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Preliminary evidence for the role of *HTR2A* variants in binge eating in young women

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Abstract

Objective—We examined the association between 15 single nucleotide polymorphisms (SNPs) in *HTR2A* and characteristics of disordered eating, including weight/shape concerns, binge eating (with or without loss of control) and compensatory behaviors (purging and non-purging). Whether a lifetime history of major depressive disorder (MDD) moderated or mediated this association was also investigated.

Method—A sample of 1533 twin women of Caucasian descent that were part of the Missouri Adolescent Female Twin Study was used. Data were collected using self-report responses to a semi-structured interview. Logistic regression analyses were used to examine the association between weight/shape concerns, binge eating and compensatory behaviors and SNPs (where carriers of the minor allele were coded as 1).

Results—Two SNPs, rs6561333 and rs2296972, showed a protective influence against binge eating, with rs2296972 being significant at a trend level after application of the False Discovery Rate. The SNP was not associated with MDD nor did MDD moderate its putative relation with binge eating.

Discussion—Pending replication, our analyses provide preliminary evidence for intronic SNPs in *HTR2A* and their association with binge eating. Given the well-documented role of serotonergic dysfunction in eating psychopathology, this report warrants considerable further study.

Keywords

HTR2A; disordered eating; binge eating

Introduction

Weight and shape concerns, binge eating and compensatory behaviors are eating disorder symptoms that cut across multiple DSM-5 diagnoses of eating disorders (American Psychiatric Association, 2013). In addition to the growing prominence of these features in DSM-5, there is accumulating evidence for heritable influences on them (Thornton *et al.*, 2011). In a longitudinal study of weight and shape concerns, Klump et al. report increasing heritability of the construct across development, with heritable factors contributing to 54%

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of the variance by age 13 (Klump *et al.*, 2010). Further, both binge eating and compensatory behaviors (Munn-Chernoff *et al.*, in press), such as self-induced vomiting have been found to be heritable, with significant overlap in the genetic factors influencing them (Sullivan *et al.*, 1998; Wade *et al.*, 2008). However, the genes that contribute to this heritable variation remain elusive (Helder and Collier, 2011).

Most gene-finding efforts have focused on diagnoses and subtypes of anorexia and bulimia nervosa in clinical populations, which may encompass a fair degree of etiological heterogeneity and may also exclude sub-threshold forms of these disorders, as well as specific eating disorder symptoms. Alterations in serotonin neurotransmission have been identified in patients with anorexia and bulimia nervosa (e.g. (Kaye, 2008; Norton and Owen, 2005; Scherag *et al.*, 2010)). For instance, acute depletion of dietary tryptophan, the precursor to 5-HT (serotonin), has been found to correspond to increased food intake in those with bulimia nervosa (Weltzin *et al.*, 1995). Furthermore, while those with bulimia have normal levels of 5-HIAA (5-hydroxyindoleatic acid, a serotonin metabolite), those in recovery show elevated levels in their cerebrospinal fluid (Bailer *et al.*, 2012).

A gene that has garnered considerable interest encodes the 5-hydroxytryptamine (serotonin) receptor 2A (*HTR2A*) (Norton and Owen, 2005; Scherag *et al.*, 2010). Generally, the serotonin receptor subtypes have been implicated in appetitive processes and satiety, as well as mood (Bailer *et al.*, 2012; Herbeth *et al.*, 2005). In particular, several studies have examined the association between the -1438G/A (rs6311) promoter polymorphism and anorexia nervosa (e.g. (Enoch *et al.*, 1998; Hinney *et al.*, 1997; Martaskova *et al.*, 2009; Nacmias *et al.*, 1999; Ricca *et al.*, 2002; Sorbi *et al.*, 1998)). Although an initial meta-analysis (Ziegler *et al.*, 1999) and a multi-center study of trios reported an absence of an association between this genetic variant and anorexia nervosa, another meta-analysis (Gorwood *et al.*, 2003) indicated an association accompanied by considerable across-sample heterogeneity. The meta-analysis concluded that variation in symptoms and clinical characteristics may obscure genetic association findings.

Research on *HTR2A* and bulimia nervosa are limited – women with bulimia nervosa tend to have normal 5-HT_{2A} receptor binding (Goethals *et al.*, 2004) although alterations have been noted in recovering patients. Furthermore, age-related changes in receptor binding tend to be absent in women recovering from bulimia nervosa and those with the binge-purge (but not restricting) subtype of anorexia nervosa (Bailer *et al.*, 2012). While human association studies have explored the relationship between *HTR2A* variants and bulimia nervosa, albeit infrequently, samples have been modest and no clear evidence for association has emerged (Kiezebrink *et al.*, 2010; Sorli *et al.*, 2008).

We examined the association between 15 single nucleotide polymorphisms (SNPs) in *HTR2A* and disordered eating characteristics, including weight/shape concerns, binge eating (with or without loss of control) and compensatory behaviors (purging and non-purging) in a sample of 1533 European-American female twins. In addition, given the well-documented comorbidity between eating disorders and major depressive disorder (MDD) (Hudson *et al.*, 2007), as well as associations between *HTR2A* variants and MDD, particularly antidepressant response (Kato and Serretti, 2010), we investigated whether MDD mediated or moderated any significant associations between *HTR2A* and these disordered eating characteristics.

Methods

Participants

Participants were drawn from the general population Missouri Adolescent Female Twin Study (MOAFTS). MOAFTS twins were born between 1975 and 1985 to parents residing in the state of Missouri. A baseline interview was conducted when the twins were adolescents (13–17 years old), but this assessment did not include measurements of eating disorders or their symptoms. All eligible twins were followed up with a detailed full-length interview in 2002–2005 (age range = 18–27 years). The full follow-up sample (N = 3787) is highly representative of the demographic characteristics of the state; 14% of twins self-identified as African-American – however, for the current analyses, only data on European-American subjects was utilized (there is no evidence for population stratification within the European-American participants). During this time, twins were also invited to provide a DNA sample (blood, buccal or saliva) for an ongoing multi-center genetic study. Saliva collection and genotyping is ongoing and currently, data on 1533 twins of European-American ancestry are available and were used in these analyses. Women who are currently genotyped did not significantly differ from the full sample on any disordered eating characteristic ($p > 0.50$). Additional details on sample recruitment and genetic data collection, quality control and tests for population stratification are available in related publications (Agrawal *et al.*, 2010; Heath *et al.*, 2002). All research was reviewed and approved by the institutional review board at the Washington University School of Medicine.

Assessment

The Semi-Structured Assessment of the Genetics of Alcoholism (SSAGA) was administered via a telephone interview to the twins (Bucholz *et al.*, 1994). The eating disorders section was adapted from the Diagnostic Interview Schedule (version 4)(Robins *et al.*, 1996). Although primarily aimed at obtaining DSM-IV diagnoses, some changes were made to the section – a detailed explanation of these modifications may be found in Duncan et al (Duncan *et al.*, 2007). Most pertinent to the current study, unlike other assessments, participants were queried about compensatory behaviors regardless of their endorsement of binge eating. All items represent lifetime assessments, were dichotomously coded and based on single items that were presented to all participants without any study-related skips. Weight/shape concerns assessed whether the individual was ever greatly concerned about eating too much, looking too fat or gaining too much weight. Binge eating was assessed as ever eating a large amount of food in a short period of time, usually less than two hours. A follow-up question on whether the binge eating was accompanied by loss of control was used to further examine promising association signals. Finally, compensatory behaviors included items that assessed whether, in an effort to either lose weight, prevent weight gain or make-up for an eating binge, the respondent had: (a) made herself vomit, (b) taken laxatives, (c) taken water pills/diuretics, (d) dieted strictly, (e) fasted (not eat anything), or (e) exercised excessively. The first three methods are considered purging compensatory behaviors whereas the last three methods are considered non-purging compensatory behaviors.

Genotyping

Typing of SNPs was conducted as part of a larger effort and was based on a panel developed by tagging genes selected primarily for studies of addiction (Hodgkinson *et al.*, 2008). We selected to examine *HTR2A* alone due to its importance in the literature. The assay was developed for Illumina Golden Gate technology and genotyping was conducted on a subset of the sample at the Centers for Inherited Diseases Research (CIDR) and subsequently, at Washington University School of Medicine (WUSM). SNP selection involved gene tagging (including gene footprints), prioritization of exonic and published variants (please see

Hodgkinson et al., 2008 for complete details; sequence information available upon request). None of the *HTR2A* SNPs showed significant deviations from Hardy-Weinberg Equilibrium ($p > 0.05$ for all but one SNP, rs1928040 with $p = 0.01$; however, this is well within the correction for multiple tests) and all had call rates greater than 99.5%. One SNP, rs6561333, was not genotyped in the second phase as the genotyping platform no longer supported the variant. Linkage disequilibrium (LD) between the SNPs in 831 unrelated women from the MOAFTS sample was calculated using Haploview (Barrett *et al.*, 2005) (Figure 1).

Statistical Analyses

Each SNP was coded as a binary variable, where being homozygous for the major allele equaled 0 and being a carrier of the minor allele equaled 1. To examine the association between each SNP and the disordered eating characteristics, logistic regressions, adjusting for zygosity (monozygotic or not), age at interview and genotyping phase (WUSM or not), were conducted in STATA (Stata Corp, 2003) using a robust variance estimator that accounted for clustering of twin data. A conservative Bonferroni correction ($p < 0.0033$) and the more common q-value, an index of the False Discovery Rate (Storey and Tibshirani, 2003), were calculated. To examine the mediating effects of MDD, (i.e. whether the effect of *HTR2A* SNPs on disordered eating characteristics was due to their effect on MDD which, in turn, influenced disordered eating characteristics) first, the association between MDD and the SNP was tested. If the SNP was not associated with MDD, there was no possibility of mediation, even if MDD and disordered eating characteristics occurred comorbidly across the lifetime. To examine the potential moderating influence of MDD, an interaction between the SNP and MDD on disordered eating characteristics was examined.

Results

Sample characteristics

Of the 1533 European-American women with genotypic data, 25.8% reported weight/shape concerns, 6.7% endorsed binge eating (with 12 missing data) without or with loss of control (reported only by 33 subjects) and 19.4% endorsed compensatory behaviors. Purging behaviors (i.e., vomiting, taking laxatives or diuretics) were endorsed by 5.7% of the sample, whereas non-purging behaviors (i.e., strict dieting, fasting or excessive exercise) were endorsed by 16.8% of the sample.

Genetic association analyses

Results for the model where carriers of minor allele were contrasted with homozygotes for the major allele are shown in Table 1. Results for other models may be found in Supplemental Tables S1–S3. There was no evidence for association between the *HTR2A* SNPs and compensatory behaviors. For weight/shape concerns, even though rs1923882 was associated at p=0.04, it did not satisfy correction for multiple testing. For binge eating, carriers of the minor alleles of two SNPs, rs6561333 and rs2296972, were less likely to report binge eating than homozygotes of the major allele (rs6561333: $p = 0.01$, q-value = 0.06; rs2296972: $p = 0.006$, q-value = 0.06), with both SNPs showing a protective effect against binge eating (rs6561333: Odds Ratio (O.R.) = 0.56, 95% Confidence Interval (C.I.) = 0.34–0.91; rs22976972: O.R. = 0.57, 95% C.I. = 0.38–0.86). These two SNPs were only in moderate LD ($r^2 = 0.32$, D' = 0.80; see Figure 1 for complete LD information). After a False Discovery Rate and a conservative Bonferroni correction, rs2296972 was only significant at a trend level.

Binge eating with or without loss of control

We examined whether rs6561333 and rs22976972 were associated with binge eating that only occurred with loss of control. For both SNPs, there was no evidence that the association was attributable to those reporting loss of control (post-hoc comparison of odds-ratios p-values > 0.05), although the modest number of subjects endorsing loss of control (N = 33) warrant caution in this post-hoc finding.

Effect of major depressive disorder

Although MDD (O.R. = 3.46, 95% C.I. 2.62–4.56) was associated with binge eating, rs2296972 was not associated with MDD (O.R. = 0.92, 95% C.I. 0.71–1.19) and consequently, there was no evidence for mediation. Evidence for moderation (genotype × MDD interaction) was also absent (interaction O.R. = 1.56, 95% C.I. 0.66–3.70), indicating the independent protective main effects of this variant on binge eating.

Discussion

In a sample of 1533 European-American female twins, we found that two SNPs in *HTR2A*, rs6561333 and rs2296972, were associated with a lower likelihood of binge eating. As these SNPs are intronic and, to our knowledge, do not correlate with functional variants in *HTR2A* or neighboring genes, the putative role of these variants will require replication and further biological validation.

A majority of human gene association studies of *HTR2A* have focused on a single promoter polymorphism (-1438G/A, rs6311) whose precise role in gene regulation remains somewhat unclear. We failed to find an association between rs4941573, which is a proxy ($r^2 = 1$, D' = 1) for the frequently studied -1438G/A promoter polymorphism (rs6311) and disordered eating characteristics. This is consistent with findings from a large multi-center family study (Gorwood *et al.*, 2002). Nonetheless, it is also possible that the lack of association is attributable to our focus on disordered eating characteristics versus a diagnosis of anorexia or bulimia nervosa. Few studies have also examined this variant in the context of bulimia nervosa. For instance, the low functioning allele of -1438G/A (G) has been found to be associated with poorer treatment response (Steiger *et al.*, 2008). Another study implicates the G allele in increased impulsivity and reduced sensitivity to post-synaptic serotonin in women with bulimia nervosa (Bruce *et al.*, 2005). One study, however, examined multiple SNPs in the gene and reported a similar protective association between rs3742278 and the binge-purge anorexia nervosa subtype (Kiezebrink *et al.*, 2010) – this SNP is in low r^2 (0.07–0.17) but high D' (1.0) with the SNPs associated with binge eating in our sample.

Some limitations of this study are worth noting. First, ours is a study of women in the Midwestern United States and may not generalize to other populations. Second, we were unable to examine clinical diagnoses of anorexia or bulimia nervosa, or severity as well as continuous indices of disordered eating due to small sample sizes. Third, we elected to exclude the African-American participants from these analyses due to concerns regarding admixture. This group is worth considerable future study as the genetic etiology of these disordered eating characteristics may differ between ethnic/racial groups. Finally, these results should be viewed as preliminary pending independent replication. Power to detect genetic main effects of less than 1.15 was less than 80%, even with minor allele frequencies of 0.4 and greater. Thus, the likelihood of false positives and negatives is a concern.

In conclusion, our examination of the genetic underpinnings of weight/shape concerns, binge eating and compensatory behaviors implicates variants in *HTR2A* for its role in binge eating. As we progress towards revised diagnostic definitions of eating psychopathology,

our study underscores the importance of examining specific eating disorder symptoms, such as binge eating, in genetic analyses (Birgegard *et al.*, 2012; Walsh, 2009).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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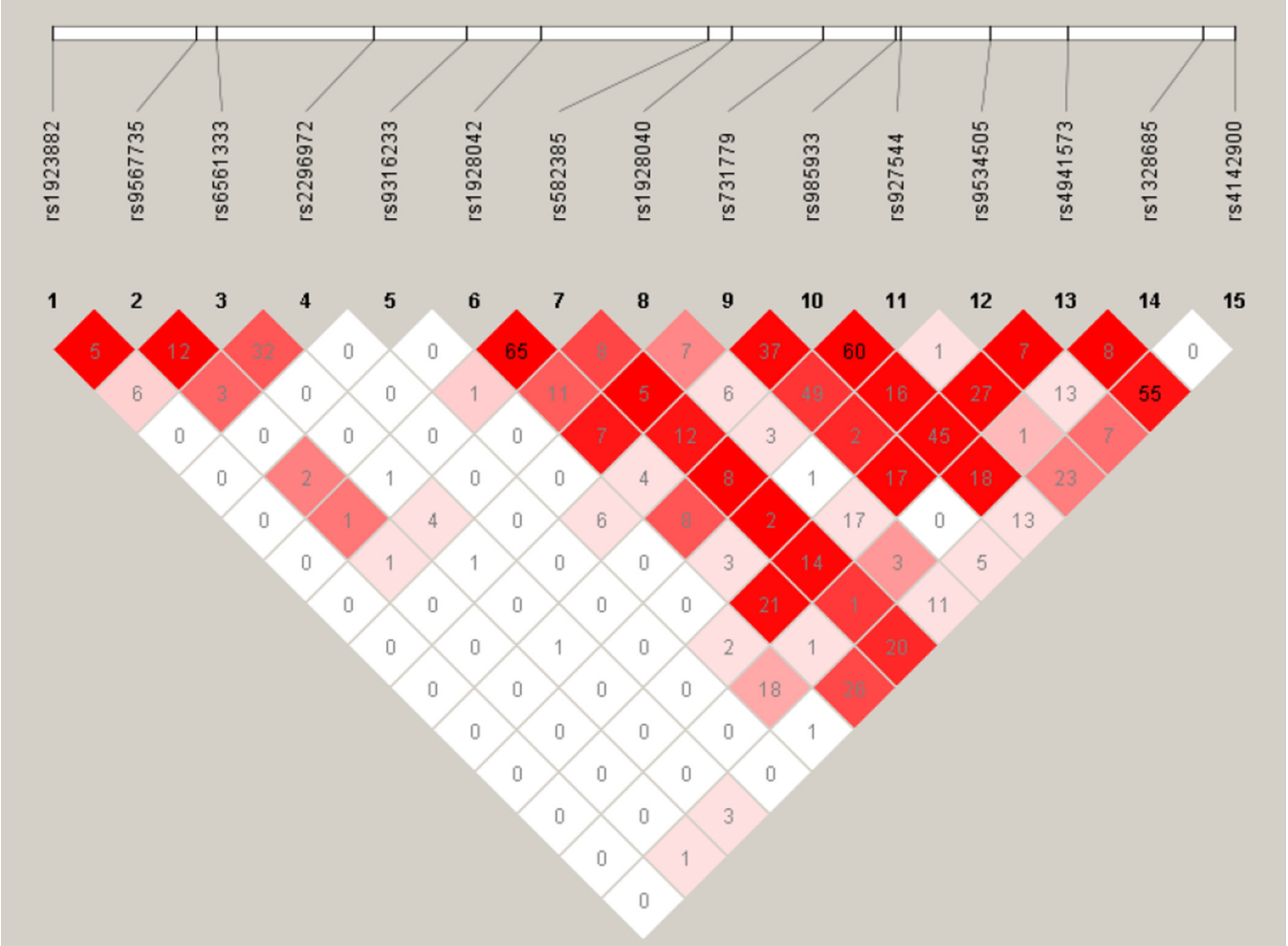

Figure 1.

Linkage Disequilibrium (LD) across 15 SNPs in *HTR2A* in 831 unrelated women from the Missouri Adolescent Female Twin Study. The colors represent D' (with darker colors representing greater LD), whereas the numeric inserts are r^2 values.

Table 1

For 15 SNPs in *HTR2A* (chromosome 13q14-q21), the percentage of women who reported weight/shape concerns, binge eating and compensatory behaviors who also carry one or more copies of the minor allele (+) and those homozygous for the major allele (−) in 1534 European-American female twins aged 18–29 years.

SNP	Base-pair	Minor Allele Frequency[#]	Weight/Shape Concerns		Binge Eating		Compensatory Behaviors	
			+	−	+	−	+	−
rs1923882	46309662	0.23 (A/G)	24.4	26.7	7.3	6.4	16.9*	21.2*
rs9567735	46317205	0.15 (G/A)	26.7	25.5	7.3	6.6	21.8	18.6
rs6561333[%]	46318313	0.45 (A/G)	24.8	25.8	5.6*	9.9*	19.8	19.5
rs2296972	46326472	0.28 (A/C)	24.1	27.4	5.0**	8.5**	19.9	19.1
rs9316233	46331356	0.18 (C/G)	24.6	26.4	7.3	6.5	19.1	19.5
rs1928042	46335217	0.24 (C/A)	26.1	25.5	6.8	6.8	18.8	19.9
rs582385	46343995	0.18 (G/A)	26.9	25.3	7.1	6.6	18.8	19.7
rs1928040	46345237	0.35 (A/G)	26.5	24.7	6.5	7.1	19.8	18.9
rs731779	46350039	0.21 (C/A)	24.0	26.8	6.1	7.2	20.3	19.0
rs985933	46353864	0.39 (A/G)	24.8	27.3	6.5	7.2	20.5	17.6
rs927544	46354052	0.30 (G/A)	25.4	26.3	6.3	7.3	20.6	18.3
rs9534505	46358745	0.09 (A/G)	23.3	26.3	6.3	6.9	18.8	19.4
rs4941573	46362858	0.42 (G/A)	25.30	26.8	6.9	6.6	19.4	19.7
rs1328685	46369891	0.10 (G/A)	24.1	26.2	7.8	6.5	19.4	19.5
rs4142900	46371551	0.48 (A/C)	25.0	28.0	6.3	8.0	19.0	20.7

[#]Alleles presented as minor/major. Positions based on NCBI build 36.3; "+" carriers of minor allele; "−" homozygous for major allele.

*p-value less than 0.05

**p-value less than 0.005;

[%]only typed in the first round of genotyping; no longer supported by assay design, N=1039