Replication of genome-wide association study (GWAS) susceptibility loci in a Latino bipolar disorder cohort

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Objectives: Recent genome-wide association studies (GWAS) have identified numerous putative genetic polymorphisms associated with bipolar disorder (BD) and/or schizophrenia (SC). We hypothesized that a portion of these polymorphisms would also be associated with BD in the Latino American population. To identify such regions, we tested previously identified genetic variants associated with BD and/or SC and ancestral haplodbloks containing these single nucleotide polymorphisms (SNPs) in a sample of Latino subjects with BD.

Methods: A total of 2254 Latino individuals were genotyped for 91 SNPs identified in previous BD and/or SC GWAS, along with selected SNPs in strong linkage disequilibrium with these markers. Family-based single marker and haplotype association testing was performed using the PBAT software package. Empirical P-values were derived from 10 000 permutations.

Results: Associations of eight a priori GWAS SNPs with BD were replicated with nominal (P ≤.05) levels of significance. These included SNPs within nuclear factor I A (NFIA), serologically defined colon cancer antigen 8 (SDCCAG8), lysosomal associated membrane protein 3 (LAMP3), nuclear factor kappa B subunit 1 (NFKB1), major histocompatibility complex, class I, B (HLA-B) and S1′-nucleotidase, cytosolic II (NT5C2) and SNPs within intragenic regions microRNA 6828 (MIR6828)—solute carrier family 7 member 14 (SLC7A14) and sonic hedgehog (SHH)—long intergenic non-protein coding RNA 1006 (LINC01006). Of the 76 ancestral haplodbloks that were tested for associations with BD, our top associated haplodblok was located in LAMP3; however, the association did not meet statistical thresholds of significance following Bonferroni correction.

Conclusions: These results indicate that some of the gene variants found to be associated with BD or SC in other populations are also associated with BD risk in Latinos. Variants in six genes and two intragenic regions were associated with BD in our Latino sample and provide additional evidence for overlap in genetic risk between SC and BD.

Keywords: bipolar disorder, Central American, family studies, genetics, lysosomal associated membrane protein 3 (LAMP3), Latinos, Mexican, Mexican-American, nuclear factor kappa B subunit 1 (NFKB1), serologically defined colon cancer antigen 8 (SDCCAG8)
1 | INTRODUCTION

The genetic contribution to psychiatric illnesses such as bipolar disorder (BD) and schizophrenia (SC) have been difficult to define due to issues of clinical heterogeneity, phenotypic overlap and lack of a simple mode of inheritance. These disorders are thought to be influenced by several genes as well as environmental factors. Family, twin, and adoption studies in BD have shown that there is a substantial genetic component [for review, see1]. BD has one of the highest heritability rates of all known psychiatric disorders, with estimates ranging from 85% to 93%.2,3 In addition, several studies have reported evidence of familial co-aggregation or comorbidity between BD and SC, mainly attributable to overlapping genetic influences.4 Over the past several years, genome-wide association studies (GWASs) have identified genetic variants that contribute to complex human disorders or physiological traits.5 To date, over 10,000 putative single nucleotide polymorphism (SNP)–phenotype associations from 1500 GWASs have been archived by the National Human Genome Research Institute (http://www.genome.gov/gwastudies/). Of these, 681 putative associations from 69 BD and/or SC studies have been reported in the National Human Genome Research Institute (NHGRI) Catalog of Published Genome-Wide Association Studies (accessed 15 June 2015),6 with a total of 186 SNP associations showing genome-wide significance ($P<5\times10^{-8}$).

GWAS results reported to date are based almost exclusively on extensive cohorts of European ancestry.7 It has been argued that the expansion of GWASs to diverse populations is needed in order for populations worldwide to benefit from medical advances resulting from genome science. There are also considerable scientific benefits to be gained from characterizing risk variants beyond what can be achieved with populations of European descent alone. Adeyemo and Rotimi confirmed that extensive variations in GWAS findings exist across populations, simply as a function of variations in allele frequencies. Therefore, studies on multiple human populations from different parts of the world are needed to better understand disease etiology and the differential distribution of diseases across ethnic groups.8 Latinos are the largest and fastest growing US minority population and represent approximately 15% of the US population.9 They have been relatively understudied in identifying the genetic underpinnings of psychiatric diseases. To the best of our knowledge, there have been no published GWASs of BD or SC based on cohorts of primarily Mexican or Central American ancestry. The present study addressed this gap in knowledge by attempting to replicate current GWAS findings in a large sample of Latino subjects with BD using a family-based approach.

Family-based association testing of single markers and haplotypes offers several advantages over GWASs. Family-based study designs are robust to the effects of spurious associations caused by population stratification, structure, and admixture.10 Family-based designs also allow the detection of Mendelian errors, which offers a level of genotyping quality control that cannot be matched by GWASs. Haplotype-based methods also represent a powerful approach to disease gene mapping based on the association between functional variants and the inherited ancestral haplotypes.11 We assume that some of the affected individuals may have inherited novel mutations from a common ancestor and that these individuals are likely to share alleles at SNPs in strong linkage disequilibrium (LD) with the disease-causing variant. It should therefore be possible to track a variant allele in the population by identifying the particular ancestral segment on which it arose.

We hypothesized that previously identified genetic variants associated with BD and/or SC and the ancestral haploblocks containing these SNPs might also show an association with BD in Latino populations. We therefore tested 91 SNPs (76 LD blocks) identified in BD and/or SC GWASs12–19 for association with BD, along with selected SNPs in strong LD with these markers, using a family-based association test for single markers and haplotypes in a Latino population.

2 | METHODS

2.1 | Subjects and methods/materials and methods

2.1.1 | Participants

DNA samples were previously collected from the National Institute of Mental Health Genetics of BD and SC in Latino Populations Studies, multi-center sibling-pair studies undertaken to find genetic linkage with BD/SC. A total of 2254 individuals from 490 pedigrees were examined from the USA, Mexico, Guatemala, and Costa Rica. Previous genetic structure analysis has shown that the population groups included in the present study, despite deriving from several countries, are closely related, with high levels of admixture from three major ancestral populations (Caucasian, Native American, and African).43 Diagnoses were made based on DSM-IV criteria44 using a best-estimate consensus procedure which reviewed Diagnostic Interview for Genetic Studies45 and the Family Interview for Genetic Studies46 assessments as well as the participants’ medical records when available. Inclusion criteria for the current analysis required a BD type I (BD-I) or schizoaffective, BD-type (SABD) proband and a minimum of two first-degree relatives willing to participate. When both parents were not available, additional siblings of the affected individuals were genotyped to help reconstruct parental genotypes. Any additional family members with BD-I and/or SABD and respective parents/first-degree relatives were also included. Subjects signed Institutional Review Board (IRB)-approved written informed consent forms in their native language prior to enrolling in the study. The procedures were approved by the IRB of Texas Tech University Health Science Center and respective IRBs in each participating site and country, and the study was performed in accordance with the Helsinki Declaration of 1975.

2.1.2 | Genotyping

Variants previously associated with BD and/or SC were identified from the NHGRI Catalog of Published Genome-Wide Association Studies (accessed 23 April 2013) and ranked by their level of significance. The top 91 ranked SNPs were genotyped along with additional SNPs found to be in strong LD with the selected SNPs. These additional SNPs were selected using the Haplovie 4.2 software11 using downloaded data from
2.2. Statistical analyses

Allele frequencies across the major ancestral HapMap populations (CEU- Utah residents with Northern and Western European ancestry from the CEPH collection, YRI- Yoruba in Ibadan, Nigeria, and CHB- Han Chinese in Beijing, China) for the 91 a priori GWAS SNPs were compared using the chi-squared test. Power calculations for family-based association tests were performed based on actual pedigree structures using a simulation computation method within the SNP & Variation Suite 8.4.4 (Golden Helix, Inc., Bozeman, MT, USA) program and assuming an additive genetic model for low and moderate odds ratios (ORs) (1.3 and 1.8, respectively) in narrow (BD-I) and broad [DSM-IV consensus diagnoses of BD-I, BD type II (BD-II), SABD, and BD not otherwise specified (BP-NOS)] BD phenotypes. Population prevalence was set at 0.01 and 0.05 for narrow and broad BD phenotypes, respectively. Family-based single marker association testing and haplotype analyses were performed using the PBAT analysis in the Golden Helix SNP & Variation Suite 8.4.4 program, assuming an additive genetic model for narrow and broad BD phenotypes. In order to maximize power in the statistical analyses, permutation procedures were implemented to calculate the empirical P-values derived from 10 000 permutations. Single marker association testing was also performed for all SNPs residing in haploblocks with nominal global-marker association with BD. ORs and 95% confidence intervals were calculated using the TDT test in Plink v1.07. Thresholds for statistical significance were set at P≤0.05 for the set of 91 a priori GWAS SNPs, P≤6.58 × 10⁻⁴ for haploblocks (based on 76 haploblocks) and P≤1.79 × 10⁻³ for single marker associations (based on 28 SNP comparisons in nominally associated haploblocks) based on Bonferroni correction for multiple testing.

3 | RESULTS

Sample distributions of participants with BD based on country of origin are described in Table 1. A total of 544 participants (318 with BD-I with psychosis; 226 with BD-I without psychosis) met the criteria for the narrow BD phenotype and 706 met the criteria for the broad BD phenotype (544 with BD-I, 110 with SABD, 12 with BD-II, and 40 with BD-NOS). Of the 2254 individuals who were genotyped, 971 were male and 1283 were female. The sample consisted of 490 Latino pedigrees (see Table 2 for a descriptive table of pedigree structures). Of the 384 markers genotyped, three markers were removed due to excessive missingness and nine markers were excluded based on HWE test, leaving 372 SNPs for analysis. Sixty-two Mendel errors were detected and set to missing. The final genotyping rate was 0.9988. Based on the pedigree structures of the current study, we had 97.8% and 97.2% power to detect associations of moderate effect (OR=1.8) and 46.7% and 44.5% power to detect associations of low effect (OR=1.3) for narrow and broad BD phenotypes (MAF=0.3), respectively (Fig. 1).

Of the 91 a priori SNPs selected from the NHGRI Catalog of Published Genome-Wide Association Studies, we were able to replicate associations of eight SNPs with BD in our Latino sample (Table 3, Supplementary Table S1). Of these, three SNPs within the nuclear factor I A (NFIA), lysosomal associated membrane protein 3 (LAMP3), and major histocompatibility complex, class I, B (HLA-B) genes were previously associated with a BD phenotype. One of the replicated SNPs, located within nuclear factor kappa B subunit 1 (NFKB1), was initially reported in an SC GWAS. Four of the replicated SNPs have been reported in multiple psychiatric phenotypes. These included variants
in serologically defined colon cancer antigen 8 (SDCCAG8) and 5′-nucleotidase, cytosolic II (NT5C2), as well as intragenic regions in chromosomes 3 (microRNA 6828 [MIR6828]—solute carrier family 7 member 14 [SLC7A14]) and 7 (sonic hedgehog [SHH]—long intergenic non-protein coding RNA 1006 [LINC01006]).

As populations vary with regard to allele frequencies and LD patterns, previously identified SNPs associated with a disease may not be the best proxy for the causal SNP in other populations. It is known that, in the presence of multiple tightly linked markers, a haplotype test may be more powerful to detect an association than concerning single-locus tests. Comparison of allele frequencies across the major ancestral HapMap populations (CEU, YRI, and CHB) for the 91 a priori GWAS SNPs revealed significant population differences in 94.5% of the SNPs tested based on the chi-squared test (Supplementary Table S2).

We therefore tested a total of 76 LD haploblocks for associations with BD in our Latino cohort. Eight of the tested haploblocks (10.5%) were nominally associated with BD based on global marker -values. Our top associated haploblock was located in the LAMP3 gene (P=9.10E−03 and P=9.68E−03 for narrow and broad BD phenotypes, respectively); however, the association did not meet the statistical threshold of significance after Bonferroni correction for multiple testing.

We next investigated if any single marker(s) from the nominally associated haploblocks was also associated with BD. Nine out of 28 (32.1%) SNPs were nominally associated under a narrow BD phenotype and five of 28 (17.9%) under a broad BD phenotype (Table 4). Of these, two markers retained statistical significance in the narrow BD phenotype after correction for multiple testing. These included rs230529 (P=9.00E−04) and rs230535 (P=3.00E−04) in NFKB1.

4 | DISCUSSION

We previously reported haplotype associations with BD in two genes (calcium voltage-gated channel subunit alpha 1 C [CACNA1C] and ankyrin 3 [ANK3] involved in calcium signaling, previously found to be associated with psychiatric disease in European populations. We reported a positive association between an eight-locus haplotype in CACNA1C and BD (permitted P=0.005; global marker permitted P=0.002) and between a six-locus haplotype block in ANK3 and BD (permitted P=0.025; global marker permitted P=0.021). The current study was designed to expand on these previous findings by testing additional markers identified through GWASs of both BD and SC in a larger Latino sample. To the best of our knowledge, this is the largest study to date to replicate BD/SC GWAS findings from primarily European and Asian populations in Latino BD cohorts. Our results indicate that some of the gene variants found to be associated with BD or SC in other populations are also associated with BD risk in Latinos.

The first goal of this project was to replicate the top BD/SC GWAS SNPs reported in the NHGRI Catalog of Published Genome-Wide Association Studies. Of the 91 SNPs tested, we were able to replicate associations with about 9% of the markers. Of the eight replicated SNPs, six fell within gene regions and two were intragenic. Seven of the replicated markers that were associated with BD in our Latino cohort had been previously reported to associate with BD or combined phenotypes including BD in other populations. SNP rs230529 was

| Power calculations based on pedigree structure were calculated for odds ratios (ORs) representing a low (OR=1.3) or moderate (OR=1.8) effect. Population prevalence (k) represents the risk for the narrow bipolar phenotype (bipolar disorder type I; k=0.01) and the broad bipolar phenotype (bipolar disorder type I/II, schizoaffective bipolar type, or bipolar disorder not otherwise specified: k=0.05) | Power | OR 1.3 k=0.01 | OR 1.8 k=0.01 | OR 1.3 k=0.05 | OR 1.8 k=0.05 |
|---|---|---|---|---|---|
| Allele frequency | 0.0 | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 |
| Power | 0.0 | 0.2 | 0.4 | 0.6 | 0.8 | 1.0 |
| OR 1.3 k=0.01 | | | | | | |
| OR 1.8 k=0.01 | | | | | | |
| OR 1.3 k=0.05 | | | | | | |
| OR 1.8 k=0.05 | | | | | | |

| FIGURE 1 | Power calculations based on pedigree structure were calculated for odds ratios (ORs) representing a low (OR=1.3) or moderate (OR=1.8) effect. Population prevalence (k) represents the risk for the narrow bipolar phenotype (bipolar disorder type I; k=0.01) and the broad bipolar phenotype (bipolar disorder type I/II, schizoaffective bipolar type, or bipolar disorder not otherwise specified: k=0.05) | Power | OR 1.3 k=0.01 | OR 1.8 k=0.01 | OR 1.3 k=0.05 | OR 1.8 k=0.05 |
|---|---|---|---|---|---|---|
| Allele frequency | 0.0 | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 |
| Power | 0.0 | 0.2 | 0.4 | 0.6 | 0.8 | 1.0 |
| OR 1.3 k=0.01 | | | | | | |
| OR 1.8 k=0.01 | | | | | | |
| OR 1.3 k=0.05 | | | | | | |
| OR 1.8 k=0.05 | | | | | | |
### TABLE 3  Association of replicated single nucleotide polymorphisms (SNPs) with bipolar disorder in the Latino cohort

| Marker       | Position | Gene            | Previous GWAS association                                      | Allele | RAF  | OR      | 95% CI     | Pperm | OR      | 95% CI     | Pperm  |
|--------------|----------|-----------------|----------------------------------------------------------------|--------|------|---------|------------|-------|---------|------------|--------|
| rs7556462    | 1p31.3   | NFIA            | Lee et al.\(^a\) (BD\(^b\))                                    | T      | 0.42 | 1.33    | 0.97–1.84  | 0.040 | 1.27    | 0.95–1.70  | 0.370  |
| rs6703335    | 1q34     | SDCAG8          | Schizophrenia PGC\(^c\) (SC\(^a\)) Steiman et al.\(^b\) (SC, SA, BD\(^b\)) | G      | 0.63 | 1.46    | 1.02–2.09  | 6.00E\(^{-04}\) | 1.40 | 1.02–1.92 | 4.00E\(^{-04}\) |
| rs644931     | 3q26.2   | MIR6828−SLC7A14 | Wang et al.\(^b\) (BD, SC\(^a\))                               | G      | 0.11 | 1.61    | 0.89–2.90  | 0.044 | 1.23    | 0.76–2.00  | 0.162  |
| rs514636     | 3q27.1   | LAMP3           | Jiang & Zhang\(^b\) (BD\(^b\))                                | G      | 0.12 | 1.63    | 0.98–2.70  | 0.026 | 2.17    | 1.33–3.56  | 0.023  |
| rs230529     | 4q24     | NFKB1           | Liou et al.\(^a\) (SC)                                        | T      | 0.55 | 1.28    | 0.95–1.74  | 3.00E\(^{-04}\) | 1.17 | 0.89–1.55 | 0.013  |
| rs9378249    | 6p21.33  | HLA-B           | Jiang & Zhang\(^b\) (BD\(^b\))                                | A      | 0.96 | 2.33    | 1.19–4.59  | 0.022 | 2.07    | 1.09–3.92  | 0.073  |
| rs10949808   | 7q36.3   | SHH−LINC01006   | Wang et al.\(^b\) (BD, SC\(^a\))                               | T      | 0.52 | 1.27    | 0.91–1.78  | 0.022 | 1.25    | 0.94–1.67  | 0.011  |
| rs11191580   | 10q24.33 | NT5C2           | Schizophrenia PGC\(^b\) (SC\(^a\)) Bergen et al.\(^a\) (SC) | C      | 0.15 | 0.73    | 0.47–1.13  | 0.040 | 0.86    | 0.58–1.26  | 0.078  |

Previous genome-wide association studies (GWASs) indicate the initial citation(s) of the association, clinical phenotype(s), and ancestry populations tested. Minor allele (based on TOP strand), minor allele frequency (MAF), odds ratio (OR), permuted P-value based on 10 000 permutation, and direction of association are listed for replicated a priori GWAS SNPs under narrow (bipolar disorder type I) and broad (bipolar disorder type I/II, schizoaffective bipolar type, or bipolar disorder not otherwise specified) bipolar phenotypes. BD, bipolar disorder; CI, confidence interval; OR, odds ratio; RAF, risk allele frequency; NFIA, nuclear factor I A; SDCAG8, serologically defined colon cancer antigen 8; MIR6828, microRNA 6828; SLC7A14, solute carrier family 7 member 14; LAMP3, lysosomal associated membrane protein 3; NFKB1, nuclear factor kappa B subunit 1; HLA-B, major histocompatibility complex, class I, B; SHH, sonic hedgehog; LINC01006, long intergenic non-protein coding RNA 01006; NT5C2, 5′- nucleotidase, cytosolic II; SC, schizophrenia; SA, schizoaffective disorder; PGC, Psychiatric Genome-wide Association Study Consortium.

Study populations: \(^a\)European; \(^b\)European, African American, Asian, other, and unknown ancestry; \(^c\)Han Chinese; \(^d\)Combined=autism spectrum disorder, attention-deficit hyperactivity disorder, BD, major depressive disorder, and SC.

P-value<.05 denoted in bold.
TABLE 4  Global haploblocks nominally associated with bipolar disorder (BD)a

| Region  | Gene                           | Previous GWAS association                  | Global P-value | Incorporated SNPs |
|---------|--------------------------------|-------------------------------------------|----------------|------------------|
|         |                                |                                           | BD narrow | BD broad |                    |
| 2q32.1  | ZNF804A                        | O’Donovan et al. 2008 (European)          | 0.036      | 0.022   | rs725617, rs1344706, rs1583048, rs11901504 |
| 3q26.2  | MIR6828–SLC7A14                 | Wang et al. 2010 (European)               | 0.033      |          | rs6444931, rs6764438, rs6789806 |
| 3q27.1  | LAMP3                          | Jiang & Zhang 2011 (European)             | 9.10E-03   | 9.68E-03 | rs514636, rs653316, rs580116 |
| 4q24    | NFKB1                          | Liou et al. 2012 (Han Chinese)            | 0.047      | 0.047   | rs2903281, rs230535, rs230530, rs230529 |
| 4q34.3  | RNA55P173–LINC00290             | Bergen et al. 2012 (European)             | 0.011      |          | rs17746001, rs1380000, rs2383393, rs10520433 |
| 13q32.3 | NALCN                         | Wang et al. 2010 (European)               | 0.022      | 0.022   | rs682767, rs682666, rs2044117, rs638732, rs2274085 |
| 15q22.2 | CYCSP38–VP513C                 | Bergen et al. 2012 (European)             | 0.028      |          | rs7497015, rs12592967, rs12908294 |
| 16p12.2 | PALB2                          | Jiang & Zhang 2011 (European)             | 0.049      |          | rs13330119, rs420259 |

GWAS, genome-wide association study; ZNF804A, zinc finger protein 804A; MIR6828, microRNA 6828; SLC7A14, solute carrier family 7 member 14; LAMP3, lysosomal associated membrane protein 3; NFKB1, nuclear factor kappa B subunit 1; RNA55P173, RNA, 5S ribosomal pseudogene 173; LINC00290, long intergenic non-protein coding RNA 290; NALCN, sodium leak channel, non-selective; CYCSP38, cytochrome c, somatic pseudogene 38; VP513C, vacuolar protein sorting 13 homolog C; PALB2, partner and localizer of BRCA2; WTCCC, Wellcome Trust Case Control Consortium.

aPrevious GWAS association indicates initial citation of association and ancestral population tested.

bDenotes GWAS reported single nucleotide polymorphism (SNP).

previously reported to associate with schizophrenia. We are the first to report a cross-disorder association of the rs230529 SNP with BD.

SNP rs670335, located on chromosome 1:243445665 within SDCCAG8, was one of the markers for which the replicated association was strongest in both narrow (P=6.00E−4, OR=0.685) and broad (P=4.00E−4, OR=0.714) BD phenotypes within our Latino population. Rs670335 has previously been associated with both BD and SC in both meta-analysis of GWASs and independent GWASs. SDCCAG8 encodes serologically defined colon cancer antigen 8, a centrosome-associated protein. This protein is believed to be involved in organizing the centrosome during interphase and mitosis. While the specific disease variant is yet to be identified, mouse gene knockdown analysis reveals that SDCCAG8 plays a role in the polarity and migration of nascent neurons in the developing cortex.

The second goal of this project was to identify Latino ancestral haploblocks associated with BD. To this end, we performed a family-based haplotype analysis for 76 genomic regions that had been previously implicated in GWASs. A three-marker haplblock in the LAMP3 gene was suggestedly associated with narrow and broad BD phenotypes (Table 4) (P=9.10 × 10−3 and P=9.68 × 10−3, respectively). LAMP3 encodes lysosomal associated membrane protein 3 and has previously been associated with BD as well as Parkinson’s disease. LAMP3 is believed to play a role in dendritic cell function and adaptive immunity. Regulation of LAMP3 enhances protein degradation and cell survival during proteasomal dysfunction. The haplblock associations in LAMP3 were much stronger than the initially reported associations for GWAS SNPs (rs514636) in the narrow (P=.0257, OR=1.63) and broad (P=.0233, OR=2.17) BD phenotypes, suggesting that causal variants associated with BD could lie within these haplblock regions in this Latino cohort.

The third goal of this project was to determine if any single marker within nominally associated haploblocks was associated with BD. Two SNPs, rs230529 and rs230535 in NFKB1, were statistically associated with BD in our Latino sample after Bonferroni correction for multiple testing (Supplementary Table S3). Our top associated SNP, rs230529, is located within chromosome 2, intronic to NFKB1. It has been implicated in treatment refractory schizophrenia within the Han Chinese population where it was associated with lower NFKB1 gene expression. Elevated NFKB1 gene expression in peripheral blood leukocytes has been proposed as a biological marker for treatment-refractory bipolar disorder. NFKB1 plays a broad role in central nervous system (CNS) function where it is involved in synaptic plasticity, neurogenesis, differentiation, and neuronal survival (reviewed in ). Meta-analysis combining SC, schizoaffective disorder, and BD GWAS data has also implicated rs230529 as being associated with a ‘broad psychosis’ phenotype. Our SNP analysis in Latino populations has identified rs230529 and the neighboring SNP rs230535 within NFKB1 as being associated with both a narrow and a broad BD phenotype. These data taken together strongly implicate the NFKB1 gene region in carrying disease-causing variants for SC and BD. Attempts to identify these variants are currently underway.

Our study is not without limitations. First, 706 subjects with BD is a small sample from the standpoint of association analysis (many of the European studies contain thousands of affected subjects). Accurate and sensitive genetic analyses of the Latino population require substantially larger samples in order to identify gene variants that might be specific to this population, as well as to confirm variants known to
be associated with BD in other populations. Second, the current study focuses on subjects of Mexican and Central American ancestry only. Depending on the origin of ancestral haploblocks, our results may or may not be generalizable to other Latino and Hispanic populations.

These results may contribute to understanding of the genetic and neurobiological functioning of BD in the Latino population. The identification of associated variants will provide insight into the perturbation of the biochemical pathways associated with these genes which have been implicated in BD. Future investigations of gene variants identified in these analyses may add to our understanding of the etiology of these disorders and could point to novel diagnostic tools and pharmaceutical treatments for BD within Latino communities. These results also provide additional evidence for overlap in genetic risk between SC and BD, a finding that has now been reported for several gene variants associated with both BD and SC. Future sequencing studies should focus on these disease-associated haplotypes co-segregating in families to identify biologically relevant variants, which may lead to the identification of population/ethnic-specific genetic biomarkers for BD. Lastly, to better identify the genetic contributions to BD in the Latino population, there is a critical need to recruit larger samples of subjects to allow for more robust association studies to be conducted in this important and understudied population.

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DISCLOSURES

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

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SUPPORTING INFORMATION

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