Association between a Vasopressin Receptor *AVPR1A* Promoter Region Microsatellite and Eating Behavior Measured by a Self-Report Questionnaire (Eating Attitudes Test) in a Family-Based Study of a Nonclinical Population

Rachel Bachner-Melman,[1,2] Ada H. Zohar,[3] Yoel Elizur,[1] Lubov Nemanov,[4] Inga Gritsenko,[4] Daphnie Konis,[2] and Richard P. Ebstein[2,4]*

[1] Department of Psychology, Mount Scopus, Hebrew University, Jerusalem, Israel
[2] Scheinfeld Center of Human Genetics for the Social Sciences, Department of Psychology, Hebrew University, Jerusalem, Israel
[3] Department of Psychology and Behavioral Sciences, Ruppin Academic Center, Emek Hefer, Israel
[4] Sarah Herzog Memorial Hospital, Jerusalem, Israel

Accepted 11 January 2004

Abstract: **Objectives:** *Considerable evidence including twin and family studies suggests that biologic determinants interact with cultural cues in the etiology of anorexia and bulimia nervosa. A gene that makes ''biologic sense'' in contributing susceptibility to these disorders, and to our knowledge not previously investigated for this phenotype, is the vasopressin receptor (*AVPR1A*), which we have tested for association with eating pathology.* **Methods:** *We genotyped 280 families with same-sex siblings for two microsatellites in the promoter region of the* AVPR1A *gene. Siblings completed the 26-item Eating Attitudes Test (EAT) and the Drive for Thinness (DT) and Body Dissatisfaction (BD) subscales of the Eating Disorders Inventory (EDI). The Quantitative Transmission Disequilibrium Test program (QTDT), which employs flexible and powerful variance-components procedures, was used to test for an association between EAT scores and the two* AVPR1A *promoter region microsatellites, RS1 and RS3.* **Results:** *A significant association (*p = *.036) was detected between the RS3 microsatellite and EAT scores. The strongest association was between RS3 and the Dieting subscale of the EAT (*p = *.011). A significant association was also observed between the EDI-DT and the RS3 microsatellit (*p = *.0450).* **Conclusions:** *We demonstrate for the first time an association between a microsatellite polymorphism in the* AVPR1A *promoter region and*

Supported, in part, by the Israel Science Foundation founded by the Israel Academy of Sciences and Humanities (RPE), the Israel Association of University Women (RB-M), and the Levin Center for the Normal and Psychopathological Development of the Child and Adolescent (RB-M).

Correspondence to: Dr. Richard P. Ebstein, Scheinfeld Center of Human Genetics for the Social Sciences, Department of Psychology, Hebrew University, P.O. Box 35300, Jerusalem 91351, Israel.
E-mail: ebstein@mscc.huji.ac.il

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/eat.20049

scores on the EAT as well as with the EDI-DT. The strongest association was observed between the RS3 microsatellite and the Dieting subscale of the EAT. The relevant phenotype appears to tap severe dietary restriction for weight loss purposes. © 2004 by Wiley Periodicals, Inc. Int J Eat Disord 36: 451–460, 2004.

Key words: AVPR1A*; Eating Attitudes Test; twin and family studies; microsatellite polymorphisms*

INTRODUCTION

Anorexia nervosa (AN) and bulimia nervosa (BN) are disorders characterized by abnormal patterns of eating behavior and by disturbances in attitudes and perceptions toward body weight and shape (Kaye, Klump, Frank, & Strober, 2000). In Western societies, sociocultural factors such as thinness norms clearly play a crucial role in shaping eating pathology (Botta, 1999; Garner & Garfinkel, 1980; Stice, Schupak-Neuberg, Shaw, & Stein, 1994). However, the low prevalence of severe eating disorders, a marked gender bias, and early age of onset suggest that other factors, namely, biologic determinants, interact with cultural cues in the etiology of AN and BN. Twin and family studies have suggested significant heritability for these disorders (Bulik, Sullivan, Wade, & Kendler, 2000; Holland, Sicotte, & Treasure, 1988; Klump, Miller, Keel, McGue, & Iacono, 2001; Walters & Kendler, 1995).

Both candidate gene (Hinney, Remschmidt, & Hebebrand, 2000; Tozzi, Bergen, & Bulik, 2002) and linkage strategies (Devlin et al., 2002; Grice et al., 2002) are currently being applied in an effort to identify genes and chromosomal regions contributing susceptibility to AN and BN, with promising preliminary results. Recently, a Japanese group used an innovative strategy in an attempt to identify genes contributing to AN and BN (Matsushita, Nakamura, Nishiguchi, & Higuchi, 2002). They found provisional evidence for an association between the serotonin transporter promoter region polymorphism (Lesch et al., 1996) and scores on the 26-item Eating Attitudes Test (EAT) in a group of unrelated female nursing students. Eating pathology in this scheme is operationalized by a score above 20 on the EAT, which is widely accepted as a reliable and valid self-report screening instrument for eating disorders (Garner, 1991; Garner & Garfinkel, 1979; Garner, Olmsted, Bohr, & Garfinkel, 1982). The clinical success of the EAT as a screening tool suggests that eating disorders may be the extremes of a behavioral spectrum, just as certain ranges in normal personality traits may indicate personality disorders (Livesley, Jang, & Vernon, 1998). Scores on the EAT show substantial heritability, with approximately one-half the variance between individuals attributable to genes (Rutherford, McGuffin, Katz, & Murray, 1993). It seems biologically meaningful to surmise that some of the quantitative trait loci partially determining EAT scores may contribute to AN and BN.

A gene of potential interest in contributing susceptibility to eating disorders, and to our knowledge not previously investigated for this phenotype, is the vasopressin receptor (*AVPR1A*). Arginine vasopressin (AVP), the endogenous ligand for the V1a vasopressin receptor, is synthesized in a number of sites in the brain, including the paraventricular, supraoptic, and suprachiasmatic nuclei of the hypothalamus (Barberis & Tribollet, 1996; Tribollet, Arsenijevic, & Barberis, 1998). Vasopressin is known for its anorectic effect in animal studies (Langhans, Delprete, & Scharrer, 1991). In the brain, AVP participates in glucose homeostasis as a neurotransmitter or neuromodulator, exciting neurons in the

paraventricular nucleus (Inenaga, Dyball, Okuya, & Yamashita, 1986; Inenaga & Yamashita, 1986) and ventromedial glucose-responsive neurons in the hypothalamus (Kow & Pfaff, 1986). Direct administration of micro doses of AVP into the nucleus of the tractus solitarius of anesthetized or awake rats rapidly increased the levels of blood glucose concentration and brain arteriovenous glucose difference (Yarkov, Montero, Lemus, Roces de Alvarez-Buylla, & Alvarez-Buylla, 2001). AVP also appears to mediate the effects of several neuropeptides on feeding behavior (Backberg, Hervieu, Wilson, & Meister, 2002; Dhillo et al., 2003; Niimi, Murao, & Taminato, 2001; Ur, Wilkinson, Morash, & Wilkinson, 2002; Wren et al., 2002).

In addition, a number of human studies suggest that vasopressin may play a role in the pathophysiology of AN and BN (Kaye, 1996). Elevated levels of AVP were observed in the cerebrospinal fluid of women recovered from AN and BN (Frank, Kaye, Altemus, & Greeno, 2000). Low serum activity of prolyl endopeptidase, a cytosolic endopeptidase that cleaves peptide bonds on the carboxyl side of proline in proteins such as vasopressin, has been observed in AN (Maes et al., 2001).

In the current study, we genotyped 280 families with same-sex siblings for two microsatellites (Thibonnier et al., 2000) in the promoter region of the *AVPR1A* gene. Scores on the EAT and the Drive for Thinness (DT) and Body Dissastisfaction (BD) subscales of the Eating Disorders Inventory-2 (EDI) were available for these subjects. The Quantitative Transmission Disequilibrium Test program (QTDT; Abecasis, Cardon, & Cookson, 2000; Abecasis, Cookson, & Cardon, 2000), which employs flexible and powerful variance-components procedures, was used to test for an association between EAT scores and the two *AVPR1A* promoter region microsatellites.

METHODS

Subjects

Respondents were primarily college students at Israeli colleges and their families, recruited by word of mouth and advertisements on campus noticeboards. The sample analyzed in the current study included 280 families, each with two parents and same-sex siblings between the ages of 14 and 34 (average age $= 22.73 \pm 4.09$). Pedigrees include 7 single-sibling families, 213 two-sibling families, 41 families with three siblings, 12 families with four siblings, 6 families with five siblings, and 1 family with six siblings.

Each contact person received a number of questionnaires (equal to the number of participating siblings) and two sterile test tubes per family member for DNA sampling, containing 10 ml of Aquafresh mouthwash. Questionnaires were completed by siblings but not parents. After a complete description of the study to the subjects, written informed consent was obtained. Completed questionnaires and DNA mouthwashes were returned by mail or hand delivered to an office. The contact person received a modest monetary incentive and the study was approved by the local institutional review board and by the genetics committee of the Israeli Ministry of Health.

Instruments

EAT

The EAT is a 26-item self-report factor-analytically derived scale, originally validated on a sample of 160 women with eating disorders and 140 female nonclinical controls (Garner et al., 1982). It is reliable and valid, correlates highly with the original 40-item

scale ($r = .98$; Garner et al., 1982), and screens for cases of eating disorders in both clinical and nonclinical populations. The EAT is scored on a 6-point Likert scale with answers ranging from *never* to *always*.

EDI

The EDI-2 is a self-report measure of symptoms generally related to eating disorders (Garner, 1991). It contains 11 standardized subscales, each independently derived and representing a unique trait. In the current study, the EDI was used to assess participants' body dissatisfaction and drive for thinness. These subscales have excellent internal consistency, content validity, criterion-based and construct validity, and good test-retest reliability in eating- disordered and healthy control subjects (Garner, 1991).

DNA Extraction and Genotyping

DNA samples were obtained from all family members and extracted using the Master Pure kit (Epicentre, Madison WI). Amplification of the RS1 and RS3 vasopressin was achieved using the following pair of primers: RS1 (corresponds to the GATA microsatellite at position −553 relative to the start site as first described by Thibonnier et al. (2000): forward (fluorescent) 5′ AGG GAC TGG TTC TAC AAT CTG C 3′; teverse 5′ ACC TCT CAA GTT ATG TTG GTG G 3′. RS3 (corresponds to the GT dinucleotide repeat at −3956 (Thibonnier et al., 2000); forward (fluorescent) 5′ CCT GTA GAG ATG TAA GTG CT 3′; reverse 5′ TCT GGA AGA GAC TTA GAT GG 3′. The two microsatellites were somewhat in linkage disequilibrium ($D' = .224$). D′ was calculated using the method of Slatkin and Excoffier (1996), which can be downloaded from the following internet site (Abecasis & Cookson, 2000): http://www.sph.umich.edu/csg/abecasis/GOLD/index.html.

Each reaction mixture contained 0.5 μM primer. A ReddyMix master mix was used (Abgene, Surrey, UK) at a magnesium concentration of 1.5–2.5 mM $MgCl_2$. The sample was initially heated at 95°C for 5′ followed by 30 cycles of 95°C (30 sec), 55°C (30 sec), 72°C (40 sec), and a final extension step of 72°C for 10 min. The polymerase chain reaction product was analyzed on an ABI 310 DNA analyzer (Applied Biosystems, Foster City, CA).

Statistical Analysis

QTDT is used to analyze quantitative or discrete traits in nuclear families, with or without parental genotypes, or in extended pedigrees. The tests described by Allison (1997), Rabinowitz (1997), Monks, Kaplan, and Weir (1998), and Fulker, Cherny, Sham, and Hewitt (1999) are also supported. Because simple models of association do not provide valid tests of linkage disequilibrium when multiple offspring per family are considered, we used the robust variance-components procedures as detailed in the QTDT package. We examined an association between two microsatellites in the promoter region of the *AVPR1A* gene (RS1 and RS3) and scores on the EAT and the DT and BD subscales of the EDI. Age and body mass index (BMI) were entered as covariates. Because entering gender as a covariate had no effect on results, gender is not shown as a covariate in Table 1. No correction was made for multiple comparisons (two microsatellites examined × two eating scales) and the results should therefore be interpreted cautiously.

We carried out a power analysis using PBAT (Lange & Laird, 2002). The following parameters were entered in the model: continuous trait, additive genetic model, allele frequency of the disease gene = .2, heritability = .05, significance level = .05, allele frequency of the marker gene = .15, P (disease allele A/marker allele A) = .9, $D' = .875$, 280 families with two siblings. Power was calculated to be .754.

RESULTS

Table 1 shows the global *p* value (corrected for multiple alleles of the microsatellite) when the *AVPR1A* microsatellites were tested for an association with the EAT and EDI scores. A significant association ($p = .036$) was detected between the RS3 microsatellite and EAT scores. Therefore, we examined the association for each of the EAT subscales. The strongest association was observed between RS3 and the Dieting subscale ($p = .011$). Because the EAT Dieting subscale and the EDI-DT subscale correlate very highly, we also examined the EDI-DT for association with the *AVPR1A* receptor polymorphism. As expected, a significant association was observed between the EDI-DT and the RS3 ($p = .0450$).

Values for individual alleles and the association with EAT scores are shown in Table 2. The allele frequencies of the RS1 and RS3 microsatellites are similar to what has previously been reported (Thibonnier et al., 2000).

Table 1. Testing for association between EAT scores and *AVPRIA* microsatellite polymorphisms

Testing trait			**EAT**			
Testing marker			RS1			
Allele	df(0)	LnLk(0)	df(T)	LnLk(T)	ChiSq	*p*
All	609	2659.62	604	2656.86	5.51	
Testing marker			RS3			
Allele	df(0)	LnLk(0)	df(T)	LnLk(T)	ChiSq	*p*
All	611	2668.15	606	2662.21	11.87	.036
Testing trait			**Dieting subscale**			
Testing marker			RS1			
Allele	df(0)	LnLk(0)	df(T)	LnLk(T)	ChiSq	*p*
All	609	2436.50	604	2434.05	4.91	
Testing marker			RS3			
Allele	df(0)	LnLk(0)	df(T)	LnLk(T)	ChiSq	*p*
All	611	2447.30	606	2439.92	14.76	.0114
Testing trait			**EDI Drive for thinness**			
Testing marker			RS1			
Allele	df(0)	LnLk(0)	df(T)	LnLk(T)	ChiSq	*p*
All	608	2190.01	603	2186.71	6.61	
Testing marker			RS3			
Allele	df(0)	LnLk(0)	df(T)	LnLk(T)	ChiSq	*p*
All	610	2201.27	605	2195.62	11.30	.0458

Note: The null and full models are evaluated. The null model: means = mu + covariate_age + covariate_BMI + B; variances = Ve + Vg + Va. The full model: means = mu + covariate_age + covariate_BMI + B + W; variances = Ve + Vg + Va.

B is a between-family component of association, whereas W is a within-family component of association. Alleles with rare frequencies of 0.05% or less are lumped together. The individual effects for all other alleles are estimated producing a single, global *p* value. A fuller explanation of these models can be found at http://www.sph.umich.edu/csg/abecasis/ as well as in the cited references. In the model, e = nonshared environment; g = polygenic effects—a function of relatedness between family members and may be due to polygenes; a = additive genetic effects. The chi-square value for determining the overall global *p* value is derived by subtracting the chi-square value of the null model from the chi-square value of the full model. EAT = Eating Attitudes Test.

Table 2. Testing for association between EAT scores and *AVPRIA* microsatellite polymorphisms individual alleles

Testing marker				**RS1**			
Allele	df(0)	LnLk(0)	df(T)	LnLk(T)	ChiSq	*p*	allele frequency
1	613	2662.75	612	2662.15	1.19		0.028
2	613	2661.75	612	2660.98	1.54		0.144
3	613	2662.22	612	2662.16	0.13		0.299
4	613	2662.04	612	2661.83	0.43		0.277
5	613	2661.18	612	2661.10	0.15		0.128
6	613	2662.72	612	2660.55	4.35	.0369	0.094
7	*** Not tested ***						0.019
8	*** Not tested ***						0.006
9	*** Not tested ***						0.004
Testing marker				**RS3**			
Allele	df(0)	LnLk(0)	df(T)	LnLk(T)	ChiSq	*p*	allele frequency
1	*** Not tested ***						0.006
2	615	2669.09	614	2669.05	0.08		0.043
3	615	2669.12	614	2667.02	4.21	.0403	0.131
4	615	2669.04	614	2668.27	1.54		0.244
5	615	2669.09	614	2666.10	5.99	.0144	0.192
6	615	2669.05	614	2668.12	1.86		0.136
7	615	2668.75	614	2668.05	1.40		0.098
8	615	2669.09	614	2664.66	8.86	.0029	0.024
9	615	2668.61	614	2668.31	0.60		0.024
10	615	2669.13	614	2667.66	2.94	.0864	0.061
11	*** Not tested ***						0.014
12	*** Not tested ***						0.002
13	*** Not tested ***						0.001
14	*** Not tested ***						0.008
15	*** Not tested ***						0.003
16	*** Not tested ***						0.009

Note: EAT = Eating Attitudes Test.

DISCUSSION

The regulation of food intake has been shown to be partially mediated by a variety of neuroregulators including neuropeptide Y, melanocortin, orexins, opioid peptides, leptins, ghrelins, cholecystokinin, and AVP (Beck, 2000; Saper, Chou, & Elmquist, 2002). In the current study, we demonstrate an association between a microsatellite polymorphism in the *AVPR1A* promoter region and scores on the EAT as well as with the EDI-DT, in respondents recruited from college campuses and the community. Significant, albeit modest, associations were observed using a robust family-based design in a variance-components framework suitable for family pedigrees of various sizes (Abecasis, Cardon, et al., 2000; Abecasis, Cookson, et al., 2000). The strongest association was observed between the *AVPR1A* promoter region microsatellite RS3 and the Dieting subscale of the EAT. No significant association was observed between the RS1 microsatellite and any of the scales administered or between the RS3 microsatellite and the Bulimia and Oral Control subscales of the EAT or the BD subscale of the EDI.

Whereas high scores on the Bulimia subscale of the EAT are indicative of bulimic but not restrictive eating disorders, high scores on the Dieting subscale are a feature of both (Garner, Olmsted, & Garfinkel, 1985). Given the high correlation between the EAT Dieting subscale and the EDI-DT ($r = .912$), it is not surprising that an association (weaker but,

nevertheless, significant) was observed between the RS3 microsatellite and both the Dieting subscale of the EAT and the EDI-DT. The behavioral phenotype in question therefore appears to be one of dietary restriction which, taken to an extreme, characterizes AN.

Several mechanisms related to the physiology of vasopressin action in the brain and its role in the regulation of food intake might explain the observed association. First, vasopressin appears to be involved in the regulation of glucose homeostasis (Kow & Pfaff, 1986), suggesting that it may be involved in the ''energy deficit'' initiation of food intake. Second, vasopressin may affect dieting behavior via its action on the reward properties of food or lack of food, which is, in turn, closely related to glucose regulation. Under certain conditions, for example, vasopressin and related peptides decrease brain reward and addictive behavior in experimental studies in animal and humans (Van Ree, 1986). Of relevance to this suggestion is the finding that eating-disordered patients, especially patients with AN, often report subjective transient symptomatic improvement or even feelings of euphoria as a result of dieting and food restriction. The food restriction is consequently reinforced by these feelings (Kaye & Strober, 1999).

Third, the *AVPR1A* receptor may contribute to eating behavior via the mechanism of stress-induced feeding problems, because vasopressin is involved in the leptin-induced activation of the hypothalamic pituitary axis (HPA) axis (Levine, 2001; Morimoto et al., 2000). The possibility of a stress axis factor is supported by publications suggesting the presence of pre-onset stressors and coping difficulties in the etiology of AN (Horesh et al., 1996; Welch, Upchurch, & Loscalzo, 1997).

Most of the information regarding the contribution of *AVPR1A* to social behavior is based on studies of the vole (Wang, Young, De Vries, & Insel, 1998). The prairie vole is highly social and monogamous, in striking contrast to the asocial and no-monogamous montane vole. There is evidence that microsatellite instability in the promoter region of this and other genes may be a major contributing factor to diversity in both region-specific gene expression and resulting behavioral phenotypes (Hammock & Young, 2002). In humans, the function of the microsatellites in regulating the *AVPR1A* gene in humans is still poorly understood. However, Hammock and Young (2002) suggested that ''minor variations in microsatellite length at the *AVPR1A* locus in humans can contribute to the diversity in human behavioral traits that are considered to be in the 'normal' range of behavior'' (p 401). Recently, the promoter region microsatellites have been linked to autism, providing preliminary evidence that the *AVPR1A* gene may play a role in social communication and behavior in humans (Kim et al., 2002).

Vasopressin also profoundly affects social interactions, social communication, and pair-bonding in a variety of vertebrate species (Insel & Young, 2000). Because there is ample evidence that eating style is influenced by social context across cultural groups (Backman, Haddad, Lee, Johnston, & Hodgkin, 2002; Clendenen, Herman, & Polivy, 1994; Monge-Rojas, Nunez, Garita, & Chen-Mok, 2002; Satia-Abouta, Patterson, Kristal, Teh, & Tu, 2002), vasopressin and its receptor could also affect human eating behavior via its action as a ''social'' hormone. It is noteworthy that in *Caenorhabditis elegans*, a neuropeptide receptor, albeit a different one, controls the choice between solitary and social feeding behavior patterns (Coates & de Bono, 2002).

Eating habits in animals and humans reflect many factors beyond simple energy requirements needed for the maintenance and growth of the organism (Levine & Billington, 1997). When, why, and how much people eat is affected by food availability and palatability, boredom, emotional state, environmental stimuli (Birch, McPhee, Sullivan, & Johnson, 1989), and the presence of others (de Castro & de Castro, 1989). Eating behavior is simultaneously primitive and sophisticated. It is inextricably

entrenched in social settings and rituals, in culinary and consumption customs, and in cultural habits and norms. Whereas in contemporary Western cultures dieting and the pursuit of thinness are desirable, fashionable, and widespread, they are also clearly predictive of the development of eating disorders (Garner & Garfinkel, 1980; Hsu, 1990; Polivy & Herman, 1987). Our results should meanwhile be interpreted cautiously and regarded as preliminary. Future research with independent samples should seek to replicate the evidence we present for the involvement of vasopressin and the *AVPR1A* receptor in feeding behavior, particularly in the socially approved, yet often maladaptive, practice of dieting and food restriction.

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