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REVIEW ARTICLE

Genetic variability in the neurobiology of nicotine dependence: effects on smoking behavior

A variabilidade genética na neurobiologia da adição à nicotina: reflexos no comportamento tabágico

Caroline de Lima Mota[1], Cristiane Barata-Silva[2], Josino Costa Moreira[1], Simone Mitri[1]

[1]*Departamento de Toxicogenética, Centro de Estudos da Saúde do Trabalhador e Ecologia Humana, Fundação Oswaldo Cruz (FIOCRUZ) - Rio de Janeiro (RJ), Brasil.*
[2]*Departamento de Química, Instituto Nacional de Controle de Qualidade em Saúde, Fundação Oswaldo Cruz (FIOCRUZ) - Rio de Janeiro (RJ), Brasil.*

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Abstract

Background: Smoking dependence is a chronic disease and a public health problem. The neurobiology of nicotine addiction can explain smoking behavior. This system has genetic variability that has been associated with vulnerability to dependence. Genetic variability in the neurobiology of smoking can help to understand why individuals exposed to drugs may or may not become addicted. **Objective:** This study aims to address genetic variability in the neurobiology of smoking addiction with a focus on polymorphic genes related to the nicotinic response and the dopaminergic reward pathway. **Method:** This work involved a search of the main scientific research on genetic variability in the neurobiology of smoking and its effects on smoking behavior. One hundred and five studies were selected, most of which highlighted polymorphisms in the genes of nicotinic receptors, dopamine receptors, and nicotine metabolism. **Results:** The majority of studies have focused on genes related to the activation of the dopaminergic reward system by nicotine. Combinations between different polymorphisms were also highlighted, showing that interactions can determine a genetic profile of predisposition to smoking addiction. Additionally, gender and ethnicity were identified as relevant factors. **Conclusion:** Knowledge of the genetic bases involved in the individual response to smoking can enable a better understanding of inter-individual differences in smoking behavior, and contribute to improving the treatment of addiction.

Keywords: smoking; genetic polymorphisms; nicotinic dependence; smoking behavior; neurobiological genetic variability.

Resumo

Introdução: A dependência nicotínica é uma doença crônica e um problema de saúde pública. O comportamento tabágico pode ser explicado pela neurobiologia da adição, cujas variações genéticas têm sido associadas à dependência. A variabilidade genética na neurobiologia do tabagismo pode ajudar a entender por que indivíduos expostos a drogas podem ou não se tornar viciados. **Objetivo:** Este estudo tem como objetivo abordar a variabilidade genética na neurobiologia do tabagismo com foco em genes polimórficos relacionados à resposta nicotínica e à via de recompensa dopaminérgica. **Método:** Uma pesquisa foi realizada nas principais bases de dados científicos sobre a variabilidade genética na neurobiologia do tabagismo e seus efeitos no comportamento do tabagismo. 105 estudos foram selecionados, em sua maioria destacando polimorfismos nos genes de receptores nicotínicos,

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Correspondence: Caroline de Lima Mota. E-mail: carolinelima_bio@yahoo.com.br
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receptores de dopamina e de metabolismo da nicotina. **Resultados:** A maioria dos estudos concentrou-se em genes relacionados à ativação do sistema de recompensa dopaminérgico pela nicotina. Determinadas combinações entre genótipos de diferentes polimorfismos também se destacaram, mostrando que interações gênicas podem determinar um perfil genético de predisposição ao tabagismo. Além disso, gênero e etnia foram identificados como fatores relevantes. **Conclusão:** O conhecimento das bases genéticas envolvidas na resposta individual ao tabagismo pode permitir uma melhor compreensão das diferenças interindividuais no comportamento tabágico e contribuir para melhoria dos tratamentos disponíveis para a dependência.

Palavras-chave: tabagismo; susceptibilidade genética; dependência nicotínica; comportamento tabágico; variabildade genética neurobiológica.

INTRODUCTION

Tobacco smoking is a public health problem internationally recognized as a chemical dependency, with industrial cigarettes being considered the most important form of consumption[1,2]. According to the *Tobacco Atlas*, 5.7 trillion cigarettes were consumed worldwide in 2016[2]. Tobacco and tobacco smoke contains more than 8 thousand substances, among which nicotine, a psychoactive substance, is responsible for the addictive effects[3]. The verification of this psychoactive role means smoking is classified, according to the *Review of the International Classification of Diseases and Related Health Problems* (ICD10), in the group of mental and behavioral disorders related to the use of psychoactive substances[4].

Tobacco smoke is the main cause of preventable mortality and morbidity in the world and accounts for the deaths of 8 million people per year. Of these, 1.2 million are non-smokers exposed to secondhand smoke[1]. For instance, in 2017, smoking was associated with 12.6% of the total deaths in Brazil[5]. According to data from Vigitel 2019, the total percentage of smokers aged 18 or over in Brazil was 9.8%, with 12.3% among men and 7.7% among women. Vigitel data points to a reduction in prevalence in both genders, although more pronounced in men[6]. This data indicates a new public health concern regarding the damage to women's health and an increase in tobacco-related diseases[1]. Although overall consumption has declined in recent years, the future path of global tobacco control is still uncertain and future projections are worrying. It is estimated that by the end of 2020, more than 10 million people will die from cardiovascular disease, chronic obstructive pulmonary disease, and lung cancer caused by tobacco use. Half of these deaths will occur during the productive years, with an individual loss of 10 to 20 years of life. In 2030, 80% of consumption-related deaths will occur in developing countries[7].

Despite knowledge of these adverse health effects, smoking addiction explains why about 70% of smokers want to quit smoking, but have not succeeded. Of these, about a third are successful for just one day and less than 10% are abstinent for twelve months[8], with cessation treatment being successful in only 35% of cases[9]. Smoking behavior is complex and multifactorial, determined by a combination of biological, psychological, and environmental factors[8]. Heredity is a strong component of tobacco use and its influence on dependence is at least 50%[10]. Genetic variations can influence up to 80% of characteristics of smoking behavior, such as initiation, persistence in smoking, and successful cessation[11].

Genetic variability in the neurobiology of smoking and other addictions can help to understand why individuals exposed to drugs may or may not become addicted. In addition, knowledge of the genetic bases involved in the individual response to smoking can contribute to improving the treatment of addiction[12]. In this sense, this study aims to address genetic variability in the neurobiology of smoking addiction, focusing on polymorphic genes related to the nicotinic response and the dopaminergic reward pathway.

METHOD

This work involved a search of the main scientific research on genetic variability in the neurobiology of smoking and its effects on smoking behavior. Bibliographic searches were carried out between 2017 and 2020 in the PubMed, Scielo, and Medline databases. The following

terms were used: genetic susceptibility, polymorphic genes, smoking, and nicotine addiction. Articles in Portuguese and English published between 2000 and 2020 were selected and qualified, according to their abstracts, as possible candidates to provide technical-scientific bases for this paper. At the end of the search, duplicate references and unavailable full studies were excluded. Two researchers analyzed and classified each abstract as being outside or within the scope.

RESULTS AND DISCUSSION

The search selected 105 articles that were used as a theoretical basis for the preparation of this work. Figure 1 presents the flowchart of the stages of the identification, selection, and inclusion of scientific articles.

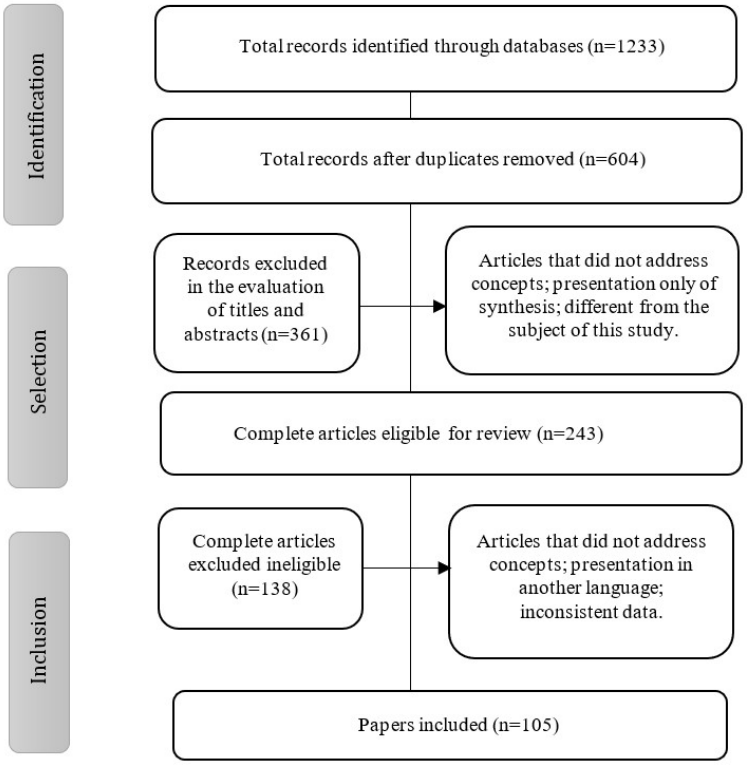

Figure 1. Flowchart of the identification, selection, and inclusion of scientific articles

Neurobiology of tobacco dependence

The neurobiology of smoking explains the molecular mechanism of the development of addiction based on the psychoactive character of nicotine. Inhaled nicotine is absorbed in the lungs from cigarette smoke and reaches the brain in 10 to 60 seconds, where it binds to nicotinic acetylcholine receptors (nAChR) in the mesolimbic system, producing the addictive effects of strengthening the smoking habit through activation of the dopaminergic reward system[13,14].

In the presence of nicotine, the flow of dopamine increases in the mesolimbic system, activating brain circuits to regulate feelings of pleasure and reward. The mesolimbic dopaminergic system is the main neurobiological structure associated with addiction to smoking and plays a crucial role in reinforcement[15]. This system is mainly composed of the ventral tegmental area and the accumbens nucleus. These regions are related to the mechanisms of addiction to nicotine, such as craving, memory, emotions related to use, tolerance, and dysphoria due to abstinence. In addition to dopaminergic hyperactivity, serotonin is released

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in the acute phase of nicotine consumption. Additionally, prolonged exposure desensitizes the gamma-aminobutyric acid system (GABAergic), an inhibitor of brain systems, which reinforces the behavior of compulsive use of nicotine[13,14].

The mechanism of activation of the dopaminergic reward system by nicotine occurs by binding nicotine to the nicotinic receptors of presynaptic neurons (nAChRs), thereby opening cationic channels and, consequently, causing neuronal depolarization. Under these circumstances, dopamine and other neurotransmitters are released in the synaptic cleft and bind to dopamine receptors (DRDs) in post-synaptic neurons, transmitting the signal between neurons. Dopamine is released from the synaptic neurons and some of it is captured by dopamine transporters (DAT) in the presynaptic neurons. After reuptake, dopamine can then be repackaged into vesicles for use in future neurotransmissions or can be degraded by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT)[14] (Figure 2).

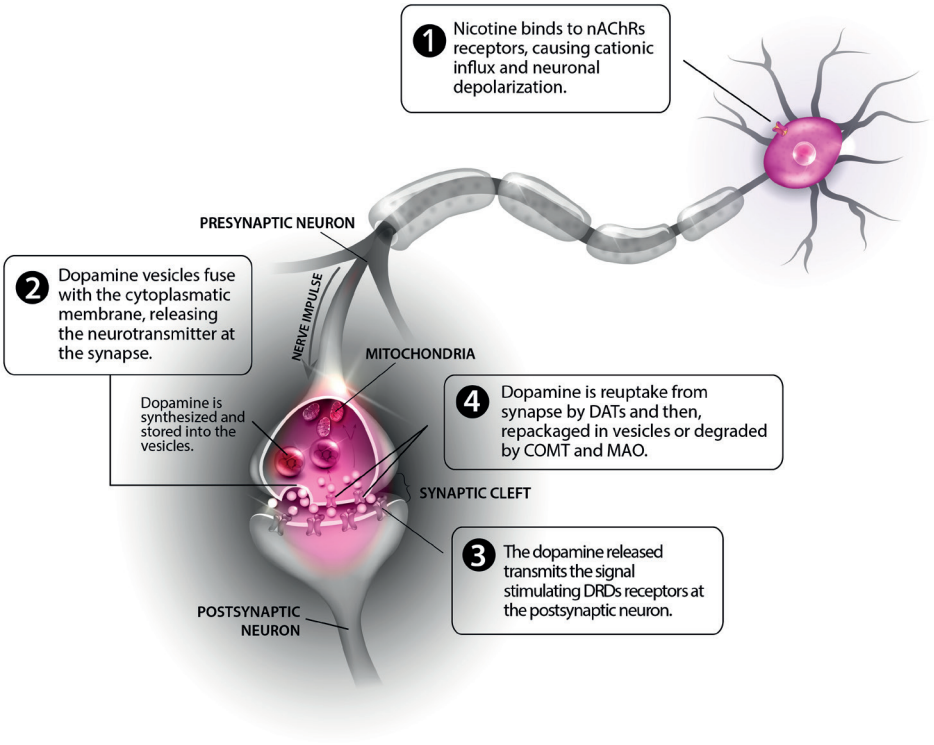

Figure 2. Activation of the dopaminergic reward system by nicotine (nAChRs: Nicotinic acetylcholine receptors; DRDs: Dopamine receptors; DATs: Dopamine transporters; MAO: Monoamine oxidase; COMT: Catechol-O-methyltransferase; NRT: Nicotine Replacement Therapy).

The genes involved in the neurobiology of smoking behavior have been investigated as candidates for individual susceptibility to smoking. Among these, special attention has been paid to those related to the nicotinic response and the neurotransmitter dopamine, considered the key to substance addiction and abuse[8,15].

The first group of genes addressed in this study is directly related to the nicotinic response and is represented by the *CYP2A6* metabolism gene (Cytochrome P4502A6) and by the genes encoding the nicotinic acetylcholine receptors, *CHRN*[8,16]. The second group includes the genes involved in the dopaminergic pathway, which are capable of interfering with the concentration of dopamine in the synaptic cleft. These are the dopaminergic receptor genes *DRD2/ANKK1* and *DRD4*, the carrier gene of dopamine transporters (*SLC6A3*), and the genes of metabolism Dopamine B-hydroxylase (*DBH*), Catechol O-methyl transferase (*COMT*) and Monoamine oxidase (*MAO*)[13,15]. Table 1 presents the main characteristics of the genes studied in this work.

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Table 1. Neurobiological genetic polymorphisms associated with smoking behavior

Polymorphism	Gene function	Variant allele	Effects on smoking behavior	References
CYP2A6	Nicotine metabolization	*2*4	Lower risk of becoming a smoker, lower degree of nicotine dependence, fewer quantity of cigarettes consumed, and greater success in cessation	17-21
CHRNA5 rs16969968	Nicotinic acetylcholine receptor	A	Higher risk of becoming a smoker, greater quantity of cigarettes consumed, greater degree of nicotine dependence, lower chance of smoking cessation	22-29
CHRNA3 rs1051730	Nicotinic Acetylcholine receptor	T	Higher risk of becoming a smoker, greater quantity of cigarettes consumed, earlier smoking initiation, higher cotinine levels, greater degree of nicotine dependence, lower chance of smoking cessation	17,22,28-33
CHRNA3 rs578776	Nicotinic acetylcholine receptor	T	Lower risk of becoming a smoker, fewer quantity of cigarettes consumed, lower degree of nicotine dependence, greater chance of smoking cessation	25,27,34
CHRNA4 rs1044396	Nicotinic acetylcholine receptor	T	Higher chance of smoking cessation, lower risk of becoming a smoker, lower degree of nicotine dependence, lower cotinine levels	19,35-39
CHRNB2 rs2072661	Nicotinic acetylcholine receptor	A	Lower chance of smoking cessation, greater degree of nicotine dependence	40-42
DRD2/ ANKK1 rs1800497	Dopamine receptor	A1 (T)	Lower chance of smoking cessation, higher risk of becoming a smoker, higher risk of regular use of tobacco, earlier smoking initiation, greater degree of nicotine dependence, greater quantity of cigarettes consumed, shorter periods of abstinence, fewer attempts to quit smoking, less effectiveness in NRT and bupropion	30,43-49
DRD4 VNTR	Dopamine receptor	Short allele	Lower risk of smoking, fewer cigarettes consumption, lower degree of dependence, higher chance of smoking cessation using NRT	50-53
SLC6A3 VNTR	Dopamine reuptake	9-repeat	Later smoking initiation, shorter period of smoking, longer periods of abstinence, greater chance of smoking cessation	54-58
DBH rs77905	Dopamine metabolizing enzymes	G	Greater persistence of smoking, less effectiveness in NRT	59,60
DBH rs3025343	Dopamine metabolizing enzymes	A	Lower chance of smoking cessation	61,62
COMT rs4680	Dopamine metabolizing enzymes	Met (A)	Decreased risk of being a smoker, later smoking initiation, lower degree of nicotine dependence, more effectiveness in NRT	60,63-69
MAOA VNTR	Dopamine metabolizing enzymes	4-repeat	Greater quantity of cigarettes consumed, greater degree of nicotine dependence	70,71
MAOA rs1137070	Dopamine metabolizing enzymes	T	decreased risk of being a smoker	60,72
MAOB rs1799836	Dopamine metabolizing enzymes	G	Decreased risk of being a smoker, later smoking initiation	70,73

GENE VARIABILITY RELATED TO NICOTINIC RESPONSE

Polymorphism of *CYP2A6*

Approximately 80% of nicotine is converted into cotinine by the action of the enzyme expressed by the Cytochrome P4502A6 gene (*CYP2A6*). Thus, variations in this gene may alter the enzymatic activity, interfering with the concentration of nicotine that reaches the target sites[16]. Apparently, CYP2A6 functional polymorphisms, in addition to affecting smoking behavior, are also associated with an increased risk of lung cancer[17].

An association between *CYP2A6* genotypes and nicotine dependence has been reported using the Fagerström Test for Nicotine Dependence (FTND) to verify the degree of nicotine dependence. Carriers of the wild allele *CYP2A6*1*, called normal metabolizers, are the most susceptible to tobacco dependence due to needing to consume a greater number of cigarettes

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to maintain satisfactory levels of nicotine in the blood[18]. Other polymorphic variants of the *CYP2A6* gene, such as the *CYP2A6*9* and *CYP2A6*12*, have smaller enzymatic activity, and the *CYP2A6*2* and *CYP2A6*4* variants are associated with a total loss of activity. So, depending on the gene variant carried, an individual is categorized as a normal, intermediate, or slow metabolizer, with 100%, less than 75%, or less than 50% enzymatic efficiency, respectively[16,18].

Wassenaar et al.[18] observed a higher quantity of cigarettes consumed per day by individuals possessing normal metabolizer genes in comparison with those having slow metabolizers. Although other studies have not reported the same association[74] or even divergent results[75,76], several works have shown a direct association between the *CYP2A6* genotype of lower enzyme activity and the lower risk of becoming a smoker, less nicotine dependence, fewer cigarettes consumed and greater success in cessation[17-21].

CHRN gene polymorphisms

The binding of nicotine to nicotinic acetylcholine receptors (nAChR) increases the concentration of dopamine and other neurotransmitters, promoting the activation of reward mechanisms, which is crucial for smoking behavior. Some variations found in the clusters of genes encoding nAChR in dopaminergic neurons are involved in the development of addiction. Special attention has been given to polymorphisms in the *CHRNA4/CHRNB2, CHRNB3/CHRNA6,* and *CHRNA5/CHRNA3/CHRNB4* gene clusters[22,23].

In 2007, an analysis of 3713 Single Nucleotides Polymorphisms (SNP) polymorphisms was published, highlighting the association of SNPs *CHRNA3* (rs578776 C>T; rs1051730 C>T) and *CHRNA5* (rs16969968 G>A) with smoking[21]. Based on this, several other studies have reported the association of gene variants of nicotinic acetylcholine receptors with nicotinic dependence in different groups, though very few have focused on the Brazilian population [24,77].

Several authors have found associations between the variant alleles of rs578776, rs1051730, and rs16969968 with characteristics of smoking behavior, such as the risk for smoking, the number of cigarettes consumed, and the degree of dependence[17,22,24-28,30,31]. These SNPs have also been associated with smoking cessation, but with inconsistent results. In general, studies have shown a significant association between the T allele of rs1051730 and the A allele of rs16969968 with a lower probability of cessation and, inversely, between the T allele of rs57877rs and a greater chance of cessation[29,32-34]. But there are contradictory findings[19,77,78]. Genetic variations in *CHRNB2* and *CHRNA4* also seem to interfere with individuals' responses to drug treatments for smoking cessation. An example is the lower incidence of abstinence symptoms related to polymorphisms in *CHRNB2* and *CHRNA4* in individuals using the drug varenicline, which acts on neuronal nicotinic cholinergic receptors by stimulating the release of dopamine[35,40]. A recent study highlights the contribution of *CHRNA4* (rs1044396 C> T) polymorphism in the choice of the best drug for anti-smoking treatment. According to this study, the effectiveness of varenicline is higher for patients with a CT or TT genotype than for those with CC[36].

Swan et al.[40] showed an association of variant A of the *CHRNB2* polymorphism (rs2072661 G> A) with nausea, an important adverse effect when discontinuing the use of varenicline[40]. Additional studies have reinforced the association of the variant T allele of rs1044396 (*CHRNA4*) and the wild G allele of rs2072661 (*CHRNB2*) with a greater possibility of quitting, lower risk of becoming a smoker, less dependence, and lower cotinine levels[19,35,37-42].

GENE VARIABILITY OF THE DOPAMINERGIC PATHWAY

Polymorphisms of the *DRD2* and *DRD4* genes

Some functional variations have been found in the genes encoding dopamine receptors (*DRDs*) related to smoking. However, the most studied, for their association with smoking, are the polymorphs *DRD2* rs1800497 and *DRD4-VNTR*[50,79]. Historically referred to as *DRD2 Taq1A*, the polymorph Taq1A (rs1800497 C>T) is a variation of the *ANKK1* gene (Ankyrin Repeat And Kinase

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Domain Containing 1), where the presence of the A1 (T) allele is related to lower expression of the DRD2 dopamine receptor, which may interfere with the synaptic concentrations of the neurotransmitter. So, individuals with the A1 allele of this gene have a higher risk of being a smoker[80], starting smoking at a lower age, have a higher degree of dependence, smoke more cigarettes, have shorter periods of abstinence, and make fewer attempts to quit smoking[30,43,44]. However, no association has been found in other studies[81,82]. Additionally, the A2 (C) allele may represent a risk in relation to the characteristics of smoking behavior[59,79].

The SNP can also interfere with the response to pharmacological therapies for cessation. David et al.[45] found that the drug bupropion was effective only in smokers with the A2/A2 (CC) genotype[45]. Swan et al.[46] also observed that A2/A2 women were less likely to stop treatment with bupropion; however, the same associations were not observed in men[46]. An identical effect was also observed in the females for Nicotine Replacement Therapy (NRT)[47]. Other studies have reported an association between the A2 allele and a higher chance of abstinence and success in cessation[45,48,49]. However, this is not a unanimous result[59].

A polymorphism of variable numerical repetition (VNTR) in the gene encoding the D4 receptor, *DRD4*, has also been investigated as a candidate for susceptibility to smoking addiction. Most studies have grouped the alleles into "long" (7 or more repetitions) or "short" (6 or less)[83]. Long alleles have been associated with lower expression of the gene in comparison with the short alleles[84]. The long allele of this polymorphism has been associated with an increased risk of smoking, greater cigarette consumption, a greater risk of initiation, and a greater degree of dependence[50-53]. The relationship between smoking cessation and these groups has also been studied by several authors, but with divergent results. Leventhal et al.[83] found that European individuals with the long allele group treated with bupropion have a greater chance of abstinence compared with a placebo group[83]. However, this result was not confirmed in other studies[85]. The influence of polymorphism was also studied for Nicotine Replacement Therapy (NRT) in individuals with European ancestors; this study showed that those possessing long alleles had a reduced probability of cessation[51]. Other studies have not confirmed the association between *DRD4* VNTR and smoking behavior[86,87]. These differences in findings reinforce the complexity of nicotine addiction and the need for future studies.

Polymorphism of the *SLC6A3* gene

The dopamine transporter (DAT), which is encoded by the SLC6A3 gene, mediates the active reuptake of dopamine from the synapse. Polymorphism of the *SLC6A3* gene is linked to dopamine transport in the synaptic cleft. It is formed by the repetition of a 40-base pair sequence, which can interfere with the expression of the *SLC6A3* gene that encodes the dopamine transport protein (D28). Alleles containing 10 and 9 repeats are the most frequent. The 10-repeats allele is associated with a higher rate of gene transcription and, therefore, with higher levels of the carrier protein[88]. Studies have shown that individuals with the 9-repeats allele are less likely to start smoking before the age of 16, have a shorter smoking time, longer periods of abstinence, and are more likely to quit smoking[54-58]. However, controversial results[89] and a lack of significant association[90] demonstrate the need for further studies on this subject.

A meta-analysis study showed that, although the genetic variations of *SLC6A3* are related to dopamine regulation, there is a lack of evidence on their influence on smoking cessation, given the multifactorial nature of smoking[88]. However, this study reinforced the importance of gene interaction in susceptibility to smoking and showed that the interaction between the *DRD2 Taq1A* and *SLC6A3* genes prolongs abstinence time and influences smoking cessation with the use of bupropion[55]. The results showed the role of gene-gene interaction in the probability of relapse: smokers possessing the A2 allele of *DRD2 Taq1A* and *SLC6A3-9* had significantly higher rates of abstinence at the end of treatment and a longer latency period for relapse[55].

Polymorphisms of the *DBH* gene

The *DBH* gene encodes the enzyme of the same name, which converts dopamine to norepinephrine; this means that lower levels of transcription or activity may result in higher

concentrations of dopamine[51]. Several studies have reported functional polymorphisms in this gene related to smoking behavior[91,92]. The literature shows an association between rs77905 (A> G) polymorphism and nicotine dependence[59,60,92]. Johnstone et al.[59] reported an association between individuals with the GG genotype, in interaction with the A2/A2 genotype of the *DRD2 Taq1A* polymorphism, and greater persistence of smoking, as well as less effectiveness of cessation due to transdermal nicotine replacement[59]. However, McKinney et al.[92] observed that homozygous smokers of the G allele smoked fewer cigarettes than smokers with the A allele[92]. Some studies found no significant association between this SNP and smoking[93]. For instance, according to some authors, the SNP rs3025343 (G> A) is associated with smoking behavior, especially the G allele, which is related to smoking cessation[61,62], but this is still controversial because other studies haven't confirmed this association[94].

Polymorphism of the *COMT* gene

Some functional polymorphisms of the *COMT* gene involved in dopamine degradation linked to smoking have already been identified[63]. The rs4680 G>A variation (Val158/108Met) resulted in less enzyme activity. Therefore, the Val allele carriers showed a low level of the neurotransmitter dopamine and increased COMT activity in comparison with the Met allele[64].

Several studies have shown an association between the Val allele and characteristics of smoking dependence, such as the risk of smoking initiation, a greater degree of dependence, and persistence[65,66]. Enoch et al.[63], analyzing a sample of 342 individuals, observed this association in female smokers[63]. A similar result was found by Nedic et al.[64] in a study with 657 Caucasian men[64]. Additionally, an association between the Met/Met genotype and greater success in cessation has been reported[67]. A survey by Colilla et al.[95], with a sample of 290 women, reported the success of NRT in smokers of Caucasian ethnicity with the homozygous genotype Met/Met in comparison with those with the Val/Val genotype. Another study of 749 Caucasians found that the Met/Met genotype is associated with higher abstinence rates[69]. However, some authors have reported different results[95-99].

Polymorphisms of the *MAOA* and *MAOB* genes

Relevant variations for smoking in both monoamine oxidase genes, *MAOA* and *MAOB*, have been reported, since both are involved in the degradation of some neurotransmitters, such as dopamine[100,101]. As for the variability of the *MAOA* gene, research has focused on polymorphisms that affect smoking. One repetition polymorphism, the *MAOA VNTR* of the promoter region of the gene, which consists of 2 to 5 repetitions of a sequence of 30 base pairs, is related to smoking. Two alleles containing 3 and 4-repeats are most common[60,66,70,71,93,102,103]. The 4-repeats allele has been associated with a greater number of cigarettes consumed, compared to the 3-repeats allele, in Caucasian men with alcohol and tobacco dependence[71]. Similarly, the 4-repeats allele has been associated with higher FTND scores and a higher degree of dependence in women[70]. However, the data are not conclusive, since these findings have not been confirmed by other studies[66,93,103].

Another polymorphism in the *MAOA* gene, called *EcoRV* rs1137070 1460C> T, is capable of altering the transcriptional activity of this gene[82,104]. In this case, the presence of the T variant reduces the risk of smoking, especially in Caucasians[72], and in women[60]. However, some studies have found otherwise[66,102].

Regarding variations in the MAOB gene, the A allele of the *MAOB* rs1799836 polymorphism (A> G) is associated with a lower risk of heavy smoking in men[72]. However, this association is contradicted by other studies[66,105]. Interactions between this SNP with other polymorphisms seem to interfere with the risk of smoking[70,73]. The association of the A allele with smoking risk was found only in association with the B12 genotype of a polymorphism known as the *TaqIB* of the *DRD2* gene[73]. Other studies have shown that Japanese men with a combination of the *MAOB* rs1799836 G allele and the 3-repeats genotype of the *VNTR MAOA* started smoking later than those with other genotypic combinations[70].

CONCLUSION

There are many genes involved in the neurobiology of smoking. Several are polymorphic and, admittedly, some of these variations can affect smoking behavior.

The majority of studies have focused on genes related to the activation of the dopaminergic reward system by nicotine present in cigarettes as candidates for susceptibility to addiction. Due to their association with a higher risk of smoking, the polymorphisms found in the genes *CYP2A6, CHRNA3, CHRNA5, CHRNA4, CHRNB2, DRD2, DRD4, SLC6A3, DBH, COMT, MAOA,* and *MAOB* were addressed. Among these, the *SNPs CYP2A6 *1, CHRNA3 rs578776, CHRNA5 rs16969968, CHRNA4 rs1044396, CHRNB2 rs2072661,* and *DRD2* Taq1A seem to most influence the development of addiction and the worsening of specific characteristics of smoking behavior, such as the number of cigarettes consumed, the age of initiation, the efficiency of drug therapy and cessation.

The relevance of genotypic combinations between different polymorphisms reinforces that interactions between genes can determine a genetic profile of predisposition to addiction. In addition, the sex and ethnicity of the studied populations proved to be important factors in the investigations, especially in the context of a diverse and mixed population. The effects of genetic variability on smoking have received great attention. Advances in the field of pharmacogenetics have enabled a greater understanding of individuality in responses to drug therapies, both in terms of efficacy and adverse effects. Knowledge of the genetic variability of the neurobiology of smoking can help elucidate the issues inherent to smoking addiction and contribute to the development of more personalized and effective forms of treatment. However, the great variability of obtained results shows that this task is not simple. Apparently, it involves several factors. Therefore, more research is needed on this topic, especially considering population differences, the interference of environmental factors, and interactions between different polymorphisms.

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