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Review article

The association of genetic polymorphisms within the dopaminergic system with nicotine dependence: A narrative review

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ABSTRACT

Nicotine, the main compound in cigarettes, leads to smoking addiction. Nicotine acts on the limbic dopamine reward loop in the midbrain by binding to nicotinic acetylcholine receptors, promoting the release of dopamine, and resulting in a rewarding effect or satisfaction. This satisfaction is essential for continued and compulsive tobacco use, and therefore dopamine plays a crucial role in nicotine dependence. Numerous studies have identified genetic polymorphisms of dopaminergic pathways which may influence susceptibility to nicotine addiction. Dopamine levels are greatly influenced by synthesis, storage, release, degradation, and reuptake-related genes, including genes encoding tyrosine hydroxylase, dopamine decarboxylase, dopamine transporter, dopamine receptor, dopamine 3-hydroxylase, catechol-*O*-methyltransferase, and monoamine oxidase. In this paper, we review research progress on the effects of polymorphisms in the above genes on downstream smoking behavior and nicotine dependence, to offer a theoretical basis for the elucidation of the genetic mechanism underlying nicotine dependence and future personalized treatment for smoking cessation.

List of Abbreviations

Abbreviation	Definition
TH	tyrosine hydroxylase
DDC	dopamine decarboxylase
DAT	dopamine transporter
DRD	dopamine receptor
DBH	dopamine decarboxylase
COMT	catechol-*O*-methyltransferase
MAO	monoamine oxidase
GWAS	genome-wide association studies
nAChRs	nicotinic acetylcholine receptors

(*continued on next page*)

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VNTR	variation in the number of tandem repeats
SNP	single nucleotide polymorphism
AA	African American
EA	European American
FTND	Fagerström Test for Nicotine Dependence
CNS	central nervous system
GABA	γ-aminobutyric acid
cAMP	cyclic AMP

1. Introduction

Tobacco use is prevalent worldwide and has caused severe health hazards over time. The *China Report on the Health Risks of Smoking, 2020* provides ample evidence that smoking causes lung cancer, malignant tumors of the oral cavity and oropharynx, as well as many other malignancies. Tobacco use is the leading preventable mortality factor in developed countries [1]. Numerous studies have demonstrated that nicotine is the primary addictive compound found in tobacco products, producing strong addiction through long-term tobacco use [2]. Nicotine induces pleasure and reduces stress and anxiety. Smokers use it to improve levels of arousal and to control mood. Smoking improves concentration, reaction time, and performance of specific tasks. Cessation of smoking causes the emergence of withdrawal: irritability, depressed mood, restlessness, and anxiety. When a person who is addicted to nicotine stops smoking, the urge to resume is recurrent and persists long after withdrawal symptoms dissipate [3]. With regular smoking, the smoker comes to associate specific moods, situations, or environmental factors — smoking-related cues — with the rewarding effects of nicotine. Typically, these cues trigger relapse [3]. The basis of nicotine dependence is a combination of positive reinforcements, including enhancement of mood and avoidance of withdrawal symptoms [3]. To our knowledge, nicotine is the only drug observed to elicit an aversive phenotype in rodents both when the drug is delivered immediately before or after the conditioning period, suggesting its unique, acutely aversive effects [4]. Furthermore, the aversive effects of nicotine can be experienced concurrently with the pleasurable effects [5] and tolerance to high doses develops over time [6], suggesting that nicotine aversion may be distinct from nicotine reward and tolerance to aversion may underlie the development of habitual nicotine consumption [7]. Nicotine dependence is a complex phenomenon [8]. It is commonly believed that a combination of sociological, psychological, and biological factors leads to the development of nicotine dependence. The results of a large sample of studies of twins have shown that genetic factors contribute up to 40–60 % to smoking behavior, suggesting a significant genetic basis for nicotine dependence [9]. Further research demonstrated that genetic factors have a considerable influence on the development and severity of nicotine dependence as well as response to treatment [10]. For instance, genome-wide association studies (GWAS) have linked a gene cluster in chromosomal region 15q25 to increased susceptibility to nicotine dependence, they highlight coding and synonymous polymorphisms in encompassing the *CHRNA5*, *CHRNA3* and *CHRNB4* genes, coding for three subunits of the nicotinic acetylcholine receptors (nAChRs) [11]. Additionally, many candidate genes involved in dopaminergic neurotransmission are essential [12,13].

After cigarette smoke inhalation, nicotine is transported through the bloodstream where it crosses the blood-brain barrier and enters the brain. Here, it acts on the midbrain limbic "dopamine reward pathway" by binding to nAChRs, promoting the release of neurotransmitters such as dopamine [14]. Dopamine is critical for the reinforcing effects (effects that promote self-administration) of nicotine and other drugs of abuse [15], as well as reward, motivation and learning [16]. Nicotine also augments both glutamate release, which facilitates the release of dopamine, and γ-aminobutyric acid (GABA) release, which inhibits the release [17,18]. As a result, GABA-mediated inhibitory tone diminishes while glutamate-mediated excitation persists, thereby increasing the excitation of dopaminergic neurons and enhancing responsiveness to nicotine, as the dopamine system is heterogeneous [19]. Inference can be drawn from this that, with long-term exposure to nicotine, some nAChRs become desensitized, but some do not.

With repeated exposure to nicotine, neuroadaptation (tolerance) to some of the effects of nicotine develops [20]. For example, the number of binding sites on the nAChRs in the brain increases, likely due to nicotine-mediated desensitization of receptors, which is believed to play a role in tolerance and dependence [21]. The symptoms of craving and withdrawal begin in smokers when desensitized [22]. In addition, nicotine withdrawal symptoms are powerful incentives to take up smoking again.

If a genetic mutation makes nicotine less rewarding, it will actually translate into increased nicotine consumption. This is indeed quite counter intuitive at first, but may explain why smokers with the 10-r allele (*SLC6A3*) show greater nicotine reward yet reduced nicotine dependence [23]. Such an effect was clearly demonstrated in mice carrying nAChRs alpha5 human SNP D398 N, which reduces the rewarding properties of nicotine, leading to greater nicotine self-administration [24].

The activity of dopamine in the brain is finely regulated. Typically, dopamine released through action potential firing is quickly reabsorbed in equal amounts. An excessive decrease in dopamine levels can lead to an aversive state [19]. Long-term excess of dopamine will induce pathological behaviors, including compulsive drug use, loss of control over drug intake, and persistence in drug-seeking despite adverse consequences [25,26]. There are considerable risks to individual health and functioning. It has been shown that chronic nicotine leads to an increase in the activity of ventral tegmental area dopamine neurons and therefore leads to a hyperdopaminergic state [27]. Dopamine levels in the body are regulated by proteins associated with the dopaminergic system, including 1) synthesis of dopamine in dopaminergic neurons; 2) release of dopamine from presynaptic neurons; 3) receptor activation in postsynaptic neurons; 4) reuptake of dopamine by presynaptic neurons, and 5) metabolic inactivation of the released dopamine [28]. Therefore, changes in the synthesis, storage, release, degradation, and reuptake processes of dopamine may alter nicotine

reinforcement by smoking and thus change smoking behaviors, such as smoking cessation, number of cigarettes per day, and smoking quantity [29].

Many candidate genes and polymorphisms related to dopaminergic neurotransmission have been identified, including tyrosine hydroxylase (*TH)* [30], dopa decarboxylase *(DDC)* [31], dopamine transporter *(DAT1/SLC6A3)* [32], dopamine receptor (*DRD)* [33, 34], monoamine oxidase *(MAO)* [35], catechol-*O*-methyltransferase *(COMT)* [36], and dopamine-β-hydroxylase *(DBH)* [37]. Dopamine synthesis, beginning with tyrosine as a raw material, is catalyzed by TH to produce levodopa (L-DOPA), which is then modified to dopamine by DDC and is finally stored in vesicles [38]. When an action potential fires, dopamine is released through volume diffusion. Typically, dopamine released by action potential firing is rapidly and equally taken up by the DAT for re-use in the nerve terminal [32]; some of the dopamine in the synaptic gap is bound to the DRD for action potential firing transmission [39]. Intraneuronal dopamine is mainly converted by MAO to dihydroxyphenylacetic acid, formed inside and outside the neuron [40]. In the presence of extracellular COMT; dihydroxyphenylacetic acid is converted to homovanillic acid; dopamine released from nerve terminals is first converted from COMT to 3-oxymethyltyrosine, and then by MAO to homovanillic acid [12]. When neurons are excited, DBH is released via the cellular efflux from nerve terminals and metabolises dopamine to noradrenaline to terminate neurotransmission [41] (Fig. 1). Association studies have demonstrated that polymorphisms of genes encoding DRD2 and SLC6A3 are significantly associated with smoking cessation [33,34]. Given that many of the studies are primarily based on Caucasian and American populations, it's important to consider that some factors, such as sample size, statistical power, and racial differences, can significantly influence the final results [42, 43]. This variation may contribute to the limited similarities observed between these findings and the results of recent GWAS on nicotine dependence [34]. Consequently, the results should be interpreted with caution and replicated in independent samples, especially considering the predominant focus on Caucasian and American populations in current research. This manuscript compiles and reviews the association results of dopaminergic gene polymorphisms with nicotine dependence across different populations. The compiled findings can help to explore the influence of related gene polymorphisms on nicotine dependence in different populations and provide a scientific basis for the elucidation of the molecular mechanism of nicotine dependence and potential personalized treatment for smoking cessation.

2. Methods

A literature search of PubMed, Web of Science, and Google was conducted to identify relevant studies published up to January 2022. We used the following search terms: "nicotine" or "smoking" or "cigarette" and "addiction" or "dependence" and "tyrosine hydroxylase" or "TH" or "dopa decarboxylase" or "DDC" or "dopamine transporter" or "DAT" or "SLC6A3" or "dopamine receptor" or "DRD1" or "DRD2" or "DRD3" or "DRD4" or "DRD5" or "catechol-*O*-methyltransferase" or "COMT" or "monoamine oxidase" or "monoamine oxidase A" or "MAO-A″ or "monoamine oxidase B″ or "MAO-B″ or "dopamine-β-hydroxylase" or "DBH" and "polymorphism" or "variation" or "single nucleotide polymorphism" or "SNP" or "variation in the number of tandem repeats "or "VNTR." The reference lists of the relevant articles were also manually searched to identify any studies potentially missed by the database search. Studies must be published in English, and population sample size, race, age, and sex were not specifically restricted to include more comprehensive information. Study should have been done on association of genetic polymorphisms within the dopaminergic

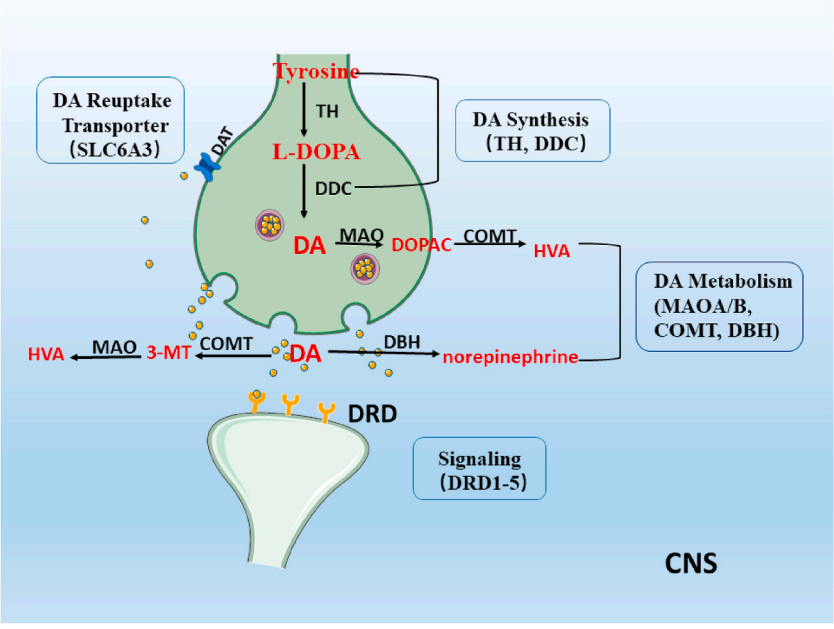

Fig. 1. Overview of genes related to the dopaminergic system [12]. CNS, central nervous system.

system with nicotine dependence. During the literature search, references related to a few dopamine-related disorders were identified, including but not limited to Parkinson's disease, attention deficit hyperactivity disorder, and others. Considering the close association of these disorders with the dopaminergic system, we found it necessary to include these relevant references. The first author collected data from each report, and all reviewers screened each record, and each report was retrieved. Risk ratio and *p*-value used in the presentation of results. A total of 143 references were included in this review.

3. Dopamine synthesis-related gene polymorphisms

3.1. TH

Tyrosine is the beginning point of dopamine synthesis. Tyrosine enters dopaminergic neurons and is converted to dihydroxyphenylalanine (levodopa, L-DOPA) by TH. TH is the rate-limiting enzyme for dopamine biosynthesis. Therefore, genes encoding TH are strong candidates to be involved in the genetic aspect of addiction. The *TH* gene is located on the telomeric end of the short arm of chromosome 11 at 11p15.5. This gene spans 8 kb of the genome and contains 13 exons with an additional alternatively spliced exon 1 [44]. Functional tetranucleotide (TCAT)-repeat sequence polymorphism (HUMTH01-VNTR) within intron 1 of the *TH* gene is a risk factor for nicotine dependence in two distinct samples from the United States and Australia [30] (Table 1). Anney et al. [30] tested the effects of HUMTH01-VNTR on nicotine dependence based on an Australian adolescent population. Addicted smokers were compared to non-addicted smokers. These data further support a protective association between the K4 (7-r) allele and nicotine-dependent smoking, with no correlation observed in any of the other three common *TH* polymorphisms (rs6356, rs6357, and HUMTH01 *Pst*I) (Table 1).

HUMTH01-VNTR is involved in the regulation of gene expression. The TCAT-motif is believed to function as one of several scaffolds or matrix attachment regions (S/MARs) [48], or as a binding site for a number of transcription factors including ZNF191, HBP1, and

Table 1
Gene polymorphisms in TH and DDC genes associated with smoking behaviors.

Genes	Gene polymorphism	Associated risk genes and genotypes/ Hapolytype	Sample Population	Crowd Results	Results of significant analysis	References
TH	HUMTH01-VNTR	K1 (11-r)Allele	Nicotine dependent and non-addicted smokers in 86 white Australian adolescents	Risk factors for nicotine dependence	OR = 2.1,95%CI= (0.98–4.6)	[30]
		K4(7-r)Allele		Protects smokers from developing nicotine dependence	P = 0.06, OR = 0.54,95%CI= (0.28–1.0)	
	rs6356	C > A,T		No correlation was observed		
	rs6357	C > T		No correlation was observed		
	rs2070762 (HUMTH01 *Pst*I)	A > G,T		Deviation from Hardy-Weinberg equilibrium		
DDC	rs921451	T > C	1590 individuals in 319 AA and 302 EA families	Related to FTND in EAs and AAs	EAs(P = 0.02), AAs(P = 0.04)	[31]
	rs921451	T > C	2037 smokers and nonsmokers (671 EAs from 200 EA families and 1366 AAs from 402 AA families)	Correlation with smoking quantity, heaviness of smoking index in EAs	smoking quantity(P = 0.01), heaviness of smoking index (P = 0.03)	[45]
	rs921451	T > C	1294 students aged 12 to 13 in the Canadian region	Related to smoking quantity.	P = 0.00568	[46]
	rs4947644	T > A,C,G		Related to nicotine dependence/Craving	P = 0.00977	
	rs11575461	G > A,C	223 high and 257 low addicted smokers in Han Chinese	Significantly correlated with FTND	$P = 1.06 \times 10^{-5}$,OR = 6.16	[34]
	rs12718541	A > G		Related to FTND in EAs and AAs	EAs(P = 0.03), AAs(P = 0.002)	
DDC	rs921451-rs3735273-rs1451371-rs2060762	C-A-T-G	1879 smokers and nonsmokers from 600 nuclear families of AA or EA	Related to heaviness of smoking index in EAs	p = 0.003	[47]
			2037 smokers and nonsmokers (671 EAs from 200 EA families and 1366 AAs from 402 AA families)	No correlation was observed	P = 0.19	[45]

Note: VNTR: Variation in the number of tandem repeats, **SNP:** single nucleotide polymorphism, **AA:** African American; **EA:** European American; **FTND:** Fagerström Test for Nicotine Dependence, Test of Nicotine Dependence scale. (When FTND ≥6, it is considered as a criterion to distinguish high nicotine dependence); ***p* value:** Statistical obtained according to the significance test method *p* value, generally $p < 0.05$ is significant, $p < 0.01$ is very significant; **OR value:** Odds ratio, OR value greater than 1, indicating that the factor is a risk factor; OR value less than 1, indicating that the factor is a protective factor.

Table 2
Polymorphisms in the SLC6A3 gene associated with smoking behaviors.

Genes	Gene polymorphism	Associated risk genes and genotypes	Sample Population	Crowd Results	Results of significant analysis	References
SLC6A3(DAT1)	VNTR	9-r Allele	19 (10 male, 32 % AAs, 43 % EAs, 21 % multi-ethnic)	Contributes to the neural and behavioral responses elicited by smoking cues	<0.001	[32]
		9-r Allele	88 AA smokers	Smokers carrying the genes had stronger cue-induced craving than non-carriers	P < 0.01	[62]
		10-r Allele	220 (108 male, 112 female) adolescents of European descent aged 14.9 years	Significantly lower intention to quit smoking among pure-sibling adolescents	p = 0.044	[64]
		9-r Allele	2155 mixed (80 % white of European ancestry) subjects	A 20 % increase in the odds of quitting smoking	OR = 1.20,95%CI= (1.01,1.43)	[63]
		9-r Allele	250 Korean smokers	The frequency of this genotype was higher in the non-abstinence group than in the abstinence group	P = 0.01	[65]
		10-r Allele	96 Japanese (75 current smokers and 21 former smokers)	The 10r/10r genotype carriers is more likely to have a lower nicotine dependence	P = 0.002, OR = 0.130,95% CI = (0.036–0.464)	[60]
		9/10-r Allele	583 British smokers	After 1 week of smoking cessation, a 10 % higher quit rate was observed in those carrying the 9-r allele than in those carrying the 10-r/10-r genotype.	P = 0.012; OR = 1.9, 95% CI=(1.1, 3.2)	[61]
		2/3 –r Allele		An 8.5 % increase in quit rate for those carrying the 2–r allele after 1 week of smoking cessation	P = 0.03; OR = 1.7, 95%CI= (1.0, 2.9)	[61]
	rs115	C > A		This SNP is not associated with smoking cessation	P = 0.896; OR = 0.959	[61]
	rs270	C > A		This SNP is not associated with smoking cessation	P = 0.635; OR = 1.136	[61]
	rs296	G > A,T		This SNP is not associated with smoking cessation	P = 0.728; OR = 1.098	[61]
	rs27072	C > A,T	668 smokers among 253 rural Chinese siblings.	The risk of early smoking onset among smokers with severe nicotine dependence carrying the A allele is almost three times greater than total smokers	OR = 11.3,95%CI= (1.5,85.6)	[66]
			476 Malay adult males (238 smokers and 238 non-smokers)	Neither genotype level nor allele level was associated with smoking behavior in the Malay male population	Genotype: P = 0.64; Allele: P = 0.75	[67]

Note: VNTR: Variation in the number of tandem repeats, **SNP:** single nucleotide polymorphism,**9-r:** 9-repeat, **AA:** African American; **EA:** European American; ***p* value**: Statistical obtained according to the significance test method *p* value, generally $p < 0.05$ is significant, $p < 0.01$ is very significant; **OR value:** Odds ratio, OR value greater than 1, indicating that the factor is a risk factor; OR value less than 1, indicating that the factor is a protective factor.

Table 3
Gene polymorphisms in DRD2/ANKK1 gene associated with smoking behaviors.

Genes	Gene polymorphism	Associated risk genes and genotypes	Sample Population	Crowd Results	Results of significant analysis	References
DRD2/ANKK1	rs1800497 (TaqIA)	G > A	220 adolescents of European descent (108 males, 112 females) aged 14.9 years	FTND scores were elevated in adolescents carrying the A1 allele.	p = 0.037	[64]
			476 Malay adult males (238 smokers and 238 non-smokers)	At the genotype level A1/A2 was significantly associated with smoking behavior.	p < 0.001	[67]
			88 AA smokers	Smokers who carry A1 allele have a stronger cue-induced craving than non-carriers.	Ps < 0.05	[62]
			389 Egyptian male smokers (average age 40 years)	There was a moderate association with smoking cessation behavior.	None	[75]
			9487 White	Smokers carrying the A2/A2 genotype were more likely to quit than smokers carrying the A1/A1 or A1/A2 genotype.	P = 3.9 × 10− 5; OR = 1.22; 95%CI = (1.11–1.34)	[33]
			732 current UK smokers	No significant correlation was detected between secondary Allele frequency and smoking status.	None	[77]
			233 Europeans	significantly correlated with nicotine dependence (FTND).	p = 0.018	[78]
			722 smokers of European ancestry	A2/A2Genes type smokers using bupropion were more than three times as likely to quit at 6 months of follow-up as placebo.	OR = 2.81,95%CI= (1.66–4.77)	[79]
			2037 subjects (671 EA from 200 EA families and 1366 AA from 402 AA families)	Significantly correlated with heaviness of smoking index under the dominant model in EAs and the combined sample, and significantly correlated with FTND in EAs.	heaviness of smoking index (P = 0.038), combined heaviness of smoking index (P = 0.042), FTND(P = 0.043)	[80]
			250 Korean male smokers	The frequency of A1/A2 genotypes was higher in the non-abstinent group than in the abstinent group.	P < 0.01	[65]
			150 smokers (Caucasian, age: 43.3 ± 11.1; 68 male, 79 female) and 228 controls	had either one or two copies of the A1-allele were 3.3 times as likely to have nicotine dependence compared to all other genotype combinations	P = 0.0003; OR = 1.626	[81]
	rs2734849	A > C,G	2037 smokers and nonsmokers (671 EAs from 200 EA families and 1366 AAs from 402 AA families)	was significantly associated with heaviness of smoking index in AAs; it was also associated with smoking quantity, heaviness of smoking index and FTND in the combined sample.	AA heaviness of smoking index (P = 0.023); combined smoking quantity(P = 0.023), combined heaviness of smoking index (P = 0.0064), combined FTND(P = 0.027)	[80]
	rs7131056	A > C,G		significantly correlated with all three nicotine dependence measurements in the EAs.	smoking quantity(P = 0.044), heaviness of smoking index (P = 0.036), FTND (P = 0.048)	[80]
	rs4274224	G > A,C		significantly correlated with all three nicotine dependence measurements in the EAs.	smoking quantity (P = 0.039), heaviness of smoking index (P = 0.040),FTND(P = 0.047)	[80]
	rs6589377	G > A,T		significantly correlated with FTND in AAs.	P = 0.049	[80]
	rs4648318	T > A,C,G		significantly correlated with FTND in EAs.	P = 0.041	[80]
	rs6278	C > A		significantly correlated with both heaviness of smoking index and FTND in EAs.	heaviness of smoking index (P = 0.040), FTND(P = 0.039)	[80]
	rs11604671	G > A,T		significantly correlated with smoking quantity and heaviness of smoking index in AAs and with smoking quantity, heaviness of smoking index and FTND in the combined sample.	AA smoking quantity(P = 0.028),AA heaviness of smoking index (P = 0.047); combined smoking quantity(P = 0.023); combined heaviness of smoking index (P	[80]

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Table 3 (*continued*)

Genes	Gene polymorphism	Associated risk genes and genotypes	Sample Population	Crowd Results	Results of significant analysis	References
					= 0.0091), combined FTND(P = 0.05).	
	rs4245150	G > C,T	1446 German adults aged 50–74 years	There was no statistically significant association between individual genotype and smoking cessation.	P = 0.54	[52]
	rs17602038	T > C		There was no statisrisk factortically significant association between individual genotype and smoking cessation.	P = 0.39	
	rs11214613	A > C,G,T	223 high and 257 low nicotine dependent Chinese Han people.	Risk factor for FTND.	P = 2.12×10^{-5}, OR = 2.18	[34]
	rs6589377	G > A,T		Risk factor for FTND.	P = 9.99×10^{-5}; OR = 1.85	[34]
	rs4648317	C > T	220 adolescents of European descent (108 males, 112 females) aged 14.9 years	T carriers were more likely to be current daily smokers than those without the allele.	p = 0.020; OR = 2.97,95%CI =(1.19–7.44)	[64]
				FTND scores were significantly higher in T allele carriers than in carriers of other alleles.	p = 0.045	[64]
	rs1079597 (Taq1B)	C > T	233 Europeans	significantly correlated with nicotine dependence (FTND).	p = 0.048	[78]
	rs6277 (C957T/ Pro319Pro)	G > A	233 Europeans	significantly correlated with nicotine dependence (FTND).	p = 0.006	[78]
			150 smokers (Caucasian, age: 43.3 ± 11.1; 68 male, 79 female) and 228 controls	957C/*Taq*I A1 haplotype was more than 3.5 times as likely to be associated with nicotine dependence compared with the 957T/*Taq*I A1 haplotype.	P = 0.003; OR = 3.540	[81]
			414 adults of European descent	Associated with abstinence after nicotine replacement therapy.	p = 0.03; OR = 0.59; 95%CI= (0.36, 0.95)	[62]
	rs1799732	−141C Ins/Del	414 adults of European descent	Smokers carrying Del C Allele had a statistically significant quit rate on nicotine replacement therapy.	P = 0.006; OR = 0.44; 95%CI= (0.25, 0.79)	
			150 smokers (Caucasian, age: 43.3 ± 11.1; 68 male, 79 female) and 228 controls	This SNP is not associated with nicotine dependence.	P = 0.813;	[81]

Note: VNTR: Variation in the number of tandem repeats, **SNP:** single nucleotide polymorphism, **AA:** African American; **EA:** European American; **FTND:** Fagerström Test for Nicotine Dependence, Test of Nicotine Dependence scale. (When FTND ≥6, it is considered as a criterion to distinguish high nicotine dependence); ***p* value:** Statistical obtained according to the significance test method *p* value, generally $p < 0.05$ is significant, $p < 0.01$ is very significant; **OR value:** Odds ratio, OR value greater than 1, indicating that the factor is a risk factor; OR value less than 1, indicating that the factor is a protective factor.

AP-1 [49–51]. Variation in the number of tandem repeats (VNTR) plays an important role in *TH* gene expression. Authors have predicted that protective alleles act in two main ways: first, increasing the relative level of endogenous dopamine, and secondly, decreasing the dopamine response to nicotine, thereby reducing perceived reward. So it can be inferred that HUMTH01-VNTR K4(7-r) allele up-regulated *TH* gene expression, and HUMTH01-VNTR K1(11-r)restrains it. However, opposite effects have been reported for these alleles in an in-vitro study. These authors suggest that *TH* transcription appears to be inhibited in in-vitro assays in proportion to the number of repeats from three to eight and with a counteracted effect for alleles above eight repeats [50]. More data are needed to test these hypotheses to elucidate the mechanisms by which *HUMTH0*1-VNTR impacts addictive smoking behavior. There is evidence of a link between *HUMTH0*1-VNTR and *TH* gene expression and HUMTH01-VNTR and smoking behavior.

3.2. *DDC*

The candidate gene *DDC* encodes dopa decarboxylase, which catalyzes the decarboxylation of L-DOPA to dopamine. Ma et al. [45] found that a *DDC* single nucleotide polymorphism (SNP) rs921451 was associated with the smoking quantity and the heaviness of smoking index (Table 1). Haplotype-based association analysis showed that a common nicotine dependence protective haplotype (T-G-T-G) was identified within African American (AA) samples and a different nicotine dependence high-risk haplotype was identified within European American (EA) samples (T-G-T-G). In addition, Yu and Colleagues [31] reported that rs921451 was correlated with nicotine dependence risk as reflected in the Fagerström Test for Nicotine Dependence (FTND) scores(The FTND is a kind of classic questionnaire closely related to the heaviness of smoking.) in a sample of 1590 individuals from 319 AA to 302 EA families, and that FTND scores were most significantly associated with rs12718541. The authors suggested that alternative splicing of *DDC* mRNA may render a functional change or provide plasticity in modulating the rate of *DDC* expression and translation. The presence of the

Table 4
Gene polymorphisms in the DRD4 gene associated with smoking behaviors.

Genes	Gene polymorphism	Associated risk genes and genotypes	Sample Population	Crowd Results	Results of significant analysis	References
DRD4	VNTR	7-r Allele	101 young adult nonsmokers of European ancestry	The presence of 7-r Allele was associated with a stronger aversive response to nicotine and reduced nicotine selection.	None	[91]
		7-r Allele	303 15-year-old German teenagers	Among men, lifetime smoking and smoking rates were higher and smoking started at an earlier age.	$p < 0.002$	[92]
		7-r Allele	792 older white smokers	There was a significant genes-treatment interaction in terms of smoking reduction rates.	P = 0.0073; HR = 1.29,95 % CI =(1.17–1.41)	[93]
		7-r Allele	220 adolescents of European descent (108 males, 112 females) aged 14.9 years	Lifetime smoking rates were significantly higher in 7-r Allele carriers compared to carriers without this Allele.	P = 0.02; OR = 1.97,95%CI= (1.11–3.50)	[64]
				7-r Allele carriers started smoking at an earlier age.	p = 0.058	
		7-r Allele	305 white 15-year-old adolescents (146 boys, 159 girls)	Among boys, 7-r Allele was associated with more smoking and alcohol consumption.	p = 0.003	[94]
				In girls, smoking and drinking activity were highest in 7-r Allele-free and 5-HTTLPR-long Allele-pure congeners.	p = 0.032	[94]
		7R + Allele	839 Australian teenagers	7R + Allele was associated with smoking initiation.	p = 0.004; OR = 1.7,95%CI=(1.2–2.3)	[95]
		Long Allele (greater than or equal to 7-r)	331 Europeans	Carriers of L Allele and the odds of withdrawal after bupropion action were higher.	P < 0.0001; OR = 1.31,95 % CI = (1.05–1.22)	[96]
		Short Allele		Purely syngeneic S Allele carriers are not associated with abstinence after bupropion action.	P = 0.23; OR = 1.06,95 % CI = (0.96–1.16)	[96]
	rs1800955	T > C,G	438 non-smokers (NS) and 1157 current smokers (Mexican mestizos)	In the comparison between HS and NS, C Allele was associated with smoking.	p = 2.34 × 10−3; OR = 1.45,95%CI = (1.19–1.76)	[98]
				In the comparison of LS with NS, C Allele was associated with smoking.	p = 1.13 × 10−3; OR = 1.47,95%CI = (1.21–1.78)	

Note: VNTR: Variation in the number of tandem repeats, **SNP:** single nucleotide polymorphism; **L Allele**: Long allele, 6 to 8 repeats; **S Allele:** Short allele, 2 to 5 repeats; **7R+**: refers to the presence of 5, 6, 7 or 8-rAllele, **HS:** heavy smokers; **NS**: never smokers; **LS:** light smokers; ***p* value:** Statistical obtained according to the significance test method *p* value, generally $p < 0.05$ is significant, $p < 0.01$ is very significant; **OR value**: Odds ratio, OR value greater than 1, indicating that the factor is a risk factor; OR value less than 1, indicating that the factor is a protective factor, **HR:** Hazard ratio.

rs12718541 A allele is predicted to disrupt the intronic splicing enhancer sequence and decrease the efficiency of splicing and, therefore, predisposition to nicotine dependence. In a study of adolescents, rs4947644 was found to be associated with nicotine dependence or craving and rs921451 was associated with smoking quantity [46]. However, in a survey of 1446 German adults aged 50–74 years, neither individual variation nor *DDC* haplotypes were found to be associated with the likelihood of overcoming nicotine dependence [52]. In a study by Zhang et al. [47] investigating a sample of AAs and EAs, none of the eight SNPs studied were found to be significantly associated with nicotine dependence, in the SNPs rs921451-rs3735273-rs1451371-rs2060762, the strongest correlation was found between heaviness of smoking index and haplotype C-A-T-G in EAs (Table 1). However, this correlation was not found in a report by Ma et al. [45] using the same sample (Table 1). The key distinction between the two analysis is that Zhang et al. analyzed the traits, including categories of smoking quantities, Heaviness of smoking index and FTND, as ordinal variables, whereas Ma and colleagues treated these scores as quantitative traits. Treating ordinal variables as if they were continuous or dichotomizing ordinal variables into binary categories decreases the power of genetic association tests [43,53]. Moreover, Zhang et al. assessed the significance of the association after adjusting for age, sex, and race in the pooled sample, as well as age and sex in each racial sample, to reduce the effect of confounding factors. Multiple comparisons using the linkage and association for ordinal traits [43,53] to determine statistical differences. These findings support the hypothesis that *DDC* indeed plays a crucial role in nicotine dependence and suggests that *DDC* is haplotype-specific across races. To address potential concerns, firstly, the pattern of association for the most significant findings should be the same across the two distinct population samples. Secondly, it is best to use within-household controls for population stratification. Thirdly, a very strict calibration should be applied to multiple tests.

In a study of Parkinson's disease, The rs921451 polymorphisms of the *DDC* gene promoter influence patients' motor response to L-

Table 5
Gene polymorphisms in DRD1, DRD3, DRD5 gene associated with smoking behaviors.

Genes	Gene polymorphism	Associated risk genes and genotypes	Sample Population	Crowd Results	Results of significant analysis	References
DRD1	rs265973	T > A,C,G	2037 smokers and nonsmokers (671 EAs	Significantly correlated with smoking quantity.	P = 0.041	[102]
	rs265975	C > G,T	from 200 EA families and 1366 AAs from 402 AA families)	There was a significant correlation with the three nicotine dependence measurements.	smoking quantity(P = 0.0078); heaviness of smoking index (P = 0.0093), FTND (P = 0.0048)。	[102]
	rs4532(*Dde*I)	C > G,T		Associated with FTND in AAs and EAs samples.	AAs(P = 0.035), EAs(P = 0.035)	[102]
	rs2168631	G > A,C,T		Nothing to do with nicotine dependence.	P > 0.05	[102]
	rs686	G > A,C,T		There was a significant correlation with the three nicotine dependence measurements.	smoking quantity(P = 0.0078); heaviness of smoking index (P = 0.0093), FTND (P = 0.0048)。	[102]
			476 Malay adult males (238 smokers and 238 non-smokers)	The prevalence of AG genotype was significantly higher in smokers in comparison with non-smokers.	p < 0.001, OR: 7.07, 95 % CI: 3.71–13.42	[67]
DRD3	rs6280	C > T	220 adolescents of European descent (108 males, 112 females) aged 14.9 years	There was a slight effect on smoking initiation, individuals with the G allele having a lower lifetime prevalence of smoking and a protective effect on adolescent smoking.	p = 0.074; OR = 0.60,95%CI = 0.34–1.05	[64]
				Adolescents carrying the G allele were significantly older when they started smoking daily.	p = 0.015	
			2037 smokers and nonsmokers (671 EAs from 200 EA families and 1366 AAs from 402 AA families)	Significantly correlated with smoking quantity, heaviness of smoking index and FTND in EAs.	smoking quantity(P = 0.00058); heaviness of smoking index (P = 0.0011),FTND(P = 0.0011)	[106]
	rs2630351	A > C,G	223 high and 257 low nicotine dependent smokers in Han Chinese	significantly correlated with FTND.	P = 2.59 × 10− 7; OR = 2.49	[34]
DRD5	rs1967550	G > A,T	223 high and 257 low nicotine dependent smokers in Han Chinese	significantly correlated with FTND.	P = 7.31 × 10− 7; OR = 2.24	[34]

Note: VNTR: Variation in the number of tandem repeats, **SNP:** single nucleotide polymorphism, **AA:** African American; **EA:** European American; **FTND:** Fagerström Test for Nicotine Dependence, Test of Nicotine Dependence scale. (When FTND ≥6, it is considered as a criterion to distinguish high nicotine dependence); ***p* value:** Statistical obtained according to the significance test method *p* value, generally $p < 0.05$ is significant, $p < 0.01$ is very significant; **OR value:** Odds ratio, OR value greater than 1, indicating that the factor is a risk factor; OR value less than 1, indicating that the factor is a protective factor.

dopa but do not significantly change peripheral pharmacokinetic parameters for L-dopa and dopamine [54]. Therefore, we predict that rs921451 may be a genetic modifier, which enhances the catalytic rate of DDC to L-DOPA and improves the reward reactivity to nicotine. Carriers of this variant may be more likely to become addicted to nicotine.

4. Dopamine reuptake-related gene polymorphisms

4.1. DAT1/SLC6A3

DAT is a membrane transporter protein encoded by the *SLC6A3* gene. Dopamine is released into the synaptic gap through calcium-mediated fusion of vesicles with the presynaptic membrane [55]. DAT uses the ionic gradient between the synaptic gap and the presynaptic neuron to drive the dopamine transport. After reuptake, dopamine is stored in vesicles. The uptake and subsequent localization of dopamine within the nerve terminal ends neurotransmission and allows for recycling of the neurotransmitter thereby enabling subsequent release. DAT is an important functional regulator, and plays a vital role in the reinforcement-reward effect during drug dependence [56]. *SLC6A3* has been linked to a number of drug dependencies, such as cocaine [57], amphetamines [58], as well as alcohol dependence [59]. There is increasing evidence that the *SLC6A3* gene polymforphism may impact dopamine transport [60]. The most studied polymorphism in the *SLC6A3* gene is the 40bp VNTR polymorphism in its 3′ untranslated region (3′ UTR). This polymorphic locus is often present as a 9-repeat (9-r) allele or a 10-r allele [32,61].

In their study, Franklin et al. [32] obtained perfusion ferromagnetic resonance images during cue exposure in 19 smokers with the 40 bp VNTR polymorphism genotype of the *SLC6A3* gene. Comparison between the two groups illustrated that the 9-r gene carriers had increased activation in response to smoking cues than the 10/10-r allele carriers in the interconnected ventral striatum, pallidum, and orbitofrontal cortex regions. Including in the other areas (anterior cingulate gyrus, parahippocampal gyrus, and insula), these results suggest that *SLC6A3* gene variants contribute to the neural and behavioral responses induced by smoking cues. Therefore, it can be inferred that brain and behavioral responses may be enhanced in smokers carrying the 9-r allele. Similarly, this finding was demonstrated in a study of 88 AAs [62] (Table 2). In a study of 583 British smokers, O'Gara et al. [61] uncovered that after one week of abstinence, carriers of the 9-r allele had 10 % higher abstinence rates than carriers of the 10/10-r allele. Moreover, during the next four weeks, the results diminished and were no longer significant. This study found a moderate effect of the *SLC6A3* genotype on the ability to quit smoking relatively early, but the evidence is limited. The same pattern was found in another study of 2155 European descent, with the difference being a 20 % increase in the odds of quitting [63] (Table 2). In adolescents of European descent, a significant decrease in the willingness to quit was found in pure 10/10-r gene carriers [64]. Gara and collaborators [61] also investigated the effect of *SLC6A3* polymorphisms in the 30 bp intron 8 VNTR on nicotine dependence, and after one week of abstinence, 2-r allele carriers had an 8.5 % higher quit rate compared to 3-r allele carriers (Table 2).

The above studies and meta-analysis suggest that individuals carrying the 9-r allele rather than the more common 10-r allele are more likely to quit smoking. However, in a systematic review of candidate gene studies of smoking behavior by Munafò et al. [23], no effect of such polymorphism on smoking behavior was uncovered. Smokers with the 10r/10r genotype were found to be more likely to have reduced ND in a study of Japanese individuals, and a similar phenomenon was found in a study of Koreans [65] (Table 2). This suggests a possible ethnographic difference in the relationship between *SLC6A3* gene polymorphisms and smoking behavior. A potential explanation for this is that the 9-r allele enhances the expression of SLC6A3 protein, resulting in reduced postsynaptic dopamine activity [60]. The 10-r allele is associated with reduced SLC6A3 protein expression. Therefore, it may minimize nicotine dependence by increasing the total amount of dopamine released into the synaptic gap, thereby allowing for greater reward from the dopaminergic effects of nicotine [60]. However, these are inferences which need to be studied in more depth.

Another polymorphism studied for this gene is a SNP. In a study of rural China, conditional logistic regression showed that the risk of early smoking onset by the rs27072-A allele was almost three times greater in severely addicted smokers than that in total smokers [66]. (Table 2). In addition, the minor alleles of rs27072 affect the risk of lethal cocaine abuse [68]. In Malay males, no association with smoking behavior was found at either the genotype or allele level [67]. O'Gara et al. [61] also studied polymorphisms in rs115, rs270, and rs296, with all three SNPs not associated with smoking cessation (Table 2). Although these findings are preliminary and require further validation, the results suggest that a polymorphism in *SLC6A3* may play an important role in smoking onset, and there may be an interactive effect between *SLC6A3* and early smoking onset on modulating the susceptibility of nicotine dependence [66] (Table 2).

5. Dopamine receptor-related gene polymorphisms

Dopamine acts through five receptor subtypes (D1-D5) [69]. Dopamine receptors are separated into two classes: D1-like receptors (D1 and D5 receptors) and D2-like receptors (D2, D3, and D4 receptors). These two types of receptors have opposite effects on signal transduction [70]. While stimulation of D1-like receptors activates cyclic AMP (cAMP), stimulation of D2-like receptors inhibits cAMP. The D2-like receptors also act as autoreceptors that reduce dopamine release. While D1 and D2 receptors are the most common dopamine receptors in the central nervous system, D2 and D4 receptors have been the focus of studies of dopamine pharmacogenetics and resultant nicotine dependence [29]. Moreover, D2 and D4 are sharply promising candidate genes of interest in substance use disorders (SUD) and polysubstance addictions.

5.1. DRD2/ANKK1

The most studied *DRD2* gene polymorphism is rs1800497 (*Taq*I A), a C > T substitution located at the 3′ UTR of the *DRD2* locus.

Table 6
Gene polymorphisms in the COMT, MAOA/B and DBH gene associated with smoking behaviors.

Genes	Gene polymorphism	Associated risk genes and genotypes	Sample Population	Crowd Results	Results of significant analysis	References
COMT	rs4680	G > A	741 Europeans	Compared to the placebo patch group, the nicotine patch group had a significant cessation-promoting effect on pure Met/Met genotype group carriers.	P = 0.05; OR = 0.43, 95%CI= (0.19,1.00)	[109]
			290 white and black female smokers	In women, Met/Met genotype carriers were more likely to be chronically abstinent due to nicotine replacement therapy compared to Val/Val genotype.	0.03; OR = 1.82, 95%CI=(1.05,3.17)	[36]
			250 Chinese smokers	At 8 weeks, the sublingual nicotine patch group was more successful in quitting smoking than the placebo group.	p = 0.0001; OR = 3.62, 95%CI=(1.94,6.75)	[110]
			250 Korean smokers	Val/Val genotype carriers were significantly associated with smoking abstinence.	P = 0.02; x2 = 8.12	[65]
	rs737865	A > G,T	430 EAs and 81 AAs smokers	The primary effect was not significant and there was no evidence of a significant genotype × EOT or treatment interaction at 6 months.	None	[111]
	rs165599	G > A,C		In EAs, there was a significant interaction with EOT, and GG genotype carriers had higher rates of smoking cessation.	p = 0.05; OR = 2.44,95%CI= (0.99–6.01)	[111]
MAO-A	VNTR	uVNTR	1822 Vietnamese males (1453 smokers and 369 nonsmokers)	significantly correlated with FTND.	P = 0.003	[112]
		4-r Allele and 3-r Allele	Chinese males(203 current smokers and 168 non-current subjects)	Individuals with the 3-r allele had a significantly increased risk of smoking compared to individuals with the 4-r allele.	p = 0.05; AOR = 1.9 95 % CI =(1.0–3.6)	[113]
		4-r Allele	504 Japanese (217 men and 287 women)	In men, no significant association was found between FTND and MAO polymorphisms.	None	[114]
				Women with 4-r Allele had a significantly lower risk of current smoking.	aOR = 0.49,95% CI=(0.26–0.93)	[114]
		4-r and 3-r Allele	121 white men with both alcohol and nicotine dependence	Highly active 4-r long Allele was associated with a significant increase in smoking compared to less active 3-r short Allele.	None	[115]
		Long Allele (3.5-r, 4-r or 5-r)	1230 Whites of Russian origin	Heterozygous S Allele carriers have a lower risk of smoking compared to pure genotypes with L Allele.	P = 0.013; AOR = 0.53,95%CI= (0.32,0.88)	[2]
				The risk of smoking was lower in the S Allele pure-allele carriers.	P = 0.043; AOR = 0.49,95%CI= (0.24,0.98)	[2]
	rs1137070	T > C	Chinese males(203 current smokers and 168 non-current subjects)	Compared to the C/O genotype, T/O genotype carriers had a significantly increased risk of smoking.	P = 0.027; AOR = 1.7,95 % CI =(1.1–2.8)	[113]
			1230 Whites of Russian origin	Among women, TT genotype carriers have a lower risk of becoming smokers.	P = 0.027; OR = 0.44,95 % CI =(0.21–0.91)	[2]
MAO-B	rs1799836	T > A,C	504 Japanese (217 male and 287 female)	In men, no significant association was found between FTND and MAO polymorphisms.	None	[114]
			1230 Whites of Russian origin	Carriers of the GG pure genotype are at higher risk of becoming smokers.	P = 0.03; OR = 2.16, 95%CI= (1.08,4.33)	[2]
DBH	rs3025343	G > A	64924 former smokers in Europe	was significantly associated with smoking cessation (cigarettes per day).	$P = 3.6 \times 10^{-8}$;OR = 1.12,95%CI= (1.08,1.18)	[37]
	rs1541333	C > A,G	793 non-Hispanic whites	High FTND subgroups were associated with smoking cessation at the 6-month follow-up.	P = 0.045,OR = 2.22,95%CI= (1.29–3.83)	[116]
	rs1076153	G > A,C,T		High FTND grouping was not associated with smoking cessation at EOT.	P = 0.3,OR = 1.49 95%CI= (1.06–2.09)	[116]
	rs2797855	G > C,T		High FTND grouping was not associated with smoking cessation at EOT.	P = 0.007,OR = 0.47, 95%CI= (0.32–0.71)	[116]

(*continued on next page*)

Table 6 (*continued*)

Genes	Gene polymorphism	Associated risk genes and genotypes	Sample Population	Crowd Results	Results of significant analysis	References
	rs1541332	G > A,C,T		High FTND grouping was not associated with smoking cessation at EOT.	P = 0.19,OR = 1.78, 95%CI= (1.12–2.83)	[116]
	rs1108580	A > G		High FTND subgroups were associated with smoking cessation at the 6-month follow-up.	P = 0.032, OR = 1.70, 95%CI= (1.22–2.38)	[116]
	rs1076150	T > C		High FTND grouping was not associated with smoking cessation at EOT.	P = 0.129, OR = 1.46, 95%CI= (1.10–1.93)	[116]

Note: EOT: End of treatment; **VNTR:** Variation in the number of tandem repeats, **SNP:** single nucleotide polymorphism, **AA:** African American; **EA:** European American; **FTND:** Fagerström Test for Nicotine Dependence, Test of Nicotine Dependence scale. (When FTND ≥6, it is considered as a criterion to distinguish high nicotine dependence); ***p* value:** Statistical obtained according to the significance test method *p* value, generally $p < 0.05$ is significant, $p < 0.01$ is very significant; **OR value:** Odds ratio, OR value greater than 1, indicating that the factor is a risk factor; OR value less than 1, indicating that the factor is a protective factor.

Two alleles, A1 and A2, were included in analyses. However, this polymorphism was later more precisely localized within the coding region of a neighboring gene, initially named X-kinase and eventually named *ANKK1* [71]. Current data show that the *Taq*I A polymorphism may be a marker of both DRD2/ANKK1 genetic variants [72].

The first association with the *DRD2* gene was alcoholism, Blum, K et al. found that the presence of the A1 allele of the *DRD2* gene correctly classified 77 % of alcoholics, and its absence classified 72 % of nonalcoholics [73]. After this, the researchers found that smokers showed a higher prevalence of A1 alleles than non-smokers, which was the first time DRD2 was associated with nicotine [74]. A modest association between *DRD2* genotype and quitting behaviors such as the number of cigarettes smoked in the past 48 h, the depth of inhalation, and FTND score was found in a study of 389 Egyptian male smokers [75] A meta-analysis of a total of 9487 Caucasians demonstrated that polymorphisms in *DRD2 Taq*I A play an important role in smoking cessation and that smokers carrying the A2/A2 genotype are more likely to quit than smokers carrying other genotypes [33] (Table 3). Bupropion is an atypical antidepressant that is effective in enhancing smoking cessation. Bupropion increases synaptic noradrenaline levels by inhibiting the noradrenaline transporter [76]. These effects may contribute to bupropion's ability to attenuate the rewarding effects of nicotine as well as nicotine withdrawal symptoms. Three studies consistently illustrated significantly higher quit rates in smokers with the A2/A2 genotype when treated with bupropion compared to placebo, while no differences were demonstrated when having one or both A1 alleles [33]. A study of Korean subjects showed that subjects carrying the A1/A1 and A2/A2 genotypes had increased withdrawal rates compared to those with the A1/A2 genotype [65], this may not stem from the presence of the A1 allele or A2 allele, but from genetic heterozygosity.

Munafò and colleagues [82] found a lack of correlation between the *DRD2 Taq*I A polymorphism and smoking cessation in a randomized trial of nicotine replacement therapy, with the central role of genotype being the opposite of previous reports, with females carrying one or more A1 alleles being less likely to quit (Table 3). In another study, neither the sample of studied women nor a meta-analysis of 29 studies found strong evidence for an association between the *DRD2 Taq*I A polymorphism and smoking behavior (including smoking initiation, smoking persistence, and smoking prevalence). Instead, it was found that there was a stronger association in males than in females [83]. Similarly, the *DRD2 Taq*I A polymorphism was not associated with smoking behavior in a healthy UK population [77] (Table 3).

Furthermore, regarding the *DRD2* SNP, Huang et al. [80] conducted a similar association analysis in the South Central Tobacco Family Cohort, including 2037 subjects in 602 core families. They selected 16 SNPs in *DRD2* and 7 SNPs in *ANKK1* and applied three commonly used measurements to determine the extent of nicotine dependence, namely smoking quantity, heaviness of smoking index, and FTND. The polymorphism of rs2734849 in *ANKK1* represents a functional causative variant for all three measures of nicotine dependence in AA and the combined sample. However, after correction for multiple tests, the variants in *DRD2* showed only a weak correlation. Furthermore, using luciferase reporter analysis, these researchers demonstrated that the polymorphism rs2734849 was associated with altered expression of NF-κB regulatory genes, which may indirectly affect DRD2 expression density. *DRD2* SNPs are more studied in Europeans, see Table 3 for details. *DRD2* gene polymorphisms were investigated in Han Chinese with two SNPs (rs11214613, rs6589377), both of which showed to be a risk factor for FTND [34] (Table 3).

Gordiev et al. [84] reported that *DRD2* rs1079597 AA carriers and *DRD2* rs1800497 CC carriers had a lower density of *DRD2* receptors. Interestingly, the *DRD2* A1 allele causes lower DRD2 expression levels in the brain [85], and has been associated with early-emerging anxious and depressive symptoms in a community sample of preschool-aged children [86]. We hypothesized that lower DRD density was the cause of higher dopamine availability. Thus, subjects carrying *DRD2* rs1079597 GG may have more need for repeated dopaminergic stimuli than those carrying *DRD2* rs1079597 AA, which induce nicotine dependence. In addition, based on the family association study, Gelernter, Joel et al. found robust evidence of an association of multiple SNPs at *TTC12* and *ANKK1* in single population and pooled sample [87].

5.2. DRD4

The structure and pharmacology of *DRD4* is similar to that of *DRD2*. DRD4 protein is predominantly expressed in the prefrontal cortex and has been extensively studied in relation to psychiatric disorders, including Attention Deficit and Hyperactivity Disorders [88], and nicotine dependence [89]. The *DRD4* gene contains two polymorphisms that have been associated with nicotine pharmacogenetics. The most studied polymorphism is the 48 bp VNTR, containing a high degree of polymorphism in exon 3. This polymorphism has been found in varying amounts between 2 and 11 repeats, with the 4-r and 7-r alleles being the most common in populations. In general, alleles with fewer than 7 repeats are considered "short alleles" (S), while alleles with 7 or more repeats are considered "long alleles" (L). Allele frequencies vary considerably among ethnic groups [90]. The 4-r allele was the most prevalent and appeared in every population with a frequency ranging from 0.16 to 0.96. The 7-r allele was the second most common, appearing quite frequently in the Americas (mean frequency = 48.3 %) but only occasionally in East and South Asia (mean frequency = 1.9 %). The diversity of the allele frequencies of this polymorphism in different populations underscores the importance of population consideration in designing and interpreting any associative studies conducted on this polymorphism.

It has been shown that AAs with at least one L allele (6–8 repeats) smoke more frequently and begin smoking earlier than those who are carriers of the S allele (2–5 repeats) [89]. Perkins et al. found that carriers of the 7-r allele may have a more robust aversive response to nicotine before developing addiction, but only in men, with no genetic association observed in women [91]. In a study examining the role of *DRD4* VNTR in regulating the relationship between nicotine dependence and neuroticism, Laucht et al. [92] determined that 15-year-old German men carrying the 7-r allele had higher lifetime smoking and smoking rates and tended to begin smoking younger than men who were carriers of another allele (Table 4). A study of two combined randomized controlled trials illustrated a significant pharmacotherapy interaction between the 7-r allele and bupropion in smoking reduction rates [93]. Both studies in adolescents found higher smoking rates in 7-r allele carriers and were also associated with heightened alcohol consumption [64,94] (Table 4). Ellis et al. [95] found that the 7R + allele (7R + refers to the presence of 5, 6, 7, or 8 repeats of the *DRD4* exon III VNTR allele) was associated with smoking initiation (Table 4). At the same time, the evidence for an association between adolescent neuroticism and the development of nicotine dependence in young adults is weaker. However, there is evidence of an interaction between neuroticism and *DRD4* 7R+. Among 7R + carriers, those with a history of neuroticism (anxiety and avoidance behaviors) are more than 3.5 times more likely to progress to nicotine dependence [95]. In a recent trial, bupropion (when compared to placebo) was a predictor of increased odds of abstinence in L-allele carriers. In contrast, bupropion was not associated with abstinence among S-allele homozygotes [96] (Table 4). This is ultimately related to an individualized pharmacogenetic treatment approach. However, this result was not replicated in a subsequent study of 416 smokers of European ancestry [97]. The differences in gene-treatment interactions between these analyses may be due to the inadequate size of the sample. Therefore, a meta-analysis of multi-treatment trials with sufficient sample size to test for primary and interactive effects of VNTR and response to multiple treatments may ultimately improve our understanding of the impact of *DRD4* exon 3 VNTR on prospective abstinence and potentially guide future treatment strategies.

Clearly, the 7-r allele is a risk factor for nicotine dependence. In a cellular assessment of *DRD4* polymorphism, Moyzis group's [99,100]findings suggest two possible reinterpretations of the existing DRD4 literature: that the 4-repeat allele is the progenitor and should be compared with the 2-r and 7-r alleles, which each show reduced cAMP activity (4 > 2>7), and that previous DRD4 findings may in fact be driven by rare variants in the 7-r allele rather than by the length polymorphism itself. Therefore, we hypothesize that rare variants in the 7-r allele lead to reduced levels of cytoplasmic cAMP, reducing protein kinase A (PKA) activity and consequently reducing neuronal excitability [101].

Another *DRD4* gene polymorphism is rs1800955 (T > C, G), located 521 bp upstream of the transcription start site, where the T allele is 40 % less transcriptionally efficient than the C allele. In a study of a mixed-race Mexican population, the C allele (risk allele) was found to be associated with cigarette smoking in heavy smokers (HS) versus never-smokers (NS) and light smokers (LS) versus NS [98] (Table 4). As a risk allele, the C allele increases the conversion efficiency of *DRD4*, and the high expression of DRD4 inhibits cAMP, thus reducing the excitability of neurons.

5.3. DRD1, DRD3, DRD5

The *DRD1* gene is located on chromosome 5q35.1 and contains two exons separated by a small intron in the 5′ UTR. Huang et al. [102] examined the association of five SNPs in, or near the dopamine D1 receptor gene (*DRD1*) with nicotine dependence, four of which were associated with nicotine dependence (Table 5). In studies of Malay males, the prevalence of the AG genotype in *DRD1* (rs686) was significantly higher in smokers compared to non-smokers [67] (Table 5). In addition, a luciferase reporter analysis demonstrated that rs686, located in the 3′ UTR caused differences in luciferase activity, indicating that rs686 is a functional polymorphism that may impact *DRD1* expression. Indeed, the genetic variation of rs686 from A to G decreases *DRD1* expression [103], which decreases phosphorylation of signaling proteins such as the dual function phosphoprotein DARPP-32, and reduces neuronal excitability, and has been associated with a variety of dopamine-related diseases, such as schizophrenia [104] and autism spectrum disorders [105].

Most studies have evaluated the *Bal*I restriction site (rs6280), which generates the Ser9Gly *DRD3* variant. The most extensive study to date assessing the impact of 13 *DRD3* SNPs with nicotine dependence was performed in a population of 2037 Americans [106]. There was a strong association between rs6280 and nicotine dependence in both the EAs and the pooled sample, and rs6280 is likely a causative functional polymorphism for the nicotine dependence association (Table 5). Interestingly, many *DRD3* SNPs appear to be associated with smoking in schizophrenics. In a study of adolescents of European descent, rs6280 was found to have a protective effect

against initiation of smoking [64]. In a study of Chinese Han people, rs2630351 was found to be a risk factor for overall FTND score [34] (Table 5).

The *DRD5* gene is located on chromosome 4p15.1-p15.3. The gene lacks introns except for a small intron in the 5′ UTR. In a study of a Chinese Han population, the *DRD5* SNP rs1967550 was shown to be a significant risk factor for the overall FTND score [34] (Table 5). An analysis of 338 European twins found that four *DRD5* markers, including the (promoter TC), repeat polymorphism, the T978C polymorphism, the C1481T polymorphism, and the D5 (CT/GT/GA)n repeat polymorphism, were not correlated for smoking initiation and nicotine dependence. However, maximum likelihood analysis pointed to the presence of a haplotype preventing smoking [107]. These data are inconsistent with a robust etiological role of *DRD5* in the cause of these complex smoking behaviors. The possible reasons for this are a poor ability to detect effects and haplotype estimation and the lack of parental genotypes to establish a more precise pathway. Although no convincing evidence was found for the involvement of *DRD5* in the main effects of the two smoking phenotypes, it remains plausible that *DRD5* may be involved etiologically through epistatic interactions. In addition, rare functional mutations in *DRD5* may be etiologically relevant from the initiation and progression of smoking to nicotine dependence.

6. Polymorphisms in genes associated with dopamine degradation

MAO and COMT enzymes convert dopamine to homovanillic acid. Both MAO and COMT are present in monoamine neurons and glial cells. DBH converts dopamine to noradrenaline in synaptic vesicles of noradrenergic neurons [41], reducing synaptic dopamine levels.

6.1. *COMT*

COMT is a key enzyme involved in dopamine metabolic inactivation, suggesting that the *COMT* gene is a possible candidate for pharmacogenetic studies of nicotine dependence and therapeutic response. The G to A mutation of *COMT* rs4680 (codon 158) converts the Val high-activity allele to the Met low-activity allele, resulting in a three-to four-fold reduction in the resultant COMT activity [108]. A randomized controlled trial of 741 smokers of European ancestry found a significant cessation-promoting effect in Met/Met genotype carriers when compared to Met/Val or Val/Val genotypes [109]. Similarly, in a clinical trial of 290 white and black female smokers, women who carried the Met/Met genotype were more likely to engage in long-term abstinence as a result of nicotine replacement therapy treatment [36] (Table 6). In contrast, in a double-blind, placebo-controlled, 8-week nicotine replacement therapy trial of 250 Chinese smokers, those carrying the Val/Val genotype had higher rates of abstinence from nicotine replacement therapy when compared to smokers carrying at least one Met allele [110]. This finding was validated in Korean smoking subjects [65] (Table 6). However, in 233 smokers, this variant was not associated with gene-drug interactions [78]. Completely opposite results were obtained in European and American populations compared to Asian populations, indicating that there may be ethnic differences in predicting pharmacogenetic differences from previous studies on nicotine replacement therapy response. Genotype frequencies of *COMT* differed significantly between ethnic groups. For example, Val/Val, Val/Met, and Met/Met genotype frequencies in the Chinese Han population were 63 %, 30 %, and 7 %, respectively, compared to 32 %, 39 %, and 30 % for EAs in the Berrettini study and 23 %, 46 %, and 32 % [111]. A possible neurobiological explanation for this result is that the Val allele determines increased COMT activity in the prefrontal cortex, which leads to lower synaptic dopamine levels. Therefore, individuals with the Val/Val genotype, may have lower baseline levels of dopamine in the frontal cortex, and may thus be responsive to nicotine replacement therapy as they are more sensitive to this enhancement than individuals carrying one or more Met alleles, which have higher baseline dopamine levels even in the absence of nicotine.

COMT variants are associated with the smoking cessation effects of bupropion. Berrettini et al. [111] studied the Val/Met polymorphism and two additional SNPs (rs737865 and rs165599), which indicated differential allele expression in a double-blind, placebo-controlled, 10-week trial of bupropion in 430 EAs and 81 AAs smokers. Smokers in the placebo group carrying the rs165599 GG genotype had increased quit rates, while smokers in the bupropion group carrying the A genotype had higher quit rates (Table 6).

6.2. *MAO*

MAO catalyzes the oxidative deamination of biogenic amines such as dopamine, noradrenaline, serotonin, and histamine [117]. Two closely linked genes on the short arm of the X chromosome encode two forms of MAO, *MAO-A* and *MAO-B* [118]. It is estimated that 70 % of neuronal MAO belongs to type A. MAO is associated with a variety of conditions, including alcohol abuse, schizophrenia, Parkinson's disease and smoking behavior [119–122]. Both *MAO-A* and *MAO-B* are suppressed in the brains of smokers [119,120]. Thus, in addition to the effect of nicotine, inhibition of MAO by smoking may be an additive mechanism of addiction [114]. In a smoking cessation trial, HS treated with a reversible MAO-A inhibitor for three months had a higher abstinence rate six months after quitting compared to HS receiving a placebo [123]. Therefore, MAO, an enzyme involved in dopamine and serotonin metabolism, may be necessary in regulating smoking behavior.

6.2.1. *MAO-A*

MAO-A polymorphisms are VNTR and *Eco*RV enzyme cut site polymorphisms (rs1137070) [113]. In the promoter and 5′ UTR regions, the *MAO-A* gene has two VNTRs [124], the proximal VNTR, uVNTR, is located approximately 1.2 kb upstream of one of the transcription start sites and consists of a repetitive 30 bp motif that can be present in 2, 3, 3.5, 4 and 5 repeats. The 3.5 and 4 repeat alleles of the uVNTR are expressed as a positive regulator 10-fold higher than other *MAO-A* gene uVNTR variants [35]. Another VNTR

known as dVNTR was identified as being 1500 bp upstream of the ATG site [125]. This variant is a 10 bp motif which can be present in 8, 9, 10, or 11 repeats, and these variants exhibit differential transcriptional activities. The authors of a preliminary study suggest that dVNTR may have a stronger regulatory function than uVNTR in terms of *MAO-A* expression [125].

Kõks et al. [112] studied the uVNTR and dVNTR polymorphisms of the *MAO-A* gene in Vietnamese male smokers and non-smokers to assess the relevance of these polymorphisms in nicotine dependence by FTND. The uVNTR carriers are more likely to become addicted to nicotine. No association was found between dVNTR and smoking behaviors. It was confirmed that low expression of MAO-A genetically predicted higher nicotine dependence. Smokers with more active enzymes are required to consume higher amounts of tobacco to achieve an inhibiting effect on MAO-A compared to smokers with genetically encoded lower enzyme activity. In our previous research, we found that harmane, a potent and selective MAO-A inhibitor present in cigarette smoke, may also play a significant role in nicotine dependence [126]. The inhibition of MAO-A activity increases the actions of dopamine and other monoamine neurotransmitters that are responsible for drug reinforcement and motivation [127], thus exacerbating susceptibility to nicotine dependence. In a study of Chinese men, a significantly increased risk of smoking was found in individuals with the 3-r gene when compared to those with the 4-r gene [113]. The same conclusion was reached in a study of Japanese female subjects [114] (Table 6). However, the opposite conclusion was found in a study of 121 white men when both alcohol and nicotine dependence were examined [115]. The variability in the results may be due to the respondents being individuals with alcohol and nicotine addiction. Further studies are required to investigate this association in smokers without concomitant alcohol dependence. A study of white individuals of Russian origin found a reduced risk of smoking in carriers of the S allele [2] (Table 6).

For the study of rs1137070, Jin et al. found [113] that individuals with the 1460T/O genotype had a significantly increased risk of smoking when compared to individuals with the 1460C/O genotype. Tiili et al. found [2] that among females, TT carriers had a lower risk generally of becoming smokers. The low-activity C allele of *MAO-A* rs1137070 was associated an increased susceptibility to heroin addiction [128]. The rs1137070 polymorphism is a synonymous variant, and allelic differences at this position do not alter the amino acid sequence but rather affect the presence or absence of restriction sites and consequent levels of MAO-A activity [129].

6.2.2. *MAO-B*

Although *MAO-B* has also been associated with nicotine dependence and psychiatric disorders, there have been fewer studies in this area [2]. The *MAO-B* gene polymorphism is present in intron 13 as the A644G polymorphism (rs1799836) [130] Tiili et al. found [2] that carriers of the rs1799836 GG genotype were at higher risk of becoming smokers. In contrast, a study of Japanese men did not find a significant association between FTND and *MAO* polymorphisms [114]. Peripheral and brain MAO-A (30 %) and MAO-B (40 %) enzyme activities were much lower in smokers compared to non-smokers [119,120]. This suggests that perhaps components of tobacco smoke (not including nicotine) may inhibit MAO and thus enhance nicotine dependence effects [131]. rs1799836 may alter MAO-B enzymatic activity [132], but how this polymorphism affects MAO-B activity remains unclear. Some studies have reported that the *MAO-B* G allele is associated with increased MAO-B activity in platelets and cultured cells [132–134], but decreased activity in the human brain [132]. This inconsistency may be due to the lack of correlation between platelet and brain MAO-B activity in the same individuals [135]. Apparently, low MAO-B activity (G allele) results in an increased risk of developing nicotine dependence.

6.2.3. *DBH*

DBH encodes a copper-dependent mono-oxygenase that converts dopamine to noradrenaline in synaptic vesicles of noradrenergic neurons [41], reducing synaptic dopamine levels. A large meta-analysis of GWAS demonstrated that rs3025343, located 23 kb upstream of *DBH*, increases cigarettes per day [37] (Table 6). Another study of 3441 chronic obstructive pulmonary disease patients of European ancestry replicated this association by demonstrating similar results [136]. Moreover, both studies were observational. In a pooled analysis of two clinical trials reported by Leventhal and colleagues, haplotypes of six *DBH* SNPs were found to predict abstinence at the conclusion of withdrawal treatment and 6-month follow-up in a high nicotine dependence study sample [116] (Table 6). Previous data have linked *DBH* gene polymorphisms to attention deficit hyperactivity disorder and associated phenotypes, including impulse control disorder [88,137] as well as altered dopaminergic and noradrenergic tone [138]. We hypothesize that individuals with *DBH* variants associated with poorer impulse control may find it difficult to resist the temptation to smoke after attempting to quit, especially when combined with the compulsive drive to smoke associated with severe nicotine dependence.

7. Conclusions and perspectives

In this review, we have endeavored to provide a comprehensive, systematic, and intuitive overview of all research on the association between genetic polymorphisms within the dopaminergic system and nicotine dependence. We have elucidated the specific effects of dopaminergic-related gene loci across different populations, delineating whether these effects manifest positively or negatively. Additionally, we have enriched our presentation with clear and very useful tables, facilitating a better understanding of the data presented. In summary, a large number of meta-analyses and linkage disequilibrium have examined the effects of dopamine -related candidate genes on nicotine dependence and have evaluated genes encoding factors including *TH*, *DDC*, *SLC6A3*, *DRD1-DRD*5, *DBH*, *COMT*, and *MAO*. Based on significant results, we can conclude that genetic polymorphisms of the dopaminergic system play an important role in nicotine addiction, in particular with DRD. From more studied adolescents, it can be found that dopaminergic pathways may have significant effects on the development of early smoking and nicotine dependence. In terms of the overall sample population, ethnic samples may be small and have unstudied genetic polymorphisms. For example, there are fewer studies on Asians and the sample sizes are minimal, so testing is prone to false positive errors. The European and American samples are relatively well-studied and comprehensive, however, some discrepancies were noted in the findings [42,43]. A series of possible explanations have

been offered to explain the results. The first reason perhaps is the impact of variations in the definition of addiction phenotypes across different studies. Because there is a large margin of error in using a questionnaire as a grading of addiction levels, using endophenotypes as the measure of addiction is highly encouraged. Additionally, both ethnicity and sex differences are contributing factors to heterogeneities across studies. As samples from different populations tend to have different allele frequencies, it is clear that the disparity of races used in different studies could produce different results. Moreover, the significance results within the same sample are different with different analytical methods. In particular, only one paper investigated association with the *TH* gene, which also reflects the differences in the relevance of different genes to nicotine addiction. To reduce the effect of confounding factors, more powerful tests are required, and the significance of the correlation needs to be assessed after adjusting for age, gender, and ethnicity in the combined sample, and age and gender in each ethnic sample. Moreover, it is preferable to investigate gene-related diseases in family lines.

Meanwhile, most studies on dopamine system-related candidate gene polymorphisms on nicotine dependence have been limited to the results of statistical analysis and have not fully investigated the mechanisms. It is important to emphasize that nicotine dependence is subject to complex multifactorial influences. Pharmacological treatments for smoking cessation aim to alleviate the discomfort of nicotine withdrawal and make it easier for smokers to quit. However, current pharmacologic smoking cessation treatments have limited effectiveness and potential adverse drug reactions. For now, there is still an urgent need to provide a better understanding of the aetiopathogeny of nicotine dependence to develop alternative prevention and intervention strategies. Firstly, understanding how different racial groups are affected by mainstream dopamine-related influences on nicotine dependence yields universal treatment strategies. Secondly, personalized precision therapies tailored to individual genetic profiles emerge as imperative for effective intervention. Accumulating evidence supports a role for epigenetics (DNA methylation; Histone acetylation; Histone methylation) in the development and maintenance of nicotine dependence to many drugs of abuse [139,140]. As more powerful sequence detection tools are developed, including analysis of common, low-frequency, and rare variants, as well as incorporating or complementing familial and environmental risk factors, this will provide even better risk stratification, unlocking the full potential of personalized treatment. Using dopamine genetic information to unlock the potential of smoking cessation is possible. Given the common risk for nicotine dependence and other addictive disorders [141] as well as mental disorders [142], it is crucial to investigate the potential to treat multiple disorders in a manner that considers this risk [143]. This is especially important considering that other dopamine-related dysfunctions may lead to various substance abuse or psychiatric disorders such as alcohol dependence [59], Parkinson's disease [54], Attention Deficit and Hyperactivity Disorders [88], schizophrenia [93] and autism spectrum disorders [94]. Understanding these interconnected mechanisms will not only lead to significant advances in the field of complex disease genetics but also provide insights into the development of effective treatment approaches.

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Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because animal experiments or clinical studies are not required for this study.

Data availability statement

Data was included in references in article. Data sharing is not applicable to this article as no new data were created or analyzed in this study. All data are from the website of https://pubmed.ncbi.nlm.nih.gov/.

CRediT authorship contribution statement

Jingjing Yang: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Investigation, Data curation, Conceptualization. **Hongjuan Wang:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization. **Huan Chen:** Validation, Supervision, Methodology, Funding acquisition, Conceptualization. **Hongwei Hou:** Validation, Supervision, Resources, Project administration, Funding acquisition. **Qingyuan Hu:** Validation, Supervision, Resources, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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