Genome-wide meta-analysis identifies seven novel susceptibility signals for nicotine dependence

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Abstract

Background: Nicotine dependence (ND) has a reported heritability of 40–70%. Genome-wide association (GWA) studies have detected multiple loci associated with ND that in aggregate account for a small fraction of the measured heritability.

Method: Low-coverage whole-genome sequencing was implemented in 1,889 samples from the UCSF Family Alcoholism study. Samples in the UCSF Family Alcoholism study and five GWA data sets through the database of Genotypes and Phenotypes (dbGaP) were categorized into genetically homogeneous groups of 14,713 European (EUR, 8,215 cases and 6,498 controls) and 3,369 African subjects (AFR, 1,869 cases and 1,500 controls) using principal component analysis of typed markers. We applied a mixed linear model to implement a genome-wide association test in each data set for ND. Inverse-variance fixed-effects meta-analysis was carried out in the EUR, AFR, and merged cohorts. We searched for rare nonsynonymous variants in the implicated loci and their aggregative effect on ND risk in the UCSF Family Alcoholism study.

Results: This study confirmed five previously reported ND susceptibility loci including the *CHRNA5-CHRNA3-CHRNB4* gene cluster region on chromosome 15. In addition, seven novel putative susceptible signals were detected: rs56247223 in the intron of *CACNA2D3* gene (odds ratio (OR) = 0.93, $P = 4.11 \times 10^{-8}$, with a minor allele frequency (MAF) = 32%) in the AFR cohort. The protective allele of rs56247223 is associated with reduced expression of the *CACNA2D3* gene expression in three human brain tissues ($P < 4.94 \times 10^{-2}$). A rare nonsynonymous variant in the *CACNA2D3* gene conferred an increased risk for ND in the UCSF Family Alcoholism study (c.C1604T, MAF = 0.16%, OR = 3.66, P = 0.01) providing further support for a role of *CACNA2D3* in ND. Six potential susceptibility loci were discovered in

the EUR and merged meta-analysis ($P < 5.00 \times 10^{-6}$). These susceptibility signals regulated the mRNA expression levels of genes *HAX1, CHRNB2*, *ADAMTSL1, PEX2, GLIS3,* and non-coding RNA *LINC00476* in human brains ($P < 0.05$). Three rare nonsynonymous variants in *HAX1, PEX2* and *GLIS3* were significantly associated with the risk of ND in the UCSF Family study ($P<0.05$). Rare nonsynonymous variants in the *HAX1* gene showed an aggregative risk effect in ND cases (gene-based association test $P = 2.80 \times 10^{-2}$). The study revealed the role of the *GABBR1* gene in the biology of ND in both single variant (rs56020557, MAF = 6%, OR = 1.05, $P = 4.50 \times 10^{-6}$ in EUR samples; rs62392942, OR = 1.06, $P = 1.28 \times 10^{-6}$ in the merged samples) and gene-base associations ($P = 6.36 \times 10^{-7}$).

Conclusions: These findings shed light on the biology of ND and the genes at the identified loci may be potential therapeutic targets for the treatment and prevention of ND.

Keywords:

Nicotine dependence; genome-wide meta-analysis; susceptibility genes; expression quantitative trait locus; nonsynonymous variants