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The impact of Taq1A ANKK1/DRD2 Polymorphism on Dopamine in Individuals with Amphetamine Use Disorder in Basra, Iraq

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ABSTRACT
The current study analyzed addictive behavior at the molecular level among amphetamine (AMP) addicts residing in the Basrah Addiction Treatment Center, during the period extending from October 2024 to July 2025. DNA was extracted from blood samples of two groups, control (20) and AMP addicts (80). Their ages ranged between 14 and 45 years and older. The DNA was then amplified using PCR. The results showed that the highest percentage of AMP addicts was 12.5% in September 2024, while the lowest percentage was 5.5% in January and February 2025, compared to the rest of the months. The results also indicated that the highest percentage of addiction was among uneducated addicts (85.5%), while the AMP addiction was 13.5% in educated addicts. The 25–34-year age group had the highest percentage (31.83%), while the age group > 45 years recorded the lowest percentage (18.8%) of AMP use. The age groups 14-24 and 35-44 years recorded percentages of 26.32% and 23.1%, respectively. Based on the PCR analysis of the TaqIA polymorphism, two mutations were identified compared to the control group (CC). These were homozygous (TT, 2.5%) and heterozygous (CT, 27.5%). In AMP addicts, the T-allele frequency was higher (83.75%) than the C-allele frequency (16.25%). The results also reported that the dopamine receptor concentrations in AMP addicts were significantly higher in the CT genotype than in the CC and TT genotypes. These results suggest the role of genetic factors in addiction susceptibility and their interaction with neurotransmitters such as dopamine.

Keywords: *Taq1A; Dopamine; Amphetamine.*

INTRODUCTION
Drug addiction is a highly complex public health issue that poses a comprehensive threat to various aspects of life at social, biological, and psychological levels. Addiction is closely linked to lower academic achievement among students, decreased productivity in the workplace, disruption of professional relationships, increased family tension, and a consequent deterioration of financial conditions (Devi & Singh, 2023)Drug addiction causes disruptions in brain and behavioral functions, negatively impacting physical, mental, and nervous health. The severity of the effects varies depending on the type of drug, its dosage, and its mechanism of action. Consumption patterns vary among individuals; some use drugs for recreational or therapeutic purposes without developing addiction, while others develop physical and psychological dependence. Susceptibility to addiction depends on individual, biological, and psychological

factors. The psychological effects of addiction arise from the initial motivations for use (such as escaping stress or relieving pain) and the neurochemical changes that result from chronic use .

Epidemiological data for 2017 indicate that 271 million people (equivalent to 5.5% of the global adult population) used illicit drugs, while 35.6 million suffered from a substance use disorder(Jabeen et al., 2018) . Cannabis (marijuana) remains the most prevalent, with 188 million people using it annually, followed by opioids, which were used by 53 million people (a 56% increase over previous estimates), and are responsible for two-thirds of drug-related disorder deaths (Akerele, 2022)

Dopamine is a monoamine neurotransmitter secreted primarily by neurons in the brain and adrenal gland. It plays a pivotal role in regulating motor, motivational, and emotional functions. Dopamine mediates its biological effects through five types of receptors (D1-D5) (Akerele, 2022)D1-D5 play vital roles in regulating brain functions, including motor control, cognition, motivation, and reward. These receptors are selectively distributed in specific brain regions, with D1 and D2 receptors concentrated in the substantia nigra and ventral tegmental area, responsible for motor control and reward processing, while D3 and D4 receptors control limbic system functions related to emotion and motivation. Studies indicate that dysregulation of these receptors is associated with multiple neuropsychiatric disorders, with genetic variations in dopamine receptors contributing to increased susceptibility to Parkinson's disease and schizophrenia. The specific tissue distribution of these receptors reveals subtle mechanisms that control various brain functions and influence neuropsychiatric health (Kawahata et al., 2024).

The dopamine receptor type 2 (DRD2) gene is of vital importance in many neuropsychiatric disorders, including schizophrenia, Parkinson's disease, and addiction-related disorders. However, current methods used to detect polymorphisms in this gene face several challenges, most notably the high cost and the inability to simultaneously detect all eight genetic variations of clinical and functional significance, which are in the coding region (Val96Ala (rs6275), Leu141Leu (rs6277), Val154Ile (rs1800498), Pro310Ser (rs6278), Ser311Cys (rs180102)) and in the non-coding regions (TaqIA (rs1800497), A-241G (rs1799978), 141C Ins/Del (rs1799732)). Genetic polymorphism TaqIA (rs1800497) in the ANKKI gene is one of the most widely studied genetic variations in the field of addiction and behavioral disorders(Frías-Delgadillo et al., 2024) .

The dopamine D2 receptor gene (DRD2) is located on chromosome 11q22-23 and spans 270 kilobases, with eight exons. The gene encodes two isoforms: a D2-short (D2S) form containing 414 amino acids, and a D2-long (D2L) form containing 443 amino acids(Jasiewicz et al., 2014) .The two isoforms are produced by alternative splicing of the 87-base-pair-long exon 6. D2L is predominantly expressed postsynaptically, while D2S is predominantly localized to the presynaptic terminal (Lira & Ahammad, 2021). The DRD2 TaqIA polymorphism is a major modulator of dopamine receptor density, affecting dopaminergic signaling and thus playing a pivotal role in cognition, motivation, reward behaviors, and emotions (Pan et al., 2021).Taq1A exists in three genotypes (A1/A1, A1/A2, A2/A2) with allele A1 prevalence in varying proportions: ~30% in Europeans, 80% in Asians, and 40% in Africans(Pan et al., 2021) .

Amphetamine (derived from alpha-methylphenethylamine) is a powerful central nervous system stimulant, used to treat narcolepsy, obesity, and attention deficit hyperactivity disorder. It is widely used as a recreational drug(Tamama & Lynch, 2019) . Amphetamine, a psycho-stimulant and sympathomimetic drug, has devastating effects on the brain and body, causing severe neurological and physical consequences (Shukla & Vincent, 2020). Its immediate effects include increased alertness, elevated heart rate, blood pressure, and body temperature, as well as loss of appetite (Daraei et al., 2019). Amphetamine stimulates the brain by affecting neurotransmitter systems such as dopamine, serotonin, and norepinephrine, which leads to a feeling of euphoria, but it is considered a highly addictive substance(Alqallaf, 2021) . Therefore, the current study aimed to investigate addictive behavior at the molecular level among drug addicts residing in the Basrah Addiction Treatment Center by the analysis of TaqIA polymorphism and its effects on dopamine concentration.

Materials and Methods

Sample Collection

Blood samples (from 100 individuals) were collected from the Basra Addiction Treatment Center. In addition to this, blood samples were also collected from volunteers (20 non-addicts). The ages of participants ranged from 14 > 45 years. Ten milliliters of urine samples were also collected from the addicts and analyzed using a urine drug screening kit to confirm amphetamine use. The blood sample (5 ml) was divided into two tubes: 2 ml into an EDTA tube and 3 ml into a gel tube. Demographic data, including age, job, education, and others, were also collected. The ethical approval was authorized by the University of Basrah and Basrah Public Health Office.

Molecular Diagnosis DNA Extraction

DNA was extracted from blood samples of AMP addicts and non-addicts using a custom extraction kit from the Taiwanese company Geneaid, according to the manufacturer's protocol. DNA concentration and purity were measured using Nanodrop. DNA was then stored at -20°C until used in subsequent steps.

Nested Polymerase Chain Reaction:

The nested polymerase chain reaction (nPCR) technique was employed to investigate the TaqIA polymorphism in AMP addicts. In the first PCR round, the primer set (5-ACGGCTGGCCAAGTTGTCT-3 and 5-ACCTTCCTGAGTGTCATCAAC-3) was previously designed to target (305 bp) the specific region that relates to DRD2 (Zahari et al., 2011). In the second PCR round, allele-specific PCR, the primer set (5-ACGGCTGGCCAAGTTGTCT-3 and 5-ATCCTCAAAGTGCTGGTCG-3) was used to target (197 bp) the wild-type allele, while the primer set (5-ACGGCTGGCCAAGTTGTCT-3 and 5-ATCCTCAAAGTGCTGGTCA-3) was utilized to target (197 bp) the mutant-type allele(Zahari et al., 2011) . The first-round reaction was performed in a total volume of 25 µL, consisting of Promega GoTaq® G2 Green Master Mix (12.5 µL), primers (1 µL each), nuclease-free water (4.5 µL), and gDNA (6 µL). The second-round reaction was similar to the first-round reaction with some exceptions. These exceptions consisted of two reactions for each sample (one with the wild-type primers and the second with the mutant-type primers), a template (3 µl of the first PCR product from the targeted sample), and nuclease-free water (7.5 µl). The cycling conditions for the first PCR were 95°C for 2 minutes, 35 (PCR1) or 15 (PCR2) cycles (95°C for 1 minute, 65°C (PCR1) or 63°C (PCR2) for 1 minute, and 72°C for 2 minutes), and 72°C for 5 minutes. The PCR products were electrophoresed on 1% (w/v) agarose gel and visualized using a UV transilluminator.

Dopamine Concentration

Dopamine concentrations were determined in the sera of AMP addicts and non-addicts using the human dopamine ELISA kit (Bioassay Technology Laboratory) according to the manufacturer’s instructions.

Statistical Analysis

Statistical analyses were performed using SPSS version 25. Data were analyzed using either the Chi-square test or one-way ANOVA. The differences were considered statistically significant when p was less than 0.01.

Results:

Demographic data

Demographic data of AMP addicts distributed by age groups are shown in Table 1. The current results showed that the age group 25 - 34 years had the highest addictive percentage (31.83%), while the age group

> 45 years had the lowest addictive percentage (18.8%). The age groups 14 - 24 and 35 - 44 years had 26.32 and 23.1%, respectively. These percentages were close among the two age groups. There are no statistically significant differences among all age groups.

Table 1: Percentages of AMP addicts over a year, distributed according to age groups.

Age group	No	%
24- 14	105	26.32
34- 25	127	31.83
44- 35	92	23.1
45>	75	18.8
Total	399	100
Chi –square value= 4.827, p value =0.1849		

Furthermore, when the addiction of AMP was distributed by months, the highest percentage of AMP addicts was recorded in September 2024, reaching 12.5%, while the lowest percentage was recorded in January and February, reaching 5.5%. The percentages for the remaining months ranged from 6 to 10.5% (Figure 1). However, there were no statistically significant differences in months for the AMP addicts.

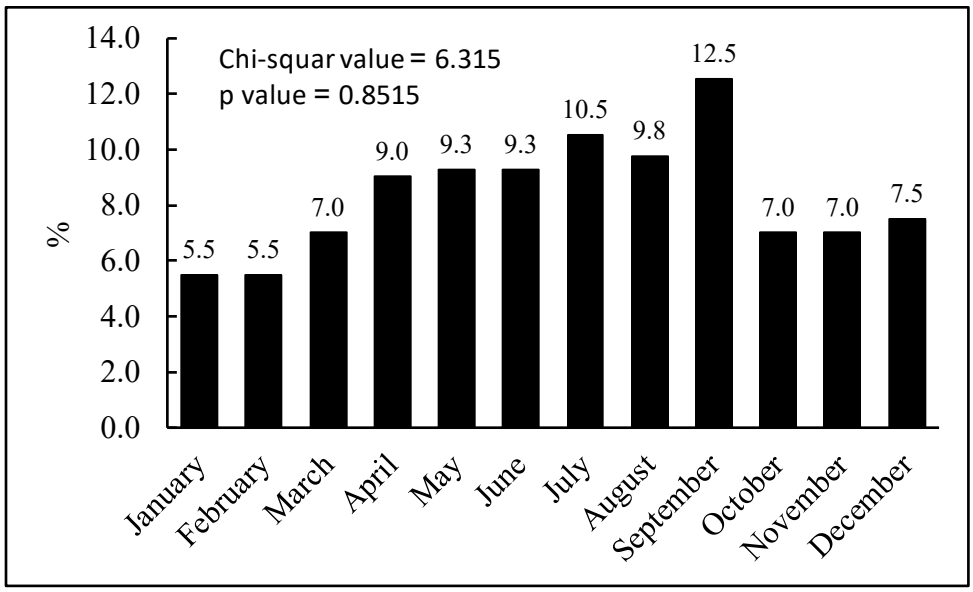

Figure 1: The percentage of AMP addicts distributed according to months.

The current results also showed that the percentage of addiction to AMP was significantly higher in the uneducated addicts (86.5%) than in the educated addicts (13.5%) (Figure 2).

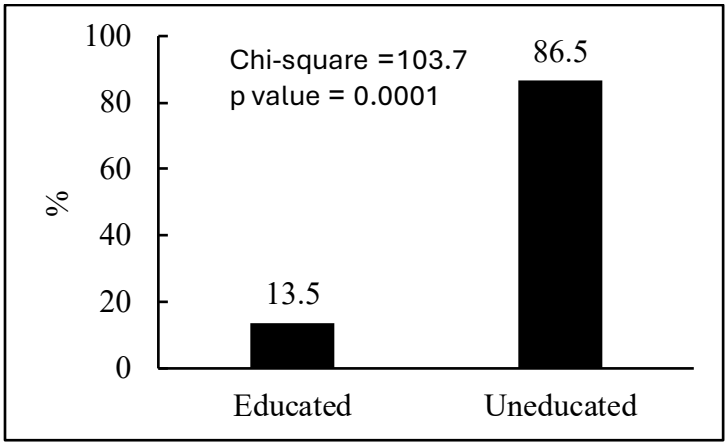

Figure 2: The percentage of AMP addicts distributed according to education.

Detection of SNP rs1800479 using nPCR

This SNP Taq1A (rs1800479), located near the dopamine D2 receptor gene, was detected in AMP and non-AMP addicts using nested-PCR (Figure 3). In this analysis, 80 samples of AMP addicts, confirmed by the urine test, and 20 control samples (not taking any drug) were used in the Taq1A (rs1800479) polymorphism analysis. The current study results clearly showed that there are two types of polymorphism in the AMP addicts (Figure 3C) compared with the non-AMP addicts (Figure 3A and 3B). These two types were homozygous mutations (TT) and heterozygous mutations (CT).

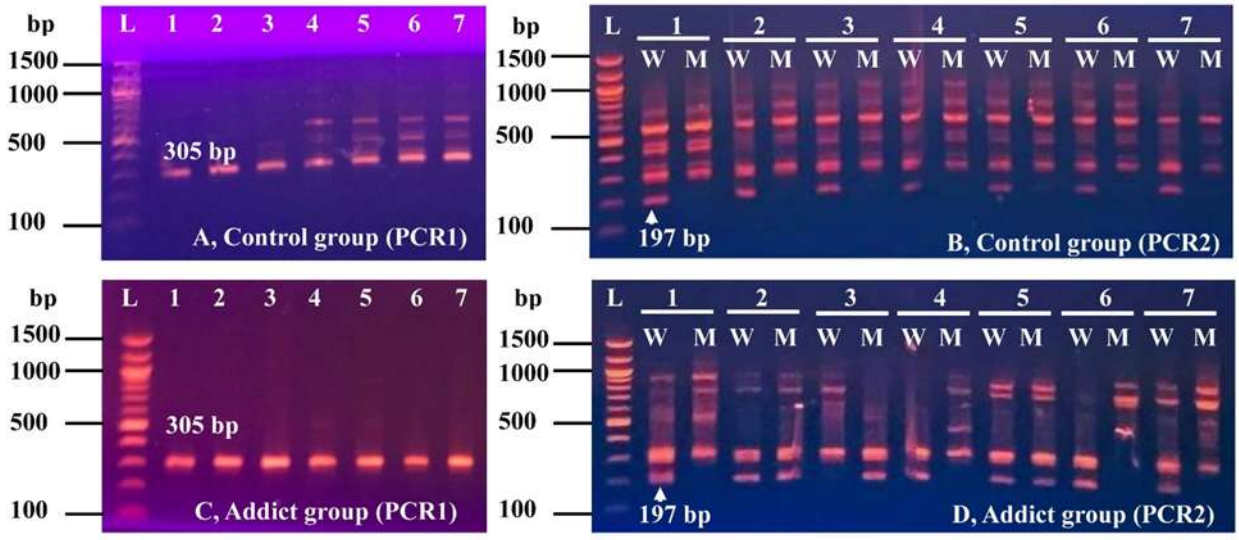

Figure 3: Agarose gel electrophoresis employed to detect Taq1A polymorphism in AMP addicts. A and B represent the control samples, while C and D represent the addicts.

DRD2/ANKK1 Taq1A polymorphism (rs1800497)

The polymorphisms of the Taq1A were investigated in the control and AMP addict groups (Table 2). The control group had only the CC genotype (100%), while the other genotypes (CT and TT) were not found. In the addict group, the highest percentage was in the CC genotype (70%), followed by 27.5% for the CT genotype, while the mutant type (TT) had the lowest percentage (2.5%). These percentages were statistically different among these three genotypes

Table 2: The percentage of Taq1A mutation in the current study samples.

Sample	NO.	Wild type		Mutant type				Total
		CC		CT		TT		
		No.	%	No.	%	No.	%	
Non addicts	20	20	100	0	0	0	0	100
Addicts	80	56	70	22	27.5	2	2.5	100
Total	100	76	76	22	22	2	2	100
Chi-square value = 22.02, p value = 0.0001								

In the addict samples, the highest percentage of the genotyping frequency was for the homozygous wild genotype (CC) (Figure 4). The homozygous mutant genotype (TT) had the lowest percentage while the heterozygous mutant genotype (CT) was 27.5%. These results were statistically significant differences.

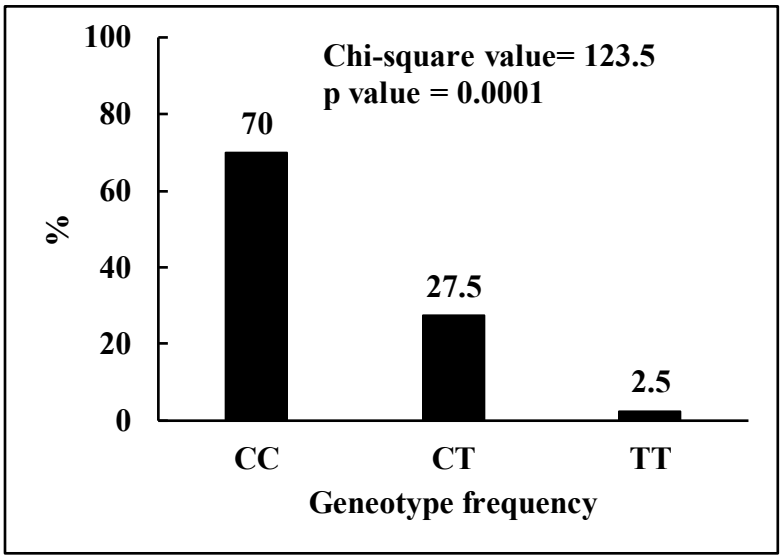

Figure 4: The percentage of recurrence of the genotypes CC, CT, and TT for AMP addicts.

The current results also revealed that the highest percentage of allele frequency was 83.75% for the C allele, which had a significant difference, while the lowest percentage was 16.25% for the T allele.

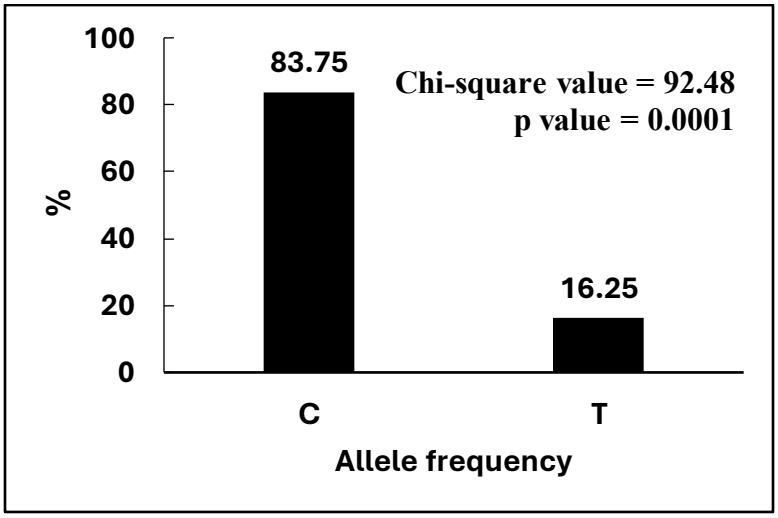

Figure 5: The percentage of T and C allele frequencies in AMP addicts.

Dopamine Concentration

Dopamine concatenations were estimated in AMP addicts within different genotypes (CC, TT and CT), and this was compared with the control group (CC) (Figure 6). The findings revealed that the dopamine concentration was different among the three genotypes of AMP addicts compared with control group. It was statistically higher in the AMP addict genotypes compared with the control genotype. In the AMP addict genotypes, The highest concentration (439 ng/ml) recorded in the CT genotype and was statistically significant. While the lowest concentration (339 ng/ml) was in the CC genotype and shared no statistical differences with the TT genotype (365 ng/ml). DRD2/ANKK1 Taq1A polymorphism (rs1800497) had a potential effect on the regulation of the DRD2 receptor in amphetamine addicts.

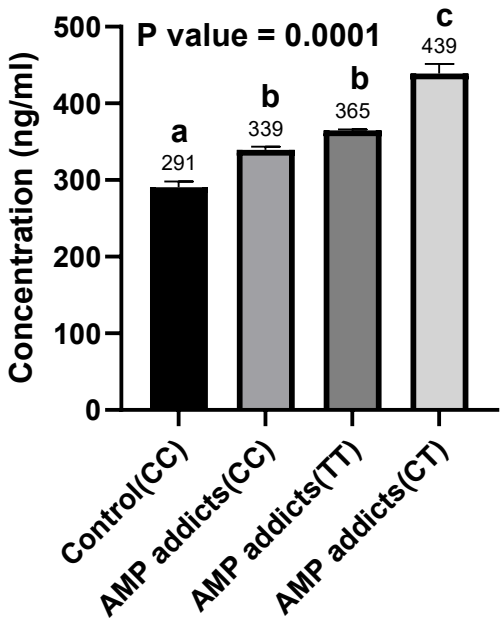

Figure 6: The effect of single-nucleotide polymorphism (Taq1A) in the ANKK1 gene on the dopamine D2 receptor (DRD2) in crystal meth (AMP) addicts.

Discussion

The current study's results indicate that the highest rate of substance abuse was observed in the 35-44 age group, at 70.33%. In contrast, the lowest rate was found among those aged 14-24, at 5.71%. The other age groups, 25-34 and 45 and above, recorded rates of 17.12% and 6.85%, respectively. These findings are consistent with a recent study conducted in the Aswan and Sohag governorates of Egypt. That study involved 372 drivers involved in road traffic accidents who were tested for drug use through laboratory analysis(Hussien et al., 2025) . It revealed that the 26-35 and 36-45 age groups were the most highly represented among substance users, with an overall prevalence of 71.8% for at least one substance.

The most commonly detected substances were cannabis (29.2%), tramadol (27.0%), and morphine (23.6%). Furthermore, 15.7% of the participants showed signs of polysubstance use (using multiple drugs). These results suggest that middle-aged drivers are at a higher risk of substance abuse. This is likely due to the use of these substances to enhance endurance and reduce drowsiness during work or driving, thereby increasing their likelihood of being involved in traffic accidents. The findings highlight the critical importance of targeted prevention and awareness programs, routine screening, and road safety education, particularly for the most vulnerable age groups.

The highest percentage of AMPH (amphetamine) addicts was recorded in September 2024 at 12.5%, while the lowest percentage was recorded in January and February at 5.5%. The remaining months showed percentages ranging between 7% and 10.5%. Despite the variation in the aforementioned percentage values, the statistical results showed no significant differences ($p < 0.05$) upon statistical analysis. Conversely, a previous study(Sara et al., 2018) .conducted a time-series analysis in New South Wales, Australia, aiming to assess monthly changes in patient admissions to mental health units for amphetamine-related disorders

between January 2000 and March 2015. The data spanned 61 months, with a monthly average of 2,482 admission cases. Of these, 128 cases (5%) were related to amphetamines, and 39 cases (1.6%) were specifically for amphetamine-induced psychosis.

The results showed a notable increase in both admissions and arrests since 2009. Amphetamine-related admissions constituted 2.7% of the total in 2009 and rose to 9.9% in the first quarter of 2015. Meanwhile, amphetamine-induced psychosis cases increased from 1.8% to 10% of all psychosis cases during the same period. The monthly average of arrests also increased, from 153 cases in 2009 to 607 cases in 2015. The study concluded that there is a clear association between amphetamine availability and increased admissions to mental health units, with significant variation based on months and years. The current results indicated that the highest rate of AMPH (amphetamine) addiction was among uneducated addicts, accounting for 86.5% of cases. In contrast, the rate of AMPH use among educated addicts was 13.5%. Consequently, the statistical analysis revealed significant differences.

This finding aligns with the work of (Borissova et al., 2022) ,whose results indicate that a low level of education is a risk factor for drug use problems and self-harming behaviors across all age groups. The analysis demonstrates that limited education is associated with an increased probability of anxiety and depression. For individuals aged 28 to 50, the risks for various psychological disorders were elevated among males, with the risk for substance use disorders reaching an odds ratio of 5.4 (95% CIs 5.1-5.7).

These findings underscore the importance of educational attainment, not only as a tool for learning but also as a potential protective mechanism against the development of certain psychological and behavioral disorders. This supports the social hypothesis that links academic failure to an increased risk of mental health issues and addiction. The Taq1 A polymorphism, located near the dopamine D2 receptor gene, was identified in AMPH addicts (80 samples) and non-AMPH addicts (20 samples) using the ARMS-PCR (Amplification Refractory Mutation System–Polymerase Chain Reaction) technique (Figure 1, partial results). The current results clearly demonstrated the presence of two polymorphism types in the AMPH addicts (Figure 1c) compared to the non-AMPH addicts (Figures 1a and 1b). These two types were a homozygous mutant (TT, sample 3) and heterozygous mutants (CT, samples 2 and 5).

These findings are consistent with those of (Grzywacz et al., 2019) ,who conducted research on 299 amphetamine addicts and 301 controls using PCR technology. The comparison between them showed that the homozygous TT mutants and heterozygous TG mutants were higher in the addicts than in the control group. This indicates that genetic variation is intricately associated with the addicted cohort.

Genetic analysis (Table 1) revealed that the wild-type CC genotype was predominant in the control group (100%, 20/20), but its frequency decreased to 70% (56/80) among AMPH addicts. Conversely, the heterozygous (CT) genotype was present in 27.5% (22/80) of addicts but was absent in the control group. The mutant homozygous (TT) genotype was the least frequent (2.5%, 2/80 in addicts; 0% in controls). Statistical analysis revealed significant differences between the two groups ($P < 0.001$).

These findings are consistent with previous research.(Ruzilawati et al., 2019) reported that the wild-type genotype (A2A2) was the most frequent in both the control (40%) and AMPH addict (49%) groups, while the mutant genotype (A1A1) was the least common in both (22% in controls, 7% in addicts). The heterozygous genotype (A1A2) was found in 25% of controls and 14% of addicts.

Further evidence was provided by (Ramadhan et al., 2020),whose study showed that carriers of the T (A1) allele were more prevalent among drug addicts (CT = 63.7%, TT = 6.6%) compared to the control group (CT = 3.3%, TT = 0%), demonstrating a strong association ($P < 0.0001$, OR = 37.3). Similarly, a study by (Lorek et al., 2024)found the TT (A1A1) genotype in 48% of opioid addicts compared to 12% of controls, while the combined frequency of T allele carriers (CT + TT) was 85% in addicts versus 42% in controls. These results strengthen the evidence that the presence of the T (A1) allele is associated with a higher

susceptibility to substance addiction. This can be explained by the fact that the Taq1A polymorphism, though located in the ANKK1 gene, has been shown to affect the availability of dopamine D2 receptors (DRD2). The presence of the T (A1) allele is associated with reduced receptor density and a diminished dopamine response to stimuli. Consequently, individuals with the CT or TT genotypes may experience a reduced normal reward response, meaning their usual "dose" of a stimulus is insufficient. This predisposes them to seek external stimulation through psychoactive substances like amphetamines(Kumar et al., 2024). This explanation is consistent with the observed increase in CT and TT genotypes among AMPH addicts in the current study.

The present study demonstrates the effect of the single nucleotide polymorphism (TaqI A) in the ANKK1 gene on the dopamine D2 receptor (DRD2) in crystal methamphetamine (AMPH) addicts, revealing clear differences in receptor concentration among groups carrying different genotypes. The control group carrying the CC genotype recorded a concentration of 291 ng/mL. In contrast, the group of AMPH addicts carrying the CT genotype showed the highest concentration of dopamine receptors, with an average of 439 ng/mL. Receptor concentrations were significantly lower in the groups carrying the TT and CC genotypes, at 365 ng/mL and 339 ng/mL, respectively.

Statistical analysis of the results showed significant differences between the groups in dopamine receptor concentration levels. This indicates a potential effect of this ANKK1 gene polymorphism on the regulation of the DRD2 receptor in amphetamine addicts (Figure 8). This finding aligns with the results of (Matsusue et al., 2018) , where the group of addicts carrying the A1A2 genotype recorded the highest dopamine receptor concentration at 62.16%. Receptor concentrations were lower in the groups carrying the A1A1 and A2A2 genotypes, at 13.51% and 24.32%, respectively. In the control group, the highest proportion carried the A2A2 genotype, at 44.26%. This study reveals that genetic predisposition, such as the Taq A1 polymorphism, can be a risk factor in the severity of methamphetamine toxicity and sudden death.

Conclusions

addiction is not related to age group, but rather that the percentage of addiction to this substance increases in uneducated individuals, in addition to its increase in the unemployed. The study showed the polymorphism of the (Taq1A) mutation and the presence of three genotypes in amphetamine addicts. The highest genotype was the CC (70%), followed by the CT (27.5%) genotype, followed by the TT (2.5%) genotype. The TC (91.6%) genotype and the TT (8.4) genotype were recorded for the first time in amphetamine addicts. The study also recorded that the percentage of the mutant allele (T) is less than 20%, which indicates that the mutant allele T affects the density of the dopamine receptor. The inferences of the relationship between the three genotypes and the concentration of dopamine in amphetamine addicts showed that the CT genotype showed the highest concentration of dopamine, which indicates that the mutation of the CT type stimulates the receptor. Dopamine produces higher levels of dopamine, which is reflected in the addict's behavior.

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