



β -2 Adrenergic receptor gene variations and coping styles in twins

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Abstract

We tested the hypothesis that the β -2 adrenergic receptor (β -2 AR) gene locus, with known effects on blood pressure regulation, is also involved in psychological coping styles. 166 pairs of monozygotic (MZ) and dizygotic (DZ) twins and DZ twin parents were investigated. We found common genetic variance for the coping factor *Emotional Coping* and blood pressure. Using three microsatellites we found linkage between the β -2 AR gene locus and the coping factor *Active Coping*. Using allele-specific PCR of all the single nucleotide polymorphisms (SNPs) in the gene causing amino acid substitutions we identified associations between the +491 G/A SNP and various coping factors. We conclude that the β -2 AR gene is relevant to coping. These preliminary findings suggest a molecular genetic underpinning of the relationship between psychological and physiological phenotypes important to cardiovascular risk. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Coping styles or “the things we do to avoid being harmed by life strains”, are complex psychological processes that have long been seen as largely learned behaviors (Costa and McCrae, 1989; Pearlin and Schooler, 1978; Feifel et al., 1987). We recently showed that genetic factors also exert important influences on coping styles in an analysis of monozygotic (MZ) and dizygotic (DZ) twin subjects (Busjahn et al., 1999). Coping styles have also been associated with risk for cardiovascular disease (Theorell, 1980). While there clearly is no ‘right’ or ‘wrong’ coping strategy, a relaxed way of putting things into perspective rather than getting upset or starting precipitant action on things past may well promote health. Specifically, maladapted coping styles may influence arterial blood pressure, a notion supported by the finding that panic disorders and panic attacks are far more common among patients with hypertension compared to normotensive persons (Davies et al., 1999). Furthermore, hopelessness, an important factor in cardiovascular morbidity and mortality, was recently found to predict the incidence of hypertension in Finnish men (Everson et al., 2000).

An association between stress and hypertension has been presumed, by patients and physicians alike, almost since blood pressure could first be measured. Weitz was the first to show that genetic factors were more strongly associated with hypertension than stress and other environmental factors by means of a case-control study (Weitz, 1922). However, since blood pressure and the ability to cope with stress are both influenced by genetic variance, the possibility exists that the same or related genes may play a role in influencing both blood pressure and the ability to deal with life strains. This hypothesis is supported by the observation that some antihypertensive drugs increase the propensity to depression (Rathmann et al., 1999), likely via an action on common physiological pathways, while it might be expected that a direct effect of blood pressure reduction would decrease the risk of depression (Shinagawa et al., 2002). Genes regulating the autonomic nervous system are candidates for such a role. We addressed this hypothesis and focused our attention on the β -2 adrenergic receptor (β -2 AR) gene. In prior analyses, we have shown significant association between this gene and resting blood pressure (Busjahn et al., 2000) as well as blood pressure regulation during stress (Li et al., 2001). We relied on microsatellite markers to test for linkage between the β -2 AR gene locus and coping factors by studying phenotyped DZ twin subjects in an identity-by-descent sib-pair linkage analysis. We then genotyped MZ and DZ twin subjects for four relevant functional polymorphisms in the β -2 AR gene and performed an allelic association study.

2. Method

2.1. Subjects

We recruited 166 pairs of twins (MZ 100 and DZ 66) by advertisement. The subjects were all German Caucasians, recruited from various parts of Germany.

With informed consent, blood was obtained for the determination of zygosity and other molecular genetic studies from all the twins and the parents of the DZ twins. Each participant underwent a medical history and physical examination. Subjects taking antihypertensive medication or being affected by any other chronic medical illness were excluded. Blood pressure and heart rate were measured in the nondominant arm by an automated oscillometric method (Dinamap; Tampa, FL) every minute.

2.2. Measures

Coping was assessed by a German questionnaire, the “Stressverarbeitungs-Fragebogen” (SVF) described previously (Jahnke et al., 1985). The questionnaire was completed by the twins under the supervision of a trained research nurse. The questionnaire includes 19 scales for different types of reactions to an unspecified range of situations that impair, adversely affect, irritate, or disturb the emotional equilibrium or balance of the subject. The questionnaire is similar to the dispositional form of the COPE questionnaire (Carver et al., 1989). Each scale consists of six items that can be answered on a five-point scale according to the probability of that reaction. Example items of the SVF are outlined in Table 1. The reliability of all scales was sufficiently high (Cronbach’s alpha Median 0.8). The validity has been tested by intercorrelations between subscales, correlations with a

Table 1
The German SVF described previously (Jahnke et al., 1985)

All questions start by the statement: “When I have been upset by anybody, disturbed by anything or somehow thrown off balance...”

- Scale 1: Play Down: *I tell myself, it is not that bad.*
 - Scale 2: Compare With Others: *I tell myself, others couldn't take it the way I do.*
 - Scale 3: Guilt Defense: *I tell myself, I'm not to blame.*
 - Scale 4: Distraction From Situation: *I try to concentrate on something else.*
 - Scale 5: Substitutional Satisfaction: *I treat myself by buying something nice.*
 - Scale 6: Ego Boost: *I think about my success in other situations.*
 - Scale 7: Situational Control: *I make a plan how to solve the problem.*
 - Scale 8: Reaction Control: *I try to keep my behavior under control.*
 - Scale 9: Positive Self Instruction: *I tell myself not to give up.*
 - Scale 10: Need For Social Support: *I try to talk to someone about the problem.*
 - Scale 11: Avoidance: *I start to avoid this kind of situation.*
 - Scale 12: Flight Tendency: *I only want to get out of this.*
 - Scale 13: Social Retreat: *I prefer to be by myself.*
 - Scale 14: Rumination: *I think about it over and over.*
 - Scale 15: Resignation: *I tend to give up.*
 - Scale 16: Self-pity: *I ask myself, why me?*
 - Scale 17: Self-Accusation: *I tell myself, after all it's my fault.*
 - Scale 18: Aggression: *I get in rage.*
 - Scale 19: Self Medication/Alcohol Use: *I'll have a few beers.*
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Example items of the coping questionnaire are given. Items are rated on a scale of 1–5.

variety of questionnaires, and by specifying different stressful situations. Normal values (T-scale, mean 50, SD 10) for the SVF for German volunteers according to gender for the 20–64 age range are available. No age-effects were found in the standardization sample.

As the subtests of the SVF questionnaire were not totally independent, secondary factors based on the intercorrelation were determined by the test's authors and confirmed in our own sample. In a four-factor solution, 61% of variance is explained, in a six-factor solution 72%. Two of the six factors are very specific and combine just two scales. We therefore elected to reduce the number of coping factors in relation to sample size and based our analysis on the four-factor solution. The four factors can be characterized as follows:

SVF1. Defense (play down, compare with others, guilt defense, ego boost).

SVF2. Emotional Coping (flight, social retreat, rumination, resignation, self-accusation, self-pity, aggression).

SVF3. Substitution (substitutional satisfaction, need for social support, self medication /alcohol abuse).

SVF4. Active Coping (situational control, reaction control, positive self instruction, avoidance).

Correlations between SVF scales and neuroticism (as reported by the test authors) ranged between 0 and 0.59, between SVF scales and extroversion between 0 and 0.36. In our sample we found significant correlation between extroversion and *Emotional Coping* (−0.26) and *Defense* (0.20), as well as neuroticism and *Emotional Coping* (0.55), *Defense* (−0.26), and *Substitution* (0.23). The significant correlations for some scales confirm the general relationship between coping and personality described by [Watson and Hubbard \(1996\)](#). At the same time it is obvious that coping styles cannot be fully explained as a linear function of personality traits.

2.3. Genotyping and sequencing

For linkage analysis three microsatellite markers spanning 2.3 cM around the β -2 locus on chromosome 5 (D5S413, D5S2090, and D5S2013) were analyzed using the ABI genotyping system. Our techniques for zygosity testing and genotyping of microsatellites have been previously described ([Becker et al., 1997](#); [Knoblauch et al., 1997](#)). We genotyped the functionally relevant polymorphisms of the β -2 AR by means of allele-specific PCR as described elsewhere ([Timmermann et al., 1998](#)).

2.4. Statistical analysis

The power of the twin model in elucidation of complex genetic disease has recently been emphasized by [Martin et al. \(1997\)](#). Analysis was done by using a structural equation modeling (SEM) approach ([Eaves et al., 1996](#)) as implemented in the MX-package ([Neale, 1997](#)). To test for common genetic factors for blood pressure

regulation and coping, Cholesky decomposition of the within- and between-subject correlation matrix of these measures was used (Neale and Cardon, 1992).

2.4.1. Linkage analysis

For linkage analysis, twin pairs were selected and used as ordinary sib-pairs, but with the advantage of perfect age matching and reduced environmental variation affecting the phenotype. From the four alleles harbored by the parents for a given locus, each child randomly inherits two. Thus, a pair of sibs may share zero, one, or two alleles identical by descent (IBD). If the locus under study is a quantitative trait locus (QTL), phenotypic similarity of sibs (measured by their covariance) should increase with the number of alleles they share. For each sib pair, the proportion of alleles IBD for the given locus is calculated based on parental genotypes using a multipoint approach as implemented in MAPMAKER/SIBS (Kruglyak and Lander, 1995). While this approach, in theory, allows for an estimate of the amount of genetic variance attributable to the locus under investigation, the current sample size is not sufficient to get reliable estimates within reasonable confidence intervals. Instead, we simply tested for the presence of a QTL effect. The difference in model fit for models with and without a QTL effect is calculated as a χ^2 statistic. Testing of multiple correlated phenotypes was used to verify the results. Thus, no adjustment for multiple testing was performed. Since we used a candidate gene approach, we accepted $P < 0.01$ to test for significant linkage in accordance with the criteria defined by Lander and Kruglyak (1995).

2.4.2. Allelic association analysis

For the allelic association analysis, a simple ANOVA based approach might be prone to false positive results due to population stratification. Therefore, a sib-pair data analysis was carried out (Fulker et al., 1999). A true allelic effect will affect the difference between phenotypic measures within a sib-pair, as well as the difference between mean values of sib-pairs, depending on their genotypes. Members of a sib-pair arise from the same stratum of the population. Thus, estimates of the allelic effect based on within-family differences are not prone to stratification influences. To test for association, maximum likelihood estimates for the allelic effect were calculated, based on within-family and between-family differences. Significance was tested by computing nested models and comparing the log-likelihood between models. To test for stratification effects, both estimates of allelic effect are constrained to be equal. In the absence of stratification, both estimates were then set to zero. In the presence of stratification effects, setting only the within-family estimate to zero will provide an unbiased test for true allelic association. We set a significance level of $P < 0.05$.

3. Results

We observed a significant inverse correlation between both systolic (-0.112 , $P < 0.05$) and diastolic (-0.156 , $P < 0.05$) blood pressure and the coping factor

Emotional Coping, indicating that a more passive, introverted way of handling stress is related to lower blood pressure. The full Cholesky model for both blood pressure measures and *Emotional Coping* had a χ^2 fit of 22.6/30df, the reduced model without genetic variance shared between the coping factor and blood pressure had a significantly worse fit (difference χ^2 11.8/2df). This confirms our expectation that some genes will influence both blood pressure and coping style. A positive correlation between *Active Coping* and diastolic blood pressure was also identified (0.117, $P < 0.05$). However, no significant evidence was found for a genetic correlation. None of the other coping factors correlated to blood pressure.

Table 2 shows the results of our linkage analysis, together with the heritability estimates. We found linkage between the β -2 AR gene locus and the coping factor *Active Coping*. In the exploratory analysis of the 19 separate questionnaire scales, subscales of *Active Coping* (Situational Control, Positive Self Instruction), and of *Emotional Coping* (Self-Pity and Aggression) were linked to the β -2 AR locus.

We originally focused on five single nucleotide polymorphisms (SNPs) in the β -2 AR gene. One SNP is in the regulatory region and four other SNP are responsible for amino acid substitutions. One of the SNPs causing an amino acid change described

Table 2

Heritability estimates for additive (a^2) and dominant (d^2) genetic influence, and results of linkage analysis (χ^2 /df for QTL-effect) for coping styles

SVF Scale	a^2	d^2	χ^2 /df	P
<i>Defense</i> (Factor 1)		0.52	0/1	n.s.
<i>Emotional Coping</i> (Factor 2)		0.23	1.55/1	n.s.
<i>Substitution</i> (Factor 3)		0.41	0/1	n.s.
<i>Active Coping</i> (Factor 4)	0.21		5.38/1	0.02
<i>Play Down</i>		0.23	0/1	n.s.
<i>Compare With Others</i>		0.43	0/1	n.s.
<i>Guilt Defense:</i>		0.68	0/1	n.s.
<i>Distraction From Situation</i>			0/1	n.s.
<i>Substitutional Satisfaction</i>	0.10	0.12	0/1	n.s.
<i>Ego Boost</i>		0.28	0/1	n.s.
<i>Situational Control</i>	0.26		9.66/1	0.002
<i>Reaction Control</i>		0.22	0/1	n.s.
<i>Positive Self Instruction</i>	0.06	0.30	8.05/1	0.005
<i>Need For Social Support</i>		0.35	0/1	n.s.
<i>Avoidance</i>	0.27		1.45/1	n.s.
<i>Flight</i>		0.48	2.96/1	0.08
<i>Social Retreat</i>		0.38	0/1	n.s.
<i>Rumination</i>	0.43		3.11/1	0.077
<i>Resignation</i>	0.34	0.20	0/1	n.s.
<i>Self-Pity</i>	0.24		6.46/1	0.01
<i>Self-Accusation</i>		0.35	0/1	n.s.
<i>Aggression</i>			4.88/1	0.03
<i>Self Medication/Alcohol Use</i>	0.23	0.21	1.70/1	n.s.

Presented are the four coping factors, followed by the 19 questionnaire scales.

by others was not encountered in our population. Thus, we focused our attention on four SNPs. Their position, consequence, and genotype frequencies are shown in Table 3.

The association analysis (Table 4) showed no indication of stratification effects ($P > 0.1$ for all variables). The most consistent results were obtained for the 491 G/A SNP in the coding region of the gene. Coping factors *Defense*, *Emotional Coping*, and *Active Coping* all revealed significant associations, while *Substitution* showed a borderline association. The +79 C/G SNP was associated with *Defense* and *Emotional Coping*. We also analyzed each individual coping scale separately as shown in Table 4; however, we are aware of the problems with multiple testing and regard these results with caution.

Fig. 1 shows the results of an allelic analysis for the 491 G/A SNP and the four coping factors. Given the complexity of the psychological traits analyzed and the underlying physiology, it is not surprising that there is no clear pattern of dominance or additive genetic influence. There is some evidence for a heterozygote effect or overdominance for *Defense* and *Active Coping*.

4. Discussion

The three important findings in this study are: (1) the observation that coping factors are correlated with resting arterial blood pressure in normal subjects, in part based on common genetic influences (*Emotional Coping*), (2) the identification of linkage between the β -2 AR gene locus and a major coping factor (*Active Coping*), and (3) allelic association between SNPs in the β -2 AR gene and various coping factors. Since the SNPs we examined have known influences on the function of the β -2 AR gene, our findings provide support for earlier studies showing associations between psychological states and β -adrenergic receptor responsiveness (Yu et al., 1999). However, we respect the complexity of the systems we are studying. Blood pressure regulation involves a host of complex pathways influenced by many genes, as Pickering proved half a century ago (Pickering, 1961). Genetic influences on coping styles can surely be no less complex. The influences of SNP variations in the β -2 AR gene we observed were modest and probably account for only a few percent of the total genetic variance.

Table 3
Position, consequence, and genotype frequencies for polymorphisms

Position (nucleotide base)	Polymorphism/frequency	Amino acid change/position
-47	C/T (38%/62%)	(regulatory)
+46	A/G (47%/53%)	Arg → Gly/16
+79	C/G (61%/39%)	Gln → Glu/27
+491	G/A (99%/1%)	Thr → Ile/164

Table 4
Association of coping scales and β -2AR

Scale	-47C/T				+49A/G				+79C/G				+491G/A			
	CC	CT	TT	p	AA	AG	GG	P	CC	CG	GG	P	GG	GA	AA	P
Defense (Factor 1)	52±6	50±6	52±7		52±7	50±6	52±7		52±7	50±6	52±7	<0.05	51±6	47±9	48±1	<0.01
Emotional Coping (Factor 2)	51±7	51±7	49±7		50±7	51±7	49±7		49±6	51±7	51±7	<0.05	50±7	49±3	46±3	<0.05
Substitution (Factor 3)	52±6	52±6	52±6		52±5	52±6	52±6		52±5	52±6	52±6		52±5	49±6	45±3	<0.10
Active Coping (Factor 4)	49±6	48±6	49±6		48±6	48±6	49±6		49±6	48±6	49±6	<0.10	48±6	44±5	51±1	<0.05
Play Down	49±9	48±9	50±10	<0.10	50±10	49±9	48±10		50±10	48±9	48±9		49±9	41±11	54±7	<0.05
Compare With Others	52±9	49±10	52±10	<0.05	51±10	50±10	53±9	<0.01	52±10	50±10	52±9	<0.10	51±10	48±5	48±7	<0.05
Guilt Defense:	53±8	51±9	53±8		53±8	51±8	53±9		53±8	51±9	53±9	<0.05	52±9	48±14	47±6	>0.01
Distraction From Situation	50±8	48±8	49±9		49±9	48±8	49±8		49±9	48±8	47±8	<0.10	48±8	55±12	46±8	<0.10
Substitutional Satisfaction	52±10	53±10	53±10		53±9	53±10	52±10		53±10	53±10	52±10		53±10	50±10	48±4	
Ego Boost	54±9	51±9	53±9		52±9	52±8	52±10		52±9	52±9	54±10	<0.10	52±9	50±11	43±7	<0.05
Situational Control	51±9	50±8	50±9		50±9	50±8	51±9		50±10	49±8	51±8		50±9	50±7	51±1	
Reaction Control	47±9	45±9	47±9		46±9	46±8	47±10		47±9	46±9	47±9		47±9	42±9	54±1	>0.10
Positive Self Instruction	50±9	46±9	49±9	<0.10	47±8	48±9	49±10		49±9	46±9	49±9	<0.05	48±9	41±11	55±8	>0.01
Need For Social Support	57±6	55±8	55±7	<0.05	54±7	56±8	55±7		55±7	55±8	56±6		55±7	53±7	49±6	
Avoidance	49±8	49±9	49±10		50±10	49±8	49±9		49±10	49±8	50±9		49±9	43±6	45±6	
Flight	51±11	50±10	48±10		49±10	50±10	49±10		48±10	50±10	51±11	<0.05	49±10	45±7	44±7	<0.05
Social Retreat	49±9	50±9	49±9		50±9	51±9	48±9	<0.05	49±9	50±9	49±10		49±9	49±8	32±3	
Rumination	51±9	51±8	49±9	<0.01	49±9	51±9	49±8	<0.05	49±9	50±9	51±9	<0.05	50±9	50±6	58±1	<0.05
Resignation	51±9	50±9	48±9		49±9	50±9	48±8		48±9	50±9	51±9	<0.05	49±9	49±5	38±4	>0.05
Self-Pity	49±10	50±9	48±8		49±9	50±9	48±9		48±8	50±9	49±10		49±9	47±10	54±3	
Self-Accusation	52±9	51±10	49±9		50±8	51±9	50±10		49±9	51±10	52±9		50±9	47±11	43±2	
Aggression	53±10	53±8	52±8		53±9	51±9	52±9		52±8	52±9	53±10		52±8	58±5	50±11	
Self Medication/Alcohol Use	48±7	47±7	47±8		47±8	47±7	47±7		47±8	46±7	48±8	<0.10	47±8	44±6	38±1	<0.10

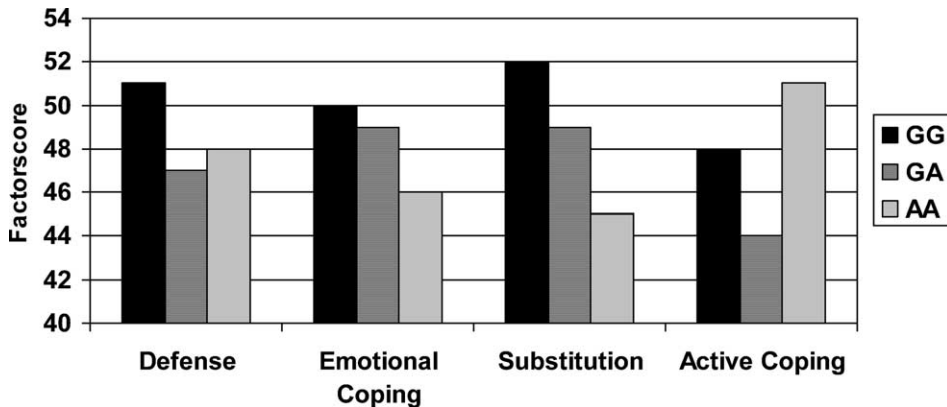


Fig. 1. The ordinate shows the scalar quantification of four coping factors (see Section 2). The effects of +491 G/A (a SNP in the coding region of the β -2 AR gene) allelic associations are given for subjects homozygous for G, heterozygous GA, and homozygous A. The effects are small but significant (except for *Substitution*).

In an earlier study of β -2 AR in which we focused on blood pressure and heart size we found linkage of the gene locus to both systolic and diastolic blood pressure and associations of blood pressure at rest and during stress and of cardiac dimensions with the +46 A/G (Arg16/Gly) polymorphism in the β -2 AR gene (Busjahn et al., 2000; Li et al., 2001). Interestingly, that particular SNP was the least informative in terms of associations with coping factors in the present study. Instead, here we found that the +491 G/A polymorphism in the fourth transmembrane-spanning domain was most robustly associated with coping factors. The -47 C/T, +46 A/G, and the +79 C/G variants are fairly close to one another and, therefore, are in relatively strong linkage disequilibrium, while +491 G/A is unrelated. The +491 G/A polymorphism has been shown to influence binding affinity for catecholamines and β -2 AR antagonists, basal and epinephrine-stimulated adenylyl cyclase activity, and agonist-promoted sequestration (Liggett et al., 1998). McGraw et al. (1998) recently reported that the Cys variant results in increased β -2 AR expression. However, on the basis of our analysis we cannot speculate on which specific SNP, or which cluster of SNPs, was responsible for the associations observed. Most likely there is an interaction between the various polymorphisms, as suggested by haplotype analysis (Drysdale et al., 2000).

The relationship between psychological parameters and blood pressure regulation is complex but compelling. The poor ability to experience and express emotions, termed alexithymia, was found to be independently associated with hypertension in a recent study (Jula et al., 1999). Verbal behavior was shown to predict blood pressure in a population-based sample (Davidson et al., 2000). In that study, the ability to constructively express a common and important emotion, anger, was associated with lower blood pressures. Similarly, five specific psychosocial domains, depression, anxiety, personality character traits, social isolation, and chronic life stress have all been shown to be contributory elements to hypertension and cardiovascular disease

(Rozanski et al., 1999). These findings are supported by evidence from experimental animal, including primate, models (Kaplan et al., 1983). Research also suggests that the disability to deal with psychosocial stress and concomitant sympathetic nervous system activity may increase blood pressure over time (Everson et al., 1996; Markovitz et al., 1998; Schnall et al., 1998). The emotions implicated include anger, anxiety, and depression (Markovitz et al., 1993).

A primary reason we selected the β -2 AR for scrutiny in our study of genetic variance on coping factors was the long-held notion that beta blocking drugs can cause depression. Paauw (1999) has recently pointed out that this idea is based primarily on a single dramatic case report and that subsequent studies have had difficulty in verifying a relationship between beta blocker treatment and depression. However, beta blockers may differ from one another in this regard. Rasanen et al. (1999) conducted an observational cohort study on 30485 persons and found that the use of pindolol was associated with a lower rate of antidepressant use, compared to other beta blockers. Furthermore, pindolol treatment was associated with a marked (29–52%) reduction in the prevalence of disability pensions resulting from major affective disorders, compared to other beta blockers. Pindolol, an otherwise nonselective beta blocker, features a so-called intrinsic isomimetic activity and may actually exert an agonist effect on certain beta adrenergic receptors.

We can only speculate on how β -2 AR variants might influence coping mechanisms; however, presumably the actions are primarily central. Adrenergic mechanisms have been linked to mood disorders since the 1960s (Nemeroff, 1998). Nevertheless, proving a molecular genetic link has been difficult. For instance, Hadley et al. (1995) could find no evidence for associations between manic-depression and variants in the norepinephrine transporter gene. Similarly, Ohara et al. (1998) found no associations between a polymorphism in the promoter region of the α_{2A} adrenergic receptor gene and mood disorders. One shortcoming in many studies is the fact that only a single polymorphism or SNP was investigated in the gene under scrutiny. Had we only relied only on the Arg16/Gly substitution in the β -2 AR gene, which has been the most frequently investigated β -2 AR gene SNP, no associations would have been found. Another weakness, which is also evident in our study, is that investigators focus on only a single gene. Central adrenergic mechanisms clearly depend on many genes involved in catecholamine synthesis, and degradation, as well as the expression and regulation of numerous receptors. In future studies, genes responsible for entire pathways will be examined in so-called “metabolic control analyses” (Bowden, 1999). Currently, a pharmaceutical industrial consortium is constructing a 300 000 SNP map across the entire human genome (Roses, 2000). This mammoth effort, to be completed in 2 years time, will provide information on several SNPs within each gene. Investigators will then be able to construct their own network analysis by analyzing a series of SNPs in several or numerous genes simultaneously, rather than concentrating only on a single gene. Clearly, much greater genotyping capacities and analytical methodologies will be required for such studies.

In summary, we performed a combined linkage and association study of the β -2 AR locus and gene, respectively. We found linkage to the coping factor *Active*

Coping expressed as a quantitative trait. We then focused on SNPs causing amino acid substitutions in the gene. The +491 G/A polymorphism in the coding region of the β -2 AR gene was the most robust in predicting associations with the coping factors (including *Active Coping*). Since we have already shown linkage and association between this gene and blood pressure in these same subjects, we suggest that the β -2 AR gene be responsible for some of the genetic variance on both these psychological and physiological phenotypes. Nevertheless, we realize that our studies are preliminary and that far more extensive analyses of the adrenergic genes in terms of a network will be necessary to elucidate these issues further.

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