Association and Linkage Analysis of Nicotine Dependence from Whole Genome Sequencing of Family Data Suggest a Novel Role for BBS5

Chris Bizon(a), Ian Gizer(b), Cindy Ehlers (c), and Kirk C Wilhelmsen (a,d)

(a) Renaissance Computing Institute, University of North Carolina at Chapel Hill
(b) Department of Psychological Sciences, University of Missouri
(c) Department of Molecular and Cellular Neurosciences, The Scripps Research Institute
(d) Department of Genetics, University of North Carolina at Chapel Hill

While genetic epidemiology shows that nicotine dependence is considerably heritable, only a small fraction of the expected genetic variance has been uncovered by single-marker GWAS studies. We collected low-coverage whole genome sequencing data on 1832 individuals from 713 families from the UCSF Family Alcoholism Study, a collection of families that are enriched for alcohol and other drug use. Individuals were assessed for nicotine dependence using the SSAGA instrument. Variants were called from this data using Thunder, a linkage-disequilibrium-aware variant caller. As expected, single-marker analysis of nicotine dependence in this data set using EMMAX found no significant results. We employed a novel genetic algorithm to calculate IBD sharing within families from the whole genome sequences; the IBD sharing was validated using previous microsatellite data. Using the calculated IBD sharing, we used SOLAR to calculate linkage for nicotine dependence, confirming a previously identified peak on chromosome 2, containing over 100 genes. In addition we calculated gene-based association for all genes in the genome using the variable threshold family analytic method as implemented in the rvtool package. The gene with the best score in this analysis is BBS5, and it is located under the linkage peak found with SOLAR. BBS5 plays a role in growing and maintaining cellular cilia, with variants known to cause Bardet-Biedl syndrome, a ciliopathy affecting multiple systems.