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ADH1A variation predisposes to personality traits and substance dependence

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Abstract

Background—Human personality traits are strong predictors or characteristics of many psychiatric disorders including substance dependence (SD). Recently, significant associations between *ADH1A* and SD have been reported, which led us to investigate the impact of *ADH1A* variation on personality traits and risk of SD.

Methods—Five hundred fifty-eight subjects with SD [398 European-Americans (EAs) and 160 African-Americans (AAs)], 517 college students (384 EAs and 133 European-origin Hispanics) and 448 healthy subjects (385 EAs, 48 AAs and 15 European-origin Hispanics) participated. Personality traits were assessed in 247 subjects with SD (179 EAs and 68 AAs), all 517 college students, and 332 healthy subjects (285 EAs, 40 AAs and 7 European-origin Hispanics). The relationships between *ADH1A* and personality traits were comprehensively examined using stepwise multivariate analysis of covariance (MANCOVA), and then decomposed by stepwise analysis of covariance (ANCOVA). The relationship between *ADH1A* and SD was examined using stepwise logistic regression analysis. Admixture effects on analyses were considered.

Results—Overall, Agreeableness and Conscientiousness were associated with the diplotypes, haplotypes, genotypes and/or alleles of *ADH1A* in three of four phenotype groups including European-American SD subjects, healthy subjects, and African-American SD subjects ($1.7\times10^{-4}\leq p\leq 0.055$), but not college students. Neuroticism was associated with diplotype, haplotypes and genotypes in African-American SD subjects ($0.001\leq p\leq 0.031$). In addition, SD was associated with diplotypes, haplotypes, genotypes and/or alleles of *ADH1A* ($0.008\leq p\leq 0.060$).

Conclusions—The present study demonstrates that the *ADH1A* variation may contribute to the genetic component of variation in personality traits and SD.

Keywords

Personality; Substance dependence; *ADH1A*

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Introduction

Personality traits are complex quantitative traits and appear to be influenced by multiple genetic loci and by environmental factors. Genetic factors have been consistently implicated as contributing to individual differences in major dimensions of personality, with about one-third to one-half of the variation in personality typically being attributed to such factors [e.g., Loehlin 1992; Ebstein et al., 2000; Bouchard and Loehlin, 2001]. A genomewide linkage study mapped five trait-influencing loci for the personality factor of Neuroticism at chromosomes 1q, 4q, 7p, 12q, and 13q [Fullerton et al., 2003]. Varying degrees of direct evidence have also been found regarding association between personality traits and specific genes, including *SLC6A4, HTR2C, HTR2A, DRD2, DRD3, DRD4, COMT, TFAP2B, ESR1* [reviewed by Luo et al., 2007a], *ADH4* [Luo et al., 2007a], *CHRM2* [Luo et al., 2007b], *ADH7* [Luo et al., 2008a], and the genes encoding the opioid receptors, *OPRs* [Luo et al., 2008b]. The present study examined the relationship between personality traits and the alcohol dehydrogenase type 1A gene (*ADH1A*); and also, the relationship between *ADH1A* and substance dependence (SD).

ADH1A is a class I ADH gene, spanning 14.6kb, located molecularly close to other two class I ADH genes, *ADH1B* and *ADH1C*. Classes I, II (*ADH4*), III (*ADH5*), IV (*ADH7*), and V (*ADH6*) map to the same ADH gene cluster at chromosome 4q21-25. The three class I genes (*ADH1A, ADH1B* and *ADH1C*) have similar sequence. For example, their proximal promoters remain 80-84% identical in sequence, with approximately the same degree of identity at synonymous sites in the coding regions of these three genes [Brown et al., 1996; Edenberg, 2000]. *ADH1A* encodes the αα ADH enzyme. αα ADH is mainly expressed in the early fetal liver. Although it is weakly expressed in adult liver [Smith et al., 1971; 1972], the density of αα ADH in adult liver is about 1000 times that in brain. Liver αα ADH has properties similar to those of ββ ADH (encoded by *ADH1B*) and γγ ADH (encoded by *ADH1C*), mainly contributing to the oxidization of ethanol (Km=4.2 mM) and retinol (Km=15-40 μM). They are also involved in several metabolic processes, e.g., norepinephrine, dopamine, serotonin and bile acid catabolism [Höög et al., 2001]. *ADH1A* and αα ADH may have some properties that differentiate it from the other two class I ADHs. For example, the *ADH1A* promoter contains an E-box–related site (CATGTG) that is not protected in DNase I footprinting assays under conditions that allow protection of the related CACGTG sites in *ADH1B* and *ADH1C* [Brown et al.,1996]; *ADH1A* is the only class I ADH gene that responds to co-transfection with hepatocyte nuclear factor-1 (HNF-1) [van Ooij et al., 1992]; the temporal expression of *ADH1A* differs from that of *ADH1B* and *ADH1C* [Smith et al., 1971; 1972; 1973]; and αα ADH is the primary form in most hepatomas [Smith, 1986].

Associations between *ADH1B* and *ADH1C* and alcohol dependence (AD) have been extensively reported [summarized in Luo et al., 2006 and Zintzaras et al., 2006], but association between *ADH1A* and AD has rarely been reported until recently – partially because there have been no reports of coding variation in *ADH1A*. However, synonymous variation or "silent" polymorphisms might potentially influence transcription levels, mRNA stability, translational efficiency, or density of αα ADH. For example, several distal *cis*-acting elements in the *ADH1A* 5′ regulatory region contribute to the regulation and tissue-specificity of αα ADH: (1) A negative element from bp -1873 to -1558, relative to the translational start site, decreased transcriptional activity to 52% in H4IIE-C3 cells and 70% in CV-1 cells. (2) A positive element from bp -2459 to -2173 doubled transcriptional activity in H4IIE-C3 cells and 1.7-fold in CV-1 cells. Gel mobility shift and supershift assays demonstrated GATA-2 binding to a region within this positive element. (3) A tissue-specific regulatory element from bp -6380 to -5403 doubled transcription in H4IIE-C3 cells while decreasing transcription to 86% in CV-1 cells. Within this tissue-specific fragment, the region from bp -5668 to -5403 increased transcription by 70% in H4IIE-C3 cells and by 30% in CV-1 cells. (4) Hepatocyte nuclear factor-3 (HNF-3) was shown to bind to a region of the tissue-specific element in CV-1 cells, contributing to tissue

specificity [Dannenberg et al., 2005]. Additionally, rs1229966 (SNP3 in this study; see below) at bp -1291 could significantly alter the secondary structure of *ADH1A* mRNA (IDT SciTools: http://www.idtdna.com/SciTools/SciTools.aspx). Thus, genetic variation in *ADH1A* has the potential to result in phenotypic variation, such as the individual genetic variability in susceptibility to the development of SD [including AD and drug dependence (DD)] or personality traits. Association between *ADH1A* variation (mostly located in the 5′ end of the gene) and SD has been reported recently. Edenberg et al. (2006) genotyped 110 SNPs across the seven ADH genes, including 14 SNPs within or near *ADH1A*, and analyzed their association with AD in a set of families with multiple AD members. Several SNPs distributed across *ADH1A* from the upstream region through exon 8 were significantly associated with AD, including rs1826909 [at bp -5601; 4.3 kb to SNP3 (rs1229966)], rs4147531 (at bp -55; 1.2 kb to SNP3), and rs2866151 [at intron 8; 3.2 kb to SNP2 (rs975833)] (see Table 1). We reported positive associations between *ADH1A* diplotypes and both AD [Luo et al., 2006] and DD [Luo et al., 2007c]. Kuo et al. (2008) genotyped 77 SNPs across the seven *ADH* genes and two *ALDH* genes (i.e., *ALDH1A1* and *ALDH2*), which included 4 SNPs within or near *ADH1A*, and analyzed their association with AD in an Irish affected sibling pair sample. They found that two SNPs in the upstream region of *ADH1A* were significantly associated with AD, including rs13134764 (at bp -31; 1.26 kb to SNP3) and rs904092 (at bp -2022; 731 bp to SNP3; interacting with rs3762894 at 5′ end of *ADH4*). These findings suggest that variation in *ADH1A* plays a role in modifying risk for SD (mainly AD). DD is one of the disorders that co-occur most commonly with AD, with which it shares a number of features. Many studies, including ours, have shown that DD and AD share susceptibility genes such as *CHRM2* [Luo et al., 2005a], *ADH4* [Luo et al., 2005b], *ADH1A*, *ADH1B*, *ADH1C*, *ADH5*, *ADH6* and *ADH7* [Luo et al., 2006; 2007c] and *OPRM1*, *OPRD1* and *OPRK1* [Luo et al., 2003; Zhang et al., 2006; 2008]. Variation in these susceptibility genes also contributes to personality traits in DD and AD subjects [Luo et al., 2007a; 2007b; 2008a; 2008b]. Thus, we examined AD and DD jointly as one phenotype (substance dependence, SD) to increase power.

Many studies have shown that personality characteristics play a role in the development of SD (including AD and opioid dependence in these studies) [e.g., Cloninger et al., 1988; Caspi et al., 1997]. Also, many previous studies suggest that common genetic factors may underlie some portion of the association between personality traits and AD [reviewed by Luo et al., 2007a]. Specifically, we have demonstrated that *ADH4*, *ADH7*, *CHRM2*, and *OPR* variation affect risk for SD and influence personality [Luo et al., 2007a; 2007b; 2008a; 2008b]. These findings highlight the role of personality as a genetically determined risk factor for SD. On the basis of this evidence, one important area of research focuses on the association between personality traits and alcohol metabolism related genes (e.g., *ADH1A*, *ADH4* and *ADH7*), especially in SD patients, due to their strong physiologic (and in some cases, genetic) contribution to SD [reviewed by Luo et al., 2007a], and due to their potential associations with levels of some specific neurotransmitters (e.g., dopamine, serotonin, and norepinephrine) [Luo et al., 2008b] that may be oxidized by, for example, the αα ADH enzyme [e.g., Höög et al., 2001]. Personality traits also exist as phenotypes independent of neuropsychiatric disorders, including SD; thus, we investigated the gene-personality relationship not only in SD patients, but also in college students, some of who had trait anxiety, and in healthy subjects who were screened to exclude individuals with Axis I mental disorders. It is predictable that gene-personality associations would differ to some extent in different phenotype groups, so that positive, although not completely consistent, associations across different phenotype groups may support the validity of the findings.

Our previous studies have demonstrated that gene effects on personality traits differed by sex, age, population, and affection status [Luo et al., 2007a; 2007b; 2008a; 2008b]. We therefore included older and younger adults, EAs and AAs, men and women, and SD and healthy

individuals in the present study, and investigated the moderating effects of sex, age, ethnicity, and affection status on the association between personality traits and *ADH1A*.

Materials and Methods

1. Subjects

Five hundred fifty-eight subjects with SD (398 EAs and 160 AAs), 517 college students (384 EAs and 133 European-origin Hispanics) and 448 healthy subjects (385 EAs, 48 AAs and 15 European-origin Hispanics) were included in the present study. Personality was assessed in 247 subjects with SD (179 EAs and 68 AAs) that were recruited at the University of Connecticut Health Center (UCHC), all college students that were recruited at the University of California San Diego (UCSD), and 332 healthy subjects (285 EAs, 40 AAs and seven European-origin Hispanics) that were recruited at the UCHC or the UCSD. Other subjects recruited from Yale University, which were included to expand the sample size to investigate the gene-SD relationship, were not assessed for personality traits. For psychiatric diagnoses, patients met lifetime DSM-III-R or DSM-IV criteria [American Psychiatric Association. 1987, 1994]. Subjects with SD had a diagnosis of alcohol dependence, cocaine dependence and/or opioid dependence. Diagnoses were made using the Structured Clinical Interview for DSM-III-R (SCID) [Spitzer et al., 1992] or DSM-IV, the computerized Diagnostic Interview Schedule for DSM-III-R (C-DIS-R) [Blouin et al., 1988] or DSM-IV, or a checklist comprised of DSM-III-R or DSM-IV symptoms. We recruited the sample of college students, aiming to get a full range of anxiety-related traits in young adults (Stein et al. 2005). Among the high anxious students, some (approximately 25% of total) were found to have generalized anxiety disorder, though nearly all have never been treated for this or any other psychiatric problem. The healthy subjects were screened using the SCID or the C-DIS-R to exclude major Axis I disorders, including AD or DD, psychotic disorders (including schizophrenia or schizophrenia-like disorders), mood disorders, and major anxiety disorders. The ages and sex distributions for these subjects are shown in Table 2. All subjects gave informed consent before participating in the study, which was approved by the Institutional Review Boards at the participating institutions.

2. Marker inclusion and genotyping

Three tagSNPs spanning the 5′ to 3′ portions of *ADH1A* (with an average inter-marker distance of 4 kb; see Table 1), one marker (rs13104485) in *ADH6* and four markers [rs1042026, rs2066702 (ADH2*3), rs2066701 and rs1229984 (ADH2*2)] in *ADH1B*, three markers [rs698 (ADH3*2), rs1693482, and rs1693427] in *ADH1C*, and thirty-eight ancestry-informative markers (AIMs) [Yang et al., 2005;Luo et al., 2005a;2005b] unlinked to *ADH1A* were included. The markers in *ADH6* and *ADH1B* were in the same haplotype block as the *ADH1A* markers (D′>0.95), and the markers in *ADH1C* were in strong LD with the *ADH1A* markers (D′>0.87). These tagSNPs fully tag each gene ($r^2 \geq 0.8$, minor allele frequency > 0.1) and were genotyped by the TaqMan technique. The three *ADH1A* tagSNPs fully tag this gene in the HapMap YRI African population also.

3. Assessment of Personality

The NEO Five-Factor inventory (NEO-FFI) [Costa and McCrae. 1997] was used to assess five personality dimensions in all subjects with SD recruited from UCHC, all college students recruited from UCSD, and all healthy individuals recruited from UCHC. The five dimensions derived from the NEO are Extraversion, Agreeableness, Conscientiousness, Neuroticism, and Openness to Experience. Every personality factor and the linear combination of all personality factors were normally distributed [Luo et al., 2007a].

4. Ancestry proportion estimation

The European and African ancestry proportions for each self-identified EA, AA and Hispanic individual were estimated by the program STRUCTURE [Pritchard et al., 2000; Falush et al., 2003] using 38 AIMs [Luo et al., 2005a,b]. The subjects were divided into "genetic" EAs (European ancestry>0.5) and "genetic" AAs (African ancestry>0.5) in the analysis described below. All Hispanics were categorized as "genetic" EAs (i.e., all had European ancestry>0.5). The ancestry proportion scores were also entered into the General Linear Models (including MANCOVA and ANCOVA) and logistic regression analysis as covariates, to exclude population stratification and admixture effects on the analysis.

5. Individual haplotype and diplotype probability estimation

The program PHASE [Stephens et al., 2001; 2003] was used to reconstruct haplotypes in each gene and estimate the probabilities (from 0-1) of all likely pairs of haplotypes (i.e., diplotypes) for every individual. These haplotype and diplotype probabilities were entered into the General Linear Models and logistic regression models as described below.

6. Data analysis

(1) Stepwise multivariate analysis of covariance (MANCOVA)—Was employed to test associations between genes and personality traits in the subjects assessed with the NEO-FFI. In the MANCOVA models, five personality factors were combined using a matrix of Sums of Squares and Cross-Products (SSCP) and served as one composite dependent variable, which was subsequently decomposed to examine the five personality factors individually. In this analysis, the diplotype or haplotype probabilities (f>0.05), genotypes or alleles of each marker served as predictor variables and age, ancestry proportions, and sex served as covariates. Age and sex as covariates were included to rule out their confounding effects on the gene-personality associations. Ancestry proportions as covariate were included to rule out the population stratification and admixture effects on the associations (Luo et al. 2005a). Additionally, the gene effects on personality traits may differ by sex and age as reviewed above, and each individual has two alleles at a single locus and two haplotypes at multiple loci; thus, we also considered the two-way interactions between the predictor variables and covariates (i.e., sex and age), between haplotypes and between any two markers as independent predictor variables in these models. The gene effects on personality traits may differ by population and affection status as reviewed above, thus, the different phenotype and population groups were analyzed separately. Statistical significance was evaluated based on the Pillai's Trace statistic. All of the above MANCOVAs were run as backward stepwise analyses. Only the variables considered statistically significant (i.e., $p<0.05$) remained in the final equations.

At a single locus, two alleles could be incorporated into a genotype. Similarly, at multiple loci, the haplotype information content could be incorporated into the diplotype. The information content of alleles and genotypes from multiple loci could be incorporated into multi-locus haplotypes and diplotypes, respectively. Therefore, the four MANCOVA models, the four ANCOVA models, and the four logistic regression models (i.e., diplotypewise, haplotypewise, genotypewise and allelewise models) are not independent of each other. Because they are equivalent to a single model, correction for multiple testing was not necessary. Among the four models, the diplotypewise model is most powerful.

Within each model, multiple predictor variables are tested. These kinds of multiple testing are accounted for by the degree of freedom. Thus, p-values derived from these models do not require further correction for multiple testing by the number of models and the significant level (α) for MANCOVA and logistic regression models is set at 0.05.

(2) Stepwise univariate analysis of covariance (ANCOVA)—Was used to assess individual personality factors to ascertain the source of positive findings resulting from the MANCOVAs. In each ANCOVA model, one personality factor served as the dependent variable and the other four personality factors served as covariates; other predictor variables, covariates, and the interaction terms were the same as those used in the MANCOVA models. Five personality factors were tested separately, so α was set at 0.01 (=0.05/5 where "5" is the number of personality factors). For each ANCOVA, a backward stepwise process was applied.

(3) Stepwise logistic regression analysis—A backward stepwise logistic regression analysis implemented in SPSS 15.0 was used to test associations between *ADH1A* and SD within "genetic" EAs and AAs (including those who were not assessed by the NEO-FFI). In the regression model, phenotypes served as the dependent variables, and the covariates included ancestry proportion, age, sex, and diplotype or haplotype probabilities, or genotypes or alleles of each marker. Two-way interactions between the predictor variables and covariates, between haplotypes, and between any two markers were also considered as predictor variables in these models. Only the variables that were statistically significant (i.e., $p<0.05$) remained in the final equations. Rare diplotypes or haplotypes ($f<0.05$ or $n<5$) were excluded and collinearity issues in the regression models were avoided [Luo et al. 2007a].

Results

1. MANCOVA indicated that the personality traits were related to age and/or sex in all subgroups ($3.3\times10^{-7}\leq p\leq0.050$), consistent with previous studies [Luo et al., 2007a; 2007b; 2008a; 2008b]. Personality traits were also related to ancestry in AAs ($7.5\times10^{-6}\leq p\leq0.035$) and Hispanics (data not shown), both of which were admixed with Europeans. MANCOVA also indicated that the *ADH1A* diplotypes, haplotypes, genotypes and alleles had significant effects on the personality traits, some of which were also modified by sex or age (Table 3) (α was set at 0.05); but the flanking genes had no significant effects on the personality traits.

There was no significant difference in the gene-personality associations among AD, cocaine dependence and opioid dependence groups (data not shown), so these three phenotype groups were combined as one SD group in the context to increase the power. In EA SD patients, diplotype TGA/TGA (frequency: $f=0.052$) at *ADH1A* had a significant main effect ($p=0.002$) and an interaction effect ($p=0.022$; modified by sex) on the composite personality trait measure. There were also significant interaction effects of haplotypes TGA × TGA ($p=0.010$), TGA × TGA × sex ($p=0.016$) and AGA × TGA ($p=0.025$) on the composite personality measure. Genotypes and alleles of SNP1 had significant main effects ($p_g=0.037$; $p_a=0.043$) and genotypes of SNP1 × SNP3 ($p_g=0.035$; modified by sex) and alleles of SNP1 ($p_a=0.037$; modified by age) had significant interaction effects on the composite personality measure.

In AA SD patients, diplotype AGA/TGA ($f=0.074$) had a significant interaction effect ($p=0.007$; modified by sex) on the composite personality measure, as did the interaction of haplotypes AGA × TGA × sex ($p=0.007$). Genotypes of SNP2 × SNP3 ($p_g=0.072$; modified by sex) and alleles of SNP1 × SNP2 ($p_a=0.050$; modified by sex) had suggestive interaction effects on the composite personality measure.

In EA healthy subjects, diplotypes AGA/TGA ($f=0.204$; $p=0.039$) and TCG/TCG ($f=0.075$; $p=0.003$) had significant effects on the composite personality measure (both modified by sex). There were also significant interaction effects of haplotypes AGA × TGA × sex ($p=0.033$) and TCG × TCG × sex ($p=0.037$) on the composite personality measure. Addition of the seven healthy Hispanic subjects to the analysis did not substantially alter these findings ($p=0.037$, 0.006, 0.029 and 0.053, respectively). Genotypes and alleles of SNP1 and SNP2 had significant interaction effects ($p_g=0.001$; $p_a=0.006$) on the composite personality measure. Addition of

the 7 healthy Hispanic subjects to the analysis did not substantially alter these findings (p=0.004 and 0.008, respectively), but SNPs 1-3 showed significant main effects (p=0.002, 0.043, and 0.007, respectively). Forty AA healthy subjects were not analyzed due to too small sample size.

If conservatively corrected by 4 MANCOVA models (i.e., allelewise, genotypewise, haplotypewise, and diplotypewise models), setting the significance level (α) at 0.05/4=0.0125, some of the above associations become suggestive, and others remain statistically significant.

In the EA college students, who have a very limited age range, no associations between *ADH1A* gene and personality were found. After combining the 133 Hispanic college students with the EA students, no positive gene-personality association was found either. (Note that by Bayesian clustering the Hispanic subjects were found to have predominantly European ancestry.)

2. ANCOVA showed that different personality factors were related to age and/or sex in all subgroups (data not shown) and related to ancestry in AAs or Hispanics (data not shown), which were admixed, consistent with previous studies [Luo et al., 2007a; 2007b; 2008a; 2008b]. ANCOVA also showed that the *ADH1A* diplotypes, haplotypes, genotypes and/or alleles had main and/or interaction effects on different personality factors in three phenotype subgroups (except for the college students) (Table 4) (α was set at 0.01).

In EA SD females, the diplotype TGA/TGA (β=-9.814; p=0.003), the interaction of haplotypes TGA × TGA (β=-10.089; p=0.001), and the interaction of genotypes SNP1ˆT/T × SNP3ˆA/A (β=-10.478; p=0.002) significantly decreased Agreeableness scores. In EA SD patients, the diplotype TGA/TGA significantly (β=6.470; p=0.004) and the interaction of haplotypes TGA × TGA suggestively (β=4.092; p=0.055) increased Conscientiousness scores.

In AA SD males, the interaction of genotypes SNP2ˆG/G × SNP3ˆG/G suggestively (β=6.664; p=0.043) increased Agreeableness scores. In AA SD females, diplotype AGA/TGA and the interaction of its two haplotypes AGA × TGA suggestively increased Conscientiousness scores (β=7.983, 31.931, respectively; both p=0.018) and decreased Neuroticism scores (β=-10.203, -40.813, respectively; both p=0.031). The interaction of genotypes SNP2ˆG/G × SNP3ˆA/A suggestively decreased Neuroticism scores (β=-10.073; p=0.030).

In EA healthy males, the diplotypes AGA/TGA (β=3.672; p=0.014) and TCG/TCG (β=7.096; p=0.005), the interactions of haplotypes AGA × TGA (β=16.726; p=0.008) and TCG × TCG (β=6.662; p=0.010), and the interaction of genotypes SNP1ˆT/T × SNP2ˆC/C (β=7.939; p=0.006) significantly or suggestively increased Agreeableness scores; the diplotype AGA/TGA (β=-3.677; p=0.019) and the interaction of its two haplotypes AGA × TGA (β=-14.741; p=0.019) suggestively decreasedConscientiousness scores. In EA healthy females, the interaction of genotypes SNP1ˆA/T × SNP2ˆC/G (β=5.744; p=0.002), the interaction of alleles SNP1ˆA × SNP2ˆC (β=3.904; p=0.004) and the interaction of alleles SNP1ˆT × SNP2ˆG (β=2.555; p=0.007) significantly increased Agreeableness scores. If combining the seven healthy Hispanic subjects, all of these effects remained almost unchanged (data not shown).

If conservatively corrected by 4 models (i.e., allelewise, genotypewise, haplotypewise, and diplotypewise models), setting the significance level (α) at 0.01/4=0.0025, some of the above associations become suggestive, and others remain statistically significant

In the EA college students, no significant associations between *ADH1A* gene and personality were found by ANCOVA, consistent with the above results by MANCOVA. This subgroup is not listed in Table 4 either.

3. Logistic regression analysis showed that SD was associated with diplotypes, haplotypes, genotypes and/or alleles of *ADH1A* (Table 5) (α was set at 0.05). (The relationship between *ADH6, ADH1B* and *ADH1C* genes and SD were reported elsewhere [Luo et al., 2006; 2007c]).

There was no significant difference in the gene-disease associations among AD, cocaine dependence and opioid dependence groups (data not shown), so these three phenotype groups were combined as one SD group in the context to increase the power. SD was significantly associated with age ($2.2\times10^{-68}\leq p\leq0.033$) and sex ($9.7\times10^{-11}\leq p\leq0.003$) in different regression models (Table 5), which reflected the asymmetrical sex and age structure of cases and controls in our samples resulting from sampling bias. Thus, confounding effects from these two covariates were controlled for in all regression analyses.

In EA females, the diplotype TCG/TCG (β=-1.387; p=0.050), the interaction of its two haplotypes TCG × TCG (β=-1.178; p=0.060), and the allele SNP2ˆC (β=-0.589; p=0.020), suggestively decreased risk for SD; the genotypes SNP3ˆA/A (β=1.461; p=0.008) and SNP3ˆA/G (β=1.229; p=0.026) and the allele SNP3ˆA (β=0.530; p=0.018) significantly increased risk for SD.

In AAs, the diplotype AGA/TCG and the interaction of its two haplotypes AGA × TCG (β=-1.518, -6.283, respectively; both p=0.029), the interaction of genotypes SNP1ˆA/T × SNP2ˆC/G (β=-1.439; p=0.031), and the interaction of alleles SNP1ˆA × SNP2ˆC (β=-1.327; p=0.037) decreased risk for SD.

All of the above |βs|<1.5. There is no outlier among these βs; that is, there is no extreme β that is hundreds or thousands of times higher than other βs in the same regression models, which is a key indicator that no multicollinearity issue occurs in these regression models.

Discussion

The findings in the present study suggest that, although modified by sex, variation in *ADH1A* may play an important role both in the development of personality traits and in the risk for SD.

ADH1A is flanked with *ADH6, ADH1B* and *ADH1C* genes. However, none of these flanking markers were significantly associated with personality factors (data not shown), which suggests that, based on the current initial evidence, it is the variation in *ADH1A*, rather than in the flanking genes, that influences personality traits.

Overall, Agreeableness and Conscientiousness were associated with the diplotypes, haplotypes, genotypes and/or alleles of *ADH1A* in three phenotype groups, including EA SD subjects, healthy subjects, and AA SD subjects. Neuroticism was associated with diplotypes, haplotypes and genotypes in AA SD females.

The diplotype AGA/TGA and the interaction of its two haplotypes AGA × TGA exerted the most robust effects. These variants had significant effects on Agreeableness, Conscientiousness and/or Neuroticism in EA healthy subjects and AA SD subjects. The second most important diplotype was TGA/TGA, which differs from AGA/TGA by a single base. This diplotype and the interaction of its two haplotypes TGA × TGA had significant effects on Agreeableness and Conscientiousness in EA SD subjects. The third most important diplotype was TCG/TCG, which is the opposite phase of AGA/AGA that differs from AGA/TGA by only one base. This diplotype and the interaction of its two haplotypes TCG × TCG had significant effects on Agreeableness in EA healthy males and decreased risk for SD in EA

females. Genotypes and/or alleles of all three SNPs and the interactions between any two of them also had significant effects on Agreeableness and/or Neuroticism.

We observed that the diplotype main effects were more significant than other gene main effects including haplotype, genotype and allele effects, consistent with previous conclusions [Luo et al., 2005a; 2006]; and as the basic biological reality is that each individual is diploid, we drew conclusions mainly from diplotypewise analysis. (1) Diplotypes and haplotypes incorporate the information of multiple markers and therefore are more powerful than single locus analysis (i.e., non-interaction analysis; data not shown). In the present study, the results from the genotypewise and allelewise analyses are consistent with those from the diplotypewise and haplotypewise analyses. For example, in EA SD females, both the diplotype TGA/TGA and the genotypes SNP1ˆT/T × SNP3ˆA/A, which can be incorporated into TGA/TGA, significantly decreased Agreeableness scores; in AA SD females, both the diplotype AGA/TGA and the genotypes SNP2ˆG/G × SNP3ˆA/A, which can be incorporated into AGA/TGA, suggestively decreased Neuroticism scores; in EA healthy males, both the diplotype TCG/TCG and the genotypes SNP1ˆT/T × SNP2ˆC/C, which can be incorporated into TCG/TCG, significantly increased Agreeableness scores. (2) Diplotypewise analysis provided much more significant results than haplotypewise main effect analysis (i.e., non-interaction analysis; data not shown), probably because more diplotypes were involved in the analysis, leading to greater sensitivity for detection. Also, in the present study, a risk/protective diplotype had effects highly consistent with effects of the interaction of its two haplotypes, suggesting that these diplotypes simply reflected the interaction effects between haplotypes (which were much stronger than the haplotype main effects), also consistent with our previous conclusions [Luo et al., 2006]. Positive diplotype-disease associations and diplotype-personality associations suggest that *ADH1A* harbors risk sites for diseases or contributory sites for personality which are in LD with these risk diplotypes.

Although diplotype AGA/TGA and its structure-similar or phase-opposite diplotypes had effects on personality across three different phenotype groups, and Agreeableness and Conscientiousness were associated with *ADH1A* gene markers across three different phenotype groups, the gene-personality associations differed somewhat among the different phenotype groups. This difference could have resulted from the variance in phenotypes (including affection status, sex, and age) and/or the variance in gene effects (including allelic heterogeneity, population specificity, and confounding effects) among these groups. Relevant considerations include the following five:

1. Phenotypic variance may be related to the difference of gene-personality association: (a) *ADH1A* may have been associated with Neuroticism only in AA SD subjects because specific facets of Neuroticism were strongly linked to SD in AAs, but not dominant in healthy subjects. For example, high Neuroticism scores (i.e., emotional instability, including self-pity, worrying, insecurity, emotionality, nervousness, quickness to anger, pessimism, longer rebound time, etc.) are strong predictors or characteristics of SD. Further, the present association signal for Neuroticism in *ADH1A* (chromosome 4q) matched the linkage signal for Neuroticism at chromosome 4q which was detected by the only published genome-scan linkage study of personality traits [Fullerton et al., 2003]. (b) The same diplotype AGA/TGA in AA SD females have opposite effects on Conscientiousness and Neuroticism, because these two personality factors are reversely correlated. (c) In EA SD subjects, there was an interaction effect of SNP1 with SNP3 on Agreeableness; in AA SD subjects, there was an interaction effect of SNP2 with SNP3 on Agreeableness and Neuroticism; and in EA healthy controls, there was an interaction effect of SNP1 and SNP2 on Agreeableness. This difference in gene effects might be related to phenotypic variance among these different groups.

2. Modification by sex may result in the difference of gene-personality association: (a) The diplotype AGA/TGA increased Conscientiousness scores in AA SD females, but decreased them in EA healthy males; this diplotype increased Agreeableness scores in EA healthy males, but the diplotype TGA/TGA that has only one base different from AGA/TGA decreased them in EA SD females, which may reflect the modification effects by sex (alternative interpretation discussed below). (b) Agreeableness and Conscientiousness are positively correlated. The diplotype TGA/TGA increased Conscientiousness scores in EA SD subjects, but when modified by sex, it decreased Agreeableness scores.

3. Age variance may be related to the difference of gene-personality association: The EA college students are young subjects in a very limited age range (18.9±2.3 years) who might have specific characters of personality traits. If *ADH1A* gene is associated with personality factors in other age ranges, it will not be associated with the personality traits in these college students. This is a possible explanation for the negative gene-personality association in this college student group, although further investigation is warranted.

4. Allelic heterogeneity or population specificity may be related to the difference of gene-personality association: (a) Diplotype TGA/TGA decreased Agreeableness scores and increased Conscientiousness scores in EA SD subjects; but diplotype AGA/TGA increased Agreeableness scores in EA healthy subjects and decreased Conscientiousness scores in EA healthy subjects. The opposite effects of two diplotypes on the same personality factors could be attributed to the opposite effects between major (SNP1^T in TGA/TGA) and minor alleles (SNP1^A in AGA/TGA) which have opposite phases. (b) Both diplotype TGA/TGA in EAs and diplotype AGA/TGA in AAs increased Conscientiousness scores in SD subjects. These two diplotypes contained opposite phase SNP1 alleles, i.e., T and A, respectively. However, the allele and diplotype frequencies are population specific, so that both diplotype TGA/TGA in EAs (f=0.052) and diplotype AGA/TGA in AAs (f=0.074) had similar frequencies and thus could exert similar effects. Both diplotype TCG/TCG in EAs (f=0.058) and diplotype AGA/TCG in AAs (f=0.056) decreased the risk for SD. These two diplotypes contained the opposite phase of haplotypes, i.e., TCG and AGA, respectively. However, these two diplotypes had similar frequencies due to population specificity and thus could also exert similar effects.

5. Confounding effects may be related to the difference of gene-personality association: In EA healthy males, the same diplotype AGA/TGA has opposite effects on Conscientiousness and Agreeableness. Conscientiousness scores are predicted only by AGA/TGA, but Agreeableness scores are predicted by both AGA/TGA and TCG/TCG; that is, the effects of AGA/TGA on Agreeableness are conditional on the existing status of the TCG/TCG, but those on Conscientiousness are not. The confounding from TCG/TCG may result in the opposite directions of the effects of AGA/TGA on these two positively-correlated personality factors.

There are three possible hypotheses to explain the personality-*ADH1A*-SD relationship: (1) The *ADH1A*-personality association and the *ADH1A*-SD association are independent of each other, which is possible because personality and SD are different phenotypes and *ADH1A*-personality association has also been detected in non-SD samples. For example, in EAs, there were “consistent” diplotype-Agreeableness and diplotype-Conscientiousness associations both in SD and healthy subjects, suggesting that affection status did not influence the *ADH1A*-personality associations [consistent with previous findings by Luo et al. (2007a)]; in other words, these *ADH1A*-personality associations were unlikely to be mediated by SD. (2) *ADH1A* bridges the association between personality and SD, which is possible and consistent with the previous findings (reviewed above or by Luo et al., 2007a) that many common genetic

factors may largely underlie the association between personality traits and SD. These findings support the theory of a shared genetic basis for personality features and SD, and that personality traits might have some underlying neurobiological mechanisms that also influence risk for SD. (3) Personality bridges the *ADH1A*-SD association, which is possible and has been supported by several lines of indirect evidence: First, as reviewed above, personality traits may play a central role in the development of SD. Specifically, some pre-morbid personality traits (i.e., those existing before the onset of SD), such as behavioral undercontrol (including impulsivity, thrill seeking, rebelliousness, irresponsibility, non-conformity, and aggressiveness), rejection of societal values, antisocial behavior, and hyperactivity, are robust predictors of AD. In other words, certain personality traits increase the likelihood that subjects who have them will develop SD or SD-related disorders. Second, consistent with our previous findings [Luo et al., 2007b], we observed that the *ADH1A*-personality associations (Tables 3 and 4) were much stronger than the *ADH1A*-disease associations in the same SD sample (Table 5), suggesting that personality traits could be a substantial heritable component of SD, serving as an intermediate phenotype for SD. Thus, personality features may be more clearly genetic in origin than SD *per se*, and personality could be a genetically determined risk factor for SD. However, more direct evidence for this hypothesis from specifically-designed studies is warranted in the future.

The *ADH1A*-personality associations in SD subjects were unlikely to be mediated by SD (as analyzed above), suggesting that the pathway by which *ADH1A* variation affects personality traits is probably not linked to ethanol metabolism pathway which involves in the *ADH1A*-alcoholism association. αα ADH enzyme encoded by *ADH1A* is mainly expressed in liver. In addition to catalyzing the oxidation of ethanol, αα ADH enzyme may oxidize retinol which is important in the maintenance of dopaminergic neurons in the brain, and some specific neurotransmitters (e.g., dopamine, serotonin, and norepinephrine) [e.g., Höög et al., 2001] which are hypothesized to be related to personality. Additionally, αα ADH enzyme is also expressed in the brain in very low density. This evidence might also help to explain the mechanism for the association between personality and *ADH1A*.

In a conclusion, the present study demonstrated that the *ADH1A* might contribute to the genetic component of variation in both personality traits and SD.

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Table 1

ADH1A marker information

Marker	rs#	Chromosome position	Distance[1]	Substitution	Location	Captured SNPs[2]
ADH1A^SNP1	rs6837311	Chr04: 100414296	0	A/T	3′	rs2866151
ADH1A^SNP2	rs975833	Chr04: 100420762	6466	C/G	intron 6	rs1229976,rs1229977, rs3819197
ADH1A^SNP3	rs1229966	Chr04: 100432456	11694	A/G	5′	rs1229967,rs4147531, rs931635,rs1826909

Rs#, reference sequence number for each SNP available from NCBI SNP database;

[1]Distance, map distance away from SNP1.

[2]Captured SNPs: the information content of those SNPs is captured by the markers studied (r^2=0.8) according to HapMap database (www.hapmap.org) in an example European population.

Table 2

Demographic data of three independent samples

	European-Americans			African-Americans			European-origin Hispanics		
Subjects	**n**	**Male%**	**Age (yrs)**	**n**	**Male%**	**Age (yrs)**	**n**	**Male%**	**Age (yrs)**
Subjects with SD	398	75.1%	39.9±9.6	160	68.8%	37.9±7.6			
Subjects with SD assessed by NEO-FFI	179	61.5%	38.6±9.8	68	48.5%	36.1±7.7			
College students assessed by NEO-FFI	384	29.7%	18.9±2.3				133	31.6%	18.5±1.4
Healthy subjects	385	40.3%	27.7±9.4	48	39.6%	34.0±11.3	15	26.7%	22.5±5.4
Healthy subjects assessed by NEO-FFI	285	37.9%	26.0±7.8	40	32.5%	33.8±10.7	7	28.6%	18.0±0.6

The indented rows in the first column represent the subsets.

Table 3

p values for MANCOVAs on the relationships between the composite personality measure and *ADH1A* gene

	Personality in EA SD subjects (n=179)				Personality in AA SD subjects (n=68)				Personality in EA students (n=384)				Personality in EA Healthy subjects (n=285)			
Variates	**Diplotype**	**Haplotype**	**Genotype**	**Allele**	**Diplotype**	**Haplotype**	**Genotype**	**Allele**	**Diplotype**	**Haplotype**	**Genotype**	**Allele**	**Diplotype**	**Haplotype**	**Genotype**	**Allele**
Age	0.022	0.025	0.043	1.8E-04	0.025	0.025		2.2E-04					4.0E-09	6.0E-09	2.7E-08	3.3E-17
Sex	0.001	0.001	0.060	8.7E-06	0.013	0.013			0.004	0.004	0.004	1.3E-06	0.003	8.5E-04		
African ancestry					0.005	0.005	0.035	7.5E-06								
TGA/TGA [or: TGA × TGA]	0.002	0.010														
TGA/TGA × Sex [or: TGA × TGA × Sex]	0.022	0.016														
AGA/TGA [or: AGA × TGA]		0.025														
AGA/TGA × Sex [or: AGA × TGA × Sex]					0.007	0.007							0.039	0.033		
TCG/TCG × Sex [or: TCG × TCG × Sex]													0.003	0.037		
SNP1			0.037	0.043												
Sex × SNP1 × SNP2								0.050							0.001	0.006
Sex × SNP1 × SNP3							0.072									
Sex × SNP1 × SNP3			0.035													
Age × SNP1				0.037												

"E-n", scientific format of "10^{-n}"; "×", interaction between.

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Table 4

ANCOVAs on the relationships between individual personality factor and *ADH1A* gene

Group	Models	Variables (sample sizes, n)	A	C	N
EA SD	Diplotypewise	TGA/TGA × Female (n=5)	*0.003*		
(n=179)		TGA/TGA (n=11)		0.004	
	Haplotypewise	TGA × TGA × Female (n=5)	*0.001*		
		TGA × TGA (n=11)		0.055	
	Genotypewise	SNP1ˆT/T × SNP3ˆA/A × Female (n=5)	*0.002*		
AA SD	Diplotypewise	AGA/TGA × Female (n=5)		0.018	*0.031*
(n=68)	Haplotypewise	AGA × TGA × Female (n=5)		0.018	*0.031*
	Genotypewise	SNP2ˆG/G × SNP3ˆA/A × Female (n=5)			*0.030*
		SNP2ˆG/G × SNP3ˆG/G × Male (n=15)	0.043		
EA controls	Diplotypewise	AGA/TGA × Male (n=26)	0.014	*0.019*	
(n=285)		TCG/TCG × Male (n=7)	0.005		
	Haplotypewise	AGA × TGA × Male (n=26)	0.008	*0.019*	
		TCG × TCG × Male (n=7)	0.010		
	Genotypewise	SNP1ˆA/T × SNP2ˆC/G × Female (n=34)	0.002		
		SNP1ˆT/T × SNP2ˆC/C × Male (n=7)	0.006		
	Allelewise	SNP1ˆA × SNP2ˆC × Female (n=34)	0.004		
		SNP1ˆT × SNP2ˆG × Female (n=152)	0.007		

"E-n", scientific format of "10^{-n}"; "×", interaction between; E=Extraversion, A=Agreeableness, C=Conscienceness, and N=Neuroticism. The italic p values denote the sign of regression coefficient (β) is negative "-"; otherwise, positive "+". Covariates of sex, age and ancestry are omitted in this table. The p values in grids are between 0.01 and 0.05; others are <0.01.EA student group is not listed in the table because no significant gene-personality association was found.

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Table 5

p values for case-control comparison on the relationships between SD and *ADH1A* gene using logistic regression analysis

	SD vs. controls in EAs (n=398 vs. 385)				SD vs. controls in AAs (n=160 vs. 48)			
Variates [sample sizes (n) of SD vs. controls]	**Diplotype**	**Haplotype**	**Genotype**	**Allele**	**Diplotype**	**Haplotype**	**Genotype**	**Allele**
Age	9.7E-37	1.5E-36	2.4E-35	2.2E-68	0.033	0.033		0.018
Male	9.7E-11	3.1E-08	2.5E-06	2.0E-12	0.002	0.002	0.003	6.1E-05
Female × TCG/TCG (or: Female × TCG × TCG) (n=5 vs. 21)	*0.050*	*0.060*						
AGA/TCG (or: AGA × TCG) (n=8 vs. 5)					*0.029*	*0.029*		
Sex × SNP3			0.031					
Female × SNP3^A/A (n=49 vs. 86)			0.008					
Female × SNP3^A/G (n=41 vs. 107)			0.026					
Female × SNP3^A (n=139 vs. 279)				0.018				
Female × SNP2^C (n=36 vs. 116)				*0.020*				
SNP1^A/T × SNP2^C/G (n=7 vs. 5)							*0.031*	
SNP1^A × SNP2^C (n=7 vs. 5)								*0.037*

"E-n", scientific format of "10-n"; "×", interaction between. The italic p values denote the sign of regression coefficient (β) is negative "-"; otherwise, positive "+". The absolute values of all regression coefficients (βs) are less than 7. EA and AA samples have 80% power to detect allele frequency difference between cases and controls down to 0.071 and 0.162, respectively (calculated by the program PAWE).

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