Neuropsychiatric Diseases Working Group (NP WG) Meeting
Ma7 20th, 2019
3:30-5pm

Attendees

Todd Lencz
Jim Knowles
Kristen Brennand
Tom Maniatis
Neville Sanjana
Michael Zody
Lara Winterkorn
Panos Roussos (remote)
Dick McCombie (remote)
Dayna Oschwald (remote)
Joseph Buxbaum (remote)

Action Items

1. Lara to send out Doodle poll for recurring meeting schedule

Meeting Notes

Welcome and Working Group Intro to invited guests –Tom Maniatis, Scientific Director and CEO, NYGC

- modelled after cancer working group
- have been effective in creating joint programs, research directions, seminars are well attended
- Polyethnic1000 came out of WG - currently funded by Mark foundation and Zuckerman institute
    - In Phase 1- retrospective samples
    - Phase II will be large scale exome or genomes
- Would like to find equivalent in this group-collaborative, complimentary projects

"Psychiatric Genetics at Zucker Hillside Hospital: An Overview" – Todd Lencz PhD, Professor, Northwell Health

- Started The Ashkenazi genome consortium (TAGC)

    - Wanted to generate an ashkenazi reference panel
    - ~1000 patients with SCZ, 1500 controls
    - All 4 grandparent ashkenazi
- Identified a new deletion near the classic 16p11.2 locus
    - 13 cases found
    - One gene in region affected zebrafish brain growth
    - Had also been IDed in neurodevelopmental disorders
- Completed WGS
    - Sequenced entire cohort- a little over 800 individuals and 600 controls
    - Better imputation than if you use the regular reference
    - Shared their reference panel with anyone who wants, working with HRC to get it incorporated
- Hoping to find a rare variant that was greatly over-represented - not the case
    - Nothing hit genome-wide level significance- now looking in synaptically expressed genes and pathways
- Interested in polygenic risk scores
- Looking for drug targets from chemoinformatic databases (pharmacogenomics)
- Looking to expand cognitive genomics, up to 300k individuals, GWAS-based,
    - Looking to do RNAseq, other functional -omics approaches
    - All healthy individuals, characterized on some test of cognitive ability- "g"
    - Many from UK biobank
    - Negative correlation btw SCZ and G is quite high
    - looking to go from global polygene scores to more specific ones related to cognition
    - Are there other polygenic risk scores related to g, educational attainment- empirically, can you select for higher intellect in IVF? 2.5IQ points, maybe
        - This is on bio archive now
- At Hillside, they do a lot of brain imaging, particularly interested in basal ganglia, have published a series of papers on cortical striatal connectivity
    - There are now some large databases with imaging and GWAS available- new wave in imaging
- Interested in sequencing in the striatum - post mortem, is there interest, are there data already available?
- Lots of intriguing variants, any of these could be CRISPR'd
- Lots of pipelines to merge data with larger databases (like PEC), always need for more functional annotation
- Interested in looking for SVs in the WGS data
    - SV- has been a big focus of the autism work at NYGC, we're now revising SV pipeline, integrating more types of calls on it, tools for identifying non-reference indels
    - Would like to use for imputation as well
    - Size of the variants we can call depends on the type of variants, generally there's a hole between the alignment-based methods and the coverage-based methods

"*Knowles Laboratory: Genomes to Post-GWAS*" – James Knowles, MD, Chair of Cell Biology, SUNY Downstate

Overall: find variants, look at how the RNA is affected, add epigenetics, understand functional implication (what did that change in the brain), finally how does that increase risk for disease

- (Genomics-> transcriptomics-> epigenomics-> behavior and brain structure)

Large cohorts with Carlos and Michele Pato at SUNY Downstate

- 30K+ DNA samples in Genomic Psychiatry cohort
- Ongoing collection: 5k OCD samples
- Funded to collect 20k SCZ samples in pakistan
    - Started in August, have 5k samples at RUCDR
- Putting in a grant to collect 3k trios in autism
- Also extending to BPD and OCD, also MDD, if funded

Transcriptomics

- NIH roadmap single cell product- 2500 samples, all patch-clamped, can make some connections between electrophysiology and genotype

PEC development paper- outgrowth of brainspan paper, sample a number of human brains (normals), 42 brains at different time points, got a number of different datatypes from a number of different regions,

- Gene expression prenatally is very different from post-natal
- There's a sample gap in the middle- partially because not many babies die in the last trimester or first 6 months
- Late third trimester is when brain expression starts to shift- need to do cat or marmoset model
    - Can't take organoid samples that far- the furthest you can get is late third trimester
- All the data is up online at development.Psychencode.org

CNON- cultured neural progenitors derived from olfactory neuroepithelium

    - SCZ is associated with deficits in olfactory perception
    - You can get these stem cells from live humans, can grow cell lines and get neural progenitors
    - You can't separate out ethnicities in gene expression in the brain- everyone is lumped together
    - If you project the data onto the brainpan PCA space, the CNON samples look like mid-late fetal brainspan samples
    - ran differential expression- there were three genes that came up as differentially expressed that were GWAS hits, two other genes were close to significance
    - Implicated the WNT signaling pathway
    - One of the members of the pathway responsible for migration is down regulated in the CNON samples
    - How much of SCZ does that account for?
        - Somewhere between 20-40% have this WNT5A "subtype" of scz
    - Have also done epigenetics (NOMe-seq, variant of WGBS), scRNAseq, Hi-C on them
    - Used a machine learning model, and combined enhancers, co-expression modules, cell fractions, eQTLs, etc and from it got a 6% increase in predictability

- One thing that needs to be done is a good eQTL map for fetal brains, we only have that for adult postmortem brains

Follow-up on previous discussions – Michael Zody, Scientific Director of Computational Biology

- Currently have 10X controller at NYGC, have access to the other two, would be open to acquiring instruments, would be open to speaking about projects and scale that would require that
- for CCDG, sequencing large autism cohort, all whole genomes, mostly done on the X so far, switching to Novaseq now
- Lots of room to do SCZ for WGS- need to be able to convince NIH that its worth it over exomes, can we make the case, maybe with SV
    - how to identify non-exonic functional loci and annotate in a way that are interpretable
- Do you need to sequence everyone to get SVs, or do you need to only sequence enough to see the ones you see in SCZ, and then can you ask is it de novo or inherited, can we genotype for them, but the cost of WGS is coming down to GT later

Regeneron Visit – Tom Maniatis, Scientific Director and CEO, NYGC

- Scheduled for July 25th
- Will look for opportunities for collaboration between the two sites

Recurring meeting schedule – Lara Winterkorn, Scientific Project Manager

- once its a recurring meeting schedule, we'll get more attendance and interest
- Lara to send out Doodle poll to pick recurring time

Buxbaum lab paper with Autism Sequencing Consortium under review (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3371405)- related to schizophrenia and educational attainment, interested in follow up of methylation and ChrX analysis