GENETICS OF ALCOHOL ADDICTION

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Abstract

A tremendous amount of attention and research has recently been concentrated on the inheritance of alcoholism and on the possibility of accounting genetically for drunken behavior. Genetic studies utilizing twins and families have demonstrated a considerable role for genetics alcohol addiction. Risk for alcoholism is likely to be the result of a large number of genes, each contributing a small fraction of the overall risk. While this review will focus on studies of role genetics in alcohol addiction. The review will briefly summarize neurobiology and genetic epidemiology that provide estimations of heritability. For each topic the data will be presented alcohol dependence, In addition, each section will review briefly some of the confounding issues in the specific type of approach utilized.

Introduction

Alcoholism and alcohol-related disorders have a marked familial inclination. There has been substantial debate over many years as to whether this represents transmission of genetic traits or the influence of family atmosphere on drinking behavior. Studies of adopted children and of monozygotic compared with dizygotic twins show a modest but definite genetic influence on drinking habits and, at least in men, on the occurrence of psychosocial problems related to alcohol abuse. Research has shown conclusively that familial spread of alcoholism risk is at least in part genetic and not just the result of family environment. The task of current science is to identify what a person inherits that increases vulnerability to alcoholism and how inherited factors interact with the environment to cause disease. This information will provide the basis for identifying people at risk and for developing behavioral and pharmacologic approaches to pre-vent and treat alcohol problems. The advances being made now are built on the discovery 50 years ago of the role in inheritance of DNA, the genetic material in cells that serves as a blue-print for the proteins that direct life processes[2].

Alcoholism: A Complex Genetic Disease

Alcoholism is a heterogeneous disease in which the expression of genetic vulnerability is modified by environmental factors. Some of the environmental influences are uniquely

experienced by the individual (noshared) and some are shared among different individuals within the family. Numerous studies have shown that alcoholism is familial [3]. Studies in recent years have confirmed that identical twins, who share the same genes, are about twice as likely as fraternal twins, who share on average 50 percent of their genes, to resemble each other in terms of the presence of alcoholism. Recent research also reports that 50 to 60 percent of the risk for alcoholism is genetically determined, for both men and women [4] [5] [6] [7]. Research suggests that many genes play a role in shaping alcoholism risk. Like diabetes and heart disease, alcoholism is considered genetically complex, distinguishing it from genetic diseases, such as cystic fibrosis, that result primarily from the action of one or two copies of a single gene and in which the environment plays a much smaller role, if any. The methods used to search for genes in complex diseases have to account for the fact that the effects of any one gene may be subtle and a different array of genes underlies risk in different people. Scientists have bred lines of mice and rats that manifest specific and separate alcohol-related traits or phenotypes, such as sensitivity to alcohol's intoxicating and sedative effects, the development of tolerance, the susceptibility to withdrawal symptoms, and alcohol-related organ damage [8] [9]. To have an alcoholic parent is a significant risk factor for the development of the disease; children of alcoholics are five times more likely to develop alcohol-related problems than children of non-alcoholics [10]. It has been shown that the transmission of the vulnerability to alcoholism from parents to their daughters is due largely or entirely because of genetics factors [11]. Studies of heritability, a measure of the genetic component of variance in interindividual vulnerability, indicate that genetic influences are substantially responsible for the observed patterns of familiality. Adoption studies have shown that alcoholism in biological parents predicts alcoholism in children even when the child is reared by unrelated adoptive parents [12] [13]. Large, well-constructed twin studies [14][15] have demonstrated that genetic factors are important in determining vulnerability to alcoholism, particularly in the more severe forms of the disease [16]

Neurobiology of Alcohol Addiction

The vital features of dependence are failure to manage over consumption, compulsion to obtain the next stimulus, and continuation of abuse despite knowledge of negative health and social consequences. Tolerance and dependence are due to neuroadaptations. Processes of reward and reinforcement play their most crucial role at the start of the path to addiction, after which long-lasting or permanent neuroadaptations occur. It is likely that genetic variation in this neurobiology predisposes some individuals to a pattern of increased craving and loss of control. Addictive substances affect a range of neurotransmitter systems in different

regions of the brain. However, a pathway that appears to be crucial to the action of all addictive drugs is the mesolimbic dopamine system, which originates in the ventral tegmental area (VTA) of the midbrain and projects to the nucleus accumbens (NAC), with projections also to the limbic system and the orbitofrontal cortex [17]. The amygdala, hippocampus, and medial prefrontal cortex send excitatory projections to the NAC. The mesolimbic dopamine pathway is associated with the ability to feel pleasure. Serotoninergic neurons originating in the dorsal and median raphe nuclei project to mesolimbic structures, including the VTA and NAC, and may exert inhibitory control on mesolimbic dopamine neuron activity [18].

Alcohol exerts its primary reinforcing or reward effects by releasing dopamine (DA) in the NAC. The acute reinforcing actions of psychostimulant drugs is mediated both by the blockade of DA binding to its transporter, preventing the reuptake of DA from the synaptic cleft [19] , and by interaction with multiple DA receptors including D1, D2, and D3 [20]. Cocaine blocks the reuptake of serotonin (5-HT) and norepinephrine in a similar fashion. A functional down-regulation of 5-HT3 receptors in the NAC may contribute to cocaine tolerance [21], whereas chronic alcohol intake increases the sensitivity of 5-HT3 receptors [22]. Chronic cocaine and alcohol administration also disrupts the endogenous opioid system [23]. Nicotine's reinforcing effect is through activation of nicotinic receptors in the VTA, ultimately leading to release of dopamine in the NA [24], but the rewarding effects are also mediated by the cholinergic and serotoninergic neurotransmitter systems. The acute reward effects of opioids are enhanced by activation of (and possibly also) receptors in the VTA.

GABA is the major inhibitory neurotransmitter in brain. The development of tolerance may be related to ethanol induced adaptive changes in the $GABA_A$ receptor system. Enhanced aminobutyric acid (GABA), glutamate, dopaminergic, opioid peptide, and serotoninergic neurotransmission have been associated with acute ethanol administration, and potentially mediate some of alcohol's reinforcing effects [25]. Ethanol appears to act on a variety of targets within the cell membrane in a less specific manner, inducing effects on neurotransmitter and neurohormone membrane receptors and receptor-gated and voltage-activated ion channels as well as modulating neurotransmitter release [26]. Alterations in calcium channels may be a major component of the changes that occurs in the physical dependence on ethanol [27].

Evidence suggests that ethanol's inhibition of the glutamatergic neurotransmitter pathways, especially at the level of the postsynaptic N-methyl-D-aspartate (NMD_A) receptor, may be an important cause of its neurotoxic effects

[28]. Glutamate is the major excitatory brain neurotransmitter with up to 40% of all synapses being glutamatergic [29]. Inhibition of GABAergic interneurons mediated via ethanol's effect on the NMD_A receptor may result in disinhibition of forebrain glutamatergic neurons that augment dopamine release [29]. Changes in the NMD_A receptor system may underlie intoxication and withdrawal symptoms [30] as well as ''blackouts'' [28]. Homotarrine (Acamprosate), a structural analogue of glutamate and an NMD_A-receptor antagonist, has been shown to almost double the abstinence rate in recovering alcoholics [31].

Genetic Epidemiology

Family Studies

Since of a high degree of familial connection, for several years, alcoholism was regarded as a separate disease that may be transmitted from generation to generations [32]. A familial connection could effect from cultural factors tending to promote heavy drinking in family members. Children try to model their actions on that of their parents and doing so may also imitate their drinking habits. On the other hand, drinking may be discouraged in some families for religious, cultural or climatic grounds while in other families constraints on heavy drinking may be virtually non-existent. So, "familial" does not necessarily mean "hereditary". A critical review of studies of the familial incidence of alcoholism summarized 39 investigations published in English that comprised family data on 6,251 alcoholics and 4,083 non-alcoholics [33]. They clearly showed that regardless of the nature of the population of non-alcoholics studied, an alcoholic is more likely to have a mother, father or a distant relative who is an alcoholic. When lifetime prevalence of alcoholism in relatives of alcoholics were compared to that in the general population, a 4-fold increased risk in first-degree relatives and a 2-fold increased risk in second-degree relatives was observed. Higher family incidence of alcohol use and abuse does not necessarily reflect a genetic determination of alcoholism. Heritable familial attributes as well as similarities in the social environment of family members also appear to play a role in familial transmission of alcoholism. Thus, family systems (family reactivity patterns, ethnic family styles, gender of the alcoholic spouse, and stages of alcoholism) are an important variable in the genesis.

Twin Studies

The twin study model is a unique method to study complex and heterogeneous trait disorders. Differences between identical twins would presumably reflect environmental influences while differences between non-identical twins may be due to heredity, environment, or both. Twin studies are based on the fact that monozygotic twins (MZ) share identical genetic material, while dizygotic twins (DZ) share the same degree of genetic similarity as non-twin siblings. If genetic

effects are present then monozygotic twins should be more similar than dizygotic twins allowing an estimation of the genetic contribution. Differences between identical twins would presumably reflect environmental influences while differences between non-identical twins may be due to heredity, environment or both [34]. . Therefore, if alcoholism has a hereditary basis, MZ twin pairs should tend to be more similar in their drinking behavior and alcohol-related problems than DZ twin pairs. In the Swedish study an increasing difference in concordance rates between the monozygotic (MZ) and dizygotic (DZ) pairs with increasing degree of alcohol abuse was found [35]. In British study the concordance rates of MZ and DZ twins did not differ significantly, but more than one-third of the twins were below age 40 years when examined, suggesting that alcohol dependence may yet develop in a proportion of co-twins [36]. In a study it is found strong evidence for genetic influences on the development of alcoholism for both sexes, while the evidence for common environmental effects was negligible [37]. Twin studies shows contribution of genetic factor on alcohol addiction

Adoption Studies

A methodical way to split "nature" from "nurture" is to learn those separated from their biological relatives soon after birth and grown by non-related foster parents and to compare them with respect to characteristics of alcohol abuse with both their biological and adoptive parents. It is based upon the premise that the genetic trait present in the affected biological parent will still be expressed in adoptee, regardless of the enotypic status and environmental circumstances of the foster parents. In studies of intact families, the effects of genetic and common environment are not separable. Adoption studies separate these effects because adoptees receive their genetic heritage from one set of parents and their rearing environment from another set. The degree to which adoptees resemble their biological relatives is a direct measure of genetic influence, while the degree to which they resemble their adoptive relatives is a measure of the influence of family environment. Extensive adoption studies conducted in Denmark and Sweden have provided substantial evidence that alcoholism is genetically influenced, and that there are distinct patterns of alcoholism with different genetic and environmental causes[38][39][40]. When the adopted away sons of an alcoholic parent were compared to their siblings raised by the alcoholic biological parent, a remarkably similar rate of alcoholism was noted in both groups. Subsequent adoption studies from other countries have clearly shown that children born to alcoholic parents but adopted away during infancy were at greater risk for alcoholism than adopted-away children born to nonalcoholic parents [41].

Gender Differences in the Transmission of Alcoholism

There is consistent evidence that relatives of women treated for alcoholism have higher risk for alcoholism than relatives of treated males [42]. This suggests that women in treatment tend to have higher liability than their male counterparts [43]. The results for untreated female alcoholics are less clear. The evidence regarding sex-specific transmission varies across studies, providing no consensus as to whether different sets of genetic factors influence the development of alcoholism in males and females [44]. Some evidence from molecular genetic studies supports the existence of sex-specific loci [45] and a definitive answer to this issue will probably come from molecular rather than epidemiological studies.

Mode of Inheritance

Although adoption and twin studies have proven useful in answering the question of nature versus nurture, the mode of inheritance of alcoholism is still an unresolved matter. None of the evidence hitherto put forward suggests that susceptibility to alcoholism is inherited via a simple Mendelian dominant, recessive or sex-linked transmission. Even if the inheritance of certain biological factors involved in alcoholism is assumed to be Mendelian, the effect of these factors on the development of complex disorders may still not fit a simple genetic model. A substantial degree of etiological heterogeneity in the alcoholism phenotype results in the ultimate manifestation of the disorder dependent on poorly understood gene-environment interactions.

Characterization of High Risk and Low Risk Individuals

In the past years, a number of investigators have tried, in prospective studies, to identify possible trait markers by studying young men and women at high risk for the future development of alcoholism based on their family history of this disorder. Having an alcoholic biological father is the best single predictor of future alcoholism in male offspring. One method of determining whether there are neuro-psychological deficits prior to the onset of alcoholism is to study children who are at risk for becoming alcoholic. In a typical prospective study young men and women at high risk for the future development of alcoholism are divided into Family History Positive (FHP) group, (who report an alcoholic parent or siblings) and Family History Negative (FHN) group (men and women who report no close alcoholic relative). The subjects are matched for demography and alcohol drinking history.

Genetics of Alcohol Metabolism

At the present time, the genes for alcohol metabolism are the only genes that are known to have a major impact on the development of alcoholism. One gene variant (allele) is protective and the other is a vulnerability allele. Alcohol dehydrogenase (ADH) metabolizes

ethanol to acetaldehyde, a toxic intermediate, which is in turn converted to acetate by aldehyde dehydrogenase (ALDH). Approximately half the population of Southeast (SE) Asian has functional polymorphisms at four different genes: ADH2, ADH3, ALDH1, and ALDH2. Across populations, the ALDH2-2 variant appears on a similar genetic background (haplotype) and thus has probably had the same evolutionary origin [46]. The most important variants are ALDH2-2) and ADH2-2. ALDH2-2 dominantly inactivates ALDH2, the ALDH that is mitochondrially localized and responsible for most acetaldehyde metabolism in cells. ADH2-2 is a superactive variant. Allelic variation at ADH3 apparently exerts no independent effect on the risk for alcoholism; however, ADH3-1 is in linkage disequilibrium with ADH2- 2 [47][48] and is thus also predictive of vulnerability. ADH2- 2 and ALDH2-2 raise the levels of acetaldehyde by increasing the rate of synthesis, by decreasing the rate of metabolism, and by interacting additively, but not synergistically [49]. The result is that ingestion of even small amounts of ethanol produces an unpleasant reaction characterized by facial flushing, headache, hypotension, palpitations, tachycardia, nausea, and vomiting [50]. In an analogous fashion, disulfiram, used in the treatment of alcoholism, and some antiprotozoal drugs such as metronidazole, inhibit ALDH2 and thereby cause a flushing reaction after alcohol consumption. Therefore, the protective effect of ALDH2 genotypes can be regarded as analogous to protection with disulfiram, as this flushing reaction, severe in homozygotes but milder in heterozygotes, deters individuals with the protective alleles from becoming alcoholic.

Conclusion

There is copious evidence of considerable heritability of both broad and narrow definitions of alcoholism in men and women. Although the quantitative role of genetic risk factors is approximately equal in both sexes, the lower concordance of opposite-sex pairs suggests some gender- specific action of genes. Genetic vulnerability to alcoholism may originate in personality or psychiatric traits that predispose to alcohol-seeking behavior, differential response to the effects of alcohol, or differential predisposition to addiction. Studies of the co-inheritance of alcoholism and other psychiatric disorders are beginning to emerge. There is evidence of co-inheritance of ASPD and alcoholism in men. Although alcoholism is associated with anxiety and affective disorders in women, it has been shown that 75% of the genetic variance of alcoholism is disease specific. Alcohol, nicotine, and other substance abuse disorders have been noted to co-occur, yet recent studies have shown that the transmission of alcoholism is largely independent of that of other drugs of abuse with the exception of nicotine, with which there is a substantial genetic correlation. The

mesolimbic dopamine system is fundamental to the neurobiology of addiction. We are only at the very beginning stages of understanding the complexities of ethanol's interactions with this system. Enhanced GABA, glutamate, dopaminergic, opioid peptide, and serotoninergic neurotransmission.

References:-

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1. Agarwal DP 2001. The Genetics of Alcohol Metabolism and Alcoholism. IJHG, 1(1): 25-32.
2. National Institute on Alcohol Abuse and Alcoholism (NIAAA). The Genetics of Alcoholism. Alcohol Alert No. 18. Rockville, MD: NIAAA, 1992.
3. Kendler KS, Davis CG, Kessler RC. The familial aggregation of common psychiatric and substance abuse disorders in the National Comorbidity Survey: a family history study. Br J Psychiatry 1997; 170:541–548.
4. Heath, A.C.; Bucholz, K.K.; Madden, P.A.F.; et al. Genetic and environmental contributions to alcohol dependence risk in a national twin sample: Consistency of findings in women and men. Psychological Medicine 27:1381–1396, 1997.
5. Heath, A.C., and Martin, N.G. Genetic influences on alcohol consumption patterns and problem drinking: Results from the Australian NH&MRC twin panel follow-up survey. Annals of the New York Academy of Sciences 708:72–85, 1994.
6. Kendler, K.S.; Neale, M.C.; Heath, A.C.; et al. A twin-family study of alcoholism in women. American Journal of Psychiatry 151:707–715, 1994.
7. Prescott, C.A., and Kendler, K.S. Genetic and environmental contributions to alcohol abuse and dependence in a population-based sample of male twins. American Journal of Psychiatry 156:34–40, 1999
8. Crabbe, J.C. Alcohol and genetics: New models. American Journal of Medical Genetics (Neuropsychiatric Genetics) 114:969–974, 2002.
9. Tabakoff, B., and Hoffman, P.L. Animal models in alcohol research. Alcohol Research & Health 24(2):77–84, 2007
10. Midanik L. Familial alcoholism and problem drinking in a national drinking survey. Addict Behav 1983;8:133–141.
11. Kendler KS, Neale MC, Heath AC, et al. A twin-family study of alcoholism in women. Am J Psychiatry 1994;151(5):707–715.
12. Goodwin DW. Alcoholism and heredity. Arch Gen Psychiatry 1979;36:57–61
13. Heath AC. Genetic influences on alcoholism risk. A review onadoption and twin studies. Alcohol Health Res World 1995;19(3): 166–171.

14. Kendler KS, Heath AC, Neale MC, et al. A population-based twin study of alcoholism in women. JAMA 1992;268(14):1877–1882.
15. Heath AC, Bucholz KK, Madden PAF, et al. Genetic and environmental contributions to alcohol dependence risk in a national twin sample: consistency of findings in women and men. Psychol Med 1997;27:1381–1396
16. Cloninger CR, Bohman M, Sigvardsson S. Inheritance of alcohol abuse: cross-fostering analysis of adopted men.
17. Arch Gen Psychiatry 1981;38:861–868Koob GF, Le Moal M. Drug abuse: hedonic homeostatic dysregulation.Science 1997;278:52–58.
18. Di Matteo V, Di Giovanni G, Di Mascio M, et al. SB 242084, a selective serotonin2C receptor antagonist increases dopaminergictransmission in the mesolimbic system.
19. Neuropharmacology1999;38 (8):1195–205. Kreek MJ. Cocaine, dopamine and the endogenous opioid system
20. Addict Dis 1996;15 (4):73–96.Koob GF, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. Science 1997;278:52–58.
21. King GR, Xiong Z, Ellinwood EH. Blockade of accumbens 5-HT3 receptor down-regulation by ondansetron administered during continuous cocaine administration. Eur J Pharmacol 1999;364(2–3):79–87..
22. Yoshimoto K, Yayama K, Sorimachi Y, et al. Possibility of 5- HT3 receptor involvement in alcohol dependence: a microdialysis study of nucleus accumbens dopamine and serotonin releasein rats with chronic alcohol consumption. Alcohol Clin Exp Res 1996;20(9 suppl):311A–319A.
23. Kreek MJ. Cocaine, dopamine and the endogenous opioid system.J Addict Dis 1996;15(4):73–96.
24. Jarvik ME, Schneider NG. Nicotine. In: Lowinson JH, Ruiz P, Millman RB, eds. Substance abuse: a comprehensive textbook, second ed. Baltimore: Williams & Wilkins, 1992:334–356
25. Markou A, Kosten TR, Koob GF. Neurobiological similarities in depression and drug dependence: a self medication hypothesis. Neuropsychopharmacology 1998;18(3):135–174
26. Little HJ. The role of calcium channels in drug dependenc Drug Alcohol Depend 1995;38:173
27. Herz A. Endogenous opioid systems and alcohol addiction. Psychopharmacology 1997; 129:99–111.–194.Tsai G, Coyle JT.

28. The role of glutamatergic neurotransmissionin the pathophysiology of alcoholism. annu Rev Med 1998;49:173–184.
29. Nestler EJ, Hope BT, Widnell KL. Drug addiction: a model for the molecular basis of neural plasticity. Neuron 1993;11:995–1005
30. Koob GF, Roberts AJ, Schulteis G, et al. Neurocircuitry targetsin ethanol reward and dependence. Alcohol Clin Exp Res 1998;22(1):3–9
31. Sass H, Soyka M, Mann K, et al. Relapse prevention by acamprosate. Results from a placebo-controlled study on alcohol dependence. Arch Gen Psychiatry 1996;53:673–680.
32. Dawson, DA, Archer L 1992. Gender differences in alcoholconsumption: effects of measurement. Brit J Addiction,87: 119-123.
33. Cotton NS 1979. The familial incidence of alcoholism: a review. J Stud Alcohol, 40: 89-116.
34. Agarwal DP 2001. The Genetics of Alcohol Metabolism and Alcoholism. IJHG, 1(1): 25-32
35. Kaij L 1960. Alcoholism in Twins. Stockholm: Almqvist and Wiksell pp. 17-21.
36. Gurling HM, Murray RM, Clifford CA 1981. Investigations into the genetics of alcohol dependence and into its effects on brain functions. Prog Clin Biol Res, 69 (Pt C): 77-87.
37. Heath AC, Bucholz KK, Madden PAF, Dinwiddie SH, Slutske WS, Bierut LJ, Statham DJ, Dunne MP, Whitfield JB, Martin NG 1997. Genetic and environmental contributions to alcohol dependence risk in a national twin sample: consistency of findings in women and men. Psychol Med, 27: 1381-1396
38. Goodwin DW, Schulsinger F, Moller N, Hermansen L, Winokur G, Guze S 1974. Drinking problems in adopted and nonadopted sons of alcoholics. Arch Gen Psychiatry, 31: 164-169.
39. Cloninger CR, Bohman M, Sigvardsson S 1981. Inheritance of alcohol abuse. Cross-fostering analysis of adopted men. Arch Gen Psychiatry, 38: 861-868
40. Bohman M, Cloninger CR, Sigvardsson S, von Knorring AL 1987. The genetics of alcoholism and related disorders. J Psychiatric Res, 21: 447-452.
41. Sigvardsson S, Bohman M, Cloninger CR 1996. Replication of the Stockholm Adoption Study of alcoholism. Confirmatory cross-fostering analysis. Arch Gen Psychiatry, 53: 681-687.
42. Prescott CA, Kendler KS 1999. Genetic and environmental contributions to alcohol abuse and dependence in a population-

based sample of male twins. Am J Psychaitry, 156: 34-40

43. McGue M, Slutske WS 1996. The inheritance of alcoholism in women. In: JM Howard, SE Martin, PD Mail, ME Hilton, ED Taylor (Eds.): Women and Alcohol: issues for Prevention Research. NIAAA Research Monograph No 32. Bethesda, MD: USDHHS pp. 65-91.
44. Hill SY 1995. Vulnerability to alcoholism in women. Genetic and cultural factors. In: M Galenter (Ed.): Recent Developments in Alcoholism, vol. 12. Women and Alcoholism. New York: Plenum Press pp. 9-28.
45. Paterson AD, Petronis A 1999. Sex-based linkage analysis of alcoholism. Genet Epidemiol, 17(Suppl 1): S289- S294
46. Peterson RJ, Goldman D, Long JC. Nucleotide sequence diversity in non-coding regions of ALDH2 as revealed by restriction enzyme and SSCP analysis. Hum Genet 999;104(2):177–87.
47. Chen CC, Lu RB, Chen YC, et al. Interaction between the functional polymorphisms of the alcohol-metabolism genes in protection against alcoholism. Am J Hum Genet 1999;65(3):795–807.
48. . Osier M, Pakstis AJ, Kidd JR el al. Linkage disequilibrium at the ADH2 and ADH3 loci and risk of alcoholism. Am J Hum Genet 1999;64(4):1147–1157.
49. . Thomasson HR, Edenburg HJ, Crabb DW, et al. Alcohol and aldehyde dehydrogenase genotypes and alcoholism in Chinese men. Am J Hum Genet 1991;48:677–681.
50. Harada S, Agarwal DP, Goedde HW. Aldehyde dehydrogenase deficiency as cause of facial flushing reaction to alcohol in Japanese. Lancet 1982;2(8253):982.
51. Goldman D, Marry Anee Enoch, Molecular and cellular genetics of alcohol addiction 1413-1423.