"A Bullet in My Blood": Genetic Predispositions for Nicotine Addiction and Implications for Smoking Prevention and Cessation Interventions their Connection to Poverty Levels

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"If I ever smell smoke on your clothes, I will never speak to you again.
If I ever see you with a cigarette in your hand, I will never let you come home.
If you ever decide to smoke, I will tell you that I hate you, because I love you.
This addiction is in my body, in my brain, in my lungs, in my hearse.
It's in yours too – you just never knew.
My girl, there is a bullet in your blood.
And I would do anything to keep my daughter from this life of suffering.

It's already too late for me."

Abstract:

Addressing nicotine addiction is a critical public health priority, as millions of individuals continue to lose their lives to tobacco-related diseases despite many wanting to quit. Both smoking initiation and subsequent nicotine dependence are highly heritable, and recent research has uncovered genetic markers of predisposition. Variation in SNP (single nucleotide polymorphisms) and alleles for dopamine transporters in the mesolimbic dopamine pathway are tied to increased risk for heavy smoking and nicotine addiction. Incorporation of discussions of individual genetic predisposition can increase the personal relevance of existing prevention intervention messaging and offer greater specificity for cessation intervention recommendations.

Introduction

Every six seconds, someone dies due to a tobacco-related disease (Action on Smoking and Health, 2016). Nicotine, the primary addictive substance in tobacco products, is a highly addictive drug that acts on the brain's reward systems and produces cycles of intoxication, withdrawal, and preoccupation (U.S. Department of Health & Human Services, 2012). By hijacking neural circuitry relating to pleasure and learning, nicotine consumption results in neurophysiological changes that compels users to seek out more. Though 68% of adult smokers want to quit, 70-85% relapse within a year of attempting to stop (Centers for Disease Control and Prevention, 2016). These statistics are highly troubling, particularly considering causal links between smoking and cancers, stroke, heart disease, diabetes, lung diseases, and premature death (Centers for Disease Control and Prevention, 2016). Though environmental factors like socioeconomic status and education can influence likelihood of smoking persistence, numerous studies have also uncovered a genetic component to nicotine addiction susceptibility (Agrawal & Lynskey, 2008; Straub et al., 1998; Li et al., 2002). As nicotine dependence is highly heritable, individuals with certain genotypes are more likely to experience greater activation of reward systems upon nicotine exposure and worse withdrawal symptoms, thus making it more difficult for them to quit (Benowitz, 2010). Current methods of measuring genetic predisposition include tracing family lineages, scanning genomes, and direct-to-consumer testing (Dingel et al., 2012; Docherty et al. 2011). Although research on isolating specific genetic markers is still emerging, strategic implementation of these methods can increase efficacy of existing smoking prevention and cessation interventions by increasing personal relevance. Current educational programs can be supplemented by incorporating opportunities for individual participants to learn about their susceptibility and develop personalized plans of action.

Neurophysiological Effects of Nicotine and Nicotine Addiction

Nicotine was first identified in the early 1800s as one of 7,000 chemicals found in tobacco smoke and serves as the primary addictive substance in tobacco (U.S. Department of Health & Human Services, 2012). Each year, millions of Americans live with a tobacco-related illness and an estimated 500,000 face premature death as a result of tobacco's harmful effects (Centers for Disease Control and Prevention, 2016). Capable of damaging almost every organ in the body and harming others through secondhand smoke, tobacco has been empirically linked to causing disability, disease, and mortality (Sullivan et al., 1999; U.S Department of Health and Human Services). Despite known health risks and aggressive public health campaigns, 36.5 million Americans still smoke and thousands of adolescents begin smoking each day (Centers for Disease Control and Prevention, 2016; Lantz et al., 2017). Although many smokers want to stop, the strong addictive power of nicotine enacts physiological and psychological changes in the body that make cessation difficult.

Inhaling smoke from a cigarette – the most popular and widely used delivery device for tobacco consumption – allows 1-2 milligrams of nicotine to enter the bloodstream and quickly diffuse into brain tissue (Benowitz, 2010; Dani & Balfour, 2011). Nicotine functions as a stimulant by triggering epinephrine release, but can also work as a sedative with increased dosages (Benowitz, 2010). As an agonist, nicotine binds selectively to nicotinic cholinergic receptors (nAChRs), opening ligand-gated ion channels, stimulating the receptors, and facilitating neurotransmitter release (Mansvelder & McGehee, 2002). Dopamine is consequently released in the mesolimbic dopamine pathway, including neurons in the ventral tegmentum, frontal cortex, and nucleus accumbens. Activation of this reward system signals the experience of pleasure, playing a crucial role in the reinforcing effects of nicotine and facilitating dependence (Benowitz, 2010). Although initial exposure to nicotine produces aversive effects such as nausea or headache, continuous nicotine consumption results in pleasure, increased concentration, and relaxation. However, because nicotine is metabolized rapidly, its positive effects wear off quickly and regular smokers must continue to consume throughout the day or else experience withdrawal – contributing to the formation of habitual smoking and dependency (Mansvelder & McGehee, 2002; Benowitz, 2010). Extended use of nicotine can also cause tolerance, where higher dosages are required to feel the same effects (Mansvelder & McGehee, 2002).

The pharmacological basis of nicotine addiction is facilitated by positive reinforcement from mood and functional enhancement, as well as avoidance of negative consequences from withdrawal (Benowitz, 2010; Mansvelder & McGehee, 2002). Nicotine withdrawal can manifest in negative emotional, physical, and cognitive symptoms. During periods of abstinence such as nighttime sleep or attempted cessation, desensitized nicotinic cholinergic receptors (nAChRs) become responsive and can trigger intense cravings for nicotine (Benowitz, 2010). In addition, deficient dopamine release can cause reduced feelings of reward and hedonic dysregulation, a loss of pleasure in once-enjoyable activities, which can persist for years after quitting (Benowitz, 2010). Other emotional symptoms can include anxiety, depressed mood, irritability, and anhedonia. Untreated individuals with nicotine addiction withdrawal can experience mood disturbances comparable to those of psychiatric outpatients with clinical depression and anxiety disorders (Hughes, 2006). Physical symptoms such as nausea, headaches, and tremors can further exacerbate withdrawal. During the addictive phase of preoccupation and anticipation where individuals begin to crave nicotine and plan for consumption, lower amounts of dopamine and glutamate in the frontal cortex result in cognitive impairments to memory, attention, motor skills, and impulse control. Combined with the powerful effects of cravings and emotional disturbances, these withdrawal symptoms can make cessation more difficult to sustain.

In addition to withdrawal symptoms, the paired association of reward (nicotine consumption) with environmental or contextual cues can provide strong urges to smoke (Mansvelder & McGehee, 2002; Dani & Balfour, 2004). Through the psychological mechanism of conditioning, once-neutral stimuli such as specific locations, habits, or people become associated with smoking over time and can function as "cues" to smoke (Benowitz, 2010). For example, if a

smoker regularly smokes a cigarette while drinking coffee, exposure to the smell, taste, or sight of coffee can remind them of smoking and subsequently trigger cravings and relapse (Benowitz, 2010). Although certain environmental cues can be avoided, others – such as a workplace or family member – can be encountered frequently and serve as a challenge to continued cessation.

Enduring nicotine consumption causes neuroadaption as the brain adapts to changing environments biologically and physiologically. As nicotine usage increases, there is an upregulation in response to nicotine-mediated desensitization of nAChr receptors and bindings sites (Benowitz, 2010). This facilitates nicotine dependence by necessitating increased amounts of nicotine to feel the same amount of pleasure. Although all regular smokers experience upregulation to some extent, a key component of interest is investigating why certain individuals experience more intense or faster upregulation than others (Mansvelder & McGehee, 2002). Recent advances in genetic sequencing technologies have shed light on several potential mechanisms of these differences.

Measures and Implications of Genetic Predisposition for Nicotine Addiction

Although nicotine has high addictive potential regardless of an individual's genetic predisposition or environmental factors, studies involving genetic epidemiology and gene-sequencing have found that liability to nicotine use and dependence are highly heritable (Dingel et al., 2012; Agrawal & Lynskey 2008; Straub et al., 1998; Hawkins et al., 1992). Data from family, adoption, and twin studies support a substantial genetic influence on nicotine addiction, and recent advances in genomic technology have enabled the identification of candidate genes implicated in susceptibility (Philibert et al., 2008). In addition to furthering understanding of the mechanisms of addiction, these methods can also be utilized in improving the personal relevance of preventative and cessation interventions.

A behavioral analysis of smoking initiation and consumption habits found strong associations in prevalence of smoking among biologically related family members (Green, 1979). However, because family studies cannot parse heritable genetic factors from familial environmental factors, adoption studies investigated the smoking habits of children who were raised by adoptive parents with no biological relation. Eaves et al.(1980) found that adoptees were more similar to their biological parents than their adoptive parents in average cigarette consumption and nicotine dependence, supporting the heritability of liability to nicotine addiction. A later meta-analysis of twin studies comparing monozygotic and dizygotic pairs found that greater genetic similarity was strongly correlated with similar measures of nicotine dependence (Li et al., 2002). Review of literature finds that the interaction of genetic and environmental factors varies for smoking initiation and nicotine dependence (Li et al, 2002; Sullivan et al., 1999; Agrawal & Lynskey, 2008). Genetic factors account for 60% of liability to initiate smoking, while environmental factors play a significant role in accounting for 30% (Agrawal & Lynskey, 2008). In contrast, nicotine dependence is determined largely by genetic factors at a rate of 70%, while environmental factors are negligible (Sullivan et al., 1999; Agrawal & Lynskey, 2008).

Since the completion of the Human Genome Project, numerous studies have implemented genome scans to identify plausible genetic markers that increase susceptibility to nicotine dependence. Though strong empirical support exists supporting the role of genetic predisposition in nicotine addiction, it has been difficult to pinpoint specific gene regions as many genes are involved. Early efforts by Straub et al. (1998) and Wang et al (2003) implicated regions on chromosomes 2, 4, 10, 16, 17, and 18. A subsequent study using transcriptional profiling to analyze 30,000 genes from DNA samples from smokers and non-smokers found 579 more activated genes and 584 less activated genes in smokers (Philibert, 2008).

Focusing further in on specific genes, Stevens et al. have found two separate groups of single nucleotide polymorphisms (SNP) in the CHRNA5-CHRNA3-CHRNB4 gene cluster associated with common variants in nicotinic receptor subunit genes that are significantly correlated with heavy smoking (2008). One group of eight SNPs was strongly associated with increased risk of heavy smoking, and a second group of SNPs was associated with decreased risk (Stevens et al., 2008). These findings of risk and protective SNP

genotype combinations define a gradient of genetic predisposition for nicotine dependence and smoking severity. In particular, the statistically significant correlation with the first SNP group and heavy smoking behaviors implicates the a5 receptor subunit and the rs16969968 SNP, where reduced activity of this receptor appears to diminish response to nicotine and may shed light on specific biological factors relating to dependence at the receptor level (Stevens et al., 2008).

Genetic variation in the mesolimbic dopamine pathway has also been implicated in mediating nicotine dependence by influencing the degree to which individuals receive greater reward from nicotine's effects on dopamine (Audrain-McGovern et al., 2004; Hall et al., 2002). Persistent smoking behavior has been linked to the rarer A1 and B1 alleles of the dopamine 2 receptor and the 10-repeat allele of the dopamine transporter gene SLC6A3. Individuals carrying the 9-repeat allele of SLC6A3 are associated with a 22% reduction in dopamine transporter protein, resulting in less clearance and greater bioavailability of dopamine; thus, they may experience less reward from nicotine and less susceptibility to dependence (Audrain-McGovern et al., 2004; Hall et al., 2002). In a study of adolescents with previous smoking experience, the presence of each additional dopamine 2 A1 allele translated to a twofold increase in likelihood to progressing to a higher level of smoking (Audrain-McGovern et al., 2004). Genetic variation in receptor structure and availability of dopamine may facilitate nicotine dependence by moderating how much nicotine affects the brain's reward system and how much behavioral reinforcement occurs upon consumption.

Implementation of Genetic Predisposition into Educational Interventions

Given advances in understanding genetic susceptibility towards nicotine addiction, interventions targeting prevention and cessation should integrate awareness of heritability of dependence liability into existing messaging. Although some policymakers have expressed concerns about diverting funding from traditional public health approaches, acknowledging how genetic predispositions can influence an individual's path to recovery can help target, individualize, and increase efficacy of existing interventions (Hall et al., 2002; Hall et al., 2008; Dingel et al., 2012). Rather than redistributing existing funds allocated for addressing tobacco use and nicotine addiction, more additional funding should be allocated for research and interventions focusing on genetic susceptibility for at-risk populations.

Countering the "Won't Happen to Me" Mentality: Prevention of Nicotine Use Initiation

From a preventative standpoint, it is imperative to target deterrence interventions towards children and adolescents to promote nicotine abstinence and prevent dependence from becoming an issue (Dingel et al., 2012; Lantz et al., 2000; Russell, 1990). In addition to genetic and environmental factors, age is particularly important in determining nicotine use initiation. 90% of adult smokers began smoking before the age of 18, and numerous longitudinal studies have linked smoking initiation in early adolescence to life-long dependence (US Department of Health & Human Services).

The proposed educational intervention builds on existing programs at elementary, middle, and high schools and incorporates discussion of genetic susceptibility to nicotine dependence, opportunities for individualized information about risk, and framing social influence resistance skills as empowerment (Lantz et al., 2000). Current models of educational interventions have been found to have modest short-term and minimal long-term effects on smoking prevention, in part because youth do not perceive health risks of smoking to be personally relevant or a cause of immediate concern (Lantz et al., 2000; Wright et al., 2003; Hawkins et al., 1992; Docherty, 2011). Though programs focusing on social influence resistance have reported modestly significant short-term reductions in smoking initiation, the efficacy of this intervention is contingent upon students recognizing that tobacco use is harmful and personally resolving to avoid it (Russell, 1990; Sullivan et al., 1999; Lantz et al., 2000). Teaching students practical skills on how to resist negative social influences, such as harmful behaviors promoted by peers, is useful but will be complemented by an improved informative component about individualized risk incurred by smoking. The goal of incorporating discussions of genetic predisposition into existing interventions is to address the shortcomings of existing educational

interventions by increasing perceptions of personal relevance, understanding of specific health risks incurred by smoking, and incentive to resist negative social influences by providing individualized information on risk of dependence.

As the intervention is to be incorporated into existing health programs to strengthen existing messaging, facilitators will be current health instructors at each school. During the informative phase of the program where students learn about the associated health risks of smoking, health class instructors will discuss how nicotine is incredibly addictive for anyone regardless of genetic predisposition - on average, people who experiment with smoking one to three times will progress to becoming regular smokers (US Department of Health & Human Services). However, they will emphasize that individuals with a genetic predisposition will face even steeper statistical odds of dependence and addiction. Measures of genetic predisposition for nicotine dependence will be modeled upon empirical methods, including an informal tracing of family history and opportunities for subsidized genetic testing. After learning about the mechanisms of genetic heritability, students will be asked to complete a worksheet about their family's health history including smoking and nicotine addiction. Pilot testing of interventions on genetic predisposition using simple methods of tracing family health histories has produced higher rates of smoking abstinence in addition to more negative attitudes towards smoking (Gartner, 2008). In addition, they have the choice of opting in to a subsidized direct-to-consumer genetic test of nicotine dependence from 23andMe, Decode, Gene Planet, Biomarker pharmaceuticals, or Lumigenix to learn about their own genetic susceptibility and potential subsequent health risks. Students will not be mandated to complete the genetic test to respect their privacy, autonomy, and financial capacities, but will be required to complete the family history activity which has been demonstrated to be an effective way to raise awareness about personal risk (Hall et al., 2012; Gartner et al., 2008). Previous research has found strong adolescent interest in testing for nicotine addiction susceptibility (Tercyak et al. 2006), and one meta-analysis has found that learning about genetic risk leads to an immediate motivational effect, greater perception of risk, and greater desire to quit smoking (Smercenik et al., 2011).

Marteau's research on the impact of informing people about genetic risk has found that positive behavioral change is most likely when they are given the opportunity to participate in effective interventions (Marteau, 2001). Although several studies incorporating genetic susceptibility testing have found that informing can lead to a decrease in motivation due to a perception of fatalism, these studies did not offer interventions that gave individuals agency to reduce harm through behavior change (Wright et al., 2003; Senior et al., 1999).

In order for interventions to be most impactful, Marteau recommends that genetic risk information be complemented by provision of concrete strategies for individuals to reduce risks of adverse health outcomes (Marteau, 2001). To empower students' sense of self-efficacy, reduce risk of increased fatalism, and increase perceptions of agency over one's health and future, students will learn strategies from current 'social influence resistance' interventions for smoking prevention (Lantz et al., 2000; Hawkins et al., 1992; Docherty, 2011). These include strategies on how to "say no" to others who may encourage smoking initiation, affirm individual values and decisions, and avoid environmental risk factors. Avoidance strategies can include brainstorming how to exit harmful environments with minimal negative social consequences (i.e, pretending to take an important phone call, saying that one has allergic reactions towards smoking/cigarette content). Value affirmation exercises that have been found to improve smoking abstinence outcomes involve asking students to brainstorm, plan, and write about why their health matters to them and why they personally choose not to smoke. Students will be more informed about their individualized health considerations and predispositions, while encouraged to maintain agency and control over environmental risk factors.

Improving Treatment Efficacy: Using Genetic Information to Optimize Cessation Strategies

Like other drugs of abuse, abstinence from smoking can be extremely difficult to achieve and maintain (Russell, 1990). Two primary factors that interact to determine smoking cessation outcomes are de-

pendence and motivation (Russell, 1990; Benowitz, 2002). Sufficient motivation is essential for permanent cessation to be achieved for all smokers, but what is 'sufficient' depends on the degree of dependence (Russell, 1990; Quaak et al., 2009). Light smokers with low dependence may stop easily once they feel motivated, but heavy smokers with high dependence may not be able to stop even with strong motivation. Research on heritability of liability has found that genetic susceptibility predicts for more severe dependence (Stevens et al., 2008; Audrain-McGovern et al., 2004; Hall et al., 2002). Having a family history of predisposition for nicotine dependence can make it more difficult for a smoker to stop once they have started. However, clinical advances in understanding the effects of different pharmacological therapies for nicotine addiction on different genetic makeups have the potential to inform, individualize, and improve the efficacy of treatment. Given that different cessation strategies (i.e., nicotine patches, bupropion administration, e-cigarettes) exhibit varying levels of efficacy for different people, analysis correlates between individuals with certain genetic markers and their most effective cessation aids can be used to streamline selection of cessation strategies for other smokers.

In translating research into practical interventions to help individuals living with nicotine addiction, Lerman et al. conducted a study on how functional genetic variants of the dopamine 2 receptor influenced the efficacy of bupropion administration and nicotine replacement therapy. The Zyban brand of bupropion is a pharmacological smoking cessation aid, acting as a nicotinic antagonist and reducing the severity of nicotine cravings and withdrawal symptoms. Nicotine replacement therapy administers nicotine without the other harmful chemicals of tobacco in the form of gum, patches, sprays, and inhalers to relieve physical withdrawal symptoms. Examining a different allele on the dopamine 2 receptor, the Ins/Del C genotype, researchers found that bupropion treatment was more effective for individuals homozygous for the Ins C allele and that nicotine-replacement therapy was more effective for carriers of the Del C allele. Quaak et al.'s study highlights the potential for assessment of genetic background to guide selection of the most effective cessation treatment for individual smokers (2009). Although these findings have yet to be widely replicated and isolate one of the many genes involved in nicotine dependence, they point towards a future where individualized pharmacotherapy could potentially identify the most effective treatments based on an individual's genetic makeup.

On a socioemotional level, utilization of genetic testing to facilitate cessation aid selection can also serve to increase smokers' perceptions of self-efficacy and motivation to quit. Many smokers have already expressed an interest in receiving genetic testing, with 60-80% reporting a desire to learn about their genetic predispositions (Smercenik, 2011). The same study found that administering genetic tests led to promising, significantly positive attitude changes and behavioral outcomes. Smokers who received genetic tests felt higher personal relevance of risk perception and expressed stronger motivation to quit (Smercenik, 2011). These results were also translated to higher cessation rates and longer periods of smoking abstinence; a proposed potential mechanism for this change is that greater belief in the specificity of treatment aid selection can result in greater belief that the treatment will work. Similarly, Wright et al. found that learning of a genetic predisposition to nicotine dependence increased motivation to overcome their illness, higher personal relevance of risk assessment, and greater interest in pursuing cessation methods (2000). Although some researchers and policymakers have expressed concern that testing negative on a risk-increasing gene can result in more negative outcomes such as decreased motivation to pursue treatment, no adverse effects were found. As in the intervention for smoking prevention, informing individuals of genetic risk must be accompanied by provision of concrete strategies for changing behavior, such as effective medical treatment options and plans to remove environmental context cues from smoking from one's life.

Conclusion

Addressing nicotine addiction is a critical public health priority, as millions of individuals continue to lose their lives to tobacco-related diseases despite many wanting to quit. As a substance with high addictive power, nicotine makes it difficult for absti-

nence to be attained and sustained. Because smoking can harm nearly every organ in the body and impact the health of others secondhand, improving and optimizing prevention and cessation interventions is imperative. Given compelling evidence substantiating the heritability of genetic predispositions toward nicotine dependence and growing understanding of how genetic makeups can influence behavioral outcomes, discussion of genetic susceptibility should be integrated into existing programs on prevention and cessation. Current prevention programs fail to elicit sufficient personal relevance for adolescents – giving them opportunities to learn highly individualized, specific information about their personal risk for nicotine dependence can increase perceptions of relevance and motivation to not smoke. In addition, advances in neurophysiological and biological understanding of the interaction of genetic variants with nicotine dependence can help optimize cessation and treatment plans with increased specificity. Though nicotine has the power to addict any individual in this world, some people are born with a "bullet in their blood", a natural genetic predisposition that may bring them harm if allowed to manifest. By using every tool that science has produced to optimize strategic interventions to prevent and treat nicotine addiction, many more will have the opportunity to live fuller, healthier lives.

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