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Titel des Beitrags: Risk gene variants for nicotine dependence in the CHRNA5-CHRNA3-CHRNB4 cluster are associated with cognitive performance.

Abstract: Recent studies strongly support an association of the nicotinic acetylcholine receptor gene cluster CHRNA5-CHRNA3-CHRNB4 with nicotine dependence (ND). However, the precise genotype-phenotype relationship is still unknown. Clinical and epidemiological data on smoking behavior raise the possibility that the relevant gene variants may indirectly contribute to the development of ND by affecting cognitive performance in some smokers who consume nicotine for reasons of "cognition enhancement." Here, we tested seven single nucleotide polymorphisms (SNPs) rs684513, rs637137, rs16969968, rs578776, rs1051730, rs3743078, rs3813567 from the CHRNA5-CHRNA3-CHRNB4 gene cluster for association with ND, measures of cognitive performance and gene expression. As expected, we found all SNPs being associated with ND in three independent cohorts (KORA, NCOOP, ESTHER) comprising 5,561 individuals. In an overlapping sample of 2,186 subjects we found three SNPs (rs16969968, rs1051730, rs3743078) being associated with cognitive domains from the Wechsler-Adult-Intelligence Scale (WAIS-R)—most notably in the performance subtest "object
assembly" and the verbal subtest "similarities." In a refined analysis of a subsample of 485 subjects, two of these three SNPs (rs16969968, rs1051730) were associated with n-back task performance/Continuous Performance Test. Furthermore, two CHRNA5 risk alleles (rs684513, rs637137) were associated with CHRNA5 mRNA expression levels in whole blood in a subgroup of 190 subjects. We here report for the first time an association of CHRNA5-CHRNA3-CHRNB4 gene variants with cognition possibly mediating in part risk for developing ND. The observed phenotype-genotype associations may depend on altered levels of gene expression. © 2010 Wiley-Liss, Inc.