Analysis of genotyped and imputed variants in the nicotinic receptor subunit genes outside CHRNA5-CHRNA3-CHRNB4 for association with nicotine dependence

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Abstract

Nicotine Dependence (ND) is identified as a complex disease and also a leading predictor of smoking continuation. Previous studies have shown distinct genetic variants in the CHRNA5-CHRNA3-CHRNB4 region on chromosome 15 that can affect the risk for develop ND in both European-Americans (EA) and African-Americans (AA). Since the family of nicotinic acetylcholine receptors (nAchRs) is considered to be a major target for nicotine in the brain, it is important to investigate gene regions in the nAchRs family outside of chromosome 15 that contain signals which are associated with ND. We hypothesized that there are single nucleotide polymorphisms associated with ND outside the CHRNA5-CHRNA3-CHRNB4 region on chromosome 15.

To evaluate this hypothesis, we carried out a case-control single-SNP association analysis in EA and AA separately by logistic regression with gender as a covariate. We analyzed 176 SNPs covering the rest of the 13 members of the nAchRs family in a sample of 2047 European-Americans (EA) and 710 African-Americans (AA). ND cases were defined by FTND $\geq 4$ while controls were FTND=0 in EA and FTND= 0 or 1 in AA. There were total of 1055 cases in EA and 461 cases in AA. We performed imputation to further evaluate two regions, CHRND-CHRNG on chromosome 2 and CHRNB3-CHRNA6 on chromosome 8, based on the presence of significantly associated SNPs from previous results.

We had 36 hits out of the 176 genotyped SNPs on chromosome 2, 8, 17, and 20 that were nominally significant with p-value less than 0.05 in EA. Rs13277254 on CHRNB3, chromosome 8, is the most significant signal for EA population. On the other hand, there are 6 hits nominally significant in AA on chromosome 2, 11, and 15. Rs1881492 in the CHRNG region is the only one which is nominally significant in both EA (p-value=0.0025) and AA (p-value=0.0035), however, the odds ratios in the two populations are in opposite directions (OR=0.7813(0.6683-0.9176) for EA and 1.552(1.155-2.084) for AA with 95% CI). Our analysis has raised attention of other signals associated with ND outside CHRNA5-CHRNA3-CHRNB4 region and it will be useful suggestive information for further follow up research.