Title

SU96. The Role of MicroRNA Expression in Cortical Development During Conversion to Psychosis

Journal

Schizophrenia bulletin, 43(Suppl 1)

ISSN

1787-9965

Authors

Zheutlin, Amanda
Jeffries, Clark
Perkins, Diana
et al.

Publication Date

2017-03-01

Peer reviewed

SU96. THE ROLE OF MICRORNA EXPRESSION IN CORTICAL DEVELOPMENT DURING CONVERSION TO PSYCHOSIS

Amanda Zheutlin*,, Clark Jeffries[2], Diana Perkins[3], Yoonho Chung[1], Adam Chekroud[1], Jean Addington[4], Carrie Bearden[5], Kristen Cadenhead[6], Barbara Cornblatt[7], Daniel Mathalon[8], Tom McGlashan[1], Larry J. Seidman[9], Elaine Walker[10], Scott Woods[1], Ming Tsuang[6], and Tyrone Cannon[1]
[1]Yale University; [2]University of North Carolina, Chapel Hill; [3]University of North Carolina; [4]University of Calgary; [5]University of California, Los Angeles; [6]University of California, San Diego; [7]Zuker Hillside Hospital; [8]University of California, San Francisco; [9]Harvard Medical School; [10]Emory

Background: In a recent report of the North American Prodrome Longitudinal Study (NAPLS), clinical high-risk individuals who converted to psychosis showed a steeper rate of cortical gray matter reduction compared with nonconverters and healthy controls, and the rate of cortical thinning was correlated with levels of proinflammatory cytokines at baseline. These findings suggest a critical role for microglia, the resident macrophages in the brain, in perturbations of cortical maturation processes associated with onset of psychosis. Elucidating gene expression pathways promoting microglial action prior to disease onset would inform potential preventative intervention targets.
Methods: We used a forward stepwise regression algorithm to build a classifier of baseline microRNA expression in peripheral leukocytes associated with annualized rate of cortical thinning in a subsample of the NAPLS cohort ($N = 74$).
Results: Our cortical thinning classifier included 9 microRNAs, $P = 3.63 \times 10^8$, $R^2 = 0.358$, permutation-based $P = .039$, the gene targets of which were enriched for intracellular signaling pathways that are important to coordinating inflammatory responses within immune cells ($P < .05$, Benjamini-Hochberg corrected). The classifier was also related to proinflammatory cytokine levels in serum ($P = .038$). Furthermore, miRNAs that predicted conversion status were found to do so in a manner partially mediated by rate of cortical thinning (point estimate = 0.078 [95% CIs: 0.003, 0.168], $P = .03$).
Conclusion: Many of the miRNAs identified here have been previously implicated in brain development, synaptic plasticity, immune function, and/or schizophrenia, showing some convergence across studies and methodologies. Altered intracellular signaling within the immune system may interact with cortical maturation in individuals at high risk for schizophrenia promoting disease onset.

SU97. ZEBRAFISH BRAIN ACTIVITY PHENOTYPES UNIFY SCHIZOPHRENIA-ASSOCIATED GENES

Summer Thyme*, Eric Li, Lindsey Pieper, Carrie Sha, Owen Randlett, Edward Soucy, Steve Zimmerman, Steve McCarroll, and Alexander Schier
Harvard University

Background: Large-scale genome-wide association studies have begun to uncover numerous candidate genes linked to schizophrenia. Yet it remains unclear how these genes function and how they contribute to the underlying molecular, cellular, developmental and behavioral processes disrupted in the disorder.
Methods: Recent technological breakthroughs in zebrafish—targeted genome editing with CRISPR/Cas9, whole-brain activity imaging, brain atlas registration, behavioral profiling—combined with the ease of studying large numbers of animals make it an ideal system for analyzing psychiatric disease genes. Combining these technologies, I have generated zebrafish mutants for over 100 schizophrenia-associated genes and am analyzing them for differences in neurological activity and morphology, as well as altered behavior. To assay these mutants for functionally altered brains, I am using a high-throughput antibody staining technique that reports integrated neuronal activity in freely swimming larvae. To determine whether these mutants have altered behavior, I am characterizing their movement rates during the day and night (sleep) and in a stressful heat condition, startle responses to both light changes and sounds, habituation to a stimulus (primitive form of learning), and level of prepulse inhibition.
Results: I have completed screening of these zebrafish mutants for altered brain activity and morphology, and over one-third display phenotypes. Comparing brain activity maps between mutants, I have discovered that multiple schizophrenia-associated genes alter activity in the same brain regions. These data have also clarified ambiguity at multi-gene loci, associated genomic regions containing multiple genes only one of which is likely involved in disease pathology, by identifying the most likely candidate genes through shared phenotypes. Observed brain abnormalities in mutants resemble known schizophrenia patient phenotypes, such as the loss of GABAergic inhibitory neurons and altered activity in olfactory and visual sensory systems. Behavioral abnormalities observed in mutant animals are also reminiscent of motor behaviors observed in patients.
Conclusion: The finding of shared phenotypes suggests that seemingly unrelated schizophrenia-associated genes may be involved in common underlying pathways. Our work illustrates how studies in a simple animal model nervous system can help uncover these pathways and elucidate gene function. Understanding the molecular, cellular, developmental and behavioral processes regulated by schizophrenia-associated genes will provide the foundation to understand the causes of schizophrenia and develop new diagnostics and therapies.This work was supported by Harvard University, NIH research grants to Alexander Schier, and a Damon Runyon Cancer Research Foundation postdoctoral fellowship to Summer Thyme.

SU98. GLUTAMATE AND GABA IN THE SUBSTANTIA NIGRA IN POSTMORTEM BRAIN

Samuel Mabry, Emma Bloom, Lesley McCollum, and Rosalinda Roberts*
University of Alabama at Birmingham

Background: Schizophrenia (SZ) is a mental illness that has positive, negative, and cognitive symptoms. The substantia nigra (SN) is one of the largest dopaminergic nuclei in the brain and projects to the striatum which is the primary locus for action of antipsychotic drugs. The SN receives both glutamatergic and GABAergic inputs that regulate the dopaminergic neuronal activity. In recent years, imaging studies that have shown hyperactivity of the SN in patients with SZ, suggesting that dysregulation of the SN may play of role in the increased amount of dopamine in the striatum in these patients.
Methods: Our study examined neurochemically defined inputs to the SN. The postmortem SN that was used was collected from the Maryland Brain Collection. There were 11 cases total that were examined in this study with schizophrenia cases ($n = 6$) being compared to matched normal control cases (SZ) ($n = 5$). In this study, immunohistochemistry was performed with 3 different antibodies: vGLUT1, vGLUT2, and GAD67, which labels glutamatergic (vGLUT1 and vGLUT2) and GABAergic (GAD67) projections to the SN. VGLUT1 labels projections coming from cortical and hippocampal regions while vGLUT2 labels projections coming from subcortical regions such as the subthalamic nucleus and the pedunculopontine nucleus. The stained tissues were mounted, cover slipped, and the entirety of the SN was imaged using a light box. Three to 4 sections were analyzed per case. Using a random coordinate generator, 20 areas were selected from each section from which 25 photos were taken for each; optical densitometry (OD) analysis was performed using ImageJ.