Taq1A and Other Genetic Variants of the Reward System Associated With Substance Use

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RESUMEN

Introducción: el polimorfismo Taq1A (rs1800497) del gen *ANKK1*, que codifica la enzima de repetición de anquirina y el dominio quinasa que contiene 1, se ha estudiado ampliamente en el consumo de sustancias de abuso y en los trastornos de conducta. Taq1A está asociado con alteraciones en el sistema de recompensa cerebral, principalmente a través de la vía dopaminérgica por el receptor de dopamina 2. **Método:** se realizó una revisión documental en la base electrónica PubMed, de los años 2008 a 2023. **Resultados:** se seleccionaron 85 artículos que cumplieron los criterios de inclusión. La presente revisión muestra la evidencia sobre los genes implicados en el sistema de recompensa cerebral y resume la importancia de diversas variantes genéticas, además de Taq1A, que están asociadas con el uso de sustancias. **Discusión y conclusiones:** los genes de riesgo asociados con el consumo de sustancias de abuso específicas, se relacionan con el sistema de recompensa mediante diversas vías de neurotransmisión, resultando en una red entrelazada de variantes genéticas que pueden interactuar entre sí para promover el desarrollo de una adicción.

Palabras clave: *ANKK1*; Asociación genética; *DRD2*; Taq1A; trastorno por consumo de sustancias; sistema de recompensa.

ABSTRACT

Introduction: the Taq1A polymorphism (rs1800497) of the *ANKK1* gene, which encodes the ankyrin repeat enzyme and the kinase domain containing 1, has been extensively studied in substance abuse and behavioral disorders. Taq1A is associated with alterations to the dopaminergic system in the brain reward system through the dopamine receptor 2. **Method:** a documentary review was performed in the electronic database PubMed between the years 2008 to 2023. **Results:** we consulted 85 articles that met the inclusion criteria. The present review shows the evidence of genes involved in the brain reward pathway that sums up the importance of the various genetic variants besides Taq1A, which are associated with substance use. **Discussion and conclusions:** risk genes associated with the consumption of specific substances of abuse are linked to the reward system through diverse neurotransmitters, resulting in a network of genetic variants that may interact between them to promote the development of addiction.

Keywords: *ANKK1; DRD2*; genetic association; reward system; substance use disorder; Taq1A.

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INTRODUCTION

Substance use disorder (SUD) is described as the compulsive use of substances of abuse and difficulties in controlling their use (Koeneke et al., 2020). SUD presents behavioral alterations due to modifications in the brain reward system (RS) that may cause a cognitive deficit in substance users. The RS alterations during the consumption of substances of abuse involve increased activation of dopamine (DA), through the dopaminergic D2 receptors (DRD2) in the ventral tegmental area (Jung et al., 2019; Singh et al., 2013), specifically in the striatum, and the nucleus accumbens (Abdulmalek & Hardiman, 2023). This increased activation has diverse effects such as gratification, pleasure, or euphoria (Kovanen et al., 2010; Mignini et al., 2012).

The dopaminergic system plays a key role in substance dependence, and it is related to arousal processes, rewarding behaviors (Deng et al., 2015), food consumption, sexual behavior and social activities (Grimm et al., 2021). Reports suggest that environmental factors, such as conduct disorders or adverse events during adolescence may predispose to the development of addiction in adulthood (Grimm et al., 2021; Koeneke et al., 2020; Lu et al., 2012). Several studies reveal that the consumption of substances of abuse has a multifactorial development. Genetic association studies in twins revealed that approximately 50% of an individual's genetics may determine the risk of SUD (Celorrio et al., 2016; Gerra et al., 2018; Kaminskaite et al., 2021).

Genetic Factors and Substance Abuse Consumption

A crucial component of SUD development is the genetic heritability (i.e., the percentage of phenotypic characteristics explained by genetic factors) that has been determined based on the type of substance of consumption (Celorrio et al., 2016). Although the individual's genetics may be a predisposing element, it is also relevant to consider the influence of environmental factors as triggers of substance use because of gene-environment interaction (Agrawal et al., 2012). Multiple genetic association studies have identified single nucleotide polymorphisms (SNPs) associated with different substances of abuse (opioids and derivatives, amphetamines, marijuana, etc.) and behavioral disorders (Agrawal et al., 2012). These SNPs can alter neurochemical pathways, e.g., SNPs in the *DRD2* gene would affect dopaminergic neurotransmission, which could increase the risk of developing dependence on substances of abuse such as alcohol, which would be explained by alterations in the RS or by increased susceptibility to the substance (Wang et al., 2013).

Currently, there are different genetic variants associated with substance use. The sum of several risk alleles of selected variants allows the calculus of polygenic risk scores (PRSs). PRSs represent the genetic risk of the individual based on the genetic variants present, and this score can serve as a biomarker of the disorder. PRSs have been calculated for smoking initiation, alcohol use disorder (AUD; Vink et al., 2014; Yang et al., 2023), opioid use disorder (OUD), and cannabis use disorder (CUD; Johnson et al., 2020).

ANKK1 and the Reward System

The *ANKK1* and *DRD2* genes are among the genes that have been studied with greater interest in relation to SUD. These genes, referred to as the *DRD2/ANKK1* complex, may interact between them because of their close genomic regions (Kaminskaite et al., 2021), in q22-q23 region of chromosome 11 (Neville et al., 2004). The variant Taq1A (rs1800497, g.32806C>T) is found in this region. It is associated with RS and the consumption of substances of abuse (alcohol, cocaine, marijuana, and tobacco, among others; Celorrio et al., 2016; Spronk et al., 2016; Singh et al., 2013; Villalba et al., 2015). This variant, previously identified as part of the *DRD2* gene, is located at ≈10 kb downstream of DRD2 gene, and was determined in the *ANKK1* gene in new genome assemblies. Taq1A produces a G713K change (Celorrio et al., 2016; Spronk et al., 2016; Singh et al., 2013; Villalba et al., 2015).

Carriers of the T (A1) allele of Taq1A (Jasiewicz et al., 2014) have reported a lower density of DRD2 in the cerebral striatum (Lee et al., 2013; Mignini et al., 2012; Singh et al., 2013) by 40% compared to carriers of the C (A2) allele (Samochowiec et al., 2016), and a tendency to present personality disorders (Kasiakogia-Worlley et al., 2011; Lu et al., 2012; Smith & Cottler, 2020). Likewise, there have been multiple meta-analysis studies (Jung et al., 2019; Schellekens et al., 2013; Swagell et al., 2012) confirming the genetic association of the Taq1A polymorphism with risk of alcohol dependence (Schellekens et al., 2013; Singh et al., 2013; Ramoz & Gorwood, 2018), and substance abuse (Jasiewicz et al., 2014; Koeneke et al., 2020) in carriers of the A1 allele (Lee et al., 2013). Thus, this work aims to review the principal genes and genetic variants that have been studied, besides Taq1A, with substance abuse in order to describe the main genetic findings that can serve as a basis for future experiments and possible clinical applications.

METHOD

A review was performed based on the Introduction, Methods, Results, and Discussion model (IMRyD; Codina, 2022) and APA Style Journal Article Reporting Standards for Qualitative Research (JARS-Qual) for review articles and research reports. To describe the article selection process, the PRISMA 2020 criteria flowchart for systematic reviews was used.

A review of articles was performed in the electronic database PubMed within the period from January 2008 to November 2023. This database contains a vast collection of full-text archives from MEDLINE (the most comprehensive database of medical literature), and other related life sciences journals. The search strategy was conducted with the keywords; "genes," "genetic association," "rs1800497," "DRD2," "ANKK1," "substance abuse," "substance use disorder," "reward system," and "human," as well as the Boolean operators' implementation. The use of a single database limits this study by excluding potentially relevant evidence. The field of genetics is continually advancing, so we suggest complementing this information with new evidence of genomic technologies in future studies.

The studies collected were cataloged by title and abstract, and the articles were read in order to determine which publications could be used. The selection of publications included indexed articles on the genetic association of substances of abuse, articles on the genetic association of the reward system applied to substance abuse, and indexed articles that included the Taq1A polymorphism (rs1800497). Articles were excluded based on the following criteria: studies not conducted in humans, experimental studies with a population under 18 years of age, content not related to substance use or abuse, not containing information on genes or genetic variants, articles not in English or Spanish, and publications with insufficient information.

RESULTS

406 publications were identified in the database, and after reading the titles and abstracts, 251 records that met the exclusion criteria were discarded. Subsequently, 155 publications were identified for evaluation and detailed reading. Finally, from these publications, 85 records were recovered that met the inclusion criteria (Figure 1).

The selected publications were categorized by type of substance of abuse: 32 for alcohol, 36 for nicotine, 6 for cannabis, 6 for cocaine, 3 for amphetamine (MDMA) and methamphetamines, 6 for heroin and 3 for opioids (Figure 2). Some of the selected publications focused on more than one substance. For each substance of abuse, we described the gene, polymorphism name, and associated effect.

Alcohol

Genetic association studies with alcohol show relevant genes that play in dopamine regulation (Table 1). The Taq1A polymorphism of *ANKK1/DRD2* has been associated with modifications in the expression of the *DRD2* gene (Grzywacz et al., 2019; Heinrich et al., 2016; Panduro et al., 2017). Its association with alcohol dependence due to decreased *DRD2* receptors in the synaptic cleft was also reported (Esposito-Smythers et al., 2009; Jasiewicz et al., 2014; Lee et al., 2013; Ramoz & Gorwood, 2015; Villalba et al., 2015; Wang et al., 2013). Another gene associat-

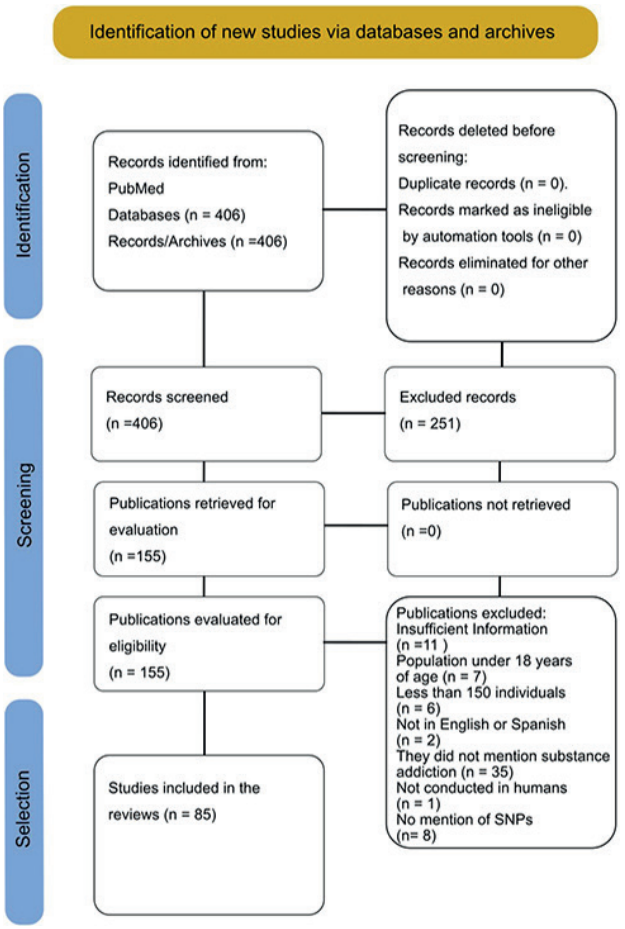

Figure 1. *Flow chart with the selection process of publications for the documentary review.*

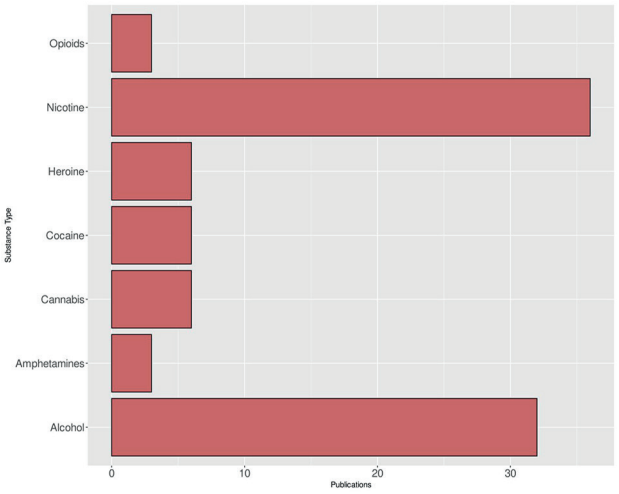

Figure 2. *Number of publications according to the substance studied.*

ed with alcohol abuse is solute transporter family-6 member-3 (*SLC6A3*), which encodes for a protein integral to the membrane of neurons and serves as a mediator of DA internalization and whose SNP rs28363170 was associated with an altered expression of the dopamine transporter gene (*DAT1*; Mignini et al., 2012; Vasconcelos et al., 2015).

The group of dopamine receptors *DRD1* (Celorrio et al., 2016; Jasiewicz et al., 2014; Ma et al., 2015b; Singh et al., 2013), *DRD2* (Celorrio et al., 2016; Grzywacz et al., 2012; Kovanen et al., 2010; Ma et al., 2015b; Ramoz & Gorwood, 2015; Singh et al., 2013; Swagell et al., 2012; Villalba et al., 2015), *DRD3* (Park et al., 2021), and *DRD4* (Villalba et al., 2015) are associated with compulsive consumption. The V58M polymorphism of the catechol-O-methyltransferase (*COMT*) gene, which encodes the enzyme responsible for regulating pain mediation by preventing DA breakdown, was associated with decreased expression of this enzyme (Celorrio et al., 2016; Kaminskaite et al., 2021; Park et al., 2021; Schellekens et al., 2013; Śmiarowska et al., 2022). In contrast, *DRD2* and *DRD3* were not associated with alcohol consumption in caucasians (Spitta et al., 2022). Clark et al., (2017) did not find common variants associated with AUD, but showed gene sets that include *ADHFE1* (alcohol dehydrogenase iron containing 1), and *ADORA1* (Adenosine A1 Receptor; Table 1).

Nicotine

We found a vast repertoire of gene polymorphisms associated with nicotine consumption. Among the most relevant associations is the Taq1A polymorphism of *ANKK1/DRD2* (Wilcox et al., 2011; Voisey et al., 2012), and the SNP rs77905 of the Dopamine β-hydroxylase (*DBH*) gene (Breitling et al., 2010), which encodes the enzyme of the same name and converts DA into noradrenaline. With dopamine receptors, a VNTR in exon III was found in *DRD4* that increased the risk of smoking, as well as SNPs rs686 (Gordiev et al., 2013; Villalba et al., 2015) and rs7653787 of the *DRD1* (Ruzilawati et al., 2020) and *DRD3* genes respectively, both associated with smoking. The A118G polymorphism of the mu-opioid receptor type 1 (*OPRM1*) was associated with more nicotine use in patients with schizophrenia (Hirasawa-Fujita et al., 2017). Of the monoamine oxidase (*MAOA*) gene, which generates the protein responsible for the degradation of some neurotransmitters such as serotonin, noradrenaline, and DA, the rs309850 variant was associated with a high risk of tobacco dependence and severe use (Huang et al., 2015; Table 2).

Cannabis

The genes found in the screening for the substance of cannabis (Cannabis Sativa) were the ANKK1 gene with SNP rs1800497 (Gerra et al., 2019; Vaske, 2013), the cannabinoid receptor gene type 1 (CNR1), and type 2 (CNR2). CNR1 and CNR2 are part of the G protein-coupled receptors, and they are found throughout the central nervous system. These receptors perform on the uptake of endocannabinoids and synthetic molecules derived from cannabis. We found studies describing an association of CNR1 and CNR2 gene SNPs and altered expression at the mRNA and protein level of both receptors (Gerra et al., 2018; 2019; Table 3).

Cocaine, Amphetamines (MDMA), Methamphetamines and Opioids

In the studies found with cocaine consumption, the Taq1A polymorphisms of *ANKK1/DRD2* (Ma et al., 2015b; Spellicy et al., 2013; 2014; Verdejo-Garcia et al., 2015) and the Taq1B SNP of *DRD2* were associated with the decrease of *DRD2* in the prefrontal cortex (Fernàndez-Castillo et al., 2010; Tsou et al., 2019; Vereczkei et al., 2013; Vizeli & Liechti, 2019; Zhang et al., 2018; Table 4). Besides, Ribeiro et al. report the transcription factor activator protein 1 (AP-1) associated with cocaine use disorder in prefrontal cortex neurons of cocaine users (Ribeiro et al., 2017). We found information related to heroin dependence based on the Taq1A (Hou & Li, 2009; Lachowicz et al., 2020; Levran et al., 2013; Vereczkei et al., 2013; Zhang et al., 2018; "Ma et al., 2015b) and H490R poly-

Table 1
Effects of the gene polymorphisms of the reward system associated with alcohol use

Gene	Polymorphism	SNP	Associated effects
ANKK1	Taq1A (C957T / G713LK)	rs1800497	Increases the risk of alcohol dependence in carriers of the Taq1A polymorphism.
		rs1800497	No association of the polymorphism with alcohol consumption was observed.
		rs1800497	No association of minor allele of the Taq1A polymorphism with striatal DRD2/3 availability in alcohol dependence.
		rs4938016	Associated with alcohol dependence.
SLC6A3 (DAT1)	40 bp 30UTR-VNTR	rs28363170	Associated with alcohol dependence.
		rs28363170	No association was observed.
DRD1		rs4532	Increases compulsive consumption in the AUD.
		rs4867798	Not associated with excessive alcohol consumption.
		rs686	Not associated with excessive alcohol consumption
		rs5326	Not associated with excessive alcohol consumption
DRD2	Taq1B	rs1079597	Decreased expression of DRD2.
		rs1079597	Associated with alcohol dependence.
	Taq1D	rs1800498	No association in subjects with alcohol dependence.
		rs4936271	Associated with excessive alcohol consumption.
		rs10891556	Associated with excessive alcohol consumption.
	-141C Ins/Del	rs1799732	Associated as a predisposing factor to alcohol dependence.
		rs1799732	Associated with the early onset of alcohol dependence.
	C957T	rs6277	No association was observed.
		rs6277	Associated with alcohol dependence.
		rs6277	No association with alcohol dependence syndrome.
		rs1799978	Associated with alcohol dependence.
		rs1799732	Associated with alcohol dependence.
		rs1076560	Associated with alcohol dependence.
	Exón 8	rs6276	Associated with the presence of alcohol withdrawal syndrome with seizures.
		rs6276	No association was observed.
		rs877138	Associated with excessive alcohol consumption in men.
DRD3		rs6280	Associated with a higher score on the obsessive-compulsive drinking scale.
DRD4	VNTR 48pb	rs6280	Associated executive dysfunction in users with excessive alcohol consumption and HIV.
COMT	Val58Met	rs4680	Associated with the severity of alcohol dependence.
		rs4680	No association was observed.
MAOA		rs5906898	Associated with excessive alcohol consumption in women.

Table 2
Effects of the gene polymorphisms of the reward system associated with nicotine use

Gene	Polymorphism	SNP	Associated effects
ANKK1	Taq1A (C957T / Glu713Lys)	rs1800497	Associated with nicotine dependence.
		rs1800497	Decrease in DRD2 in men with schizophrenia who smoke .
		rs1800497	Associated with greater response in nicotine replacement therapy in smoking.
		rs1800497	Associated with the initiation of smoking.
		rs1800497	Associated with smoking abstinence.
		rs1800497	Not associated with nicotine dependence.
		rs11604671	Associated with nicotine dependence.
		rs11604671	Not associated with nicotine dependence.
		rs4938015	Associated with nicotine dependence.
		rs4938016	Associated with nicotine dependence.
		rs2734849	Associated with nicotine dependence.
		rs4938013	Associated with nicotine dependence.
		rs17115439	Risk of nicotine dependence.
		rs17115439	Not associated with nicotine dependence.
		rs877138	Associated with nicotine dependence.
		rs877138	Not associated with nicotine dependence.
		rs4938012	Associated with nicotine dependence.
		rs2282511	Associated with nicotine dependence.
DBH		rs77905	Not associated with nicotine dependence.
DRD1		rs686	Associated with tobacco consumption.
DRD2	Taq1B	rs1079597	Associated with nicotine dependence.
		rs1079597	Not associated with nicotine dependence.
	Taq1D	rs1800498	Associated with nicotine dependence.
	C957T	rs6277	Associated with nicotine dependence.
		rs6277	Not associated with nicotine dependence.
		rs7131056	Not associated with nicotine dependence.
		rs2283265	Association of TT genotype with better response to smoking in individuals who received nicotine replacement therapy.
		rs4274224	Not associated with nicotine dependence.
		rs6589377	Associated with nicotine dependence.
		rs6589377	Not associated with nicotine dependence.
		rs1799978	Associated with nicotine dependence.
		rs1799732	Associated with nicotine dependence.
		rs1799732	Not associated with nicotine dependence.
		rs4648318	Associated with nicotine dependence.
		rs1076560	Associated with smoking.
		rs4581480	Not associated with nicotine dependence.
		rs4648317	Increased smoking prevalence.
		rs4648318	Associated with nicotine dependence.
		rs6278	Associated with severe smoking.
	-141C Ins/Del	rs1799732	Better response with nicotine replacement therapy.
		rs1799732	Not associated with nicotine dependence.

Table 2 (continued)
Effects of the gene polymorphisms of the reward system associated with nicotine use (continued)

DRD3		rs7653787	Associated with the CT genotype for tobacco consumption.
DRD4	Exón III VNTR		Associated with the risk of smoking in carriers of the short allele and the A2 Taq1A allele.
TTC12	Alelo G	rs2236709	Decreased expression of DRD2.
		rs2303380	Associated with smoking.
		rs2282511	Associated with automatic tobacco consumption.
SLC6A3 (DAT1)	40 bp 30UTR-VNTR	rs28363170	Associated with severe smoking.
		rs28363170	Not associated with smoking.
		rs28363170	Associated with difficulty quitting nicotine.
	3'UTR VNTR	rs27072	Associated with nicotine dependence.
		rs27072	Not associated with smoking.
OPRM1	A118G	rs1799971	Association of the GG and GA genotype with greater cigarette consumption per day in individuals with schizophrenia.
		rs1799971	No association was observed.
HTR2A		rs6313	Association of the G and GA genotype with greater cigarette consumption per day in individuals with schizophrenia.
COMT	Val158Met	rs4680	Associated with nicotine dependence.
		rs4680	Not associated with nicotine dependence.
		rs165599	Better effect for nicotine cessation in carriers of the A allele.
		rs737865	Better response for smoking cessation with the use of medications.
CNR1	C3764G	rs6928499	Not associated with smoking.
CHRNB2		rs2072658	Associated with the age of initiation of smoking and dependence.
CHRNA3		rs1051730	Associated with continued smoking during pregnancy.
		rs1317286	Not associated with smoking.
		rs1317286	Associated with susceptibility to severe smoking prevalence.
	C546T	rs578776	Related to reward and nicotine dependence.
CHRNA4		rs2236196	Associated with smoking dependence.
		rs2236196	Not associated with smoking.
		rs2273504	Associated with early onset of smoking and consumption of cigarettes per day.
CHRNA5	G1192A	rs16969968	Associated with susceptibility to the prevalence of smoking.
		rs16969968	Not associated with smoking.
		rs8034191	Associated with smoking and severe smoking.
HTR2A	-1438 A/G	rs6311	Not associated with nicotine dependence.
MAOA	MAOA VNTR	rs309850	The 3R variant was associated with severe smoking in young people.
	EcoRV	rs1137070	It is not related to smoking.
		rs2235186	Higher allele frequency in susceptibility SNP in the population of Rome.

Table 3
Effects of the gene polymorphisms of the reward system associated with cannabis use

Gene	Polymorphism	SNP	Associated effects
ANKK1	Taq1A (C957T / Glu713Lys)	rs1800497	Associated with cannabis use.
		rs1800497	Not associated with cannabis use.
CNR2		rs2501431	Possible risk factor for cannabis use in men.
FAAH		rs324420	Not associated with cannabis use.
		rs6277	No significant association with cannabis use.
COMT	Val158Met	rs4680	No significant association with cannabis use.

Table 4
Effects of the gene polymorphisms of the reward system associated with cocaine use

Gene	Polymorphism	SNP	Associated effects
ANKK1	Taq1A (C957T / Glu713Lys)	rs1800497	Associated with cocaine dependence.
		rs1800497	Not associated with cocaine dependence.
DRD2		rs2283265	Associated with cocaine dependence.
	Taq1B	rs1079597	Not associated with cocaine dependence.
	C957T	rs2283265	Associated with cocaine dependence.

Table 5
Effects of the gene polymorphisms of the reward system associated with heroin use

Gene	Polymorphism	SNP	Associated effects
ANKK1	Taq1A (C957T / Glu713Lys)	rs1800497	Associated with heroin dependence.
		rs11214598	Associated with heroin dependence.
	His490Arg	rs2734849	Associated with heroin dependence.
DRD2	C957T	rs2283265	Associated with heroin dependence.
		rs1799978	Associated with heroin dependence.
		rs1799732	Associated with heroin dependence.
	Taq1B	rs1079597	Associated with heroin dependence.
		rs2245805	Associated with heroin dependence.
	Taq1D	rs1800498	Associated with heroin dependence.

morphisms of the *ANKK1* gene (Levran et al., 2013; Zhang et al., 2018). An interesting report showed a mutation in the *DRD2* gene was associated with a protective effect against heroin consumption in its carriers (Ma et al., 2015b; Tsou et al., 2019; Verecz-kei et al., 2013; Zhang et al., 2018). Also, variable number tandem repeats (VNTR) of *DAT1* were associated with dopamine re-accumulation in the brain synapse in individuals who used heroin (Vizeli & Liechti, 2019; Table 5).

Amphetamines (MDMA) had very similar results to heroin, as there is extensive evidence for association with Taq1A and B polymorphisms and decreased expression of DRD2 in dopaminergic neurons of MDMA-using users. In studies of dependence on this substance, variants of the *DAT1* gene were also associated with the presence of psychosis after the consumption of this substance of abuse (Vizeli & Liechti, 2019; Table 6). Finally, in opioid research, the Taq1A polymorphism of *ANKK1/DRD2* was associated with an increased risk of opioid dependence (Deng et al., 2015; Table 7). However, a decrease in DRD2 expression was found only in the Caucasian population (Cai et al., 2015).

Table 6
Effects of the gene polymorphisms of the reward system associated with amphetamine, methamphetamine and MDMA use

Gene	Polymorphism	SNP	Associated effects
ANKK1	Taq1A (C957T / Glu713Lys)	rs1800497	No association was observed.
DRD2	Taq1B	rs1079597	No association was observed.
	C957T	rs6277	No association was observed.
DAT1	3'UTR VNTR	rs28363170	No association was observed.
	VNTR	rs3836790	No association was observed.
		rs6347	No association was observed.
		rs11133767	No association was observed.
		rs11564774	No association was observed.
		rs460000	No association was observed.
		rs463379	No association was observed.
COMT	Val158Met	rs4860	Associated with amphetamine and methamphetamine dependence.

Table 7
Effects of the gene polymorphisms of the reward system associated with opioid use

Gene	Polymorphism	SNP	Associated effects
ANKK1	Taq1A (C957T / Glu713Lys)	rs1800497	Associated with risk of opioid dependence.
		rs1800497	No association was observed.

DISCUSSION AND CONCLUSIONS

The development of substance use disorder is multifactorial, with a relevant genetic component (Celorrio et al., 2016). Because of this, different genetic association studies have been performed with candidate genes containing polymorphisms associated with the consumption of diverse substances of abuse, such as opioids (Abdulmalek & Hardiman, 2023), amphetamines, marijuana, and nicotine (Agrawal et al., 2012). In the majority, these polymorphisms are associated with altered neurochemical pathways or dopamine turnover in the RS (Wang et al., 2013). Within the etiology of SUDs, the individual's genetics are a predisposing factor, while environmental factors could trigger the onset of the disorder. This interaction is categorized as a gene-environment interaction (Agrawal et al., 2012). Our aim in this review is to learn about the genes and polymorphisms that have been studied alongside the Taq1A, associated with substance abuse, in order to create a specific line of knowledge for future experimental studies in addictions, with particular emphasis on the reward system.

Reports suggest that the Taq1A polymorphism is in a high state of linkage disequilibrium with the Taq1B SNP of the *DRD2* coding gene (Chmielowiec et al., 2022; Śmiarowska et al., 2022; Tsou et al., 2019). Because of their chromosomal proximity, both SNPs occur together in an individual with a higher frequency than if it were by random probability of recombination. The *ANKK1* gene is adjoining to the *DRD2* gene (Esposito-Smythers et al., 2009; Jasiewicz et al., 2014; Villalba et al., 2015; Wang et al., 2013), and functions as a regulator of DRD2 expression indirectly (Lee et al., 2013; Ramoz & Gorwood, 2015), through activation of the transcription factor NF-kB (Herman et al., 2014; Huang et al., 2009; Ma et al., 2015a; Stapleton et al., 2011). It has been widely associated with alterations of the RS (Jasiewicz et al., 2014).

Several works address the study of dopamine receptor genes for their crucial role in the development of SUDs, in particular with cocaine and heroin use. Taq1A has also been associated with psychiatric disorders related to SUD (Fernàndez-Castillo et al., 2010; Spellicy et al., 2013; Verdejo-Garcia et al., 2015) and conditioning behaviors to substance dependence

(Spellicy et al., 2014). Alcohol consumption has been associated with various genetic variants, mainly of the *SLC6A3, DRD2, COMT,* and *DAT1* genes. The evidence collected so far has led to the conclusion that a history of conduct disorder in adolescence, combined with the presence of risk genetic variants, could predispose the individual to the development of SUD (Lu et al., 2012).

The RS is involved in the pathogenesis of AUD by a dysregulation in the mechanisms of action of several neurotransmitters (García-Gutiérrez et al., 2022; Park et al., 2021). The latter translates into impairment of DA neuronal turnover in individuals with AUD who exhibit withdrawal and impulsivity following discontinuation of alcohol use (Gullo et al., 2014). Studies on dopamine expression address the SNP 40 bp 30UTR-VNTR (rs28363170) of the *SLC6A3* gene, associated with increased expression of the DAT1 (Mignini et al., 2012; Vasconcelos et al., 2015). Likewise, the SNP-141C Ins/Del (rs1799732) of the *DRD2* gene contains a deletion reported in severe alcohol dependence, probably because of the decrease of DRD2 in the striatum (Grzywacz et al., 2012). Meanwhile, the Catechol-O-methyltransferase (*COMT*) gene, a promoter of the inactivation of catecholamine-derived neurotransmitters such as DA, adrenaline, and noradrenaline (Schellekens et al., 2013; Śmiarowska et al., 2022), has the Val-158Met polymorphism, which was associated with decreased COMT enzymatic activity. Val158Met has been documented in impaired impulse control and alcohol abuse (Celorrio et al., 2016; Kaminskaite et al., 2021; Park et al., 2021; Śmiarowska et al., 2022).

The addictive effects of nicotine operate through the RS. Exposure to the substance increases DA neurotransmitter turnover, mainly in mesocorticolimbic reward pathways (Huang et al., 2009). The addictive potential of tobacco is presented by the low ability to stop using it (Stapleton et al., 2011; Ohmoto et al., 2014; Tomaz et al., 2015), as only 7% of users stop using it for more than one year (Huang et al., 2009). Nicotine addiction is multifactorial (Munafò et al., 2009; Bidwell et al., 2015b; Huang et al., 2015) with SNPs associated with smoking that are involved in dopaminergic, serotonergic, cannabinoid, and opioid pathways, e.g., the 40bp VNTR (rs28363170; Weafer et al., 2017; Liu et al., 2020) and rs27072, polymorphisms of the *SLC6A4* gene (Ruzilawati et al., 2020), and the rs6313 variant of the 5-HT2A receptor gene (*HTR2A*), which has been associated with long periods of smoking cessation. Other reports suggest that the mu-opioid receptor-1 gene (*OPRM1*) is a gene that could show interesting results on RS and dependence on various substances of abuse, including nicotine and opioids. The A118G polymorphism (rs1799971) of *OPRM1* was associated with higher cigarette consumption per day (Verde et al., 2011). Finally, the cluster of genes on chromosome 11q23 (*NCAM1-TTC12-ANKK1-DRD2*) has a critical role in DA receptors and smoking ("Bidwell et al., 2015a; 2015b; Lobo et al., 2012; Macare et al., 2018; Herman et al., 2014; Mayer et al., 2015; Doran et al., 2013; Radwan et al., 2007).

Regarding cannabis use, reports with the cannabinoid receptor 1 (*CNR1*) mention the association of the genetic variant G1359A (rs1049353) with memory dysfunction, impulsivity, anxiety disorder, depression, and cognitive impairment (García-Gutiérrez et al., 2022; Gerra et al., 2018; Forrester & Jahan, 2020). Cocaine association studies show that the RS is a critical component of the development of SUD (Spellicy et al., 2014). It was determined that genetic heritability with risk variants for cocaine abuse can be as high as 72% (Koeneke et al., 2020). Within these genetic risk factors, only the *DRD2* gene presented significance with the T allele of the rs2283265 polymorphism, because the variant is found in higher frequency in cocaine users and is associated with decreased expression of DRD2 (Spellicy et al., 2013). The Taq1B variant (rs1079597) was also associated with decreased DRD2 receptors (Fernàndez-Castillo et al., 2010).

In association studies with heroin use, the *DRD2* gene has been analyzed the majority of times, followed by *DRD4* and *DAT1*. The consumption of this substance and its derivatives causes high brain stimulation in the SR (Hou & Li, 2009; Tsou et al., 2019). Analysis of heroin properties in the RS is related to changes in the mesolimbic dopaminergic system (Tsou et al., 2019). *ANKK1* is involved in the development of behavioral changes that increase the risk of heroin dependence. Other genetic variants of the *DRD2* gene, widely studied in heroin dependence, are SNPs analyzed in European and Asian populations, such as Taq1D and C957T -141C Ins/Del (Fiatal et al., 2016; Lachowicz et al., 2020; Levran et al., 2013; Tsou et al., 2019), with effect on DRD2 expression.

Central nervous system stimulants have been described to function as a reuptake inhibitor for various neurotransmitters, such as serotonin, norepinephrine, and DA neurotransmition, resulting in a euphoric effect. Similar to heroin, amphetamines increase DA levels in the synapse of the nucleus accumbens (Chmielowiec et al., 2022; Vizeli & Liechti, 2019). These substances of abuse have different de-

rivatives such as amphetamines, methamphetamines (crystal) and MDMA (ecstasy). With the latter, the study of polymorphisms of genes involved in neurotransmitter pathways affected by amphetamines may help with the study of the modulation of MDMA effects (Vizeli & Liechti, 2019). Finally, opioid addiction could be caused mainly by medically derived products, such as heroin and morphine, which interact with the RS ("Cai et al., 2015; Deng et al., 2015). Unlike opioids, amphetamine-type stimulants block DAT1 or increase the release rate of synaptic vesicles (Abdulmalek & Hardiman, 2023). Evidence suggests that this addiction originates due to deficiencies in the reward system dependent on dopamine receptors. This deficiency will cause the need for a higher concentration of the opioid substance in order to feel satisfaction, which results in the sensation of pleasurable experiences (Cai et al., 2015).

The DA neurotransmission has been affected in different ways by gender (Harp et al., 2020), high or excessive substance use, adverse childhood experiences and multiple genetic variants. These are risk factors but not definitive conditions for developing an addiction. Therefore, it is important to trace the effects of drug abuse in the different pathways of the reward system while taking into account both environmental factors and the ancestry of specific populations. The growing evidence in this field allows the implementation of new prevention and treatment approaches which will benefit the mental health (Esposito-Smythers et al., 2009; Smith & Cottler, 2020).

This review describes the main genetic factors, especially the Taq1A polymorphism of the *ANKK1* gene, as well as the psychosocial factors related to the development of addictions. The review focused mainly on the diversity of polymorphisms involved in the reward pathway and their biological effects, which may have a relevant role as either a risk or a protective factor regarding substance abuse leading to the development of SUD. Finally, this information expands our knowledge concerning the polymorphisms associated with these mental disorders, which could bring us closer to the search and validation of candidate genes in substance users in order to seek early intervention and prevention of addictions.

Limitations of the Study

Animal studies, which could explain the expression of some genes involved in the reward pathway, were not used because its effects on humans have not yet been studied, and it would be difficult to know its scope for its translation into the clinic. We only found four studies of the Latino population related to the reward system and substance use disorder, two from Mexico and two from Brazil. More studies on the Latino population are needed to complement the findings.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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