

**Review Article**

Genetic Basis of Idiosyncratic Responses to Alcoholism

Charles Ejike Osuji

Biotechnology Advanced Research Center, Sheda Science and Technology Complex (SHESTCO), Abuja, Nigeria

Email address:

charleschuks@gmail.com

To cite this article:Charles Ejike Osuji. Genetic Basis of Idiosyncratic Responses to Alcoholism. *European Journal of Clinical and Biomedical Sciences*. Vol. 2, No. 6, 2016, pp. 63-68. doi: 10.11648/j.ejcs.20160206.12**Received:** October 7, 2016; **Accepted:** November 11, 2016; **Published:** December 12, 2016

Abstract: Aim: The scientific viewpoint of genetic polymorphisms associated with risk of alcoholism and its adverse individual behavioural reactions is the main focus of this review. A complex syndrome like alcoholism and its idiosyncrasy may not be entirely understood on the basis of pathophysiological concept of neurotransmission alone. While neuropharmacology explains the mechanism behind molecular basis of alcoholism, the variation in alcohol induced abnormal neurotransmission due to presence or absence of different gene variants or isoenzymes of a particular gene on the other hand is a strong indication of genetic predisposition to alcoholism. In this article the term alcohol is used as a generic name for ethanol, which is the main subject of this discussion. Conclusion: The concomitant untoward intrinsic toxicity associated with alcoholism that makes it a potential trigger to a myriad of abnormal behavioural reactions in not only dose dependent pattern but with strong genetic disposition arises majorly due to different modes and levels of genetic variation in metabolic enzymes.

Keywords: Alcoholism, Genetic, Polymorphism Neurotransmission, Enzymes, ALDH, ADH, Cytochrome P₄₅₀

1. Introduction

Ethanol which is generically called alcohol has been a part of human culture with a universal history across almost all societies in which it is consumed, experiencing net health and social problems [1, 2]. Alcohol is one of the commonly available and widely abused substances and its beverages are one of the most widely consumed drinks [3]. It is the third-most popular drink overall, after water and tea [4] and viewed by some to be the oldest fermented beverage [5-8]. With the industrialization of alcohol production and the globalization of its marketing, alcohol consumption and its related problems have increased worldwide [9].

The volumes, patterns and concentrations of alcohol consumption are likely a risk factor to some chronic diseases and conditions. In some traditions, ethanol consumption is recommended as an antidote for people who have consumed ethylene glycol, as it inhibits its oxidation to the toxic ethanal (aldehyde) and subsequently to oxalate, allowing time for the glycol to be eliminated from the body unchanged [9]. Rather than having nutritional value, complications of alcohol nutritional implications abound. In small doses it stimulates appetite while larger amounts suppress hunger, which deprives the body of nutrients leading to malnutrition and

anaemia. This is because it displaces nutritious foods like protein, carbohydrate, etc from the diet due to its high calorific value (but devoid of nutritional content) which can satisfy caloric requirements but easily leads to malnutrition.

The relatively high solubility of ethanol in water to its fat absorption tendency helps it to distribute itself mostly in tissues rich in water (muscle) than in those rich in fat [10]. This could also account for slight differences in alcoholism among people with different body mass indices (BMI). Alcohol is one of the most widely used groups of pharmacologic active agents that are of important medical uses with multiple psychoactive actions in varying doses in different individuals ranging from loss of integrative role by the cortex, resulting to confused and disorganized thinking to disruption of adequate motor control [11]. The effects of alcoholism in humans can be very devastating even to psychiatric disorders and increasing the risk of other diseases like hypertension, epilepsy, foetal alcohol syndrome, e. t. c., which mostly occur secondary to alcohol intoxication [12, 13]. Alcohol crosses the blood placental barrier to affect the foetus in the womb causing some negative effects on the cells. These effects lead to impairment of some structures responsible for spatial memory, cognitive and coordination function in the brain. It also diminishes thiamine absorption in the intestine

and depletes hepatic stores of this healthy vitamin. This leads to impairment of active thiamine in the body leading to thiamine deficiency in alcoholics [14, 10].

Alcohol idiosyncrasy may not be entirely understood on the basis of neurophysiological functioning alone but also from the genetic angle. The genetic polymorphisms associated with alcohol-induced flushing in alcoholism are through molecular mechanisms that include accumulation of acetaldehyde, release of histamine [15] and genetic influence of transmitter chemicals and their metabolic enzymes. These in turn influence alcohol consumption and have been viewed as high risk factors for developing alcohol abuse and dependence [16-18]. The drug-related mechanisms generating cumulative changes in neurotransmission are majorly genetic in nature since the presence of different gene variants can lead to diverse reactions to a particular chemical agent. While a drug may not really change a person's genes, it can stimulate some genes to amplify their production of proteins, causing alteration in cellular physiology and morphology [19].

2. Alcohol Consumption and Effects

Consumption and intoxication of alcohol can cause a serious damage to tissues in the brain and many organs in the body as it affects some important and vulnerable areas of the brain like the cerebral cortex, the hippocampus and the cerebellum. Alcoholism remains one of the most rife and devastating forms of substance abuse in the United States and the rest of the world [20]. While a short-term intoxicating alcohol consumption may be associated with decreased attention, alterations in memory and sedation, continued acute consumption may result in lethargy, confusion, amnesia, loss of sensation, difficulty in breathing, and even death. Alcohol's excitatory actions with behavioural manifestations of intoxication seem to be caused by suppression of inhibitory neurotransmitter systems [21].

The nervous system is one of the major means that coordinates the body physiology through high-level processes controlled in the brain. It utilises the chemical transmission pathway between one nerve cell to another and to receptors in the effector cells. Alcohol is thought to produce its effect not only by binding to specific receptors but also by its lipophilicity which is believed to decrease transmitter release and post-synaptic responsiveness by interacting with membrane lipids as well as membrane proteins. The chemical transmission takes place through the release of small amounts of transmitter substances called neurotransmitters from the nerve terminals into the synaptic cleft to effect a post-synaptic action by binding to specialised receptor molecules. Most of the neurotransmitters are destroyed by enzymes while some undergo "reuptake" in the sending neurone for re-use. The genetic variation in the enzymes that destroy these neurotransmitters is of great importance in alcoholism. Ethanol like some other drugs of abuse mimics the natural transmitter substances to stimulate transmission of abnormal messages in the excitatory or inhibitory systems. Monoamine oxidase (MAO) is an important enzyme in the

metabolism of most brain neurotransmitters that affect behaviour such as dopamine, norepinephrine, and serotonin. The genetic and physiological variation of this enzyme and its likes in humans is key to alcoholism idiosyncrasy.

Alcohol is a known product of the addiction that alters brain function by interacting with multiple neurotransmitter systems and positively reinforces drinking through several neurochemical systems that lead to dependence, tolerance and withdrawal syndromes.

Alcohol's interaction with neurotransmitter produces neurochemical effects like magnifying the effect of gamma-aminobutyric acid (GABA), glycine, serotonin and endorphins alongside an antagonising effect on glutamate activities, increased turnover of norepinephrine and dopamine, decreased transmission in acetylcholine. This makes alcoholics to try drinking to achieve an ecstatic mood or to relieve a moody state like anxiety and in the process, increase the frequency and quantity of consumption to achieve the same effect which eventually culminates to unsuccessful attempts to stop consumption without experiencing negative physical symptoms (alcohol withdrawal syndrome). The decline in GABA function which usually results from a decrease in receptor levels or a change in the protein composition of the receptor in long-term alcohol consumption leads to decreased sensitivity to neurotransmission. Similarly, glutamate receptors appear to adapt to the inhibitory effects of alcohol by increasing their excitatory activity [22, 23]. Additional studies show a compensatory decline in adenosine activity following continuing alcohol exposure [23]. It also directly or indirectly interacts with the brain's reward system by flooding the circuit with dopamine leading to their reinforcing characteristic. Dopamine is a neurotransmitter in the brain that is involved in regulation of emotion, motivation and pleasurable feelings that reward our natural behaviours.

The liver is the primary site of alcohol metabolism [24] where several biochemical agents called enzymes help to convert it to other compounds (or metabolites), which can be easily processed by the body. Alcohol is also metabolized in non-liver (extrahepatic) tissues [25] that do not contain alcohol dehydrogenase (ADH) enzyme, such as the brain, by other enzymes like cytochrome P_{450} and catalase. Alcohol metabolism can be categorised into two pathways viz; oxidative and nonoxidative pathways. ADH, present in the cytosol, converts alcohol to acetaldehyde (CH_3CHO). The acetaldehyde is generally short-lived as it is quickly metabolised to a less toxic acetate (CH_3COO^-) by another enzyme called aldehyde dehydrogenase (ALDH) [26]. The activities of these enzymes may lead to variation in alcohol elimination rates among individuals [27]. The amount of alcohol metabolised in the body varies widely among individuals and depends on a range of factors including liver size, body mass, learned behaviours [28], age of onset in consumption of alcohol, environment [29] and most importantly genetic factor. Reports of some analytical studies such as genome-wide association studies (GWAS), Collaborative Studies of Genetics of Alcoholism (COGA), Single nucleotide polymorphism (SNP) etc, have suggested

the occurrence of novel micro loci implicated in alcohol consumption and dependence [30]. Research has shown that different people carry different forms of ADH and ALDH enzymes. These different versions can be traced to variations in the same gene [31] as subtypes of the same receptor may respond differently among individuals depending on the location and genetic mediated structure activity relationship of neurotransmitters with the effector cells [32].

3. Alcoholism and Genetics

Although alcohol intoxication is largely dose dependent, but not all individuals who consume alcohol become alcoholics even at a given dose. Vulnerability to intoxication, addiction and tolerance has been largely linked to some genetic factors. Research findings aggregately indicate that genetic factors have a lot of influence in development of alcoholism with increase in risk for close relatives of alcoholics developing alcohol dependency among the general population [33-36]. Goodwin and colleagues suggest a stronger genetic influence than environmental influence on alcohol dependence [37]. Sensitivity to alcohol intoxication is a potent factor suggesting that both sensitivity and dependency are genetically influenced [38]. This predisposition to alcoholism is somewhat in traced to a gene in chromosome 11 that controls a type of dopamine receptor. The risk of alcohol abuse is seven times greater among the first-degree relatives of alcoholics than among first-degree relatives of non problem drinkers [33]. Other major genetic causes are mostly neurotransmitter based which is highly linked to genetic variation in most neurotransmitters involve in alcohol interaction especially dopamine receptors mediated [39] metabolism rate of alcohol in the brain. According to Yingmei Zhang and Jun Ren (2012) [20], twin case studies projects a strong genetic predisposition for alcoholism and female twin studies demonstrate that females have much lower concordance rates than males [40] for gender differences [41] which may be probably due to difference in water- fat-concentrations and BMI. Some individual genes in neurotransmitter signalling pathways linked with the ventral tegmental area (VTA) and nucleus accumbens in human studies have been identified with alcohol addiction. They include cholinergic (muscarinic and nicotinic) receptor genes [42, 43], GABA A receptor, [44], glutamate receptor [45], serotonin (5-HTT) [46], [47], dopamine [48], opioid receptors [49], etc. The effect of genetics on the degree of alcohol intoxication lies more in the basis of alcohol enzymatic metabolism in the body. The genetic variation of ADH, ALDH, cytochrome P450 (CYP2E1), and catalase in humans is a major genetic influence in alcohol consumption, intoxication, dependence and even alcohol-related tissue damage. Seven different ADH genes and nine different ALDH genes exist in humans and they have varying effects on alcohol metabolism [50]. Out of the seven forms of ADH protein, the ADH2 also known as ADH1B form is expressed in three polymorphic versions and accounts for most of the alcohol metabolism [51]. One of ADH2 polymorphism is linked with a high

susceptibility to alcohol intoxication. This could account for high alcohol elimination rates seen in African Americans [52] and Native Americans[53] with the ADH1B*3 allele who metabolize alcohol at a faster rate than those with ADH1B*1. Also people of Jewish origin carrying the ADH1B*2 allele show an elevated alcohol elimination rates compared with people with ADH1B*1 [54]. On the other hand, the ADH7 gene is monomorphic in the human population and is highly expressed in the stomach and metabolizes about 30% of the alcohol before it is absorbed into the blood [50]. The ADH7 gene in females is not transcribed and translated to protein hence it is silent and this actually why females are generally more sensitive than males in response to alcohol intoxication

The ALDH that detoxifies the toxic acetaldehyde by breaking it down to acetic acid has a variant form, (ALDH2) which allele carries a single base mutation that renders it non-functional [50]. Among the 18 genes encoding members of the ALDH enzyme family, only ALDH2 plays a major role in oxidizing acetaldehyde in the liver [55]. Individuals expressing this non-functional variant form of ALDH2 have elevated levels of acetaldehyde upon consumption of alcohol which produces unpleasant feeling of intoxication like flushed face, headache, nausea, and a rapid heart rate. This makes alcohol consumption either repulsive to people with ALDH2 or highly intoxicated with very little quantity. [50]. Rivera-Meza *et al.*, (2012) [56], showed that gene carriers of fast ADH or slow ALDH, which delay the processing of acetaldehyde in the body, tend to be non alcoholics and while carriers of slow ADH or fast ALDH that favours accumulation of acetaldehyde in the system are not only alcoholics but are also at very high risk of other concomitant intrinsic health consequences of alcoholism. Thus ALDH2 is the single genetic factor that most strongly correlates with the incidence of alcoholism in humans. Genetic differences in these enzymes may help to explain why some ethnic groups have higher or lower rates of alcohol-related problems [57-61]. For example, one version of the ADH enzyme, called ADH1*2, is common in people of Chinese, Japanese, Korean descent but are in people. These enzymes protect against alcoholism [62] by metabolizing alcohol to acetaldehyde very efficiently, leading to elevated acetaldehyde levels that make drinking unpleasant [63]. Also genetic variation in CYP2E1 has been identified to affect alcohol metabolism. Enhanced alcohol metabolism by CYP2E1 contributes to alcoholics' metabolic tolerance for ethanol, thereby promoting further alcohol consumption. Genes coding for GABA receptors or associated proteins may also be critical determinants of individual differences in ethanol sensitivity [64]. Functional polymorphism in some important neurotransmitters and metabolic enzymes involve in alcohol neurotransmission processes such as serotonin transporter gene, gene encoding for the enzyme monoamine oxidase (MAO), gene encoding for the enzyme catechol-O-methyltransferase (COMT), [65] is clearly implicated in genetic basis of alcohol idiosyncrasy. MAO is an important enzyme in the metabolism of most brain neurotransmitters that affect behaviour such as dopamine, norepinephrine, and serotonin. Roland D. Ciaranello, Richard

E. Boehme 1982 [66] also reported genetic control of dopamine receptors in the nigrostriatal and mesolimbic pathways in inbred mice. COMT is involved in catabolizing catecholamines such as dopamine which is the major neurotransmitter implicated in alcohol induced rewarding process [67]. It also catalyzes the O-methylation metabolism of S-adenosylmethionine to catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine which results in one of the major degradative pathways of the catecholamine transmitters [68]. The biochemical mechanism of these gene regulatory actions on the enzymes is on proteolysis rather than synthesis [66]. Non alcoholics have been found to have low platelet MAO activity levels than alcoholics [69-71]. Hence, genetic differences in the alcohol metabolic enzymes like mono amine oxidase and receptor genes helps to explain why some people have higher or lower rates of alcohol-related problems.

4. Conclusion

Idiosyncratic alcohol-induced responses arise majorly due to different modes and levels of genetic variation leading to functional polymorphism in some important neurotransmitters and metabolic enzymes involve in alcohol neurotransmission pathways. It is however not without untoward intrinsic toxicity which makes alcoholism a potential trigger to a myriad of abnormal reactions in not only dose dependent pattern but with strong genetic disposition.

References

- [1] McGovern 2009; McGovern, P. *Uncorking the Past: The Quest for Wine, Beer, and Other Alcoholic Beverages*. Berkley; Los Angeles; London: The Regents of the University of California, 2009.
- [2] Tramacere et al. 2012b, c). Tramacere, I.; Pelucchi, C.; Bonifazi, M.; et al. A meta-analysis on alcohol drinking and the risk of Hodgkin lymphoma. *European Journal of Cancer Prevention* 21(3): 268–273, 2012b.
- [3] Volume of World Beer Production. *European Beer Guide*. Archived from the original 2006. [European BeerGuide. net](http://EuropeanBeerGuide.net).
- [4] Nelson, Max. *The Barbarian's Beverage; A History of Beer in Ancient Europe*. Abingdon, Oxon: Routledge. 2005 p. 1. ISBN 0-415-31121-7.
- [5] Rudgley, Richard. *The Alchemy of culture. Intoxicants in the society*. London: British Museum Press. 1993; p. 411. ISBN 978-0-7141-1736-2.
- [6] Arnold, John P. *Origin and History of Beer Brewing. From Prehistoric Times to the Beginning of Brewing Science and Technology*. Cleveland, Ohio: Reprint Edition by BeerBooks. 2005; p. 411. ISBN 0-9662084-1-2.
- [7] Joshua J. Mark. *Beer*. *Ancient History Encyclopedia*. 2011.
- [8] Google Books. *World's Best Beers 2009*. ISBN 978-1-4027-6694-7.
- [9] Kevin D. Shield, Charles, Parry and Jürgen Rehm. *Chronic Diseases and Conditions Related to Alcohol Use*. Alcohol research; current reviews 2013 vol. 35 No 2.
- [10] <http://emedicine.medscape.com>. Alcohol intoxication
- [11] *Brain & Mind Magazine*. An Initiative by the Centre for Biomedical Informatics; 3 (8) 1999.
- [12] Rehm J, Room R, Graham K, Monteiro M, Gmel G, Sempos CT: The relationship of average volume of alcohol consumption and patterns of drinking to burden of disease: an overview. *Addiction*. 2003, 98: 1209-1228.10.1046/j.1360-43.2003.00467.
- [13] Sulik KK: Genesis of alcohol-induced craniofacial dysmorphism. *Exp Biol Med*. 2005, 230: 366-375
- [14] Chopra K, Tiwari V. Alcoholic neuropathy: possible mechanisms and future treatment possibilities. *Br J Clin Pharmacol*. 2012 Mar; 73(3): 348–362. Published online 2011 Oct 11. doi: 10.1111/j.1365-2125.2011.04111.
- [15] Thomasson HR, Crabb DW, Edenberg HJ, Li TK: Alcohol and aldehyde dehydrogenase polymorphisms and alcoholism. *Behav Genet*. 1993, 23: 131-136. 10.1007/BF01067417.
- [16] Hendershot CS, Lindgren KP, Liang T, Hutchison KE: COMT and ALDH2 polymorphisms moderate associations of implicit drinking motives with alcohol use. *Addict Biol*. 2011, 17: 192-201.
- [17] Edenberg HJ, Xuei X, Chen HJ, Tian H, 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, Foroud T: Association of alcohol dehydrogenase genes with alcohol dependence: a comprehensive analysis. *Hum Mol Genet*. 2006, 15: 1539-1549. 10.1093.
- [18] Goldman D, Oroszi G, Ducci F: The genetics of addictions: uncovering the genes. *at. Rev Genet*. 2005, 6: 521-532.
- [19] Carl, Sherman., *Impacts of Drugs on Neurotransmission*; NIDA 2007.
- [20] Yingmei Zhang and Jun Ren -ALDH2 in Alcoholic Heart Diseases: Molecular Mechanism and Clinical Implications. doi: 10.1016/j.pharmthera.2011.05.008.
- [21] Pohorecky, L. A. Biphasic action of ethanol. *Biobehavioral Reviews* 1: 231–240, 1977. Shepherd, G. M. *Neurobiology*. 3d ed. New York: Oxford University Press, 1994.
- [22] Tabakoff, B., and Hoffman, P. L. Alcohol addiction: An enigma among us. *Neuron*. 1996 16: 909–912.
- [23] Valenzuela, C. F., and Harris, R. A. Alcohol: Neurobiology. In: Lowinson, J. H.; Ruiz, P.; Millman, R. B.; and Langrod, J. G., eds. *Substance Abuse: A Comprehensive Textbook*. Baltimore: Williams & Wilkins, 1997. pp. 119–142.
- [24] Ramchandani, V. A.; O'Connor, S.; Neumark, Y. D.; et al. The alcohol clamp: Applications, challenges and new directions. *Alcoholism: Clinical and Experimental Research*. 2006; 30: 155–164.
- [25] O'Connor, S.; Morzorati, S., Christian, J.; and Li, T.-K. Clamping breath alcohol concentration reduces experimental variance: Application to the study of acute tolerance to alcohol and alcohol elimination rate. *Alcoholism: Clinical and Experimental Research* 1998; 22: 202–210.

- [26] Alcohol Research & Health, Vol. 30, No. 1, 2007.
- [27] Martin, N. G.; Perl, J.; Oakeshott, J. G.; Gibson, J. B.; Starmer, G. A.; and Wilks, A. V. A twin study of ethanol metabolism. *Behavioural Genetics*. 1985; 15: 93–109.
- [28] Zucker RA, Kincaid SB, Fitzgerald HE, Bingham CR. Alcohol schema acquisition in preschoolers: Differences between children of alcoholics and children of nonalcoholics. *Alcoholism: Clinical and Experimental Research*. 1995; 19: 1011–1017.
- [29] Ron Weathermon, and David W. Crabb. Alcohol and Medication Interactions. niaaa.nih.gov/publication 1999 Vol. 23, No. 1.
- [30] Tatiana V Morozova and David Goldman, The genetic basis of alcoholism: multiple phenotypes, many genes, complex networks 2012.
- [31] Hurley, T. D.; Edenberg, H. J.; Li, T.-K. The Pharmacogenomics of alcoholism. In: *Pharmacogenomics: The Search for Individualized Therapies*. Weinheim, Germany: Wiley-VCH, 2002, pp. 417–441.
- [32] Thompson, R. F. *The Brain: A Neuroscience Primer*. New York: Worth Publishers 2000.
- [33] Merikangas KR. The genetic epidemiology of alcoholism. *Psychological Medicine* 1990; 20: 1122.
- [34] Pickens RW, Svikis DS, McGue M, Lykken D, Heston M, Clayton P. 1991. Heterogeneity in the inheritance of alcoholism: A study of male and female twins. *Archives of General Psychiatry* 48: 19-28.
- [35] Cadoret RJ, Cain C, Grove W. 1980. Development of alcoholism in adoptees raised apart from alcoholic biologic relatives. *Archives of General Psychiatry* 37: 561-563.
- [36] Grove W, Eckert E, Heston L, Bouchard T, Segal N, Lykken D. 1990. Heritability of substance abuse and antisocial behavior: A study of monozygotic twins reared apart. *Biological Psychiatry* 27: 1293-1304.
- [37] Goodwin, Donald W. "Hereditary" Alcoholism the facts. New York: Oxford University Press.
- [38] Whitfield, John B. "Genes for Alcohol Metabolism and Alcohol Sensitivity Their Role in the Genetics of Alcohol Dependence" *Alcohol in Health and Disease*. New York: Marcel Dekker, Inc., 2001.
- [39] Research Institute on Addictions, Washington Post, 1998.
- [40] Morse, RM; Flavin, DK. The definition of alcoholism, The joint committee of the national council on Alcoholism and Drug dependence and The American Society of Addiction Medicine to study the the definition and criteria for diagnosis of Alcoholism". *The Journal of the American Medical Association*. 1992 268 (8): 1012. doi: 10.1001/jama..03490080086030.
- [41] Carlson, Neil R.; Buskist, William; Enzle, Michael E.; Heth, C. Donald. *Psychology: The Science of Behaviour* 3rd Canadian Edition. Pearson. 2005. pp. 75–76. ISBN 0-205-45769.
- [42] Luo X, Kranzler HR, Zuo L, Wang S, Blumberg HP, Gelernter J: CHRM2 gene predisposes to alcohol dependence, drug dependence and affective disorders: results from an extended case-control structured association study. *Hum Mol Genet*. 2005.
- [43] Ehringer MA, Clegg HV, Collins AC, Corley RP, Crowley T, Hewitt JK, Hopfer CJ, Krauter K, Lessem J, Rhee SH, et al. Association of the neuronal nicotinic receptor beta2 subunit gene (CHRNA2) with subjective responses to alcohol and nicotine. *Am J Med Genet B Neuropsychiatr Genet*. 2007; 144B(5): 596–604. doi: 10.1002/ajmg.b.3046444.
- [44] Agrawal A, Edenberg HJ, Foroud T, Bierut LJ, Dunne G, Hinrichs AL, Nurnberger JI, Crowe R, Kuperman S, Schuckit MA, et al. Association of GABRA2 with drug dependence in the collaborative study of the genetics of alcoholism sample. *Behav Genet*. 2006; 36(5): 640–650. doi: 10.1007/s10519-006-9069-4.
- [45] Chen AC, Tang Y, Rangaswamy M, Wang JC, Almasy L, Foroud T, Edenberg HJ, Hesselbrock V, Nurnberger J, Jr, Kuperman S, et al. Association of single nucleotide polymorphisms in a glutamate receptor gene (GRM8) with theta power of event-related oscillations and alcohol dependence. *Am J Med Genet B Neuropsychiatr Genet*. 2009; 150B(3): 359–368. doi: 10.1002/ajmg.b.30818.
- [46] Van Der Zwaluw CS, Engels RC, Vermulst AA, Rose RJ, Verkes RJ, Buitelaar J, Franke B, Scholte RH: A serotonin transporter polymorphism (5-HTTLPR) predicts the development of adolescent alcohol use. *Drug Alcohol Depend*. 2010, 112: 134-139. 10.1016/j.drugalcdep.2010.06.001.
- [47] Cao J, LaRocque E, Li D. Associations of the 5-hydroxytryptamine (serotonin) receptor 1B gene (HTR1B) with alcohol, cocaine, and heroin abuse. *Am J Med Genet B Neuropsychiatr Genet*. 2013; 162B(2): 169–176. doi: 10.1002/ajmg.b.32128.
- [48] Kohnke MD, Batra A, Kolb W, Kohnke AM, Lutz U, Schick S, Gaertner I. Association of the dopamine transporter gene with alcoholism. 2005; 40(5): 339–342. doi: 10.1093/alcac/agh179.
- [49] Ashenhurst JR, Bujarski S, Ray LA. Delta and kappa opioid receptor polymorphisms influence the effects of naltrexone on subjective responses to alcohol. *Pharmacol Biochem Behav*. 2012; 103(2): 253–259. doi: 10.1016/j.pbb.2012.08.019.
- [50] Biological Factors Influence Alcohol. The Alcohol Pharmacology Education Partnership is powered by Word Press at Duke Word Press. The ABCs of Intoxication » Content: Biological Factors Influence Alcohol Intoxication Pt. 2.
- [51] Alcohol Metabolism: An Update. Alcohol Alert. National institute of alcohol abuse and alcoholism (NIAAA publication) 2007.
- [52] Thomasson, H. R.; Beard, J. D.; and Li, T. K. ADH2 gene polymorphisms are determinants of alcohol pharmacokinetics. *Alcoholism: Clinical and Experimental Research* 19: 1494–1499, 1995.
- [53] Wall, T. L.; Garcia-Andrade, C.; Thomasson, H. R.; et al. Alcohol elimination in Native American Mission Indians: An investigation of interindividual variation. *Alcoholism: Clinical and Experimental Research* 20: 1159–1164, 1996.
- [54] Neumark, Y.; Friedlander, Y.; O'Connor, S.; et al. The influence of alcohol dehydrogenase polymorphisms on alcohol metabolism among Jewish males in Israel (Abstract). *Alcoholism: Clinical and Experimental Research* 2001; 25: 126A, 2001.
- [55] Edenberg HJ. Genetics of alcohol use disorders. In: Miller PM, editor. *Biological research on addiction*. London: Elsevier Science & Technology Books/Academic Press; 2013. pp. 500–508.

- [56] Rivera-Meza M, Quintanilla ME, Tampier L. Reduction of ethanol consumption in alcohol-preferring rats by dual expression gene transfer. *Alcohol Alcohol*. 2012; 47(2): 102–108. doi: 10.1093/alcalc/agr161.
- [57] Curtis, G. Steinmetz, Peiguang Xie, Henry Weiner, Thomas D. Hurley. Structure of mitochondrial aldehyde dehydrogenase: The genetic component of ethanol aversion. 1997 DOI: 10.1016/S0969-2126(97)00224-4.
- [58] Mulligan CJ, Robin RW, Osier MV, Sambuughin N, Goldfarb LG, Kittles RA, Hesselbrock D, Goldman D, Long JC. Allelic variation at alcohol metabolism genes (ADH1B, ADH1C, ALDH2) and alcohol dependence in an American Indian population. *Hum Genet*. 2003; 113(4): 325–336. doi: 10.1007/s00439-003-0971-z.
- [59] Birley AJ, James MR, Dickson PA, Montgomery GW, Heath AC, Martin NG, Whitfield JB. Adh snp associations with alcohol metabolism in vivo. *Hum Mol Genet*. 2009; 8(8): 1533–1542. doi: 10.1093/hmg/ddp060.
- [60] Bierut LJ, Goate AM, Breslau N, Johnson EO, Bertelsen S, Fox L, Agrawal A, Bucholz KK, Gruzca R, Hesselbrock V. ADH1B is associated with alcohol dependence and alcohol consumption in populations of European and African ancestry. *Mol. Psychiatry*. 2012; 17(4): 445–450. doi: 10.1038/mp.2011.124.
- [61] Hurley TD, Edenberg HJ. Genes encoding enzymes involved in ethanol metabolism. *Alcohol Res*. 2012; 34(3): 339–344.
- [62] Ehlers, C. L.; Gilder, D. A.; Harris L.; and Carr L. Association of the ADH2*3 allele with a negative family history of alcoholism in African American young adults. *Alcoholism: Clinical and Experimental Research* 25: 1773–1777, 2001.
- [63] Crabb, D. W. Ethanol oxidizing enzymes: Roles in alcohol metabolism and alcoholic liver disease. *Progress in Liver Disease Progress in Liver Disease* 13: 151–172, 1995.
- [64] KA Wafford, DM Burnett, TV Dunwiddie, RA Harris. Genetic differences in the ethanol sensitivity of GABAA receptors expressed in *Xenopus* oocytes, 1990.
- [65] Marco Catalano. Functionally gene linked polymorphic regions and genetically controlled neurotransmitters metabolism. The impact of genomic studies on neuropsychopharmacology Volume 11, Issue 6 2001.
- [66] Roland D. Ciaranello and Richard E. Boeh Genetic regulation of neurotransmitter enzymes and receptors: Relationship to the inheritance of psychiatric disorders Volume 12, Issue 1 1982; pp 11–35; doi: 10.1007/BF01065738.
- [67] Arqam Qayyum, Clement C. Zai Yuko Hirat, Arun K. Tiwari Sheraz Cheema Behdin Nowrouzi, Joseph H. Beitchman, and James L. Kennedy current neuropharmacology The Role of the Catechol-o-methyltransferase (COMT) Gene Val158Met in Aggressive Behavior, A Review of Genetic Studies 2015. doi: 10.2174/1570159X13666150612225836.
- [68] <http://www.ncbi.nlm.nih.gov/gene/1312>; COMT catechol-O-methyltransferase Homo sapiens (human). updated sept 2016.
- [69] Von Knorring AL, Bohman M, von Knorring L, Oreland L. Platelet MAO activity as a biological marker in subgroups of alcoholism. *Acta Psychiatrica Scandinavica* 1985. 72(52): 51-58.
- [70] Pandey GN, Fawcett J, Gibbons R, Clark DC, Davis JM. Platelet monoamine oxidase in alcoholism. *Biologic Psychiatry* 1988. 24: 15-24.
- [71] Tabakoff B, Hoffman PL, Lee JM, Saito T, Willard B, De Leon-Jones F. Differences in platelet enzyme activity between alcoholics and nonalcoholics. *New England Journal of Medicine* 1988; 318: 134-139 Edenberg HJ. The genetics of alcohol metabolism: role of alcohol dehydrogenase and aldehyde dehydrogenase variants. *Alcohol Res Health*. 2007; 30(1): 5–13.