W011

Inflammation and pruning may inform risk to psychiatric disorders. lessons from large genetic data

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Background It's known that psychiatric disorders are caused to either environmental and genetics factors. Through the years several hypotheses were tested and many genes were screened for association, resulting in a huge amount of data available for the scientific community. Despite that, the molecular mechanics behind psychiatric disorders remains largely unknown. Traditional association studies may be not enough to pinpoint the molecular underpinnings of psychiatric disorder. We tried to applying a methodology that investigates molecular-pathway-analysis that takes into account several genes per time, clustered in consistent molecular groups and may successfully capture the signal of a number of genetic variations with a small single effect on the disease. This approach might reveal more of the molecular basis of psychiatric disorders.
Methods i)We collected data on studies available in literature for the studied disorder (e.g. Schizophrenia, Bipolar Disorder);ii)We extracted a pool of genes that are likely involved with the disease;iii)We used these genes as starting point to map molecular cascades function-linked. The molecular cascades are then analyzed and pathways and sub-pathways, possibly involved with them, are identified and tested for association.
Results/discussion We obtained interesting results. In particular, signals of enrichment (association) were obtained multiple times on the molecular pathway associated with the pruning activity and inflammation. Molecular mechanics related to neuronal pruning were focused as a major and new hypothesis for the pathophysiology of psychiatric disorders and the role of inflammatory events has been extensively investigated in psychiatry. intersting, inflammatory mechanics in the brain may also play a role in neuronal pruning during the early development of CNS.
Disclosure of interest The author has not supplied his declaration of competing interest.

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W012

Combined analysis of large genetic samples: new statistical approaches improve gene discovery

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Introduction Cognitive dysfunction is recognized as a core feature of schizophrenia and is considered an important predictor of functional outcomes. Despite this, current treatment strategies largely fail to ameliorate these cognitive impairments. In order to develop more efficient treatment strategies, a better understanding of the pathogenesis of cognitive dysfunction is needed. Accumulating evidence indicates that genetic risk of schizophrenia contributes to cognitive dysfunction. However, the precise genetic variants jointly influencing schizophrenia and cognitive function remain to be determined.
Aims Here, we aimed to identify gene loci shared between schizophrenia and general cognitive function, a phenotype that captures the shared variation in performance across several cognitive domains.
Methods Using a Bayesian statistical framework, we compared genome-wide association study (GWAS) data on schizophrenia from the Psychiatric Genomics Consortium cohort ($n = 79{,}757$) with GWAS data on general cognitive function from the CHARGE Consortium ($n = 53{,}949$). By conditioning the false discovery rate (FDR) on shared associations, this statistical approach increases power to detect gene loci.
Results We observed substantial polygenetic overlap between schizophrenia and general cognitive function, which replicated across independent schizophrenia sub-studies. Using the conditional FDR approach we increased discovery of gene loci and identified 13 loci shared between schizophrenia and general cognitive function. The majority of these loci (11/13) shows opposite directions of allelic effects in the phenotypes, in line with previous genetic studies and the observed cognitive dysfunction in schizophrenia.
Conclusions Our study extends the current understanding of the genetic etiology influencing schizophrenia and general cognitive function by identifying shared gene loci between the phenotypes.
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W013

RNA sequencing in bipolar disorder: from long non-coding to circular rnas

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Bipolar disorder (BPD) is a highly debilitating psychiatric disorder. The underlying molecular mechanisms of BPD remain largely unknown. Studies targeting postmortem brain tissues of BPD patients have identified very few consistently replicated differences in the expression levels of protein-coding RNAs across different areas of the brain. Since differential expression of the human genome produces a wide spectrum of protein-coding and noncoding RNAs, we hypothesized that major molecular deficits associated with BPD could reflect dysregulation of multiple classes of RNA. To test this hypothesis, we obtained postmortem human medial frontal gyrus tissue from BPD patients and healthy controls ($n = 16$). To survey the implication of both protein-coding and long non-coding RNAs (lncRNAs) in BPD, we then performed RNA sequencing, PCR validation and replication experiments adopting a case-control design. Thirty-six genes and fifteen lncRNA transcripts not previously implicated in BPD were detected as differentially expressed (FDR < 0.1). Functional analyses identified enrichments of angiogenesis, vascular system development and histone H3-K4 demethylation. In addition, we report extensive alternative splicing defects in the brains of BPD subjects compared to controls. Finally, we describe for the first time a large reservoir of circular RNAs (circRNAs) that populate the medial frontal gyrus and report significantly altered levels of two circular transcripts (cNEBL and cEPHA3) from the NEBL and EPHA3 loci in BPD. Our findings may not only contribute to gain insight into the pathophysiology of BPD but may be tested in the near future as potential biomarkers for diagnostics.
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