Admixture Mapping Implicates ROBO2 as Bipolar Disorder Risk Gene in African Americans

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Introduction

Great strides have been made in identifying the genetic underpinnings of bipolar disorder (BD) in populations with European ancestry; however, there has been a great paucity of studies focused on admixed population such as African Americans. Populations of European descent contain only a subset of human genetic variation, and populations vary in terms of disease-allele frequencies, linkage disequilibrium (LD) patterns, disease prevalence, and effect size; therefore, diverse populations are needed to reveal the underlying biological variation in complex genetic disorders such as BD. Studies focusing on admixed populations present unique opportunities to explore the genetic etiology of BD and may identify ancestry specific risk loci using genetic methods such as admixture mapping.

Methods

Data was obtained from the GAIN study through the database of genotypes and phenotypes (dbGaP) platform (study accession: phs000017.v3.p1). Subjects were filtered for African American ancestry, resulting in to 686 African American controls, 265 African Americans with BD and 150 with schizoaffective, bipolar type (SABP). Genotype data was formatted using PLINK and intersected with the 1000 Genome project and the Human Genome Diversity Project reference panels and overlapping SNPs retained using BCFtools. Global African and European ancestry was estimated using the ADMIXTURE software[1]. Local ancestry at each SNP was estimated using the ELAI software[2].

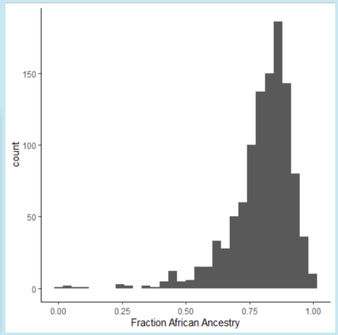
Methods

We performed genome-wide admixture mapping to identify local African or European ancestry regions associated with BD in African Americans using linear regression models in R, adjusting for sex. P-value threshold analysis was performed with STEAM: Significance Threshold Estimation for Admixture Mapping (https://github.com/kegrinde/STEAM). Power analysis was conducted using PAMAM: Power analysis in multiancestry admixture mapping[3].

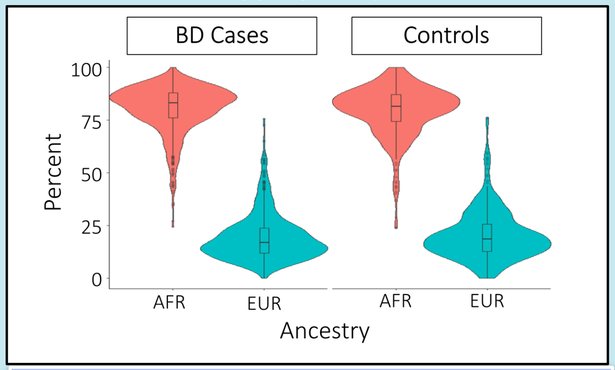
Results

Distribution of Global African Ancestry of 1,101 African American GAIN subjects

- Mean = 79.8%
- Median = 82.6%

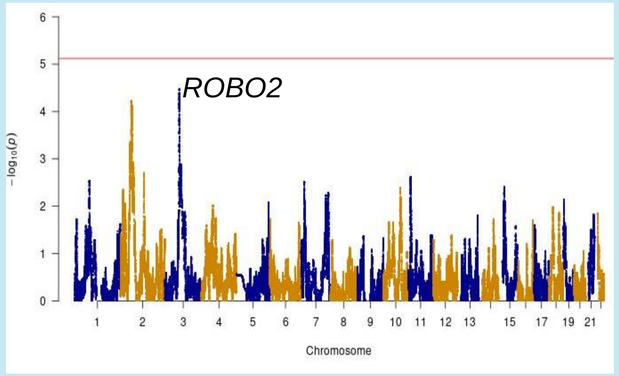


1,084 individuals and 810,371 variants were retained passed QC and were included in the final admixture mapping analyses.



Estimated Admixture Proportions of African American BD Cases and Controls. African (AFR) and European (EUR) ancestral populations. No significant differences in ancestry means (p = 0.187, t-test).

Results



Admixture Mapping Results. Manhattan plot indicates chromosomal regions where local ancestry is associated with BD. The top nominally associated ancestry specific SNP was rs4327364 (Z= -4.147, p= 3.36e-5). Analytical p-value = 7.57e-6 (red line).

Power analysis indicates the current study is underpowered and a combined case-control sample size of 2,540 is needed to achieve 80% power.

Discussion

Although no variants reached statistical threshold of significance, we report suggestive evidence that rs4327364 within the ROBO2 gene is associated with BD risk in African Americans. ROBO2 encodes the Roundabout Guidance Receptor 2 protein, which functions in axon guidance and cell migration and is critical for the maintenance of inhibitory synapses in the adult brain[4]. Previous GWAS indicate that variants within the ROBO2 are associated with schizophrenia, depression and depressive symptoms, response to ketamine in bipolar disorder/major depression, brain volume, and chronotype[5].

Conclusions

Our findings suggests that population-specific genetic variation contributes to BD in African Americans, and that the genetic underpinnings of BD may differ between racial/ethnic groups. Future, larger studies utilizing independent and joint admixture mapping/association techniques may elucidate novel population specific susceptibility loci in BD as well as common loci associated with BD across diverse ancestral populations.

References

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