Review

From Men to Mice: CHRNA5/CHRNA3, Smoking Behavior and Disease

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Abstract

Introduction: The nicotinic acetylcholine receptor (nAChR) gene cluster CHRNA5-A3-B4 on chromosome 15 has been the subject of a considerable body of research over recent years. Two highly correlated single nucleotide polymorphisms (SNPs) within this region—rs16969968 in CHRNA5 and rs1051730 in CHRNA3—have generated particular interest.

Methods: We reviewed the literature relating to SNPs rs16969968 and rs1051730 and smoking-related phenotypes, and clinical and preclinical studies, which shed light on the mechanisms underlying these associations.

Results: Following the initial discovery of an association between this locus and smoking behavior, further associations with numerous phenotypes have been subsequently identified, including smoking-related behaviors, diseases, and cognitive phenotypes. Potential mechanisms thought to underlie these have also been described, as well as possible gene × environment interaction effects.

Conclusions: Perhaps counter to the usual route of scientific inquiry, these initial findings, based exclusively on human samples and strengthened by their identification through agnostic genome-wide methods, have led to preclinical research focused on determining the mechanism underlying these associations. Progress has been made using knockout mouse models, highlighting the importance of α5 nAChR subunits in regulating nicotine intake, particularly those localized to the habenula—interpeduncular nucleus pathway. Translational research seeking to evaluate the effects of nicotine challenge on brain activation as a function of rs16969968 genotype using neuroimaging technologies is now called for, which may point to new targets for novel smoking cessation therapies.

Discovery of the Association between SNP rs16969968/ rs1051730 and Smoking Behaviors

An association between SNP rs16969968 in CHRNA5 and nicotine dependence (ND) was first reported in 2007 in a candidate gene study conducted by Saccone and colleagues (Saccone et al., 2007), with the minor A allele found to confer increased risk. The following year, the same locus (tagged by SNP rs1051730 in CHRNA3, a variant highly correlated with rs16969968) was also found to be associated with smoking quantity, this time identified in a genome-wide association study (GWAS) conducted by Thorgerisson et al. (2008). This study also demonstrated an association between rs1051730 and ND and two smoking-related diseases, namely lung cancer and peripheral arterial disease. Notably, while the candidate gene study was published first, it was the GWAS that made much more of an impact. This may have been because CHRNA5 was not recognized as a particularly strong candidate at the time, given the then known neurobiology of tobacco dependence—more emphasis had been placed on genes encoding α4 and β2 subunits which had been implicated by

Introduction

Nicotinic acetylcholine receptors (nAChRs), to which nicotine binds, serve as the “gateways” through which nicotine exerts its effects on the brain. Recent years have witnessed a rapid growth in research focused on the nAChR gene cluster CHRNA5-A3-B4 on the long arm of chromosome 15 (15q24-25.1), responsible for encoding three nAChR subunits (α5, α3, and β4). One locus within this cluster has generated particular interest—that marked by the single nucleotide polymorphisms (SNPs) rs16969968 in CHRNA5 and rs1051730 in CHRNA3. These highly correlated SNPs, which have been broadly studied, are now firmly established predictors of multiple smoking-related behaviors and diseases, and form the focus of this review. Within this review, we discuss the initial discovery of an association between these variants and smoking behavior, the numerous phenotypes with which they have been subsequently associated (smoking-related behaviors, diseases, and cognitive phenotypes; see Supplementary Tables 1, 2, and 3, respectively), and potential mechanisms purported to underlie such associations. Gene × environment interactions are also discussed, alongside issues relating to phenotype definition and measurement precision.

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animal models as critical to the experience of nicotine’s reinforcing effects (e.g., Picciotto et al., 1998). In contrast, the GWAS did not require a strong prior hypothesis regarding gene selection, as this approach is inherently agnostic with respect to candidacy. Furthermore, the simultaneous demonstration of an association between this locus and two smoking-related diseases lent further authority to this finding. These initial studies were followed by a number of others documenting a range of associations between this locus and smoking-related behaviors and diseases.

**Phenotypes Associated With SNP rs16969968/rs1051730**

**Smoking Behavior**
The 15q locus has primarily been associated with measures of heaviness of smoking, including ND and smoking quantity, although there is some evidence for other phenotypes.

SNPs rs1051730 and rs16969968 have been repeatedly associated with ND, typically assessed using the Fagerström Test for Nicotine Dependence (FTND; Chen, Johnson, et al., 2009; Chen, Chen, et al., 2009; Gruca et al., 2010; Johnson et al., 2010; Saccone, Saccone, et al., 2009; Saccone, Wang, et al., 2009; Saccone et al., 2007; Thorgeirsson et al., 2008; Wassenaar et al., 2011; Winterer et al., 2010). The impact of this locus on ND (and other smoking-related phenotypes) may be modified by different factors. The relationship has, for instance, been shown to be modified by age of smoking onset, although with inconsistent findings. Gruca et al. (2010) found that SNP rs16969968 exhibited a larger effect in late-onset smokers (post 16 years), while in contrast Weiss et al. (2008) noted an association between this locus and severity of ND only in individuals who became regular smokers before the age of 16. Reasons underlying this disparity are unclear. A parsimonious explanation would be that these were chance findings. However, they do illustrate the potential importance of age of smoking onset, which is plausibly supported by research highlighting differential effects of nicotine exposure in adolescent and adult rats (e.g., Schochet, Kelley, & Landry, 2004).

Another related issue to be considered concerns the impact of these SNPs at different ages. Both Rodriguez et al. (2011) and Ducci et al. (2011) have sought to address this question, comparing the effects of this locus on smoking behavior during adolescence and adulthood. Although phenotype definition and ages studied vary between these studies and are not directly comparable, both draw a similar conclusion—the effect of this locus on smoking behavior appears to be consistent during both adolescence and adulthood. Rodriguez et al. (2011) found that rs16969968 was associated with continued smoking in individuals who have experimented with tobacco, with similar effects noted at ages 13–15 years and at 18 years. Ducci et al. (2011) found that rs1051730 was associated with regular/heavy smoking, again with similar effects noted at ages 14 and 31 years.

Environmental factors have also been shown to impact upon the relationship between rs1051730/rs16969968 and smoking-related behaviors, such as parental monitoring (Chen, Johnson, et al., 2009), peer smoking (Johnson et al., 2010), and childhood adversity (Xie et al., 2011). Gene × environment interactions are discussed in detail in Text Box 1.

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**Text Box 1.** The study of gene × environment (G × E) interactions in the context of behavioral phenotypes has proved controversial (Flint & Munafò, 2008; Riley, 2008; Uher, 2008) but smoking is one case where there is a priori evidence of interaction—whatever one’s genetic risk, it is not possible to become tobacco dependent without first exposing oneself to tobacco. The unequivocal evidence of association of CHRNA5-A3-B4 variants with heaviness of smoking and other tobacco use phenotypes also addresses one concern raised regarding G × E effects, namely the presence of interaction effects in the absence of main effects (Flint & Munafò, 2008). What remains is to consider what environmental factors may plausibly influence the probability of exposure to tobacco (i.e., experimentation) and thereby moderate the expression of genetic liability for subsequent dependence. One such factor is parental monitoring (i.e., the extent to which parents are aware of their child’s activities, peer group, etc.), which is independently known to be associated with the likelihood of smoking experimentation and initiation (Forrester, Biglan, Severson, & Smolkowski, 2007). Recent work indicates that parental monitoring may indeed moderate the association of CHRNA5-A3-B4 variants with the subsequent development of tobacco dependence and heavy smoking (Chen, Johnson, et al., 2009), although this study relied on retrospective self-report of parental monitoring and requires replication in a prospectively assessed sample. Similar moderating effects of parental monitoring have been reported in relation to genetic associations with externalizing behaviors (Dick et al., 2009, 2011) and alcohol use (Kendler, Gardner, & Dick, 2011). This is consistent with evidence from twin studies, which suggests that at high levels of parental monitoring, environmental influences are the dominant influence on adolescent smoking, but at low levels genetic influences are more important (Dick et al., 2007). While parental monitoring therefore appears to be a promising environmental factor, which may moderate the expression of genetic effects, the challenge will be to identify other factors, which may operate in similar ways. Environmental factors influencing the likelihood of initiation, such as peer smoking (Scherrer et al., 2011), are likely targets. It is also possible that there may be particular developmental risk windows when smoking initiation is more likely to result in the expression of genetic influences on dependence liability, based on known relationships between early smoking initiation and subsequent dependence (Klueter, Dayal, & Mutgi, 1999). In addition, it will be important to identify further variants beyond the CHRNA5-A3-B4 cluster which robustly associate with tobacco use phenotypes, a project which is rapidly making progress (Fürberg et al., 2010; Liu et al., 2010; Thorgeirsson et al., 2010).

Smoking quantity, typically assessed in terms of self-reported daily cigarette consumption, is also a well established as a correlate of rs1051730 and rs16969968 genotypes (Breetvelt et al., 2011; Caporaso et al., 2009; Freathy et al., 2009; Kaur-Knudsen, Bojesen, Tybjaerg-Hansen, & Nordestgaard, 2011; Keskitalo et al., 2009; Lips et al., 2010; Marques-Vidal et al., 2011; Sargison et al., 2011; Siedlinski et al., 2011; Sorice et al., 2011; Thorgeirsson et al., 2008; Wassenaar et al., 2011). Further, several meta-analyses
have consistently documented this relationship (Furberg et al., 2010; Liu et al., 2010; Thorgerisson et al., 2010; Ware, van den Bree, & Munafò, 2011). Each copy of the minor (risk) allele appears to account for approximately one cigarette per day in terms of variance in smoking quantity (Ware et al., 2011). Given the above, it is perhaps unsurprising that levels of cotinine (the primary metabolite of nicotine) have also been found to associate with rs1051730 and rs16969968 genotype (Keskitalo et al., 2009; Le Marchand et al., 2008; Timofoeva et al., 2011). What is interesting, however, is that the relationship between this locus and nicotine metabolite levels appears to be stronger than the relationship noted between this locus and daily cigarette consumption. Keskitalo et al. (2009) for instance found that rs1051730 was associated with both daily cigarette consumption and circulating cotinine levels, but, critically, also noted that the proportion of variance accounted for by this SNP was nearly five times greater for cotinine relative to daily cigarette consumption (see Text Box 2).

Evidence for an association between rs1051730/rs16969968 and smoking cessation has been observed, although evidence for this relationship is weaker than that observed for ND and smoking quantity. Freathy et al. (2009) found an association between rs1051730 and reduced ability of women to quit smoking during pregnancy, an effect subsequently replicated by Thorgerisson and Stefansson (2010). In further support, Munafò et al. (2011) found weak evidence of an association between rs1051730 and short-term cessation outcome in a combined analysis of two prospective clinical trial samples, although no evidence of association was noted at later follow-up. However, Breetvelt et al. (2011) and Lips et al. (2010) found no association between rs16969968 and smoking cessation, while Breitling et al. (2009) also failed to note an association between rs16969968 and rs1051730 and cessation, as assessed in ever-heavy smokers (>20 cigarettes/day). In a similar vein, De Ryck et al. (2010) found no association between rs1051730 and the presence of withdrawal symptoms or smoking cessation outcome following short-term nicotine patch treatment. Furthermore, Marques-Vidal et al. (2011) found no evidence for association between rs1051730 and willingness, attempt, or preparation to quit.

It is unclear whether or not rs1051730/rs16969968 is associated with smoking initiation. Lips et al. (2010) and Kaur-Knudsen et al. (2011) found no association between this locus and smoking initiation. Similarly, we found no association between rs1051730 and smoking initiation in a prospectively assessed cohort (unpublished data). Furthermore, a recent twin study (Maes et al., 2011) suggested that this locus plays a much more prominent role in ND relative to smoking initiation/experimentation. However, Sherva et al. (2008), found an association between rs16969968 and smoking status (regular smoker vs. never-smoker). Of particular interest, they also found an association between rs16969968 and positive first smoking experience, specifically experience of a “pleasurable buzz.” This may mediate the association between this SNP and increased risk of regular smoking. Inconsistencies in the definition of the “initiation” phenotype may have hampered progress in this area—for example, the genes influencing initial experimentation (i.e., first puff) may differ from those underlying progression from experimentation to regular use.

Cancer

Many diseases have been associated with SNPs rs16969968 and rs1051730, among which lung cancer is certainly the most frequently reported, and has been noted across a range of histology types (adenocarcinoma; squamous cell; large cell; small cell), and in European, Asian, and Black samples (Amos et al., 2010; Amos et al., 2008; Hung et al., 2008; Jaworowska et al., 2011; Kaur-Knudsen et al., 2011; Lips et al., 2010; Liu et al., 2008; Saccone et al., 2010; Sakoda et al., 2011; Schwartz, Cote, Wenzlaff,
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Land, & Amos, 2009; Shiraiishi et al., 2009; Spitz, Amos, Dong, Lin, & Wu, 2008; Timofeeva et al., 2011; Truong et al., 2010; Wang et al., 2010; Wassenaar et al., 2011; although see Yang et al., 2010). There is considerable debate as to whether this association is direct or mediated via the variants’ association with smoking quantity. Briefly, the former (direct) argument is supported by studies demonstrating a relationship between this locus and cancer following adjustment for smoking quantity (e.g., Kaur-Knudsen et al., 2011; Wassenaar et al., 2011), while the latter (indirect) is supported by studies which fail to note an association between this locus and cancer in never-smokers (e.g., Girard et al., 2010), and the inadequacy of self-reported smoking measures in capturing true tobacco exposure (Munafò et al., 2012; see Text Box 2). Several lung cancer specific phenotypes have also been associated with this locus, age of cancer onset/diagnosis being most predominantly reported (Lips et al., 2010; Sakoda et al., 2011; Spitz et al., 2008; Truong et al., 2010)—presence of the minor allele is consistently associated with earlier age of onset/diagnosis (although see Jaworowska et al., 2011). SNP rs1051730 has also been associated with larger tumor size at diagnosis for squamous cell carcinoma (Chen, Gorlov, et al., 2011). However, it does not appear to be associated with survival time in lung cancer patients (Xun et al., 2011). Additional cancers linked to this locus include upper aerodigestive tract cancers (e.g., those of the oral cavity, larynx, esophagus; Lips et al., 2010), although this association has not been consistently shown (Hung et al., 2008), and more recent work suggests that it may be limited to women only (Chen, Truong, et al., 2011). Bladder cancer has also been associated with this locus (Gago-Dominguez et al., 2011; Kaur-Knudsen et al., 2011), although, again, this finding has not been consistently shown (Jaworowska et al., 2011; Spitz et al., 2008). Finally, Chen, Wu, et al. (2011) found no association between rs1051730 and pancreatic cancer risk.

Alcohol and Substance Use

Alongside tobacco dependence, rs1051730 and rs16969968 have been linked to dependence upon other drugs of abuse, including opiates (Erlich et al., 2010), cocaine (Gruca et al., 2008), and alcohol (Chen, Chen, et al., 2009; Wang et al., 2009). Erlich et al. (2010) found that the minor allele of rs16969968 was associated with opioid dependence severity, the same allele that has consistently been associated with ND. In contrast, Gruca et al. (2008) found this same minor allele to be protective for cocaine dependence. Similarly, Chen, Chen, et al. (2009) found that the major alleles of rs16969968 and rs1051730 were associated with symptoms of alcohol abuse/dependence, while simultaneously demonstrating an association between the minor alleles and ND. They found no evidence for an association between these variants and cannabis dependence. While these opposing effects are intriguing, they are based on a very limited number of studies and therefore require replication.

Other Disease Outcomes

Chronic obstructive pulmonary disease/emphysema, a common smoking-related disease, has also been associated with rs16969968 and rs1051730 (Kaur-Knudsen et al., 2011; Kim et al., 2011; Lambrechts et al., 2010; Pillai et al., 2009; Wang et al., 2010; Young et al., 2008). Arguments as to whether this association is direct or mediated via the association with smoking quantity are also common here (see Text Box 2). An association between this locus and cardiovascular disease has also been demonstrated. For instance, Thorgerisson et al. (2008) observed an association between rs1051730 and peripheral arterial disease, also a known smoking-related disease. Finally, Hong et al. (2011) have demonstrated an association between rs16969968 and schizophrenia.

Other Nondisease Outcomes

How do we explain the associations noted between SNP rs16969968/rs1051730 and smoking-related behaviors? Several studies investigating associations between these variants and cognitive and personality-related phenotypes offer some insight. Etter et al. (2009) found marginal evidence of an association between rs16969968 and novelty seeking. Individuals with the AA (ND risk) genotype had higher novelty seeking scores than individuals of GG or AG genotype, suggesting mediation by personality trait (of note, however, no association was observed with ND). Winterer et al. (2010) reported an association between both rs1051730 and rs16969968 and cognitive performance as assessed by the Wechsler-Adult-Intelligence Scale and an n-back task measure of executive function. The alleles associated with lower cognitive performance were also those associated with increased risk for ND. Against a background of previous research highlighting the role of nicotine as a cognitive enhancer (Warburton, 1992), the authors postulate that this locus may indirectly increase a subject’s liability to ND as a result of cognitive augmentation by nicotine consumption. Indeed, the increased prevalence of smoking noted in samples of individuals with neurocognitive disorders (e.g., attention-deficit hyperactivity disorder) has been attributed to nicotine’s beneficial effect on cognitive performance (e.g., improving attention; Sacco, Bannon, & George, 2004). It has also been proposed that genetic effects on smoking behaviors may be mediated in part by their effect on reactivity to smoking cues. James et al. (2011) found an association between rs16969968 and brain reactivity to smoking-related cues assessed by functional magnetic resonance imaging. They found that women without the risk allele for ND showed greater reactivity to smoking cues in regions such as the hippocampus and dorsal striatum relative to women possessing this allele. The authors speculate that smokers without the ND risk allele may thus continue to smoke due to heightened cue reactivity. The results of this study are counter intuitive in comparison with previous research. However, differences in ND were controlled for when comparing smokers with and without the ND risk allele. Other studies have not done this when investigating the effects of this variant, which may partly explain these results. However, the sample size was small, which increases the possibility that statistically significant results may reflect false positives (Green et al., 2008), and so these results should be interpreted with particular caution until they have been replicated.

Determining the Mechanism Linking SNP rs16969968/rs1051730 to Smoking Behaviors

The evidence linking SNPs rs1051730 and rs16969968 to smoking-related behaviors is compelling. What is less clear, however, is the fundamental mechanism linking the two. Exactly how do these polymorphisms exert their effect? Let us first consider their functional significance. SNP rs1051730 in CHRNA3 is a coding, synonymous variant (http://genome.ucsc.edu/), that is,
a variant which does not result in an amino acid change in the subsequent protein, which is therefore unlikely to be of any functional significance. This SNP may act as a proxy or tag for a functional SNP however, which may underlie the observed associations (rs1051730 is highly correlated with rs16969968). In contrast to rs1051730, SNP rs16969968 in CHRNA5 is a missense mutation, resulting in an amino acid change (aspartate to asparagine) in the resultant α5 nAChR subunit protein. This variant is of definite functional significance—in vitro studies have demonstrated that α5 receptor complexes with the aspartic acid variant exhibit a twofold greater maximal response to a nicotine agonist compared with α5 receptor complexes containing the asparagine variant (i.e., the risk variant robustly associated with ND; Bierut et al., 2008). Building upon this foundation of research, Fowler, Lu, Johnson, Marks, and Kenny (2011) sought to establish the underlying mechanism through an elegant series of experiments involving α5 knockout mouse models (analogous to individuals with reduced α5 receptor function, i.e., carriers of the rs16969968 risk allele). They noted that knockout mice responded more vigorously than wild-type mice for nicotine infusions at high doses. While wild-type mice appeared to titrate delivery of nicotine dose (through self-administration) to achieve a consistent, desired level, knockout mice did not, consuming greater amounts as dosage increased. This led the authors to propose that deficient α5 signaling attenuates the negative effects of nicotine that serve to limit its intake, a conclusion which fits well with human research (i.e., smokers carrying the rs16969968 risk allele are likely to smoke more heavily than their counterparts without the risk allele). Furthermore, they also demonstrated that this effect could be “rescued” in α5 knockout mice through injection of a lentivirus vector into the medial habenula (MHb), rescuing expression of α5 subunits in this region. The knockout mice did not appear to differ from wild-type mice in experience of the rewarding effects of nicotine, but the inhibitory effect of high nicotine doses on the activity of reward circuitries observed in wild-types appeared to have been largely abolished in knockout mice. This observation is complemented by a previous study by Jackson et al. (2010), where the differential effects of nicotine dose on reward between α5 knockouts and wild-types was illustrated using a conditioned place preference task. Fowler et al. (2011) further determined that this effect appeared to be mediated via the pathway between the MHb and the interpeduncular nucleus (IPN, to which the MHb projects) through α5 containing nAChRs. Diminished IPN activity in response to nicotine was observed in knockouts, and additionally, disruption of IPN activity increased nicotine self-administration. In short, it appears that high doses of nicotine stimulate the MHb–IPN tract through nAChRs containing α5 subunits. This results in the relay of an inhibitory motivational signal serving to limit further drug intake. This pathway acts alongside the classic “reward” pathway.

Conclusions and Future Directions

There is now a compelling body of evidence linking SNPs rs16969968 and rs1051730 to smoking-related behaviors and a host of smoking-related diseases. These two SNPs have generated interest in a region which is proving highly illuminating—rapid progress is now being made in identifying further loci which robustly associate with tobacco-use phenotypes within the CHRNA5-A3-B4 cluster (i.e., independent SNPs within this region which provide a secondary signal when conditioned on rs1051730/rs16969968, such as SNP rs6495308 in CHRNA3, as identified by Liu et al. [2010]). Solid progress is also being made in identifying additional loci associated with smoking-related phenotypes beyond this gene cluster (Furberg et al., 2010; Liu et al., 2010; Thorgeirsson et al., 2010).

Perhaps counter to the usual route of scientific inquiry, these exciting initial findings, based exclusively on human samples and strengthened by their identification through agnostic genome-wide methods, have led to preclinical research focused on determining the mechanism underlying these associations. Exciting progress has been made using knockout mouse models, highlighting the importance of α5 nAChR subunits in regulating nicotine intake, particularly those localized to the MHb–IPN pathway. Translational research seeking to evaluate the effect of nicotine challenge on brain activation as a function of rs16969968 genotype using neuroimaging technologies is now called for, which may point to new targets for novel smoking cessation therapies.

Supplementary Material

Supplementary Tables 1, 2, and 3 can be found online at http://www.ntr.oxfordjournals.org

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Declaration of Interests

The authors have no competing interests to declare. This publication is the work of the authors and Jennifer Ware will serve as guarantor for the contents of this paper.

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