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Genome-Wide Association Study of Treatment Response to Venlafaxine XR in Generalized Anxiety Disorder

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Abstract

We conducted the first genome-wide association study (GWAS) in Generalized Anxiety Disorder (GAD) to identify potential predictors of venlafaxine XR treatment outcome. Ninety-eight European Americans (EA) patients participated in a venlafaxine XR clinical trial for GAD, with Hamilton Anxiety Scale (HAM-A) response/remission at 24 weeks as the primary outcome measure. All participants were genotyped with the Illumina PsychChip, and 266,820 common single nucleotide polymorphisms (SNPs) were analyzed. Although no SNPs reached genome-wide significance, 8 SNPs were marginally associated with treatment response/remission and HAM-A reduction at week 12 and 24 ($p < 0.00001$). Several identified genes may indicate markers crossing neuropsychiatric diagnostic categories.

Keywords

pharmacogenetics; generalized anxiety disorder; venlafaxine XR

1. Introduction

Generalized anxiety disorder (GAD), a chronic psychiatric disorder characterized by a state of excessive worry, afflicts roughly 4.1% of American adults (Grant et al., 2005). GAD is marked by significant morbidity and mortality. Recent studies found that compared to those without anxiety, individuals with GAD had a significantly higher likelihood of suicidal ideation (odds ratios (ORs) = 1.78 – 4.81) and attempted suicides (ORs = 2.70 – 5.59) (Cougle et al., 2009; Kanwar et al., 2013). GAD is most often treated with selective

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Conflict of Interest

The authors declare no conflict of interest.

serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). However, antidepressant treatment response is highly variable in individuals with GAD; while antidepressant treatments are effective for some GAD patients, up to 34% of patients fail to respond favorably (Baldwin and Nair, 2005; Gelenberg et al., 2000; Rickels et al., 1993). Pharmacogenetic studies investigating the effect of antidepressant drugs on mood disorders have primarily focused on major depressive disorder (MDD), while research on pharmacogenetic treatments for anxiety disorders is limited (Kato and Serretti, 2010; Multani et al., 2012; Tiwari et al., 2009). Because the research on pharmacogenetic treatment response in anxiety disorders is sparse, the genetic component underlying pharmacotherapy response remains unknown.

To identify genetic variants contributing to the etiology of primary anxiety disorders, a meta-analysis of genome-wide association studies (GWASs) with large, independent samples found multiple novel genetic variants to be significantly associated with anxiety disorder phenotypes (Otowa et al., 2016). GWASs could be useful for examining the pharmacogenetics of antidepressant treatment response in GAD to detect small effect sizes of associated genetic variants.

In this study, we tested the hypothesis that single nucleotide polymorphisms (SNPs) are associated with treatment response outcome in GAD. Treatment responses were quantified based on Hamilton Anxiety Scale (HAM-A) and Clinical Global Impressions-Severity (CGI) scale reductions following 24-week treatment with venlafaxine XR. Identifying genetic variants which potentially contribute to GAD could better inform pharmacological treatments based on individual genetic profiles.

2. Methods

2.1 Subjects

Participants with a diagnosis of GAD were enrolled in an 18-month relapse prevention study which included three treatment phases (Rickels et al., 2010): The first phase 24-week open-label venlafaxine XR flexible-dose treatment phase (75–225 mg day^{-1}) was used to conduct primary pharmacogenetic analyses (supplementary materials). Overall, 156 patients (European-Americans [EA] n =112; African-Americans n =41; others n= 3) were evaluated for treatment response to venlafaxine XR. However, due to ethnic differences in allele frequencies and consequent population stratification, only the EA population (n= 112) was used in the pharmacogenetic analysis. The HAM-A score was used as a primary outcome measure, and the CGI of Improvement (CGI-I) score at 24 weeks was used as a secondary outcome measure.

2.2 Genotype and Quality Controls

All participants were genotyped using the Illumina PsychChip capturing 571K SNPs. Among those SNPs, only common variants SNPs whose minor allele frequency is greater than 5% were selected due to our sample size. Common variants are defined by over 1% of a minor allele frequency with decent sample size such as 1,000 (Schork et al., 2009), but we

selected common SNPs having 5% or greater because at least 5 out of 100 samples were needed for a suitable statistical analysis due to our sample size of 96.

Quality control (QC) procedures were applied to individual samples and SNPs. Using common SNPs (n = 146,257) available in both our samples, and in samples in the 11 populations of HapMap phase 3 data (n = 1,184), we performed principal components analysis to determine non-European ancestry by Eigenstrat (Price et al., 2006). Non-European ancestry samples were removed. Samples were excluded if the missing rate exceeded 2%. Related or duplicated samples were identified through identity-by-state sharing analysis and removed. SNPs were excluded if the missing rate exceeded 5%, their minor allele frequency was < 5%, or they showed departure from the Hardy Weinberg equilibrium test (p-value < 1.0E-5). After the series of QC, 98 European samples with 266,820 common SNPs remained for further statistical analysis (supplementary materials).

2.3 Statistical Analysis

The HAM-A reduction scores from baseline to 24 weeks and from baseline to 12 weeks respectively were tested for association with each SNP using a linear regression model based on an additive model. Response and remission to venlafaxine XR at 12 and 24 weeks, including CGI-I response and remission, were tested using an allelic based chi-square test that compared allele frequency between two groups. Instead of using Fisher Exact test that is more accurate than the chi-square test when the sample size is small and a genetic variant is rare, we utilized chi-square test because our sample size of 98 and common variants provide a reasonable approximation of test statistics[reference].

3. Results

None of the SNPs were identified with genome-wide significance (1.9×10^{-7} = 0.05/266,820 by Bonferroni correction based on the number of SNPs, 266,820 SNPs) for either the main outcome measures or secondary outcome measures at the main study end point at week 24. All p-values except HAM-A reduction score were driven by an allelic comparison test without any assumption of genetic model such as a co-dominant model. Additional results are available in the supplementary materials. Table 1 illustrates the 8 SNPs associated with all treatment response/remission measures and HAM-A score at week 24 and 12 by a threshold of p-value < 0.01: rs10483832 (*MED6*), rs13216187 (*SGK1*), rs17154827, rs1993919 (*STAB2*), rs2136474 (*SPATA3*), rs7060140 (*OPHN1*), rs7342064 and rs7897283 (*PARD3*).

4. Discussion

In this study, we conducted the first GWAS analysis of antidepressant treatment response in GAD. We found that none of the SNPs tested reached a genome-wide significance threshold, either in categorical outcomes or HAM-A response/remission. We did not explore demographic and clinical characteristics, such as sex, age, and time spent in treatment, as covariates in the association analysis of our sample due to the overall negative result. The following 8 SNPs were marginally associated with treatment response/remission and HAM-A scores at both week 12 and 24 ($p < 0.00001$): rs10483832-*MED6*, rs13216187-*SGK1*,

rs17154827, rs1993919-*STAB2*, rs2136474-*SPATA3*, rs7060140-*OPHN1*, rs7342064-*PARD3*, and rs7897283-*PARD3* (Table 1). The finding that these 8 SNPs were consistently associated with treatment outcome across HAM-A measures and time points indicates encouraging trends to pursue for further study.

SGK1 is the most clinically notable of the identified genes. A growing body of literature indicates that *SGK1* may be involved in the pathophysiology of mood, anxiety, and trauma-related disorders. Chronic stress exposure in mice has been found to increase *SGK1* in corpus callosum oligodendrocytes via hypothalamus-pituitary-adrenal axis activation, inducing morphological changes which may contribute to the pathogenesis of major depressive disorder (Miyata et al., 2015). Furthermore, downregulation of *SGK1* in the hippocampus resulted in a reversal of corticosterone-induced depressive symptoms in a rodent model of depression (Li et al., 2015).

Recent studies have also shown that the effect of glucocorticoid signaling on glucocorticoid receptor function may be mediated by *SGK1* upregulation, which has been demonstrated in both rodents and humans (Anacker et al., 2011; Sato et al., 2008; Yuen et al., 2011). Traumatic stress has been shown to induce learned helplessness and anhedonic-like behaviors in rats through decreased expression of *SGK1* and synaptic significant decrease in spine density in medial prefrontal cortex (PFC) neurons (Licznerski et al., 2015). The same study found the *SGK1* gene to be down-regulated by more than 80% in postmortem PFC samples of PTSD individuals compared to healthy controls (Licznerski et al., 2015). Thus these studies support an association between glucocorticoid-induced increases in *SGK1* and the development of anxiety and mood disorders. Although a larger sample is needed to replicate the present study's findings, *SGK1* genetic variants may contribute to treatment response and GAD susceptibility.

STAB2 and *OPHN1*, two additional genes associated with antidepressant treatment outcome in GAD in the present study, have been identified as potential genetic determinants of schizophrenia. An Identify candidate Causal SNPs and Pathways (ICSNPathway) analysis on a schizophrenia GWAS data set implicated *STAB2* as a candidate gene in schizophrenia susceptibility. Though *OPHN1* has largely been associated with mental retardation (Nakano-Kobayashi et al., 2014), intellectual disability (Powell et al., 2014), and autism spectrum disorders (Piton et al., 2011; Won et al., 2013), reductions in gamma oscillatory activity observed in *OPHN1* knockout mice have also been associated with Alzheimer's disease, aging, and schizophrenia phenotypes, suggesting that reductions in *OPHN1* expression increase the likelihood of cognitive and psychiatric pathology (Powell et al., 2014). The common correlations between *STAB2* and *OPHN1* genetic variants and neuropsychiatric illnesses suggest an underlying genetic basis for the symptomatology shared by these disorders.

Because *SGK1, STAB2*, and *OPHN1* have been associated with a) treatment response in GAD in our study, and b) MDD, PTSD, and schizophrenia across studies, these results suggest that some genetic markers might cross diagnostic categories for multiple psychiatric disorders.

From the standpoints of both genetics and clinical experimental design, the current study may have been limited by several factors, including the retroactive collection of DNA, the absence of a placebo arm in the first phase of the trial, and the use of pill counts as the only measure of medication adherence. It should also be noted that the Illumina PsychChip array is designed on the basis of literature findings, and it contains at least 50,000 markers which have been previously associated with common psychiatric disorders. Hence, it is possible that our method of genotyping increased the probability of identifying genes of prior association with psychiatric disorders.

Limiting factors in the present study were small sample sizes and lack of statistical power for a genome-wide association study. At the same time our phenotypic characteristics were a response/remission to the drug which often drives relatively larger effects by genetic variants than complex disease status does. Considering our study as an exploratory study, the sample size of 98 was suitable enough to provide nominal association signals of SNPs on treatment outcomes of venlafaxine XR due to relatively large effects of SNPs selected from psychiatric disease genetic studies. In addition, instead of using a mixed effective model incorporating different time points for HAM-A score, we took into account HAM-A reduction scores from a baseline of HAM-A to investigate how genetic variants contributed to an improvement of HAM-A scores.

The Illumina Psych Chip that we used for genotyping was customized SNPs selected from results of psychiatric disease GWAS and many Exome studies, therefore SNP markers were not well-covered by common variants. Accurate imputation requires well-covered common variants with strong linkage disequilibrium (LD) across whole genomes (Halperin and Stephan, 2009)(Marchini and Howie, 2010). Due to our customized common SNPs screened by 5% of minor allele frequency with our samples size, the accuracy of imputation was not guaranteed to improve statistical power to discover associations.

In summary, we conducted the first GWAS of antidepressant treatment response in GAD. Although we found no significant genome-wide association results, it is promising that 8 SNPs were marginally associated with treatment response/remission and HAM-A at both months 3 and 6 ($p < 0.00001$). Because three genes (*SGK1, STAB2*, and *OPHN1*) included in our SNPs of interest have been previously associated with mood and anxiety disorders, our results suggest that certain genetic markers may underlie the shared phenotypic characteristics of comorbid psychiatric pathologies. Avenues for future research include the replication of results with larger samples sizes to increase statistical power and further elucidate the treatment effects of antidepressant venlafaxine XR on GAD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Results (p-values) of significant SNPs across all outcomes at both week 24 and week 12 at significance level of 1.9×10^{-5}.

CHR[a]	SNP	Physical location[b]	A1	A2	Week	RESPONSE	CGI RESPONSE	REMISSION	CGI REMISSION	HAM-A	GENE symbol	SNP function
14	rs10483832	71060837	G	A	24	0.0008	1.22E-05	0.0020	0.0086	0.0030		
					12	0.0010	0.001	0.0083	0.0010	0.003	MED6	Intronic
6	rs13216187	134627600	G	A	24	0.0001	0.0033	0.0001	2.99E-05	4.42E-05		
					12	0.0016	0.0033	0.0053	0.0012	0.0018	SGK1	Intronic
10	rs17154827	44490532	C	A	24	1.36E-05	2.80E-05	0.0017	0.0002	4.36E-05		
					12	0.0007	2.80E-05	0.0024	0.0029	4.07E-05	LINC00841[c]	Intergenic
12	rs1993919	104027817	G	A	24	0.0024	0.0038	0.0063	0.0085	0.0071		
					12	0.0082	0.0005	0.0008	0.0017	0.0022	STAB2	Intronic
2	rs2136474	231864289	C	A	24	0.0028	0.0015	0.0005	0.0007	0.0047		
					12	6.36E-05	0.0004	0.0095	0.0012	0.0065	SPATA3	Intronic
X	rs7060140	67407442	C	A	24	0.0015	0.0058	0.0008	0.0043	0.0004		
					12	0.0004	0.0004	0.0086	0.0016	6.36E-05	OPHN1	Intronic
10	rs7342064	35099799	A	G	24	6.01E-05	0.0002	0.0023	0.0003	0.0009		
					12	0.0005	0.0047	3.27E-05	0.0019	0.0003	PARD3	Intronic
10	rs7897283	35075817	C	A	24	7.40E-05	0.0002	0.0014	0.0003	0.0010		
					12	0.0006	0.0053	2.01E-05	0.0023	0.0003	PARD3	Intronic

[a] CHR stands for Chromosome

[b] the chromosome position was obtained from hg19 (GRCh37).

[c] rs17154827 is intergenic SNP between LINC00841(distance = 25177) and C10orf142(distance = 297666)