

Genetic risk, nicotine dependence, and the clinical benefit of cessation pharmacotherapy

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Background: Recent meta-analyses show that genetic variants have been associated with nicotine dependence. We tested whether or not composite of these variants could ascertain the risk of nicotine dependence, delayed smoking cessation, and identify individuals who derive greater clinical benefit from cessation pharmacotherapy.

Methods: A community-based study (N=5,155) and a randomized controlled trial (N=1,084) were included in analyses. We studied the association of a genetic risk score based on multiple GWAS-level genetic variants (*CHRNA5*, *DNMT3B*, *CHRNA4*, *CYP2A6*) with nicotine dependence. We then examined their effects on smoking cessation (self-reported quit age in a community study and point-prevalence abstinence at end-of-treatment in a clinical trial) and response to pharmacotherapy.

Results: The *DNMT3B* variant rs910083 that predicts nicotine dependence also predicts a later age of smoking cessation in a community-based sample (HR=0.95, p=0.048). In the smoking cessation trial, the same variant predicts abstinence at end-of-treatment in individuals receiving placebo medication, but not amongst individuals receiving active medication. The genetic variant interacts with treatment in affecting cessation success ($X^2=7.67$, df=1, p=0.0056). When we combined multiple GWAS-level variants, the genetic scores predict a later age of smoking cessation in a community-based sample ($X^2=8.46$, df=2, p=0.015), and interact with treatment in affecting cessation success ($X^2=15.0$, df=1, p=0.00011). Specifically, the number needed to treat was >1000 in people with low genetic risk, and 20 in those with intermediate genetic risk, and 2.5 in those with high genetic risk.

Conclusions: Smokers with the *DNMT3B* high risk genetic variants have an increased likelihood of responding to pharmacologic cessation treatments, compared to smokers with the low risk genetic variants. People with the highest burden of genetic risk derive the largest relative and absolute clinical benefit from cessation pharmacotherapy. The high-risk genetic scores increase the risk of cessation failure, and this increased risk can be ameliorated by cessation pharmacotherapy.

Keywords: smoking cessation, pharmacogenetics, nicotine dependence