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Candidate Genes for Alcohol Dependence: A Review of Genetic Evidence From Human Studies

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FAMILY, TWIN, AND adoption studies have convincingly demonstrated that genes play an important role in the development of alcohol dependence, accounting for approximately 50–60% of the population variance (McGue, 1999). Additionally, patterns of alcohol use seem to be under genetic influence. Twin studies have demonstrated that dimensions of alcohol use, such as quantity of alcohol consumed on a typical drinking occasion, frequency of use, and frequency of intoxication, and alcohol metabolism measures, such as time to peak blood alcohol concentration and rate of elimination, are under substantial genetic influence (Heath, 1995). Furthermore, there is evidence of genetic effects on patterns of alcohol use as early as adolescence, and these effects seem to increase over time (Rose et al., 2001). It is unclear to what extent the genes that influence patterns of alcohol use overlap with those that influence alcohol dependence.

Despite strong evidence for genetic effects contributing to alcoholism susceptibility, detecting the specific genes that increase or decrease the risk for alcoholism has proven difficult. Many factors contribute to the slow progress in isolating the genes involved in drinking behavior. Many genes are thought to contribute to alcoholism susceptibility, and different genes are likely contributing to alcohol dependence in different individuals. Additionally, the environment plays a substantial role in drinking patterns, with nearly half of the variance in drinking patterns and alcohol dependence attributed to environmental factors. Furthermore, these genes and environments probably interact. Data from a Finnish twin study of alcohol use among adolescents demonstrated that the magnitude of genetic influences can vary dramatically between environments, with up to 5-fold differences demonstrated in different environments (Dick et al., 2001). This suggests that some environments may exacerbate the expression of genetic predispositions, whereas others may be protective. Finally, there is substantial phenotypic heterogeneity in the manifestation of alcohol dependence, with alcoholics differing on dimensions such as age of onset of problems, alcohol symptoms, drinking history, and comorbid disorders. Some evidence suggests that genes may be more important in certain subtypes of alcoholics (Cloninger et al., 1981). Other investigators have studied endophenotypes as a means to deal with the substantial heterogeneity involved in alcohol dependence. Endophenotypes are phenotypes that are thought to be intermediaries between a particular disorder and the biological processes that lead to the manifestation of this disorder. For example, brain wave activity, as measured by electroencephalogram (EEG) and event-related potential (ERP), has been studied as an endophenotype for both alcohol dependence and schizophrenia. It is possible that genes act more directly on an endophenotype, as compared with a diagnostic classification, and, therefore, the study of endophenotypes may more efficiently lead to the identification of genes. All of these factors considerably complicate efforts to identify the genes involved in alcohol dependence and to understand the contribution of any specific gene that is identified.

A number of genetic strategies have been used in the study of alcohol dependence. These include both linkage and association studies. Linkage studies involve the ascertainment of families with multiple affected individuals; genotyping of segments of DNA that exhibit variation, called polymorphic markers, is often used to detect chromosomal regions in which affected individuals within a family demonstrate increased sharing of a particular marker allele, suggesting that there may be a gene nearby involved in the disorder. Association studies can use either families or unrelated controls; they test the association between a particular allele at a candidate gene and a specific outcome across families. Association methods typically can detect significant effects over much smaller physical distances as compared with linkage studies. For a more extensive review of the methods used in genetic studies, see Dick and Foroud (2003).

Here we review the evidence for candidate genes that have been implicated in genetic studies of alcohol dependence and related phenotypes, such as quantitative indices of alcohol use, and endophenotypes, such as EEG. This review is not meant to be exhaustive in reporting all candidate genes, but, rather, covers in detail many of the candidate genes currently thought to be most promising.

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We focus primarily on evidence from human studies and supplement these findings with evidence from animal studies. More extensive and thorough reviews of findings from the animal literature are available elsewhere (Belknap and Atkins, 2001; Crabbe et al., 1994; McBride and Li, 1998). Additionally, see the accompanying article by Schumann et al. (2003b) for more detailed information on animal studies.

ALCOHOL DEHYDROGENASE (*ADH*) GENES

The only genes that have been consistently replicated to contribute to alcoholism susceptibility are polymorphisms in the alcohol-metabolizing enzymes: ADH and aldehyde dehydrogenase (ALDH). ADH oxidizes ethanol to acetaldehyde. There are multiple forms of ADH, but the class I isozymes are thought to play the major role in ethanol metabolism (Edenberg and Bosron, 1997). There are three ADH class I isozymes—*ADH1A*, *ADH1B*, and *ADH1C* (formerly called *ADH1*, *ADH2*, and *ADH3*)—that are closely linked on chromosome 4q22. Genetic polymorphisms have been identified in two of the three ADH class I enzymes: *ADH1B* has three different alleles, and *ADH1C* has two different alleles, each of which differs in kinetic properties. The *ADH1B*2* and *ADH1B*3* alleles and the *ADH1C*1* allele code for subunits of proteins which, in vitro, have greater enzymatic activity, suggesting faster conversion of ethanol to acetaldehyde in individuals carrying these alleles. However, the enzymes encoded by the different alleles of the *ADH1B* gene have a more dramatic effect, altering the kinetic constants more than 30-fold (Bosron et al., 1983).

Allele frequencies for the *ADH* genes differ substantially among populations. The *ADH1B*2* allele is virtually nonexistent in blacks and is rare (<5%) in most white populations; however, it predominates in Asian populations (Goedde et al., 1992). The *ADH1B*3* allele is largely limited to populations of African descent, occurring with a frequency of 15–20% (Bosron and Li, 1987), and to some American Indian tribes (Wall et al., 1997). The frequency of the *ADH1C*1* allele is 55–60% in populations of European decent but is >90% in the Han Chinese (Shen et al., 1997).

A number of studies have reported lower frequencies of both the *ADH1B*2* and *ADH1C*1* alleles among alcoholics, as compared with nonalcoholics, in a variety of East Asian populations (Chen et al., 1996b; Higuchi, 1994; Maezawa et al., 1995; Muramatsu et al., 1995; Nakamura et al., 1996; Shen et al., 1997; Thomasson et al., 1991, 1994). A meta-analysis concluded that the *ADH1B*1* allele is associated with an almost 3-fold increase in risk for alcohol dependence as compared with the *ADH1B*2* allele (Whitfield, 1997).

Relatively few studies have found protective effects of the *ADH* genes among non-Asian populations, in large part due to the rarity of the protective alleles among other populations. However, a study of Jewish men living in Israel found that the *ADH1B*2* allele was related to a reduced level of peak weekly alcohol intake (Neumark et al., 1998). Additionally, *ADH1B*2* was associated with lower levels of both alcohol dependence and consumption in men, but not in women, in a European population (Whitfield et al., 1998). A genome-wide screen of alcoholism in the Collaborative Study of the Genetics of Alcoholism (COGA), which is largely a Caucasian population, has found evidence of linkage among unaffected individuals to the chromosome 4 region containing the *ADH* gene cluster (Reich et al., 1998), suggesting that a particular genetic variant may be protective. Additionally, linkage has been reported in this region to the phenotype "maximum number of drinks in a 24-hr period" in the COGA sample (Saccone et al., 2000). Finally, a genome scan comparing the frequency of the alleles at single nucleotide polymorphisms (SNPs) between unrelated control individuals and individuals with histories of illegal substance use and/or dependence found a significant difference for a SNP located near the *ADH* gene cluster. Together, these findings suggest that the effects of the *ADH* genotype on alcohol use (and perhaps other drug use) are not unique to Asian individuals. Rather, it seems that the substantial role of the *ADH1B* locus was detected in the Asian population due to the higher frequency of the protective allele in that group.

There is debate regarding whether the effect of the *ADH1C* genotype is independent of the *ADH1B* genotype or whether the observed differences between alcoholics and controls with the *ADH1C* genotype can be attributed solely to linkage disequilibrium between the *ADH1B* and *ADH1C* genes (Whitfield, 1997). A large investigation of 340 alcoholics and 545 controls in a Han Chinese population was undertaken to resolve this question (Chen et al., 1999). That study concluded that polymorphisms at *ADH1C* exerted no significant effect on the risk for alcohol dependence and attributed previous reports of the effect of *ADH1C* to linkage disequilibrium with *ADH1B*. A subsequent analysis of haplotype frequencies in Taiwanese Chinese alcoholic individuals and controls also concluded that the association with alcoholism was due to *ADH1B* and that associations shown with *ADH1C* were most likely due to linkage disequilibrium with *ADH1B* (Osier et al., 2002).

The *ADH1B*3* allele, found almost exclusively in black populations, seems to be protective against alcohol-related birth defects and, indirectly, against alcoholism in this population. Drinking during pregnancy was associated with lower scores on an infant mental development index, but only in the offspring of African American mothers without an *ADH1B*3* allele. Children of mothers who drank during pregnancy, but who had an *ADH1B*3* allele, scored no differently than children of mothers who did not drink during pregnancy (McCarver et al., 1997). This may illustrate a gene × environment interaction, whereby the deleterious effects of a potentially dangerous in utero environment are enhanced in the presence of a particular genetic

variant. It was proposed that this protective effect was afforded by the more efficient alcohol metabolism provided by the *ADH1B*3* allele. In another sample of young adult African Americans, the *ADH1B*3* allele was significantly associated with a negative family history of alcoholism (Ehlers et al., 2001). Because family history of alcoholism is a strong predictor of alcohol problems, this association suggests that the *ADH1B*3* allele may be protective against the development of alcoholism. Although there was no association between the *ADH1B*3* allele and self-reported history of drinking in the sample, more than half of the small, young sample of 97 individuals did not drink regularly, limiting the power to directly test for this association. Finally, in a sample of individuals of mixed ancestry from the Western Cape Province of South Africa, where fetal alcohol syndrome (FAS) is particularly common, the *ADH1B*2* allele was significantly increased among individuals in a control group, as compared with individuals with FAS and their mothers (Viljoen et al., 2001). These findings suggest that the *ADH1B*2* allele may confer protective effects against FAS in this population. The *ADH1B*3* allele was infrequent and not significantly different between groups in this study.

ALDH *Genes*

After the metabolism of ethanol to acetaldehyde by the ADH enzymes, acetaldehyde is converted to acetate by ALDH. There are nine major gene families coding for human ALDH (Agarwal, 2001). Only class I and class II isozymes (*ALDH1* and *ALDH2*) are thought to be centrally involved in the oxidation of acetaldehyde (Ramchandani et al., 2001). ALDH2, the low-K_m form of ALDH found in mitochondria, is thought to be primarily responsible for acetaldehyde oxidation, because it has high catalytic efficiency, which *ALDH1* does not (Ramchandani et al., 2001). Thus, genetic studies have focused largely on *ALDH2*, which has been localized to chromosome 12 and exhibits notable genetic variation. The enzyme subunit produced by the *ALDH2*2* allele renders enzyme tetramers into which it is incorporated comparatively inactive, and, thus, it acts as a dominant negative allele. Heterozygotes have facial flushing and other aversive symptoms when alcohol is consumed. The *ALDH2*2* allele is nearly absent in whites and blacks, but it is considerably more common in Asians, with up to 43% of the Japanese population carrying this allele (Goedde et al., 1992). Although the other *ALDH* gene families have not been studied to the extent that *ALDH2* has, genetic variation has been found in several additional *ALDH* genes (Agarwal, 2001), raising the possibility that other ALDH genes may also be involved in alcohol consumption and related disorders.

A potential role for the involvement of *ALDH2* in alcohol dependence was detected as early as 1982, when Harada et al. (1982) reported that ALDH2 deficiency was substantially lower among Japanese alcoholics, suggesting that the deficient *ALDH2*2* allele may play a protective role by reducing the risk of alcohol dependence. Subsequent studies have also reported reduced rates of the *ALDH2*2* allele among alcoholics in Asian populations (Chen et al., 1996b; Higuchi, 1994; Lee et al., 2001; Maezawa et al., 1995; Muramatsu et al., 1995; Nakamura et al., 1996; Shen et al., 1997; Thomasson et al., 1991, 1994). *ALDH2*2* confers up to a 10-fold reduction in the risk of alcohol dependence (Thomasson et al., 1994), giving it a stronger protective effect than either the *ADH1B* or *ADH1C* genes (Chen et al., 1996b; Shen et al., 1997). The effect of the *ADH1B* genotype seems to be independent from, and additive to, that of the *ALDH2* locus (Chen et al., 1996b; Nakamura et al., 1996).

γ-*Aminobutyric Acid (GABA) Receptor Genes*

GABA is the major inhibitory neurotransmitter in the human central nervous system. There are two primary types of GABA receptors: $GABA_A$ receptors and $GABA_B$ receptors. The $GABA_A$ receptors act through intrinsic ion channels; the receptor is composed of multiple subunits, designated α, β, γ, δ, ρ, and ϵ, with several identified genes coding for these subunits (Buck, 1996). Most of the $GABA_A$ receptor genes are organized into clusters. Chromosome 4 contains the genes *GABRA2*, *GABRA4*, *GABRB1*, and *GABRG1*; chromosome 5 contains *GABRA1*, *GABRA6*, *GABRB2*, and *GABRG2*; and chromosome 15 contains *GABRA5*, *GABRB3*, and *GABRG3* (National Center for Biotechnology Information, LocusLink). The $GABA_B$ receptors act through G proteins; less is known about their genetic architecture.

Several lines of evidence suggest that GABA is involved in many of the behavioral effects of alcohol, including motor incoordination, anxiolysis, sedation, withdrawal signs, and ethanol preference (Buck, 1996; Grobin et al., 1998). $GABA_A$ receptor agonists tend to potentiate the behavioral effects of alcohol, whereas $GABA_A$ receptor antagonists attenuate these effects. $GABA_A$ receptors have also been implicated in ethanol tolerance and dependence (Grobin et al., 1998). The precise mechanisms by which GABA reception is involved in these actions of ethanol remain unknown (Grobin et al., 1998). The role of $GABA_B$ receptors in the actions of ethanol has not been studied nearly as extensively as that of $GABA_A$ receptors.

A large genome-wide scan of multiplex families segregating for alcohol dependence has yielded evidence of linkage to a chromosomal region containing genes coding for GABA receptors. Long et al. (1998) found evidence of linkage to chromosome 4p, near the β1 GABA receptor gene (*GABRB1*), among a population of Southwestern American Indians. By use of a case-control design, *GABRB1* was also significantly associated with alcohol dependence (Parsian and Zhang, 1999); this association remained significant when the analyses were limited to a smaller sample of alcoholics who were characterized by an

earlier age of onset of problems, antisocial behavior, and high novelty seeking (Cloninger, 1987). Association of the *GABRB1* gene with alcoholism has also been investigated with a family-based design as part of the COGA study (Song et al., 2003). Family-based association tests avoid the potential problems with population stratification that may exist in population-based, case-control designs. Modest linkage disequilibrium was found between *GABRB1* and alcohol dependence, as defined by the COGA criteria of concurrent DSM-III-R and Feighner diagnoses. Additional evidence of association was also observed with the more restrictive ICD-10 criteria for alcohol dependence (Song et al., 2003). A study by Uhl et al. (2001) of SNP differences between drug abusers and controls also found evidence of association with a SNP near the $GABA_A$ receptor gene region implicated in the Long et al. (1998) and COGA studies.

The COGA study has also collected electrophysiological data in families of alcoholics. There is evidence suggesting that EEG and ERP differences exist in families of alcoholics (Porjesz et al., 1998). These findings support the use of these brain wave variations as endophenotypes for the study of the genetics of alcoholism susceptibility. Using these quantitative phenotypes in linkage analyses may be more powerful than using a dichotomous disease status (affected/unaffected), for several reasons. First, information from all family members can be used in the genetic analyses, rather than limiting the analyses to only affected individuals. In addition, some endophenotypes, such as the EEG or ERP, have substantially higher heritability as compared with the dichotomous alcoholism phenotype and so may prove to be a more powerful phenotype for genetic studies. In the COGA study, analysis of EEG phenotypes has provided evidence of linkage and association to chromosome 4 at a marker in the *GABRB1* gene (Porjesz et al., 2002).

There is also evidence of association between $GABA_A$ receptor genes on chromosome 15 and alcohol dependence. In a case-control study of Caucasian alcoholics and controls, an association was reported between *GABRB3* and severe alcoholism, as defined by documented alcohol-induced bodily damage, such as cirrhosis (Noble et al., 1998). Furthermore, there was a significant, progressive decrease in the prevalence of the most frequent allele of *GABRB3* as one considered nonalcoholics, less-severe alcoholics, and severe alcoholics, respectively. Following evidence from a study demonstrating that GABRB3, GABRA5, and GABRG3 were only expressed from the paternal alleles in hybrid mouse A9 cells containing a single human chromosome 15 (Meguro et al., 1997), Edenberg and colleagues tested for paternal transmission of *GABRA5* and *GABRB3* in the COGA sample (Song et al., 2003); they found significant evidence of association of both genes with ICD-10–defined alcoholism when only paternal transmission of alleles was studied.

A number of groups have investigated the role of the $GABA_A$ receptor genes located on chromosome 5, with mixed results. Hsu et al. (1998) found no significant association of *GABRG2* with a case-control association design among the Han Chinese in Taiwan. Subsequently, positive findings were reported for *GABRG2* by using a case-control design among Japanese individuals meeting criteria for DSM-III-R alcohol dependence, when dependence was comorbid with antisocial personality disorder (Loh and Ball, 2000). *GABRG2* has also been linked to alcohol dependence in a Finnish population (Radel et al., 1999). No association was found by Loh and Ball (2000) with the other $GABA_A$ receptor subunit genes located on chromosome 5q: *GABRA6*, *GABRA1*, and *GABRB2*. Sander et al. (1999a) investigated polymorphisms of the chromosome 5 $GABA_A$ receptors in a German population and found an association between *GABRA6* and alcohol dependence with comorbid antisocial personality disorder. No associations were reported for *GABRB2* and *GABRG2*. In a small case-control study, Schuckit et al. (1999) found that a genetic polymorphism in *GABRA6* was associated with a lower level of response to alcohol and higher rates of alcoholism. In a Scottish population, associations were found between *GABRA6* and *GABRB2* and alcohol dependence (Loh et al., 1999). The genes encoding *GABRA6* and *GABRA1* were also investigated by using a family-based design as part of the COGA study (Song et al., 2003); neither of these genes provided evidence of association. Finally, Parsian and Cloninger (1997) compared allele frequencies at the *GABRA1* gene on chromosome 5 and *GABRA3* on chromosome X between unrelated alcoholics and psychiatrically normal controls. No difference was found for *GABRA1*; however, a significant difference was found for *GABRA3*. A small sample of alcoholics and their parents was also genotyped for within-family analyses, and neither gene was significant in the haplotype relative risk analyses, suggesting that the results on chromosome X may be spurious. Notably, neither of the genome-wide screens for alcohol dependence mentioned previously (Long et al., 1998; Reich et al., 1998) found evidence of linkage to the cluster of GABA receptor genes on chromosome 5q.

To our knowledge, only one study has investigated the role of $GABA_B$ receptor genes and alcohol dependence. The $GABA_B$R1 receptor gene was cloned in 1997 and has been localized to chromosome 6p21.3. The frequencies of three polymorphisms in this gene were investigated in a sample of German ICD-10 alcohol-dependent individuals and controls (Sander et al., 1999c). None of the tested variants differed significantly between the groups, although trends toward association were found with alcoholics who also met criteria for ICD-10 dissocial personality disorder.

Evidence for the involvement of the GABA receptors in alcohol consumption can also be found in animal studies by using strains that differ in alcohol preference and other behaviors related to alcohol consumption (Crabbe et al., 1994). Genes related to alcohol-withdrawal severity have been mapped to murine chromosome 11, which contains

the *Gabra6, Gabra1,* and *Gabrg2* $GABA_A$ receptor genes (Buck et al., 1997). A polymorphism has been identified in the *Gabrg2* receptor gene that is correlated with alcohol-withdrawal severity, ethanol-conditioned taste aversion, ethanol-induced motor incoordination, and ethanol-induced hypothermia (Buck and Hood, 1998; Hood and Buck, 2000). Linkage has also been reported on mouse chromosome 2, near the *Gad1* gene, which encodes the enzyme synthesizing GABA (Buck et al., 1997; Hitzemann et al., 1998; Rodriguez et al., 1995). Additionally, quantitative trait loci involved in alcohol consumption, locomotor activation, and alcohol withdrawal severity have been mapped to murine chromosomes 5, 6, 7, and X in the vicinity of $GABA_A$ receptor genes [reviewed in Buck (1996)].

Thus, several converging lines of evidence suggest a role of the GABA receptors in alcohol use and dependence. Table 1 summarizes the genetic studies that have investigated the $GABA_A$ receptor genes in humans; animal studies that found complementary evidence are also included. There is consistent support for the involvement of *GABRB1* on human chromosome 4 and the $GABA_A$ receptor genes on chromosome 15, although only a limited number of studies have investigated these genes. There is less consistent evidence for the involvement of the chromosome 5 $GABA_A$ receptor genes in humans, although animal work performed on homologous chromosomal regions in mice has provided consistent positive evidence. Further studies are needed to elucidate the exact nature of GABA involvement and the specific receptor genes that are involved.

DOPAMINE

Dopamine Receptors

Dopamine has long been believed to play an important role in alcoholism due to its involvement in reward behavior (Wise and Rompre, 1989). It is thought that alcohol's rewarding effects are mediated through the mesolimbic dopamine system. There are five dopamine receptors. The dopamine D2 receptor gene (*DRD2*) is located presynaptically and regulates dopamine release and synthesis. It has been most widely studied in relation to alcohol dependence and has been the focus of substantial controversy. Blum et al. (1990) first reported an association between *DRD2* and alcoholism. Studying 70 brain samples from alcoholics and nonalcoholics, the A1 allele of *DRD2* correctly classified 77% of the alcoholics, and the absence of the A1 allele correctly classified 72% of the nonalcoholics. This association has been replicated by several groups (Amadeo et al.,

Table 1. Summary of Evidence From Genetic Studies of $GABA_A$ Receptor Genes

Chromosome	Gene	Phenotype	Method	Positive reports	Negative reports
4	*GABRB1*	Alcohol dependence	Linkage analysis	Long et al., 1998	
		Alcohol dependence	Case control	Parsian and Zhang, 1999	
		Alcohol dependence	Family based Case control	Song et al., 2003	
		Drug abuse	Genome scan	Uhl et al., 2001	
		EEG	Genome scan	Porjesz et al., 2002	
5	*GABRG2*	Alcohol dependence with ASPD	Case control	Loh and Ball, 2000	
		Alcohol dependence with criminality	Linkage analysis	Radel et al., 1999	
		Alcohol dependence	Case control		Hsu et al., 1998
		Alcohol dependence with ASPD	Case control		Sander et al., 1999a
(11)	*Gabrg2*	Alcohol withdrawal severity	B6, D2, BXD RI	Buck et al., 1997; Buck and Hood, 1998; Hood and Buck, 2000	
	GABRA6	Alcohol dependence with ASPD	Case control	Sander et al., 1999a	
		Lower level of response to alcohol; higher alcoholism	Case control	Schuckit et al., 1999	
		Alcohol dependence; dependence with Korsakoff's syndrome	Case control	Loh et al., 1999	
		Alcohol dependence with ASPD	Case control		Loh and Ball, 2000
		Alcohol dependence	Family based		Song et al., 2003
(11)	*Gabra6*	Alcohol withdrawal severity	BXD RI and F2	Buck et al., 1997	
	GABRA1	Alcohol dependence with ASPD	Case control		Loh and Ball, 2000
		Alcohol dependence	Family based		Song et al., 2003
		Alcohol dependence	Case control		Parsian and Cloninger, 1997
(11)	*Gabra1*	Alcohol withdrawal severity	BXD RI and F2	Buck et al., 1997	
	GABRB2	Alcohol dependence; dependence with Korsakoff's syndrome	Case control	Loh et al., 1999	
		Alcohol dependence with ASPD	Case control		Loh and Ball, 2000
		Alcohol dependence with ASPD	Case control		Sander et al., 1999a
15	*GABRB3*	Severe alcoholism	Case control	Noble et al., 1998	
		ICD-10 alcoholism, paternal transmission	Family based	Song et al., 2003	
	GABRA5	ICD-10 alcoholism, paternal transmission	Family based	Song et al., 2003	
X	*GABRA3*	Alcohol dependence	Case control	Parsian and Cloninger, 1997	
		Alcohol dependence	Family based		Parsian and Cloninger, 1997

The chromosomes for mouse homologs of the corresponding human genes are indicated in parentheses.
ASPD, antisocial personality disorder.

1993; Blum et al., 1991; Comings et al., 1991; Higuchi et al., 1994; Ishiguro et al., 1998; Kono et al., 1997; Neiswanger et al., 1995a; Noble et al., 1994; Parsian et al., 1991). Studies in mice also have found that several responses to alcohol link to a region on murine chromosome 9, containing the gene coding for the dopamine D2 receptor (Crabbe et al., 1994). However, many studies in humans have failed to replicate an association between *DRD2* and alcohol dependence (Arinami et al., 1993; Bolos et al., 1990; Chen et al., 1996a, 2001; Cook et al., 1992; Cruz et al., 1995; Gelernter and Kranzler, 1999; Gelernter et al., 1991; Goldman et al., 1992, 1997; Lee et al., 1999; Lobos and Todd, 1998; Lu et al., 1996; Parsian et al., 2000; Sander et al., 1995, 1999b; Schwab et al., 1991; Suarez et al., 1994; Turner et al., 1992; Waldman et al., 1999).

There has been considerable debate regarding the inconsistent findings for *DRD2*. It has been suggested that several factors contribute to inconsistencies between studies, including the type of alcoholics selected and the type of controls selected for comparison. Blum et al. (1996) have argued that the association exists only among severe alcoholics; however, several groups have stratified the subjects on the basis of severity and still failed to find an association (Arinami et al., 1993; Chen et al., 2001; Edenberg et al., 1998a). Positive associations are also more frequent among groups that screen alcoholics out of their comparison control group, rather than selecting the control group at random. Nonalcoholics have a lower *DRD2* A1 allele frequency than the general population; this suggests that perhaps *DRD2* is not influencing alcoholism per se, but rather a related phenotype that has not been accurately defined (Neiswanger et al., 1995b). Indeed, the authors of the original *DRD2* report have expanded their position on the role of dopamine to suggest that it is involved in what they term *reward deficiency syndrome*, a collection of addictive, impulsive, or compulsive behaviors, including alcoholism, polysubstance abuse, smoking, obesity, attention-deficit disorder, and gambling (Blum et al., 1996).

Another possible reason for inconsistency between studies is that the frequency of the *DRD2* A1 allele, which has been associated with alcoholism, differs substantially among populations (Edenberg et al., 1998a). This creates difficulties with population-based association studies, because controls must be very carefully matched. Because such case-control studies are potentially subject to spurious associations due to population stratification, four family studies of *DRD2*, which avoid this potential confound, are noteworthy. All four of these family-based studies were negative and found no association between the *DRD2* locus and alcoholism (Bolos et al., 1990; Edenberg et al., 1998a; Neiswanger et al., 1995a; Parsian et al., 1991). Interestingly, two of the studies also conducted population-based analyses, in which they found positive associations with *DRD2* that were not subsequently confirmed in the family-based tests (Neiswanger et al., 1995a; Parsian et al., 1991).

Together, these studies suggest that if *DRD2* plays a role in alcohol dependence, it is likely a small one and certainly cannot account for 27% of the genetic diathesis to alcohol dependence, as some of the original authors have suggested (Noble, 2000). Furthermore, it is more likely that perhaps *DRD2* is involved in some alcohol-related phenotype, rather than in alcohol dependence per se.

Other dopamine receptors have also been studied in relation to alcohol dependence, with largely negative results. In three independent samples, no association was found between alcohol dependence and the D3 dopamine receptor gene (*DRD3*; Gorwood et al., 1995). This group recently conducted a follow-up study in a new sample of French alcoholic cases and controls and again found no significant difference in *DRD3* polymorphisms (Gorwood et al., 2001). Additionally, no association was found by using both population-based (Dobashi et al., 1997; Parsian et al., 1997) and family-based (Parsian et al., 1997) designs for the dopamine D3 and D4 receptor genes. Another group found a positive association between a *DRD3* variant and alcohol dependence with delirium, but no associations were found between the D3 or D1 receptor genes and the entire group of alcoholics (Sander et al., 1995). Finally, no association was found between the dopamine D4 receptor gene and alcohol dependence when this was tested in three groups of Taiwanese alcoholics (Chang et al., 1997).

Dopamine Transporter (DAT)

Animal studies have found that chronic alcohol consumption alters *DAT* functioning, suggesting involvement of *DAT* in the development of alcohol tolerance (Yoshimoto et al., 2000). A small number of groups have investigated the role of *DAT* in alcohol dependence. Comparing Japanese alcoholics with controls, there was a trend toward an association between *DAT* and alcohol dependence (Dobashi et al., 1997). Another group tested *DAT* densities among late-onset type 1 alcoholics versus healthy controls; they found *DAT* occupancy ratios to be significantly lower among alcoholics (Repo et al., 1999). However, with a family-based approach, no association was detected between *DAT* and alcoholism, even when alcoholics were stratified on the basis of severity (Franke et al., 1999). Additionally, a study comparing alcohol-dependent individuals who had withdrawal symptoms and healthy controls found no significant difference in a polymorphism in the *DAT* gene among four aboriginal groups and the Han Chinese in Taiwan (Chen et al., 2001). Additional research is needed to clarify any role of *DAT* in alcohol dependence.

SEROTONIN (5-HYDROXYTRYPTAMINE; 5-HT)

5-HT is thought to be involved in many aspects of alcohol consumption, abuse, and dependence. Pharmacological agents that increase 5-HT cause a reduction in alcohol self-administration in both rats and humans (Sellers et al., 1992). The gene encoding the 5-HT transporter (*HTT*) has been mapped to human chromosome 17q11.2 (Gelernter et

al., 1995). It exhibits functional polymorphism, with the shorter allele demonstrating lower transcriptional efficiency. An association between the short allele of *HTT* and anxiety-related personality traits has been reported (Lesch et al., 1996), supporting the idea that *HTT* may play a role in alcohol use via its involvement in harm avoidance (Cloninger, 1987).

A number of studies have investigated the role of *HTT*, with contradictory results (Table 2). In a case-control study of German alcohol-dependent subjects with a history of withdrawal seizure or delirium, the frequency of the short allele was found to be increased among alcoholic subjects (Sander et al., 1997). A subsequent study comparing alcohol-dependent patients and controls also found a higher frequency of the short allele of *HTT* among patients (Hammoumi et al., 1999). Another study found an increased frequency of the short allele among habitually violent type 2 alcoholics, as compared with type 1 alcoholics and normal controls (Hallikainen et al., 1999). A family-based association study also found support for an association between the short allele of *HTT* and alcohol dependence (Lichtermann et al., 2000). However, a number of studies have found positive results supporting the role of the long allele of *HTT* in alcohol use. A small, preliminary study of the level of response to alcohol found that individuals homozygous for the long *HTT* allele had lower levels of response to alcohol and the sample had a higher proportion of alcoholics (Schuckit et al., 1999). A case-control study of alcoholics also found a higher frequency of the long allele among alcoholics as compared with controls; this association became more significant when limited to type II alcoholics (Parsian and Cloninger, 2001). However, no associations remained significant after correcting for multiple testing. A study of children of alcoholics found that children homozygous for the long allele had higher levels of behavioral disinhibition and negative affect and had an earlier age of onset of alcohol use (Twitchell et al., 2001). Finally, a case-control study of Japanese alcoholics found that alcoholics with the long allele had a significantly earlier onset of alcohol dependence than individuals who were homozygous for the short allele (Ishiguro et al., 1999); no association was found between the short allele and a diagnosis of alcoholism or antisocial alcoholism.

Other studies have found no evidence of association with *HTT*. With a family-based design in the COGA project, no support was found for either linkage or association between the *HTT* gene and alcohol dependence, defined by using a variety of diagnostic systems (Edenberg et al., 1998b). In a large case-control study of Japanese alcoholics, no differences in the frequencies of the long or short alleles were found between alcoholic and control subjects; however, alcoholic binge drinkers had a significantly higher frequency of homozygous short alleles than alcoholics who did not binge drink (Matsushita et al., 2001).

A very limited number of studies have also tested polymorphisms in other 5-HT genes. A sample of alcoholics and normal controls was tested for differences in polymorphisms in a variety of the other genes involved in the serotonergic pathway, specifically, variations in tryptophan hydroxylase, the 5-HT receptors *5-HT$_{2A}$* and *5-HT$_{2C}$*, and monoamine oxidase A genes (Parsian and Cloninger, 2001). The allele frequencies of *5-HT$_{2A}$* differed between alcoholics and normal controls, and a monoamine oxidase A gene polymorphism differed between type II alcoholics and controls; however, neither association was significant after correcting for multiple testing (Parsian and Cloninger, 2001). The Schuckit study, previously mentioned in relation to *HTT* (Schuckit et al., 1999), found no evidence of association with the *5-HT$_{2A}$* and *5-HT$_{2C}$* receptor genes with a low level of response to alcohol or a diagnosis of alcoholism. Two recent case-control studies have also investigated the role of the *5-HT$_{1B}$* receptor gene and failed to show an association with *5-HT$_{1B}$* and alcohol dependence (Cigler et al., 2001; Gorwood et al., 2002), even when limited to alcoholism comorbid with antisociality (Gorwood et al., 2002). However, linkage has been reported to mouse chromosome 9 with a variety of alcohol-related phenotypes, such as alcohol consumption and alcohol-induced hypothermia, in a region containing the *5-HT$_{1B}$* receptor gene (Crabbe et al., 1994).

Thus, the role of the 5-HT genes in alcohol use and dependence remains unclear. The role of the *HTT* gene is controversial, with studies reporting association to alcohol dependence and drinking behavior with each of the two alleles. Furthermore, significant findings with subtypes of alcoholism should be interpreted cautiously due to the possibility of spurious association resulting from multiple comparisons and data mining. There is currently little sup-

Table 2. Summary of Evidence From Genetic Studies of *HTT*

Chromosome	Gene	Associated allele	Phenotype	Method	Positive reports	Negative reports
17	*HTT*	Short	Alcohol dependence with withdrawal	Case control	Sander et al., 1997	
		Short	Alcohol dependence	Case control	Hammoumi et al., 1999	
		Short	Violent type 2 alcoholics	Case control	Hallikainen et al., 1999	
		Short	Alcohol dependence	Family based	Lichtermann et al., 2000	
		Long	Level of response to alcohol; alcoholism	Case control	Schuckit et al., 1999	
		Long	Alcohol dependence	Case control		
		Long	Behavioral disinhibition; negative affect	Children of alcoholics	Twitchell et al., 2001	
		Long	Earlier onset alcohol dependence	Case control	Ishiguro et al., 1999	
		Short or long	Alcohol dependence	Family based		Edenberg et al., 1998b
		Short or long	Alcohol dependence	Case control		Matsushita et al., 2001

port for the role of the 5-HT receptor genes and additional genes involved in the serotonergic pathway.

NEUROPEPTIDE Y (NPY)

Relative to genes involved in alcohol metabolism or GABAergic, dopaminergic, and serotonergic function, NPY has only recently been proposed as a candidate gene for alcohol dependence. Studies in selectively bred rats and knock-out mice have provided evidence that genetic variation in NPY contributes to alcohol consumption (Carr et al., 1998; Thiele et al., 1998, 2002). An association of alcohol use and NPY has also been demonstrated in humans: a genetic variant in NPY was associated with higher alcohol consumption in samples ascertained from eastern Finland (Kauhanen et al., 2000). This finding has been replicated in a recent case-control study of European Americans, in which the Pro7 allele of NPY was more than twice as prevalent in two independently collected samples of alcohol-dependent individuals than in controls (Lappalainen et al., 2002). However, another case-control study found that the same genetic variant was significantly lower in alcoholic subjects than in controls (Ilveskoski et al., 2001). An additional case-control study found no association between genetic variants in NPY in male Japanese alcoholics and controls; however, there was a significant difference between alcoholic patients with and without seizures (Okubo and Harada, 2001). These studies differ methodologically in several ways, including the use of quantitative versus qualitative indices of alcohol use/dependence, the use of nonselected and selected samples, and the use of individuals of different ethnicities. However, the contrasting results underscore the need for further research to elucidate the role of this potentially promising gene in human drinking behavior and alcohol dependence. Recently, it has also been demonstrated that NPY plays a role in the human stress response, providing another interesting pathway by which NPY may be involved in alcohol use (Heilig and Thorsell, 2002; Morgan et al., 2000, 2002).

CONCLUSIONS

Although a substantial genetic component for drinking behavior and alcohol dependence has been established, the complexity of alcohol-related traits has made the path to specific gene identification arduous. Despite this, several promising candidate genes are emerging. *ADH1B* and *ALDH2* remain the only genes with definitively established contributions to alcohol dependence. The effects of these genes seem to be additive, with *ALDH2* having a stronger effect. There is also a preliminary suggestion that the *ADH1B*3* allele, found primarily in black populations, and, perhaps, the *ADH1B*2* allele may be protective against adverse alcohol-related outcomes, such as impaired mental ability and FAS.

Evidence from both human and animal studies is accumulating to implicate the $GABA_A$ receptor genes as likely candidates in alcohol use and dependence. There is consistent evidence for the involvement of the $GABA_A$ receptor genes on chromosomes 4 and 15, and there is more mixed evidence for the GABA receptors on chromosome 5, with both positive and negative reports. Only a limited number of studies have investigated the chromosome 4 and 15 $GABA_A$ receptor genes; clearly, continued research is needed on these potentially promising genes.

There has been considerable debate regarding the role of the dopamine D2 receptor in alcohol dependence. The bulk of the current evidence, especially accumulating negative reports from family-based studies, does not seem to support a strong role for *DRD2*; rather, it seems that if *DRD2* is involved in alcohol dependence it is through a broader, as yet undefined, addictive/compulsive phenotype. There is little evidence to support the role of other dopamine receptor genes in alcohol dependence. Modest evidence of association with *DAT* in a small number of studies warrants further research to understand whether *DAT* plays a role in alcohol dependence.

The role of the *HTT* gene in alcohol dependence remains controversial, with several positive reports of association to each of the *HTT* alleles and with other investigators finding no association at all. If *HTT* plays a role in alcohol dependence, it is clearly a complex one, of which we have limited understanding. There is currently no evidence of association with the 5-HT receptor genes that have been studied.

Promising new candidate genes, such as *NPY* (Carr et al., 1998; Thiele et al., 1998, 2002), cyclic adenosine monophosphate/protein kinase A (Heberlein, 2000), and protein kinase C (Bowers et al., 1999), are also emerging from the animal literature, and their involvement in drinking behavior and alcohol dependence in humans warrants further study. Although this review has concentrated on the candidate genes that have received the most study thus far, other candidate genes certainly exist and are only beginning to be characterized. For example, a variant in the enzyme fatty acid amide hydrolase has been recently associated with problematic drug and alcohol use in humans (Sipe et al., 2002). Additionally, a cannabinoid CB1 receptor antagonist recently has been demonstrated to abolish the increase in alcohol intake that occurs in rats after a period of imposed abstinence, suggesting that this receptor may play a role in alcohol relapse (Serra et al., 2002). An analysis of genetic variations of protein tyrosine kinase fyn showed an association of a fyn genotype with alcohol dependence in a group of 430 patients and 365 controls (Schumann et al., 2003). Protein tyrosine kinase fyn has been shown to modulate the activity of the alcohol-sensitive NR2A and NR2B subunits of the NMDA receptor (Cheung and Gurd, 2001), suggesting that it may be important for mediating the glutamatergic effects of ethanol. There is also some suggestion that genetic variation in the glutamate transporter *EAAT2* gene might contribute to vulnerability to risk-taking behav-

ior in alcoholics (Sander et al., 2000). Thus, many other promising genes likely still have yet to be defined.

Until recently, researchers have been limited in their genetic studies by the availability of potential candidate genes in their linked regions. In addition, very little was known of the genetic variation within potential candidate genes. The sequencing of the human genome will make the cataloging of human genes and genetic variation available to all researchers. It is anticipated that this will then rapidly advance the association of candidate genes with alcoholism (see discussion of methodology in the accompanying Schumann article). Once replicable associations are established, it will still remain a challenge to identify the causative genetic variant responsible for the role of that gene in alcohol dependence. In vitro studies will be needed to conclusively demonstrate that a genetic variant is causally related to variation in a gene's product, function, or level of expression. However, identifying these genes and understanding their pathways may lead to early intervention for individuals at risk for alcohol dependence and may lead to the development of more effective treatment of alcoholic patients, making this an important research pursuit.

REFERENCES

Agarwal DP (2001) Genetic polymorphisms of alcohol metabolizing enzymes. Pathol Biol 49:703–709.

Amadeo S, Abbar M, Fourcade ML, Waksman G, Leroux MG, Madex A, Selin M, Champiat J-C, Brethome A, Leclaire Y, Castelnau D, Venisse J-L, Mallet J (1993) D2 dopamine receptor gene and alcoholism. J Psychiatr Res 27:173–179.

Arinami T, Itokawa M, Komiyama T, Mitsushio H, Mori H, Mifune H, Hamaguchi H, Toru M (1993) Association between severity of alcoholism and the A1 allele of the dopamine D2 receptor gene TaqI A RFLP in Japanese. Biol Psychiatry 33:108–114.

Belknap JK, Atkins AL (2001) The replicability of QTLs for murine alcohol preference drinking behavior across eight independent studies. Mamm Genome 12:893–899.

Blum K, Cull JG, Braverman ER, Comings DE (1996) Reward deficiency syndrome. Am Sci 84:132–145.

Blum K, Noble EP, Sheridan PJ, Finley O, Montgomery A, Ritchie T, Ozkaragoz T, Fitch RJ, Sadlack F, Sheffield D (1991) Association of the A1 allele of the D2 dopamine receptor gene with severe alcoholism. Arch Gen Psychiatry 48:409–416.

Blum K, Noble EP, Sheridan PJ, Montgomery A, Ritchie T, Jagadeeswaran P, Nogami H, Briggs AH, Cohn JB (1990) Allelic association of human dopamine D2 receptor gene in alcoholism. JAMA 263:2055–2060.

Bolos AM, Dean M, Lucase-Derse S, Ramsburg M, Brown GL, Goldman D (1990) Population and pedigree studies reveal a lack of association between the D2 receptor gene and alcoholism. JAMA 264:3156–3160.

Bosron WF, Li T-K (1987) Catalytic properties of human liver alcohol dehydrogenase isoenzymes. Enzyme 37:19–28.

Bosron WF, Magnes LJ, Li T-K (1983) Kinetic and electrophoretic properties of native and recombined isoenzymes of human liver alcohol dehydrogenase. Biochemistry 22:1852–1857.

Bowers BJ, Owen EH, Collins AC, Abeliovich A, Tonegawa S, Wehner JM (1999) Decreased ethanol sensitivity and tolerance development in gamma-protein kinase C null mutant mice is dependent on genetic background. Alcohol Clin Exp Res 23:387–397.

Buck KJ (1996) Molecular genetic analysis of the role of GABAergic systems in the behavioral and cellular actions of alcohol. Behav Genet 26:313–323.

Buck KJ, Hood HM (1998) Genetic association of a GABA-A receptor gamma2 subunit variant with severity of acute physiological dependence on alcohol. Mamm Genome 9:975–978.

Buck KJ, Metten P, Belknap JK, Crabbe JC (1997) Quantitative trait loci involved in genetic predisposition to acute alcohol withdrawal in mice. J Neurosci 17:3946–3955.

Carr LG, Foroud T, Bice P, Gobbett T, Ivashina J, Edenberg HJ, Lumeng L, Li T-K (1998) A quantitative trait locus for alcohol consumption in selectively bred rat lines. Alcohol Clin Exp Res 22:884–887.

Chang FM, Ko HC, Lu R-B, Pakstis AJ, Kidd KK (1997) The dopamine D4 receptor gene (DRD4) is not associated with alcoholism in three Taiwanese populations: six polymorphisms tested separately and as haplotypes. Biol Psychiatry 41:394–405.

Chen C-C, Lu R-B, Chen Y-C, Wang M-F, Chang Y-C, Li T-K, Yin S-J (1999) Interaction between the functional polymorphisms of the alcohol-metabolism genes in protection against alcoholism. Am J Hum Genet 65:795–807.

Chen C-H, Chien SH, Hwu HG (1996a) Lack of association between TaqI A1 allele of dopamine D2 receptor gene and alcohol-use disorders in atayal natives of Taiwan. Am J Med Genet 67:488–490.

Chen WJ, Chen C-H, Huang J, Hsu Y-PP, Seow S-V, Chen C-C, Cheng ATA (2001) Genetic polymorphisms of the promoter region of dopamine D2 receptor and dopamine transporter genes and alcoholism among four aboriginal groups and Han Chinese in Taiwan. Psychiatr Genet 11:187–195.

Chen WJ, Loh E-W, Hsu Y-PP, Cheng ATA, Chen C-C, Yu J-M (1996b) Alcohol-metabolising genes and alcoholism among Taiwanese Han men: independent effect of ADH2, ADH3, and ALDH2. Br J Psychiatry 168:762–767.

Cheung HH, Gurd JW (2001) Tyrosine phosphorylation of the N-methyl-D-aspartate receptor by exogenous and postsynaptic density-associated Src-family kinases. J Neurochem 78:524–534.

Cigler T, LaForge KS, McHugh PF, Kapadia SU, Leal SM, Kreek MJ (2001) Novel and previously reported single-nucleotide polymorphisms in the human 5-HT1B receptor gene: no association with cocaine and alcohol abuse or dependence. Am J Med Genet 105:489–497.

Cloninger CR (1987) Neurogenetic adaptive mechanisms in alcoholism. Science 236:410–416.

Cloninger CR, Bohman M, Sigvardsson S (1981) Inheritance of alcohol abuse: cross-fostering analysis of adopted men. Arch Gen Psychiatry 38:861–868.

Comings DE, Comings BG, Muhleman D, Dietz G, Shahbahrami B, Tast D, Knell E, Kocsis P, Baumgarten R, Kovacs BW (1991) The dopamine D2 receptor locus as a modifying gene in neuropsychiatric disorders. JAMA 266:1793–1800.

Cook BL, Wang ZW, Crowe RR, Hauser R, Freimer M (1992) Alcoholism and the D2 receptor gene. Alcohol Clin Exp Res 16:806–809.

Crabbe JC, Belknap JK, Buck KJ (1994) Genetic animal models of alcohol and drug abuse. Science 264:1715–1723.

Cruz C, Camarena B, Mejia JM, Paez F, Eroza V, de la Fuente JR, Kershenobich D, Nicolini H (1995) The dopamine D2 receptor gene TaqI A1 polymorphism and alcoholism in a Mexican population. Arch Med Res 26:421–426.

Dick DM, Foroud T (2003) Overview of genetic strategies to detect genes involved in alcoholism and related traits. Alcohol Res Health, in press.

Dick DM, Rose RJ, Viken RJ, Kaprio J, Koskenvuo M (2001) Exploring gene-environment interactions: socioregional moderation of alcohol use. J Abnorm Psychol 110:625–632.

Dobashi I, Inada T, Hadano K (1997) Alcoholism and gene polymorphisms related to central dopaminergic transmission in the Japanese population. Psychiatr Genet 7:87–91.

Edenberg HJ, Bosron WF (1997) Alcohol dehydrogenases, in *Comprehensive Toxicology (Vol 3: Biotransformation)* (Guengerich FP ed), pp 119–131. Pergamon, New York.

Edenberg HJ, Foroud T, Koller DL, Goate A, Rice J, Van Eerdewegh P, Reich T, Cloninger CR, Nurnberger JI, Kowalczuk M, Wu B, Li T-K, Conneally PM, Tischfield JA, Wu W, Shears S, Crowe R, Hesselbrock V, Schuckit M, Porjesz B, Begleiter H (1998a) A family-based analysis of the association of the dopamine D2 receptor (DRD2) with alcoholism. Alcohol Clin Exp Res 22:505–512.

Edenberg HJ, Reynolds J, Koller DL, Begleiter H, Bucholz KK, Conneally PM, Crowe R, Goate A, Hesselbrock V, Li T-K, Nurnberger JI Jr, Porjesz B, Reich T, Rice J, Schuckit M, Tischfield JA, Foroud T (1998b) A family-based analysis of whether the functional promoter alleles of the serotonin transporter gene HTT affect the risk for alcohol dependence. Alcohol Clin Exp Res 22:1080–1085.

Ehlers CL, Gilder DA, Harris L, Carr LG (2001) Association of the ADH2*3 allele with a negative family history of alcoholism in African American young adults. Alcohol Clin Exp Res 25:1773–1777.

Franke P, Schwab SG, Knapp M, Gansicke M, Delmo C, Zill P, Trixler M, Lichtermann D, Hallmayer J, Wildenauer DB, Maier W (1999) DAT1 gene polymorphism in alcoholism: a family-based association study. Biol Psychiatry 45:652–654.

Gelernter J, Kranzler HR (1999) D2 dopamine receptor gene (DRD2) allele and haplotype frequencies in alcohol dependent and control subjects: no association with phenotype or severity of phenotype. Neuropsychopharmacology 20:640–649.

Gelernter J, O'Malley S, Risch N, Kranzler HR, Krystal J, Merikangas K, Kennedy JL, Kidd KK (1991) No association between an allele at the D2 dopamine receptor gene (DRD2) and alcoholism. JAMA 266:1801–1807.

Gelernter J, Pakstis AJ, Kidd KK (1995) Linkage mapping of serotonin transporter protein gene SLC6A4 on chromosome 17. Hum Genet 95:677–680.

Goedde HW, Agarwal DP, Fritze G, Meier-Tackman D, Singh S, Beckman G, Bhatia K, Chen LZ, Fang B, Lisker R, Paik YK, Rothhammer F, Saha N, Segal B, Srivatava LM, Czeizel A (1992) Distribution of ADH2 and ALDH2 genotypes in different populations. Hum Genet 88:344–346.

Goldman D, Dean M, Brown GL, Bolos AM, Tokola R, Virkkunen M, Linnoila M (1992) D2 dopamine receptor genotype and cerebrospinal fluid homovanillic acid, 5-hydroxyindoleacetic acid and 3-methoxy-4-hydroxyphenylglycol in alcoholics in Finland and the United States. Acta Psychiatr Scand 86:351–357.

Goldman D, Urbanek M, Guenther D, Robin R, Long JC (1997) Linkage and association of a functional DRD2 variant (Ser311Cys) and DRD2 markers to alcoholism, substance abuse and schizophrenia in Southwestern American Indians. Am J Med Genet 74:386–394.

Gorwood P, Aissi F, Batel P, Ades J, Cohen-Salmon C, Hamon M, Boni C, Lanfumey L (2002) Reappraisal of the serotonin 5-HT1B receptor gene in alcoholism: of mice and men. Brain Res Bull 57:104–107.

Gorwood P, Limoson F, Batel P, Duaux E, Gouya L, Ades J (2001) The genetics of addiction: alcohol-dependence and D3 dopamine receptor gene. Pathol Biol 49:710–717.

Gorwood P, Martres MP, Ades J, Sokoloff P, Noble EP, Geijer T, Blum K, Neiman J, Jonsson E, Feingold J, Schwartz, JC (1995) Lack of association between alcohol dependence and D3 dopamine receptor gene in three independent samples. Am J Med Genet 60:529–531.

Grobin AC, Matthews DB, Devaud LL, Morrow AL (1998) The role of GABA-A receptors in the acute and chronic effects of ethanol. Psychopharmacology 139:2–19.

Hallikainen T, Saito T, Lachman HM, Volavka J, Pohjalainen T, Ryynanen OP, Kauhanen J, Syvalahti E, Hietala J, Tiihonen J (1999) Association between low activity serotonin transporter promoter genotype and early onset alcoholism with habitual impulsive violent behavior. Mol Psychiatry 4:385–388.

Hammoumi S, Payen A, Favre J-D, Balmes J-L, Benard J-Y, Husson M, Ferrand J-P, Martin J-P, Daoust M (1999) Does the short variant of the serotonin transporter linked polymorphic region constitute a marker of alcohol dependence? Alcohol 17:107–112.

Harada S, Agarwal DP, Goedde HW, Tagaki S, Ishikawa B (1982) Possible protective role against alcoholism for aldehyde dehydrogenase isozyme deficiency in Japan. Lancet 2:827.

Heath AC (1995) Genetic influences on drinking behavior in humans, in *The Genetics of Alcoholism* (Begleiter H, Kissin B eds), pp 82–121. Oxford University Press, New York.

Heberlein U (2000) Genetics of alcohol-induced behaviors in Drosophila. Alcohol Res Health 24:185–188.

Heilig M, Thorsell A (2002) Brain neuropeptide Y (NPY) in stress and alcohol dependence. Rev Neurosci 13:85–94.

Higuchi S (1994) Polymorphisms of ethanol metabolizing enzyme genes and alcoholism. Alcohol Alcohol 2:19–34.

Higuchi S, Muramatsu T, Murayama M, Hayashida M (1994) Association of structural polymorphism of the dopamine D2 receptor gene and alcoholism. Biochem Biophys Res Commun 204:1199–1205.

Hitzemann R, Cipp L, Demarest K, Mahjubi E, McCaughran J Jr (1998) Genetics of ethanol-induced locomotor activation: detection of QTLs in a C57BL/6J × DBA/2J F2 intercross. Mamm Genome 9:956–962.

Hood HM, Buck KJ (2000) Allelic variation in the GABA A receptor gamma2 subunit is associated with genetic susceptibility to ethanol-induced motor incoordination and hypothermia, conditioned taste aversion, and withdrawal in BXD/Ty recombinant inbred mice. Alcohol Clin Exp Res 24:1327–1334.

Hsu Y-PP, Seow S-V, Loh E-W, Wang Y-C, Chen C-C, Yu J-M, Cheng ATA (1998) Search for mutations near the alternatively spliced 8-amino-acid exon in the GABA-A receptor gamma 2 subunit gene and lack of allelic association with alcoholism among four aboriginal groups and Han Chinese in Taiwan. Mol Brain Res 56:284–286.

Ilveskoski E, Kajander OA, Lehtimaki T, Kunnas T, Karhunen PJ, Heinala P, Virkkunen M, Alho H (2001) Association of neuropeptide Y polymorphism with the occurrence of type 1 and type 2 alcoholism. Alcohol Clin Exp Res 25:1420–1422.

Ishiguro H, Arinami T, Akazawa S, Enomoto M, Mitushio H, Fujishiro H, Tada K, Akimoto Y, Mifune H, Shioduka S, Hamaguchi H, Toru M, Shibuya H (1998) Association study between the −141C Ins/Del and TaqI A polymorphisms of the dopamine D2 receptor gene and alcoholism. Alcohol Clin Exp Res 22:845–848.

Ishiguro H, Saito T, Akazawa S, Mitushio H, Tada K, Enomoto M, Mifune H, Toru M, Shibuya H, Arinami T (1999) Association between drinking-related antisocial behavior and a polymorphism in the serotonin transporter gene in a Japanese population. Alcohol Clin Exp Res 23:1281–1284.

Kauhanen J, Karvonen MK, Pesonen U, Koulu M, Tuomainen T-P, Uusitupa MIJ, Salonen JT (2000) Neuropeptide Y polymorphism and alcohol consumption in middle-aged men. Am J Med Genet 93:117–121.

Kono Y, Yoneda H, Sakai T, Nonomura Y, Inayama Y, Koh J, Sakai J, Inada Y, Imamichi H, Asaba H (1997) Association between early-onset alcoholism and the dopamine D2 receptor gene. Am J Med Genet 74:179–182.

Lappalainen J, Kranzler HR, Malison R, Price L, Van Dyck C, Rosenheck RA, Cramer J, Southwick S, Charney D, Krystal J, Gelernter J (2002) A functional neuropeptide Y Leu7Pro polymorphism associated with alcohol dependence in a large population sample from the United States. Arch Gen Psychiatry 59:825–831.

Lee HC, Lee H-S, Jung S-H, Yi SY, Jung HK, Yoon J-H, Kim CY (2001) Association between polymorphisms of ethanol-metabolizing enzymes and susceptibility to alcoholic cirrhosis in a Korean male population. J Korean Med Sci 16:745–750.

Lee JF, Lu RB, Ko HC, Chang FM, Yin S-J, Pakstis AJ, Kidd KK (1999) No association between DRD2 locus and alcoholism after controlling the ADH and ALDH genotypes in Chinese Han population. Alcohol Clin Exp Res 23:592–599.

Lesch K-P, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Muller CR, Hamer DH, Murphy DL (1996) Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 274:1527–1531.

Lichtermann D, Hranilovic D, Trixler M, Franke P, Jernej B, Delmo C, Knapp M, Schwab S, Maier W, Wildenauer DB (2000) Support for allelic association of a polymorphic site in the promoter region of the serotonin transporter gene with risk for alcohol dependence. Am J Psychiatry 12:2045–2047.

Lobos EA, Todd RD (1998) Association analysis in an evolutionary context: cladistic analysis of the DRD2 locus to test for association with alcoholism. Am J Med Genet 81:411–419.

Loh E-W, Ball D (2000) Role of the GABA-A B2, GABA-A alpha 6, GABA-A alpha 1, and GABA-A gamma 2 receptor subunit genes cluster in drug responses and the development of alcohol dependence. Neurochem In 37:413–423.

Loh E-W, Smith I, Murray R, McLaughlin M, McNulty S, Ball D (1999) Association between variants at the GABA-A B2, GABA-A A6, and GABA-A G2 gene cluster and alcohol dependence in a Scottish population. Mol Psychiatry 4:539–544.

Long JC, Knowler WC, Hanson RL, Robin RW, Urbanek M, Moore E, Bennett PH, Goldman D (1998) Evidence for genetic linkage to alcohol dependence on chromosomes 4 and 11 from an autosome-wide scan in an American Indian population. Am J Med Genet 81:216–221.

Lu R-B, Ko HC, Chang FM, Castiglione CM, Schoolfield G, Pakstis AJ, Kidd JR, Kidd KK (1996) No association between alcoholism and multiple polymorphisms at the dopamine D2 receptor gene (DRD2) in three distinct Taiwanese populations. Biol Psychiatry 39:419–429.

Maezawa Y, Yamauchi M, Suzuki TG, Sakurai S (1995) Alcohol-metabolizing enzyme polymorphisms and alcoholism in Japan. Alcohol Clin Exp Res 19:951–954.

Matsushita S, Yoshino A, Murayama M, Kimura M, Muramatsu T, Higuchi S (2001) Association study of serotonin transporter gene regulatory region polymorphism and alcoholism. Am J Med Genet 105:446–450.

McBride WJ, Li T-K (1998) Animal models of alcoholism: neurobiology of high alcohol-drinking behavior in rodents. Crit Rev Neurobiol 12: 339–369.

McCarver DG, Thomasson HR, Martier SS, Sokol RJ, Li T-K (1997) Alcohol dehydrogenase-2*3 allele protects against alcohol-related birth defects among African Americans. J Pharmacol Exp Ther 283:1095–1101.

McGue M (1999) The behavioral genetics of alcoholism. Curr Dir Psychol Sci 8:109–115.

Meguro M, Mitsuya K, Sui H, Shigenami K, Kugoh H, Nakao M, Oshimura M (1997) Evidence for uniparental, paternal expression of the human GABAA receptor subunit genes, using microcell-mediated chromosome transfer. Hum Mol Genet 6:2127–2133.

Morgan CA III, Rasmusson A, Wang S, Hoyt G, Hauger RL, Hazlett G (2002) Neuropeptide-Y, cortisol, and subjective distress in humans exposed to acute stress: replication and extension of previous report. Biol Psychiatry 52:136–142.

Morgan CA III, Wang S, Southwick SM, Rasmusson A, Hazlett G, Hauger RL, Charney DS (2000) Plasma neuropeptide-Y concentrations in humans exposed to military survival training. Biol Psychiatry 47:902–909.

Muramatsu T, Wang ZC, Fang YR, Hu KB, Yan H, Yamada K, Higuchi S, Harada S, Kono H (1995) Alcohol and aldehyde dehydrogenase genotypes and drinking behavior of Chinese living in Shanghai. Hum Genet 96:151–154.

Nakamura K, Iwahashi K, Matsuo Y, Miyatake R, Ichikawa Y, Suwaki H (1996) Characteristics of Japanese alcoholics with the atypical aldehyde dehydrogenase 2*2. I. A comparison of the genotypes of ALDH2, ADH2, ADH3, and cytochrome P-4502E1 between alcoholics and non-alcoholics. Alcohol Clin Exp Res 20:52–55.

Neiswanger K, Hill SY, Kaplan BB (1995a) Association and linkage studies of the TAQI A1 allele at the dopamine D2 receptor gene in samples of female and male alcoholics. Am J Med Genet 60:267–271.

Neiswanger K, Kaplan BB, Hill SY (1995b) What can the DRD2/alcoholism story teach us about association studies in psychiatric genetics? Am J Med Genet 60:272–275.

Neumark YD, Friedlander Y, Thomasson HR, Li T-K (1998) Association of the ADH2*2 allele with reduced ethanol consumption in Jewish men in Israel: a pilot study. J Stud Alcohol 59:133–139.

Noble EP (2000) Addiction and its reward process through polymorphisms of the D2 dopamine receptor gene: a review. Eur Psychiatry 15:79–89.

Noble EP, Syndulko K, Fitch RJ, Ritchie T, Bohlman MC, Guth P, Sheridan PJ, Montgomery A, Heinzmann C, Sparkes RS (1994) D2 dopamine receptor TaqI A alleles in medically ill alcoholic and nonalcoholic patients. Alcohol Alcohol 29:729–744.

Noble EP, Zhang X, Ritchie T, Lawford BR, Grosser SC, Young RM, Sparkes RS (1998) D2 dopamine receptor and GABA-A receptor B3 subunit genes and alcoholism. Psychiatry Res 81:133–147.

Okubo T, Harada S (2001) Polymorphism of the neuropeptide Y gene: an association study with alcohol withdrawal. Alcohol Clin Exp Res 25: 59S–62S.

Osier MV, Pakstis AJ, Soodyall H, Comas D, Goldman D, Odunsi A, Okonofua F, Parnas J, Schulz LO, Bertranpetit J, Bonne-Tamir B, Lu R-B, Kidd JR, Kidd KK (2002) A global perspective on genetic variation at the ADH genes reveals unusual patterns of linkage disequilibrium and diversity. Am J Hum Genet 71:84–99.

Parsian A, Chakraverty S, Fisher L, Cloninger CR (1997) No association between polymorphisms in the human dopamine D3 and D4 receptors genes and alcoholism. Am J Med Genet 74:281–285.

Parsian A, Cloninger CR (1997) Human GABA-A receptor alpha 1 and alpha 3 subunits genes and alcoholism. Alcohol Clin Exp Res 21:430–433.

Parsian A, Cloninger CR (2001) Serotonergic pathway genes and subtypes of alcoholism: association studies. Psychiatr Genet 11:89–94.

Parsian A, Cloninger CR, Zhang Z-H (2000) Functional variant in the DRD2 receptor promoter region and subtypes of alcoholism. Am J Med Genet 96:407–411.

Parsian A, Todd RD, Devor EJ, O'Malley KL, Suarex BK, Reich T, Cloninger CR (1991) Alcoholism and alleles of the human D2 dopamine receptor locus. Arch Gen Psychiatry 48:655–663.

Parsian A, Zhang Z-H (1999) Human chromosomes 11p15 and 4p12 and alcohol dependence: possible association with the GABRB1 gene. Am J Med Genet 88:533–538.

Porjesz B, Almasy L, Edenberg HJ, Wang K, Chorlian DB, Foroud T, Goate A, Rice J, O'Connor SJ, Rohrbaugh J, Kuperman S, Bauer LO, Crowe R, Schuckit M, Hesselbrock V, Conneally PM, Tischfield JA, Li T-K, Reich T, Begleiter H (2002) Linkage disequilibrium between the beta frequency of the human EEG and a GABAA receptor gene locus. Proc Natl Acad Sci USA 99:3729–3733.

Porjesz B, Begleiter H, Reich T, Van Eerdewegh P, Edenberg HJ, Foroud T, Goate A, Litke A, Chorlian DB, Stimus A, Rice J, Blangero J, Almasy L, Sorbell J, Bauer LO, Kuperman S, O'Connor SJ, Rohrbaugh J (1998) Amplitude of visual P3 event-related potential as a phenotypic marker for a predisposition to alcoholism: preliminary results from the COGA project. Alcohol Clin Exp Res 22:1317–1323.

Radel M, Vallejo RL, Long JC, Goldman D (1999) Sib-pair linkage analysis of GABRG2 to alcohol dependence (abstract). Alcohol Clin Exp Res 23:59A.

Ramchandani VA, Bosron WF, Li T-K (2001) Research advances in ethanol metabolism. Pathol Biol 49:676–682.

Reich T, Edenberg HJ, Goate A, Williams JT, Rice JP, Van Eerdewegh P, Foroud T, Hesselbrock V, Schuckit MA, Bucholz K, Porjesz B, Li T-K, Conneally PM, Nurnberger JI, Tischfield JA, Crowe RR, Cloninger CR, Wu W, Shears S, Carr K, Crose C, Willig C, Begleiter H (1998) Genome-wide search for genes affecting the risk for alcohol dependence. Am J Med Genet 81:207–215.

Repo E, Kuikka JT, Bergstrom KA, Karhu J, Hiltunen K, Hiihonen J (1999) Dopamine transporter and D2 receptor density in late-onset alcoholism. Psychopharmacology 147:314–318.

Rodriguez LA, Plomin R, Blizzard DA, Jones BC, McClearn GE (1995) Alcohol acceptance, preference and sensitivity in mice: quantitative trait

loci mapping analyses using BXD recombinant inbred strains. Alcohol Clin Exp Res 19:367–373.

Rose RJ, Dick DM, Viken RJ, Kaprio J (2001) Gene-environment interaction in patterns of adolescent drinking: regional residency moderates longitudinal influences on alcohol use. Alcohol Clin Exp Res 25:637–643.

Saccone N, Kwon JM, Corbett J, Goate A, Rochberg N, Edenberg HJ, Foroud T, Li T-K, Begleiter H, Reich T, Rice JP (2000) A genome screen of maximum number of drinks as an alcoholism phenotype. Neuropsychiatr Genet 96:632–637.

Sander T, Ball D, Murray R, Patel J, Samochowiec J, Winterer G, Rommelspacher H, Schmidt LG, Loh E-W (1999a) Association analysis of sequence variants of the GABAA A6, B2, and G2 gene cluster and alcohol dependence. Alcohol Clin Exp Res 23:427–431.

Sander T, Harms H, Lesch K-P, Dufeu P, Kuhn S, Hoehe M, Rommelspacher H, Schmidt LG (1997) Association analysis of a regulatory variation of the serotonin transporter gene with severe alcohol dependence. Alcohol Clin Exp Res 21:1356–1359.

Sander T, Harms H, Podschus J, Finckh U, Nickel B, Rolfs A, Rommelspacher H, Schmidt LG (1995) Dopamine D1, D2, and D3 receptor genes in alcohol dependence. Psychiatr Genet 5:171–176.

Sander T, Ladehoff M, Samochowiec J, Finckh U, Rommelspacher H, Schmidt LG (1999b) Lack of an allelic association between polymorphisms of the dopamine D2 receptor gene and alcohol dependence in the German population. Alcohol Clin Exp Res 23:578–581.

Sander T, Ostapowicz A, Samochowiec J, Smolka M, Winterer G, Schmidt LG (2000) Genetic variation of the glutamate transporter EAAT2 gene and vulnerability to alcohol dependence. Psychiatr Genet 10:103–107.

Sander T, Samochowiec J, Ladehoff M, Smolka M, Peters C, Riess O, Rommelspacher H, Schmidt LG (1999c) Association analysis of exonic variants of the gene encoding the GABA-B receptor and alcohol dependence. Psychiatr Genet 9:69–73.

Schuckit M, Mazzanti C, Smith TL, Ahmed U, Radel M, Iwata N, Goldman D (1999) Selective genotyping for the role of 5-HT2A, 5-HT2C, and GABA alpha6 receptors and the serotonin transporter in the level of response to alcohol: a pilot study. Biol Psychiatry 45:647–651.

Schumann G, Spanagel R, Mann K (2003b) Candidate genes for alcohol dependence: animal studies. Alcohol Clin Exp Res, in press.

Schwab S, Soyka M, Niederecker M, Sackenheil M, Scherer J, Wilderauer DB (1991) Allelic association of human dopamine D2-receptor DNA polymorphism ruled out in 45 alcoholics. Am J Hum Genet (Suppl) 49:203.

Sellers EM, Higgings GA, Sobell MB (1992) 5-HT and alcohol abuse. Trends Pharmacol Sci 13:69–75.

Serra S, Brunetti G, Pani M, Vacca G, Carai MAM, Gessa GL, Colombo G (2002) Blockade by the cannabinoid CB1 receptor antagonist, SR 141716, of alcohol deprivation effect in alcohol-preferring rats. Eur J Pharmacol 443:95–97.

Shen YC, Fan JH, Edenberg HJ, Li T-K, Cui YH, Wang YF, Tian CH, Zhou CF, Zhou RL, Wang J, Zhao ZL, Xia GY (1997) Polymorphism of ADH and ALDH genes among four ethnic groups in China and effects upon the risk for alcoholism. Alcohol Clin Exp Res 21:1272–1277.

Sipe JC, Chiang K, Gerber AL, Beutler E, Cravatt BF (2002) A missense mutation in human fatty acid amide hydrolase associated with problem drug use. Proc Natl Acad Sci USA 99:8394–8399.

Song J, Koller DL, Foroud T, Rice J, Nurnberger JI Jr, Begleiter H, Porjesz B, Smith TL, Schuckit M, Edenberg HJ (2003) Association of GABA-A receptors and alcohol dependence and the effects of genetic imprinting. Am J Med Genet 117B:39-45.

Suarez BK, Parsian A, Hampe CL, Todd RD, Reich T, Cloninger CR (1994) Linkage disequilibria at the D2 dopamine receptor locus (DRD2) in alcoholics and controls. Genomics 19:12–20.

Thiele TE, Koh MT, Pedrazzini T (2002) Voluntary alcohol consumption is controlled via the neuropeptide Y Y1 receptor. J Neurosci 22:1–6.

Thiele TE, Marsh DJ, Marie LS, Bernstein IL, Palmiter RD (1998) Ethanol consumption and resistance are inversely related to neuropeptide Y levels. Nature 396:366–369.

Thomasson HR, Crabb DW, Edenberg HJ, Li T-K, Hwu HG, Chen C-C, Yeh EK, Yin S-J (1994) Low frequency of the ADH2*2 allele among Atayal natives of Taiwan with alcohol use disorders. Alcohol Clin Exp Res 18:640–643.

Thomasson HR, Edenberg HJ, Crabb DW, Mai X-L, Jerome RE, Li T-K, Wang S-P, Lin Y-T, Lu R-B, Yin S-J (1991) Alcohol and aldehyde dehydrogenase genotypes and alcoholism in Chinese men. Am J Hum Genet 48:677–681.

Turner E, Ewing J, Shilling P, Smith TL, Irwin M, Schuckit M, Kelsoe JR (1992) Lack of association between an RFLP near the D2 dopamine receptor gene and severe alcoholism. Biol Psychiatry 31:285–290.

Twitchell GR, Hanna GL, Cook EH, Stoltenberg SF, Fitzgerald HE, Zucker RA (2001) Serotonin transporter promoter polymorphism genotype is associated with behavioral disinhibition and negative affect in children of alcoholics. Alcohol Clin Exp Res 25:953–959.

Uhl GR, Elmer GI, La Buda MC, Pickens RW (1995) Genetic influences in drug abuse, in *Psychopharmacology: The Fourth Generation of Progress* (Bloom FE, Kupfer DJ eds), pp 1793–1806. Raven Press, New York.

Uhl GR, Liu Q-R, Walther D, Hess J, Naiman D (2001) Polysubstance abuse-vulnerability genes: genome scans for association, using 1004 subjects and 1494 single-nucleotide polymorphisms. Am J Hum Genet 69:1290–1300.

Viljoen DL, Carr LG, Foroud T, Brooke L, Ramsay M, Li T-K (2001) Alcohol dehydrogenase-2*2 allele is associated with decreased prevalence of fetal alcohol syndrome in the mixed ancestry population of the Western Cape Province, South Africa. Alcohol Clin Exp Res 25:1719–1722.

Waldman ID, Robinson BF, Rhee SH (1999) A logistic regression extension of the transmission disequilibrium test for continuous traits: application to linkage disequilibrium between alcoholism and the candidate genes DRD2 and ADH3. Genet Epidemiol (Suppl 1) 17:S379–S384.

Wall TL, Garcia-Andrade C, Thomasson HR, Carr LG, Ehlers CL (1997) Alcohol dehydrogenase polymorphisms in Native Americans: identification of the ADH2*3 allele. Alcohol Alcohol 32:129–132.

Whitfield JB (1997) Meta-analysis of the effects of alcohol dehydrogenase genotype on alcohol dependence and alcoholic liver disease. Alcohol Alcohol 32:613–619.

Whitfield JB, Nightingale BN, Bucholz KK, Madden PAF, Heath AC, Martin NG (1998) ADH genotypes and alcohol use and dependence in Europeans. Alcohol Clin Exp Res 22:1463–1469.

Wise RA, Rompre P-P (1989) Brain dopamine and reward. Annu Rev Psychol 40:191–225.

Yoshimoto K, Ueda S, Nishi M, Yang Y, Matsushita H, Takeuchi Y, Kato B, Kawai Y, Noritake K, Kaneda S, Sorimachi Y, Yasuhara M (2000) Changes in dopamine transporter and c-Fos expression in the nucleus accumbens of alcohol-tolerant rats. Alcohol Clin Exp Res 24:361–365.