



The Genetics of Smoking and Nicotine Addiction

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Abstract:

Globally, tobacco smoking is responsible for the deaths of five million people each year and increases the risk of developing numerous disorders, particularly pulmonary and cardiovascular disease, as well as many cancers. It has long been known that several environmental factors influence the decision to smoke. However, in recent years, we have learned more about the role that genes play in the development of nicotine dependence. Twin and family studies have shown that there is not one specific gene that determines who will develop a smoking addiction but rather several genes that cause an individual to become more susceptible to being addicted to nicotine. These genes are responsible for how certain neurotransmitters are produced and metabolized, the number of receptors that are available to act on and how rapidly nicotine is metabolized by the individual. The more we understand these processes, the better the opportunity will be to formulate effective treatments. This review discusses the role genetics plays in the decision to smoke, the ability to quit and how human genetic variation can influence the success of therapeutics in the treatment of smoking behavior

Introduction

It has long been known that several environmental factors influence the decision to smoke. In recent years, we have learned more about the role that genes play in the development of nicotine dependence. There is not one specific gene that determines who will develop a smoking addiction, but rather several genes that cause an individual to become more susceptible to being addicted to nicotine.

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Genes and Environmental Interactions

Smoking and nicotine addiction are complex multi-factorial



FIGURE 1: Single Nucleotide Polymorphisms (SNPs)

Slight variations in our DNA sequences can have a major impact on whether or not we develop a disease and on our particular responses to such environmental insults as bacteria, viruses, and toxins. They also impact our reactions to drugs and other therapies. One of the most common types of sequence variation is the single nucleotide polymorphism (SNP). SNPs are sites in the human genome where individuals differ in their DNA sequence, often by a single base. For example, one person might have the base A (adenine) where another might have C (cytosine), and so on. Researchers in public and private sectors are generating maps of these sites, which can occur in genes as well as in noncoding regions. Scientists believe such SNP maps will help them identify the multiple genes associated with such complex diseases as cancer, diabetes, vascular disease, and some forms of mental illness. SNP maps provide valuable targets for biomedical and pharmaceutical research. *Image was gratefully provided by the U.S. Department of Energy Genome Programs. <http://genomics.energy.gov>.*

behaviors involving several stages, including initiation, regular use, dependence, cessation and lapse.¹² These are all influenced by environmental factors, such as smoking status of family and peers, economic class and cultural and educational background. Though these environmental factors influence smoking behavior, genetics is still a major determinant of whether an individual continues to smoke following initiation, becomes nicotine dependent or is able to quit.

During the past two decades, twin and adoption studies that estimate the extent to which genes and environment contribute to an observed variation have shown heritability

for smoking ranging from approximately 12 percent to 80 percent, varying according to assessment methods.³⁻¹¹ Further, multivariate analyses of genetic influences on the specific stages of smoking behavior have suggested not only common heritable factors but also stage-specific genetic factors.⁹⁻¹² Taken together, these studies further the notion that intricate gene X environment interactions exist in the etiology of smoking behavior and nicotine addiction.¹³ Though the elegant studies referenced above have identified genetic and environmental components influencing smoking behavior, our understanding of the interaction of gene X gene and gene X environment have yet to be fully elucidated.

Recently, the wealth of information and the advances in genomics made available due to the Human Genome Mapping Project (HGMP) have allowed scientists to localize and implicate more genes involved in complex and multifactorial diseases than ever before. The HGMP identified millions of genetic variations throughout the genome known as Single Nucleotide Polymorphisms (SNPs) (Figure 1). These may or may not have any functional effect on a gene, but, more importantly, they can be used as genetic markers. The discovery of SNPs, combined with micro-array technology, has allowed the simultaneous genotyping of hundreds of thousands of markers allowing genome wide association studies (GWAS) to be conducted. It also has led to the recent discovery of common genetic variants associated with complex diseases such as coronary heart disease¹⁴⁻¹⁶ and type II diabetes^{17,18} and nicotine dependence, smoking cessation and abstinence.¹⁷⁻²⁰ The influence of the allelic variations found in these loci then can be investigated in candidate gene association studies.

Most recent candidate gene association studies in smoking behavior and nicotine addiction have been focused on targets identified by prior linkage analysis and, surprisingly, have not been concentrated on genes of neurotransmitter pathways in the brain reward system and nicotine metabolism.

This review aims to provide an overview of the advances in the field of the genetics of smoking and nicotine addiction, discussing past and recent family, twin and GWAS, candidate gene association studies and the future direction of genetic research of complex disorders and behaviors.

Family and Twin Studies

The considerable evidence that smoking behavior and nicotine dependence have both genetic and environmental influences originate from twin and adoption studies. There have been numerous twin studies dating back to Fisher in 1958, who was the first to report that the concordance for

smoking was higher in monozygotic than dizygotic twin pairs in the German population.²¹ Subsequently, these results later were confirmed and replicated in various countries and populations, and although early studies suggested the role of heredity was fairly small, more recent reports of larger numbers of better characterized phenotypes in conjunction with major advances in statistical analyses have revealed a significant genetic impact on many aspects of smoking behavior. These include initiation,^{3,22,23} persistence²⁴⁻²⁶ and number of cigarettes smoked (For detailed reviews of this literature, the reader should refer to Sullivan and Kendler, 1997, Heath et al., 1998 and Li et al., 2003²⁷⁻²⁹). However, when considering these findings, one of the most notable observations of this literature is the consistent evidence for mid- to high heritability across a wide range of ages, countries and gender.³⁰

Genome Wide Association Studies

In the last few years, there has been a dramatic increase in the publication of GWAS for numerous diseases. The timing of these publications reflects the enormous technological advances in genotyping technology by companies such as Affymetrix and Illumina, but the groundswell behind these studies also can be traced back to two groundbreaking publications from 1996.^{31,32} These papers argued that common variants underlie most common diseases and that these would be more easily detected using population-based association studies, rather than family based linkage analysis. (Though this may necessitate analyzing every gene in our genome and, thus, all known common variants in our genes should be identified). These hypotheses gained support and led to the International HapMap Project³³ with the goal of cataloging all common genetic variants. Therefore, with the latest SNP genotyping platforms that allow simultaneous genotyping of hundreds of thousands of SNPs, the HapMap has made GWAS possible. GWAS enables the detection of allelic variants in genes that were perhaps not anticipated and has already identified previously unanticipated addiction-susceptibility at-risk genes that may contain polymorphisms that could contribute to individual differences in vulnerability to substance dependence.^{20,34-38}

Candidate Gene Association Studies

Nicotine, the predominant psychoactive agent in cigarettes, readily crosses the blood-brain barrier and targets nicotinic acetylcholine receptors (nAChRs). That, in turn, leads to an increase in the release of dopamine. Furthermore, repeated nicotine administration results in neuronal changes such as an upregulation of nAChRs.^{39,40} Thus, it is not surprising that the majority of candidate gene studies have concentrated on genes in neurotransmitter

pathways for drug reward and nicotine metabolism. The major candidate genes, the associated polymorphisms and the resulting phenotypes are listed in Table 1.

Dopamine Receptors

The role of the dopaminergic system in the rewarding properties of nicotine is well established and has received considerable interest in candidate gene studies.^{41,42} The dopamine receptor family is a group of G-protein-coupled receptors comprised of five members and are encoded by the genes DRD1-5. In particular, linkage studies have implicated a chromosomal region near 11q23, which is close to DRD2, with cigarette consumption.⁴³ Subsequent analysis of the variation in the DRD2 gene has revealed an SNP in a kinase gene, ANKK1 downstream of the DRD2 locus.⁴⁴ However, there has been conflicting evidence that this C>T SNP firstly results in a lower number of D2 receptors and secondly is a risk factor for smoking behaviors.⁴⁵⁻⁴⁷

Polymorphisms in the DRD4 gene, specifically a 48-base pair (bp) Variable Number of Tandem Repeat (VNTR) found in exon 3 of DRD4 and located on chromosome 11p15.5, also have shown association with habitual smoking.⁴⁸ Interestingly, the varying number of repeats found in the VNTR also has been associated with different smoking phenotypes. For example, in African Americans the long (L) allele containing 6-10 repeats has been associated with a shorter time before the first cigarette in the morning, compared to the short (S) allele of 2-5 repeats.⁴⁹ Further, individuals possessing the L allele has also been shown to exhibit a greater craving for cigarettes and attention to smoking cues than individuals with the S allele.⁵⁰

There is also some evidence that DRD1, DRD3 and DRD5 have a role in smoking behavior. For example, a region on chromosome 5 close to DRD1 has shown linkage to both smoking initiation and cigarette consumption.^{48,51,52} Additionally, as part of a study examining dopamine receptor genes among smokers, Tourette syndrome probands and pathologic gamblers, there was a significant increase in the frequency of specific DRD1 genotypes (1/1) in all three groups when compared to controls. These results, therefore, suggest that there may be an overlap in genetic susceptibility to addictive behaviors, possibly mediated by specific alleles in DRD1.⁵³

Dopamine Transporter

The dopamine transporter (DAT) is a transmembrane protein that is a critical regulator of dopamine transmission, and variations in the gene SLC6A3 that encodes DAT have been reported to mediate concentrations of and responses to synaptic dopamine. A 40bp VNTR polymorphism

Table 1. List of Candidate Genes Associated with Smoking and Nicotine Addiction.

Candidate Gene	Genetic Association	Phenotype	Reference
Dopaminergic system: <i>Dopamine Receptors,</i> DRD2	Linkage to Chromosomal region 11q23.	Increased cigarette consumption.	[43]
DRD4	48bp VNTR in Exon 3	Habitual smoking, greater craving, Shorter time before first morning cigarette.	[48] [50] [49]
<i>Dopamine Transporter,</i> DAT 1	40bp VNTR in 3' UTR	Lower risk of current smoking and starting smoking before age 16, longer periods of abstinence and increased quitting.	[59] [60]
<i>Dopamine Metabolism,</i> Tyrosine Hydroxylase (TH)	Linkage to Chromosomal region 11.15.5.	Habitual smoking.	[48]
Dopamine β -hydroxylase (DBH)	Linkage to Chromosomal region 9q43.	Habitual smoking and cigarette consumption.	[52] [65]
Monoamine oxidase (MAOA)-A	VNTR in promoter region	Higher levels of nicotine dependence and lower risk of smoking.	[66]
Catechol-o-Methyl Transferase (COMT)	G>A SNP corresponding to Val108/158Met	Protective against smoking in women, protective against nicotine dependence.	[70] [71]
Serotonergic System <i>Serotonin Transporter,</i> 5-HTT	44bp insertion/deletion in promoter	Association is via genetic effects on personality.	[83]
<i>Serotonin Metabolism,</i> Tryptophan Hydroxylase	Linkage of Chromosomal region 11p15	Habitual smoking.	[48]
Cholinergic Receptors CHRNA4 CHRNA7	Alpha-4 subunit variation Polymorphism in intron 2, Linkage to Chromosomal region 15q13.1	Lower risk of nicotine dependence in Chinese men. Smoking status in schizophrenics. Habitual smoking	[87] [91]
Nicotine Metabolism CYP450 2A6	Multiple polymorphisms. CYP2D6*1or*2	Wide range of enzyme activity affecting metabolism of nicotine to cotinine. Extensive metabolizers of nicotine and heavy smoking.	[95] [96,97]

(3-13 repeats) has been located in the 3' untranslated region (UTR) of SLC6A354 with the 9-10 repeat alleles the most frequently occurring in humans.⁵⁵ The 9 repeat allele has been associated with dopamine excess disorders and the 10 repeat allele linked to dopamine deficiency conditions.⁵⁶⁻⁵⁸ Interestingly, studies of the 9 repeat allele in smoking behavior have been linked with a lower risk of current smoking and starting smoking before the age of 16 years, longer periods of abstinence during previous quit attempts and increased quitting.^{59,60} Unfortunately, in both studies, the effect size was small, a mixed sample of subjects was recruited and these studies have not been replicated.^{61,62}

Genes Involved in Dopamine Metabolism

Several enzymes including Tyrosine hydroxylase (TH), Dopamine β -hydroxylase (DBH), Catechol-o-methyl Transferase (COMT) and Monoamine oxidase (MAO)-A and B are involved in the metabolism of dopamine.⁶³

TH encodes tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis. A region close to the TH gene on Chromosome 11.15.5 has been linked with habitual smoking in genome wide-linkage scans.⁴⁸ It has been suggested that a 4bp VNTR in the promoter region of the gene affects gene expression due to the disruption of a number of transcription factor binding sites.⁶⁴ DBH catalyzes the conversion of dopamine to norepinephrine, and genome scans also have implicated its chromosomal locus on 9q43 to both habitual smoking and cigarette consumption.^{52,65} Another VNTR found in the promoter region of MAO-A has been associated with higher levels of nicotine dependence in Japanese males and a reduced risk of being a current smoker in Japanese females.⁶⁶

The role of COMT in the degradation of catecholamines is well known and the association with various behavioral disorders of a functional G>A SNP corresponding to Val108/158Met within the gene has been well-documented in the literature. Individuals who are Val/Val homozygotes have a three- to four-fold higher enzyme activity compared with those with a Met/Met genotype.^{67,69} Reports have suggested that the low activity Met allele is protective against current smoking in women⁷⁰ and that several gender and specific haplotypes are protective against nicotine dependence.⁷¹ However, other studies have not found any associations between this polymorphism and smoking initiation, cessation or consumption.^{72,73}

Serotonin System

Serotonin Transporter

There is substantial evidence that nicotine intake increases serotonin levels in the brain and that a withdrawal of

nicotine causes a decrease in serotonin levels. The serotonin transporter (5-HTT) not only regulates the level and duration of the neurotransmission of serotonin but also modulates the release of dopamine.^{74,75} The serotonin transporter 5-HTT has been associated with a number of psychiatric disorders including depression and schizophrenia which are co-morbid with smoking.⁷⁶⁻⁷⁸ A polymorphism in the 5' promoter region of 5-HTT (*5-HTTLPR*), which involves a 44bp insertion or deletion, results in two alleles, Long (L) or Short (S), with the S allele causing a reduction in gene expression.⁷⁹ The studies that have examined the impact of the polymorphism on smoking have produced contradictory results, with the S allele showing a lower frequency in current smokers to former smokers in a Japanese study,⁸⁰ but in another study, no associations were found.⁸¹ An interesting aspect of the role of the *5-HTTLPR* polymorphism in smoking is the strong relationship of the SS genotype with irritability and temperament traits. This suggests that the *5-HTTLPR* polymorphism is associated with smoking via genetic influences on personality, and, therefore, is greatly influenced by population composition.⁸² This can be supported by studies in adults with the S allele who have high levels of neuroticism and also have increased difficulty in quitting smoking.⁸³

Serotonin Metabolism and Tryptophan Hydroxylase

Tryptophan Hydroxylase is the rate-limiting enzyme for serotonin synthesis, and, thus, is a good candidate gene for smoking behavior. Further, the gene that encodes Tryptophan Hydroxylase (TPH1) is located on chromosome 11p15 in a chromosomal region associated with habitual smoking in a genome wide-linkage study.⁴⁸ However, the evidence for associations with smoking again has been mixed.^{84,85}

Cholinergic Receptors

Our understanding of cholinergic receptor function and activation following nicotine administration results from extensive animal studies and the use of knockout mice. We know that a large proportion of nicotine's psychoactive properties are a result of binding to and the activation of neuronal nicotinic cholinergic receptors (nAChR). These are pentameric multi-subunit (α 2-10, β 2-4) ligand-gated cation channels, with the α 4 and β 2 subunits comprising approximately 90 percent of the high affinity nicotine-binding sites in the brain.⁸⁶ Mice lacking both subunits exhibit a lack of nicotine self-administration and nicotine-induced dopamine release in the VTA.⁸⁶

Genetic variants of CHRNA4, which encodes the α 4 subunit, have been associated with smoking and a lower risk

of nicotine dependence in Chinese men but has not been replicated in either males or females of other ethnic groups.^{87,88} As the prevalence of smoking in schizophrenics is very high (80 percent),^{89,90} several genetic studies have examined genes associated with smoking in this patient population. A polymorphism in intron 2 of CHRNA7 has been associated with smoking status in schizophrenics, and interestingly, the region near CHRNA7 on chromosome 15q13.1 has been linked to habitual smoking.⁹¹

Genes Influencing Metabolism of Nicotine

Cytochrome P450 2A6

Following the smoking of a cigarette, 80 percent of the nicotine is metabolized in the liver to cotinine⁹² with the highly polymorphic enzyme cytochrome P450 2A6 (CYP2A6) responsible for 90 percent of this reaction.⁹³ Subsequently, cotinine is metabolized to trans-3-hydroxycotinine in a reaction controlled entirely by CYP2A6. Further, the gene for CYP2A6 is found on 19q13.2 adjacent to a region associated in a genome scan with smoking frequency.⁹⁴

There exist multiple genetic variations of CYP2A6 between individuals and ethnic groups, which result in a wide activity range for this enzyme. An excellent review of the role of the CYP2A6 polymorphisms and smoking behavior can be found in an article by Malaiyandi et. al.⁹⁵

Another P450 enzyme, CYP2D6, also is involved in the conversion of nicotine to cotinine. Individuals who are homozygous for the recessive alleles of this gene CYP2D6, *3,*4 and *5 are considered poor metabolizers, while individuals possessing one or two copies of CYP2D6 *1 or *2 are known as extensive metabolizers. Those with two more copies are considered ultrarapid metabolizers.⁹⁶ The involvement of this genotype in smoking has support from reports that the prevalence of ultrarapid metabolizers among heavy smokers was four times higher compared to nonsmokers and twice as high compared to smokers with variable consumption.⁹⁷

Pharmacogenetics of Smoking Behavior and Treatment

The progress in our understanding of genetic variation within individuals has led to a greater awareness of the variability of an individual's response to specific medications. Pharmacogenetic studies of the medications used in the treatment of smoking and nicotine addiction have revealed that specific genotypes are predictive of therapeutic response.⁹⁸ Preliminary studies have focused on the CYP2B6 gene, which is potentially involved with nicotine metabolism and also is the primary enzyme involved in the

metabolism of the drug bupropion.^{99,100} Studies which examined the 1459 C>T SNP, which decreases enzyme activity, showed that smokers with at least one T allele possessed the so-called poor metabolizer genotype SNP: TC or TT and exhibited greater cravings and increased rates of failure following attempts to quit than smokers who had the wild type CC genotype with no mutations. However, women with the poor metabolizer genotype (TT or TC) who were treated with bupropion had much fewer intense cravings and had better success at quitting smoking.^{99,101} Further studies have investigated the efficacy of bupropion treatment in smokers with specific DRD2 genotypes and found a much more favorable outcome associated with the 141InsC genotype.¹⁰² Overall, this and other data show that although drugs such as bupropion are efficient in the treatment of smoking and nicotine dependence, there is substantial evidence that the genotypic variations between individuals play a critical role in the therapeutic response of the patient. Therefore, pharmacogenetic studies and testing can and will lead to higher rates of success and fewer adverse effects in the treatment of nicotine addiction and smoking behavior.

Conclusions

Smoking still continues to have an enormous impact on human health, despite the well-documented health problems associated with this behavior. However, a better understanding of the genetic influences on smoking behavior and nicotine addiction will provide clinicians and scientists with better tools to understand the complex mechanisms involved in this hazardous behavior.

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APPENDIX 1. Glossary of Genetic Terms**Allele**

One of two or more alternate forms of a gene.

Association Study

Genetic association studies aim to test whether single-locus alleles or genotype frequencies (or more generally, multilocus haplotype frequencies) are different between two groups (usually diseased subjects and healthy controls).

Genome Wide Association Study (GWAS)

A genome-wide association study is an approach that involves rapidly scanning markers across the complete sets of DNA, or genomes, of many people to find genetic variations associated with a particular disease.

Genotype

Complete set of genes of an organism.

Exon

Coding region of a gene interrupted by introns. Exons remain in the messenger RNA following processing.

Haplotype

Combination of alleles at multiple loci that are transmitted together on the same chromosome. Haplotype may refer to as few as two loci or to an entire chromosome depending on the number of recombination events that have occurred between a given set of loci. In a second meaning, haplotype is a set of single nucleotide polymorphisms (SNPs) on a single chromatid that are statistically associated.

HapMap

The International HapMap Project is an organization whose goal is to develop a haplotype map of the human genome (the HapMap), which will describe the common patterns of human genetic variation. The HapMap is expected to be a key resource for researchers to find genetic variants affecting health, disease and responses to drugs and environmental factors.

Heterozygous

Refers to an individual that possesses two different alleles at a locus.

Homozygous

Refers to an individual that possesses two identical alleles at a locus.

Intron

Intervening sequence between exons. Introns are removed from the RNA following transcription.

Linkage Analysis

Study aimed at establishing linkage between genes. Linkage is the tendency for genes and other genetic markers to be inherited together because of their location near one another on the same chromosome.

Locus

Position on a chromosome where a specific gene is located.

SNP

One of the most common types of sequence variation is the single nucleotide polymorphism (SNP). SNPs are sites in the human genome where individuals differ in their DNA sequence, often by a single base.

SNP nomenclature

SNPs are written with a prefix, period and greater than sign showing the wild-type and altered nucleotide or amino acid; for example, 76A>T.

VNTR

Variable Number of Tandem Repeats. Short sequences repeated in tandem that vary greatly among individuals.

Phenotype

Appearance or manifestation of a trait or characteristic.

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