Research Article

RGS2 AND GENERALIZED ANXIETY DISORDER IN AN EPIDEMIOLOGIC SAMPLE OF HURRICANE-EXPOSED ADULTS

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Background: *Generalized anxiety disorder (GAD) is a common and sometimes disabling condition often associated with stressful life events that involve significant loss or danger. The disorder appears moderately heritable. Polymorphisms in the RGS2 (regulator of G-protein signaling 2) gene were recently associated with anxious behavior in mice and panic disorder and trait anxiety in humans. We examined whether rs4606, a single nucleotide polymorphism (SNP) in the 3′ UTR of RGS2, was associated with GAD in an epidemiologic sample of adults exposed to the 2004 Florida Hurricanes.* ***Methods:*** *The sample for the current study is 607 adults from the 2004 Florida Hurricane Study who returned buccal DNA samples via mail. Participants were selected via random digit dial procedures and interviewed via telephone about hurricane exposure, social support, and GAD symptoms. The outcome measure was DSM-IV diagnosis of GAD derived from structured interviews.* ***Results:*** *RGS2 SNP rs4606 was significantly associated with GAD in this sample. In logistic regression analyses, each C allele was associated with a 100% (P = .026) increased risk of GAD after controlling for age, sex, ancestry, hurricane exposure, and social support.* ***Conclusions:*** *These findings are consistent with a previously published study showing a higher prevalence of the C allele among panic disorder patients than controls. This study points toward a relevant polymorphism for GAD at the 3′ end of the RGS2 gene; and suggests that studying a recently disaster-exposed sample is both feasible and may improve*

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INTRODUCTION

Generalized anxiety disorder (GAD) is characterized by exaggerated and uncontrollable worry or tension about everyday events at a level more severe than warranted by the situation. Symptoms of GAD also include restlessness, being easily fatigued, having difficulty concentrating, irritability, muscle tension, and sleep disturbance (APA, 1994). GAD is common and sometimes debilitating, with a lifetime prevalence of 5.7% and a 12-month prevalence of 3.1% in the United States.[1–3] Family and twin studies support the role of genetic factors in the etiology of GAD; a meta-analysis of twin studies reported the heritability of GAD to be 31% (95% CI: 24–39%;[4]). However, little progress has been made in identifying specific genes that increase the risk of GAD.

GAD is common after natural disasters[5,6] and stressful life events, particularly those involving loss and danger, have been particularly associated with increased risk of GAD.[7] Hurricanes, having the potential to produce widespread property damage, physical injury, and death, are stressful life events involving both loss and danger, a fact that was dramatically demonstrated by the widespread devastation produced by Hurricanes Katrina and Rita in the Gulf Coast regions of the United States in 2005. Prior genetic association studies of GAD have not included stress-exposed samples. Moffitt et al. recently suggested the exposed-cohort design as an efficient way of testing genotype-environment interaction: "If a good candidate gene is available, such an exposed sample could be used to test the hypothesis that genotype-risk individuals develop psychopathology but genotype-controls do not."[8].

We hypothesized that rs4606, a polymorphism in the 3′ untranslated region of the *RGS2* (regulator of G-protein signaling 2) gene, would be associated with GAD in an epidemiologic sample of older adults who were exposed to one or more hurricanes during the 2004 Florida Hurricane season.[9–12] Regulators of G-protein signaling bind to Gα subunits and increase their GTPase activity, which then attenuates the downstream signaling.[13] *RGS2*, a potent regulator that reduces G-protein activity, selectively inhibits Gqα,[14] therefore increasing the GTPase activity. G-protein coupled receptors comprise one of the largest groups of signaling proteins; nearly 2% of our genes code for these receptors.

The *RGS2* gene has been associated with anxiety in animal models and in human correlational studies. *RGS2* knockout mice, both hetero- and homozygous, have increased hypertension,[15] excitability in CA1 neurons in the hippocampus,[16] and anxiety-related traits.[17] A targeted genome screen found modest evidence for linkage between markers in a region including *RGS2* and anxiety disorder proneness.[18] Recently, Leygraf and others[19] found that polymorphisms in *RGS2* were associated with panic disorder in humans with the strongest association being observed for a haplotype containing single nucleotide polymorphisms (snps) rs4606 and rs3767488. Specifically, for rs4606, the authors found a higher prevalence of the C allele among panic disorder patients than controls.[19] A significant association has also been found between rs4606 and anxiety-related temperament, personality, and brain function, however, the G allele was found to be the risk allele.[20] Similarly, the distribution of rs4606 genotypes was found to be significantly different in suicide victims versus controls; the G allele was more prevalent in suicide victims.[21] Rs4606 is of particular interest because it is functional. Variation in rs4606 is associated with variation in peripheral blood mononuclear cell and cultured fibroblast *RGS2* mRNA expression.[22]

MATERIALS AND METHODS

DATA COLLECTION AND SAMPLE

This article focuses on 607 participants in the 2004 Florida Hurricane Study who completed structured telephone interviews and provided saliva samples through the mail that yielded genotype data for the rs4606 polymorphism.

Verbal consent was obtained from the participants; the participants were sent a letter documenting the elements of verbal consent and providing them with contact information for the principal investigator. Participants who completed the diagnostic interview and returned saliva samples were paid $20. The institutional review boards at the relevant institutions approved all procedures.

ASSESSMENT PROCEDURE

Telephone interviews were conducted with a probability sample of English- and Spanish-speaking adults from telephone households in 38 counties in Florida within 6–9 months of the 2004 Florida hurricane season, between April 5 and June 12, 2005. Older adults (ages 60 and older) were oversampled to address research questions specific to this age group. Sample selection and telephone interviewing were performed by Schulman, Ronca, Bucuvalas, Inc., a national survey research firm with considerable experience conducting diagnostic interviews by telephone.[23] Random-digit-dial procedures were used to locate households within the sampling frame. Respondents were randomly selected by using the most recent birthday method when multiple eligible adults were present within a household. Assessments were conducted via highly structured interview using computer-assisted telephone interview (CATI) format. The CATI format uses a computer program that projects instructions and questions on a computer screen that are read verbatim by

interviewers to participants over the telephone. Interviewers then recorded participants' responses on a computer with closed-ended response options. Supervisors randomly monitored interviews in progress, thereby providing considerable quality control over data collection. Interviews averaged 26.5 min in length.

More details about the sampling procedure and methodology for the Florida Hurricane Study are provided elsewhere.[9–12]

Presence of GAD since the hurricanes was measured using a slightly modified version of the Structured Clinical Interview for DSM (SCID-IV)[24] structured interview questions that correspond directly to DSM-IV criteria using yes/no response options. The diagnosis required excessive and poorly controlled anxiety and worry occurring more days than not for a period of 6–9 months ("since the hurricanes"), as well as three of six hallmark GAD symptoms (restlessness, fatigue, concentration problems, irritability, tension, and sleep disturbance). This scale showed good internal consistency in the current sample among individuals screening into the module (Cronbach's $\alpha = .85$).

PTSD since the hurricanes was assessed with the National Women's Study PTSD module, a widely used measure in population-based epidemiological research originally modified from the Diagnostic Interview Schedule. Research on the National Women's Study PTSD module has provided support for concurrent validity and several forms of reliability (e.g., temporal stability, internal consistency, diagnostic reliability[25]). The National Women's Study PTSD module was validated in the DSM-IV PTSD field trial against the SCID, in which the interrater κ coefficient was .85 for the diagnosis of PTSD and comparisons between scores on the National Women's Study PTSD module and the SCID yielded a κ coefficient of .71 for current and .77 for lifetime PTSD.[26] Research also has found high correspondence between telephone versus in-person administration of the PTSD module as well as the depression module described below.[27] We operationalized PTSD diagnosis based on DSM-IV symptom requirements, including functional impairment.

Major depression since the hurricanes was assessed with modified questions from the SCID-IV. Following DSM-IV criteria, the respondents met criteria for major depression if they had five or more depressive symptoms for at least 2 weeks, including endorsement of one or both of the symptoms relating to depressed mood or loss of interest or pleasure. Past-year major depression identified by this measure is associated with lower reported work quality and mental health treatment-seeking after the addition of control for demographic characteristics, assault history, and PTSD diagnoses.[28]

Hurricane exposure and social support were found to be associated with GAD in this sample[9] and are included as covariates in logistic regression models. *Hurricane exposure* was assessed with five important indicators identified in previous research on Hurricanes Hugo and Andrew[29] on the basis of their relation to posthurricane mental health functioning: (1) present during hurricane-force winds or major flooding; (2) lack of adequate access to food, water, electricity, telephone, or clothing for a week or longer; (3) two or more hurricane-related losses of furniture, sentimental possessions, automobile, pets, crops, trees, or garden; (4) displacement from home for 1 week or longer; and (5) out-of-pocket losses of $1,000 or more that were not reimbursed by insurance or other sources. Hurricane exposure was defined as having experienced none, one, two, three, or four or more of these five indicators. High hurricane exposure was defined as having experienced two or more of these five indicators.

Social support during the 6 months before the hurricanes was assessed with a modified five-item version of the Medical Outcomes Study module[30] that assesses emotional, instrumental, and appraisal social support (sample range = 0–20; mean = 15.9, $SD = 4.8$). Low social support was operationalized as a score of 15 or less based on the cutoff score derived from prior work.[23] This scale had good reliability (Chronbach's $\alpha = .86$).

COLLECTION OF DNA SAMPLES

Saliva samples were obtained via a mouthwash protocol and returned via mail to the Yale University laboratory where DNA extraction and analyses was conducted. Saliva samples were provided by 651 participants (42.2% response rate). Of these, valid genetic ancestry data were available for 623 cases (95.7%), and valid genotype data were available for 607 cases (93.2%). The likelihood of submitting a saliva sample did not differ in relation to sex, level of hurricane exposure, level of social support, or GAD status. Additional details on response rate and correlates of participation are summarized elsewhere.[11]

GENOTYPING

DNA was extracted from saliva using PUREGENE (Gentra Systems, Minneapolis) kits. SNPs were genotyped with a fluorogenic 5' nuclease assay method ("TaqMan") using the ABI PRISM 7900 Sequence Detection System (ABI, Foster City, CA). All genotypes were assayed in duplicate; discordant genotypes were discarded.

In addition, 36 markers were genotyped to provide ancestry information.[31–33] We added one additional highly informative SNP marker, *SLC24A5*[34] to the panel described previously.

ANCESTRY PROPORTION SCORES

Participants' ancestries were estimated by Bayesian cluster analysis with the marker panel described above on the procedures and STRUCTURE software developed by Pritchard and colleagues.[35, 36] For the STRUCTURE analysis, we specified the "admixture" and "allele frequencies correlated" models and used 100,000 burn-in and 100,000 Markov chain Monte Carlo iterations. Ancestry proportion scores were computed and included in analytic models to avoid spurious associations that can result from population stratification.

STATISTICAL ANALYSES

We used χ^2 analyses to test whether demographic factors, low social support, hurricane exposure, the rs4606 polymorphism in *RGS2*, and posthurricane major depression and posttraumatic stress disorder were associated with posthurricane GAD. We then conducted logistic regression analyses to determine whether any observed association between rs4606 and GAD persisted after adjusting for sex, age, ancestral proportion scores, social support, and hurricane exposure. To determine whether the association between *RGS2* and GAD was modified by the level of stress exposure, we reran the logistic regression analyses including an interaction term for rs4606 × hurricane exposure. Because we had limited power to detect interaction effects, we also ran the logistic regression analyses stratified by hurricane exposure so we could observe whether the odds ratios for the association between rs4606 and GAD were comparable across high and low levels of hurricane exposure.

RESULTS

PREVALENCE OF GAD AND RGS2 GENOTYPE

Table 1 presents the demographic, trauma exposure, and clinical correlates of GAD. The prevalence of GAD since the hurricane was 6.8% ($n = 41$). RGS2 SNP rs4606 genotype frequencies were in Harvey-Weinberg equilibrium. Genotype frequencies were similar to those reported by Leygraf et al.[19] Female sex, age, and self-reported race were not

TABLE 1. Sample descriptives and unadjusted association between risk factors and current GAD diagnosis

Variable	Overall ($n = 607$) % (N)	Current GAD ($n = 41$) % (N)	No GAD ($n = 566$) % (N)	χ^2 ($df = 1$)	P-value
Female sex	64.9	82.9	63.6	6.27	.12
	(394)	(34)	(360)		
Age less than 60 years	22.6	28.6	22.3	0.46	.50
	(137)	(11)	(126)		
Race/ethnicity					
White	90.6	82.9	91.1		
	(547)	(34)	(513)		
Other[a]	9.4	17.1	8.9	3.00	.08
	(57)	(7)	(50)		
Low social support	37.0	51.2	36.0	3.80	.05
	(224)	(21)	(203)		
Hurricane exposure				10.39[b]	.001
0	9.7	4.9	10.1		
	(59)	(2)	(57)		
1	45.6	36.6	46.3		
	(277)	(15)	(262)		
2	23.7	17.1	24.2		
	(144)	(7)	(137)		
3	13.8	22.0	13.3		
	(84)	(9)	(75)		
4	7.1	19.5	6.2		
	(43)	(8)	(35)		
RGS2 rs4606				4.42[b]	.04
G/G	7.7	2.4	8.1		
	(47)	(1)	(46)		
G/C	36.4	26.8	37.1		
	(221)	11)	(210)		
C/C	55.8	70.7	54.8		
	(339)	(29)	(310)		
Major depression	5.9	31.7	4.1	52.37	<.001
	(36)	(13)	(23)		
Posttraumatic stress disorder	3.1	19.5	1.9	38.92	<.001
	(19)	(8)	(11)		

GAD, generalized anxiety disorder; *RGS2*, regulator of g-protein signaling.
[a]Other includes African-American, Hispanic, and Asian.
[b]χ^2 linear-by linear association test.

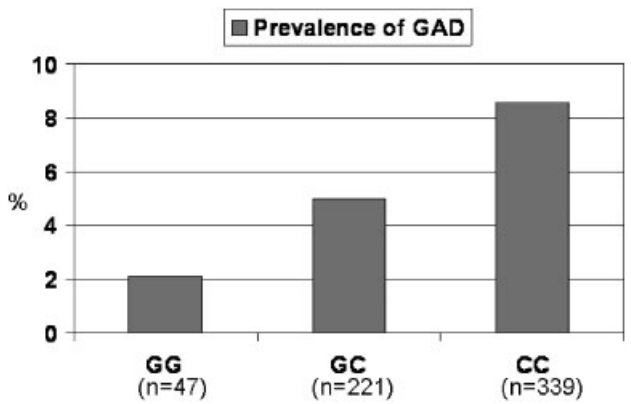

Figure 1. Prevalence of generalized anxiety disorder by rs4606 genotype

significantly associated with GAD in unadjusted analyses. Both low social support and level of hurricane exposure significantly predicted GAD. Moreover, the χ^2 linear-by-linear association test supported a significant association between rs4606 and GAD. As self-reported race was not significantly associated with GAD or with genotype frequencies ($\chi^2[2, n = 587] = 3.53$, $P = .47$), it is not likely that population stratification is a cause of false-positive findings.

ASSOCIATION BETWEEN GAD AND RGS2 GENOTYPE

Figure 1 shows the dose–response association between rs4606 and GAD. Table 2 shows the results of the logistic regression analyses. Both female sex and hurricane exposure were significantly associated with GAD. For rs4606, each "C" allele at rs4606 was associated with a 100% increased risk of being diagnosed with posthurricane GAD. Comparable results were found when we restricted the sample to Whites only (OR = 1.91, 95% CI: 1.00, 3.76). The effect of RGS2 genotype on risk of GAD was similar for those with low (OR = 2.61, 95% CI: 0.88,

TABLE 2. Final logistic regression analysis of the association between RGS2 genotype and generalized anxiety disorder (GAD)

Variable	GAD diagnosis		
	Adjusted odds ratio	95% CI	*P*
Female sex	2.6	1.1–6.1	0.025
Age less than 60 years	1.1	0.5–2.3	0.878
Ancestral proportion score	0.5	0.06–3.6	0.452
Hurricane exposure	1.8	1.2–2.2	0.001
Low social support	1.9	1.0–3.6	0.065
RGS2 rs4606 (C is risk allele)	2.0	1.1–3.8	0.026

7.78) and high (OR = 1.87, 95% CI: 0.84, 4.12) hurricane exposure. Moreover, the interactions term for rs4606 × hurricane exposure was not significant (interaction OR = 0.60, 95% CI: 0.32, 1.12).

DISCUSSION

Our results support a significant association between SNP rs4606 in the RGS2 gene and GAD in this epidemiologic sample of older adults exposed to the 2004 Florida Hurricane Season. These findings are consistent with those of Leygraf et al.[19] who found a significant association between the same SNP and panic disorder in a clinical sample. In contrast, Smoller et al.[20] also found an association between rs4606 and anxiety-related traits but the G allele was the risk allele. Taken together, these findings point toward a relevant polymorphism for anxiety-related disorders at the 3′ end of the RGS2 gene. However, the inconsistency with regard to the risk allele among studies raises questions as to whether rs4606 is the causal variant in RGS2 as related to anxiety it is possible rs4606 is in linkage disequilibrium with some different functional variant, and the direction of LD differs by population. Alternatively, multiple testing, population stratification, or some other form of confounding may account for the association between rs4606 and outcomes in some studies.

The biological mechanism via which variation in RGS2 increases the risk of GAD remains to be elucidated. It is noteworthy that suicide victims showed elevated RGS2 immunoreactivity in postmortem brain tissue from their amygdala and prefrontal cortex.[21] The neural circuitry connecting the amygdala and prefrontal cortex is thought to regulate emotional behavior, particularly responses to fear and anxietyinducing stimuli.[37] RGS2 is expressed in these brain regions.[38, 39] A recent study demonstrated pathological activation of the amygdala-prefrontal fear circuit among adolescents with GAD.[40] Thus, the possibility that RGS2 is associated with GAD via fear-circuit dysregulation should be explored in future studies.

We identified five potential limitations of the data presented in this article. First, individuals who relocated outside of the 38 hurricane-affected counties or lacked telephone service 6–9 months after the hurricanes were excluded from the study. However, telephone service was restored to the vast majority of Florida households several months before the study, and these hurricanes did not result in the type of massive evacuation outside the affected area that occurred following Hurricane Katrina. Second, the return rate of saliva samples was 42%, which is lower than optimal, but nonparticipation was not significantly related to major study variables of hurricane exposure, social support, and GAD. Third, we used a slightly modified version of the SCID-IV administered by lay interviewers over the telephone rather than from in-person clinical interviews. However, there is substantial evidence supporting the reliability and validity of the SCID-IV[41–44] and the validity of this measure as a lay screener for GAD.[45, 46] Moreover, the reliability of this measure in the current study was high (.85). Furthermore, prior research comparing telephone and in-person assessment with similar measures found no significant difference between the two methods.[27] Fourth, the study was cross-sectional, and therefore, we are unable to determine with certainty whether posthurricane GAD represents new onsets of the disorder or recurrence among individuals who might have had prior episodes. From an epidemiologic perspective, predisaster psychopathology could be a confounder in studies concerned with relations between risk factors and postdisaster outcomes. However, in the context of a genetic association analysis, we suggest that it is unlikely that predisaster psychopathology could substantially influence the results documented here. Finally, we also note that the number of affected individuals was relatively small, in the context of a reasonably large sample. Thus, we had very limited power to test for interaction effects.

CONCLUSIONS

This is the first genetic association study of GAD of which we are aware to examine gene–disorder relations within a sample that was recently exposed to a significant stressor. It is worth noting that the 6-month prevalence of GAD in this sample is 6.8%, which is more than twice the 12-month prevalence in the general population (3.1%) and almost twice the lifetime prevalence (3.6%) among adults over aged 60.[1, 2] The nature of the population makes this finding less vulnerable to ascertainment or recall biases than for a clinical sample or one using lifetime diagnoses. Additional research is needed to replicate our methodology and findings, but our results suggest that studying a recently disaster-exposed sample is both feasible and may improve power to find gene–disorder

associations. Moreover, our findings in conjunction with data from mouse models and an emerging literature on RGS2 and anxiety in humans suggest that pharmacological agents targeting RGS2 may provide novel treatments for anxiety disorders.

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