Description of research project for internship

Title of research project: Building a molecular landscape of schizophrenia: from human genetic and transcriptomics data to biological significance

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Start internship: ~ September 2019

Background

Schizophrenia (SZ) is a neurodevelopmental disorder that is present in around 0.5% of the population[1]. Brain development in SZ patients is disturbed by a combination of genetic and environmental risk factors, which results in cognitive and behavioral symptoms during adolescence and early adulthood[2]. These symptoms can be divided into three categories: positive symptoms, including delusions, hallucinations and abnormal motor behavior; negative symptoms, including diminished emotional expression and avolition; and cognitive symptoms, including reduced communicative and executive functioning[3]. Currently available SZ medications target the positive symptoms, while there is still a lack of knowledge about the etiology of the negative and cognitive symptoms and how to treat them[4]. The cognitive symptoms are hypothesized to arise from the prefrontal cortex (PFC), in which functional dysconnectivity and redox imbalance play a role[4].

Aim of the project

Big "omics" data for complex diseases are generally analysed using bioinformatics-based tools and computational modelling, which leads to so-called 'networks'. We have developed a method to integrate big genetic and other genome-wide data for a complex disease into a model that we have termed a 'molecular landscape'. Our starting point is to apply bioinformatics-based gene enrichment, protein-protein interaction and pathway analysis tools. This initial analysis is followed by manual curation and iterative integration of corroborating evidence and findings from extensive systematic literature evaluations. First, we analyse the top-ranked genes that have been identified through several types of genetic studies, including genome-wide association studies (GWAS) and mostly based on expression quantitative trait loci (eQTLs), yielding a 'level 1' molecular landscape that represents the causal mechanisms underlying the disorder. Next, we analyse genome-wide expression data, yielding a 'level 2' molecular landscape that represents the - dysregulated - biological processes operational during the course of the disease.
Genetic data from a GWAS meta-analysis and transcriptomics data from PFC and hippocampus of human SZ patients and control individuals[5] will be analyzed to build a 'level 1' and 'level 2' molecular landscape that will reveal the pathological pathways involved in SZ.

Literature

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3. Patel KR, Cherian J, Gohil K, Atkinson D. Schizophrenia: overview and treatment options. *P T*. 2014;39(9):638-645. http://www.ncbi.nlm.nih.gov/pubmed/25210417. Accessed June 5, 2019.
4. Maas DA, Vallès A, Martens GJM. Oxidative stress, prefrontal cortex hypomyelination and cognitive symptoms in schizophrenia. *Transl Psychiatry*. 2017;7(7):e1171.
5. Leonardo Collado-Torres, Emily E. Burke, Amy Peterson, ..., Joel E. Kleinman, Daniel R. Weinberger, Andrew E. Jaffe (2019) Regional Heterogeneity in Gene Expression, Regulation, and Coherence in the Frontal Cortex and Hippocampus across Development and Schizophrenia. Neuron 103, 203–216; July 17, 2019; https://doi.org/10.1016/j.neuron.2019.05.013.