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Genomics and personalized medicine: *CHRNA5-CHRNA3-CHRNB4* and smoking cessation treatment

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A B S T R A C T

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 review the significance of variants in the nicotinic receptor gene cluster (*CHRNA5–CHRNA3–CHRNB4*) in the prediction of smoking quantity, smoking cessation, and response to cessation medication in multiple studies of smoking cessation. Three common haplotypes (low-risk, intermediate-risk, and high-risk) in the *CHRNA5–CHRNA3–CHRNB4* region are defined by rs16969968 and rs680244. The genetic variants in the *CHRNA5–CHRNA3–CHRNB4* region that predict nicotine dependence also predicted a later age of smoking cessation in a community-based sample. In a smoking cessation trial, these variants predicted abstinence at the end of treatment in individuals receiving placebo medication, but not among individuals receiving active medication. Pharmacological treatments moderate the genetic risk in affecting cessation success. These pharmacogenetic interactions have been reproduced by a recent meta-analysis of smoking cessation trials. The number needed to treat was four for smokers with the high-risk haplotype, seven for smokers with the intermediate-risk haplotype, and $>$ 1000 for smokers with the low-risk haplotype. The wide variation in number needed to treat between smokers with different haplotypes supports the notion that personalized smoking cessation intervention based upon genotype could meaningfully increase the efficiency of such treatment. In summary, variants in the *CHRNA5–CHRNA3–CHRNB4* region identify individuals at increased risk of cessation failure, and this increased risk can be ameliorated by cessation pharmacotherapy.

1. Introduction

Cigarette smoking is a major global public health problem. Nicotine dependence is a classic addictive disorder with symptoms of craving, withdrawal syndrome, and heavy, uncontrollable use [1]. Nicotine dependence is also manifested by both quitting difficulty [2] and a high likelihood of lapses or relapses after a quit attempt [3–6]. Therefore, identification of

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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.

Genomic research can lead to personalized medicine [7]. 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. In clinical practice, it is common for different patients to show different efficacy or side effects with the same medication regimen, such as tamoxifen for breast cancer risk reduction in patients with selected biomarkers [8]. Increasing evidence suggests that the risk/benefit ratio of the medication may vary with a person's genetic makeup. The goal of personalized medicine is to tailor treatments for each patient to maximize benefits and minimize side effects.

2. Genetics of nicotine dependence

Multiple, recent, large genetic meta-analyses based on tens of thousands of individuals of European descent have confirmed the association of 15q25.1 with smoking heaviness, defined by cigarettes per day [9–12], with the most robust associations being reported for rs16969968 and rs1051730; two highly correlated variants ($p < 5.57 \times 10^{-72}$) [11]. In the *CHRNA5–CHRNA3–CHRNB4* region, at least two independent signals have been identified [10,13]. The first signal tagged by rs16969968, a variant that results in an amino acid change in the α5 nicotinic cholinergic receptor (*CHRNA5*), alters nicotinic receptor conductance *in vitro* [14,15]. A second, distinct signal tagged by rs680244 is associated with variability in *CHRNA5* mRNA levels [16]. Individuals of European descent have one of the three common haplotypes in the region spanning *CHRNA5* and the 3′ end of *CHRNA3* [13], which can be defined by these two variants: rs16969968 and rs680244 [16]. These three haplotypes represent different risk levels of nicotine dependence: low-risk (H1, 21%), intermediate-risk (H2, 44%), and high-risk (H3, 36%) haplotypes.

3. Genetics of smoking cessation

The *CHRNA5–CHRNA3–CHRNB4* variants have been less consistently associated with cessation outcomes than with smoking heaviness measures. Five studies have shown an association between the *CHRNA5–CHRNA3–CHRNB4* region and successful smoking cessation [17–21]. All five found that the same genetic risk variants that contribute to smoking heaviness and nicotine dependence also predicted smoking cessation. Yet, other studies failed to confirm this association [22–24]. Uhl et al [24], in a genome-wide association of three treatment cohorts, did not identify any nicotinic receptor genes as predictors of prospectively measured smoking cessation. 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 [11]. Variations in study design (with or without a placebo group), ascertainment, and definitions of smoking cessation (time to relapse, abstinence, or the contrast of former vs. current smoker) may explain these inconsistent findings.

3.1. *CHRNA5–CHRNA3–CHRNB4 genetic variants predict age of smoking cessation*

CHRNA5–CHRNA3–CHRNB4 haplotypes were associated with age of self-reported smoking cessation in a community-based

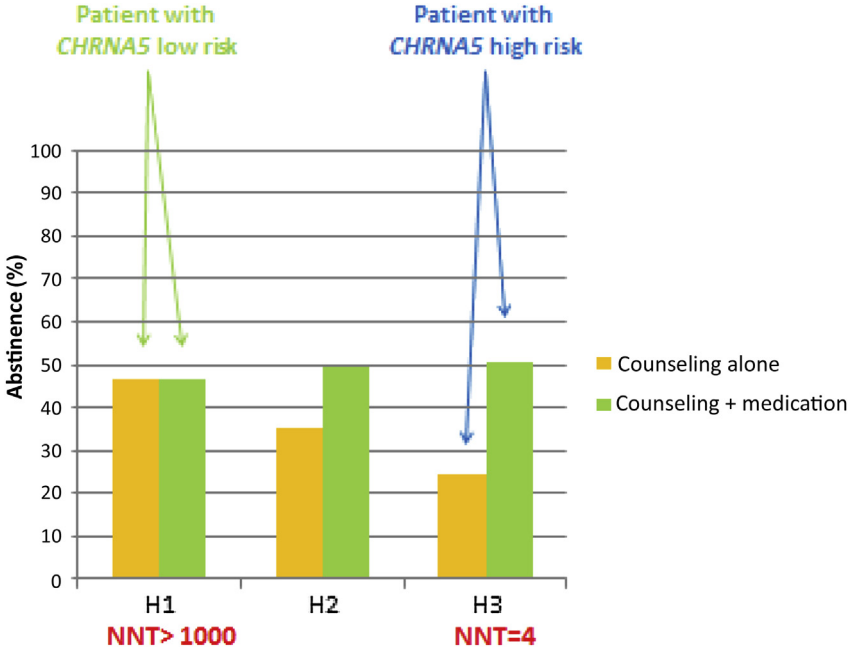

Fig. 1 – *CHRNA5* predicts smoking cessation and response to medication: number needed to treat (NNT) varies with haplotypes. H1 = G_C (20.8%); H2 = G_T (43.7%); H3 = A_C (35.5%). NNT = number of patients to treat for one to benefit.

sample [25]. Compared to the low-risk haplotype (H1), the high-risk haplotype (H3) was associated with a later quitting age. The median age of smoking cessation was 57 years for those with haplotype H3, and 55 years for those with haplotypes H2 and H1. This study showed that the genetic variants in the chromosome 15q25 region that predicted heavy smoking and nicotine dependence also predicted a later age of smoking cessation in a large community-based sample. Those with the high-risk genetic variants quit later than those at low genetic risk, manifested as a 2-year delay in median quit age.

3.2. *CHRNA5–CHRNA3–CHRNB4 genetic variants predict smoking relapse and response to medication*

In a large smoking cessation trial of smokers receiving cessation counseling with placebo medication, the high-risk haplotype (H3) that was associated with heavy smoking predicted failed abstinence in comparison to the low-risk haplotype (H1) [25]. Pharmacological treatment significantly increased the likelihood of abstinence in individuals with the high-risk haplotype (H3) but exerted little effect in individuals with the low-risk haplotype (H1). This was reflected by a significant interaction between treatment (placebo vs. active treatment) and haplotypes (Fig. 1). Across the active pharmacological 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 mitigates the genetic risks for cessation difficulty [26]. A recent meta-analysis of the Pharmacogenetics of Nicotine Addiction Treatment (PNAT) Consortium reported a similar pharmacogenetic interaction, in that patient responses to nicotine replacement therapy (NRT) were moderated by *CHRNA5* genetic variants [27].

Medication efficacy is often represented by the number needed to treat (NNT) [25]. The NNT is seven 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 four for smokers with the high-risk haplotype, seven for smokers with the intermediate-risk haplotype, and $>$ 1000 for smokers with the low-risk haplotype. An NNT of four is an impressive finding, compared to the NNTs of many existing pharmacotherapies [28–30]. 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.

4. Conclusions

Multiple studies have underscored the relation between the targeted haplotypes, nicotine dependence, and smoking cessation. There is a significant interaction among these *CHRNA5–CHRNA3–CHRNB4* haplotypes and treatment on cessation success, and this reveals that cessation treatment effectiveness is modulated by the haplotypes. These findings strengthen the case for the development and rigorous testing of treatments that target patients with different genetic risk profiles based on the chromosome 15q25 region that includes the genes encoding the nicotinic receptor subunits. Those with the high/intermediate-risk haplotypes appear more biologically predisposed to having difficulty quitting without pharmacological treatment, and this risk may be ameliorated by effective pharmacological treatment. Smoking cessation pharmacotherapy such as NRT, bupropion, and varenicline is moderately effective, yet it does have side effects. Identifying genes related to responsiveness to pharmacological treatment for nicotine addiction may lead to improved treatment algorithms that further the promise of personalized medicine [31].

Disclosure of conflicts of interest

Dr. Bierut is an inventor on the patent "Markers for Addiction" (US 20070258898) covering the use of certain SNPs in determining the diagnosis, prognosis, and treatment of addiction. Dr. Chen declares no potential conflict of interest.

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