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Assessing the association between ADH5 and ALDH1A1 genetic variants and substance use disorder risk in a Jordanian male population

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Abstract

Background Substance Use Disorder (SUD) is a severe global problem that is influenced by both environmental and genetic factors. The genetic etiology of addiction can be complex and overlapping. This study aimed to investigate the association between two genes, *ADH5* and *ALDH1A1*, and drug addiction in Jordanian males.

Methods This study included 496 addicted patients and 496 healthy controls of Arab descent. The addicted participants were identified as Jordanian males with dependence on substances such as amphetamines, synthetic cannabinoids, benzodiazepines, alcohol, opiates, cocaine, and multiple substances. The participants' DNA was extracted, and 20 selected SNPs within *ADH5* and *ALDH1A1* were genotyped using the MassARRAY™ system. The statistical analysis was carried out using SPSS.

Results The study investigated associations between 20 variants within the *ADH5* and *ALDH1A1* genes and substance use disorder in Jordanian males. No statistically significant association was observed between individual polymorphisms and addiction ($P > 0.05$). However, the haplotypes *CCGTTTTGTTTGG* and *CCCTTGTGTTCGG* within the *ALDH1A1* gene were significantly associated with an increased risk of addiction, with P-values of 0.0022 and 0.049 and odds ratios (OR) of 2.34 and 1.91, respectively.

Conclusion This study did not find a significant association between *ADH5* and *ALDH1A1* gene polymorphisms with addiction in Jordanian males. The authors suggest replicating this type of study with larger sample sizes and more variants in the same or different genes to confirm their findings.

Keywords *ADH5*, *ALDH1A1*, Polymorphisms, Drug, Addiction, Jordan

Introduction

Substance Use Disorder (SUD) is one of the chronic complicated illnesses characterized by compulsive and repetitive use of drugs to achieve provisional euphoria, animates the person with an addiction to tolerance, and elevates the danger of withdrawal signs upon decreasing the absorption of the drug [1, 2]. Consequently, individuals with addiction may experience cravings, tolerance, and relapse due to neurological changes that lead to psychological and physical dependence [3]. According to the United Nations Office on Drugs and Crime (UNODC) statement, almost 5% of the world's adult people used

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illegitimate drugs at least once in 2010, and more than 0.6% of the population are deemed "problem drug users. Besides, over 200 thousand deaths yearly are recorded due to continuing drug addiction [4, 5]. The average drug abuse is a growing trend in various developing societies, although it is constant in some countries [4]; for instance, Iran is facing a rising number of drug abusers who have adverse health and social influences [6]. Various agents such as physicochemical and pharmacological features of drugs, risk-seeking, psychiatric discords, and exhausting life and dominantly genetic makeup may make a person abuse drugs [7]. Addiction is a dangerous worldwide problem with significant environmental and genetic influences. It has been joined to environmental factors together with genetic ones [8]. Examining the role of genetic mutations in the etiology of addiction may enhance response to the medications and play a vital role in illness protection [9, 10]. Genetic and environmental factors play an essential role in contributing to the beginning of the use of addictive agents and the transmission from use to addiction. Addictions are medium to highly heritable [11].

Although numerous genes have been involved in drug addiction, only some of them have either been replicated to have an association or to have a recognized functional mechanism linked to the specific impacts of abused drugs. Identifying genes and vulnerable chromosomal regions is a crucial first step in understanding the genetic factors contributing to addiction susceptibility. Over the past three decades, several technologies have been applied to create such as candidate genes or weak chromosome regions [12].

Genome-wide association studies (GWAS) on alcohol use disorder (AUD) have been carried out across multiple populations. The largest GWAS on problematic alcohol use (PAU) involved 435,563 European individuals and identified 29 independent risk variants [13]. However, East Asian studies have included far fewer participants, with the largest analysis encompassing only 3,381 subjects (533 cases) [14], leading to limited power for identifying AUD-related genetic variants in this population. The genetic findings indicate significant variability across populations, making polygenic risk scores less transferable [15]. Among East Asians, ADH1B and ALDH2 are the most consistently implicated loci. Specifically, ADH1B rs1229984 and ALDH2 rs671 have shown strong associations with alcohol dependence in candidate studies within this group [16, 17].

The alcohol dehydrogenase (ADH) gene family, especially the *ADH1B*, *ADH1C*, and *ADH5 genes*, is crucial in the genetic understanding of alcohol use disorder, with extensive research supporting their role in alcohol metabolism and addiction susceptibility. These genes encode enzymes that metabolize ethanol into acetaldehyde, which can influence an individual's predisposition to alcohol dependence. Specific genetic variants, such as the ADH1B rs1229984 variant, have been linked to a protective effect against alcohol dependence. This variant is associated with heightened enzymatic activity, leading to increased production of acetaldehyde, which can cause adverse reactions to alcohol and, consequently, discourage alcohol consumption [18].

ADH5 (Alcohol Dehydrogenase 5, Chi Polypeptide) is a protein-coding gene. This gene encodes a member of the alcohol dehydrogenase family; members play a vital role in metabolizing an extended group of substrates, including retinol, ethanol, hydroxysteroids, other aliphatic alcohols, and lipid peroxidation products [19]. The *ADH5* gene comprises nine exons and eight introns on chromosome 4q23–q24 [20]. Some diseases associated with the *ADH5* gene include proliferative-type fibrocystic change of the breast and methanol poisoning. Also, among its relevant pathways are drug metabolism - cytochrome P450 and glucose metabolism [21]. In the various ethnic groups of the Chinese Han population, the study showed that (rs1154414) SNP has no significant association with the expression of the *ADH5* gene induced by formaldehyde and drugs [22].

On the other hand, haplotype trend regression analysis revealed that rs1154400 within the *ADH5* gene is associated with drug dependence in European Americans and African Americans [23]. Many genes code for aldehyde dehydrogenase (ALDH) enzymes found on various chromosomes; 19 putatively functional genes and three pseudogenes in the *ALDH* gene superfamily have been recognized to encode ALDH isozymes [24]. However, one of them, *ALDH1* (*ALDH1A1*, 9q21.13, cytosolic isozyme), is thought to be significantly implicated in acetaldehyde oxidation [25]. Several functional polymorphisms for the *ADH* and *ALDH* genes have significantly less minor allele frequency (MAF) in European populations [26–28]. Consequently, the roles of the *ADH* and *ALDH* genes in the progress of Alcohol Dependence are less clear in Caucasians. Significant associations described with AD included the *ADH5* gene and haplotypes of the *ADH1A1* gene, although the associated genotypes or haplotypes were altered in European and African American individuals [29].

Studies have shown that multiple genes are correlated with drug addiction susceptibility and are considered candidates for personalized medicine development in the Jordanian population [30–33]. Therefore, in this current project, we examined the genetic susceptibility to substance use disorder by investigating the association of ADH5 and ALDH1A1 gene variants with substance use disorder in Jordanians. We screened and analyzed

20 candidate SNPs selected from these genes based on criteria such as clinical importance and depending on early published implications of these variants with drug dependence among other peoples. The results of the current study aim to spread knowledge about the correlation between genetic polymorphisms and increased susceptibility toward substance use and drug addiction. The goal of the current study is to provide enough information that could aid in the development of modern personalized medicine approaches toward drug addiction treatments.

Materials and methods

Study design and patients

The study included a total sample size of 992 participants, comprising equal cases and controls. The statistical software G*Power was employed to calculate the actual power of the study. Using an alpha level (α) of 0.05 and an effect size (d) of 0.50, considered a moderate effect size, the calculated actual power of the study was found to be 0.80. This result indicates that the study is sufficiently powered to detect a moderate effect size, as it meets the commonly accepted threshold of 80% power. This suggests a strong likelihood of correctly rejecting the null hypothesis, should an effect truly exist.

The study group consisted of 496 drug addicts chosen based on the drug abuse criteria according to the Manual of Mental Disorders (DSM-IV) criteria (APA, 2013). All participants were males from Jordan and were hospitalized in 2018 for eight months in the Drug Rehabilitation Centre of the Jordanian Public Security Directorate (DRC-PSD) and the National Centre for Rehabilitation of Addicts (NCRA) of the Ministry of Health in Jordan. Cases were classified as drug-dependent based on their dependence on various substances, including amphetamines (5.8%), synthetic cannabinoids (48%), cannabinoids (20%), benzodiazepines (4.3%), alcohol (5.3%), opiates (4.5%), cocaine (1.1%), and mixed substances (dependence on two or more substances) (11.3%). Marital status, employment status, and smoking status were also considered in this project; 87.8% of the patients were smokers, 70.9% were single, and 29.6% were unemployed. In addition, 496 healthy Jordanian male participants with no history of psychiatric disorders or drug addiction were collected as controls. 66.2% of the controls were smokers, 41% were single, and 20.6% were unemployed. The inclusion/exclusion criteria for patient selection were limiting the patient's disorders to drug addiction and excluding any other neurological and mental disorders. For the controls, the inclusion/exclusion criteria included healthy participants with no history of drug addiction or family history of addiction and substance use. Structured questionnaires and clinical data were obtained according to the Human Ethics Committee of the Jordanian Ministry of Health (MOH/REC/180057) and the Institutional Review Board/Human Research Ethics Committee at Jordan University of Science and Technology (43/114/2018). Written informed consent was obtained from all participants in this study as their approval of participation.

Genes and SNP selection

The gene and SNP selections for the current study were based on published results from different populations. The *ADH5* gene and its polymorphisms have been associated with drug addiction [23]. ALDH1A1 polymorphisms have also been linked with susceptibility to drug addiction in several populations [34]. Finally, for further confirmation of SNP selection, globally available databases were used as a resource for SNP information and validation of the selection [35, 36]. This study includes seven polymorphisms of *ADH5* (rs17595424, rs1154414, rs7683704, rs7684986, rs1154405, rs1154401, and rs1154400) and 13 SNPs of *ALDH1A1* (rs8187876, rs1888202, rs348457, rs2773806, rs1424482, rs63319, rs4745209, rs6560311, rs4406477, rs11143443, rs1364451, rs1418187, and rs2249978) to assess their correlation with drug addiction in the Jordanian population.

DNA Extraction and Genotyping

The Wizard® Genomic DNA Purification Kit (Promega Corporation, USA) was used to purify the genomic DNA of the collected venous blood samples. The agarose gel electrophoresis technique and the Nano-Drop ND-1000 UV-Vis Spectrophotometer (BioDrop, UK) were also used to detect the quantity and quality of the extracted genetic material. The candidate SNPs within (*ADH5* and *ALDH1A1*) genes were selected using the sequencing procedure. Using nuclease-free water, chosen DNA samples for genotyping were diluted with an ultimate concentration of 20ng/µl (50-500µl) and shipped on wet ice to the Australian Genome Research Facility (AGRF) (Australia). At the AGRF, the samples were genotyped using the Agena Bioscience MassARRAY® on a Compact Spectrometer, IPLEX GOLD chemistry. The complete processed SNP genotypic data for the *ADH5* and *ALDH1A1* genes is available as a supplementary file.

Statistical analysis

Identifying if the decided variants fulfill the (HWE) equation was done using the *P*-value of Hardy-Weinberg equilibrium (HWE). Genetic association, genotypic and allelic frequencies, haplotypic analyses, and multiple genetic models were conducted using SNPStats software (2006 Institut Català d'Oncologia). Moreover, regression analysis was done using the Statistical Package for the Social Sciences (SPSS), version 25.0 (SPSS, Inc., Chicago,

IL). The *P*-values of less than 0.05 were considered to be statistically significant.

Results

Clinical characteristics of participants

In this project, all participants were Jordanian males of Arab descent. Four hundred ninety-six cases were classified as drug addicts based on their dependence on various substances. Age, employment status, smoking status, and marital status showed significant associations between controls and patients, with $P < 0.05$. The percentage of unemployed individuals was nearly 1.5 times higher in SUD patients (29.6%) compared to healthy controls (20.6%). SUD patients exhibited higher rates of single status (70.9%) and smoking (87.8%) compared to controls (41% single and 66.2% smokers).

Hardy-Weinberg Test for Selected SNPs

The list of chosen genetic variants of the two genes (*ADH5* and *ALDH1A1*) is summarized in Table 1). The table also exhibits the chromosomal positions of SNPs, minor alleles and their frequencies, and the *P*-value of HWE for drug addiction patients and healthy controls. The results indicate that all the included SNPs are in Hardy-Weinberg Equilibrium (HWE), as evidenced by the *P-values* larger than 0.05. Based on the outcome of this test, all the candidate SNPs of both *ADH5* and *ALDH1A1* genes were included in the following tests of this study.

Genetic association analyses of ADH5 and ALDH1A1 gene polymorphisms with Drug Addiction

Table 2 demonstrates the allelic and genotypic distribution of the SNPs between cases and healthy individuals. Our results exposed that there was no significant association between the studied SNPs and addiction. The results of the current study show that there was no association between ADH5 gene polymorphisms and drug addiction. The test also uncovered an allelic association of rs1424482 of the *ALDH1A1* gene with drug addiction in this study (*P*-values = 0.05), where 41% of patients carried the (C) allele, and 45% of healthy participants had the same variant. However, for this SNP, no significant association was found between the genotypes and drug addiction.

Table 1 ADH5 and ALDH1A1 SNPs, their positions (GRCh38 genome build), minor allele frequencies among drug addiction patients and healthy controls, and HWEc P-values for the candidate gene polymorphisms

Gene	SNP-ID	SNP Position[a]	Cases ($n = 496$)		Controls ($n = 496$)		
			MA[b]	MAF[c]	MA[b]	MAF[c]	HWE[d] *P*-value
ADH5	rs17595424	4:99072718	0	0.12	T	0.1	0.63
	rs1154414	4:99078985	C	0.16	C	0.15	0.86
	rs7683704	4:99083075	T	0.16	T	0.14	0.35
	rs7684986	4:99070525	T	0.11	T	0.1	0.3
	rs1154405	4:99087599	G	0.25	G	0.26	0.73
	rs1154401	4:99088587	G	0.33	G	0.33	0.84
	rs1154400	4:99088859	C	0.33	C	0.32	0.92
ALDH1A1	rs8187876	9:72950038	T	0.12	T	0.13	0.17
	rs1888202	9:72904335	G	0.44	G	0.93	0.93
	rs348457	9:72915638	G	0.47	G	0.49	0.15
	rs2773806	9:72936384	C	0.11	C	0.1	0.81
	rs1424482	9:72948641	C	0.41	C	0.45	0.32
	rs63319	9:72909868	G	0.47	G	0.45	0.09
	rs4745209	9:73025189	C	0.3	C	0.32	0.53
	rs6560311	9:72997266	T	0.32	T	0.36	0.09
	rs4406477	9:73037542	C	0.43	C	0.46	0.65
	rs11143443	9:73041134	C	0.03	C	0.02	1
	rs1364451	9:72993844	T	0.13	T	0.15	0.21
	rs1418187	9:73022744	A	0.32	A	0.33	0.48
	rs2249978	9:73012182	A	0.38	A	0.4	0.71

[a] Chromosome positions are based on NCBI Human Genome Assembly Build

[b] MA: minor allele

[c] MAF: minor allele frequency

[d] HWE: Hardy-Weinberg equilibrium. N/A: not applicable.

Table 2 Allele and genotype distributions of ADH5 and ALDH1A1 SNPs in drug addiction patients and controls

Gene	SNP-ID	Allelic and Genotypic Frequencies in Cases and Controls				
		Allele/Genotype	Cases ($n = 496$)	Controls ($n = 496$)	Chi-square	*P*-value*
ADH5	rs1759542	G	860(0.88)	881(0.9)	0.96	0.33
		T	116(0.12)	101(0.1)		
		GG	381(0.78)	396(0.81)	1.1	0.59
		GT	98(0.2)	89(0.18)		
		TT	9(0.02)	6(0.01)		
	rs1154414	T	804(0.84)	825(0.85)	0.33	0.57
		C	158(0.16)	151(0.15)		
		TT	340(0.71)	349(0.72)	0.97	0.62
		TC	124(0.26)	127(0.26)		
		CC	17(0.04)	12(0.02)		
	rs7683704	C	828(0.84)	852(0.86)	1.19	0.27
		T	154(0.16)	138(0.14)		
		CC	353(0.72)	369(0.75)	1.18	0.55
		CT	122(0.25)	114(0.23)		
		TT	16(0.03)	12(0.02)		
	rs7684986	C	855(0.89)	873(0.9)	0.65	0.42
		T	105(0.11)	95(0.01)		
		CC	378(0.79)	391(0.81)	0.74	0.69
		CT	99(0.21)	91(0.19)		
		TT	3(0.01)	2(0.00)		
	rs1154405	A	736(0.75)	729(0.74)	0.26	0.61
		G	248(0.25)	259(0.26)		
		AA	277(0.56)	267(0.54)	0.64	0.72
		AG	182(0.37)	195(0.39)		
		GG	33(0.07)	32(0.06)		
	rs1154401	C	659(0.67)	665(0.67)	0.0009	0.98
		G	321(0.33)	323(0.33)		
		CC	226(0.46)	225(0.46)	0.21	0.89
		CG	207(0.42)	215(0.44)		
		GG	57(0.12)	54(0.11)		
	rs1154400	T	666(0.67)	669(0.68)	0.02	0.88
		C	322(0.33)	319(0.32)		
		TT	228(046)	227(0.46	0.20	0.90
		TC	210(0.43)	215(0.44)		
		CC	56(0.11)	52(0.11)		
ALDH1A1	rs8187876	C	868(0.88)	858(0.87)	0.64	0.42
		T	118(0.12)	130(0.13)		

Table 2 (continued)

Gene	SNP-ID	Allelic and Genotypic Frequencies in Cases and Controls				
		Allele/Genotype	Cases ($n = 496$)	Controls ($n = 496$)	Chi-square	*P*-value*
		CC	388(0.79)	376(0.76)	3.43	0.48
		CT	92(0.19)	106(0.21)		
		TT	13(0.03)	12(0.02)		
	rs1888202	C	552(0.56)	580(0.59)	1.37	0.24
		G	430(0.44)	406(0.41)		
		CC	154(0.31)	171(0.35)	1.41	0.49
		CG	244(0.5)	238(0.48)		
		GG	93(0.19)	84(0.17)		
	rs348457	C	518(0.53)	507(0.51)	0.76	0.38
		G	456(0.47)	483(0.49)		
		CC	146(0.3)	138(0.28)	0.71	0.69
		CG	226(0.46)	231(0.47)		
		GG	115(0.24)	126(0.25)		
	rs2773806	T	883(0.89)	888(0.9)	0.06	0.80
		C	105(0.11)	102(0.1)		
		TT	396(0.8)	397(0.8)	0.86	0.64
		TC	91(0.18)	94(0.19)		
		CC	7(0.01)	4(0.01)		
	rs1424482	T	578(0.59)	542(0.55)	3.4	0.05
		C	404(0.41)	448(0.45)		
		TT	179(0.36)	154(0.31)	3.42	0.18
		TC	220(0.45)	234(0.47)		
		CC	92(0.19)	107(0.22)		
	rs63319	T	501(0.53)	526(0.55)	1	0.31
		G	447(0.47)	428(0.45)		
		TT	141(0.3)	154(0.32)	0.93	0.62
		TG	219(0.45)	218(0.44)		
		GG	114(0.24)	105(0.22)		
	rs4745209	T	686(0.7)	650(0.68)	1.68	0.19
		C	288(0.3)	310(0.32)		
		TT	245(0.5)	223(0.46)	15.66	0.33
		TC	196(0.4)	204(0.42)		
		CC	46(0.09)	53(0.11)		
	rs6560311	G	662(0.68)	623(0.64)	2.21	0.13
		T	318(0.32)	345(0.36)		
		GG	231(0.47)	209(0.43)	13.07	0.52
		GT	200(0.41)	205(0.42)		
		TT	59(0.12)	70(0.14)		
	rs4406477	T	554(0.57)	534(0.54)	1.36	0.24
		C	416(0.43)	446(0.46)		
		TT	173(0.36)	148(0.3)	3.93	0.13
		TC	208(0.43)	238(0.49)		

Table 2 (continued)

Gene	SNP-ID	Allelic and Genotypic Frequencies in Cases and Controls				
		Allele/Genotype	Cases ($n = 496$)	Controls ($n = 496$)	Chi-square	*P*-value*
		CC	104(0.21)	104(0.21)		
	rs11143443	T	957(0.97)	967(0.98)	1.98	0.15
		C	31(0.03)	21(0.02)		
		TT	464(0.94)	473(0.96)	2.36	0.30
		TC	29(0.06)	21(0.04)		
		CC	1(0)	0(0)		
	rs1364451	C	859(0.87)	839(0.85)	2.56	0.10
		T	125(0.13)	149(0.15)		
		CC	377(0.77)	360(0.73)	2.26	0.32
		CT	105(0.21)	119(0.24)		
		TT	10(0.02)	15(0.03)		
	rs1418187	G	670(0.68)	660(0.67)	0.2	0.65
		A	318(0.32)	330(0.33)		
		GG	231(0.46)	223(0.45)	0.30	0.85
		GA	208(0.43)	214(0.43)		
		AA	55(0.11)	58(0.12)		
	rs2249978	G	601(0.62)	584(0.6)	1.04	0.30
		A	365(0.38)	390(0.4)		
		GG	196(0.41)	177(0.36)	1.981	0.37
		GA	209(0.43)	230(0.47)		
		AA	78(0.16)	80(0.16)		

P-value <0.05 was considered as significant

Genetic Models and Drug Addiction

Genetic modeling was employed to understand the genotypes' inheritance mode further. Table 3 summarizes the introduced genetic models for ADH5 and ALDH1A1 gene polymorphisms. The tested models included Codominant, Dominant, Recessive, and Over-dominant models. The results show that there was no significant association between different models of inheritance and dominancy within the *ADH5* and *ALDH1A1* genes and drug addiction in general.

Regression analysis

Binary logistic regression analysis assessed the association between disease status and genotype frequencies of the studied polymorphisms, along with various demographic and clinical covariates, including age, smoking status, employment, and marital status. The results, detailed in Supplementary Table 1, identify the factors most likely to predict disease risk. The genotypes of all polymorphisms were not significantly associated with addiction ($P > 0.05$). However, smoking status and employment were significantly associated with SUD. A significant association was found between smoking and an increased risk of addiction ($P < 0.05$), while employed individuals had a lower likelihood of addiction compared to unemployed individuals ($P < 0.05$).

Genetic Haplotype analysis

Haplotyping was also examined as a part of the genetic association analyses in this project. The test was done to assess the effect of the polymorphisms in a block and their relationship with drug addiction. Tables 4 and 5 describe the haplotype blocks within the *ADH5* and *ALDH1A1* genes. The haplotypes CCGTTTTGTTTG G and CCCTTGTGTTCGG of the *ALDH1A1* gene are considered risk factors, as they showed a significant association with drug addiction (P-values = 0.0022 and 0.049, OR = 2.34 and 1.91, respectively). However, the haplotype analysis of *ADH5* variants showed no significant association with addiction.

Table 3 Genetic association analysis of the polymorphisms in drug addiction cases and controls using different genetic models

Gene	SNP-ID	Model	Genotype	Cases (496 %)	Controls (496%)	OR (95% CI)	*P*-Value
ADH5	rs17595424	Codominant	G/G G/T T/T	381 (78.1%) 98 (19.9%) 9 (1.8%)	398 (80.4%) 91 (18.4%) 6 (1.2%)	1.00 0.90 (0.65-1.23) 0.64 (0.23-1.83)	0.59
		Dominant	G/G G/T-T/T	385 (78.2%) 107 (21.8%)	398 (80.4%) 97 (19.6%)	1.00 0.88 (0.64-1.19)	0.4
		Recessive	G/G-G/T T/T	483 (98.2%) 9 (1.8%)	489 (98.8%) 6 (1.2%)	1.00 0.66 (0.23-1.86)	0.43
		Over Dominant	G/G-T/T G/T	394 (80.1%) 98 (19.9%)	404 (81.6%) 91 (18.4%)	1.00 0.91 (0.66-1.24)	0.54
	rs1154414	Codominant	T/T C/T C/C	340 (70.7%) 124 (25.8%) 17 (3.5%)	349 (71.5%) 127 (26%) 12 (2.5%)	1.00 1.00 (0.75-1.33) 0.69 (0.32-1.46)	0.62
		Dominant	T/T C/T-C/C	340 (70.7%) 141 (29.3%)	349 (71.5%) 139 (28.5%)	1.00 0.96 (0.73-1.27)	0.78
		Recessive	T/T-C/T C/C	464 (96.5%) 17 (3.5%)	476 (97.5%) 12 (2.5%)	1.00 0.69 (0.33-1.46)	0.32
		Over Dominant	T/T-C/C C/T	357 (74.2%) 124 (25.8%)	361 (74%) 127 (26%)	1.00 1.01 (0.76-1.35)	0.93
	rs7683704	Codominant	C/C C/T T/T	353 (71.9%) 122 (24.9%) 16 (3.3%)	369 (74.5%) 114 (23%) 12 (2.4%)	1.00 0.89 (0.67-1.20) 0.72 (0.33-1.54)	0.55
		Dominant	C/C C/T-T/T	353 (71.9%) 138 (28.1%)	369 (74.5%) 126 (25.4%)	1.00 0.87 (0.66-1.16)	0.35
		Recessive	C/C-C/T T/T	457 (96.7%) 16 (3.3%)	483 (97.6%) 12 (2.4%)	1.00 0.74 (0.35-1.58)	0.43
		Over Dominant	C/C-T/T C/T	369 (75.2%) 122 (24.9%)	381 (77%) 114 (23%)	1.00 0.90 (0.68-1.21)	0.5
	rs7684986	Codominant	C/C C/T T/T	378 (78.8%) 99 (20.6%) 3 (0.6%)	391 (80.8%) 91 (18.8%) 2 (0.4%)	1.00 0.89 (0.65-1.22) 0.64 (0.11-3.88)	0.69
		Dominant	C/C C/T-T/T	378 (78.8%) 102 (21.2%)	391 (80.8%) 93 (19.2%)	1.00 0.88 (0.64-1.21)	0.43
		Recessive	C/C-C/T T/T	477 (99.4%) 3 (0.6%)	482 (99.6%) 2 (0.4%)	1.00 0.66 (0.11-3.97)	0.65
		Over Dominant	C/C-T/T C/T	381 (79.4%) 99 (20.6%)	393 (81.2%) 91 (18.8%)	1.00 0.89 (0.65-1.22)	0.48
	rs1154405	Codominant	A/A G/A G/G	277 (56.3%) 182 (37%) 33 (6.7%)	267 (54%) 195 (39.5%) 32 (6.5%)	1.00 1.11 (0.85-1.45) 1.01 (0.60-1.68)	0.72
		Dominant	A/A G/A-G/G	277 (56.3%) 215 (43.7%)	267 (54%) 227 (46%)	1.00 1.10 (0.85-1.41)	0.48
		Recessive	A/A-G/A G/G	459 (93.3%) 33 (6.7%))	462 (93.5%) 32 (6.5%)	1.00 0.96 (0.58-1.59)	0.88
		Over Dominant	A/A-G/G G/A	310 (63%) 182 (37%)	299 (60.5%) 195 (39.5%)	1.00 1.11 (0.86-1.44)	0.42
	rs1154401	Codominant	C/C C/G G/G	226 (46.1%) 207 (42.2%) 57 (11.6%)	225 (45.5%) 215 (43.5%) 54 (10.9%)	1.00 1.04 (0.80-1.36) 0.95 (0.63-1.44)	0.9
		Dominant	C/C C/G-G/G	226 (46.1%) 246 (53.9%)	225 (45.5%) 269 (54.5%)	1.00 1.02 (0.80-1.32)	0.86
		Recessive	C/C-C/G G/G	433 (88.4%) 57 (11.6%)	440 (89.1%) 54 (10.9%)	1.00 0.93 (0.63-1.38)	0.73
		Over Dominant	C/C-G/G C/G	283 (57.8%) 207 (42.2%)	279 (56.5%) 215 (43.5%)	1.00 1.05 (0.82-1.36)	0.69
	rs1154400	Codominant	T/T C/T C/C	228 (46.1%) 210 (42.5%) 56 (11.3%)	227 (46%) 215 (43.5%) 52 (10.5%)	1.00 1.03 (0.79-1.34) 0.93 (0.61-1.42)	0.9

Table 3 (continued)

Gene	SNP-ID	Model	Genotype	Cases (496 %)	Controls (496%)	OR (95% CI)	*P*-Value
		Dominant	T/T C/T-C/C	228 (46.1%) 266 (53.9%)	227 (46%) 267 (54%)	1.00 1.01 (0.79-1.29)	0.95
		Recessive	T/T-C/T C/C	438 (88.7%) 56 (11.3%)	442 (89.5%) 52 (10.5%)	1.00 0.92 (0.62-1.37)	0.68
		Over Dominant	T/T-C/C C/T	284 (57.5%) 210 (42.5%)	279 (56.5%) 215 (43.5%)	1.00 1.04 (0.81-1.34)	0.75
ALDH1A1	rs8187876	Codominant	C/C C/T T/T	388 (78.7%) 92 (18.7%) 13 (2.6%)	376 (76.1%) 106 (21.5%) 12 (2.4%)	1.00 1.19 (0.87-1.63) 0.95 (0.43-2.11)	0.54
		Dominant	C/C C/T-T/T	388 (78.7%) 105 (21.3%)	376 (76.1%) 118 (23.9%)	1.00 1.16 (0.86-1.56)	0.33
		Recessive	C/C-C/T T/T	480 (97.4% 13 (2.6%)	482 (97.6%) 12 (2.4%)	1.00 0.92 (0.42-2.04)	0.84
		Over Dominant	C/C-T/T C/T	401 (81.3%) 92 (18.7%)	388 (78.5%) 106 (21.5%)	1.00 1.19 (0.87-1.63)	0.27
	rs1888202	Codominant	C/C C/G G/G	154 (31.4%) 244 (49.7%) 93 (18.9%)	171 (34.7%) 238 (48.3%) 84 (17%)	1.00 0.88 (0.66-1.16) 0.81 (0.56-1.17)	0.49
		Dominant	C/C C/G-G/G	154 (31.4%) 337 (68.6%)	171 (34.7%) 322 (65.3%)	1.00 0.86 (0.66-1.12)	0.27
		Recessive	C/C-C/G G/G	398 (81.1%) 93 (18.9%)	409 (83%) 84 (17%)	1.00 0.88 (0.63-1.22)	0.44
		Over Dominant	C/C-G/G C/G	247 (50.3%) 244 (49.7%)	255 (51.7%) 238 (48.3%)	1.00 0.94 (0.74-1.21)	0.66
	rs348457	Codominant	C/C C/G G/G	146 (30%) 226 (46.4%) 115 (23.6%)	138 (27.9%) 231 (46.7%) 126 (25.4%)	1.00 1.08 (0.80-1.45) 1.16 (0.82-1.63)	0.7
		Dominant	C/C C/G-G/G	146 (30%) 341 (70%)	138 (27.9%) 357 (72.1%)	1.00 1.11 (0.84-1.46)	0.47
		Recessive	C/C-C/G G/G	372 (76.4%) 115 (23.6%)	369 (74.5%) 126 (25.4%)	1.00 1.10 (0.83-1.48)	0.5
		Over Dominant	C/C-G/G C/G	261 (53.6%) 226 (46.4%)	264 (53.3%) 231 (46.7%)	1.00 1.01 (0.79-1.30)	0.93
	rs2773806	Codominant	T/T C/T C/C	396 (80.2%) 91 (18.4%) 7 (1.4%)	397 (80.2%) 94 (19%) 4 (0.8%)	1.00 1.03 (0.75-1.42) 0.57 (0.17-1.96)	0.64
		Dominant	T/T C/T-C/C	396 (80.2%) 98 (19.8%)	397 (80.2%) 98 (19.8%)	1.00 1.00 (0.73-1.36)	0.99
		Recessive	T/T-C/T C/C	487 (98.6%) 7 (1.4%)	497 (99.2%) 4 (0.8%)	1.00 0.57 (0.16-1.95)	0.36
		Over Dominant	T/T-C/C C/T	403 (81.6%) 91 (18.4%)	401 (81%) 94 (19%)	1.00 1.04 (0.75-1.43)	0.82
	rs1424482	Codominant	T/T C/T C/C	179 (36.5%) 220 (44.8%) 92 (18.7%)	154 (31.1%) 234 (47.3%) 107 (21.6%)	1.00 1.24 (0.93-1.64) 1.35 (0.95-1.92)	0.18
		Dominant	T/T C/T-C/C	179 (36.5%) 312 (63.5%)	154 (31.1%) 341 (68.9%)	1.00 1.27 (0.98-1.66)	0.076
		Recessive	T/T-C/T C/C	399 (81.3%) 92 (18.7%)	388 (78.4%) 107 (21.6%)	1.00 1.20 (0.88-1.63)	0.26
		Over Dominant	T/T-C/C C/T	271 (55.2%) 220 (44.8%)	261 (52.7%) 234 (47.3%)	1.00 1.10 (0.86-1.42)	0.44
	rs63319	Codominant	T/T G/T G/G	141 (29.8%) 219 (46.2%) 114 (24.1%)	154 (32.3%) 218 (45.7%) 105 (22%)	1.00 0.91 (0.68-1.22) 0.84 (0.59-1.20)	0.63
		Dominant	T/T G/T-G/G	141 (29.8%) 333 (70.2%)	154 (32.3%) 323 (76.7%)	1.00 0.89 (0.67-1.17)	0.4
		Recessive	T/T-G/T G/G	360 (76%) 114 (24.1%)	372 (78%) 105 (22%)	1.00 0.89 (0.66-1.21)	0.46

Table 3 (continued)

Gene	SNP-ID	Model	Genotype	Cases (496 %)	Controls (496%)	OR (95% CI)	*P*-Value
		Over Dominant	T/T-G/G G/T	255 (53.8%) 219 (46.2%)	259 (54.3%) 218 (45.7%)	1.00 0.98 (0.76-1.26)	0.88
	rs4745209	Codominant	T/T C/T C/C	245 (50.3%) 196 (40.2%) 46 (9.4%)	223 (46.5%) 204 (42.5%) 53 (11%)	1.00 1.14 (0.88-1.49) 1.27 (0.82-1.95)	0.44
		Dominant	T/T C/T-C/C	245 (50.3%) 242 (49.7%)	223 (46.5%) 257 (53.5%)	1.00 1.17 (0.91-1.50)	0.23
		Recessive	T/T-C/T C/C	441 (90.5%) 46 (9.4%)	427 (89%) 53 (11%)	1.00 1.19 (0.78-1.81)	0.41
		Over Dominant	T/T-C/C C/T	291 (59.8%) 196 (40.2%)	276 (57.5%) 204 (42.5%)	1.00 1.10 (0.85-1.42)	0.48
	rs6560311	Codominant	G/G G/T T/T	231 (47.1%) 200 (40.8%) 59 (12%)	209 (43.2%) 205 (42.4%) 70 (14.5%)	1.00 1.13 (0.86-1.48) 1.31 (0.88-1.94)	0.36
		Dominant	G/G G/T-T/T	231 (47.1%) 259 (52.9%)	209 (43.2%) 275 (56.8%)	1.00 1.17 (0.91-1.51)	0.21
		Recessive	G/G-G/T T/T	431 (88%) 59 (12%)	414 (85.5%) 70 (14.5%)	1.00 1.24 (0.85-1.79)	0.26
		Over Dominant	G/G-T/T G/T	290 (59.2%) 200 (40.8%)	279 (57.6%) 205 (42.4%)	1.00 1.07 (0.83-1.37)	0.63
	rs4406477	Codominant	T/T C/T C/C	173 (35.7%) 208 (42.9%) 104 (21.4%)	148 (30.2%) 238 (48.6%) 104 (21.2%)	1.00 1.34 (1.00-1.78) 1.17 (0.82-1.66)	0.14
		Dominant	T/T C/T-C/C	173 (35.7%) 312 (64.3%)	148 (30.2%) 342 (69.8%)	1.00 1.28 (0.98-1.67)	0.07
		Recessive	T/T-C/T C/C	381 (78.6%) 104 (21.4%)	386 (78.8%) 104 (21.2%)	1.00 0.99 (0.73-1.34)	0.93
		Over Dominant	T/T-C/C C/T	277 (57.1%) 208 (42.9%)	252 (51.4%) 238 (48.6%)	1.00 1.26 (0.98-1.62)	0.08
	rs11143443	Codominant	T/T C/T CC	464 (93.9%) 29 (5.9%) 1 (0.2%)	473 (95.8%) 21 (4.2%) 0 (0%)	1.00 0.71 (0.40-1.26) NA (0.00-NA)	0.25
		Dominant	T/T C/T-C/C	464 (93.9%) 30 (6.1%)	473 (95.8%) 21 (4.2%)	1.00 0.69 (0.39-1.22)	0.19
		Recessive	T/T-C/T C/C	493 (99.8%) 1 (0.2%)	494 (100%) 0 (0%)	1.00 NA (0.0-NA)	0.24
		Over Dominant	T/T-C/C C/T	465 (94.1%) 29 (5.9%)	473 (95.8%) 21 (4.2%)	1.00 0.71 (0.40-1.27)	0.24
	rs1364451	Codominant	C/C T/C T/T	377 (76.6%) 105 (21.3%) 10 (2%)	360 (72.9%) 119 (24.1%) 15 (3%)	1.00 1.19 (0.88-1.60) 1.57 (0.70-3.54)	0.32
		Dominant	C/C T/C-T/T	377 (76.6%) 115 (23.4%)	360 (72.9%) 134 (27.1%)	1.00 1.22 (0.91-1.63)	0.18
		Recessive	C/C-T/C T/T	478 (98%) 10 (2%)	475 (96.9%) 15 (3%)	1.00 1.51 (0.67-3.39)	0.31
		Over Dominant	C/C-T/T T/C	387 (78.9%) 105 (21.3%)	375 (75.9%) 119 (24.1%)	1.00 1.17 (0.87-1.58)	0.27
	rs1418187	Codominant	G/G G/A A/A	231 (46.8%) 208 (42.1%) 55 (11.1%)	223 (45%) 214 (43.2%) 58 (11.7%)	1.00 1.07 (0.82-1.39) 1.09 (0.72-1.65)	0.86
		Dominant	G/G G/A-A/A	231 (46.8%) 263 (53.2%)	223 (45%) 272 (55%)	1.00 1.07 (0.83-1.38)	0.59
		Recessive	G/G-G/A A/A	439 (88.9%) 55 (11.1%)	437 (88.3%) 58 (11.7%)	1.00 0.92 (0.62-1.37)	0.77
		Over Dominant	G/G-A/A G/A	286 (57.9%) 208 (42.1%)	281 (56.8%) 214 (43.2%)	1.00 0.99 (0.77-1.27)	0.72

Table 3 (continued)

Gene	SNP-ID	Model	Genotype	Cases (496 %)	Controls (496%)	OR (95% CI)	*P*-Value
	rs2249978	Codominant	G/G G/A A/A	196 (40.6%) 209 (43.3%) 78 (16.1%)	177 (36.3%) 230 (47.2%) 80 (16.4%)	1.00 0.82 (0.62-1.08) 0.88 (0.61-1.28)	0.37
		Dominant	G/G G/A-A/A	196 (40.6%) 287 (59.4%)	177 (36.3%) 310 (63.7%)	1.00 0.84 (0.65-1.08)	0.18
		Recessive	G/G-G/A A/A	405 (83.8%) 78 (16.1%)	407 (83.6%) 80 (16.4%)	1.00 0.98 (0.70-1.38)	0.91
		Over Dominant	G/G-A/A G/A	274 (56.7%) 209 (43.3%)	257 (52.8%) 230 (47.2%)	1.00 0.85 (0.66-1.10)	0.22

P-value <0.05 was considered as significant

OD Odd ratio, *CI* Confidence interval

Table 4 Haplotype analysis of ADH5 gene variants (rs1759542, rs1154414, rs7683704, rs7684986, rs1154405, rs1154401, rs1154400)

4	Frequency	OR (95% CI)	*P*-value
GTCCACT	0.5134	1	---
GCCCACT	0.1549	0.95 (0.74 - 1.23)	0.71
GTCCGGC	0.1431	1.19 (0.91 - 1.55)	0.2
TTTTGGC	0.1058	0.87 (0.65 - 1.18)	0.37
GTTCAGC	0.0371	0.91 (0.56 - 1.46)	0.68
GTCCAGC	0.0262	0.73 (0.41 - 1.28)	0.27

P value < 0.05 was considered significant

Table 5 Haplotype analysis of ALDH1A1 gene variants (rs8187876, rs1888202, rs348457, rs2773806, rs1424482, rs63319, rs4745209, rs6560311, rs4406477, rs1114344, rs1364451, rs1418187, and rs2249978)

Haplotype	Frequency	OR (95% CI)	*P-value*
CGCTTGTGTTCGG	0.2757	1	----
CCGTCTCTCTCAA	0.1374	1.10 (0.82 - 1.49)	0.51
CCGTTTTGTTCGG	0.1096	0.93 (0.67 - 1.30)	0.68
TCGTCTCTCTCAA	0.0671	1.19 (0.81 - 1.76)	0.37
CCGTTTTGTTTGG	0.0369	2.34 (1.36 - 4.02)	0.0022
CCGTCTTTCTCGA	0.0308	1.55 (0.91 - 2.63)	0.11
CCCTTGTGTTCGG	0.0284	1.91 (1.00 - 3.64)	0.049
TGCCCGCTCTCAA	0.0259	1.32 (0.74 - 2.36)	0.34
CGCTTGTGCTCGG	0.0217	1.18 (0.64 - 2.20)	0.59
CCCTTTTGTTCGG	0.0206	1.32 (0.69 - 2.51)	0.4
CCGTTTTGCTTGG	0.0115	1.07 (0.44 - 2.60)	0.87
CGCCCGTGTTTGG	0.0105	1.98 (0.73 - 5.35)	0.18
CCCTCGCTCTCAA	0.0103	2.09 (0.75 - 5.86)	0.16

P value < 0.05 was considered significant

The linkage disequilibrium (LD) analysis

The linkage disequilibrium (LD) analysis of 13 SNPs within the *ALDH1A1* gene, as presented in Supplementary Table 2, reveals varying degrees of association among the genetic markers, with strong LD observed between several SNP pairs. Notably, rs8187876 and rs1424482 exhibit near-complete LD (D' = 0.9993), indicating a high likelihood of co-inheritance. Similarly, rs8187876 and rs11143443 display strong LD (D' = 0.9876), suggesting close linkage in this genomic region. Statistically significant P-values for most SNP pairs ($P < 0.05$) underscore the relevance of the observed LD, particularly for pairs such as rs8187876/rs1888202 ($P = 1e\text{-}04$) and rs348457/rs2773806 ($P = 0$), confirming their non-random association. In contrast, weaker LD is observed between some SNPs, such as rs348457 and rs1364451 (D' = 0.0423, $P = 0.4328$), indicating minimal correlation between these loci.

The linkage disequilibrium (LD) analysis of 7 SNPs within the *ADH5* gene, as presented in Supplementary Table 3, reveals a strong correlation between most SNP pairs, as indicated by high D' values approaching 1. This suggests that most SNP combinations exhibit strong LD, implying a high probability of co-inheritance. Statistically significant *P*-values ($P < 0.001$) for all pairs further confirm that these LD patterns are unlikely to occur by chance. Notably, one SNP pair, rs7683704 and rs1154405, show moderate LD (D' = 0.6314), while all other pairs display powerful LD, such as rs17595424 and rs1154414 (D' = 0.9961). These findings suggest that the SNPs are likely located within the same haplotype block, characterized by low recombination rates, and may be inherited together in population studies.

Discussion

Genetic polymorphisms of the enzymes that are involved in alcohol metabolism are an essential factor in developing alcoholism, alcohol damage to the digestive organs, and drug addiction. It is highly ethnically and race-dependent. Several studies showed that *ADH* genes are important risk factors for alcohol dependence in different

populations, specifically *ADH5*, *ADH6, ADH1A, ADH1B, ADH1C, and ADH7* also have moderate risk for drug addiction. This study examined the association between twenty SNPs from *ADH5* and *ALDH1A1* and drug addiction in the Jordanian population for the first time.

This study was composed of 496 addicted male participants and 496 healthy controls from the Jordanian Arab population. The relationship between *ADH5* and *ALDH1A1* and alcohol dependence has been reported in several linkage studies of diverse ethnic groups, including Native Americans [37]. Several studies on the Jordanian population have suggested a potential correlation between different genetic polymorphisms and drug addiction [38–40].

However, there was no observed correlation between ADH5 and ALDH1A1 polymorphisms and drug addiction in Jordanian males. This could be explained by the cultural awareness towards drug addicts, thus leading to fewer chances of marriage with a gene polymorphism carrier. This will eventually lead to less continuity of the polymorphism in the population, which could lead to the isolation of related polymorphisms from the population over time.

It was observed that rare genotypes of six polymorphisms of the *ALDH1A1* gene, including rs1424482, rs1888202, rs348461, rs63319, rs7027604, and rs722921, were associated with poorer overall survival among Hispanics [41]. In our study, no significant association was observed between these variants and addiction in the Jordanian population. The *ALDH1A1* gene is associated with alcohol-induced flushing, alcohol sensitivity, and dependence in Finnish Caucasians [41]. The MAF of rs1154414 subjects in the IASPSAD study was 0.09 and 0.15 in the Finnish Caucasians. However, the MAF in controls was the same in both studies (0.12). In our research, the MAF of these SNPs was 0.33 for both controls and patients in the Jordanian population [42, 43].

Another coding SNP that has previously shown an association with alcoholism in Irish populations was rs1154414, located in intron 4 of the *ADH5* gene (OR = 1.48, $p = 0.004$) [29, 42]. Another study in both European- and African Americans reported a significant association for ADH5 marker rs1154400 using genotypic tests [29], but these associated genotypes were opposite to those found in our study, which showed no significant association in the Jordanian population; this may be because of a multi-locus effect in *ADH5*.

According to Liu et al., a study on ALDH1A1 SNPs (rs3819197, rs1229967, rs13134764, rs904092) revealed a significant association between an ALDH1A1 haplotype and alcohol dependence (AD) in Southwest American Indians. In Finnish populations, haplotypes from blocks 1 and 2 (spanning intron 5 to the 3' UTR) showed significant association with AD, driven by SNPs rs3764435 and rs2303317. A similar association in Southwest Indians was found in block 3 (which includes the promoter region), with five SNPs showing allelic identity [42]. In our study, two haplotypes of the *ALDH1A1* gene were found to be associated with substance use disorder (SUD) and identified as risk factors (*P*-values = 0.0022 and 0.049, OR = 2.34 and 1.91, respectively). Additionally, the linkage disequilibrium (LD) analysis of SNPs within the *ALDH1A1* gene revealed varying degrees of association among genetic markers, with a particularly strong LD observed between rs8187876 and rs1424482 (D' = 0.9993) and between rs8187876 and rs11143443 (D' = 0.9876), indicating a high likelihood of co-inheritance and close genomic linkage.

Future research should include a broader spectrum of drug addiction-related genes, neurodevelopment genes, and even tumor suppressor genes, as these biological processes have long been correlated with substance abuse as a post-effect. Although no significant association was discovered in the Jordanian population, the results of the current study could aid in the development of a new personalized medicine approach for drug addiction and substance dependence.

Conclusion

In this study, the result of the association study was presented between 20 variants of two candidate genes (*ADH5* and *ALDH1A1*) and substance abuse in the Jordanian population. The analysis revealed no significant association between the studied SNPs and Jordanian-addicted participants. One problem with the case-control design is that genotype and haplotype frequencies vary between ethnic or geographic populations. Suppose the case and control populations must be better matched for ethnicity or geographic origin. Although the effect of the genetic factors on the overall problem of drug dependence is modest, these polymorphisms likely contribute to the inter-individual variation in substance abuse disorder susceptibility and subsequent risk for addiction. Combinations of polymorphisms in genes involved in both stages of drug metabolism may also interact to affect substance abuse-related behavior. Our study group is small, and genetic stratification is possible. Therefore, it is essential to replicate these results in larger samples and different populations. In addition, further genotyping of the other ADH gene polymorphisms will be required to investigate the possible linkage with addiction.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12864-025-11379-2.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

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Authors' contributions
L.N.A.: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Visualization, Supervision, Project administration, Funding acquisition, Writing – review & editing. A.H.M.: Formal analysis, Investigation, writing review, and editing. M.A.A: Formal analysis, Investigation, Resources, writing – original draft, writing review, and editing.

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Data availability
All data generated or analyzed during this study are included in this published article and the supplementary information.

Declarations

Ethics approval and consent to participate
The study and methodology were approved by the Human Ethics Committee of the Jordanian Ministry of Health (MOH/REC/180057) and the Institutional Review Board/Human Research Ethics Committee at Jordan University of Science and Technology (43/114/2018). The Public Security Directorate reviewed and approved the study (C/2/46/21546). Written informed consent was obtained from all participants in this study as their approval of participation. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki/).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Zou Z, Wang H, d'Oleire Uquillas F, Wang X, Ding J, Chen H. Definition of Substance and Non-substance Addiction. Adv Exp Med Biol. 2017;1010:21–41.
2. Volkow ND, Li T-K. Drug addiction: the neurobiology of behaviour gone awry. Nature Reviews Neuroscience. 2004;5(12):963–70.
3. Day E. Facing addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, OFFICE OF THE SURGEON GENERAL Washington, DC, USA: U.S. Department of Health and Human Services, 2016 382 pp. Online (grey literature): https://addiction.Surgeongeneral.Gov/. Drug Alcohol Rev. 2018;37(2):283-284.
4. United Nations Office on Drugs and Crime. 2012. World Drug Report 2012. Vienna: United Nations.
5. Jadidi N, Nakhaee N. Etiology of drug abuse: a narrative analysis. J Addict. 2014;2014:352835–352835.
6. Nakhaee N, Jadidi N. Why Do Some Teens Turn to Drugs? A Focus Group Study of Drug Users' Experiences. Journal of Addictions Nursing. 2009;20(4):203–8.
7. Crabbe JC. Genetic Contributions to Addiction. Annual Review of Psychology. 2002;53(1):435–62.
8. Prom-Wormley EC, Ebejer J, Dick DM, Bowers MS. The genetic epidemiology of substance use disorder: A review. Drug Alcohol Depend. 2017;180:241–59.
9. Al-Eitan L, Tarkhan A. Practical Challenges and Translational Issues in Pharmacogenomics and Personalized Medicine from 2010 Onwards. Current Pharmacogenomics and Personalized Medicine. 2017;14(1):7–17.
10. Al-Eitan L, Jaradat S, Hulse G, Tay G. Pharmacogenetic Approach to Treating Drug Dependence: Serotonin Transporter Gene (SLC6A4) Promoter Polymorphisms as Treatment Predictors in Jordanian Arabs. Current Pharmacogenomics and Personalized Medicine. 2012;10(4):293–305.
11. Bevilacqua L, Goldman D. Genes and addictions. Clin Pharmacol Ther. 2009;85(4):359–61.
12. Goldman D, Oroszi G, Ducci F. The genetics of addictions: uncovering the genes. Nature Reviews Genetics. 2005;6(7):521–32.
13. Zhou H, Sealock JM, Sanchez-Roige S, Clarke TK, Levey DF, Cheng Z, Li B, Polimanti R, Kember RL, Smith RV, et al. Genome-wide meta-analysis of problematic alcohol use in 435,563 individuals yields insights into biology and relationships with other traits. Nat Neurosci. 2020;23(7):809–18.
14. Sun Y, Chang S, Wang F, Sun H, Ni Z, Yue W, Zhou H, Gelernter J, Malison RT, Kalayasiri R, et al. Genome-wide association study of alcohol dependence in male Han Chinese and cross-ethnic polygenic risk score comparison. Transl Psychiatry. 2019;9(1):249.
15. Martin AR, Gignoux CR, Walters RK, Wojcik GL, Neale BM, Gravel S, Daly MJ, Bustamante CD, Kenny EE. Human Demographic History Impacts Genetic Risk Prediction across Diverse Populations. Am J Hum Genet. 2017;100(4):635–49.
16. Li D, Zhao H, Gelernter J. Strong association of the alcohol dehydrogenase 1B gene (ADH1B) with alcohol dependence and alcohol-induced medical diseases. Biol Psychiatry. 2011;70:504–12.
17. Li D, Zhao H, Gelernter J. Strong protective effect of the aldehyde dehydrogenase gene (ALDH2) 504lys (*2) allele against alcoholism and alcohol-induced medical diseases in Asians. Hum Genet. 2012;131:725–37.
18. Edenberg HJ. The genetics of alcohol metabolism: role of alcohol dehydrogenase and aldehyde dehydrogenase variants. Alcohol Res Health. 2007;30(1):5–13.
19. Walter MC, Rattei T, Arnold R, Güldener U, Münsterkötter M, Nenova K, Kastenmüller G, Tischler P, Wölling A, Volz A, et al. PEDANT covers all complete RefSeq genomes. Nucleic Acids Res. 2009;37(Database issue):D408–11.
20. Yokoyama H, Baraona E, Lieber CS. Molecular Cloning and Chromosomal Localization of theADH7Gene Encoding Human Class IV (σ) ADH. Genomics. 1996;31(2):243–5.
21. Rieder MJ, Livingston RJ, Stanaway IB, Nickerson DA. The Environmental Genome Project: Reference Polymorphisms for Drug Metabolism Genes and Genome-Wide Association Studies. Drug Metabolism Reviews. 2008;40(2):241–61.
22. Zhang J, Yin LH, Pu YP. Using Immortalized Human Lymphocytes Cell Lines to Screen the Genetic Markers of ADH5 to Formaldehyde. Applied Mechanics and Materials. 2012;195–196:465–8.
23. Luo X, Kranzler HR, Zuo L, Wang S, Schork NJ, Gelernter J. Multiple ADH genes modulate risk for drug dependence in both African- and European-Americans. Hum Mol Genet. 2007;16(4):380–90.
24. Vasiliou V, Nebert DW. Analysis and update of the human aldehyde dehydrogenase (ALDH) gene family. Hum Genomics. 2005;2(2):138–43.
25. Ramchandani V, Bosron W, Li T. Research advances in ethanol metabolism. Pathologie Biologie. 2001;49(9):676–82.
26. Goedde HW, Agarwal DP, Fritze G, Meier-Tackmann D, Singh S, Beckmann G, Bhatia K, Chen LZ, Fang B, Lisker R, et al. Distribution of ADH2 and ALDH2 genotypes in different populations. Hum Genet. 1992;88(3):344–6. https://doi.org/10.1007/BF00197271.

27. Oota H, Pakstis AJ, Bonne-Tamir B, Goldman D, Grigorenko E, Kajuna SLB, Karoma NJ, Kungulilo S, Lu RB, Odunsi K, et al. The evolution and population genetics of the ALDH2 locus: random genetic drift, selection, and low levels of recombination. Annals of Human Genetics. 2004;68(2):93–109.
28. Osier M, Pakstis AJ, Kidd JR, Lee JF, Yin SJ, Ko HC, Edenberg HJ, Lu RB, Kidd KK. Linkage disequilibrium at the ADH2 and ADH3 loci and risk of alcoholism. Am J Hum Genet. 1999;64(4):1147–57.
29. Kuo P-H, Kalsi G, Prescott CA, Hodgkinson CA, Goldman D, van den Oord EJ, Alexander J, Jiang C, Sullivan PF, Patterson DG, et al. Association of ADH and ALDH genes with alcohol dependence in the Irish Affected Sib Pair Study of alcohol dependence (IASPSAD) sample. Alcohol Clin Exp Res. 2008;32(5):785–95.
30. Al-Eitan LN, Jaradat SA, Qin W, Wildenauer DMB, Wildenauer DD, Hulse GK, Tay GK. Characterization of serotonin transporter gene (SLC6A4) polymorphisms and its association with drug dependence in a Jordanian Arab population. Toxicology and Industrial Health. 2014;30(7):598–610.
31. Al-Eitan LN, Jaradat SA, Su SY, Tay GK, Hulse GK. Mu opioid receptor (OPRM1) as a predictor of treatment outcome in opiate-dependent individuals of Arab descent. Pharmgenomics Pers Med. 2012;5:99–111. https://doi.org/10.2147/PGPM.S33351.
32. Al-Eitan L, Jaradat S, Dadour I, Tay G, Hulse G. Polymorphisms in the u-opioid receptor gene in Jordanian arabs with opiate drug dependence. ScienceMED. 2012;3(2):91–7.
33. N Al-Eitan L, A Haddad Y: Emergence of pharmacogenomics in academic medicine and public health in Jordan: History, present state and prospects. Current Pharmacogenomics and Personalized Medicine (Formerly Current Pharmacogenomics) 2014,12(3):167-175.
34. Lind PA, Eriksson CP, Wilhelmsen KC. The role of aldehyde dehydrogenase-1 (ALDH1A1) polymorphisms in harmful alcohol consumption in a Finnish population. Hum Genomics. 2008;3:1–12.
35. National Center for Biotechnology Information. dbSNP: Short Genetic Variations. National Library of Medicine, National Institutes of Health. 2024. https://www.ncbi.nlm.nih.gov/snp/.
36. Ensembl. Ensembl Genome Browser. European Bioinformatics Institute (EMBL-EBI). 2024. https://asia.ensembl.org/.
37. Ehlers CL, Gizer IR. Evidence for a genetic component for substance dependence in Native Americans. Am J Psychiatry. 2013;170(2):154–64.
38. Al-Eitan L, Shatnawi M, Alghamdi M. Investigating CHRNA5, CHRNA3, and CHRNB4 variants in the genetic landscape of substance use disorder in Jordan. BMC psychiatry. 2024;24(1):436.
39. Al-Eitan LN. Rababa'h DM, Alghamdi MA: Genetic susceptibility of opioid receptor genes polymorphism to drug addiction: A candidate-gene association study. BMC psychiatry. 2021;21:1–14.
40. Al-Eitan LN, Jaradat SA, Hulse GK, Tay GK. Custom genotyping for substance addiction susceptibility genes in Jordanians of Arab descent. BMC Res Notes. 2012;5:1–11.
41. Xia Z, Baumgartner KB, Baumgartner RN, Boone SD, Hines LM, John EM, Wolff R, Slattery ML, Connor AE. Associations between ALDH1A1 polymorphisms, alcohol consumption, and mortality among Hispanic and non-Hispanic white women diagnosed with breast cancer: the Breast Cancer Health Disparities Study. Breast Cancer Research and Treatment. 2018;168:443–55.
42. Liu J, Zhou Z, Hodgkinson CA, Yuan Q, Shen PH, Mulligan CJ, Wang A, Gray RR, Roy A, Virkkunen M: Haplotype-based study of the association of alcohol-metabolizing genes with alcohol dependence in four independent populations. Alcoholism: Clinical and Experimental Research 2011, 35(2):304-316.
43. Li D, Zhao H, Gelernter J. Strong association of the alcohol dehydrogenase 1B gene (ADH1B) with alcohol dependence and alcohol-induced medical diseases. Biol Psychiatry. 2011;70(6):504–12.

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