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A Season-of-Birth/DRD4 Interaction Predicts Maximal Body Mass Index in Women with Bulimia Nervosa

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We have earlier reported that season of birth interacts with the hypofunctional 7-repeat (7R) allele of the dopamine-4 receptor gene (DRD4) to promote weight gain and obesity in women with seasonal affective disorder (SAD). This study examined whether this gene–environment interaction influences body weight regulation in women with bulimia nervosa (BN). In 188 female probands with BN, we performed an analysis of covariance predicting maximum lifetime body mass index (BMI) using season-of-birth, DRD4 genotype (7R present/absent), and past history of anorexia nervosa (yes/no) as independent variables, and age at maximum weight as the co-variate. Consistent with our SAD study, the birth-season × DRD4 interaction was a significant predictor of maximal BMI. Although in SAD, the *spring*-birth/7R+ group had markedly elevated maximal BMIs and high rates of obesity, in this BN sample, the *fall*-birth/7R+ group exhibited the highest BMI values ($N = 17$: mean maximal BMI = 28.2 kg/m^2 (SE 0.9) *vs* 25.2 kg/ m^2 (SE 0.3) for all other probands combined ($N = 171$); $p = 0.002$). The lifetime rate of obesity (BMI > 30) was also higher in the fall-birth/7R+ *vs* 'other' group (29.9 *vs* 8.8%, respectively, $p = 0.008$). These data offer further evidence that season of birth interacts with the 7R allele of DRD4 to influence body weight regulation in female overeating populations.

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INTRODUCTION

Developmental plasticity refers to the process by which genetic programs are modified in response to environmental conditions to shape physiology and behavior. In human beings, much of the work in this area has focused on the early origins of obesity and metabolic disorders, and is based on the fundamental notion that over the course of evolution, developing organisms would greatly enhance their chance of survival by matching long-term energy intake and metabolism to environmental conditions anticipated after birth. For example, the *thrifty phenotype hypothesis of* Hales and Barker (2001) proposes that a low-birth weight and long-term insulin resistance are adaptive if food supplies are scarce and likely to remain so over time. A thrifty phenotype is thought to be triggered by one or more signals of maternal malnutrition passing across the placenta to the developing fetus, thus providing the fetus with a forecast of a sparse nutritional environment. If the prediction proves wrong and food supplies become abundant, the thrifty phenotype becomes a risk factor for obesity, diabetes, and cardiovascular disease.

We have recently proposed a *seasonal thrifty hypothesis* to explain the early developmental origins of obesity in the context of winter seasonal affective disorder (SAD; Levitan *et al*, 2006), a recurrent form of mood disorder characterized by overeating and weight gain in a majority of cases (Rosenthal *et al*, 1984). According to our model, one phenotype of SAD reflects the vestigial expression of a genetic program designed to preserve body mass in the face of predictable seasonal famines. The proposed trigger is an early signal of latitude transmitted *in utero* through maternal melatonin and/or diet (Levitan *et al*, 2006). As is the case with the original thrifty phenotype, such a process becomes maladaptive in a plentiful food environment, leading to high rates of obesity in SAD patients with this vulnerability.

The specific finding that inspired our thrifty model was an interaction between season-of-birth and the 7-repeat (7R) allele of the dopamine-4 receptor gene (DRD4) in predicting obesity in women with SAD (Levitan *et al*, 2006). DRD4 is of particular interest as a putative 'thrifty gene' for several reasons: (1) the 7R variant of DRD4 is hypofunctional

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(Asghari *et al*, 1995), and low-dopamine activity is thought to have a major function in overeating and obesity (Wang *et al*, 2001; Volkow and Wise, 2005; Stice *et al*, 2008); (2) there is mounting evidence that 7R carriers may have a unique ability to adapt appetitive behavior and body composition to anticipated climactic conditions (Levitan *et al*, 2006; Eisenberg *et al*, 2008); (3) there has been strong positive selection of the 7R allele in the last 40 000 years of human evolution (Ding *et al*, 2002). It has been suggested that the ability of 7R to optimize weight and energy regulation under extreme environmental conditions, particularly in migrating populations, might have had a function in this regard (Levitan *et al*, 2004, 2006; Eisenberg *et al*, 2008).

This study looks at whether season of birth interacts with the 7R allele of DRD4 to predict weight gain and obesity in a second group of female overeaters, that is women with bulimia nervosa (BN). It was hypothesized that in a heterogenous group of women with BN, the interaction of DRD4 genotype (defined by the presence or absence of the hypofunctional 7R allele) and birth season (spring/summer/fall/winter) would be associated with increased maximal lifetime body mass indices (BMIs), thus replicating our overall findings in women with SAD.

MATERIALS AND METHODS

Sample

The current sample consisted of 188 consecutive female probands, 16–50 years of age, with DSM IV-defined BN with or without a past history of anorexia nervosa (AN). Ancestral information was available for 182 probands. Of these, 165 (90.7%) were Caucasian, 10 (5.5%) Oriental, 4 (2.2%) West Indian, 2 (1.1%) Native Canadian, and 1 (0.5%) African American. To limit the impact of morbid obesity because of rare genetic variants on the current results, individuals with a maximal lifetime BMI of >50 were excluded. To simplify the interpretation of results, BN probands meeting full DSM-IV criteria for SAD were also excluded. Subjects were recruited from a well-established eating disorder treatment program or from the community through newspaper advertisements. They were initially screened on the telephone and then personally interviewed using the structured clinical interview for DSM IV (First *et al*, 2002) and the eating disorder examination (Cooper *et al*, 1989). Maximum and minimum weight achieved from age 16 years onward (excluding pregnancy) with corresponding heights and ages were obtained through self-report. BMI was calculated for each subject based on the formula (weight in kilograms/corresponding height in meters^2).

Each subject was given an oral and written summary of the purposes, procedures, and potential risks of the project and gave informed written consent. The protocol was approved by the University of Toronto and University of British Columbia research ethics committees.

Laboratory Methods

Blood samples were sent to the Centre for Addiction and Mental Health neurogenetics laboratory. Genomic DNA was extracted from white blood cells using the high-salt method. All genotyping of the DNA was performed blind to psychiatric diagnosis and vice versa. This was facilitated through a standard patient identification coding system used by our laboratory. The 48 base pair VNTR region in the third exon of *DRD4* was amplified using polymerase chain reaction (PCR) techniques with primers and conditions earlier published (Lichter *et al*, 1993). The PCR products were visualized through gel electrophoresis performed in 3.5% agarose prepared with ethidium bromide and 1X TBE (Tris, boric acid, EDTA).

Statistical Methods

The same statistical approach as described in our earlier manuscript was used (Levitan *et al*, 2006), except that a dichotomous categorical variable (history of AN *vs* no history of AN) was added as a factor to the current analysis. In summary, to study the main effect of genotype, two genotypic groups were defined based on whether a given proband did or did not carry at least one version of the hypofunctional 7R allele of DRD4 (designated the 7R and no7R groups, respectively). To study the main effect of birth season, four season-of-birth groups were defined based on the calendar year, that is spring births had occurred between 22 March and 21 June inclusive, summer births were between 22 June and 21 September inclusive, fall births between 22 September and 21 December inclusive, and winter births between 22 December and 21 March inclusive. The genotype $\times$ birth-season interaction thus included eight groups, including four with the 7R allele (7R/spring, 7R/summer, 7R/fall, and 7R/winter) and four without this allele (no7R/spring, no7R/summer, no7R/fall, and no7R/winter).

A 2 [genotype] $\times$ 4 [season of birth] $\times$ 2 [history of AN] analysis of covariance (ANCOVA) was carried out with maximum lifetime BMI as the dependent variable and age at maximal BMI as the co-variate. Where applicable, *post hoc* analyses used the least significant difference test.

The significance level for the main ANCOVA was set at $p<0.01$. Given the large number of study groups, which limits statistical power, a significance level of 0.05 was set for the main and interaction effects and *post hoc* tests, as was performed in our prior analyses of SAD probands.

RESULTS

Sample Characteristics

Error terms for unadjusted means are SDs and BMI measures are in kg/m^2. The mean current age of the sample was 25.2 ($\pm$6.2) years. The mean current BMI was 22.4 ($\pm$4.1), the mean minimal lifetime BMI was 18.6 ($\pm$2.6), and the mean maximum BMI was 25.5 ($\pm$4.3). Eighty probands (42.6%) had a past history of AN.

The frequency of the common 4R and 7R alleles was 69.1 and 17.3%, respectively, highly consistent with our prior study in women with SAD (Levitan *et al*, 2006). There was no deviation from Hardy–Weinberg equilibrium. There were 61 probands (32.4%) with at least one version of the 7R allele.

Table 1 General Linear Model Predicting Maximum Lifetime Body Mass Index (BMI) with DRD4 Genotype, Birth Season, and Past History of Anorexia Nervosa (AN), Co-varied by Age at Maximal BMI in 188 Women with Bulimia Nervosa

	df	F	*p*-value	Partial η^2	Power
Overall model	16	5.56	<0.0001	0.342	1.00
Source					
Age at maximal BMI	1	46.44	<0.0001	0.214	1.00
DRD4 genotype[a]	1	7.39	0.007	0.041	0.77
Birth season[b]	3	3.20	0.025	0.053	0.73
Past AN	1	5.81	0.017	0.033	0.67
DRD4 × birth season	3	2.92	0.036	0.049	0.69
DRD4 × past AN	1	0.11	0.743	0.001	0.06
Birth season × past AN	3	2.08	0.105	0.035	0.53
DRD4 × birth season × past AN	3	1.94	0.125	0.033	0.50
Error	171				
Total	188				

Abbreviation: df, degrees of freedom.
[a]Genotype defined by the presence or absence of the 7-repeat allele of DRD4.
[b]Spring = 22 March–21 June; Summer = 22 June–21 September; Fall = 22 September–21 December; Winter = 22 December—21 March.

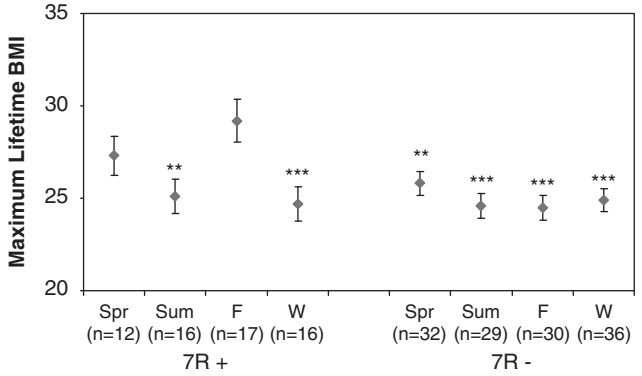

Figure 1 Marginal means for maximal lifetime BMI (±SEM) in groups defined by the interaction of DRD4 genotype (7R present/absent) and season of birth in 188 women with Bulimia Nervosa. ** <7R+ fall-birth group at $p \leqslant 0.01$; *** <7R+ fall-birth group at $p \leqslant 0.001$.

Maximal BMI, DRD4, Season of Birth, and Past AN

The mean maximal BMIs for carriers and non-carriers of the 7R allele were 26.4 ± 5.3 and 25.0 ± 3.6, respectively. The mean maximal BMIs based on birth-season groupings were spring 26.0 ± 5.8 ($N = 44$); summer 24.6 ± 2.8 ($N = 45$); fall 26.6 ± 5.2 ($N = 47$); and winter 24.8 ± 2.9 ($N = 52$). The mean maximal BMIs in probands with and without a history of AN were 24.4 ± 3.8 and 26.3 ± 4.4, respectively.

The results of the general linear model predicting maximal BMI with genotype, birth season, and AN history, with age at maximal BMI as a co-variate are summarized in Table 1. As shown, the overall model was highly significant ($F = 5.56$, df = 16, 171; $p < 0.0001$), accounting for 34.2% of the variance in maximal lifetime BMI in this sample. The genotype × birth-season interaction and the main effects of genotype, birth season, and AN history were all statistically significant. None of the other interaction terms met statistical significance. *Post hoc* testing of birth-season effects revealed that BN probands with a fall birth had a greater mean maximal BMI than did probands born in either summer or winter at $p < 0.05$. No other pairwise group differences related to birth season were identified at this step.

Post hoc Testing of the DRD4/Birth-Season Interaction

Figure 1 summarizes the marginal means for maximal BMI in the eight subgroups defined by the interaction of DRD4 genotype (7R present or absent) and season of birth (spring, summer, fall, and winter). *Post hoc* testing revealed that all of the significant pairwise group differences were attributable to the high mean maximal BMI in 7R carriers born in the fall (ie the 7R/fall-birth group). As indicated, this group had a significantly higher value than four of the other interaction groups at $p \leqslant 0.001$, and two of the interaction groups at $p \leqslant 0.01$. The 7R/spring-birth group, which had by far the highest maximal BMI in our SAD sample (Levitan *et al*, 2006), did not differ significantly from any of the other interaction groups in this BN sample.

Rates of Obesity

On the basis of these findings, lifetime rates of obesity were next compared in the 7R/fall-birth and 'other' groups using Pearson χ^2. The corresponding rates of obesity were 7R/fall-birth group = 5/17 (29.4%) *vs* 'other' group = 15/171 (8.8%); $\chi^2 = 6.93$, df = 1; $p = 0.008$; ODDS ratio = 4.33, 95% CI = 1.34–13.96.

Analysis of Caucasian Probands

To determine whether population stratification might have accounted for the current findings, we repeated our main analyses in the subgroup of probands of Caucasian ancestry ($N = 165$). In this sub-sample, the overall statistical model remained highly significant ($F = 4.89$, df = 16, 148, $p < 0.001$), accounting for 34.6% of the variance in maximal lifetime BMIs, whereas the genotype by birth-season interaction met a trend level of significance ($F = 2.16$, df = 3, 148, $p = 0.095$). *Post hoc* analysis revealed that the 7R-fall-birth group had a significantly higher mean maximal BMI than five of the other interaction groups at $p \leqslant 0.01$ and one of the interaction groups at $p < 0.05$. The marginal means for maximal BMI in the 7R/fall-birth ($N = 14$) and 'other' ($N = 151$) groups defined above were 27.9 kg/m^2 (SE 1.0) and 25.2 kg/m^2 (SE 0.3), respectively ($F = 6.64$, df = 2, 162, $p = 0.011$). It would thus seem that limiting the analysis to Caucasian probands only did not have a major effect on the overall pattern of results.

DISCUSSION

In showing that the 7R allele of DRD4 interacts with birth season to predict maximal BMI and obesity in women with BN, the current results extend our prior findings in overeating women with SAD (Levitan *et al*, 2006). In this BN sample, 7R carriers born in the *fall* exhibited the highest maximal BMI values, whereas in our SAD sample, it was the 7R/*spring*-birth group who accounted for all of the significant effects. It would seem that during fetal and/or perinatal development, unknown factors tied to birth season interact with the hypofunctional 7R allele to influence maximal extremes of body weight in these female overeating populations. The overall pattern of results across our two studies suggests that different seasonal mechanisms might operate in these two disorders.

To explain why the season-of-birth effects found in BN were 6 months out-of-phase to our SAD data, more information on maternal eating disorders, food intake in pregnancy, birth weights, early feeding patterns, and the growth trajectories of our probands would be of great interest (Stewart *et al*, 1987; Treasure and Russell, 1988; Conti *et al*, 1998; Bulik *et al*, 1999, 2009; Sollid *et al*, 2004). Unfortunately, these variables were not included in the current protocol. Although important seasonal patterns of eating behavior, food preferences, and dieting exist in the population at large (Zahorska-Markiewicz, 1980; Zifferblatt *et al*, 1980; Attazardeh, 1983; Hardin *et al*, 1991; Yanovski *et al*, 2000), and in eating disorders *per se* (Lam *et al*, 1991; Brewerton *et al*, 1994; Levitan *et al*, 1994), no studies to date have examined these seasonal changes during pregnancy. It should be noted that both low and high extremes of birth weight can be associated with obesity over the lifespan (Hales and Barker, 2001; Phillips and Young, 2000). We speculate that in families with SAD, spring births may be associated with an increased risk of higher-birth weights because of fall/winter increases in total caloric intake in mothers during pregnancy. On the other hand, particularly in mothers with eating disorder pathology, fall births may be associated with sub-optimal weight gain and lower-birth weights because of lower-caloric intake and increased physical activity in the warmer months. In either case, the long-term risk for weight gain and obesity in the offspring should be increased, particularly for carriers of the 7R allele. Future prospective studies starting in fetal development are needed to test this and other seasonal hypotheses directly.

Plasticity Models of the DRD4 Gene

It has recently been suggested that the 7R allele of DRD4 is an example of a 'plasticity gene' variant which magnifies environmental influences on phenotypic development (Belsky *et al*, 2009). The more specific notion that climactic conditions can interact with the 7R allele to influence weight regulation over time is also an area of emerging interest. For example, a recent study in Africa showed that 7R is associated with increased fat-free mass in Ariaal men who migrate over long distances, but not in their sedentary relatives (Eisenberg *et al*, 2008). Taken together with our findings in SAD and BN, this suggests that the 7R allele may enable human beings to match nutritional intake and anthropomorphic makeup with anticipated climactic conditions relevant to food availability, energy storage, and energy usage. This adaptive function could help explain the rapid increase in the frequency of the 7R allele in recent human evolution (Ding *et al*, 2002). Although adaptive in strained environments and in migrating populations, this plasticity becomes a risk factor for obesity when circumstances change, leading to the widespread availability of highly palatable foods and the sedentary lifestyle typical of modern developed countries.

Limitations and Future Directions

The overall sample size for this study was small, particularly as it relates to G $\times$ E effects, and much larger studies are needed to replicate the current findings. Notwithstanding, this was a replication sample based on our earlier findings in SAD, and the overall pattern of results is highly consistent with our prior data. The specific finding of a 7R/fall-birth interaction predicting high BMIs and obesity was not predicted *a priori*.

As a group, BN patients are more heterogenous than SAD patients, suggesting that many factors merit consideration when interpreting the overall results. On the basis of the high rate of past AN in probands with BN, we included past AN in the current analyses. Although the three-way interaction of genotype, season of birth, and AN history did not reach statistical significance, a general trend in this direction suggests that a three-way effect might emerge in future work. This is of potential relevance in that prior research has found season-of-birth effects in the AN population *per se* (Rezaul *et al*, 1996; Crisp *et al*, 2007). Another factor that was not part of the current protocol relates to the potential function of medications in shaping maximal BMIs. For example, many BN probands would have been on one or more anti-depressants over time, which can lead to weight gain and/or prevent weight gain in many cases. Lifetime medication histories will thus be an important consideration in future work of this type.

If replicated in larger samples, the current results might have implications for the prevention of obesity in eating-disordered families. For example, in families with high-dietary restraint and a high frequency of the 7R allele, seasonally based dietary management during pregnancy might prevent unusually low (or high) birth weights and at least some cases of obesity in the next generation. For fall births occurring at northern latitudes, limiting infants' exposure to cold temperatures in the first 6 months of life might also have a function in this regard (Phillips and Young, 2000). Pending future investigation of these G $\times$ E interactions in the population at large, broader application of such strategies might also prove useful in future years.

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DISCLOSURE

The authors declare no conflict of interest.

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