-mitotic?