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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.