Genetic associations with cognitive performance in psychotic disorders from the Bipolar-Schizophrenia Network on Intermediate Phenotypes consortium

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Abstract

Background: Cognitive deficits are known to be present and familial in schizophrenia and bipolar disorder. Understanding the genetic contributors to cognitive impairments in psychotic disorders as well as healthy controls can contribute to our understanding of disease pathophysiology and its behavioral consequences.

Methods: The Brief Assessment of Cognition in Schizophrenia (BACS) was administered to 1059 participants (schizophrenia N=299, schizoaffective disorder N=179, psychotic bipolar disorder N=236, and controls N=345) in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. Participants were 15-65 years of age, clinically stable outpatients (if probands), and without significant neurological disorder, or recent substance abuse or dependence. Participants were genotyped using the Illumina PsychChip followed by imputation using the 1000Genomes reference panel resulting in 4,322,238 SNP markers. A mixed modeling GWAS approach (EMMAX) was performed using BACS total composite Z scores examined as a quantitative trait phenotype in relation to genetic data while controlling for genetically-driven ancestry measures, age, and sex. Probands and controls were grouped together for primary analyses and then also stratified by the top two genetically-derived ancestry groups.

Results: When all participants were examined together, the most prominent region associated with BACS performance was the *SFMBT1* locus on chromosome 3 (lowest p=1.110E-7; N=10 SNPs p<1.0E-5). Analyses stratified by ancestry also revealed a robust association of *SFMBT1* in participants of predominantly Caucasian ancestry (lowest p=2.410E-7). Robust associations with the LCO101928516 locus on chromosome 6 (lowest p=4.6x10E-8; N=18 SNPs p<1x10E-5) were identified in participants of predominantly African ancestry. Additionally there were N=30 genes or defined genetic loci harboring SNPs with suggestive (p<1E-5) associations with BACS performance. Notable trends in top associations include genes previously associated with risk for schizophrenia or bipolar disorder (*CDH12, DNM3, ITIH1, ITIH4, LRFN5, NMBR, NTRK3*); brain structure, white matter, or development (INPP5D, *LRFN5, NTRK3*); and cognition (*AKAP6, TNFSF10*).

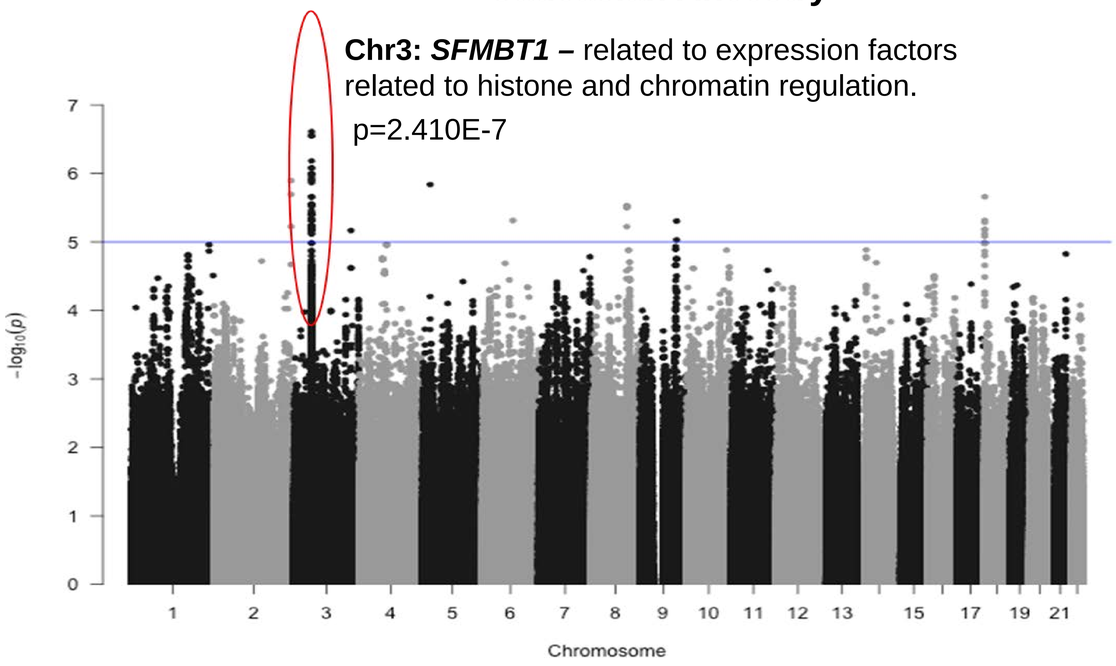
Conclusion: We identified SNPs in genes potentially associated with neuropsychological performance as measured by the BACS. The most robust association was in participants of predominantly African ancestry at a gene locus on chromosome 6 (LCO101928516) that is to date not well characterized for molecular function or relationships with brain-related phenotypes. Additionally, many SNPs at the *SFMBT1* locus on chromosome 3 also appear to be associated with cognitive performance in our study sample. This gene is related to expression factors related to histone and chromatin regulation. Other genes harboring SNPs with suggestive associations include those previously associated with risk for psychotic disorders, brain structure or development, and cognition. These data suggest that cognitive impairments in psychotic disorders may be influenced by genes also known to be risk factors for psychiatric disorders, but also other genes related to brain processes or epigenetic gene regulation. These findings as well as novel loci identified herein require validation and will be further investigated in the BSNIP2 study.

Entry Criteria
15-65 years of age
WRAT-RT>65
English proficiency
No history of seizures or head injury with loss of consciousness > 10 minutes
Negative urine toxicology screen
No history of medical condition known to significantly affect cognition
Clinically stable with no recent medication changes (6wks)
Clinical Evaluations
DSM-IV diagnoses assigned via consensus diagnostic meetings using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), medical charts, and interviews with relatives
Positive and Negative Syndrome Scale (PANSS)
Young Mania Rating Scale (YMRS)
Montgomery-Åsberg Depression Rating Scale (MADRS)
Schizo-Bipolar Scale (SBS)
Neuropsychological Performance
Brief Assessment of Cognition in Schizophrenia (BACS) adjusted for age, sex, and race

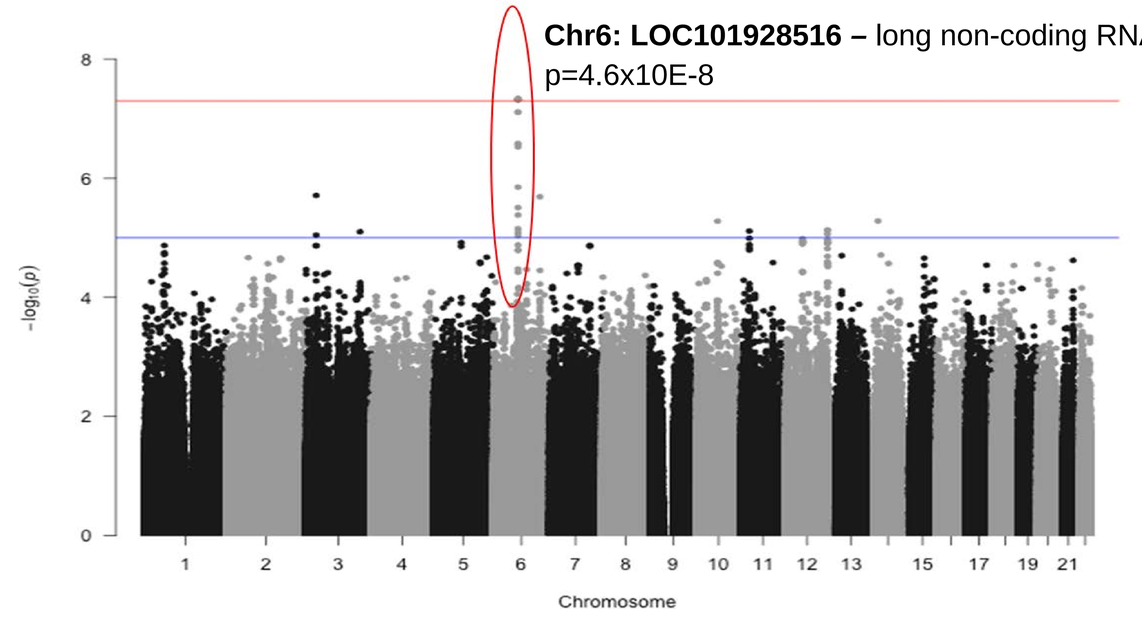
Genetic Analyses
Participants were genotyped using the Illumina PsychChip followed by imputation using the 1000 Genomes reference panel
4,322,238 SNP markers
Mixed modeling GWAS approach (EMMAX) was performed using BACS total composite Z scores examined as a quantitative trait phenotype while accounting for genetically-driven ancestry measures, age, and sex
Probands and controls were grouped together for primary analyses and then also stratified by the top two genetically-derived ancestry groups

Genome-wide association study of BACS performance

Caucasian Ancestry



African Ancestry



Findings

- The most robust association was in participants of predominantly African ancestry at a gene locus on chromosome 6 (LCO101928516) that is to date not well characterized for molecular function or relationships with brain-related phenotypes
- Additionally, many SNPs at the ***SFMBT1*** locus
  - Related to expression factors related to histone and chromatin regulation.
- Additionally there were N=30 genes or defined genetic loci harboring SNPs with suggestive (p<1E-5) associations with BACS performance. Notable trends in top associations include genes previously associated with risk for schizophrenia or bipolar disorder (*CDH12, DNM3, ITIH1, ITIH4, LRFN5, NMBR, NTRK3*); brain structure, white matter, or development (INPP5D, *LRFN5, NTRK3*); and cognition (*AKAP6, TNFSF10*).

Conclusions

These findings suggest that cognitive impairments in psychotic disorders may be influenced by genes also known to be risk factors for psychiatric disorders, but also other genes related to brain processes or epigenetic gene regulation

Acknowledgments and Disclosures

This study was supported by National Institute of Health (NIH) grants MH078113, MH077945, MH077852, MH077851, MH077862, MH072767, and MH083888. The contents of this work are solely the responsibility of the authors and do not necessarily represent the official views of NIH. Dr. Keefe receives royalties for the BACS testing battery and the MATRICS Battery (BACS Symbol Coding), and he is a shareholder in NeuroCog Trials. The other authors report no disclosures or potential conflicts of interest.