Investigation of Relationships Between Bipolar Disorder Phenotypes And Genome-Wide Significant Loci From PGC2 Schizophrenia

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Background

Schizophrenia (SZ) and Bipolar disorder (BD) show evidence for partial overlap in phenotypic and genetic influences based on family, twins, adoption and Psychiatric Genetic Consortium (PGC) studies. They have lifetime prevalence of about 1% and 2.4%, and heritability estimates of 60-80% and 40-70%, respectively. In the last decade BD has been investigated using dimensional structuring of psychoses based on symptomatic-functional checklists that provides reliable approach to phenotypic assessment. Recent research suggests moving towards developing Phenotype-based Genetic Association Studies. In this approach, patients will only be put into groups consisting of others with symptoms similar to their own. Canonical Correlation Analysis (CCA) is statistical technique designed to identify relationships (usually hidden) between two sets of variables. We use CCA to combine genotypic and phenotypic variables and measure correlation between those sets. This analysis estimates canonical correlation between psychotic symptoms measured using validated item check list (OPCRIT), and genome-wide significant (GWS) loci from PGC2 schizophrenia.

Methods

For our analysis we used phenotype and genetic data for 5,507 BD cases. Imputation of genetic data was performed with 1000Genomes (Phase 3, 2014) then quality control was applied (INFO>0.8, HWE>1e-6, MAF>0.01). Additional quality control was performed on phenotypic symptom coverage. CCA was employed as implemented in R, using package “CCA” with GWS loci from PGC2 SZ and OPCRIT items. SNPs were standardised and adjusted for 10 population covariates calculated from imputed data using principal component approach prior to CCA.

Results

Canonical correlation analysis was run on 4422 cases on 89 available GWS PGC2 SZ SNPs or their proxies (with r2>0.6). 60 phenotypic variables were taken from OPCRIT measurements including mood disturbance, biological indices, atypical depression, substance use, psychosis and social functioning. We found no significant canonical correlations indicating absence of hidden sub-clusters at individual symptom level of BD associated with SZ GWS loci.

Discussion

Our analysis was focused to find correlation from bipolar phenotype by using OPCRIT questionnaire and GWS SZ loci from PGC2. We have shown that

there were no significant canonical correlation coefficients suggesting that there is no direct association between SZ associated genetic loci and BP at individual symptom level.

CCA is canonical correlation analysis is one of potential of data-driven approaches to identify hidden genotype-phenotype relationships. It provides opportunities to generate and test different hypotheses and understand more about complex architecture of psychiatric disorders. In the next stage we plan to extend our analysis to more fine grained systematic descriptors of BD and test for correlation with genetic profiles from a number of co-morbid disorders, as well as the full range of phenotypic and genetic data that are available.