M39. INVESTIGATING THE ROLE OF TREATABLE GENETIC DISEASES IN SCHIZOPHRENIA AND BIPOLAR DISORDER POPULATIONS AND ITS CLINICAL DIAGNOSTIC IMPACT

Clement Zai[1], Venuja Sriretnakumar[1], Ricardo Harripaul[1], Kirti Mittal[1], James L. Kennedy[1], Joyce So[1]
[1]Centre for Addiction and Mental Health

Background Many rare genetic syndromes are known to phenotypically manifest with psychiatric symptoms that can be indistinguishable from primary psychiatric disorders. While the majority of ongoing psychiatric genetic research has been dedicated to the identification and characterization of genes involved in primary psychiatric disorders, little research has been done to determine the extent to which rare genetic variants contribute to the overall psychiatric disease load. Within schizophrenia and bipolar populations, we are conducting the first study of its kind to determine the prevalence of four treatable genetic syndromes (Niemann Pick disease type C (NPC), Wilson disease, acute intermittent porphyria (AIP), and homocystinuria (HOM)) manifesting as primary psychiatric disorders.

Methods We are screening 1323 schizophrenia and 1200 bipolar disorder samples, along with 980 sex- and age-matched healthy controls, all with available DNA and extensive phenotype data. We are using a matrix-type pooled targeted deep sequencing of the genes NPC1, NPC2, ATP7B, HMBS, and CBS to screen for the four genetic diseases. Pathogenic variants within the targeted genes will be identified using an in-house analytic pipeline with quality control, variant discovery designed specifically for identifying variants in the matrix pooled targeted sequencing approach, and functionality prediction programs (i.e. Polyphen, SIFT, Scone) to determine variant pathogenicity. Sanger sequencing will be used to validate identified mutations and decrease false positive calls.

Results We hypothesize that a significant sub-population of patients with psychiatric disorders have underlying rare genetic conditions. Preliminary screening of 1023 schziophrenia patients for possible pathogenic variants resulted in the identification of 11 previously known pathogenic variants from the ClinVar database, with 2 pathogenic variants for NPC, 2 for HOM, and 7 for WD. Additionally, 34 variants were predicted to be pathogenic based on whether three or more pathogenicity prediction softwares (PolyPhen2, SIFT, MutationTaster and Condel) identified the variant to be damaging, of which 3 are predicted nonsense mutations.

Discussion Identification of known and predicted pathogenic variants within the schizophrenia and bipolar populations strongly suggests the role of rare genetic diseases within psychiatric populations as hypothesized. Screening for treatable genetic diseases, such as NPC, WD, AIP and HOM, within schizophrenia and bipolar samples could provide a possible explanation for severe treatment resistance and treating the genetic condition can effectively "cure" patients of their otherwise difficult-to-treat psychiatric symptoms. Ultimately, this proof-of-principle study will lead to the development of molecular diagnostic tools for detection of underlying genetic disorders in psychiatric patients and will allow for precision medicine.

Disclosure:
Patent application - JLK, CCZ