A Genome-wide association meta-analysis of the nicotine metabolite ratio and five other smoking related traits in smokers of European descent

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Smoking behaviour is influenced by the nicotine metabolism rate, which varies among individuals and is highly heritable. We present the largest (N=5185) genome-wide association study (GWAS) to date of a biomarker of nicotine metabolism rate, the nicotine metabolite ratio (NMR, ratio of 3-hydroxycotinine to cotinine). Among Finnish, North American and Australian smokers, we also ran GWASs for two self-reported tobacco exposure measures (cigarettes smoked per day (CPD) and pack-years (CPD x years smoked)), two objective exposure biomarkers (plasma cotinine (Cot), and a more sensitive biomarker constructed as the sum of cotinine and 3-hydroxycotinine (Cot+3HC)), and one biomarker of smoking intensity (Cot/CPD). Cot and 3HC were determined by liquid chromatography/mass spectrometry. To our knowledge, these represent the first GWASs of Cot/CPD and Cot+3HC. In total, we found 1902 genome-wide significant SNPs located in six distinct loci. For NMR the chr 19 top SNP, rs56113850, was in CYP2A6 (p=5*E-259) and the chr 4 top SNP, rs34638591, in TMPRSS11E (p=1*E-10). The total phenotypic variance explained by the top SNPs was 24.8% for NMR, 4.8% for cotinine and 4.6% for COT+3HC. We found 6-13 SNPs with a direct effect on the NMR via fine-mapping analyses with GCTA and FINEMAP (www.christianbenner.com). The chr 4 association for NMR is novel, and TMPRSS11E has previously only been reported in GWASs of corpuscular haemoglobin and volume. This is also the first GWAS to find associations for addiction phenotypes in CNN3, TENM2 and SMARCA2, among others. Our study reveals novel genetic loci associated with smoking-related traits.