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Genetic Expression of *ALDH2* and *ADH1B* in Alcoholic Dependent Individuals in Iraqi Population

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Abstract

Alcohol addiction is a public health concern that affects communities all over the world, especially those with distinct genetic traits, such as the Iraqi community. This study investigates the genetic factors that contribute to alcohol dependence, focusing on the expression levels of Alcohol Dehydrogenase 1B (*ADH1B*) and Aldehyde Dehydrogenase 2 (*ALDH2*) genes in individuals from diverse regions of Iraq. A total of 250 blood samples were collected from males, ranging in age from 18 to 55, including 200 alcohol-dependent individuals and 50 samples as controls in the Iraqi population. The data showed a considerable increase in the expression level of the *ADH1B* (P -value < 0.0001 ; $t = 6.447$) among alcohol-dependent individuals compared to the control group. At the same time, the expression level of the *ALDH2* gene is significantly downregulated (P -value < 0.0001 ; $t = 6.447$) in alcohol-dependent individuals compared to the control. In alcohol dependence, *ADH1B* and *ALDH2* transcripts demonstrate different patterns that enable more efficient alcohol breakdown and protection against toxic aldehyde buildup. Alcohol detoxification roles of these enzymes demonstrate an extremely positive correlation through the result of $r = 0.8347$ with $p > 0.0001$. The protective mechanism between *ADH1B* and *ALDH2* becomes less effective when alcohol addiction continues, causing metabolic problems as well as disease development. The research confirms the essential metabolic interactions between *ADH1B* and *ALDH2* regarding alcohol dependence while showing the requirement for additional studies about their medical applications for prevention and therapy. Finally, the work reinforces the importance of genetic screening of these markers as possible tools for diagnosing individuals at risk for alcohol use disorders and establishing personalized therapy strategies to address the metabolic disturbances associated with alcohol dependency.

Keywords: Gene Expression, *ALDH2*, *ADH1B*, Alcohol dependent.

في الأفراد المدمنين على الكحول في المجتمع العراقي *ADH1B* و *ALDH2* التعبير الجيني عن

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الخلاصة:

يعتبر الإدمان على الكحول مشكلة صحية عامة تؤثر على المجتمعات في جميع أنحاء العالم ولاسيما في المجتمعات ذات الخصائص الوراثية الفريدة مثل المجتمع العراقي تهدف هذه الدراسة الى فهم العوامل الوراثية التي تسهم في الإدمان على الكحول مع التركيز بشكل خاص على مستويات التعبير الجيني عن جينات انزيم لإنزيم الكحول ديهيدروجينيز (*ADH1B*) وإنزيم الأدهيد ديهيدروجينيز (*ALDH2*) لدى الأفراد المدمنين على الكحول في مناطق مختلفة من ولتحقيث هذا الهدف تم جمع 250 عينة دم من الذكور الذين تتراوح اعمارهم بين 18 و 55 عاما و كان عدد الاشخاص المدمنين على الكحول 200 و عدد الاشخاص الاصحاء 50. اظهرت النتائج زيادة كبيرة في تعبير انزيم الكحول ديهيدروجينيز ($P\text{-value} < 0.0001; t = 6.447$) بين الافراد المدمنين على مقارنة بمجموعه الاشخاص الاصحاء بينما لوحظ انخفاض ملحوظا في التعبير الجيني لانزيم وإنزيم الأدهيد ديهيدروجينيز ($P\text{-value} < 0.0001; t = 6.447$) في حالة الاعتماد على الكحول، تُظهر جينات *ADH1B* و *ALDH2* أنماط تعبير مختلفة تسهم في تعزيز تفكيك الكحول بشكل أكثر كفاءة وتوفير الحماية ضد تراكم الأدهيد السام. تُظهر أدوار هذه الإنزيمات في إزالة السموم من الكحول ارتباطاً إيجابياً قوياً، حيث بلغت قيمة معامل الارتباط ($r = 0.8347, p > 0.0001$). ومع ذلك، يصبح هذا التأثير الوقائي أقل فاعلية مع استمرار إدمان الكحول، مما يؤدي إلى اضطرابات في التمثيل الغذائي وتطور الأمراض. تؤكد هذه الدراسة على التفاعل الأيضي الأساسي بين *ADH1B* و *ALDH2* فيما يتعلق بالاعتماد على الكحول، مع التأكيد على الحاجة إلى مزيد من الأبحاث حول تطبيقاتهما الطبية للوقاية والعلاج. وأخيراً، تسلط الدراسة الضوء على أهمية الفحص الجيني لهذه العلامات كأدوات محتملة لتشخيص الأفراد المعرضين لخطر اضطرابات استخدام الكحول، وتطوير استراتيجيات علاجية مخصصة لمعالجة الاضطرابات الأيضية المرتبطة بالإدمان على الكحول.

Introduction

Alcohol impairs mental functioning in stages, beginning with judgment and reasoning and progressively impacting more basic functions as consumption increases. Initially, alcohol diminishes judgment and reasoning, followed by impairments in motor skills and reaction times. At blood alcohol concentrations (BAC) of 0.06-0.09, coordination is significantly compromised, rendering activities such as driving hazardous. Moreover, alcohol is strongly associated with heightened aggression and violent behavior, playing a role in approximately half of all violent crimes and sexual assaults worldwide. It is also a significant contributor to suicides, second only to depression [1,2]. Other research shows that individuals with a family history of alcohol abuse were more likely to develop similar problems, with twin and adoption studies supporting the presence of a genetic component [3]. Genetic research identified specific gene polymorphisms, particularly those related to alcohol metabolism, that influenced an individual's susceptibility to alcohol dependence and replicated [4,5].

Alcohol Dehydrogenase (ADH), a crucial enzyme in human alcohol metabolism, was found to vary in activity as people aged. Research indicates that hepatic cytosolic ADH activity decreases as people age. This decrease in ADH activity most likely led to older persons' greater vulnerability to the harmful effects of alcohol [6]. After alcohol consumption, approximately 20% was absorbed by the stomach, while the intestines absorbed the remainder. The liver primarily metabolizes the alcohol, converting it into fatty acids and other byproducts [7]. Only a tiny portion of the alcohol was excreted through breath, urine, or sweat. As alcohol was metabolized, it could result in the accumulation of triglycerides in the liver, leading to fatty liver disease and, over time, cirrhosis [8]. *ALDH2* genes have been identified as significant epigenetic markers linked to problematic drinking and alcohol use disorder (AUD), with risk variations in these genes being associated with a variety of psychiatric diseases altered by stress [9]. Genetic studies revealed that specific individuals had a natural predisposition to alcohol dependence due to variations in genes responsible for alcohol metabolism [10]. The central

genes involved were alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). Variants such as *ADH1B-2*, *ADH1B-3*, *ADH1C-1*, and *ALDH2-2* were associated with lower rates of alcohol dependence, as they influenced the breakdown of alcohol and the accumulation of acetaldehyde, which could produce unpleasant effects and reduce alcohol consumption [11]. This genetic variation was common among East Asians, with about 40% carrying it, but was rare in Europeans. This genetic trait helped limit alcohol intake and reduced the risk of alcohol dependence [12,13]. Association between genetic polymorphism of ADH3 exon 8 and ADH2 exon 9 genes and specific enzymes with Alcoholism in Iraq. While studies have been conducted on the Alcohol Dehydrogenase genotypes, specifically *ADH2* and *ADH3*, in the Iraqi population [14], no research has been conducted on the gene expression of ADH in this group. As a result, this study sought to fill this gap by studying the gene expression of *ALDH2* and *ADH1B* in alcohol-dependent individuals from diverse regions of Iraq. This study sheds light on the molecular mechanisms of alcohol dependence in the Iraqi population.

Subjects, materials, and methods

Subjects

This study aimed to investigate the gene expression of alcohol metabolism by examining the responsible enzymes. The sample included alcohol-dependent individuals aged 18 to 55 years from three regions of Iraq. A total of 250 samples were intentionally categorized into three groups based on an analysis of their housing environments in relation to their place of residence. The groups included 50 samples from alcohol-dependent individuals in southern Iraq (specifically from Basra, Nasiriya, and A 'Amara), 50 samples from alcohol-dependent individuals in central Iraq (including Najaf, Karbala, Samawah, and Diwaniyah), 50 samples from alcohol-dependent individuals in Baghdad, and 50 samples from alcohol-dependent individuals in northern Iraq (comprising Mosul, Salahuddin, and Diyala). Additionally, 50 samples were included as a control group. All alcohol-dependent and controlled samples of these individuals who volunteered to participate in the study provided informed written consent. Between January and August 2024, research was conducted at Al-Nahrain University's Forensic DNA Centre and Training. The Medical City Hospital Ethics Committee and the University of Baghdad's Committee for Postgraduate Studies (CSEC/1124/0105) approved the experiment.

Exclusion Criteria

Men who consumed alcohol inconsistently or intermittently, as well as those who were both alcoholics and drug addicts, were excluded from the study. Additionally, men with chronic diseases such as cardiovascular disease, diabetes mellitus, kidney failure, or hypertension were omitted.

Sample Collection

Peripheral blood (PB; 4 mL) was collected from each participant, and 0.3 mL of PB was used for gene expression analysis.

The RNA quantification and qPCR

The RNA was extracted according to the protocol of the TRIzol reagent (ELK Biotechnology, China). The quantification of RNA was carried out using a Quantus Fluorometer. For this process, 2 μ L of RNA was combined with 198 μ L of diluted Quantifluor Dye. The RNA concentration values were recorded after incubating the mixture at room temperature in the dark for 5 minutes. The qPCR reaction is a two-step process that involves converting RNA into complementary DNA (cDNA) in the first reaction, followed by a separate polymerase chain reaction (PCR) to amplify the cDNA in the second reaction. The cDNA reaction was prepared as follows: a total volume of 20 μ L, consisting of 10 μ L of the reaction mixture, 1 μ L of the MMLV-RT enzyme,

500 ng of RNA, 1 μ L of the oligo primer, and the final volume was completed with nuclease-free water.

The reaction program is as follows: an annealing step at 25°C for 5 minutes, an extension step at 42°C for 60 minutes, enzyme inactivation at 70°C for 15 minutes, and a hold step at 4°C for 10 minutes.

For the second reaction, the qPCR calculation was done with the following master mix components: 10 μ L of Luna® Universal qPCR, 0.5 μ L each of forward and reverse primers as shown in Table 1, 6 μ L of nuclease-free water, and 3 μ L of cDNA, making a total volume of 20 μ L.

The qPCR program began with an initial denaturation at 95°C for 1 minute, followed by 45 cycles of denaturation at 95°C for 15 seconds and annealing at 58-63°C for 30 seconds. At the end of the reaction, a melt curve analysis was done to ensure that the amplification was specific. The $2^{-\Delta\Delta Ct}$ Livak method was used for data analysis.

Table 1: Primers used in this study.

Primer Name	Primer Sequence	Tm	References
RPL27-F	ATCGCCAAGAGATCAAAGATAA	58	[15]
RPL27-R	TCTGAAGACATCCTTATTGACG		
ADH1B-F	GGGAAGCCCATTCACTT	63	Designed in this study
ADH1B-R	TAGAGCCTGGGGTGACCTTG		
ALDH2-F	GCGACTGTGTGGGTCAACT	63	Designed in this study
ALDH2-R	GAGGGAGGAAGCTTGCATGA		

Statistical analysis

Statistical evaluation was done with Prism-Graph Pad. An unpaired *t*-test was used to compare the two sample groups, and a *P*-value of less than 0.05 was judged statistically significant, resulting in the rejection of the null hypothesis. The Pearson correlation coefficient test was used to calculate the correlation between the gene expression of *ALDH2* and *ADH1B*.

Results

The findings showed that the expression level of *ALDH2* in alcohol-dependent individuals was significantly downregulated and the fold change of around 0.5 with (*p*-value < 0.0001; *t* = 6.447) compared to the control sample, which showed a fold change of about 1.0, and serving as a baseline for comparisons. as shown in Figure 1.

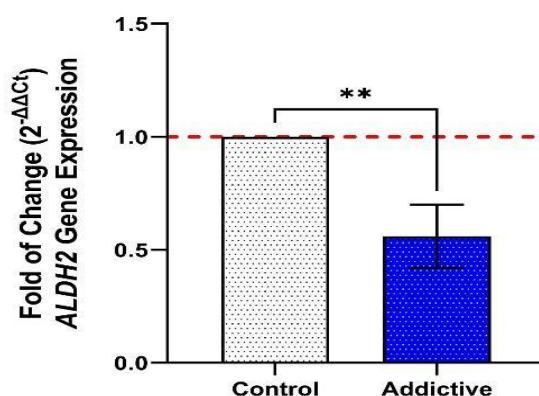


Figure 1: Real-time PCR analysis in alcohol-dependent individuals representing the expression levels of an *ALDH2* gene. The figure shows a significant decrease in expression levels of *ALDH2* in alcohol-dependent individuals compared to the controls. *t*-test, N=250, *P*<0.0001.

The expression level of the *ADH1B* gene revealed significant upregulation (P -value < 0.0001; $t = 6.447$) with a nearly 30-fold change in alcohol-dependent individuals compared to the control sample, which showed a fold change of about 2.73, as shown in Figure 2. The fold change follows the method $2^{-\Delta\Delta Ct}$, where the $\Delta\Delta Ct_{(patients)} = \Delta Ct_{(patients)} - \Delta Ct_{(Control)}$.

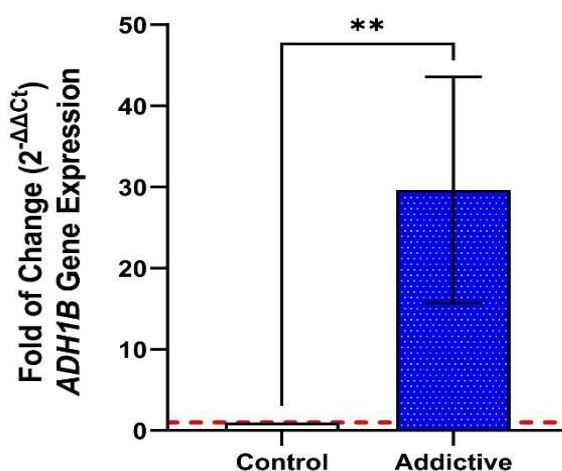


Figure 2: Real-time PCR analysis in alcohol-dependent individuals representing the expression levels of an *ADH1B* gene. The figure shows significantly upregulated levels of *ADH1B* expression in the alcohol-dependent individuals compared to the control. t -test, $N=250$, $P<0.0001$.

The results of the correlation between the gene expression of *ALDH2* and *ADH1B* in alcohol-dependent individuals, using Pearson correlation, showed a substantial and significant positive relationship between these two variables at ($r(250) = .835$, $p < .001$), as shown in Table 2. A strong positive correlation exists between the genes because the Pearson correlation coefficient equals 0.8347, which indicates that enhanced gene expression in one element matches higher expression in the other. One gene's expression variation can be attributed to nearly 70% of the expression level of the other gene based on the coefficient of determination ($r^2 = 0.6967$). The P -value ($1.913e-12$) demonstrates extremely strong evidence of statistical importance because the correlation occurs infrequently by chance. This correlation strength matches the magnitude of covariance, which amounts to 4496.702. The increase in data points to 44 provides stronger reliability to the correlation analysis. The correlation statistics of 9.822 demonstrate knowledge of the high statistical significance of the relationship.

Table 2: Pearson correlation results from the *ALDH2* and *ADH1B* gene expression.

Parameter	Value
Pearson correlation coefficient (r)	0.8347
r^2	0.6967
P-value	1.913e-12
Covariance	4496.702
Sample size (n)	250
Statistic	9.822

Discussion

The results of this study indicate significant alterations in the gene expression of *ALDH2* and *ADH1B* in alcohol-dependent individuals, highlighting their potential importance in alcohol metabolism and dependency. Samples were collected from different Iraqi regions; choosing

samples from the various areas of Iraq helps capture the genetic and environmental diversity that may impact alcohol metabolism and dependence. This strategy ensures that the study reflects a more comprehensive picture of the population, acknowledging regional variations that could influence gene expression and the overall findings.

The *ADH1B* expression increased significantly in alcohol-dependent individuals, which showed a fold change of 30, contrary to 2.37 in control samples, indicating that overexpression of this gene can accelerate acetaldehyde production. The findings also showed that alcohol-dependent individuals had significantly lower levels of *ALDH2* expression than the control group, which was approximately 50%. This is because *ALDH2* converts acetaldehyde, a toxic byproduct of alcohol metabolism, to acetate [16,17,18].

The higher levels of *ADH1B* expression indicate faster ethanol metabolism. Nonetheless, acetaldehyde synthesis may exceed detoxification capacity, resulting in a dangerous accumulation. Since *ADH1B* promotes the oxidation of ethanol into acetaldehyde, a toxic result of alcohol metabolism [19,20]. Meanwhile, *ADH1B* gene expression in other research shows decreased expression levels in different types of cancer [21, 22]. The decreased expression of *ADH1B* in metabolism can potentially generate inflammatory tumor conditions, which lead to cancer. This is opposite to the increased *ADH1B* expression, which occurs with alcohol dependence. The MAPK signaling pathway becomes inactive after *ADH1B* overexpression, which leads to tumor suppression and prevents tumor proliferation, invasion, and migration [23].

The observed downregulation of *ALDH2*, which is commonly associated with alcoholism due to its function in acetaldehyde detoxification, could still be a compensatory mechanism that fails over time. In alcohol-dependent individuals, the body may attempt to manage acetaldehyde levels at first, but continuous downregulation of *ALDH2* results in insufficient acetaldehyde clearance. This causes toxic buildup, increasing the damaging effects of alcohol [24]. As the expression of *ALDH2* decreases, the body's ability to convert acetaldehyde to the less harmful acetate is compromised, leading to its accumulation [25,26]. This buildup triggers oxidative stress and sets off a cascade of damaging effects on cellular structures and organ function. In addition, it causes toxic consequences such as headaches, nausea, and an increased risk of long-term tissue damage, notably in the liver, cellular damage, and inflammation [27]. Acetaldehyde's continuous presence may enhance addictive behaviors, probably due to the disruption of neurotransmitters in the brain. Research indicates that high levels of acetaldehyde impact dopamine pathways, which reinforces addictive behavior and sustains alcohol use despite negative consequences [28]. This produces an endless cycle in which alcohol intake persists despite its negative consequences, fueled by both addiction and the body's decreased ability to handle acetaldehyde poisoning [29,30]. This led to the current medical treatment, which is converting alcohol to acetaldehyde or acetate, like naltrexone and other drugs that help in alcohol treatment [31,32]. As a result, individuals with *ALDH2* downregulation build acetaldehyde in their bodies after consuming alcohol, which is a similar feature to *LUAD* and *CRC* cancers, as poorly expressed *ALDH2* fuels toxic aldehyde buildup and inflammatory conditions and raises tumorigenic potential [33,34]. The enzyme regulates critical metabolic intermediates to control immune responses and stemness pathways. In alcohol-dependent individuals, its deficiency results in impaired mitochondrial fatty acid oxidation and reduced energy expenditure while increasing lipid accumulation [35]. Research into *ALDH2* activators has shown clinical success across various cancer diseases and metabolic illnesses, which demonstrates that targeting *ALDH2* represents a promising method to control illness development, improve patient medical results, and decrease inflammatory processes [36,37].

Alcohol-dependent individuals have *ADH1B* overexpression, which leads to increased acetaldehyde synthesis; here comes the role of *ALDH2* that converts acetaldehyde to acetate, but the reduced expression of *ALDH2* leads to the accumulation of acetaldehyde and not only contributes to the deleterious consequences of alcohol, but it also encourages additional alcohol consumption, hence prolonging addiction. These findings suggest that genetic factors, such as *ADH1B* overexpression and *ALDH2* downregulation, play a crucial role in the development of alcohol-related disorders. *ADH1B* and *ALDH2* transcript levels were linked with regulating metabolism, cell cycle, DNA repair, and cancer-associated pathways [38].

Research shows that alcohol dependence creates intricate relationships between the *ADH1B* and *ALDH2* genetic factors. The enzymes demonstrate high levels of coordinated activity based on their positive correlation of 0.8347, which indicates they adjust together when exposed to long-term alcohol use. The data shows increased activity of the *ADH1B* gene because cells adapt their responses to elevated ethanol concentrations. The simultaneous decrease of the detoxifying enzyme *ALDH2* results in the buildup of toxic byproducts because of its fundamental role in clearing acetaldehyde. The short-term decrease of *ALDH2* expression seems beneficial, but proves unsuccessful as alcohol consumption persists. This expression failure creates an environment with elevated toxicity while simultaneously promoting inflammatory reactions that increase the chance of pathophysiological deterioration. The research results demonstrate a coordinated expression pattern between *ADH1B* and *ALDH2*. However, the diminished *ALDH2* function indicates an unfavorable impact on its protective capacity against alcohol-induced tissue damage.

Understanding the genetic interplay between *ADH1B* and *ALDH2* not only sheds light on the pathophysiology of alcohol dependence but also opens the door to targeted genetic or pharmacological interventions that could improve treatment outcomes [39].

This study has several limitations. The study uses 250 male participants based on their regional categorization but excludes female participants, limiting potential generalization beyond Iraqi males. A cross-sectional study methodology restricts researchers from noting temporal changes or adjusting for changing lifestyle variables. Multiple complicated aspects, such as nutrition, health conditions, and genetic differences, prove difficult to manage, and their effect on enzyme expression remains unclear. The dependent nature of alcohol use information from participants introduces possible reporting bias along with potential matching differences between the small control sample and alcohol-dependent groups [40].

Conclusion

Finally, this study showed considerable excessive activity of both *ADH1B* and *ALDH2* in alcohol-dependent individuals, highlighting a complicated genetic interaction that has a significant impact on alcohol metabolism. *ADH1B* promotes the conversion of ethanol into the risky byproduct acetaldehyde, but *ALDH2*, despite its high activity, is unable to eliminate the accumulating acetaldehyde adequately. This continuous discrepancy causes high acetaldehyde levels, which increase alcohol's adverse effects and prolong addicted tendencies. Chronic alcohol exposure seems to regulate both *ADH1B* and *ALDH2* since alcohol-dependent patients present a strong positive correlation ($r=0.8347$) between these enzymes. The findings highlight the need to incorporate both genes when assessing genetic susceptibility to alcohol dependency, as well as indicate that tailored treatment techniques targeting these metabolic abnormalities may be required for successfully controlling alcohol use disorders. More research is needed to establish the potential uses of these genetic markers in therapy, especially in Iraqi populations.

Conflict of interest

I pledge that I have no conflict of interest with other researchers.

References

- [1] G. F. Koob, "Alcohol use disorder treatment: Problems and solutions," *Annual Review of Pharmacology and Toxicology*, vol. 64, no. 1, pp. 255–275, 2024.
- [2] A. W. Jones, "Dubowski's stages of alcohol influence and clinical signs and symptoms of drunkenness in relation to a person's blood-alcohol concentration—Historical background," *Journal of Analytical Toxicology*, vol. 48, no. 3, pp. 131–140, Apr. 2024, doi: 10.1093/jat/bkae008.
- [3] P. D. Gonçalves, S. S. Martins, N. M. Gebru, S. R. Ryan-Pettes, N. Allgaier, A. Potter, W. K. Thompson, M. E. Johnson, H. Garavan, and A. Talati, "Associations Between Family History of Alcohol and/or Substance Use Problems and Frontal Cortical Development From 9 to 13 Years of Age: A Longitudinal Analysis of the ABCD Study," *Biological Psychiatry Global Open Science*, vol. 4, no. 2, p. 100284, 2024.
- [4] F. Schmid, A. Henry, F. Benzerouk, S. Barrière, C. Portefaix, J. Gondrexon, A. Obert, A. Kaladjian, and F. Gierski, "Neural activations during cognitive and affective theory of mind processing in healthy adults with a family history of alcohol use disorder," *Psychological Medicine*, vol. 54, no. 5, pp. 1034–1044, 2024.
- [5] R. Bowns, J. E. Loeffelman, D. Steinley, and K. J. Sher, "A brief young adult alcohol problems screening test: Short form development using combinatorics," *Journal of American college health*, vol. 72, no. 6, pp. 1857–1863, 2024.
- [6] M. Turner, "Genomic markers and psychological health outcomes of drinking behaviours in veterans," 2022, *Queensland University of Technology*.
- [7] C. C. Smith, J. Stevens, M. Novelli, D. Maskey, and G. T. Sutherland, "Phosphatidylethanol in post-mortem brain: Correlation with blood alcohol concentration and alcohol use disorder," *Alcohol*, vol. 119, pp. 17–22, 2024, doi: <https://doi.org/10.1016/j.alcohol.2024.05.001>.
- [8] T. Lehner, B. Gao, and B. Mackowiak, "Alcohol metabolism in alcohol use disorder: a potential therapeutic target," *Alcohol and Alcoholism*, vol. 59, no. 1, p. agad077, 2024.
- [9] V. Patel, "A Rudimentary Study On Aging And Alcohol Sensitivity In A Mouse Model," *Indian Journal of Forensic Medicine & Toxicology*, vol. 14, no. 2, 2023.
- [10] H. Zhou and J. Gelernter, "Human genetics and epigenetics of alcohol use disorder," *The Journal of Clinical Investigation*, vol. 134, no. 16, 2024.
- [11] M. Hatami, S. Zia, A. Kanjorpor, H. Nemati, and M. Sadeghi, "Impact of alcohol dehydrogenase 3 (ADH3 or ADH1C) genetic variation on head and neck cancer susceptibility: A systematic review, meta-analysis, functional analysis, and trial sequential analysis," *Pathology-Research and Practice*, vol. 262, p. 155561, 2024.
- [12] A. Y.-H. Woo and L. Jia, "ALDH2 mutations and defense against genotoxic aldehydes in cancer and inherited bone marrow failure syndromes," *Mutation Research-Fundamental and Molecular Mechanisms of Mutagenesis*, p. 111870, 2024.
- [13] A. A. Abdulla, "Association between Genetic Polymorphism of ADH3 exon 8 and ADH2 exon 9 Genes and Specific Enzymes with Alcoholism in Iraq," *Indian Journal of Forensic Medicine & Toxicology*, vol. 15, no. 2, 2021.
- [14] D. Cozzoli, A. Daponte, S. De Fazio, V. Ariano, M. R. Quaranta, V. Leone, A. Ostuni, M. Casanova, C. R. Catacchio, M. Ventura, and F. Montinaro, "Genomic and Personalized Medicine Approaches for Substance Use Disorders (SUDs) Looking at Genome-Wide Association Studies," 2024. doi: 10.3390/biomedicines9121799. *Journal of American college health*, vol. 71, no. 6, pp. 1857–1863, 2024.
- [15] C. Dunstan-Harrison, I. M. Morison, and E. C. Ledgerwood, "Inherited thrombocytopenia associated with a variant in the FLI1 binding site in the 5' UTR of ANKRD26," *Clinical Genetics*, 2024 *Journal of Integrative Neuroscience*, vol. 24, no. 6, p. 111, 2024..
- [16] R. Polimanti and J. Gelernter, "ADH1B: From alcoholism, natural selection, and cancer to the human phenome.," *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*, vol. 177, no. 2, pp. 113–125, 2018, doi: 10.1002/ajmg.b.32523.
- [17] P. Gombo, P. K. Yadav, and M. Yadav, "Structural and Functional Aspects of Alcohol Dehydrogenase-A minireview".
- [18] L. O. Dannenberg, H. Chen, H. Tian, and H. J. Edenberg, "Differential regulation of the alcohol dehydrogenase 1B (ADH1B) and ADH1C genes by DNA methylation and histone deacetylation," *Alcoholism: Clinical and Experimental Research*, vol. 30, no. 6, pp. 928–937, 2006.

- [19] A. Cieslik-Starkiewicz, K. Noworyta, J. Solich, A. Korlatowicz, A. Faron-Górecka, and R. Rygula, "Identification of genes regulated by trait sensitivity to negative feedback and prolonged alcohol consumption in rats," *Pharmacological Reports*, vol. 76, no. 1, pp. 207–215, 2024.
- [20] D.-P. Gao, L.-W. Wang, D.-L. Xie, Q. Li, Z.-P. Yu, Z.-H. Tang, K.-K. Cui, and Y. Cai, "Chronic Alcohol Exposure Alters the Levels and Assembly of the Actin Cytoskeleton and Microtubules in the Adult Mouse Hippocampus," *Journal of Integrative Neuroscience*, vol. 23, no. 6, p. 118, 2024.
- [21] C. Jiang, R. Liu, and X. Wu, "Alcohol dehydrogenase-1B represses the proliferation, invasion and migration of breast cancer cells by inactivating the mitogen-activated protein kinase signalling pathway.," *Journal of Physiology & Pharmacology*, vol. 74, no. 5, 2023.
- [22] R. Villéger, M. Chulkina, R. C. Mifflin, N. S. Markov, J. Trieu, M. Sinha, P. Johnson, J. I. Saada, P. A. Adegboyega, B. A. Luxon, E. J. Beswick, D. W. Powell, and I. V Pinchuk, "Loss of alcohol dehydrogenase 1B in cancer-associated fibroblasts: contribution to the increase of tumor-promoting IL-6 in colon cancer," *British Journal of Cancer*, vol. 128, no. 4, pp. 537–548, 2023, doi: 10.1038/s41416-022-02066-0.
- [23] Y. Zhou, L. Yu, P. Huang, X. Zhao, R. He, Y. Cui, B. Pan, and C. Liu, "Identification of afatinib-associated ADH1B and potential small-molecule drugs targeting ADH1B for hepatocellular carcinoma," *Frontiers in Pharmacology*, vol. 14, p. 1166454, 2023.
- [24] Q. Wang, B. Chang, X. Li, and Z. Zou, "Role of ALDH2 in Hepatic Disorders: Gene Polymorphism and Disease Pathogenesis.," *Journal of clinical and translational hepatology*, vol. 9, no. 1, pp. 90–98, 2021, doi: 10.14218/JCTH.2020.00104.
- [25] A. Kuhlemeier, Y. Desai, A. Tonigan, K. Witkiewitz, T. Jaki, Y.-Y. Hsiao, C. Chang, and M. L. Van Horn, "Applying methods for personalized medicine to the treatment of alcohol use disorder.," *Journal of consulting and clinical psychology*, vol. 89, no. 4, p. 288, 2021.
- [26] Y. Shen, Y. Hong, X. Huang, J. Chen, Z. Li, J. Qiu, X. Liang, C. Mai, W. Li, X. Li, and Y. Zhang, "ALDH2 regulates mesenchymal stem cell senescence via modulation of mitochondrial homeostasis," *Free Radical Biology and Medicine*, vol. 223, pp. 172–183, 2024, doi: <https://doi.org/10.1016/j.freeradbiomed.2024.07.040>.
- [27] A. Marley, M. Bakali, and C. Simpson, "Effect of a moderate alcohol dose on physiological responses during rest and prolonged cycling," *Alcohol and Alcoholism*, vol. 59, no. 2, p. agad079, 2024.
- [28] N. B. Morris, N. Ravanelli, and G. K. Chaseling, "The effect of alcohol consumption on human physiological and perceptual responses to heat stress: a systematic scoping review," *Environmental Health*, vol. 23, no. 1, p. 73, 2024.
- [29] K. K. Nutfilloevich and K. D. Akhrovovna, "MORPHOLOGICAL CHANGES IN THE LIVER IN NORMAL AND CHRONIC ALCOHOL POISONING," *ОБРАЗОВАНИЕ НАВКА И ИННОВАЦИОННЫЕ ИДЕИ В МИРЕ*, vol. 36, no. 3, pp. 77–85, 2024.
- [30] I. Karunarathna, K. De Alvis, P. Gunasena, and A. Jayawardana, "Alcohol and its effects on cognitive function and mental health: A systematic review," 2024. *Journal of Integrative Neuroscience*, vol. 23, no. 6, p. 118, 2024.
- [31] R. C. K. Yen, "Detoxification preparations with reinforced boosters to treat alcohol intoxication," 2024, *Google Patents*.
- [32] W. B. Bowen Jr and D. S. Daniel, "Method and composition for the accelerated in vivo removal of ethanol," Dec. 21, 2004, *Google Patents*.
- [33] T.-O. Tran, T. H. Vo, L. H. T. Lam, and N. Q. K. Le, "ALDH2 as a potential stem cell-related biomarker in lung adenocarcinoma: Comprehensive multi-omics analysis," *Computational and Structural Biotechnology Journal*, vol. 21, pp. 1921–1929, 2023, doi: <https://doi.org/10.1016/j.csbj.2023.02.045>.
- [34] L. Wang, X. Zhou, H. Yan, Y. Miao, B. Wang, Y. Gu, W. Fan, K. Xu, S. Huang, and J. Liu, "Deciphering the role of tryptophan metabolism-associated genes ECHS1 and ALDH2 in gastric cancer: implications for tumor immunity and personalized therapy.," *Frontiers in immunology*, vol. 15, no.1 p. 1460308, 2024, doi: 10.3389/fimmu.2024.1460308.
- [35] H. Lei, J. Liao, X. Wang, R. Huang, C. Ying, and J. Yang, "ALDH2 is a novel biomarker and exerts an inhibitory effect on melanoma," *Scientific Reports*, vol. 14, no. 1, p. 4183, 2024.
- [36] P. Wei, G. M. S. H. Prince, U. Batzorig, C. Huang, and Y. Chang, "ALDH2 promotes cancer stemness and metastasis in colorectal cancer through activating β -catenin signaling," *Journal of cellular biochemistry*, vol. 124, no. 6, pp. 907–920, 2023.

- [37] Y.-C. Chang, H.-L. Lee, W. Yang, M.-L. Hsieh, C.-C. Liu, T.-Y. Lee, J.-Y. Huang, J.-Y. Nong, F.-A. Li, H.-L. Chuang, Z.-Z. Ding, W.-L. Su, L.-Y. Chueh, Y.-T. Tsai, C.-H. Chen, D. Mochly-Rosen, and L.-M. Chuang, "A common East-Asian ALDH2 mutation causes metabolic disorders and the therapeutic effect of ALDH2 activators," *Nature Communications*, vol. 14, no. 1, p. 5971, 2023, doi: 10.1038/s41467-023-41570-6.
- [38] Y. Zhang, J. Ma, H. Du, Y. Shi, S. A. G. Willis-Owen, M. F. Moffatt, and Y. Zhang, "The prognostic effect of ADH1B and ALDH2 in lung adenocarcinoma," *Journal of Clinical Oncology*, vol. 41, no. 16_suppl, pp. e15167–e15167, 2023, doi: 10.1200/JCO.2023.41.16_suppl.e15167.
- [39] S.A.A. Hamid and R.M. Khoshabeh, "Antibiotic Resistance, Biofilm Formation, and Identification of FimH and FimA Adhesion Genes in Uropathogenic *Escherichia Coli* (UPEC) Isolated from Patients in Baghdad Province," *Iraqi Journal of Science*, vol.65, no.10 pp.5546-5554,2024.
- [40] A.M. Salih, I.H. Aziz, and F.Y. Mohsin, "Estimation of miRNA 208 Effects in Inducing Epithelial-Mesenchymal Transition by Targeting CDH2 in Breast Cancer Patients of Iraqi Population," *Iraqi Journal of Science*, vol.66, no.1, pp.103-113,2025