2022 Molecular Psychiatry Association (MPA) Conference Report

By Clara Liao and Victor Ekuta

The COVID-19 pandemic has been a formidable obstacle to accessible scientific discourse. The 2022 MPA conference, in contrast, was a welcome reprieve from virtual meetings and a much-needed opportunity to reengage in transformative scientific exchange. Such close-knit conferences are fertile ground for revealing the dialogue behind the results -- an often-overlooked facet that drives scientific progress. The conference enabled us to invoke unstructured musings and organic discussions at moments ranging from plenary Q&A to coffee breaks, all situated against the beautiful backdrop of the Maui sunshine. This year's symposium schedule featured a variety of themes, encompassing every level of analysis, from genetic variants and cellular changes to alterations in brain structure, circuitry, and behavior. In parallel, speakers also highlighted several newly developed tools and their applications.

Throughout three days of presentations, we held in our minds what Dr. David Lewis, Distinguished Professor of Psychiatry and Neuroscience, Thomas Detre Professor of Academic Psychiatry, Chair, Department of Psychiatry implored us to consider in our scientific interpretations – to question which of the 5 "C's" a disease-related alteration represents: an upstream cause, a downstream detrimental consequence of a cause, a compensatory response to a cause or a consequence, a comorbid factor, or a confound due to experimental limitations. By discussing the connections across each level of analysis – from molecule to clinical presentation – we can best verify which "C's" our findings represent. Doing so reveals a blend of convergence and divergence, contextualizes perturbations and consequences, highlights clinical implications, and ultimately spurns fundamental updates to our approach to psychiatric healthcare. Here we highlight just a handful of the notable subjects presented that underscore these themes at each level of analysis.

Genetic Variants

Amidst the vast landscape of genetic variants implicated in neuropsychiatric disorders, researchers face challenges when studying rare Copy Number Variations or CNVs - particularly in addressing where (brain region? cell type?) and when (what stage of development?) to look. A key question is whether these variants converge and diverge into subtypes or ultimately impact the same cell type. Answering such a sophisticated question will require us to leverage novel technologies that can disentangle the relationship between gene function and development. For this reason, Dr. Xin Jin, Assistant Professor from the Dorris Neuroscience Center at Scripps Research created perturb-seq, a scalable method to test gene function across a range of cell types and developmental events. This method reveals potentially convergent pathways in corticogenesis, which are implicated in autism spectrum disorders (ASD). In a

similar fashion, Dr. Ellen Hoffman, Assistant Professor in the Child Study Center at Yale School of Medicine, presented a pipeline for screening autism risk genes in parallel using large-scale behavior-based screens on zebrafish. This novel strategy does not try to recapitulate clinical behaviors but instead leverages high system throughput to understand how these genes affect fundamental neural circuits. Such high-throughput, scalable strategies are key to progressing from a list of risk genes to identifying mechanistically convergent pathways that can represent a therapeutic target.

Zebrafish. Shutterstock.com/NERYXCOM

A talk by Dr. Sundari Chetty, Assistant Professor, Psychiatry and Behavioral Sciences at Stanford University, took this concept one step further, illustrating the power of using human-induced pluripotent stem cells to model psychiatric disorders. In Autism Spectrum Disorder (ASD), a larger brain, indicated by an increase in both grey and white matter - precedes the first clinical signs of the disease. By using human-induced pluripotent stem cells (iPSCs), Chetty et al. were able to model brain overgrowth in the context of ASD. Notably, the researchers discovered several genes potentially implicated in regulating head size, providing a possible avenue for understanding the underlying mechanism of this phenomenon and identifying novel therapeutic targets for the treatment of neurodevelopmental disorders (i.e., CD47, CD99).

Brain Structure and Circuity

Dr. David Lewis' presentation during the Tianqiao and Chrissy Chen Plenary, focused on dissecting the neural circuitry and disease process of schizophrenia, highlighting its association with genetic and transcriptomic alterations in the regulation of actin filament dynamics that impair the capacity to form and maintain dendritic spines. This genetic vulnerability could be moderated by cell-type-specific gene expression patterns, which begets the question– at what point during development do cortical

alterations engender symptom onset? This question emphasizes mapping convergence and distinctions in etiology, pathogenesis, and clinical syndrome.

Dr. Lin Tian, Professor and Vice Chair of the UC David School of Medicine, introduced a particularly exciting tool that tackles the need for high-resolution imaging of neuromodulator activity. dLight, a family of intensity-based, genetically encoded sensors, enables optical recording of neuromodulator dynamics in behaving mice. Such a tool revolutionizes the way we can measure neuronal circuits.

Dr. Scott Russo, Professor of Neuroscience and Psychiatry at the iCahn School of Medicine at Mount Sinai, discussed his work distinguishing cell-type-specific signaling in a local circuit, revealing a mechanism for providing context by integrating information. While the lateral habenula is a potential modulator of aggressive social interactions, his work has provided the first functional evidence for an orexin-driven local inhibitory circuit.

Dr. Jennifer Mulle, Associate Professor in the Rutgers Department of Psychiatry and Department of Neuroscience and Cell Biology, demonstrated the tantalizing prospect of utilizing deep phenotyping as a strategy for uncovering mechanistic hypotheses. Using neuroimaging, her group studied the brains of individuals with 3q29 deletion syndrome, a strong genetic risk factor for Schizophrenia as well as ASD and intellectual disability. By collecting numerous domains of pathology for phenotypic measures, Dr. Mulle performed a systematic evaluation of multiple potential medical manifestations, documenting common features of the syndrome aimed at highlighting the convergent consequences of the deletion. They found that these individuals had critical structural changes in the cerebellum, such as smaller cerebellums, decreased cortical volumes, and arachnoid cysts. Furthermore, these structural changes to the cerebellum were associated with domains of phenotypic disability, such as the association of worse executive function and lower IQ with smaller cerebellar volumes. Taken together, these data point to the cerebellum as a region of priority for mechanistic investigation, ultimately suggesting that data from deep phenotyping can drive mechanistic hypotheses.

Clinical

While molecular psychiatry is intrinsically satisfying, it also has a pivotal role to play in driving clinical medicine forward. Several talks highlighted the inherent power of this approach. Researchers address the understudied connections between psychiatric conditions and other physiological contexts in the session, *Linking Mental Health and Physical Health Using Genetics, Functional Genomics, and Large-*

Scale Electronic Health Record Data. Here, we heard of bidirectional relationships between endometriosis and mental health, shared genetic enrichment in cardiomyopathy-associated pathways, and the power of harnessing a large-scale biobank to examine weight cycling and clinical complications.

A talk by Dr. Stephan Sanders, Associate Professor, Psychiatry at the UCSF Weill Institute for Neurosciences, highlights the need for a more rigorous classification of disease phenotypes. His group found that genetic variants overlap between several neuropsychiatric disorders, such as ASD, schizophrenia, and developmental delay. This finding raises an important question: could neuropsychiatric disorders ultimately be captured by a "holy grail" of genetic variants? Answering this question will require large population cohorts with systematic phenotypes and detailed functional analysis. This is especially critical to overcoming the ascertainment bias, the notion that inconsistent reporting of phenotypes is a major obstacle to interpreting genotype-phenotype relationships.

Similarly, Dr. David Glahn, Ph.D. Harvard Medical School/Boston Children's Hospital pointed out that low diagnosis stability can be attributed to the conflation of psychosis with schizophrenia. A broader net for diagnosis may be achievable through clinical genomic screens for children with presenting symptoms, filling the gap for more studies needed on early-onset psychosis and early-onset schizophrenia.

If the 2022 MPA meeting is any indication, scientists are poised to tackle these emerging challenges. Overall, the compelling talks we've highlighted here cover the topic of molecular psychiatry broadly, from transcriptomic alterations to clinical insights. Through this thematic diversity, the 2022 MPA meeting showcases the field on a synergistic and collaborative upwards trajectory.

Clara Liao is a third-year Neuroscience Ph.D. student at Yale University; Victor Ekuta is a MIT linQ Catalyst Healthcare Innovation Fellow and MD Candidate. They wrote this meeting report as part of the Tianqiao and Chrissy Chen Institute Science Writers Fellowship which aims to extend the conversation beyond the meeting with the hopes of sparking new ideas and collaborations.

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