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REVIEW

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Association of *OPRM1* with addiction: a review on drug, alcohol and smoking addiction in worldwide population

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Abstract

Background: Drugs are chemicals which can disrupt the nerve cell functions of the brain. The present study aims to investigate the addiction related gene (*OPRM1*) in three types of addiction—drugs, alcohol and smoking. Pathway for the addiction was ascertained through KEGG database, and the hotspot mutations for various populations were identified from Gnomad-exomes database. In silico analyses like SIFT, Polyphen, Hope, I-mutant and mutation taster were performed to understand the amino acid substitution, protein function, stability and pathogenicity of the variants.

Main body: Addiction-related variants were found in exons 1, 2 and 3, while the exon 4 did not exhibit any addiction related variation. Among all the variants from this gene, rs1799971 (A118G) polymorphism was the most commonly studied variation for addiction in different populations worldwide. Population-wise allele and genotype frequencies, demographic and epidemiological studies have also been performed from different populations, and the possible association of these variants with addiction was evaluated.

Conclusion: Our findings suggest that *OPRM1* polymorphism impact as pharmacogenetic predictor of response to naltrexone and can also address the genetic predisposition related to addiction in human beings.

Keywords: *OPRM1* gene, Addiction, Gnomad-exomes database, Smoking, Drug, Alcohol

Background

The epidemic of narcotic addiction is emerging as the most serious clinical issue of current generation as it ruins families, society and countries. Addiction is defined as the inability to stop taking a substance or engaging in an activity, despite the fact that it is harmful to one's mental and physical health. It is about the way our body craves for a substance especially if it causes obsessiveness. Different single nucleotide polymorphisms (SNPs) in the *OPRM1* gene have been reported in many populations which has an association with narcotic addiction. We reviewed on three types of addiction which are Drug/Substance addiction, smoking addiction and alcohol addiction related to *OPRM1*. *OPRM1* encodes the mu opioids receptors, which is the primary site of action for the most commonly used opioids including morphine, heroin, fentanyl, etc. It gives the instruction for making the protein called mu opioid receptor. The endogenous opioid system plays a key role in narcotic addiction and mediates the analgesic and reward properties of drugs. The *OPRM1* receptor is a membrane of the G-coupled receptor family [1]. This receptor spans more than 80 kbp of nucleotide sequences on chromosome 6q24-25 and is composed of transcript regulatory region, introns and exons [2]. The mu opioid receptor is the

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major site of action for endogenous opioids, opiate and opioid analgesic drugs and also the exogenous opioids drugs such as heroin, methadone [3]. Particularly, the genomic organization of the human *OPRM1* gene locus is highly similar to the mouse locus. However, alternative splicing events display some substantial differences between human and mouse [4].

Addiction can be caused by genetic factors although environmental factors cannot be underestimated as it is also implicated to the development of the opioid addiction [5]. Among all receptors involved in opioid addiction, mu opioid receptor (MOR) has the major role in mediating opioid tolerance and independence [6]. Research findings have suggested that non-opioid drugs like alcohol, cocaine, etc., may again wield some of their effects through the activation of the opioids receptors. The receptors mediate drug-induced feeling and increases the production of chemicals which can lead to feelings of euphoria, analgesia, pleasure and withdrawal [7], and thus it plays a crucial role in reinforcing and rewarding the substance used to include alcohol. Alcohol dependence is a common disorder which might also lead to psychiatric disorder, and there are about 76 million people suffering from alcohol dependence worldwide.

The other non-opioid substances like nicotine/tobacco are also associated with the up-or down-regulation of the encephalic opioid receptor levels and enhance the endorphinis mu receptor mRNA and protein expression in the brain. It also stimulates endogenous opioid release resulting in the mu opioid receptor activation. Smoking remains very common among people with mental health problems, particularly among those who have substance abuse disorders [8]. Nicotine is the primary reward component in tobacco products, and therefore genes involved in the metabolism of nicotine are biologically plausible candidates for genetic studies of smoking behaviour because they determine the levels and persistence of nicotine in the body. Tobacco dependence occurs through nicotine which is the main psychoactive component in tobacco [9].

In the present study, we have conducted a literature review on addiction causing mutations in the *OPRM1* gene related to drugs, alcohol and smoking addiction. We have also found the mutational hotspots in this gene in 4 exons from the Ensembl Genome browser and used the genome version of GRch37. Further, we conducted the HOPE, POLYPHEN-2, SIFT, MUTATION TASTER and i-MUTANT assay to test their pathogenicity and protein structure change followed by exploring the addiction pathways of *OPRM1*gene.

Main text

Association and pathway studies

A huge amount of studies has been reported in the association of opioids drugs/substance addiction with the *OPRM1* gene, but the results are not always consistent. Some inconsistent result may be because of the small sample size, inadequate statistics or different diagnostic criteria's (Table 1). The study included a range of phenotype for narcotic addiction like heroin addiction, cocaine addiction, methamphetamine addiction and amphetamine addiction. On the other way, in case of a long-term exposure, the brain starts to adapt to some amount of dopamine (DA) that can bind to dopamine transporter (DAT) which helps in transporting dopamine back to the nerve terminal. So, higher doses are needed to produce the same level of pleasure. Activation of PKA signalling pathway through D1R receptor results in activation of ΔFosB which plays a role in development and maintenance of addiction. Activation of this cdk5 and activators p35 and DARPP32 leads to activation of protein called postsynaptic density protein 95 (PSD 95) which results in reduction in the synaptic clustering of NMDARs (N-methyl-d-aspartic acid receptor) (Fig. 1).

Amphetamine Addiction pathway

Amphetamine is a psychostimulant drug that exerts persistent addictive effects. Most addictive drugs increase extracellular concentrations of DA in nucleus accumbens (NAc) and medial prefrontal cortex (mPFC), projection areas of mesocorticolimbic DA neurons and key components of the "brain reward circuit". Amphetamine achieves this elevation in extracellular levels of DA by promoting efflux from synaptic terminals.

Normal condition

Tyrosine hydroxylase (TH) catalyses the hydroxylation of tyrosine to L-DOPA (L-dihydroxyphenylalanine). TH is activated to make more DOPA which after decarboxylation by AADC (aromatic amino acid decarboxylase) the DA is transferred to synaptic cleft by Vesicular Monoamine Transporter (VMAT). At the same time, some amount of DA is converted to dihydroxyphenylacetic acid (DOPAC) and hydrogen per oxide by monoamine oxidase (MOA) in pre-synaptic cleft. DAT helps in transport of DA back to nerve terminal.

Acute amphetamine

Amphetamine-induced tyrosine hydroxylase (TH) results in increased production of DA from L-DOPA through ADCC. DA is transported to synaptic cleft by

Table 1 Association and pathway studies of drug addiction

S No	Population/ethnicity	Addiction-dependent cases				Controls	Genes				Reference
		OD/HD	CD	MD	AmD		*OPRM1*		*OPRK1*	*OPRD1*	
1	Swedish	139				170	√				[10]
2	Asian	473					√				[6]
3	Asian	87				82	√				[11]
4	African Americans	336	503							√	[12]
5	European Americans	1007	336							√	
6	Caucasian				162		√				[13]
7	Asian (Manipur, India)	132				147	√				[14]
8	Mix (7)	79	202			116	√				[15]
9	African Americans	33	125			51	√				[16]
10	Asian (Japanese)				128	232	√				[17]
11	European Americans	412				184	√		√	√	[18]
12	African Americans	202				167	√		√	√	[19]
13	Pakistan	100				100	√				[20]
14	European Americans	83				832	√		√	√	[21]
15	European Americans	91	171			338	√				[22]
16	European Americans	111	225			443			√	√	[23]
17	European Americans	21								√	[24]
18	Caucasian	56				83		√			[25]
19	Caucasian	236				84		√			[26]
	African Americans	74				34		√			
20	Asian (China)	145				48		√			[27]
21	Iran	100				100		√	√	√	[28]
22	Han Chinese (Taiwanese)	72						√	√	√	[29]
23	European Americans			117		76		√			[30]
24	Malaysians Malays	459				543				√	[31]

The table depicts the association and pathway studies of drug addiction cases and dependent cases which have been analysed for *OPRM1*, *OPRK1* and *OPRD1* genes studies from different countries

VMAT, but amphetamine inhibits the activity of MAO. Glutamate binds to its receptor NMDA (N-methyl-D-aspartate) receptor and AMPA. Activation of these receptor allows positive ions to flow through the membrane (Ca^{2+} and Na^{+}). At the same time, released DA bind to D1R receptor. Influx of positive ions result in depolarization which leads to increased Ca^{2+} concentration. Activated D1R binds to Gs which leads to induced activation of Adenyl Cyclase, an enzyme which convert ATP to cAMP which in-turn activate PKA signalling pathway. The cAMP binds to CREB protein that regulates expression of genes and thus induces PDYN, *arc, c-fos* gene expression, which is responsible for induction and maintenance of addiction (Fig. 2).

Chronic amphetamine

In case of chronic abuse, amphetamine-induced TH activity results in production of high concentration of DA from L-DOPA through ADCC. DA is transported to synaptic cleft through VMAT, but MAO activity is inhibited and reuptake of DA by DAT is blocked which leads to increased concentration of DA in synaptic cleft. Glutamine binds to its receptor NMDA and AMPA. Exposure to ethanol also influences the expression of Ca^{2+}/calmodulin-dependent protein kinase IV (CaMKIV), where the CaMKIV main role is to activate the CREB, and thereby CREB phosphorylation occurs in the NAC. Not only is CREB phosphorylated upon activation of D1 cAMP-PKA signalling but also DARPP-32, which is a 32-kDa protein that is expressed predominantly in the synaptic neurons. The central action of nicotine is mediated by nicotine acetylcholine nACh receptor. In normal condition, GABA neurons are transported to synaptic vesicle by Vesicular GABA Transmitter (VGAT). GABA mediates its effect via its receptor GABAA. GABAA receptor present in postsynaptic cell contains chloride ions channel (OCl^{2-}), calcium ions channel (OCa^{2+}) and sodium ions channel (Na^{+}) (Fig. 3).

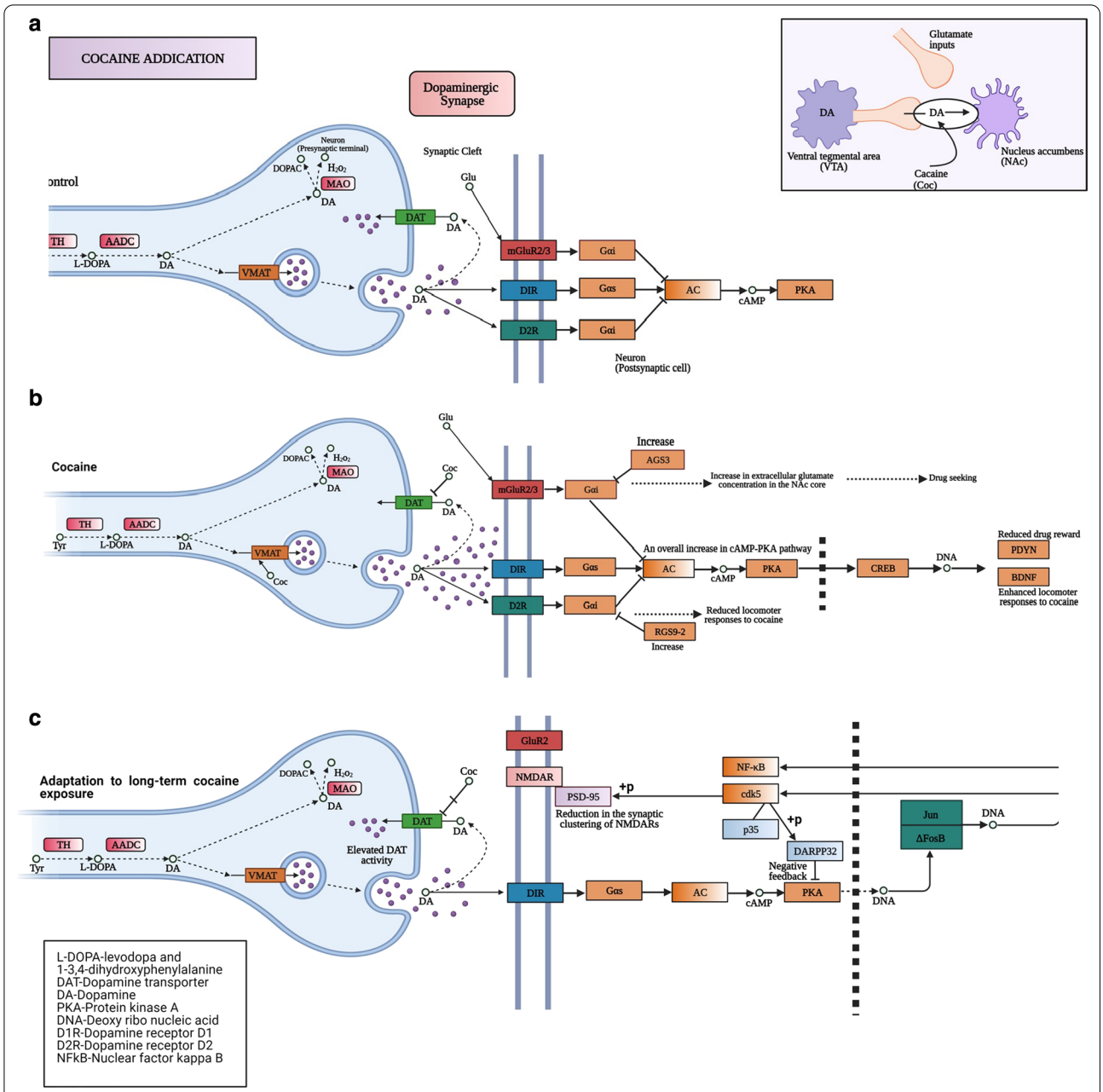

Fig. 1 Addiction and its related signalling pathway: Long-term exposure, on the other hand, causes the brain to adapt to a certain level of dopamine (DA) that can bind to the dopamine transporter (DAT), which aids in the transit of dopamine back to the nerve terminal. To achieve the same level of enjoyment, greater doses are required. When the PKA signalling pathway is activated via the D1R receptor, FosB is activated, which plays a role in the development and maintenance of addiction. The activation of this cdk5 as well as the activators p35 and DARPP32 causes the protein Postsynaptic density protein 95 (PSD 95) to be activated, resulting in a reduction in NMDAR synaptic cluster

Hotspot mutations

Ensembl Genome Browser of version 37 was used to explore the different variations present in the four exons of the *OPRM1*. Focus was given to the variant frequency which contains information about sample size, reference and alternate alleles in populations. In the present study, Gnomad-Exomes database was used to find hotspot mutations. The addiction genes were selected separately from all of the variants present in Gnomad-Exomes (Exons 1, 2, 3 and 4), and there were no addiction variants in exon4 from this database. We have seen three addiction variants in exon1, four in exon2 and five in exon3. These addiction variants were tested by using

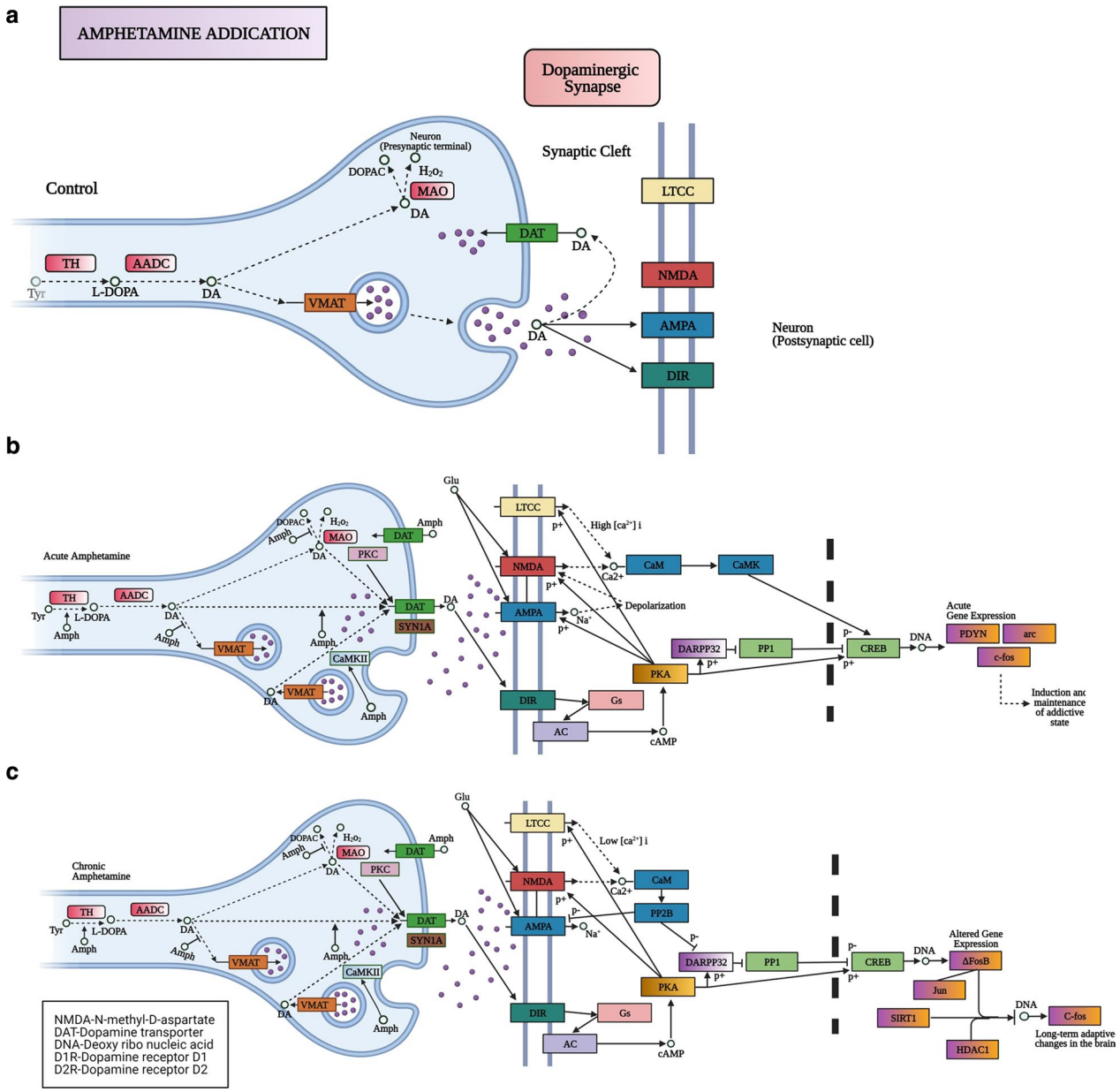

Fig. 2 Amphetamine and its related signalling pathway: Positive ions (Ca^{2+} and Na^{+}) can pass through the membrane when these receptors are activated. Released DA binds to the D1R receptor at the same time. Depolarization occurs as a result of positive ion flux, resulting in an increase in Ca^{2+} concentration. When activated D1R binds to Gs, it causes adenyl cyclase, an enzyme that converts ATP to cAMP, to become activated, which activates the PKA signalling pathway. The cAMP binds to the CREB protein, which regulates gene expression and thereby induces the expression of PDYN, arc and c-fos genes, which are responsible for the induction and maintenance of addiction

in silico analysis-HOPE, SIFT, POLYPHEN-2, MUTATION TASTER and i-MUTANT (Table 5).

Demographic and epidemiological studies in different populations

A case–control study was performed on addicted patients using opioid, cocaine, ecstasy, alcohol, cannabis and sedative substances and statistical diagnostic of DSM IV [32]. Alblooshi et al. (2018) clinically diagnosed for substance used disorder by DSM V and the epidemiological characteristics appeared to correlate with marital status, and the single males were the highest percentage in the cohort [33]. Coller et al. compared genotyped frequencies between opioid-dependent and control groups,

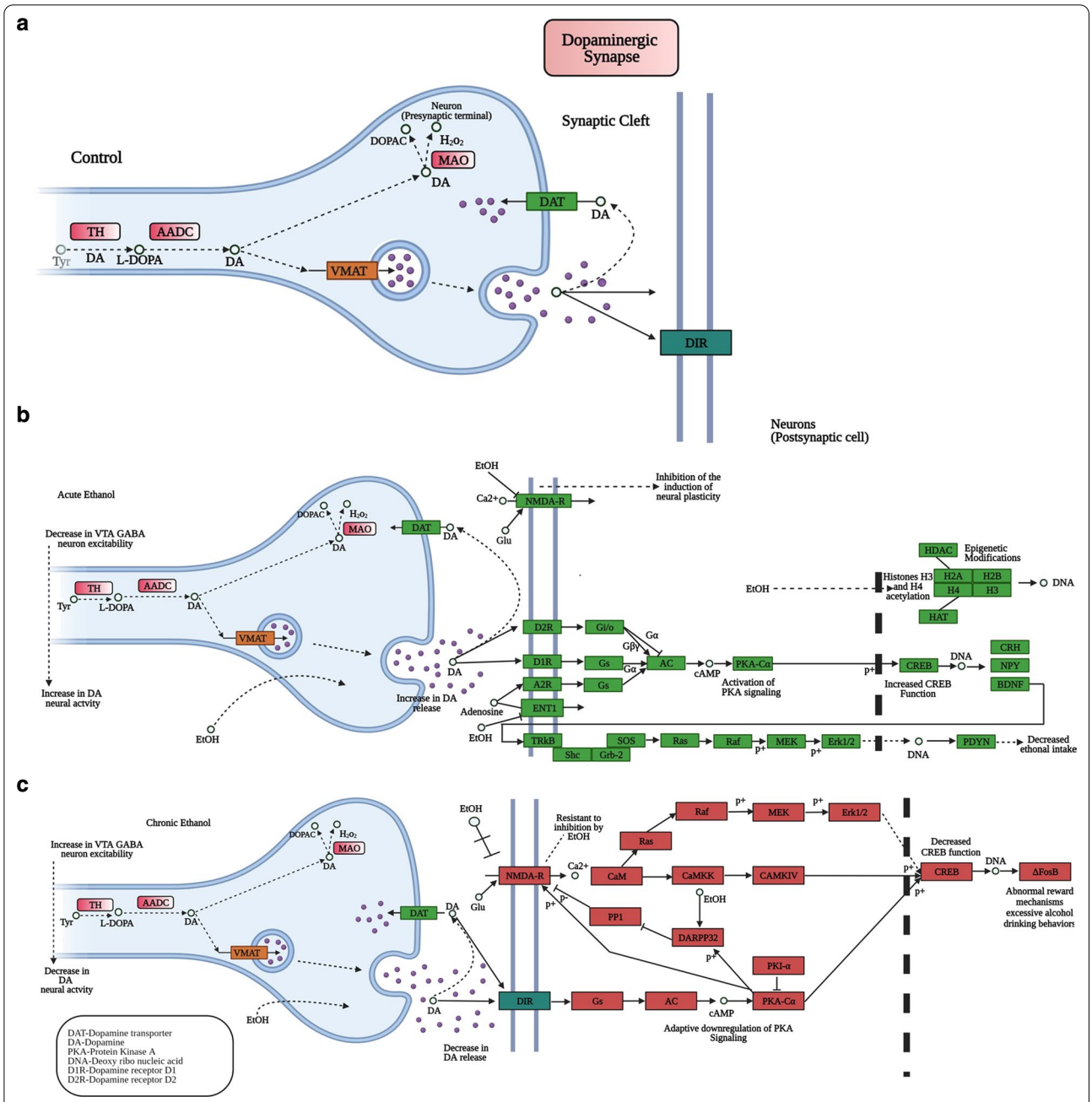

Fig. 3 Chronic amphetamine and its related signalling pathway: Ethanol also affects the production of Ca^{2+}/calmodulin-dependent protein kinase IV (CaMKIV), a protein kinase whose major function is to activate CREB, resulting in CREB phosphorylation in the NAC. When D1 cAMP-PKA signalling is activated, not only CREB, but also DARPP-32, a 32-kDa protein produced mostly in synaptic neurons, is phosphorylated. Nicotine's central effect is mediated by the nicotine acetylcholine nACh receptor. Vesicular GABA transmitter transports GABA neurons to synaptic vesicles in normal conditions (VGAT). GABA's action is mediated via the GABAA receptor. Chloride ions channel (OCl2-), calcium ions channel (OCa^{2+}) and sodium ions channel (Na^{+}) are all present in the GABAA receptor in the postsynaptic cell

and no difference was observed with a pooled OR (95% CI), from the 13 studies of 1.28 (0.77–2.11), $p=0.34$, and the comparison of allele frequencies in case and controls has also no difference with a pooled OR (95% CI) of the 16 studies of 1.16 (0.91–1.47), $p=0.23$ [25]. Puspitasari et al. used cross-sectional method and compared the participants as gender (male and female). The G allele tends to be higher in males ($p=0.029$) (Table 6) [34].

Population based studies

The Genome Aggregation Database (gnomAD) is used to aggregate and harmonize exome and genome sequencing data from a variety of large-scale sequencing projects and to make summary data available for the wider scientific community (https://gnomad.broadinstitute.org/about). We observed population-based hotspot mutation for each of the variants selected for our review. Among all the 12 variants, rs1799971, rs17174794 and rs62638690 were reported in Clinvar as clinically significant, and among them the variant rs1799971 was associated with all the three types of addiction (drugs, alcohol and nicotine/smoking). Variant Asp-40 does not show altered binding affinities for most opioid peptides and alkaloids tested, but it binds to beta-endorphin, an endogenous opioid that activates the mu opioid receptor approximately 3 times more than the most common allelic form. The rs9282819 and rs9282817 are shown virtually monomorphic, and Clarke et al. showed that rs17174794 has no significant association, while rs17174801 and rs62638690 have shown a significant association for narcotic addiction [35] (Table 4).

Narcotic addiction

Drug/substance addiction is widely studied in different populations in various genes. In the case of the *OPRM1* gene, overall there are about 273 SNPs, where variant rsID1799971 from exon1 (also known as A118G, Asn40Asp) are the common polymorphism and mostly studied for addiction [32]. It is the mutational hotspot for the Asian Population and is non-synonymous mutation which indicates the change in amino acid. Turkan et al. included 103 patients addicted to opioids and cocaine and have 83 healthy volunteers with similar demographic features as controls [32]. Their finding includes the genotyping where addicted patients scored 32.0% and control 16.9%, respectively (p value = 0.027), the prevalence of G allele was 16.1% in patient and 8.1% in control group (p value = 0.031) which shows that there is an association between A118G and substance addiction, while there is no result with psychiatric disorder. Schwantes-An et al. performed genetic meta-analysis and has demonstrated that the G allele of rs1799971 has a modest protective effect on substance dependence scoring. The *OPRM1* (A118G) polymorphism in Indonesian population and genotype analysis was carried out by a modified allele-specific polymerase chain reaction (PCR) method [36]. Ahmed et al. performed SNPs genotyping of rsID1799971 (A118G) with PCR–RFLP method and found 13% controls and 7% addicts in heterozygous condition, and 8% controls and 22% addicts in homozygous condition [20]. Drakenberg et al. found the association between heroin and A118G SNP in *OPRM1* in Caucasian European subjects [37].

Besides, the variant S147C (rs17174794) genotyped in European American was found to increase the potency of Morphine, N152D (rs17174801) mutant leads to the reduced expressions of the receptors [38], and N40D (rs1799971) leads to the loss of a glycosylation site in the extracellular N-terminal domain of the MOR, and association was found in many populations, but not found any of these three variants association with narcotic addiction in this paper. Nikolov et al. (2011) also studied heroin addiction in the Bulgarian population from the ethnic Bulgarian and Roma where allelic and genotyping analysis was done [39]. Different statistical analyses method was done to know the allele and genotype frequency. Various polymorphisms were studied from *OPRM1* gene with different substance addiction. In allele frequency, the mutant allele and the wild-type allele frequency were recorded with the OR and p-value. Genotype frequency can be calculated using Hardy–Weinberg equilibrium. The level of statistical significance can be expressed by p-value. A p-value less than 0.05 (typically ≤ 0.05) is said to be statistically significant. The p value higher than 0.05 (>0.05) is not statistically significant and indicates strong evidence for the null hypothesis.

Alcohol addiction

Frances et al. studied the association between the mu opioid receptor gene and alcohol and tobacco consumption in Spanish population [40]. Lara et al. studied the association between the alcohol and *OPRM1* using an intravenous alcohol administration paradigm to investigate the association between sensitivity of *OPRM1* and alcohol and the results showed that the alcohol would be higher in the carrier of the G-allele and they were almost three times more likely to have a family history of AUD [41]. The G-allele carriers were linked with higher urgency and regulation of impulsivity. Alblooshi et al. studied DRD2 and *OPRM1* as candidate genes and performed a cross-sectional case–control cohort in United Arab Emirates (UAE) population [33] (Table 2). Another study investigated the association between *OPRM1* and alcohol dependence in Taiwanese Han where three types of receptor genes were examined by the differences in allele frequency and genotype frequency distribution between cases–control as well as HWE was examined using Fisher's exact tests.

Nicotine addiction

Nicotine is a chemical found in tobacco, and most smokers use tobacco regularly as they are addicted to nicotine. It is an addictive substance which can affect the lungs through smoking tobacco. Nicotine also increases the levels of endogenous opioids that bind to mu opioid

Table 2 Association and pathway studies of alcohol addiction

S. No	Population/ethnicity	Alcohol-dependent cases	Controls	Genes			Publication
				OPRM1	OPRK1	OPRD1	
1	US Caucasian	100		√			[42]
	Finnish	324		√			
	American Indians	367		√			
2	Asian	53	82	√			[11]
3	American Indians	251		√			[43]
4	Mix (7)	100	116	√			[15]
5	European Americans	179	297	√			[44]
6	European Americans	219			√		[45]
7	European Americans	219	832	√	√	√	[21]
8	European Americans	318	338	√			[22]
9	European Americans	557	443		√	√	[23]
10	Finnish	512	511	√			[46]
11	Caucasian	236	84	√			[26]
	African Americans	74	34	√			
12	Los Angelas (White, AfricanAmerican, Asian, Latino, NativeAmerican)	295		√			[41]
13	Spanish (Caucasian)	763		√			[40]
14	Korean	112	140	√			[47]

The table explains the association and pathway studies of alcohol-dependent cases and controls in the genes *OPRM1*, *OPRK1* and *OPRD1* in different populations

Table 3 Association and pathway studies of nicotine/smoking addiction

Population/ethnicity	Nicotine-dependent cases	Genes			Publication
		OPRM1	OPRK1	OPRD1	
European	288	√			[22]
Chinese	284	√			[52]
Caucasian	688	√			[22]
Spanish	763	√			[40]
Caucasian + Asian	3313	√			[49]
Caucasian	179	√			[44]
Caucasian	62	√			[50]
UK	633	√			[53]
Netherland	1399	√			[51]
Pennsylvania	44	√			[41]
Caucasian + Asian		√			[2]

This table explains the association and pathway studies of nicotine/smoking addiction in different populations *OPRM1*, *OPRK1* and *OPRD1* in different ethnic groups

receptors on GABA interneurons in the VTA, and the mu opioid receptor (*OPRM1*) ASN40ASP functional variant has been associated with response to NRT; however, the direction of association in different populations has not been consistent [48]. The association between the nicotine dependence and the *OPRM1* was systematic reviewed, and meta-analysis was performed [49]. The odd ratios (OR) and 95% confidence interval (95% CIs) were calculated in allele, homozygote, heterozygote, dominant and recessive allele. Lechner et al. (2016) found the influence of A118G polymorphism in *OPRM1* gene and VNTR polymorphism in DRD2 gene on cigarette cravings after alcohol drinking where genotyping and analysis were done for these polymorphisms. Naltrexone may be

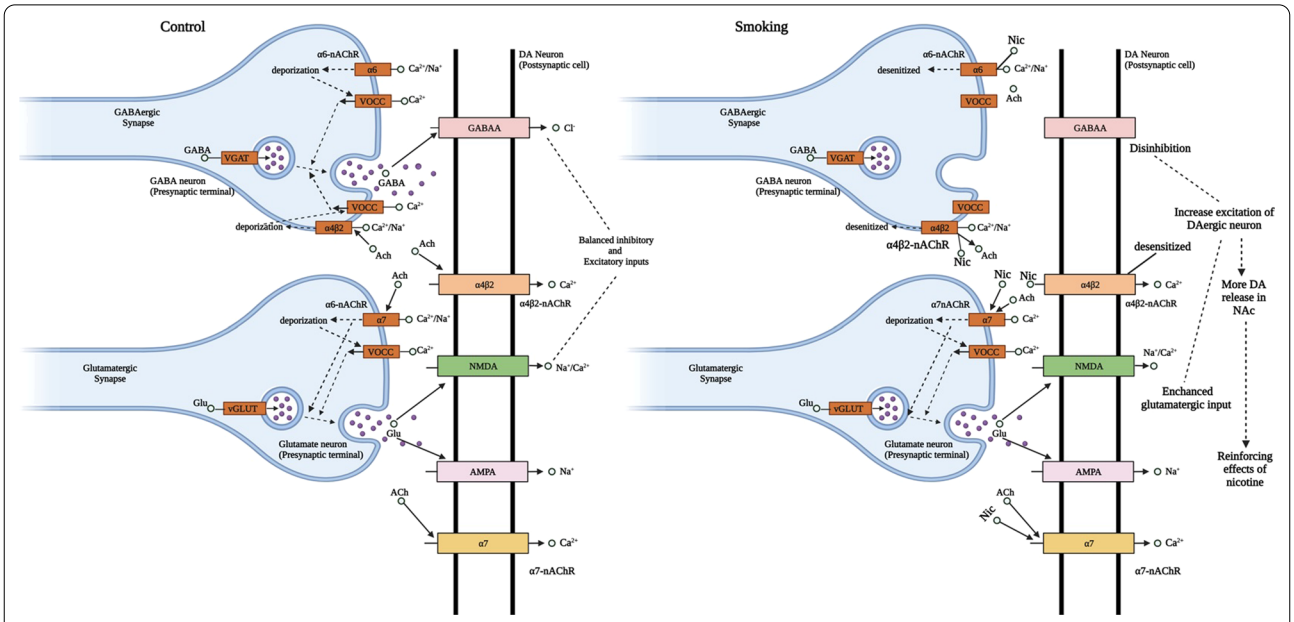

Fig. 4 Signalling pathway related to nicotine addiction: Nicotine is a substance contained in tobacco, and most smokers are addicted to nicotine; therefore, they use tobacco on a regular basis. It is an addictive drug that can harm your lungs if you smoke tobacco. The mu opioid receptor (OPRM1) ASN40ASP functional variant has been associated with response to NRT, but the direction of association in different populations has not been consistent. Nicotine also increases the levels of endogenous opioids that bind to mu opioid receptors on GABA interneurons in the VTA

Table 4 Population-based variants in the *OPRM1*

S. No	rsID	Exon	Hotspot (population)
1	rs1799971	1	Asian
2	rs9282819	1	European
3	rs9282817	1	African
4	rs17174794	2	European
5	rs17174801	2	African
6	rs79910351	2	European
7	rs62638690	2	Ashkenazi Jewish
8	rs1799974	3	European
9	rs17174822	3	African
10	rs200811844	3	African
11	rs17174829	3	European
12	rs11575856	3	Asian

This table explains the different exons and hotspot regions in population-based variants

an important and helpful in aiding smoking cessation for those who are having a heavy drink of alcohol [50]. Zhang et al. examined the association of smoking initiation and nicotine dependence with mu opioid receptor where the sample was drawn from two population-based twin studies (Table 3) [22]. Kleinjan et al. studied the development of nicotine craving in adolescence smokers who have smoked from the parental exposure of smoking. Three types of genes are genotyped—*DRD2, DRD4* and *OPRM1* (Fig. 4) [51] (Tables 4, 5 and 6).

Conclusion

Taken collectively, our review shows that rs1799971 in exon 1 is the most commonly studied addiction variants in different population in substance addiction. Although there are many studies, the association between addiction and *OPRM1* is not fully catalogued [55]. Based on previous studies, males have more chances to become addicted compared to females and different substance addiction was influenced by 60% genetics as well as environmental factor [56]. The identification of genes which involve in addiction pathway may prove our understanding of the disorder and may allow the development of treatment process. As the literature review covers only few exons of *OPRM1*, the full-length gene sequence data will throw more light for such types of studies. To conclude, as different studies showed conflicting results, researchers may need to study a larger sample size to have a better conclusion. The potential clinical utility of *OPRM1* polymorphism which is influenced as a pharmacogenetic predictor of response to naltrexone needs much more study. Thus, it may be necessary to address the genetic predisposition and delineate the association with the clinical problems in future studies.

Table 5 OPRM1 variants allele frequency and genotype frequency in different worldwide population

S. No	Author	Location	Population	rsID	Controls	Patients	Substance	Allele frequency				Genotype frequency	
								A	G	OR	*P* value	OR	*P* value
1	[32]	Europe	Turkish	rs1799971	83	103	General substance	0.839	0.084	2.07	0.031	2.32	0.027
						96	Opioid	–	–	–	–	2.217	0.081
						96	Cocaine	–	–	–	–	0.635	0.484
2	[10]	Europe	Swedish	rs1799971	120	67	Heroin	0.828	0.172	**2.72****	0.0025	2.97	0.0031
3	[36]	Europe	European Ancestry	rs1799971	–	–	Substance dependence	–	–	–	–	0.90	**0.952****
4	[34]	Asia	Indonesian	rs1799971	–	158	Opioid	0.396	0.604	**0.029***	**1.659****	1.19	0.092
5	[20]	Asia	Pakistan	rs1799971	100	100	Opioid	0.74	0.26	–	–	3.06(GG)	0.016
6	[37]	Europe	Caucasian European	rs1799971	–	65	Heroin	–	–	–	–	**0.061***	0.013
7	[35]	North America	European American	rs62638690	–	1377	Heroin/cocaine	©	0.99 (F)	0.47	0.02	0.94	0.796
				rs17174794	–			C	0.38 G	1.49	0.19		
			African American	rs17174801	–			A	0.9 G	1.14	0.65	0.94	0.74
				rs1799971	–				**2.62****	0.57	0.57		
8	[33]	European	UAE	rs1799971	262	512	SUD	–	–	–	–	0.78	0.12
9	[39]	Europe	Bulgarian	rs1799971	3293	Heroin	Roma	–	0.202	–	0.0009	–	–
							Non-Roma	–	0.138	–	–	–	–
10	[40]	Europe	Spanish	rs1799971	763 women (465) Men (298)	Alcohol	Women					0.55	0.049
							Men	–	–	2.25	0.046	–	0.280
11	[41]	Europe	Caucasian	rs1799971	295	Alcohol		–	–	–	–	–	0.056
12	[49]			rs1799971	9613	Alcohol		–	–	–	–	1.261	0.042
13	[46]	Europe	Finnish	rs1799971									
14	[47]	Asia	Korean	rs1799971	140 112	Alcohol		0.603	0.397	1.40	0.105	1.21	0.045
15	[33]	Europe	UAE	rs1799971	262 512	SUD		0.189	0.154	0.78	0.12	–	–
			Egypt Arabs	rs1799971				0.007	**0.052***	0.73	0.54	–	–
			Combine of UAE& Egypt Arabs	rs1799971				0.17	0.13	0.73	0.04	–	–
16	[40]	Europe	Spanish	rs1799971	763 (Unrelated Subject)	Smoking		–	–	–	–	–	0.716
17	[49]	Europe + Asia	Caucasian + Asian	rs1799971	3313	Nicotine dependence		–	–	1.000	0.999	1.261	0.042
18	[50]	Europe	Caucasian	rs1799971	62	Cigarette craving		–	–	–	–	–	0.008
19	[2]	Europe	Caucasian	rs1799971	–	Smoking		–	–	–	–	**3.26****	**0.00***

This table explains the OPRM1 variants allele frequency and genotyped frequency in different worldwide population compared to patients and controls

Table 6 Demographic studies in different populations

S. No	Subject categorized	No. of participants	Age	Age at addiction	Gender		Ethnicity	Marital status				Family history
					Male	Female		M	UM	W	D	
1	A118A	–	23–45	19–25	57	31	–					6.56
	A118G		20–28	12–22	12	3						17.2
2	15–58	26	15–58		23	33						
	19–46	39	19–46		3	6						
3	Control		36.5 years			52%						
	Heroin		45.6 years			23%						
4	Control		31.8 years		54.3%							
	Substance dependence		37.9 years		71.2%							
5	Control	2324			78%							
	Opioid	2845			56%							
6			Below 20–12 20–29: 144 30–39: 54 40–49: 32 Above 50: 8				Ajam-17 Arab-56 Bloush-18 Mixed-48 None-10	89	146	1	14	142
7	Current smoker		Mean age 56.4 ± 14.8									
	Ex-smoker		Mean age 68.5 ± 8.3									
8	Male	39.9 ± 14.7						158	108		3	
	Female	36.7 ± 14.8						148	176		177	
	Male	42.3 ± 12.7						43	22	–	2	
	Female	39.6 ± 12.7						58	41	4	3	
9	OH dependent		19.6%		94.6%							
	Non-alcohol dependent		41.4%		57.1%							

Table 6 (continued)

S. No	Subject categorized	Smoking history	Alcohol	Education						Disease history/ cause of death/ stress related	Employment	References
				P	HS	S	Dip	U	Doc			
1	A118A	12.5		50	28.1			12.5	9.3			[54]
	A118G	20.0		38.7	22.5			16.1	22.5			
2	15–58									Alcohol intoxication (n 2), electric shock (n 2), pulmonary emboli (n 1), myocardial infarct (n 17), pneumonia (n 2), sudden death (n 2)		[37]
	19–46									Heroin overdose		
3	Control											[10]
	Heroin											
4	Control											[15]
	Substance dependence											
5	Control											[25]
	Opioid											
6		Current smoker—239 Ex-smoker—11 Never smoke—0		135	71		30				Employed: 82 Unemployed: 116 Student: 31 Master degree: 2 Bachelor degree: 11	[33]
7	Current smoker	Mean age: 23.6 ± 8.0Cigarette consume (per day)—22.3 ± 11.9 Smoking years—32.9 ± 14.3		35.5	64.5					Cardiovascular and cerebrovascular—58.7 Respiratory disease—27.5 Diabetes mellitus—13.8		[52]
	Ex-smoker	Mean age: 28.3 ± 10.8 Cigarette consume (per day)—19.9 ± 9.9 Smoking years -31.7 ± 12.3		34.9	65.1					Cardiovascular and cerebrovascular—62.3 Respiratory disease—30.8 Diabetes mellitus—6.8		

Table 6 (continued)

S. No	Subject categorized	Smoking history	Alcohol	Education						Disease history/ cause of death/ stress related	Employment	References
				P	HS	S	Dip	U	Doc			
8	Male			44		136		91		Stress at work: 5.85 ± 2.54 Life stress: 4.94 ± 2.17 OH intake g/d: 7.50 ± 8.78 AUD (AUDIT ≥ 8): 10.6		[40]
	Female			63		169		123		Stress at work: 5.39 ± 2.65 Life stress: 5.17 ± 2.29 OH intake g/d: 4.75 ± 6.50 AUD (AUDIT ≥ 8): 7.3		
	Male			21		30		17		Stress at work: 6.30 ± 2.62 Life stress: 5.13 ± 2.21 Cigrette intake n/d: 12.9 ± 10.3 Fragestrom score: 3.38 ± 2.96		
	Female			30		46		31		Stress at work: 5.90 ± 2.93 Life stress: 6.05 ± 2.44 Cigrette intake n/d: 11.2 ± 8.7 Fragestrom score: 2.89 ± 2.09		

Table 6 (continued)

S. No	Subject categorized	Smoking history	Alcohol	Education						Disease history/ cause of death/ stress related	Employment	References
				P	HS	S	Dip	U	Doc			
9	OH dependent		Age of onset of alcohol problems—35 First hospitalization for alcohol problems (years)— 42.5 Average drinking days per month—16.3 Drinks per drinking day—12.4 Family history of alcohol problems—47.3 History of severe alcohol withdrawal – 22.3	8.7%								[47]
	Non-alcohol dependent		N/A	N/A								

This table explains the demographic studies in different populations

M: married; UM: unmarried; W: widow; D: divorced; P: primary; S: secondary; HS: high school; Dip: diploma; U: university; Doc: doctorate; Fam: family; Frd: friends; Eco: economic

Abbreviations
OPRM1: Mu (μ) opioid receptor; KEGG: Kyoto Encyclopedia of Genes and Genomes; SNPs: Single nucleotide polymorphisms; MOR: Mu opioid receptor; mRNA: Messenger ribonucleic acid; DA: Dopamine; DAT: Dopamine transporter; D1R receptor: Dopamine receptor D1; p35: Cyclin-dependent kinase 5 activator protein; PKA: CAMP-dependent protein kinase; NMDARs: N-methyl-d-aspartic acid receptor; NAc: Nucleus accumbens; mPFC: Medial prefrontal cortex; TH: Tyrosine hydroxylase; L-DOPA: L-Dihydroxyphenylalanine; AADC: Aromatic amino acid decarboxylase; VMAT: Vesicular monoamine transporter; DOPAC: Dihydroxyphenylacetic acid; MOA: Monoamine oxidase; NMDA: N-methyl-D-aspartate; CaMKIV: Ca^{2+}/calmodulin-dependent protein kinase IV; VGAT: Vesicular GABA transmitter; OCl2: Chloride ions channel; OCa2+: Calcium ions channel; gnomAD: The genome aggregation database; CI: Confidence interval; PCR: Polymerase chain reaction; PCR–RFLP: Polymerase chain reaction–restriction fragment length polymorphism; HWE: Hardey Weinberg equilibrium; *DRD2*: Dopamine receptor D2; *DRD4*: Dopamine receptor D4; DST: Department of Science and Technology.

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NSK, VH, CV and HPS performed conceptualization of the manuscript; VB, IM, SMD and KRSSR revised and edited the manuscript. All authors have reviewed the manuscript.

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