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Effects of fat mass and obesity-associated (*FTO*) gene polymorphisms on binge eating in women with binge-eating disorder: The moderating influence of attachment style

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ABSTRACT

Objectives: The genetics of binge-eating disorder (BED) is an emerging topic and one candidate pathway, namely the fat mass and obesity-associated (*FTO*) gene, may be implicated because of its role in food reward sensitivity and self-regulation of eating. The aims of this study were to examine the independent effects of variants of *FTO* on binge frequency in women with and without BED and to examine the moderating role of interpersonal attachment in this association.

Methods: Secondary data analysis was conducted on a cross-sectional comparison of three groups of women in a trial of group treatment for BED: BED with obesity (n = 73), BED without obesity (n = 55), and normal weight without BED (n = 50). Women were genotyped for five of the most common *FTO* single-nucleotide polymorphisms, *rs9939609, rs8050136, rs3751812, rs1421085*, and *rs1121980*, which have been related to body mass index and energy intake. Binge frequency (Eating Disorder Examination), body composition (bio-electric impedance), and attachment (Attachment Style Questionnaire) were assessed.

Results: There were no significant between-group differences for frequencies of *FTO* alleles, nor were there any significant anthropometric associations. The *FTO* × attachment interaction was significant whereby, relative to a low-risk *FTO* genotype, individuals with a high-risk genotype for the SNP *rs1421085* and high-avoidant attachment had higher mean binge frequency than those with high genetic risk but low-avoidant attachment ($\beta = -7.96$; $t = -2.07$; $P = 0.042$).

Conclusions: FTO genotypes associated with risk for obesity and loss of control of eating, specifically *rs1421085*, may interact with insecure attachment in a way that may exacerbate binge eating among women with BED.

Introduction

Binge-eating disorder (BED) is the most prevalent eating disorder [1] and is characterized by persistent episodes of overeating accompanied by loss of control (i.e., binge eating) and significant distress over binge eating, but with no compensatory behaviors such as vomiting, excessive exercise, or laxative misuse. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defined BED by one binge episode per week, on average, for 3 mo [2]. Furthermore, it is estimated that 8% of individuals with obesity, and 20% to 30% of patients with obesity participating in weight loss programs, meet criteria for BED [3], indicating that BED is more common among individuals living with overweight and obesity or in clinical populations seeking treatment for weight loss [4].

Overall, it has been shown with considerable agreement that BED aggregates in families, with heritability estimates (liability owing to additive genetic effects) of ~45% [5,6], leaving the

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remaining variance attributable to unique environmental factors. To date, the strongest known susceptibility locus for obesity is the fat mass and obesity-associated (*FTO*) gene, where single-nucleotide polymorphisms (SNPs) that cluster in the first intron show the strongest association with body mass index (BMI; effect size of ~0.35 kg/m^2 per allele) and obesity risk [7,8]. Although the mechanisms by which *FTO* variants influence obesity are unclear, recent research is emerging that shows *FTO* associations with anorexia nervosa and bulimia nervosa [9] and with BED [10,11]. Indeed, variants of the *FTO* gene are related to poor behavioral regulation and BED, suggesting a genetic role in the pathogenesis of BED.

One important theoretical framework that is grounded in environmental and social influences of BED is research on attachment theory [12]. Attachment is important to the healthy development of regulatory behaviors, such as emotion regulation, the regulation of feeding and eating, and reward sensitivity [13,14]. It is known that impaired self-regulatory behaviors are a risk factor for obesity and BED. More specifically, attachment theory describes how variations in child–caregiver rearing environment can determine a person's later relationship patterns and affect regulation and attachment style [12]. Attachment is often conceptualized as secure or insecure. Securely attached individuals have more stable relationships and are better able to regulate emotional distress, sensations of hunger and satiety, and eating behavior [13]. Insecure attachment style is subcategorized as anxious or avoidant, and both have been associated with poor regulation of emotions, disordered eating, weight gain, and obesity [15,16]. Attachment anxiety may confer risk for eating-disorder severity because of an upregulation of negative emotions (i.e., anxiety and depression), poor body image, and associated problematic eating behaviors [17]. On the other hand, attachment avoidance also may lead to greater eating-disorder symptoms by maladaptive downregulation of emotions, alexithymia, and restrained eating [17].

It is well accepted that the function of individual SNPs may interact with obesity phenotypes such as food reinforcement, reward sensitivity, and overeating [18–20]. However, there is a paucity of data examining the putative associations of these polymorphisms in the clinical population of BED. As such, we examined individual genetic associations based on five of the most common *FTO* SNPs (*rs9939609, rs8050136, rs3751812, rs1421085*, and *rs1121980*) [19] that are related to BMI and energy intake. Thus, in this cross-sectional analysis of secondary data of women living with overweight and obesity and with BED, compared with age- and weight-matched controls of women without BED and age-matched normal-weight women without BED, we aimed to examine whether the prevalence of polymorphisms at the *FTO* locus differ between women living with obesity with and without BED and normal-weight controls and to examine whether attachment style in women with BED moderates the association between variants of *FTO* genes and binge-eating frequency. We predicted that the frequency of *FTO* SNPs associated with disordered feeding and reward would be higher in women with BED than in the the two non-clinical control groups. Moreover, we predicted that attachment style and *FTO* polymorphisms would interact such that individuals with *FTO* risk genotypes and with anxious or avoidant attachment styles would report greater binge frequency than those women with the *FTO* no-risk genotype who have less anxious or avoidant attachment.

Methods

Ethics statement

This research project was approved by the Ottawa Health Science Network Research Ethics Board. All participants signed informed consent forms before enrollment into the study. Once enrolled, participants were assigned a unique study code, which allowed for de-identification and confidentiality throughout the study.

Study design and participants

In a secondary analysis of data, we performed cross-sectional comparisons between three groups:

1. Overweight and obese women (BMI ≥27 kg/m^2) with BED who responded to an invitation or advertisement to participate in a trial of group psychological treatment for BED (n = 73).
2. Age- and weight-matched overweight women without BED (n = 55).
3. Age-matched normal-weight women (BMI ≥ 20 and BMI ≤ 27 kg/m^2) without BED (n = 50).

Participants in the two groups of women without BED were matched to the BED sample on age so that there were equal proportions of individuals in each decade (i.e., 18–20, 21–30, and 31–40 y, etc.). Participants without BED in the overweight group were also matched to the BED sample on BMI so that there were equal proportions in each weight class (i.e., BMI 27–29.9, 30–34.9, 35–39.9, and ≥40 kg/m^2). These three groups of women were asked to provide data at one time point for the cross-sectional comparisons. Exclusion criteria for all participants included the inability to speak or read English, current or past inappropriate compensatory behaviors (e.g., vomiting), drug or alcohol abuse in the previous 6 mo, a diagnosis of bipolar disorder or a psychotic disorder, pregnancy, a diagnosis of diabetes, and a past or current history of cancer. Control condition participants could not have a current or past eating disorder, including BED. More details can be found elsewhere [21].

Procedure

BED participants were women referred from a tertiary care eating disorders program or respondents to community newspaper advertisements for treatment of binge eating. Women without BED (overweight and normal weight) responded to community newspaper advertisements to participate in a study on women's health. A research coordinator screened participants by phone for exclusion criteria, described the nature of the study, and assessed for the presence of BED using the Structured Clinical Interview for DSM-IV Axis I Disorders [22].

Measures

Binge eating

The primary outcome variable was the number of days binged in the previous 28 d. Days binged were assessed by a research coordinator unaware of the individuals' levels of attachment anxiety, using the Eating Disorder Examination (EDE) [23] semistructured interview. The first assessment of binge days was conducted over the phone before the women attended an in-person interview, and subsequent assessments were conducted in person. All Eating Disorder Examination interviews were audio recorded.

Weight, BMI, and fat percentage

Participants were all weighed on the same standard scale (Tanita Body Composition Analyser, BC-418). Participants were asked to step onto the sanitized scale with bare feet for the purpose of estimating body composition. Height and waist circumference was measured with the same measuring tape for each participant.

Attachment anxiety

The Attachment Styles Questionnaire (ASQ) [24] was used to assess attachment and is a self-reported measure with 40 items rated on a scale from 1 to 6. The ASQ can be scored as five scales including Confidence in Relationships (8 items), in which higher scores indicate greater attachment security. For this study we were interested in the effects of attachment anxiety and avoidance, so we focused on the four attachment insecurity scales. The Relationships as Secondary (7 items) and Discomfort with Closeness (10 items) scales are indices in which higher scores indicate greater attachment avoidance. Preoccupied (8 items) and Need for Approval (7 items) are scales in which higher scores indicate greater attachment anxiety. Questions on the ASQ include: "Overall I am a worthwhile person" (Confidence); "My relationships with others are generally superficial" (Relationships as Secondary), "I find it difficult to depend on other people" (Discomfort with Closeness), "I worry a lot about my relationships" (Preoccupied), and "Sometimes I think I am no good at all" (Need for Approval). In a previous study, internal consistency of ASQ scales within BED samples were good and ranged from coefficient α of 0.70 to 0.83 and mean interitem correlations of 0.20 to 0.41 [25].

Genotyping

Whole blood was collected from participants through a peripheral venipuncture, and aliquots of 1 mL whole blood was frozen for DNA extraction and

Table 1
Demographic data (means ± standard deviation) for women living with obesity with BED, women living with overweight or obesity without BED, and normal-weight women without BED

Characteristic	BED* (n = 73)	Overweight or obese (n = 55)	Normal weight (n = 50)
Age (y)	44.2 (11.2)	46.1 (11.9)	43.8 (11.9)
Body weight (kg)	103.3 (20.3)	98.5 (19.2)	62.3 (6)
Height (cm)	164.4 (7)	163 (6.5)	164 (5.4)
BMI (kg/m^2)	38.1 (6.7)	37 (6.5)	23.2 (2)
Waist (cm)	112.5 (15)	109.4 (14.8)	77.2 (7)
Fat mass (kg)	48.3 (14.4)	45.9 (14.1)	18.1 (4.4)
Body fat (%)	20.8 (2.5)	20.7 (2.6)	13.1 (2.3)
Family income (%)			
$10 000–$19 000	2 (2.9)	1 (1.9)	1 (2.1)
$20 000–$29 000	4 (5.7)	0 (0)	0 (0)
$30 000–$39 000	5 (7.1)	2 (3.9)	0 (0)
$40 000–$49 000	13 (18.6)	2 (3.9)	3 (6.3)
$50 000–$59 000	7 (10)	8 (15.4)	3 (6.3)
$60 000–$69 000	8 (11.4)	4 (7.7)	5 (10.4)
$70 000–$79 000	10 (14.3)	7 (13.5)	6 (12.5)
≥$80 000	21 (30)	28 (53.9)	30 (62.5)

BED, binge-eating disorder; BMI, body mass index.
*BED measured by clinical interview.

genotyping analysis. Multiplex SNP genotyping was performed using the MassARRAY system with iPLEX technology (Agena Bioscience Inc., San Diego, CA, USA). Five SNPs were assayed by primer extension and mass spectrometry. A custom Agena Bioscience primer assay was used for primer extension. Polymerase chain reaction extension primers were designed using MassARRAY Assay Design software v3.0.2.0. Genotypes were called automatically using MassARRAY Typer software v4.0 and were visually inspected.

Statistical analysis

Participant characteristics are presented as means with standard deviations (SDs) for continuous data and frequencies with percentages for categorical data. Genotype frequencies for *FTO* SNPs were compared in BED, overweight or obese non-BED, and normal-weight non-BED samples using the χ^2 test statistic, and effects sizes were reported as Cramer's V. Anthropometric variables were compared between *FTO* risk alleles within BED, non-BED, and normal-weight groups using the χ^2 tests. Binge frequency was assessed across *FTO* genotype and ASQ attachment insecurity scale scores to determine any effects of level of attachment insecurity and genotype on binge eating. We categorized individuals with BED into high or low levels on each of the four ASQ attachment insecurity scales by using a median split of the sample based on their score on the respective scale. Interaction terms were created in a linear multiple regression model with binge frequency as the dependent variable, and genotype, ASQ insecurity scale level (high vs low), and genotype × ASQ insecurity scale level as independent variables.

Table 2
Allele and genotype frequencies for fat mass and obesity-associated (*FTO*) gene in women living with obesity with BED (n = 73), women living with overweight or obesity without BED (n = 55), and normal-weight women without BED (n = 50)

Group	*FTO* rs1121980								Cramer's V
	Allele			Genotype		χ^2			
	GG	GA	AA	GG/GA (risk)	AA	DF	Value	*P*-value	
BED* (%)	15 (20.6)	41 (56.2)	17 (23.3)	56 (76.7)	17 (23.3)	2	1.22	0.54	0.083
Normal (%)	7 (14)	27 (54)	16 (32)	34 (68)	16 (32)				
Overweight/Obese (%)	9 (16.4)	30 (54.6)	16 (29.1)	39 (70.9)	16 (29.1)				
Group	*FTO* rs1421085								Cramer's V
	Allele			Genotype		χ^2			
	CC	TC	TT	CC/TC (Risk)	TT	DF	Value	*P*-value	
BED* (%)	15 (20.6)	39 (53.4)	19 (26)	54 (74)	19 (26)	2	2.45	0.29	0.11
Normal (%)	7 (14)	24 (48)	19 (38)	31 (62)	19 (38)				
Overweight/Obese (%)	9 (16.4)	26 (47.3)	20 (36.4)	35 (63.6)	20 (36.4)				
Group	*FTO* rs3751812								Cramer's V
	Allele			Genotype		χ^2			
	TT	GT	GG	TT/GT (Risk)	GG	DF	Value	*P*-value	
BED* (%)	14 (19.2)	39 (53.4)	20 (27.4)	53 (72.6)	20 (27.4)	2	2.36	0.31	0.11
Normal (%)	6 (12)	24 (48)	20 (40)	30 (60)	20 (40)				
Overweight/Obese (%)	9 (16.4)	26 (47.3)	20 (36.4)	35 (63.6)	20 (36.4)				
Group	*FTO* rs8050136								Cramer's V
	Allele			Genotype		χ^2			
	AA	CA	CC	AA/CA (Risk)	CC	DF	Value	*P*-value	
BED* (%)	14 (19.2)	39 (53.4)	20 (27.4)	53 (72.6)	20 (27.4)	2	1.65	0.44	0.09
Normal (%)	6 (12)	25 (50)	19 (38)	31 (62)	19 (38)				
Overweight/Obese (%)	9 (16.4)	27 (49.1)	19 (34.6)	36 (65.5)	19 (34.6)				
Group	*FTO* rs9939609								Cramer's V
	Allele			Genotype		χ^2			
	AA	AT	TT	AA/AT (Risk)	TT	DF	Value	*P*-value	
BED* (%)	14 (19.2)	39 (53.4)	20 (27.4)	53 (72.6)	20 (27.4)	2	1.65	0.44	0.09
Normal (%)	6 (12)	25 (50)	19 (38)	31 (62)	19 (38)				
Overweight/Obese (%)	9 (16.4)	27 (49.1)	19 (34.6)	36 (65.5)	19 (34.6)				

BED, binge-eating disorder; BMI, body mass index; *FTO*, fat mass and obesity-associated gene.
Risk genotypes for *FTO* are associated with elevated BMI, body fat, loss of control of eating, and energy intake.
*BED measured by clinical interview.

Results

Participant characteristics are reported in Table 1.

Genotype frequencies for *FTO* genes are summarized in Table 2 and demonstrate that there were no significant differences in the frequencies of *FTO* alleles by group, and effects sizes were small. As well, there were no significant associations between *FTO* risk alleles and anthropometric variables by group (results not shown).

There was a significant interaction for the *FTO rs1421085* risk genotype and the ASQ Relationships as Secondary scale level ($\beta = -7.96$; $t = -2.07$; $P = 0.042$; Table 3). Here the *FTO rs1421085* risk score showed higher binge frequency in the subgroup of individuals with high ASQ Relationships as Secondary, and the effect was reversed in those with low Relationships as Secondary where individuals had lower binge frequency with the *FTO rs1421085* risk score. Similarly, there was an interaction trend for the *FTO rs1121980* risk genotype and ASQ Relationships as Secondary level ($\beta = -7.84$; $t = -1.96$; $P = 0.054$; Table 3). Here the *FTO rs1121980* risk genotype showed highest binge frequency in the subgroup of individuals with high level of ASQ Relationships as Secondary (i.e., high-avoidant attachment). The effect was reversed in those with low scores on the Relationships as Secondary subscale where individuals had lower binge frequency with the *FTO rs1121980* risk genotype. No other significant *FTO* interactions emerged with ASQ attachment insecurity variables.

Discussion

To our knowledge, this is the first study to examine these *FTO* polymorphisms in a clinical sample of patients with BED as diagnosed with the current gold standard of interview-based assessment. Contrary to our first hypothesis, when comparing women living with overweight or obesity and with BED to age- and weight-matched controls of women without BED and age-matched normal-weight women without BED, we found there were no significant group differences in the frequencies of polymorphisms of the *FTO* gene. However, our second hypothesis was partially confirmed as individuals with the *FTO rs1121980* and *rs1421085* risk genotypes demonstrated higher binge frequency in the subgroup of individuals when they had high attachment avoidance as measured by the ASQ Relationship as Secondary scale. This trend was reversed in those with low attachment avoidance, where individuals with the *FTO* risk genotypes had lower binge frequencies than the *FTO* non-risk genotype (Table 3).

Eating disorders show a multifactorial etiology, including psychological, environmental, and biological factors [22]. Indeed, heritability estimates of ~45% [5,6] have been established, indicating a near equal influence of genes and environment on the expression of BED. Although several candidate genes (e.g., dopamine, serotonin, melanocortin, etc.) [26] and circulatory factors (e.g., insulin-like growth factor 2) [27] have been investigated regarding the genetics and neurobiology of BED, more recently the *FTO* gene has generated great interest [26], owing in part to the significant associations with BMI and obesity risk [7,8] and more directly with recent associations with BED [10,11]. Overall, in the current sample we did not observe any associations between individual *FTO* SNPs (related to obesity risk) and anthropometric variables. There were no significant differences in the frequencies of *FTO* alleles by group, nor were there differences across groups (see Table 2). It has been pointed out by other groups that ethnicity can explain null findings, whereby *FTO* SNPs in the Asian and black populations explain less variation in BMI or energy intake [28], but our sample was largely of European decent. Thus, overall our data on genetic associations of risk genotype with BED were not significant.

Table 3
Binge frequency by *FTO* risk genotypes and attachment style in women with BED* (n = 73)

Genotype	ASQ Discomfort			ASQ Relationship as Secondary			ASQ Preoccupation			ASQ Need for Approval		
	0–38 (n = 38)	>38 (n = 35)	*P*-value	0–19 (n = 37)	>19 (n = 36)	*P*-value	0–31 (n = 41)	>31 (n = 32)	*P*-value	0–29 (n = 38)	>29 (n = 35)	*P*-value
FTO rs1121980												
GG/GA (Risk)	14 (7.6)	15.3 (7.4)	0.39	14 (5.7)	15.3 (9)	0.05	14.7 (7.5)	14.6 (7.6)	0.56	13.4 (7.8)	15.8 (7.1)	0.26
AA	16.3 (7.1)	14 (6.5)		18.6 (7.8)	12 (3.3)		14.6 (6.3)	17 (8)		16.3 (6.7)	13.6 (7.4)	
FTO rs1421085												
CC/TC (Risk)	14.4 (7.5)	15.1 (7.4)	0.85	14 (5.7)	15.5 (8.9)	0.04	14.7 (7.5)	14.8 (7.4)	0.77	13.8 (7.7)	15.6 (7.1)	0.64
TT	15.2 (7.8)	15.1 (6.6)		18.6 (7.8)	12.1 (5.3)		14.6 (6.3)	15.9 (8.7)		15.2 (7.4)	15 (7.5)	
FTO rs3751812												
TT/GT (Risk)	14.4 (7.5)	15.4 (7.3)	0.6	14.3 (5.6)	15.5 (8.9)	0.09	15 (7.4)	14.8 (7.4)	0.6	14.1 (7.7)	15.6 (7.1)	0.8
GG	15.2 (7.8)	14.1 (6.8)		17.4 (8.2)	12.1 (5.3)		14 (6.4)	15.9 (8.7)		14.6 (7.4)	15 (7.5)	
FTO rs8050136												
AA/CA (Risk)	14.4 (7.5)	15.4 (7.3)	0.6	14.3 (5.6)	15.5 (8.9)	0.09	15 (7.4)	14.8 (7.4)	0.6	14.1 (7.7)	15.6 (7.1)	0.8
CC	15.2 (7.8)	14.1 (6.8)		17.4 (8.2)	12.1 (5.3)		14 (6.4)	15.9 (8.7)		14.6 (7.4)	15 (7.5)	
FTO rs9939609												
AA/AT (Risk)	14.4 (7.5)	15.4 (7.3)	0.6	14.3 (5.6)	15.5 (8.9)	0.09	15 (7.4)	14.8 (7.4)	0.6	14.1 (7.7)	15.6 (7.1)	0.8
TT	15.2 (7.8)	14.1 (6.8)		17.4 (8.2)	12.1 (5.3)		14 (6.4)	15.9 (8.7)		14.6 (7.4)	15 (7.5)	

BED, binge-eating disorder; BMI, body mass index; *FTO*, fat mass and obesity-associated gene.
Risk genotypes for *FTO* are associated with elevated BMI, body fat, loss of control of eating, and energy intake.
*BED measured by clinical interview.

This study had several methodological strengths and weaknesses. Strengths of this study include the clinical sample of women with the gold standard diagnosis of BED, along with carefully matched control groups. In addition, we believe this was the first study to examine and document that *FTO* polymorphisms interact with attachment style to affect binge-eating frequency in a clinical population, which are novel findings that warrant replication and further investigation. The sample size was comparable to other studies examining the genetics of BED, but nonetheless may have limited our statistical power to identify statistically significant genetic associations.

Conclusions

We found that two *FTO* SNPs previously associated with obesity and eating behavior (i.e., *rs1121980* and *rs1421085*) also interacted with anxious attachment in a way that manifested by increased binge frequency, which to our knowledge are novel findings. This would suggest that certain *FTO* polymorphisms appear to interact with attachment style to exacerbate binge eating in women with obesity and BED. Indeed, data from twin studies have suggested that attachment is driven primarily by environmental causes [29], but the majority of attachment studies have focused on very young children [30], and more recent studies including older populations have found strong evidence of genetic influence on attachment security [31], leaving Fearon and Roisman [30] to suggest that genetic and environmental influences might shift over the course of development in favor of genetics. In other words, carrying specific genes or having a specific genetic polymorphism at a particular gene locus might be associated with developing a particular attachment style in a particular kind of social environment. Overall, our findings need to be replicated with larger samples in order to determine the independent and interactive effects of *FTO* polymorphisms on attachment style, and other environmental factors, in the etiology and maintenance of BED. Moreover, our findings support the conduct of intervention studies to determine whether targeting attachment-based therapies in treatment would optimize outcomes in those with BED compared with either treatment modality alone.

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