Serotonin-System Polymorphisms (5-HTTLPR and –1438G/A) and Responses of Patients With Bulimic Syndromes to Multimodal Treatments

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Background: We tested the hypothesis that individuals carrying low-function alleles of the serotonin transporter (5-HTTLPR) and 5-HT_{2A} receptor gene (–1438G/A) promoter polymorphisms would show relatively poor treatment responses on indices of bulimic and concurrent symptoms.

Method: Participants included 111 women with bulimia-spectrum eating disorders (DSM-IV-TR criteria), 98 of whom were followed through 4- to 8-month spans of specialized multimodal treatment to enable examination of relationships between genotypes and prospective changes in eating and general psychiatric symptoms. Given a hierarchically structured dataset and a desire to control for effects of variations in adjunctive pharmacotherapy, individual therapy, group therapy, or day treatment, we used multilevel modeling techniques. The study was conducted between October 2001 and May 2007.

Results: After effects of treatments were removed, 5-HTTLPR low-function allele carriers showed smaller treatment reductions in binge eating ($p < .01$) and in anxiety and depression ($p < .05$), whereas low-function –1438G/A G carriers showed smaller reductions in binge eating ($p < .01$) and impulsivity ($p < .05$).

Conclusions: This study documents an expected association between poorer bulimia-treatment response and low-function alleles of 5-HTTLPR and –1438G/A—and suggests that such effects cannot be attributed to mediating influences of medication or psychotherapy responsiveness alone. A better understanding of hereditary, serotonin-mediated factors affecting bulimic individuals' progress during therapy may facilitate the development of more effective treatments.

(J Clin Psychiatry 2008;69:1565–1571)

Received Dec. 20, 2007; accepted Feb. 22, 2008. From the Eating Disorders Program (Drs. Steiger, Bruce, and Israel and Mss. Richardson, Anestin, and Groleau) and Research Center (Drs. Steiger, Joober, Bruce, and Israel and Mss. Richardson, Anestin, and Groleau), Douglas Mental Health University Institute; the Psychiatry Department (Drs. Steiger, Joober, Bruce, and Israel) and Psychology Department (Drs. Steiger and Bruce and Ms. Richardson), McGill University; and the Department of Social and Preventive Medicine, University of Montreal (Dr. Gauvin), Montreal, Quebec, Canada.

This research was supported in part by grant no. SR-4306 awarded to Drs. Steiger and Joober and colleagues by the Quebec government's Joint Conseil qué bécois de la Recherche Social–Fonds de la Recherche en Santé du Québec (CQRS-FRSQ) Program in Mental Health and in part by grants no. MOP-79490 and MOP-57929 awarded to Dr. Steiger and colleagues by the Canadian Institutes for Health Research.

Preliminary results from this study were presented at the annual meeting of the Eating Disorders Research Society, Oct 27, 2007, Pittsburgh, Pa.

Dr. Joober has received honoraria for consultations from Janssen-Ortho and Pfizer Canada. Drs. Steiger, Gauvin, Bruce, and Israel and Mss. Richardson, Anestin, and Groleau report no additional financial or other relationships relevant to the subject of this article.

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Findings in subjects with bulimic syndromes reveal heterogeneous response patterns, but consistently associate "borderline" or "impulsive" traits with less favorable outcome.[1,2] Suggesting a biological substrate, in bulimic and nonbulimic populations alike, borderline or impulsive manifestations have been linked to pronounced dysregulation of the serotonin (5-hydroxytryptamine: 5-HT) system.[3] Correspondingly, molecular-genetic studies in bulimic patients associate low-function alleles of serotonin-linked polymorphisms (5-HTTLPR or –1438G/A) with impulsivity and borderline personality disorder.[4–6] One study, based on a very small sample, has linked the 5-HTTLPR S allele with unfavorable response of bulimic symptoms to pharmacotherapy.[7] Another study, involving an atypical "low comorbidity" inpatient sample, has not.[8] Moderating effects of 5-HTTLPR upon response to pharmacotherapy have, however, been demonstrated in such non–eating disordered populations as individuals undergoing treatment for major depressive disorder.[9]

We tracked responses of bulimic women through 4-month to 8-month spans of specialized, multimodal

treatment (involving individual and group psychotherapy and, optionally, pharmacotherapy). We expected low-function 5-HTTLPR or –1438G/A allele carriers to show poorer treatment response. Outcome indices were selected to tap bulimia-specific symptoms and common, concurrent psychiatric problems. Naturally occurring treatment variations (e.g., presence of adjunctive group or pharmacotherapy) afforded us the chance of conducting a preliminary exploration into the extent to which genetic factors moderated responses to either psychological or pharmacologic interventions (e.g., influenced selective serotonin reuptake inhibitor [SSRI] responsiveness). However, we assumed that genetic effects shape the expression of general psychopathologic tendencies (e.g., instability of mood or behavior), and therefore expected prognostic effects to be generalized, rather than being mediated solely by such factors as lesser medication responsiveness in low-function allele carriers.

METHOD

Participants

This institutional ethics board–approved study, conducted between October 2001 and May 2007, recruited 111 consecutive, consenting women with bulimia-spectrum disorders through a specialized eating disorders program. Participants had a body mass index (BMI) of 17.5 to 35 kg/m^2, and DSM-IV-TR[10] bulimia nervosa or an eating disorder not otherwise specified (EDNOS) characterized by bingeing and/or purging. Individuals with anorexia nervosa or binge eating disorder, or who were pregnant, were excluded. We felt our sample to be typical of women seeking treatment for a bulimia-spectrum disorder and note previous findings showing that bulimia nervosa and EDNOS bulimic variants are equivalent on many clinical dimensions.[11]

The sample described was organized into 2 subgroups: The first consisted of 98 completers of at least a first (and usually a second) 4-month span of treatment. Of these individuals, 90 provided assessment data after 4 months of treatment, and 62 after 8 months. The 98 treated cases had a mean (SD) age of 26.81 (7.15) years and a mean BMI of 22.38 (3.90) kg/m^2 and included the following diagnostic classes: 72 (73.5%) meeting DSM-IV criteria for bulimia nervosa–purging subtype, 3 (3.1%) for bulimia nervosa–nonpurging subtype, and 23 (23.5%) for a bulimia-spectrum EDNOS. Of the EDNOS group, 16 (16.3%) showed binge-purge syndromes, but binged or purged at less than the requisite twice weekly, and 7 (7.1%) purged but had subjective binges. Mean (SD) number of weekly binge episodes (averaged over the preceding 4 weeks) was 4.87 (4.79). Mean number of days per week of vomiting or purging (also averaged over 4 weeks) was 3.35 (2.63) and 4.46 (3.20), respectively. Ethnic origins were 92 (93.8%) West European white, 2 (2.0%) East European white, 1 (1.0%) Middle East white, 2 (2.0%) Latin American white, and 1 (1.0%) mixed West European white/Asian.

A remaining 13 women met inclusion criteria and were recruited into the study but did not pursue the treatments offered. These individuals formed a dropout comparison group, with a mean (SD) age of 24.92 (5.82) years and a mean BMI of 23.33 (5.17) kg/m^2. The group included 8 women (61.5%) with bulimia nervosa–purging subtype, 1 (7.7%) with bulimia nervosa–nonpurging subtype, and 4 (30.8%) with a bulimia-spectrum EDNOS (because they binged or purged at less than the requisite twice weekly). In the dropout group, the mean for weekly binge episodes was 8.94 (13.78), and the mean weekly vomit or purge days were 2.88 (3.11) and 4.81 (4.20), respectively. Ethnic origins were 11 (84.6%) West European white, 1 (7.7%) East European white, and 1 (7.7%) mixed East and West European white.

Measures

Eating disorder diagnoses and symptoms were assessed using the Eating Disorders Examination (EDE[12]) interview and/or the Eating Disorders Examination Questionnaire (EDE-Q).[13] The EDE is a "gold standard" interview for assessing anorexic and bulimic symptoms, with solid discriminant validity and internal consistency (with Cronbach α's ranging from 0.67 to 0.90).[12] Derived from the EDE, the EDE-Q uses 38 self-report questions to assess presence and severity of criterion eating disorder symptoms. The EDE-Q indices reportedly correspond well with those obtained using the EDE.[14] On the basis of practical considerations, some of our participants completed the EDE-Q, some the EDE, and some both assessments. When available, we gave precedence to the EDE. Numbers of cases in whom eating disorder diagnoses and symptom severities were assessed using the EDE or EDE-Q were as follows: pretreatment, 79 versus 19 (total of 98); 4-month treatment, 48 versus 42 (total of 90); 8-month treatment, 29 versus 29 (total of 58). Spearman rank-order correlations between EDE and EDE-Q estimates for pretreatment (N = 82), 4-month (N = 48), and 8-month (N = 24) measures of bingeing, vomiting, and purging were as follows: $r_{baseline} = 0.66$ ($p < .01$), $r_{4\text{-month}} = 0.73$ ($p < .01$), and $r_{8\text{-month}} = 0.43$ ($p < .05$) for bingeing; $r_{baseline} = 0.83$ ($p < .01$), $r_{4\text{-month}} = 0.80$ ($p < .01$), and $r_{8\text{-month}} = 0.81$ ($p < .01$) for vomiting; $r_{baseline} = 0.64$ ($p < .01$), $r_{4\text{-month}} = 0.83$ ($p < .01$), and $r_{8\text{-month}} = 0.75$ ($p < .01$) for purging.

We used 3 additional questionnaires to study comorbid symptoms: (1) The Center for Epidemiologic Studies Depression Scale (CES-D),[15] a 20-item questionnaire with α of .90, was used for the measurement of depressive mood and symptoms. (2) The Behavior and Symptom Identification Scale (BASIS-32)[16] was used to provide an overall assessment of psychiatric symptoms and functional

abilities. Internal consistency of the full BASIS-32 is reportedly .89; test-retest reliabilities reportedly range from .65 to .81 across subscales.[16] We analyzed BASIS-32 subscales measuring anxiety/depression, daily living, impulsivity, and self/other relations, excluding a fifth subscale (psychosis) given lack of relevance to our population. (3) The Barratt Impulsivity Scale-version 11 (BIS-11),[17] which evinces good internal consistency and discriminant validity, was used for the measurement of (a) motoric impulsivity (or proneness to reckless actions), (b) cognitive/attention impulsivity (or inability to maintain focused attention), and (c) non-planning impulsivity (or lack of concern for the future).

We used DNA (from whole blood) to assay –1438G/A and 5-HTTLPR. Given evidence that 5-HTTLPR may be either "biallelic" (i.e., having low-function short, S, and high-function long, L, alleles) or "triallelic" (i.e., having a low-function short, S allele; a high-function long allele variant, L_A, with an adenine to guanine substitution; and a less common, low-function long allele, L_G, without this substitution),[18] this polymorphism was modeled both ways. Genotyping procedures are detailed elsewhere.[4,5]

Treatment

Treatments were administered through a large-scale, specialized eating disorders program for adults. Psychotherapeutic aspects of treatment were guided mainly by cognitive-behavioral principles with demonstrated efficacy in the treatment of bulimic symptoms and concurrent areas of disturbance, in individuals with threshold and subthreshold (EDNOS) bulimic variants.[19] All participants received individual therapy (mean ± SD = 14.93 ± 6.31 sessions, range = 6 to 34 sessions); 86 (87.8%) participated in weekly 1½ hour groups (mean ± SD = 14.00 ± 7.49 sessions, range = 1 to 32 sessions); 29 (29.6%) participated in 6- to 10-hour day treatments, 4 days per week (mean ± SD = 28.45 ± 18.25 sessions, range = 1 to 69 sessions); and 62 (63.3%) received adjunctive medication at some point during their treatment.

Of those receiving adjunctive medication, 30 (30.6%) received an SSRI (citalopram, fluoxetine, sertraline, or paroxetine); 6 (6.1%) received a serotonin-norepinephrine reuptake inhibitor (SNRI: venlafaxine); 23 (23.5%) received an SSRI or SNRI, but in combination with an adjunctive mood stabilizer, anxiolytic, serotonin antagonist/reuptake inhibitor, noradrenergic and specific serotonergic reuptake inhibitor, or atypical antipsychotic; 1 (1.0%) received a monoamine oxidase inhibitor plus mood stabilizer and atypical antipsychotic; and 1 (1.0%) received a tricyclic antidepressant plus anxiolytic. A final case shifted from an SSRI to an anxiolytic between the 4-month and 8-month assessments. The decision to initiate (or maintain) medications was made by the team's attending psychiatrist (a 10-year specialist in eating disorder treatment) in conjunction with each patient and (usually) her primary therapist/case manager. Decision making involved a systematic assessment of eating and psychiatric symptoms. In our protocol, patients are not generally medicated at the outset of treatment, unless there is significant psychiatric comorbidity or a well-indicated, preexisting prescription (pertinence of which is assessed at the initial psychiatric examination). The later introduction of pharmacotherapy is generally determined by the failure of the first treatment module to produce acceptable improvements in symptoms or by an emergent need to treat incipient ones. All treatment decisions respected patient preferences and informed consent principles. Statistical procedures (described below) were used to control effects owing to medication.

Treatments were offered in 16-week segments, with patients invited (when indicated) to continue for a second 16 weeks. The second block of therapy was approved following a judgment that extended therapy was warranted—based on review of improvement, ongoing eating disorder symptoms, and/or evidence of proneness to relapse, involving the primary therapist, the patient, and the multidisciplinary team. Such decisions balanced the desire to limit the duration and intensity of treatments offered against the goal of optimizing treatment efficacy. In our program, ongoing empirical outcome assessments (conducted over many years) have confirmed that the approach yields gains consistent with those expected of effective treatments for bulimia nervosa. At 4 months, we obtained data from 90 of the 98 patients. At 8 months, 62 were assessed (51 having completed 8-month treatments, and 11 having finished planned treatments at 4 months, but returning for an 8-month follow-up). Among 36 remaining cases, 11 completed treatment but missed the 8-month assessment; 10 dropped out after 4 months and submitted no further data; and 15 were still treated but had not yet reached the 8-month mark. Dropping out of therapy was defined as failure to complete a contracted 4-month segment of treatment.

Statistical Analysis

Our principal analysis sought to examine genetic influences upon progress of treatment outcomes while controlling for extent of psychotherapy and medication received. Since unequal numbers of repeated measures were obtained across participants, we used multilevel modeling analyses. Multilevel modeling, a generalization of the general linear model used in multiple regression, handles missing data without listwise deletion and allows for the specification of random and fixed effects.[20] We conceptualized repeated reports of eating or psychological symptoms (level-1 variables) as being nested within participants (level-2), and modeled effects for each dependent measure (i.e., binge episodes/week, vomiting days/week, CES-D, BASIS-32 anxiety/depression subscale, etc.) across time in incremental

steps. Time was modeled by creating 2 dummy variables (level 1)—one that represented reports measured after the first 4 months of treatment and another that represented reports at 8 months.

Effects of genotype were assessed by adding to both the intercept and the time dummy variables a level-2 variable that differentiated people with and without a target genotype. Emphasis on the distinction between low-function and high-function alleles in past research of this type, and results of our own preliminary analyses (not reported here), led us to structure analyses for genetic effects to compare individuals who did or did not carry at least 1 low-function allele of the respective polymorphism of interest. Thus, for the biallelic 5-HTTLPR, we contrasted SS or SL genotypes to LL genotypes. For the triallelic 5-HTTLPR, we set up a contrast that compared individuals who were homozygous for low-function alleles (i.e., SS, SL_G, or L_GL_G—designated S′S′) or heterozygous for a low-function allele (i.e., SL_A or L_GL_A—designated S′L) versus individuals who had only high-function alleles (i.e., L_AL_A—designated LL). For –1348G/A, we contrasted GG or GL genotypes to the AA genotypes.

Next, we ran models that controlled potential confounding effects of psychoactive medications and psychotherapy. Possible effects of medications were controlled using a level-1 variable that registered medication use as a dichotomous (present/absent) time-varying factor in the interval leading up to each assessment interval. (Given sample size, and the variations found in medication regimens, we felt it unrealistic to attempt to control for effects owing to individual medication families, types, or dosages.) Since it was more feasible to control for variations owing to different types and intensities of psychosocial treatments, we introduced control variables upon psychological aspects of treatment, as follows: Intensities of individual, group, and day treatment therapies were first quantified by number of sessions. Distributions of these variables showed departures from normality, so we transformed data into categorical indicators, creating 5 level-1 (time varying) dummy variables: (1) a dummy variable contrasting people attending day treatments (6-hour day program or 10-hour day hospital groups) to those who did not, (2) 2 dummy variables contrasting people in the highest or middle tertile of "number of individual therapy sessions" to those in the lowest tertile, and (3) 2 dummy variables contrasting people in the highest or middle tertile of "number of group therapy sessions" to those in the lowest tertile.

Analyses on bingeing and vomiting called for Poisson outcomes; other multilevel modeling analyses were for continuous outcomes. Analyses were performed using HLM 6.04 software (Scientific Software International, Chicago, Ill., available at www.ssicentral.com) and the model:

Level-1 Model

$Y_{ij} = \beta_{0j} + \beta_{1j}$ (4 months) + β_{2j} (8 months) + β_{3j} (presence medication) + β_{4j} (day treatment) + β_{5j} (highest tertile individual sessions) + β_{6j} (middle tertile individual sessions) + β_{7j} (highest tertile group sessions) + β_{8j} (middle tertile group sessions) + e_{ij}

Level-2 Model

$\beta_{0j} = \gamma_{00} + \gamma_{01}$ (low function allele of 5-HTTLPR or –1438G/A) + υ_{0j}

$\beta_{1j} = \gamma_{10} + \gamma_{11}$ (low function allele of 5-HTTLPR or –1438G/A)

$\beta_{2j} = \gamma_{20} + \gamma_{21}$ (low function allele of 5-HTTLPR or –1438G/A)

$\beta_{3j} = \gamma_{30}$

$\beta_{4j} = \gamma_{40}$

$\beta_{5j} = \gamma_{50}$

$\beta_{6j} = \gamma_{60}$

$\beta_{7j} = \gamma_{70}$

$\beta_{8j} = \gamma_{80}$.

Thus, significant coefficients for the parameters γ_{11} and γ_{21} reflected genotype effects at 4 or 8 months, respectively.

A secondary set of analyses compared the group of "completers" to "dropouts" on the variables of mean age, BMI, binge-purge frequency, scores on psychopathologic indices, and, most importantly, frequencies of 5-HTTLPR and –1438G/A genotypes. We conducted a third set of analyses to determine whether genotypes were associated with differential rates of dropping out of treatment (among treated patients) during the second segment of treatment.

RESULTS

In our sample of treated patients, distributions of genotypes (and corresponding results of Hardy-Weinberg tests) were as follows: ***5-HTTLPR biallelic***: SS, N = 20 (20.4%), SL, N = 44 (44.9%), LL, N = 34 (34.7%); χ^2 = 0.68, df = 2, p = .41; ***5-HTTLPR triallelic***: S′S′ (designating 2 low-function alleles—i.e., SS, SL_G, or L_GL_G), N = 27 (27.5%), S′L (designating 1 low-function allele—SL_A, SL_G, or L_AL_G), N = 44 (44.9%), or LL (designating 2 high-function alleles—L_AL_A), N = 27 (27.5%); χ^2 = 1.02, df = 2, p = .31; and ***–1438G/A***: GG, N = 19 (19.4%), GA, N = 55 (56.1%), AA, N = 24 (24.5%); χ^2 = 1.54, df = 2, p = .21. No deviations from expected population rates were obtained.

Table 1 shows coefficients (SEs) and estimated means for variables that yielded statistically significant gene effects (obtained first without controls and then with controls for treatment effects). On weekly bingeing, whether or not controls for treatment were applied, significant

Table 1. Results of Multilevel Modeling Analyses Examining the Effects of 5-HTTLPR (biallelic and triallelic) and –1438G/A on Response to Treatment[a]

Outcome Variable	Baseline γ_{00}	4 months γ_{10}	8 months γ_{20}	Baseline γ_{01}	4 months γ_{11}	8 months γ_{21}
Weekly bingeing (N = 98)						
	No S-Allele (biallelic)			S-Allele (biallelic)		
Unadjusted coefficient (SE)	1.31 (0.19)	–0.77 (0.14)	–1.41 (0.25)	–0.11 (0.23)	0.04 (0.17)	**0.74 (0.27)*****
Unadjusted estimated mean	3.71	1.72	0.90	3.32	1.60	1.70
Adjusted coefficient (SE)[b]	1.41 (0.22)	–0.53 (0.19)	–1.44 (0.26)	–0.14 (0.24)	–0.09 (0.18)	**0.92 (0.29)*****
Adjusted estimated mean[b]	4.09	2.41	0.97	3.56	2.20	2.43
	No S-Allele (triallelic)			S-Allele (triallelic)		
Unadjusted coefficient (SE)	1.29 (0.21)	–0.73 (0.16)	–1.34 (0.27)	–0.08 (0.25)	–0.01 (0.19)	**0.63 (0.29)****
Unadjusted estimated mean	3.63	1.75	0.95	3.35	1.60	1.65
Adjusted coefficient (SE)[b]	1.38 (0.24)	–0.54 (0.20)	–1.34 (0.28)	–0.08 (0.26)	–0.12 (0.19)	**0.74 (0.31)****
Adjusted estimated mean[b]	3.97	2.32	1.04	3.67	2.05	2.10
	No G-Allele			G-Allele		
Unadjusted coefficient (SE)	1.08 (0.23)	–0.73 (0.17)	–1.61 (0.29)	0.21 (0.26)	–0.01 (0.20)	**0.94 (0.31)*****
Unadjusted estimated mean	2.94	1.42	0.59	3.63	1.73	1.86
Adjusted coefficient (SE)[b]	1.11 (0.25)	–0.56 (0.20)	–1.42 (0.30)	0.32 (0.27)	–0.16 (0.21)	**0.75 (0.32)****
Adjusted estimated mean[b]	3.03	1.73	0.73	4.18	1.48	1.55
BASIS-32 anxiety/depression subscale (N = 89)						
	No S-Allele (biallelic)			S-Allele (biallelic)		
Unadjusted coefficient (SE)	2.23 (0.21)	–0.78 (0.24)	–0.71 (0.29)	–0.28 (0.25)	**0.58 (0.29)****	0.30 (0.35)
Unadjusted estimated mean	2.23	1.45	1.52	1.95	1.75	1.54
Adjusted coefficient (SE)[b]	2.22 (0.25)	–0.79 (0.27)	–0.66 (0.29)	–0.21 (0.25)	**0.55 (0.28)***	0.11 (0.35)
Adjusted estimated mean[b]	2.22	1.43	1.56	2.01	1.77	1.46
BIS-11 total (N = 86)						
	No G-Allele			G-Allele		
Unadjusted coefficient (SE)	73.71 (2.44)	–1.65 (1.96)	–7.28 (2.17)	–1.67 (2.84)	–0.09 (2.39)	**6.56 (2.83)****
Unadjusted estimated mean	73.71	72.06	66.43	72.04	70.30	71.32
Adjusted coefficient (SE)[b]	75.92 (2.70)	–0.74 (2.16)	–6.75 (2.35)	–0.98 (2.89)	0.94 (2.46)	**7.02 (2.84)****
Adjusted estimated mean[b]	75.92	75.18	69.17	74.94	75.14	75.21
BIS-11 attentional (N = 86)						
Unadjusted coefficient (SE)	2.62 (0.09)	–0.15 (0.11)	–0.33 (0.12)	–0.02 (0.11)	0.00 (0.13)	**0.30 (0.15)****
Unadjusted estimated mean	2.62	2.47	2.29	2.60	2.45	2.57
Adjusted coefficient (SE)[b]	2.66 (0.11)	–0.13 (0.12)	–0.33 (0.13)	0.01 (0.11)	0.01 (0.14)	**0.34 (0.16)****
Adjusted estimated mean[b]	2.66	2.53	2.33	2.67	2.55	2.68
BIS-11 non-planning (N = 86)						
Unadjusted coefficient (SE)	2.35 (0.10)	0.04 (0.08)	–0.15 (0.09)	–0.15 (0.12)	–0.01 (0.10)	**0.25 (0.12)****
Unadjusted estimated mean	2.35	2.39	2.20	2.20	2.23	2.30
Adjusted coefficient (SE)[b]	2.42 (0.11)	0.07 (0.09)	–0.12 (0.10)	–0.15 (0.12)	0.04 (0.11)	**0.25 (0.12)****
Adjusted estimated mean[b]	2.42	2.49	2.30	2.27	2.38	2.40

[a]Significant effects appear in bold font. The table displays results for only those variables for which significant effects were obtained.
[b]Adjusted for medication and dose of therapy.
*p < .10.
**p < .05.
***p < .01.
Abbreviations: 5-HTTLPR = serotonin transporter promoter polymorphism, BASIS-32 = Behavior and Symptom Identification Scale, BIS-11 = Barratt Impulsiveness Scale-version 11.

low-function versus high-function allele differences were obtained at 8 months with biallelic and triallelic 5-HTTLPR and –1438G/A. On the BASIS-32 anxiety/depression subscale, the biallelic 5-HTTLPR comparison was significant at 4 months, regardless of treatment effects. Likewise, regardless of treatments, –1438G/A contrasts yielded significant effects on the BIS total, attentional, and non-planning scores at 8 months. Throughout, presence of a low-function allele was associated, not with greater initial symptoms, but with significantly more symptoms at 4 or 8 months.

To ensure that apparent differences in response between carriers of low-function and high-function alleles were not confounded by differences in treatments received, we performed ancillary analyses aimed at predicting membership in the most intense treatment categories (highest tertile of individual therapy sessions, highest tertile of group therapy sessions, participation in day treatment, or receipt of medication) as a function of the presence of a low-function allele. In all instances but 1 (patients with a low-function allele of –1438G/A being more likely to be in the highest tertile of group therapy sessions at 4 months), statistically significant effects were not observed. In other words, lesser response of low-function allele carriers observed could not have been attributable to these individuals having received smaller doses of treatment.

Analyses using t tests to compare treatment completers (N = 98) to dropouts (N = 13) on the variables weekly binge episodes (mean ± SD = 4.88 ± 4.79 vs. 8.94 ± 13.78), weekly vomit days (mean ± SD = 3.36 ± 2.63 vs. 2.88 ± 3.11), weekly purge days (mean ± SD = 4.46 ± 3.20 vs. 4.81 ± 4.20), CES-D score (mean ± SD = 29.53 ± 12.21 vs. 28.43 ± 11.18), BIS total score (mean ± SD = 72.30 ± 11.06 vs. 65.14 ± 9.14), and BASIS-32 subscale scores for anxiety/depression (mean ± SD = 2.09 ± 0.98 vs. 2.06 ± 1.11), daily living (mean ± SD = 1.96 ± 0.77 vs. 2.15 ± 1.20), impulsivity (mean ± SD = 1.32 ± 0.76 vs. 1.52 ± 0.82), and self/other relations (mean ± SD = 2.24 ± .84 vs. 2.16 ± .92) yielded no significant effects. Likewise, the respective numbers (and percentages) of low-function allele carriers in completer and dropout groups were as follows: 5-HTTLPR biallelic: N = 64 (65.3%) versus N = 10 (76.9%); 5-HTTLPR triallelic: N = 71 (72.4%) versus N = 11 (84.6%); –1438G/A: N = 75 (76.5%) versus N = 13 (100%), and pairs of proportions never differed significantly.

A final analysis aimed at detecting genetic correlates of the tendency to leave therapy during the segment of therapy between 4-month and 8-month assessments. To do so, we compared proportions of individuals carrying low-function alleles across a group of 10 patients who dropped out between 4-month and 8-month assessments to corresponding proportions in 88 cases who successfully completed their prescribed course of treatment at 4 months, or who continued in therapy through the eighth month. Respective proportions of carriers of at least 1 copy of the 5-HTTLPR S allele (biallelic model) were 9 of 10 (or 90.0%) versus 55 of 88 (62.5%), of the 5-HTTLPR S′ alleles (triallelic model) were 9 of 10 (90.0%) versus 62 of 88 (70.5%), and of the –1438G/A G allele were 8 of 10 (80.0%) versus 67 of 88 (76.1%). Although available numbers provide limited power, Fisher exact tests revealed no significant differences in any case. There was, however, a trend toward higher dropping out among carriers of the biallelic S allele ($p < .08$).

DISCUSSION

We observed bulimic women who carried low-function alleles of 5-HTTLPR or –1438G/A to show lesser reduction in weekly frequency of binge episodes at roughly 8 months of therapy (in the case of both polymorphisms), slower response on a measure of anxiety and depression at 4 months of therapy (in 5-HTTLPR S-allele carriers), and absence of improvements on measures of impulsivity at 8 months (in –1438G/A G-allele carriers). Cognitive (attentional and planning) components of impulsivity seemed to account for the latter effect.

Effects obtained on measures of binge eating could reflect serotonergic influences upon appetite regulation, which might (in theory) render low-function allele carriers prone to greater difficulties with satiety and, in turn, with abstinence from binge eating. Alternatively, since there was evidence of greater persistence of anxiety, depression, and impulsivity in our low-function allele carriers, lesser response of bulimic symptoms in these patients could have been enacted through mediating effects (on binge eating) of ongoing depressive or impulsive symptoms. Regardless, an implication seems to be that 5-HTTLPR and –1438G/A low-function alleles predict lesser (or less rapid) treatment response in bulimic patients.

Our findings help rule out a third possibility—namely, that effects observed were mediated specifically by factors that impeded the responsiveness of low-function allele carriers to benefits of pharmacotherapy. Were findings attributable to this factor alone, genetic effects should have been "erased" by controls for medication effects—but this was not the case. Indeed, statistical measures applied suggest that any effects attributable to genetic factors occurred independently of effects owing to variations in medication or psychotherapy. In this respect, results point to hereditary, serotonin-mediated factors affecting bulimic individuals' general progress in therapy, independently of therapy form or intensity. Along with the latter interpretation, we offer the caveat that our study had relatively low power for the specific examination of effects owing to treatment variations. Results bearing upon these factors should, therefore, be interpreted with reserve.

Regardless of the mechanism that underlies an apparent association between genotypes and treatment response, we are intrigued by the way in which our findings point to a plausible biological substrate for the already known association between heightened impulsivity or affectivity, on the one hand, and poor bulimia treatment response, on the other.[1,2] Previous work by our group has associated the low-function alleles of both 5-HTTLPR and –1438G/A with heightened impulsivity and affective instability.[4,5] It is thus not surprising to note that genotypes believed to correspond (on average) to elevated impulsivity/affective instability may also be associated with poorer treatment response. Indeed, this observation provides a degree of external validation, based on genetic indicators, for the notion that impulsivity may have an unfavorable connotation for bulimia-treatment outcome. If our speculations on the role of serotonergic mechanisms in mediating prognostic effects are correct, then our findings may help elucidate causal mechanisms underlying an association between heightened impulsivity and poorer bulimia-treatment response.

Limitations

Our naturalistic design allowed us to examine influences of genotypic factors upon responses of bulimic

individuals to real-life treatments, and hence had the benefit of producing findings that promise to generalize to real-life clinical settings. However, the design also created the risk that outcomes might have been influenced by uncontrolled treatment variations. For example, more-symptomatic or less-responsive cases might have tended to be recalcitrant, to avoid treatment, or to receive less of it. Providing reassurance that this was not the case, statistical measures applied help separate effects of treatment variations from effects owing to genetic factors, and suggest that genetic effects obtained were not attributable to confounds owing to treatment factors. Similarly, analyses that tracked the association between allelic variations and treatment quantities administered argued (if anything) that low-function allele carriers, who were expected to (and actually did) do more poorly in treatment, received (if anything) more (and not less) of it.

There might also be the concern that attrition at the 8-month assessment might have distorted outcome findings, especially should there have been disproportionate attrition aligned with different genotypes. While the preceding necessitates conservative interpretation of our 8-month treatment results, we note that ancillary analyses conducted to determine whether genotypes were associated with differential rates of dropping out of treatment (among treated patients) during the second 4-month segment of treatment found no such differences. In a related vein, attrition at 8 months reduces sample size and may, correspondingly, reduce stability of findings. Nonetheless, correspondence of our findings to those in related studies[7,9] and to expectations derived from theory encourage us to interpret 8-month differences as reflecting genuine effects of the genetic factors explored.

Clinical Implications

In linking hereditary factors associated with the 5-HT system with different response patterns, our findings point to various clinically relevant potentials: First, our findings corroborate the speculation, raised by various authors,[21,22] that genetic variations may define etiologically and clinically distinct subgroups within the bulimic population—seen in the present study to differ on indices of response to clinical treatment. Second, one could envisage future applications of genetic information of the type derived here (once further refined) that might guide treatment protocols (both pharmacologic and psychotherapeutic) in a way that might improve the "fit" of treatments to the needs of a constitutionally "compromised" (and hence typically less responsive) subgroup of bulimic patients.

Drug names: citalopram (Celexa and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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