Objective: Low monoamine oxidase (MAO) activity and the neurotransmitter dopamine are 2 important factors in the development of alcohol dependence. MAO is an important enzyme associated with the metabolism of biogenic amines. Therefore, the present study investigates whether the association between the dopamine D2 receptor (DRD2) gene and alcoholism is affected by different polymorphisms of the MAO type A (MAOA) gene.

Methods: A total of 427 Han Chinese men in Taiwan (201 control subjects and 226 with alcoholism) were recruited for the study. Of the subjects with alcoholism, 108 had pure alcohol dependence (ALC) and 118 had both alcohol dependence and anxiety, depression or both (ANX/DEP ALC). All subjects were assessed with the Chinese Version of the Modified Schedule of Affective Disorders and Schizophrenia-Lifetime. Alcohol dependence, anxiety and major depressive disorders were diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria.

Conclusion: The genetic variant of the DRD2 gene was only associated with the ANX/DEP ALC phenotype, and the genetic variant of the MAOA gene was associated with pure ALC. Subjects carrying the MAOA 3-repeat allele and genotype A1/A1 of the DRD2 were 3.48 times (95% confidence interval = 1.47–8.25) more likely to be ANX/DEP ALC than the subjects carrying the MAOA 3-repeat allele and DRD2 A2/A2 genotype. The MAOA gene may modify the association between the DRD2 gene and ANX/DEP ALC phenotype.

Huang, Lin, Wan, Chang, Lu — Department of Psychiatry, Tri-Service General Hospital; Wang — Graduate Institute of Medical Sciences, National Defense Medical Center, National Defense Medical Center, Taipei; Chang — Program of Clinical Psychology, Department of Psychology, National Taiwan University, Taipei; Ko, Lu — Institute of Behavioral Medicine; Lu — Department of Psychiatry, College of Medicine, National Cheng Kung University, Tainan; Wang — Department of Health, Nantau Psychiatric Center, Nantau, Taiwan, ROC.
Introduction

Family, twin and adoption studies suggest that heredity plays an important role in alcohol dependence and drinking behaviour and, therefore, that there are genetic risk factors for alcoholism.1,2 Alcohol dependence is a complex disorder that is probably regulated by several genes.3 Although several candidate genes have been studied, the results of these studies are controversial4–12; the gene-to-gene interaction approach might be more revealing than the single-gene approach in the study of alcoholism.

Monoamine oxidase (MAO) is an important enzyme associated with the metabolism of biogenic amines and neurotransmitters, including dopamine as well as 5-hydroxytryptamine (5-HT) and norepinephrine.13,14 Cloninger15 proposed that the catecholamine neurotransmitters including dopamine, 5-HT and norepinephrine are related to some personality traits that might put an individual at increased risk for drinking behaviour and developing alcohol dependence. For example, low MAO activity might also be a risk factor for impulsive behaviour, personality disorder and alcoholism.16–19 Therefore, MAO activity may play a critical role in the regulation of catecholamines and in the pathogenesis of psychiatric disorders.20 A functional 30-base pair (bp) repeat polymorphism in the promoter region of the MAOA gene may alter transcriptional efficiency; the allele with 3 copies of the repeat sequence was transcribed about 2 times less efficiently than the allele with 4 copies of the repeat motif.20,21 The MAOA gene is considered to be a candidate gene of alcohol dependence susceptibility, because alcohol dependence is sensitive to allelic variation in the MAOA gene.22–25 Samochowiec and colleagues26 and Schmidt and colleagues27 reported that a low-activity 3-repeat allele of the MAOA promoter polymorphism is associated with antisocial alcoholism among German men, and Contini and colleagues28 confirmed that the 3-repeat allele increased susceptibility to alcohol dependence and antisocial behaviours in a Brazilian sample. However, the existence of an association between the MAOA gene and alcoholism with or without antisocial behaviour is not consistently reported. Further, several studies have found no association between alcoholism and the MAOA gene.29–32

In animal studies, alcohol can stimulate dopaminergic neurons in the ventral tegmental area,27,28 and the density of dopamine D2 receptors in the limbic system is lower in alcohol-prefering rats than in nonpreferring rats.29,30 Likewise, the number of striatal dopamine D2 receptors is less in alcohol-prefering humans than in healthy control subjects.31 Moreover, brain imaging studies of healthy volunteers have shown that individuals with an A1 allele of the DRD2 gene have a reduced number of dopamine D2 receptors.32,33 The A1 polymorphism of the DRD2 Taq1 A loci has been considered as a risk factor for alcohol dependence,34–36 but the association between alcoholism and the DRD2 gene remains equivocal.37–39 The confounding effects of MAOA and DRD2 genes on alcohol dependence might be partly due to different definitions of control groups, ethnically or racially mixed study populations and phenotypic heterogeneity of alcoholism.39,40

To overcome these possible confounding effects and to reduce the probability of type I and type II errors, we recruited 2 different subtypes of patients dependent on alcohol: a group with pure alcohol dependence and no other comorbid diagnosis (pure ALC) and a group with alcohol dependence and comorbid anxiety, depression or both (ANX/DEP ALC). Our intent was to reduce the phenotypic heterogeneity of the overall sample. We also recruited unrelated healthy control subjects to evaluate the association between MAOA and DRD2 and alcohol dependence in the Han Chinese population of Taiwan.

We hypothesized that, if both the MAOA and DRD2 genes are associated with alcohol dependence, this would be revealed by an association study comparing subjects with pure ALC to well-matched control subjects. However, alcoholism is usually comorbid with anxiety or depression or both, and the mood disturbance might increase drinking behaviour. Thus, we hypothesized that the MAOA and DRD2 genes might increase susceptibility to ANX/DEP ALC. Dopamine is oxidatively deaminated by MAOA and, in a rat model, 90% of the metabolism is via deamination by MAOA in the corpus striatum to form 3,4-dihydroxyphenyl-acetaldehyde (DOPAL).34,35 These observations led us to hypothesize that the MAOA and DRD2 genes might interact to increase susceptibility to alcohol dependence and/or its subgroup. We therefore tested whether the relation between the DRD2 gene and alcoholism is affected by different polymorphisms of the MAOA gene.

Methods

Subjects and clinical assessments

The protocol of this study was approved by the Institutional Review Board for the Protection of Human Subjects at Tri-Service General Hospital (TSGH), a medical teaching hospital affiliated with the National Defence Medical Center in Taipei, Taiwan. Written informed consent was obtained from all participants after a full explanation of the study procedures.

To minimize the effects of ethnic differences on gene frequencies, all 427 subjects were recruited from the Han Chinese population in Taiwan; all participants were unrelated and were matched for ethnicity and geographic origin. Alcohol dependence was diagnosed and classified into 2 groups: pure ALC (108 participants) and ANX/DEP ALC (118 participants). A total of 201 participants were healthy control subjects. Subjects with pure ALC had a past or current history of alcohol dependence but no history of other mental disorders, including personality, anxiety, depressive, or affective disorders or illegal drug use disorders. Those with ANX/DEP ALC had a past or current history of major depression or anxiety disorder or both, as well as a diagnosis of alcohol dependence, but no history of other mental disorders or illegal drug use disorders. The healthy control subjects had no past or present major or minor mental illnesses (including addictive disorder, schizophrenia, anxiety disorder, personality disorder or substance use disorders) and no family history of alcohol dependence or heavy alcohol consumption in first-degree relatives.
Subjects with alcohol dependence were recruited from the psychiatric clinical population, and control volunteers were recruited from the community. Each subject was interviewed by an attending psychiatrist, who made an initial evaluation, and then by a well-trained research psychologist, who identified the clinical subtype of alcohol dependence and selected the control subjects. All diagnoses of alcohol dependence, anxiety, major depressive disorders and other mental disorders were made according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria. A well-trained research psychologist interviewed participants, using the Chinese Version of the Modified Schedule of Affective Disorders and Schizophrenia-LifeTime (SADS-L), in order to meet a DSM-IV diagnosis and to exclude other mental disorders (antisocial personality disorder and drug use disorder) in control subjects and in individuals with pure ALC. The interrater reliability kappa values of the Chinese Version of SADS-L were good-to-excellent for major depression (0.79), bipolar disorder (0.71), anxiety disorder (0.86), schizophrenia (0.95), alcohol abuse and dependence (1.00), and substance abuse and dependence (0.82).

**Blood samples and DNA extraction**

With the informed consent of each participant, 20 mL of whole blood was drawn from the peripheral vein with vacutainer tubes containing 15% (K) Ethylenediaminetetraacetic acid (EDTA) solution (Becton Dickinson vacutainer systems). Genomic DNA was extracted from the leukocytes using standard methods.

**Genotyping of MAOA and DRD2 genes**

The 30-bp repeat polymorphism of the MAOA-uVNTR gene (variable number of tandem repeats located upstream of the promoter region) was investigated with a modification of the polymerase chain reaction (PCR) method described by Zhu and colleagues. The EcoRV polymorphisms in exon 14 of the MAOA gene were detected with the modified PCR-RFLP (restriction fragment length polymorphism) method described by Hotamisligil and Breakefield. The MAOA EcoRV (−) polymorphism remained intact and was 703 bp long, whereas the MAOA EcoRV (+) polymorphism was cut into 2 DNA fragments of 340 bp and 363 bp by the EcoRV restriction enzymes.

**TaqI “A” and TaqI “B”** polymorphisms of the DRD2 gene were genotyped with the PCR-RFLP method. Cycling protocols, which were modified from those described by Castiglione and colleagues and Grandy and colleagues, were carried out on a Perkin Elmer 9700 thermal cycler (Boston, MA). The 310-bp A1 allele remained uncut, whereas the A2 allele was cut into 2 DNA fragments of 130 bp and 180 bp. The 459-bp TaqI B1 allele remained intact, and the TaqI B2 allele was cut into 2 DNA fragments of 267 bp and 192 bp.

**Statistical analyses**

The differences in the genotype and allele frequencies of the MAOA and DRD2 genes between the pure ALC and ANX/DEP ALC groups and the control groups were calculated with Pearson’s chi-square (2-tailed), and Hardy–Weinberg equilibrium was assessed for each group. Fisher’s exact test was substituted for the chi-square test when sample cell sizes were smaller than expected (< 5 subjects). One-way analysis of variance and Bonferroni post hoc test were employed to determine the difference of mean age among these subtypes. The Bonferroni post hoc test, Pearson’s chi-square, Fisher’s exact test and multiple logistic regression analyses were performed with SPSS (version 11.5, Taipei, Taiwan) for Windows. A p value of less than 0.05 was considered statistically significant. The frequency of the 2-repeat polymorphism of the MAOA gene was found in 0 subjects in the ANX/DEP ALC group, 1 subject in the pure ALC group and 4 subjects in the control group. Therefore, we did not include subjects with 2-repeat polymorphism of MAOA-uVNTR for data analysis.

Differences in haplotype frequencies, linkage disequilibrium coefficients (D), and standardized linkage disequilibrium coefficients (D′) between the TaqI A and TaqI B systems of the DRD2 gene were estimated with the Estimating haplotypes and Permutation and Model Free Analysis computer programs. Differences in haplotype frequency between study variables were estimated with Fisher’s exact test when the cells were small. Moreover, the power analysis was performed with the use of G*Power computer software, and the effect size conventions were determined according to the method of Erdfelder and colleagues.

**Results**

There were significant differences in mean age among these 3 study groups (F = 13.661; p < 0.001) and between the control and pure ALC groups (36.58 [standard deviation {SD} 9.57 yr] v. 42.09 [SD 9.82 yr]; p < 0.001) but not between the control and ANX/DEP ALC groups (36.58 [SD 9.57] yr v. 35.99 [SD10.51] yr; p = 0.611).

As shown in Table 1, the haplotype frequencies of A1B2 and A2B1 were less than 5%, and strong linkage disequilibrium between the TaqI A and TaqI B polymorphisms in the DRD2 gene (p = 0.001) was evident in each of the 3 study groups. Genotype distributions of TaqI A and TaqI B polymorphism of the DRD2 gene were in the Hardy–Weinberg equilibrium, both in the patients and in the control subjects (p > 0.1). There are significant differences in the haplotype frequencies of the DRD2 gene among the 3 study groups (p = 0.020). The frequency of the A1B1 haplotype was significantly higher in the ANX/DEP ALC group than in the control group (p = 0.006) but was not significantly different in the pure ALC group versus the normal control group (Table 1).

There were no significant differences in the genotype frequencies of MAOA-uVNTR (in the promoter region of the gene) and in EcoRV (in exon 14) polymorphisms among the 3 groups or the ANX/DEP ALC group versus the control group. However, the MAOA gene was significantly associated with pure ALC (p = 0.030 in MAOA-uVNTR and p = 0.039 in MAOA EcoRV, respectively; see Table 2).
After stratifying the MAOA-uVNTR 3-repeat and MAOA-EchoRV (+) genotypes, the only significant difference in DRD2 haplotype was between the ANX/DEP ALC group and the control group. When the MAOA-uVNTR 4-repeat and MAOA-EchoRV (−) genotypes were stratified, respectively, there were no significant differences in the DRD2 haplotype between healthy control subjects and each of the other groups, respectively (Table 3).

Logistic regression analysis of the DRD2 TaqI A polymorphism as a risk factor for alcohol dependence and correction for age showed that the DRD2 A1/A1 and A1/A2 genotypes were associated with higher risk for ANX/DEP ALC than the DRD2 A2/A2 genotype (approximately 1.98–2.59-fold), but the DRD2 A1/A1 genotype was not significantly associated with pure ALC (model 1, Table 4). After stratifying MAOA genotypes and correcting for age, the association of the DRD2 A1/A1 and A1/A2 genotypes with ANX/DEP ALC persisted after stratification by MAOA-uVNTR 3-repeat (odds ratio [OR] = 3.48, p = 0.008 for A1/A1 genotype; OR = 2.53, p = 0.017 for A2/A2 genotype) and MAOA-EchoRV (+) genotypes (OR = 2.80, p = 0.017 for EchoRV (+) genotype), but the association had not been found under stratification of the MAOA-uVNTR 4-repeat and MAOA-EchoRV (−) genotypes, respectively (Table 4). These results led us to suggest that the DRD2 gene plays an important role in the ANX/DEP ALC group and that the MAOA gene might modify the association between the DRD2 gene and alcoholism.

The study power was around 0.41–0.56 to detect a small effect and 0.99 to detect a medium and large effect. In the present power analysis, effect size conventions were determined according to the method of Erdfelder and colleagues, as follows: small effect size = 0.10, medium effect size = 0.30, large effect size = 0.50 (α = 0.05).

Discussion

We found that the DRD2 gene is associated with ANX/DEP ALC and that the frequency of the A1/B1 haplotype is higher in subjects with alcohol dependence. These results are consistent with our previous studies in mixed-sex subjects, but results differ from those of the small study of 20 subjects with alcoholism and mood disorder. We hypothesized that, if the DRD2 gene is associated with alcohol dependence, this would be revealed by an association study of subjects with pure ALC and well-matched control subjects, but these results do not support this association. The foregoing observations led us to suggest that the DRD2 gene is associated with alcoholism only in patients with anxiety and depression among the Han Chinese population of Taiwan. Thus, it may be easier to detect an association between the DRD2 gene and alcohol dependence in specific population subgroups.

The association of MAOA EcoRV polymorphism with alcoholism has been reported in the Han Chinese population but remains controversial. We found that the polymorphism of

---

**Table 1: Haplotype frequency and linkage disequilibrium of the DRD2 TaqI A and TaqI B polymorphism in Han Chinese men with alcohol dependence and in control subjects**

<table>
<thead>
<tr>
<th>Groups/haplotypes</th>
<th>Sample size (2n)</th>
<th>Haplotype frequency, %</th>
<th>Linkage disequilibrium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A1B1</td>
<td>A1B2</td>
</tr>
<tr>
<td>Control subjects</td>
<td>402</td>
<td>0.333</td>
<td>0.018</td>
</tr>
<tr>
<td>Pure ALC</td>
<td>216</td>
<td>0.356</td>
<td>0.005</td>
</tr>
<tr>
<td>ANX/DEP ALC</td>
<td>236</td>
<td>0.470</td>
<td>0.009</td>
</tr>
</tbody>
</table>

DRD2 = dopamine D receptor; TaqI A = rs1800497; TaqI B = rs1079596; 2n = double strain; D = linkage disequilibrium coefficients; D′ = standard linkage disequilibrium coefficients; pure ALC = pure alcohol dependence; ANX/DEP ALC = alcohol dependence and anxiety or depression or both.

* p value of Fisher’s exact test.
† p value of linkage disequilibrium in each of the 3 study groups.
‡ Control subjects v. pure ALC v. ANX/DEP ALC; χ² value = 14.388, df = 6.
§ Control subjects v. pure ALC.
** Control subjects v. ANX/DEP ALC.

**Table 2: Genotype frequencies of MAOA polymorphism in Han Chinese men with alcoholism and control subjects**

<table>
<thead>
<tr>
<th>Groups/genotypes</th>
<th>Sample size, no.</th>
<th>Promoter-VNTR (no and %)</th>
<th>χ²</th>
<th>p value</th>
<th>Sample size, no.</th>
<th>EcoRV, no. (and %)</th>
<th>χ²</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3-repeat</td>
<td>4-repeat</td>
<td></td>
<td></td>
<td>+</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Control subjects</td>
<td>197</td>
<td>123 (62.4)</td>
<td>74 (37.6)</td>
<td>5.160</td>
<td>0.160*</td>
<td>201</td>
<td>125 (62.2)</td>
<td>76 (37.8)</td>
</tr>
<tr>
<td>Pure ALC</td>
<td>107</td>
<td>53 (49.5)</td>
<td>54 (50.5)</td>
<td>4.736</td>
<td>0.030†</td>
<td>108</td>
<td>54 (50.0)</td>
<td>54 (50.8)</td>
</tr>
<tr>
<td>ANX/DEP ALC</td>
<td>118</td>
<td>72 (61.0)</td>
<td>46 (39.0)</td>
<td>0.063</td>
<td>0.802‡</td>
<td>118</td>
<td>73 (61.9)</td>
<td>45 (38.1)</td>
</tr>
</tbody>
</table>

MAOA = monoamine oxidase-A; VNTR = variable number of tandem repeats; EcoRV = restriction enzyme rs1137070; pure ALC = pure alcohol dependence; ANX/DEP ALC = alcohol dependence and anxiety or depression or both.

* Control subjects v. pure ALC v. ANX/DEP ALC; df = 3.
† Control subjects v. pure ALC.
‡ Control subjects v. ANX/DEP ALC.

---

Rev Psychiat Neurosci 2007;32(3)
promoter and EcoRV in the MAOA gene are associated with pure ALC but not with other subgroups of alcohol dependence. The significant association between the MAOA gene and pure ALC is consistent with previous studies on alcoholism, but contradicts certain other reports. Moreover, our finding of no MAOA gene association with ANX/DEP

<table>
<thead>
<tr>
<th>Table 3: DRD2 haplotype frequencies of the TaqI A and TaqI B polymorphisms in the 4 groups with stratification of the MAOA genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Groups/haplotypes</strong></td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Control subjects</td>
</tr>
<tr>
<td>Pure ALC</td>
</tr>
<tr>
<td>ANX/DEP ALC</td>
</tr>
<tr>
<td>Control subjects</td>
</tr>
<tr>
<td>Pure ALC</td>
</tr>
<tr>
<td>ANX/DEP ALC</td>
</tr>
<tr>
<td>Control subjects</td>
</tr>
<tr>
<td>Pure ALC</td>
</tr>
<tr>
<td>ANX/DEP ALC</td>
</tr>
<tr>
<td>Control subjects</td>
</tr>
<tr>
<td>Pure ALC</td>
</tr>
<tr>
<td>ANX/DEP ALC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4: Multiple logistic regression analysis of the TaqI A polymorphisms of the DRD2 gene for risk of alcohol dependence with stratification of the MAOA genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Groups/variables</strong></td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Model 1</td>
</tr>
<tr>
<td>DRD2 A1/A1</td>
</tr>
<tr>
<td>DRD2 A1/A2</td>
</tr>
<tr>
<td>Model 2</td>
</tr>
<tr>
<td>DRD2 A1/A1</td>
</tr>
<tr>
<td>DRD2 A1/A2</td>
</tr>
<tr>
<td>Model 3</td>
</tr>
<tr>
<td>DRD2 A1/A1</td>
</tr>
<tr>
<td>DRD2 A1/A2</td>
</tr>
<tr>
<td>Model 1</td>
</tr>
<tr>
<td>DRD2 A1/A1</td>
</tr>
<tr>
<td>DRD2 A1/A2</td>
</tr>
<tr>
<td>Model 3</td>
</tr>
<tr>
<td>DRD2 A1/A1</td>
</tr>
<tr>
<td>DRD2 A1/A2</td>
</tr>
</tbody>
</table>

DRD2 = dopamine D2 receptor; TaqI A = rs1800497; TaqI B = rs1079596; MAOA = monoamine oxidase A; ANX/DEP ALC = alcohol dependence or anxiety or depression or both; MAOA = pure alcohol dependence; ANX/DEP ALC = alcohol dependence and anxiety or depression or both; EcoRV = restriction enzyme rs1137070.

*Control subjects v. Pure ALC v. ANX/DEP ALC.
†Control subjects v. Pure ALC.
‡Control subjects v. ANX/DEP ALC.
§p value of Fisher’s exact test.

MAOA and DRD2 genes in anxiety-depression alcoholism
ALC is consistent with the some reports but not others. There are several possible reasons for these contradictory results. First, definition of the “normal control” group varies between studies. Some studies use a “super-control” (that is, the healthy control subjects had no past or present major or minor mental illnesses, including affective disorder, schizophrenia, anxiety disorder, personality disorder or substance use disorders), while others do not. In genetic association studies, use of suitable control subjects is very important. Several studies have shown that the MAOA and DRD2 genes are associated with several substance abuse or mood disorders. Previous studies suggested that the prevalence of the A1 allele is significantly higher in unscreened control subjects (not excluding people with alcoholism or nicotine addiction) than in assessed control subjects (with exclusion). Using unscreened individuals as control subjects may unwittingly include an excess of patients with A1 alleles and further attenuate the association between the DRD2 A1 allele and alcohol dependence. Thus, the control group should probably exclude subjects with substance use disorders, other major or minor mental disorders and/or a family history of mental disorders. In this study, all potential control subjects were screened by an attending psychiatrist and interviewed by a well-trained psychologist to reduce the confounding factors. If comorbid disorders were found, these participants were excluded. In the study by Lu and colleagues, patient subtype of alcohol dependence was not determined, even though alcohol dependence is a complex phenotype with a heterogeneous etiology. To establish a precise phenotype, Cloninger proposed a neurobiological learning model that subdivided alcoholism into 2 subtypes. People with type I alcoholism (late-onset) often have a high incidence of comorbidity with mood disorders; they show high harm-avoidance and low novelty-seeking behaviors. People with type II alcoholism (early-onset) often have antisocial personality traits and show low harm-avoidance and high novelty-seeking. Cloninger’s classification was not confirmed by subsequent studies. The use of Cloninger’s Tri-dimensional Personality Questionnaire (TPQ) lacks a cut-off point to distinguish the various subtypes of alcoholism, and the definition of personality traits may vary according to sociocultural differences. In recent studies, the DSM-IV criteria have been considered more reliable for clinical use and have also been used in clinical research. It is important to use a well-defined or quantitative phenotype in the association studies of candidate genes of complex disorders because it can lead to a dramatic increase in statistical power. Thus, we suggest that using the SADS-L for initial assessment and the DSM-IV diagnosis to further subgroup patients might reveal novel associations between candidate genes and specific subtypes of alcohol dependence. Another potential confounding factor in prior studies is that there are racial and ethnic differences in gene frequency. The frequencies of DRD2 and MAOA genes are known to vary among different racial or ethnic groups. The DRD2 Taq1 A polymorphism of the A1 allele frequency in our control samples (35.1%) is similar to other Asian populations (35%-37%) but is much higher than in Caucasian samples (11%-20%). Finally, the MAOA promoter polymorphism, high-activity allele (4-repeat) has a prevalence of 40% in Asian populations but in Caucasian populations is as high as 60%-70%. These differences may be partially responsible for the divergent association results.

Several findings from our study suggest that MAOA genes modify the association between the DRD2 gene and alcoholism. The DRD2 gene was associated with ANX/DEP ALC before stratifying by MAOA genotype; after stratification, an association with the MAOA 3-repeat and MAOA EcoRv(+) genotypes was revealed, even though the DRD2 gene was not associated with ANX/DEP ALC in those with MAOA 4-repeats and EcoRv(-) genotypes (Table 3). After stratifying MAOA genotypes and correcting for age, multiple logistic regression analysis showed that the risk of alcohol dependence differed in people with different DRD2 Taq1 A genotypes. The risk for ANX/DEP ALC was much higher in subjects with A1/A1 and A1/A2 genotypes (2.53–3.48 times) than in those with the A2/A2 genotype. That difference in risk was significant only after stratification into the MAOA-uVNTR 3-repeat genotype and into those with the EcoRv(+) genotype (Table 4). Thus, the MAOA genes appear to modulate the effect of the DRD2 gene in the ANX/DEP ALC group but not in the pure ALC group. A possible reason for this result is that dopaminergic tone might be lower in people with alcoholism who have mood disorders than in control subjects and others with different subtypes of alcohol dependence. The lower reinforcement of the dopamine-related reward system might be compensated for by the low-enzyme activity genotype of the MAOA gene. Our results seem to favour a hypothesis that MAOA genes modulate the relation between the DRD2 gene and ANX/DEP ALC, but additional studies are needed. Such studies should use large samples in different populations to determine whether DRD2 and MAOA genes are jointly involved in the development of alcohol dependence.

A potential weakness of our study is that only men were recruited. This is because men with alcoholism are about 10 times more frequent than women with alcoholism in the Han Chinese population in Taiwan, and the MAOA gene locus is located on the short arm of the X chromosome (Xp11.23). Therefore, the relation is easier to study in men than in women. Nevertheless, alcoholism is more frequent in women with depression and anxiety than in women without mood disorders. Thus a study is needed to investigate the relation between the MAOA gene and the DRD2 gene in women with alcoholism.

The ANX/DEP ALC subtype of alcohol dependence might play an important role in a candidate gene study of alcoholism. The present study suggests that the MAOA VNTR allelic variants may modify the effect of the DRD2 gene in subjects with ANX/DEP ALC. However, dopamine is not only degraded by MAO but is also subjected to O-methylation by catechol-O-methyltransferase (COMT) and aldehyde dehydrogenase (ALDH). Our results suggest that the effect of other genes on alcoholism, including gene variants of metabolic enzymes involved in the metabolism of dopamine (e.g., ALDH and COMT genes), should be further investigated.
References


44. Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. Arch Gen Psychiatry 1978;35:837-44.


