

# IS THERE A GENETIC BASIS FOR ALCOHOLISM?

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## ABSTRACT

This paper reviews studies done on the correlation of alcoholism and genetics. Evidence of this correlation can be seen in high heritability of alcoholism. The main methods used in determining genetic risk factors are candidate gene studies and genome wide studies. This review focuses mainly on findings related to specific neurotransmitters and receptors in relation to alcoholism. Evidence has shown that specific neurotransmitters and receptors can play a role in increased susceptibility to alcoholism. The neurotransmitters and receptors discussed in this paper include GABA, glutamate, and endogenous opioids. There is also a discussion focused on mutations of specific enzymes (ADH and ALDH) used to metabolize alcohol and its possible effects on developing alcoholism. When applicable, findings include a potential pharmacological treatment targeting the possible causation for alcoholism. Results from the studies conducted by the Collaborative Studies on Genetics of Alcoholism (COGA) have been discussed as well. COGA findings include specific chromosomes and their relationships with alcoholism, namely 1, 4, 7, 11, and a possible indicator for increased susceptibility, or level of response (LR).

The World Health Organization (WHO) estimates that alcohol results in 2.5 million deaths each year and in 9% of all deaths between the ages of 15 and 29. The WHO further concludes that alcohol is the world's third largest risk factor for disease burden; it is the leading risk factor in the Western Pacific and the Americas, and the second largest in Europe (World Health Organization 2011). An American survey by Hasin and colleagues (2007) concludes that alcoholism affects 4-5 % of the population at any given time. As a result of these widespread ramifications, alcoholism has been a subject of much research. This paper will primarily deal with the studies of genetic influences that affect alcoholism risk. Locating a genetic link can lead to possible alcoholism prevention of those genetically susceptible and help better treat those who have already developed the problem.

## DISCUSSION

In order for researchers to compare and contrast their findings, they must agree on the definition of an alcoholic. Most researchers rely on the definition of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, [DSM-IV] (APA 1994) and the World Health Organization's International Classification of Diseases (ICD-10). The Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, fourth edition (DSM-IV) defines alcohol dependence, to be equated with alcoholism, as:

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1. Tolerance, as defined by either of the following:

- A need for markedly increased amounts of the substance to achieve intoxication or desired effect.
- Markedly diminished effect with continued use of the same amount of substance.

2. Withdrawal, as manifested by either of the following:

- The characteristic withdrawal syndrome for the substance.

- The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.
- 3. The substance is often taken in larger amounts or over a longer period than was intended.
- 4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
- 5. A great deal of time is spent in activities to obtain the substance, use the substance, or recover from its effects.
- 6. Important social, occupational or recreational activities are given up or reduced because of substance use.
- 7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

The ICD-10 criteria for alcoholism are similar to that of the DSM-IV (Baber 1992). A main difference is that ICD-10 doesn't include a category on alcohol abuse, but rather refers to the same diagnosis as "harmful use." The change is meant to prevent an underreporting of alcohol abuse (Baber 1992). "Harmful use" includes psychical or mental damage due to alcohol dependence (Baber 1992).

A possible indication that a genetic predisposition for alcoholism exists is the fact that an alcoholic's biological offspring are approximately three to five times more likely to develop alcoholism during their lifetime than the biological offspring of nonalcoholics (Cotton 1979). One can argue, however, that the increased rate of alcoholism in alcoholics' biological offspring is due to environmental influences; a positive family history can merely be the result of shared environmental influences. Therefore, behavioral geneticists use twin and adoption studies to identify the separate contributions of genetics and shared environmental factors.

Researchers use analyses of genetically identical monozygotic twins (MZ) and fraternal dizygotic (DZ) twins to measure the heritability of alcoholism. There are eight major twin studies of alcoholism in men, and in all but one of these studies the concordance (same trait in both members of a pair of twins) rate for alcoholism was significantly greater in MZ than DZ twins (McGue1999). For example, in a study by Kendler, Prescott, Neale, and Pedersen (1997) on 8,939 Swedish male twins born from 1902 to 1949, the MZ twin concordance rate is significantly higher than the DZ twin concordance rate. Overall, the studies' concordance rates in monozygotic twins are approximately 47.9%, and in dizygotic twins, 32.8%.

Adoption studies also allow researchers to better separate genetics from environmental influences on the development of alcoholism. Seminal research by Cloninger and colleagues (1987) uses a large-scale adoption study in Sweden to identify genetic and other variables that predict alcohol abuse in adoptees. This study, coined the Stockholm Adoption Study, was done on 862 men and 913 women adopted by non-relatives at an early age in Sweden. The study distinguishes between two forms of alcoholism: Type I is characterized as late onset of alcoholism, after age 25, and marked by frequent psychological dependence; Type II alcoholism is characterized as a relatively early onset of alcoholism, before age 25, and marked by spontaneous alcohol seeking and aggressive behavior. Analysis of data from male

adoptees shows that although Type II alcoholism has an approximate heritability of 90%, Type I alcoholism has a heritability estimate of less than 40%. Many of the key results from the original Stockholm Adoption Study were independently replicated in a second Swedish city, Gothenburg (Sigvardsson et al. 1996). The replication study was carried out on a slightly smaller group (577 men and 660 women) but concludes that the risk of Type 2 alcoholism is increased 6-fold in adopted sons with a Type 2 genetic background compared with others, while Type I alcoholism has only a 4-fold increase in adopted men with Type I genetic backgrounds of alcoholism.

Due to the evidence that alcoholism is heritable, the next step is to identify the possible genetic factors that lead to the heritability. Two basic strategies are used to identify genetic risk factors for alcoholism: candidate gene approach and genome-wide studies (Sloan et al. 2008). The candidate gene approach involves assessing the association between a particular allele (or set of alleles) of a gene that may be involved in the disease (i.e. a candidate gene) and the disease itself (Kwon and Goate 2000). This approach often begins with the knowledge of potential physiological mechanisms that might be related to the endophenotype and makes educated guesses about which of the known genes might be important (Schuckit 2000). The genes most extensively examined by candidate gene studies are those involved in alcohol (i.e. ethanol) metabolism and in neurological pathways responsible for increased risk taking and “reward” stimulation from ethanol (Sloan et al. 2008).

A genome-wide study scans all genomes of individuals and identifies genetic polymorphisms. The two main approaches to genome-wide analysis are association and linkage (Sloan et al. 2008). Association studies examine genetic polymorphisms associated with case or control status, whereas linkage studies investigate the inheritance of specific locations on a chromosome within family lines (Sloan et al. 2008). In association studies, one tests if a given allele contributes to the risk for alcohol dependence. For example, if a researcher hypothesizes that Gene A plays a role in alcoholism, he would expect this allele to differ between the case and the control subjects.

Linkage analysis scans the genome using a type of genetic variation called microsatellites. Microsatellites are nucleotide pair combinations of DNA which repeat themselves and form groupings. Microsatellites can be highly polymorphic, making them useful for comparative genetic studies of organisms. Then, the pattern of transmission of disease (e.g. alcoholism) in families with multiple affected members is compared with the pattern of transmission of certain microsatellites (Foroud et al. 2010). The principal hypothesis in linkage analysis is that alcoholics within a family share many risk alleles; therefore, genes containing alleles that increase the risk for alcoholism reside within chromosomal regions that are inherited by most or all alcoholic family members (Foroud et al. 2010).

A prime example of specific genes related to the risk of alcoholism are those that control the production of the enzymes that metabolize ethanol (i.e. alcohol). Ethanol is metabolized in the liver, where it is converted to acetaldehyde by the enzyme alcohol dehydrogenase (ADH). ADH is responsible for 80% of ethanol’s metabolism to acetaldehyde (Gemma et al. 2006). About 10% of ethanol is metabolized by CYP2E1; the percentage increases when ADH is saturated (Gemma et al. 2006). Acetaldehyde is then converted to acetate by the enzyme aldehyde dehydrogenase (ALDH). High levels of acetaldehyde in the blood causes nausea, dizziness, and

headaches; therefore, variation in the genes coding for the ADH and ALDH enzymes are expected to be associated with alcoholism risk (Edenberg 2007).

There are at least six isoenzymes of ALDH (Schuckit 2000). ALDH2\*2, an isoenzyme of ALDH, involves a point mutation that results in the exchange of the amino acid glutamate at position 487 of the ALDH protein for the amino acid lysine (Edenberg 2007; Foroud et al. 2010). This mutation acts in a nearly dominant manner to render the enzyme almost inactive (Foroud et al. 2010). As a result, homozygous carriers of ALDH2-2 exhibit highly elevated levels of acetaldehyde, which produces aversive reactions, including flushing, tachycardia and nausea after consuming even a small amount of alcohol (Eng et al. 2007). Studies have shown that ALDH2-2 influences a person's drinking levels, and, consequently, the risk of developing alcohol abuse or dependence (Edenberg 2007; Hurley et al. 2002). There are almost no documented cases of homozygous carriers of ALDH2-2 being diagnosed as alcoholics (Luczak et al. 2006). Even people who are heterozygous for this mutation produce an ALDH enzyme with extremely low enzyme activity (Crabb et al. 1989).

Approximately 10% of Asian men and women (e.g. Japanese, Chinese, and Koreans) are homozygous for the mutation of ALDH2\*2, although it is not known to be found in any other racial group (Wall and Ehlers 1995). An additional 40% of Asians are heterozygotes for the ALDH mutated enzyme (Wall and Ehlers 1995). Compared with a Chinese man carrying two active ALDH alleles, the odds ratio of an alcoholism risk for a Chinese man carrying one inactive ALDH2-2 allele is 0.33 (Edenberg 2007). Furthermore, although heterozygote ALDH2-2 carriers represent almost half of the general population in their countries, they comprise less than 10% of Asian alcoholics, further supporting the conclusion that even heterozygotes have a relative protection from alcoholism (Murayama et al. 1998).

There are also coding variations in the ADH gene, called ADH2-2 and ADH2-3, which encode highly active enzymes which increase the production rate of acetaldehyde (Li 2000). These variations also reduce the risk for alcohol dependence (Edenberg 2007; Thomasson et al. 1991). For example, a pilot study by Neumark and colleagues (1998) was the first example of association between alcohol consumption patterns and a polymorphism at the ADH2 locus in a Jewish population. The study compares ADH loci in 92 non-drinkers (control) versus 53 heavy drinkers (case). Neumark furthered the study in 2004 by testing the effect of ADH2-2 on alcohol-elimination rates (AER) under experimental conditions. The study is based on the above-cited hypothesis that ADH2-2 increases the rate at which alcohol is metabolized, thereby increasing the production rate of acetaldehyde and producing aversive reactions. The study confirms that the rate of alcohol elimination is significantly associated with the *ADH2* genotype of Jewish males (Neumark 2004).

The evidence that an increase of acetaldehyde can be a deterrent to the development of alcohol abuse has led researchers to develop pharmacological treatments. Disulfiram blocks the enzyme aldehyde dehydrogenase, leading to an accumulation of acetaldehyde following an intake of alcohol (Heilig and Egli 2006). The accumulation of acetaldehyde then causes flushing, shortness of breath, tachycardia and other unpleasant symptoms. The point of disulfiram is not that patients actually experience adverse symptoms, but that the anticipation of these symptoms helps patients abstain from consuming alcohol (Heilig and Egli 2006). The logic is that an accumulation of acetaldehyde poses a possible medical risk. However,

disulfiram has a limited and largely negative documentation for efficacy (Heilig and Egli 2006). For example, a controlled multisite study of disulfiram treatment of alcoholism in 605 men concludes that although disulfiram may help reduce drinking frequency after relapse, it does not reduce the probability of abstinence from alcohol (Fuller et al. 1986).

Researchers have also done candidate gene studies on genes for receptors in the neurotransmitter gamma-aminobutyric acid (GABA), opioid receptor and components of the pathways for the neurotransmitters serotonin, dopamine, and glutamate (Sloan et al. 2008). A full discussion of each neurotransmitter surpasses the scope of this paper; therefore, but a few neurotransmitters and receptors and their relation to alcoholism will be discussed.

There is evidence supporting a link between the endogenous opioid system and excessive alcohol consumption (Gianoulakis 2001; Herz 1997). This evidence, linking the endogenous opioid system to alcoholism, led to several theories regarding the possible nature of an opioid abnormality in this disorder (Oswald and Wand 2004). The Opioid Deficit Hypothesis postulates that physiological cravings for alcohol may be the result of a deficiency of naturally occurring opiate like substances (Trachtenberg and Blum 1987). Conversely, the Opioid Surfeit Hypothesis maintains that excess (i.e. surfeits), not deficits, in opioidergic activity increases one's propensity to consume alcoholic beverages (Reid et al. 1991).

The first study to suggest a possible link between endogenous opioid and ethanol was conducted by Davis and Walsh (1970), who discovered that morphine-like alkaloids (tetrahydroisoquinolones) are formed *in vivo* as a result of the interaction between ethanol metabolite, acetaldehyde, and certain metabolites of dopamine. Due to Davis and Walsh's findings, further research sought to demonstrate that these alkaloids could bind to opioid receptors and produce opioid-like effects (Blum et al. 1978; Fertel et al. 1980). However, the pharmacological relevance of these compounds in opioidergic processes remains unclear because their concentrations in brain tissues is extremely low (Oswald and Wand 2004).

The best evidence of the linkage between endogenous opioid systems and ethanol consumption is that pharmacological blockades of opioid receptors reduce alcohol drinking in a dose-related fashion. Naltrexone is an opioid receptor antagonist that reduces alcohol cravings and relapses to heavy drinking, but it does not necessarily produce total abstinence. The initial study done by Altshuler and colleagues (1980) reports on the dose-related effect of naltrexone on decreasing ethanol drinking in 10 of 21 rhesus monkeys who were willing to self-administer alcohol. The treatment results were replicated by O'Malley et al. in 1992. In a 12-week, double-blind, placebo-controlled trial conducted on seventy male alcohol-dependent patients, Volpicelli and colleagues (1992) found that only 23% of alcoholic subjects who were administered naltrexone relapsed to heavy drinking, compared with 54.3% of subjects taking a placebo. Based, in part, on the findings of these studies, naltrexone was approved by the Food and Drug administration (FDA) in 1995 for the treatment of ethanol dependence. Since naltrexone's approval for the treatment of alcoholism, the opioid antagonist has been tested in 29 controlled clinical trials in unselected participants with alcoholism (Pettinati et al. 2006). The study concludes that "19 (70%) of 27 clinical trials that measured reductions in 'heavy or excessive drinking' demonstrated an advantage for prescribing naltrexone over placebo, whereas

only 9 (36%) of 25 clinical trials that measured abstinence or ‘any drinking’ found an advantage for medication over placebo” (Pettinati et al. 2006).

The effects of naltrexone have led to candidate gene studies on opioid receptors. There are three types of opioid receptors (mu, delta and kappa) that represent respective targets of the major opioid peptides (Herz 1997). Naltrexone acts as an antagonist at opioid receptors, with a relative selectivity for the  $\mu$ -opioid receptor (Oswald and Wand 2004). There are more than 25 identified allelic variants of the gene that codes for the  $\mu$ -opioid receptor (O’Brien 2008). In a human laboratory study (Ray and Hutchison 2004), volunteers with Asp40 allele (*OPRM1*) reported greater subjective euphoria at a given ethanol blood level. In a more recent study of heavy drinkers, naltrexone attenuated the increased alcohol stimulation in those carrying the Asp40 allele (Ray and Hutchison 2007).

Additionally, GABAergic mechanisms mediate many of the behavioral effects of ethanol, including its anticonvulsant, sedative-hypnotic, cognitive-impairing, and fine motor skill damaging effects (Kumar et al. 2009). The two classes of GABA receptors are GABA-A and GABA-B. GABA-A receptors are ligand-gated ion channels (i.e. ionotropic) that confer fast synaptic inhibition (Enoch 2007). GABA-A receptors undergo allosteric modulation by several structurally unrelated drugs, most with their own binding sites, including ethanol and benzodiazepines (Enoch 2007). Initial evidence that alcoholism is related to GABA-A receptors is because benzodiazepines show effectiveness in treating alcohol withdrawal (Enoch 2007).

GABA-A receptors are composed of five subunits (Sigel et al. 2006). Most receptors consist of two  $\alpha$  (alpha), two  $\beta$  (beta), and one  $\gamma$  (gamma) subunits (Sigel et al. 2006). The GABA-A receptor ion channel is lined by the transmembrane (TM) segments from each of the five subunits that form the receptor (Enoch 2007). Specific mutations in transmembrane domains 2 and 3 of the alpha subunit can abolish or markedly reduce the effects of ethanol on these receptors without necessarily affecting receptor function; therefore, alcohols may bind in a cavity located between TM2 and TM3 (Mascia et al. 2000).

Topiramate, which has a complex effect on GABA-A receptors, is hypothesized to decrease alcohol reinforcement and the propensity to drink (Johnson et al. 2007). A double-blind, randomized, placebo-controlled, 14-week trial of 371 men and women concludes that “topiramate was significantly more efficacious than placebo at reducing the percentage of heavy drinking days,” and “topiramate is a safe and consistently efficacious medication for treating alcohol dependence” (Johnson et al. 2007).

GABA inhibits hypothalamic-pituitary-adrenal axis responses to stress whereas glutamate activates the response (Herman et al. 2004). Prime targets of ethanol are the *N*-methyl-D-aspartate (NMDA) receptors in the glutamate system (Spanagel 2009). NMDA is an amino acid derivative that acts as a specific agonist at the NMDA receptor, mimicking the action of glutamate. Acute alcohol exposure inhibits the excitatory action of glutamate at the *N*-methyl-d-aspartate (NMDA) receptor, whereas chronic alcoholism results in increased NMDA receptor expression so that abrupt withdrawal produces a hyperexcitable state that leads to seizures (Guochuan and Coyle 1998). These findings have led to the formulation of the glutamate homeostasis hypothesis of addiction which suggests that enhanced

glutamate-mediated neuronal excitability during withdrawal and prolonged abstinence contributes to craving and relapse (Kalivas 2009).

Further, “Metabotropic glutamate (mGlu) receptors, which include mGlu1–8 receptors, are a heterogeneous family of G-protein-coupled receptors which function to modulate brain excitability via presynaptic, postsynaptic and glial mechanisms” (Schoepp 2001). In contrast to ionotropic receptors, metabotropic receptors influence the activity of a cell indirectly by first initiating a metabolic change in the cell. Studies provide evidence that activation of group II mGluRs (predominantly presynaptic) by a selective mGlu 2/3 agonist (LY379268) dose dependently blocks the effects of both stress and drug related environmental stimuli on the recovery of extinguished ethanol-seeking behavior (Zhao et al. 2006). A similar study on group I mGluRs (predominantly located postsynaptically) in alcohol-preferring P-rats, a well-defined genetic model of excessive alcohol consumption, shows that infusion of the mGluR5 antagonist 2-methyl-6(phenylethynyl) pyridine (MPEP) in the nucleus accumbens reduces ethanol-reinforced responding (Besheer et al. 2010). Besheer et al. (2010) concludes that the data “confirms the importance of mGluR5 activity in the nucleus accumbens in regulating drug reinforcement and emphasizes the potential therapeutic utility of targeting this receptor system in individuals with genetic risk for excessive drinking.”

The interaction of ethanol and glutamate led to candidate gene studies on glutamate. An association study that tested the candidate gene hypothesis of allelic variants of the ionotropic glutamatergic N-methyl-D-aspartate receptor (NMDAR) provides evidence that they are associated with vulnerability to alcoholism (Wernicke et al. 2003). Wernicke and colleagues studied variants of the ionotropic glutamatergic N-methyl-d-aspartate receptor (NMDAR the silent G2108A and C2664T polymorphisms of the NMDAR1 and the NMDAR2B genes), in exon 5 of the EAAT2 gene in 702 subjects of German descent, comprising 367 alcohol-dependent subjects and 335 control subjects. Genotype frequencies of the NMDAR1 polymorphism differed significantly between control and alcoholic subjects and the NMDAR2B polymorphism revealed a significantly reduced T allele in Cloninger type 2 alcoholics and in patients reporting an early onset compared with control subjects.

In 1989, the National Institute on Alcohol Abuse and Alcoholism initiated the Collaborative Study on the Genetics of Alcoholism (COGA), a large, systematic effort to identify the genes that predispose to alcoholism. COGA’s goal is to elucidate the genetic mechanisms that contribute to a person’s susceptibility to alcohol abuse and dependence (Begleiter et al. 1995). COGA generated a dataset of 1,857 families consisting of 16,062 individuals as of March 2010 (Foroud et al. 2010). Due to the genetic complexity of alcoholism, COGA researchers chose an unbiased survey of the entire genome (i.e. genotyping) (Edenberg 2002). Using microsatellite markers, more than 1.2 million genotypes were generated on 2,310 people from families of alcoholics and 1,238 people from control families (Edenberg 2002). This information enables researches to monitor the inheritance pattern of marker alleles within families with alcoholics and therefore helps identify chromosomal regions that show genetic linkage with alcoholic related traits (Edenberg 2002). To be categorized as a “family of alcoholics” the family must comprise at least three first-degree relatives who met lifetime criteria for *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM–III–R) (Foroud et al. 2010).

COGA data collected from families with alcoholism are used for both linkage and association analyses (Sloan et al. 2008). In 1998, COGA researchers published their initial linkage findings based on an analysis of 291 markers in 987 individuals from 105 families (Reich et al. 1998). Substantial evidence points to a susceptibility loci for alcohol dependence on chromosomes 1 and 7. In addition, there is suggestive evidence for a protective locus on chromosome 4 near the *ADH* gene (Reich et al. 1998). At the same time as the COGA findings were published, a second large-scale linkage study of alcoholism, based on a sample of Native Americans, reported suggestive evidence of the existence of a predisposing gene on Chromosome 11p, in close proximity to the *DRD4* dopamine receptor (Long et al 1998). Evidence also suggests a protective gene on Chromosome 4p, near the beta1 GABA receptor gene (Long et al. 1998). Although only the Chromosome 4 findings overlapped, the two studies sampled different ethnic groups, and the genes that underlie alcoholism risk might be expected to vary for groups having distinct evolutionary history (McGue 1999). A more recent COGA study by Yang and colleagues (2005) found potential candidate regions on chromosomes 1, 2, and 7 linked with alcoholism susceptibility. Overall, Yang viewed his findings as consistent with Reich's findings (Yang et al. 2005).

Due to prior evidence for the role of the *ADH* genes in alcoholism susceptibility, the COGA investigators did several studies to determine the specific nature of the link (Foroud et al. 2010). In one particular study, COGA researchers genotyped 110 DNA markers known as single nucleotide polymorphisms (SNPs) across the seven *ADH* genes located on chromosome 4q and analyzed their association with alcoholism in a set of families (n= 262) with multiple alcoholic members (Edenberg et al. 2006). The analyses show strong evidence that 12 SNPs located in and around the *ADH4* gene are significantly associated with alcoholism (Edenberg et al. 2006).

Evidence of a molecular interaction between ethanol and GABA receptors led COGA researchers to study the link between variation in GABA receptors and alcoholism. Edenberg and colleagues (2004) performed a linkage analyses of 69 single-nucleotide polymorphisms (SNPs) within a cluster of four GABA (A) receptor genes located in chromosome 4p: *GABRG1*, *GABRA2*, *GABRA4*, and *GABRB1*. The analyses found thirty-one SNPs in *GABRA2* associated with alcohol dependence. Edenberg concludes his study by stating, " the convergence of evidence from different analyses and phenotypes, along with the biological data on its function, provides strong evidence that *GABRA2* is a key gene affecting the risk for alcoholism." Interestingly, the *GABRA2* is part of the GABA-A  $\alpha$  subunit that was mentioned before as a possible binding spot for alcohol.

The genome-wide association studies (GWAS), also known as the whole genome association studies, are examinations of all or most of the genes (the genome) of different individuals of a particular species to see how much the genes vary from individual to individual. Different variations are then associated with different traits, such as diseases. In humans, hundreds or thousands of individuals are tested for single-nucleotide polymorphisms (SNPs). The advantage of GWAS is that it allows a comprehensive test for associations across the genome, rather than testing only one gene at a time.

The genome-wide association studies (GWAS) examine up to a millions SNPs through the human genome in a single experiment (Foroud 2010). The different variations of SNPs between individuals is then associated with different traits, such as diseases. An advantage of GWAS is its hypothesis-free strategy and its suitability for the discovery of novel genetic contributors to disease (Bierut et al. 2010).

This first genome-wide significant association study in alcohol dependence was published in 2009 (Treutlein et al. 2009). The GWAS included 487 male inpatients with alcohol dependence as defined by the *DSM-IV* and 1,358 population-based control individuals (Treutlein et al. 2009). The GWAS tested 524 396 single-nucleotide polymorphisms (SNPs) (Treutlein et al. 2009). The analyses found two closely linked SNPs located on chromosome 2 (Treutlein et al. 2009). However, a recent GWAS of 1,897 European-American and African-American subjects with alcohol dependence compared with 1,932 unrelated, alcohol-exposed, nondependent controls did not replicate the finding reported by Treutlein and colleagues (Bierut et al. 2010). Interestingly, Bierut's GWAS found SNPs genotyped in *GABRA2* that overlap with SNPs reported by Edenberg et al. (2004).

The level of reaction to alcohol has been a useful tool to indicate a possible increase in susceptibility to alcoholism. Studies have found a correlation between level of response (LR) to alcohol and the risk of developing alcohol dependency (Schuckit 1999). Numerous alcoholics have reported an ability to consume large amounts of alcohol with relatively little effect from early in their drinking careers (Schuckit 1999). A low LR is usually evaluated by giving alcohol to individuals and determining the intensity of response at a given blood alcohol concentration (BAC), or by indirectly measured through a self-report of a history of a higher number of drinks required to produce a specific effect (Schuckit 2000). A study of 453 sons of alcoholics and controls as conducted over a period of 15 years demonstrated that a low LR was a significant predictor of later alcoholism (Schuckit and Smith 1996).

There are several indications that LR is genetically influenced. For example, a study on 3,810 adult twin pairs reported a higher level of similarity on some aspects of LR in identical twins than in fraternal twins, with an estimated heritability between 40 and 60 percent (Martin 1988). A pilot study (Mazzanti et al. 1999) evaluated 17 men with low LR scores, comparing results to 24 individuals who were clearly higher on the LR scale. The high LR and low LR groups were then evaluated for the patterns of 5 candidate genes relating to serotonin and gamma-aminobutyric acid functions. The 14 men with the LL genotype of the serotonin transporter (5-HTT) polymorphism and the seven with the genotype of the *GABAA* alpha 6 polymorphism had demonstrated lower LR scores at about age 20, and had significantly higher proportions of alcoholics than the other genotypes for those loci. These studies show that low LR can be a potential indicator to a genetic risk of alcoholism.

## CONCLUSION

In conclusion, evidence has shown that there exists a genetic susceptibility to alcoholism. However, it is clear that there are environmental factors, possible as high as 50% (Dick and Beirut 2006), that can attribute to alcoholism. The main focus of this paper is to show that the genetic component of alcoholism exists as well, though it is clear that alcoholism is a complex disease that involves various mechanisms and pathways. Susceptibility to alcoholism cannot be attributed to one single gene,

neurotransmitter, or receptor. Other possible neurotransmitters that haven't been discussed but yet can play a vital role are serotonin and dopamine (DRD2). This paper is only a brief overview of possible genetic contributions to alcoholism. There is much more research that has been done and more that will be done in the near future.

## REFERENCES

- Altshuler HL, Phillips PA, Feinhandler DA. 1980. Alteration of ethanol self-administration by naltrexone. *Life Sci* 26(9):679-688.
- American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. Washington D.C.: American Psychiatric Association. pp. 181-183.
- Baber TF. 1992. Substance-related problems in the context of international classificatory systems. In: Lader M, Edwards G, Drummond DC, editors. *The Nature of Alcohol and Drug Related Problems*. New York: Oxford University Press
- Begleiter H, Reich T, Hesselbrock V. 1995. The Collaborative Study on the Genetics of Alcoholism. *Alcohol Health & Research World* 19:228-236.
- Besheer J, Grondin JJ, Cannady R, Sharko AC, Faccidomo S, Hodge CW. 2010. Metabotropic glutamate receptor 5 activity in the nucleus accumbens is required for the maintenance of ethanol self-administration in a rat genetic model of high alcohol intake. *Biol Psychiatry* 67:812-822.
- Bierut LJ, Agrawal A, Bucholz KK, Doheny KF, Laurie C, Pugh E, Fisher S, Fox L, Howells W, Bertelsen S, Hinrichs AL, Almasy L, Breslau N, Culverhouse RC, Dick DM, Edenberg HJ, Foroud T, Gruzza RA, Hatsukami D, Hesselbrock V, Johnson EO, Kramer J, Krueger RF, Kuperman S, Lynskey M, Mann K, Neuman RJ, Nöthen MM, Nurnberger Jr. JI, Porjesz B, Ridinger M, Saccone NL, Saccone SF, Schuckit MA, Tischfield JA, Wang JC, Rietschel M, Goate AM, Rice JP. 2010. A genome-wide association study of alcohol dependence. *Proc. Natl Acad. Sci. USA* 107:5082-5087.
- Blum D, Hamilton MG, Hirst M, Wallace JE. 1978. Putative role of isoquinoline alkaloids in alcoholism: a link to opiates. *Alcohol Clin Exp Res* 2:113-20.
- Cloninger CR. 1987. Neurogenetic adaptive mechanisms in alcoholism. *Science* 236: 410-416.
- Cotton NS. 1979. The familial incidence of alcoholism: A review. *Journal of Studies on Alcohol* 40:89-116.
- Crabb DW, Edenberg HJ, Bosron WF, Li TK. 1989. Genotypes for aldehyde dehydrogenase deficiency and alcohol sensitivity. The inactive ALDH2(2) allele is dominant. *Journal of Clinical Investigation* 83:314-316.
- Davis VE, Walsh MJ. 1970. Alcohol, amines and alkaloids: a possible biochemical basis for alcohol addiction. *Science* 167:1005-7.
- Dick DM, Bierut LJ. 2006. The Genetics of Alcohol Dependency. *Current Psychiatric Reports* 8(2):151-7.
- Edenberg HJ. 2002. The collaborative study on the genetics of alcoholism: An update. *Alcohol Research & Health* 26:214-218.
- Edenberg HJ. 2007. The genetics of alcohol metabolism: Role of alcohol dehydrogenase and aldehyde dehydrogenase variants. *Alcohol Research & Health* 30:5-13.
- Edenberg HJ, Dick DM, Xuei X. 2004. Variations in GABRA2, encoding the alpha 2 sub unit of the GABA(A)receptor, are associated with alcohol dependence and with brain oscillations. *American Journal of Human Genetics* 74:705-714.
- Edenberg HJ, Xuei X, Chen HJ, Huijun T, Wetherill LF, Dick DM, Almasy L, Bierut L, Bucholz KK, Goate A, Hesselbrock V, Kuperman S, Nurnberger J, Porjesz B, Rice J, Schuckit M, Tischfield J, Begleiter H and Foroud T. 2006. Association of alcohol dehydrogenase genes with alcohol dependence: A comprehensive analysis. *Human Molecular Genetics* 15:1539-1549.
- Eng MY, Luczak SE, Wall TL. 2007. ALDH2, ADH1B, and ADH1C genotypes in Asians: A literature review. *Alcohol Research & Health* 30:22-27.
- Enoch MA. 2007. Genetics, stress and the risk for addiction. In: al'Absi M, editor. *Stress and addiction: biological and psychological mechanisms*. New York: Elsevier Neuroscience. pp. 127-46
- Fertel RH, Greenwald JE, Schwarz R, Wong L, Bianchine J. 1980. Opiate receptor binding and analgesic effects of the tetrahydroisoquinolines salsolinol and tetrahydro-papaveroline. *Res Commun Chem Pathol Pharmacol* 27:3-16.

- Foroud T, Edenberg H, Crabbe J. 2010. Genetic Research: Who Is At Risk for Alcoholism? *Alcohol Research and Health* 33(1/2):64-75.
- Fuller RK, Branchey L, Brightwell DR, Derman RM, Emeric CD, Iber FL. 1986. Disulfiram treatment of alcoholism: A Veterans Administration cooperative study. *JAMA* 256:1449-1455
- Gemma S, Vichi S, Testai E. 2006. Individual susceptibility and alcohol effects: Biochemical and genetic aspects. *Annali dell'Istituto Superiore di Sanità* 42:8-16.
- Gianoulakis C. 2001. Influence of the endogenous opioid system on high alcohol consumption and genetic predisposition to alcoholism. *J Psychiatry Neurosci* 26:304-18.
- Guochuan T, Coyle JT. 1998. The role of glutamatergic neurotransmission in the pathophysiology of alcoholism. *Annual Review of Medicine* 49:173-84.
- Hasin DS, Stinson FS, Ogburn E, Grant BF. 2007. Prevalence, correlates, disability, and comorbidity of DSMIV alcohol abuse and dependence in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of General Psychiatry* 64:830-842.
- Heilig M, Egli M. 2006. Pharmacological treatment of alcohol dependence: target symptoms and target mechanisms. *Pharmacol Ther* 111:855-876.
- Herman JP, Mueller NK, Figueiredo H. 2004. Role of GABA and glutamate circuitry in hypothalamo pituitary-adrenocortical stress integration. *Ann NY Acad Sci* 1018:35-45.
- Herz A. 1997. Endogenous opioid systems and alcohol addiction. *Psychopharmacology* 129:99-111.
- Hurley TD, Edenberg HJ, Li TK. 2002. The Pharmacogenomics of Alcoholism. In: Lucinio J, Wong ML, editors. *Pharmacogenomics: The Search for Individualized Therapies*. Weinheim, Germany: Wiley-VCH pp. 417-441.
- Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L, Beyers K. 2007. Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA* 298:1641-51.
- Kalivas P. 2009. The Glutamate Homeostasis hypothesis of addiction. *Nature Reviews Neuroscience* 10(8):561-72.
- Kendler KS, Prescott CA, Neale MC, Pedersen NL. 1997. Temperance Board registration for alcohol abuse in a national sample of Swedish male twins, born 1902 to 1949. *Archives of General Psychiatry* 54:178-18.
- Kwon JM, Goate AM. 2000. The candidate gene approach. *Alcohol Res. Health* 24:164-168.
- Li T-K. 2000. Pharmacogenetics of responses to alcohol and genes that influence alcohol drinking. *J Stud Alcohol* 61:5-12.
- Long JC, Knowler WC, Hanson RL, Robin RW, Urbanek M, Moore E, Bennett PH, Goldman D. 1998. Evidence for genetic linkage to alcohol dependence on chromosomes 4 and 11 from an autosome-wide scan in an American Indian population. *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 81:216-221.
- Luczak SE, Glatt SJ, Wall TJ. 2006. Meta analyses of ALDH2 and ADH1B with alcohol dependence in Asians. *Psychological Bulletin* 132(4):607-621.
- Martin NG. 1988. Twin studies of alcohol consumption, metabolism, and sensitivity. *Australian Drug and Alcohol Review*. 1988; 7:9-12.
- Mascia MP, Trudell JR, Harris RA. 2000. Specific binding sites for alcohols and anesthetics on ligand-gated ion channels. *Proc Natl Acad Sci USA* 97:9305-10.
- Mazzanti C, Schuckit MA, Smith TL, Ahmed U, Radel M, Iwata N, Goldman D. 1999. Selective genotyping for the role of 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, and GABA<sub>A</sub> 6 receptors and the serotonin transporter in the level of response to alcohol: a pilot study. *Bio Psychiatry* 45:647-651.
- McGue M. 1999. The behavioral genetics of alcoholism. *Current Directions in Psychological Science* 8:109-115.
- Murayama M, Matsushita S, Muramatsu T. 1998. Clinical characteristics and disease course of alcoholics with inactive aldehyde dehydrogenase-2. *Alcohol Clin Exp Res*. 22:524-527.
- Neumark YD, Friedlander Y, Thomasson HR. 1998 Association of the ADH2\*2 allele with reduced ethanol consumption in Jewish men in Israel: a pilot study. *J Stud Alcohol* 59:133-139.
- Neumark YD, Friedlander Y, Durst R, Leitersdorf E, Jaffe D, Ramchandani VA, O'Connor S, Carr LG, Li T.-K. 2004. Alcohol Dehydrogenase Polymorphisms Influence Alcohol-Elimination Rates in a Male Jewish Population. *Alcoholism: Clinical and Experimental Research* 28:10-14.
- O'Brien CP. 2008. Prospects for a genomic approach to the treatment of alcoholism. *Arch. Gen. Psychiatry*. 65:132-133

- O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. 1992. Naltrexone and coping skills therapy for alcohol dependence: a controlled study. *Arch Gen Psychiatry*. 49(11):881-887.
- Oswald LM, Wand GS 2004. Opioids and alcoholism. *Physiology Behavior* 81:339–358.
- Pettinati HM, O'Brien CP, Rabinowitz AR, Wortman SP, Oslin DW, Kampman KM, Dackis CA. 2006. The status of naltrexone in the treatment of alcohol dependence: specific effects on heavy drinking. *J Clin Psychopharmacol*. 26(6):610-625.
- Ray LA, Hutchison KE. 2004. A polymorphism of the mu-opioid receptor gene (OPRM1) and sensitivity to the effects of alcohol in humans. *Alcohol Clin Exp Res* 28:1789-1795.
- Ray LA, Hutchison KE. 2007. Effects of naltrexone on alcohol sensitivity and genetic moderators of medication response: a double-blind placebo-controlled study. *Arch Gen Psychiatry* 64(9):1069-1077.
- Reich T, Edenberg HJ, Goate A, William JT, Rice JP, Van Eerdewegh P, Foroud T, Hesselbrock V, Schuckit MA, Bucholz K, Porjesz B, Li TK, Conneally PM, Nurnberger JI, Tischfield JA, Crowe RR, Cloninger CR, Wu W, Shears S, Carr K, Crose C, Willig C, Begleiter H. 1998. Genome-wide search for genes affecting risk for alcohol dependence. *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 81:206-215.
- Reid LD, Delconte JD, Nichols ML, Bilsky EJ, Hubbell CL. 1991. Tests of opioid deficiency hypotheses of alcoholism. *Alcohol* 8:247-57.
- Schoepp DD. 2001. Unveiling the functions of presynaptic metabotropic glutamate receptors in the central nervous system. *J Pharmacol Exp Ther* 299:12–20.
- Schuckit MA. 1998. Biological, psychological, and environmental predictors of the alcoholism risk: a longitudinal study. *J Stud Alcohol* 59:485-494.
- Schuckit MA. 2000. Genetics of the risk for alcoholism. *Am J Addict* 9:103–112.
- Schuckit MA, Smith TL. 1996. An 8-year follow-up of 450 sons of alcoholic and control subjects. *ArchGen Psychiatry* 53:202-210.
- Sigel E, Baur R, Boulineau N, Minier F. 2006. Impact of subunit positioning on GABAA receptor function. *Biochem Soc Trans* 34:868–71.
- Sigvardsson S, Bohman M, Cloninger CR. 1996. Replication of the Stockholm Adoption Study of alcoholism: Confirmatory cross fostering analysis. *Archives of General Psychiatry* 53:681-687.
- Sloan C, Sayarath V, Moore JH. 2008. Systems genetics of alcoholism. *Alcohol Research and Health* 31:14-25.
- Spanagel R. 2009. Alcoholism: A systems approach from molecular physiology to addictive behavior. *Physiol Rev* 89(2):649–705.
- Trachtenberg MC, Blum K. 1987. Alcohol and opioid peptides: neuropharmacological rationale for physical craving of alcohol. *Am J Drug Alcohol Abuse* 13:365-72.
- Treutlein J, Cichon S, Ridinger M, Wodarz N, Soyka M, Zill P, Maier W, Moessner R, Gaebel W, Dahmen N, Fehr C, Scherbaum N, Steffens M, Ludwig KU, Frank J, Wichmann HE, Schreiber S, Dragano N, Sommer WH, Leonardi-Essmann F, Lourdasamy A, Gebicke-Haerter P, Wienker TF, Sullivan PF, Nothen MM, Kiefer F, Spanagel R, Mann K, Rietschel M. 2009. Genome-wide association study of alcohol dependence. *Arch Gen Psychiatry* 66:773–784.
- Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. 1992. Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry* 49:876–880.
- Wall TL, Ehlers CL. 1995. Genetic influences affecting alcohol use among Asians. *Alcohol Health & Research World* 19(3):184-189.
- Wernicke C, Samochowiec J, Schmidt LG, Winterer G, Smolka M, Kucharska-Mazur J, Horodnicki J, Rommelspacher H. 2003. Polymorphisms in the N-methyl-D-aspartate receptor 1 and 2B subunits are associated with alcoholism-related traits. *Biological Psychiatry* 54(9):922-928.
- World Health Organization. 2011, February. Alcohol Fact Sheet. Retrieved 22 May 2011 from: <http://www.who.int/mediacentre/factsheets/fs349/en/index.html>
- Yang HC, Chang CC, Lin CY. 2005. A genome-wide scanning and fine mapping study of COGA data. *BMC Genetics* 6(Suppl 1):S30
- Zhao Y, Dayas CV, Auja H, Baptista MA, Martin-Fardon R, Weiss F. 2006. Activation of group II metabotropic glutamate receptors attenuates both stress and cue-induced ethanol-seeking and modulates c-Fos expression in the hippocampus and amygdala. *J Neurosci* 26:9967–9974.