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The Forensic Genetic Profiling of Alcoholism within the Iraqi Population

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Abstract

Background. Alcoholism is a multifaceted condition shaped by the interaction of hereditary, environmental, and behavioral elements, affecting gene expression and cellular pathways. Short tandem repeats (STRs) function as essential genetic markers, providing insights into genetic predispositions and population-level changes linked to alcohol consumption. **Aim.** This study examines the genetic diversity and forensic utility of STR markers in Iraqi communities. **Methods.** The examined autosomal STRs, encompassing essential CODIS loci, through a five-color fluorescence detection technique to evaluate allele frequency, heterozygosity, and regional genetic variation. The findings indicate considerable variability in allele frequencies, with departures from Hardy-Weinberg equilibrium (HWE) at specific loci, implying effects from genetic drift, population structure, or selective pressures. **Results**. There was not much difference between areas regarding allelic variation, average allele count, and allelic size ranges. However, some loci (DYS391) showed changes in regional frequency that past migration patterns and demographic effects may have caused. Hardy-Weinberg equilibrium calculation revealed that loci 7 and 23 regularly deviated from equilibrium across all regions. This could be because of selection pressures or non-random mating. Statistical tests of forensic efficiency parameters such as MP, PD, and PE showed that loci like Penta E, D16S539, and D18S51 help exclude individuals. At the same time, markers like DYS391 had lower exclusion capacity, especially in certain areas. **Conclusion**. This work elucidates the relationship between regional genetic variation and environmental influences, enhancing comprehension of the genetic underpinnings of alcohol dependency in ethnically varied communities. These findings have implications for personalized therapy and the development of predictive biomarkers for alcohol dependence.

Keywords: Y-STR, genetic diversity, Forensic statistical parameter, Iraq, population genetics.
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Introduction

Short tandem repeats (STRs) are highly variable sequences distributed across the human genome, consisting of repeated units of a 1–6 base pair motif. More than 1 million variable STR loci have been identified, some of which modulate gene expression and affect complex phenotypes, including height. Short tandem repeats (STRs) are extensively variable sequences within the human genome (1). Short tandem repeats (STRs) exhibit mutation rates significantly higher than those of base substitutions and are prevalent in functional regions of genomes (2, 3). Some studies have indicated that variations in STR tract lengths may be associated with differences in environmental factors (4, 5).

Y chromosome markers are crucial instruments in forensic

genetics, providing significant insights into genetic identity for criminal investigations and legal proceedings. Additionally, these genetic markers are extensively utilized in genealogical research, anthropology, and population genetics, aiding in tracing paternal lineages and understanding population structures and migrations (6, 7).

STR detection technology has rapidly become a cornerstone of forensic DNA analysis due to its ability to identify individuals based on genetic differences. STRs repeat relatively short DNA sequences, making them ideal for multiplex amplification since the annealing temperatures for these fragments are similar. This technology has evolved by incorporating fluorescent markers and advanced genetic analyzers, allowing for fully automated and high-throughput forensic DNA testing. It enhances the discriminatory power linked to their typing and analytical methods. The enhancement of discriminatory power has primarily been achieved by introducing novel, highly polymorphic STRs and advancing larger multiplex panels. The discrimination power can be enhanced through additional characterization beyond the nominal length of alleles at existing loci. STR alleles are characterized by the number of units in their repeat motifs, a distinction typically determined through size separation via capillary electrophoresis (CE). Other detection methods, including Sanger sequencing and mass spectrometry, have been employed to ascertain STR alleles' size and nucleotide composition (8, 9). With advancements in CE technology, commercial kits that detect 20–27 Y-STRs in a single reaction were introduced in 2015(10). This study aims to investigate the association between specific short tandem repeat (STR) loci and alcohol addiction to identify potential genetic markers that contribute to susceptibility. By analyzing the frequency and distribution of these loci in alcohol-dependent individuals compared to a control group, we aim to understand their role in predisposing factors, uncover possible biological mechanisms, and explore their potential as predictive biomarkers for early detection and personalized interventions.

Methods

Study design and ethical aseptic

This study sought to examine the forensic genetic profiling of alcoholism within the Iraqi population, focusing on autosomal short tandem repeat frequencies at 23 loci. The samples 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 about their residence. The groups included 50 samples from alcohol-dependent individuals in southern Iraq (specifically from Basra, Nasiriya, and A 'Amara), 100 samples from alcohol-dependent individuals in central Iraq or called Furat awsat (including 50 from Najaf, Karbala, and 50 samples from Samawah), and Diwaniyah, and 50 samples from alcohol-dependent individuals in northern Iraq (comprising Mosul, Salahuddin, and Diyala). Additionally, 50 samples as a control group. Peripheral blood samples were collected using FTA cards from 250 unrelated individuals. This study excluded participants who consumed alcohol inconsistently or intermittently, as well as individuals who were both alcoholics and drug addicts. Moreover, the study excluded men

with chronic conditions such as cardiovascular disease, diabetes mellitus, kidney failure, or hypertension. As well as all alcohol-dependent and controlled participants in the study provided informed written consent. The research was undertaken at Al-Nahrain University's Forensic DNA Centre and Training from January to August 2024. The Ethics Committee of the Medical City Hospital and the University of Baghdad's Committee for Postgraduate Studies both sanctioned the experiment.

Sample collection and selection

Each participant provided about 4 mL of peripheral blood for the sample collection. The 3 mL of peripheral blood (PB) was transferred to an EDTA tube for further molecular analysis. The PB samples were preserved at -20 °C to facilitate further DNA extraction.

Molecular analysis

DNA extraction methods

DNA was extracted using the Chelex extraction method and differential lysis. The sample and 1 ml of TE buffer were combined in an autoclaved tube and stirred gently. Subsequently, incubate at room temperature for 15 to 30 minutes, with frequent agitation. After centrifugation for three minutes, the majority of the supernatant was cautiously removed. Chelex (5%) was added into a final volume of 200 µl. The specimen was incubated at 56ºC for 15 to 30 minutes, vortexed at high velocity for 5 to 10 seconds, and incubated in a boiling water bath for 8 minutes. The sample was vortexed again and centrifuged for 2 to 3 minutes. The supernatant was used for measurement and/or PCR amplification. The remainder was preserved at 2 to 8°C or frozen for subsequent use(11).

DNA quantification methods

DNA quantification was carried out using the qPCR method. Calibration standards were often created using the human DNA standard used for qPCR quantification. The concentrations applied were: 50 ng/µl, 5 ng/µl, 0.5 ng/µl, 0.05 ng/µl, and a TE-4 blank. A 100 ng/µl standard may also be prepared optionally.

The calibration standards were prepared using the 200 ng/µl human DNA standard. For DNA quantification, the qPCR master mix was formulated with an additional approximately 5% to accommodate pipetting variability. According to the reaction volume, either 23 µl (for 25 µl reactions) or 11.5 µl (for 12.5 µl reactions) of the PCR mixture was allocated to each well of the optical plate. Subsequently, 2 µl (for 25 µl reactions) or 1 µl (for 12.5 µl reactions) of the sample, standard, or control was introduced into the designated wells, generally in duplicate. The response plate was sealed with an optical adhesive cover, and if air bubbles were suspected, it was audible. A plate record was generated in the 7500 SDS program utilizing a specified naming convention and stored on the assigned computer.

PCR amplification

Y-chromosome molecular markers were amplified using the PCR (Polymerase Chain Reaction) technique with the AmpFlSTR Yfiler™ kit (Promega, USA). For the amplification of autosomal short tandem repeat (STR) markers, the AmpFlSTR Identifiler™ and PowerPlex Fusion (Promega®) kits were utilized, following the manufacturer's protocols.

Capillary electrophoresis

The amplified products were separated using the capillary electrophoresis Genetic Analyzer 3130xl or Genetic Analyzer 3500 (Applied Biosystems, USA). The results were analyzed using GeneMapper® ID Software (Applied Biosystems, USA).

Data analysis

For the study objective, association analysis can be used to identify statistically significant relationships between specific alleles and addiction. This involves comparing the frequencies of these alleles between individuals with addiction and a control group to detect potential differences.

Results

Table (1) revealed The Hardy-Weinberg equilibrium (HWE) calculation for the South region of Iraq, which is a broad spectrum of observed heterozygosity (Obs. Het) and expected heterozygosity (Exp. Het) among populations. Meanwhile, the frequency of the south population ranges from (0.44) DYS391 to (0.01) FGA.

Table (1): Hardy-Weinberg equilibrium of the south region individuals.

Hardy -Weinberg equilibrium : (South)				
Locus	**Obs. Het.**	**Exp. Het.**	**P-value**	**s. d.**
1	0.8	0.78141	0.28506	0.00037
2	0.84	0.83778	0.55202	0.00048
3	0.88	0.80101	0.02853	0.00014
4	1	0.78283	0.00057	0.00002
5	0.72	0.76545	0.01143	0.00009
6	1	0.91212	0.23965	0.00027
7	1	0.80141	0.00088	0.00003
8	1	0.87596	0.4681	0.00047
9	1	0.8804	0.05534	0.00016
10	0.56	0.71253	0.06421	0.00026
11	0.82	0.78182	0.488	0.00043
12	0.78	0.80505	0.11284	0.00029
13	0.72	0.76545	0.01065	0.00012
14	0.7	0.8103	0.03017	0.00018
15	0.84	0.86606	0.20336	0.00027
16	0.78	0.83475	0.54004	0.00044
17	0.8	0.79071	0.48601	0.00051
18	0.74	0.71677	0.16506	0.00032
19	0.8	0.87091	0.03182	0.00019
20	0.76	0.76485	0.37384	0.00046
21	1	0.86303	0.6781	0.00053
22	0.82	0.87495	0.15544	0.00025
23	1	0.80929	0.02701	0.00014

Table (2) shows a notable deviation from Hardy-Weinberg equilibrium (HWE) in the Furat Awsat population. While the frequency of The Furat Awsat population ranges from the lowest frequency (0.01) FGA to the highest frequency (0.48) DYS391.

Table (2): Hardy-Weinberg equilibrium of furat awsat region individuals.

Hardy Weinberg equilibrium : (furat awsat)				
Locus	**Obs. Het.**	**Exp. Het.**	**P-value**	**s. d.**
1	0.8	0.82889	0.47148	0.00057
2	0.84	0.83838	0.39307	0.00042
3	0.72	0.80646	0.40951	0.00039
4	0.86	0.86303	0.00023	0.00002
5	0.86	0.79596	0.75284	0.00036
6	1	0.91253	0.17275	0.0003
7	1	0.80566	0.00937	0.00008
8	1	0.87798	0.46761	0.00035
9	1	0.88364	0.06054	0.0002
10	0.74	0.75758	0.16235	0.00044
11	0.76	0.77859	0.20935	0.00043
12	0.84	0.80788	0.98929	0.00011
13	0.86	0.79596	0.74316	0.00042
14	0.76	0.82566	0.50336	0.00054
15	0.8	0.86283	0.47491	0.00033
16	0.92	0.84848	0.695	0.00033
17	0.78	0.80788	0.1138	0.0003
18	0.7	0.64263	0.23997	0.00044
19	0.84	0.85515	0.2193	0.00036
20	0.72	0.71717	0.76818	0.00038
21	1	0.84404	0.69229	0.00033
22	0.82	0.86343	0.00985	0.00011
23	1	0.80687	0.01574	0.0001

Meanwhile, the North population Hardy-Weinberg equilibrium results in Table 3, while the frequency of the north population ranges from (0.38) D13S317 to (0.01) FGA.

Table (3): Hardy-Weinberg equilibrium of North region individuals.

Hardy-Weinberg equilibrium : (North)				
Locus	**Obs. Het.**	**Exp. Het.**	**P-value**	**s. d.**
1	0.8	0.80889	0.41435	0.0005
2	0.84	0.86525	0.74898	0.00039
3	0.76	0.79515	0.96169	0.00019
4	0.64	0.73091	0.35923	0.00042
5	0.84	0.79596	0.96535	0.00018
6	1	0.90929	0.31203	0.00032
7	1	0.79677	0.00246	0.00005
8	1	0.87293	0.49994	0.00038
9	1	0.87939	0.06403	0.00025
10	0.72	0.72323	0.16389	0.00036
11	0.78	0.77535	0.58901	0.0005
12	0.8	0.79758	0.891	0.0003
13	0.84	0.79596	0.96576	0.00019
14	0.76	0.7699	0.38985	0.0004
15	0.86	0.88121	0.88684	0.00028
16	0.8	0.85071	0.29009	0.00042
17	0.76	0.79798	0.7506	0.00035
18	0.66	0.65737	0.80576	0.00036
19	0.86	0.86788	0.49192	0.00047
20	0.76	0.76465	0.62881	0.00042
21	1	0.8503	0.62508	0.00035
22	0.98	0.88	0.70973	0.00056
23	1	0.82263	0.01629	0.00012

Discussion

The STR analysis provides in-depth insights into the genetic diversity among alcohol-dependent individuals and control individuals in Iraq. Short Tandem Repeats (STR) markers were evaluated, and the assessment of sizing precision aimed for a standard deviation of less than 0.1 for all alleles. This result indicates that the precision of the 23 Y-STR panel exceeds that of other Y-STR kits reported in validation studies, making it adequate for distinguishing micro-variants or ladder peaks (12, 13).

The Hardy-Weinberg equilibrium (HWE) test results show a broad spectrum of observed heterozygosity (Obs. Het) and expected heterozygosity (Exp. Het) among populations in the south, furat awsat, and north regions. The South exhibited slightly higher matching probabilities, reflecting reduced diversity, potentially due to factors like limited gene flow or a higher prevalence of in-group marriages. These differences in diversity are significant because of greater genetic variability, and the heterozygosity ranges from 0.56 at locus 10 to 1.00 at several loci, including loci 4, 6, 7, 8, 9, and 23. Notable deviations from Hardy-Weinberg equilibrium ($p < 0.05$) were observed at loci 3, 4, 7, 13, 14, 19, and 23. Locus 4 exhibited a significant deviation ($p = 0.00057$), with an observed heterozygosity of 1.00, markedly exceeding the expected heterozygosity of 0.78 as shown in table (1).

The Furat Awsat population exhibits a comparable trend, with heterozygosity values reported between 0.72 at locus 10 and 1.00 at loci 6, 7, 8, 9, and 21. Notable deviations from Hardy-Weinberg equilibrium (HWE) were identified at loci 4 ($p = 0.00023$), 7 ($p = 0.00937$), 22 ($p = 0.00985$), and 23 ($p = 0.01574$). In contrast, most loci exhibited non-significant *p*-values, indicating that equilibrium is predominantly upheld. As shown in Table (2), High heterozygosity may indicate genetic variability potentially linked to factors such as alcohol metabolism, addiction resistance, or susceptibility. This diversity may suggest that these populations possess a range of genetic traits that could differentially affect alcohol dependence among individuals.

The North population exhibits heterozygosity values between 0.66 at locus 18 and 1.00 at loci 6, 7, 8, 9, 21, and 23. Notable deviations were observed at loci 7 ($p = 0.00246$) and 23 ($P= 0.0129$), as shown in table (3), indicating potential non-random mating or other genetic influences within.

The Hardy-Weinberg equilibrium test results offer essential insights into the genetic structure of these populations, particularly regarding deviations from equilibrium that may indicate underlying evolutionary factors. Loci 7 and 23, which often deviate from Hardy-Weinberg equilibrium in various populations, may be influenced by selective pressures or other genetic factors.

A comparison of populations indicates that the South populations exhibit more loci deviating from Hardy-Weinberg equilibrium than the Furat Awsat and North populations. This suggests that genetic drift, selective pressures, and population structure may be more pronounced in the south populations. The Furat Awsat population exhibits less significant deviations, suggesting more excellent

genetic stability or reduced environmental influences on this group.

Patterns of heterozygosity indicated significant genetic variability among regions. The Furat awsat shows higher matching probabilities (0.243 for DYS391) even though this locus has a high matching probability across all different populations in contrast to the north population, which shows the lowest matching probability (0.039 for the D7S820 locus. suggesting greater diversity, in contrast to the South, which showed slightly higher probabilities. Loci like Penta E demonstrated significant discrimination power across all regions at about (0.95), whereas DYS391 displayed diminished discriminatory potential, particularly in Furat Awsat at about (0.75). The Power of Exclusion (PE) values indicate that markers such as Penta E, D16S539, D2S1338, D19S433, and D18S51 demonstrate consistent robustness for exclusion purposes across various regions since their power of discrimination is 1, whereas CSF1PO and DYS391 exhibit reduced effectiveness about (0.46-0.75).

Alcohol is a psychoactive substance, and it shows its effect through the interplay of genetic and environmental factors and the variations in traits associated with its consumption (14, 15). Genetic markers include D3S1358 (LARS2), D1S1656 (RGS4), TH01 (Tyrosine Hydroxylase), and D7S820 (Semaphorin 3A) influence interrelated pathways that govern mitochondrial efficiency(16, 17), neurotransmitter signaling (18, 19), immunological regulation (20, 21), and neuroplasticity (22, 23). These pathways do not operate in isolation but are profoundly affected by environmental factors such as stress, alcohol accessibility, and culture and social context, ultimately determining an individual's risk for alcohol dependence and risky behaviors.

The marker D3S1358 encodes LARS2, which plays an important role in mitochondrial protein synthesis for efficient energy production and alcohol detoxification. In the liver, alcohol is metabolized into acetaldehyde by alcohol dehydrogenase (ADH), which is further converted to acetate by mitochondrial ALDH2. Variations in LARS2 impair mitochondrial activity, causing acetaldehyde accumulation, a very toxic intermediate (24). Which in turn led to systemic acetaldehyde poisoning, causing nausea, liver damage, and oxidative stress. Reduced alcohol detoxification efficiency can increase oxidative damage, leading to liver fibrosis and systemic inflammation when combined with persistent alcohol usage (25, 26, 27).

In the brain, RGS4 (D1S1656) and TH01 (Tyrosine Hydroxylase) are essential for dopamine signaling, which controls reward and reinforcement. TH01 encodes the enzyme tyrosine hydroxylase that converts tyrosine into dopamine, while RGS4 controls GPCR signaling to modulate neurotransmitter activity precisely. Alcohol stimulates the brain to produce excessive dopamine release; Dopamine production may improve alcohol's rewarding effects and reinforce drinking (28, 29). Impairment of RGS4 signaling can also affect neurotransmitter activity, increasing impulsivity and risk-taking. Dopamine pathway disturbances can lead to impaired decision-making, leading to increased alcohol consumption and dangerous behaviors like drinking and driving (30,

31). Neuroplasticity and Synaptic Adaptation

Neuroplasticity, run by Semaphorin 3A (D7S820), is another critical pathway affected by alcohol since it regulates axonal development and synaptic plasticity, which is crucial for learning, memory, and behavioral adaption (32). Alcohol impairs these processes by disrupting synaptic signaling, diminishing the brain's ability to adapt to external stimuli. Chronic alcohol use increases the risks, particularly in individuals with D7S820 variants, leading to impaired cognitive control and motor coordination by disrupting semaphorin-related plasticity (33, 34).

Alcohol metabolism and clearance also involve markers such as vWA (von Willebrand Factor) and FGA (Fibrinogen Alpha), which regulate vascular function and blood coagulation. Chronic alcohol consumption impacts vascular health by affecting the distribution of alcohol in the bloodstream and its subsequent elimination via the liver and kidneys. Compromised vascular dynamics may delay the transfer of alcohol metabolites, hence elevating systemic exposure and toxicity (35), (36). Simultaneously, CSF1R, encoded by CSF1PO, modulates macrophage function and immunological responses(37). Variants in this gene may intensify liver inflammation, diminishing the organ's ability to metabolize and eliminate alcohol effectively. This heightened inflammation state extends alcohol toxicity and hinders systemic elimination.

Environmental factors further modify these genetic predispositions, with stress playing a significant role. stress stimulates the hypothalamic-pituitary-adrenal (HPA) axis, releasing cortisol and modifying dopamine and serotonin pathways (38). Variations in RGS4 and TH01 interact with stress response, amplifying impulsivity and increasing alcohol consumption as a coping mechanism. Frequent alcohol drinking to alleviate stress can disrupt the HPA axis, impairing neurotransmitter imbalance and promoting addictive behaviors. Population-specific genetic diversity also contributes to this outcome (39, 40). For instance, regions with high genetic heterozygosity, such as southern Iraq, exhibit more significant behavioral variability, which may reduce uniform susceptibility to alcohol dependence. Conversely, genetically homogenous regions, like parts of Furat Awsat and the North, show higher prevalence rates of alcohol dependency traits due to the dominance of specific alleles.

These findings highlight the intricate interplay between genetic predispositions and environmental influences in shaping alcohol-related behaviors (41)

Conclusion

Research on STR markers reveals how alcohol metabolism, stress, social context, and regional genetic diversity impact susceptibility to alcohol dependence. It also highlights the distinct allele distributions and genetic diversity in Iraq, enhancing our understanding of population structure, genetic drift, and evolutionary factors affecting allele frequencies and heterozygosity in Iraqi populations.

The STR analysis highlights significant genetic diversity across Iraqi regions. Higher heterozygosity and deviations from Hardy-Weinberg equilibrium suggest varied genetic

structures shaped by selective pressures. Regions like the South show greater allelic diversity, which may lead to increased behavioral variability and a lower risk of traits like alcohol dependence. In contrast, areas with genetic homogeneity, such as parts of Furat Awsat and the North, may have a higher prevalence of certain dependent traits. These findings enhance our understanding of the genetic factors influencing behavior in Iraq.

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Conflict of interest

No conflict of interest

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