Combined genetic influence of the nicotinic receptor gene cluster *CHRNA5/A3/B4* on nicotine dependence

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Background: The *CHRNA5/A3/B4* gene locus is associated with nicotine dependence and other smoking related disorders. While the non-synonymous *CHRNA5* variant rs16969968 appears to be the main risk factor, linkage disequilibrium (LD) blocks in the cluster under evolutionary selection carry frequent variants that regulate expression of the genes in the cluster. Previously reported, interactions between *CHRNA5* and *CHRNA3* enhancer haplotypes (tagged by rs880395 and rs1948, respectively) and rs16969968 cause combined effects on nicotine dependence that are significantly different compared to rs16969968 alone [1]. Here we address further contributions by variants affecting *CHRNB4*.

Results: We identify a fourth LD block (tagged by rs4887074) that regulates expression of *CHRNB4*, a possibly limiting component of nicotinic receptors, and evaluate the effect of rs4887074 on nicotine dependence singly as well as combined with rs880395/rs16969968/rs1948. Additive logistic regression models indicate that rs4887074 is associated with nicotine dependence and modulates the effect of rs16969968 in GWAS datasets (COGEND, UW-TTURC, SAGE). Haplotype and diplotype analyses of the four variants reveal a pattern of nicotine dependence risk for individuals that further differentiate those obtained with rs16969968 alone or in combination with rs488035 and rs1948. Moreover, both rs16969968 and rs4887074 represent significant variance QTLs, supporting the hypothesis that they interact with other variants, genes, or other factors in an allele-specific fashion.

Conclusions: These results indicate that genetic variants in a gene cluster region under evolutionary constraints must be considered jointly for accurate analysis of genetic influence on complex traits in individuals. Supported by NIH grant U01 GM092655

[1] ES Barrie, et al. The *CHRNA5/CHRNA3/CHRNB4* nicotinic receptor regulome: genomic architecture, regulatory variants, and clinical associations. Human Mutation 38:112 (2016).