Anthropology is a discipline, which serves the infinite curiosity about human beings. Etymologically the term ‘Anthropology’ is derived from two Greek words ‘Anthropos’ which means man and the ‘logos’ which refers to study. Therefore anthropology is defined as a discipline studying human beings scientifically in time and space. The subject matter of anthropology deals with human variation and evolution, humans not as individuals but ethnic groups or populations as a unit of study. Anthropologists ideally study man holistically taking into account both the biological and socio-cultural aspects.

In the beginning, anthropology was divided into two major branches according to the scope of study. They were Physical/Biological Anthropology and Cultural/Social Anthropology. The biological aspect of man was dealt solely under physical anthropology and the cultural anthropology included the whole of mental, rational and material-technological processes and products of the human being in an integrated pattern. With development, more divisions in the subject have been noted. Cultural Anthropology has given rise to three major sub-fields such as Archaeological Anthropology, Linguistic Anthropology and Social Cultural anthropology. However, Physical Anthropology continues to be one of the major fields of anthropology.

Physical Anthropology is defined as a science whose objective is the “study of humanity considered as a whole, in its parts and in relationship to the rest of nature” according to biologists Paul Broca (1871) (Lindee and Santos, 2012). Initially Physical Anthropology studied human origins and evolution and their physical
characteristics. Interest was in the comparative study of man considering the past, present and even future. It also focuses the biosocial adaptation of different human populations living in different geographical and ecological zones. The major areas of interest in Physical Anthropology have been Human Paleontology (Paleoanthropology), Primate Behaviour, Racial History and Human Genetics.

In the beginning, Physical/Biological anthropologists developed anthropometric and anthroposcopic techniques to study human variation throughout the world and classified humans into different races. The discovery of genetically determined red blood cell polymorphism in the beginning of twentieth century and later on protein polymorphism provided Physical Anthropologist with new tools to study human variation both at the regional and global levels (Crawford, 1973). Cavalli-Sforza et al., (1994) attempted a synthesis of the classical genetic marker data available on populations from different parts of the world. Such classical genetic markers, particularly serological, were used extensively to investigate the role of different evolutionary forces like drift, selection, mutation, migration and gene flow in shaping the genetic makeup of populations.

The development of physical anthropology is intimately related with the theoretical development of general biology. Anthropology uses genetics as a tool to understand human variation and evolution involving focus on health and evolutionary aspects. Genetics is an important aspect, which throws light on the ways of inheritance. The term anthropological genetics is a synthetic discipline that applies the methods and theories of genetics concerning the process of human evolution, variation and biocultural involvement in complex diseases (Crawford, 2007). It differs from its kin discipline human genetics since it emphasise on smaller, reproductively isolated, non-western populations, bio-cultural perspective on evolution and on complex disease etiology and transmission. Anthropological geneticists also attempt to measure environmental influences through co-variants of quantitative phenotype. The roots of the field of anthropological genetics are closely related with the developments in evolutionary biology, population genetics and biological anthropology. According to O’Rourke (2003), it was cross-fertilized by molecular biology and bioinformatics.

In the late 1950s and early 1960s, with the publication of Sewell Wright’s insight into the actions of stochastic processes, physicians and medical genetics discovered the
usefulness of small, genetically isolated populations for the understanding of rare genetic diseases and anomalies. Thus, knowledge about population became an important and compulsory for geneticist to understand the nature of disease and its development. It opens the door of anthropological genetics to enter in the field of human genetics. Therefore, anthropological genetics can play an integral role in identifying natural experiments in human populations (Terwilliger and Goring, 2000 and Terwilliger, 2003).

With the discovery of the helical structure of deoxyribonucleic acid (DNA) by Watson and Crick in 1953 and the advent of polymerase chain reaction (PCR) techniques in the 1980s along with the use of restriction enzymes for identifying polymorphisms at the DNA level provided anthropologists with new and more powerful techniques and genetic markers for testing different anthropological hypotheses. Here, genetic marker is defined as ‘discrete segregating, genetic traits which can be used to characterize populations by virtue of their presence, absence or high frequency in some populations and low frequency in others’ (Crawford, 1973).

Anthropological genetics of the late 1960s and early 1970s were preceded by almost a century of discovery and development in evolutionary theory and genetics. More attraction was made by its variation, polymorphic nature and differed in allele frequencies in human regional populations. They also started studying rare human genetic anomalies distributed in various populations. During this process, Anthropological geneticists have faced the challenges of clear understanding of mode of inheritance and their variation in different populations. Population structure in anthropological genetics is a much broader concept. An attempt was made to define the population structure and have good knowledge about the pattern of distribution and their disease mechanisms. According to them it is a broader concept, implying a variety of mechanisms that influence the degree and pattern of genetic variation in a population (Cavalli-Sforza, 1959).

Moreover, with the recent advancements in science and technology determined the sequence of the human genome and identified the genes that contain all of the information needed to build and maintain human body. Human Genome Project (HGP) reported that in human there are more than 3 billion DNA base pairs
comprising approximately 100,000 genes that make up human DNA (IHGSC, 2001). Such databases of DNA sequence (GeneBank) have been made freely accessible without restrictions to all scientists in industry and academia bringing a paradigm shift in studying human genetic variations among different populations. The availability of known genomic variations coupled with easy to type technologies facilitated the use of genomic markers for studying intra and inter population variations. Such studies intensively helped in understanding the human evolution and migrations. Based on the reported and available data on the prevalence of diseases and also certain genomic markers one can understand that the distribution of diseases and genomic markers are to be community specific at some extent. Thus, Anthropological Genetics/Genomics faced a paradigm shift from understanding genetic variation for evolutionary purposes to understanding genetic variations in relation to various non-communicable complex disorders. Anthropological geneticists started focusing on the genetic variation and susceptibility to various diseases among different populations. The extent of genetic variation and their manifestation are found to vary in different ethnic groups. Some populations are found to be more prone to a particular disease while others are not, as genetic structure of a particular population is shaped by their environmental/geographical position, life style, matting pattern and other genetic factors which are population specific. This suggests that a clear understanding of genetic structure of both ancestral and contemporary populations is compulsory while investigating any disease association studies. Therefore, anthropological genetics has emerged as a useful tool for studying various multifactorial complex diseases since the knowledge of human variations and its underlying genetic and environmental factors specific to populations is the primary goal of anthropological geneticists. Moreover, understanding genetic variation in disease risks and mapping candidate genes associated with the complex disease may provide new insight into the disease etiology which could lead to genetic screening programmes to identify the populations at higher risk. One of the best examples of complex disease, where the phenotypic expression is the interplay of gene-gene and gene-environment interaction is alcohol dependence. Here, both gene and environment act importantly in developing the disease profile (Enoch, 2006). It is found to be population specific and its prevalence is widely
different across the world. The World Health Organization (WHO) estimates that about 140 million people throughout the world suffer from alcohol dependence (WHO, 2001). It is one of the leading health risks and becomes world’s third largest risk factor for disease and disability. Alcoholism turns out to be the greatest risk among middle income countries (and ranks third in industrialized nations) and is estimated to be 6.5% lifetime prevalence in the general population. Approximately 2.5 million deaths each year are attributable to alcohol resulting 4% of all deaths worldwide according to the WHO (2011). Moreover, 5% of all deaths worldwide of young people between the ages of 15 and 29 were attributable to alcohol use. Globally alcohol was estimated to cause 20-30% of oesophageal cancer, liver disease, epilepsy, motor vehicle crashes, and homicide and other intentional injuries, reports WHO (2003). Alcohol takes a heavy toll - damaging public and private life with countless traffic fatalities and injuries, home fires, drowning, suicides and violent crimes. Moreover alcohol is also reported to cause debt problems, ruined careers, divorces, birth defects, and children with permanent emotional damage.

1.1 Alcohol
The term ‘alcohol’ describes various compounds composed of carbon, hydrogen and oxygen. It contains a hydroxyl group, ‘OH’, attached to a carbon molecule, which itself is connected to various combinations of carbon and hydrogen molecules. Originally, the word alcohol originates in the 16th century from the Arabian term ‘al-kuhul’ meaning ‘the kohl’ a powder used as eyeliner. Alcohol was a powder form and it was discovered by famous Persian alchemist Muhammad ibn Zakariya Razi. Now, the word came to refer to any fluid obtained by the process of distillation and the meaning became restricted to "spirit of wine". According to WHO (2003), alcohol is defined as a generic term for many different chemical compounds, each with its own distinct properties.

1.1.a Types of Alcohol
There are different types of alcohols used in various laboratories, industries and for drinking purposes by human beings for its intoxicating and mind-altering effects. The three most commonly encountered alcohols are - isopropyl alcohol (isopropanol),
methyl alcohol (methanol) and ethyl alcohol (ethanol). Isopropanol also commonly known as “rubbing alcohol” is used in industrial processes, home cleaning products as well as in cosmetic products such as skin lotions. Methanol is commonly available as methylated spirit and has been used as industrial solvents like cleaning solvents, paint removers, photocopier developer and anti-freeze solutions. Chemically, it is similar to ethanol and often available in large quantities inexpensively. However, end product after it is metabolized is poisonous and even can cause poisoning leading to blindness or even death.

Ethanol is a thin and clear liquid with high volatility. Usually it is consumed in diluted concentrations of absolute ethyl alcohol i.e. 100 percent. It is also found to use as a reagent in some industrial applications after combining with small quantities of methanol to prevent from direct consumption. Ethanol is the kind of alcohol consumed by humans which is produced by the process of fermentation in which yeast feeds on sugar of starch and produces alcohol along with carbon dioxide. According to manufacturing mechanisms, alcohol can be of following types -

**Wine:** It is made from variety of fruits such as grapes, peaches, plums or apricots. The most common wines are produced from grapes. The soil in which grapes are grown and the weather conditions in the growing season determine the quality and taste of the grapes which in turn affects the taste and quality of wines. When ripe, the grapes are crushed and fermented in large vats to produce wine.

**Beer:** It is also made by the process of fermentation. A liquid mix, called wort, is prepared by combining yeast and malted cereal such as corn, rye, wheat or barely. While fermenting, this liquid mix produces alcohol and carbon dioxide. The process of fermentation is stopped before it is completed to limit the alcohol content. The alcohol so produced is called beer containing around 4 to 8% of alcohol.

**Whisky:** It is made by distilling the fermented juice of cereal grains such as corn, rye or barley. Scotch whisky was originally made in Scotland. The word “Scotch” has become almost synonymous with whisky of good quality.

**Rum:** It is a distilled beverage made from fermented molasses or sugarcane juice and is aged for at least three years. Caramel is sometimes used for colouring.

**Brandy:** It is distilled from fermented fruit juices. It is usually aged in oak casks. The colour of brandy comes either from the casks or from caramel that is added.
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**Gin:** It is a distilled beverage made by combining alcohol, water and various flavours. It does not improve with age, so it is not stored in wooden casks.

**Liqueur:** It is made by adding sugar and flavouring such as fruits, herbs or flowers to brandy or to a combination of alcohol and water. Most liqueurs contain 20-65% alcohol. They are usually consumed in small quantities after dinner.

**Local Beverage (Country Liqueur):** It is a distilled alcoholic beverage made from locally available material such as sugarcane, rice, palm, coconut and cheap grains with alcohol content around 40%. Some of the common varieties are ‘arrack’, ‘desi sharab’ and ‘tari’ (toddy).

**Table 1.1: Types of alcoholic beverages, their sources and alcohol content (WHO, 2003)**

<table>
<thead>
<tr>
<th>Beverage</th>
<th>Types of Alcoholic Beverages</th>
<th>Source</th>
<th>Alcohol Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brandy</td>
<td>Fruit Juices</td>
<td></td>
<td>40-50</td>
</tr>
<tr>
<td>Whisky</td>
<td>Cereal grains</td>
<td></td>
<td>40-55</td>
</tr>
<tr>
<td>Rum</td>
<td>Molasses or Sugarcane</td>
<td></td>
<td>40-55</td>
</tr>
<tr>
<td>Wines</td>
<td>Grapes</td>
<td></td>
<td>10-22</td>
</tr>
<tr>
<td>Beer</td>
<td>Cereals</td>
<td></td>
<td>4-8</td>
</tr>
</tbody>
</table>

**1.2 History of Alcohol Production and Use**

The term alcohol was found to be existing ever since the rise of human evolution. Archaeologists around the globe try to explore the evidence of alcohol production and consumption in the past by using advanced techniques for detecting alcohol production and consumption in the archaeological records (Biers and McGovern, 1990 and Michel et al., 1993). It also includes the ethno archaeological investigation of alcohol, in which researchers undertake ethnographic studies that pay systematic attention to the material dimension of alcohol. The best results come from triangulating multiple strands of data including the excavated material-culture traces...
of consumption, production, trading practices and the chemical traces of alcoholic beverages preserved in ancient vessels using archaeometric techniques.

Use of alcohol has been mentioned since the discovery of fermentation plant products 6000-4000 Before Christ (BC). The world’s earliest known wine jar (dated back to 5400-5000 BC) was found in Hajji Firuz Tape, Iran by Archaeologists from the University of Pennsylvania, USA. Descriptions of the use of alcoholic beverages exist in almost all civilizations of the world dating as far back as 3000-200 BC. Archaeological findings like wine jars and beer jugs from various parts of the world suggest old history of alcohol use and was believed to be existing from as early as 5000 BC (McGovern et al., 1995). The evidence of alcohol production in Neolithic China from fermented beverage of rice, honey, and fruit were discovered and dated as early as the seventh millennium Before Common Era (BCE). It is also believed to be the precursor of the cereal-based alcohol preserved inside sealed bronze vessels of the 2nd millennium Shang and Western Zhou dynasties (McGovern et al., 2004).

Historically alcoholic drinks have been an intricate part of the civilization in India, China, Western Asia and Europe but modes of alcohol consumption vary from one culture to another. It had been mainly associated with various socio-cultural practices like medicinal preparations, wars, marriages and religious rituals across different cultures. Alcohol beverage production was quite common among different cultural and religious groups probably only after the appearance of agriculture.

In Europe, credible evidence for alcoholic beverages, especially drinking vessels in funerary contexts dates back to at least the Neolithic or may have existed even earlier (Dietler, 1996). Wine was also introduced to Early Bronze Age Greece in the third millennium BCE and subsequently spread to Italy with Greek colonization during the eighth and seventh centuries BCE (Wright, 2004). By the second to first centuries BCE, the Mediterranean wine trade had expanded dramatically. During the sixteenth century, production of alcohol distillation began to shift from apothecaries and monasteries to merchants and commercial distillers. By the seventeenth century, consumption was widespread and production increased dramatically, especially cheaper sugar and grain based alcohols began to be produced in northern Europe (Matthee, 1995).
1.2.a History of Alcohol Use in India

Alcoholic beverages have been mentioned in ancient Indian literature and the earliest reference to alcohol can be traced back to 2000 BC (Samhita, 1949; Dikshitar, 1951; Prakash, 1961 and Chopra and Chopra, 1995). Archaeological materials (particularly pottery remains) support early history of alcohol production and use in India. The ancient Indian society had the knowledge of how to prepare alcohol beverage, but did not support routine alcohol use and regarded abstinence as a virtue for most people. Textual evidences also demonstrate that barley and rice beers extend back to at least the Vedic period (second millennium BCE), and alcoholic beverages made from a variety of grasses, fruits and other substances are also attested in ancient texts (Prakash, 1961). For example, the preparation of ‘‘toddy’’ from palm tree tapping was prevalent in southern India in prehistoric times (Singh and Lal, 1979). It proves the widespread use of alcohol as well as the presence of long histories of alcohol consumption as traditions have been observed in India at least since Vedic times (Benegal, 2005).

The historical pattern of alcohol use behaviours and attitudes are very complicated and many faceted in India because of its various events taken place in the history. The evolution of alcohol use patterns can be broadly divided into four broad historical periods such as –

1.2.a.i The Vedic Period (1500-700 BC) use of alcohol has been referred in various sources during Rig Veda. It was a part of religious festivals (Singh and Lal, 1979; Achaya, 1991, Parkar et al., 2001 and Benegal, 2005) as well as widely used among the nobility, Kshatriya warriors and some other sectors of society. Soma & Sura are two common beverages used in India from the early period and it continued to the period of the Indus Valley Civilization (1500 BC) and the Vedas (1800 BC). Soma (sacred drink) has been described as alcoholic beverage for the upper classes of humans and the Gods. It is also described as celestial nectar and drink of gods and believed to be immortality (Singh and Lal, 1979). Soma experience was of enlightening, creating euphoric states stimulating mind and body (Chand, 1972). It has been restricted to Saints & elite of society. Sura is a form of beer manufactured
from rice, jiggery, barley, or other ingredients and popular in the general populace. It has been allowed to warriors (Kshatriyas) fighting ethos and day-to-day consumption common men. It was considered for lower classes of human society to relieve from physical hardships.

1.2.a.ii Post-Vedic Period (700-1100) - Traditional drinking patterns seem to have continued and have mainly been used by warriors and rulers, however drinking was not considered a daily event. Alcoholic beverages were served to guests on certain occasions such as moving into a new house and weddings (Praskara, 1956 and Singh and Lal, 1979). Ritual drinking was considered as an essential component of practices in certain religious sects. Two important religious movements, Buddhism and Jainism, strongly condemned use of alcohol. Budhism, prohibited drinking by monks and in monasteries as well as Budha counseled general abstinence from alcohol.

According to Hindu mythology (2000 BC), there were strict rules and guidelines on who is allowed to drink and under what circumstances. Manu, for instance, strictly forbade drinking by Brahmins whereas other classes of society were allowed to drink, but only on specific occasions (like wars, religious events and festivals). Hindu religion (some sects) permitted alcohol use for the practice of magical rituals. Abstinence was considered the norm for the common man (Tekchand, 1972). A dichotomous division of the society into “the bad” (alcohol and non-vegetarian) and “the good” (not alcohol and vegetarian) were practiced in early history. Both abstinence and drinking co-existed in different contexts and strata of the society (Sharma, 1996).

Historical evidences suggest that alcohol use did not pose a significant health or social problem in ancient and medieval periods in India. During this period, Charaka and Susruta wrote about alcohol as a medicine and as a social drink. Susruta’s writings have been dated anywhere from 600 BCE to 500 CE, and include many reflections on alcohol use and abuse. It suggests the origin of alcohol distillation in India many centuries earlier than it developed in Europe in the 10th century (Sharma et al., 2010).
1.2.a.iii Islamic Invasions and Moghul Rule (1100-1800) - This period in the history of India begins with the incursions of Muslim invaders in the 11th century, initiated by Mahmud of Ghazni’s brutal conquests in north India (Wolpert, 1997). The Muslims were officially puritanical in approach to alcohol, as the Quran specifically prohibits all alcohol use. However, wine remained a part of court life during most periods of Islamic rule, and the Muslim overlords did not usually interfere with the social habits, including alcohol use, of the Hindu (and Christian) populace (Sharma et al., 2010).

Throughout the period of Islamic rule in India, regardless of the occasional imposition of strict prohibitions, it appears that drinking of “country liquor” and homebrewed beers (often rice beer), as well as toddy (in south India), continued to be common among the lower income, lower caste people, especially in rural areas. Also, considerable numbers of middle and upper classes in both Hindu and Muslim communities continued to use alcohol in varying degrees (Sharma et al., 2010).

1.2.a.iv Period of British Rule (1800-1947) - When the British and other European colonial powers came to India in the 16th and 17th centuries, the consumption of alcohol gradually increased (Saxena, 1999; Parkar et al., 2001 and Benegal, 2005). Under British rules, India witnessed a slow and steady rise in licit alcohol availability and consumption. There was a change in the types of beverages consumed, in the patterns of drinking as well as in the attitude of the society towards drinking alcohol. During the colonial period distilled beverages of a much higher alcohol content gradually replaced traditional fermented beverages. The first commercial distillery in India was established in 1805 and “Indian Pale Ale” came to be the special brew in India. Various branches of distillation centres and new breweries were developed in north and south India (Statemaster, 2010).

The another factor that opened new avenues for alcohol consumption in India was the participation of Indian soldiers in World Wars and westernization.
Westernization influences on the life styles of educated Indians which drive western style of alcohol use as a status symbol (Sharma et al., 2010).

1.2.a.v Post Independence - Since the 1970s there has been a strong increase in the use of alcoholic beverages in Indian society (Mohan and Sharma, 1995; Saxena, 1999 and Parkar et al., 2001). The contemporary alcohol consumption pattern has been changing its themes and images from ritualistic and occasional to become a part of everyday social intercourse and entertainment at regional and local levels. Traditional drinking patterns have continued among many sectors of tribal populations and other marginal, low income populations. Across most tribal populations, alcohol plays an important role in all stages from negotiation to celebration of marriage, as well as other major life events.

The availability of alcoholic beverages in India is mainly from industrialized sector. However, home brewed alcohol is also available in some parts of the country. Both beer and wine have been produced in industrialized sector (WHO, 2003). Besides the beer and wine, spirit industry has grown fully under two broad categories namely Indian made foreign liquor (IMFL) made by large industrial houses and India made country liquor (IMCL). There are over 50 manufacturers, 1500 wholesalers and 28,000 retail outlets for IMFL and beer in the country mostly concentrated in cities (WHO, 2003). Country liquors are distilled beverages made by small manufacturers under license from the government. Such beverages are made from locally available raw materials and marketed locally such as arrack, desi sharab, tari, tharra, etc. These country liquor being the cheapest available legal drinks are reported to be consumed in large quantities all over the country.

Beside the above categories of alcohol beverages, illicit liquor is also produced in small industries all over the country. Such liquor is produced without following standard rules and regulations given by government and excise duty is also not paid on these beverages. It has become the cheapest liquor in the country and thus enjoys substantial popularity. The raw materials are usually locally available cheap materials such as sugar, rice, grains etc. Both country liquor and illicit liquor outlets are predominant in rural areas.
1.3 Distribution of Alcohol Dependence

Alcohol consumption is highly prevalent in many cultures and contributes to the global burden of disease constituting 3.2% of deaths worldwide (Ker and Ivers, 2006). In fact, there is a causal relationship between alcohol consumption and more than 60 types of diseases and injuries including cancer, cardiovascular diseases, liver cirrhosis, neuropsychiatric disorders, homicide, epileptic seizures and motor vehicle accidents worldwide. Alcohol dependence which has been proven to have a high genetic basis, is one potentially fatal consequence of chronic heavy alcohol consumption, and may be regarded as one of the most prevalent neuropsychiatric diseases afflicting our society today. The desire for alcohol drinking with time and availability of alcoholic beverages will be leading to pathological craving for alcohol. On availability of alcohol only some individuals become alcohol dependant (AD) whereas other don’t. Even among AD individuals or chronic alcoholics, susceptibility to alcohol related diseases like liver cirrhosis, cardiovascular diseases, neuropsychiatric disorders etc. vary differentially. Apart from this, the onset of the alcohol dependence or chronic alcoholism and their biological consequences also vary from person to person.

1.3.a World Scenario

Alcoholic beverages are widely consumed throughout the world. The great majority of high-income modern society regularly consumes alcohol. According to the global status report on alcohol and health (WHO, 2011), the world’s highest alcohol consumption levels (aged 15 years or older), risky patterns of drinking, are found in the developed world (western and eastern Europe) mostly the Northern Hemisphere, but also in Argentina, Australia and New Zealand. Luxemburg has the highest level of consumption worldwide at more than 13 liters per year. In fact, Europeans countries have high rate of alcohol consumption per capita of 10 liters of pure ethanol per year (Spanagel, 2009). In Southern Africa and North and South America medium consumption levels is reported. Low alcohol consumption levels are found in the countries of North Africa and sub-Saharan Africa, the Eastern Mediterranean region, and southern Asia and the Indian Ocean where large populations are of Islamic faith (WHO, 2011). Nine countries report a complete ban on alcohol - Afghanistan, Brunei
Darussalam, the Islamic Republic of Iran, Maldives, Mauritania, Pakistan, Saudi Arabia, Somalia and Sudan. Four other countries report partial bans on alcohol such as Bangladesh, Comoros, India (in five states) and Qatar.

![Alcohol consumption map](image)

**Figure 1.1:** Alcohol consumption by total adult (15+) per capita in liters of pure ethanol (Best estimates of 2005 using average recorded alcohol consumption 2003-2005), WHO 2011.

### 1.3.b Indian Scenario
Alcoholic beverages become the most important commodities worldwide due to common beliefs of stress-relieving effect and also thought to produce positive mood states (Spanagel, 2009). Alcohol consumption has been steadily increasing in developing countries like India and decreasing in developed countries since the 1980s. India is generally regarded as a traditional ‘abstaining’ culture (Bennet et al, 1993). However, alcohol consumption seems to be accelerated by influence of west and global cultural pressures. India also has one of the largest alcohol beverage industries in the world contributing to 65 percent of alcohol production and nearly 7 percent of imports into the South Asian region. The amount of alcohol produced in India during 2006-07 was approximately 4 million metric tons.
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Figure 1.2: Recorded adult per capita consumption (age 15+) of alcohol in India
(Sources: FAO (Food and Agriculture Organization of the United Nations), World Drink Trends 2003, WHO 2004)

Patterns of alcohol consumption vary widely through the country and the pattern of drinking to intoxication is also increasing in the country which leads to higher proportion of harmful use and dependence leading to adverse impact on health aspects. Simultaneously, there is an affect of alcohol dependence on socio-economic and burden on the nation. Approximately around 62.5 million alcohol users were estimated in India. About 80% of alcohol consumption is in the form of hard liquor or distilled spirits showing that the majority drinks beverages with a high concentration of alcohol. Branded liquor accounts for about 40% of alcohol consumption while the rest is in the form of country liquor. A large portion of this consumption was homemade and illegally produced alcohol or in other words, unrecorded alcohol.

Punjab, Andhra Pradesh, Goa and the North-Eastern states have a much higher proportion of male alcohol consumers than the rest of the country. Women tend to drink more in the states of Arunachal Pradesh, Assam and Sikkim in North-East; Madhya Pradesh, Chhattisgarh, Orissa and Andhra Pradesh in central and east India; and Goa in the west, compared to other states (NFHS, 2007). A very high frequency of alcohol consumption has been recorded among tribal, rural and lower socio-economic urban sections. The unrecorded consumption of alcohol still remains high in India.
1.3.c Pattern of Alcohol use in Manipur

From the time immemorial, the people of Manipur use *yu* (fermented rice brew) the local liquor for various purposes as described by various folk tales and historical facts. It is deeply embedded in the culture and social activities like worship of god, birth rites and marriage negotiation since it is considered as a good omen. It is equally important during festive occasions and even dead mourning (Ghosh and Ghosh, 1997). A pot of *yu* is invariably kept near the dead body when buried. Traditionally it is used as a drug and prescribes to patients only by traditional healers (*Maiba* and *Maibi*) (Singh and Singh, 2006). Consumption of alcohol was not a taboo during pre-Hinduism according to various folk tales and historical facts (Ghosh and Ghosh, 1997). But drinking was restricted and follows strict rules and guidelines under *Yupalpa*, governing who could drink under what circumstances. *Yupalpa* is a post reserved in the Meitei ancient king’s court that looks after overall administration of
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The yu. After entering Hindu tradition (Hinduism) and Christianity some two centuries back, social taboo were brought against consumption of alcoholic beverages, ensuring stoppage of production of distilled liquor from the society, but the process still continued in villages mainly inhibited by schedule caste and tribes (Singh and Singh, 2006). As a consequence consumption of alcohol has won social acceptance in spite of the social taboo during various occasions, social or domestic.

At present, alcohol is used as a compulsory delicious item in every aspect of daily routine work where people are gathered like party, functions and agricultural practices. If it is not served in any field then it is considered as meaningless, so there is no party (big/small) where alcohol is not served. Most of the households have one or two alcohol abusers which may range from normal users to dependence. Old or middle aged individuals use to drink before having meal in most of the time with the conception that, it is good for health and helps in digestion too. However, alcohol consumption by women is socially unacceptable in this society (Singh et al., 2005). On the other side alcohol use among youth becomes a serious problem in the state.

Data from regional surveys (male subjects 15 years and above) conducted in 1997 show that the rate of heavy drinking among male current drinkers was 89% in Thoubal District, Manipur (WHS, 2004). Here, it can be said that most of the youth in this particular district had used or tasted alcohol once in their adolescent life. 81.1% of men were not able to limit the use of alcohol and 80.3% reported being often intoxicated when required to fulfill major obligations. About 40.1% of the population in Thoubal district reported giving up social, occupational or recreational activities due to alcohol (WHO, 2004). In a very recent study conducted by Ningombam et al. (2011) reported higher (54%) prevalence of tobacco and alcohol use among higher school students of Manipur.

At the moment the use of alcohol is infrequent among women who also tend to resist the habit among male family members. One of the contributing factors of alcohol dependence in Manipur has been cited as widely available in every nook and corner despite the fact that it is officially declared “dry” state. By dry state, selling and consumption of alcohols in shop or market is banned. But it is still available in the locales. Every locality has at least 5 to 6 vendor within 1km radius of boundary. Frequencies of such vendors are more in rural areas while compared to urban. Most of
the common brands of alcohol are also available besides the local liquor. These vendors are not only the source of alcohol, some army canteens where many kinds of foreign liquor are available are also other sources of alcohol. It is also imported from neighbouring state, Assam where a lot of manufacturing companies are legally situated. On the other hand, it is also imported from the neighbouring country Myanmar via Moreh, a town sharing border with other Asian countries like China, Thialand and Myanmar.

1.4 Alcohol Metabolism
Alcohol is easily absorbable substance and can be easily absorbed without any change in structure along the whole length of the digestive tract. Absorption takes place from stomach where around 20% is absorbed and remaining 80% (approximately) is rapidly absorbed in intestine. From intestine, it is directly absorbed into blood stream from where it is distributed quickly throughout the body until all the alcohol consumed has been metabolized affecting the brain and other tissues (Bosron et al., 1993). Alcohol thus absorbed is further metabolized in the body through oxidation reaction to get rid of from the body. The distribution of alcohol throughout the body is largely governed by the water content of various organs and tissues due to its small molecular size and completely water soluble nature. The volume of distribution of alcohol is comparable to total body water (Marshall et al., 1983 and Holford, 1987). Unmetabolised alcohol around 2-8% is excreted unchanged in the breath (0.7%), through urine (0.3%) and sweat (0.1%) (Holford, 1987). Elimination of alcohol occurs mainly via hepatic oxidation and is governed by the catalytic properties of the alcohol metabolizing enzymes.
1.4.4 Alcohol and Liver

Ethanol (CH\(_3\)CH\(_2\)OH) is predominantly metabolized in the liver cell cytosol and it is also metabolized to a lesser extent in kidneys, lungs and other tissues by the enzyme alcohol dehydrogenase (ADH) producing acetaldehyde (CH\(_3\)CHO), with nicotinamide adenine dinucleotide (NAD) acting as the hydrogen acceptor. Ethanol is also metabolized in a low percentage by a family of liver endoplasmic reticulum
(microsome) enzymes known as cytochrome P450 (CYP) (Roberts et al., 1994). As a third route of ethanol metabolism, catalase in the peroxisomes of liver and in other cells metabolizes a small amount of ethanol when sufficient hydrogen peroxide \((H_2O_2)\) is available without requiring NAD as a cofactor. All three of these means of metabolizing ethanol result in acetaldehyde. Acetaldehyde is then further metabolized in mitochondria by the enzyme acetaldehyde dehydrogenase to acetic acid \((CH_3COOH)\), which can be further metabolized into carbon dioxide and water finally releasing energy (von Wartburg, 1971).

Daily drinking of alcohol increases liver metabolism of ethanol by as much as a third but acetaldehyde is not always rapidly metabolized. Acetaldehyde released into the bloodstream can drift to other organs, notably the brain, where it can damage proteins and DNA as well as cause lipid peroxidation in membranes. Accumulation of high doses of acetaldehyde may cause facial flushing, headache, nausea, vomiting and other side effects. Excessive drinking may also lead to triglyceride accumulation resulting fatty liver due to increase of Nicotinamide Adenine Dinucleotide - Hydrogen (NADH) quantities. High alcohol and fat consumption along with low protein and carbohydrate consumption helps turn fatty liver into alcoholic liver cirrhosis, a cause of death for some alcoholics. Ethanol also increases the release of arachidonic acid from cell membranes, increasing oxidative stress. In ethanol-damaged livers there is a decrease in activity of S-AdenosylMethionine (SAMe) synthetase, the enzyme that synthesizes SAMe from methionine. Deficiency of SAMe results in membrane damage, which further worsens liver damage (Lieber, 2000a).

### 1.4.b Alcohol and Brain

Ethanol exerts its primary effects through modulation of action of a number of brain neurotransmitters, notably subtypes of receptors for dopamine, gamma-aminobutyric acid (GABA) and glutamate. Ethanol also alters the activity of the brain signaling chemicals serotonin, acetylcholine, noradrenaline, endorphin, encephalin and neuropeptide (Israel and Kalant, 1963). When alcohol reaches brain, it increases dopamine release in the nucleus accumbens, a brain "pleasure center" similarly activated by cocaine. It enhances reward or pleasure phenomenon. However, chronic and or high levels of alcohol will eventually lead to a decrease in dopamine release.
This imbalance in chemicals can result in negative feelings such as anxiety, anger or in a carving for a substance. Therefore, alcohol tolerance and dependence can be attributed to compensatory synaptic plasticity, particularly an adaptive increase in dopamine receptors enhancing reward or pleasure phenomenon (Gilpin and Koob, 2008).

GABA is the major inhibitory neurotransmitter in the brain. GABA\textsubscript{A} receptors are a family of chloride ion channels that predominately mediate rapid inhibitory neurotransmission throughout the central nervous system (CNS). The neurotransmitter GABA binds to these receptors, changing their conformation state and thereby opening the pore to allow chloride ions (Cl\textsuperscript{-}) to pass down an electrochemical gradient. The flux of chloride ions hyperpolarizes the membrane leading to neuronal inhibition. Ethanol augments the influx of chlorine ions due to GABA, which has much to do with the sedative, tranquilizing and/or anaesthetic properties of beverage alcohol. The motor incoordination due to ethanol is caused by potentiation of GABA\textsubscript{A}-associated adenosine A\textsubscript{2A} receptors in the striatum (Meng et al., 1997). The effects of chronic ethanol administration are influenced by adaptations in GABA\textsubscript{A} receptor function, expression, trafficking, and sub-cellular localization that contribute to ethanol tolerance, dependence, and withdrawal hyperexcitability.

The third brain neurotransmitter receptor most strongly affected by ethanol is the NMDA (N-Methyl-D-Aspartate) receptor for glutamic acid (glutamate). It is associated with memory formation through a process known as LTP (Long-Term Potention) in hippocampus. Ethanol, especially heavy drinking, is a potent inhibitor of the NMDA receptor can block LTP almost entirely causing/resulting memory lost (Givens and Mcmahon, 1995).

1.5 Factors Influencing Alcohol Metabolism

The rate of absorption after drinking is influenced by various factors such as -

1.5.a Food – presence of food and type of food in the gastrointestinal tract influence the absorption process. Higher the dietary fat, protein and
carbohydrates content, longer the time for absorption since more time is required for emptying the stomach (Jones and Jonsson, 1994).

1.5.b Gender and Body Composition - men and women absorb alcohol differently. Women are found to have higher blood alcohol concentrations (BAC’s) after consuming the same amount of alcohol as men. This difference has been attributed to women’s smaller amount of body water (Mumenthaler et al., 1999) and lower activity of the alcohol metabolizing enzyme (Frezza et al., 1990 and Seitz et al., 1993). In general, low weight individuals are more affected by a given amount of alcohol than the heavier individuals. However, for people of the same weight, a well muscled individual will be less affected than someone with a higher percentage of fat since fatty tissue does not contain much water and will not absorb much alcohol.

1.5.c Nature and Concentration of the Alcoholic Beverage - The nature and concentration of the alcoholic beverage that one ingests can have a slight effect on the peak alcohol concentration, due to the differences in absorption rate of different concentrations of alcohol. It is most rapidly absorbed when the concentration of the drink is between 10% and 30% alcohol (O’Neill et al., 1983).

1.5.d Rate of Ingestion - blood alcohol concentration depends on the amount of alcohol consumed and the rate at which the user's body metabolizes alcohol. Because the body metabolizes alcohol at a fairly constant rate (somewhat more quickly at higher and lower alcohol concentrations), ingesting alcohol at a rate higher than the rate of elimination results in a cumulative effect and an increasing blood alcohol concentration (O’Neill et al., 1983 and Dubowski, 1985).

1.6 ALCOHOL DEPENDENCE: Definition, its History and Development
When definitions of alcoholism are concerned there are many definitions since there are different types of alcoholics or alcohol related problems. The term alcoholism is very broad and has been associated with many problems in defining since it is a member of a heterogeneous population afflicted with an ailment that is multi factorial
in origin. The term alcoholism was first used in 1849 by the Physician Magnus Huss to describe the systematic adverse effects of alcohol (Magnus, 1852). The definitions of alcoholism vary significantly between the medical, treatment programs, laws and the general public since there are many pattern (light, moderate and heavy drinkers) and facets of alcoholism (such as biochemical, psychiatric, moral, sociological and legal). To overcome such difficulties in defining the term alcoholism, other words have been used to describe the disease phenotype such as - alcoholics, alcohol dependents, alcohol addiction and problem drinkers.

Trotter, (1788) a Scottish physician for the first time defined excessive drinking of alcohol as a disease or medical condition. The term “addiction” was used in defining for those who lose control on drinking alcohol, by Benjamin Rush in 1800s (Katcher, 1993). Researchers started defining alcohol dependence as maladaptive behaviours that result in the persistent, compulsive and uncontrolled use of alcohol. Thus, intermittent or continual ingestion of alcohol is thought to be a risk leading to dependency.

In the 1930s and 40s, the role of genetic factors in the etiology of alcoholism was almost totally dismissed. However various research works on the topic make it regain acceptance in the 1950s and has remained popular since. World Health Organization (1952) defines alcoholics in a broad sense as “Those excessive drinkers whose dependence on alcohol has attained such a degree that it shows a noticeable mental disturbance or an interface with their bodily and mental health, their interpersonal relations, and their smooth social and economic functioning; or who show the prodromal signs of such development. They therefore require treatment”. It emphasizes various influencing factors such as interpersonal relations, and social and economic functioning but it is lengthy and weighty definition as well as it relies on the use of the word ‘excessive drinking’ which is problematic in defining. There are many definitions of alcoholism reflecting the difficulties associated with describing a phenomenon in which social and physiological factors play varying parts. Jellinek, (1956) put forward the modern theory of alcoholism as a disease in his famous book "The Disease Concept of Alcoholism". In the same year the American Medical Association (AMA) had declared that alcoholism was an illness. Alcoholism is also
defined as “a heterogenous set of behaviour that includes the pattern of alcohol intake that causes medical and / or social complications (Cloninger et al., 1981)

According to National Council on Alcoholism and Drug Dependence (NACDD), alcoholism is a primary, chronic disease with genetic, psychological and environmental factors influencing its development and manifestation. The disease is often progressive and fatal (Morse and Flavin, 1992). World Health Organization (1993) redefined the term alcoholism as a multi factorial disease with complex mode of inheritance in addition to the influence of psychological and social factors.

Proper diagnosis, identifying and labeling of specific conditions became equally important and useful to clinicians and researchers in studying/understanding the etiology of the disease. It allows clinicians to monitor and plan treatment and also enables public health planners to ensure the availability of treatment facilities and also help in health care. Diagnostic criteria for alcohol abuse and dependence have evolved over time. It reached a turning point in 1980 with the publication of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) (American Psychiatric Association, 1980). Researchers revised the criteria to improve their reliability, validity and precision.

At present, clinicians, international health agencies and researchers are able to categorize people with alcohol dependence, abuse and harmful use, since the publication of revised and improved diagnostic criteria of alcohol dependence by American Psychiatric Association’s (1994) Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV). According to this criteria, for the first time the term “alcoholism” was dropped in favour of two distinct categories labelled “alcohol abuse” and “alcohol dependence” (Nathan, 1991; Babor, 1992; Schuckit, 1994 and Cottler et al., 1995). This DSM IV criterion for alcohol dependence and abuse is usually relied by most of the researchers and clinicians in the United States.

World Health Organization also developed diagnostic criteria (International Classification of Disease 10 (ICD-10) for the purpose of compiling statistics on all causes of death and illness, including those related to alcohol abuse or dependence, worldwide (Grant, 1989; Babor, 1992 and Rounsaville et al., 1993). ICD-10 is an international diagnostic and classification system for all causes of death and disability, including psychiatric disorders (Rounsaville et al., 1993). Here, alcohol dependence is
defined in a way that is similar to the DSM. The diagnosis focuses on an interrelated cluster of psychological symptoms (craving), physiological signs (tolerance and withdrawal) and behavioural indicators such as the use of alcohol to relieve withdrawal discomfort (Babor, 1992). The use of alcohol takes on a much higher priority for a given individual than other behaviours that once had greater value. However, ICD-10 includes the concept of “harmful use” rather than alcohol abuse. Harmful use of alcohol is defined as “a pattern of psychoactive substance use that is causing damage to health”. Damage – may be physical (e.g. Liver damage) or mental (e.g. Episodes of depression) (ICD-10, WHO, 1992).

In the present study, DSM-IV criteria for classifying alcohol dependence have been used for selecting the case (alcohol dependence) and control individuals.

Alcohol dependence according to DSM-IV criteria could be summarized as a maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by three or more of the following seven criteria, occurring at any time in the same 12 month period.

1. **Tolerance** - a need for markedly increased drinking amounts of alcohol to achieve intoxication or desired effects. In other words markedly diminish alcohol effect with continued use of the same amount of alcohol.

2. **Alcohol withdrawal signs or symptoms** - Alcohol is taken to relieve or avoid withdrawal symptoms such as delirium, convulsion, anxiety, fatigue, depression etc.

3. **Drinking more than intended** - alcohol is often taken in larger amounts or over a longer period than was intended.

4. **Unsuccessful attempts to cut down on use** - a persistent desire or there are unsuccessful efforts to cut down or control alcohol use.

5. **Excessive time related to alcohol** - a great deal of time is spent in activities necessary to obtain alcohol, use alcohol or recover from its effects for example hangover.
6. **Impaired social or work activities due to alcohol** - important social, occupational, or recreational activities are given up or reduced because of alcohol use.

7. **Use despite physical or psychological consequences** – continued alcohol use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the alcohol for example continued drinking despite recognition that alcohol liver disease may develop by alcohol consumption.

Thus, alcoholism refers to the persistent consumption of alcoholic beverages despite the associated detrimental effects on health (physiologic and psychological) and social relationships.

### 1.7 Etiology of Alcohol Dependence

Alcoholism is an extremely complex disease resulting from the complex interaction between the socio-environmental context, the individual at risk (genetic) and availability of alcohol (Sloan et al., 2008). Heritability, genetic factors, estimates for alcoholism range from 50% to 60% signifying the importance of genetic factors as well as environmental in the etiology of alcoholism (Goldman, 1993; Rose, 1998 and Dick and Bierut, 2006). Development of alcoholism by some individuals depends on the presence of genetically controlled predisposing factors interacting with environmentally determined precipitating factors (Agarwal, 2001). Here, we can quote the finding of Rose and Dick (2005) that is environment is most important for initiation of drinking, whereas genetic influences are more important for establishing drinking patterns. Thus, the search for potential causative genes is rather complicated; an unknown number of genes as well as environmental factors may be involved in the development of alcohol dependence.

#### 1.7.a Environmental Factors

Environmental factors are important in understanding the etiology of alcohol dependence. Environmental vulnerability to alcoholism is likely to be due to
numerous factors like alcohol availability, peer group, parental attitudes, education, occupation, early onset age of alcohol consumption, etc. For example, drinking at an early age (early onset of drinking) has been associated with later alcoholism and other drinking problems. Since, adolescence is a critically vulnerable time for the development of risky drinking habits that may lead to permanent neurobiological changes with significant consequences including the development of addiction.

Individuals consuming alcohol before the age of 15 years are found to be associated with fourfold increased risk for lifetime alcoholism compared with starting at the age of 21 years (Grant and Dawson, 1998). Study in Indian population (Ajmer district, Rajasthan) observed the significant association of alcohol abuse with age (higher in age group more than 20 years) (Sundaram et al., 1984). Other studies also suggest that environmental influences (like peer pressure, alcohol availability etc), strongly influence if and when a child starts to drink. Bonomo et al. (2004) as well reported that frequent drinking in adolescence shown independent increase risk for alcoholism since, drinking during adolescence can impair brain development (particularly the hippocampus) and its function (De Bellis et al., 2000 and Hiller-Sturmhofel and Swartzwelder, 2004). Enoch, (2006) notes down that adolescence is a critically vulnerable time for the development of risky drinking habits that may lead to permanent neurobiological changes with significant consequences including the development of addiction.

Now, early onset of alcohol consumption has become an important issue globally. Reports of youth risk behavior survey (by Centers for Disease Control and Prevention) reveals that more than 20% of high school students drink alcohol before age of 13 years in United States (Grunbaum et al., 2003). Monitoring the Future (MTF) - a long term study of American adolescents, college students and adults through age 50 reveals that the drinking tends to start in the teenage (11 to 13 years) among adolescent Americans (Johnston et al., 2005). One reason for this could be sheer enjoyment and to get relief of social anxiety.

Education level has been found to have an impact on the risk of drug or alcohol abuse. Studies on education level and substance abuse relationship reported that high school dropping out students was associated with elevated risk of alcohol disorders relative to those with higher degree students among African Americans and white Americans.
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(Crum and Anthony, 2000). In another study in Netherlands, abstinence was found to be decreased significantly by increasing in educational level. Moreover, excessive drinking, and notably very excessive drinking, was found to be more prevalent in the lowest educational group. Furthermore, after controlling for differences in drinking behavior they also found the evidence for higher prevalence of alcohol-related problems in lower educational levels (van Oers et al., 1999). Higher socioeconomic status and educational aspiration have been shown to protect against heavy drinking in adolescence (Tiet et al., 1998). In general, a lower socioeconomic status (SES) is related to a lower health status, more health problems, and a shorter life expectancy.

In a large scale study including over 30,000 men and women aged 20-93 in Copenhagen found that those with the lowest level of schooling were most frequently heavy smokers, heavy drinkers and the most physically inactive (Schnohr et al., 2004). Similarly, it has been reported that nearly half of all clients in treatment for drug or alcohol abuse never went to school or only completed primary school (European Monitoring Centre for Drugs and Drug Addiction, National Reports (EMCDDA, 2002). These results suggest that education level may have some influence on those who would abuse alcohol and drugs, but it is not a definite indicator. In an epidemiological survey conducted by department of psychiatry, Government Medical College and Hospital, Chandigarh estimating the pattern of alcohol and other substance dependence in rural and slum dwellers population of Chandigarh revealed that majority of the individuals who consume alcohol or other substance were found to be illiterate (37.67%) (Chavan et al., 2007).

Epidemiological studies also reveal that prevalence of alcohol and other substance use increases in rural areas. Spence and Wallisch, (2007) reported an increasing trend in illicit drug use and substance related problems in rural but not in urban areas in Texas. According to National household survey on drug abuse (NHSDA) prevalence of illicit drug use reveals an emergent trend among rural youths (Vega et al., 2007). However, on an average across all age groups highest rate of illicit drug use was observed among residents of large metropolitan areas followed by nonmetropolitan areas and completely rural countries. Cronk and Sarvela (1997) also propose higher rates of alcohol usage and other substances like methamphetamines and inhalants among rural youths than urban youths. Data from National Survey of Drug Use and Health (2008-
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2009) examines alcohol use among rural and urban adolescents between the ages of 12 and 17 reveals that rural adolescents exhibited higher alcohol use than their urban counterparts among adolescents of USA (Gale et al., 2012). Studies on rural population of Uttar Pradesh (India) reported that alcohol consumption was commonest substance abuse (82.5%) followed by cannabis (16.1%) (Sethi and Trivedi, 1979). In a survey of 4 villages in Punjab, majority of the population (78.28%) consumed alcohol (Deb and Jindal (1974) suggesting the elevated prevalence among rural population.

Gender also plays an important role in drug taking behavior in India. No female was reported for use of any substance (Chavan et al., 2007). Epidemiological surveys conducted in different parts of India, similar findings had been documented by Lal and Singh (1979). Ghulam et al. (1996) highlighted that gender is an important factor in drug taking behavior. On the other side, several studies reveal apparent associations between occupations and alcohol-related disorders. Analyses of the data from individuals currently employed and not employed in their occupation reveals reduction in risk for those who leave some occupations and increased risk for those who leave other occupations (Mandell et al., 1992). Harford et al. (1992) provides estimates of alcohol consumption and alcohol dependence among employed men and women in the United States. The prevalence of alcohol dependence was highest in certain blue-collar occupations (craftsmen, laborers, and service workers among men; machine operators, laborers, and service workers among women) than white-collar jobs. Findings of such studies reveal that employment in some occupations may be protective for Alcohol Dependence.

Alcohol consumption and tobacco use are closely linked behaviours. Studies have found that people who drink alcohol often also smoke and vice versa (Bobo and Husten, 2000). People who are dependent on alcohol are three times more likely than those in the general population to be smokers, and people who are dependent on tobacco are four times more likely than the general population to be dependent on alcohol (Grant et al., 2004).

In fact, smoking rates among alcoholics have been estimated to be as high as 90 percent, with approximately 70 percent of alcoholics smoking at least one pack of cigarettes per day (NIAAA, 1998). Similarly, smokers are far more likely to consume
alcohol than are nonsmokers, and smokers who are dependent on nicotine have a 2.7 times greater risk of becoming alcohol dependent than nonsmokers (Breslau, 1995). Alcohol dependence and smoking, individually and in combination, are complex forms of addictive behavior that may be influenced by a variety of genetic, neurobiological, conditioning, and psychosocial mechanisms (Drobes, 2002).

**Figure 1.5: Alcoholism: Gene and Environmental Factors**

### 1.7.b Genetics of Alcohol Dependence

Cultural and Biological factors are two important factors in understanding the study of alcoholism. Studies on genetic predisposition mainly focus on the familial, in particular genetic, determinants of disease and the joint effects of genes and non-genetic determinants (Burton et al., 2005). The familial nature of alcohol dependence has been recognized since the time of ancient Greeks. Goldman et al. (2005) emphasizes that alcohol dependence runs in families and its heritability excess of 50%.

Innumerable epidemiological studies have been trying to demonstrate the vital role of genetic propagation of the disease alcoholism, which was commonly believed to be environmental, depends on ones behaviour as well as believed to be disease of middle age. It can be said that genetic evidence for the disease alcoholism comes from basically four different methods of studies such as family studies of biologically related individuals; twin studies; adoption studies and genetic linkage studies.
1.7.b.i Family Studies

A trend of transmission of alcoholism, from alcoholic parents to their children has been observed from different family studies on alcoholism suggesting a high degree of familial association. In early days, alcoholism was also classified into two forms - familial and non-familial suggesting the predisposition as well as inheritance of the disease (Cotton, 1979). Several family studies have provided high prevalence of alcohol dependence among family members of alcoholics than in relatives of non alcoholics (Goodwin, 1976 and Cotton, 1979). Risk of developing alcohol dependence ranges from two fold (Dawson et al., 1992) to five fold in first degree relatives of alcoholic parents (Cotton, 1979). If a second or third degree relative is affected than risk of developing alcohol dependence reaches upto third fold (Dawson et al., 1992). However, such familial resemblance could be due to shared family environment rather than shared heredity.

1.7.b.ii Twin Studies

Twin studies have been used as a powerful method in understanding the genetic basis of disorders. It is well known that if any differences are found between identical twins that would be due to environmental influences while differences between non-identical twins may be due to heredity, environment or both (Aggarwal, 2001). A disorder is likely to be under genetic influence if concordance rates are higher in monozygotic (MZ) twins, who share 100% of their genes, than dizygotic (DZ) twins, who share 50% of their genes on average. The heredity basis of alcoholism has been first explored in Sweden and Finland twin studies (Kaij, 1960 and Partanen et al., 1966). Studies on over 16,000 twin pairs found higher concordance rates among monozygotic twins for alcoholism as compared to dizygotic twins (Loehlin, 1972 and Pickens et al., 1991). According to various epidemiological twin studies, risk of hereditary transmission of alcoholism ranges between 50 to 64% and heritability was stable over time (Heath et al., 1997 and Prescott and Kendler, 1999). Applying tetrachoric correlation and model fitting, Gelernter et al. (2009) documented twin resemblance of developing alcoholism to genetic factors (54%), family environment factors (14%) and non-shared environmental factors (remainder 32%). Findings of such twin studies strongly suggested the role of genetic effect in alcohol dependence.
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However, it should be viewed in the light of adoption studies to further disentangle the genetics from environmental effects.

1.7.b.iii Adoption Studies

It is an approach to understand the development of the disease by studying individuals separated from biological parents and raised by foster parents living in a different environment. Researchers were trying to prove the genetic basis of alcoholism through such studies which are believed to be the most powerful way to disentangle the genetic and environmental factors predisposing to the disease. According to Prescott and Kendler (1999), relatives of alcoholics have a four times greater risk of alcohol dependence showing the evidence that genetics plays an important role in developing alcoholism (Cloninger et al., 1981). Children of alcoholic parents were at greater risk for alcoholism while comparing with children born to nonalcoholic parents when they were adopted away from their respective family (Sigvardsson et al., 1996). Remarkably similar rates of alcoholism was also established among siblings of alcoholic parents regardless of whether they were brought up by their biological parents or were adopted (Cadoret et al., 1986).

Such studies on alcoholism, point out that alcoholism is a complex disease that most likely results from the interplay between genetic predisposition and socio-environmental factors (Cloninger, 1987 and Merikangas, 1990). Alcoholism is also considered as a common but etiologically disorder involving several gene(s) with gene and environmental interactions (Enoch, 2006). Various methods of genetic studies have come up with advancement in the field of science and technology which have been trying to find out the true genetic basis of alcoholism. Of which disease-marker association studies, an approach to understand the development of the disease if the cause is really genetic in nature, have become increasingly more popular because of the ambiguity of the definition of phenotypes as well as mode of inheritance and the possibility of multiple gene involvement (Crowe, 1993; Hodge, 1994 and Chen et al., 1997)

In the search for genetic basis for such a complex disorder, a large number of genetic markers have been studied to find an association with alcohol dependence. As yet, no comprehensive, well-powered study has been published in association with the
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Alcoholism: Its Genetics and Impact on Health – A study among Meiteis of Manipur, India

As the genetic predisposition to alcoholism and its related morbidity is undeniable, the research in this time has picked up momentum targeting various pathways involved in alcohol consumption and metabolism. Therefore, genetic predisposition to alcoholism can be studied under two broad aspects such as –

i) Genetics of alcohol Metabolism – understanding genetic behaviour of genes/markers responsible for alcohol metabolism might help in revealing the genetic aspects of alcohol metabolism leading to alcoholism.

ii) Genetics of Neurocognitive functions related to alcohol – understanding role of genes which are associated with neurobehavioral pathways could lead to better understanding of the complexity of alcoholism.

Aversion to alcohol, wanting to have alcohol, craving to have alcohol and addiction to alcohol are characteristics which talk about the cognitive behaviours of a person. Above parameters knowingly or unknowingly lead to consumption of alcohol which needs to be metabolized in the body of an individual. Thus both metabolic and neurological pathways go hand in hand in the onset of alcohol related diseases/phenotypes. Therefore genes involved in these two pathways are expected to be vital in terms of genetic etiology of alcohol dependence.

1.8 Genetic Markers for Alcohol Dependence: Candidate Gene Studies

Candidate gene approach can be defined as the study of the genetic influences on a complex trait by: generating hypotheses about, and identifying candidate genes that might have a role in, the etiology of the disease (Tabor et al., 2002). Selected important genetic markers for the present study covering the above two broad aspects which are associated with alcoholism and its ill impacts on health are mentioned below:

1.8.a Genes related with Alcohol Metabolism

Understanding metabolism of alcohol can suggest the causes of alcoholism. Individuals differ in the rate at which alcohol is metabolized (pharmacokinetics) and in the extent to which they are affected by a given dose of alcohol.
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(pharmacodynamics). These individual differences affect drinking behavior, the potential for the development of alcohol dependence, and the risk for developing alcohol induced organ damage. Of special interest is the finding that the metabolism of alcohol varies among people and that variations in metabolism are particularly noticeable among certain ethnic groups (Suddendorf, 1989 and Goedde et al., 1992). Elimination of ethanol from the human body occurs through several pathways, including oxidative metabolism, pulmonary and renal excretion. Ethanol is first oxidized to acetaldehyde by the enzyme alcohol dehydrogenase (ADH) and acetaldehyde is oxidized to acetate by aldehyde dehydrogenase (ALDH) (Mulligan et al., 2003). Acetate thus produced is converted to acetyl coenzyme A (CoA) and enters either the citric acid cycle, where it is ultimately oxidized to carbon dioxide and water, or is involved in other metabolic functions. At present, the researcher has focused on understanding the potentially important role of alcohol and acetaldehyde metabolizing enzymes in the causation of alcoholism. The genes coding for ethanol metabolism enzymes (ADH and ALDH) have been widely studied as such liver enzymes are believed to be related to increased risk alcohol dependence (Kuo et al., 2008).

1.8.a.i Alcohol Dehydrogenase (ADH)
Alcohol dehydrogenase (ADH) catalyzes the oxidation of ethanol to acetaldehyde. In humans, there are five classes (I-V) of ADH (Jornvall and Hoog, 1995) coded by seven genes, characterized and mapped to a gene cluster, located on chromosome 4(q21-24) (Edenberg, 2000). Class I (ADH1, ADH2, ADH3) and II (ADH4) ADH are found to code for enzymes catalyzing the initial step in the pathway for the metabolism of ethanol (Crabb et al., 2004). Class I enzymes are mainly expressed in liver and contribute about 70% of the ethanol oxidizing capacity (Lee et al., 2004). According to kinetic property class I ADH is sub-divided into 3 subunits viz ADH1A (α), ADH1B (β) and ADH1C (γ). These genes encoding alpha, beta and gamma subunits are tandemly organized in a genomic segment as a gene cluster on chromosome 4 (Riess et al., 1994). The different isoenzymes of ADHs have been classified based on enzymatic and DNA/protein sequence characteristics (Duester et al., 1999 and Edenberg, 2000). The enzymes are very similar in sequence and
structure but differ in preferred substrates (Edenberg and Bosron, 1997). Two of the three class I genes (ADH1B and ADH1C) are known to have alleles producing enzymes that catalyze the oxidation of ethanol at different rates (Borson et al., 1980). These differences are thought to be underlying a part of the threefold variation in alcohol elimination rates among individuals (Bennion and Li, 1976 and Wagner et al., 1976), of which 50% is thought to be genetic in origin (Martin et al., 1985). Variation at these genes due to mutation may have allele possessing high enzyme activity for ethanol oxidation. This could lead to high concentration of acetaldehyde accumulation in the body (normal acetaldehyde in body is 9µM or 40µg percent). It is generally characterized by various syndromes such as reddening of the face and skin, increase heart rate, warmth, sleepiness, and light headedness. Thus, kinetic properties of such genes and their important role in the metabolism of ingested alcohol suggest an etiological role in the development of alcohol related health problems. Therefore, genes for class I and IV ethanol oxidizing ADH have been extensively studied in association studies of alcoholism.

Figure 1.6: Diagrammatic depiction of ADH gene location on chromosome no. 4 (q23)
Alcohol Dehydrogenase 1B (ADH1B Arg47His) Polymorphism

ADH1B is one of the ADH I class gene involved in oxidation of alcohol metabolism. It has three known functional variant ADH1B*1, ADH1B*2 and ADH1B*3. The functional variants of allele ADH1B*2 (47His) and ADH1B*3 (369Cys) have high enzyme activity and usually rapid conversion of ethanol to acetaldehyde. ADH1B gene exhibit single nucleotide polymorphisms (SNPs) resulting in critical single amino acid exchanges at different sites in the NADP coenzyme-binding domain (Yin, 1994). These functionally different alleles are the result of a single amino acid substitution at residue 47 in exon 3 (Arginine in ADH1B*1 and Histidine in ADH1B*2). Accordingly, the enzymes encoded by polymorphic forms of ADH1B display different maximal activities (Vmax) and affinities (Km) for ethanol (Bosron and Li, 1986 and Yin, 1994). The β2β2 isozyme resulting from the ADH1B*2 form of ADH1B Arg47His polymorphism has a significantly higher Vmax value (340 µM/min) for ethanol, and a maximal activity 40-fold that of β1β1 (9 µM/min) (Edenberg and Bosron, 1997). Therefore, ADH1B*2 homozygotes are predicted to produce higher levels of acetaldehyde, than any other ADH1B genotype. Increase in acetaldehyde may cause various side effects leading towards a protective role against alcohol dependence. This characteristic of ADH1B variation effects have been widely studied on alcohol use and dependant subjects among various populations.

Most early genetic association studies on the effects of ADH1B Arg47His polymorphism were performed in China, where the frequency of the ADH1B*2 allele is higher than elsewhere (Osier et al., 2002). Various association studies in Asian populations reported higher frequencies of ADH1B*2 allele in controls than in alcoholics (Thomasson et al., 1991; Chen et al., 1996; Shen et al., 1997 and Tanaka et al., 1997). Tsuchihashi-Makaya et al. (2009) also reported a significant association (p<0.001) with drinking behavior for ADH1B Arg47His polymorphism. A study on Israeli Jews by Neumark et al. (1998) indicated that the ADH1B Arg47His polymorphism accounted for 20-30% of variation in alcohol intake, and the less common ADH1B*2 served as a protective factor against alcohol dependence. Similar effects on alcohol consumption have been reported in young age group (33years), but not older among Israeli Jews (Spivak et al., 2007). Whitfield et al. (1998) also found
an association between ADH1B*2 and alcohol intake and dependence among Australians of European descent. Statistically significant differences were found among European alcohol dependent cases and controls (p=0.0016). ADH1B*2 frequency was higher in nonalcoholics (3.8%) than in alcoholics (1.3%) suggesting ADH1B*2 allele decreases the risk for alcohol dependence (Borra’s et al., 2000). In an integrated analysis of large sample size among Australian populations conducted by Macgregor et al. (2009) reported that the variation at rs1229984, the well known ADH1B Arg47His polymorphism, is highly significantly associated with more frequent alcohol reactions and lower alcohol intake. However, this polymorphism is not significantly associated with AD cases. In a recent study conducted by Tan et al. (2010) among Chinese and Indian population reported higher frequencies of ADH1B*2 allele among controls as compared to the alcohol-dependent subjects. They also reported higher frequency of this particular allele among Chinese population than Indian. Interestingly, individuals with homozygous ADH1B*2*2 genotype i.e. protective were found to be non alcohol dependent (Tan et al., 2010). The common ADH variants show distinct population distributions. ADH1B*2 is present at frequencies >0.59 (~90%) in East Asian populations (Eriksson et al., 2001), with the exception of a frequency of 0.33 among Thais. Very low frequency of this allele (<0.25) has been reported in European and Middle East populations. Moreover, African populations have been found to almost absent of this allele (Goedde et al., 1992; Neumark et al., 1998 and Goldman et al., 2005).

Figure 1.7: Diagrammatic depiction of ADH1B Arg47His gene polymorphism and protection from alcohol dependence
Alcohol Dehydrogenase 1C (ADH1C Ile349Val) Polymorphism
ADH1C gene encodes class I alcohol dehydrogenase, gamma subunit, which is a member of the alcohol dehydrogenase family. ADH1C has two functional variants ADH1C*1 (Isoleucine) and ADH1C*2 (Valine) which is the result of a single-nucleotide difference that causes an amino acid substitution in exon 8 (Edenberg and Bosron, 1997). The ADH1C encoded γ1 and γ2 homodimers also show a difference in their Vmax activities. The enzyme produced by ADH1C*1 (γ1 subunit) has a higher Vmax (88 mM/min) than that for the enzyme (γ2) produced by ADH1C*2 (35 mM/min) (Edenberg and Bosron, 1997). This amino acid substitution within ADH1C gene upon in vitro enzyme kinetics is well documented (Edenberg and Bosron, 1997). Individuals carrying ADH1C*1 have a faster predicted elimination rate for alcohol. Therefore, ADH1C*1 also plays an important role in protection against alcohol dependence.

The ADH1C*1 allele is generally found at higher frequencies in controls than in alcoholics (Chen et al., 1996). Zintzaras et al. (2006) found a significant association of higher risk of alcoholism with person having ADH1C*2 (OR=1.91). Conflicting reports have also been published on the association between ADH1C Ile349Val polymorphism and alcohol dependence. Borra’s et al. (2000) found an association between ADH1B Arg47His but not ADH1C Ile349Val polymorphism with alcohol dependence in Caucasian people. Other studies have observed a small protective function for ADH1C*1 in Caucasians (Thomasson et al., 1994 and Chao et al., 1994). Some recent studies indicate that both ADH1C Ile349Val and ADH1B Arg47His polymorphism independently affect drinking habits in European (Tolstrup et al., 2008) and Japanese (Matsuo et al., 2007) people. The strong linkage disequilibrium (LD) between ADH1B Arg47His and ADH1C Ile349Val has been reported (Osier et al., 1999) suggesting gene-gene interaction in propagating the disease phenotype.

Association studies of alcohol chronic pancreatitis caused by alcohol addiction among the Polish population found statistically more frequent of both heterozygous and homozygous conditions of ADH1B*1 and ADH1C*2 alleles among the patients than the controls (Cichoz-Lach et al., 2008). This study concludes that ADH1C*1 and ADH1B*2 alleles may be risk factors for the development of alcohol dependence.
Allele frequency distribution of ADH1C \( \text{Ile}_349\text{Val} \) gene polymorphism was found to be population specific. The ADH1C*2 allele is present in East Asia at frequencies of 0.12-0.24 (Thomasson et al., 1991; Chen et al., 1996 and Shen et al., 1997), whereas in a sample of mixed Europeans it was reported at a frequency of 0.39 (Whitfield et al., 1998). However, both ADH1C*1 and ADH1C*2 allele are found in equal frequency among Caucasian population and ADH1C*1 allele is predominant among black and oriental population (Agarwal and Godde, 1989).

1.8.a.ii Aldehyde Dehydrogenase (ALDH)

Human aldehyde dehydrogenase (ALDH) gene is a family of nineteen functional genes and three pseudo-genes which provide instructions for making enzymes that are involved in the breakdown (metabolism) of various molecules within cells (Vasiliou and Nebert, 2005). ALDH is tetrameric enzymes which play an important role in the metabolism of many molecules including certain fats (cholesterol and other fatty acids) and protein building blocks (amino acids). Additional ALDH enzymes detoxify substances, such as alcohol, pollutants and toxins that are formed within cells (Sladek, 2003). The specific role of aldehyde dehydrogenase enzymes is to change the aldehyde groups (i.e. groups of oxygen, carbon, and hydrogen atoms) that are attached to other molecules. These aldehyde groups can be beneficial or damaging to cells and tissues, depending on the molecule to which they are attached. Though, molecules that produce (NADPH and NADH) during the alteration of aldehyde groups via ALDH enzymes are necessary for many cellular processes (Vasiliou and Nebert, 2005).

Aldehyde dehydrogenase enzymes are primarily found in liver and kidney cells but they are also located in other cells throughout the body. Within cells, aldehyde dehydrogenase enzymes are located in a structure involved in protein processing and transport (endoplasmic reticulum), the energy-producing center of cells (mitochondria), the internal fluid of the cell (cytosol), and the nucleus (Vasiliou and Nebert, 2005). The ALDH enzymes are differentiated on the basis of their kinetic properties, localization within the cell, tissues and distribution and their
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Electrophoretic mobility (Agarwal, 2001). Out of these, only three families have significant role in acetaldehyde oxidation viz ALDH1, ALDH2 and ALDH3 (Agarwal, 2001). Except ALDH2, which is found in mitochondria, other isoymes/families are found in cystosol and it is found to be highly expressed in liver and stomach. It has very low Km (<5uM) i.e. high affinity for alcohol, not exceeding the in vivo acetaldehyde level making the most prominent enzyme significantly involved in alcohol-associated acetaldehyde oxidation (Crabb et al., 2004).

Common variations (polymorphisms) in ALDH genes can affect the function of the enzymes that are produced. Any polymorphisms of these ethanol-metabolizing enzymes may be associated with inter-individual difference in alcohol metabolism and susceptibility to alcoholic liver disease. Polymorphisms in the ALDH2 gene, for example, affect the breakdown of alcohol. People who have a certain polymorphism in the ALDH2 gene that disrupts the functioning of the enzyme have a decreased tolerance for alcohol (Vasiliou and Nebert, 2005). Diseases caused by mutations in ALDH genes typically involve the buildup of substances in the body that are harmful in large amounts or that impair the function or production of other necessary molecules.

**Aldehyde Dehydrogenase 2 (ALDH2 Glu487Lys) Polymorphism**

Aldehyde Dehydrogenase 2 (ALDH2) gene belongs to the aldehyde dehydrogenase family and it is second enzyme of the major oxidative pathway of alcohol metabolism. In humans there are two major liver isoforms of aldehyde dehydrogenase, cytosolic and mitochondrial, which can be distinguished by their electrophoretic mobilities, kinetic properties, and subcellular localizations. Mitochondrial isoyme ALDH2 is located on the long arm of chromosome 12 (12q24.2) encoding 517 amino acid residues with 13 exons (Hsu et al., 1988). The ALDH2 izoenzyme is the main form of aldehyde dehydrogenase responsible for acetate aldehyde oxidation (Goedde et al., 1979).
A functional polymorphism as a result of single nucleotide change G/A in exon 12 at mRNA nucleotide position 1510 causes a glutamic (Glu) to lysine (Lys) amino acid substitution at amino acid position 487 (Yoshida et al., 1985). This generates the deficient variant ALDH2*487Lys which is the dominant negative variant that is found to be strongly associated with resistance to alcoholism and the flushing reaction to ethanol. In traditional usage the 487Glu allele is number 1 (i.e. ALDH2*1) and the 487Lys allele is number 2 (i.e. ALDH2*2).

The ALDH2*1 allele encodes an active subunit while ALDH2*2 allele encodes a subunit that is essentially inactive consequently causing a build-up of acetaldehyde in the blood and other tissues. The effect of the inactive ALDH2*2 enzyme was first investigated by Wolff (1972) who observed racial differences in the facial flushing response during alcohol consumption. Individuals with heterozygous and homozygous for ALDH2*2 allele are therefore deficient in the conversion of acetaldehyde to acetate. Loss of the enzyme activity in ALDH2*2 alters the acetaldehyde metabolism resulting rapid accumulation of toxic acetaldehyde in the body causing/developing adverse reactions to alcohol. For example, certain abnormal behaviour patterns such as - facial flushing (reddenning of face), nausea, palpitations, headache and other dysphoric reactions (Wolff, 1972; Suddendorf, 1989 and Takeshita et al., 1999). Finally it acts as protection against further heavy drinking and finally alcoholism (Chen et al., 1999 and Yin and Agarwal 2001). Two fold increase in alcohol dependence was observed among those possessing the wild type ALDH2*1 allele.

**Figure 1.8: Diagrammatic depiction of ALDH2 gene location on chromosome 12**
Presence of ALDH2*2 allele has been reported to be protective variants against developing alcohol dependence and alcohol liver disease due to adverse effects caused by accumulation of toxic acetaldehyde inside the body. However, higher frequency of acute alcohol intoxication is reported among Orientals than among Caucasians. It could be due to the absence of a catalytically active form of the mitochondrial isozymes. Most Caucasians are found to have two major isozymes, while approximately 50% of Orientals have the cytosolic isozyme but not the mitochondrial isozyme. The increased exposure to acetaldehyde in individuals with the catalytically inactive form may also confer greater susceptibility to many types of cancer.

Figure 1.9: Diagrammatic representation of facial flushing before and after alcohol consumption (Source: http://www.geneticsandsociety.org/article.php?id=5313)

Genetic variation of ALDH2 and risk of alcohol dependence has been well established among Asian populations. Individuals possessing ALDH2*1 allele in heterozygous condition are at reduced risk of AD compared to ALDH2*1 homozygotes, while individuals homozygous for ALDH2*2 have a very low risk for alcohol dependence (Chen et al., 1996 and Chen et al., 1999). Lee et al. (2001) reported that ALDH2*2 gene protects against the development of alcoholism among Korean alcoholic patients. In a recent study Hendershot et al. (2009) reported the association of ALDH2 genotype with drinking behaviour and its consequences. They also looked at the level
of ethnicity and there were significant differences in drinking outcomes. For example, Korean ethnicity predicted higher drinking rates and lower alcohol sensitivity than Chinese adults (Hendershot et al., 2009).

![Diagram](image)

**Figure 1.10: Diagrammatic depiction of ALDH2 Glu487Lys gene polymorphism and protection from alcohol dependence**

Frequency distribution of the ALDH2 alleles varies among different populations. ALDH2*2 has been reported in East Asian populations at high frequencies (as high as 30.0%) but has not been seen in other population studies such as Caucasians (Shibuya and Yoshida, 1988; Crabb et al., 1989 and Peterson et al., 1999). This particular variant (ALDH2*2 allele) occurs mainly in oriental populations, i.e. Japanese, Chinese, inhabitants of Taiwan and Korea (Chao et al., 1994; Chao et al., 1997; Lee et al., 1997 and Osaka et al., 2003). Investigations of the Caucasian race have found an almost totally homozygotic character of ALDH2*1 (Day et al., 1991; Goedde et al., 1992; Gilder et al., 1993 and Cichoz-Lach et al., 2008).

### 1.8.b Genes related with Neurocognitive Function

Brain balances the activity of inhibitory neurotransmitters (which work to delay or stop nerve signals) with that of excitatory neurotransmitters (which work to speed up these signals). Alcohol abuse alters the balance among different types of neurotransmitters, small molecules involved in the brain communications, leading to abnormality in neuronal functions and hence impairs brain function associated with alcohol intoxication (Koob et al., 1998; Nestler, 2001 and Koob, 2003). Therefore,
pathway of alcohol intoxication and dependence is believed to be originated from brain.
Chronic alcohol use influences almost all neurotransmitter systems like dysfunctioning of dopamine, serotonin and glutamine neurotransmitter system affecting reward, obsessive and relief craving respectively (Valenzuela, 1997). As the brain adapts to alcohol's presence over time, it compensates for alcohol's slowing effects by speeding up signal transmission (Lovinger, 2008). In this way, our brain attempts to restore itself to a normal state in the presence of alcohol resulting into alcohol's effects on health including alcohol tolerance and withdrawal symptoms associated with alcohol dependence.

Figure 1.11: Human Brain showing the dopamine pathways (Source: Wikipedia, the free encyclopedia. http://en.wikipedia.org/wiki/Dopaminergic_pathways)

The indications for a genetically defined predisposition responsible for AD are examined in the field of different candidates for neurotransmitter genes (Adinoff, 2004 and Dodd et al., 2004). Among them dopaminergic neurotransmission plays a crucial role in the genesis and maintenance of alcohol dependence (Hillemacher et al., 2009). Dopamine D2 receptor gene (DRD2) has most recently been the focus of attention which is generally known to play a significant role in substance dependence development (Wozniak et al., 1991; Koob et al., 2001; Munafo et al., 2001; Lingford-
Hughes and Nutt, 2003 and Zigmond, 2004). Alcohol increases dopamine release which supposedly enhances reward or pleasure phenomenon (Wise and Rompre, 1989 and Koob et al., 1992). However, chronic and/or high levels of alcohol eventually lead to a decrease in dopamine release. This chemical imbalance results in negative feelings such as anxiety, anger or in a craving for a substance like alcohol (Dick and Foroud 2003 and Tupala and Tiihanene, 2004). Therefore dopamine is one of the primary receptor genes which are considered as a possible candidate gene for susceptibility to alcoholism (Pfefferbaum et al., 2001 and Tupala et al., 2001, 2003). Alcohol acts on many neurotransmitter systems besides dopamine receptors like alteration of serotonin receptors activity which seems to be implicated in dependency development (Lovingier, 1997). It also modifies the GABA$_A$, which is an inhibitory neurotransmitter, contributing to alcohol tolerance and dependence (Kumar et al., 2009). However, the exact neurobiological changes leading to uncontrollable substance seeking phenomenon (craving) are unknown making more complexity in understanding the neuroreceptor system of alcoholism (Koob and Le Moal, 2006).

1.8.b.i Dopamine D2 Receptor (DRD2)

Dopamine is an important neurotransmitter, chemical messengers, in the mammalian central nervous system. It is the primary endogenous ligand for dopamine receptors. There are two families of dopamine receptors as D1-like family (D1 and D5) and D2-like family (D2, D3 and D4) according to their ligand specificities and their effects on G protein-mediated messenger systems (Hess and Creese, 1987 and Vallar and Meldolesi, 1989). D1-like family receptors activate adenylyl cyclise (AC), which increases the cyclic adenosine monophosphate (cAMP) resulting neuron excitation and induces an action by modulating the activity of ion channels. Contrary D2-like family receptors directly inhibit the formation of cAMP by inhibiting the enzyme AC (Morris and Malbon, 1999). Dopamine is transmitted via three major pathways namely nigrostriatal, tubero-infundibular and Mesolimbic. Each pathway concerned with different sense functions in different regions of the brain is shown in Table (1.2).
Table 1.2: Functions of different dopamine receptor pathways in different regions of the brain and its associated diseases

<table>
<thead>
<tr>
<th>Dopamine Pathway</th>
<th>Position in the Brain</th>
<th>Function</th>
<th>Associated Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nigrostriatal</td>
<td>Substantia Nigra - Striatum</td>
<td>Motor control (sensory stimuli and movement)</td>
<td>Parkinson’s Disease, Chorea</td>
</tr>
<tr>
<td>Tubero-infundibul</td>
<td>Hypothalamus – Pituitary gland</td>
<td>Neuronal control of the hypothalamic-pituitary endocrine system, hormone regulations etc</td>
<td>Hyperprolactinaemia</td>
</tr>
<tr>
<td>Mesolimbic</td>
<td>Ventral Tegmental area – Nucleus (includes accumbens, amygdale &amp; hippocampus and prefrontal cortex)</td>
<td>Memory, motivation, cognitive, reward &amp; desire, emotional etc response</td>
<td>Schizophrenia and Drug addiction</td>
</tr>
</tbody>
</table>

Ankyrin repeat and kinase domain containing 1 (ANKK1 TaqI A) Polymorphism

Dopamine D2 receptor gene was located to the short arm of chromosome number 11 (11q22-23) (David et al., 1989). It spans 270 kb long with eight exons and an intron of approximately 250kb separating the first exon from the exon encoding the receptor protein (Eubanks et al., 1992). Recently, TaqI A polymorphism has been located in a protein coding region (exon 8) nearby novel gene named ankyrin repeat and kinase domain containing (ANKK1) gene (Neville et al., 2004). Earlier, TaqI A polymorphism was lied over 10kb downstream of the termination codon and 250kb away from the transcriptional start site of DRD2 gene. The ANKK1 TaqI A polymorphism also reported to cause a missense substitution increasing the striatal activity of dopamine biosynthesis enzyme, L-amino acid decarboxylase (Laakso et al., 2005).
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Dopamine D2 receptor gene is one of the primary receptor genes which are considered as a possible candidate gene for susceptibility to alcoholism (Pfefferbaum et al., 2001 and Tupala et al., 2003). Any polymorphism that affects the expression of D2 dopamine receptor may be a possible candidate for susceptibility to alcoholism (Parsian et al., 1991 and Uhl et al., 1992). Restriction of TaqI yields polymorphic fragment lengths identifying alleles A1 and A2 that differ in average amounts of receptor sites (Blum et al., 1993). A1 allele is associated with 40% reduction in the expression of D2 dopamine receptors. Therefore, people possessing A1 allele become more susceptible for alcohol dependence (Prasad et al., 2010).

For the first time, Blum et al. (1990) found possible association of A1 allele of the TaqI A polymorphism (Grandy et al., 1989) with alcoholism encouraging the researchers in the study of genetic basis of alcoholism (Noble et al., 1991; Smith et al., 1992 and Arinami et al., 1993). Various association studies on alcoholism found A1 allele, regulating synthesis of D2 receptor, associated and high rates of this allele in alcoholics compared with non-alcoholics (Blum et al., 1990 and Noble, et al., 1991). Inconsistent association results of A1 allele with alcohol dependence have been reported by many authors from different populations groups. Bolos et al. (1990)

Figure 1.12: Diagrammatic depiction of DRD2 gene location on chromosome 11
reported no significant difference in the prevalence of the A1 allele between unrelated white alcoholics and controls. A study from Caucasian alcoholics reported a positive association with the A1 allele of the DRD2 locus. However, the significant results occurred only among severe medical complications of alcoholism (Parsian et al., 1991). Subsequently Comings et al. (1991) also demonstrated a significant association between the A1 allele and alcoholism among American whites.

A study by Gelernter and co-workers compared 44 unrelated white alcohol dependence (DSM-III criteria) with random population control group of the same Caucasian ethnic origin. No significant differences in A1 allele frequencies between alcoholics and controls for the DRD2 locus were found (Gelernter et al., 1991).

Such inconsistent results could be due to other functional allelic variants located on the gene or could be due to linkage disequilibrium with functional allelic variants in the regulatory regions of the DRD2 gene that affect receptor expression (Comings et al., 1991). Hauge et al. (1991) suggested strong linkage disequilibrium between the TaqI A and TaqI B system in European ancestry sample, a similar result was also reported by O’Hara et al. 1993. Lu et al. (1996) also reported strong linkage disequilibrium for the haplotype of these DRD2 systems in the Chinese Han, Atayal and Ami. Such findings indicate that A1 allele might be in linkage disequilibrium with a mutation in the promoter/ regulatory gene that affects dopamine D2 receptor expression. An association between A1 allele and low D2 receptor availability in healthy subjects was also reported by Pohjalainen et al. (1998). Such influence on dopamine D2 receptor expression was further correlated with risk conferring nature of the A1 allele in subsequent association studies in different populations like Caucasians, Han Chinese, and Europeans (Shaikh et al., 2001).

Lu et al. (1996) studied three distinct Taiwanese populations to examine the genetic association of alcoholism and DRD2 TaqI A, TaqI B and short tandem repeat polymorphisms (STRP). No significant association was observed between any of the three polymorphisms at the DRD2 locus and alcoholism. A borderline association was reported between TaqI A1 and alcoholism among the Ami and Han Chinese (Chen et al., 1997). However, Laruelle et al. (1998) did not find association between A1 allele and lower D2 receptor expression and suggested that D2 receptors binding potential is not affected by TaqI A polymorphism at the D2 receptor gene. Though, a marginal
association of allele *TaqI* A1 is in concurrence with the meta-analysis carried out by Munafo et al. 2001 where association of the DRD2 *TaqI* A polymorphism with alcoholism suggests that A1 allele confers modest increase in risk. Samochowiec et al. (2006) did not find any association of *TaqI* A1 with alcohol dependence in a Polish population. In the same year, Berggren et al. (2006) recruited a large number of subjects (1207) of Scandinavian origin, 375 alcohol-dependent individuals, who were treated as inpatients for alcohol withdrawal symptoms and 578 individuals screened and 254 individuals unscreened for alcohol consumption were used. DRD2 *TaqI* A1 allele frequency was significantly overrepresented in the alcohol-dependent subjects as compared with both the total and screened control groups (OR=1.34). The findings in this study lend further support to the notion of an association between the DRD2 A1 allele and alcohol dependence, although the effect size of the DRD2 A1 allele is small.

However, such association findings remained controversial. Inconsistent results have been observed in different studies contributing to biasness of the role of dopamine receptor (DRD2 *TaqI*) in developing the disease. Such inconsistency in results may arise from difference in study design, selection of cases and controls due to phenotypic variation, variation in sampling and difference in ethnic background. Association of *TaqI* A1 allele with alcohol dependence has been found to vary from one population to other. For example, Noble (1998) reported a negative association of *TaqI* A1 allele with alcohol dependence among East Asian, European and Caucasian populations. An important confounding factor in an association study is that different populations have different allele frequencies at many loci (Bowcock et al., 1987, 1991; Kidd et al., 1991 and Barr and Kidd 1993). One of the reasons could be due to the difference in allele frequency distribution. The A1 allele frequency ranges between 0.06 and 0.18 in populations with European ancestry, while a significantly higher frequency (0.7) is seen in native South American populations. Whereas, the allele frequency observed in East Asian populations is 0.45.

DRD2 is also implicated in the etiology of other addictive disorders such as drug abuse (Noble, 2000), movement disorders (Lee et al., 1978; Comings and Blum, 2000) and mental health disorders like schizophrenia (Kukreti et al., 2006). It is also reported to be clinically significant because of its physical properties for example
antipsychotic drugs display high affinities (Seeman and Lee 1975 and Creese et al., 1976). Certain studies have also been conducted to understand the pharmacology and neurophysiology of the dopamine D2 receptors extending molecular works as gene expression and associated human diseases (Ogawa, 1995). On the other side, haplotype of dopamine D2 receptor has been extensively studied to understand the human evolutionary history and their migratory pattern since relative distribution of haplotype can provide more accurate information on the genetic diversity and similarity among the populations (Castiglione et al., 1995; Kidd et al., 1998; Tishkoff et al., 2000; Vishwanathan et al., 2003; Bhaskar et al., 2008; Prabhakaran et al., 2008 and Saraswathy et al., 2009 a,b).

The most commonly studied SNPs at DRD2 locus in association with alcohol dependence in addition to TaqI A are TaqI B and TaqI D (Prasad et al., 2010). Beside the above DRD2 sites, -141C Ins/Del polymorphism is also extensively investigated in association with AD to understand the genetic mechanism of alcohol dependence (Konishi et al., 2004). However, findings of the above said genetic markers are highly inconsistent for their association with alcohol dependence (Wiesbeck et al., 2006).

**Dopamine D2 receptor (DRD2 TaqI B and TaqI D) polymorphism**

DRD2 TaqI B site, G to A transversion, is a functional variant (Jonsson et al., 1999) and is closer to the regulatory and structural coding regions (5’ region) of the gene (Hauge et al., 1991) and is believed to play an important role in transcription regulation. However, DRD2 TaqI D system (Parsian et al., 1991) maps between exons 2 and 3 with unclear functional significance (Parsian et al., 1991 and Suarez et al., 1994). TaqI B has been examined in numerous association studies, and this system has long been known to be in strong linkage disequilibrium (LD) with the A system (Hauge et al., 1991). It has also been suggested that the mutation causing TaqI A and TaqI B polymorphisms are in LD with functional allelic variants in the regulatory regions of the DRD2 gene that affects receptor expression (Comings et al., 1991 and O’Hara et al., 1993). However, it has been rarely investigated for its association with AD. The only positive study of the TaqI B system reports genotypes with TaqI B1 allele more prevalent among alcoholics (Blum et al., 1993). Two studies (Konishi et al., 2004a, 2004b) carried out in Mexican-American population reported conflicting
results with regard to association of this polymorphism with alcohol dependence. No positive association was found for TaqI B with AD in Mexican-Americans. However in a subsequent study, they reported an association of TaqI B polymorphism with early age of onset for alcohol drinking in Mexican-Americans (Konishi et al., 2004a). A very recent study from north Indian population (Prasad et al., 2010) also reported no allelic or genotypic association of TaqI B polymorphism with AD. Bhaskar et al. (2010) also reported no association of TaqI B with alcohol dependence. However, they reported significant association of TaqI D with alcohol dependence among Kota population of Tamil Nadhu.

**Dopamine 2 receptor (DRD2 -141C Ins/Del) polymorphism**

Inconsistent findings of dopamine D2 receptor (TaqI A) with alcohol dependence hint the existence of a functional variant, perhaps located in the DRD2 promoter, possibly affecting mRNA expression or stability, which could account for some genetic association of alcohol dependence (Uhl et al., 1993 and Gejman et al., 1994). Recently Arinami et al. (1997) has reported the association of promoter polymorphism (-141C Ins/Del) of the DRD2 gene involving the insertion (Ins)/deletion (Del) with dopamine receptor density. In vitro -141C Ins/Del polymorphism alters its transcriptional activity and thus regulates the expression of DRD2 receptor. -141C Ins allele is considered as wild type and variant Del allele is found to have lower transcription activity and higher striatal dopamine receptor density (Jonsson et al., 1999). This polymorphism has been extensively investigated for its association with alcohol dependence in several studies across different populations since it has been found to be associated with Schizophrenia (Ishiguro et al., 1998; Gelernter and Kranzler, 1999; Sander et al., 1999; Blomqvist et al., 2000; Chen et al., 2001; Wiesbeck et al., 2003; Konishi et al., 2004; Johann et al., 2005 and Prasad et al., 2010). However, the results are inconsistent.

In a genetic association study Ishiguro et al. (1998) reported positive association of -141C Ins allele with alcohol dependence among Japanese population (p< 0.002). Another association study among German alcoholics suggested a possible role of -141C Ins/Del polymorphism (Samochowiec et al., 2000). However, it failed to replicate the association in a family based case-control study of a Polish population
Alcoholism: Its Genetics and Impact on Health – A Study Among Meiteis of Manipur, India (Samochowiec et al., 2006). Sander et al. (1999) reported no-association of this particular polymorphism with alcohol dependence among the Caucasian population. Similar findings were also reported by Wiesbeck et al. (2003) among the Caucasian population. Other genetic association studies among different population across the world did not find any association of -141C Ins/Del with alcohol dependence (Blomqvist et al., 2000; Chen et al., 2001 and Wiesbeck et al., 2003). Johann et al. (2005) studied the association of a -141C Del variant of the DRD2 gene in well-characterized, primary chronic alcoholics of German descent and found an excess of the -141C Del alleles in alcoholics with a paternal and grand-paternal history of alcoholism. They concluded that though the -141C Del variant of DRD2 might be a protective factor against the development of withdrawal symptoms, it might also be a risk factor in a highly burdened subgroup of alcoholics with a paternal and grand-paternal history of alcoholism (Johann et al., 2005).

In contrast, -141C Ins allele of DRD2 gene were found significantly higher among alcohol dependence indicating -141C Ins allele as a genetic risk factor for alcohol dependence in Mexican-Americans (Konishi et al., 2004). A recent study among Indian males (Prasad et al., 2010) also reported a significant association of -141C Ins with alcohol dependence (P<0.05; OR 0.19, 95%, CI 0.06-0.6) suggesting the presence of -141C Ins allele is a predisposing subject to alcohol dependence.

1.8.b.ii Dopamine D1 Receptors (DRD1)

DRD1 gene encodes the D1 subtype of the dopamine receptor. The D1 subtype is the most abundant dopamine receptor in the central nervous system. This G-protein coupled receptor stimulates adenylyl cyclase (AC) and activates cAMP dependent protein kinases. The sequence of the dopamine D1 receptor gene has been determined by researchers (Dearry et al., 1990; Sunahara et al., 1990 and Zhou et al., 1990) and mapped to 5q35.1 (Grandy et al., 1990). Several polymorphisms have been detected in the DRD1 gene like EcoRI and TaqI restriction fragment length polymorphism (Grandy et al., 1990) along with four polymorphisms produced by MstNI, Ddel, PvuI and Bsp1286I in the 5’ and 3’ UTR of the DRD1 gene (Cichon et al., 1994).
The D1 receptors regulate neuronal growth and development, mediate some behavioral responses, and modulate dopamine receptor D2-mediated events. It involved in many brain functions, including motor control (Dreher and Jackson, 1989 and Meyer and Shults, 1993), inattentive symptoms of attention deficit/hyper active disorder and reward and reinforcement mechanisms. Therefore, it is considered as candidate gene in the study of the etiology of neuropsychiatric diseases that may involve dopaminergic abnormalities. These disorders include Tourette’s syndrome (TS) (Gelernter et al., 1993 and Comings, 1997), Alcohol dependence (George et al., 1995), attention deficit-hyperactivity disorder (ADHD) (Cook et al., 1994), Schizophrenia (Seeman et al., 1984; O’Hara et al., 1993 and Karlsson et al., 1994) and affective disorders (Shah et al., 1995).

Rinaldi et al. (2007) reported that DRD1 is an important gene in alcohol dependence, particularly regarding its role within the prefrontal cortex in the modulation of cognitive processes. Among the different polymorphisms of DRD1 gene, the D1.1 marker/rs4532 (a -48A/G Ddel polymorphism) in the 5’UTR (untranslated region) of exon 2 at the bp -48 (-48A/G) of DRD1 gene display a modest role in a large set of phenotypes including addictive behaviours (Comings, 1997).

Kim and co-workers (2007) examine the genetic effects of the dopamine receptor gene family (DRD1-5) in 535 alcohol dependent subjects and 273 control subjects among Korean population. None of the DRD1-5 gene polymorphisms was found to be associated with the risk of alcoholism except one 5’ UTR polymorphism in the DRD1 (-48A>G) gene which was significantly associated with severity of alcohol related
problem. They also reported association of -48A>A genotype with novelty seeking, harm avoidance and persistence (Kim et al., 2007). Moreover, recent studies confirmed an association of two DRD1 sites i.e. haplotype rs686*T – rs4532*G (OR = 4.06) with alcoholic dependence, rather than the individual sites (Batel et al., 2008). The T allele of rs686 SNP is found to be frequent among the severe alcohol dependence (Batel et al., 2008). The T allele of the rs686 within DRD1 gene is a nonspecific risk factor for a trait related to attention deficit and impulsivity (Malloy-Diniz et al., 2007) which may increase the risk for earlier initiation, higher consumptions of alcohol and or more deleterious consumption of alcohol, increasing the risk for alcohol dependence (Batel et al., 2008).

*Therefore, one can quote that environments probably moderate the effects of genes and genes probably moderate the effects of environments (Ridley, 2003 and Rutter, 2006).*

**1.9 Alcohol and Medical/Health Problems**

Alcohol consumption is found to be related to wide range of physical, mental and social harms. Most health professionals agree that alcohol affects practically every organ in the human body. Alcohol consumption was linked to more than 60 disease conditions in a series of recent meta-analyses (English et al., 1995; Single et al., 1999; Gmel and Rehm, 2001 and Ridolfo and Stevenson, 2001).

The relation of alcohol consumption and health effects could be broadly divided into two sub categories. Firstly, on the two main dimensions of alcohol consumption - average volume of consumption and patterns of drinking and secondly on the mediating mechanisms - biochemical effects, intoxication, and dependence. Alcohol is a toxic substance that can affect each and every organ of human body particularly stomach, liver, brain and heart. Some of the major health problems associated with excessive alcohol intake is shown in Figure 1.14. When alcohol is consumed excessively it slows down functioning of stomach and interferes with the process of digestion. Further drinking may cause gastric ulcers and increases the incidence of cancer.
1.9. Alcohol and Liver

Daily drinking of alcohol increases liver metabolism of ethanol by as much as a third but acetaldehyde is not always rapidly metabolized. Thus, high doses of acetaldehyde cause flushing, headache, nausea, vomiting and other side effects. Excessive alcohol consumption may also cause alcoholic fatty liver which is one of the major threats to public health which is caused by accumulation of fat in the liver due to improper functioning of liver. Chronic heavy drinking may also cause inflammation and destruction of liver cells leading to alcoholic hepatitis and further drinking of alcohol leads to the critical stage called cirrhosis where liver get irreversible lesions, scarring and damage of liver cells. Alcoholism has been estimated as the leading cause of liver cirrhosis (English et al., 1995; Corrao et al., 1997, 1998). In India or China, liver cirrhosis is mainly caused by other factors such as viral infections. The relationship between alcohol consumption and liver cirrhosis seems to be mainly dependent on the volume of drinking and independent of patterns of drinking (Lelbach, 1975).
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However, some research also indicates a potential effect of occasions of heavy drinking (Rhodés et al., 1993). Therefore, at this cirrhosis stage liver cells cannot work properly and impair the ability to remove yellow pigment and thus skin appears yellow forming another disease phenotype commonly called Jaundice. Liver damage also causes fluid to build in extremities i.e. edema and decreases the production of blood-clotting factors leading to uncontrolled bleeding.

1.9.b Alcohol and Brain
Alcohol is a depressant, which slows down the central nervous system depressing the nerve cells in the brain and alters their ability to respond appropriately. It also impairs regions of brain controlling fine motor skills, behavior and emotions. Alcohol can cause drowsiness, dulled smell and taste (reducing the desire to eat), relieve pain, anesthesia, induce sleep, respiratory failure. Light drinking increases social conversation and reduces inhibition among virtually all people who consume alcoholic beverages on social occasions. The effects are particularly dramatic for some people suffering from high anxiety. Light drinking can also increase violent aggression in some people. Alcohol users also experience mild euphoria, loss of inhibition, judgment, memory, concentration and coordination (shortened attention span, impaired problem solving abilities), as well as inducing extreme mood swings, visual ability and hearing (affects ability to distinguish between sounds and perceive the direction they are coming from). Long term drinking may result in permanent brain damage, addiction to alcohol and serious mental disorders triggering psychiatric problems, coma and even death. The fatty acid ethyl esters produced in the brain from ethanol are particularly damaging to the hippocampus (Gubitosi-Klug and Gross, 1996) Even low to moderate consumption of alcohol was associated with brain atrophy in a study of middle-aged men (Ding et al., 2004). Ethanol can also increase release of arachidonic acid from cell membranes and (with increased cyclooxygenase activity) can cause oxidative stress in the brain (Sun et al., 2002).

1.9.c Alcohol and Heart
Alcohol interferes with normal heart rhythm, abnormal heart signals and enlargement of heart. It has been suggested that the changes found in the cardiovascular system in
alcoholics may arise from the myocardial and adrenal release of catecholamines due to acetaldehydes (James and Bear, 1977). Continuous alcohol drinking increases blood pressure and hence increases the risk of heart attack and stroke. Chronic heavy drinking weakens the heart muscle and ability to pump blood leading to disease phenotype called Cardiomyopathy.

1.9.d Alcohol and Stomach & Intestine
Alcohol consumption effects most of the organs involved in digestive processes and nausea, diarrhea, vomiting, sweating and loss of appetite are most of the common outcomes. Irritation and damage of esophagus lining induce severe vomiting and hemorrhaging. It can further affect stomach lining causing peptic bleeding lesions. Such minute blood loss may deplete the body's iron stores, causing irritability, lack of energy, headaches and dizziness among the excessive alcohol users. Moreover, the pancreas becomes stressed from having to create insulin to metabolize the sugar present in alcohol. This creates a significant risk of pancreatitis, a chronic inflammation that can be fatal. Chronic drinking may result in inflammation, ulcers, and cancers of the intestines and colon.

1.9.e Alcohol and Cardiovascular Disease
Cerebrovascular disease (stroke) consists of several subtypes, the most common subtypes being ischaemic stroke and haemorrhagic stroke, which are affected differently by alcohol. For ischaemic stroke, the predominant type of stroke, the weight of evidence including biological mechanisms - suggests that low to moderate consumption may offer some protection (Beilin et al., 1996; Knuiman and Vu, 1996; Wannamethee and Shaper, 1996; Keil et al., 1997; Thun et al., 1997; Yuan et al., 1997; Hillbom, 1998; Kitamura et al., 1998 and Sacco et al., 1999). In contrast, hypertension and other cardiovascular disorders such as cardiac arrhythmias or heart failure are adversely affected by alcohol (Klatsky, 1995; Friedman, 1998; Rosenqvist, 1998; Wood et al., 1998 and Puddey et al., 1999). There are some indications that hypertension may be related to the pattern of heavy drinking occasions (Wannamethee and Shaper, 1991; Puddey et al., 1999 and Murray et al., 2002).
For haemorrhagic stroke, the weight of evidence suggests an increase in risk for males even at low levels of consumption (Jackson, 1994; You et al., 1997; Berger et al., 1999 and Sacco et al., 1999). Patterns of drinking not only play a role in any protective effects of alcohol on CHD, drinking patterns are also relevant to risks of stroke (Hillbom et al., 1998) and for sudden cardiovascular death or cardiovascular death in general (Wannamethee and Shaper, 1992 and Kauhanen et al., 1997) with heavy drinking occasions and intoxication resulting in increased risk.

1.9.f Alcohol and Cancer
Alcohol has consistently been related to the risk of cancer of the mouth (lip, tongue), pharynx, larynx, hypopharynx, oesophagus and liver (English et al., 1995; Corrao et al., 1999 and Single et al., 1999). Female breast cancer is also reported to be associated with alcohol consumption. Moreover, various types of cancers are also found to be linked with alcohol such as stomach, pancreas, colon, rectum, prostate, salivary glands, ovarium, endometrium and bladder cancer.

1.9.g Effects of Prenatal Alcohol Exposure
Chronic alcohol consumption also affects other body organs and particularly the reproductive system of both male and female. Long term use can impair the sexual functioning and it may result impotence and infertility. In men, it may lead to sterility, atrophy of the testes and enlargement of the breasts. Early menopause and menstrual irregularities are common in women who drink excessively.

Alcohol consumption during pregnancy is related to various risks to the fetus, which include gross congenital anomalies and Fetal Alcohol Spectrum Disorders (FASD), a condition characterized by facial disfigurement, growth retardation and brain damage (particularly to the corpus callosum, basal ganglia and cerebellum) (Alvear et al., 1998; Faden et al., 1997; Habbick et al., 1997; Larkby and Day, 1997; Mattson et al., 1997 and Passaro and Little, 1997). FASD ranges from individual anomalies at one end and serious neurobiological dysfunctions, including mental retardation, on the other. Some of the important symptoms of FASD are such as small head, possible
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brain damage, abnormal facial features, poor muscle tone, speech and sleep disorders, and retarded growth and development.

The prenatal teratogenic effects of alcohol also include lethal consequences. They comprise spontaneous abortion, low birth weight, fetal damage, prematurity, and intrauterine growth retardation (Abel, 1997 and Windham et al., 1997).

1.9 Alcohol and Malnutrition

Alcohol contributes to malnutrition by replacing foods needed for essential nutrients and by interfering with absorption, storage or metabolism of the essential nutrients (Lieber, 2000). It inhibits the breakdown of nutrients into usable molecules by decreasing secretion of digestive enzymes from the pancreas. Alcohol also impairs nutrient absorption by damaging the cells lining the stomach and intestines, and disabling transport of some nutrients into the blood. Even if nutrients are digested and absorbed, alcohol can prevent them from being fully utilized by altering their transport, storage and excretion. Alcohol also interferes with the body's ability to absorb calcium, resulting in bones being weak, soft, brittle and thinner (Osteoporosis). Nutritional deficiency is also certainly a factor in alcoholic brain damage. Alcohol amnesic disorder (Korsakoff's Disease) is usually associated to a deficiency of Vitamin B1 (Thiamine) (Brust, 2007). Even without thiamine deficiency, nearly a fifth of the neurons in the frontal association cortex are lost in chronic alcohol consumption (Kril et al., 1997).

1.9.1 Alcohol and Mental Conditions

Alcohol is implicated in a variety of mental disorders which are not alcohol-specific. The co-morbidity of alcohol dependence with other mental conditions is high, both in clinical and in general population samples (Grant and Harford, 1995). Low dose of alcohol reduces response-time and increases performance error-rate. Moderate doses of ethanol induce "a significant deterioration of capacity to detect the activation of erroneous responses" (Ridderinkhof et al., 2002). Alcohol consumption plays a positive causal role in depression, a common mental disorder. Alcohol use disorders are linked to depressive symptoms, and that alcohol dependence and depressive disorders co-occur to a larger degree than expected by chance. However, it is not clear
in the individual case whether the depression is caused by alcohol problems, whether the alcohol consumption or alcohol problem is caused by depression, or whether both could be attributed to a third cause (Vaillant, 1993). A shared third cause could be certain neurobiological mechanisms (Markou et al., 1998) or genetic predisposition may also cause the disorder.

1.9.j Alcohol and Other Chronic Conditions
Other risks of alcohol consumption include epilepsy (Jallon et al., 1998), acute and chronic pancreatitis (Skinazi et al., 1995; Ammann et al., 1996; Robles-Diaz and Gorelick, 1997 and Damström-Thakker, 1998) and psoriasis (English et al., 1995).

1.9.k Alcohol and Social Problems
Alcohol use has been associated with increased risk of injury in a wide variety of settings including road traffic accident (vehicles, bicycles, pedestrians), falls, fires, injuries related to sports and recreational activities, self-inflicted injuries or injuries resulting from interpersonal violence (Cherpitel, 1992; Martin, 1992; Freedland et al., 1993; Hingson and Howland, 1993; Hurst et al., 1994 and Martin and Bachman, 1997). Changes in drinking level could also relate with changes in homicide level in the society.

Alcohol consumption is also linked to many harmful consequences for the individual drinker, the drinker’s immediate environment and society as a whole. Such social consequences as traffic accidents, workplace-related problems, family and domestic problems, and interpersonal violence (Klingeman and Gmel, 2001). On the other hand, however, social consequences affect individuals other than the drinker e.g. passengers involved in traffic casualties, or family members affected by failure to fulfil social role obligations, or incidences of violence in the family. Ultimately, however, these events have an impact on society as a whole as they affect economic productivity or require the attention and resources of the criminal justice or health care system, or of other social institutions (Gmel and Rehm, 2003).
Alcohol also equally affects in a variety of social, family, parents and child relationship as well as economic problems in the society. Research has found that alcohol is present in a substantial number of domestic violence inside and outside
home is commonly associated with alcohol use. The most common pattern is husband-to-wife violence. Drinking frequently has been associated with intrafamily violence. Excessive alcohol use is a strong and consistent correlate of marital violence.

Most of the heavy drinkers give up or reduce their important social, occupational, or recreational activities because of long term alcohol effects. Individuals belong to low socio-economic status spent a large proportion of their income on alcohol consumption resulting poverty and lack of other primary necessities such as food, housing and education. This often leads to a vicious cycle of heavy drinking, poverty and illness. The economic consequences of expenditures on alcohol are significant especially in high poverty areas. Besides money spent on alcohol, a heavy drinker also suffers other adverse economic effects. These include lowered wages (because of missed work and decreased efficiency on the job), lost employment opportunities, increased medical expenses for illness and accidents, legal cost of drink-related offences, and decreased eligibility of loans

1.10 Origin of Research Proposal

Alcohol dependence, once considered to be abnormal health behaviour, became an important topic of research. It is categorised under complex disorders, the causes for which could be at socio-cultural and biological levels. Under both level genetic parameters were studied at biochemical and molecular levels. At molecular level gene polymorphisms involved in alcohol metabolism and neurocognitive function were exclusively explored. However, the candidate gene approach gave varied results. This could possibly be because of varied ethnicity, geography and study design. Since, each ethnic population has different genetic composition and their genetic structure is significantly influenced by its socio-cultural phenomenon for example matting pattern. Such difference in matting pattern could shape a population with a distinct gene pool. Therefore, one should consider ethnic background of the studied population to have a better understanding of the complexity of disease.
In light of the present scenario, the present study focuses on anthropogenetics, a comprehensive approach, to understand the disease etiology of alcohol dependence among Meitei community, a Mendelian population, with special reference to environmental and genetic factors as well as ill effects of alcohol consumption on health with special reference to anthropometric, physiological and biochemical variables. Alcohol consumption is found to be very frequent among Meitei community of Manipur (from secondary literature). Thus in the present study, alcohol dependent cases and controls are selected from a Mendelian population i.e. Meitei, to have a common genetic, geographic and environmental background.

1.11 Rationale

In India, few genetic association studies have been reported to date to unravel the genetic predisposition to alcohol dependence (Shaikh et al., 2001, Vaswani et al., 2009; Prasad et al., 2010 and Bhaskar et al., 2010, 2012, 2013). Most of the studies were conducted in Southern and Northern population of India. To my knowledge, this is the first study attempted to understand both genetic and environmental factors as well as their interaction in predisposing an individual towards alcohol dependence among a specific Mendelian population.

Present study emphasises not only to on the genetic and environmental risk factors for alcohol dependence, but also to have an insight into the reasons behind the predisposition of alcohol consumers to various adverse health variables. Identification of genetic and environmental risk factors responsible for developing/causing alcohol dependence and understanding the dynamic interaction of gene-gene and gene-environmental interactions would help in understanding the etiology of such complex disease phenotype. Moreover, it would also throw light on community based pharmacogenomics approach facilitating health management programmes in near future.
1.12 Hypothesis

Variation/Mutation in the selected genes i.e. ADH1C Ile349Val, ADH1B Arg47His, ALDH2 Glu487Lys, DRD2 (TaqI/B, TaqI/D, -141C Ins/Del), DRD1 -48A/G and ANKK1 TaqI A are expected to be more common among the alcohol dependent cases as compared to controls, influencing the susceptibility to alcohol dependence. This effect will be more pronounced under certain environmental conditions like early onset of alcohol consumption, rural setting, smoking, lower education level and unemployment.

![Diagram showing genetic and environmental factors in alcoholism]

Figure 1.15 Hypothesis
1.13 Aim
The present study aims to understand the etiology of alcohol dependence (environmental and genetic variables) and also its effects on health among Meiteis of Manipur.

1.14 Objectives

- **To estimate the occurrence of alcohol dependence and the associated environmental risk factors**
  It will be achieved by generating data on household survey from different villages of the selected four districts (Thoubal, Imphal East, Imphal West and Bishnupur) where Meities are predominantly inhabited.

- **To understand the association of selected gene polymorphisms with alcohol dependence**
  It will be achieved by generating data on molecular markers/gene polymorphism like that of ADH1B Arg47His, ADH1C Ile349Val, ALDH2 Glu487Lys, DRD1 -48A/G, ANKK1 TaqI A and DRD2 (TaqI B, TaqI D and -141C Ins/Del).

- **To understand the dynamic gene-gene and gene-environment interactions with special reference to alcohol dependence**
  Relevant statistical software like SPSS, Odd ratio calculator, SNP Stat and MS Excel will be used to achieve the dynamic interrelationship between environment and genetic variables leading to alcohol dependence.

- **To understand the effect of alcohol consumption on health with special reference to anthropometric, physiological and biochemical variables**
  It will be achieved by generating data on anthropometric (BMI, WC and WHR), physiological (DBP and SBP) and biochemical variables (lipid profile and liver enzyme levels).