Published in final edited form as:
Am J Med Genet B Neuropsychiatr Genet. 2008 March 5; 147B(2): 179–186. doi:10.1002/ajmg.b.30589.

ADH7 variation modulates Extraversion and Conscientiousness in substance dependent subjects

Xingguang Luo[1,2,*], **Henry R. Kranzler**[3], **Lingjun Zuo**[1,2,*], **Huiping Zhang**[1,2], and **Joel Gelernter**[1,2]

[1]Department of Psychiatry, Yale University School of Medicine, New Haven, CT

[2]VA Connecticut Healthcare System, West Haven Campus, CT

[3]University of Connecticut School of Medicine, Alcohol Research Center, Department of Psychiatry, Farmington, CT

Abstract

Background—Human personality traits have been closely linked to substance dependence (SD), and are partially genetically determined. Recently, associations between *ADH7* and SD have been reported, which led us to investigate the relationship between *ADH7* variation and personality traits.

Methods—We assessed dimensions of the five-factor model of personality and genotyped four *ADH7* markers and thirty-eight unlinked ancestry-informative markers in 244 subjects with SD [178 European-Americans (EAs) and 66 African-Americans (AAs)] and 293 healthy subjects (253 EAs and 40 AAs). The relationships between *ADH7* markers and personality traits were comprehensively examined using multivariate analysis of covariance (MANCOVA), and then decomposed by Roy Bargmann Stepdown analysis of covariance (ANCOVA).

Results—Generally, older individuals, AAs, and males had significantly lower personality scores ($4.7\times10^{-5}\leq p\leq 0.032$), as reported previously. In SD subjects, Extraversion was most significantly associated with *ADH7* haplotypes ($3.7\times10^{-4}\leq p\leq 0.001$), diplotypes ($0.007\leq p\leq 0.012$), and genotypes ($p=0.001$), followed by Conscientiousness ($0.005\leq p\leq 0.033$). The contributory haplotype and diplotypes contained the alleles and genotypes of rs284786 (SNP1) and rs1154470 (SNP4). In healthy subjects, other personality factors (except Extraversion) were associated with *ADH7* diplotypes ($0.005\leq p\leq 0.016$) and genotypes ($0.002\leq p\leq 0.052$). Some of the gene effects on personality factors were modified by sex.

Conclusions—The present study demonstrated that the *ADH7* variation may contribute to the genetic component of variation in personality traits. Personality traits and SD have a partially overlapping genetic basis.

Keywords

Personality; Substance dependence; *ADH7*

Corresponding author and reprints: Xingguang Luo, MD and Lingjun Zuo, MD; Yale University School of Medicine; VA Psychiatry 116A2; 950 Campbell Avenue; West Haven, CT 06516. Xingguang.Luo@yale.edu and Lingjun.Zuo@yale.edu; Tel: 203-932-5711 ext 3590; Fax: 203-937-4741.

Introduction

The gene encoding alcohol dehydrogenase 7 (*ADH7*) is a class IV ADH gene, located at 4q23-24, at the 5′ end of the ADH gene cluster that contains seven ADH genes in a head-to-tail array from qter towards the centromere in the following order: *ADH7-ADH1C-ADH1B-ADH1A-ADH6-ADH4-ADH5*. *ADH7* has 9 exons and 8 introns that span about 22 kb, encoding the μμ or σσ ADH enzyme (374 amino acids). σσADH has an overall three-dimensional structure more similar to the class I ADHs than the other classes of ADHs. σσADH (called retinol dehydrogenase) is the most efficient among all classes of ADHs in catalyzing the metabolism of the longer chain aliphatic alcohols (such as retinol) [Satre et al., 1994]. It converts retinol (the major vitamin A precursor) to retinal; retinal is then synthesized to retinoic acid (RA; the active form of vitamin A). RA is a pleiotrophic regulator of gene expression used by vertebrates [Chambon, 1993]. It regulates transcriptional control through the retinoic acid receptors RAR and RXR [Zetterström et al., 1994]. RA, bound to their receptors, functions in the brain and pituitary by regulating the expression of the dopamine D2 receptor, which is a component of the dopaminergic system [Wolf, 1998]. RA is involved in regulating embryonic development (including development of the brain) and adult epithelial cell differentiation [Satre et al., 1994]. Dopamine neurons contain all the necessary components for this regulation. Proper development and maintenance of the dopaminergic system may be strongly dependent on the supply of RA, not only during embryogenesis, but also in adulthood [Zetterström et al., 1994], so that there is an important role of ADHs in the development and maintenance of the dopaminergic system.

ADHs (except those of Class III) also catalyze ethanol metabolism (Km value in the mM range) [Satre et al., 1994]. Class IV ADH is mainly distributed in the upper digestive tract (from mouth to stomach) and esophagus, but not in the liver [Moreno and Pares, 1991; Pares et al., 1994]. The stomach Class IV ADH is believed to contribute to the decreased bioavailability of imbibed alcohol after oral ingestion because of gastric first-pass metabolism, which may represent an important first line barrier against ethanol toxicity [Gentry et al., 1994]. The activity of the class IV ADHs towards ethanol is reported to be even higher than that of the classical liver enzymes (mainly Class I ADHs) in some studies (e.g., Pares et al. (1992) and Yin et al. (1997) reported that σσADH had the highest maximal activity for ethanol among the ADHs, which may be because σσADH is the first of the ADHs to start metabolizing ingested alcohol while still in the upper gastrointestinal tract]. Besides metabolizing retinol and ethanol, σσADH may be involved in the metabolism of some specific aldehydes, dopamine and other substances [Boleda et al., 1993; Yokoyama et al., 1995; Buervenich et al. 2000; Höög et al., 2001]. Interindividual genetic differences in σσADH may lead to variation in uptake of potentially harmful exogenous agents that may eventually interact with the dopamine system of the brain [Buervenich et al., 2005]. Additionally, the non-retinol substrates can compete for ADHs with retinol, e.g., high levels of ethanol inhibit retinol metabolism [Ang et al., 1996] – this suggests the possibility that a deficit exists in the synthesis of RA in alcoholics and drug abusers *per se*, even in the absence of an overall deficit in ADH activity. If a deficit in the overall ADH activity is present too, the deficit in the synthesis of RA should be more severe in such subjects than the healthy subjects. This deficit may result in dopaminergic dysfunction, as described above. It has long been hypothesized that the dopaminergic system is related to the development of alcohol dependence (AD), drug dependence (DD), and personality, which suggests a potentially important role of σσADH in the development of these phenotypes.

Important residues in the coenzyme-binding and substrate-binding sites of σσADH differ from those of other ADH classes, which may affect substrate binding or coenzyme binding, resulting in distinct ethanol turnover, expression in stomach, and possible emergence of

σσADH from other enzymes [Farres et al., 1994; Pares et al., 1994]. These structural changes are believed to result in a human class IV ADH with more activity for ethanol under physiological conditions [Farres et al., 1994]. Variation in *ADH7* introns may potentially influence the transcription levels, mRNA stability, translational efficiency, and density or affinity of σσADH as well. In summary, the structure in *ADH7* sequence, including coding regions, introns, and regulatory regions, may determine the properties of σσADH; variation in these regions may modulate its enzymatic function, with consequent effects on the metabolism of ethanol, retinol, aldehydes, dopamine, and other substances, which may eventually be related to risk for AD, DD, and personality, as described above. However, only recently have direct associations between *ADH7* and these phenotypes been reported. Osier et al. (2004) found that a polymorphism (rs1154458) in intron 6 of *ADH7* was significantly associated with AD in an unrelated Chinese sample. Edenberg et al. (2006) reported that rs284779 in intron 7 and rs28478 in the 3′-UTR were significantly associated with AD in a pedigree sample including European-American (EA) and African-American (AA) subjects. We [Luo et al., 2006a] reported that rs1573496 (SNP3 in the present study; a nonsynonymous SNP) in exon 3 and rs284786 (SNP1; a synonymous SNP) in exon 9 were suggestively associated with AD in AAs, and multiple diplotypes were suggestively associated with AD both in EAs and AAs. We [Luo et al., 2007a] also reported that rs1573496 (SNP3) in exon 3 was suggestively and rs971074 (SNP2) in exon 6 was significantly associated with DD in AAs, and multiple diplotypes were suggestively (in EAs) or significantly (in AAs) associated with DD. No studies have yet examined the association between *ADH7* and personality; such an association, if present, could underlie the associations with SD phenotype, either entirely, or, more likely, in part. The present study aimed to investigate this association.

DD (including cocaine dependence and opioid dependence) and AD have been demonstrated to share genetic risk related to ADH genes [Luo et al., 2006a; b; 2007a]. Therefore, in the present analysis, AD and DD were combined as “substance dependence” (SD), in order to increase the overall power to detect an effect. Many previous studies have provided evidence that personality characteristics may play a central role in the development of SD (including AD and opioid dependence in these studies) [e.g., Cloninger et al., 1988; Caspi et al., 1997], and common genetic factors may underlie some portion of the association between personality traits and AD [reviewed by Luo et al., 2007b]. We also demonstrated that variation in *ADH4* and *CHRM2* affected “risk” for both SD and personality features [Luo et al., 2007b, in press]. These findings highlight the role of personality as a genetically determined risk factor for SD.

Personality traits are among the most complex quantitative traits, which are usually governed by several genetic loci and influenced by environmental factors. Genetic factors have been consistently implicated as contributing to individual differences in major dimensions of personality (evidence was summarized in details by Luo et al. [2007b]). It is very promising to detect positive association between personality traits and alcohol metabolism related genes (e.g., *ADH4* and *ADH7*), especially in SD patients, because personality traits have strong genetic link to SD (described above), and have associations with levels of dopaminergic activity that may be directly or indirectly affected by σσADH (reviewed above).

The bioavailability of ethanol has been reported to be greater in women, which has been at least in part attributed to lower levels of σσADH [Frezza et al., 1990; Thomasson et al., 1995]. Glucocorticoid response element (GRE) in *ADH7*, through which androgens (but not estrogens) upregulate gene expression [Lange et al., 1992], may account for the observed sex difference in first-pass metabolism due to higher gastric ADH activity in male than in female subjects [Frezza et al., 1990]. Therefore, we predicted the presence of sex-specific

gene effects on personality scores for this locus. Additionally, Asians have lower σσADH activity than EAs and AAs, e.g., approximately 80% of Japanese men and women lack σσADH activity, whereas all EAs and AAs exhibit activity [Baraona et al., 1991; Thomasson et al., 1993]. Our previous studies have demonstrated that the genetic effects on personality traits were modified by sex, age, population, admixture, and affection status [Luo et al., 2007b, in press]. Consequently, we 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 *ADH7*. Our previous studies (Luo et al., 2007b; in press) indicated that the personality scores were significantly different between the SD and healthy subjects; in the present study, healthy subjects with no Axis I psychiatric disorders served as a basis for replication and as controls for SD subjects.

Materials and Methods

1. Subjects

Two hundred forty-four subjects with SD (178 EAs and 66 AAs) and 293 healthy subjects (253 EAs and 40 AAs) were included in the present study. The SD subjects (142 males; 102 females) met lifetime DSM-III-R criteria [American Psychiatric Association 1987] for AD (n=194) and/or DD (n=142 for cocaine dependence; n=92 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 healthy subjects (109 males; 184 females) 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 average ages were 37.9±9.3 years for SD subjects and 27.6±8.6 years for healthy subjects. The populations here were identified using ancestry proportions. All subjects were recruited at the University of Connecticut Health Center (UCHC) and gave informed consent before participating in the study, which was approved by the UCHC Institutional Review Board.

2. Marker inclusion and genotyping

We examined four markers spanning the 5′ to 3′ regions of *ADH7* (with an average inter-marker distance of 5590bp; see Table 1) and 38 ancestry-informative markers (AIMs) unlinked to *ADH7* [Yang et al., 2005; Luo et al., 2005a,b]. The four *ADH7* markers cover all haplotype blocks in *ADH7*, with SNPs 2 and 3 in one haplotype block both in EAs and AAs; SNP4 (rs1154470) belongs to this block only in EAs, and SNP1 is independent of the other three SNPs both in EAs and AAs [Luo et al., 2006a]. These *ADH7* markers were selected because, at the time of genotyping, they were all available as validated assays from Applied Biosystem, Inc. (ABI, Foster City, CA, USA) and they fully tagged the *ADH7* locus. The *ADH7* markers and AIMs were genotyped as in our initial study [Luo et al., 2006a].

3. Assessment of Personality

The NEO Five-Factor inventory (NEO-FFI) [Costa and McCrae. 1997] was used to assess five personality dimensions in both affected and healthy individuals, including Extraversion, Agreeableness, Conscientiousness, Neuroticism, and Openness to Experience. The personality scores for the different factors were: Extraversion (4–48, mean 28.7±6.9), Agreeableness (10–46, mean 31.0±6.6), Conscientiousness (0–48, mean 31.8±7.8), Neuroticism (2–48, mean 20.4±9.4), and Openness to Experience (9–45, mean 28.4±6.5). Every personality factor and the linear combination of all personality factors were normally distributed [Luo et al., 2007b]. As reported previously, these five factors are significantly intercorrelated, i.e., Neuroticism is negatively correlated with the other personality factors

and all of the other personality factors are positively correlated with one another [Luo et al., 2007b].

4. Ancestry proportion estimation

The proportions of European and African ancestry for each EA and AA individual were estimated using a set of 38 AIMs [Luo et al., 2005a,b] and the program STRUCTURE [Pritchard et al., 2000; Falush et al., 2003]. The ancestry proportion scores were entered into General Linear Models (including MANCOVA and ANCOVA) 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 and estimate the probabilities (from 0 to 1) of all likely pairs of haplotypes (i.e., diplotypes) for every individual. For analysis, these haplotype and diplotype probabilities were entered into the General Linear Model described below. The frequencies of allele, genotype, and common haplotypes and diplotypes are shown in Table 2.

6. Data analysis

(1) Stepwise multivariate analysis of covariance (MANCOVA)—MANCOVA was employed to test associations between genes and personality traits. In the haplotypewise and diplotypewise MANCOVA models, five correlated personality factors that served as one composite dependent variable; haplotype or diplotype probabilities served as predictor variables; age, ancestry proportions, and sex served as covariates; and two-way interactions between the predictor variables and covariates and between haplotypes were also considered as independent predictor variables. SD subjects and healthy subjects were analyzed separately. Statistical significance was evaluated based on the Pillai's Trace statistic (Pillai, 1954). When we obtained positive findings from the haplotypewise or diplotypewise analysis, we further performed allelewise and genotypewise MANCOVA using allele or genotype data to fine-map the contributory loci for personality. Alleles or genotypes of each marker, instead of haplotype or diplotype probabilities, served as predictor variables; two-way interactions between the predictor variables and covariates and between any two markers were also considered as independent predictor variables in these models. All of the MANCOVAs used backward stepwise elimination, with only the variables considered statistically significant (i.e., $p<0.05$) retained in the final equations.

(2) Stepwise Roy Bargmann Stepdown Analysis [see Tabachnick and Fidell. 1996]—Positive findings using MANCOVA were followed by stepwise Roy Bargmann Stepdown Analysis (a stepdown ANCOVA) of each personality factor to determine the factors contributing to the positive findings. In these ANCOVA models, each personality factor served as a dependent variable and the predictor variables, covariates, and interaction variables were the same as for the MANCOVA models. For the first step, we tested the highest-priority personality factor with a univariate ANCOVA. The priority order was the same as that in previous studies [Luo et al., 2007b, in press]: Neuroticism (F4) > Agreeableness (F2) > Conscientiousness (F3) > Extraversion (F1) > Openness (F5). We tested each personality factor with ANCOVA, using all higher-priority personality factors as covariates. To address the inflation of type I error due to multiple tests for the Roy Bargmann Stepdown Analysis, α was set at 0.01, though some suggestive gene effects ($0.01<p<0.05$) are also presented. These analyses also used a backward stepwise elimination process.

Results

1. MANCOVA indicated that the personality traits were related to age, ancestry, and sex; and the haplotypes, diplotypes, and genotypes had significant effects on the personality traits, some of which were moderated by sex (Table 3).

Haplotypewise, diplotypewise, and/or genotypewise MANCOVAs showed that there were significant associations between the personality traits and age, ancestry, and sex, both in SD and healthy individuals ($6.9\times10^{-6}\leq p\leq0.042$; Table 3).

In SD subjects, haplotypewise MANCOVA showed that the haplotype TCGA had a significant main effect (p=0.011) and an interaction effect (with TCGG: p=0.006) on the composite personality trait set. Diplotypewise MANCOVA showed that the diplotypes TCGA/TCGG (p=0.041), TTCG/TCGG (p=0.020), and ACGA/ACGG (p=0.041) had a significant main effect on the composite personality trait set. Genotypewise MANCOVA showed that the genotypes of SNP1 and SNP4 had a significant interaction effect (p=0.014) on the composite personality trait set. In healthy subjects, diplotypewise MANCOVA showed that the diplotypes TCGA/TCGG had a significant effect on the composite personality trait set (modified by sex: p=0.001). Genotypewise MANCOVA showed that the genotypes of SNP1 and SNP4 had a significant interaction effect (p=0.013) on the composite personality trait set. Genotypes of SNP4 also had a significant effect on the composite personality trait set, moderated by sex (p=0.037).

2. Roy Bargmann Stepdown Analyses showed that different personality factors were related to age, ancestry, and/or sex, and that the haplotypes, diplotypes, and genotypes had main and/or interaction effects on different personality factors (Table 4).

The haplotypewise, diplotypewise, and genotypewise Roy Bargmann Stepdown Analyses showed that different personality traits were related to age, ancestry, and/or sex, all of which were reported previously [Luo et al., 2007b]. Neuroticism was significantly higher in females than in males among SD subjects ($4.7\times10^{-5}\leq p\leq1.1\times10^{-4}$); Agreeableness was significantly higher in females than in males among healthy individuals (p=0.001). Extraversion decreased with age in both SD and healthy subjects ($\beta<0$; $4.6\times10^{-4}\leq p\leq0.002$). Openness to Experience decreased ($\beta<0$; $4.9\times10^{-4}\leq p\leq1.2\times10^{-4}$), but Agreeableness increased with age in healthy individuals ($\beta>0$; $0.001\leq p\leq0.002$). Extraversion increased with European ancestry proportions both in SD and healthy subjects ($\beta>0$; $0.003\leq p\leq0.032$). Agreeableness increased with European ancestry proportions in SD subjects ($\beta>0$; $0.003\leq p\leq0.010$). Additionally, Neuroticism was negatively correlated with the other four personality factors, which were all positively correlated to each other, consistent with our previous findings [Luo et al., 2007b].

In SD subjects, the haplotype TCGA significantly increased Extraversion scores ($\beta>0$, p=0.001), but the interaction between this haplotype and TCGG ($\beta<0$, $p=3.7\times10^{-4}$), the diplotype constructed by these two haplotypes (i.e., TCGA/TCGG) ($\beta<0$, p=0.007), and the diplotype TTCG/TCGG ($\beta<0$, p=0.012) significantly or suggestively decreased Extraversion scores. Diplotypes TTCG/TCGG ($\beta>0$, p=0.033) and ACGA/ACGG ($\beta>0$, p=0.018) suggestively increased Conscientiousness scores. Additionally, the interaction between genotypes SNP1^T/T and SNP4^A/A ($\beta>0$, p=0.001) significantly increased Extraversion scores, but genotypes SNP1^A/A × SNP4^G/G ($\beta<0$, p=0.005) and SNP1^A/T × SNP4^A/G ($\beta<0$, p=0.016) significantly decreased Conscientiousness scores. In healthy individuals, the diplotype TCGA/TCGG increased Conscientiousness scores in females ($\beta>0$, p=0.007) and Openness scores in males ($\beta>0$, p=0.001), but decreased Neuroticism scores in males ($\beta<0$, p=0.013). The genotypes SNP1^T/T × SNP4^A/A significantly increased Agreeableness scores ($\beta>0$, p=0.005), and the genotype SNP4^A/G significantly increased both

Agreeableness scores (β>0, p=0.002) and Neuroticism scores (β>0, p=0.003) in females. No completely identical personality-gene associations were seen in both SD and healthy subjects.

Discussion

The findings in the present study suggest that *ADH7* variation may play an important role in the development of personality traits, with rs284786 (SNP1) and rs1154470 (SNP4) being the most important of the variants we studied directly. Personality traits and SD partially share genetic "risk" and might have intrinsically-related neurobiological mechanisms related to σσADH activity.

Quantitative personality traits are genetically complex and multigenic. A composite personality trait set usually can only be weakly associated with the main effect of a single haplotype, diplotype, genotype, or allele, as observed by MANCOVA in the present study. However, their interaction effects (as detected using MANCOVA) could be much stronger, and certain single personality factor could be strongly associated with a gene (as shown using ANCOVA).

Using MANCOVA, we found that the five personality traits measured by the NEO-FFI were strongly related to age, ancestry, and sex [Luo et al., 2007b]. Decomposing these findings with ANCOVA, we found that, generally, older individuals, AAs, and males had significantly lower personality scores in both SD and healthy subjects; an exception to this was that older healthy individuals had significantly higher scores on the Agreeableness measure. MANCOVA also indicated that the multi-locus haplotypes and diplotypes had significant effects on the personality traits, which suggests that *ADH7* might harbor sites that contribute to the development of personality traits. Genotypewise MANCOVA suggested that these contributory sites might be close to SNP1 or SNP4. Decomposition of these findings using ANCOVA showed that, in SD subjects, Extraversion was most significantly affected by *ADH7*, followed by the effect of Conscientiousness. The contributory haplotype and diplotypes contained the alleles and genotypes of SNP1 and SNP4. In healthy subjects, other personality factors (except Extraversion) were affected by *ADH7*. Basically, the gene effects in healthy subjects were weaker than in SD subjects, consistent with the hypothesis that the *ADH7* gene effects should be more significant in the SD subjects than in the healthy subjects (summarized in the Introduction).

Some of the gene effects on personality factors were modified by sex, which may reflect the sex-specificity of σσADH activity (reviewed in Introduction). However, these modifications appear only in the healthy sample (that is, the gene effects are significant only in males or in females in this sample – see Table 4), but not in the SD sample. Our previous study (Luo et al., 2007b) showed that the gene variation could be associated with some specific ranges of personality scores. Males and females have different personality scores, that is, the personality scores in males and females are located in different (overlapping) ranges. When dividing the whole sample by sex, it is easier to detect the gene-personality association in males or in females, especially when the gene-personality association is not strong enough in the whole sample, as for the healthy subjects. This might explain why in the healthy sample some gene effects can be detected only when modified by sex, although this explanation might not be comprehensive.

Several important initial studies, using independent population-based or family-based samples, reported strong associations between *ADH7* variation and SD (summarized in the *Introduction*). This evidence suggested that *ADH7* might be a shared risk locus for both SD and personality traits. The gene-personality association was also present in healthy subjects,

where it differed a little from that in SD subjects, suggesting that the "risk" sites in *ADH7* for personality traits could be independent of those for SD. In the present sample, we found that rs284786 (SNP1) and rs975833 (SNP2) were modestly associated with SD ($p<0.05$; see Table 2), but the "risk" site for personality seemed to be closest to SNP1 and SNP4 (rs1154470), leading to the interpretation that the "risk" sites for these two different phenotypes could be located in different positions within the same gene. These "risk" sites might alter the properties of σσADH, thereby affecting dopaminergic activity, which is postulated to contribute to the development of both SD and personality (as detailed in the Introduction).

In conclusion, the present study demonstrated that *ADH7* might contribute to the genetic component of variation in personality traits, with the risk for SD and personality traits being partially shared.

Acknowledgments

This work was supported in part NIH grants R01-DA12849, R01-AA016015, R01-DA12690, K24-DA15105, R01-AA11330, P50-AA12870, K08-AA13732, K24-AA13736, K02-MH01387, and M01-RR06192 (University of Connecticut General Clinical Research Center), by funds from the U.S. Department of Veterans Affairs (the VA Medical Research Program, and the VA Connecticut–Massachusetts Mental Illness Research, Education and Clinical Center [MIRECC], and the VA Research Enhancement Award Program [REAP] research center), and Alcoholic Beverage Medical Research Foundation (ABMRF) grant award R06932 (X Luo).

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3. Washington, DC: American Psychiatric Press; 1987.

Ang HL, Deltour L, Zgombic-Knight M, Wagner MA, Duester G. Expression patterns of class I and class IV alcohol dehydrogenase genes in developing epithelia suggest a role for alcohol dehydrogenase in local retinoic acid synthesis. Alcohol Clin Exp Res. 1996; 20:1050–1064. [PubMed: 8892527]

Baraona E, Yokoyama A, Ishii H, Hernandez-Munoz R, Takagi T, Tsuchiya M, Lieber C. Lack of alcohol dehydrogenase isoenzyme activities in the stomach of Japanese subjects. Life Sci. 1991; 49:1929–1934. [PubMed: 1745108]

Blouin AG, Perez EL, Blouin JH. Computerized administration of the diagnostic interview schedule. Psychiat Res. 1988; 23:335–344.

Boleda MD, Saubi N, Farrés J, Parés X. Physiological substrates for rat alcohol dehydrogenase classes: aldehydes of lipid peroxidation, omega-hydroxyfatty acids, and retinoids. Arch Biochem Biophys. 1993; 307:85–90. [PubMed: 8239669]

Buervenich S, Sydow O, Carmine A, Zhang Z, Anvret M, Olson L. Alcohol dehydrogenase alleles in Parkinson's disease. Mov Disord. 2000; 15:813–818. [PubMed: 11009184]

Buervenich S, Carmine A, Galter D, Shahabi HN, Johnels B, Holmberg B, Ahlberg J, Nissbrandt H, Eerola J, Hellstrom O, Tienari PJ, Matsuura T, Ashizawa T, Wullner U, Klockgether T, Zimprich A, Gasser T, Hanson M, Waseem S, Singleton A, McMahon FJ, Anvret M, Sydow O, Olson L. A rare truncating mutation in ADH1C (G78Stop) shows significant association with Parkinson disease in a large international sample. Arch Neurol. 2005; 62:74–78. [PubMed: 15642852]

Caspi A, Begg D, Dickson N, Harrington HL, Langley J, Moffitt TE, Silva PA. Personality differences predict health-risk behaviors in adulthood: Evidence from a longitudinal study. J Pers Soc Psychol. 1997; 73:1052–1063. [PubMed: 9364760]

Chambon P. The molecular and genetic dissection of the retinoid signalling pathway. Gene. 1993; 135:223–228. Review. [PubMed: 8276261]

Cloninger CR, Sigvardsson S, Bohman M. Childhood personality predicts alcohol abuse in young adults. Alcohol Clin Exp Res. 1988; 12:494–505. [PubMed: 3056070]

Costa PT, McCrae RR. Stability and change in personality assessment: the revised NEO Personality Inventory in the year 2000. J Pers Assess. 1997; 68:86–94. [PubMed: 9018844]

Edenberg HJ, Xuei X, Chen HJ, Tian H, Wetherill LF, Dick DM, Almasy L, Bierut L, Bucholz KK, Goate A, Hesselbrock V, Kuperman S, Nurnberger J, Porjesz B, Rice J, Schuckit M, Tischfield J, Begleiter H, Foroud T. Association of alcohol dehydrogenase genes with alcohol dependence: a comprehensive analysis. Hum Mol Genet. 2006; 15:1539–1549. [PubMed: 16571603]

Farres J, Moreno A, Crosas B, Peralba JM, Allali-Hassani A, Hjelmqvist L, Jornvall H, Pares X. Alcohol dehydrogenase of class IV (sigma sigma-ADH) from human stomach. cDNA sequence and structure/function relationships. Eur J Biochem. 1994; 224:549–557. [PubMed: 7925371]

Falush D, Stephens M, Pritchard JK. Inference of Population Structure Using Multilocus Genotype Data: Linked Loci and Correlated Allele Frequencies. Genetics. 2003; 164:1567–1587. [PubMed: 12930761]

Frezza M, Di Padova C, Pozzato G, Terpin M, Baraona E, Lieber CS. High blood alcohol levels in women: The role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. N Engl J Med. 1990; 322:95–99. [PubMed: 2248624]

Gentry RT, Baraona E, Lieber CS. Agonist: gastric first pass metabolism of alcohol. J Lab Clin Med. 1994; 123:21–26. Review. [PubMed: 8288957]

Höög JO, Hedberg JJ, Stromberg P, Svensson S. Mammalian alcohol dehydrogenase - functional and structural implications. J Biomed Sci. 2001; 8:71–76. [PubMed: 11173978]

Lange AJ, Espinet C, Hall R, el-Maghrabi MR, Vargas AM, Miksicek RJ, Granner DK, Pilkis SJ. Regulation of gene expression of rat skeletal muscle/liver 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase. Isolation and characterization of a glucocorticoid response element in the first intron of the gene. J Biol Chem. 1992; 267:15673–15680. [PubMed: 1339434]

Luo X, Kranzler HR, Zuo L, Yang BZ, Lappalainen J, Gelernter J. ADH4 gene variation is associated with alcohol and drug dependence in European Americans: results from family-controlled and population-structured association studies. Pharmacogenet Genomics. 2005b; 15:755–768. [PubMed: 16220108]

Luo X, Kranzler HR, Zuo L, Wang S, Blumberg HP, Gelernter J. CHRM2 gene predisposes to alcohol dependence, drug dependence, and affective disorders: results from an extended case-control structured association study. Hum Mol Genet. 2005a; 14:2421–2434. [PubMed: 16000316]

Luo X, Kranzler HR, Zuo L, Wang S, Gelernter J. Personality traits of Agreeableness and Extraversion are associated with ADH4 variation. Biol Psychiatry. 2007b; 61:599–608. [PubMed: 17069770]

Luo X, Kranzler HR, Zuo L, Zhang H, Wang S, Gelernter J. CHRM2 variation predisposes to personality traits of Agreeableness and Conscientiousness. Hum Mol Genet. In press.

Luo X, Kranzler HR, Zuo L, Wang S, Lappalainen J, Schork NJ, Gelernter J. Diplotype trend regression (DTR) analysis of the ADH gene cluster and ALDH2 gene: Multiple significant associations for alcohol dependence. Am J Hum Genet. 2006a; 78:973–987. [PubMed: 16685648]

Luo X, Kranzler HR, Zuo L, Wang S, Lappalainen J, Schork NJ, Gelernter J. Drug dependence is associated with multiple ADH and ALDH genes. Hum Mol Genet. 2007a; 16:380–390. [PubMed: 17185388]

Luo X, Kranzler HR, Zuo L, Lappalainen J, Yang BZ, Gelernter J. ADH4 gene variation is associated with alcohol and drug dependence in European Americans: results from HWD tests and case-control association studies. Neuropsychopharmacology. 2006b; 31:1085–1095. [PubMed: 16237392]

Moreno A, Pares X. Purification and characterization of a new alcohol dehydrogenase from human stomach. J Biol Chem. 1991; 266:1128–1133. [PubMed: 1985938]

Osier MV, Lu RB, Pakstis AJ, Kidd JR, Huang SY, Kidd KK. Possible epistatic role of ADH7 in the protection against alcoholism. Am J Med Genet B Neuropsychiatr Genet. 2004; 126:19–22. [PubMed: 15048643]

Pillai, KCS. Institute of Statistics Mimeo Series NO. 88. University of North Carolina; Chapel Hill: 1954. On some distribution problems in multivariate analysis.

Pares X, Cederlund E, Moreno A, Saubi N, Hoog JO, Jornvall H. Class IV alcohol dehydrogenase (the gastric enzyme). Structural analysis of human sigma sigma-ADH reveals class IV to be variable and confirms the presence of a fifth mammalian alcohol dehydrogenase class. FEBS Lett. 1992; 303:69–72. [PubMed: 1592118]

Pares X, Cederlund E, Moreno A, Hjelmqvist L, Farres J, Jornvall H. Mammalian class IV alcohol dehydrogenase (stomach alcohol dehydrogenase): structure, origin, and correlation with enzymology. Proc Natl Acad Sci USA. 1994; 91:1893–1897. [PubMed: 8127901]

Pritchard JK, Stephens M, Donnelly P. Inference of population structure using multilocus genotype data. Genetics. 2000; 155:945–959. [PubMed: 10835412]

Spitzer RL, Williams JBW, Gibbon M, First MB. The structured clinical interview for DSM-III-R (SCID), I: History, rationale, and description. Arch Gen Psychiat. 1992; 49:624–629. [PubMed: 1637252]

Stephens M, Donnelly P. A comparison of bayesian methods for haplotype reconstruction from population genotype data. Am J Hum Genet. 2003; 73:1162–1169. [PubMed: 14574645]

Stephens M, Smith NJ, Donnelly P. A new statistical method for haplotype reconstruction from population data. Am J Hum Genet. 2001; 68:978–989. [PubMed: 11254454]

Satre MA, Zgombic-Knight M, Duester G. The complete structure of human Class IV alcohol dehydrogenase (retinol dehydrogenase) determined from the ADH7 gene. J Biol Chem. 1994; 269:15606–15612. [PubMed: 8195208]

Tabachnick, BG.; Fidell, LS. Using multivariate statistics. 3. HarperCollins College Publishers; New York, New York, USA: 1996.

Thomasson HR, Cutler C, Stone CL, Bosron WF, Li T-K. Multiple forms of gastric alcohol dehydrogenase consistently identified in gastric biopsies. Gastroenterology. 1993; 104:1007A. [PubMed: 8385040]

Thomasson HR, Dean RA, Cerimele B, Kalbfleisch JH, Rudy A, Li T-K. Gender and ethnic differences in ethanol first-pass metabolism. Alcohol Clin Exp Res. 1995; 19:76A.

Wolf G. Vitamin A functions in the regulation of the dopaminergic system in the brain and pituitary gland. Nutr Rev. 1998; 56:354–355. [PubMed: 9884583]

Yang BZ, Zhao H, Kranzler HR, Gelernter J. Population Group Assignment: Effects of Markers and Methods. Genet Epidemiol. 2005; 28:302–312. [PubMed: 15782414]

Yokoyama H, Baraona E, Lieber CS. Upstream structure of human ADH7 gene and the organ distribution of its expression. Biochem Biophys Res Commun. 1995; 216:216–222. [PubMed: 7488092]

Yin SJ, Liao CS, Wu CW, Li TT, Chen LL, Lai CL, Tsao TY. Human stomach alcohol and aldehyde dehydrogenases: comparison of expression pattern and activities in alimentary tract. Gastroenterology. 1997; 112:766–775. [PubMed: 9041238]

Zetterström RH, Simon A, Giacobini MM, Eriksson U, Olson L. Localization of cellular retinoid-binding proteins suggests specific roles for retinoids in the adult central nervous system. Neuroscience. 1994; 62:899–918. [PubMed: 7870312]

Table 1

ADH7 marker information

Marker	rs#	Chromosome position	Distance[1]	Substitution	Location
ADH1A^SNP1	rs284786	Chr04: 100792371	0	A/T	exon 9
ADH1A^SNP2	rs971074	Chr04: 100800255	7884	C/T	exon 6
ADH1A^SNP3	rs1573496	Chr04: 100808063	15692	C/G (Ala/Gly)	exon 3
ADH1A^SNP4	rs1154470	Chr04: 100814731	22360	A/G	intron 1

Rs#, reference sequence number for each SNP available from NCBI SNP database; Distance, map distance away from SNP1.

Am J Med Genet B Neuropsychiatr Genet. Author manuscript; available in PMC 2011 August 24.

Table 2

Genotype, allele, haplotype, and diplotype frequencies

		European-Americans				African-Americans			
		Case		Control		Case		Control	
Marker	**Genotype or Allele**	**N**	***f***	**N**	***f***	**N**	***f***	**N**	***f***
SNP1	TT	92	0.523	122	0.498	20	0.299	7	0.175
	TA	70	0.398	94	0.384	37	0.552	19	0.475
	AA	14	0.080	29	0.118	10	0.149	14	0.350[g1]
	T	254	0.722	338	0.690	77	0.575[a1]	33	0.413
	A	98	0.278	152	0.310	57	0.425	47	0.588
SNP2	CC	136	0.773	181	0.751	49	0.742[g2]	20	0.513
	CT	37	0.210	56	0.232	16	0.242	16	0.410
	TT	3	0.017	4	0.017	1	0.015	3	0.077
	C	309	0.878	418	0.867	114	0.864[a2]	56	0.718
	T	43	0.122	64	0.133	18	0.136	22	0.282
SNP3	GG	140	0.782	194	0.776	63	0.969	36	0.923
	GC	36	0.201	51	0.204	2	0.031	3	0.077
	CC	3	0.017	5	0.020	0	0.000	0	0.000
	G	316	0.883	439	0.878	128	0.985	75	0.962
	C	42	0.117	61	0.122	2	0.015	3	0.038
SNP4	GG	71	0.425	108	0.444	47	0.783	30	0.750
	GA	77	0.461	103	0.424	12	0.200	9	0.225
	AA	19	0.114	32	0.132	1	0.017	1	0.025
	G	219	0.656	319	0.656	106	0.883	69	0.863
	A	115	0.344	167	0.344	14	0.117	11	0.138
Haplotype	TCGG	74	0.417	102	0.404	28	0.429	8	0.194
	TCGA	35	0.195	46	0.183	4	0.067	3	0.066
	ACGA	27	0.150	40	0.160	3	0.050	3	0.068
	ACGG	20	0.110	29	0.116	21	0.317	16	0.391
	TTCG	18	0.101	24	0.094	1	0.013	1	0.035
	ATCG	2	0.011	6	0.022	0	0.002	0	0.002

		European-Americans				African-Americans			
		Case		Control		Case		Control	
Marker	**Genotype or Allele**	**N**	***f***	**N**	***f***	**N**	***f***	**N**	***f***
	ATGG	1	0.007	2	0.009	3	0.046	5	0.125
	TTGG	0	0.002	2	0.009	5	0.074	5	0.114
Diplotype	TCGG/TCGG	30	0.168	44	0.173	12	0.182	0	0.000
	TCGA/TCGG	28	0.158	37	0.145	2	0.030	2	0.050
	ACGA/TCGG	23	0.131	30	0.117	5	0.069	2	0.038
	ACGG/TCGG	17	0.098	20	0.080	19	0.286	5	0.125
	TTCG/TCGG	17	0.096	21	0.084	0	0.000	2	0.049
	ACGA/TCGA	8	0.046	16	0.062	0	0.001	1	0.025
	TCGA/TCGA	8	0.044	10	0.039	1	0.015	0	0.000
	ACGG/TCGA	8	0.044	10	0.038	4	0.068	1	0.037
	ACGA/ACGG	7	0.042	11	0.042	0	0.004	2	0.050
	TTCG/TCGA	6	0.034	8	0.033	0	0.000	0	0.000
	ACGA/TTCG	5	0.028	6	0.024	1	0.012	0	0.000
	ACGA/ACGA	5	0.025	8	0.030	0	0.000	0	0.000
	ACGG/TTCG	3	0.017	6	0.024	1	0.013	1	0.021
	ATCG/TCGG	2	0.011	4	0.015	0	0.002	0	0.003
	ACGG/ACGG	1	0.006	4	0.017	6	0.087	8	0.191
	ATGG/ACGG	1	0.006	0	0.000	2	0.030	4	0.108
	ATGG/TCGG	1	0.003	2	0.008	3	0.048	2	0.046
	ACGG/TTGG	0	0.001	0	0.002	4	0.058	2	0.054
	TTGG/TCGG	0	0.000	3	0.013	4	0.058	3	0.075

N, number of individuals (for genotypes) or chromosomes (for alleles); *f*, frequency; case, SD subject; control, healthy subject. [g]Genotypewise and [a]allelewise case-control comparison for frequency distributions: p_{a1}=0.024, p_{a2}=0.011, p_{g1}=0.048, and p_{g2}=0.035.

Table 3

p values for MANCOVAs on the relationships between composite personality trait and *ADH7* gene

	Substance-dependent Subjects			Healthy subjects	
Variates	**Haplotypewise**	**Diplotypewise**	**Genotypewise**	**Diplotypewise**	**Genotypewise**
Age	0.002	0.008	0.002	6.9×10^{-6}	1.8×10^{-5}
European ancestry	0.003	0.002	0.012	0.001	0.010
Sex	0.029	0.016	0.034	0.033	0.042
TCGA	**0.011**				
TCGG × TCGA	**0.006**				
TCGG/TCGA		**0.041**			
TCGG/TTCG		**0.020**			
ACGA/ACGG		**0.041**			
Sex × TCGG/TCGA				**0.001**	
SNP1 × SNP4			**0.014**		**0.013**
Sex × SNP4					**0.037**

"×", interaction between. Bold color corresponds to the gene effects.

Am J Med Genet B Neuropsychiatr Genet. Author manuscript; available in PMC 2011 August 24.

Table 4

Roy Bargmann Stepdown ANCOVAs on the relationships between each personality factor and predictor variables

		F1		F2		F3		F4		F5	
	Variables	***â***	**p**	***â***	**p**	***â***	**p**	***â***	**p**	***â***	**p**
Haplotypewise (Cases)	Age	−0.145	4.6E-04								
	European ancestry			2.547	0.003						
	Sex (Male=1,Female=0)								1.1E-04		
	Female							4.637	1.1E-04		
	Extraversion									0.197	4.6E-04
	Conscientiousness	0.271	1.1E-05								
	Neuroticism	−0.175	2.8E-04	−0.221	2.8E-08	−0.402	7.6E-18				
	TCGA	6.450	**0.001**								
	TCGG × TCGA	−19.242	**3.7E-04**								
Diplotypewise (Cases)	Age	−0.142	0.001								
	European ancestry	2.561	0.006	2.547	0.003						
	Sex (Male=1,Female=0)								1.1E-04		
	Female							4.637	1.1E-04		
	Extraversion									0.197	4.6E-04
	Conscientiousness	0.258	3.1E-05								
	Neuroticism	−0.163	0.001	−0.221	2.8E-08	−0.408	1.5E-18				
	TCGA/TCGG	−3.265	**0.007**								
	TTCG/TCGG	−3.866	**0.012**			3.347	**0.033**				
	ACGA/ACGG					5.532	**0.018**				
Genotypewise (Cases)	Age	−0.145	0.001			−0.088	0.059				
	European ancestry	2.254	0.032	2.314	0.010						
	Sex (Male=1,Female=0)								4.7E-05		
	Female							5.148	4.7E-05		
	Extraversion									0.205	4.7E-04
	Conscientiousness	0.261	9.4E-05								
	Neuroticism	−0.185	0.001	−0.213	2.0E-07	−0.457	1.5E-19				
	SNP1 × SNP4		**0.030**				**0.005**				
	SNP1^T/T × SNP4^A/A	7.436	**0.001**								

		F1		F2		F3		F4		F5	
	Variables	***â***	**p**	***â***	**p**	***â***	**p**	***â***	**p**	***â***	**p**
	SNP1^A/A × SNP4^G/G					−6.392	**0.005**				
	SNP1^A/T × SNP4^A/G					−2.943	**0.016**				
Diplotypewise (Controls)	Age	−0.129	0.002	0.127	0.001					−0.142	4.9E-04
	European ancestry	3.218	0.003								
	Sex (Male=1,Female=0)				0.001						
	Female			2.214	0.001						
	Extraversion									0.214	1.2E-04
	Agreeableness	0.166	0.006			0.191	0.006				
	Neuroticism	−0.240	9.3E-06	−0.426	1.6E-18	−0.341	1.0E-07				
	Sex × TCGA/TCGG						**0.016**		**0.007**		**0.005**
	Female × TCGA/TCGG					4.157	**0.007**				
	Male × TCGA/TCGG							−4.518	**0.013**	4.853	**0.001**
Genotypewise (Controls)	Age	−0.130	0.002	0.118	0.002					−0.159	1.2E-04
	European ancestry	3.231	0.003								
	Sex (Male=1,Female=0)				0.002						
	Female			2.122	0.002						
	Extraversion									0.201	3.3E-04
	Agreeableness	0.166	0.006			0.212	0.002				
	Neuroticism	−0.247	4.4E-06	−0.402	1.0E-15	−0.305	1.0E-06				
	SNP1 × SNP4				**0.052**						
	SNP1^T/T × SNP4^A/A			5.466	**0.005**						
	Sex × SNP4								**0.003**		
	Female × SNP4^A/G							3.788	**0.003**		

"E-n",scientific format of "10^{-n}"; "×", interaction between; F1 to F5: personality factors, i.e., F1=Extraversion, F2=Agreeableness, F3=Conscienceness, F4=Neuroticism, and F5=Openness. β, regression coefficient; p, p-value; the indented lines in "Variables" column correspond to post-hoc decomposition analysis. Bold color corresponds to the gene effects.