The influence of genetics on nicotine dependence and the role of pharmacogenetics in treating the smoking habit*

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ABSTRACT
Despite the considerable efforts made in the fight against smoking in the last decades, there are still substantial numbers of people who, in full knowledge of the health hazards, begin smoking or continue smoking. Recent studies have focused on the genetic bases of the nicotine addiction. Various genetic polymorphisms have been associated with smoking. However, environmental factors have also been shown to play a role. In this review, we present some of the principal data collected in genetic studies of smoking behavior. The results obtained through this line of research will eventually aid clinicians in individualizing the type, dosage and duration of treatment for patients with nicotine dependence in accordance with the genotype of each smoker, thereby maximizing the efficacy of the proposed treatment regimen.

Keywords: Smoking; Tobacco use cessation; Nicotine; Tobacco use disorder

INTRODUCTION

The harmful effects of smoking and the number of deaths it causes are widely known. Any moderately well-informed person knows that smoking leads to innumerable health problems. However, those who continue to smoke, together with those who try or start smoking, constitute a large percentage of the global population. In addition, a significant portion of smokers, despite having the desire to quit smoking and making attempts to do so, find it difficult and typically do not succeed.(1)

Traditionally, experimentation with and the initiation of the smoking habit were related to issues such as rebellious adolescent behavior, a need to affirm maturity, challenging authority, imitating idols, peer group pressure (from friends or relatives who are smokers) and associating smoking with being successful from a professional, financial or sexual point of view. More recently, other perspectives, such as the specific personality pattern typified by the search for challenges and the characteristics of neuropsychological

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development, also began to be considered. The reasons that smokers have such difficulty in ceasing smoking are probably similar and are compounded by the problem of organic dependence.

Nicotine dependence explains why approximately 70% of smokers who want to quit smoking do not succeed. Of these, approximately one-third succeed for only one day and less than 10% remain abstinent for twelve months. The definitive cessation of smoking generally only occurs after various attempts, and the relapse rate is very high. The percentage of smokers in which relapse occurs is similar in almost all social classes, even that including individuals, such as health care professionals, who are more informed about tobacco-related diseases. The prevalence of smoking among doctors can be seen as an interesting marker of the dimension of the problem.

It is interesting to note that only a portion of smokers develop such dependence. Why is it that not all smokers present the same evolution? Currently, one of the great questions in the study of smoking is why people exposed to drugs either become or do not become addicted to them. Smoking is a complex multifactorial behavior in which genetic and environmental contributions are significant determinants for both the initiation and maintenance of the habit. Some of those genetic factors will be discussed herein.

GENETIC BASES OF SMOKING

Epidemiological studies examining genetic issues, environmental issues, individual factors (such as neurological development and concomitance with eventual mental diseases) and the interrelationships among these factors, as well as the responses to certain drugs, have shown that the genetic component can play a significant role in the smoking habit, being responsible for 40% to 60% of the variability in the risk of addiction. Some authors estimate that this contribution is more than 80%. It seems that the contribution of heredity to the maintenance of the dependence is approximately 67%.

The first studies relating genetics to smoking date from 1958. One study reported the possibility that the genome is associated with tobacco consumption and lung cancer. The authors of that study suggested the existence of genes that, in youth, predispose individuals to become smokers and, later, to present pulmonary neoplasia.

The analysis of the genetic contribution to smoking began with studies of individuals that share genes, i.e., parents and children, with special emphasis on twins and the adopted members of those families. The role of the environment in the initiation and maintenance of smoking was also evaluated by studying the influence of raising one of a set of twins by biological parents and the other by adoptive parents as well as by studying the peculiarities of the smoking habits of adopted children in relation to the smoking habits of their parents. Those ideas were expanded and studied in depth in the late 1990s. The genetic contribution to smoking was initially considered to be modest, possibly as a result of the complexity of the analysis of the problem and of the multiple interrelationships between genes and the environment.

The role of heredity in smoking addiction continues to be studied through the fundamental aspects of initiation and maintenance of the behavior, with special attention to the difficulty of quitting the smoking habit.

There are innumerable twin concordance studies indicating that genetic inheritance plays a role in smoking addiction. Such studies have demonstrated a higher concordance rate in relation to smoking among monozygotic twins than among dizygotic twins, regardless of whether they were raised together or separately. More recent publications, involving larger study samples, a better classification of phenotypes and more sophisticated statistical models, indicate a rather significant influence of the genome in the determination of the smoking phenotype. Similar results were reported in the USA, Scandinavia, Australia, Great Britain and Japan. In Scandinavia, an association was found between adopted smokers and their biological siblings, as well as between female smokers and their biological mothers (as opposed to their adoptive mothers), underscoring the role of heredity and decreasing the relative importance of the environment in this behavior.

It is currently estimated that this contribution is on the order of 56% for the initiation and 67% for the maintenance of the smoking habit. The genetic influence is also being evaluated in other variables related to smoking such as the age of...
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Even though those twin studies provided convincing data regarding heredity in smoking, the majority were not delineated to identify the genes responsible for those effects.21

This search for the genes specifically associated with smoking has been carried out according to two principal lines of research: identification of the alleles that interfere in the neurobiology of transmitters such as dopamine, serotonin and noradrenaline; and identification of genes that might influence the response to nicotine, thereby interfering with the receptors or with the metabolism of nicotine.

Genetic variation in the dopamine pathway presents biological variation in the studies on smoking dependence, since there are innumerable studies that show the role of this neurotransmitter in the rewarding effects of nicotine and of various other addictive drugs.1,6,22 Nicotine stimulates the release of dopamine in the accumbens nucleus, possibly through the activation of specific receptors. Therefore, various studies have sought to investigate the association between dopamine-regulating genes and nicotine dependence.

The most extensively studied genes of the dopaminergic pathway are those that regulate the flow of dopamine in the central nervous system. Five different dopamine receptors are known, and the genes that encode them have been cloned (DRD1, DRD2, DRD3, DRD4 and DRD5). Among those, the DRD2 receptor has been the most widely studied, due to its association with other addictive behaviors, such as the abuse of licit or illicit drugs, compulsive gambling and compulsive eating, as well as to the known fact that nicotine has a dopamine-releasing effect.23 A meta-analysis evaluated thirteen studies involving the DRD2 polymorphism and smoking, in addition to many other factors that could not be included in its systematic review.9 Certain polymorphisms in DRD2 alleles are more common among smokers than among nonsmokers, and individuals with such polymorphisms present a deficit in the regulation of dopamine and therefore require external stimuli, such as exogenous nicotine, to release sufficient quantities of neurotransmitters and produce a sensation of pleasure or well-being.24 Patients with these genetic characteristics have a lower number of dopaminergic receptors, start smoking earlier, consume greater quantities of cigarettes per day and have more difficulty in quitting smoking.

The idea that DRD1, DRD3 and DRD5 polymorphisms are associated with smoking has been controversial in the literature. Polymorphism in the DRD4 gene, possibly related to the onset of smoking, has been associated with a greater predisposition toward smoking among individuals of African descent but not among Caucasians.25

Polymorphisms associated with dopamine transport in the synaptic fissure have also been studied. Some authors16 found that the SLC6A3 genotype is responsible for encoding the dopamine transporter protein. Individuals that present the SLC6A3-9 polymorphism have a lower predisposition to become smokers, consume less tobacco and have less difficulty in quitting the smoking habit.16

There is evidence that nicotine increases the secretion of serotonin, and that its withdrawal decreases serotonin release, thereby possibly being involved in the mood changes associated with smoking abstinence. Therefore, the serotoninergic pathway has also recently come to be associated with smoking. Studies of the polymorphisms that might be related to smoking, i.e., those involved in the biosynthesis or reuptake of serotonin, are in the initial phase. Depression and anxiety are clinical situations that are both linked to smoking.20,26 Polymorphism of the 5-HT2A serotonin gene receptor increases the chance of the maintenance of smoking to 1.63 for individuals with CC alleles, compared with 0.88 for those with TT alleles.20 A highly significant association between polymorphism in the serotonin transporter gene and the categorical definition of smoking (nonsmoker versus smoker, adjusted according to degree of dependence) has been found, suggesting that this gene influences the initiation of smoking.27

In relation to the pathways involving noradrenaline, it is known that the quantity of cigarettes consumed is associated with polymorphisms of the monoamine oxidase (MAO) genes (MAO-A and MAO-B),28 by which MAO inhibitors can come to play an adjuvant role in the treatment of smoking.29 There is a possible association between the genetics of the enzyme related to the metabolism of dopamine and noradrenaline, beta-dopamine hydroxylase and the
symptoms of tobacco withdrawal syndrome.\(^{10}\) It is known that nicotine has a high affinity for cholinergic receptors, and the relationship between the genes that encode those receptors and smoking might therefore eventually be shown.\(^{22}\)

Genes involved in the metabolism of nicotine are also plausible candidates for studies of smoking behavior. Therefore, individuals that metabolize nicotine more slowly are less likely to start smoking, since they tend to experience more prolonged and intense adverse effects upon initiating the use of tobacco. After becoming regular smokers, such individuals generally smoke less, since they maintain high serum levels of nicotine for longer periods of time. Polymorphism in the CYP2A6 gene, responsible for the hepatic regulation of the nicotine transporter enzyme into cotinine, has been widely studied.\(^{31-34}\)

There is evidence that other systems involved in neuronal transmission are related to different smoking phenotypes. It is known that the consumption of opioids such as heroin and others is associated with the consumption of tobacco. The \(-\)opioid receptor is the primary locale of action of the \(-\)endorphins by promoting the rewarding effects. Nicotine stimulates those endogenous opioid receptors in the brain. The A118G polymorphism of the \(-\)opioid receptor (OPRM1) is associated with the risk of dependence on various drugs, including nicotine.\(^{36}\)

The chronic administration of nicotine increases the quantity of GABA-ergic receptors in animal models whereas that of GABA-B agonists decreases the self-administration of nicotine in rats, possibly due to the reduction of the rewarding effect caused by nicotine. However, the role of the genetics of the GABA receptors in nicotine dependence and in its treatment has yet to be proven.\(^{37-38}\)

Studies attempting to demonstrate such a role have presented various limitations. The inadequate adjustment of the classification of the studied population among the cases and controls plays an important role in the lack of reproducibility in the various studies. Ethnic and cultural factors might influence practices related to smoking in a manner that has not been fully evaluated, since the extent of this type of bias in phenotypes associated with the behavior and drug use remains unknown.

Another limitation is that the simplistic classification of individuals as smokers or nonsmokers may not be satisfactory in describing the multiple phenotypes connected with tobacco consumption such as age of onset, daily tobacco intake, environmental and family influence, individual experiences, previous attempts to cease smoking, signs, symptoms, degree of dependence and many others.\(^{23,35}\)

Complex characteristics such as smoking, which probably result from the interaction of various genes with environmental factors, indicate the need for a more precise definition of phenotypic patterns. This has not been universally achieved, which makes comparison of the results difficult.\(^{23}\)

**Pharmacogenetics of Smoking**

The significant advances in genetics have enabled the investigation of the variability of individual responses to medications, with respect to their efficacy as well as to the rate of adverse effects they provoke, through a new field of science, pharmacogenetics, i.e., the study of the genetic bases of the pharmacological response.\(^{39}\)

The polymorphism of the genes involved in encoding the metabolizing enzymes of drugs and the variability of the transport proteins or receptors are included in these investigations.

The first pharmacogenetic studies involving medications used in the treatment of smoking appeared in recent years. These studies identified, in a preliminary manner, which specific alleles are predictive of the therapeutic response.\(^{40}\)

The first article about the pharmacogenetics of smoking focused on the role of the CYP2B6 gene, which is involved in the biotransformation of bupropion and in the metabolism of nicotine in the central nervous system. It has been shown that smokers presenting the poor metabolizer phenotype (1459 C>T: TC or TT) present greater cravings upon abandoning smoking, and that their failure rates are higher than those of smokers presenting no mutations (CC phenotype). These effects were modified by the interaction between the treatment, genotype and gender of the patient, i.e., the use of bupropion attenuated the genetic tendency toward relapse among the carriers of this polymorphism, but only among women.\(^{41-42}\)

Another study founded on this same clinical trial examined genetic variation in the dopaminergic pathway by studying the polymorphisms in the
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Dopamine (SLC6A3) transporter gene and in its DRD2 receptor. That study was based on the premise that the effects of bupropion are attributable, in part, to the inhibition of dopamine reuptake. The results revealed a gene-gene interaction in the probability of relapse, i.e. smokers with the DRD2-A2 and SLC6A3-9 alleles presented significantly higher abstinence rates at the end of the treatment and a longer latency period for relapse. Among smokers with DRD2-A1 alleles, the effect of the polymorphism on the SLC6A3 gene was not significant.\(^{24}\)

Another study showed that carriers of the DRD2-A1 allele exhibited significantly higher food rewarding rates than the others, and that such rates are attenuated by bupropion. These results show that the weight gain related to smoking cessation might be related to compensation (food reward), and that this can also be associated with specific genetic characteristics.\(^{43}\)

There have been few pharmacogenetic studies of nicotine replacement therapy. The first such study,\(^{44}\) based on data from an earlier study on nicotine patches, concluded that nicotine patches were more effective than placebos among carriers of the DRD2-A1 allele, but not among those who were homozygotic for the DRD2-A2 allele. That study also evaluated another common polymorphism in the gene that encodes the enzyme responsible for the conversion of dopamine into noradrenaline, dopamine beta-hydroxylase. The patches were significantly more effective among smokers presenting the DRD2-A1 and DBH-A polymorphisms concomitantly. These results were confirmed at six and twelve months of follow-up evaluation, although only in women.\(^{45}\)

In relation to the polymorphisms that involve the DRD2 gene, there is data showing that carriers of the A1 variant are more likely to present tobacco withdrawal syndrome and shorter latency periods prior to relapses, and that the nicotine patch is more efficacious in such individuals. The A1 variant has also been correlated with a lower number of receptors and reduced binding capacity.\(^{46}\)

There is evidence that the genetic and biological factors influencing the efficacy of drug therapy for smoking cessation in men are different from those at work in women.\(^{15}\)

A study involving the genetic analysis of smokers in relation to the polymorphism in the genes that encode endorphin receptors in the brain showed that, upon quitting smoking, individuals with the OPRM1 Asp40 polymorphism, by virtue of the greater affinity that endorphin has for its receptor, presented higher success rates, fewer symptoms of tobacco withdrawal syndrome and less weight gain than did those with the Asn40 polymorphism. In addition, those in the Asp40 group responded better to nicotine patches, principally at the dose of 21 mg, than to nicotine replacement spray. Therefore, these individuals apparently could obtain more favorable results if treated with patches at this dose and for longer periods of time. That was one of the first studies showing that genotypes interact with the formulation/presentation of drugs and with the dose to be used.\(^{47}\)

In a study conducted in 2006, an interaction was found between the DRD2 genotype (141Ins/Del) and the treatment given: the InsC homozygotes presented a more favorable response to bupropion, whereas DelC homozygotes presented the best therapeutic response to nicotine replacement therapy, in any of its presentations.\(^{47}\)

There have been few pharmacogenetic studies related to the serotonergic pathway. Preliminary results show that the CC polymorphism of the 5-HT2A gene is associated with therapeutic failure of treatment regimens in which bupropion or nortriptyline are used to promote smoking cessation. Carriers of TC alleles have higher success rates with the use of bupropion than with that of nortriptyline.\(^{48}\)

However, although the drugs available for the treatment of smoking are efficient, there are substantial interindividual differences in the therapeutic responses. Pharmacogenetic studies can lead to higher rates of success and fewer adverse effects, thereby identifying predictive genetic variants of the therapeutic response. Tests that can predict the therapeutic response are in the evaluation phase and, therefore, still awaiting their introduction into clinical practice.\(^{49}\)

REFERENCES

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