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J Am Acad Child Adolesc Psychiatry. Author manuscript; available in PMC 2010 December 9.

Published in final edited form as:
J Am Acad Child Adolesc Psychiatry. 2010 January ; 49(1): 33–41.

A Genome-Wide Association Study of Amygdala Activation in Youths With and Without Bipolar Disorder

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Abstract

Objective—Functional magnetic resonance imaging is commonly used to characterize brain activity underlying a variety of psychiatric disorders. A previous functional magnetic resonance imaging study found that amygdala activation during a face-processing task differed between pediatric patients with bipolar disorder (BD) and healthy controls. We undertook a genome-wide association study to explore the genetic architecture of this neuroimaging phenotype.

Method—Thirty-nine patients with BD and 29 healthy controls who had previously undergone functional magnetic resonance imaging when viewing a neutral face were genotyped using a genome-wide single-nucleotide polymorphism (SNP) array. After quality control, 104,043 SNPs were tested against normalized amygdala activation scores obtained from the right and left hemispheres. Genetic association was tested with covariates to control for race and ethnicity. Patients and controls were grouped together in the primary analyses.

Results—Right amygdala activation under the hostility contrast was most strongly associated with an SNP in the gene DOK5 (rs2023454, $p = 4.88 \times 10^{-7}$, false discovery rate = 0.05). DOK5 encodes a substrate of tropomyosin-related kinase B/C receptors involved in neurotrophin signaling. This SNP accounted for about 33% of the variance in youths with BD and 12% of the variance in healthy youths. Other results (false discovery rate <50%) were also observed at SNPs near several other genes.

Conclusions—To our knowledge, this is the first genome-wide association study of amygdala activation in adolescents with BD. Although preliminary, these data suggest that DOK5 and perhaps several other genes influence the magnitude of amygdala activation during face processing, particularly in those with BD. Further studies are needed to replicate these findings and characterize the mechanisms involved.

Keywords

amygdala; bipolar disorder; DOK5; functional magnetic resonance imaging

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The high temporal and spatial resolution of functional magnetic resonance imaging (fMRI) provides a unique glimpse into the neural activity associated with cognitive and emotional processes.[1] Functional MRI is commonly used to characterize brain activity and search for neuroimaging phenotypes that may act as biomarkers for psychiatric disorders.[2] Functional

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Disclosure: Drs. Liu, Brotman, Leibenluft, and McMahon, Ms. Akula, and Ms. Skup report no biomedical financial interests or potential conflicts of interest.

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neuroimaging techniques such as fMRI allow the acquisition of measurements of brain function within a single subject in a single session.[3]

Previous fMRI studies have shown that patients with bipolar disorder (BD) often show brain activation patterns during a facial affect discrimination task that differ from those of healthy controls.[4] In these studies, subjects typically view human faces expressing a range of affective states (e.g., neutral, happy, sad, angry, or fearful); some studies ask subjects to identify the predominant emotion. Recently, an event-related fMRI study examined amygdala activation in children when attention was directed to emotional aspects of faces (hostility, subjects' fearfulness) as opposed to nonemotional aspects (nose width). Compared to controls, youths with BD perceived greater hostility in neutral faces and experienced more fear when viewing them. Also compared to controls, youths with BD had greater activation in the left amygdala, accumbens, putamen, and ventral prefrontal cortex when rating facial hostility and greater activation in the left amygdala and bilateral accumbens when rating their own fear of the face.[5] These data suggest that amygdala activation as measured by fMRI may provide important insights into the neurobiology of mood disorders.[6]

To explore the genetic architecture of amygdala activation in children, we undertook a genome-wide association study (GWAS). GWASs offer a powerful approach to the study of complex, genetically influenced traits by sampling genetic variation throughout the genome without resorting to genetic linkage or candidate gene methods. GWASs have successfully identified genetic variants that contribute to the risk of type 2 diabetes,[7] Crohn disease,[8] and heart disease,[9] among others.[10] Neuropsychiatric disorders have proven more challenging, perhaps owing to their heterogeneity and genetic complexity.[11-13] Although their heritability has been little studied, neuroimaging phenotypes might be less genetically complex than clinical disorders[14] and may be good GWAS targets, even in relatively small samples.

Method

Participants

As detailed elsewhere,[5] outpatients aged 9 to 19 years (mean ± SD, 14 ± 2.9 years) who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria[15] for BD (n = 39) were studied along with 29 psychiatrically healthy volunteers (Table 1). Compared to the study by Rich and colleagues,[5] the sample in the present study included 25 additional subjects who were collected under the same inclusion criteria and scanned using the same paradigm. Psychiatric diagnosis was established by the Kiddie-Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version.[16]

To determine mood state in patients, the Children's Depression Rating Scale (CDRS; 29.13 ± 9.30)[17] and the Young Mania Rating Scale (YMRS; 9.82 ± 6.44)[18] were collected within 48 hours of scanning. More than half of patients (n = 21, 53.9%) were euthymic (CDRS <40 and YMRS <12) at the time of testing; 33.3% (n = 13) were hypomanic (CDRS <40 and YMRS >12 but <26); 7.7% (n = 3) were depressed (CDRS >40 and YMRS <12); and 5.1% (n = 2) were in a mixed (CDRS >40 and YMRS >12) mood state.

Most (n = 29, 74.4%) patients were medicated when scanned. Medications received were anticonvulsants (n = 22, 56.4%), atypical antipsychotics (n = 17, 43.6%), antidepressants (n = 13, 33.3%), lithium (n = 12, 30.8%), and stimulants (n = 8, 20.5%).

Patients who had unstable medical illness, substance abuse within the previous 2 months, or pervasive developmental disorder were excluded. Healthy volunteers were excluded if they or their first-degree relatives had a positive psychiatric history. Subjects were self-identified

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as white (n = 57), African-American (n = 6), or unknown (n = 5). All protocols were approved by the National Institute of Mental Health institutional review board. All parents gave written consent for their children's participation, and children gave written assent.

Behavioral Task, fMRI Data Acquisition, and Analysis

As described elsewhere,[5,19] participants viewed a series of 32 gray-scale adult faces (eight happy, eight angry, eight fearful, eight neutral) selected from standardized sets (www.uphs.upenn.edu/bbl/pubs/downloads/nptasks.shtml; www.macbrain.org/faces/index.htm). This event-related design consisted of four blocks: view each face passively, rate the perceived threat (“How hostile is this face?”), rate subjective fear (“How afraid are you of this face?”), and rate the width of the nose (“How wide is the nose?”). Using a five-key button box (MRI Devices, Waukesha, WI), ratings (1 = not at all, 5 = very) were recorded while subjects viewed the face. Given the significant between-group results reported by Rich et al.,[5] the contrasts of interest compared activation during an emotional task (rating perceived threat or subjective fear) versus a nonemotional task (rating nose width). Thus, the primary contrasts, all with neutral faces, were perceived threat versus nose width (“hostile versus nose”) and subjective fear versus nose width (“afraid versus nose”).

Whole-brain fMRI data were acquired on a General Electric Signa 3-T scanner (Milwaukee, WI). T2-weighted images were acquired by use of echoplanar single-shot gradient echo imaging with spatially normalized T1-weighted anatomic imaging. To ensure consistency with previous analyses, fMRI data were analyzed using SPM99 (Wellcome Department of Neurology, University College, London). Details regarding data acquisition and analysis are reported by Rich et al.[5] During preprocessing, we corrected functional data for slice timing and motion, coregistered functional and anatomic data, and spatially normalized the data to the Montreal Neurological Institute T1-weighted template image in SPM99. At the individual subject level, event-related blood oxygen level–dependent response amplitudes were estimated using the general linear model. Blood oxygen level–dependent signal changes were averaged across all voxels in each amygdala structure, providing a single average amygdala value for each event type in each subject. The analysis focused on the amygdala region of interest and used the Gaussian random field threshold ($p < .05$, corrected) and a small volume correction.

Amygdala boundaries were defined using standard anatomic criteria[20] on a single Montreal Neurological Institute template and applied to all normalized brains at the group level. The boundaries of the amygdala were defined anteriorly by the white matter of the parahippocampal gyrus (which provided the anterior, lateral, and inferior borders of the anterior part of the amygdala) and posteriorly by the temporal horn of the lateral ventricle (inferior border), the basal ganglia (superior border), the uncus (medial border), the white matter of the temporal lobe (lateral border), and the alveus of the hippocampus (posterior border).

Genotyping

DNA samples were extracted from fresh peripheral blood using the Puregene kit (Gentra Systems, Inc., Minneapolis, MN) according to the manufacturer's instructions. DNA concentrations were determined using the NanoDrop system (NanoDrop Technologies, Wilmington, DE) and adjusted to 50 ng/μL. Each sample was loaded onto the Human-1 SNP BeadChip (Illumina, Inc., La Jolla, CA), which assays 109,365 single-nucleotide polymorphisms (SNPs) enriched for exon-centric and putative functional SNPs located directly within coding, promoter, and highly conserved noncoding regions.[21,22] Genotyping was performed according to the manufacturer's protocol with 750 ng of each DNA sample.

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Genotypes were assigned with Illumina Beadstudio 3.0 software (Illumina, Inc.), using default parameters.

Genotype Quality Control

Genotyped samples were gender-verified based on heterozygosity of X-linked markers. Graphical representation of relationships[23] was used to check for cryptic relatedness between individuals, all of whom were expected to be unrelated. A set of 1,093 unlinked SNPs was assembled from the total data by randomly selecting one of every 200 SNPs, assessing linkage disequilibrium between adjacent pairs of SNPs, and excluding one of each pair where $r^2 > 0.3$. No cryptically related individuals were detected.

This same set of unlinked SNPs was used to assess individual ancestry by use of STRUCTURE software.[24,25] STRUCTURE infers allele frequencies in each of k ancestral populations on the basis of multilocus genotypes and assigns a posterior probability of ancestry for each of the inferred populations to each individual. Because our study subjects reportedly came from at least three ethnic groups and a $k = 3$ model produced a good fit to the data by the likelihood ratio test, estimated posterior probabilities from a $k = 3$ model (admixture model, 20,000 burn-ins and 20,000 replicates) were used as covariates in the association analysis to correct for ethnicity. Reported ancestry was not considered explicitly in the analysis.

Association Analysis—Association analysis was carried out using PLINK software.[26] Data were filtered for minor allele frequencies under 1%, missing genotype rates over 5%, or Hardy-Weinberg Equilibrium p values $\leq .001$. A total of 104,043 SNPs passed all quality control filters. Because the neuroimaging data were a quantitative phenotype that was determined without regard to case status, we grouped all cases and controls together for all primary analyses to maximize power.

After interesting markers were identified, cases were separated from controls in post hoc analyses to provide separate estimates of the regression coefficients for marker genotype versus amygdala activation in the case and control groups. We regressed normalized amygdala activation values against genotype by use of the '—linear' command in PLINK. Interesting results (defined below) were further evaluated with post hoc tests[27] with depressive symptoms, as measured by the CDRS, and genotype as independent variables.

To check for residual bias in the final results, we generated quantile-quantile plots,[28,29] which graph the observed p values against those expected under a null distribution (Figure 1). As a further test of potential population stratification, we used PLINK to estimate the genomic inflation factor based on the median χ^2 value.

Because amygdala activation was scored on the left and right and with two contrasts, we essentially carried out four GWASs, creating a formidable multiple-testing problem. Correction for multiple testing was based on the false discovery rate (FDR),[30] as estimated by the program Q-Value.[31] This procedure does not control the experiment-wise error rate, but instead estimates the proportion of false positive results among the rejected null hypotheses. For this exploratory study, an FDR less than or equal to 5%, within a particular side and contrast, was set as the threshold of interest for further study.

Post hoc analyses examined associations between mood state and medications versus amygdala activity within the BD group. Specifically, Pearson correlations were used to examine the relation between amygdala activation and hypomania and depression scores and the number of medications taken by each patient.

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Results

The mixed ethnicity of the sample was effectively controlled for in the primary association analysis (Figure 1), with no substantial inflation of the distribution of the test statistic. Consistent with these results, all genomic inflation factor values were lower than 1.02, close to the ideal value of 1.00.

Only one marker met the FDR 5% threshold of interest. This SNP, rs2023454, was associated with amygdala activation under the hostility contrast in the right amygdala ($p = 4.88 \times 10^{-7}$, FDR = 0.05). This SNP resides in the 3′ untranslated region (UTR) of the gene DOK5. DOK5 encodes a membrane protein that interacts with phosphorylated receptor tyrosine kinases to mediate neurite outgrowth and activation of the mitogen-activated protein kinase pathway.[32]

Inspection of the scatter plot revealed an approximately linear relation between genotype at rs2023454 and right amygdala activation scores in the hostility versus nose-width contrast (Figure 2). Overall, about 20% of the variance in this trait could be explained by this SNP in this sample ($r^2 = 0.2164$). The highest trait values were observed in carriers of the “GG” genotype.

The preceding results were based on analysis of the entire sample, regardless of BD diagnosis. To evaluate any impact of diagnosis on these findings, we divided the sample into cases and controls and regressed genotype at rs2023454 on right amygdala activation scores in the hostility contrast. Genotype at rs2023454 accounted for about 33% of the variance in youths with BD and 12% of the variance in healthy youths in this sample (Figure 3). However, no significant main effect of diagnosis ($p > .13$) and no significant diagnosis × genotype interaction ($p > .17$) was detected by analysis of variance. This shows that the association we observed applied to the entire sample, but was nonsignificantly stronger in subjects with BD.

Results for all markers with an FDR lower than 50% are listed in Table 2. Like rs2023454, several of these markers showed relatively large effect sizes (Figure 1). This may be consistent with the idea that neural activity measured by blood flow is less genetically complex than clinical phenotypes. However, the true effect sizes may be smaller due to the “winner's curse,”[33] and some of these signals may represent multiple testing artifacts.

Of note, we detected nominally significant evidence of an association between an SNP in the 5′ UTR of the serotonin transporter and left amygdala activation under the hostility contrast (rs6354, $p = .0043$, $r^2 = 0.11$). This fell well short of our FDR threshold for declaring novel findings of interest, but is consistent with previous studies that have found an association between genetic variation in this region of the serotonin transporter gene and amygdala activation.[34-36]

Functional MRI signals may be influenced by medications and mood state. To evaluate these potential confounds, we examined associations between amygdala activation and current medication use and between amygdala activation and current mood state as assessed by the YMRS and CDRS. All control subjects were medication-free, and mood ratings were not available in controls (but would be expected to be unremarkable); therefore, these analyses were run in patients only. There was no relation between amygdala activation and number of current medications or YMRS scores. However, right amygdala activation during the hostility contrast correlated negatively with CDRS scores ($r = -0.39$, $p = .01$). Thus, we repeated the genetic association analysis for rs2023454 with CDRS score as a covariate. The inclusion of this potential confounder had little effect on the regression coefficient (−0.0014 versus −0.0015). Although these post hoc analyses suggest that our findings are not

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attributable solely to medications or mood state, they do not eliminate the potential effect of these confounding variables.

Discussion

To the best of our knowledge, this is the first GWAS of amygdala activation in subjects with BD. Previously, Potkin and colleagues[37,38] used fMRI for quantitative phenotyping in a GWAS of adults with schizophrenia. In the present study, we detected interesting preliminary evidence that a 3′ UTR SNP in the gene DOK5 is a modulator of right amygdala activity when subjects rate hostility in neutral faces. Although the most significant findings reported meet our prior FDR thresholds, the findings fall short of typical thresholds for genome-wide significance.[10] Still, these results suggest that a novel gene may regulate amygdala activation in the human brain during face processing.

DOK5 plays an important role in neurotrophin signaling pathways, neuronal development, and differentiation. Docking proteins are substrates of tyrosine kinases and function to recruit and assemble specific signal transduction molecules.[39] DOK5 acts as substrate of tropomyosin-related kinase B/C receptors and is involved in neurotrophin-induced mitogen-activated protein kinase activity. The tropomyosin-related kinase family of receptors is a group of high-affinity receptors for neurotrophin growth factors, with pivotal functions in many physiologic processes of the central nervous system. Tropomyosin-related kinase receptors dimerize and auto-phosphorylate upon neurotrophin stimulation and then recruit multiple adaptor proteins to modulate transduction signals.[40] DOK5 is mainly expressed in the nervous system, especially in the neural tube, dorsal root ganglia, and cranial ganglia. Studies also have shown that DOK5 is involved in insulin and glial-derived neurotrophic factor signaling and mediates glial-derived neurotrophic factor–induced neurite outgrowth in PC12 cells.[32] Glial-derived neurotrophic factor is a small protein that potently promotes neuronal survival. In mice, DOK5 proteins have been shown to mediate neurite outgrowth.[40] Thus, DOK5 is a plausible candidate in the pathophysiology of a neurodevelopmental disorder such as BD. However, the detailed regulatory mechanisms and functions of DOK5 in these pathways remain unknown.

DOK5 is highly expressed in brain, with the greatest expression in fetal brain, whole brain, and amygdala (http://expression.gnf.org). A microarray expression study of DOK5 showed specific expression in brain and spinal cord (GeneNote).[41] The Stanley Medical Research Institute Online Genomics Database (https://www.stanleygenomics.org, gene_id 11543) lists DOK5 among many genes that are slightly downregulated in brain tissue from patients with BD (fold change = 1.13, $p < .01$).

This study has several limitations. The SNP with the strongest statistical evidence of association, rs2023454, results in a DNA sequence variation of unknown functional significance. Variation in the 3′ UTR may play a role in regulating DOK5 expression, including mRNA stability, mRNA localization, and translational efficiency. More work is needed to elucidate the mechanism of the observed association findings.

In addition, the interpretation of the findings is limited by the choice of regions of interest, medication effects, comorbidity, and task performance. Although some interesting association signals were detected in this study, sample size, although relatively large for an fMRI study, was small for a GWAS. This was a major reason that we elected to carry out the primary analyses only in the combined sample of cases plus controls. The main limitation we see in the attempt to integrate GWAS with neuroimaging is that GWASs are best conducted in large samples, which are at present very expensive to image. It is possible that imaging measures such as fMRI, acting as biomarkers, may provide a genetically more

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tractable target than clinical diagnoses.[34,36] For this reason, initial studies even in relatively small samples such as this are justified.

Subjects who participate in imaging studies may be unrepresentative of the larger population. Furthermore, children who were unable to remain still for the imaging procedures were excluded from the sample we studied. However, because all participants were evaluated and scanned using the same criteria, and genotyping and quality control filters were applied under our standard protocol regardless of imaging phenotype, selective participation was unlikely to introduce a bias into the genetic analysis. We also implemented a thorough adjustment for population stratification, which can be a particular hazard in genetic association studies.

The relatively small sample of this study also means that we may have missed true signals due to lack of power. In this regard, it is reassuring that we did detect a nominally significant association between amygdala activation and an SNP in the 5′ UTR of the serotonin transporter, near the well-studied linked polymorphic region, consistent with previous reports.[35,42,43] However, because this was an SNP-based study, we did not genotype the linked polymorphic region directly.

Environmental variables such as medication exposure may influence amygdala activity. For example, the mood stabilizer lithium may cause morphologic and functional changes that affect fMRI signals,[44] and medications may alter the magnitude of the blood oxygen level–dependent signal in fMRI data by mechanisms unrelated to the disease process.[45,46] Medication use by cases is unlikely to account for our results, which are not based on case–control comparisons and appear to be independent of diagnosis. Nevertheless, replication in additional samples is needed to demonstrate the robustness of these findings and better estimate effect sizes.

Amygdala activation during a face-processing task is an intriguing phenotype, but its stability[47] and relation to clinical variables[48] remain unknown. In fact, amygdala activation did not differ between patients and controls in this sample, unlike in previous published work that used a smaller and partially overlapping sample.[5] Although BD is heritable, the heritability of amygdala activation has not been studied directly. It is presently unclear whether amygdala hyperactivity in response to face-emotion processing fulfills the classical criteria for an endophenotype,[36,45] including heritability, stability, and familial aggregation with illness. However, increased amygdala activation has been shown to be present in children with BD,[5,49] and amygdala hyperactivity may be related to the deficits in face-emotion processing observed in pediatric BD.[50,51] Moreover, unaffected youths at risk for BD show face-emotion processing deficits,[52,53] suggesting that face-emotion processing deficits have a familial relation with BD. Previous candidate-gene studies have suggested that variation in the genes encoding the serotonin transporter and brain-derived neurotrophic factor[54] affect amygdala activation, further supporting the idea that this trait is under some genetic control.

All of the association signals that we detected at an FDR lower than 50% were present in cases and controls. Although the DOK5 association may be stronger in cases, we did not find evidence that the impact of genotype on amygdala activation differs significantly by diagnosis. There may be a subset of BD cases characterized by increased amygdala activity, and genetic variants that influence amygdala activity may be risk factors in this subset, even though those same variants may not be detectable risk factors for all cases of BD. This may be one reason why, to the best of our knowledge, none of the genes reported in Table 2 have previously been found to contain variants associated with BD in unselected samples.

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Despite these limitations, this first GWAS of an fMRI phenotype in BD revealed some interesting and potentially important signals that warrant further study. Given our small sample, attempts at replication in larger samples is critical. Our results suggest that such larger-scale studies, using denser sets of SNPs that are now routinely available for GWAS, might uncover additional signals to provide a more complete picture of the genetic determinants of amygdala activation in vivo and of possible links to BD.

Acknowledgments

This study was supported by the Intramural Research Program of the National Institute of Mental Health at the National Institutes of Health.

The authors thank the patients and healthy control subjects who underwent fMRI imaging. They thank the Stanley Foundation Brain Consortium for gene expression data. They thank Jo Steele and Ioline Henter for their data preparation and editorial assistance.

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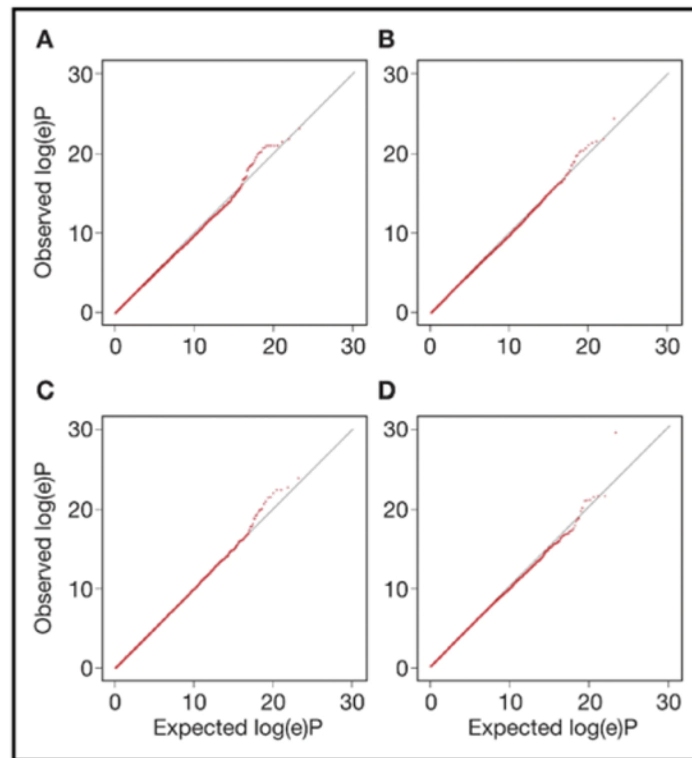

FIGURE 1.

Probability (quantile–quantile) plots of genome-wide association study (GWAS) results. No substantial biases were detected. Quantile–quantile plots of GWAS result for (A) afraid versus nose in left amygdala, (B) afraid versus nose in right amygdala, (C) hostile versus nose in left amygdala, and (D) hostile versus nose in right amygdala. *Note:* X axis = expected log(e)P; y axis = observed log(e)P.

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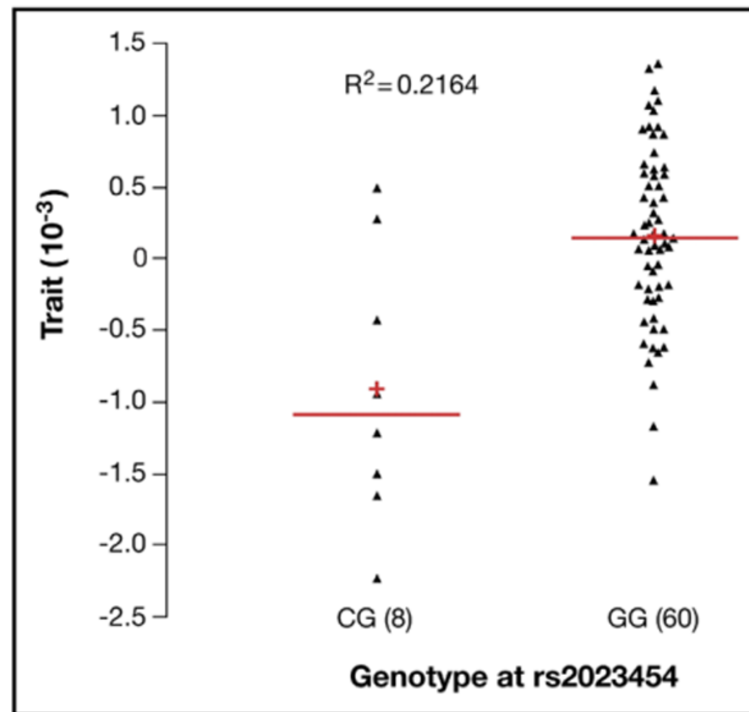

FIGURE 2.
Correlation between genotype at rs2023454 and right amygdala activation (hostility contrast). This single-nucleotide polymorphism has a C-allele frequency of 0.058 in this sample, and no CC homozygotes were observed. *Note:* All data points are shown, along with mean (−) and median (+). For rs2023454, eight subjects had the CG genotype and 60 subjects had the GG genotype.

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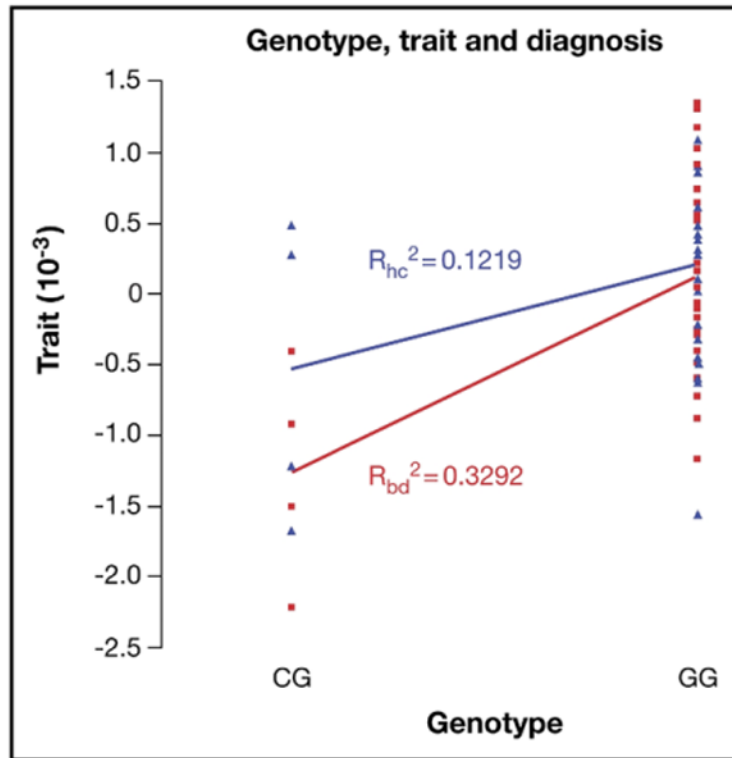

FIGURE 3.
Correlation between genotype at rs2023454 and right amygdala activation (hostility contrast), broken down into cases with bipolar disorder (bd; red, n = 39) and healthy controls (hc; blue, n = 29).

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TABLE 1
Demographics and Clinical Characterization of Study Samples

Subjects	Healthy (n = 29)	Bipolar Disorder (n = 39)	Total (N = 68)
Number of males (proportion)	11 (0.38)	15 (0.39)	26 (0.38)
Age (mean ± SD)	9–18 (13 ±2.9)	9–19 (15 ±2.8)	9–19 (14 ± 2.9)
Ethnicity counts			
White	21	36	57
African American	5	1	6
Unknown	3	2	5

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TABLE 2

Selected Genome-Wide Association Study Results for Activation Phenotypes in Left and Right Amygdala

SNP	Nearest Gene	Role	FDR	R^2	*P*	Phenotype
rs2023454	DOK5	3′ UTR	0.05	0.22	4.88×10^{-7}	HR
rs10407640	KIAA0355	intron	0.33	0.31	6.56×10^{-6}	HL
rs328406		intron (boundary)	0.33	0.27	1.18×10^{-5}	HL
rs1669263		intron	0.36	0.26	2.80×10^{-5}	HL
rs807846		intron	0.38	0.2	3.34×10^{-5}	HL
rs4979326	ZNF618	intron	0.33	0.23	1.35×10^{-5}	HL
rs7858120		intron	0.33	0.22	1.38×10^{-5}	HL
rs4979327		intron	0.33	0.22	1.69×10^{-5}	HL
rs2157786	ATBF1	intron (boundary)	0.33	0.23	2.14×10^{-5}	HL
rs2836368	ERG	intron	0.33	0.19	2.21×10^{-5}	HL
rs2836362		intron	0.45	0.2	5.64×10^{-5}	HL
rs12471108	UGCGL1	intron	0.36	0.25	1.99×10^{-5}	FL
rs9973651		3′ UTR	0.36	0.24	2.94×10^{-5}	FL
rs11542865		3′ UTR	0.36	0.24	2.94×10^{-5}	FL
rs1054317		downstream	0.36	0.24	2.94×10^{-5}	FL
rs2290110		intron (boundary)	0.36	0.24	2.94×10^{-5}	FL
rs13405489		intron	0.36	0.24	2.94×10^{-5}	FL
rs10803593		intron	0.36	0.24	3.30×10^{-5}	FL
rs11687190		intron	0.36	0.24	3.46×10^{-5}	FL
rs11903649		intron	0.36	0.25	4.34×10^{-5}	FL
rs7577867		intron	0.36	0.24	4.69×10^{-5}	FL
rs744265		intron (boundary)	0.36	0.24	4.87×10^{-5}	FL
rs3738923		intron	0.39	0.23	5.66×10^{-5}	FL
rs797509	DLEU7	downstream	0.36	0.19	4.20×10^{-5}	FL
rs1126671	ADH4	coding exon	0.43	0.24	4.54×10^{-5}	HL
rs155202	BICD1	intron	0.43	0.19	4.75×10^{-5}	HL
rs1044305	LOC91461	3′ UTR	0.43	0.21	4.96×10^{-5}	HL

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SNP	Nearest Gene	Role	FDR	R^2	*P*	Phenotype
rs11085900	FLJ45910	3′ UTR	0.48	0.19	6.47×10^{-5}	HL
rs5952987	PHF16	intron (boundary)	0.48	0.12	8.46×10^{-5}	FL
rs2239791		intron	0.48	0.12	9.08×10^{-5}	FL
rs150857	CARKL	coding exon	0.48	0.2	1.01×10^{-4}	FL
rs6675647	AGBL4	intron	0.49	0.19	5.13×10^{-6}	FR
rs6927681	MCMDC1	intron	0.49	0.13	2.19×10^{-5}	FR
rs2806218	C6orf151	3′ UTR	0.49	0.25	2.37×10^{-5}	FR
rs1539537		3′ UTR	0.49	0.24	2.70×10^{-5}	FR
rs2757598		3′ UTR	0.49	0.24	3.84×10^{-5}	FR
rs5926442	NR_002784	exon	0.49	0.2	3.29×10^{-5}	FR
rs12842916		exon	0.49	0.2	3.84×10^{-5}	FR
rs2730078	ADAMTSL3	promoter	0.49	0.3	4.21×10^{-5}	FR
rs7168338	UACA	intron	0.49	0.21	1.13×10^{-4}	FL
rs1010820	HOMER2	intron	0.5	0.21	1.20×10^{-4}	FL

Note: Only SNPs near genes are shown, sorted by minimum FDR for any SNP in that gene. All results with an FDR lower than 0.5 are listed. FDR = false discovery rate; FL = fearfulness, left amygdala; FR = fearfulness, right amygdala; HR = hostility, right amygdala; HL = hostility, left amygdala; SNP = single nucleotide polymorphism; UTR = untranslated region.