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Genetics and Smoking Cessation: Improving Outcomes in Smokers at Risk

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Abstract

This article reviews evidence supporting the potential utility of a pharmacogenetic approach to the treatment of nicotine dependence. There is substantial evidence that nicotine dependence and smoking persistence are heritable, and are determined by a complex interplay of polygenic and environmental influences. The most robust evidence for specific genetic influences on nicotine dependence is found in studies of genetic variation in nicotine-metabolizing enzymes. Data also support the role of genes in the dopamine and opioid pathways as predictors of dependence and smoking relapse; however, the evidence for genetic associations is not always consistent. Emerging data from pharmacogenetic trials of nicotine-dependence treatment are promising, suggesting that genetic profiles of smokers someday may be used by providers to choose the type, dose, and duration of treatment for individual smokers. However, additional trials including larger and more diverse populations are needed before such data can be translated to practice to reduce smoking prevalence and tobacco-related disease.

Introduction

Despite progress made in the treatment of tobacco dependence, currently available treatments are effective for only a fraction of smokers. Although current guidelines recommend the use of nicotine patch as a firstline treatment for tobacco dependence,[1] about 70%–80% of smokers treated with the patch relapse to their former smoking practices in the long-term.[2,3] Bupropion has been shown to produce higher quit rates than nicotine replacement therapy,[4,5] yet the large majority of smokers do not quit nor do they remain abstinent. The newly FDA-approved medication for treating nicotine dependence, varenicline, which outperforms bupropion significantly, yields a 1-year abstinence rate of 22%. However, these quit rates were achieved with behavioral counseling lasting for almost 1 year, which may not reflect real-world treatment.[6,7] Thus, research is needed to identify those smokers who are at increased risk for relapse following a cessation attempt, and to tailor smoking-cessation treatments to smokers' individual risks and needs.

Pharmacogenetics research is generating new knowledge about genetic factors that influence nicotine dependence and smoking-cessation treatment outcomes. The basic premise of this approach is that inherited differences in drug metabolism (pharmacokinetics) and drug targets (pharmacodynamics) have important effects on treatment outcome.[8,9] These concepts and key

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variables are illustrated for nicotine-dependence treatment in Figure 1. Efforts to increase the understanding of the role that inherited variation plays in response to pharmacotherapy for nicotine dependence someday may help practitioners to individualize treatment type, dose, and duration based on genotype, thereby minimizing adverse reactions, increasing treatment compliance, and maximizing treatment efficacy.[10,11] This article reviews evidence supporting the potential utility of a pharmacogenetic approach to smoking-cessation treatment. Portions of this paper were adapted from a recent book chapter on this topic.[12]

Genetic Influences on Smoking Persistence and Relapse

While the initiation of tobacco use, the progression from use to nicotine dependence, and the ability to quit smoking are influenced by a range of environmental factors (e.g., parental and peer influence, depression), twin studies have shown that genes play a critical role as well.[13,14] In twin studies, evidence of heritability is based on evaluating the similarity between monozygotic twins (who share 100% of their genes) on a phenotype, compared to dizygotic twins (who share 50% of their genes, similar to nontwin siblings). These studies have shown that approximately 60%–70% of the variability in nicotine dependence and smoking persistence is due to genetic influences.[13,15–21] Two recent studies examined smoking-cessation data from twin pairs from the Vietnam Twin Registry[22,23] and concluded that 51%–54% of the variance in the ability to quit smoking given a quit attempt, was attributable to genetic factors.

Given consistent evidence for the heritability of nicotine dependence, attention has shifted to investigations of specific genetic influences.[24–26] Genetic variation in enzymes (e.g., CYP2A6) that metabolize nicotine to its inactive forms (cotinine and 3-hydroxycotinine) influence peripheral levels of nicotine and smoking behaviors.[25] Genetically faster metabolizers of nicotine (two *1 alleles; ~80% of smokers)[27] smoke more cigarettes per day and are more dependent on nicotine than slower metabolizers (carriers of *2 *4, *9A, and *12A alleles; ~20% of smokers)[27,28] Fast metabolizers are also two times less likely to quit smoking,[29] are more likely to relapse following transdermal nicotine-replacement treatment,[30] and report higher levels of withdrawal symptoms following cessation.[31]

Candidate genes in neurobiological pathways mediating drug reward have been extensively studied for associations with nicotine dependence. Nicotine binds to neuronal nicotinic acetycholine receptors (nAChRs) expressed on dopamine and gamma-aminobutyric acid (GABA) neurons in the ventral tegmental area (VTA), resulting in increased dopamine release in the nucleus accumbens.[32,33] Despite the importance of nAChRs in nicotine dependence, particularly the *CHRNA4* and *CHRNB2* subtypes,[34] functional polymorphisms in these subunit genes have yet to be identified. Selected genetic polymorphism and haplotypes in *CHRNA4* have been associated with nicotine dependence,[35,36] while studies examining the role of *CHRNB2* in smoking behavior have been negative.[35,37,38]

Given the central role of dopamine signaling in the rewarding effects of nicotine, alcohol, and other addictive drugs,[39–41] many initial studies focused on the common Taq1A polymorphism, originally thought to be in the dopamine D2 receptor (*DRD2)* gene, but later determined to be in a neighboring gene, *ANKK1*.[42] With respect to smoking behavior, some association studies have reported a higher prevalence of the low-activity *DRD2* Taq1'A1 allele among smokers compared to nonsmokers,[43,44] while other findings have been negative.[45] Positive results have also been reported for associations of a variable number tandem repeat (VNTR) polymorphism in the 3″ end of the dopamine transporter *(SLC6A3)* gene with smoking behavior[46,47]; however, this has not been replicated in other studies.[48] Finally, two independent studies have provided evidence for interacting effects of the *DRD2* Taq1A and *SLC6A3* variants on the likelihood of cessation.[49,50] A separate study found associations of

SLC6A3 genotypes with cessation following treatment with either nicotine replacement therapy (NRT) or bupropion.[51]

More robust findings have been observed for polymorphisms shown to alter protein transcription or translation. For example, the reduced-activity 7-repeat allele of the *DRD4* gene VNTR has been associated with smoking persistence in African Americans.[52] The high-activity (Val) allele of the catechol-o-methyl-transferase (*COMT*) gene, associated with more rapid degradation of dopamine, has been associated with smoking persistence in a retrospective case-control study and in a prospective smoking-cessation study.[53]

Nicotine also increases levels of endogeneous opioids that bind to mu opioid receptors on GABA interneurons in the VTA.[41] Consistent with neurobiological evidence, the mu opioid receptor (*OPRM1*) Asn40Asp functional variant (low-activity Asp40 allele) has been associated with smoking persistence,[54] as well as reduced nicotine reward among women.[55] A recent study comparing smokers with high vs low levels of nicotine dependence did not find associations with this *OPRM1* variant; however, haplotype analysis suggests that other variants, that may be in linkage disequilibrium with the Asn40Asp polymorphism, are linked with this smoking phenotype.[56] Finally, despite effects of nicotine on serotonin neurotransmission, there is no strong evidence linking smoking cessation with genes in the serotonin pathway,[57–59] although associations with nicotine dependence have been reported.[60] Thus, it has proven difficult to identify candidate genes with robust, replicable associations with nicotine dependence and smoking persistence.

Pharmacogenetic Investigations of Treatment for Nicotine Dependence

Pharmacogenetic clinical trials, in which the type and dose of treatment are under experimental control, may provide a stronger signal for genetic effects on smoking cessation and shed light on individual differences in the efficacy of treatments for nicotine dependence (see Table 1).[61] The emerging field of pharmacogenetics is based on the premise that inherited genetic variants contribute to individual variability in treatment toxicity and efficacy.[8,9] Although this field is in its formative years, identifying genes related to responsiveness to treatments for nicotine addiction can lead to clinical guidelines for tailoring treatments to genetic profiles to increase treatment efficacy.[10,61]

Nicotine Replacement Therapy Trials

To date, two pharmacogenetic trials of NRT have been conducted. The first of these, conducted in the United Kingdom, compared transdermal nicotine patch to placebo patch among 755 of 1500 smokers who consented to provide DNA following the initial efficacy trial.[62,63] Based on previous evidence that nicotine's rewarding effects are mediated, in part, by dopaminergic mechanisms,[64,65] initial pharmacogenetic analyses focused on genes in the dopamine reward pathway. The patch was found to be superior to placebo for carriers of the Taq1 A1 allele of the *DRD2 (ANKK1*) gene, but not those homozygous for the more common A2 allele.[62] Further, the short-term efficacy of the transdermal nicotine patch was modulated by synonymous single-nucleotide polymorphism (SNP) in the dopamine beta hydroxylase (*DBH)* gene, which codes for an enzyme involved in the conversion of dopamine to norepinephrine.[63] A longer-term follow-up of this analysis supported the association of the *DRD2* Taq1A variant with abstinence at 6- and 12-month follow-ups; however, the effect was observed only among women.[62] These findings suggest that the efficacy of pharmacotherapy may be influenced by different genetic and biological factors in men and women.

In the United States, an open-label randomized trial compared transdermal nicotine and nicotine nasal spray. A recent pharmacogenetic analysis from this trial focused on two functional genetic variants in *DRD2*.[66] A promoter variant (–141C *Ins/Del*) is associated with

altered transcriptional efficiency.[67] Another functional SNP in *DRD2* (C957T) alters mRNA stability and protein synthesis.[68] Smokers carrying the reduced activity *Del* C allele of the –141C had statistically significantly higher quit rates on NRT compared to those homozygous for the *Ins* C allele, independent of NRT type. The C957T variant also was associated with abstinence following NRT. Thus, smokers carrying variants associated with reduced transcriptional efficiency or translation responded better to NRT, perhaps because of nicotine's effects on dopamine release. Separate analyses from this trial reported that success with NRT was predicted by an interaction between the *DRD2* –141 *Ins/Del* SNP and the *NCS-1* gene, coding for a *DRD2* interacting protein.[69]

The role of the *COMT* Val/Met functional polymorphism was also explored for effects on response to NRT in this trial.[53] COMT is the primary enzyme involved in the degradation and inactivation of the neurotransmitter dopamine. A polymorphism in *COMT* results in conversion of a Val high-activity allele to a Met low-activity allele, resulting in a three- to four-fold reduction in *COMT* activity. In the NRT trial, the Met/Met genotype was associated with a higher probability of abstinence with either nicotine nasal spray or nicotine patch, among women, but not in men.[53]

The role of the *OPRM1* gene was also examined in the U.S. trial.[54] The Asp40 variant (G allele) is associated with reduced MRNA and protein levels[70] and is carried by 25%–30% of individuals of European ancestry. In the NRT trial, smokers carrying the *OPRM1* Asp40 variant were significantly more likely than those homozygous for the Asn40 variant to be abstinent at the end of the treatment phase. The differential treatment response was most pronounced among smokers receiving transdermal nicotine.[54] In contrast to positive associations for *DRD2* and *OPRM1*, there was no evidence for moderation of treatment response by the serotonin transporter (*5-HTTLPR*) gene in the NRT trial.[58] Likewise, David et al.[57] reported that response to NRT was not associated with variants of the *5-HTTLPR* gene.

Finally, a recent paper reported the effects of SNPs in *CHRNA4* (α4 subunit of the acetycholine nicotinic receptor) in response to NRT in the U.S. clinical trial.[71] Individuals with the TC genotype for this SNP, which is associated with greater α4β2 binding and greater sensitivity to the acute effects of smoking, were more likely to maintain abstinence on nasal spray, but not transdermal patch.

Bupropion Trials

To date, three independent bupropion pharmacogenetic trials have been conducted in the U.S. An initial report from a placebo-controlled trial focused on the *CYP2B6* gene, which has been implicated in bupropion kinetics[72] as well as in brain metabolism of nicotine.[73] Participants in this trial provided blood samples and received bupropion (300 mg/day for 10 weeks) or placebo, plus counseling. Smokers with a decreased-activity variant of *CYP2B6* (slower metabolizers) reported greater increases in cravings for cigarettes following the target quit date and had significantly higher relapse rates.[74] These effects were modified by a significant gender × genotype × treatment interaction, suggesting that bupropion attenuated the effects of genotype among female smokers. The absence of a genotype association with bupropion side effects suggests that the genotype effect is not due to bupropion pharmacokinetics, but may be attributable to *CYP2B6*-mediated differences in nicotine metabolism in the central nervous system (CNS). For example, slower metabolizers of CNS-nicotine may experience neuroadaptive changes that promote dependence and abstinence-induced craving. In a subsequent analysis of a novel functional *CYP2B6* *6 variant (a genotype combining 2 SNPs), smokers with this genotype had significantly lower quit rates on placebo, and responded very well to bupropion; in contrast, smokers with the wildtype genotype performed equally well on placebo and bupropion.[75]

Inhibition of dopamine reuptake is one putative mechanism for the beneficial effects of bupropion.[76,77] Therefore, an analysis of response to bupropion has been conducted relative to two functional genetic variants in *DRD2*. There was a statistically significant interaction between the *DRD2* –141C *Ins/Del* genotype and treatment, at the end of the treatment phase, indicating a more favorable response to bupropion among smokers homozygous for the *Ins* C allele compared to those carrying a *Del* C allele.[66] The C957T variant was not associated with bupropion response. Given that the –141 *Ins* C allele results in higher transcriptional efficiency compared to the *Del* (N) allele,[67] individuals with the –141C *Ins/Del* CC genotype may have more D2 receptors available to bind dopamine, yielding a more rewarding experience of the nicotine-induced dopamine release. Blockade of dopamine reuptake by bupropion may be more effective in promoting abstinence in the *Ins C* genotype group due to greater ability to bind dopamine.

David et al.[78] examined the *DRD2*, the dopamine transporter gene *SLC6A3*, and the *CYP2B6* (C1459T) genotypes as moderators of treatment response in a placebo-controlled bupropion trial with 283 smokers of European ancestry. Smokers with the *DRD2* Taq1-A2/A2 genotype had a significantly better treatment response (35% for bupropion and 12% for placebo), compared to smokers with A1/A1 or A1/A2 genotypes (21% for bupropion and 24% for placebo). Cinciripini and colleages[79] examined the *DRD2* Taq1A polymorphism in a placebo-controlled trial of venlafaxine (a serotonin reuptake inhibitor) and reported that smokers carrying the A1 allele were less likely to quit.

Swan and colleagues[80] examined the role of the *DRD2* Taq1A polymorphism in an open-label, randomized effectiveness trial comparing 150mg and 300 mg doses of bupropion. Compared to women homozygous for the A2 allele, women with at least one A1 allele were significantly less likely to quit smoking and more likely to report having stopped taking bupropion due to treatment side effects. Finally, a recent analysis from the bupropion placebo-controlled trial provides preliminary evidence for associations of a *COMT* haplotype with bupropion response.[81]

Summary, Clinical Implications, and Future Research Directions

Initial findings presented in this review support the role of genetic variation in response to bupropion and NRT for smoking cessation (see Table 1). Variations in genes in the dopamine and opioid pathways, and in nicotine-metabolizing enzymes, appear to play a role in the efficacy of nicotine-replacement therapy, while genetic variation in the dopamine pathway also appears to be important for response to bupropion. Many of these studies also provide evidence for gender heterogeneity in these genetic associations.

While the integration of genetic testing into standard clinical practice would be premature at this time, pharmacogenetic studies of treatments for nicotine dependence eventually may guide individualized smoking-cessation treatments. For instance, carriers of genetic variants that increase nicotine metabolism may not respond as well to standard NRT doses, whereas carriers of reduced-activity variants in *DRD2* (e.g., Taq 1A, –141 DelC) may respond particularly well to NRTs. Selecting smokers with reduced-activity *DRD2* variants for NRT or selecting smokers with genetic variants that increase nicotine metabolism for a higher dose of NRT may enhance long-term quit rates. Importantly, many of the genetic variants linked to nicotine dependence and poor response to treatments are very common, such as *CYP2A6*1* (77%)[27] and *DRD2* A1 (43%),[50] suggesting that genetically-tailored treatment approaches could have a substantial population-level impact on treatment outcomes. In addition, the effect size associated with the presence of genetic alleles linked to smoking phenotypes is typically meaningful. For instance, 35% of smokers homozygous for the *Ins* C allele were abstinent following bupropion treatment, compared to only 20% of smokers carrying a *Del* C allele.[66] Likewise, at the end of NRT

treatment, 23% of carriers of the Taq1 A1 allele of the *DRD2* (*ANKK1*) gene were abstinent, compared to 13% of those homozygous for the more common A2 allele.[62] Further, pharmacogenetic studies also may help researchers understand the neurobiology of nicotine dependence which, in turn, could guide the development of new treatments. Thus, given the frequency and impact of genetic alleles linked to smoking phenotypes, using genetic information to tailor the selection of treatments may ultimately have a substantial impact on overall rates of smoking.

The use of genetic information to tailor the selection of treatments for nicotine dependence is feasible, yet there are several important policy issues that must be addressed before this technology will become standard clinical practice. First, while genetic testing for smoking genotypes increasingly is becoming more affordable and efficient with advances in technology, testing largely remains confined to the context of research programs. Decisions about how the costs of testing will be covered and whether or not insurance companies will absorb these costs have yet to be bridged. Further, given the limited resources of middle- or low-income countries, it appears likely that the potential benefits of using genetic information to treat nicotine dependence would only be realized in high-income countries. Even with adequate resources in high-income countries to implement genetic testing into treatment for nicotine dependence, researchers will need to demonstrate that such a treatment approach is cost-effective. To date, cost-effectiveness analysis of genetic testing for nicotine-dependence treatment has only recently begun,[82] and remains as a critical priority for future research.

Further, as genetic testing for nicotine dependence is incorporated into clinical practice, researchers and clinicians must be mindful of the role of race/ethnicity as factors that influence smoking phenotypes and genes related to nicotine dependence. To date, the vast majority of studies have been conducted with Caucasians to avoid population stratification bias. Race/ethnicity influence smoking behavior (e.g., age of initiation, smoking rate, level of dependence)[83] and there are large racial differences in allele frequencies for nicotine-metabolizing genes[25,84] and dopaminergic genes.[85] Further, since access to healthcare and socioeconomic status vary with race/ethnicity, the potential implementation of genetic testing clinical services may need to consider race/ethnicity as an important variable if the potential for this technology is to be realized.[84]

Third, there is substantial comorbidity between nicotine dependence and other substance abuse conditions and psychiatric disorders, including depression, schizophrenia, attention-deficit hyperactivity disorder, anxiety, and personality disorders.[33] In addition, genes linked to smoking behavior and treatment response may be related to psychiatric conditions and other addictions.[87] Thus, genetic testing to tailor treatment for nicotine dependence simultaneously could identify individuals with other dependence or psychiatric disorders,[88] and treatment programs may need to be prepared to provide more comprehensive interventions to ensure efficacy and to address comorbid psychiatric conditions.

Fourth, several genes and environmental factors likely combine to influence response to treatments for nicotine dependence. To date, most studies have focused on single genes and have not evaluated gene–environment interaction. The development of effective individualized treatments for nicotine dependence and moving beyond a “one size fits all” model may depend on future pharmacogenetic studies that include sufficiently large samples to evaluate gene–gene and gene–environment interactions.

Finally, if genetic testing for nicotine dependence is to be incorporated into clinical practice, primary care physicians, who are often the first point of contact for patients seeking assistance with quitting, will need to be appropriately trained. Many physicians lack confidence to provide

genetic testing,[89] underscoring the need for guidelines to help physicians integrate genetic testing into their practice.

Additional work is needed to validate these findings across independent trials. Meta-analytic techniques also may be applied to overcome issues related to the relatively small sample sizes of the initial trials.[90] Future studies also should explore the use of more refined outcome measures that account for the longitudinal trajectories of smoking cessation, including multiple lapses, relapses, and changes in smoking rates over time.[91] Increased attention to gender heterogeneity in genetic associations[55] as well as ethnic heterogeneity is needed. In addition, future studies should also explore the influence of genetic variation in additional genetic pathways relevant to nicotine dependence, including GABA and glutamate. Such studies may hold great promise for the identification of novel biological targets for drug development and improvement in the delivery of nicotine-dependence treatment to reduce the morbidity and mortality caused by smoking.

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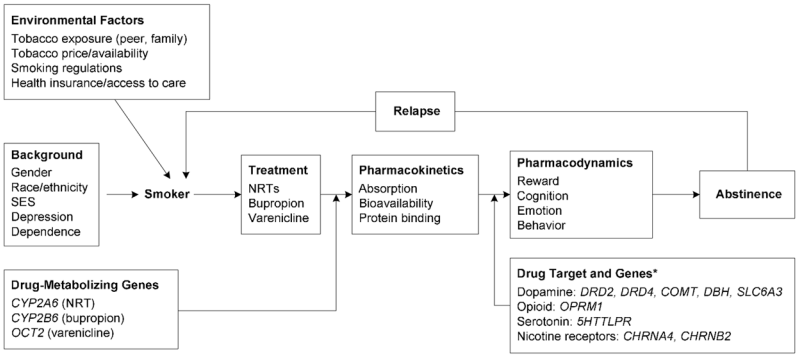

Figure 1.

A pharmacogenetic model of nicotine-dependence treatment. * indicates that genes shown include the subset examined for pharmacogenetic effects.

nAChRs, nicotinic acetylcholine receptors; NRT, nicotine replacement therapy; SES, socioeconomic status.

Table 1

Summary of pharmacogenetic effects in nicotine-dependence clinical trials

Genes	Treatment	Gender interaction	Main finding	Citation
Pharmacokinetics/drug metabolizing enzymes				
CYP2A6	NRT	Not reported	Genotypes related to 3-HC/cotine ratio; slow metabolizers smoke fewer cigarettes and are less nicotine dependent; in patch condition, slow metabolizers had higher plasma nicotine but equal patch use; in spray condition, fast metabolizers used more spray but had equal plasma nicotine	28
CYP2A6 (3-HC/ Cotinine Ratio)	NRT	Not reported	3-HC/cotinine ratio predicted nicotine patch efficacy butnot nasal spray; there was a 30% reduction in chance of cessation following patch therapy with each increasing quartile of metabolite ratio	30
CYP2B6	Bupropion	Yes	Slow metabolizers had increased cravings after quitting and higher relapse rates; bupropion attenuated theses effects among females	74
	Bupropion	No	Among smokers with decreased bupropion metabolism, bupropion produced significantly higher abstinence rates than placebo; bupropion was no more effective than placebo for smokers with normal bupropion metabolism	75
Pharmacodynamics/drug target genes				
DRD2 (Taq 1A)	NRT	Yes	Quit rates from patch therapy were higher for women with the Taq1 A1 allele, but there was no genotype effect for men	62
	NRT	No	Quit rates from patch therapy were significantly greater for smokers with the Taq1 A1 allele and the *DBH* A allele	63
	Bupropion	Yes	Women with the *DRD2* A2/A2 allele were more likely to quit smoking, compared to women with A1 alleles	80
	Bupropion	No	Those with *DRD2* A2/A2 alleles showed better treatment response, versus those with A1/A1 or A1/A2 alleles	78
	Venlafaxine		Smokers with the *DRD2* A1 allele (A1/A1/A2) quit significantly less often than the homozygous A2s	79
DRD2 (-141 *Ins/ Del*)	NRT	No	Smokers homozygous for the *Del* C allele responded better to NRT than carriers of the *Ins* C allele	66
	Bupropion	No	Smokers homozygous for the *Ins* C allele had higher quit rates following bupropion, versus smokers with the *Del* C allele; smokers with the *Del* C allele had higher quit rates on placebo	66
	NRT	No	Smokers with at least one copy of the -141 *Del* allele and two copies of the *FREQ* rs1054879 A allele were more likely to quit smoking, compared to smokers with other alleles	69
DRD2 (C957T)	NRT	No	Smokers with CT/CC genotypes were less than two-thirds as likely to be abstinent, versus participants with TT genotypes	66
	Bupropion	No	Variants of C957T were not associated with quit rates following bupropion therapy	66
DBH	NRT	No	Smokers with the *DBH* GA/AA genotype had higher quit rates, compared to those with GG alleles	63
COMT	NRT	Yes	Women with the Met/Met genotype showed higher quit rates following NRT, versus women with the Val/Val allele	53
	Bupropion	No	COMT haplotype from SNPs rs165599 and rs373865 affected response to bupropion, with higher quit rates among smokers carrying the A allele of the rs165599 (A/G) SNP	82
SLC6A3	Bupropion	No	Smokers with *DRD2-A2* genotypes and *SLC6A3*-9 genotypes, versus *SLC6A3*-10 genotypes, had significantly higher quit rates and a longer latency to relapse	50
	NRT or bupropion	No	Smokers with the 9-repeat allele were more likely to quit smoking following treatment than those with 10/10 repeats	51
	Bupropion	No	There were no main effects for *DRD2* and *SLC6A3* genotypes on smoking cessation; those with DRD2 A1 and *SLC6A3* 9-repeat alleles show poorer response to bupropion	49
OPRM1	NRT	Yes	Quit rates following treatment were higher for carriers of the *OPRM1* Asp40 variant, versus carriers of the Asn40	54
5-HTTLPR	NRT	No	*5-HTTLPR* alleles were not related to NRT response	58
	NRT	No	*5-HTTLPR* alleles were not related to NRT response	57
CHRNA4	NRT	No	Smokers with the TC genotype were more likely to maintain abstinence on nasal spray, but not transdermal patch	71

NRT, nicotine replacement therapy; 3-HC, 3-hydroxycotinin