

Genetics of Alcohol Use in Humans: An Overview

Jayanta Kumar Nayak¹, B. N. Sarkar¹, P. K. Das² and V. R. Rao¹

1. Anthropological Survey of India, Kolkata, India,

2. Department of Anthropology, Utkal University, Bhubaneswar, India

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ABSTRACT Alcoholism is an extremely complex disease for which no generally accepted definition exists. There is a complex interaction between the socio-environmental context, the individual at risk, and the availability of alcohol. The result of family, twin and adoption studies suggest a significant genetic predisposition to the disease. Identifying novel genetic risk factors for common diseases is a global challenge in the post genomic era. Recent molecular genetic research into the causes of alcoholism has drawn attention to the potential role of alcohol and acetaldehyde metabolizing enzymes. Functional polymorphisms have been observed at various genes encoding these enzyme proteins that act as one of the biological determinants significantly influencing drinking behavior and the development of alcoholism and alcohol-induced organ damage. Most ethanol elimination occurs by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) systems via oxidation of ethanol to acetaldehyde and acetic acid. However, the legacy of alcoholism among certain ethnic groups suggests that genetic factors can increase an individual's vulnerability for this disease. An association study in patient cohorts and controls, from large populations involving whole genome scans, is the preferred approach for complex traits. To understand the molecular epidemiology and role of cofactors in alcoholism the standard phenotype-genotype correlation may be a useful tool. The present paper reviews various aspects of alcoholism including both the behavioural and molecular etiologies.

INTRODUCTION

A necessary condition for the development of alcoholism is the availability of alcohol. Humans have probably been alcohol users from the pre-historical times. After the introduction of agriculture (between 10,000 to 5,000 B.C.), systematic alcohol production became possible by fermentation of barley, honey, milk and grapes by various populations. At that time, alcohol was mainly used as a food because of its vitamin and mineral content. The preserving qualities of alcoholic solutions enabled long-term storage of food, an important property in the early stages of civilization. Presumably, an essential motivation for utilizing the psychotropic effects of alcohol was to cope with existential fear, which certainly was omnipresent in 'primitive' societies. This might also have been the cause for early integration of alcohol use in religious rites. Invention of the method of distillation of alcohol around 1000 AD made the production of concentrated alcoholic beverages possible.

During the thirteenth and fourteenth centuries this technique spread over Europe and paved the way for alcohol abuse and the development of alcoholism.

Alcoholism is thought to be a multifactorial disease with complex mode of inheritance in addition to the influence of psychological and social factors (WHO 1993). Many family, adoptee and twin-based studies in relation to alcoholism revealed hereditary factors as important determinants of alcoholism. Genetics and pharmacokinetics of alcohol determine variations of alcohol metabolism among alcohol users and therefore, influence alcohol drinking behavior and risk of alcoholism. As per the definition proposed by National Council on Alcoholism and Drug Dependence (NACDD) and the American Society of Addiction Medicine (ASAM), alcoholism is a primary, chronic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is well recognized that the primary alcohol, ethanol, can be absorbed unchanged along the whole length of the digestive tract, that absorption takes place rapidly from the stomach (about 20%), and most rapidly from the small gut (about 80%). The rate of absorption after drinking is affected by several factors, for example the volume, concentration (10 – 20% solutions are most rapidly absorbed) and nature of the alcoholic drink, the presence or

Address for correspondence: Dr V. R. Rao,
Director-in-Charge, Anthropological Survey of India,
Government of India, 27, Jawaharlal Nehru Road,
Kolkata 700 016, West Bengal, India
Telephone: 91 33 2286 1796, 2286 1781
Fax: 91 33 2286 1799
E-mail: drraovr@yahoo.com

absence of food in the stomach, rate of gastric emptying, pylorospasm, permeability of the gastric and intestinal tissues, individual variations. After absorption into the blood stream, alcohol is distributed quickly throughout the total body water (Pawan 1972). The disease is often progressive and fatal. It affects so many vital organs of our body like liver and heart. It is characterized by continuous or periodic impaired control over drinking, pre-occupation with the drug alcohol, use of alcohol despite adverse consequences, and distortions in thinking, most notably denial. Alcoholism is a common etiologically complex disorder (Kessler et al. 1994) involving complex gene-with-gene and gene with environmental interactions (Chen et al. 1999). The genes underlying human alcohol metabolism

provides a rare example of how allelic variations contribute to a complex disease through intervening physiology and behavior. Ethanol elimination occurs mostly by alcohol dehydrogenase (ADH) (Eriksson et al. 2001) and aldehyde dehydrogenase (ALDH) systems via oxidation of ethanol to acetaldehyde and acetic acid (Bosron and Li 1986). Most of the metabolism of alcohol and aldehyde is carried out in the liver, although extra-hepatic metabolism has also been demonstrated in the stomach, gut and upper aerodigestive tract (Wight and Ogden, 1998) including some potential metabolism due to oral microflora in the oral cavity (Homann et al. 1997, 2000 and Muto et al. 2000). Pawan (1972) clearly sketched the pathways of alcohol metabolism in man (Fig. 1). Genetic variation in alcoholic liability can be

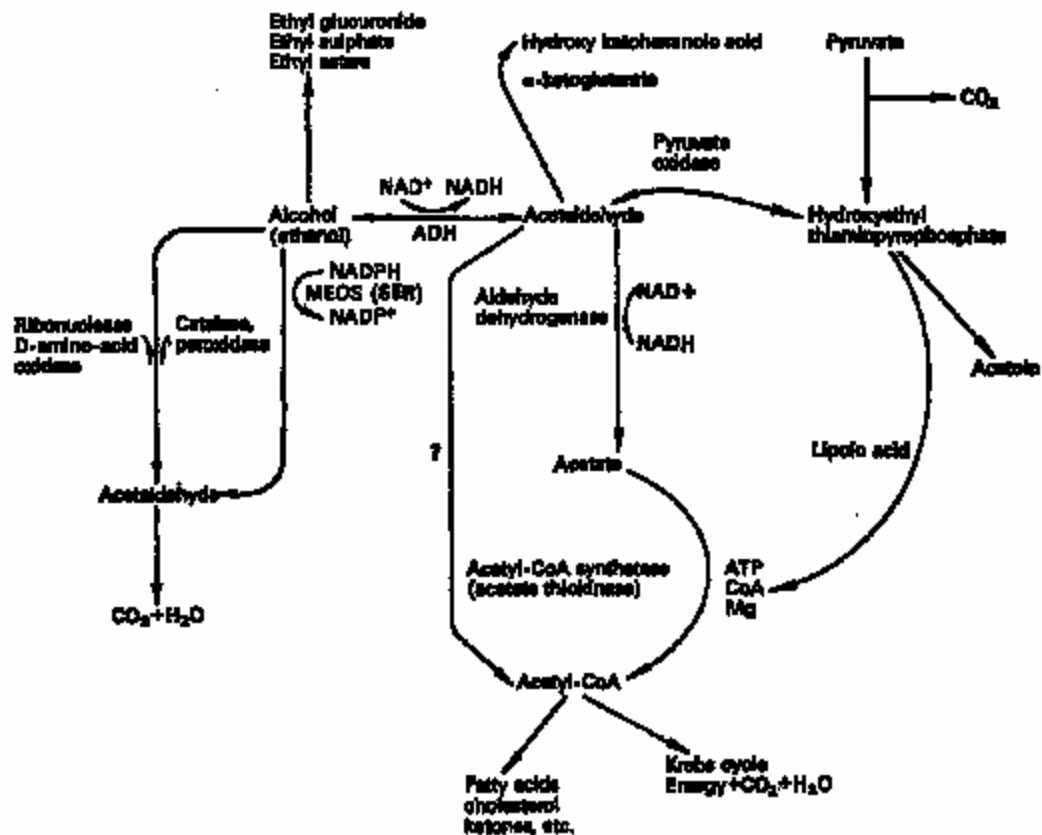


Fig. 1. Pathways of alcohol (ethanol) metabolism in man. ADH: Alcohol Dehydrogenase; MEOS: Microsomal Ethanol Oxidizing System; SER, Smooth Endoplasmic Reticulum.

used to investigate some of the underlying mechanisms, which may aid in identifying individuals at increased risk and provide information about systems involved in the health consequences of alcohol dependence. In addition, genetic variations are being investigated with respect to treatment with the goal of personalizing treatment approaches, hence minimizing adverse reactions and optimally identifying novel treatment approaches. Findings from the human genome project, and large investments in biotechnology, have strengthened the belief of scientists and the public in realizing this goal in the near future (Weiland 2000). Genetic studies utilizing twin and family approaches have clearly shown considerable role of genetics in alcohol dependence, albeit only few gene variants have been identified unambiguously (Stoltenberg and Burmeister 2000 and Nestler 2000). Risk for alcohol dependence is likely to be the result of a large number of genes, each contributing a small fraction to the overall risk. The problem of genetic heterogeneity has been overcome in other areas of medicine and thus we are optimistic that this will also be true for investigations of alcohol dependence (Stoltenberg and Burmeister 2000; Wahlsten 1999; and Crabbe 2002).

TYPOLOGY OF ALCOHOLISM

Alcohol addiction is a common, complex disorder; many other traits that are associated with the risk for alcoholism also cluster in families and have genetic underpinnings. Addictions are psychiatric disorders that are associated with maladaptive and destructive behaviors, and that have in common the persistent, compulsive and uncontrolled use of alcohols or an activity. Addictive agents induce adaptive changes in brain function. These changes are the basis for tolerance and for the establishment of craving, withdrawal and affective disturbance, which persist long after consumption ceases (Roberts and Koob 1997). This self-maintaining and progressive neurobiology of addictions makes them chronic and relapsing disorders.

The alcohol addiction is a worldwide public-health crisis, and exerts corrosive effects at family and societal levels, leading even to the narco-political and narco-economic domination of countries and religions. World Health Organization in the year 1983 declared Alcohol related problems as major health problems which

are responsible for 3.5% of disability adjusted life years (DALYs) lost globally (Murray and Lopez 1996). Alcohol affects all aspects of human life and causes hazards to health and welfare. Heavy alcohol reduces life expectancy by 10 – 12 years besides affecting productivity in developed and developing nations (Grant 1985). Alcohol as a disease agent causes acute and chronic intoxication, cirrhosis of liver, toxic psychosis, gastritis, pancreatitis, cardiac myopathy and peripheral neuropathy. Also mounting is the evidence that it is related to cancers of mouth, pharynx, larynx and oesophagus. Alcohol is an important etiological factor in suicide, accidents, social and family disorganization, crime and loss of productivity. Increasing percentage of young people have started drinking alcohol in increased frequency and quantity thus constituting serious hazards to health, welfare and life (WHO, 1980). The World Health Organization (WHO) estimated that there are two billion alcohol users (WHO-Global Status Report on alcohol, 2004: http://www.who.int/substance_abuse/publications/en/global_status_report_2004_overview.pdf). Drinking prevalence, mortality and morbidity from alcohol use in South-East Asia Region and some parts of India is furnished in Table 1. Traits, or phenotypes, include a person's response to alcohol, the maximum amount of alcohol a person consumes on a single occasion and biological measurements, such as brain electro-physiological measures. Researchers rely on personality questionnaires to determine the alcoholic category of the subjects. Seven frequently used questionnaires are: the Minnesota Multiphasic Personality Inventory (MMPI), the MaC Andrew Alcoholism Scale (MAC), the Eysenck Personality Questionnaire (EPQ), the Tri-dimensional Personality Questionnaire (TPQ), the Connecticut Typology Questionnaire (CTQ), the Alcohol Use Disorders Identification Test (AUDIT) and the Michigan Alcoholism Screening Test (MAST).

Alcoholism is categorized into three types: type-I, II, and III. Cloninger (1990) distinguished type-I of alcoholism (low novelty seeking, high harm avoidance, high reward dependence) from type-II (male-limited) alcoholism (high novelty seeking, low harm avoidance, low reward dependence). Hill (1992) proposed a third type of alcoholism. Like type-II alcoholism, it is significantly influenced by genetic factors, but is not associated with any abnormal behavior.

Table 1: Drinking prevalence, mortality and morbidity from alcohol use in South-East Asia Region and some parts of India.

Country	Parts of country or population	Prevalence rate	Alcohol dependency rate	Mortality	Morbidity due to alcohol consumption	Reference
India		16.7% - 58.3%	1% - 2%	11.5 %	16% liver cirrhosis, 1.43% cancer, 25% accident, 10% suicide	Saxena 2004 WHO 2004
India	Arunachal Pradesh Goa Andhra Pradesh Rural Punjab Northern India Western India Southern India	50.2% 49% 21% 74% 60% 24.7% 26%-50%	3%			Deswal et al. 2006 Dhupadale et al. 2006 WHO 2004 Deb and Jindal 1975 Varma et al. 1980 Sundaram et al. 1984 Chakravarthy 1990 and Bang and Bang 1991 Mohan et al. 1992
Bangladesh	Delhi	26%				WHO 2004
Indonesia	Balinese and Jakarta populations	40%	0.2% 2.7%		20%	WHO 2004 WHO 2004
Myanmar		10%	10%		~10%	WHO 2004
Nepal					~8%	WHO 2004
Sri Lanka		25% -34%		6%	0.12% liver cirrhosis	WHO 2004
Thailand		31.4%			0.6 Cancer 4.7%	WHO 2004

Genetic Epidemiology of Alcoholism

1) Family Studies: Alcoholism was regarded as a distinct disease that may be transmitted from generation to generation (Dawson and Archer 1992). A familial association could result from cultural factors tending to encourage heavy drinking in family members. On the other hand, drinking may be discouraged in some families for religious, cultural or climatic grounds while in other families constraints on heavy drinking may be virtually non-existent. So "familial" does not necessarily mean "hereditary". A critical review of studies of the familial incidence of alcoholism summarized 39 investigations published in English that comprised family data on 6,251 alcoholics and 4,083 non-alcoholics (Cotton 1979). They clearly showed that regardless of the nature of the population of non-alcoholics studied, an alcoholic is more likely to have a mother, father or a distant relative who is an alcoholic. When lifetime prevalence of alcoholism in relatives of alcoholics was compared to that in the general population, a four-fold increased risk

in first-degree relatives and a two-fold increased risk in second-degree relatives were observed. Higher family incidence of alcohol use and abuse does not necessarily reflect a genetic determination of alcoholism. Heritable familial attributes as well as similarities in social environment of family members also appear to play a role in familial transmission of alcoholism.

2) Twin Studies: The twin study paradigm is a powerful method to understand complex and heterogeneous trait disorders. Twin studies are based on the fact that monozygotic twins (MZ) share identical genetic material, while dizygotic twins (DZ) share the same degree of genetic similarity as non-twin siblings. If genetic effects are present then monozygotic twins should be more alike than dizygotic twins allowing an estimation of the genetic contribution. Differences between identical twins would presumably reflect environmental influences while differences between non-identical twins may be due to heredity, environment or both (Agarwal 2001). Therefore, if alcoholism has a hereditary basis, MZ twin pairs should tend to be more similar in

their drinking behavior and alcohol-related problems than DZ twin pairs (Pickens et al. 1991). It has been clearly demonstrated that both genetic and environmental factors influence alcohol dependence (Heath et al. 1999). These studies examine traits that are not inherited in a Mendelian fashion, but nevertheless show non-random familial distributions indicating genetic contributions (Vanyukov and Tarter 2000; and Jacob et al. 2001). Twin studies strongly indicate the presence of genetic risk factors for multiple aspects of alcohol dependence including initiation, contribution, amount consumed and cessation. In addition to estimating genetic liability, these studies provide further information about environmental contributions, identifying that which is shared and that which is non-shared.

3) Adoption Studies: A systematic approach to separate “nature” from “nurture” is to study individuals separated from their biological relatives soon after birth and raised by non-related foster parents and to compare them with respect to characteristics of alcohol abuse with both their biological and adoptive parents. It is based upon the premise that the genetic trait present in the affected biological parent will still be expressed in adoptees, regardless of the genotypic status and environmental circumstances of the foster parents. In studies of intact families, the effects of genetic and common environment are not separable. Adoption studies separate these effects because adoptees receive their genetic heritage from one set of parents and their rearing environment from another set. The degree to which adoptees resemble their biological relatives is a direct measure of genetic influence, while the degree to which they resemble their adoptive relatives is a measure of the influence of family environment. Adoption studies are capable of delimiting almost completely genetic and environmental influences on the variation in the liability to a disorder (except contributions of ante- and early postnatal environmental factors) (Heath et al. 1998). Extensive adoption studies conducted in Denmark and Sweden have provided substantial evidence that alcoholism is genetically influenced, and that there are distinct patterns of alcoholism with different genetic and environmental causes (Goodwin et al. 1974; Cloninger et al. 1981; Bohman et al. 1987). When the adopted away sons of alcoholic parents were compared to their siblings raised by the alcoholic biological parent, a remarkably similar rate of alcoholism was

noted in both groups. Subsequent adoption studies from other countries have clearly shown that children born to alcoholic parents but adopted away during infancy were at greater risk for alcoholism than adopted-away children born to nonalcoholic parents (Sigvardsson et al. 1996).

4) Gender Differences in Transmission of Alcoholism: There is consistent evidence that relatives of women treated for alcoholism have higher risk for alcoholism than relatives of treated males (Prescott and Kendler 1999). Twin studies provide estimates of heritability of the liability to alcoholism in the range of 51% - 65% in females and 48% - 73% in males (Johnson et al. 1998; Prescott et al. 1999; Prescott and Kendler 1999; Kendler et al. 1994). Early studies found that genetic influences on alcoholism risk were clear in men but were less certain in women (McGue et al. 1992). However, subsequent studies, which explicitly addressed gender difference, found evidence for 64% heritability for women and men, even when data were weighted to adjust for selective attrition (Prescott et al. 1999). In addition, it has been noted that the genetic sources of vulnerability to alcoholism are partially, but not completely overlapping in men and women (Prescott et al. 1999). Heritability estimates were 66% in women and 42% - 75% in men for frequency of alcohol consumption, and 57% in women and 24% - 61% in men for average quantity consumed when drinking. Men (but not women) who are at increased genetic risk of alcohol dependence exhibited reduced alcohol sensitivity (Heath et al. 1999). This suggests that women in treatment tend to have higher liability than their male counterparts. Some evidence from molecular genetic studies supports the existence of sex-specific loci (Paterson and Petronis 1999), and a definitive answer to this issue will probably come from molecular rather than epidemiological studies.

5) Mode of Inheritance: Although adoption and twin studies have proven useful in answering the question of nature versus nurture, the mode of inheritance of alcoholism is still an unresolved issue. Heritability estimates vary somewhat depending on diagnostic criteria, with the highest heritability estimates obtained for Feighner Probable alcoholism (63%), Cloninger type II alcoholism (54%), and DSM - III alcohol dependence (52%) (Van den Bree et al. 1998). Certain diagnostic systems are more sensitive for detecting genetic influences and may be more

appropriate for studies attempting to find genes for alcoholism (Van den Bree et al. 1998). While environmental effects explain most of the variation in initiation of drinking, genetic factors are more important in explaining frequency of intoxication (Viken et al. 1999). This study also observed similar genetic risk for males and females in the initiation of drinking, but suggested that either different genetic factors or different shared environmental factors were influencing the two sexes (Viken et al. 1999). It was also noted that specific genes are influencing the heritability for alcohol withdrawal syndrome (Schuckit 2000). None of the evidence hitherto put forward suggests that susceptibility to alcoholism is inherited via a simple Mendelian dominant/recessive or sex-linked transmission. Even if the inheritance of certain biological factors involved in alcoholism is assumed to be Mendelian, the effect of these factors on the development of complex disorders may still not fit a simple genetic model. A substantial degree of etiological heterogeneity in the alcoholism phenotype results in the ultimate manifestation of the disorder dependent on poorly understood gene-environment interactions.

6) Characterization of High Risk and Low Risk Individuals: It is not clear if genetic risk is a major factor in initiation of drinking or drinking during adolescence (Stallings et al. 1999). In the past years, a number of investigators have tried, in prospective studies, to identify possible trait markers by studying young men and women at high risk for the future development of alcoholism based on their family history of this disorder. Having an alcoholic biological father is the best single predictor of future alcoholism in male offspring. One method of determining whether there are neuro-psychological deficits prior to the onset of alcoholism is to study children who are at risk for becoming alcoholic. In a typical prospective study young men and women at high risk for the future development of alcoholism are divided into Family History Positive (FHP) group, (who report an alcoholic parent or siblings) and Family History Negative (FHN) group (men and women who report no close alcoholic relative). The subjects are matched for demography and alcohol drinking history.

Gene Identification

Family, twin and adoption studies have

indicated that alcoholism has a strong genetic component (Reich et al. 1999). In searching for genes that contribute to alcoholism risk, several approaches like a) polymorphic markers, b) linkage mapping and c) the candidate gene approach, may be utilized in order to identify the genetic loci underlying alcoholism susceptibility.

a) Polymorphic Markers: As part of the Human Genome Project, a large number of markers called micro-satellites have been mapped on the human genome. These markers are short stretches of two to four nucleotides and are repeated several times. These markers are highly polymorphic and transmitted across successive generations of a family. To find chromosomal regions and genes influencing alcoholism, researchers look for certain micro-satellite markers that may co-inherit with the disease across multiple generations.

b) Identifying Chromosomal Locations of Interest (Linkage Studies): Linkage mapping, also called positional cloning, is the process of systematically scanning the entire DNA contents (i.e., the genomes) of various members of families affected by the disorder using regularly spaced, highly variable (i.e., polymorphic) DNA segments whose exact position is known (i.e., genetic markers). Using those families, investigators can identify genetic regions associated or "in linkage" with the disease by observing that affected family members share certain marker variants (i.e., alleles) located in those regions more frequently than would be expected by chance. These regions can then be isolated, or cloned, for further analysis and characterization of the responsible genes. Linkage mapping techniques have already resulted in the identification of several potential DNA regions that may contain susceptibility genes for alcoholism (Reich et al. 1999). The primary advantage of linkage mapping is that investigators need no prior knowledge of the physiology or biology underlying the disorder being studied, which is important for complex disorders like alcoholism.

A very close location of the alcohol dehydrogenase (ADH) genes was identified on chromosome 4q (Long et al. 1998; Reich et al. 1998; Saccone et al. 2000); the ADH genes have been associated with protective effects in Asians (Reich et al. 1998). Evidence for linkage to chromosome 4q in both a South-Western American Indian tribe and in Americans of European descent strongly supports a role for

genes in this location in influencing risk for alcohol dependence. Linkage to chromosome 4p has also been seen near the $\beta 1$ GABA receptor gene (Long et al. 1998). In a Finnish sib-pairs study (Lappalainen et al. 1998), antisocial alcoholism showed weak evidence of linkage with a location on chromosome 6 and significant evidence of linkage to the Serotonin receptor 1B G861C. In a South-Western American Indian tribe, significant sib-pair linkage to chromosome 6 was also seen (Lappalainen et al. 1998). Multipoint methods provided the strongest suggestions of linkage with susceptibility loci for alcohol dependence on chromosomes 1 and 7, and more modest evidence for a locus on chromosome 2 (Reich et al. 1998). The best evidence for linkage has been seen on chromosome 11p (D11S1984), in close proximity to the DRD4 dopamine receptor and tyrosine hydroxylase (TH) genes (Long et al. 1998). Results from numerous studies analyzing sib-pair linkage for alcoholism are published in an issue of *Genetic Epidemiology*, 1999; 17 Supplement 1; many identified sites on chromosome 10q, which may be related to genetic variation in the CYP2E1 gene (10q24.3) that can inactivate ethanol.

To understand genetic contributions to alcohol drinking behaviors many aspects of the behavior need to be assessed as independent endo-phenotypes since different gene variants may affect these various behavioral aspects of alcohol dependence differentially. Large studies of multiple gene variants and clearly defined phenotypes will lead to better understanding of the specific genes and the mechanisms involved. Whereas the linkage mapping approach is an unbiased search of the entire genome without any preconceptions about the role of a certain gene, the candidate gene approach allows researchers to investigate the validity of an "educated guess" about the genetic basis of a disorder. This approach involves assessing the association between a particular allele (or set of alleles) of a gene that may be involved in the disease (i.e., a candidate gene) and the disease itself. The major difficulty with this approach is that in order to choose a potential candidate gene, researchers must have an understanding of the mechanisms underlying the disease (i.e., disease pathophysiology). In contrast with linkage mapping studies, however, studies of candidate genes do not require large families with both affected and unaffected members, but can be

performed with unrelated cases and control subjects or with small families (e.g., a proband and parents). Further more, candidate gene studies are better suited for detecting genes underlying common and more complex diseases where the risk associated with any given candidate gene is relatively small (Collins et al. 1997; Risch and Merikangas 1996).

c) Candidate Genes Involved in Alcohol Dependence: Candidate gene studies are better suited for detecting genes underlying common and more complex diseases where the risk associated with any given candidate gene is relatively small. Association studies with candidate genes remain conceptually the simplest of genetic studies where specific biological hypotheses can be tested in a design similar to a classical case-control study (Kwon and Goate 2000; Stoltenberg and Burmeister 2000). Candidate gene studies often test one gene, and often one allele, at a time. More recently, multiallelic / multigenic interactions have been examined by testing for the effect of two markers and their statistical interaction (Longmate 2001). This new approach makes particular sense when the genes / proteins studied are known to belong to interacting systems and when the phenotype, such as dependence, is thought to be oligogenic (e.g., dopamine receptors and dopamine biosynthetic and degradative enzymes). As novel techniques develop (e.g., single nucleotide polymorphisms (SNPs) scored on DNA chips), extremely large datasets will be required for sufficient statistical power, but the findings will be much more informative than testing single alleles and single genes (Stoltenberg and Burmeister 2000). Currently the best candidate allelic variants (as everyone has the same genes) fulfill at least two criteria: a) the variant has been shown to alter function or regulation, and b) the variant has a good likelihood of being biologically relevant (Stoltenberg and Burmeister 2000) (Table 2).

GABA: The principal inhibitory neurotransmitter in the brain is γ -aminobutyric acid (GABA_A). Binding of GABA to ionotropic GABA_A receptors causes the opening of an integral chloride ion channel, thus changing the membrane potential of neurons and thereby exerting a crucial role in regulating brain excitability. GABA_A receptors are sensitive to ethanol and are believed to mediate many of its effects, including anxiolysis, sedation, motor in-coordination, tolerance, and dependence (Grobin et al. 1998).

Table 2: Different genes implicated in alcoholism.

<i>Gene</i>	<i>Variant(s)</i>	<i>Phenotype</i>	<i>Reference</i>
ADH2 (ADH1B)	Arg47His	Protects from alcoholism	Chen et al. 1999; Osier et al. 2002;
ADH3 (ADH1C)	Ile349Val	Protects from alcoholism	
ALDH2	ALDH2*2	Protects from alcoholism Decreases amount of alcohol consumed	Okamoto et al. 2001; Nakamura et al. 1996; Maczawa et al. 1995;
CYP2E1	5' variant *1D repeat polymorphism Dra 1-C c2	Increased risk for alcoholism Alcoholism Alcoholic liver disease	Chen et al. 1999; Lee et al. 2001.Sun et al. 1999; Howard et al. 2002.
GABA _A receptor α 1	repeat polymorphism	Alcoholism	Parsian and Cloninger 1997
GABA _A receptor α 3	repeat polymorphism	Alcoholism	Sander et al. 1999
GABA _A receptor α 6	P385S	Alcoholism	Parsian and Zhang 1999
GABA _A receptor β 1		Alcoholism and Type II	
GABA _A receptor β 2	BanI RFLP	Alcohol dependence	Sander et al. 1999
GABA _A receptor β 3	G1 allele	Severe Alcoholism	Noble et al. 1998
GABA _A receptor γ 2	NciI RFLP	Alcohol dependence with antisocial personality	Loh et al. 2000
GABA _A receptor R1	S489 exon 7, exon 11	Alcoholism and personality disorders	Sander et al. 1999
Dopamine receptor (DR) D1	A48G	Alcohol Use	Sander et al. 1995; Hietala et al. 1997
DRD2	A1	Alcoholism	Hietala et al. 1997
DRD3	S9G	Alcoholic delirium	Sander et al. 1995
DRD4	VNTR in exon3	Alcoholism	Hutchison et al. 2002
Dopamine transporter	SLC6A3-93'- UTR G2319A	Alcoholism Alcoholism	Pastorelli et al. 2001 Ueno et al. 1999

GABA_A receptors are pentameric assemblies of subunits; 17 mammalian subunits are known, which are classified into α (1-6), β (1-3), γ (1-3), δ , ϵ , and ρ (1-3) types. In addition, the β_2 , β_3 , and γ_2 varieties occur in alternatively spliced forms. Most GABA receptors contain α , β and γ subunits (Mehta and Ticku 1992). Most of the genes encoding human GABA_A receptor subunits are organized in clusters. GABRA2, GABRA4, GABRB1 and GABRG1 on chromosome 4p¹² (Russek 1999). GABRA5, GABRB3 and GABRG3 encoding the α_5 , β_3 and γ_3 subunits, are on chromosome 15q11.2-q12 (Sinnott et al. 1993). The findings of Wallner et al. (2003) demonstrate that high alcohol sensitivity of GABA_A receptors requires the co-expression of either δ or the β_3 subunit with β_2 , markedly decreases the alcohol sensitivities of GABA_A receptors. The δ subunit may play an important role in determining the enhancing actions of modulatory agents other than alcohol.

There have been several studies of the potential association of genes encoding GABA_A receptor subunits with alcoholism. Parsian and Cloninger (1997) examined microsatellite polymorphisms in GABRA1 and GABRA3 in a

sample of alcoholics and controls of Western European descent, and found no significant association with alcoholism or with type I and type II subunits of alcoholics. Parsian and Zhang (1999) found association between a microsatellite polymorphism in the GABRB1 gene and alcoholism in the same population. There have been several papers examining the gene cluster on chromosome 5. Sander et al. (1999) examined single nucleotide polymorphisms in GABRA6, GABRB2 and GABRG2 in 349 German alcoholics and 182 ethnically matched controls, and found no significant association with alcohol dependence or withdrawal or familial alcoholism. Loh et al. (2000) carried out association studies of five polymorphisms in GABA subunit genes on chromosome 5 in Japanese, and found no association of any with alcoholism or alcoholism without concurrent antisocial personality disorder, but a marginal association of one polymorphism in GABRG2 for alcoholism with antisocial personality disorder. In a Scottish population, Loh et al. (1999) reported association between alcoholism and polymorphisms in GABRA6 and GABRB2.

Dopamine System: Polymorphisms of genes

in the dopamine system are plausible functional candidate genes for alcohol dependence. An association was made between a 5' polymorphism (A48G) and alcohol use, but not all studies conform a role for Dopamine receptor D1 (DRD1) in alcohol use (Sander et al. 1995; Hietala et al. 1997). The results for both the DRD1 and DRD2 genes, which have opposing effects on cyclic AMP, were consistent with negative and positive heterosis, respectively. These results suggest a role for genetic variants of the DRD1 gene in some addictive behaviors, and suggest an interaction of genetic variants at the DRD1 and DRD2 genes.

The DRD2 minor A1 allele was, a decade ago, first reported to have association with severe alcoholism (Hietala et al. 1997; Dobashi et al. 1997). Although many studies have not found an association with dependence, some association with severity of drinking may exist (Pastorelli et al. 2001; Sander et al. 1995; Noble et al. 2000). However, no association was found between the A1 polymorphism and age at onset of alcohol dependence (Anghelescu et al. 2001). In family association studies no evidence for a role of DRD2 was found (Edenberg et al. 1998; Goldman et al. 1997). In summary, DRD2 may not alter risk for alcohol dependence, but alcohol-dependent patients with the DRD2 A1 allele may have greater severity of their disorder across a range of the drinking problem indices (Connor et al. 2002). There are few examples where the DRD2 genetic variation has been examined in conjunction with other genes. For example variants of both the DRD2 and GABA_A receptor subunit genes were associated with risk for alcoholism; however, when combined, the risk for alcoholism was more robust than when these variants were considered separately (Noble et al. 1998). Likewise there was a stronger association of a DRD2 and ADH2 variants together on risk for alcoholism than either gene variant alone (Amad et al. 2000).

Reddy et al. (2007) studied SNPs at the two sites of NPY and DRD2-Taq1 loci among 28 hierarchical caste and tribal groups of India and try to correlate with their traditionally known average drinking behaviors. Assuming that NPY-C confers protection against alcoholism and DRD2-TaqA1 allele is susceptible to alcoholism, they concluded that although the trend of allele frequency in the hierarchical groups suggests an association with their drinking behaviors, case

control studies are required to infer the nature of this association. As these two alleles at NPY and DRD2-Taq1 show opposing trends of average allele frequency with hierarchical positions of the studied populations the authors have tested further for possible co-adaptation of these alleles but could not find convincing evidence.

Studies of DRD3 and alcoholism demonstrated no significant association (Parsian et al. 1997; Henderson et al. 2000), regardless of sensation seeking score, addictive or psychiatric co morbidity, alcoholism typology, and clinical specifics of alcoholism. Even when tested in alcoholics in the presence of active or inactive ALDH2, no association with DRD3 was observed (Higuchi et al. 1996). One study found a significantly increased allele frequency of DRD3 S9 in alcohol-dependent individuals with delirium suggesting it may confer genetic susceptibility to some aspects of the effects of alcohol (Sander et al. 1995).

Van Tol et al. (1992) described the existence of at least 3 polymorphic variations in the coding sequence of the human D4 receptor. A 48-bp sequence in the putative third cytoplasmic loop of the receptor was found to exist either as a direct repeat sequence (D4.2), as a 4-fold repeat (D4.4), or as a 7-fold repeat (D4.7). Two other variant alleles were detected. Expression of the cDNA for the 3 cloned receptor variants showed different properties for the long form (D4.7) as contrasted with the shorter forms with respect to clozapine and spiperone binding. These variations among humans may underlie individual differences in susceptibility to neuropsychiatric disease and in responsiveness to antipsychotic medication.

Human personality traits that can be reliably measured by rating scales show a considerable heritable component. One such instrument is the tridimensional personality questionnaire (TPQ), which was designed by Cloninger et al. (1993) to measure 4 distinct domains of temperament—novelty seeking, harm avoidance, reward dependence, and persistence—that are hypothesized to be based on distinct neurochemical and genetic substrates. Cloninger et al. (1993) proposed that individual variations in the novelty seeking trait are mediated by genetic variability in dopamine transmission. Individuals who score higher than average on the TPQ novelty seeking scale are characterized as impulsive, exploratory, fickle, excitable, quick-tempered, and extravagant,

whereas those who score lower than average tend to be reflective, rigid, loyal, stoic, slow-tempered, and frugal.

Hutchison et al. (2002) found an association between alcoholism and DRD4 receptor variation. In a study of 20 abstinent alcohol-dependent men, a significant correlation was found between apomorphine-induced growth hormone release and the 'novelty seeking' score of the individual (Wiesbeck et al. 1995). This supported Cloninger's hypothesis by giving neuroendocrine evidence that this personality dimension is related to dopaminergic activity, albeit in the tubero-infundibular dopaminergic system which is not directly associated with human personality traits. In two groups of Finnish subjects (193 psychiatrically screened normal controls and 138 alcoholic offenders), Malhotra et al. (1996) determined DRD4 genotypes and assessed novelty seeking with the TPQ. In the control individuals, they found no significant association between novelty seeking and the 7-repeat allele despite similar allele frequencies and the use of the same personality measure as employed by Ebstein et al. (1996). The group of alcoholic offenders had significantly higher novelty seeking than control individuals; however, Malhotra et al. (1996) could not replicate the previous association in this group. They suggested that DRD4 may require reevaluation as a candidate gene for personality variation.

The ALDH2*2 allele of the aldehyde dehydrogenase-2 gene is considered to be a genetic deterrent for alcoholism; however, Muramatsu et al. (1996) found that 80 of 655 Japanese alcoholics had the mutant allele. They postulated that these alcoholics had some other factor which overcame the adverse effects of acetaldehydemia and that this factor might reside in the 'reward system' of the brain in which dopamine plays a crucial role. Therefore, Muramatsu et al. (1996) studied variation at the DRD4 locus and found in the alcoholics a higher frequency of a 5-repeat (5R) allele of the DRD4 receptor 48-bp repeat polymorphism in alcoholics with ALDH2*2 than in 100 other alcoholics and 144 controls. They found that alcoholics with the 5R allele also abused other drugs more often. Chang et al. (1996) presented data that urged caution in the interpretation of DRD4 association studies in mixed populations. They focused particularly on the expressed polymorphism in exon 3 which may have functional relevance. This

polymorphism (an imperfect 48-bp tandem repeat coding for 16 amino acids; alleles had been reported with 2 to 10 repeats) was found to be universal, suggesting that it is ancient and arose before the global dispersion of modern humans. They described diversity of allele frequencies for this expressed polymorphism among different populations and emphasized the importance of population considerations in the design and interpretation of association studies using the polymorphism.

DRD4 is one of the most variable human genes known. Most of this diversity is the result of length and single-nucleotide polymorphism (SNP) variation in a 48-bp VNTR in exon 3, which encodes the third intracellular loop of this dopamine receptor. Variant alleles containing 2 (2R) to 11 (11R) repeats are found, with the resulting proteins having 32 to 176 amino acids at this position. The frequency of these alleles varies widely. The 7R allele, for example, has an exceedingly low incidence in Asian populations yet a high frequency in the Americas (Chang et al. 1996). Although initial studies suggested that the 7R allele of the DRD4 gene might be associated with the personality trait of novelty seeking (Ebstein et al. 1996; Benjamin et al. 1996), the most reproduced association is that between the 7R allele and attention deficit-hyperactivity disorder. Ding et al. (2002) stated that 8 separate replications of the initial observation of an increased frequency of the DRD4 7R alleles in ADHD probands had been reported.

Dopamine transporter (DAT) 7 repeats tended to be higher, and that of 9 repeats lower, in alcoholic Japanese patients (Dobashi et al. 1997); however, no association was found between DAT and alcoholism (Pastorelli et al. 2001; Parsian and Zhang 1997) even in family-based studies (Schmidt et al. 1998). An increased prevalence of the 9-repeat allele in alcoholics displaying withdrawal seizures or delirium has been observed (Schmidt et al. 1998). A polymorphism in the 3'-UTR (G2319A) of the DAT gene was associated with alcoholism (Ueno et al. 1999).

CYP2E1: Cytochrome P450 2E1 (CYP2E1) is an enzyme that is also able to metabolize ethanol to acetaldehyde and acetaldehyde to acetate (Howard et al. 2002). In humans, the levels of hepatic CYP2E1 were found to vary 50-fold *in vitro* while *in vivo* CYP2E1 activity was found to vary by 15-fold. The CYP2E1 gene is genetically

polymorphic and CYP2E1 variant alleles have been associated with altered ethanol metabolism (Sun et al. 1999).

Aldehyde Dehydrogenase: So far 17 ALDH genes have been identified in nine ALDH genotype groups (Brennan et al. 2004). The isozyme mainly responsible for acetaldehyde oxidation is the mitochondrial class II ALDH (ALDH2) that has a micro molar Km value and high affinity for acetaldehyde (Lands, 1998) located on chromosome 12q24.2. The ALDH2 enzyme is polymorphic in humans, having two allelic forms, ALDH2*1 and ALDH2*2 caused by a point mutation at amino acid position 487, where substitution of Lysine for Glutamic acid that results from a transition of G to A at nucleotide 1510 (Hsu et al. 1985; Yoshida et al. 1991). The ALDH2 deficiency leads to an aversive response to alcohol due to elevated levels of acetaldehyde resulting in increased hangover symptoms (Wall et al. 2000) and the alcohol flush response (Li, 2000; Tanaka et al. 1997). ALDH2*1 is a very active form found at high frequency among most ethnic groups, while the ALDH2*2 is inactive (or has very low activity) and is found at high frequency

among Asians (e.g. Chinese, Japanese, Koreans). The ALDH2*2 has been demonstrated to be associated with substantial protection from alcoholism in Japanese (Okamoto et al. 2001; Nakamura et al. 1996; Maczawa et al. 1995), Han Chinese (Chen et al. 1999) and Koreans (Lee et al. 2001). Genetic variation in ALDH2, tested in multiple ethnic groups, alters the amount of ethanol consumed (Tanaka et al. 1997; Okamoto et al. 2001; Sun et al. 1999) and risk for binge drinking (Luczak et al. 2001). An association with alcoholic liver disease was observed in some but not all studies, and may be due to the effect on levels of consumption. ALDH2*2 homozygous individuals are unable to oxidize acetaldehyde and who are heterozygous do so inefficiently (Yoshida et al. 1984; Novoradovsky et al. 1995). About 50% of oriental people are deficient in the ALDH2 isozyme that can most efficiently detoxify acetaldehyde (Harada et al. 1981; 1985). ALDH2 genotype and gene frequency among various populations of Mongoloid and Caucasoid and other Indian origins including different linguistic groups are presented in Table 3.

Alcohol Dehydrogenase: Alcohol dehydro-

Table 3: Distribution of ALDH2 genotype and gene frequency among various populations of Mongoloids and Caucasoids origin.

Subjects	n	Genotype frequency			Gene frequency		Reference
		ALDH2 *1/*1	ALDH2 *1/*2	ALDH2 *2/*2	ALDH2 *1	ALDH2 *2	
<i>Mongoloids</i>							
Thais(Northeast)	124	113	11	0	0.956	0.044	Mongconthawornchai et al. 2002
Thais(North)	111	100	11	0	0.95	0.05	Goedde et al. 1992
Phillipinos	86	85	1	0	0.994	0.006	Goedde et al. 1992
Malays	73	68	5	0	0.966	0.034	Goedde et al. 1992
Koreans	218	156	58	4	0.849	0.151	Goedde et al. 1992
Chinese	132	92	38	2	0.841	0.159	Goedde et al. 1992
Chinese	50	26	18	6	0.7	0.3	Thomasson et al. 1991
Taiwanese aborigine	58	56	2	0	0.98	0.02	Chen et al. 1998
Japanese	53	29	23	1	0.764	0.236	Goedde et al. 1992
Japanese	58	32	21	5	0.73	0.27	Yamamoto et al. 1993
Japanese	424	235	160	29	0.743	0.257	Takeshita et al. 1994
Japanese	129	70	48	11	0.729	0.271	Yuasa et al. 1997
<i>Caucasoids</i>							
Germans	193	193	0	0	1	0	Goedde et al. 1992
Swedes	99	99	0	0	1	0	Goedde et al. 1992
Hungarians	117	114	3	0	0.987	0.013	Goedde et al. 1992
Indians	179	173	5	1	0.98	0.02	Goedde et al. 1992
Onge	40	40	0	0	1	0	Bhasker et al. 2007
Pattapu	95	95	0	0	1	0	Bhasker et al. 2007
Gond	47	47	0	0	1	0	Bhasker et al. 2007
Korku	133	133	0	0	1	0	Bhasker et al. 2007
Bhil	34	34	0	0	1	0	Bhasker et al. 2007
Sahariya	48	48	0	0	1	0	Bhasker et al. 2007

genase (ADH) metabolizes alcohol to acetaldehyde. It exists as a polygene family on chromosome 4q, which has been linked to alcoholism. Variants of different class I ADH genes have been shown to be associated with an effect that is protective against alcoholism (Osier et al. 2002). There are seven ADH genes with two polymorphic genes, ADH2 and ADH3 (Li, 2000). All seven genes exist in a cluster extending $\cong 380$ kb on the long arm of chromosome 4 (i.e., 4q21-23) (Osier et al. 2002). The class I ADH genes [ADH1A(α), ADH1B(β), ADH1C(γ)] exist in a tighter cluster of $\cong 77$ kb, flanked upstream by ADH7(μ or σ) in class IV and downstream by ADH6 in class V, ADH4(π) in

class II and ADH5(x) in class III, in the order of magnitude (Rao et al. 2007). Although the greatest similarity seen among the class I genes, all seven ADH enzymes are very similar in amino-acid sequence and structure but differ in preferred substrates (Edenberg 2000). Two of the three class I genes are known to have alleles that produce enzymes that catalyze the oxidation of ethanol at different rates (Edenberg and Bosron 1997). At the protein level, the allelic series for ADH1B (previously called "ADH2") encodes the β subunit of the dimeric enzyme and is generated by variation at two different sites at the genomic level: the ADH1B*1 allele is composed of 47Arg and 369Arg, the ADH1B*2 allele is composed of

Table 4: Gene frequency of ADH1B and ADH1C gene of some Indian populations.

Population	Gene frequency of ADH1B*47 (ADH2*2)		Gene frequency of ADH1C*349 (ADH3*349)		Reference
	A allele	G allele	A allele	G allele	
Onge	0.000	1.000	1.000	0.000	Rao et al. 2007
Pattapu	0.045	0.955	0.750	0.250	Rao et al. 2007
Gond	0.000	1.000	0.5714	0.4286	Rao et al. 2007
Korku	0.000	1.000	0.5791	0.4209	Rao et al. 2007
Bhil	0.000	1.000	0.6250	0.3750	Rao et al. 2007
Sahariya	0.020	0.980	0.5918	0.4082	Rao et al. 2007
Brahmin	0.000	1.000	0.556	0.444	Reddy et al. 2006
Kshatriya	0.000	1.000	0.692	0.308	Reddy et al. 2006
Vysya	0.000	1.000	0.583	0.417	Reddy et al. 2006
Akuthota	0.000	1.000	0.697	0.321	Reddy et al. 2006
Kamma	0.000	1.000	0.767	0.233	Reddy et al. 2006
Kapu	0.000	1.000	0.667	0.333	Reddy et al. 2006
Pokanati	0.000	1.000	0.603	0.397	Reddy et al. 2006
Panta	0.000	1.000	0.541	0.459	Reddy et al. 2006
Vanne	0.000	1.000	0.683	0.317	Reddy et al. 2006
Baliya	0.000	1.000	0.79	0.21	Reddy et al. 2006
Ekila	0.000	1.000	0.667	0.333	Reddy et al. 2006
Kurava	0.000	1.000	0.645	0.355	Reddy et al. 2006
Thogata	0.000	1.000	0.688	0.313	Reddy et al. 2006
Yadava	0.000	1.000	0.683	0.317	Reddy et al. 2006
Ediga	0.000	1.000	0.533	0.467	Reddy et al. 2006
Gandla	0.000	1.000	0.583	0.417	Reddy et al. 2006
Jangam	0.000	1.000	0.5	0.5	Reddy et al. 2006
Devangapattur	0.000	1.000	0.559	0.441	Reddy et al. 2006
Chakli	0.000	1.000	0.673	0.327	Reddy et al. 2006
Mangali	0.000	1.000	0.577	0.423	Reddy et al. 2006
Vadde	0.000	1.000	0.619	0.381	Reddy et al. 2006
Madiga	0.000	1.000	0.672	0.328	Reddy, et al. 2006
Mala	0.000	1.000	0.663	0.337	Reddy et al. 2006
Erukala	0.000	1.000	0.56	0.44	Reddy et al. 2006
Sugali	0.000	1.000	0.703	0.297	Reddy et al. 2006
Yanadi	0.000	1.000	0.652	0.348	Reddy et al. 2006
Dudekula	0.000	1.000	0.7	0.3	Reddy et al. 2006
Sheik	0.000	1.000	0.81	0.19	Reddy et al. 2006

47His and 369Arg, and the ADH1B*3 allele is composed of 47Arg and 369Cys. Osier et al. 2002, had not seen the “double variant” (composed of 47His and 369Cys), but they assumed that it could exist. ADH1B*1 have high affinity and low capacity in contrast to ADH1B*2 and ADH1B*3 which have low affinity for ethanol and high capacity. The functional variants in the corresponding metabolic enzymes make the class I ADH genes obvious candidates for risk of developing alcoholism. Alleles at two ADH genes that encode enzymes with higher V_{max} values—namely, ADH1B*47His (previously called “ADH2*2”), at the Arg47His (exon 3) SNP, and ADH1C*349Ile (previously called “ADH3*1”), encodes the γ subunits and at the Ile349Val (exon 8) SNP – have consistently been found at significantly lower frequencies in alcoholic individuals than in non-alcoholic controls in Eastern-Asian samples (Thomasson et al. 1991; Chen et al. 1996; Shen et al. 1997; Tanaka et al. 1997; Osier et al. 1999; Li et al. 2001).

ADH1B*2 / (ADH2*2) allele frequency is lower in alcoholic populations indicating a protective role (Nakamura et al. 1996; Maczawa et al. 1995; Chen et al. 1999; Thomasson et al. 1994): the influence of this genetic variant is easier to demonstrate in populations which have low prevalence of the ALDH2*2 (Li 2000). There is evidence that ADH1C*349Ile may play an important role related to alcohol abuse, health and disease. Hines et al. (2001) demonstrated that ADH1C*349Ile homozygous individuals are more protected from heart disease by moderate drinking than ADH1C*349Val homozygotes. In contrast to it Visapaa et al. (2004) reported highest ADH1C*349Ile allele frequency in patients with oral cancer and cancer of the larynx. The allele ADH1C*349Ile is a considerable risk factor for female breast cancer, especially when ethanol consumption is high (Freudenheim et al. 1999). The gene frequency of the protecting ADH1B and ADH1C genes in some Indian populations is presented in Table 4. Altogether 34 different population groups were studied from India (Reddy et al. 2006 and Rao et al. 2007) of which majority of the groups were from the southern part of India.

CONCLUSION

The genetic data can be, and have been, used to improve our understanding of the etiology of alcohol dependence and inter-individual

variation in the risk for alcoholism. Once genes are identified which alter the predisposition to alcohol dependence, a major challenge will be to understand how the functions of these genes interact with the environmental influences on dependence. The unique Indian population structure with strictly defined endogamous castes and tribes maintaining isolated gene pools may aid in precise understanding of the genetic mechanisms underlying the alcoholic phenotypes. Analysis of specific genes will allow a rational exploration of biochemical underpinnings of the actions of alcohol and makes possible a link between behavioral change, genetic predisposition and biochemical action. Such genes, and the proteins they encode, will become primary targets for creating novel diagnostic tools as well as the basis of novel behavioral and pharmacological treatments. Genetic information may be useful for identifying individuals at increased risk for alcohol dependence and for the health consequences of alcohol dependence. By gaining a better understanding of genes that are involved in initiation, maintenance and cessation of alcohol dependence, novel pharmacological and behavioral treatment approaches may be designed. In summary, the improved understanding of genetic influences on alcohol dependence promises to increase our understanding of addictive processes, and should provide novel prevention and treatment possibilities.

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