Meta-Analysis of the Association of the Taq1A Polymorphism with the Risk of Alcohol Dependency: A HuGE Gene-Disease Association Review

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The human dopamine 2 receptor Taq1A allele has been implicated as a vulnerability factor for alcohol dependence in a number of studies and reviews. To determine whether this allele is associated with alcoholism, the authors conducted a Human Genome Epidemiology review and meta-analysis. Forty-four studies with 9,382 participants were included. An odds ratio of 1.38 (95% confidence interval: 1.20, 1.58; heterogeneity, 50.5%) was found for the A1A1 + A1A2 versus the A2A2 genotype. Sensitivity analyses suggested lack of ethnic matching as a possible source of heterogeneity; a small, significant association was detected in studies with ethnic-matched controls (odds ratio = 1.26, 95% confidence interval: 1.02, 1.56; heterogeneity, 37%). Significant associations were also found in analyses restricted to studies reporting use of blinding and those with adequate screening of controls for alcohol dependency. For the A1A1 versus the A1A2 + A2A2 genotype, the odds ratio was 1.22 (95% confidence interval: 1.05, 1.43; heterogeneity, 37%). Sensitivity analyses on groups of studies reporting use of ethnic-matched controls and those that screened controls for alcohol dependency still showed significant associations. The relatively small effect for the association of the A1 allele, or another genetic variant linked to it, with alcohol dependence indicates a multigene causality for this complex disorder.

alleles; association; dependency (psychology); DRD2; epidemiology; meta-analysis; review (gene-disease association); Taq1A

Abbreviations: CI, confidence interval; DRD2, dopamine receptor D2 gene; GABA, γ-aminobutyric acid; OR, odds ratio.

Editor’s note: This paper is also available on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/).

GENE

Alcohol is known to increase dopaminergic function in the mesolimbic system, a brain reward system thought to be crucial in drug-mediated reinforcement behavior, and therefore may be involved in the pathogenesis of alcohol dependence. The dopamine receptor D2 gene (DRD2) has been one of the most extensively studied in addictive disorders, with the Taq1A polymorphism being the most frequently studied. The DRD2 Taq1A polymorphism is located more than 10 kilobase-pairs downstream from the coding region of the DRD2 gene at chromosome 11q23, and a mutation in this noncoding region would not be expected to produce a structural change in the dopamine receptor (1, 2). Therefore, the functional significance of the polymorphism is...
unclear. It is suggested that the Taq1A polymorphism may be in linkage disequilibrium with an upstream regulatory element or another functional gene that confers susceptibility to alcoholism. More recently, this DRD2-associated polymorphism has been more precisely located within the coding region of a neighboring gene, ANKK1 (ankyrin repeat and kinase domain containing 1), which may confer a change in the amino acid sequence (3).

DISEASE

DRD2 has been implicated as a vulnerability factor for alcohol dependence in a number of studies and previous reviews. Blum et al. (4) were the first to report a significantly higher frequency of the A1 allele of the Taq1A polymorphism near the DRD2 gene in alcoholics compared with nonalcoholic controls. This finding suggests an increased susceptibility to alcohol dependence in people with a particular variant of the DRD2 gene. Later studies supported this initial finding (5–7). Other studies, reviews, and meta-analyses, however, have generally been less positive about the evidence for an association between DRD2 and alcohol dependence (1, 8–10) because more robust association methods did not support the original report. It has been suggested that the nature of the control group may determine whether significant population-based associations are found (6). Therefore, the association of the DRD2 Taq1A allele with alcohol dependence remains unclear and controversial.

The Taq1A allele has also been implicated in other addictive disorders such as polysubstance abuse (11); cocaine (12–14); methamphetamine (15, 16, 17), and nicotine dependence (18); and gambling (19) as well as in other mental health disorders such as mood disorders, schizophrenia, and posttraumatic stress disorder (20, 21). However, no conclusive linkage or association has been found. Other candidate genes (alleles) implicated in alcohol dependency are the alcohol-metabolizing enzymes alcohol dehydrogenases and acetaldehyde dehydrogenase, and γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the human brain (22). GABA acts via two receptor types, A and B. GABA_A receptors are activated by benzodiazepines, which have pharmacologic properties similar to alcohol; thus, GABA_A receptor genes are strong candidates. Several association studies point to the involvement of GABA_A receptor subunit genes clustered on chromosome 5 and the development of alcohol dependence (23–29).

Prevalence data from population surveys in the United States have shown that about 6 percent of men and 2 percent of women are classified as alcohol dependent (30). Although a predisposition to alcohol dependency is thought to be partly attributable to genetic factors, a role for other risk factors has also been suggested. Previous work has linked alcohol abuse and dependence to an earlier age at drinking onset (31–38); being male (31, 33); being divorced, separated, or never married (31); having an early history of antisocial behavior (33, 39, 40); and belonging to a lower socioeconomic group (41). However, these findings are mostly from cross-sectional surveys, which are susceptible to recall bias, and there are few data confirming the association between specific risk factors and alcohol dependency from robust prospective studies with sufficient duration of follow-up and adequate control for confounding (31).

OBJECTIVES

The aim of this Human Genome Epidemiology review was to systematically review and perform a meta-analysis of all available evidence from observational studies regarding the association of the DRD2 Taq1A allele with alcohol dependence.

METHODS

Inclusion criteria

Studies were selected if they evaluated an association between the Taq1A allele of the DRD2 gene and alcohol dependency and included a non-alcohol-dependent concurrent control group. Only studies published in the English language were considered.

Identification and eligibility screening of studies

We identified eligible studies by searching Medline (National Library of Medicine, Bethesda, Maryland), Embase (Elsevier, Amsterdam, the Netherlands), and BIOSIS (Thomson Scientific, Stamford, Connecticut) from their inception to August 2006. We used the following thesaurus search terms (exploded): “alcohol-related disorders” OR “alcoholic beverages” OR “alcoholic drinking” combined with the free-text terms “allele*” OR “gene” OR “genes” OR “locus” OR “loci” OR “receptor*” OR “genotype*” OR “polymorphi*” OR “RFLP” OR “genetic*” OR “mutation*” OR “variant*” AND “alcohol*” OR “drink*” AND “DRD2” OR “Taq1A.” Two reviewers (L. S. and M. W.) screened the title and abstract of each electronic citation; full-text copies of potentially relevant studies were obtained. Each full-text copy was screened for eligibility (L. S. and M. W.). References from retrieved study reports and reviews were also screened for additional studies.

Data extraction

Two investigators (L. S. and M. W.) independently extracted data by using a structured form. Discrepancies were resolved by discussion and consultation with a third reviewer (D. F.). The following information was sought from each report: selection and diagnostic criteria of the alcohol-dependent group; selection and classification criteria of the control group; demographic information including ethnicity, age, and sex; all alleles investigated; method of ascertainment of genotype; blinding of personnel performing genotyping to clinical status of the study participants; methods used to create balanced groups (matching procedures or statistical adjustment methods); genotype and allelic frequencies; and statement of Hardy-Weinberg equilibrium. Studies were categorized as Caucasian based on the original study’s use of the term to describe ethnic group or for studies conducted on White North Americans or Europeans.
Data analysis

We estimated unadjusted odds ratios for published genotype frequencies. Pooled odds ratios were calculated by using a random-effects model (42) stratified by geographic region/ethnicity. Geographic regions/ethnic groups were Caucasian, Native American, Japanese, Chinese, Hispanic, Indian, and Korean. Studies with mixed populations were added to the group that represented the majority of the participants. We quantified the extent of heterogeneity by using $I^2$, which represents the proportion of variability between studies attributable to true variability rather than chance (43). There are several approaches to analyzing gene-disease association studies. We conducted two analyses; one assumed a dominant model of gene action (homozygous wild type vs. heterozygous and homozygous variant), the other a recessive model of gene action (homozygous wild type plus heterozygous vs. homozygous variant). We chose not to compare allele frequencies (codominant model) between cases and controls, because this process double-counts people, or to perform several pair-wise comparisons, because each pair-wise comparison leaves out valuable information. In addition, both analyses increase the likelihood of a type 1 error. We tested whether the genotype frequencies in the controls were in agreement with the expected distribution (Hardy-Weinberg equilibrium) by using Pearson’s $\chi^2$ with 1 degree of freedom, with Yates’s correction for cells with values of less than 5.

We investigated heterogeneity through a number of pre-planned sensitivity analyses in which studies were eliminated from analyses if they significantly deviated from Hardy-Weinberg equilibrium, did not use ethnic-matched controls, did not report use of blinding of case-control status and/or genotyping, and did not report adequate screening of control groups to exclude alcohol dependency. Cumulative meta-analyses were also performed. We used Stata software, version 8 (Stata Corporation, College Station, Texas) for cumulative meta-analyses and Hardy-Weinberg analysis, and the computer program RevMan, version 4.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) for all other analyses.

RESULTS

Description and quality of included studies

We screened 1,056 titles and abstracts and obtained 116 full-text papers. Of these, 44 met our eligibility criteria. We included 44 studies with a total of 9,382 participants. Forty-two were case-control studies, and two were cross-sectional surveys (44, 45). Characteristics of included studies are summarized in table 1. Three studies reported allelic frequencies only (6, 46, 47), but we were able to extract genotype frequencies from a review published by Noble (48) for the Bolos et al. (46) and Neiswanger (6) studies. All others reported genotype frequencies.

Alcohol dependency was determined by using different diagnostic criteria: the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised; Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Revised; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; and Feighner criteria (precursor to modern psychiatric classification criteria). Two studies also used autopsy-confirmed alcohol misuse cases (4, 49). Fourteen studies excluded patients with other addictions and major psychiatric disorders (5, 46, 50–61). Controls were classified as not alcohol dependent, but the thoroughness of this diagnosis varied across studies, and some studies may not have screened the controls adequately to eliminate possible cases (45–47, 56, 60, 62–71). Blinding of clinical investigators assessing case-control status to genotype was reported by only 10 studies (4, 5, 45, 46, 56, 57, 72–75).

Matching for sex was described in 10 studies (44, 51, 52, 59, 64, 69, 74, 76–78), for age in two (76, 77), and for ethnicity in 30 (5, 6, 44–46, 49, 52, 54, 56–60, 62, 64, 66–70, 75–84). Few (nine) studies reported blinding to case or control status of personnel who performed the genotyping (4, 5, 52, 56, 62, 65, 75, 85). Polymerase chain reaction was used for genotyping in 25 studies (5, 45, 49, 50, 54, 57–61, 63, 64, 67, 69–71, 73, 74, 76–79, 81, 86, 87) and hybridization in 16 studies (4, 6, 46, 51–53, 55, 56, 62, 65, 66, 68, 72, 75, 84, 85); three did not report the method used (44, 47, 83). Genotyping was conducted in duplicate by only six studies (52, 57, 62, 67, 75, 76); in one study (87), 10 percent of the sample was checked; and in one study, samples were genotyped in triplicate (4).

Overall effects

Forty-three studies, including a total of 5,273 cases and 3,995 controls, reported genotype frequencies for the TaqIA polymorphism and alcohol dependency.

We found evidence suggesting that genotypes in control groups were not in Hardy-Weinberg equilibrium ($p < 0.05$) in three studies (46, 68, 74).

For all studies combined, when we assumed the dominant model of gene action ($A_1A_1 + A_1A_2$ vs. $A_2A_2$), a small but significant association of alcohol dependency with being homozygote or heterozygote for the $A_1$ allele was detected. The odds ratio was 1.38 (95 percent confidence interval (CI): 1.20, 1.58) when random effects were used, although substantial statistical heterogeneity was detected between studies ($I^2 = 50.5$ percent, $p = 0.0001$). Stratifying the studies into subgroups by ethnic group produced similar results, with significant associations detected in the two largest subgroups: Caucasian (odds ratio (OR) = 1.57, 95 percent CI: 1.29, 1.91) with substantial heterogeneity ($I^2 = 57.2$ percent, $p = 0.0001$) and Chinese (OR = 1.35, 95 percent CI: 1.04, 1.75) with no heterogeneity ($I^2 = 0$ percent, $p = 0.71$) (Web figure 1; this information is shown in the first of four supplementary figures; each is referred to as “Web figure” in the text and is posted on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/reviews.htm) as well as on the Journal’s website (http://aje.oupjournals.org/)).

Pooling the results of the same studies, but assuming the recessive model of gene action ($A_1A_1$ vs. $A_1A_2 + A_2A_2$), also showed a small but significant positive association of...
### Table 1. Characteristics of studies included in a meta-analysis of the association of the Taq1A polymorphism with the risk of alcohol dependency

<table>
<thead>
<tr>
<th>Study (first author, year (reference no.))</th>
<th>Participant characteristics</th>
<th>Genotype and method</th>
<th>Hardy-Weinberg (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amadeo, 2000 (86)</td>
<td>Polynesian, Polynesian/Caucasian, Polynesian/Chinese hospitalized for alcohol dependence; 38 with cannabis abuse/dependence; DSM-III-R* criteria; interview; n = 71 (61 men, 10 women); mean age, 40.8 years</td>
<td>Taq1A, PCR*; no information on blinding</td>
<td>0.104</td>
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<tr>
<td>Amadeo, 2001 (50)</td>
<td>German alcohol dependents; DSM-IV* criteria; admitted for detoxification; 56% nicotine dependent; M-CIDI,* interview, and ASI* conducted by psychiatrist; psychotic disorders and substance abuse other than nicotine excluded; n = 243 (187 men, 56 women)</td>
<td>Taq1A, PCR; no information on blinding</td>
<td>0.436</td>
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<tr>
<td>Arinami, 1993 (51)</td>
<td>Japanese alcoholics; hospital inpatients; randomly selected; unrelated; DSM-III-R criteria; assessed by psychiatrist; major affected disorder, schizophrenia, or psychoses excluded; interview for family history of alcoholism; n = 78 (74 men, 4 women); mean age, 51 (range, 25–79) years</td>
<td>Group 1: unrelated volunteers selected from staff, students, and routine patients and relatives of patients; unscreened, n = 100; mean age, 44 (SEM,* 1.2) years; group 2: gender-matched, nonalcoholics recruited from care staff; did not meet criteria for alcoholism; nonsmokers; n = 35; mean age, 45 (SEM, 1.5) years</td>
<td>0.096</td>
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<tr>
<td>Bau, 2000 (63)</td>
<td>Unrelated Caucasian, alcoholic, Brazilian hospital detoxification patients; DSM-III-R criteria and interview; n = 115; males; mean age, 41 (range, 20–63) years</td>
<td>Taq1A, PCR; no information on blinding</td>
<td>0.572</td>
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<tr>
<td>Blum, 1990 (4)</td>
<td>Caucasian cadavers of alcoholics; cause of death related to alcohol abuse; samples obtained from National Neurological Research Bank, United States; alcohol dependence or alcohol abuse or nonalcoholic status determined independently by two psychiatrists using medical records and relative or treatment center staff, 100% agreement; n = 35 (32 men, 3 women); 22 White, 13 Black; mean age, 51.0 (SEM, 2.3) years</td>
<td>Taq1A; hybridization; three independent samples blind to clinical status</td>
<td>0.181</td>
</tr>
<tr>
<td>Blum, 1991 (72)</td>
<td>Caucasian alcoholics receiving treatment for alcohol dependence; volunteers; living in Texas; classified as severe (dependent with medical complications) or less severe (dependent only) based on three questionnaires, DSM-III-R criteria for alcohol dependence and abuse; n = 96 (65 men, 31 women); 89 White, 7 Black; mean age, 44.8 (SEM, 1.4) years</td>
<td>Taq1A; hybridization; no information on blinding</td>
<td>0.463</td>
</tr>
<tr>
<td>Bolos, 1990 (46)</td>
<td>Unrelated Caucasian alcoholics all admitted to NIAAA* unit; DSM-III-R and RDC* criteria for alcohol dependence by two independent clinical interviewers blind to genotype status; no major psychiatric disorder or major drug abuse; n = 40 (36 men, 4 women); mean age, 44 (SEM, 2) years</td>
<td>Taq1A; hybridization; no information on blinding</td>
<td>0.024</td>
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*Note: DSM-III-R and DSM-IV are diagnostic criteria for mental disorders, while RDC is a research diagnostic criteria system. Taq1A is a genetically determined polymorphism.
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<th>Study (first author, year)</th>
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<tbody>
<tr>
<td>Chen, 1996 (81)</td>
<td>Atayal Taiwanese (aboriginal); alcohol dependent; DSM-III-R criteria and Chinese diagnostic interview, alcoholism section; n = 85; mean age, 40 years</td>
<td>Taq1A, PCR; no information on blinding</td>
<td>0.510</td>
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<tr>
<td>Chen, 1997 (64)</td>
<td>Han Chinese and four aboriginal groups in Taiwan from community and clinical settings, DSM-III-R criteria for alcohol dependence, assessed by psychiatrist or trained nurses, semi-structured clinical interview, defined as severe by liver function, peripheral neuropathy and hallucinations; n = 203, 178 men 35 women; age 41.2–51.1 years</td>
<td>Taq1A and NcoI, PCR + Taq digestion</td>
<td>0.772</td>
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<td>Comings, 1991 (65)</td>
<td>North American; Caucasian; attending an addiction clinic; DSM-III-R criteria for alcohol dependence and an additional 13 cases from brain tissue from NNRB*; n = 104</td>
<td>Taq1A; hybridization; genotype read blind to clinical status</td>
<td>0.177</td>
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<td>Cook, 1992 (52)</td>
<td>Male Caucasian alcoholics in a VA* alcohol treatment unit in nonurban areas of Iowa and neighboring states according to DSM-III-R criteria obtained by structured interview; no other substance dependence or psychiatric conditions; n = 20; mean age, 66.9 (SD, 15.3) years</td>
<td>Taq1A; duplicate genotyping by hybridization; blind to clinical status</td>
<td>0.451</td>
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<td>Cruz, 1995 (53)</td>
<td>Unrelated male Mexican alcoholics hospitalized for hallucinosis, with withdrawal symptoms, or delirium; DSM-III-R and AUDIT* and Eysenck Personality Questionnaire, major mental disorders excluded except major depression or psychosocial substance abuse; n = 38; mean age, 34 (range, 21–47) years</td>
<td>Taq1A; hybridization; no information on blinding</td>
<td>0.192</td>
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<tr>
<td>Finckh, 1996 (54)</td>
<td>Unrelated Caucasian alcoholics of German origin recruited from three different sources: hospital detoxification unit, homeless not receiving treatment, hospitalized in a psychiatric addiction unit; ICD-10* criteria for alcoholism; structured interview; other drug addictions and major psychiatric comorbidities excluded; n = 312 (273 men, 39 women); mean age, 42 (SD, 9.4) years</td>
<td>Taq1A, and exon 7 C/G SerCys polymorphism PCR; no information on blinding</td>
<td>0.698</td>
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<tr>
<td>Foley, 2004 (49)</td>
<td>Brain tissue collected at autopsy from Caucasians, alcoholics, 34% with cirrhosis; alcohol-related end-organ damage confirmed pathologically at autopsy; alcohol consumption ascertained by medical records, in excess of 80 g/day most of adult life; N = 87</td>
<td>Taq1A, Taq1B, ADH1C, EA AT2G 603A, SHTTL-PR, NMDAR2B, DAT1 SLC6A3, SLC6A4, PCR; no information on blinding</td>
<td>0.570</td>
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Table continues
### TABLE 1. Continued

<table>
<thead>
<tr>
<th>Study (first author, year)</th>
<th>Participant characteristics</th>
<th>Genotype and method</th>
<th>Hardy-Weinberg (p value)</th>
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<tbody>
<tr>
<td>Geijer, 1994 (55)</td>
<td>Scandinavian alcoholics from an inpatient detoxification program; DSM-III-R criteria plus interview; excluded if history of psychiatric disorders or dependence on psychoactive substances other than alcohol; criminal and social security registers used to verify alcoholism and exclude mental/nervous disorders; psychoactive substance detection at autopsy excluded; ( N = 74 ) (64 men, 10 women); mean age, 46 (range, 29–71) years; plus 19 autopsy samples from alcoholics (18 men, 1 woman); mean age, 51.1 (range, 25–75) years</td>
<td>Persons screened for alcohol dependence or abuse; DSM-III-R criteria and medical record review to verify clinical status and exclude those with substance misuse; ( N = 81 ) (43 men, 38 women) mean age, 39.5 (range, 29–56) years</td>
<td>Taq1A, Taq1B; hybridization; no information on blinding</td>
</tr>
<tr>
<td>Gelernter, 1991 (56)</td>
<td>Unrelated Caucasian alcohol-dependent subjects participating in pharmacotherapy trials for alcoholism; no comorbid psychiatric disorder or opiate abuse or dependence; DSM-III-R criteria and structured clinical interview; diagnosis blind to genotype status; ( N = 44 ) (34 men, 10 women); mean age, 40.5 (range 23–62) years</td>
<td>Unrelated White patients from family pedigree studies, mixed European ancestry, described as a random sample; no psychiatric interview; ( N = 68 )</td>
<td>Taq1A; hybridization; genotyping blind to case status</td>
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<tr>
<td>Gelernter, 1999 (83)</td>
<td>European Americans seeking treatment for substance misuse; DSM-III-R criteria; 7–9 criteria met = severely affected, 3–6 = affected; ( n = 160 )</td>
<td>European Americans screened by various questionnaires including DSM-III-R and SADS-L* or interview to exclude substance use and psychotic, anxiety; and mood disorders; ( N = 136 )</td>
<td>Taq1A, Taq1B, Taq1D, and 141C InsDel; genotyping methods described in Gelernter (98); no mention of blinding</td>
</tr>
<tr>
<td>Goldman, 1992 (66)</td>
<td>Finnish violent alcoholics imprisoned, unrelated, and with Finnish parents; ( N = 46 ); all male; mean age, 29.2 (SEM, 1.3) years</td>
<td>Finnish nonalcoholics, unrelated with Finnish parents; paid volunteers recruited through newspaper advertisements; ( N = 36 ); all male; mean age, 30.1 (SEM, 2.5) years</td>
<td>Taq1A; hybridization; no information on blinding</td>
</tr>
<tr>
<td>Goldman, 1997 (45)</td>
<td>Southwestern American Indian population, interrelated pedigrees; DSM-III-R criteria for alcohol dependence, substance misuse (excluding alcohol), or schizophrenia; clinical interview blind to genotype; ( N = 459 ) (121 women, 155 men) with alcohol dependence</td>
<td>( N = 161 ) unaffected from the same sample population as cases</td>
<td>ser311cys, Taq1A, intron 2 STR,* PCR; no information on blinding</td>
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<tr>
<td>Gorwood, 2000 (57)</td>
<td>Males alcoholics of French origin from the psychiatric department and outpatient clinic of two general hospitals; DSM-III-R criteria plus interview; schizophrenia and dementia excluded; analysis blinded; ( n = 113 ); mean age, 43.6 (SD, 10.3) years</td>
<td>Male blood donors of French origin; no alcohol dependence; DSM-III-R criteria, classified as social drinkers; ( n = 49 ); minimum age, 35 years</td>
<td>Taq1A, PCR; duplicate genotyping blind to clinical status</td>
</tr>
<tr>
<td>Heinz, 1996 (58)</td>
<td>Unrelated individuals, German nationality of European descent; alcohol dependent in a detoxification outpatient clinic; ICD-10 criteria; no comorbid psychiatric disorders; no other substance misuse; ( N = 97 )</td>
<td>Nonalcoholics; ethnically matched; at least age 26 years; no addictive disorder or previous psychiatric treatment ascertained by questionnaire; ( N = 113 ) (50 addictive, 63 women)</td>
<td>Taq1A, PCR; no information on blinding</td>
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<tr>
<td>Hietala, 1997 (84)</td>
<td>Finnish unrelated male alcoholics in a detoxification program; DSM-III-R criteria for alcohol dependence; clinical interviews; ( n = 70 ); mean age, 42.1 (SD, 8.5) years</td>
<td>Unrelated male volunteers from two industrial corporations in Finland; screened to exclude alcohol abuse and major mental disorders by interview and medical record review; ( n = 50 ); mean age, 44.1 (SD, 8.3) years</td>
<td>Taq1A; hybridization; no information on blinding</td>
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* SADS-L: Schedule for Affective Disorders and Schizophrenia for Longitudinal Studies in Psychiatric Epidemiology.
<table>
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<tbody>
<tr>
<td>Ishiguro, 1998 (59)</td>
<td>Unrelated, Japanese alcoholic patients diagnosed according to DSM-III-R criteria for alcohol dependence and withdrawal symptoms; other addictions excluded; N = 209 (195 men, 14 women); mean age, 52.0 (range, 29–75) years</td>
<td>Unrelated, healthy age- and sex-matched Japanese with no history of addictive disorder or psychiatric treatment determined by questionnaire; N = 152 (137 men, 15 women); mean age, 50.8 (range, 25–65) years</td>
<td>Taq1A, PCR; no information on blinding</td>
</tr>
<tr>
<td>Kaaoguz, 2004 (74)</td>
<td>Turkish, unrelated alcoholic males, severe drinkers of Raki (45% ethanol) per DSM-IV criteria; psychiatrists blind to genotype; type II characterized by fighting when drinking, automobile accidents, arrest for reckless driving, hospitalization for alcoholism; and inability to abstain before aged 25 years; N = 82; males; mean age, 43 (range, 28–63) years</td>
<td>Healthy males: no psychiatric or organic diseases; no history of alcohol or drug dependency; N = 93; males; mean age, 29.8 (range, 17–50) years</td>
<td>Taq1A, PCR; no information on blinding</td>
</tr>
<tr>
<td>Konishi, 2004 (87)</td>
<td>Mexican Americans living in Los Angeles, California, recruited from human service agencies, treatment programs, mental health clinics, AA* groups, Hispanic churches and organizations, and medical emergency rooms; DSM-IV criteria for alcoholism; structured clinical interview; N = 200; mean age, 39.0 (SD, 10.8) years</td>
<td>Nonalcoholics: structured clinical interview; N = 251; mean age, 32.5 (SD, 9.2) years</td>
<td>Taq1A, Taq1B, intron 6, intron 7, 141C ins/del, ADH1C, ADH2 PCR for ADH genotypes, 10% of each genotype duplicated; no information on blinding</td>
</tr>
<tr>
<td>Kono, 1997 (73)</td>
<td>Native Japanese: unrelated; DSM-III-R criteria: 7–9 criteria met = severely affected, 3–6 = affected; subtyped by age at onset (&lt;25 years) and family history of alcohol dependence; also by mood disorder, hallucinosis, withdrawal delirium, or seizures; two independent psychiatrists blind to genotype; n = 100 (78 men, 22 women); mean age, 48.7 (SD, 9.4) years</td>
<td>Unrelated; alcoholism and family history of alcoholism excluded; n = 93 (70 men, 23 women); mean age, 42.5 (SD, 13.3) years</td>
<td>Taq1A, PCR; no information on blinding</td>
</tr>
<tr>
<td>Lawford, 1997 (5)</td>
<td>Unrelated Australian volunteers of Caucasian descent, age not given; sample A: N = 68 (63 men, 5 women admitted to an acute detoxification unit); sample B: N = 90 (85 men, 5 women admitted to a psychiatric unit for alcohol rehabilitation); sample C: N = 43 (36 men, 7 women admitted for alcohol-induced gastrointestinal disease but excluded if they had dementia, delirium, psychosis, or other CNS* impairment); fulfilled DSM-III-R criteria for alcohol abuse/dependence; detailed interview and questionnaire; all interviews blind to genotype status</td>
<td>Unrelated Australian volunteers of Caucasian descent; hospital staff; nonsmokers; no current daily alcohol consumption above 6 g for men and 4 g for women; structured interview; N = 46 (16 men, 30 women)</td>
<td>Taq1A, PCR; genotyping blind to clinical status</td>
</tr>
<tr>
<td>Lee, 1999 (71)</td>
<td>Chinese Han with alcohol dependence: 19 hospitalized with withdrawal symptoms or medical complications of alcoholism, 109 outpatients with complications of alcoholism; DSM-III-R–defined alcohol dependence; structured clinical interview; N = 128 (120 men, 8 women); mean age, 39.11 (SD, 10.78) years</td>
<td>Nonalcoholics; unrelated; selected from community and hospital; same ethnic group; N = 85 (75 men, 10 women); mean age, 36.95 (SD, 12.32) years; 19 alcoholics and 24 nonalcoholics included in earlier Lu study (68)</td>
<td>Taq1A, Taq1B, ADH2, ADH3, and ALDH2 PCR, duplicate tests; no information on blinding</td>
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<th>Genotype and method</th>
<th>Hardy-Weinberg (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limosin, 2002 (79)</td>
<td>French Caucasian, alcohol-dependent; detoxification inpatients; DSM-III-R criteria plus interview; $n = 120$; 62 men (mean age, 44.4 years), 58 women (mean age, 46.3 years)</td>
<td>Taq1A, PCR; no information on blinding</td>
<td>0.786</td>
</tr>
<tr>
<td>Lu, 1996 (68)</td>
<td>Taiwanese male alcoholics from three ethnic groups; Chinese Han: $n = 21$, Atayal (aboriginal): $n = 20$; some related individuals in both groups because of small communities; DSM-III-R criteria for “severe” alcohol dependence based on clinical interview</td>
<td>Taq1A, Taq1B and intron 2 STR polymorphism; hybridization, no information on blinding</td>
<td>0.011</td>
</tr>
<tr>
<td>Lu, 2001 (60)</td>
<td>Han Chinese in Taiwan hospital patients; DSM-III-R–defined alcohol dependence; clinical interview plus interview with family member to confirm diagnosis; major mental illness and conduct disorder excluded; $n = 97$ (88 men, 9 women)</td>
<td>Taq1A and Taq1B, PCR; no information on blinding</td>
<td>0.361</td>
</tr>
<tr>
<td>Lee, 1997 (67)</td>
<td>Korean alcoholics selected from two hospitals; DSM-III-R criteria; $N = 67$; male; mean age, 46 (SD, 9.28) years, range, 27–70 years</td>
<td>Taq1A, PCR; no information on blinding</td>
<td>0.235</td>
</tr>
<tr>
<td>Matsushita, 2001 (77)</td>
<td>Japanese inpatients hospitalized for 2–4 weeks for alcohol dependence or abuse, DSM-III-R criteria, clinical interview, 376 with active ALDH2, 74 with inactive ALDH2; plus 133 male alcoholics from detoxification unit, DSM-III-R, with inactive ALDH2; $n = 583$ (541 men, 42 women); mean age, 50.2 years</td>
<td>Taq1A, PCR; no information on blinding</td>
<td>0.249</td>
</tr>
<tr>
<td>Neiswanger, 1995 (6)</td>
<td>Unrelated Caucasian alcoholics; DSM-III-R plus Feighner diagnostic interview schedule; current and lifetime history of drinking and drug use; 20% also drug dependent; psychopathologies minimal; $n = 52$ (20 men, 32 women); mean age, 33.8 (SD, 5.7) years</td>
<td>Taq1A, hybridization; no information on blinding</td>
<td>0.449</td>
</tr>
<tr>
<td>Noble, 1994 (85)</td>
<td>Caucasian, hospitalized alcoholics with alcohol-induced chronic organ disease, SAAST* score at least 11, and DSM-III-R criteria for alcohol abuse/dependence; Severity of Alcohol Dependence Questionnaire also used; drug abuse/dependence not excluded; $N = 73$ (63 men, 10 women); 44 Caucasian, 21 Hispanic, 8 Black; mean age, 44.0 (SD, 1.0) years</td>
<td>Taq1A, hybridization; genotyping blind to clinical status</td>
<td>0.630</td>
</tr>
<tr>
<td>Ovchinnikov, 1999 (69)</td>
<td>Slavic-surnamed patients with alcohol dependence; group 1: age at onset &gt; 25 years, negative family history, less severe disease; group 2: age at onset &lt; 25 years, family history positive, severe alcohol abuse; according to ICD-10 criteria, group 1: $n = 18$, group 2: $n = 24$; men; mean age; 39.8 (SD, 10.3) years</td>
<td>Taq1A, Taq1B, exon 3 DRD4, PCR; no information on blinding</td>
<td>0.561</td>
</tr>
</tbody>
</table>
### TABLE 1. Continued

<table>
<thead>
<tr>
<th>Study (first author, year)</th>
<th>Participant characteristics</th>
<th>Genotype and method</th>
<th>Hardy-Weinberg (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alcohol-dependent cases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parsian, 1991 (75)</td>
<td>Unrelated alcoholics taking part in a larger alcoholism study; Caucasian; diagnosed according to Feigner criteria; diagnosis blind to genotype status; (N = 32; 81% \text{ men; mean age, 34.6 (SD, 7.6) years} )</td>
<td>Taq1A, hybridization; genotyping in duplicate, blind to case status</td>
<td>0.441</td>
</tr>
<tr>
<td>Pastorelli, 2001 (76)</td>
<td>White Italians; alcohol dependent; seeking treatment or admitted for medical reasons; 80% smokers; 27% polysubstance abusers; interview; (N = 60) (45 men, 15 women); mean age, 46.4 (SD, 10.8) years</td>
<td>Taq1A and Taq1B, PCR; genotyping in duplicate; no information on blinding</td>
<td>0.412</td>
</tr>
<tr>
<td>Samochowiec, 2000 (70)</td>
<td>Unrelated, Caucasian, German alcoholic patients recruited from two hospitals; ICD-10; structured clinical interview; (N = 292) (233 men, 50 women); mean age, 43 (SD, 9) years</td>
<td>–141C ins/del, exon 8 AG, Taq1A, PCR; no information on blinding</td>
<td>1.000</td>
</tr>
<tr>
<td>Sander, 1999 (61)</td>
<td>Unrelated, German, alcohol-dependent individuals diagnosed according to ICD-10 and structured interview; no comorbid substance dependence bar nicotine; (N = 310) (261 men, 49 women); mean age, 42.4 (SD, 9.4) years</td>
<td>–141C Ins/del and Taq1A, PCR; no information on blinding</td>
<td>0.893</td>
</tr>
<tr>
<td>Schwab, 1991 (47)</td>
<td>Alcohol dependents in detoxification; Caucasians living in Germany; diagnosis by clinical examination; (n = 45)</td>
<td>Taq1A; no information on blinding</td>
<td>Not tested</td>
</tr>
<tr>
<td>Shaikh, 2001 (78)</td>
<td>Alcohol dependents from southern India admitted to a mental health hospital; SCAN* criteria and ICD-10 for alcohol dependence (Schedules for Assessment of Neuropsychiatry) plus interview; age at dependence &lt;25 years; &gt;2 first-degree relatives with alcohol dependence; (n = 50)</td>
<td>Taq1A, PCR; no information on blinding</td>
<td>0.124</td>
</tr>
<tr>
<td>Suarez, 1994 (62)</td>
<td>Unrelated Caucasian alcoholics, mainly probands in an ongoing study of genetics and alcoholism; alcoholism determined according to Feigner criteria, structured clinical interview, and medical record review; (n = 88)</td>
<td>Race-matched controls all unrelated and all psychiatrically normal from three sources: spouses of alcoholics ((n = 14)), subjects in a bipolar study ((n = 12)), and subjects from a catchment's area survey; interview ((n = 63)); (n = 89); aged 40–55 years</td>
<td>0.708</td>
</tr>
<tr>
<td>Young, 2002 (44)</td>
<td>Unrelated male Caucasian PTSD* patients (Australian armed forces veterans) consuming harmful alcohol levels; interviewers blinded to case-control status; assessed for PTSD; interviewed for alcohol consumption; (n = 38); mean age, 52 (SEM, 0.7) years</td>
<td>Taq1A; no information on blinding</td>
<td>0.188</td>
</tr>
</tbody>
</table>

* DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised; PCR, polymerase chain reaction; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Revised; M-CIDI, Munchner Composite International Diagnostic Interview; ASI, Addiction Severity Index; SEM, standard error of the mean; NIAAA, National Institute on Alcohol Abuse and Alcoholism; RDC, research diagnostic criteria; NNRB, National Neurological Research Bank; CEPH, Centre d’etude du Polymorphisme Humain; VA, Veterans Administration; SD, standard deviation; MAST, Michigan Alcohol Screening Test; AUDIT, Alcohol Use Disorders Interview Test; ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; SADS-L, Schedule for Affective Disorders and Schizophrenia, Lifetime Version; STR, short tandem repeat; AA, Alcoholics Anonymous; CNS, central nervous system; KAST, Kurihama Alcoholism Screening Test; SAAST, Self-Administered Alcohol Screening Test; SCAN, Schedule for Assessment of Neuropsychiatry; PTSD, posttraumatic stress disorder.

alcohol dependency with being homozygote for the $A1$ allele (Web figure 2). The combined odds ratio was 1.22 (95 percent CI: 1.05, 1.43) using random effects this time, with no statistical heterogeneity detected between studies ($I^2 = 0\%$, $p = 0.92$). Again, subgroup analyses showed no notable differences between different populations, with a significant association detected in the Caucasian subgroup (OR = 1.40, 95 percent CI: 1.03, 1.91) with no heterogeneity ($I^2 = 0\%$, $p = 0.92$) and in the Chinese subgroup (OR = 1.41, 95 percent CI: 1.00, 2.00) with no heterogeneity ($I^2 = 0\%$, $p = 0.52$).

**Sensitivity analyses**

Statistically significant departures from Hardy-Weinberg equilibrium were detected in three studies (46, 68, 74). Exclusion of these three studies from both analyses did not change the overall effect for the recessive model (OR = 1.22, 95 percent CI: 1.05, 1.43; $I^2 = 0\%$, $p = 0.89$) or remove heterogeneity between studies for the dominant model (OR = 1.38, 95 percent CI: 1.20, 1.60; $I^2 = 53.1\%$, $p < 0.0001$). There was a slight increase in heterogeneity in the Caucasian subgroup ($I^2 = 59.7\%$) with removal of the two studies, with significant departures from Hardy-Weinberg equilibrium. An overall significant association was still detected using the dominant model in analyses restricted to studies reporting use of ethnic matching of controls (table 2), blinding (table 3), and screening of the control group to exclude alcohol dependents (table 4). Sensitivity analyses had little impact on heterogeneity, with the exception of the Caucasian subgroup when the analysis was restricted to studies using ethnically matched controls, where it was markedly reduced (37 percent, table 2). Similarly, for the recessive model, significant associations were still detected when restricting the analyses to studies with ethnically matched controls (table 3) and screened controls (table 4), with negligible heterogeneity.

Results for the cumulative meta-analysis after each study from 1990 to 2004, and for each genetic model, are shown in Web figures 3 and 4. For the dominant model, the cumulative meta-analysis shows that, with each additional study, although being significantly greater than one since 1990, the magnitude of the effect decreased over time; the odds ratio came closer to one and remained relatively stable beginning in 2000. For $A1$ homozygotes versus both other genotypes (recessive model), the odds ratio became greater than one after 1991 and has remained so since then, reaching significance in 2001. The pooled odds ratio has changed very little since 2001.

**TABLE 2. Effect estimates in studies that reported use of a control group matched for ethnicity**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of studies</th>
<th>OR* dominant†</th>
<th>95% CI*</th>
<th>I²%‡</th>
<th>No. of studies</th>
<th>OR recessive§</th>
<th>95% CI</th>
<th>I²%‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>11</td>
<td>1.26</td>
<td>1.02, 1.56</td>
<td>37.0</td>
<td>11</td>
<td>1.26</td>
<td>0.84, 1.91</td>
<td>0</td>
</tr>
<tr>
<td>Native American</td>
<td>1</td>
<td>0.95</td>
<td>0.57, 1.58</td>
<td>1</td>
<td>0.83</td>
<td>0.56, 1.24</td>
<td>0.92</td>
<td>0.56, 1.24</td>
</tr>
<tr>
<td>Japanese</td>
<td>4</td>
<td>1.12</td>
<td>0.71, 1.77</td>
<td>69.3</td>
<td>4</td>
<td>1.25</td>
<td>0.89, 1.76</td>
<td>1.76</td>
</tr>
<tr>
<td>Chinese</td>
<td>5</td>
<td>1.35</td>
<td>1.04, 1.75</td>
<td>0</td>
<td>5</td>
<td>1.41</td>
<td>1.00, 2.00</td>
<td>0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2</td>
<td>1.07</td>
<td>0.73, 1.57</td>
<td>0</td>
<td>2</td>
<td>1.31</td>
<td>0.78, 2.00</td>
<td>19.5</td>
</tr>
<tr>
<td>Korean</td>
<td>1</td>
<td>1.10</td>
<td>0.58, 2.06</td>
<td>1</td>
<td>0.96</td>
<td>0.42, 2.20</td>
<td>0.42, 2.20</td>
<td>19.5</td>
</tr>
<tr>
<td>Indian</td>
<td>1</td>
<td>0.84</td>
<td>0.36, 1.95</td>
<td>1</td>
<td>1.25</td>
<td>0.42, 3.75</td>
<td>0.42, 3.75</td>
<td>19.5</td>
</tr>
<tr>
<td>Polynesian</td>
<td>1</td>
<td>0.97</td>
<td>0.48, 1.96</td>
<td>1</td>
<td>0.99</td>
<td>0.39, 2.49</td>
<td>0.39, 2.49</td>
<td>19.5</td>
</tr>
<tr>
<td>Overall</td>
<td>26</td>
<td>1.18</td>
<td>1.04, 1.34</td>
<td>22.3</td>
<td>26</td>
<td>1.18</td>
<td>1.01, 1.39</td>
<td>1.39</td>
</tr>
</tbody>
</table>

* OR, odds ratio; CI, confidence interval.
† $A1A1 + A1A2$ vs. $A2A2$ genotype.
‡ Variability between studies due to heterogeneity rather than chance.
§ $A1A1$ vs. $A1A2 + A2A2$ genotype.

**TABLE 3. Effect estimates in studies that reported use of blinding measures**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of studies</th>
<th>OR* dominant†</th>
<th>95% CI*</th>
<th>I²%‡</th>
<th>No. of studies</th>
<th>OR recessive§</th>
<th>95% CI</th>
<th>I²%‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>11</td>
<td>1.76</td>
<td>1.25, 2.48</td>
<td>50.6</td>
<td>11</td>
<td>1.29</td>
<td>0.69, 2.40</td>
<td>0%</td>
</tr>
<tr>
<td>Native American</td>
<td>1</td>
<td>0.95</td>
<td>0.57, 1.58</td>
<td>1</td>
<td>0.83</td>
<td>0.56, 1.24</td>
<td>0.56, 1.24</td>
<td>0</td>
</tr>
<tr>
<td>Japanese</td>
<td>1</td>
<td>0.83</td>
<td>0.46, 1.48</td>
<td>1</td>
<td>1.95</td>
<td>0.85, 4.44</td>
<td>0.85, 4.44</td>
<td>0%</td>
</tr>
<tr>
<td>Overall</td>
<td>13</td>
<td>1.54</td>
<td>1.12, 2.12</td>
<td>57.9</td>
<td>13</td>
<td>1.05</td>
<td>0.77, 1.43</td>
<td>0%</td>
</tr>
</tbody>
</table>

* OR, odds ratio; CI, confidence interval.
† $A1A1 + A1A2$ vs. $A2A2$ genotype.
‡ Variability between studies due to heterogeneity rather than chance.
§ $A1A1$ vs. $A1A2 + A2A2$ genotype.
DISCUSSION

This large meta-analysis of mainly case-control studies found a small but significant association of the Taq1A polymorphism with alcohol dependency in both a dominant and a recessive model of gene action. Given the modest effect size found by our meta-analysis, many of the individual studies were obviously underpowered. However, there were substantial variations between studies, particularly in the Caucasian subgroup. The observed heterogeneity could be due to differences in how the samples were selected and screened or to methods of genotyping or interaction with other risk factors.

We tested whether genotype frequencies in the control groups were in agreement with Hardy-Weinberg equilibrium because it has been reported that this is miscalculated in many studies (88), and departure from Hardy-Weinberg equilibrium may point to genotyping error or other biases resulting in heterogeneity and misleading results (89). Exclusion of the three studies with significant deviation from Hardy-Weinberg equilibrium did not account for the heterogeneity or significantly change the pooled estimate. For many studies, although significant deviations were not found, agreement with Hardy-Weinberg equilibrium cannot be implied because there may have been insufficient information to detect a difference.

All of the studies had one or more serious methodological shortcomings: lack of matching for or adequate description of ethnicity of the control group, lack of blinding, inconsistent screening of control groups for alcohol dependence, inadequate description of genotyping methods, and potential variations in case definition due to imprecision of the different diagnostic criteria used. Selection of the control groups was especially problematic and in many studies included convenience samples rather than population-based controls. Population stratification cannot be ruled out because ethnicity was self-reported, and self-reported ancestry has been shown to be unreliable in outbred populations such as in the United States (90). One or more of these factors may have led to the observed heterogeneity in our meta-analysis. It is likely that each of these biases would affect the overall pooled estimate to a different extent, but it is unclear whether they would all work to bias the result in the same direction.

We investigated the impact of including studies with a greater likelihood of bias on the overall estimate by conducting a series of sensitivity analyses. Overall pooled estimates or heterogeneity values did not change markedly when potentially biased studies were excluded; however, heterogeneity was reduced substantially in the Caucasian subgroup and the overall group when the analysis was restricted to studies with ethnically matched controls.

An additional factor that has been cited as a probable cause of heterogeneity between studies is severity of alcohol dependency. We were unable to investigate the impact of severity of alcohol dependency on the pooled estimate because there was no consistent use of the term “severe.” Medical complications, withdrawal symptoms, and Michigan Alcohol Screening Test scores were all used as criteria for defining the cases as severe. Severity of illness may reflect the duration of illness if based on an accumulation of complications and thus be unreliable.

The cumulative meta-analysis showed that, as more studies were published, the pooled odds ratio approached one, suggesting that one reason earlier studies showed strong associations may be chance because of small sample sizes. This finding is in agreement with an investigation of 55 meta-analyses of genetic association studies of various disease outcomes that showed that positive findings of early association studies do not adequately predict establishment of an association (91). Although we made a considerable effort to find published studies, the possibility of publication bias cannot be overlooked. It is difficult to predict the likely effect on the estimate. Most frequently, publication bias is due to preferential publication of favorable results, which tends to overestimate effects or associations; however, because of the polarity of opinion on the role of Taq1A, studies showing no association may not have been suppressed. We did not formally investigate publication bias through the use of funnel plots...
because it is unclear whether the assumptions for their interpretation are valid when observational studies, rather than randomized controlled trials, are pooled (92, 93).

Authors of previous reviews, meta-analyses, and primary studies have presented contrasting findings on the role of Taq1A and alcoholism. Reviews by Noble et al. (7, 48, 94, 95) reported on meta-analyses, mainly in Caucasian populations, and concluded that there is a strong association, particularly among people with “severe” alcohol dependency. These analyses were all based on comparing allele frequencies in people with alcohol dependency and nonalcoholic controls, analogous to the codominant model. This type of analysis tends to produce spurious associations or overinflate p values because of doubling of the sample size. It is also not clear whether, in these reviews, correct methods for pooling frequencies were used, which weights each study appropriately, or whether frequencies were pooled simply by adding them all and treating the data as if they were all from one large study.

A more cautious conclusion was drawn by Gelernter et al. (10), whose meta-analysis of studies published up to 1993 failed to confirm that a strong association was found. They suggested that factors contributing to the heterogeneity were lack of careful screening to exclude problem alcohol use by the control groups and lack of matching for ethnicity rather than the use of simple racial matching.

Although the modest strength of association found in this study is of a similar magnitude to odds ratios reported for meta-analyses of other candidate genes and mental health disorders (96, 97), because of the numerous potential sources of bias in the primary studies, overestimation of the association cannot be ruled out.

While there is convincing evidence for a genetic contribution to alcohol dependence derived from family, twin, and adoption studies, it cannot be explained by a single gene operating under Mendelian laws of inheritance.

Therefore, a single gene predisposing to alcoholism is not anticipated, and the likelihood is that many, of relatively modest influence, interact with environmental factors and operate during a process of development. As such, the relatively small effect identified by this study regarding the A1 allele or another genetic variant linked to it is much more in keeping with the current understanding of the genetic contribution to such complex disorders and behaviors.

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REFERENCES


