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Personality Traits of Agreeableness and Extraversion are Associated with *ADH4* Variation

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Abstract

Background—Personality traits are associated with substance dependence (SD); genetic factors may influence both. Strong associations between ADH4 variation and SD have been reported. We aimed to investigate the relationship between ADH4 variation and personality traits in the present study.

Methods—We assessed dimensions of the five-factor model of personality in 243 subjects with SD (175 European Americans [EAs] and 68 African Americans [AAs]) and 296 healthy control subjects (256 EAs and 40 AAs). We also genotyped 7 ADH4 markers (spanning the locus) and 38 unlinked ancestry-informative markers in these subjects. The relationships between the diplotypes, alleles, and genotypes at ADH4 and personality traits were examined using multivariate analysis of covariance (MANCOVA), controlling for potential confounders.

Results—Generally, SD patients, older individuals, and male subjects scored higher on neuroticism and lower on other personality factors. Personality factors were associated with the diplotypes. The allele A or genotype A/A of single nucleotide polymorphism (SNP)6 (rs1800759 at the gene promoter) was significantly associated with agreeableness scores. There were associations between extraversion and SNP1 (hcv2033010 at the 3′ end) and SNP2 (rs1042364 in exon 9) in subjects with higher conscientiousness scores.

Conclusions—The personality traits of agreeableness and extraversion are related to ADH4 polymorphism. Among the ADH4 markers that appear to predispose to certain personality traits, the functional variant rs1800759 (SNP6) in the promoter region is most important. We conclude that personality traits and SD have a partially overlapping genetic basis.

Keywords

ADH4; MANCOVA; personality traits; substance dependence

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According to the five-factor model of personality (Digman 1990), the full range of personality traits can be well defined in terms of five basic dimensions. These dimensions are: factor I (extraversion or surgency), which contrasts such traits as talkativeness, assertiveness, and activity level with silence, passivity, and reserve; factor II (agreeableness or pleasantness), which contrasts kindness, trust, and warmth with hostility, selfishness, and distrust; factor III (conscientiousness or dependability), which contrasts organization, thoroughness, and reliability with carelessness, negligence, and unreliability; factor IV (neuroticism versus emotional stability), which includes nervousness, moodiness, and temperamentality; and factor V (openness to experience or intellect), which contrasts imagination, curiosity, and creativity with shallowness and imperceptiveness (Goldberg 1993).

This structure of traits in the five-factor model is consistent among highly diverse cultures with distinct languages and between men and women, older and younger adults, and European Americans (EAs) and non-European Americans (Costa et al 1991; McCrae and Costa 1997). This universality could reflect a common biological basis of personality traits across distinct cultures, populations, ages, and sexes. Based on its wide applicability and consistency, the five-factor model has been widely accepted.

Genetic factors have been implicated as contributing to individual difference in major dimensions of personality traits, evidenced by a linkage study and many association studies. A genomewide-scan linkage study mapped five trait-influencing sites for neuroticism at chromosomes 1q, 4q, 7p, 12q, and 13q (Fullerton et al 2003). Subjects expressing one or both S alleles of a regulatory region polymorphism at the serotonin transporter gene (*SLC6A4*) tended to score lower on the NEO Five-Factor Inventory factor of agreeableness than subjects homozygous for the L allele; within this factor, the facet subscale of tendermindedness was lower for subjects expressing one or both S alleles compared with subjects homozygous for the L allele ($p = .003$) (Wand et al 2002). There have also been reports of an association between this polymorphism and harm avoidance (Wiesbeck et al 2004), neuroticism (Du et al 2000; Lesch et al 1996), violent behavior (Retz et al 2004), or other anxiety-related personality traits (Melke et al 2001). Many other studies have also reported on the relationship of personality traits with other candidate loci, such as variation at the *5-HT2C* gene (Ebstein et al 1997), the *5-HT2A* gene (Golimbet et al 2002), the *DRD2* gene (Jonsson et al 2003; Lee et al 2003; Ponce et al 2003; Rosmond et al 2001), the *DRD3* gene (Thome et al 1999), the *DRD4* gene (Bau et al 1999; Gelernter et al 1997; Lee et al 2003), the *COMT* gene (Rujescu et al 2003; Tsai et al 2004), the *BDNF* gene (Itoh et al 2004; Lang et al 2004, 2005; Sen et al 2003), the *OPRM1* gene (Wand et al 2002), the *TFAP2B* gene (Damberg et al 2000), and the *ESR1* gene (Westberg et al 2003). These findings provide additional support for the hypothesis that personality traits are influenced by genetic factors.

Personality traits may play a central role in the development of substance dependence (SD; including alcohol dependence and opioid dependence in the studies by Caspi et al 1997; Cloninger 1987; Cloninger et al 1988; Loper et al 1973; Verheul et al 2004; Zucker and Lisansky Gomberg 1986). Specifically, some premorbid personality traits, such as “behavioral under-control” (including impulsivity, thrill seeking, rebelliousness, irresponsibility, nonconformity, and aggressiveness) (Sher et al 1991), rejection of societal values, antisocial behavior, and hyperactivity, are robust predictors of alcohol dependence (Cox et al 1983; Otter and Martin 1996). In contrast, it has been argued that personality traits, especially “negative emotionality” (anxiousness, inhibition, moodiness, and unhappiness), may be a consequence rather than a cause of alcohol dependence (Schuckit 1986).

Common genetic factors may largely underlie the association between personality traits and alcohol dependence. For example, in a community sample of 2682 twins, Slutske et al (1998) found that 70% of the association between antisociality and alcohol dependence was

explained by common genetic factors; this study also showed that alcohol dependence and conduct disorder shared many personality traits (also confirmed by Krueger et al 2000; Sher and Trull 1994) that could be accounted for by common genetic risk factors. In a follow-up study, these authors confirmed the finding that these personality dimensions shared genetic risk factors with alcohol dependence (Slutske et al 2002). Studies of the offspring of alcoholics suggested that behavioral undercontrol might be related to the familial diathesis underlying alcohol dependence risk (e.g., Finn et al 2000; Sher et al 1991, 1999). There is also direct evidence that personality traits and alcohol dependence are linked to polymorphisms in the serotonin transporter gene (*SLC6A4*) and the μ-opioid receptor gene (*OPRM1*) (Sander et al 1998a, 1998b). These findings support the idea of a shared genetic basis for personality features and alcohol dependence.

The development of alcohol dependence depends on heavy ethanol consumption, which appears to be influenced by alcohol dehydrogenase (ADH) activity. Increased ADH activity can increase the rate of alcohol metabolism, thereby increasing the production of the toxin acetaldehyde. If acetaldehyde is not metabolized quickly, it accumulates, resulting in an aversive "flushing reaction," which can limit alcohol consumption and, hypothetically, thereby reduce the risk for alcohol dependence (Hasin et al 2002; Muramatsu et al 1995; Thomasson et al 1994). Conversely, decreased ADH activity may increase the risk for alcohol dependence (Hasin et al 2002; Thomasson et al 1994). Human ADH4 enzyme mainly contributes to liver ADH activity, and at intoxicating levels of alcohol, it may account for as much as 40% of the total ethanol oxidation rate (Ditlow et al 1984). A polymorphism mapped to the promoter region of the *ADH4* locus at 4q22 (e.g., single nucleotide polymorphism [SNP]6: −75A/C [rs1800759]) could modulate ADH activity (Edenberg et al 1999). Guindalini et al (2005) reported that promoter variants, including −75A/C and −159A/G, were significantly associated with alcohol dependence in European Brazilians and African Brazilians. We (Luo et al 2006a) found that seven *ADH4* markers (including −75A/C) were in strong linkage disequilibrium (LD) to form a haplotype block in EA and African American (AA) substance dependent subjects and healthy control subjects. The genotype frequency distributions of the seven *ADH4* markers were in Hardy-Weinberg Disequilibrium (HWD) in the EA patients with SD but were in Hardy-Weinberg Equilibrium (HWE) in the EA healthy control subjects and the AA cases and control subjects. The genotypes of seven *ADH4* markers were significantly associated with alcohol and/or drug dependence in EAs. Among these markers in EAs, SNP6 and SNP2 (rs1042364) were most significant HWD in cases with alcohol dependence and drug dependence, respectively; also, these two markers were most significantly associated with alcohol dependence and drug dependence, respectively. Fine mapping the risk loci with an HWD measure (Feder et al 1996) revealed that these two markers were closest to the risk loci for alcohol dependence and drug dependence, respectively. After correcting for the effects of allele frequencies of markers on HWD (Jiang et al 2001), SNP6 was the marker closest to the risk loci for both alcohol dependence and drug dependence.

We hypothesized that personality traits would also be associated with *ADH4* variation, due to their strong genetic link to SD and the strong association between SD and *ADH4*. The present study aimed to investigate the role of these seven *ADH4* markers in determining differences in personality traits among individuals.

Methods and Materials

Subjects

Two hundred forty-three subjects with SD (175 EAs and 68 AAs) and 296 healthy control subjects (256 EAs and 40 AAs) were included in the present study. This is a subsample of the subjects among whom we previously studied the relationships between SD and *ADH4* (Luo et al 2006a). The patients (140 male patients; 103 female patients) met lifetime DSM-III-R or

DSM-IV criteria (American Psychiatric Association 1987, 1994) and had a diagnosis of alcohol dependence (n = 192) and/or drug dependence (n = 144 for cocaine dependence; n = 95 for opioid dependence). Diagnoses were made using the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al 1992), the computerized Diagnostic Interview Schedule for DSM-III-R (C-DIS-R) (Blouin et al 1988), or a checklist comprised of DSM-III-R symptoms. The control subjects (111 male subjects; 185 female subjects) were recruited by advertisement from the general population, with many recruited from local college campuses. The control subjects were screened using the SCID or the C-DIS-R to exclude major Axis I mental disorders, including alcohol or drug dependence, psychotic disorders (including schizophrenia or schizophrenia-like disorders), mood disorders, and anxiety disorders. The average ages were 37.9 ± 9.3 years for cases and 27.6 ± 8.6 years for control subjects.

The subjects were recruited at the University of Connecticut Health Center. All subjects gave informed consent before participating in the study, which was approved by the Institutional Review Board.

Marker Inclusion

Seven single nucleotide polymorphisms (all of those available from the public Applied Biosystems, Inc., ABI, Foster City, California, at the time of genotyping, designated by hcv# or rs#) were included in this study. These markers included SNP1 (hcv2033010 at the 3' end), SNP2 (rs1042364 in exon 9), SNP3 (rs1126671 in exon 7), SNP4 (rs1126670 in exon 6), SNP5 (rs7694646 in intron 4), SNP6 (rs1800759 in the promoter region), and SNP7 (rs1984362 at the 5' end). The allele frequencies and polymerase chain reaction (PCR) conditions for these markers have been validated by ABI. These markers, spanning the full length of *ADH4*, cover a range of 28,752 base pairs (bp), with an average spacing of 4792 bp. We have previously reported the relationships between these markers and risk for drug and alcohol dependence in a larger sample that includes these subjects (Luo et al 2005b, 2006a).

Thirty-eight ancestry-informative markers unlinked to *ADH4*, including 37 short tandem repeats (STR)s and one Duffy antigen gene (*FY*) marker (rs2814778), were genotyped to detect the population structure and obtain the ancestry proportions of our sample. These marker sets have been employed in the studies by Stein et al (2004), Kaufman et al (2004), Zhang et al (2006), and Luo et al (2005a, 2005b, 2006b), and their characteristics were described in the studies by Yang et al (2005) and Luo et al (2005b).

Genotyping

The seven *ADH4* SNPs were genotyped with a fluorogenic 5′ nuclease assay method, i.e., the TaqMan technique (Shi et al 1999), using the ABI PRISM 7900 Sequence Detection System (ABI, Foster City, California). Polymerase chain reaction was performed in a final volume of 3 μL, including 1.5 μl 2X TaqMan Universal PCR Master Mix (ABI), .075 μL 20X Assays-on-Demand or .0375 μL 40X Assays-by-Design (ABI), .03 μL 100X BSA (New England Biolabs, Inc., Beverly, Massachusetts), and 1 ng DNA. All genotyping was performed in duplicate and compared to ensure validity of the data. Mismatched genotypes, which constituted<.5% of the total number of duplicate genotypes performed, were discarded. The 38 ancestry-informative markers were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique or fluorescence capillary electrophoresis technique (more details are provided by Luo et al 2005b).

Assessment of Personality

Personality dimensions in patients and healthy individuals were assessed with the NEO Five-Factor Inventory (NEO-FFI), a 60-item self-report questionnaire. This questionnaire is rated on a five-point scale to yield scores in five major domains of personality and requires a sixth-

grade reading level. Usually, this questionnaire requires 10 to 15 minutes to complete. Internal consistency values (Cronbach's alpha coefficient) for the NEO-FFI Form S ranges from .68 to .86 (Costa and McCrae 1997). Pairwise correlation analysis was performed on these traits by Pearson's method. Some of the personality phenotype data were included in our earlier reports addressing the relationship of personality to *DRD4* (Gelernter et al 1997) and *SLC6A4* (Gelernter et al 1998).

Estimation of Ancestry Proportions and Reconstruction of Haplotypes

To detect admixture, measure its extent in our sample, and estimate ancestry proportions for each individual, we used the ancestry information content from the set of 38 ancestry-informative markers through the program STRUCTURE, which is based on the Bayesian approach (Falush et al 2003; Pritchard et al 2000).

The program PHASE was used to reconstruct haplotypes in this study (Niu et al 2002; Stephens et al 2001; Stephens and Donnely 2003). This program is based on a combination of the Bayesian statistical method and the so-called "divide-and-conquer" (i.e., partition ligation) strategy and has no requirement for the assumption of Hardy-Weinberg equilibrium. Diplotype (i.e., haplo-type pair) probabilities for each individual were estimated by PHASE.

Data Analysis

Multivariate Analysis of Covariance—Multivariate analysis of covariance (MANCOVA), implemented in SPSS 13.0 (SPSS Inc, Chicago, Illinois), was employed to test associations between *ADH4* and personality factors. In the MANCOVA model, five personality factors that are correlated served as one composite response variable; diplotype probabilities served as predictor variables; diagnosis, age, ancestry proportions, and sex served as covariates; and the two-way interactions between each predictor variable and each covariate were also considered as independent predictor variables in this model. Statistical significance was based on the value of Pillai's Trace statistic.

These seven markers were all in HWD. We have demonstrated that diplotypes based on such markers could be more powerful and valid than haplotypes in association analysis (Luo et al 2005b). Thus, only diplotypewise analysis was considered in this study.

The gene frequency distributions are highly significantly different between EAs and AAs (see Table 1), and EAs and AAs were both observed to be admixed populations (Luo et al 2005b). The population stratification and admixture effects could be important in our mixed sample and should be considered. Thus, ancestry proportions were included in the MANCOVA model to exclude both population stratification and admixture effects. Diagnosis (i.e., affection status), age, and sex were included in the model to exclude their potential confounding effects on associations. They have been reported to influence personality scores (Hernandez-Avila et al 2004); thus, it is reasonable and predictable that gene effects on personality scores could be different in different diagnosis, age, or sex subgroups. The probabilities, rather than the categories, of diplotypes were included because the probabilities preserve more information than directly using the categorical variables.

After we obtained positive findings from the above diplotypewise analysis, we performed allelewise and genotypewise MANCOVA using allele or genotype data, instead of diplotype data, to fine-map the trait loci for personality. Two-way interactions between the predictor variables and covariates and between any two *ADH4* markers were also considered as independent predictor variables in these models.

Univariate Analysis of Covariance—A series of univariate analysis of covariance (ANCOVA) tests was employed to assess the unique contribution of each personality factor to the association between the overall personality traits and covariates and genes. In these models, each personality factor served as one response variable in a univariate ANCOVA test. The predictor variables, covariates, and interaction variables were the same as those used in the aforementioned MANCOVA models.

This series of separate univariate ANCOVA tests was considered exploratory, because they ignored the correlations between personality factors and could reflect the same underlying phenomenon or inflate the probability of type I error. However, these univariate ANCOVA tests helped us to prioritize the theoretical importance of the five personality factors in their associations with *ADH4*, enabling us to perform the Roy-Bargmann stepdown analysis.

Roy-Bargmann Stepdown Analysis—Following positive findings from the MANCOVA, we sought to identify the genetic factors underlying the positive findings. This effort used the Roy-Bargmann stepdown analysis, a stepwise univariate ANCOVA (Tabachnick and Fidell 1996). First, we tested the highest priority personality factor using univariate ANCOVA. Then, we tested the next personality factor with ANCOVA, and used all the higher priority personality factors as covariates. This stepdown process decomposed the findings from MANCOVA without neglecting the correlations among the personality factors. We limited the Roy-Bargmann stepdown analysis to allele-wise and genotypewise models, so that we could fine-map the trait-influencing loci and decompose the sources of associations by the following methods. Two-way interactions between the predictor variables and covariates (including the higher priority personality factors) and between any two *ADH4* markers were also considered as new independent predictor variables in these allelewise and genotypewise models. To be conservative in multiple testing and to avoid inflating the type I error rate in these analyses, we set the significance level (α) at .01.

If there are strong correlations between markers, between personality factors, or between markers and personality factors in these stepwise ANCOVA models, these independent variables will have a near-linear relationship that might lead to multicollinearity. During ANCOVA calculations, multicollinearity causes a division by zero (or a very small quantity), which, in turn, causes the calculations to be aborted (or to be distorted), creating inaccurate estimates of the regression coefficients, inflating the standard errors of the regression coefficients, and deflating the partial *t* tests for the regression coefficients, giving false, nonsignificant *p*-values and degrading the predictability of the model. Hence, during each step of ANCOVA, multicollinearity was detected first. First, pairwise correlation analysis between personality factors (see above) and pairwise linkage disequilibrium between markers (Luo et al 2006a) were tested, looking for near-linear relationships (although multicollinearity does not always show up when considering the variables two at a time). Second, the variance inflation factors, a measure of multicollinearity, were calculated (Haan 2002). Variance inflation factors over 10 indicate collinear variables. Third, eigenvalues of the correlation matrix of the independent variables and condition numbers were calculated. Eigenvalues of the correlation matrix near zero indicate multicollinearity. The condition number is the largest eigenvalue divided by each corresponding eigenvalue. Large condition numbers (>1000) indicate a severe multicollinearity problem. Fourth, if severe multicollinearity was detected, we planned to use the linear ridge regression method for ANCOVA; otherwise, we used general linear regression for ANCOVA.

***T* Test, One-Way Analysis of Variance, and Post Hoc Tests—**After we obtained multiple risk predictor variables (including covariates, markers, and their interactions) using the Roy-Bargmann stepdown analysis, we decomposed them into a single variable and analyzed the specific risk covariates, risk alleles, and risk genotypes for every personality

factor, using *t* test (for covariates and alleles) or one-way analysis of variance (ANOVA) (for genotypes) followed by post hoc tests. To make the post hoc testing feasible, all the continuous covariates were converted into categorical variables. That is, ancestry proportions were converted into dichotomous population categories, i.e., "genetic" EAs (European ancestry proportion > .5) and "genetic" AAs (African ancestry proportion > .5), and age data were converted into dichotomous age categories, i.e., older subjects (> mean age of 32 years) and younger subjects (≤32 years), based on the cutoff point used by Koppes et al (2001) to differentiate younger and older individuals. Because of the strong correlation between personality factors, we would expect that an association between a gene and one specific individual personality factor might be observed independent of other personality factors only rarely; instead, an association with a personality factor might be dependent on other personality factors. That is, gene-personality association would be modified by another individual personality factor. However, due to the lack of published standard cutoff points available for the personality factors, there was no clear criterion for converting the continuous personality factor scores into categories. Thus, most personality factors were not decomposed using post hoc testing, except for one specific personality factor (i.e., conscientiousness) that was found to modify the gene-phenotype association (see Results below) and whose cutoff point was set at 22 on an exploratory basis.

Results

The scores for the different personality factors were: extraversion (range = 4–48, mean [± standard deviation] = 28.5 ± 6.9), agreeableness (range = 10–46, mean = 31.0 ± 6.6), conscientiousness (range = 0–48, mean = 31.8 ± 7.8), neuroticism (range = 2–48, mean = 20.4 ± 9.4), and openness to experience (range = 9–45, mean 28.4 ± 6.4). Neuroticism was negatively correlated with the other personality factors and all of the other personality factors were positively correlated with one another ($p < .01$). The genotype, allele, haplotype, and diplotype frequencies in the whole sample are shown in Table 1.

Multivariate analysis of covariance indicated that the personality factors were related to diagnosis, age, sex, ancestry, and *ADH4* variation (Table 2). Diplotypewise MANCOVAs showed that 1) the personality factors were related to diagnosis, sex, age, and ancestry; 2) there was a significant association between the personality factors and the diplotype TTACAAA/TCACTAG ($p = .030$); this association was alternatively modified by ancestry ($p = .028$) or age ($p = .019$), that is, this association varied between different populations or age subgroups; and 3) there was a significant association between the personality factors and the diplotype TTACAAA/CCGATCG; this association was modified by diagnosis ($p = .034$) or by sex ($p = .039$), that is, this association is different for the different diagnosis subgroups or sex subgroups.

Allelewise and genotypewise MANCOVAs showed that 1) the personality factors were related to diagnosis, age, and ancestry; 2) the marker SNP6 had a significant effect on the personality factors (modified by sex; $p = .030$, 5.4×10^{-4} for alleles and genotypes, respectively); and 3) inclusion in the model of both sex and age increased the observed effect of SNP6 on personality factors, such that $p = 2.5 \times 10^{-13}$ (for alleles) and 2.2×10^{-5} (for genotypes), respectively.

Univariate ANCOVAs identified the priority of the personality factors. A series of univariate ANCOVAs (including diplotypewise, allelewise, and genotypewise analyses [data not shown]) showed the priority order of the personality factors as follows: neuroticism (F4) > agreeableness (F2) > conscientiousness (F3) > extraversion (F1) > openness (F5). The priority was decided using the following criteria: 1) personality factors with higher priorities were associated with more diplotypes or markers and interaction variables than those with lower priorities; and 2) personality factors with higher priorities were more significantly affected by

genetic factors than were those with lower priority. This priority order was also confirmed by testing other genes (unpublished data).

Roy-Bargmann stepdown analyses showed that different personality factors were related to diagnosis, age, and/or sex and that the *ADH4* markers had effects on different personality factors (Table 3). First, although there were strong correlations between personality factors, all the correlation coefficients (|r|) were less than .6; all the variance inflation factors were less than 10; and all the condition numbers were less than 1000. Thus, the multicollinearity was not severe in any of the stepwise ANCOVA models, making it possible to examine a general regression model.

The allelewise and genotypewise Roy-Bargmann stepdown analyses based on the observed priority order showed that different personality factors were related to diagnosis, age, and/or sex and that *ADH4* markers had effects on different personality factors. In summary, the following findings were obtained: 1) conscientiousness, neuroticism, and openness to experience were significantly related to diagnosis ($1.2 \times 10^{-43} \leq p \leq .004$); extraversion, agreeableness, neuroticism, and openness to experience were significantly related to age ($2.4 \times 10^{-9} \leq p \leq .006$); and agreeableness and neuroticism were significantly related to sex ($1.6 \times 10^{-6} \leq p \leq .006$); 2) SNP1 alleles and SNP2 alleles had effects on extraversion (F1) ($p = .009$ and $p = .003$, respectively), which were modified by conscientiousness (F3); 3) SNP6 had significant effects on agreeableness ($p = 5.0 \times 10^{-4}$ for alleles; $p = 1.9 \times 10^{-4}$ for genotypes), which were modified by sex; and 4) no significant interaction effects were detected between different *ADH4* SNPs on personality factors.

Generally, substance dependent patients, older individuals, and male subjects had significantly higher neuroticism and significantly lower scores on other personality factors. There were associations between extraversion and SNP1 and SNP2 in subjects with higher conscientiousness scores. Allele A or genotype A/A of SNP6 was significantly associated with agreeableness scores (around 31.0 ± 6.8), which were lower in female subjects, especially younger female subjects, and higher in male subjects, especially older male subjects (Table 4).

Decomposing the risk variables obtained from the Roy-Bargmann stepdown analysis, we found the following: 1) patients had lower scores on agreeableness, conscientiousness, and openness to experience and higher scores on neuroticism than did control subjects; older individuals had lower scores on extraversion, agreeableness, and openness to experience and higher scores on neuroticism than did younger individuals; male subjects had lower scores (30.2 ± 6.3) on agreeableness than did female subjects (31.7 ± 6.8); and female patients had higher scores on neuroticism than did male patients (all $p < .05$); 2) in the subgroups with higher conscientiousness scores (>22), alleles of SNP1 or SNP2 were associated with extraversion ($p < .05$); 3) male subjects with allele A of SNP6 had higher scores on agreeableness (30.8 ± 5.9) than those with allele C (29.7 ± 6.8; $p = .041$); and female subjects with allele A or genotype A/A of SNP6 had lower scores on agreeableness (31.0 ± 6.8 for allele A, 29.5 ± 6.6 for genotype A/A) than those (32.2 ± 6.9 for allele C, 32.3 ± 6.9 for genotypes C/A+C/C) with allele C or other genotypes ($p = .039$ and $p = .003$, respectively). These higher agreeableness scores in male subjects (30.8 ± 5.9) are close to the lower scores in female subjects (31.0 ± 6.8), and both are associated with allele A. If decomposed by age, associations became more significant both in older male subjects (30.2 ± 5.9 versus 28.3 ± 6.4 for allele A vs. C, $p = .013$) and in younger female subjects (30.7 ± 6.5 versus 32.2 ± 6.9 for allele A vs. C, $p = .028$; 29.0 ± 6.0 versus 32.2 ± 6.8 for A/A versus C/A+C/C, $p = .005$, respectively). These higher agreeableness scores in older male subjects (30.2 ± 5.9) are closer to the lower scores in younger female subjects (30.7 ± 6.5); both are significantly associated with allele A.

Discussion

The present study provides strong evidence that personality traits are related to *ADH4* variation. Several *ADH4* markers contribute to variation in personality traits, among which the functional variant SNP6 (rs1800759) in the promoter region is the most important, as predicted. Using MANCOVA and the Roy-Bargmann stepdown ANCOVA analyses, we were able to correlate personality factors, the interactions among markers, and the interactions between markers and covariates, while controlling for potential biases. In these two analyses, subjects that differed on affection status, age, population, and sex were combined in a single model, thus maximizing the statistical power of the analysis. Use of MANCOVA made it possible to examine diplotypes, which incorporate the LD information between markers, in addition to the information from all single markers and unknown markers and thus are likely to be more representative of a "whole gene" than any single marker. Our use of quantitative, rather than categorical, phenotypic information is also an important advantage of this analytic approach.

Diplotypewise analysis showed that the personality factors were associated with the diplotypes TTACAAA/TCACTAG and TTACAAA/CCGATCG (which harbor the allele A or genotype A/A of SNP6; associations were modified by diagnosis, sex, age, or ancestry), suggesting that *ADH4* harbors risk loci for the variation observed in the personality traits. Allelewise and genotypewise MANCOVAs, which in decomposing the findings from diplotypewise analysis also provided support for those analyses, demonstrated that the personality factors were related to diagnosis, age, and ancestry and that the marker SNP6 was the most important genetic variant affecting the personality factors.

The Roy-Bargmann stepdown ANCOVAs, which were used to decompose the overall personality traits to identify more specific sources of association, sometimes were more powerful than MANCOVAs. This is evidenced by the facts that at this step in the analysis: 1) in the genotypewise analyses, the associations between covariates and personality factors became more significant (Table 3 versus Table 2); and 2) markers (i.e., SNPs 1 and 2), in addition to SNP6, were found to be associated with personality traits. This analysis also demonstrated that a personality factor (i.e., extraversion) was affected by two *ADH4* markers (i.e., SNPs1 and 2), although these associations were modified by another specific personality factor (i.e., conscientiousness), which may be because of the strong correlation ($p = 1.2 \times 10^{-15}$) between these two personality factors.

We also decomposed every risk covariate and marker revealed by the Roy-Bargmann stepdown analysis to identify the sources of association (i.e., specific risk covariates, risk alleles, and risk genotypes), using *t* test, one-way ANOVA, and post hoc tests (Table 4). However, because the interaction effects between markers and covariates and between markers were ignored in these analyses, the effects of markers became less significant or nonsignificant (Table 4 versus Table 3), which is consistent with the conclusion by Marchini et al (2005) that interaction analysis is more powerful than noninteraction analysis. In view of this point and other issues described above, our conclusions should be drawn primarily from the Roy-Bargmann stepdown analyses, the findings from which show very high levels of statistical significance ($1.2 \times 10^{-43} \leq p \leq .009$; Table 3), although some findings from decomposing analyses become considerably less strong or nonsignificant (Table 4).

Our analyses demonstrated that of the markers studied, SNP6 had the most significant effect on personality traits. This is a functional variant at the promoter that leads to an alteration of *ADH4* promoter activity, significantly affecting the expression of π ADH; the A allele has promoter activity more than twice that of the C allele (Edenberg et al 1999). This variant has been reported to be associated with risk for alcohol dependence in European Brazilians and African Brazilians (Guindalini et al 2005). We (Luo et al 2006a) have reported that this variant

was also strongly associated with SD and was the marker closest to the putative disease locus for SD; its minor A/A genotype increases risk for SD, that is, this is an SD-risk variant. In the present study, we observed that minor allele A increased the agreeableness score in male subjects (especially in older individuals), and allele A genotype A/A decreased the agreeableness score in female subjects (especially in younger individuals). This does not conflict in the sense that agreeableness scores in older male subjects and younger female subjects are very similar to one another; both groups of subjects have scores around 30.8 ± 5.9. The moderating effect of age on this marker between male subjects and female subjects indicates that the gene effect on personality traits is modified by sex and age, which is consistent with the extant literature on the topic. First, associations between personality traits and SD have been shown to be modified by sex. For example, the "positive emotionality" (outgoing, lively, persistent, and warm; measured by Tridimensional Personality Questionnaire [TPQ] and Eysenck Personality Questionnaire-Revised [EPQ-R]) may be more strongly associated with alcohol dependence among women than among men (Slutske et al 2002); "negative emotionality" accounts for a portion of the genetic risk for alcohol dependence among men but not among women; and "behavioral undercontrol" accounts for significantly more of the genetic risk for alcohol dependence among women than among men (Slutske et al 2002). Second, these associations may be modified by age. For example, 1) the relationship between rigidity and alcohol consumption was found to be modified by age; it appears that a rigid adolescent refrains from drinking a second, third, or fourth drink, whereas a rigid young adult refrains from initiating drinking; in adulthood, rigid persons are less subject to influence to drink (Koppes et al 2001); and 2) in women only, especially adults, dominance was positively related to the level of wine consumption (Koppes et al 2001).

Single nucleotide polymorphism 2 (SNP2) is a nonsynonymous variant (Gly→Arg) in exon 9. Single nucleotide polymorphism 2 is in strong LD with SNP6 and was, like SNP6, strongly associated with SD (Luo et al 2005b, 2006a). Single nucleotide polymorphism 2 was also the marker closest to the risk locus for drug dependence (Luo et al 2005b, 2006a). In this study, SNP2 was associated with extraversion, although this association appeared only in subjects with higher conscientiousness scores. Single nucleotide polymorphism 1 had similar effects to those of SNP2. The modulating role of conscientiousness in the effects of SNPs 1 and 2 on extraversion indicates that there was a strong correlation between these two personality traits, and that this correlation makes it difficult to detect gene effects on extraversion independent of conscientiousness; thus, this correlation needs to be considered in studying these gene effects.

Both SD (Luo et al 2005b, 2006a) and personality traits (present article) were demonstrated to be strongly associated with *ADH4*. We, therefore, conclude that personality traits and SD have a partially shared genetic basis, consistent with the extant literature. Both phenotypes are influenced by the environment as well. It is probable that being substance dependent exerts some influence on personality structure during the course of the illness (Verheul et al 2004). If the influence of *ADH4* variation on personality were mediated through an effect on SD (that is, if it were a secondary phenomenon), then findings in substance dependent subjects would be expected to differ from those in control subjects. We therefore divided the subjects into case and control groups and tested the relationship between *ADH4* and personality within each group, and most of the results were similar (data not shown). That is, diagnosis does not generally affect the relationship between *ADH4* and personality. Thus, some specific personality traits could be taken as phenotypes independent of SD, though mediated by *ADH4* as SD. This is understandable because personality traits might have some underlying neurobiological mechanisms similar to those influencing risk for SD. The ADH4 enzyme (π ADH) catalyzes certain endogenous substrates (i.e., norepinephrine aldehydes, including 3,4-dihydroxymandelaldehyde [DHMAL] and 4-hydroxy-3-methoxymandelaldehyde [HMMAL]) to synthesize the intermediary glycols of norepinephrine metabolism, including

3,4-dihydroxyphenylglycol (DHPG) and 4-hy-droxy-3-methoxyphenylglycol (HMPG), respectively. The enzyme π ADH has 9- to 29-fold greater efficiency as a catalyst for this reaction than any class I isozyme (α, β, and γ ADHs); class III ADH (χ ADH) does not have any detectable catalytic activity for these substrates (Mardh et al 1986). Activated π ADH attributable to *ADH4* gene variation, e.g., allele A of SNP6 (Edenberg et al 1999), would be predicted to increase levels of DHPG and HMPG, and this could result in a very high turnover of norepinephrine aldehydes. To block the turnover of norepinephrine aldehydes, an individual could self-administer alcohol to compete with DHPG and HMPG anabolism, because alcohol is an exogenous competitor for endogenous DHPG and HMPG on π ADH (Mardh et al 1986). Over time, this could lead to alcohol dependence. Alternatively, to mitigate the lower norepinephrine levels, an individual could self-administer cocaine, which partially functions as a norepinephrine reuptake inhibitor and can increase plasma norepinephrine concentrations (Sofuoglu et al 2001), or opiates, which stimulate norepinephrine release in cerebrospinal fluid (Bouaziz et al 1996). Over time, such self-administration of drugs (cocaine and opiates) could, similarly, lead to drug dependence. Norepinephrine is also well known to play a role in the development and expression of various personality traits (Coccaro et al 2003). A low level of norepinephrine is usually hypothesized to cause aggressive behavior (Coccaro et al 2003) that could be most closely predicted by (low) agreeableness (Gleason et al 2004). Agreeableness-related personality traits and aggression might be the outcome of a self-regulatory process predicated on a low level of norepinephrine (Gleason et al 2004). Thus, personality trait development might have a similar mechanism to SD risk, potentially mediated by norepinephrine levels, which are affected by ADH4 enzyme activity. Alternatively, other mechanisms via other pathways, e.g., a dopaminergic pathway, might be possible.

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Table 1

Frequency Distributions of Genotypes, Alleles, and Common Haplotypes and Diplotypes in EAs, AAs, and the Entire Sample

	EAs		AAs		Total		EA vs. AA
	n	*f*	*n*	*f*	*n*	*f*	*p*-Value
SNP1 (hcv2033010)							
T/T	41	.096	3	.029	44	.083	
T/C	185	.434	33	.314	218	.411	
C/C	200	.469	69	.657	269	.507	.001
T	267	.313	39	.186	306	.288	
C	585	.687	171	.814	756	.712	2.4E-04
SNP2 (rs1042364)							
T/T	37	.089	2	.019	39	.074	
T/C	168	.403	20	.187	188	.359	
C/C	212	.508	85	.794	297	.567	2.0E-07
T	242	.290	24	.112	266	.254	
C	592	.710	190	.888	782	.746	2.0E-08
SNP3 (rs1126671)							
A/A	44	.103	4	.038	48	.090	
A/G	189	.443	32	.305	221	.415	
G/G	194	.454	69	.657	263	.494	.001
A	277	.324	40	.190	317	.298	
G	577	.676	170	.810	747	.702	1.0E-04
SNP4 (rs1126670)							
C/C	44	.104	3	.028	47	.089	
A/C	185	.436	34	.318	219	.412	
A/A	195	.460	70	.654	265	.499	4.1E-04
C	273	.322	40	.187	313	.295	
A	575	.678	174	.813	749	.705	7.7E-05
SNP5 (rs7694646)							
A/A	37	.087	3	.029	40	.075	
A/T	175	.410	18	.171	193	.363	
T/T	215	.504	84	.800	299	.562	1.2E-07
A	249	.292	24	.114	273	.257	
T	605	.708	186	.886	791	.743	3.2E-08
SNP6 (rs1800759)							
A/A	71	.168	73	.689	144	.273	
A/C	196	.464	27	.255	223	.422	
C/C	155	.367	6	.057	161	.305	< 2.2E-16
A	338	.400	173	.816	511	.484	
C	506	.600	39	.184	545	.516	< 2.2E-16
SNP7 (rs1984362)							
A/A	37	.087	0	.000	37	.070	
A/G	172	.405	19	.181	191	.360	
G/G	216	.508	86	.819	302	.570	2.5E-09
A	246	.289	19	.090	265	.250	
G	604	.711	191	.910	795	.750	1.5E-10
Haplotype							
CCGATCG	520	.603	40	.184	559	.519	
TTACAAA	239	.277	17	.078	256	.237	
CCGATAG	60	.070	133	.616	193	.179	
TCACTAG	28	.033	17	.079	45	.042	
CTACAAA	9	.011	1	.005	10	.010	
TTACAAG	2	.002	5	.023	7	.007	< 2.2E-16
Diplotype							
CCGATCG/CCGATCG	161	.374	6	.056	167	.310	
TTACAAA/CCGATCG	140	.324	2	.021	142	.263	
CCGATAG/CCGATCG	34	.078	21	.198	55	.102	
CCGATAG/CCGATAG	1	.003	42	.384	43	.079	
TTACAAA/TTACAAA	33	.078	0	.000	33	.062	
TTACAAA/CCGATAG	20	.047	13	.116	33	.061	
TCACTAG/CCGATCG	17	.040	2	.018	19	.035	
TCACTAG/CCGATAG	3	.007	13	.120	16	.029	
TTACAAA/TCACTAG	6	.014	0	.000	6	.011	

	EAs		AAs		Total		EA vs. AA
	n	***f***	***n***	***f***	***n***	***f***	***p*-Value**
CTACAAA/ CCGATCG	5	.012	0	.000	5	.009	7.9E-07

n, individual numbers (for genotypes, haplotypes, and diplotypes) or chromosome number (for alleles); *f*, frequency; EA, European American; AA, African American; EA vs. AA, exact tests for the comparisons of genotype, allele, haplotype, and diplotype frequency distributions between EAs and AAs; SNP, single nucleotide polymorphism; E, scientific format of 10^{n}.

Table 2

MANCOVAs Reflecting the Relationships Between Personality Traits and *ADH4* Variation

Models	Sources	*p*-Values
Diplotypewise	Diagnosis	9.0E-32
	Sex	9.2E-05
	Age	4.9E-08
	Ancestry	1.2E-05
	“TTACAAA/TCACTAG”	.030
	Ancestry × “TTACAAA/TCACTAG”	.028
	Age × “TTACAAA/TCACTAG”	.019
	Dx × “TTACAAA/CCGATCG”	.034
	Sex × “TTACAAA/CCGATCG”	.039
Allelewise	Diagnosis	2.4E-69
	Age	2.2E-16
	Ancestry	2.7E-11
	Sex × SNP6	.030
	(or) Sex × Age × SNP6	2.5E-13
Genotypewise	Diagnosis	2.0E-35
	Age	4.5E-08
	Ancestry	5.0E-05
	Sex × SNP6	5.4E-04
	(or) Sex × Age × SNP6	2.2E-05

MANCOVA, multivariate analysis of covariance; E, scientific format of 10^{n}. × denotes interaction.

Table 3

Roy-Bargmann Stepdown ANCOVAs for the Relationship Between Each Personality Factor and Predictor Variables

Sources	F1	F2	F3	F4	F5
Allelewise					
Age	2.4E-09	5.9E-05		8.0E-04	.006
Diagnosis			1.5E-04	1.2E-43	.004
Sex		1.6E-06			
F2			.002		
F1					3.8E-05
F4	1.9E-14	1.3E-34	6.8E-27		
Sex × SNP6		5.0E-04			
F3 × SNP1	.009				
F3 × SNP2	.003				
Genotypewise					
Age	3.5E-05				
Diagnosis				1.5E-22	
Sex		.006		.001	
F4	1.7E-06	1.8E-11	2.4E-15		
Sex × SNP6		1.9E-04			

Only significant relationships are shown; statistical significance threshold = .01.

F1, Extraversion; F2, Agreeableness; F3, Conscientiousness; F4, Neuroticism; F5, Openness; X, interaction between; SNP, single nucleotide polymorphism; E, scientific format of 10^{n}.

Table 4

Decomposition Analysis of the Relationship Between Each Personality Factor and Each of the Predictors of Risk

		Lower F1		Lower F2		Lower F2		Lower F3		Higher F4		Lower F5	
Sample	**Covariates**	**RF**	***p***	**RF**	***p***	**RF**	***p***	**RF**	***p***	**RF**	***p***	**RF**	***p***
Whole	Diagnosis			SD	7.3E-16			SD	5.4E-17	SD	3.6E-32	SD	3.6E-12
	Age	Older	8.5E-11	Older	.035					Older	.001	Older	1.5E-10
	Sex			Male	.009					Female in SD	1.0E-04		
Male subjects	SNP6			Allele C	.041	Allele C in older subjects	.013						
	SNP6			Allele A	.039	Allele A in younger subjects	.028						
Female subjects				Genotype A/A	.003	Genotype A/A in younger subjects	.005						

RF, risk factor; *p*, *p*-values; SD, substance dependence; E, scientific format of 10^{n}; SNP, single nucleotide polymorphism.