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Examining Associations between Disordered Eating and Serotonin Transporter Gene Polymorphisms

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Abstract

Objective—The serotonin system has been implicated in mood and appetite regulation, and the serotonin transporter gene (*SLC6A4*) is a commonly studied candidate gene for eating pathology. However, most studies have focused on a single polymorphism (*5-HTTLPR*) in *SLC6A4*; little research has utilized multiple single nucleotide polymorphisms (SNPs) to investigate associations between *SLC6A4* and eating pathology more comprehensively.

Method—Family-based association tests were conducted for seven polymorphisms in or near *SLC6A4*, using families from the Colorado Center for Antisocial Drug Dependence. Data were available for 135 families, with phenotypic data available for female twins and female nontwin siblings. Seven items assessed two disordered eating characteristics: weight and shape concerns and behaviors (WSCB) and binge eating (BE).

Results—No significant associations were found between any genetic variant and the two disordered eating characteristics.

Discussion—This study suggests that utilizing polymorphisms in and near *SLC6A4*, including *5-HTTLPR*, may not be useful in identifying genetic risk factors for disordered eating.

Keywords

eating disorders; disordered eating; serotonin transporter; family-based association; *5-HTTLPR*; SNPs

Introduction

Twin studies have indicated moderate genetic influences on eating pathology, including clinical eating disorders^{1,2} and disordered eating characteristics (e.g., body dissatisfaction and binge eating)^{1,3}, yet specific genetic variants contributing to these disorders and behaviors have not been clearly identified. Of interest in the eating disorder literature are genes in the serotonin system, as serotonin is known to be involved in mood and appetite

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regulation⁴. One putative gene in this system influencing eating disorders is the serotonin transporter gene (*SLC6A4*) since it regulates serotonin reuptake from the synaptic cleft. However, an important limitation of the literature investigating associations between *SLC6A4* variants and eating disorders is that most studies have only investigated a single polymorphism within *SLC6A4*, the 43 base pair insertion/deletion polymorphism in the promoter region (*5-HTTLPR*)⁵.

Variations in *5-HTTLPR* have been shown to regulate basal transcription rates⁵ and are typically characterized as consisting of a short-allele, which leads to reduced transcriptional efficiency compared with the long-allele⁶. Although there have been inconsistent single study findings for both eating disorders, two recent meta-analyses^{7,8} showed that having at least one *5-HTTLPR* short-allele increased the risk for anorexia nervosa but not bulimia nervosa. In addition, few studies have examined *5-HTTLPR* with disordered eating^{9–11}, despite evidence to suggest that it precedes the development of clinical eating disorders¹². Thus, even though accumulating research suggests that *5-HTTLPR* influences the risk for AN, it is not yet clear whether it increases the risk for BN or disordered eating.

Furthermore, although other genetic variants have been identified in this gene, few studies have explored their association with eating disorders. Earlier work investigated both a variable number tandem repeat polymorphism and *5-HTTLPR*^{13,14}, whereas more recent studies utilized single nucleotide polymorphisms (SNPs) to detect associations between *SLC6A4* genetic variants and eating pathology. In the latter studies, no significant associations were found between *SLC6A4* SNPs and anorexia nervosa or between these SNPs and anorexia nervosa subtypes^{15,16}. Still, it is unknown if particular features commonly seen in women with anorexia and bulimia nervosa (e.g., weight concerns and binge eating) are associated with *SLC6A4* variants.

We tested the feasibility of using a gene-based approach to investigate associations between multiple *SLC6A4* polymorphisms and two disordered eating characteristics¹⁷. The use of multiple polymorphisms allows for a more comprehensive evaluation of the role of genetic variation in *SLC6A4* and eating pathology. Moreover, the use of disordered eating characteristics rather than clinical eating disorders could provide valuable insight into risk factors for more general eating attitudes and behaviors.

Materials and Methods

Participants

Participants were adolescent and young adult female twins and female nontwin siblings (mean age: 17.30 ± 1.25 years; range: 16.00–21.00), as well as their male siblings and parents from the Colorado Center for Antisocial Drug Dependence (CADD)¹⁸. This is a population-based community sample that assesses substance use, personality traits, and psychopathology from families whose twins were born in the state of Colorado¹⁸. The CADD twin sample was drawn from two studies- the Colorado Community Twin Study (CTS) and the Longitudinal Twin Study (LTS)¹⁸. For CTS families, twins were recruited by birth records obtained from the Colorado Department of Health, Division of Vital Statistics or through primary and secondary schools beginning in 1983. Twins born from 1986 onwards were invited to participate in the CTS and willing participants born between 1980 and 1990 were included in the CADD study. Families from the LTS were recruited only from the Colorado Department of Health, Division of Vital Statistics, only from the greater Denver metropolitan area, and only from families whose twins had healthy birth weights and gestational ages born between 1984 and 1990. The CADD sample was comparable with the larger sample of twin families from which it was drawn¹⁸.

Overall, 135 families (465 individuals) from our previous biometrical twin analyses¹⁷ were included in the current study. The number of families included in the analyses was smaller than the 838 families from our previous study because we wanted to include only those families that could potentially be informative for the within-family association test between disordered eating characteristics and genetic variants. Thus, families were excluded if: 1) no genotyping was completed for an entire family; 2) only one member of the family had genotypic information (since there must be at least two family members for a within-family association test); 3) genotypic information was only available for *5-HTTLPR* (since we were particularly interested in *SLC6A4* SNPs, we wanted to make sure the families also had SNP information); and 4) monozygotic (MZ) twins had to have a nontwin sibling with genotype information (because MZ twin pairs alone are not informative for within-family testing). The final sample consisted of 43 MZ, 61 dizygotic, and 31 opposite-sex twin pairs.

The number of family members ranged from two to five and could include one or both twins, a full nontwin sibling (male or female), and the biological parents. Notably, phenotypic data were only available for female offspring, whereas genotypic data were available for male and female offspring and biological parents. The self-reported ethnicity composition of the sample was as follows: 88.6% White, 5.1% more than one race, 1.2% American Indian, 0.8% Asian, 0.8% Native Hawaiian, 0.8% Black, and 2.7% unknown. Study protocol was approved by the University of Colorado's Institutional Review Board. Participants 18 years old or older gave informed consent to participate; participants under age 18 gave assent. Parents also provided informed consent for participants under age 18.

Assessment

A seven-item eating pathology screening tool^{19,20} assessed eating attitudes and behaviors. Phenotypic exploratory and confirmatory factor analyses revealed two disordered eating characteristics: weight and shape concerns and behaviors (WSCB; which assessed feeling fat, thinking about staying thin, eating less than usual when upset, and self-induced vomiting) and binge eating (BE; which assessed eating in secret, finding it hard to stop eating, and eating more than usual when upset)¹⁷. The two disordered eating characteristics were scored from 0 to 3+, reflecting the number of items endorsed on each factor (note: WSCB had a possible range from 0 – 4 but was truncated at 3+ to create a four-category ordinal scale for both WSCB and BE)¹⁷. Biometrical model-fitting showed that these characteristics were moderately heritable ($h^2 = 0.43$ [95% confidence interval: 0.33–0.52] for WSCB and 0.49 [0.36–0.58] for BE)¹⁷. In the current study, 52.0% of the participants with available phenotypic data (i.e., female offspring) endorsed at least one WSCB item and 30.6% endorsed at least one BE item; the nonparametric phenotypic correlation between WSCB and BE was significant ($r = 0.26, p < 0.001$).

In addition, we conducted an independent study to assess the validity of the seven-item eating pathology screening tool by comparing it to a widely used disordered eating measure—the Eating Disorder Examination Questionnaire (EDE-Q²¹). Results from 133 female undergraduate students (mean age: 18.91 ± 1.26 ; range: 18.00 – 26.00) suggested that the correlation between a total score of the seven-item assessment and the EDE-Q Global Score was 0.63 ($p < 0.05$). Furthermore, using an EDE-Q clinical cut-off score of four²¹, the mean total score of the seven-item assessment was higher in individuals who met the clinical cut-off score ($n = 17$; mean = 5.06 ± 1.20) compared with females who did not meet the clinical cut-off score ($n = 116$; mean = 3.18 ± 1.60). Thus, this seven-item eating pathology screening tool provides useful information to detect disordered eating in young adult females.

Zygosity and Genotyping

Zygosity information was obtained using a combination of physical similarity ratings and genotyping. Zygosity was initially assigned using a modified version of the Nichols and Bilbro questionnaire²². For most participants, zygosity was subsequently confirmed using a minimum of 11 highly informative short tandem repeat polymorphisms. Any discrepancies between similarity ratings and genotyping were resolved¹⁸.

DNA samples were obtained via cheek swab buccal cell collection. For both CTS and LTS families, *5-HTTLPR* was genotyped according to modified protocols^{23,24}. The recently identified SNP (rs25531) in the *5-HTTLPR* long-allele was not examined in this sample because genotypic information was not available. All SNPs in CTS families were genotyped using a 32-SNP, ABI Taqman® OpenArray® (Carlsbad, CA). All SNPs in LTS families were genotyped with the Illumina® (San Diego, CA) GoldenGate 96-SNP assay²⁵ using their BeadXpress™ system. *SLC6A4* SNP selection was based on the following criteria: 1) coverage of the gene from the region upstream of *5-HTTLPR* to the 3' UTR (47 kilobases); 2) an acceptable Golden Gate assay²⁵ design score; 3) a minor allele frequency of at least 0.10; 4) HapMap²⁶ validation; and 5) if possible, a reported association with a behavioral phenotype. Genotype frequencies for the seven polymorphisms in parents and offspring are presented in Table 1.

Although our 32-SNP assay (for CTS) and 96-SNP assay (for LTS) included variants in other loci, we examined only *SLC6A4* variants for three reasons. First, the SNP panel was not designed for eating pathology research, so we focused on polymorphisms related to *SLC6A4* given prior interest in *5-HTTLPR*. We wanted to expand on this body of literature by examining other polymorphisms in *SLC6A4*. Second, our inclusion of *5-HTTLPR* and other genetic variants using a family-based design provides additional within-family information to the *SLC6A4* and eating pathology literature. Finally, the number of families included in this study is small. Examining associations between the disordered eating characteristics and genetic variants in other loci would have reduced our statistical power.

Statistical Analyses

Haploview²⁷ was utilized to determine linkage disequilibrium (LD) patterns among the genetic variants. Hardy-Weinberg Equilibrium (HWE) was calculated using Merlin²⁸. Because our sample population was a relatively small subset of the total CADD sample, HWE calculations were based on the founders of the full sample, who were also genotyped for these SNPs ($n = 222$) and for *5-HTTLPR* ($n = 499$)¹. Family-based association tests operationalized in FBAT²⁹ were then used to conduct all association analyses. FBAT is an extension of the Transmission Disequilibrium Test that utilizes both within- and between-family information²⁹. Because MZ twin pairs share 100% of their genetic make-up and are not informative for within-family testing (although they are informative for between-family testing), one MZ twin was randomly selected from each MZ twin pair to be included in the analyses. FBAT accommodates ordinal data that are not normally distributed²⁹.

We examined associations between each polymorphism and the two phenotypes (i.e., WSCB and BE) independently. An additive mode of inheritance was assumed throughout all models, and the offset value was allowed to be freely estimated in order to minimize the variance of the test statistic³⁰. As specified by FBAT²⁹, the default number of informative families (at least 10 for a given analysis) was utilized. An initial p -value of 0.05 was used to

¹Parental genotypes for CTS families were not available. Thus, HWE was calculated only on LTS founders. However, we also examined HWE in Haploview using both offspring and parents from the 135 families. These results were not different from HWE in founders only (which are reported in the text).

determine statistical significance. However, in order to correct for multiple testing (seven polymorphisms times two phenotypes equals 14 tests; see Results section), we used the Bonferroni correction³¹, where the corrected critical p -value was 0.004.

Results

Figure 1 shows the location of the six SNPs in and near *SLC6A4* included in this study, as well as *5-HTTLPR* (and rs25531 that lies within *5-HTTLPR*). None of the seven polymorphisms showed Mendelian errors or were in Hardy Weinberg Disequilibrium. Minor allele frequencies for the genetic variants ranged from 0.09 (rs140700) to 0.48 (rs1042173) (Table 2).

The r^2 values were generally low (i.e., ≤ 0.48), suggesting that the information these SNPs provided were relatively independent. One exception was the r^2 value of 0.82 between rs1042173 and rs2054847, indicating that these two SNPs were associated with each other. Figures of the LD patterns are provided in Figure 2.

Association results for WSCB and BE are presented in Table 2. When testing for an association between each of the seven polymorphisms and WSCB, no genetic variants were significant even before correcting for multiple testing (all p -values > 0.05). Similarly, no associations between SNPs in or near *SLC6A4* and BE were detected (all p -values > 0.05). These data suggest that genetic variants in and near *SLC6A4* are not associated with weight and shape concerns/behaviors or binge eating.

Discussion

This study sought to determine the feasibility of utilizing a gene-based approach to examine the association between multiple polymorphisms in and near *SLC6A4* and disordered eating. We did not find significant associations between *SLC6A4* polymorphisms and weight and shape concerns and behaviors (WSCB) or between these same variants and binge eating (BE). Despite recent meta-analyses^{7,8} suggesting that the *5-HTTLPR* short-allele is significantly associated with anorexia nervosa, we found no allele to be associated with eating disorder symptoms. This finding is similar to prior research^{9,10} that reported no main effects for binge eating or drive for thinness with *5-HTTLPR* alleles. It is possible that including polymorphisms from other loci and exploring epistasis would yield significant findings, as has been shown between *5-HTTLPR* and MAO genotypes with eating disorders and their symptoms^{10,32}. However, our sample size was too small to perform these analyses. Even though our findings were not significant, it is interesting that the *5-HTTLPR* risk allele for WSCB was the short-allele and for BE it was the long-allele. Prior studies reported that the long-allele was associated with abnormal eating behaviors in a Japanese sample of women¹¹ and in Caucasian women with binge eating disorder³³. More studies are clearly needed to determine if there is a differential risk allele for specific disordered eating characteristics.

With respect to *SLC6A4* SNPs, our findings corroborate prior studies that did not find significant associations with anorexia nervosa and anorexia nervosa subtypes^{15,16}. Of particular interest is the fact that three of our SNPs- rs6354, rs140700, and rs1042173- overlapped with genetic variants included in the study by Pinheiro et al¹⁶ (C. M. Bulik and L. M. Thornton, personal communication, March 25, 2011). Furthermore, two genome-wide association studies did not detect significant associations between anorexia nervosa and *SLC6A4* SNPs^{34,35}. Thus, *SLC6A4* SNPs may not represent genetic risk factors for eating pathology.

In conclusion, we did not find significant associations between disordered eating and polymorphisms in and near *SLC6A4*. The lack of significant findings could be due to the small sample size, the age of our sample (given that individuals may not be past the risk period for eating disorder symptoms), or the use of disordered eating symptoms rather than clinical diagnoses (we do not have clinical diagnoses of eating disorders in our twin samples). It will be important for future research to include multiple polymorphisms in many loci, including other neurotransmitter systems, in order to fully understand the role of genes on eating related behaviors.

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FIGURE 1.

Serotonin transporter gene (*SLC6A4*) polymorphism information. The serotonin transporter gene is typically read from the 3-prime to 5-prime end. However, the expanded portion of the figure has been inverted for ease of interpretation. The marker position is located under the polymorphism and was obtained from HapMap.

FIGURE 2.
 D' (left) and R^2 (right) values for polymorphisms in and near *SLC6A4*.

TABLE 1

Genotype frequencies

Genotype Frequency				
Polymorphism	Genotype	Parents* (n = 137)	Offspring* (n = 285)	Total* (n = 422)
rs12945042	AA	20	31	51
	AG	53	107	160
	GG	55	117	172
5-HTTLPR	LL	27	64	91
	SL	48	92	140
	SS	15	32	47
rs6354	AA	66	159	225
	AC	27	67	94
	CC	0	4	4
rs2020942	AA	26	40	66
	AG	50	112	162
	GG	43	101	144
rs140700	AA	2	3	5
	AG	21	45	66
	GG	102	204	306
rs2054847	AA	24	48	72
	AG	50	129	179
	GG	51	82	133
rs1042173	AA	45	62	107
	AC	47	130	177
	CC	31	54	85

Note:

* The maximum number of individuals for whom genotypic data could be available. Only one member of a MZ twin pair was included in the genotype frequencies.

TABLE 2
Descriptive *SLC6A4* polymorphism information and results for association analyses

SNP	Allele	MA (Freq)	WSCB		BE	
			#Fam	p	#Fam	p
rs12945042	A/G	A (0.34)	63	0.14	A	60 0.18 A
5- <i>HTTLPR</i>	S/L	S (0.46)	40	0.64	S	38 0.66 L
rs6354	A/C	C (0.14)	42	0.31	C	39 0.45 C
rs2020942	A/G	A (0.39)	57	0.80	A	58 0.40 A
rs140700	A/G	A (0.09)	32	1.00	A	30 0.58 A
rs2054847	A/G	A (0.44)	63	0.94	A	62 0.86 G
rs1042173	A/C	C (0.48)	57	0.93	C	58 0.32 A

Note: WSCB = weight and shape concerns and behaviors; BE = binge eating; SNP = single nucleotide polymorphism; MA = minor allele; Freq = frequency; #Fam = number of informative families; RA = risk allele. The *p*-values presented in the table are before applying Bonferroni correction ($p = 0.004$).