
In Search of Causality: From Neuropsychiatric Genetics to Pathophysiology

**Open workshop organized as a joint effort between
New York Genome Center (NYGC), Columbia University, UCSF, University of Oxford,
UCLA, and Simons Foundation Autism Research Initiative (SFARI)**

Conference Chairs:

Kelsey Martin (SFARI, UCLA) • **Stephan Sanders** (Oxford, UCSF) • **Thomas Lehner** (NYGC)

The past decade has seen immense progress in identifying hundreds of causal factors for neuropsychiatric disorders, mostly in the form of genetic variants. However, limited progress has been made in identifying the pathophysiological processes that connect cause to phenotypic effect. Should such causal processes be established, they would hold considerable potential for therapeutic development in a field where advances are desperately needed. Establishing these causal relationships is complicated by the limited ability to assay the living human brain, the absence of clear endpoints in experimental model systems, and the tendency of the causal factors towards pleiotropic effects, only some of which contribute to neuropsychiatric phenotypes. In the face of these challenges, how do we establish causality?

Exploring this question is made more challenging by the complexity of the brain and insufficiently accurate models of how behavior is encoded in cells and circuits. Fundamental questions remain about which developmental stages, brain regions, cell types, biological pathways, and circuits are involved and whether these are adequately represented in cellular and animal model systems. The absence of clear answers to these questions makes it hard to isolate one variable for study (e.g., investigating a circuit necessitates a decision about which developmental stages to query; investigating developmental stages require choices of brain regions) and leads to heterogeneous data, which complicates integrative analysis.

This workshop will explore the challenges and opportunities in delineating the etiology of neuropsychiatric disorders, and the inherent conceptual and epistemological limitations of developing causal models of brain function in health and disease. Participants will explore the nature of causality against our limited understanding of brain function across levels of organizational complexity including integrating information across levels of analyses from genes to cells to circuits to behavior.

This meeting will take place on **September 23rd, 2022** and will be **virtual**.

Expected outcomes are a critical assessment of the state of the art, a prioritized list of recommendations for future research and the identification of areas in need of collaboration across specialties. The proceedings will be summarized in a position paper.

Conference Schedule

10:00 am Introductory Remarks - **Kelsey Martin** (SFARI, UCLA) • **Thomas Lehner** (NYGC)

10:10 am Perspectives - **John Ngai** (Brain Initiative, NIH) • **Josh Gordon** (Director, NIMH)

10:30 am State of the Field - **Stephan Sanders** (UCSF, Oxford)

10:50 am Keynote Address - **Ken Kendler** (VCU)

11:20 am Discussion

11:30 am Break

11:40 am **Gene Regulation**

This panel will discuss molecular mechanisms that underlie the pathophysiology of neuropsychiatric disorders, and how they work together across integrated pathways to regulate RNA and protein levels. Panelists will discuss approaches towards establishing criteria for what constitutes a causal unit and what knowledge is lacking for the field to progress from characterized causal factors to pathology.

Chairs: **Geetha Senthil** (NIMH) • **Katie Pollard** (Gladstone Institutes, UCSF) • **Len Pennacchio** (Lawrence Berkeley National Lab)

Panelists: **Carl de Boer** (University of British Columbia) • **Christopher Walsh** (Harvard, HHMI) • **Kaitlin Samocha** (MGH, Broad Institute) • **Olga Troyanskaya** (Princeton) • **Sergiu Pasca** (Stanford) • **Tom Nowakowski** (UCSF) • **Tuuli Lappalainen** (NYGC, SciLifeLab, KTH) • **Yin Shen** (UCSF)

1:00 pm Lunch

1:30 pm **Cell Types and Brain Regions**

This panel will discuss approaches towards identifying the subcellular regions, cell types, and brain regions involved in the pathophysiology of neuropsychiatric disorders, including what we know about the mechanisms that underlie cellular differentiation, cell communication, neuronal activity, and brain development, and how their disruption can lead to pathophysiology.

Chairs: **Aviv Regev** (Genentech) • **Ed Lein** (Allen Institute) • **Nenad Sestan** (Yale)

Panelists: **Evan Macosko** (Harvard, Broad Institute) • **Flora Vaccarino** (Yale) • **Hongkui Zeng** (Allen Institute) • **Kira Poskanzer** (UCSF) • **Kristen Brennand** (Yale) • **Mark McCarthy** (Genentech) • **Paola Arlotta** (Harvard, Broad Institute) • **Samuel Aparicio** (NYGC, University of British Columbia) • **Yoshua Bengio** (University of Montreal, Mila-Quebec AI Institute)

2:50 pm Break

2:55 pm **Brain to Behavior to Brain**

This panel will discuss how neuronal circuits encode and influence behaviors related to neuropsychiatric disorders. It will include a discussion about establishing definitions and criteria for what constitutes a disease-related phenotype, whether such phenotypes are or can be represented in cellular and/or animal model systems, and how the underlying circuitry can be modulated to probe their effects on behavior.

Chairs: **Kafui Dzirasa** (Duke, HHMI) • **Kelsey Martin** (SFARI, UCLA) • **Samuel Wang** (Princeton)

Panelists: **Ann Kennedy** (Northwestern) • **Conor Liston** (Weill Cornell) • **Helen Mayberg** (Mount Sinai) • **Kay Tye** (Salk Institute, HHMI) • **Loren Frank** (UCSF, HHMI) • **Nicole Rust** (UPenn) • **Rui Costa** (Allen Institute) • **Susanne Ahmari** (U Pitt)

4:15 pm **Break/Survey of approaches** - break to allow people to digest and respond to an online survey to invite feedback

4:30 pm **Establishing Causality**

This panel will attempt to define fundamental principles for establishing causality across the broad spectrum of determinants of brain function in health and disease. It will aspire to integrate the discussions that will have taken place throughout the day, and explore the opportunities, as well as challenges, in delineating the etiology and pathophysiology of neuropsychiatric disorders. From a clinical perspective, panelists will discuss how best to leverage studies in humans to guide investigations in model systems, and vice versa, across all levels of analyses. The panel will aim to identify verifiable and falsifiable criteria for establishing the causality of defined determinants, and how the field might use such criteria as guidance for where we should be prioritizing scientific focus.

Chairs: **Shafali Jeste** (CHLA, USC) • **Steven Kushner** (Columbia U) • **Steven McCarroll** (Harvard)

Panelists: **Caroline Uhler** (MIT) • **Catherine Dulac** (Harvard, HHMI) • **Cori Bargmann** (Rockefeller) • **Daniel Geschwind** (UCLA) • **Lea Davis** (Vanderbilt) • **Mark Daly** (U of Helsinki, Broad Institute) • **Michel Nivard** (VU Amsterdam)

5:50 pm Closing statement: **Stephan Sanders** (Oxford, UCSF)

Overall panel structure: 2-3 panelists will provide short talks at the start of the panel, followed by a panel discussion moderated by the panel chairs.