Neuropsychiatric genetic variation shapes brain architecture by modulating gene expression

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Symposium

Neuropsychiatric conditions represent a significant health burden, and the genetic contribution to these conditions ranges from 50 to 80%. Rare and common genetic variants both contribute substantially to disease and studies have associated over 1000 genes with autism, schizophrenia and other neuropsychiatric disorders. As a result of the routine implementation of genomic testing in medical diagnostics, rare genetic variants with large effect sizes are identified in 10 to 30% of children with neuropsychiatric disorders. However, large scale brain networks that may mediate the effects of mutations on risk for disease remain largely unknown. Recent genetic neuroimaging studies have shown that common and rare genetic variants modulate brain structure and functional connectivity. Alterations associated with these mutations overlap with those previously observed in individuals with idiopathic psychiatric conditions.

The molecular mechanisms linking genetic variation to these neuroanatomical differences are mostly unknown. Rare coding variants such as deletions and stop mutations affect expression. Non-coding variation may alter specific regulatory elements, also leading to alterations in gene expression and downstream impacts on neuroanatomy. Levels of gene expression across the brain are distributed according to spatial patterning that mirrors the spatial gradients observed at the cellular, structural and functional connectivity levels. It has been hypothesized that information on brain-wide gene transcription data will help to bridge the gap between gene mutations and large-scale structural and functional alterations. In particular, mutations altering genes whose spatial expression exhibit robust topological patterns may lead to changes in brain structure and function alterations following similar spatial patterns. This symposium will bring together experts covering the latest studies on associations between genomic variants and neuroimaging phenotypes and their relationship with gene transcription.

Objective

Understand the nature and effect-size of common and rare mutations on neuroimaging measures.
Understand how cellular gene expression varies across the human cortex and between primates and mice.

Target Audience

Any researcher interested in understanding the relationship between microscopic molecular factors and large scale structure and function of the brain.

Presentations

The effect on functional brain networks of high-risk variants identified in the neurodevelopmental disorder clinic.

Genomic Copy Number Variants (CNVs) are among the most highly penetrant risk factors for neuropsychiatric conditions but almost nothing is known about their impact on functional connectivity (FC). As many CNVs confer risk for both ASD and SZ, we hypothesized that CNVs and these idiopathic conditions may converge on a smaller set of FC alteration dimensions. We analyzed resting-state functional MRI data from 442 carriers of 12 neuropsychiatric CNVs, 755 individuals with ASD or SZ, and 4,960 controls. The effect sizes of each FC profile are correlated to the gene content of CNVs measured by constraint scores. Exploratory factor analyses highlight 3 latent factors explaining 40% of the variance across all CNVs and psychiatric conditions. They mainly involved thalamic, cerebellar, orbitofrontal, and caudate functional seed regions. We also show overlapping brain patterns of gene co-expression across the 12 CNVs, which may explain FC similarities. We conclude that a parsimonious set of FC dimensions may explain the effects of high-risk genomic variants and mechanisms by which they increase risk for mental illnesses.

Presenter

Clara Moreau, University of Montreal
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Genetic Determinants of brain structure

P. Thompson will discuss the latest studies of the genetic determinants of brain structure generated by the ENIGMA consortium. A decade of studies fueled by vast global partnerships (among ENIGMA, CHARGE, UK Biobank, and others) has harmonized worldwide brain mapping data (MRI, dMRI, rs-fMRI, EEG) with imputed genome-wide genomic data to yield over 200 common genetic variants associated with structural and functional brain metrics. Brain GWAS and psychiatric GWAS can then be assessed for overlap using an approach akin to connectomics, where matrices of genetic correlations across diseases, brain signals, and locations in the brain are clustered to home in on “modules” or clusters of genetic effects on the cortex. In parallel, ENIGMA’s 50 working groups also published the largest neuroimaging studies of 10 brain disorders (schizophrenia, bipolar disorder, MDD, PTSD, SUDs, ADHD, ASD, OCD, epilepsy, and 22q deletion syndrome). They have begun to relate common and distinct profiles across all these disorders to colocalized gene expression maps, epigenetic information, and CNVs, offering mechanistic insight into the brain maps.

Presenter

Paul Thompson, University of Southern California Los Angeles, CA
United States

From SNPs to cortical structure: Molecular mechanisms by which common genetic variation leads to changes in brain structure

Work from the ENIGMA consortium has demonstrated that genetic variation associated with changes in cortical surface area is enriched within gene regulatory elements active during cortical neurogenesis in prenatal development. The strongest enrichments were found in neural progenitor cells, a cell-type that produces the excitatory neurons of the cortex. In order to determine the impact of genetic variation on gene regulation within neural progenitors and their differentiated neuronal progeny, we profiled chromatin accessibility (via ATAC-seq) and gene expression (via RNA-seq) in a population of 92 genotyped human neural progenitor cell lines. Using these data, we identify several loci where genetic variation demonstrates cell-type specific impacts on regulatory elements and gene expression, leading to alterations in brain structure. In this way, we explain some of the molecular mechanisms associated with changes in brain structure and risk for neuropsychiatric disorders.

Presenter

Jason Stein, University of North Carolina - Chapel Hill Chapel Hill, NC
United States

Molecular variation of cortical cell types across human cortex and between primates and mice

Trygve Bakken will discuss the molecular diversity of cell types in human cortex, neuronal specialization across areas, and cell type homologies between human, monkey, and mouse. High-throughput RNA-sequencing of single nucleus transcriptomes from postmortem frozen tissue provides a powerful method to characterize cellular diversity in human brain. We have applied snRNA-seq to seven cortical areas, with an initial focus on middle temporal gyrus and primary motor cortex (M1). We find broad conservation of neuronal and non-neuronal cell types between areas, similar layer distributions and proportions, and shared marker expression. Excitatory neurons show more dramatic specialization, such as large Betz cells in layer 5 of M1 that also have highly distinctive physiological and morphological features. We compared human to marmoset and mouse M1, using snRNA-seq and epigenetic data generated by members of the BRAIN Initiative Cell Census Network. We demonstrate a broadly conserved cellular makeup whose similarity mirrors evolutionary distance. The core molecular identity of these types allowed us to generate a consensus cell type classification and infer cell type properties across species. Many species-specific features were also observed in gene expression, methylation, and relative proportions, and may help inform the effective use of model organisms.

Presenter

Trygve Bakken, Allen Institute for Brain Science Seattle, WA
United States