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Supplementary Methods

Nicotine Dependence (ND) Study Descriptions, Quality Control (QC), and 1000 Genomes (1000G) Imputation

Our study included European (EUR) and African American (AA) ancestry ever smokers from 23 independent studies. Data were contributed by original study investigators or obtained via the database of Genotypes and Phenotypes (dbGaP). Fifteen of the studies (total N=38,062) were included in our prior genome-wide association study (GWAS) meta-analysis of ND.[1] The present study included the same sample size for 10 prior studies, an updated size for 5 of the prior studies, and 8 newly added studies. Additional details of each study are provided below and in **Supplementary Table 3**. As before,[1,2] ever smokers were defined by having reported smoking 100 or more cigarettes in their lifetime, unless otherwise stated, and ND was defined by the Fagerström Test for Nicotine Dependence (FTND).[3]

Our standard QC pipeline was applied to each study, unless otherwise stated. All studies were imputed to 1000G phase 3, except for deCODE as detailed below. Participants were removed due to missing rate >3%, sample duplication (identity-by-state >90%), first-degree relatedness (identity-by-descent >40%), gender discordance (F_{st} <0.2 for chromosome X single nucleotide polymorphisms (SNPs) to confirm females and F_{st} >0.8 to confirm males), excessive homozygosity (F_{st} >0.5 or F_{st} <-0.2), or chromosomal anomalies. SNPs were removed due to missing rate >3% or Hardy-Weinberg equilibrium (HWE) $P<1\times10^{-4}$. Genotyped SNPs passing QC were used as input for imputation with reference to 1000G phase 3 across all studies,[4] unless otherwise stated.

African American Nicotine Dependence (AAND). The community-based AAND study was designed to compare nicotine dependent smokers with smokers who never developed ND symptoms. Recruitment focused on AAs from the Chicago area between 2010 and 2013.

Participants reported smoking >100 cigarettes during their lifetime, and their ND was assessed using the FTND. Genotyping was performed on the Illumina Omni Express array. Following standard QC, the final analysis data set included 1,687 AAs with complete data on lifetime FTND (i.e., FTND based on when they reported smoking the most) and covariates—age, sex, and principal component (PC) eigenvectors. PC eigenvectors were computed to remove any residual bias due to population stratification.

Alcohol Dependence in African Americans: A Case-Control Genetic Study (ADAA). Data for the ADAA study were collected between 2009 and 2013. Alcohol dependent cases, who met Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition (DSM-IV) criteria as assessed using a modified version of the Semi-Structured Assessment for the Genetics of Alcoholism, were recruited from treatment centers in St. Louis, Missouri. Alcohol dependent controls, who had consumed at least 12 alcohol beverages in their lifetime but did not meet DSM-IV criteria for alcohol abuse or dependence, were recruited from households in neighborhoods located in proximity to neighborhoods where the alcohol dependent cases resided. Participants were genotyped on a custom array that is based on an Illumina HumanOmniExpressExome background, and QC steps were applied with procedures that largely mimic our standard QC, excluding participants with call rate >1%, gender discrepancy, ancestry discrepancy, chromosomal anomalies, duplicate samples, or first-degree relatives and excluding SNPs with call rate >2%, no mapping, >2 discordant calls in duplicated samples, >5 discordant calls at the same position, or HWE $P<1\times10^{-4}$. The ND GWAS analysis included 1,145 current and former smokers, and covariate adjustments were made for age, sex, alcohol dependence (DSM-IV), cocaine dependence (DSM-IV), and PC eigenvectors.

Collaborative Genetic Study of Nicotine Dependence (COGEND and COGEND2). AAND was modeled after its predecessor, COGEND. Beginning in 2001, COGEND compared nicotine dependent smokers to smokers who never developed dependences symptoms.[5] Participants included EURs and AAs, who were aged 25 to 44 years old and recruited from St. Louis and Detroit. The FTND was administered to determine study eligibility as either nicotine dependent cases (current smokers who reported an FTND score of $\geq$4) or controls (smokers who reported >100 cigarettes during their lifetime but reported an FTND score $\leq$1). Participants were genotyped on either the Illumina Human1M-Duo array as part of the Study of Addiction: Genetics and Environment (SAGE)[6] or the Illumina HumanOmni2.5 array as part of the Gene Environment Association Studies Initiative (GENEVA).[7] The genotyping data are available via dbGaP accession numbers phs000092.v1.p1 and phs000404.v1.p1, respectively. We retained genotyped SNPs surpassing call rate >98% and HWE $P \geq 1 \times 10^{-4}$ thresholds in each subset, combined the subsets, removed duplicated participants and first-degree relatives, and retained only the SNPs genotyped at the intersection of the different arrays to circumvent potential bias.[8] After applying standard QC on the combined COGEND subsets, the final dataset included 1,935 EAs and 704 AAs with lifetime FTND scores and covariates (age, sex, and PC eigenvectors) for analysis.

Our analyses also included COGEND2 participants who were recruited more recently (2011–2014) following the COGEND study design. COGEND2 participants were genotyped on the Illumina Omni Express array, alongside the AAND participants, but analyzed separately. Following standard QC, there were 292 EURs and 313 AAs from COGEND2 for analysis with lifetime FTND scores and covariates (age, sex, and PC eigenvectors).

Center for Oral Health Research in Appalachia 1 (COHRA1)

COHRA1 was primarily designed to conduct GWAS analyses of dental caries,[9] as one contributing site of a four-site study. COHRA1 was the only site that collected FTND data. COHRA1 recruited families beginning in 2003 from Appalachian regions: four rural counties (West Virginia and Pennsylvania) and an urban area. Eligible families included at least one adult and one biological child residing in the same household. We obtained COHRA1 genotyping data, as assayed on the Illumina Human610 array, via dbGaP accession number phs000095.v2.p1. We obtained FTND phenotype data from the original study investigators. When FTND data were available on parent(s) and children, we selected a single person from each relative pair/cluster based on the following criteria: (1) FTND data availability and (2) highest call rate if more than one relative had FTND data available. Following standard QC, we retained 243 EAs with current FTND scores and covariates (age, sex, and PC eigenvectors) for our final analysis dataset. Twelve of the participants were <18 years old.

Chronic Obstructive Pulmonary Disease Gene (COPDGene and COPDGene2)

COPDGene is a longitudinal observational study of COPD with participants ascertained at multiple centers across the United States.[10] Participants, aged 45 to 80 years old, reported a current or former history of smoking and 10 or more cigarette pack-years. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria were used to stage disease severity among COPD cases based on their post-bronchodilator pulmonary function measures: GOLD = 1–2 for mild cases and 3–4 for moderate/severe cases. COPD controls had pulmonary function measures in the normal range for their sex, age and height. Acute and chronic respiratory disease, cancer and other conditions were used as exclusion criteria.

Our prior GWAS included 2,211 Non-Hispanic white (henceforth referred to as EUR) and 2,115 AA current smokers with current FTND data available from the baseline examination and with a determinant COPD case/control status.[1] For the present study, we added participants from the same examination with current FTND data available and an indeterminant COPD status (GOLD = -1). Together, we included 2,549 EUR and 2,534 AA current smokers from the baseline examination (denoted COPDGene1).

In a further expansion of COPDGene for the present study, we included participants who were not captured in COPDGene1 but had lifetime FTND data collected as part of the phase 2 follow-up examination (denoted COPDGene2; total N=2,630 EURs and 267 AAs). COPDGene2 comprised mostly former smokers but some current smokers, who had missing FTND at the baseline examination. Both COPDGene1 and COPDGene2 participants were genotyped on the Illumina HumanOmni1-Quad array and made available via dbGaP accession number phs000765.v1.p2. We conducted QC, imputation, and GWAS analysis for each ancestry in each of the two study phases, separately. Covariates for the GWAS analysis included age, sex, GOLD stage (-1 for indeterminant status, 1 or 2 for mild cases, and 3 or 4 for moderate/severe cases, with 0 for controls as the reference category), and PC eigenvectors.

deCODE**.** deCODE Genetics is a large population-based study from Iceland with data collection spanning 1996 to 2014. It was approved by the Data Protection Commission of Iceland and the National Bioethics Committee of Iceland. Participants were originally recruited to conduct genetic studies of smoking-related and a range of other phenotypes along with population controls. Personally identifiable information that was associated with phenotypic information and blood samples were encrypted by a third-party system.[11] Collection of smoking

data has been described elsewhere.[12] Briefly, questionnaires were used to gather data on cigarettes per day (CPD) and the other FTND items.

Our prior ND GWAS meta-analyses included 9,090 smokers from deCODE.[1,2] The present analysis used an expanded sample size of 15,312 smokers using new smoking data collected in deCODE. Participants were genotyped on Illumina SNP arrays, and QC was applied as described before.[13] The ND definitions mimicked our prior analyses,[1,2] whereby mild dependence included smokers with lifetime FTND data (here, N=6333) as well as low-intensity smokers with CPD, but not the full-scale FTND, data available (N=8979). Smokers defined as moderately and severely dependent all had the full-scale FTND data available. See "FTND and categorical ND definitions for discovery GWAS" for further details. Association tests were carried out using a linear mixed model implemented in BOLT-LMM[14]. The FTND score was corrected for age and sex. LD score regression[15] was applied to account for inflation in test statistics due to cryptic relatedness and stratification. The $\chi 2$ statistics from the GWAS was regressed against LD score with a set of 1.1 M variants, and the intercept was used as the correction factor. The LD scores were downloaded from a LD score database (ftp://atguftp.mgh.harvard.edu/brendan/1k_eur_r2_hm3snps_se_weights.RDS; accessed 23 June 2015).

Environment and Genetics in Lung Cancer Etiology Study (EAGLE). EAGLE is a population-based study of newly diagnosed lung cancer cases and matched controls, who were aged 35 to 79 years old and recruited from the Italian region of Lombardy.[16,17] Genotyping was done on the Illumina HumanHap550v3 array, as part of GENEVA.[7] We obtained the genome-wide genotype, phenotype, and covariate data via dbGaP accession number phs000093.v2.p2 as well as the original study investigators. Lifetime FTND scores were collected among current and

former smokers. Following our standard QC steps, the final analysis data set for EAGLE included 3,006 participants with complete data available on FTND scores and covariates (age, sex, and PC eigenvectors). As before,[1,2] lung cancer case/control status was not included as a covariate, because FTND scores were collected among current and former smokers based on lifetime and not current smoking habits.

Electronic Medical Records and Genomics (eMERGE) network**.** We obtained data from eMERGE participants in "A Genome-Wide Association Study on Cataract and HDL in the Personalized Medicine Research Project Cohort**"** via dbGaP accession number phs000170.v2.p1. These eMERGE participants were recontacted to collect data on a broad range of phenotypes and exposures to facilitate harmonization with other studies as part of the PhenX Rising project (https://www.genome.gov/27549243/phenx-rising/). FTND data were collected in this study based on current habits among current smokers and on period of maximum usage (i.e., lifetime) among former smokers. We combined the data from current and former smokers, given our prior findings that any measurement variance in the FTND has negligible effects on genetic association results, with very similar patterns observed between current and lifetime FTND.[18] The final analysis data set included 730 EURs. Covariates for GWAS analysis included age, sex, and PCs.

FINRISK**.** The population-based FINRISK study was initiated in 1972 with follow-up taking place every 5 years until 2012. Recruitment occurred in several geographic areas across Finland, making FINRISK a nationally representative study as previously described.[19] Genotyping was performed on the Illumina Human610-Quad or HumanCoreExome array, followed by QC and imputation with reference to the all-Finnish panel from the Sequencing Initiative Suomi project,[20] as described before.[21] The final analysis data set included 2,211

unrelated participants, including current and former smokers, with complete data on lifetime FTND scores and covariates (age, sex, and PC eigenvectors).

Finnish Twin Cohort (FTC)**.** As before,[1] FTC participants originated from these sub-cohorts: the Nicotine Addiction Genetics study of adult twins, born 1938–1957 and concordant for being ever smokers, and their relatives (mainly siblings); and population-based longitudinal studies of five consecutive Finnish twin birth cohorts from 1983–1987 (FinnTwin12) and 1975–1979 (FinnTwin16).[22,23] The FTC sample size has increased from our prior GWAS analyses[1] due to new genotyping data. Genotyping was done using Illumina's Human610-Quad, Human670-QuadCustom, or HumanCoreExome array. QC was performed in two batches—(1) Human610-Quad and Human670-QuadCustom together and (2) HumanCoreExome—with variants removed for low call rate (<97.5% in batch 1 or <95% in batch 2), MAF<1%, or HWE $P<1\times10^{-6}$ and participants removed for low call rate (<98% for batch 1 or <95% for batch 2), excessive heterozygosity, discordant sex, or ancestry outlier. Imputation was conducted separately by genotyping array with Minimac3 v2.0.1 using the Michigan Imputation Server.[24] Imputed variants were merged across batches to construct the final analysis dataset of 2,507 participants with complete data on lifetime FTND scores and covariates (age, sex, birth cohort, and PC eigenvectors). Their kinship matrix was taken into account as a random effect in a linear mixed model. Imputation quality scores were re-calculated across the merged batches using the impute-info plugin for BCFtools.

Molecular Genetics of Schizophrenia—Genetic Association Information Network (GAIN) and nonGAIN studies**.** The overarching Molecular Genetics of Schizophrenia study was designed as a United States-based case-control study of schizophrenia/schizoaffective disorder. Cases were diagnosed with schizophrenia or schizoaffective disorder according to

DSM-IV criteria, whereas controls were assessed and determined to have no history of these illnesses. One subset of the study participants were genotyped as part of GAIN[25] with data obtained via dbGaP accession number phs000021.v3.p2, whereas the other subset was genotyped separately and denoted nonGAIN with data obtained via dbGaP accession number phs000167.v1.p1. Both subsets were genotyped using the Affymetrix 6.0 array. For the prior[1] and present ND GWAS analyses, we applied our standard QC steps and used only the schizophrenia controls. The final analysis datasets included 774 EAs from GAIN, 477 AAs from GAIN, and 471 EAs from nonGAIN with complete data available on lifetime FTND scores and covariates (age, sex, and PC eigenvectors for each dataset analyzed separately).

German Nicotine Cohort study (NCS) (German study). The German study is a population-based case-control study specifically conducted to assess the genetics of ND[26]. Data collection occurred from 2007-2009 at 7 recruitment centers across Germany (Departments of Psychiatry at the Universities of Aachen, Berlin, Bonn, Düsseldorf, Erlangen, Mainz, Mannheim). Probands were randomly selected from the local population via residents' registers at each site, and subjects were required to meet the following inclusion criteria: age 18-65 years; current smoker or occasional smoker (>=7 cigarettes per week or 1 cigarette per day) or never smoker (<=20 cigarettes over lifetime); grandparents born in Germany or adjacent country; native-level German language proficiency; letter invitation via official local residents' register. Furthermore, the following exclusion criteria were applied: former smoker; alcohol or substance abuse within previous six months (DSM-IV); a history of alcohol or substance dependence (DSM-IV); DSM-IV axis-1 psychiatric diagnosis within previous six months; non-German origin; not native-level proficient in German language; pregnant; any medical condition that may interfere with the study; CNS-relevant medication within previous 6 months; CNS-relevant

(neurological) illnesses (lifetime). Out of 55,000 subjects contacted, 2,396 were enrolled in the study.

DNA extracted from whole-blood samples acquired from study subjects were genotyped using the Illumina InfiniumOmniExpressExome-8v1-3_A array. Genotype QC steps included missing rate (missing rate>=0.05 and MAF>=0.05 or missing rate>=0.03 and MAF<0.05) and HWE $P<5.38\times10^{-8}$. Subject QC steps included missing rate >=5%, excess heterozygosity (plink --het, F more than 2*sigma deviations from the mean), high degree of relatedness (plink –genome full, pi_hat>=0.26), and PCA-based ancestral outlier removal (1000 Genomes Phase 3 reference). Following QC, imputation was performed using IMPUTE2 with the 1000 Genomes Phase 3 reference panel. The final analysis dataset with complete phenotype and genotype information included 991 current smokers of EUR ancestry.

Jackson Heart Study (JHS) / Atherosclerosis Risk in Communities (ARIC)**.** The longitudinal JHS was designed to evaluate cardiovascular disease risk among AAs from the general population in Jackson, Mississippi and its surrounding area.[27] JHS was an extension of the ARIC study of EURs and AAs from 4 communities across the United States (Jackson, Mississippi; Forsyth County, North Carolina; suburbs of Minneapolis, Minnesota; and Washington County, Maryland).[28] JHS recruited AAs were aged 35 to 84 years old, alongside their relatives who were aged 21 to 34 years old. Across JHS and ARIC, smokers were defined based on reports of having smoked 400 or more cigarettes in their lifetime. In parallel with the approach taken in deCODE, we included smokers with lifetime FTND data (N=682, all from JHS) and augmented the sample size by including 461 low-intensity AA smokers from ARIC with only CPD data available in the mild ND category (see “FTND and categorical ND definitions for discovery GWAS” for additional details).

Genotyping for both JHS and ARIC were performed on the Affymetrix 6.0 array, and we obtained these data via dbGaP (accession numbers phs000286.v3.p1 for JHS and phs000090.v1.p1 for ARIC). After applying our standard QC, there were 1,143 AA smokers with FTND scores or CPD reported and covariate (age, sex, and PC eigenvectors) data available: N=628 from JHS and 515 from ARIC. We confirmed that no participants were duplicated across the JHS and ARIC subsets in our final analysis data set, with identity-by-state estimates <0.9 for all pairwise comparisons.

Minnesota Center for Twin and Family Research (MCTFR)**.** MCTFR is composed of two longitudinal studies, the Minnesota Twin Family Study and the Sibling Interaction and Behavior Study. The Minnesota Twin Family Study recruited three studies of twin pairs and their parents and the Sibling Interaction and Behavior Study recruited adoptive and biological siblings and their parents. Families were initially recruited as a community study to study a broad range of psychological domains. Altogether, we included data for 1,073 current and former smokers, with lifetime FTND data available, who were genotyped on the Illumina 660W-Quad. Their genotyping protocols and QC were described previously.[29,30] Sex and age were included as covariates and to account for family relatedness, we used a kinship matrix and included PC eigenvectors as covariates. Additional covariates were included based on sample ascertainment and structure; we used four dummy coded variables to account for each of the three Minnesota Twin Family Study intake studies and the Sibling Interaction and Behavior Study, and a variable indicating if an individual was a parent.

Netherlands Twin Registry (NTR)**.** The NTR began in 1987 as a longitudinal study of twins and other multiple birth siblings. The NTR is comprised of two collections: (1) adult twins and their family members, and (2) younger twins recruited at birth or in early life, their parents,

and their siblings.[31] Genome-wide genotyping was performed on a subset of NTR participants using various Affymetrix and Illumina arrays,[32,33] followed by QC as described elsewhere.[33] Genotyped SNPs passing QC were merged across different arrays and used for imputation. Imputed SNPs were filtered out for the following reasons: MAF<0.5%, HWE $P<1\times10^{-5}$, estimated $r^2<0.3$, Mendelian error rate<2%, or absolute reference frequency allele difference>0.15 between NTR and 1000G. With an increased sample size from before due to a continued increase in the number of NTR participants who were genotyped, the present analysis included 4,489 NTR participants who had lifetime FTND[34] and covariate (age, sex, dummy variables to correct for genotyping array, and PC eigenvectors) data available.

GWAS of Alcohol Use and Alcohol Use Disorder in Australian Twin-Families (OZ-ALC) Study. Data for the present study were obtained from dbGaP study "International Consortium on the Genetics of Heroin Dependence" (accession number phs000277.v1.p1), for which OZ-ALC participants served as a source of DSM-IV-assessed non-opioid dependent controls. No other components of the heroin dependence study had FTND data. The OZ-ALC study data were derived from telephone diagnostic interviews of Australian twins from the general population and their spouses. Alcohol dependent cases from OZ-ALC were minimized for inclusion in the heroin dependence study made available in dbGaP. We began with the 1,172 participants, who were all of Australian European ancestry, genotyped on the CIDR370v1 or CIDR370v3 array, and had lifetime FTND data available.[35] Genotype imputation was based on the overlap of the two arrays. The final analysis dataset included 1,138 unrelated participants. Our statistical analyses included adjustment for age, sex, and PCs.

Study of Addiction: Genetics and Environment (SAGE)**.** SAGE was assembled from three case-control studies collected in the United States for addictive disorders: COGEND, the

Collaborative Study on the Genetics of Alcoholism (COGA),[36] and the Family Study of Cocaine Dependence (FSCD).[37] Genotyping was conducted using the Illumina Human1M-Duo array, from which we obtained via dbGaP accession number phs000092.v1.p1. COGEND participants were removed to avoid participant overlap; all other participants from COGA and FSCD (henceforth referred to as SAGE*) were analyzed together as previously done.[1,2,6] Following our standard QC, there remained 832 EAs and 633 AAs with lifetime FTND scores and covariates (age, sex, DSM-IV-defined cocaine dependence, DSM-IV-defined alcohol dependence, and PC eigenvectors) for GWAS analysis.

Spit for Science**.** Spit for Science, is an ongoing longitudinal study of Virginia Commonwealth University students. Briefly, incoming students age 18 or older were eligible to complete phenotypic assessments, which covered a wide range of topics but focused on alcohol use.[38] Study data were collected and managed using REDCap electronic data capture tools[39] hosted at Virginia Commonwealth University. Follow-up assessments were completed in subsequent spring semesters. Individuals who did not participate in the first wave of data collection (including those who turned 18 after the end of the first wave of data collection) had the opportunity to join the study the following spring; those who participated during their first year were eligible to complete follow-up assessments each spring. Participants who completed the phenotypic assessments were eligible to provide a DNA sample. There was a total of 7,603 participants across three studies, which matriculated in Fall 2011 (N=2,714), 2012 (N=2,486), and 2013 (N=2,403). Of these, 98% provided a DNA sample. The current analyses are based on FTND data captured after the Spring 2014 survey, with data available for up to 4 waves per participant. Lifetime FTND data were collected among current and former smokers, using the FTND with the heaviest smoking reported when data were available from more than one wave.

Genotyping was performed on the Affymetrix BioBank array, and QC steps were applied as detailed elsewhere.[40] For this study, we used only genotyped EURs, which was the largest ancestry group and had sufficient representation in each of the three ND categories (mild/moderate/severe). Following QC, there were 1,717 individuals with FTND scores and covariate data (age, sex, and PCs) available.

University of Wisconsin-Transdisciplinary Tobacco Use Research Center (UW-TTURC)**.** UW-TTURC represents a collection of smokers recruited from Madison and Milwaukee, Wisconsin, beginning in 2001, for smoking cessation treatment clinical trials.[9] Participants were deemed eligible, based on having smoked at least 10 CPD and reported being motived to quit smoking. Genotyping was performed using the Illumina HumanOmni2.5 array. We obtained their genotypes, FTND scores, and covariate data via dbGaP accession number phs000404.v1.p1. After applying standard QC, there remained 1,534 EAs and 247 AAs with current FTND scores and covariate data (age, sex, and PC eigenvectors) for analysis.

Yale-Penn**.** The Yale-Penn study was designed to conduct genetic studies for addiction using mostly unrelated individuals but also small nuclear families, all of whom were recruited from the eastern United States.[41-43] ND was not considered in the inclusion or exclusion criteria, but lifetime FTND data were collected among smokers.[44] Genotyping was conducted on the Illumina HumanOmni1-Quad array. QC mimicked prior analysis,[1] except that ancestry assignments were refined using K-means clustering to assign individuals based on the nearest centroid across the first 10 PC eigenvectors with reference to 1000G EUR or AFR population. There were 1,579 EAs and 2,637 AAs in the final analyses, which included adjustment for age, sex, and PC eigenvectors.

FTND and categorical ND definitions for discovery GWAS

Our discovery GWAS meta-analyses included studies with ND defined by the full 6-item FTND. The FTND[3] queries the following six items:

(1) **How soon after you wake up do/did you smoke your first cigarette?** Categorical responses: within 5 minutes, 6–30 minutes, 31–60 minutes, or after 60 minutes.

(2) **Do/Did you find it difficult to refrain from smoking in places where it is forbidden, e.g., in church, at the library, in a cinema, etc.?** Binary response: yes or no.

(3) **Which cigarette would you hate most to give up?** Binary response: the first one in the morning or all others.

(4) **How many cigarettes per day do/did you smoke?** Categorical response: 10 or less, 11–20, 21–30, or 31 or more.

(5) **Do/did you smoke more frequently during the first hours after waking than during the rest of the day?** Binary response: yes or no.

(6) **Do/did you smoke if you are so ill that you are in bed most of the day?** Binary response: yes or no.

Additional details on the protocol and scoring algorithm are provided in the PhenX Toolkit[45], a catalog of commonly ascertained phenotype and exposure measures: https://www.phenxtoolkit.org/protocols/view/31001. Briefly, FTND scores range from 0 (no dependence) to 10 (highest dependence level). FTND can be administered on current or former smokers based on the time period when they reported smoking the most (i.e., lifetime FTND) or among current smokers based around the time of interview (i.e., current FTND). We used lifetime FTND collected among current and former smokers in AAND, ADAA, EAGLE, COGEND, COGEND2, COPDGene2, deCODE, eMERGE, FINRISK, FTC, GAIN, JHS/ARIC,

MCTFR, nonGAIN, NTR, OZ-ALC, SAGE*, Spit for Science, and Yale-Penn. We used current FTND that was available in COHRA1, COPDGene, eMERGE, German, and UW-TTURC.

We used the FTND to derive a categorical variable for ND: scores of 0–3 for mild, 4–6 for moderate, and 7–10 for severe. We relied solely on the FTND to define ND, except in two of the 23 studies (deCODE and JHS/ARIC) where we included smokers with FTND data available as well as low-intensity smokers who had only CPD data that we used as a proxy measure to define mild dependence (CPD ≤10) as done before.[1,2] Our prior assessment showed high concordance of CPD ≤10 and FTND scores 0–3 (86.4%),[1] suggesting that CPD can be used to define mild dependence with little phenotype misclassification. However, any phenotype misclassification would be expected to conservatively bias results, leading to reduced statistical power, attenuated effect size estimates, and thus underestimate SNP associations with ND.[46,47] Moderate and severe dependence was defined solely by FTND scores across all studies, as our prior assessment showed lower concordance between FTND and CPD for defining these categories.[1] In follow-up analyses of lead SNPs from novel loci, we tested associations of each specific FTND item, using linear regression models for items with categorical responses (items #1 and 4) and logistic regression models for items with binary responses (items #2, 3, 5, and 6), followed by meta-analysis of results across studies. Due to varying genotype and phenotype data availability for the novel loci and specific FTND items, some studies could not utilize the full sample set for specific FTND item testing. These studies include AAND, COGEND, COGEND2, deCODE, Dental Caries, GAIN, German, JHS/ARIC, and nonGAIN.[48,49]

Heaviness of smoking index (HSI) in the UK Biobank for independent testing

Since there are no other datasets with comparably large sample sizes, we relied on the HSI that is available in the UK Biobank for independent testing of our genome-wide significant

FTND-based GWAS meta-analysis findings. The UK Biobank collected data on two of the 6 FTND items (CPD and time to first cigarette in the morning [TTFC]) among current smokers, who reported smoking on most or all days. These two items comprise the HSI, which has historically been considered a suitable proxy for the full-scale FTND.[3] To evaluate the agreement in our FTND categories (score range = 0–10; mild [scores 0–3], moderate [scores 4–6], and severe [scores 7–10] as we have routinely used before[1,2]) with HSI categories (score range = 0–6; mild [scores 0–2], moderate [scores 3–4], and severe [scores 5–6], in accordance with the scoring algorithm by the American Society of Clinical Oncology[50]), we used EURs in COGEND, which was ascertained specifically for ND. We compared FTND and HSI categories based on lifetime FTND (i.e., FTND based on time smoked most). Results are presented in **Supplementary Table 15**. Concordance was highest for mild dependence at 94.9%; i.e., among those defined as having mild dependence by the HSI, 94.87% also had mild dependence as defined by the full-scale FTND. We observed concordance of 81.2% for moderate dependence and 84.9% for severe dependence. Overall concordance was high (89.3%), corroborating the utility of the HSI categories as a proxy for defining ND in the UK Biobank.

Genome-wide significant SNP associations from our GWAS meta-analysis were tested for association using 33,791 current smokers with HSI data available in UK Biobank: 18,063 mild (HSI scores 0–2), 13,395 moderate (HSI scores 3–4), and 2,333 severe (scores 5–6) dependence. This final analysis data set included only unrelated individuals, as we removed 844 third-degree or closer relatives prior to analysis; for each related pair/cluster, individuals who had more relatives and who were light smokers were prioritized for removal. For our SNP-HSI association testing, we followed the model employed by systemic GWAS analyses for a multitude of phenotypes (see http://www.nealelab.is/uk-biobank/), adjusting for the following

covariates: sex, age, age^2, age × sex, age^2 × sex, and PC eigenvectors, with the age^2 and interaction terms among the age and sex variables intended to account for non-linear associations.

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Supplementary Table 1. Genome-wide significant single nucleotide polymorphism (SNP) and insertion/deletion (indel) associations from the cross-ancestry genome-wide association study (GWAS) meta-analysis (total N=58,000).
The SNPs and indels span five loci: chromosomes 5q34, 7q21, 9q34, 15q25, and 20q13. "Direction" indicates the association of the "Allele1" allele, corresponding to the "Effect" (β coefficient, with + corresponding to increased risk and – corresponding to decreased risk of nicotine dependence), across the 23 studies.

See attached spreadsheet for results.

Supplementary Table 2. Leave-one-study-out analyses of lead single nucleotide polymorphisms (SNPs) discovered in the cross-ancestry genome-wide association study (GWAS) meta-analysis of nicotine dependence (ND).

Study (ancestry) removed	Remaining N	rs1862416-T association with ND			rs2714700-T association with ND		
		β	SE	P	β	SE	P
AAND (AA)	56,313	0.039	0.0069	1.2×10^{-8}	-0.023	0.0041	2.2×10^{-8}
ADAA (AA)	56,855	0.038	0.0069	2.6×10^{-8}	-0.022	0.0041	6.6×10^{-8}
COGEND (EUR)	56,065	0.039	0.0069	2.5×10^{-8}	-0.023	0.0041	3.4×10^{-8}
COGEND (AA)	57,296	0.039	0.0068	1.3×10^{-8}	-0.022	0.0041	4.3×10^{-8}
COGEND2 (EUR)	57,708	0.038	0.0068	2.2×10^{-8}	-0.022	0.0041	3.6×10^{-8}
COGEND2 (AA)	57,687	0.038	0.0068	2.2×10^{-8}	-0.023	0.0041	1.4×10^{-8}
COHRA1 (EUR)	57,757	0.039	0.0068	1.2×10^{-8}	-0.023	0.0041	2.3×10^{-8}
COPDGene1 (EUR)	55,451	0.038	0.0070	4.0×10^{-8}	-0.024	0.0041	9.8×10^{-9}
COPDGene1 (AA)	55,466	0.038	0.0069	3.6×10^{-8}	-0.024	0.0041	7.4×10^{-9}
COPDGene2 (EUR)	55,370	0.038	0.0070	5.3×10^{-8}	-0.022	0.0042	1.2×10^{-7}
COPDGene2 (AA)	57,733	0.038	0.0068	2.8×10^{-8}	-0.022	0.0041	3.2×10^{-8}
deCODE (EUR)	42,688	0.036	0.0078	3.9×10^{-6}	-0.024	0.0047	3.0×10^{-7}
EAGLE (EUR)	54,994	0.039	0.0070	2.9×10^{-8}	-0.021	0.0042	3.1×10^{-7}
eMERGE (EUR)	57,270	0.038	0.0070	6.2×10^{-8}	-0.023	0.0042	7.4×10^{-8}
FINRISK (EUR)	55,789	0.039	0.0071	4.7×10^{-8}	-0.022	0.0042	1.3×10^{-7}
FTC (EUR)	55,493	0.040	0.0070	7.2×10^{-9}	-0.023	0.0042	5.6×10^{-8}
GAIN (EUR)	57,226	0.038	0.0068	2.0×10^{-8}	-0.023	0.0041	1.6×10^{-8}

GAIN (AA)	57,523	0.039	0.0068	1.6×10^{-8}	-0.023	0.0041	3.1×10^{-8}
German (EUR)	57,009	0.036	0.0069	1.3×10^{-7}	-0.023	0.0041	1.7×10^{-8}
JHS/ARIC (AA)	56,857	0.039	0.0069	1.6×10^{-8}	-0.022	0.0041	8.4×10^{-8}
MCTFR (EUR)	56,927	0.040	0.0069	7.2×10^{-9}	-0.022	0.0041	4.9×10^{-8}
nonGAIN (EUR)	57,329	0.039	0.0068	1.3×10^{-8}	-0.022	0.0041	7.3×10^{-8}
NTR (EUR)	53,511	0.040	0.0070	1.0×10^{-8}	-0.023	0.0042	4.0×10^{-8}
OZ-ALC (EUR)	56,862	0.038	0.0070	6.6×10^{-8}	-0.023	0.0041	2.7×10^{-8}
SAGE (EUR)	57,168	0.038	0.0069	2.5×10^{-8}	-0.023	0.0041	3.0×10^{-8}
SAGE (AA)	57,367	0.039	0.0068	1.1×10^{-8}	-0.022	0.0041	3.7×10^{-8}
Spit for Science (EUR)	56,283	0.039	0.0072	6.0×10^{-8}	-0.022	0.0043	2.1×10^{-7}
UW-TTURC (EUR)	56,466	0.040	0.0069	1.1×10^{-8}	-0.023	0.0041	4.1×10^{-8}
UW-TTURC (AA)	57,753	0.038	0.0068	2.2×10^{-8}	-0.023	0.0041	2.1×10^{-8}
Yale-Penn (EUR)	56,421	0.040	0.0069	5.6×10^{-9}	-0.023	0.0041	1.9×10^{-8}
Yale-Penn (AA)	55,363	0.038	0.0069	4.4×10^{-8}	-0.022	0.0042	1.2×10^{-7}

Abbreviations: AA, African American ancestry; EUR, European ancestry; SE, standard error.

Supplementary Table 3. Characteristics of participants included in the genome-wide association study (GWAS) meta-analyses of nicotine dependence (ND), separated into each of the 23 studies and the two ancestry groups.

				European ancestry (total N=46,213)				African American ancestry (total N=11,787)			
Study	**Total N**	**N (%), females**	**Mean age (SD)**	**N (%), mild ND**	**N (%), moderate ND**	**N (%), severe ND**	**GWAS λ**	**N (%), mild ND**	**N (%), moderate ND**	**N (%), severe ND**	**GWAS λ**
AAND	1,687	969 (57.4)	41.2 (10.3)	NA	NA	NA	NA	526 (31.2)	830 (49.2)	331 (19.6)	1.00
ADAA	1,145	472 (41.2)	41.2 (10.3)	NA	NA	NA	NA	526 (31.2)	830 (49.2)	331 (19.6)	1.01
COGEND [a]	2,639	1,628 (61.7)	36.6 (5.57)	941 (48.6)	521 (26.9)	473 (24.4)	1.01	248 (35.2)	283 (40.2)	173 (24.6)	1.01
COGEND2	605	324 (53.6)	34.4 (5.87)	60 (20.5)	91 (31.2)	141 (48.3)	1.01	13 (4.2)	137 (43.8)	163 (52.1)	1.03
COHRA1	243	129 (53.1)	32.1 (9.1)	79 (32.5)	127 (52.3)	37 (15.2)	1.01	NA	NA	NA	NA
COPDGene1 [a]	5,083	2,817 (55.4)	55.4 (7.3)	743 (29.1)	1,118 (43.9)	688 (27.0)	1.03	711 (28.1)	1,149 (45.3)	674 (26.6)	1.00

COPDGene2 [a]	2,897	1,395 (48.2)	63.7 (8.0)	955 (36.3)	1,172 (44.6)	503 (19.1)	1.03	146 (54.7)	103 (38.6)	18 (6.7)	1.00
deCODE [a,b]	15,312	9,127 (59.6)	66.5 (15.4)	11,494 (75.1)	2,250 (16.6)	1,268 (8.3)	1.12	NA	NA	NA	NA
EAGLE	3,006	478 (15.9)	NA [c]	1,416 (47.1)	1,027 (34.2)	563 (18.7)	1.00	NA	NA	NA	NA
eMERGE [a]	730	319 (43.7)	72.1 (9.2)	487 (66.7)	193 (26.4)	50 (6.8)	1.02	NA	NA	NA	NA
FINRISK	2,211	1,025 (46.4)	50.5 (13.3)	1,401 (63.4)	614 (27.8)	196 (8.9)	1.02	NA	NA	NA	NA
FTC [a]	2,507	1,111 (44.3)	45.5 (16.2)	1,436 (57.3)	828 (33.0)	243 (9.7)	1.00	NA	NA	NA	NA
GAIN	1,251	655 (52.4)	52.0 (15.2)	327 (42.2)	280 (36.2)	167 (21.6)	1.01	221 (46.3)	176 (36.9)	80 (16.8)	0.99
German	991	543 (54.8)	36.3 (12.6)	565 (57.0)	313 (31.6)	113 (11.4)	1.00	NA	NA	NA	NA
JHS/ARIC [b]	1,143	641 (56.1)	52.9 (9.2)	NA	NA	NA	NA	867 (75.9)	218 (19.1)	58 (5.1)	1.01
MCTFR [a]	1,073	492 (45.9)	20.6 (5.4)	687 (64.0)	293 (27.3)	93 (8.7)	1.01	NA	NA	NA	NA
nonGAIN	671	322 (48.0)	52.9 (15.5)	298 (44.4)	234 (34.9)	139 (20.7)	1.02	NA	NA	NA	NA

NTR [a]	4,489	2,750 (61.3)	45.5 (15.0)	2,842 (63.3)	1,276 (28.4)	371 (8.3)	1.01	NA	NA	NA	NA
OZ-ALC	1,138	379 (33.3)	45.6 (9.3)	976 (85.8)	125 (11.0)	37 (3.3)	1.01	NA	NA	NA	NA
SAGE	1,465	649 (44.3)	40.9 (9.9)	243 (29.2)	295 (35.5)	294 (35.3)	1.01	211 (33.3)	272 (43.0)	150 (23.7)	1.00
Spit for Science	1,717	994 (57.9)	20.4 (1.5)	1,532 (89.2)	158 (9.2)	33 (1.9)	0.99	NA	NA	NA	NA
UW-TTURC	1,781	1,040 (58.4)	43.4 (11.2)	311 (20.3)	723 (47.1)	500 (32.6)	1.01	40 (16.2)	119 (48.2)	88 (35.6)	1.01
Yale-Penn	4,216	1,833 (43.5)	40.1 (9.42)	284 (18.0)	751 (47.6)	544 (34.4)	1.01	837 (31.7)	1,346 (51.0)	454 (17.2)	1.04

Abbreviations: NA, not available; SD, standard deviation

[a] European ancestry participants were included in the GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN) consortium.[48] [b] ND was categorized according to Fagerström Test for Nicotine Dependence (FTND) scores: mild (FTND score 0–3), moderate (FTND score 4–6) or severe (FTND score 7–10). For deCODE and JHS/ARIC only, the mild category included participants with FTND score 0–3 as well as low-intensity smokers with no FTND data available but with ≤10 cigarettes per day (CPD). [c] Age was only available as a categorical variable: 23.2% aged 59 or less, 18.2% aged 60–64, 22.4% aged 65–69, 21.4% aged 70–74 and 14.8% aged 75–79.

Supplementary Table 4. Associations of the novel nicotine dependence (ND)-implicated single nucleotide polymorphisms (SNPs) with other smoking traits in the GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN) consortium[48]—initiation (ever vs. never smoking), age at initiation, cigarettes per day, and cessation (current vs. former smoking).

SNP associations at P<0.05 are bolded.

SNP (effect allele)	**Initiation (N=1,232,091)**		**Age at initiation (N=341,427)**		**Cigarettes per day (N=337,334)**		**Cessation (N=547,219)**	
	β (SE)	**P**	**β (SE)**	**P**	**β (SE)**	**P**	**β (SE)**	**P**
rs1862416 (T)	**0.005 (0.003)**	**0.033**	-0.01 (0.005)	0.080	0.001 (0.003)	0.61	-6.6×10^{-5} (0.004)	0.50
rs2714700 (T)	**-0.003 (0.002)**	**0.016**	-4×10^{-4} (0.003)	0.80	**-0.004 (0.002)**	**0.045**	-0.001 (0.002)	0.31

Abbreviation: SE, standard error.

Supplementary Table 5. Linkage disequilibrium (LD) structure and conditional association testing of the nicotine dependence (ND)-associated *TENM2* single nucleotide polymorphism (SNP) rs1862416 (chr. 5: 167,394,595) and the nearby lead SNPs implicated at genome-wide statistical significance for smoking initiation (ever vs. never smoking) by the GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN) consortium.[48]

LD was determined using the LDlink tool,[51] and conditional modeling was conducted using ND GWAS meta-analysis summary statistics as input into the Genome-wide Complex Trait Analysis (GCTA) tool.[52,53]

			LD in 1000G European panel		**LD in 1000G African panel**		**rs1862416 associations with ND conditioned on GSCAN lead SNP(s)**		
GSCAN lead SNP	**chr. 5 position (NCBI build 37)**	**P, cross-ancestry meta-analysis for ND**	**r^2**	**D'**	**r^2**	**D'**	**P, European ancestry-specific meta-analysis**	**P, African American-specific meta-analysis**	**P, cross ancestry meta-analysis**
rs3909281	165,096,435	0.12	0.0020	0.11	0.00090	0.041	7.5×10^{-7}	7.0×10^{-3}	2.2×10^{-8}
rs3843905	165,427,280	0.55	0.00010	0.025	0.00080	0.065	6.2×10^{-7}	7.3×10^{-3}	1.8×10^{-8}
rs79476395	166,063,680	0.018	0.00030	0.20	0.0014	0.46	1.6×10^{-6}	6.7×10^{-3}	4.6×10^{-8}
rs6890961	166,778,503	9.9×10^{-4}	0.0047	0.24	0.00030	0.048	2.9×10^{-6}	6.1×10^{-3}	7.9×10^{-8}
rs4044321	166,989,513	0.78	0.00040	0.040	0.00050	0.072	6.7×10^{-7}	6.9×10^{-3}	1.9×10^{-8}
rs2173019	167,614,971	0.036	0.0017	0.024	0.0017	0.16	1.0×10^{-6}	6.0×10^{-3}	2.7×10^{-8}
						All SNPs	7.2×10^{-6}	6.6×10^{-3}	2.2×10^{-7}

Abbreviations: 1000G, 1000 Genomes; NCBI, National Center for Biotechnology Information.

Supplementary Table 6. Independent testing of novel nicotine dependence (ND)-associated single nucleotide polymorphisms (SNPs) with heaviness of smoking (HSI) in the UK Biobank.

SNP (effect allele)	Chr:position (NCBI build 37)	Gene / closest genes	HSI in UK Biobank (N=33,791)				Meta-analysis of FTND GWAS and UK Biobank HSI results (total N=91,791)	
			Effect allele freq.	estimated r^2	β (SE)	P	β (SE)	P
rs1862416 (T)	5:167,394,595	*TENM2*	0.89	1	-0.0064 (0.0075)	0.39	0.018 (0.0050)	3.0×10^{-4}
rs2714700 (T)	7:79,367,667	*MAGI2 / GNAI1*	0.47	1	-0.012 (0.0047)	0.014	-0.018 (0.0031)	7.7×10^{-9}

Abbreviations: FTND, Fagerström Test for Nicotine Dependence (FTND); GWAS, genome-wide association study; NCBI, National Center for Biotechnology Information; SE, standard error.

Supplementary Table 7. Genome-wide H-MAGMA results using the nicotine dependence GWAS meta-analysis of European ancestry participants in the iNDiGO consortium with reference to chromatin interaction maps from fetal brain tissue.

Results are sorted by the H-MAGMA P value.

See the attached spreadsheet for results.

Supplementary Table 8. Genome-wide H-MAGMA results using the nicotine dependence GWAS meta-analysis of European ancestry participants in the iNDiGO consortium with reference to chromatin interaction maps from adult brain tissue.

Results are sorted by the H-MAGMA P value.

See the attached spreadsheet for results.

Supplementary Table 9. Statistically significant H-MAGMA results from the nicotine dependence GWAS meta-analysis of European ancestry participants in the iNDiGO consortium, based on $P<2.7\times10^{-6}$ (Bonferroni correction for testing 18,655 genes), with look-up in the UK Biobank using heaviness of smoking index as a proxy for nicotine dependence.

H-MAGMA was applied in both the iNDiGO consortium and the UK Biobank using chromatin interaction maps in fetal and adult brain tissues, separately, as the reference datasets. Results are sorted, within each tissue, by H-MAGMA p-values in the iNDiGO consortium. H-MAGMA p-values in the UK Biobank that surpass Bonferroni correction for testing 16 unique genes ($P<0.0031$) are shown in bold.

Gene	Chr. band	iNDiGO (N=46,213)		UK Biobank (N=33,791)	
		No. SNPs annotated to gene	**P**	**No. SNPs annotated to gene**	**P**
Fetal brain tissue as chromatin interaction mapping reference in H-MAGMA					
CHRNA5	15q25	17	2.6×10^{-28}	19	$\mathbf{8.9\times10^{-26}}$
IREB2	15q25	40	1.7×10^{-27}	42	$\mathbf{3.3\times10^{-22}}$
HYKK	15q25	16	2.4×10^{-27}	20	$\mathbf{4.8\times10^{-25}}$
CHRNA3	15q25	82	6.4×10^{-24}	84	$\mathbf{5.7\times10^{-25}}$
CHRNB4	15q25	93	1.8×10^{-14}	101	$\mathbf{2.3\times10^{-15}}$
ADAMTS7	15q25	30	1.6×10^{-12}	32	$\mathbf{2.9\times10^{-14}}$
CHRNA4	20q13	264	7.7×10^{-12}	282	1.0×10^{-2}
PSMA4	15q25	52	2.3×10^{-11}	58	$\mathbf{1.3\times10^{-10}}$
MORF4L1	15q25	60	2.9×10^{-11}	63	$\mathbf{1.7\times10^{-11}}$
ADAMTSL2	9q34	277	3.4×10^{-8}	296	$\mathbf{3.2\times10^{-8}}$
DBH	9q34	114	1.7×10^{-6}	127	$\mathbf{1.1\times10^{-4}}$
Adult brain tissue as chromatin interaction mapping reference in H-MAGMA					
CHRNA5	15q25	17	2.6×10^{-28}	19	$\mathbf{8.9\times10^{-26}}$
WDR61	15q25	31	3.5×10^{-22}	32	$\mathbf{1.8\times10^{-20}}$
IREB2	15q25	130	4.2×10^{-18}	139	$\mathbf{2.1\times10^{-13}}$
CHRNA3	15q25	101	5.4×10^{-15}	115	$\mathbf{6.6\times10^{-16}}$
HYKK	15q25	143	2.2×10^{-14}	158	$\mathbf{2.1\times10^{-14}}$
ACSBG1	15q25	117	8.0×10^{-14}	126	$\mathbf{9.4\times10^{-13}}$
ADAMTS7	15q25	71	2.3×10^{-11}	76	$\mathbf{2.0\times10^{-13}}$
PSMA4	15q25	52	2.3×10^{-11}	58	$\mathbf{1.3\times10^{-10}}$
CHRNA4	20q13	96	1.0×10^{-10}	99	$\mathbf{7.0\times10^{-5}}$
CHRNB4	15q25	53	1.7×10^{-9}	59	$\mathbf{1.7\times10^{-10}}$
AFG1L	6q21	281	1.1×10^{-6}	319	0.54
AK2	1p35	60	1.3×10^{-6}	68	0.38
RBBP8NL	20q13	172	2.1×10^{-6}	178	8.6×10^{-3}

Supplementary Table 10. Genome-wide Summary-MultiXcan (S-MultiXcan)[54] results from the European ancestry-specific nicotine dependence GWAS meta-analysis summary statistics with reference to imputed genetically driven gene expression across the 13 adult brain tissues in GTEx.

S-MultiXcan provides gene-level association results based on aggregating *cis*-eQTL evidence across multiple tissues, while also presenting gene-based results from the best and worst single-tissue models. Results are sorted by the multi-tissue P value.

See attached spreadsheet for results.

Supplementary Table 11. Genetic correlations of nicotine dependence (ND) with other phenotypes using linkage disequilibrium (LD) score regression (LDSC).

Phenotypes are sorted by disease or measurement category. Phenotypes that have statistically significant correlations with ND, as determined by Bonferroni correction (α=0.05/46 phenotypes, P_1<0.0011), are bolded.

Category	**Phenotype**	**Reference**	**h^2 (single trait SNP heritability)**	**Cross-trait comparison with ND**				
				gcov_int[a]	**r_g**	**SE**	**P_1 (H_0: r_g = 0)**	**P_2 (H_0: r_g = 1)**
Brain volume	Accumbens volume	[55]	0.092	0.0020	0.13	0.15	0.37	6.5×10^{-9}
	Caudate volume	[55]	0.25	0.0067	-0.091	0.094	0.33	3.4×10^{-22}
	Hippocampus volume	[55]	0.14	0.0062	-0.15	0.13	0.25	2.2×10^{-11}
	Intracranial volume	[55]	0.18	0.00040	-0.24	0.12	0.036	5.2×10^{-11}
	Pallidum volume	[55]	0.16	0.0050	-0.075	0.11	0.50	2.0×10^{-16}
	Putamen volume	[55]	0.30	-0.0010	0.17	0.083	0.045	8.8×10^{-24}
	Thalamus volume	[55]	0.14	-0.0017	-0.092	0.12	0.43	1.1×10^{-14}
Cancer	**Lung adenocarcinoma**	**[56]**	**0.069**	**0.0037**	**0.48**	**0.11**	**8.6×10^{-6}**	**1.1×10^{-6}**
	Lung cancer (overall)	**[56]**	**0.087**	**0.0065**	**0.68**	**0.089**	**3.4×10^{-14}**	**2.9×10^{-4}**
	Small cell lung cancer	[56]	0.11	0.0085	0.40	0.13	0.0024	7.5×10^{-6}
	Squamous cell lung cancer	**[56]**	**0.053**	**0.0065**	**0.75**	**0.11**	**3.0×10^{-11}**	**0.03**
Cardiometabolic	Adiponectin	[57]	0.12	-0.0051	0.035	0.11	0.74	2.6×10^{-20}
	Coronary artery disease	**[58 b]**	**0.080**	**-0.0032**	**0.32**	**0.064**	**6.0×10^{-7}**	**4.6×10^{-26}**
Cigarette smoking	**Age of smoking initiation**	**[48]**	**0.047**	**-0.042**	**-0.55**	**0.066**	**1.7×10^{-16}**	**8.9×10^{-12}**

	Cigarettes per day	**[48]**	**0.075**	**0.14**	**0.95**	**0.054**	**3.1×10^{-70}**	**0.35**
	Cotinine levels	[59]	0.22	0.020	0.46	0.23	0.051	0.021
	Smoking cessation (current vs. former)	**[48]**	**0.032**	**0.032**	**0.51**	**0.063**	**3.4×10^{-16}**	**8.2×10^{-15}**
	Smoking initiation (ever vs. never)	**[48]**	**0.069**	**0.012**	**0.40**	**0.049**	**3.2×10^{-16}**	**2.8×10^{-34}**
Cognitive / education	Childhood IQ	[60]	0.28	0.00080	-0.17	0.10	0.11	2.1×10^{-15}
	College completion	[61]	0.079	-0.024	-0.23	0.070	0.0012	4.3×10^{-28}
	Intelligence	[62]	0.19	0.0024	-0.17	0.056	0.0031	1.3×10^{-50}
	Years of schooling	**[63] [c]**	**0.11**	**-0.012**	**-0.34**	**0.041**	**9.2×10^{-17}**	**8.6×10^{-58}**
Drug and alcohol	**Alcohol dependence**	**[64]**	**0.096**	**0.025**	**0.57**	**0.13**	**6.3×10^{-6}**	**1.4×10^{-4}**
	Alcohol drinks per week	[48]	0.049	0.017	0.13	0.054	0.016	1.4×10^{-58}
	Cannabis use disorder	[65]	0.027	0.0029	0.40	0.15	0.010	9.4×10^{-5}
	Lifetime cannabis use (ever vs. never)	[66]	0.067	-0.0057	0.057	0.056	0.31	3.9×10^{-63}
Neurologic	Alzheimer's disease	[67]	0.045	-0.0043	-0.087	0.12	0.48	1.5×10^{-13}
	Amyotrophic lateral sclerosis	[68]	0.049	0.0010	-0.060	0.12	0.62	1.3×10^{-14}
	Parkinson's disease	[69]	0.41	6.3×10^{-7}	0.074	0.092	0.42	9.2×10^{-24}
Personality	Conscientiousness	[70]	0.073	-0.014	0.052	0.18	0.77	1.6×10^{-7}
	Neuroticism	**[71]**	**0.089**	**0.0054**	**0.28**	**0.067**	**3.2×10^{-5}**	**1.4×10^{-26}**
	Openness to experience	[70]	0.11	-0.0077	-0.12	0.13	0.35	2.8×10^{-12}
Psychiatric	Anorexia nervosa	[72]	0.18	-0.014	0.098	0.066	0.14	5.0×10^{-43}

	Attention deficit hyperactivity disorder	[73]	**0.24**	**-0.0033**	**0.49**	**0.063**	**5.7×10^{-15}**	**9.1×10^{-16}**
	Autism spectrum disorder	[74]	0.20	-0.0068	0.23	0.078	0.0024	2.7×10^{-24}
	Bipolar disorder	[75]	**0.35**	**-0.0024**	**0.25**	**0.050**	**3.3×10^{-7}**	**2.6×10^{-52}**
	Depressive symptoms	[71]	**0.047**	**-0.00080**	**0.40**	**0.075**	**9.6×10^{-8}**	**1.1×10^{-15}**
	Major depressive disorder	[76]	**0.038**	**-0.0046**	**0.38**	**0.051**	**6.1×10^{-14}**	**1.7×10^{-33}**
	Posttraumatic stress disorder	[77]	**0.017**	**-0.0077**	**0.72**	**0.15**	**6.5×10^{-7}**	**0.056**
	Psychiatric cross-disorder	[78]	0.17	0.0021	0.17	0.080	0.031	4.6×10^{-25}
	Schizophrenia	[79]	**0.46**	**0.0077**	**0.18**	**0.043**	**3.2×10^{-5}**	**1.3×10^{-65}**
	Subjective well being	[71]	0.025	-0.0092	-0.24	0.075	0.0016	9.4×10^{-25}
Respiratory	COPD	[80]	0.10	-0.0065	0.18	0.088	0.033	1.8×10^{-20}
	Forced expiratory volume in 1 second (FEV_1)	[81]	0.27	-0.0048	-0.0017	0.060	0.98	1.4×10^{-63}
	Forced vital capacity (FVC)	[81]	0.26	-0.0054	-0.0073	0.057	0.90	4.2×10^{-69}
	FEV_1/FVC	[81]	0.26	-0.0020	0.012	0.059	0.84	6.1×10^{-63}

[a] Deviation of the cross-trait intercept term from 0 is indicative of study overlap in the GWAS results being compared.

[b] Results are based on cross-ancestry meta-analysis results that are available in LDHub; results for all other results correspond to European-specific meta-analyses.

[c] The GWAS results for educational attainment (years of schooling) include all discovery cohorts, except for 23andMe, resulting in a total sample size of 766,345.

Supplementary Table 12. Credible set analysis and annotation of the novel nicotine dependence (ND)-associated loci.

For the novel ND-associated loci (chromosomes 5q34 and 7q21), we applied a Bayesian method[82] implemented via LocusZoom[83] to identify a credible set likely to contain the causal variant at each loci. The calculated posterior probability for each variant is provided as well as the cross-ancestry, European ancestry-specific, and African American ancestry-specific meta-analysis results for comparison. HetPval is the heterogeneity p-value from the meta-analysis. The credible set was annotated using GTEx,[84] BrainSeq,[85] and HaploReg.[86]

See attached spreadsheet for results.

Supplementary Table 13. Tissues and cell types evaluated for shared genetics with nicotine dependence (ND) using stratified linkage disequilibrium (LD) score regression, as applied to specifically expressed genes (LDSC-SEG).

Tissues and cell types are sorted by data origin (RNA-sequencing in the Genotype-Tissue Expression [GTEx] project or array-based in Gene Expression Omnibus [GEO]) and then by p-value. Tissues/cell types that have statistically significant correlations with ND, as determined by Bonferroni correction (α=0.05/205 phenotypes, $P<2.4\times10^{-4}$), are bolded.

See attached spreadsheet for results.

Supplementary Table 14. Look-up of genome-wide significant single nucleotide polymorphisms (SNPs) in the GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN) consortium[48] for association with nicotine dependence (ND) in our cross-ancestry GWAS meta-analysis.

Results are sorted by GSCAN smoking phenotype in descending $|r_g|$ with ND (cigarettes per day [r_g=0.95], age at initiation [r_g=-0.55], cessation [current vs. former smoking, r_g=0.51], and initiation [ever vs. never smoking, r_g=0.40], shown in alternating grey shading) and then by FTND GWAS meta-analysis p-value. For SNPs implicated at genome-wide significance for more than one phenotype in GSCAN, the results from the phenotype with the smallest p-value are presented. β estimates correspond to the effect alleles. No SNPs from novel loci for ND surpassed Bonferroni correction for multiple testing ($P<1.1\times10^{-4}$, α=0.05/452 SNPs available in the iNDiGO cross-ancestry FTND GWAS meta-analysis). Abbreviations: AI, age at initiation; CPD, cigarettes per day; NA, not available; SC, smoking cessation; SE, standard error; and SI, smoking initiation.

See attached spreadsheet for results.

Supplementary Table 15. Agreement between heaviness of smoking index (HSI) and Fagerström Test for Nicotine Dependence (FTND) categories for mild, moderate, and severe nicotine dependence (ND) in COGEND participants of European ancestry.

		FTND category[a], N (% of total N in HSI category)			
		Mild	***Moderate***	***Severe***	**Total**
HSI category [b]	***Mild***	998 (94.9)	54 (5.1)	0 (0)	1,052
	Moderate	3 (0.6)	417 (81.9)	89 (17.5)	509
	Severe	0 (0)	72 (15.1)	404 (84.9)	476

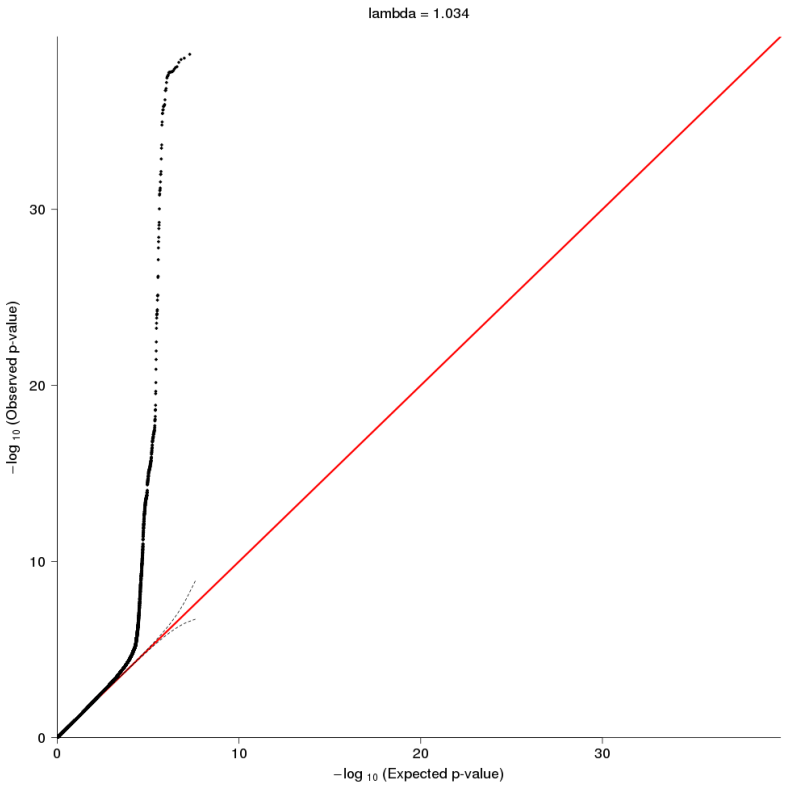
[a] Categories for the full-scale, 6-item FTND (score range = 0–10) were defined as follows: mild (scores 0–3), moderate (scores 4–6), or severe (scores 7–10).

[b] Categories for the 2-item HSI (score range = 0–6) were defined as follows: mild (scores 0–2), moderate (scores 3–4), or severe (scores 5–6).

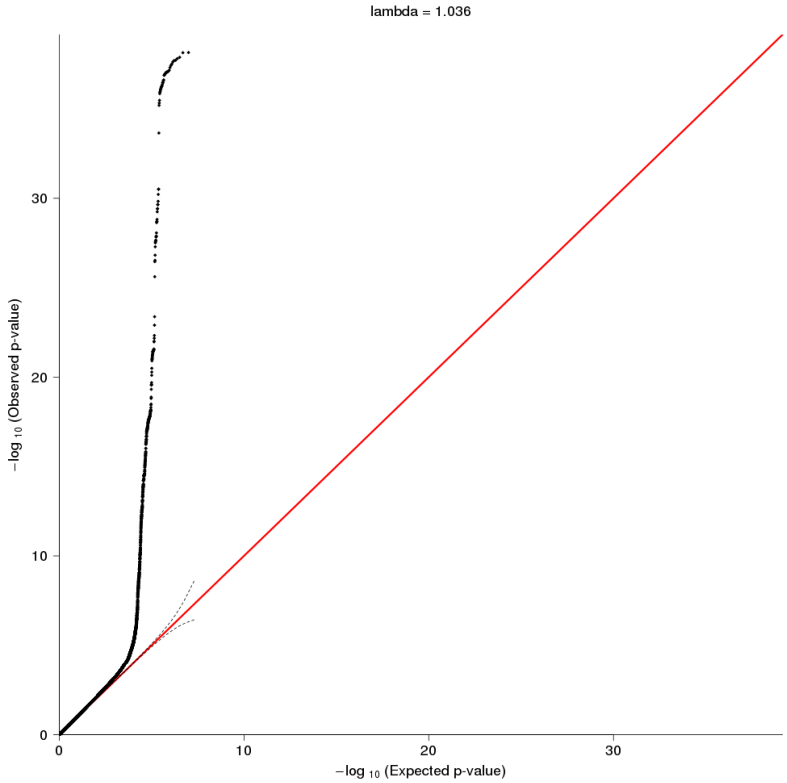
Supplementary Figure 1. Quantile-quantile plots for nicotine dependence genome-wide association study (GWAS) meta-analyses.

Results are shown for (A) the cross-ancestry meta-analysis (European ancestry and African American participants from all studies), (B) the European ancestry-specific meta-analysis, and (C) African American-specific meta-analysis. The observed vs expected meta-analysis $-\log_{10}$ p-values (black dots) are plotted along the identity line (red) with the corresponding genomic inflation factor (λ) indicated.

(A)



(B)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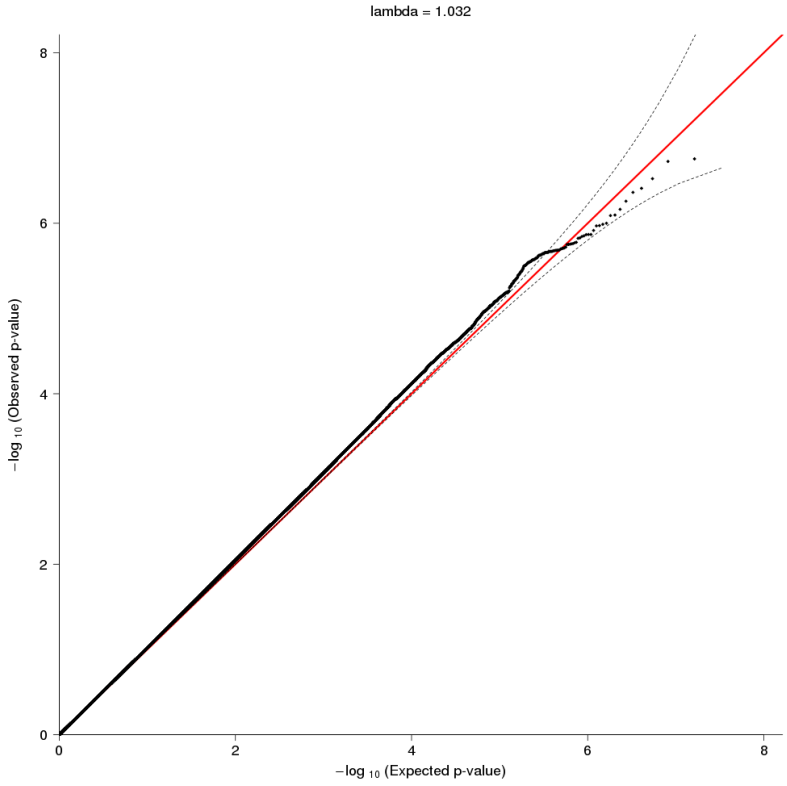
−log 10 (Observed p-value)
−log 10 (Expected p-value)
0
10
20
30

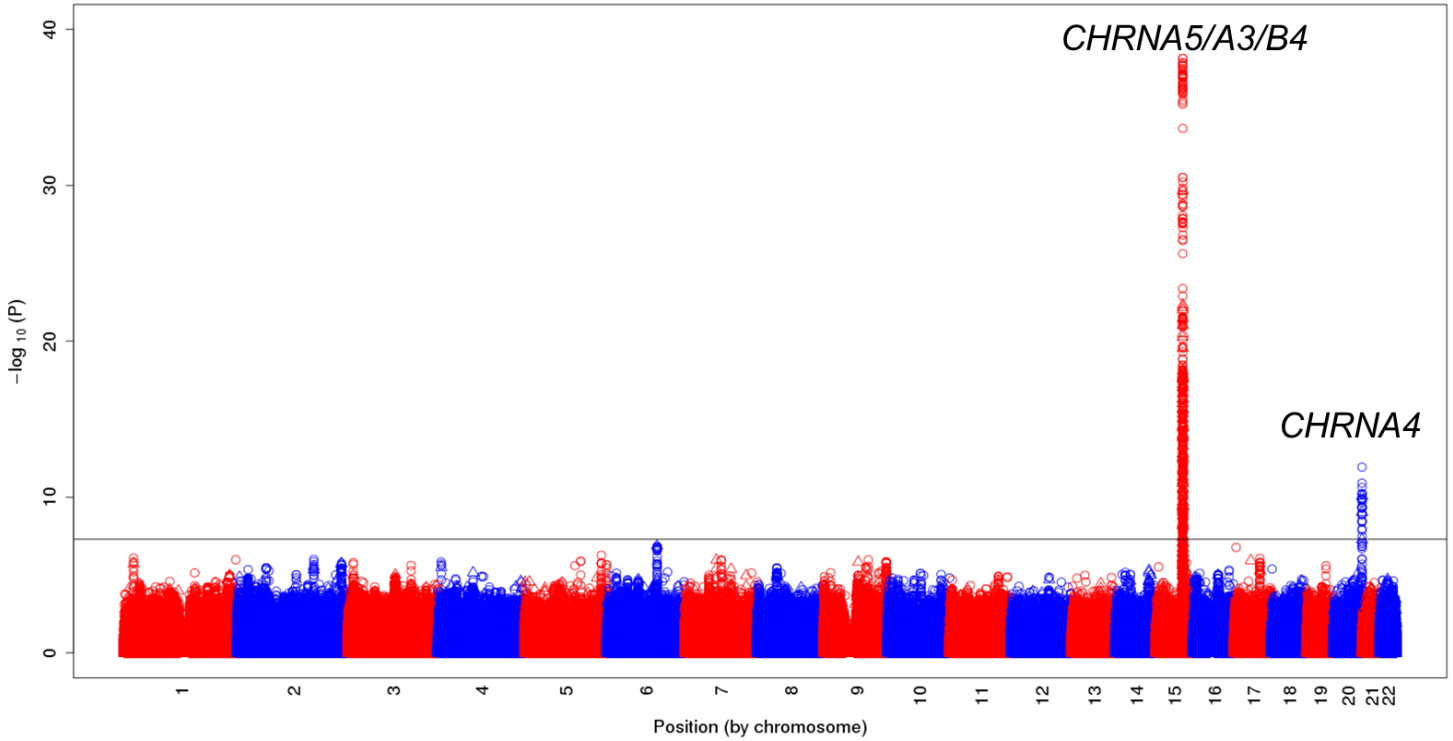
(C)


lambda = 1.032
−log 10 (Observed p-value)
−log 10 (Expected p-value)
0
2
4
6
8

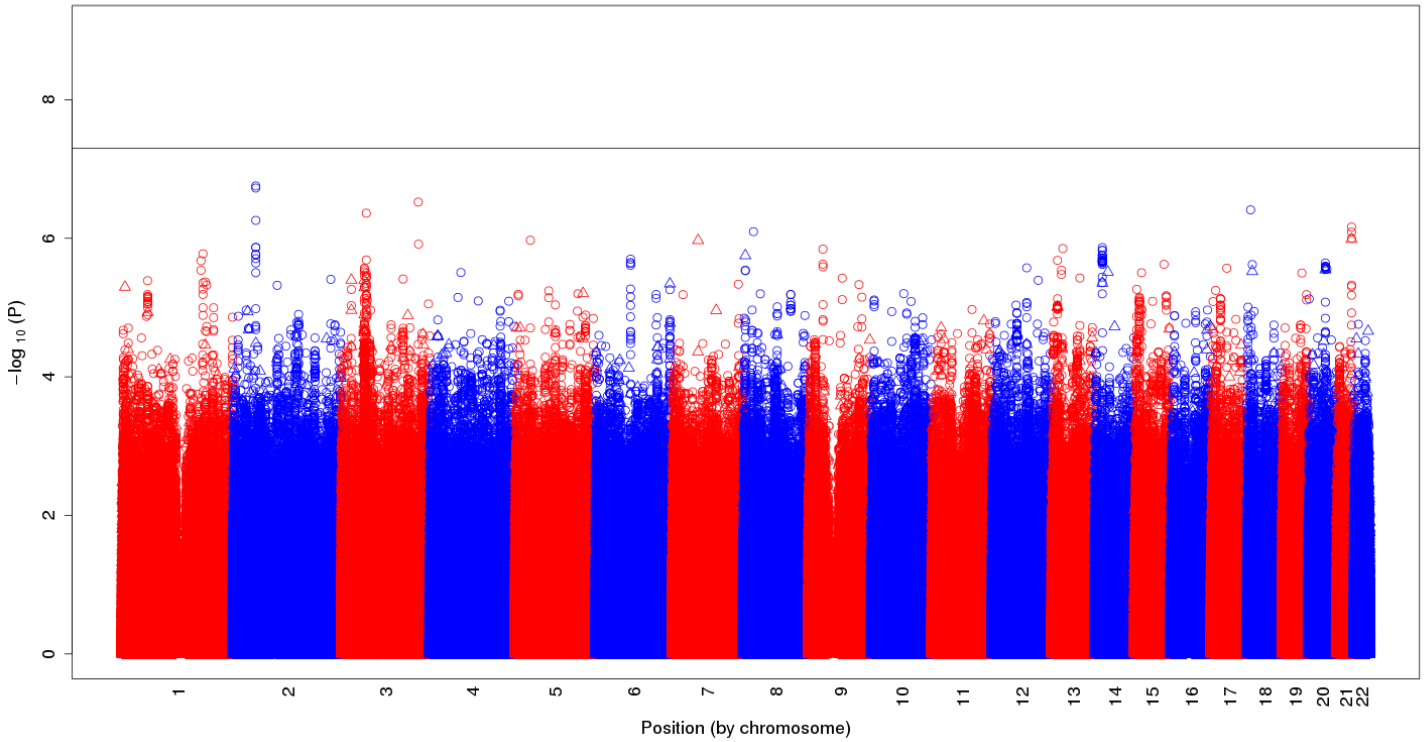
Supplementary Figure 2. Manhattan plots for ancestry-specific nicotine dependence genome-wide association study (GWAS) meta-analyses.

Results are shown for (A) the European ancestry-specific (total N=46,213) and (B) African American-specific (total N=11,787) meta-analyses. The $-\log_{10}$ meta-analysis p-values are plotted by chromosomal position of single nucleotide polymorphisms (SNPs; depicted as circles) and insertions/deletions (indels; depicted as triangles). The genome-wide statistical significance threshold ($P<5\times10^{-8}$) is shown as a solid black line.

(A)



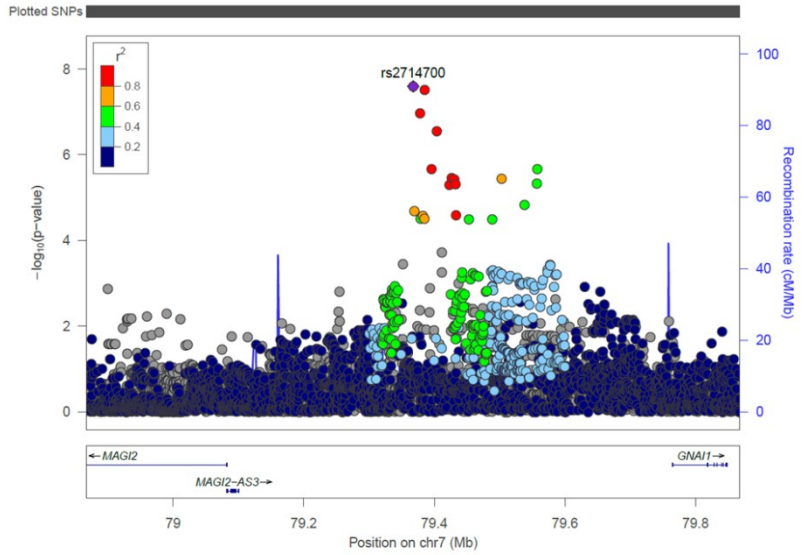
(B)


−log 10 (P)
0
2
4
6
8
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Position (by chromosome)

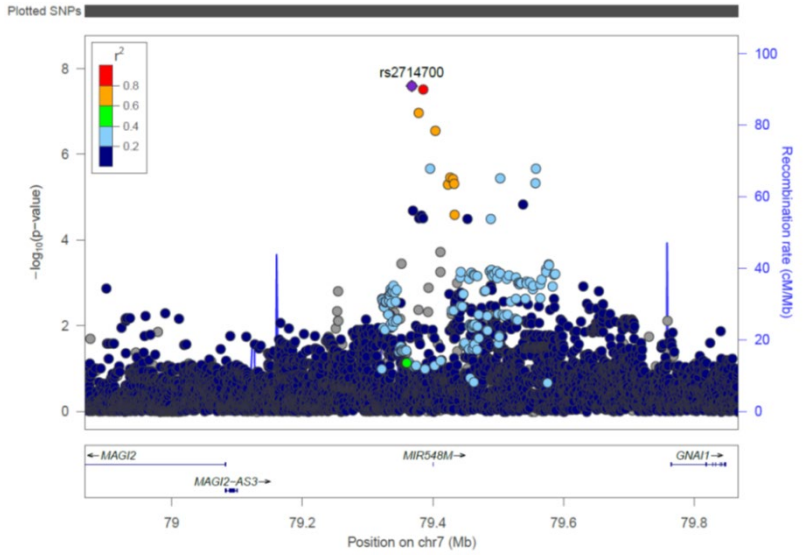
Supplementary Figure 3. Regional association plots for two novel loci identified at genome-wide significance in the cross-ancestry nicotine dependence genome-wide association study (GWAS) meta-analyses.

Results are shown for rs2714700 on chromosome 7 in reference to the 1000 Genomes (A) European and (B) African superpopulation panels and rs1862416 on chromosome 5in reference to the same (C) European and (D) African panels. The $-\log_{10}$ meta-analysis p-values are plotted by chromosomal position with r^2 values between the lead single nucleotide polymorphism (SNP; in purple) and nearby SNPs indicated in 0.2 increments (e.g., 0.8–1 in red).

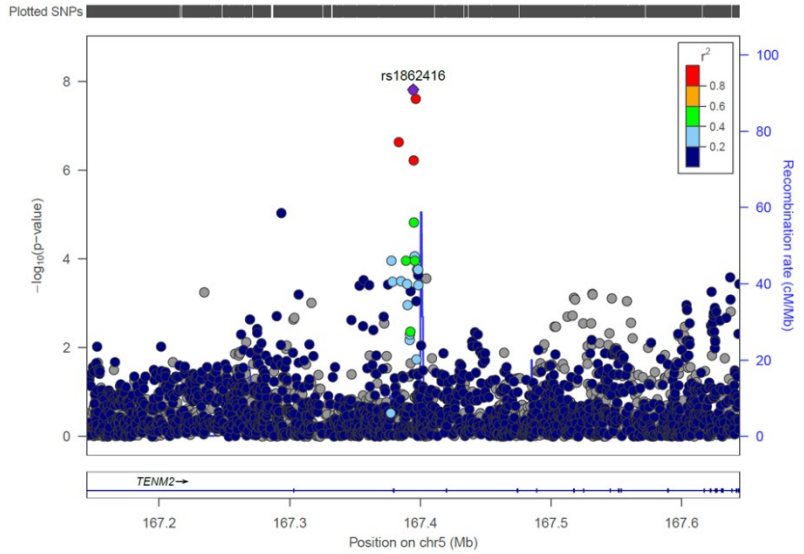
(A)



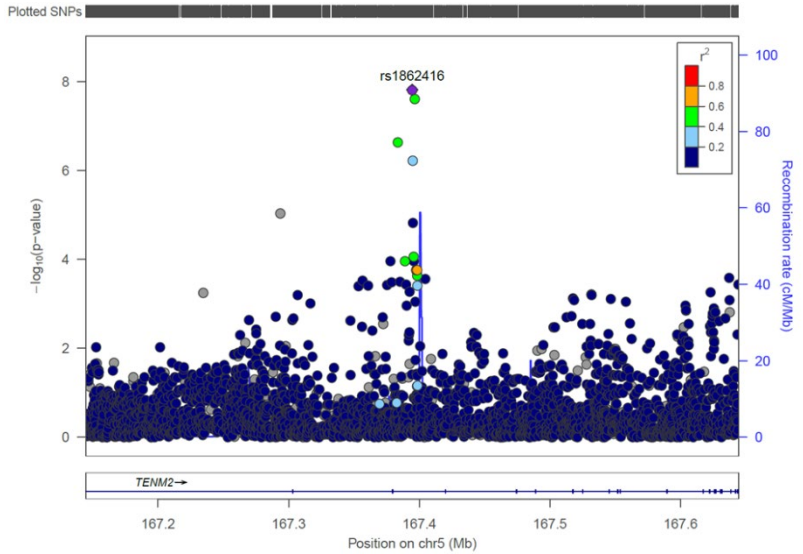
(B)



(C)


Plotted SNPs
rs1862416
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
TENM2
167.2
167.3
167.4
167.5
167.6
Position on chr5 (Mb)

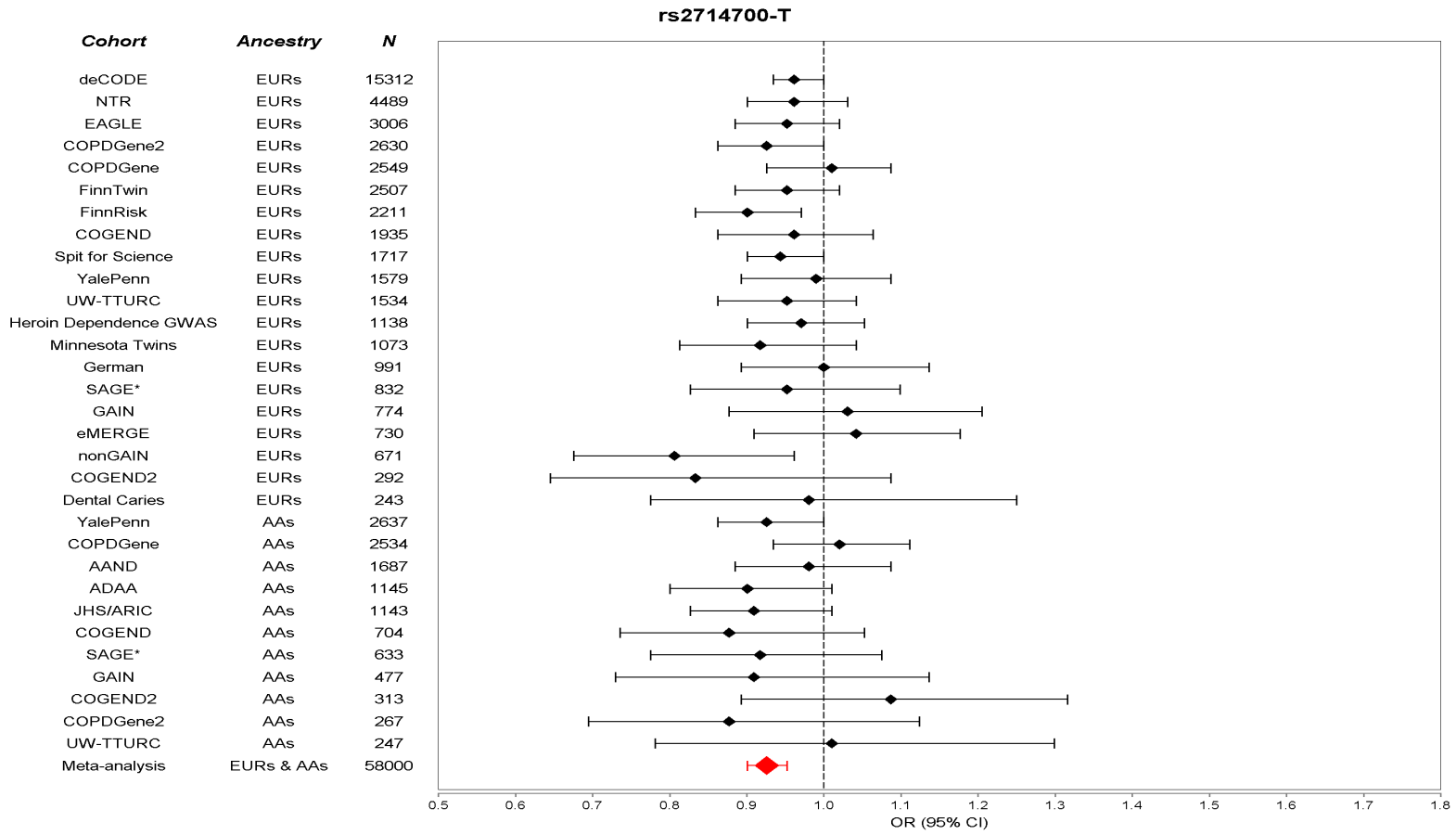
(D)


Plotted SNPs
rs1862416
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
TENM2
167.2
167.3
167.4
167.5
167.6
Position on chr5 (Mb)

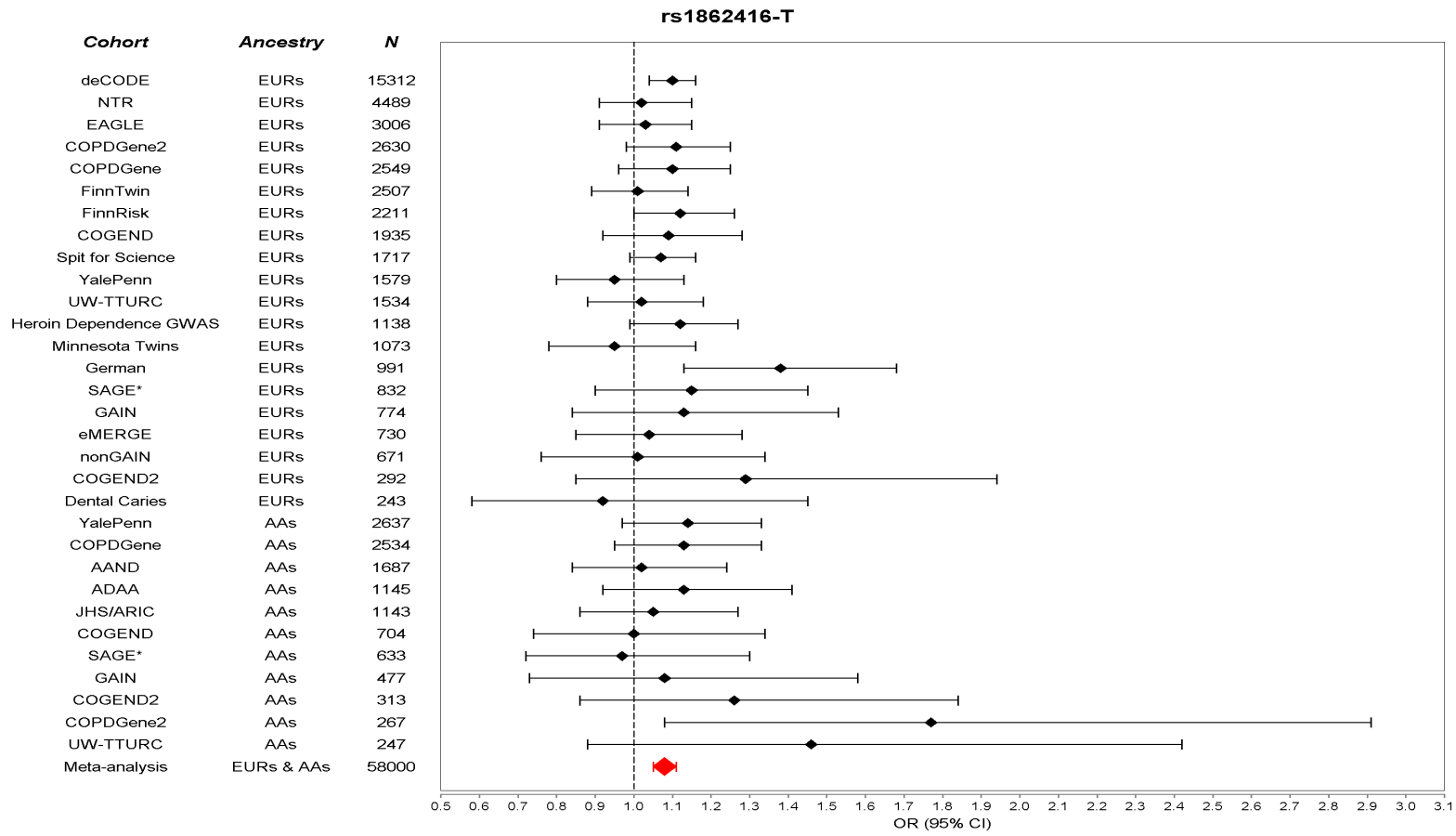
Supplementary Figure 4. Novel single nucleotide polymorphism (SNP) associations with nicotine dependence (ND) by study and ancestry group.

Associations are presented for the (A) *MAGI2/GNAI1* SNP allele rs2714700-T and (B) *TENM2* SNP allele rs1862416-T with severe vs. mild ND, by calculating odds ratio (OR) and 95% confidence interval (CI) estimates using the regression coefficients from the discovery genome-wide association study analyses of categorical FTND (i.e., OR=exp[2×β_{SNP}] for severe vs. mild ND).

(A)

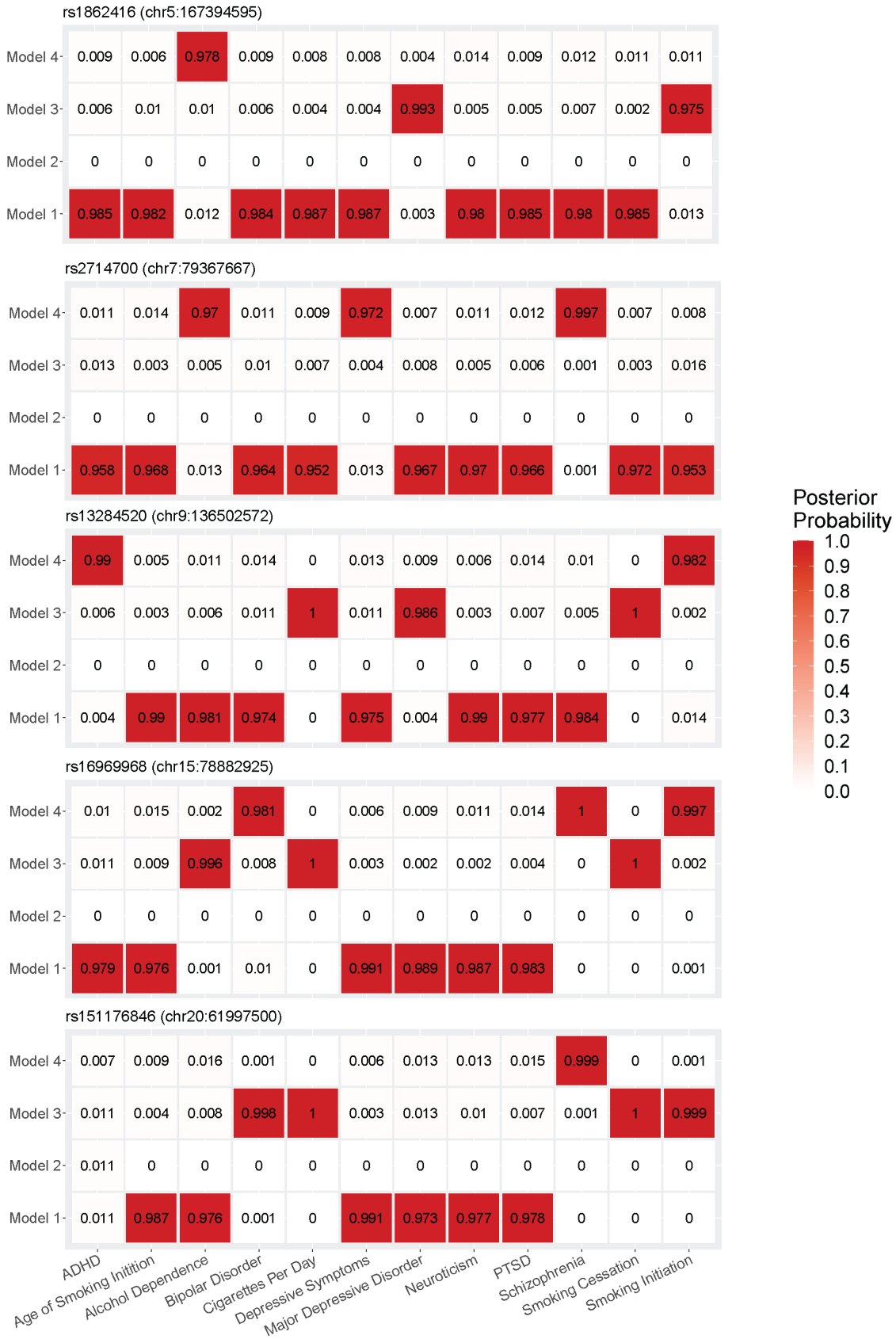


(B)

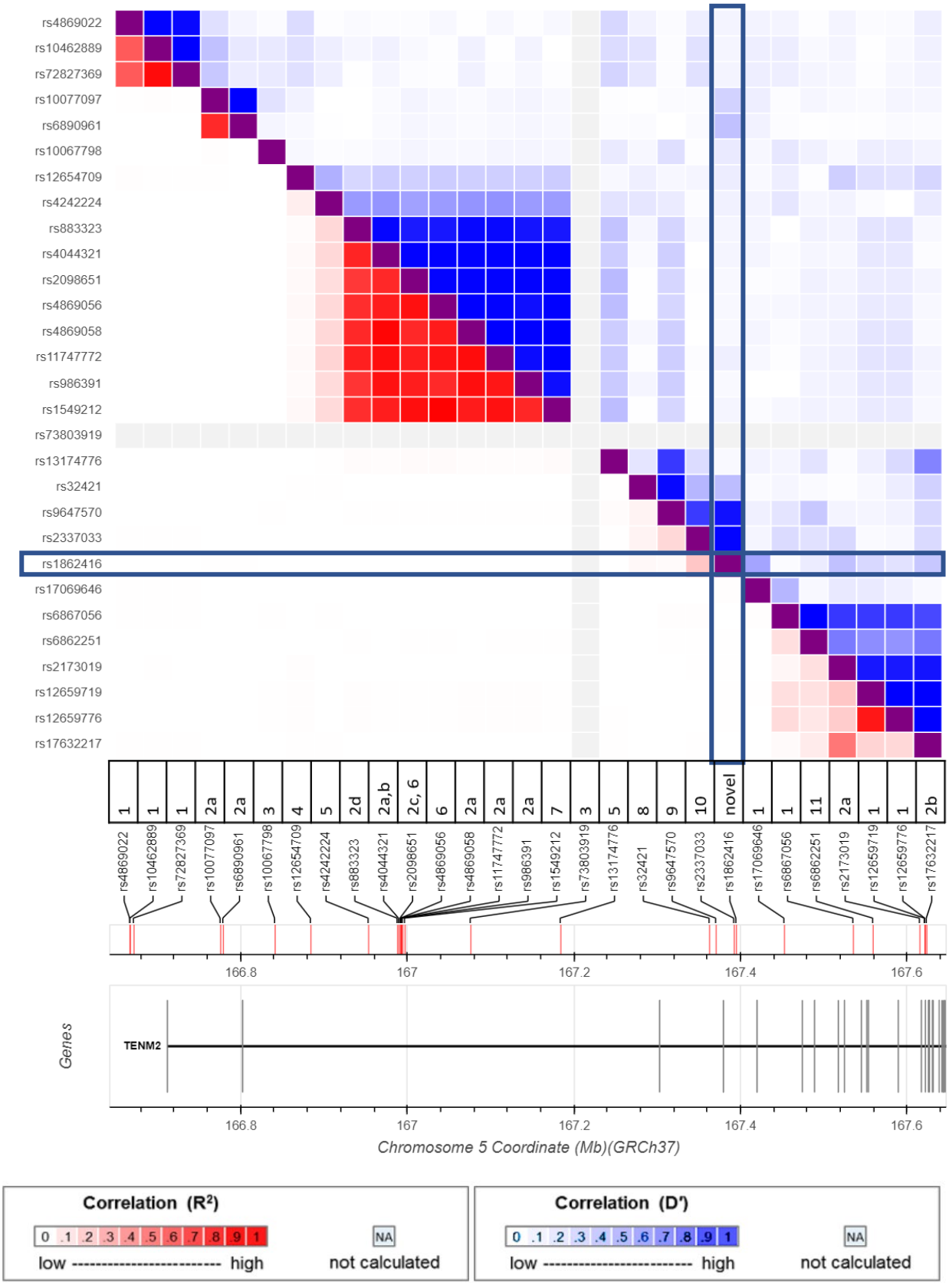

rs1862416-T
Cohort
Ancestry
N
deCODE EURs 15312
NTR EURs 4489
EAGLE EURs 3006
COPDGene2 EURs 2630
COPDGene EURs 2549
FinnTwin EURs 2507
FinnRisk EURs 2211
COGEND EURs 1935
Spit for Science EURs 1717
YalePenn EURs 1579
UW-TTURC EURs 1534
Heroin Dependence GWAS EURs 1138
Minnesota Twins EURs 1073
German EURs 991
SAGE* EURs 832
GAIN EURs 774
eMERGE EURs 730
nonGAIN EURs 671
COGEND2 EURs 292
Dental Caries EURs 243
YalePenn AAs 2637
COPDGene AAs 2534
AAND AAs 1687
ADAA AAs 1145
JHS/ARIC AAs 1143
COGEND AAs 704
SAGE* AAs 633
GAIN AAs 477
COGEND2 AAs 313
COPDGene2 AAs 267
UW-TTURC AAs 247
Meta-analysis EURs & AAs 58000
0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 2.0 2.1 2.2 2.3 2.4 2.5 2.6 2.7 2.8 2.9 3.0 3.1
OR (95% CI)

Supplementary Figure 5. Posterior probability matrices for traits evaluated for shared genetics with ND using GWAS-PW at the 5 FTND-associated genome-wide significant loci.

For the 12 traits, variants in LD (r^2>0.2 in 1000 Genomes EUR populations) with the lead SNP from each genome-wide significant FTND locus was analyzed using GWAS-PW to find shared genetic influences between FTND and each trait. Shown are GWAS-PW posterior probabilities that the genomic region surrounding a lead GWAS SNP contains a variant that influences ND (Model 1); contains a variant that influences the other trait (Model 2); contains a variant that influences both traits (Model 3); or contains a variant that influences ND and a separate variant that influences the other trait (Model 4). The genomic position for each lead GWAS SNP is in reference to GRCh37.


rs1862416 (chr5:167394595)
Model 4 0.009 0.006 0.978 0.009 0.008 0.008 0.004 0.014 0.009 0.012 0.011 0.011
Model 3 0.006 0.01 0.01 0.006 0.004 0.004 0.993 0.005 0.005 0.007 0.002 0.975
Model 2 0 0 0 0 0 0 0 0 0 0 0 0
Model 1 0.985 0.982 0.012 0.984 0.987 0.987 0.003 0.98 0.985 0.98 0.985 0.013
rs2714700 (chr7:79367667)
Model 4 0.011 0.014 0.97 0.011 0.009 0.972 0.007 0.011 0.012 0.997 0.007 0.008
Model 3 0.013 0.003 0.005 0.01 0.007 0.004 0.008 0.005 0.006 0.001 0.003 0.016
Model 2 0 0 0 0 0 0 0 0 0 0 0 0
Model 1 0.958 0.968 0.013 0.964 0.952 0.013 0.967 0.97 0.966 0.001 0.972 0.953
rs13284520 (chr9:136502572)
Model 4 0.99 0.005 0.011 0.014 0 0.013 0.009 0.006 0.014 0.01 0 0.982
Model 3 0.006 0.003 0.006 0.011 1 0.011 0.986 0.003 0.007 0.005 1 0.002
Model 2 0 0 0 0 0 0 0 0 0 0 0 0
Model 1 0.004 0.99 0.981 0.974 0 0.975 0.004 0.99 0.977 0.984 0 0.014
rs16969968 (chr15:78882925)
Model 4 0.01 0.015 0.002 0.981 0 0.006 0.009 0.011 0.014 1 0 0.997
Model 3 0.011 0.009 0.996 0.008 1 0.003 0.002 0.002 0.004 0 1 0.002
Model 2 0 0 0 0 0 0 0 0 0 0 0 0
Model 1 0.979 0.976 0.001 0.01 0 0.991 0.989 0.987 0.983 0 0 0.001
rs151176846 (chr20:61997500)
Model 4 0.007 0.009 0.016 0.001 0 0.006 0.013 0.013 0.015 0.999 0 0.001
Model 3 0.011 0.004 0.008 0.998 1 0.003 0.013 0.01 0.007 0.001 1 0.999
Model 2 0.011 0 0 0 0 0 0 0 0 0 0 0
Model 1 0.011 0.987 0.976 0.001 0 0.991 0.973 0.977 0.978 0 0 0
ADHD
Age of Smoking Initition
Alcohol Dependence
Bipolar Disorder
Cigarettes Per Day
Depressive Symptoms
Major Depressive Disorder
Neuroticism
PTSD
Schizophrenia
Smoking Cessation
Smoking Initiation
Posterior Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0

Supplementary Figure 6. Linkage disequilibrium (LD) matrix of rs1862416 (marked by blue boxes) and other *TENM2* single nucleotide polymorphisms (SNPs) included in the genome-wide association study (GWAS) catalog[87] (https://www.ebi.ac.uk) for their genome-wide significant associations ($P<5\times10^{-8}$). r^2 values, as obtained from LDlink[51], correspond to the 1000 Genomes European panel. Numerical values correspond to the originally reported GWAS: 1, educational attainment[63]; 2a, smoking initiation (ever vs. never smoking)[48,88-90]; 2b, age of smoking initiation[48]; 2c, smoking cessation (current vs. former smoking)[48]; 2d, alcohol consumption (drinks per week)[48]; 3, lung function[90,91]; 4, height[90]; 5, number of sexual partners[88]; 6, depression[92,93]; 7, risk taking tendency[88]; 8, body mass index[90]; 9, menarche (age at onset)[94]; 10, cigarette pack-years[95]; and 11, regular attendance at a religious group[96]. rs11739827, associated with alcohol consumption[48], was not available for comparison with rs1862416 in LDlink.


rs4869022
rs10462889
rs72827369
rs10077097
rs6890961
rs10067798
rs12654709
rs4242224
rs883323
rs4044321
rs2098651
rs4869056
rs4869058
rs11747772
rs986391
rs1549212
rs73803919
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rs32421
rs9647570
rs2337033
rs1862416
rs17069646
rs6867056
rs6862251
rs2173019
rs12659719
rs12659776
rs17632217
1 1 1 2a 2a 3 4 5 2d 2a,b 2c, 6 6 2a 2a 2a 7 3 5 8 9 10 novel 1 1 11 2a 1 1 2b
166.8 167 167.2 167.4 167.6
Genes
TENM2
Chromosome 5 Coordinate (Mb)(GRCh37)
Correlation (R²)
0 .1 .2 .3 .4 .5 .6 .7 .8 .9 1
low ---------- high
NA
not calculated
Correlation (D')
0 .1 .2 .3 .4 .5 .6 .7 .8 .9 1
low ---------- high
NA
not calculated

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