Variants Weakly Correlated with CHRNA5 D398N Polymorphism Should be Considered in Transcriptional Deregulation at the 15q25 Locus Associated with Lung Cancer Risk

To the Editors: A recent article by Falvella et al. (1) reports a significant up-regulation of CHRNA5 transcript levels in lung adenocarcinomas, a confirmation of an association between the CHRNA5 D398N variant and lung cancer risk, and an association of the D398N variant (rs16969968) with CHRNA5 mRNA levels in lung tissue. This study highlights the candidacy of CHRNA5 as the 15q25 locus associated with lung cancer risk. The authors reported that CHRNA5 mRNA levels are up-regulated 30-fold in lung adenocarcinoma compared with normal lung tissue and that CHRNA5 mRNA levels were about 2.5-fold lower in individuals homozygous for the risk allele (N398) compared with individuals homozygous for the nonrisk allele. However, there is insufficient evidence to conclude that the risk allele of the D398N variant is biologically associated with higher CHRNA5 mRNA expression in lung adenocarcinoma. Our work provides evidence for two distinct biological mechanisms altering the risk related to developing nicotine dependence and lung cancer. One mechanism involves the variant rs16969968 (D398N), which likely alters protein structure and receptor function in vitro (2). A second potential mechanism is altered mRNA expression of CHRNA5. In our study using human brain tissue, we showed that several variants located upstream of the coding region of CHRNA5 (i.e., rs588765) are much more strongly associated with the variability in CHRNA5 mRNA expression observed in human frontal cortex than rs16969968 (3, 4). Subjects homozygous for the minor allele of rs588765 showed a 2.9-fold increase in CHRNA5 mRNA expression compared with subjects homozygous for the major allele (3, 4). The polymorphism rs588765 and highly correlated variants are only weakly correlated with the D398N variant. Using diplotype analysis, we observed that the variant N398, which greatly increases risk for nicotine dependence and lung cancer, primarily occurs on the background of low mRNA expression of CHRNA5. The nonrisk variant D398 occurs on both high and low expression alleles. When D398 occurs on the background of low CHRNA5 mRNA expression, the risk for nicotine dependence and lung cancer is significantly lower compared with those with the high CHRNA5 mRNA expression (4). Thus, for an optimal translational application of their findings, variants tagged by rs588765 are recommended in further testing of the association observed between the D398N variant and CHRNA5 mRNA levels in lung tissue.

Jen C. Wang
Laura J. Bierut
Alison M. Goate
Department of Psychiatry,
Washington University School of Medicine,
St. Louis, Missouri

Disclosure of Potential Conflicts of Interest

Drs. L.J. Bierut, A.M. Goate, and J.C. Wang are listed as inventors on a patent (US 20070258898) held by Perlegen Sciences, Inc., covering the use of certain single nucleotide polymorphisms in determining the diagnosis, prognosis, and treatment of addiction. Dr. Bierut has acted as a consultant for Pfizer, Inc., in 2008.

References
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Jen C. Wang, Laura J. Bierut and Alison M. Goate


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