Published in final edited form as:

Neurosci Lett. 2018 March 16; 669: 83–92. doi:10.1016/j.neulet.2016.05.033.

Pathways to Precision Medicine in Smoking Cessation Treatments

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Abstract

Cigarette smoking is highly addictive and modern genetic research has identified robust genetic influences on nicotine dependence. An important step in translating these genetic findings is to identify the genetic factors affecting smoking cessation in order to enhance current smoking cessation treatments. We reviewed the significant genetic variants that predict nicotine dependence, smoking cessation, and response to cessation pharmacotherapy. These data suggest that genetic risks may predict smoking cessation outcomes and moderate the effect of pharmacological treatments. Some pharmacogenetic findings have been replicated in meta-analyses or multiple smoking cessation trials. The variation in efficacy between smokers with different genetic markers supports the notion that personalized smoking cessation intervention based upon genotype could maximize the efficiency of such treatment while minimizing side effects, thus influencing the number needed to treat (NNT) and the number needed to harm (NNH). In summary, as precision medicine is revolutionizing health care, smoking cessation may be one of the first areas where genetic variants identify individuals at increased risk. Genetic variants predict cessation failure, and this increased risk may be ameliorated by cessation pharmacotherapy.

Keywords

Smoking cessation; precision medicine; pharmacogenetics

1. INTRODUCTION

Cigarette smoking is a major global public health threat [1–4], and smoking cessation greatly diminishes the increased risk of mortality[3]. Nicotine dependence is a classic addictive disorder with symptoms of craving, withdrawal syndrome and heavy,

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DISCLOSURES

Dr. Bierut is listed as an inventor on Issued U.S. Patent 8,080,371, "Markers for Addiction" covering the use of certain SNPs in determining the diagnosis, prognosis, and treatment of addiction.

uncontrollable use [5]. Nicotine dependence is also manifested by both quitting difficulty [6] and a high likelihood of lapses or relapses after a quit attempt [7–10]. Therefore, identification of the factors that contribute to smoking cessation difficulties is a critical step in understanding the biology of nicotine dependence, enhancing prediction of prognosis and treatment outcomes, and informing more effective cessation treatments.

Leveraging advances in genomics and data science, the goal of precision medicine is to tailor treatments based on an individual's unique characteristics to maximize benefits and minimize side effects [11]. Growing research in understanding human genomes and identifying specific genetic markers for a disease will not only lead to improved understanding of the biology underlying the disease, but also improved clinical care. For example in clinical practice, it is common for patients to vary in efficacy or side effects to the same medication regimen such as tamoxifen for breast cancer risk reduction in patients with selected biomarkers [12]. Increasing evidence suggests that the risk benefit ratio of the medication may vary with a person's genetic makeup.

Recent research has begun to determine biomarkers (such as genotype, nicotine and metabolite levels) that may have utility in predicting smoking cessation. Use of biomarkers in smoking cessation treatments has great promise as summarized by multiple reviews [13–16]. Different pharmacokinetic and pharmacodynamic markers have been implicated in personalized therapeutic approaches including variation in Cytochrome P450 2A6 (*CYP2A6*), nicotinic acetylcholine receptor genes (*nAChRs*) and other genes based on the Genome Wide Association Study (GWAS) discovery, although the precise mechanisms underlying many of these findings remain unknown [17, 18]. For example, variants in the genes encoding the $\alpha 5$ - $\alpha 3$ - $\beta 4$ nicotinic receptor subunits show promise as a biomarker for predicting risk for developing nicotine dependence [19–22], lung cancer [23, 24], chronic obstructive pulmonary disease (COPD) [25], delayed smoking cessation [26], and possibly a differential response to pharmacologic treatment [27, 28].

Biomarkers are useful if they predict disease course or treatment outcomes. David and colleagues suggested key factors to consider when evaluating biomarkers: (1) analytical validation: determination of whether or not a biomarker is able to be measured accurately, precisely and reliably; (2) qualification: assessment of available evidence on associations between the biomarker and disease states; and (3) utilization: determination of adequate evidence to support applying the biomarker for a specific use [29]. For smoking cessation treatment, Bough and colleagues suggested 3 types of biomarkers: (1) diagnostic biomarkers, which can be used to identify the presence or absence of a specific disease state and aid in patient selection; (2) pharmacodynamics biomarkers, which can be used to report on the downstream effects of a pharmacotherapy and determining optimal dosing; (3) predictive biomarkers, which can be used to select patients who are likely to respond to therapy [30].

Opinions differ as to whether pharmacogenetic testing should be implemented in the clinic at this time because clinical utility and cost-effectiveness require further investigation. However, allowing physicians to select medications for individuals based, at least in part, on genetic factors that predispose to treatment success or failure rather than on a trial and error

basis may ultimately improve successful smoking cessation rates [31]. In the post-GWAS era, translational research from several disciplines, including behavioral science, ethics and economics, should be performed in parallel with ongoing genome-wide association studies for smoking behavior and pharmacogenetic trials. This critical step will enable translation and implementation of genetic insights into clinical practice to reduce the global burden of smoking [32].

2. Genetics of Nicotine Dependence

Multiple recent large scale genetic meta-analyses based on tens of thousands of subjects of European descent confirmed the association of 15q25.1 with smoking heaviness, defined by cigarettes per day [19–22], with the most robust associations being reported for rs16969968 and rs1051730, two highly correlated variants ($p < 5.57 \times 10^{-72}$) [21]. In the *CHRNA5-A3-B4* region, at least two independent signals have been identified [20, 33]. The first signal, tagged by rs16969968, a variant that results in an amino acid change in the $\alpha 5$ nicotinic cholinergic receptor (*CHRNA5*), alters nicotinic receptor conductance *in vitro* [34, 35]. A second, distinct signal tagged by rs680244 is associated with variability in *CHRNA5* mRNA levels [36]. Animal studies of the association between *CHRNA5* and nicotine dependence has shed light on potential biological mechanisms underlying addiction [37–39]. Individuals of European descent have one of the three common haplotypes in the region spanning *CHRNA5* and the 3' end of *CHRNA3* [33], which can be defined by these two variants: rs16969968 and rs680244 [36]. These three common haplotypes represent different risk levels of nicotine dependence: low-risk (H1, frequency 21%), intermediate-risk (H2, frequency 44%), and high-risk (H3, frequency 36%) haplotypes. The association of *CHRNA5* and heavy smoking extends from individuals of European ancestry to diverse ancestry backgrounds [40]. In a recent large meta-analysis of cigarettes per day (CPD) in 32,389 individuals of African ancestry, rs2036527 in *CHRNA5* is found as associated with heavy smoking [41].

More genome wide association studies (GWAS) examined different smoking phenotypes. Growing GWAS evidence supports *CHRNA5* as a robust top predictor for different smoking phenotypes defined as cigarettes smoked per day [19–22], nicotine dependence as defined by Fagerstrom Test for Nicotine Dependence (FTND) [42], carbon monoxide levels [43], or cotinine levels [44].

Dissection of phenotypic features associated with *CHRNA5* reveals that *CHRNA5* risk gene is associated with a smoker profile of compulsive heavy smoking with craving which is best captured by high cigarettes per day instead of a DSM diagnosis of tobacco dependence [45]. Research suggests nicotinic receptor variants are associated with greater odds of nicotine dependence according to cigarettes per day (CPD) and to a lesser extent Time to First Cigarette (TTF) [46]. It is possible different phenotypic characteristics of nicotine dependence are associated with different risk genes discovered in recent GWAS of nicotine dependence [47]. Identification of such a phenotypic cluster can be a pivotal step for further pharmacogenetic studies with specific genetic targets [48].

Additional genes (*CYP2A6* and other nicotinic receptor genes) have also been shown as associated with heavy smoking. Multiple signals are independently associated with heavy smoking and nicotine dependence. For example, variants in *CYP2A6* has been shown to predict risk for developing nicotine dependence [21, 22, 49], possibly lung cancer [50, 51] and chronic obstructive pulmonary disease (COPD) [52], delayed smoking cessation [53–55], and possibly a differential response to pharmacologic treatment [56]. Moreover, evidence suggests that a metabolic biomarker, nicotine metabolism ratio (NMR), and *CHRNA5* may have independent and additive effects on nicotine dependence [57]. A recent GWAS of a nicotine metabolism biomarker, NMR, identified variants in *CYP2A6* which explained 30% of variance in the nicotine metabolism biomarker, NMR [58].

3. Genetics of Smoking Cessation

Compared to smoking quantity as defined by cigarettes per day, smoking cessation is a much more complex behavioral phenotype, which may be defined variably as a simple contrast of former versus current smokers, age of quitting smoking, or days to relapse in a well-controlled smoking cessation trial. Using a crude phenotypic contrast (current vs. former smokers), genome wide association study of smoking cessation identified *DBH* as associated with cessation [21]. Using more refined definitions of smoking cessation such as days to relapse in smoking cessation treatment trials or age of quitting smoking, the *CHRNA5-CHRNA3-CHRNA4* variants have been shown as associated with cessation outcomes, although the level of association is not as strong as the genetic association with smoking heaviness measures. Multiple studies show an association between the *CHRNA5-CHRNA3-CHRNA4* region and successful smoking cessation [26–28, 59–64]. These studies found that the same genetic risk variants that contributed to smoking heaviness and nicotine dependence also predicted smoking cessation. Yet, other studies failed to confirm this association [65–68]. One large genome-wide association meta-analysis, that strongly supported the association between 15q25.1 and smoking heaviness, reported a modest association with current versus former smoking as a measure of smoking cessation below genome wide level of significance [21]. Uhl and colleagues [67], in a genome-wide association of three treatment cohorts, did not identify any nicotinic receptor genes as predictors of smoking cessation in smokers receiving nicotine replacement therapy. Variations in study design (with or without a placebo group), ascertainment, definitions of smoking cessation (time to relapse, abstinence, or the contrast of former vs. current smoker), and study power may explain these inconsistent findings.

3.1. *CHRNA5-CHRNA3-CHRNA4* and smoking cessation

3.1.1. *CHRNA5-CHRNA3-CHRNA4* Genetic Variants Predict lung cancer, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), and mortality—GWAS of lung cancer reveals *CHRNA5* as one of the top signals for increased lung cancer risks [23]. However, whether the risk gene exerts a direct or indirect effect via smoking on increased lung cancer risk is still unknown [24, 69, 70]. *CHRNA5* has been shown to not only predict increase in lung cancer risk, but also predict earlier age of lung cancer diagnosis [71]. In a large meta-analysis, Chen and colleagues [26] showed the clinical significance of the *CHRNA5* variant rs16969968 and that it predicts

delayed smoking cessation and an earlier age of lung cancer diagnosis. Among smokers with lung cancer diagnoses, the rs16969968 genotype (AA) was associated with a four-year earlier median age of diagnosis compared with the low-risk genotype (GG). Smokers with high-risk AA genotypes were diagnosed with lung cancer at age 61, four years earlier than age 65 for those with low-risk GG genotypes. These findings underscore the potential clinical and public health importance of rs16969968 in *CHRNA5* in relation to smoking cessation success and lung cancer risk [26]. Importantly, *CHRNA5* is also associated with chronic obstructive pulmonary disease (COPD) [25, 72], coronary artery disease (CAD) [73, 74], and increased mortality in large scale population studies [75, 76].

3.1.2. *CHRNA5-CHRNA3-CHRNA4* Genetic Variants Predict Age of Smoking Cessation—*CHRNA5-CHRNA3-CHRNA4* haplotypes have been found to be associated with age of self-reported smoking cessation in a community-based sample [27]. In a large meta-analysis, Chen and colleagues [26] showed the clinical significance of the *CHRNA5* variant rs16969968 in predicting smoking cessation. The rs16969968 genotype (AA) was associated with a four-year delay (age 52 delayed to 56) in median age of smoking cessation compared with the low-risk genotype (GG). *CHRNA5* predicts delayed smoking cessation even in special high-risk population such as patients with myocardial infarction (MI). Among patients who were ever smokers and hospitalized with acute MI, the high-risk *CHRNA5* allele was associated with lower likelihood of quitting before hospitalization and significantly less abstinence one year after hospitalization with MI. The *CHRNA5* rs16969968 genotype may therefore identify patients who would benefit from aggressive, tailored smoking cessation intervention [77].

3.1.3 *CYP2A6* and smoking cessation—Variation in nicotine metabolism, and variation in the gene that encodes the primary nicotine metabolism enzyme, cytochrome P450 2A6 (*CYP2A6*), are robustly associated with cigarette consumption [22, 78–80]. Several studies have reported an influence of nicotine metabolic rate upon cessation [53–55], although the predictive relation between nicotine metabolism and different treatment regimens remains unclear. In general, smokers who are slow nicotine metabolizers (both genetic and phenotypic) had significantly higher plasma nicotine levels and higher quit rates with both placebo and nicotine gum treatments [54, 81, 82].

4. Gene-environment Interplay of Smoking Cessation

The genetic risk association varies with potential moderators for the genetic risk such as the impact of disease/symptom, use of cessation medication, and influence of environmental risk factors. Some studies show an association between *CHRNA5* and smoking cessation [59–63], whereas other studies do not [65–67]. It is likely that the expression of this genetic risk on cessation varies with several factors, such as developing a smoking-related disease such as COPD or lung cancer [26], use of cessation pharmacotherapy [27], and environmental influences on smoking cessation such as living with a partner who smokes [83]. The effect of this genetic locus is seen most clearly in subjects who have strong environmental influences to quit smoking, no smoking-related disorder, and no use of cessation medicine. If *CHRNA5* risk alleles causes early development of smoking-related disease such as lung cancer, the disease development encourages earlier quitting than would

otherwise occur. Therefore, the genetic effect of delaying cessation is offset by its effect of accelerating disease development which may promote quitting [26]. Similarly, use of cessation pharmacotherapy may reduce the effect of *CHRNA5* on cessation difficulty since pharmacotherapy appears to alter this genetic risk [27].

5. Genetics of Smoking Cessation Treatment Response

Recent evidence suggests that the efficacy of smoking cessation pharmacotherapy can vary across patients based on their genotypes or metabolic markers.

5.1. *CHRNA5-CHRNA3-CHRNA4* predicts response to medication

Growing evidence suggests that *CHRNA5* predicts response to cessation pharmacotherapy. Sarginson and colleagues [62] conducted a pharmacogenetic analysis that showed a significant association between rs8192475 (R37H) in *CHRNA3*, higher craving after quitting, and increased withdrawal symptoms over time. They identified two markers for point prevalence abstinence, *CHRNA5* SNP rs680244 and *CHRNA4* SNP rs12914008, and provided support for the role of the *CHRNA5/A3/B4* subunits in determining number of cigarettes smoked and response to smoking cessation therapy. Munafo and colleagues [61] reported a weak association between *CHRNA5* variant and short-term smoking cessation in treatment seeking smokers, which does not seem to operate only among those receiving nicotine replacement therapy. Further, in a retrospective candidate pharmacogenetics analysis, several genes were examined with respect to different pharmacotherapies: In the treatment arm with varenicline, continuous abstinence (weeks 9–12) was associated with multiple nAChR subunit genes (including *CHRNA2*, *CHRNA5*, and *CHRNA4*). In the treatment arm with bupropion, abstinence was associated with *CYP2B6*. Incidence of nausea was associated with several nAChR subunit genes [63]. More recently, both *CHRNA4* promoter SNP rs3813567 and *CHRNA5* rs680244 genotypes were associated with both point prevalence abstinence and post-quit craving in a selegiline trial. These findings highlight the potential of *CHRNA5-CHRNA3-CHRNA4* genetic markers in identifying those likely to respond to pharmacotherapy for smoking cessation [84]. In a recent examination of a large smoking cessation trial by Chen and colleagues [27], smokers receiving cessation counseling with placebo medication, the high-risk *CHRNA5* rs16969968-rs680244 haplotype that is associated with heavy smoking predicts failed abstinence in comparison to the low-risk haplotype. Pharmacological treatment significantly increased the likelihood of abstinence in individuals with the high-risk haplotype, but exerted little effects in individuals with the low-risk haplotype. This is reflected by a significant interaction between treatment (placebo versus active treatment) and *CHRNA5* haplotypes. Across the active pharmacologic treatment conditions, these genetic variants do not predict abstinence, and this reduced genetic effect with pharmacological treatments suggests that cessation treatments differ in effectiveness across the haplotypes and most strongly mitigate the genetic risks for cessation difficulty. A subsequent meta-analysis of the Pharmacogenetics of Nicotine Addiction Treatment (PNAT) Consortium confirms a similar pharmacogenetic interaction that patient responses to nicotine replacement therapy (NRT) are moderated by *CHRNA5* genetic variants [28].

Medication efficacy is often represented by the number-needed-to-treat (NNT). The NNT is 7 when computed across all individuals regardless of their haplotype status, supporting the established effect of pharmacotherapy. However, the NNT varies widely depending on the individual's haplotype. Based on their absolute risks, the NNT is 4 for smokers with the high-risk haplotype, 7 for smokers with the intermediate-risk haplotype, and >1000 for smokers with the low-risk haplotype [27, 85]. An NNT of 4 is an impressive finding, compared to the NNT's of many existing pharmacotherapies [86–88]. The wide variation in NNT between smokers with different haplotypes supports the notion that personalized smoking cessation intervention based upon genotype, could meaningfully increase the efficiency of such treatment.

The pharmacogenetic associations could be ameliorated by different factors such as effective treatments or extremely high or low cessation rates. This is reflected in a recent meta-analysis to examine only smokers receiving nicotine replacement therapy without a control group where rs16969968 or rs1051730 showed no association with smoking abstinence [89]. In another recent trial of smokers of European ancestry, *CHRNA5-A3-B4* gene variants exhibited a trending, but not significant association with smoking cessation in smokers receiving placebo; however, there was no association with another robust predictor, nicotine metabolism ratio (NMR), in this same group [68]. In an effort to synthesize existing pharmacogenetics findings, Chen and colleagues [90] examined results from two large smoking cessation trials conducted in different institutes and demonstrated inconsistent genotypic associations in the placebo arms across these different trials. This inconsistency highlights the need to compare the most effective pharmacotherapies in the same trial with the same placebo control to establish pharmacogenetic evidence to aid decisions on medication choice for patients trying to quit smoking. In fact, interpretation of any results of pharmacogenetics analyses highlights the importance of a placebo control group in testing whether medication efficacy differ with genetic markers [91].

Pharmacogenetic evidence beyond European ancestry is important but quite limited at this time. In recent clinical trials of African Americans, Zhu and colleagues reported that *CHRNA5-A3-B4* variants influence smoking abstinence during active pharmacotherapy [64]. Medication adherence, another important predictor for cessation outcome, also has been examined for genetic associations in smokers of European ancestry. Secondary analysis of data from a pharmacogenetic smoking cessation trial showed a weak potential association between *CHRNA5* rs1051730 genotype and adherence to prescribed NRT dose [92].

5.2. Nicotine metabolism biomarkers (NMR, *CYP2A6*, *CYP2B6*) predicts response to treatment

Previous studies of nicotine metabolism and cessation treatment have examined a proxy for *CYP2A6* activity, Nicotine Metabolite Ratio (NMR), the ratio of two stable nicotine metabolites, cotinine: 3-hydroxycotinine, measured in the blood, urine, or saliva of current smokers [53–55, 93, 94]. *CYP2A6* is highly polymorphic, with reduced function alleles producing significantly slower rates of nicotine metabolism. Relatively common variants define multiple *CYP2A6* haplotypes in European populations [95], and the large majority of inter-individual variation in metabolism of nicotine to cotinine can be explained by seven

polymorphisms among European Americans [96]. Chen, Bloom, and colleagues showed that *CYP2A6*-defined nicotine metabolic function moderated the effect of smoking cessation pharmacotherapy on smoking relapse with pharmacotherapy significantly slowing relapse in fast, but not slow, metabolizers. Nicotine replacement therapy was effective amongst individuals with fast, but not slow, *CYP2A6*-defined nicotine metabolism. In contrast, the effect of bupropion on relapse likelihood was unlikely affected by nicotine metabolism as estimated from *CYP2A6* genotype [56].

Metabolic markers, rather than genetic variants, may be used to optimize treatment choice for individual smokers and to improve treatment outcomes. Lerman and colleagues examined nicotine metabolism ratio (NMR) and reported findings from a recent trial that at end of treatment, varenicline was more efficacious than nicotine patch in normal metabolizers, but not in slow metabolizers [97]. This study suggested that treating normal metabolizers with varenicline and slow metabolizers with nicotine patch could optimize quit rates while minimizing side-effects [97]. However, in this trial normal vs. slow metabolizers did not differ in abstinence, which raised concern of inconsistency with existing evidence suggesting a higher quit rate for slow metabolizers [81, 82]. Another study of a community-based sample of treatment seeking smokers who received transdermal nicotine showed that faster nicotine metabolizers were significantly less likely to quit smoking although there is no control comparison in this trial [82].

Another study of smokers who received behavioral counseling and drug therapy (bupropion, nicotine replacement therapy, and/or varenicline) showed that patients with *CYP2B6**4 (rs2279343) variant had lower success rate with bupropion. Likely, the *CYP2B6**4 variant influences the pharmacological activity of bupropion, and *CYP2B6**4 may be a genetic marker for individualized bupropion pharmacotherapy [98].

5.3. Other markers and smoking cessation treatment response

Additional genetic and imaging biomarkers reported in respect to smoking cessation treatment response requires further evidence of replication and biological investigation [99–106]. However, few of these candidate genes are present within regions of suggestive or significant linkage or overlap with genome-wide linkage or association studies of tobacco dependence or smoking cessation [107].

There have been attempts to create polygenic risk scores to predict smoking cessation or treatment response, although their variant selection is based on candidate gene studies, or subthreshold associations, and not based on genetic signals surpassing GWAS association thresholds. For example, an ‘additive genetic efficacy score’ (AGES) based on dopamine functional polymorphisms appears to predict lapse to smoking following a quit attempt [108]. Rose, Uhl, and colleagues developed quit-success genotype score based on many variants arising from pooled GWAS results in smokers receiving nicotine replacement therapy [109, 110]. Different neuroimaging markers have also been examined [111]. For example, lower pre-treatment brain nAChR density has been shown as associated with a greater chance of quitting smoking with NRT or placebo [112]. Cigarette smoking leads to upregulation of nicotinic acetylcholine receptors (nAChRs) in the human brain, including the common $\alpha 4\beta 2^*$ nAChR subtype. Smokers with less upregulation of available $\alpha 4\beta 2^*$

nAChRs have a greater likelihood of quitting with treatment than smokers with more upregulation. While the costly, time-consuming PET procedure used here is not likely to be used clinically, simpler methods for examining $\alpha 4\beta 2^*$ nAChR upregulation may be developed in the future to help determine which smokers need more intensive treatment [113].

6. Translation and Feasibility

Despite growing evidence of genetic markers as predictor of prognosis and treatment response, translation into clinical practice requires much work due to many factors such as inconsistent evidence, little data in diverse ancestry populations, lack of available CLIA-certified fast genotyping for clinical use, and need for research on cost-effectiveness [2, 14, 17, 44, 54, 114, 115]. To implement precision medicine for smoking cessation treatment, there are potential barriers. Some people remain skeptical for the value of genetic testing while proven interventions for treating tobacco dependence, including simple cost-effective measures, such as quit lines which are underutilized [116]. Furthermore, whether the use of personalized genomic information can be used to promote behavior change remains a topic of debate [117].

7. CONCLUSIONS

Multiple studies underscore the relation between the genetic markers, nicotine dependence, smoking-related diseases, and smoking cessation. First, current evidence demonstrates that smokers with the high-risk $\alpha 5$ nicotinic cholinergic receptor *CHRNA5* genotypes appear more biologically predisposed to have difficulty quitting without pharmacologic treatment and acceleration of multiple health risks including earlier mortality, and this risk may be ameliorated by effective pharmacological treatment. Second, current evidence strongly suggests a significant interaction between *CHRNA5* genotypes or nicotine metabolism ratio (NMR) and pharmacotherapy on cessation success. This evidence reveals that cessation pharmacotherapy effectiveness is modulated by these biomarkers. These findings strengthen the case for the development and rigorous testing of treatments that target patients with different biological risk profiles based on the chromosome 15q25 region that includes the genes encoding the nicotinic receptor subunits or nmetabolic biomarkers. Additional research on prospective replication of these pharmacogenetics findings in diverse populations is needed before clinical translation.

Smoking cessation pharmacotherapy such as nicotine replacement therapy (NRT), bupropion, and varenicline are moderately effective yet with side effects. Identifying genes related to responsiveness to pharmacologic treatment for nicotine addiction may lead to improved treatment algorithms that further the promise of personalized medicine [118]. Additional research on related topics such as epigenetic markers and personalized risk communication is also needed in the future. To implement precision medicine for smoking cessation treatments, we need collaborative, prospective research on pharmacogenetics, well-designed meta-analyses of diverse populations, cost-effectiveness analyses, and useful polygenetic risk scores linked to clinical indicators such as number needed to treat (NNT) in order to match smokers with treatments of maximal efficacy and minimal side effects.

Acknowledgments

The authors thank Nina Smock for the assistance in project coordination and editing/preparing the manuscript.

FUNDING SUPPORT

This research was supported by R01 DA038076, and K08 DA030398 (LSC) from the National Institute on Drug Abuse, and sub-award KL2 RR024994 (LSC) from the National Center for Research Resources. Dr. Bierut (LJB) is supported by National Institute on Drug Abuse grant R01DA036583 and National Cancer Institute grant P30CA091842.

Abbreviations

AGES	Additive genetic efficacy score
CAD	Coronary artery disease
CHRNA5	$\alpha 5$ nicotinic cholinergic receptor
COMT	Catechol-O-methyltransferase
COPD	Chronic Obstructive Pulmonary Disease
CPD	Cigarettes per day
CYP2A6	Cytochrome P450 2A6
FTND	Fagerstrom Test for Nicotine Dependence
GWAS	Genome Wide Association Study
MI	Myocardial infarction
nAChRs	Nicotinic Acetylcholine Receptor Genes
NMR	Nicotine metabolism ratio
NNT	Number Needed-To Treat
NNH	The Number Needed To Harm
NRT	Nicotine replacement therapy
PNAT	Pharmacogenetics of Nicotine Addiction Treatment
TTF	Time to First Cigarette

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Highlights

- Genetic research has identified robust genetic influences on nicotine dependence
- These same genetic risk factors that influence the development of nicotine dependence are the strongest risk factors for the development of lung cancer and chronic obstructive pulmonary disease.
- Genetic research has identified prognostic predictor for cessation failure
- Genetic research has identified predictors for response to treatment
- Tailored cessation treatments may reduce side effects and increase cessation success