20.3 OPEN CHROMATIN ANALYSES INFORM FUNCTIONAL NONCODING GWAS VARIANTS IN HIPSC MODEL OF MENTAL DISORDERS

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Background: Neuropsychiatric disorders, including schizophrenia (SZ), afflict a significant fraction of the population. Recent genome-wide association studies (GWAS) under the framework of the Psychiatric Genomics Consortium (PGC), along with large-scale sequencing efforts, have identified a plethora of disease risk loci with common and/or rare risk variants. Translating these exciting genomic findings into causation and disease biology offers the promise of developing more tailored therapies in psychiatry. However, understanding the disease biology underlying most GWAS findings remains challenging: (1) The paucity of disease-relevant biological materials for assaying molecular and cellular phenotypes associated with risk loci; (2) Most disease variants lie within poorly-annotated noncoding parts of the genome for which functional interpretation is challenging; and (3) Each locus often contains many genes/variants equivalently associated with the disease due to linkage disequilibrium, and it is difficult to identify which are the likely causal gene/variant. Human neurons derived from induced pluripotent stem cells (iPSCs), both monolayer cultures (2D model) and the emerging brain organoids (3D model), provide a promising alternative to human brains for recapitating cellular phenotypes relevant to psychiatric disorders. CRISPR/Cas9 editing further strengthens the utility of these models by enabling the generation of isogenic lines with essentially the same genetic background on which allelic effects of a risk variant can be directly compared, thus increasing the sensitivity to detect typically small effects of a GWAS variant.

Methods: To functionally assess the relevance of noncoding sequences in neuropsychiatric disorders, we hypothesized that disease-relevant noncoding sequences likely overlap with cell-specific open chromatin regions (OCRs). We have carried out a genome-wide OCR profiling of excitatory neuronal differentiation from human iPSCs using an Assay for Transposase-Accessible Chromatin by sequencing (ATAC-seq).

Results: We found that OCRs in neurons were enriched SZ risk variants in neural OCRs and can help prioritize putatively functional SZ risk variants that may impact OCRs and consequentially, cellular development. At a leading SZ-risk locus flanking MIR137, we further examined the functional effects of a prioritized common GWAS SNP rs1198588 in CRISPR/Cas9-edited hiPSCs, and found that SZ-risk allele of rs1198588 altered MIR137 expression, OCR dynamics and dendrite arborization/synapse maturation. To systematically identify such disease risk variants that may affect OCR, we further carried out a proof-of-concept analysis of allele-specific open chromatin (ASoC) of in hiPSC-derived neurons. We found that Heterozygous SNPs showing ASoC are more prevalent in neurons than in hiPSCs. Out of the 12 schizophrenia GWAS-implicated SNPs that we found in neuronal OCRs of this single individual, two SNPs showed ASoC and are thus putatively functional: one lies within the 5'-UTR of CHRNA5 (cholinergic receptor, nicotinic, alpha 5) and the other is in the promoter region of VPS45, a Sec1 family gene involved in synaptic transmission. We are currently in the process of replicating the observed landscape of ASoC in iPSC-derived neurons from a larger sample pool.

Discussion: Our study suggests that OCR profiling in a human iPSC model of neuronal differentiation can predict functional noncoding sequences that regulate neurodevelopment.

20.4 MODELING THE CONTRIBUTION OF COMMON VARIANTS TO SCHIZOPHRENIA RISK

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Background: Schizophrenia (SZ) is a debilitating psychiatric disorder for which the complex genetic mechanisms underlying the disease state remain unclear. Whereas highly penetrant variants have proven well-suited to human induced pluripotent stem cell (hiPSC)-based models, the power of hiPSC-based studies to resolve the much smaller effects of common variants within the size of cohorts that can be realistically assembled remains uncertain.

Methods: We reprogrammed fibroblasts from SZ patients into hiPSCs and subsequently differentiated these disorder-specific hiPSCs into neural progenitor cells (NPCs) and neurons. Our hiPSC neural cells, from controls and patients with SZ, better resemble fetal rather than adult brain tissue, indicating that hiPSC-based models may be best suited for studies of disease predisposition. At the cellular level, we have previously reported aberrant migration in SZ hiPSC NPCs, together with diminished neuronal connectivity and impaired synaptic function in SZ hiPSC neurons.

Results: We identified microRNA-9 as having significantly downregulated levels and activity in a subset of SZ hiPSC-derived neural progenitor cells (NPCs), a finding that was corroborated by a larger replication cohort and further validated by an independent gene-set enrichment analysis of the largest SZ genome-wide association study (GWAS) to date. Overall, this demonstrated a remarkable convergence of independent hiPSC- and genetics-based discovery approaches. In developing this larger case/control SZ hiPSC cohort of hiPSC-derived NPCs and neurons, we identified a variety of sources of variation, but by reducing the stochastic effects of the differentiation process, we observed a significant concordance with two large post-mortem datasets.

Discussion: We predict a growing convergence between hiPSC and post-mortem studies as both approaches expand to larger cohort sizes. Meanwhile, we have been integrating CRISPR-mediated gene editing, activation and repression technologies with our hiPSC-based neural platform, in order to develop a scalable system for testing the effect of a manipulating the growing number of SZ-associated variants and genes in NPCs, neurons and astrocytes. Altogether, our objective is to understand the cell-type specific contributions of SZ risk variants to disease predisposition.

21. IDENTIFYING INDIVIDUALS AT HIGH RISK FOR SCHIZOPHRENIA: LJ SEIDMAN MEMORIAL SYMPOSIUM

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Overall Abstract: Lawrence J. Seidman was born and grew up in New York City. He obtained a PhD from Boston University in Psychology and stayed in Massachusetts to work for many years in the Harvard affiliated hospitals, such as the VA-Boston Healthcare System, Massachusetts General Hospital and at his untimely passing, he was Professor of Psychology in the Department of Psychiatry at Beth Israel-Deaconess Hospital and the Massachusetts Mental Health Center. He was about to move to a new phase in his career, assuming a position at Children's Hospital, Boston. He was a pioneer in the fields of the neuropsychology of schizophrenia, ADHD and related disorders, of using the tools of cognitive assessments and brain imaging to understand the genetic predisposition for serious mental illness, and in the last several years—prediction of conversion to psychosis in individuals at high risk. He contributed to many multicenter collaborations and had several collaborators world-wide, playing an important role in their work. This symposium is conducted in his honor with contributions from key collaborators on different aspects of his work. Drs. Tyrone Cannon and Elaine Walker will both represent the North American Prodrome Longitudinal Study (NAPLS) consortium by reviewing its findings in brain imaging and cognition. Dr. David Bragg will review the work of the Consortium on the Genetics of Schizophrenia (COGS) multicenter collaboration, in which Dr. Seidman led one of its sites, and Dr. TianHong Zhang from Shanghai will present current data from the Shanghai-Boston SHARP collaboration on early detection of
Concurrent Symposia

21.1 STRESS AND COGNITION IN YOUTH AT CLINICAL RISK FOR SCHIZOPHRENIA

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Background: Heightened Stress has been shown to have acute adverse effects on cognitive function, and both stress and cognitive deficits have been found to be inversely associated with hippocampal volume reduction in both healthy and clinical samples. Further, heightened stress and cognitive deficits have been observed in individuals at clinical high risk (CHR) for psychosis in the North American Prodrome Longitudinal Study (NAPLS-2) as well as other studies of CHR groups. The present study utilizes data from NAPLS-2 to examine the relation of acute stress and hippocampal volume with cognitive performance in healthy youth and those at CHR for psychosis. Both the independent and additive relations of daily stress and hippocampal volume (HV) on cognition are examined.

Methods: The sample was 666 participants (CHR=476; HC=190) who completed MRI scans, as well as measures of stress and cognitive function at the NAPLS-2 baseline assessment. The self-report stress measure was the Daily Stress Inventory (DSI) and cognitive performance was assessed with tests from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery (the Brief Assessment of Cognition in Schizophrenia [BACS]; Symbol Coding, Category Fluency; Animal Naming Trail Making Test: Part A [TMT], Continuous Performance Test—Identical Pairs [CPT-IP], Hopkins Verbal Learning Test—Revised [HVLT-R]). Hierarchical Linear regression analyses were conducted controlling for subject age, sex and intracranial volume (ICV) with test scores as the dependent measures and DSI scores and hippocampal volume as the predictors.

Results: As expected, across subject groups, age was positively associated with performance on all of the cognitive measures, and females scored higher than males on the CPT-IP, WMS, and TMT. ICV was positively linked with performance on the TMT, WMS, NAB Mazes, CPT-IP, and BACS. For HC and CHR subjects combined, after entering covariates (sex, age and ICV), DSI, but not HV, was inversely associated with performance on the BVMT, HVLT, CPT-IP, and WMS. Neither DSI nor HV predicted performance on the NAB mazes or the BACS, beyond the variance accounted for by covariates. When analyses were conducted separately for the HC and CHR groups, DSI was not predictive of performance.

Discussion: The present findings indicate that self-reported daily stress is inversely associated with cognitive performance on a variety of measures, and that this relation is not mediated by HV or any of the covariates in the combined sample of HC and CHR youth. Because the two groups differ in DSI scores, with CHR youth showing significantly higher stress scores, the combined samples represent a broader range of scores than either group alone. Thus, the within-group range of DSI scores is constrained and DSI is not predictive of performance within group. Instead, it appears that elevated stress is one factor contributing to cognitive deficits in CHR youth.

Background: Larry Seidman, Ph.D. was a key contributor to the Consortium on the Genetics of Schizophrenia (COGS) with its focus on understanding the genetic substrates of quantitative endophenotypes in schizophrenia patients. With his deep knowledge of neurocognition related to psychosis, Larry was able to help steer the COGS-1 family study of over 300 families. The subsequent COGS-2 case-control study used the same well curated, quality controlled extensive battery of testing with 1411 schizophrenia patients and 1500 extensively tested healthy control subjects. Larry was first author on the 2015 paper “Factor structure and heritability of endophenotypes and schizophrenia: findings from the Consortium on the Genetics of Schizophrenia.” It is important to note that related association studies examined the relationship of quantitative endophenotypes and genetic loci, and this is complementary to but distinct from case-control studies. These COGS studies identified a 42-gene network with a NRGL-ERBB4 hub underlying schizophrenia neurocognitive deficits. Thus, these NS, modest for case-control studies, are quite powerful for gene finding using quantitative phenotype markers related to core “thought disorder” neurocognitive deficits in schizophrenia. These quantitative measures are up to 100 X more efficient and 10 X more powerful for gene finding than case-control studies as explained by Blangero, Williams and Almasy as early as 2005. Genes for SZ overlap with genes for key functionally important quantitative endophenotypes as shown by many groups, including COGENT and COGS, so case-control and endophenotype studies are best viewed as complementary in nature.

Methods: Seidman et al (2015) examined 12 heritable neurocognitive and neuropsychological domains (including the Penn CNB Battery), as well as three neuropsychological measures reflecting inhibitory reprocessing from EEG and eye movements. Seidman et al’s analysis revealed five distinct factors in the composite COGS battery. These were 1-episodic memory, 2-working memory, 3-perceptual vigilance, 4-visual abstraction and 5-inhibitory processing. The five factors had similar structures across probands, siblings and controls. Also, heritability was significant for all 5 factors. These composite endophenotype factors will be used to enhance our neurobiological and genetic understanding of schizophrenia and its treatment as we move forward, and are related to the Biotype concept of psychosis. Larry Seidman was also an important contributor to the COGS mission as described below.

Results: The COGS PsychChip GWAS of quantitative endophenotypes has now identified six regions of association with quantitative neurocognitive measures exceeding genome-wide significance (e.g. NRGL-3-Abstraction and Mental Flexibility on the CNB). In addition, many associations between endophenotypes and specific loci exceed the suggestive threshold for further investigation.

Discussion: These data will be presented implicating synaptic plasticity and other crucial CNS processes in endophenotype dysfunction in SZ. NB: COGS interrogates the genetic architecture of endophenotypes associated with SZ and its functional outcome, not schizophrenia per se. Still, there is much overlap between risk genes for SZ and neurocognitive endophenotypes. Also neurocognitive endophenotypes are endorsed by the FDA and MATRICS as treatment targets for schizophrenia itself. This allows for data-guided drug and sensory-cognitive remediation of neurocognitive deficits to improve functional outcome in schizophrenia. Using this genomic information to enhance precision based selection of treatment options now seems to be an exciting and viable new treatment pathway.

21.3 NEUROIMAGING MARKERS OF RISK FOR AND PROGRESSION TO FULL PSYCHOSIS IN THE NAPLS PROJECT

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Background: Dr. Larry Seidman made numerous impactful contributions to our understanding of the roles of disrupted neurocognition and brain function in individuals with or at risk for schizophrenia. Based

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