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Genes, the Environment, and Cigarettes

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Abstract

Tobacco use remains the leading cause of preventable death in the United States, emphasizing the need to understand what genes and environments are involved in the establishment of cigarette use behaviors. However, to date, no comprehensive review of the influence of genes, the environment, and their interaction on cigarette use exists. This narrative review provides a description of gene variants and environmental factors associated with cigarette use, as well as an overview of studies investigating gene-environment interaction (GxE) in cigarette use. GxE studies of cigarette use have been useful in demonstrating that the influence of genes changes as a function of both the phenotype being measured and the environment. However, it is difficult to determine how the effect of genes contributing to different phenotypes of cigarette use changes as a function of the environment. This suggests the need for more studies of GxE, to parse out the effects of genes and the environment across the development of cigarette use phenotypes, which may help to inform potential prevention and intervention efforts aimed at reducing the prevalence of cigarette use.

Keywords

Cigarette use; genes; environment; gene-environment interaction; twin studies; genetic association studies

INTRODUCTION

Tobacco use remains the leading cause of preventable death in the United States and results in nearly \$170 billion in direct medical care for adults and greater than \$156 billion in lost

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DECLARATION OF INTEREST

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productivity due to premature death and exposure to secondhand smoke (1). These costs emphasize the need to understand what genes and environments are involved in the establishment of cigarette use behavior (2). Knowing what genes and environmental risk factors impact cigarette use can help to reduce its prevalence by shaping prevention and intervention efforts. However, to date, many studies on cigarette use have focused solely on genes and environments contributing independently to risk for cigarette use and its health consequences. Fewer studies have investigated the effects of gene-environment interaction (GxE), which can be conceptualized as the difference in the contribution of genetic factors, conditional on environmental exposure (3). Since cigarette use involves both motivational and reward systems that develop through interactions between genes and the environment, studies of the joint effects of multiple genetic mutations across different environments could be useful in understanding the range of genetic susceptibility to environmental risk factors influencing cigarette use and its health consequences (4). GxE studies have been useful in determining whether genetic effects are more or less important under particular environmental conditions (5). For example, restricting the availability of tobacco has been found to reduce the effect of genes influencing whether individuals initiate and maintain smoking behaviors. Alternatively, under environments where there are fewer restrictions, the importance of the role of genes is expected to increase since individuals are able to express the full range of phenotypes (6), inclusive of nicotine dependence and tobacco-related health conditions such as heart disease and cancer. Quitting cigarette use can effectively reduce the risk of these tobacco-related outcomes for each individual smoker, while also substantially reducing excess health-care utilization and improved labor supply on a larger scale (4). However, to improve strategies for disease prevention and intervention efforts focused on smoking cessation, a better understanding of genetic, social environment, and individual determinants of risk contributing to cigarette use are needed. In other words, we need to be able to disentangle the etiology of cigarette use and identify the conditions under which genes, the environment, and their interaction impact cigarette use behaviors. Through this narrative review, we seek to integrate twin and molecular genetic studies of GxE in cigarette use. Specifically, this narrative review provides a brief overview of studies investigating genetic and environmental factors influencing cigarette use separately, and then summarizes gene-environment interactions in cigarette use behaviors.

Phenotypic Measures of Cigarette Use

It is important to understand how cigarette use has been measured before getting into details about how we can determine how much of cigarette use is attributed to genes, the environment, and their interactions. The most common phenotypic measures of cigarette use include: initiation; adolescent smoking; cigarettes per day; regular smoking; nicotine dependence; and smoking cessation. Initiation is usually a self-report measure that is assessed using a yes or no question, such as “Have you ever smoked an entire cigarette?” (7). Although adolescent smoking is often treated as binary (yes/no) variable, the way in which it is assessed differs across studies. One study may measure adolescent smoking by asking the question, “Have you ever smoked (or tried smoking)?” to which adolescents can respond either yes or no (8). While another study may ask adolescents to choose from a nine-point scale with multiple response categories, ranging from “I have never smoked, not even one puff” to “I smoke at least once a day” and recode responses to either no (non-

smoker) to yes (smoker) (9,10). There is also some variation in how to assess cigarettes per day: some studies collect the average number of cigarettes smoked per day, while others collect the maximum number of cigarettes per day (11). Nicotine dependence is most often assessed using the Fagerstrom Test for Nicotine Dependence (12). Smoking cessation is assessed in a variety of ways, though the most common seems to be through self-reports of abstinence (e.g. 7-day point prevalence abstinence, 30-day prolonged abstinence, 6-month prolonged abstinence) or by asking about quit attempts. These different stages of cigarette use vary in their heritability, suggesting that different points along smoking trajectories may be influenced by different etiological factors (13). Distinguishing between these phenotypes helps to provide insight into the nature of cigarette use, which may provide guidance for potential interventions and treatments (14).

Quantitative Studies of Inferred Genetic Susceptibility for Cigarette Use

Classic twin methodologies have been useful in quantifying genetic and environmental factors associated with cigarette use phenotypes. Generally, twin study methods have been used to compare the agreement in the behavior of monozygotic or identical twins that share the same genetic make-up and dizygotic or fraternal twins who share, on average, 50% of their genetic make-up. Statistical models estimate the percentage of variance in the trait explained by genes (i.e. heritability) and by common environment (i.e. experiences that render family members more alike) and unique environment (i.e. experiences that cause dissimilarity between family members) (15). Heritability estimates differ according to phenotype and age. For the initiation of cigarette use, shared environmental factors account for a small proportion of the liability (16), relative to additive genetic factors, which account for ~60% of the variance (17). Data from one meta-analysis showed differences in the heritability of initiation by sex, suggesting that genetic and environmental factors may contribute differently to individual differences in initiation in male and female smokers. Whereas the weighed mean heritability for females reached ~50%, the weighted mean heritability for males was ~40% (18). Meanwhile, heritability estimates for smoking persistence range from 50% to 70%, for smoking quantity from 40% to 60%, for nicotine dependence from 60% to 80%, and for smoking cessation ~50% (19–21). It has also been suggested that the liability to smoking initiation, regular tobacco use, and nicotine dependence are correlated. Specifically, more than 80% of the variance in liability to initiation and regular use is shared, while a smaller proportion is shared between regular use and nicotine dependence (17). Added to this, age-dependent genetic effects have been identified, whereby the genetic liability influencing later cigarette use behaviors is more influential when cigarette use is initiated during adolescence (22), implying a gene-environment interaction with E being operationalized as age.

Gene-Finding Efforts for Cigarette Use

While twin and family studies were able to establish that cigarette use phenotypes were heritable, technological advances made it possible to sequence the human genome and look for the genes underlying these twin and family heritability estimates. Gene finding methods are used to determine the locations of gene variants that differentially impact the liability to traits. In general, these gene-finding methods are statistical in nature, such that researchers infer the probability that a locus in the genomic region under investigation contributes to

liability for the trait (e.g. cigarette use phenotypes) from an examination of the distribution of genetic markers within either families, as in linkage studies, or populations, as in genome-wide association studies (GWAS) (23). Genome-wide linkage studies were first used to identify chromosomal regions that could have contained loci contributing to cigarette use phenotypes, involved with either the neurotransmission of neuromodulators or the rewarding efforts of nicotine on the mesolimbic system (24). Candidate gene studies investigated associations between measures of cigarette use initiation, intensity, and dependence and genes involved with nicotine receptors, dopaminergic transmission, and serotonin transporters. Despite some regions showing suggestive linkage in multiple studies, results have been heterogeneous. Added to this, genes implicated in candidate gene studies have not been reliably associated with cigarette use phenotypes in larger GWAS, the effects of most candidate genes for cigarette use remain largely ambiguous. Replication of candidate gene studies remains a problem because of small sample sizes in each individual study, differences in measures of cigarette use, and differences in genetic and environmental backgrounds (25). GWAS simultaneously analyzes common genetic variants across the entire genome and has been used since the early 2000s to identify genetic variants contributing to cigarette use phenotypes (26). Gene-finding efforts have identified associations between a variety of cigarette use phenotypes and single nucleotide polymorphisms (SNPs) within neuronal nicotinic acetylcholine receptor genes (nAChRs), the initial physiological targets of nicotine in the central and peripheral nervous system (27–29), and variable-number-of-tandem-repeats (VNTR) polymorphisms located in dopaminergic genes and serotonin transporter genes (30).

Nicotinic receptor genes—Although nAChRs in *CHRNA7*, *CHRNA9*, *CHRNA5*, *CHRNA3*, and *CHRNA4* were found to be significantly associated with nicotine addiction in early candidate gene studies, GWAS failed to provide support for these findings (31). Instead, independent GWAS have provided evidence for association between common variants within the *CHRNA5-CHRNA3-CHRNA4* gene cluster located on chromosome 15 and nicotine dependence (29,32). The studies identified in this review investigated the following SNPs within this cluster: *rs16969968* (33,34), *rs680244* (34), *rs3743078* (33), and *rs1051730* (35,36) which is in near-perfect linkage disequilibrium with *rs16969968* in Caucasian samples. Numerous studies have demonstrated the association between functional variant *rs16969968* and cigarettes per day (CPD) and nicotine dependence (27,29,37), heavy smoking (28,38) and decreased response to nicotine antagonists in vitro (35). The same locus was associated with the risk of lung cancer and chronic obstructive pulmonary disease in several GWAS (22). SNP *rs680244* has been associated with variability in *CHRNA5* mRNA levels (34). SNP *rs3743078* is a proxy for variant *rs578776*, which has also been associated with nicotine dependence (33). Gene variant *rs1051730* has been previously associated with smoking quantity and increased susceptibility for lung cancer and vascular disease among smokers (35).

Dopaminergic genes—The dopaminergic system is also believed to play an important role in nicotine dependence, since nicotine increases dopaminergic activity in the brain to induce feelings of pleasure or reward. Candidate genes include: dopamine receptors (*D2* and *D4*), dopamine transporter gene (*DAT1*), ankyrin repeat and kinase domain containing 1

(*ANKK1*), tetratricopeptide repeat domain 12 (*TTC12*), and the serotonin transporter gene (*5-HTTLPR*). *ANKK1* contains a TaqIA1 C>T polymorphism (rs1800497) that has previously been associated with reduced dopamine D2 receptor availability and binding capacities in the brain, which is believed to cause carriers of the allele to compensate for the reduced state of reward following nicotine use. It is also weakly associated with adolescent smoking initiation (9). Dopamine receptor D₄ is a G protein-coupled receptor encoded by the *DRD4* gene that is activated by the neurotransmitter dopamine. The 48-base pair variable-number-of-tandem-repeats polymorphism in exon III of the *DRD4* gene ranges from 2 to 11 repeats. Previous studies have indicated that the longer the repeat, the more dampened the response to dopamine. The *DAT1* transporter gene regulates re-uptake of dopamine into presynaptic terminals, terminating dopaminergic neurotransmission, and maintaining dopamine homeostasis. *DAT1* contains a polymorphic 40-base pair VNTR which has been previously associated with lower risk of early smoking onset and current smoking (10). The gene cluster *TTC12-ANKK1-DRD2* plays a central role in modulating dopamine reward system, by mediating the reinforcing effect of all known addictive substances (35).

Serotonin transporter gene—It has been demonstrated that *5-HTTLPR* plays a role in nicotine dependence via mediating rewarding effects in the dopaminergic reward system; two common variants (a 14-repeat short (S) variant having less transcriptional activity and lower serotonin uptake and a 16-repeat long (L) variant) seem to have differential effects. While the S allele has a significant effect on smoking behavior, the L allele contributes more to smoking rate (39). It has been suggested that the differential effects are due to interactions with other polymorphisms, though results are inconclusive (40).

Meta-Analyses, Missing Heritability, and Why Studying GxE is Important

Although independent genome wide association studies have identified variants associated with cigarette use, these variants currently explain very little of the phenotypic variation because genetic effects due to common alleles are quite small and the detection of signals requires very large sample sizes. GWAS are underpowered to detect these effects. To overcome the issue of power and false-positive findings, meta-analysis statistically synthesizes information from multiple studies (41). The largest genetic meta-analysis of cigarette use conducted by the Tobacco and Genetics Consortium included sixteen GWAS and found five significant loci. Each of the five loci was associated with only one specific smoking phenotype: nonsynonymous *rs6265* on *BDNF* and smoking initiation (OR = 1.06, 95% CI: 1.04, 1.08, p-value = 1.8×10^{-8}); nonsynonymous *rs1051730* in 15q25 on nicotinic receptor gene *CHRNA3* ($\beta = 1.03$, SE = 0.053, p-value = 2.8×10^{-73}), *rs1329650* on 10q25 ($\beta = 0.367$, SE = 0.059, p-value = 5.7×10^{-10}), and *rs3733829* in 9p13 of *EGLN2* ($\beta = 0.333$, SE = 0.058, p-value = 1.0×10^{-8}) and number of cigarettes per day, and *rs3025343* near *DBH* on chromosome 9 and smoking cessation (OR = 1.12, 95% CI: 1.08–1.18, p-value = 3.6×10^{-8}) (11). Still, the variance attributed to these genetic variants only explains a small proportion of phenotypic variation in cigarette use, which does not correspond to estimates of heritability calculated from twin and family studies. A portion of this “missing heritability” might be explained by gene-environment interaction (42), emphasizing the importance of studying GxE. Although reliable demonstration of GxE requires very large

sample sizes, studies of GxE can be helpful in determining why heritability estimates for cigarette use phenotypes vary, and could explain why the search for susceptibility genes from GWAS have not been especially successful. Identified genetic loci from the current literature contribute only modestly to the variability in cigarette use phenotypes. Once we are able to identify more genes contributing to cigarette use, studies of GxE could be used to shape smoking cessation therapies and tobacco control efforts, through interventions tailored to genotypes or environmental factors contributing to tobacco use.

Social and Environmental Risk Factors for Cigarette Use

Although it is clear from the literature that genes influence cigarette use, the motivation to begin smoking is also strongly impacted by the social environment, especially during adolescence (43). As twin and family studies have demonstrated, shared environmental factors also account for a replicable proportion of the variation in initiation specifically (16), and smoking behaviors more generally (44). Thus, research on genetics and cigarette use should take into account social and environmental factors that may modify genetic risk, especially when we consider cigarette use as a dynamic process in which individuals can move from initiation, to intermittent use, to regular use, and/or dependence. Understanding the genetic and environmental factors that interrupt progress along this trajectory or potentiate continued use could be useful for intervening with cigarette use and promoting either prevention of initiation or cessation after continued cigarette use (45). Below, we review epidemiological findings of key environmental covariates that may influence cigarette use and should be considered for genetic research on cigarette use.

Sociodemographic Characteristics—Sociodemographic characteristics should be considered potential environmental covariates in genetic research on cigarette use because the prevalence of smoking tends to be higher among disadvantaged groups. Additionally, disadvantaged users of cigarettes may be more likely to initiate use, less likely to be successful in quit attempts and face higher exposure to the harms of tobacco (46). Groups that are at higher risk for smoking include the poor, semi-skilled manual occupation groups, the unemployed, poor educational achievers, and single mothers (12,47). Smoking prevalence among these groups may be due to reduced support for quitting, low motivation to quit, stronger addiction to tobacco, targeted marketing by tobacco companies, and psychological differences regarding self-efficacy in the ability to quit (46), which could be intensified by high feelings of anxiety (48), hopelessness, lack of social, communication, and refusal skills, and low-self esteem (49), or experiencing highly stressful events in childhood (50). These are all potential points of intervention for cessation efforts and have the potential to reduce health costs associated with cigarette use. Cigarette use also varies by sex between countries, making it difficult to determine whether males or females are more likely to smoke (51). However, according to a review paper of 12 studies published between 1980 and 2010 assessing smoking initiation, boys had a lower age of smoking initiation relative to girls (52). Meanwhile, according to longitudinal studies, girls and boys have similar levels of overall substance use during early adolescence, but boys have greater increases in substance use during middle and late adolescence after initiation (53). Studies of adult smokers have also demonstrated that women tend to smoke fewer cigarettes per day, use cigarettes with lower nicotine content, and do not inhale as deeply as men. However, it

remains uncertain whether this may be due to differences in sensitivity to nicotine or differences in other social factors associated with the experience of cigarette use (54).

Family Cigarette Use—Although family influences play an important role on the development of cigarette use, most of the research done has focused the role of parents and siblings on experimentation with and the onset of cigarette use (55–57). As evidenced by previous studies, negative family environments characterized by low connectedness or cohesion (58) high levels of parent-child conflict, inadequate parental monitoring, and family violence contribute to tobacco use (59). Individuals with negative family environments may be less likely to comply with parental requests to abstain from smoking and their initial use may go undetected or unpunished (60). Alternatively, an authoritative, positive parental style (61), and parental anti-smoking socialization (i.e. messages about smoking, reactions to smoking, household smoking rules), parental expectations and opinions about the choice to smoke (62–64) may help prevent early adolescents from smoking. Added to this, there is consistent evidence demonstrating that parental smoking is a risk factor for adolescent smoking (59,65). However, one study found that the effect of parental disapproval both in smoking and nonsmoking parents was stronger and more robust than that of parental smoking and even attenuated the effect of peer smoking, suggesting that parental disapproval makes adolescents more resistant to peer smoking (66). However, it remains unclear to what extent this is pure environment and passive gene-environment correlation. The presence of gene-environment correlation would imply that non-smoking parents pass on their “non-smoking” genes but also create a non-smoking environment. Siblings also influence the initiation and escalation of cigarette use, such that having older siblings who smoke increases a child’s risk of smoking even after adjusting for parents’ smoking (67). Risk of initiation increases substantially as the number of smokers in an adolescent’s environment increases, with adolescent females more likely to smoke than adolescent males (57,68). Besides their smoking behavior, social connectedness between siblings appears to moderate shared environmental influences on smoking frequency and any subsequent changes on smoking frequency (69). Given that few longitudinal studies have examined how these family influences shape cigarette use following experimentation and initiation, information that could inform the development of effective cigarette use prevention programs addressing family influences remains limited (55).

Peer Cigarette Use—Peer relationships, especially those during adolescence, contribute to an individual’s initiation, progression, and trajectories of cigarette use (70). In fact, adolescent smoking is more strongly associated with peer smoking, relative to parents’ smoking (57,71–73). It has also been suggested that parental smoking does not moderate the association between friends smoking and adolescent smoking; although, parental behaviors may effect smoking progression through their impact on the selection of friends (74) and limiting increases in the number of friends who smoke (62). It has been previously suggested that adolescents who frequently smoke in the presence of others, use smoking as a way to achieve social belonging (75) and are more likely to smoke when their best friends smoke. However, there is debate about whether peer influence leads to smoking (e.g. socialization) or whether individuals who smoke tend to seek out other smokers (e.g. selection) (76). Added to this, cigarette use initiation is more likely to occur in schools with

higher smoking rates (77), since smoking may seem more normative and acceptable (78) and more social sources of cigarettes may exist (79). This might explain why, despite legislation that prohibits tobacco sales to minors, adolescents are still able to acquire cigarettes through direct purchase from others or from older friends (80). It is also unclear to what extent this is pure environment, rather than active gene-environment correlation whereby individuals are acting on their propensity to use cigarettes by seeking out friend groups that permit cigarette use. Longitudinal study designs of adolescents and their peer groups may help to determine whether gene-environment correlation is present, while disentangling whether socialization or selection has a stronger impact on trajectories of cigarette use. Findings from these longitudinal studies may be helpful in the design of interventions. For example, interventions may want to focus on cognitive factors as a means to mitigate effects of peer group influences on cigarette use through social skills or altering social norms (70).

Age of onset—Approximately 90% of adult smokers first tried cigarettes before the age of 18, and practically all began using cigarettes before the age of 26 (81). In addition to being at higher risk for nicotine dependence (82), individuals who have an earlier onset of cigarette use are at increased risk for heavy smoking (22) and worse tobacco-related health outcomes in adulthood (83). Added to this, one study conducted on students in grades 9–12 in Canada found that a delay of one year in the age of smoking onset was associated with lower odds of being a current smoker (adjusted OR = 0.76, 95% CI= 0.73–0.79). Increasing the age of onset also seems to increase the likelihood of successful smoking cessation, as results from another study found that the likelihood of smoking cessation was greater in smokers who had begun cigarette smoking after age 13, relative to individuals who had begun earlier (84). These findings suggest that early prevention and intervention are needed to avoid early-onset cigarette use to reduce negative consequences associated with cigarette use, such as nicotine dependence and tobacco-related health outcomes in adulthood (83).

Public policy—Given the toll taken by cigarette use, a number of public policies have been implemented to control tobacco use. The choice of public policy varies considerably between and within countries, allowing for a natural experiment in the study of the effects of tobacco control on the demand for and use of cigarettes. Examples of tobacco control policies include prohibition of paid-for advertising for tobacco products, promotion of smoke-free policies, and excise taxes on tobacco products (85). Since countries do differ greatly in the prevalence of cigarette use, potentially due to differences in cultural norms and attitudes towards cigarette use, results might not replicate across countries. In general, studies have found that smoking restrictions in public places have a negative effect on average cigarette consumption by smokers, such as smoking restrictions in restaurants, limited cigarette sale through vending machines, and smoking restrictions in shopping areas (86) and workplaces (87). And, as summarized from one systematic review, increasing taxes on tobacco products independently reduces smoking prevalence among youth and adults, while banning smoking in public places reduces the prevalence of smoking among the general population, and mass media campaigns reduce the initiation of smoking in youths and prevalence in adults (88).

Religion—Although religion seems to be inversely related to all measures of tobacco use (i.e. lifetime, occasional, and regular use), findings suggest that religion's primary influence on cigarette use is the negative effect it has on ever use (89). Importance of religion and attendance in worship services are negatively associated with smoking, such that the more religious a teenager perceives him or herself to be, the less likely it is that he or she would smoke (90). Furthermore, private religiosity is protective against initiation of regular smoking among nonsmokers as well as the initiation of experimental smoking, but only when the young person attends religious services or a religious youth group frequently. Meanwhile, public religiosity predicts the reduction and cessation of cigarette use among regular smokers (91). It has been suggested that religiosity may discourage the use of substances through adolescents' exposure to religious doctrines discouraging the use of substances, which implies that religious individuals may be more likely to hold conservative attitudes towards substance use, such as cigarette use, and will affiliate with peers that are similar to them (92).

Evidence of Gene-Environment Interaction in Cigarette Use

From the previous sections of this manuscript, it is clear that genes and environments contribute to risk for cigarette use. However, it is important to remember that cigarette use phenotypes are complex traits arising from interactions among social-environmental, psychological, and genetic factors (93) and these interactions need to be taken into consideration when developing downstream public health interventions. Despite progress made in the prevention of and treatment for cigarette use, available treatments are effective for only a portion of smokers. Whereas the identification of specific genetic variants is necessary in determining the underlying biological mechanism of risks for cigarette-related health outcomes, understanding how these variants interact with aspects of the environment to influence cigarette use has the potential to more effectively tailor interventions to smokers' individual risks and needs (94). In studies of gene-environment interaction, genetic effects can be modeled either as latent variables in twin and family studies or as genuine measured genes in molecular genetic studies. When genetic effects are modeled latently, the contribution of gene effects is inferred based on observed correlations between people with different degrees of sharing across genes or the environment (5). These correlations are used to study whether the heritability is the same in different groups. Meanwhile, molecular genetic studies focus mostly on one specific gene of interest, rather than the aggregate effect of genes influencing a trait. Despite awareness of the importance of gene-environment interactions in tobacco use, studies available on the subject are currently limited. Evidence from twin studies have predominantly focused on the importance of genetic factors influencing cigarette initiation, as it relates to family environment, school environment, neighborhood characteristics, and religion, while molecular genetic studies of social policy and the environment have investigated whether genetic influences on initiation, daily smoking, and cessation are moderated by social policy and the environment. All studies discussed in this section still await replication.

Family environment—One Finnish twin study demonstrated that at age 14, the effect of genes on cigarette use increased and common environmental effects decreased as adolescents reported less parental monitoring. Specifically, genetic factors accounted for

more than 60% of the variance at the extreme low end, but less than 15% at the extremely high end of parental monitoring. Meanwhile, common environmental effects accounted for 20% and 80% of the variance at extremely low and high ends of parental monitoring, respectively (8). Parental monitoring seems to have an effect on genes contributing to nicotine dependence as well, as demonstrated by a significant interaction found between *rs169169968* and parental monitoring ($p = 0.009$) in the Collaborative Genetic Study of Nicotine Dependence, whereby nicotine dependence increased with the risk genotype when combined with the lowest quartile of parental monitoring (33). This suggests that parents moderate the likelihood of an individual at genetic risk for adolescent smoking and nicotine dependence in later life, through the restrictiveness of the social environment provided by parents. Variation in *rs3743078* did not contribute to this association, as no significant interaction was found between parental monitoring and *rs3743078* ($p = 0.80$). Meanwhile, whether or not parents smoke may have less of an effect on adolescent smoking, as interactions between measures of environmental smoking, conceptualized as paternal smoking, maternal smoking, or sibling smoking, and genetic variants of *DRD2*, *DRD4*, or *DAT1* of the dopaminergic system did not significantly contribute to variation in adolescent smoking (9). Furthermore, only one significant interaction found between maternal smoking and *rs1051730* influenced occasional smoking at 14 years (35). One study investigated the effect of smoking-specific parenting messages across: how often parents talked with their child about smoking-related issues in the past 12 months (e.g. “frequency”), how respectful parents were to children about communicating about smoking-related issues (e.g. “quality”), and whether there were smoking-specific rules at home (e.g. “house rules”). The effect of these smoking-specific parenting messages seems limited, as the Dutch study found no evidence for interaction between smoking-specific parenting in terms of frequency, quality, or house rules, and dopaminergic genes on adolescent smoking behavior (10). Dopaminergic genetic variants *DRD2*, *DRD4*, and *DAT1* were chosen for their associations with smoking from previous studies.

School environment—Two twin studies investigated the moderating effect of school-level variables on heritability of adolescent smoking behavior (95,96). Findings from Daw et al. (2013) suggest that an individual’s susceptibility to school-level patterns of smoking is conditional on the number of short alleles in *5-HTTLPR*. The greater the number of short alleles, the stronger the individual’s response to the school health behavioral environment (39). No interaction effects were found between dopaminergic genes and peer smoking (9). Institutional control, which incorporated measures of school smoking policies implemented by adults and whether teachers could smoke on school grounds, was not found to significantly interact with genetic influences on daily smoking among youth (95). There was also no evidence for interaction between state-level smoking by adults, measured by the percentage of adults reporting regular use in the Behavioral Risk Factor Surveillance System (1992–1993), and genetic influences on regular use during adolescence. This was not the case for state-level smoking by youth, measured by the percentage of 9th to 12th graders reporting frequent smoking, which was found to be negatively associated with genetic influences on regular smoking. Within schools, the effect of genes on daily smoking decreased as the prevalence of smoking among popular students increased, suggesting that social pressures within schools moderate the heritability of daily smoking. These

interactions were not found for smoking onset (95). One study also tested whether the response to a substance use prevention/intervention program varied based upon a set of five markers (*rs16969968*, *rs1948*, *rs578776*, *rs588765*, and *rs684513*) and found that there was a main effect of both the intervention ($b = -0.24$, $p\text{-value} < 0.05$) and genotype at *rs16969968* ($b = 0.14$, $p\text{-value} < 0.05$) on high school smoking. The genotype $\times$ intervention interaction effect was also found, where those with the A/A and G/A genotypes reduced their levels of smoking to levels similar to those with G/G genotypes following the intervention phenotype (G/G vs. A/A: $b = -0.67$, $p < 0.05$; A/G vs. A/A: $b = -0.61$, $p < 0.05$; G/G vs. A/G n.s.) (97).

Neighborhood environment—Neighborhood-level factors have previously been associated with the risk of smoking initiation. In order to test whether genetic factors and social context influence cigarette use, one molecular study investigated the interaction between an aggregated genotypic risk score (GRS) combining the top genetic variants (i.e. all SNPs reaching a $p\text{-value}$ threshold of $< 5 \times 10^{-7}$) from a meta-analysis previously conducted on African Americans, and neighborhood-level effects on smoking behavior. Among individuals who had ever smoked cigarettes, the GRS significantly predicted the number of cigarettes smoked per day (measured by “In the past 30 days, on those days when you smoked, on average, how many cigarettes did you smoke per day?”) and accounted for ~3% of the variance. Significant interactions were observed between the GRS and number of traumatic events experienced and average neighborhood social cohesion, but not neighborhood physical disorder. The association between the GRS and cigarettes per day increased with increasing number of traumatic events and decreased with increasing levels of neighborhood social cohesion (98).

Religion—Most studies investigating the effect of religion on cigarette use have focused on the association between measures of religiosity and smoking initiation. Only one twin study investigating the moderating effect of religion on cigarette use was identified, which investigated the interaction between self-rated religiousness, religious affiliation, and organizational religious activity and smoking initiation heritability. This study provided no evidence for interaction between religious affiliation or organizational religious activity and genetic influences of smoking initiation. It did, however, find that high levels of self-rated religiousness attenuated the additive genetic component for smoking initiation (7).

Public Policy—Given that smoking ranks highly among public health problems in the world, public policy initiatives have been implemented to decrease smoking prevalence, while also emphasizing the negative health consequences of cigarette use. Examples of legal and regulatory policies related to tobacco include prohibition of smoking in public places and workplaces, restrictions on sale and marketing of tobacco products (especially to children), and federal legislation giving government agencies the authority to regulate tobacco (99). One study conducted in the Netherlands explored whether a change in environmental conditions – that is, smoking policies such as cigarette pack warnings about health consequences and bans on smoking advertisements – led to a change in the relative contribution of genetic factors to smoking initiation by comparing data on two cohorts of young adult twins. This study found that although the changes in policies and attitudes

towards smoking led to a decrease in the prevalence of smoking, it did not change the heritability of smoking. These findings did not provide support for GxE between initiation and public policy initiatives (100). Meanwhile, a few studies demonstrate interactions between policy initiatives and the heritability of daily and regular smoking have found evidence for GxE (96,101,102), suggesting that historical time periods can be characterized as distinct social environments that moderate the contribution of genes to cigarette use (103). One study using twin pairs from the National Survey of Midlife Development in the United States found that the timing of the first Surgeon General's Report coincides with an increase in the genetic influences on regular smoking, but subsequent legislation prohibiting smoking in public places reduced these influences (101). Another study conducted using data from the National Longitudinal Study of Adolescent Health, investigated interactions between state-level measures characterizing social and institutional effects on smoking and daily smoking and smoking onset of adolescents. At the state level, the effect of genes on daily smoking were lower in states with relatively high taxes on cigarettes and greater controls on vending machine and cigarette advertising, while there was no variation in heritability estimates for smoking onset among adolescents (96). Fletcher (2012) also found that variation in the SNP *rs2304297* of nicotinic acetylcholine receptor *CHRNA6* moderated the influence of tobacco taxation on multiple measures of tobacco use, such that individuals with the protective G/G polymorphism responded to taxation while others had no response. Only one study investigated GxE between policy and cessation, as a study by Boardman et al. (2011) demonstrated that the genetic influences on smoking desistance (measured using a pair-wise measure indicating the length of time in years for a twin to quit smoking after his/her sibling had quit) increased in importance following restrictive legislation on smoking behaviors during the early and mid-1970s (103).

Pharmacological treatment—Studies provide support for the role of genetic variation in response to bupropion and nicotine replacement therapy for smoking cessation. Generally, variations in genes within the dopamine and opioid pathways and in nicotine-metabolizing enzymes appear to play a role in the efficacy of nicotine-replacement therapy, while variation in dopamine pathway genes are important for response to bupropion (94). In the one study investigating pharmacological treatment on genetic risk for smoking cessation, genetic variants *rs16969968* and *rs680244* were used to categorize patients into three haplotypes: (1) low smoking risk allele at *rs16969968* and low mRNA expression allele at *rs680244*, (2) low smoking risk and high mRNA expression, and (3) high smoking risk and high mRNA expression. These haplotypes are located *CHRNA5-CHRNA3-CHRNA4* on chromosome 15 and were chosen for their consistent association with measures of smoking heaviness and nicotine dependence in other studies, and potential relation with cessation likelihood. In the smoking cessation trial, haplotype interacted with treatment in affecting success of cessation, in that active treatment was strongly associated with a lower risk of relapse in individuals with haplotype 3 (relative hazard = 0.48, p-value = 9.7×10^{-7}) and haplotype 2 (relative hazard = 0.48, p-value = 2.7×10^{-8}), but not haplotype 1 (relative hazard ratios = 0.83, p-value = 0.36). No significant differences were found in the effect of haplotype on abstinence/relapse between bupropion only, nicotine replacement therapy only, and combined therapies treatment groups (34). Exposure to environmental smoking-related cues may also play an important role in promoting relapse, as individual differences in

response to the sight or smell of a lit cigarette may be mediated by the *DRD4* VNTR polymorphism. Participants who were homozygous or heterozygous for the seven repeat or longer allele demonstrated significantly higher craving, more arousal, less positive affect, and more attention to the smoking cues than participants for whom this polymorphism was absent (104). The integration of genetic testing into standard clinical practice would be premature at this time, but pharmacologic studies of treatments for nicotine dependence eventually may guide individualized smoking-cessation treatments.

DISCUSSION AND CONCLUSION

Both twin/family and molecular genetic studies provide preliminary evidence that gene-environment interactions have differential effects on cigarette use over the course of development. Twin and family studies demonstrate that the relative contributions of genetic and environmental factors to cigarette use changes across time from adolescence, when most smokers initiate cigarette use, through adulthood, when many smokers have established patterns of cigarette use. Familial and environmental factors contribute to whether individuals initiate cigarette use. However, as individuals move from initiation to more established patterns of use, the importance of common environmental factors decreases while the influence of genes increases. As the contribution of genes to cigarette use increases, the influence of environmental factors does not go away, but rather, environmental factors begin playing a different, but still important role – that is, as a moderator of the influence of genetic susceptibilities (105). This implies the presence of a gene-environment interaction, such that certain environments allow for greater expression of genetic effects, possibly due to the availability of opportunities for individuals to show their genetic predispositions (6). While twin studies of gene-environment interaction have been useful in explaining how the effect of genes may change as a function of the environment, molecular genetic studies of gene-environment interaction have been useful in parsing out the role of specific genes influencing cigarette use behaviors through the testing of the main effect of a specific gene of interest from candidate and genome wide association studies on a given cigarette use phenotype and the testing of interactions between the specific genes of interest and the environment.

From this review of the literature on the influence of genes, environments, and their interaction on cigarette use, we find that significant GxE interactions vary across cigarette use phenotypes. Let us first consider gene-environment interactions contributing to cigarette initiation. Religion was the only environmental variable found to moderate genetic influences on initiation during adolescence (7). More specifically, of the studies investigating gene-environment interaction contributing to initiation (7,95,96,106), only one twin study yielded a significant interaction between aggregated genetic risk and self-rated religiousness (7). The Timberlake et al. (2006) study was the only twin study that included this very specific environmental factor on smoking initiation, even though previous associations have been found between religion and decreased risk for smoking initiation in epidemiological studies. To our knowledge, the interaction between specific genetic variants and self-rated religiousness has not been tested in molecular genetic studies and none of the genetic association studies investigating gene-environment interaction contributing to initiation yielded positive GxE results (9,10). These findings suggest a few different things:

either the contribution of genes on initiation remains consistent across different environmental contexts, the effect of GxE in twin studies is quite small, and/or current genetic association studies investigating GxE in cigarette initiation are underpowered to detect effects. Under the first scenario, the environment would have no effect on genetic influences contributing to initiation and encouraging a change in the environment (e.g. increasing self-rated religiousness) would not necessarily reduce cigarette prevalence. The second scenario suggests that the effect of gene-environment interaction is small and certain environments provide only a minimally greater expression of genetic effects. In the context of religiousness, this might be explained by the fact that genetic influences on smoking have been found to be low or nonexistent among individuals raised with a strong religious upbringing (7). The third scenario implies a problem with power, so investigators will need to look towards increasing their sample sizes in future studies of gene-environment interaction in cigarette initiation to detect an effect if it is there.

Gene-environment interactions contributing to other cigarette use behaviors, such as adolescent smoking, cigarettes smoked per day, nicotine dependence, and cessation have yielded significant findings as well. A couple of measures of the parental environment moderated genetic influences on adolescent smoking (8,35). Specifically, significant interactions were found between parental monitoring and *rs16969968* of *CHRNA5* (33) and maternal smoking during pregnancy and *rs1051730* of *CHRNA3* (35) for smoking at age 14. Meanwhile, social pressures to smoke, prevalence of smoking among popular students, marketing and vending restrictions on the sale of cigarettes, and school-level smoking moderated the heritability of daily smoking among adolescents (39,95,96). Only one molecular genetic study investigated and found a significant interaction between *5-HTTLPR* and school tobacco use in influencing tobacco use frequency, such that the greater the number of short alleles, the stronger the individual's response to the school health behavioral environment (39). In adulthood, the experience of traumatic events and neighborhood social cohesion interacted with aggregated genetic risk to influence the number of cigarettes smoked per day. The interaction between the experience of traumatic events and neighborhood social cohesion and aggregated genetic risk seemed to be largely driven by a single variant (*rs203652*) located on the *CHRNA5-CHRNA3-CHRNA4* gene cluster (98). Parental monitoring also interacted with genetic variant, *rs16919968*, to determine nicotine dependence in adulthood (33), while treatment status interacted with genetic risk for smoking cessation (34).

From these studies we can see that the environment moderates the effect of genes across different cigarette use phenotypes. However, the extent to which the environment moderates the genetic influences across different cigarette use phenotypes varies. There are a couple of different reasons why it is the case that GxE is found for some cigarette use phenotypes and not others. It could be that the genes influencing initiation may be different from the genes influencing other cigarette use behaviors (96,107,108), such as adolescent smoking, daily smoking, number of cigarettes smoked per day, nicotine dependence, and smoking cessation. It is also possible that, the effect of certain environmental measures of smoking that are potentially influenced by both genes and environment [e.g. smoking status of father, sibling, friend, or best friend (35)] seems to vary among carriers of nicotinic receptor genes, but not among carriers of dopaminergic gene variants - possibly, suggesting that either: the effect of

However, we are unable to conclude from some small GxE studies that the phenotypes are not genetically the same, as long as GWAS on the same phenotypes do not come up with the same list of associated genes. As such, we remain unable to make definitive claims regarding the nature of changing gene-environment interaction contributing to cigarette use due to the limited availability of studies investigating this phenomenon. Each study reviewed here examined the association between specific cigarette use phenotypes and a given environmental measure within either adolescents or adults. This made it difficult to determine how environmental contexts differentially influence genetic factors that contribute to cigarette use phenotypes such as initiation, daily use, nicotine dependence, and cessation and demonstrates how the use of various cigarette use phenotypes may complicate the literature and comparability of findings across studies. Added layers of complexity are found in the fact that there is a great deal of variability in heritability across each cigarette use phenotype (96) and heritability estimates may be contingent on social and institutional characteristics of the environment, such as temporal changes in genetic epidemiology of smoking, changes in smoking norms, changes in the cost of smoking, and legal limits placed upon smokers (103). Using longitudinal data with repeated measures of different cigarette use phenotypes and environmental contexts would allow researchers to evaluate genetic contributions to the inter-individual variability of each cigarette use phenotype and assess the stability or change of individual differences in each cigarette use phenotype over time. The same longitudinal data could be used to predict cigarette use behaviors over time (113). Future studies might also want to include a range of nicotinic receptor, dopaminergic, and serotonergic gene variants to parse out the effect sizes of main effects on cigarette use phenotypes and interaction effects with different environmental contexts.

In this review of the literature, only a handful of significant gene-environment interactions influencing cigarette use were identified and none were replication studies. To ensure that these findings are not false positives, replication studies using alternative samples are needed. It has been suggested elsewhere that gene-environment interaction studies will be underpowered to detect effects under the following conditions: when the estimated main effects of genes are weak, when the genetic effect is found only among individuals exposed to a particular environmental risk, and when environmental influences are not detected because risk is only conferred among individuals with genetic liability (6). Replications of findings from studies that have identified significant gene-environment interactions influencing cigarette use would imply that the under-examined role of genetic factors in response to particular environments would be an important step in efforts to further reduce smoking rates (102).

Currently, efforts to reduce smoking rates have focused on the implementation of policies that restrict availability or use of cigarettes in public places. Anti-smoking policies directed at adolescents address onset of cigarette use, while emphasizing the role of immediate social influences and refusal skills, which have been shown to reduce initiation by 30% (114). However, it is possible that these policies may only be effective for those who are not genetically susceptible to smoking. Furthermore, although restrictions on smoking in public places, anti-tobacco ads, and increased costs of purchasing cigarettes through excise taxes have also aided smokers in quitting, there remain concerns that policies have focused too heavily on implementing social restrictions on cigarette use, while doing less to help genetically vulnerable smokers quit (96). To address this gap in the literature and further reduce smoking rates, greater focus needs to be placed on determining the extent to which individual differences are due to genes, environmental factors, or their interaction. Gene-environment interaction studies may help us to better understand how prevention and intervention efforts can be tailored to genotypes under different environmental contexts at the level of family, school, neighborhood, and public policy.

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KEY MESSAGES

- No comprehensive reviews of the influence of genes, the environment, and their interaction on cigarette use exist currently.
- The influence of genes may change as a function of the environment and the phenotype being measured.
- It is difficult to determine how the effect of genes contributing to different phenotypes of cigarette use changes according to environmental context, suggesting the need for more studies of gene-environment interaction related to cigarette use to parse out effects.