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Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence

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Supplementary Note for

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1. Supplementary Information

1.1 Study Cohort Descriptions and Methodology

We meta-analyzed genome-wide association studies of intelligence measures in 14 cohorts, which are described in detail below.

1.1.1 UK Biobank (UKB)

The UK Biobank Study (<http://www.ukbiobank.ac.uk>) is a large population-based cohort that includes over 500,000 participants¹. The aim of the UK Biobank is to study health-related determinants and outcomes by large-scale data-collection within the general population. The study protocol was approved by the National Research Ethics Service Committee North West–Haydock (reference 11/NW/0382), and all procedures were performed in accordance with the ethical principles for medical research declared in the World Medical Association Declaration of Helsinki. Access to the UK Biobank data was obtained under the UK Biobank application number 16406. Participants were recruited by invitation letters that were sent out to approximately 9.2 million individuals between 37-72 years who were living within 25 miles distance from one of the 22 study assessment centers and were registered with the National Health Service (NHS). In total, 503,325 participants were subsequently recruited into the study¹. Large-scale data collection was performed that included a wide array of phenotypic data, such as registry-based phenotypic information, extensive self-reported baseline data collected by questionnaire, brain imaging, and anthropometric assessments, in addition to genotype data ascertained from blood samples.

We analyzed imputed genotype data from the second release by UK Biobank (July 2017), which includes 92,693,895 genetic variants in 487,442 individuals². Genotyping was divided over 106 batches using two custom Affymetrix genotyping platforms (UK BiLEVE Axiom array $n \sim 50,000$; UK Biobank Axiom array $n \sim 450,000$). Quality control of the genotype data was performed locally by UK Biobank (details available at <http://www.biorxiv.org/content/early/2017/07/20/166298>). Genotypes were imputed using a combination of two reference panels. The first panel consisted of a merged reference panel that included the UK10K haplotype panel and the 1000 Genomes reference panel. In addition, the genotype data was imputed using the Haplotype Reference Consortium³ (HRC) reference panel. If variants were imputed in both panels, the HRC imputation was retained. Following recommendations from UK Biobank, we excluded variants imputed based on the combined UK10K/1000 genomes panel.

For the current GWAS, we only included individuals of European ancestry, defined by projecting ancestry principal components from the 1000 Genomes reference populations⁴ onto the called genotypes available in UK Biobank, and grouping individuals into their closest ancestral population identified by the minimum Mahalanobis distance from the projected principal component scores⁵. We excluded subjects with a Mahalanobis distance >6 SD from their empirically assigned population. Additional filtering of individuals was based on UKB-provided information on genomic relatedness (subjects with most inferred relatives, 3rd degree or closer, were removed until no related subjects were present), discordant sex, sex aneuploidy, missing phenotype or covariate data, and withdrawn consent.

Imputed variants were converted to hard calls at a certainty threshold of 0.9, filtering by an imputation INFO threshold of <0.9 and excluding multi-allelic SNPs, indels, SNPs without a unique rsID, and SNPs with minor allele frequency (MAF) <0.0001 , resulting in a total of 10,847,151 remaining SNPs for analysis. To correct for population stratification, we computed European-specific principal components based on a set of 145,432 independent ($r^2 < 0.1$) autosomal SNPs with MAF >0.01 and INFO=1 using FlashPCA2⁶.

Genome-wide analysis was performed on two fluid intelligence scores available in UK Biobank, that were collected by questionnaire either on a touch-screen device at the assessment center ('touchscreen', field 20016) or by an online questionnaire from home ('web-based', field 20191). The measures indicate the number of correct answers out of 13 questions of verbal and mathematical fluid intelligence. We used the test score that was collected during the first research visit (2006-2010), or during subsequent assessments in case data was missing at the first visit (N=19,831). Test results were available for N=185,317 (touch-screen; ts) and N=123,665 (web-based; wb) individuals. In case individuals had completed both the touch-screen and the web-based test (N=57,450), only the touchscreen test scores were used. In total, 251,532 individuals completed either the web-based (UKB-wb) or touchscreen (UKB-ts) version of the fluid intelligence score and 195,653 European ancestry individuals (142,077 ts/53,576 wb) with available genotype and phenotype data after quality control were included in the analysis (**Supplementary Table 1**).

GWAS was conducted separately for the two phenotypes in PLINK v1.9⁷ using an additive linear regression model and controlling for covariates of age, sex, twenty European-based ancestry

principal components, genotyping array, socioeconomic status assessed by the Townsend deprivation index⁸, and, for UKB-ts, assessment center where the measure was collected.

1.1.2 Cognitive Genomics Consortium (COGENT)

The Cognitive Genomics Consortium (COGENT) data comes from a large consortium that meta-analyzed GWAS results on general cognitive functioning from 24 independent studies (ACPRC, ADNI, ASPIS, CAMH, CHS, CNP, DCC, DNS, DUBLIN, FHS, GCAP, GENADA, HBCS, IBG, LBC1936, LOAD, LOGOS, MCTFR, MUNICH NCNG, PNC, TOP, ZHH). Full descriptions of these cohorts and the analytic methods are provided in Trampush et al⁹, from which the reported GWAS summary stats were obtained. The samples were primarily adults (age range 8-96, $M=46$) and all of European ancestry, from the United States, United Kingdom, and Europe. All studies were approved by their relevant institutional ethics review board. Participants were excluded based on presence of dementia or other neuropsychiatric disorder, where relevant to the study sample. To be included in the COGENT meta-analysis, participants had to have at least one neuropsychological measure available across at least three domains of cognitive performance (e.g. working memory, verbal memory, processing speed, executive function) or a validated g factor measure such as a full-scale IQ test. Common neuropsychological measures used by the studies included the digit symbol, digit span, verbal memory for words/stories, semantic/phonemic fluency, vocabulary, and trail-making tests, as described in Trampush et al⁹. GWAS meta-analysis was performed on a score derived from the first unrotated principal component of the neurocognitive measures. This principal component explained on average 42% (SD=11%) of the variance in overall cognitive test performance. Participants in the

individual samples were genotyped on either Affymetrix or Illumina SNP arrays. After quality control steps including SNP filtering on MAF <0.01 , call rate $<98\%$, Hardy-Weinberg Equilibrium (HWE) $P < 10^{-6}$; and individual filtering on call rate $<98\%$, ancestry outliers, sex mismatch, and cryptic relatedness, samples were imputed to the HRC reference panel. Association analyses were conducted in each cohort using either PLINK v1.9 or BOLT-LMM¹⁰ (for studies whose design included related individuals), using a linear allelic association test with imputed dosages and adjusting for age, sex, and ancestry principal components. Cohort results were meta-analyzed in METAL¹¹ and filtered for minimum imputation INFO score <0.6 , MAF <0.1 , and minimum N $<10,000$.

1.1.3 Rotterdam Study (RS)

The Rotterdam Study is a population-based cohort in the area of Rotterdam, the Netherlands including individuals of 45 years and older¹². The current study included all participants for whom genotypic data was available and who had undergone cognitive testing at the study center from 2002 onwards. The Rotterdam Study protocol has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands, and written informed consent was obtained from all participants. Participants underwent extensive cognitive testing with a neuropsychological battery comprising of the letter-digit substitution task (number of correct digits in one minute), the verbal fluency test (animal categories), the Stroop test (error-adjusted time in seconds for Stroop reading and interference tasks), and a 15-word learning test (delayed recall). Principal component analysis was performed on the test results to estimate a

g-factor, which explained 66.0% of the variation in cognitive test scores. Genotyping was performed on either Illumina 550, Illumina 550 duo or Illumina 610 quad SNP arrays. Variants were filtered on call rate <95%, MAF<0.01, and HWE $P<10^{-6}$. Individuals were filtered based on individual call rate <95%, gender mismatch, outlying heterozygosity, non-European ancestry and relatedness (pairwise IBD >0.185). Genotypes were imputed to the HRC reference panel. Genome-wide analysis of the g-factor was performed in PLINK v1.9 in 6,182 individuals, while correcting for age, sex, genotype array and ancestry principal components.

1.1.4 Generation R Study (GENR)

The Generation R Study is a large birth cohort in the area of Rotterdam, the Netherlands, that investigated approximately 10,000 children born between 2002 and 2006¹³. The study was approved by The Medical Ethical Committee of the Erasmus Medical Center, and parents provided informed consent for their enrolled children. Cognitive testing was done when children were around the age of 6 using the two subtests of the Snijders-Oomen Non-Verbal Intelligence test revised (SON-R)¹⁴. The subsets 'mosaics' and 'categories' were used, which assess spatial visualization abilities and abstract reasoning abilities, respectively. The correlation between the total score derived from these two subsets and IQ scores of the complete test was 0.86 in a subsample of children (N=626). A nonverbal IQ score was derived from the cognitive test scores using normal values tailored to exact age. DNA was extracted either from cord blood at birth or from venipuncture during a later visit to the research center. Genotyping was performed on Illumina 550K or Illumina 610K SNP arrays. An extensive description of the calling procedures and subsequent quality control have been described previously¹⁵. SNP-level

filtering included genotype call rate $<95\%$, MAF <0.01 , and HWE $P < 10^{-6}$. Individuals were filtered on based on individual call rate $<95\%$, outlying heterozygosity, non-European ethnicity, missing phenotype, and relatedness (pairwise IBD >0.185). Genotype data were subsequently imputed to the HRC reference panel. Genome-wide analysis of the derived IQ score in 1,929 individuals was performed using linear regression in PLINK v1.9, while correcting for age, gender, genotype array and ancestry principal components.

1.1.5 Swedish Twin Registry (STR)

The Swedish Twin Registry (STR) is a large epidemiological resource established in 1950s to study smoking and alcohol consumption and disease risk¹⁶. In a subset of this sample ($n = 3,125$), records from the Military Archives of Sweden were matched to participant data to obtain a measure of intelligence that was assessed during military conscription at age 18, as described in Rietveld et al¹⁷. Participants provided written informed consent and the study was approved by the local ethics review board. The assessment included 4 subtests of logical, verbal, spatial, and technical ability, from which the first principal component was extracted for analysis. Participants were genotyped on the Illumina HumanOmniExpress-12v1_A, and genotypes were imputed to the HapMap2 CEU reference population using IMPUTE2¹⁸ after excluding variants with call rate $<95\%$, MAF <0.01 , and HWE $P < 10^{-6}$, and individuals with phenotypic/genotypic sex discordance, outlying heterozygosity (>5 S.D.), relatedness, or non-European ancestry. Genetic analysis with a linear model was conducted using Merlin-offline¹⁹ to account for the relatedness of the twin sample, using an age/sex standardized cognitive

performance score and ancestry principal components as covariates. GWAS summary statistics for this analysis were obtained from previous reports^{17,20}.

1.1.6 Spit for Science (S4S)

The Spit for Science study aims to study genetic, environmental, and developmental influences on substance use and emotional health in a representative sample of college students at a large, urban, public university in the United States²¹. All participants provided written informed consent and the study was approved by the local institutional review board. The study enrolled four cohorts of incoming freshman students to participate in an online self-report survey. Participant data was also matched to university records, from which a measure of intelligence was obtained from scores on the SAT, a standardized test that is widely used for college admission and includes two primary domains of fluid intelligence: critical reading/writing and mathematics. Scores on the SAT are highly correlated with other intelligence tests and provide a good index of g ²². The sample has little variation in age at enrollment ($M=18.5$), although exact age at SAT assessment was not available. However, the SAT is a standard prerequisite for college admissions in the United States and is nearly always taken in the year prior to college enrollment, when participants would have been aged 17-18. Participants were required to be at least age 18 to enroll in the study, and 98% were between 18.0-19.5 at the initial freshman fall assessment.

DNA was isolated from saliva and subsequent genotyping was performed on the Axiom Biobank 650k V2 array. Following removal of poor quality SNPs with call rates $<95\%$, HWE $P < 10^{-6}$, and samples with call rates $<98\%$, sex discordance, outlying heterozygosity, or relatedness,

genotypes were imputed to the 1000 Genomes phase 1 v.3 reference panel. Individuals from this multi-ethnic sample were each assigned to continental super-population groups best reflecting their genetic ancestry by projecting ancestry principal components from the 1000 Genomes reference populations onto the S4S samples and identifying the most closely-related population based on Mahalanobis distances (as described in section 1.1.1; see also Webb et al.⁵). Genetic association analyses were then conducted separately within each of five ancestral super-population groups to avoid spurious association results due to population stratification. Included here are results from the European subset (N=2,818). Analyses were conducted in SNPTESTv2²³ using an additive linear model with sex and within-ancestry principal components (selected via step-wise linear regression association with the phenotype) as covariates.

1.1.7 High IQ / Health and Retirement Study (HiQ/HRS)

This study used an extreme sampling design to compare individuals with high intelligence with unascertained population controls²⁴. The HiQ sample included individuals with exceptionally high IQ (top 0.03% of the IQ distribution) that were identified by the Duke University Talent Identification Program (TIP), a program that identifies high-achieving youth who take the SAT at age 12 instead of the usual age 18. The project received ethical approval from the King's College London Research Ethics Committee (PNM/11/12–51) and the European Research Council Executive Agency ((2012)56321) and informed consent was obtained from all subjects. DNA was derived from buccal swabs and subsequent genotyping was done on the Illumina Omni Express genotyping array. In total, 1,238 high-IQ individuals of European descent were genotyped and passed quality control.

As a population comparison group, individuals were obtained from the publically available University of Michigan Health and Retirement Study (HRS) sample, a representative population-based sample of individuals in the United States aged 50 years and older. Given that these participants come from an epidemiological birth cohort unselected for cognitive or other health-related outcomes, it is presumed that intelligence follows a typical normal distribution in this sample. Genotype data was based on saliva, and genotyping was performed on Illumina Human Omni-2.5 Quad Beadchip. These data were obtained through dbGaP (accession: phs000428.v2.p2, https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000428.v2.p2). After quality control and ancestry-matching to the HiQ participants, genotypes were available for 8,172 European ancestry individuals.

Quality control steps, performed separately in the two samples, included filtering SNPs with call rate <98%, HWE $P < 10^{-6}$, or MAF <0.005 and samples with call rate <98%, outlying heterozygosity (>4 SD), relatedness, or outlying ancestry. Samples from both studies were imputed to the HRC reference panel. High IQ individuals were used as cases and population comparisons as controls in a logistic regression model in SNPTESTv2 using imputed dosages of SNPs with MAF >0.01 and INFO >0.9, controlling for sex and ancestry principal components. Therefore, unlike the rest of the cohorts, the phenotype for this cohort was status as a high-IQ or unselected individual, rather than a measured intelligence score.

1.1.8 Twin Early Development Study (TEDS)

The Twins Early Development Study (TEDS)²⁵ is a longitudinal cohort study investigating over 11,000 twin pairs from England and Wales between 1994 and 1996. The study was approved by

the ethics committee of the Institute of Psychiatry (05/Q0706/228), and consent was obtained from parents of the participants. Cognitive testing was performed at the age of 12, using the WISC-III-PI Multiple Choice Information (General Knowledge) and Vocabulary Multiple Choice subtests²⁶, and two nonverbal reasoning tests, the WISC-III-UK Picture Completion²⁶ and Raven's Standard and Advanced Progressive Matrices^{27,28}, which were all administered online²⁹. g-scores were derived as the arithmetic mean of the four standardized test scores. DNA was obtained from saliva and buccal cheek swabs. Genotyping was performed on either an Affymetrix GeneChip 6.0 (N=2,241) or Illumina HumanOmniExpressExome SNP array (N=1,173), which were imputed and analyzed separately (referred to as TEDS1 and TEDS2, respectively, throughout the manuscript). Individuals were filtered from subsequent analysis based on call rate <0.99%, non-European ancestry, outlying heterozygosity, poor array signal intensity, and relatedness. SNPs were filtered on MAF <0.05, and genotype call rate of <99%, and HWE $P < 10^{-5}$. Genotype data were imputed to the HRC reference panel. GWAS was conducted with a linear regression model using hard-called imputed dosage data in PLINK v1.9, correcting for sex, age at assessment and ancestry principal components.

1.1.9 Danish Twin Registry (DTR)

The Danish Twin Registry sample (DTR) included 990 participants that were collected as part of two studies: the study of Middle-Aged Danish Twins (MADT, n=737) and the Longitudinal Study of Aging Danish Twins (LSADT, n=253). Written informed consent was obtained from all participants. Collection and use of biological material and survey information were approved by the Regional Scientific Ethical Committees for Southern Denmark, and the study was approved

by the Danish Data Protection Agency. MADT was initiated in 1998 and includes 4,314 twins randomly chosen from the birth years 1931-1952³⁰. Surviving participants were revisited from 2008 to 2011³¹, where blood samples and cognitive test data were collected. LSADT was initiated in 1995 and includes twins aged 70 years and older. Follow-up assessments were conducted every second year through 2005³². The individuals included in the present study all participated in the 1997 assessment, where blood samples and cognitive data were collected from same sex twin pairs. The phenotype in both MADT and LSADT was a composite cognitive score that included tests of verbal fluency, forward and backward digit span, and immediate and delayed recall³³. In both studies, independent samples (excluding co-twins within a pair) were used for analysis.

Samples from MADT (N=737) were genotyped using the Illumina Infinium PsychArray (Illumina San Diego, CA, USA). Genotyping was conducted by the SNP&SEQ Technology Platform, Science for Life Laboratory, Uppsala, Sweden (<http://snpseq.medsci.uu.se/genotyping/snp-services/>). Pre-imputation quality control included filtering SNPs on genotype call rate <98%, HWE $P < 10^{-6}$, and MAF=0, and individuals on sample call rate <99%, relatedness and gender mismatch. Pre-phasing and imputation to the 1000 Genomes phase I v.3 reference panel was performed using IMPUTE2 and a chunk-size of 1 MB. GWAS was conducted using hard-called imputed dosage data in PLINK v1.9 using age and sex as covariates in a linear regression model. Samples from LSADT (N=253) were genotyped on the Illumina Infinium PsychArray BeadChip and underwent quality control procedures including filtering SNPs on call rate of <98%, HWE $P < 10^{-6}$, and filtering individuals based on individual call rate <99%, relatedness and gender mismatch, before imputation to the 1000 Genomes phase I v.3 reference panel. GWAS was conducted

using a linear regression model with hard-called imputed dosage data in PLINK v1.9 using age, sex, and ancestry principal components as covariates.

1.1.10 IMAGEN

The IMAGEN study is an international collaboration that studies mental health in adolescents from the UK, France, Ireland and Germany³⁴ and collects data from self-report questionnaires, behavioral assessment, interviews, brain imaging and genetic data. The study protocol was approved by the local ethics committees and all participants and their parents provided written informed consent/assent. The study conducted a neurocognitive test battery in subjects from three subsamples. Principal component analysis was performed to obtain a general factor of cognition based on WISC IV²⁶ subtests (matrix reasoning, block design, digit span backward and forward, similarities and vocabulary) and the CANTAB battery³⁵ (pattern recognition, rapid visual information processing and spatial working memory). The first principal component explained more than twice as much variance as compared to the following components, and was used as a general factor of IQ (g-factor). DNA was collected from blood obtained by venipuncture and genotyping was performed using Illumina Quad 610 chips. Data was collected from eight different study sites and genotyped in three batches, for which quality control, imputation, and analysis were performed separately. In each batch, SNPs were filtered based on call rate <0.98 and HWE $P < 10^{-6}$ and individuals were filtered based on individual call rate $<98\%$, outlying heterozygosity rate (<0.2), pairwise IBD >0.2 , and non-European ancestry. Genotype imputation was performed using the pre-phasing/imputation stepwise approach implemented in IMPUTE2/SHAPEIT2³⁶ (chunk size of 3 Mb and default parameters) with the

1000 Genomes Project reference panel phase I v3. Post-imputation, SNPs were additionally filtered for INFO > 0.8 and missingness < .01. GWAS was conducted on each dataset using an additive linear model in PLINK with ancestry principal components as covariates and results were meta-analyzed across the three subsamples (N=1,343 individuals) using METAL with an inverse variance-weighted fixed effects scheme.

1.1.11 Brisbane Longitudinal Twin Study (BLTS)

The Brisbane Longitudinal Twin Study (BLTS) was initiated in 1992 at the Queensland Institute of Medical Research (QIMR)³⁷. Twelve year old twins and their non-twin siblings were recruited from primary and secondary schools, and were followed over time, including cognitive testing at the age of 12 and 16. Cognitive phenotypes included IQ scores from the Multi-dimensional Aptitude Battery II (MAB)³⁸ at age 16 and the first factor score from the Verbal and Spatial Reasoning Test for Children (VSRT-C)³⁹ at age 12. Participants were genotyped using Illumina 610-Quadv1 or Illumina HumanCoreExome-12v1 chips using DNA extracted from blood samples in the majority of the cases. Data was screened for genotyping quality (GenCall < .7 from the 610k chip), SNP call rates (< 0.95% or < 0.99% for exome markers), HWE $P < 10^{-6}$, MAF < 0.01, individual call rate < 0.95%, non-European ancestry, and pedigree, sex, and Mendelian errors. Data from the two genotype arrays were phased separately using SHAPEIT2 and imputed to the HRC reference panel. The GWAS was performed separately in children (QIMR-C, N=530) and adolescents (QIMR-A; N=2,598) using RareMetalWorker⁴⁰ software to account for relatedness, with sex, age, ancestry principal components and imputation run included as covariates in a linear model.

1.1.12 Netherlands Study of Cognition, Environment and Genes (NESCOG)

The Netherlands Study of Cognition, Environment and Genes (NESCOG), is a population-based study of adults that investigates genetic and environmental determinants of cognitive function⁴¹. For the current study a population-based family sample of NESCOG was used including 560 participants (330 females) that participated in a gene-environment interaction study on cognition. The study was approved by the institutional review board of Vrije Universiteit Amsterdam and participants provided informed consent. General cognition was measured using the full Wechsler Adult Intelligence Scale (WAIS)⁴². Genotype data was generated on the Illumina PsychChip array with HumanCore, Human Exome, and custom content. Pre-imputation SNP filtering included MAF <0.05, and genotype call rate of <99% and HWE $P < 10^{-6}$. Individuals were filtered on outlying heterozygosity, genotype call rate <95% and non-European ancestry. Genotypes were subsequently imputed to the HRC reference panel. GWAS was conducted on the age- and sex-standardized scores using hard-called dosages in a linear model in PLINK v1.9 with ancestry principal components as covariates for 252 individuals with available phenotypic and genotypic data.

1.1.13 Genes for Good (GfG)

Genes for Good (GfG) is an online genetic study (<http://genesforgood.org>) hosted at the University of Michigan investigating health-related traits through the Facebook App Platform. The study is open to anyone in the US over the age of 18. The study methods were approved by the University of Michigan institutional review board and all participants provided written

informed consent. Participants were asked to fill out various health-related surveys including the ICAR 16 item Verbal Reasoning Test⁴³ (<https://icar-project.com/>), consisting of questions related to vocabulary, general knowledge, and logical deduction. The final phenotype is a factor extracted from a 2-parameter item response theory model on participant responses to the Verbal Reasoning Test. Genotyping on saliva samples was conducted on a standard Illumina HumanCoreExome BeadChip and Illumina HumanCoreExome BeadChip with custom content. Pre-imputation quality control included filtering SNPs with MAF <0.05, genotype call rate <99%, ambiguous SNPs with MAF >0.4, HWE $P < 10^{-3}$, and individuals with sex discordance, individual call rate <99%, and non-European ancestry based on principal component analysis. Genotypes were imputed to the HRC reference panel. Genome-wide analysis was run on 5,084 individuals using a linear regression model in PLINK v1.9, and results were corrected for age, sex and ancestry principal components.

1.1.14 Swedish Twin Studies of Aging (STSA)

The Swedish Twin Studies of Aging include three studies grouped into two analytic cohorts, all samples of older adults with no history of stroke or dementia. All participants provided informed consent and the study was approved by the Regional Ethics Board in Stockholm and the Institutional Review Board at the University of Southern California. The Swedish Adoption/Twin Study of Aging (SATSA) and the “Sex differences in health and aging” (GENDER) studies include twins born, respectively, between 1886-1958 (SATSA)⁴⁴ and 1906-1925 (GENDER)⁴⁵. The SATSA sample of like-sex twins and the GENDER sample of unlike sex twins were assessed at an in-person visit on a neurocognitive battery. The first principal component

was extracted from four ability tests available in 703 participants from the combined SATSA and GENDER samples, spanning verbal (Synonyms), spatial (Block Design), episodic memory (Thurstone Picture Memory), and processing speed (Digit Symbol) domains. This factor accounted for 60.79% of the variance in the four tests. DNA was extracted from blood samples and genotyped using the Illumina Infinium PsychArray. Data was cleaned for sample call rate <99%, SNP call rate <98%, HWE $P < 10^{-6}$, and non-European ancestry samples. Samples were phased and imputed to the 1000 Genomes phase 1 v.3 reference panel using SHAPEIT2+IMPUTE2. Association analysis was conducted using a linear model in PLINK v1.07⁴⁶ with age, sex, and ancestry principal components as covariates and cluster-robust standard errors to correct for twin pair dependency.

The Study of Dementia in Swedish Twins (HARMONY) includes twin pairs of like and unlike sex born before 1935 who completed a full clinical workup⁴⁷. The first principal component was extracted from five intelligence tests in 448 participants, spanning verbal (WAIS Information subtest), executive functioning (Verbal Fluency), spatial (WAIS Block Design), episodic memory (Word List Learning-Delayed Recall), and processing speed (Digit Symbol) domains, and this factor accounted for 55.6% of the variance in task performance. Genotyping, quality control, and data analysis followed the same procedures as in the SATSA+GENDER cohort but were conducted separately.

1.2 Operationalization of intelligence

The various cohorts used different measures to assess intelligence (see **Supplementary Figure 2**). However, decades of research have firmly established that virtually all aspects of cognitive

functioning – verbal and mathematical ability, abstract reasoning, processing speed, executive functioning, spatial reasoning, memory, etc. – are captured primarily by a single underlying latent factor, labeled general intelligence or Spearman's g ⁴⁸. This is known as the positive manifold of cognitive ability or intelligence. Cognitive tests may comprise a single complex task that simultaneously taps into facets from each of these domains, or may be a constellation of multiple sub-tests each from a single domain. Regardless of the specific construction, correlations between performance on all such validated cognitive tests are high⁴⁹. Further, the g factor underlying multiple different test batteries has been shown to be identical⁵⁰, indicating that different tests or different configurations of sub-tests index the same construct. While there are specific genetic and environmental influences on sub-domains of intelligence (for example, mathematics versus vocabulary), the covariance between these domains is best captured by a higher-order g factor, and this g factor accounts for most of the genetic influences on specific domains⁵¹. Phenotypes which extract the commonalities across multiple domains of cognitive functioning will thus be most informative for genetic association analyses. Meta-analysis of such phenotypes will improve power to detect variants that either have direct effects on individual variation in the g factor (i.e., a single system underlying global cognitive functioning), or variants which have pleiotropic effects across multiple domains of cognitive functioning that are indirectly captured by g . Unfortunately, as GWAS is simply a statistical association technique, it can only point to which genetic variants demonstrate a significant association and not what the mechanism for this association might be, requiring follow-up with functional testing and phenotypic refinement to determine how these variants and genes are linked to intelligence.

In the present study, all cohorts except HiQ/HRS used a quantitative measure of intelligence consisting of either a principal component extracted from multiple tests from different cognitive sub-domains (*g* factor), or a score from a composite measure with multiple sub-domain tests included by design (full-scale IQ scores from the WISC, WAIS, MAB, or SON-R; fluid intelligence measure summed over verbal and mathematical reasoning items; or the SAT college entrance exam which has both verbal and mathematical reasoning components). The GfG cohort is slightly more limited than the others in that its *g* factor was derived primarily from the verbal reasoning domain, and may capture somewhat less (but still a substantial proportion⁴⁹) of the influence of the general intelligence factor. As the HiQ/HRS study sampled individuals from the extremely high and normal ranges of the Gaussian IQ distribution, it can be expected that the two sub-samples of this study differ on mean levels of the same *g* factor that underlies IQ scores. With the exception of severe intellectual disability caused by rare, usually Mendelian, mutations, high and low intelligence form a part of the same spectrum of variation as the normal range of intelligence⁵²⁻⁵⁵, and so the “cases” and “controls” in this sample are expected to differ only quantitatively and not qualitatively in the genetic variants that influence intelligence.

We note that while differences in assessment methods across cohorts may reduce power to detect true associations in meta-analysis, it simultaneously reduces type I error by removing sources of measurement error that may be correlated between assessments when they are derived from the same method. Results therefore will more likely reflect genetic variants with robust associations to the common latent factor underlying general cognitive test performance across multiple methods and not those confounded by correlated measurement error.

2. Supplementary Results

2.1 Cohort-Specific Analyses

2.1.1 GWAS results per cohort

For each cohort, an individual GWAS was run after cohort-specific quality control was performed, as described in detail in **Supplementary Information 1.1**. Results were inspected for inflation possibly due to insufficiently corrected population stratification, by calculating the lambda inflation factor as well as the LD score intercept using LD score regression⁵⁶. A lambda > 1 suggests an inflation of the genetic effects which can be due to both spurious and genuine effects. It is likely to increase with sample size and degree of polygenicity of the trait, as the distribution of effect sizes begins to differ substantially from a null distribution when more variants have true associations. An LD score intercept > 1 suggests that there is spurious association, and an intercept <1.10 is generally considered to suggest that the signal is mostly due to genuine association effects. For all cohorts except the HiQ/HRS cohort the LD intercept was < 1.04, and the intercept for the meta-analysis was 1.08 (compared to inflation of $\lambda_{GC}=1.92$), suggesting the genetic signal is mostly due to polygenicity and unlikely to be driven by population stratification (**Supplementary Table 4**).

For HiQ/HRS, the intercept was a bit higher at 1.14, although this is not outside the range reported for methodologically sound GWAS studies⁵⁶. The HiQ/HRS was unusual among the meta-analysis cohorts in that it used a case-control design with samples recruited from two quite different populations, and it is possible that this influenced how well the LD reference population was matched and thus inflated the intercept. However, we note that there was no

evidence of inflation in a similar analysis with this sample using hard-called genotypes²⁴. Further, when excluding this sample from the meta-analysis, 78% of genome-wide significant (GWS; $P < 1 \times 10^{-8}$) SNPs from the full meta-analysis retain a GWS association and 100% retain at least suggestive significance ($P < 5 \times 10^{-5}$), indicating that this sample is not contributing any additional spurious association signals. We see that this follows an expected pattern in which the increase in sample size boosts existing signal beyond a GWS threshold rather than identifying wholly distinct loci, as 94% of GWS SNPs remained significant and 100% were suggestive when excluding the smaller S4S sample (N=2,818), and 56% and 98% were GWS and suggestive, respectively, when excluding the larger set of non-adult samples (N=65,639) in the age group-specific meta-analyses.

2.1.2 Genetic correlations between cohorts

Genetic correlations between the GWAS results from all cohorts included in the meta-analysis, except 6 cohorts with $N < 800$, were calculated with LD Score regression (**Supplementary Table 2**). This method does not limit estimates of correlations between -1 and 1 , to avoid bias in standard errors, but an r_g that is out of bounds (< -1 or $> +1$) usually means that one of the h^2 estimates was very close to zero^{56,57}. Estimates of r_g ranged from -0.309 to 2.033 , with lower or out of bound r_g 's coming almost exclusively from cohorts with small sample size ($N < 3,000$). LD score regression estimates are highly variable and subject to chance fluctuation in small samples, thus a low or inconsistent r_g in these samples is not necessarily troubling on its own. No single cohort showed consistent low r_g 's with all of the other cohorts, and thus we kept all cohorts in the meta-analysis. Capping the out-of-bound estimates at $[-1, 1]$, the average

correlation between cohorts was 0.67. The three largest cohorts ($N > 10,000$: UKB-ts, UKB-wb, COGENT) were all very highly correlated, $r_g > 0.90$, and each of the smaller cohorts showed a correlation of at least 0.56 with one of these three. Of the 21 pairwise correlations involving cohorts with $N > 3000$, 20 were statistically significant (at $P < .05$) and all were positively correlated ($r^2 > 0.56$), indicating that substantial genetic overlap exists between cohorts so long as the sample size is large enough to obtain stable standard errors. Notably, despite having a different type of phenotype than the rest of the quantitative samples, the case/control HiQ/HRS sample was highly genetically correlated with the other cohorts ($r_g > 0.72$ with UKB-ts, UKB-wb, and COGENT; mean $r_g = 0.71$ with all cohorts).

2.1.3 SNP heterogeneity between cohorts

In addition to the primary fixed-effects meta-analysis, we conducted a random-effects meta-analysis to test for heterogeneity in the SNP association effects between cohorts. In the phase 1 meta-analysis (all cohorts except HiQ/HRS), no SNP had a heterogeneity test P -value below the GWS threshold, and 5.1% of all SNPs had a P -value less than a nominal threshold of 0.05. Among the 242 GWS lead SNPs reported here (see [Supplementary Results 2.3](#) below), none had a heterogeneity test P -value less than 0.05/242. In the phase 2 meta-analysis (phase 1 plus HiQ/HRS), a single SNP (rs7670286; meta-analysis $P = 0.59$) had a heterogeneity test P -value below the GWS threshold, and 4.3% of all SNPs had a P -value less than a nominal threshold of 0.05. Among the 242 GWS lead SNPs reported here, none had a heterogeneity test P -value less than 0.05/242. Further, 15.5% of all meta-analysis SNPs, 29.3% of GWS SNPs, and 33.0% of lead SNPs were sign-concordant in more than 80% of available cohorts. Assuming that 10 cohorts

were available for meta-analysis (this number differs per SNP but is conservative when the number is larger), the expectation of observing >80% sign concordance by chance in a binomial distribution is 1.1%. Based on this expected proportion, the observed sign concordance rates for all SNPs, GWS SNPs, and lead SNPs were all significantly higher than that expected by chance (χ^2 test $P_s < 3 \times 10^{-20}$). Although a visual comparison of the individual cohort GWAS results (**Supplementary Figure 1**) shows clear differences in the associations detected in each cohort, these results are consistent with such effects being driven by differences in sample size/power rather than qualitative differences in the associated variants between cohorts. As noted in **Supplementary Results 2.1.1**, the consistency of significant/suggestive loci when excluding various subsets of the meta-analytic sample also corroborates to the homogeneity of genetic association effects between cohorts.

2.2 Age Group Comparisons

The vast majority of subjects included in the meta-analysis were adults, yet the relatively small child (N=9,814), young adult (N=6,033), and older adult (N=8,323) sub-samples were highly genetically correlated with the adult sample (**Supplementary Table 3**) suggesting that the same genetic effects are important across age groups. Although the point estimates of heritability were slightly larger in children (0.22), young adults (0.21), and older adults (0.23) versus adults (0.20), standard errors of the estimates in these subsets were overlapping, indicating that these could not be differentiated from equality.

2.3 Meta-analysis Results

2.3.1 Genomic risk loci

The meta-analysis resulted in 12,110 SNPs with a GWS association ($P < 5 \times 10^{-8}$), representing 524 *independent significant SNPs* in distinct LD regions ($r^2 < 0.6$). These signals were indexed by 242 *lead SNPs* ($r^2 < 0.1$) in 213 independent *genomic risk loci* after merging regions < 250 KB apart into a single locus (**Supplementary Table 5**). The borders of the genomic risk loci were defined by taking all independent GWS SNPs in a locus and then identifying all SNPs that were in LD with one of these SNPs in the reference panel, as detailed in the **Online Methods**. Annotated *candidate SNPs* ($N=21,403$) used for the follow-up analyses detailed below are all SNPs that are located in a risk locus and that are in LD with one of the independent GWS SNPs. Of the 12,110 GWS SNPs, 30 SNPs were not available in the UKB reference panel; 17 of these were within the positional boundaries of a risk locus and were included as such, and 13 were outside of bounds of defined risk loci (**Supplementary Table 6**).

Close visual examination of the regional association plots for each GWS locus (**Supplementary Figure 4**), which provide a zoomed in view of the SNPs contributing to the association signal in a linkage disequilibrium block, indicated 8 loci (#s 8, 40, 66, 82, 124, 134, 197, and 200) for which the patterns of association appeared suspicious (**Supplementary Figure 5**). Specifically, these regions had only one or two SNPs whose association was GWS, in contrast to a pattern of broad enrichment for SNPs in a local region that is seen in the majority of credibly associated loci due to the correlation of test statistics between SNPs in linkage disequilibrium. We investigated these loci further (**Supplementary Table 7**) and did not find obvious signs that would indicate genotyping errors or other statistical artefacts, such as poor imputation quality, inconsistent association statistics between cohorts (comparing our three largest cohorts, UKB-ts, UKB-wb,

COGENT, since test statistics can fluctuate substantially in small samples), major allele frequency differences from a reference panel, or patterns of regional LD that differed from a known reference panel. These SNPs generally also did not have low MAF, which might have explained the absence of LD proxies. These 8 loci appeared to be regions for which there were simply few other SNPs in strong LD with the lead SNP, and so there is a lack of information available to infer whether these represent credible association signals. None of the SNPs in these regions have been previously reported to have an association with intelligence or other cognitive phenotypes, and none were implicated in the proxy replication. We therefore have less confidence that these loci represent true genetic associations until they are replicated in future research, and so we report the total number of robustly associated genomic loci for intelligence as 205 (213-8). We do, however, include these eight more tentative loci in all tables for reference and future replication, with a notation of any results that stem from their inclusion.

These loci were mapped to genes *TTL7* (locus 8, positional mapping), *ZNF385B* (locus 40, positional mapping), *ANAPC4* (locus 66, eQTL mapping), *CCDC149* (locus 66, positional and eQTL mapping), *SREK1IP1* (locus 82, positional mapping), *RIMS2* (locus 124, positional mapping), *DCC* (locus 197, positional mapping, although this gene also overlapped a second nearby locus, 198, that included many GWS SNPs), and *MAN2B1* (locus 200, eQTL mapping but also implicated via eQTL mapping from nearby locus 201). Of these genes, three genes (*ANAPC4*, *DCC*, *RIMS2*) also had a significant MAGMA gene-based *P*-value ($P=1.67\times 10^{-7}$, $P=9.17\times 10^{-23}$, and $P=8.08\times 10^{-9}$ respectively, **Supplementary Table 15**) as they included multiple SNPs with *P*-values around the suggestive threshold of association, even though only a single SNP in these genes was GWS by

itself. *CCDC149* and *DCC* have been previously linked to intelligence in gene-based tests, although no SNPs had individually been associated^{20,58}. None of these genes were found in the set of 92 genes implicated by all four mapping strategies (**Supplementary Table 16**). *RIMS2* was included in the *neurogenesis*, *regulation of nervous system development*, and *positive regulation of nervous system development* gene-sets that showed significant enrichment, and *DCC* was included in the *neurogenesis*, *neuron differentiation*, *central nervous system neuron differentiation*, and *regulation of nervous system development* gene-sets (**Supplementary Table 18**).

The 205 (i.e. 213-8) identified genomic risk loci were spread throughout the genome, with one or more risk loci found on every autosome. Of these, 190 were novel, which we defined as loci for which no SNPs within the positional bounds of the genomic risk locus (including SNPs that were not analyzed in the meta-analysis) had been previously linked to “intelligence”, “cognition”, or “cognitive ability” in the NHGRI-EBI catalog or in our manual lookup of recently published GWAS for these phenotypes (**Supplementary Table 24**). The genomic risk loci and their functional consequences are described further below in **Supplementary Results 2.3.5**.

Although chromosome X was included in the meta-analysis, we only had genotyped SNPs (N=14,847) on this chromosome available in the two UKB cohorts (N=195,653) (**Online Methods**). We did not find any GWS association on chromosome X with the currently available N for X, yet, given the difference in sample size and number of SNPs examined in comparison with the autosomes, their results are not directly comparable. We note that the current lack of GWS results does not necessarily imply there are no relevant genetic variants located on chromosome X. Current challenges with genotyping, imputation, and quality control of the X

chromosome often result in a disproportionately small number of high quality SNPs available for analysis, making its potential genetic contributions difficult to uncover⁵⁹.

2.3.2 Proxy replication

We tested for replication of the identified SNPs/loci using the proxy phenotype of educational attainment. Although replication would be more direct with the same measured intelligence phenotype, there are not, to our knowledge, other equally large independent cohorts with well-characterized assessments of intelligence. A sample size on par with that of the discovery sample is necessary to independently validate variants with very small effects, especially given the common occurrence of larger-than-expected associations being identified in the first discovery sample in a phenomenon known as “winner’s curse”.

Educational attainment is an easily and reliably measured phenotype and so has been collected in many hundreds of thousands of available samples. The genetic correlation between educational attainment and intelligence is among the largest observed between any pair of complex cognitive/psychiatric traits ($rg > .70$)^{9,20}, and there is evidence that intelligence directly impacts later educational attainment⁶⁰ and that (some of) the genetic effects on educational attainment are mediated through intelligence⁶¹. Educational attainment is therefore well-suited for use in validating genetic associations with intelligence and has been successfully applied as a proxy phenotype in several previous reports^{17,20}.

SNP-based proxy replication was conducted in a GWAS of educational attainment using a large, non-overlapping subset of the UKB sample (N=188,435; **Online Methods**), which included UKB subjects for which data on intelligence was not available and who were not genetically related

to any of the subjects for whom intelligence data was available. The GWAS results on educational attainment in UKB showed a high genetic correlation with previously published results of a GWAS meta-analysis of educational attainment⁶² (LDscore regression $r_g=0.93$, $SE=0.013$), as well as a robust genetic correlation with the intelligence meta-analysis results ($r_g=0.73$, $SE=0.020$). Out of the 12,110 GWS SNPs for intelligence, 12,093 were available for look-up, as were all of the 242 independent lead SNPs. We found that the effects of 11,280 out of 12,093 total SNPs (93%; exact binomial $P=5\times 10^{-324}$) and the effects of 226 out of 242 independent lead SNPs (93%; exact binomial $P=1\times 10^{-48}$) were sign concordant between educational attainment and intelligence (**Supplementary Table 8**). This approach resulted in 48 proxy-replicated loci (with $P<0.05/242$ for educational attainment). In 38 of these loci, the lead SNP for intelligence in the locus was significantly associated with educational attainment, while in the other 10 an LD proxy of the intelligence lead SNP was associated with educational attainment (**Supplementary Table 8**).

2.3.3 Polygenic score validation

To evaluate the replicability and predictive utility of our SNP-based results, we estimated the variation in intelligence that could be explained by the current GWAS meta-analysis by calculating a polygenic score (PGS) in four independent cohorts using LDpred⁶³ and PRSice⁶⁴ (**Online Methods**). The four cohorts were each separately excluded from the meta-analysis, which was then re-run so the results could be used to calculate PGS in each independent hold-out sample.

There was good concordance between the two methods, with LDpred PGS explaining 2.4% - 4.7% ($P < 1 \times 10^{-21}$) of the variance in intelligence in each sample at the best prior of $p=1.0$ /infinitesimal and PRSice PGS explaining 2.0% - 5.2% of the variance in each sample ($P < 2 \times 10^{-19}$) when filtering the included SNPs by meta-analysis p thresholds of $< .11$ (**Supplementary Table 9**), an increase in maximum explained variance of 0.4% compared to the previous largest GWAS meta-analysis²⁰. Surprisingly, the proportional increases in number of associated loci found with this sample size relative to previous studies (205 versus 18 loci with sample $N=269,867$ versus 78,303) did not translate to a similarly large increase in variance explained by PGS ($r^2=5.2\%$ versus 4.8%).

2.3.4 Stratified heritability

Stratified heritability analyses showed enrichment of several functional genomic categories (**Supplementary Table 10**), including conserved regions of the genome (Enrichment of 16.44, proportion $h^2=.428$, $P=2.01 \times 10^{-12}$), coding regions (Enrichment of 8.19, proportion $h^2=.120$, $P=1.67 \times 10^{-6}$), H3K9ac histone regions (Enrichment of 2.44, proportion $h^2=.307$, $P=6.25 \times 10^{-5}$), and the narrow H3K9ac peaks in these regions (Enrichment of 6.18, proportion $h^2=.239$, $P=2.04 \times 10^{-5}$). H3K9ac is a histone mark that indicates an active promoter or enhancer region⁶⁵. These annotations are not mutually exclusive, and in fact there is high evolutionary conservation for both protein-coding regions and regions of distal regulatory activity^{66,67}. These results suggest that biological processes relevant for intelligence include those that are common across species, those that directly affect protein structure/function, as well as those that have indirect effects via regulatory mechanisms. These genetic effects come

disproportionately from variants that are very common, with greatest enrichment for SNPs with a minor allele frequency (MAF) between 0.4 and 0.5 ($P=1.34\times 10^{-12}$) in human populations (**Supplementary Figure 6**) but they are spread proportionally across the genome (**Supplementary Figure 7**), likely reflecting a high degree of polygenicity and the involvement of a large proportion of the genome in variation in intelligence. However, we note that our MAF filtering criteria during the quality control stage reduces the number of variants available with low (mostly <0.01) frequency, and so may not be an accurate representation of the effects of these variants.

2.3.5 Description and functional annotation of genomic risk loci

Using FUMA, we annotated all 21,403 SNPs that were in LD (≥ 0.6) with one of the independent significant SNPs, allowing further inspection of these variants. Functional annotations included ANNOVAR⁶⁸, which identifies the SNP's genic position (e.g. intron, exon, intergenic), Combined Annotation Dependent Depletion (CADD)⁶⁹ scores, which predict how deleterious the effect of a SNP is on protein structure/function, RegulomeDB⁷⁰ (RDB) scores, which predict likelihood of regulatory functionality, and chromatin states from the Roadmap ChromHMM model^{67,71}, which predict transcription/regulatory effects from chromatin states at the SNP locus.

Of the 21,403 candidate SNPs, 21,368 were available for lookup in the annotation databases. These SNPs were mostly located in intronic ($n=10,961$; 51.3%) and intergenic areas ($n=7,149$; 33.4%) (**Supplementary Table 6; Figure 1c**), yet 5.2% (1,103 SNPs) were annotated to functional genic regions, with 1.4% (293 SNPs) being exonic. The most likely genetic variants to have a substantial impact on a phenotype are those that have a direct consequence on a protein,

specifically variants located in coding exons that have a nonsynonymous change resulting in a change to the protein's amino acid sequence (ExNS SNPs). Of the annotated SNPs in GWS loci, we identified 146 ExNS located in 113 unique genes (**Supplementary Table 11**). Eighteen genes included more than 1 ExNS: *AKAP6*, *ALMS1*, *BSN*, *BTN2A1*, *CELSR3*, *DDX27*, *GNL3*, *ITHIH1*, *LINC02089*, *MST1R*, *MTMR4*, *PCDHA1*, *PCDHA3*, *RECQL4*, *RNF43*, *STAB1*, *TRIOBP*, and *ZNF638*. Sixty-four ExNS had CADD scores above 12.37 (the threshold suggested by Kircher et al.⁶⁹ to be deleterious) and 18 had a RDB score of 1d or 1f, suggesting they were likely affecting binding sites and gene expression. Apart from the protein consequences of ExNS variants, the rest of the implicated SNPs also showed evidence of indirect effects on gene products: 2.9% had a RegulomeDB⁷⁰ score of 1a-1f (**Figure 1d**), suggesting a regulatory function, and the majority of candidate SNPs (80.0%) were in open chromatin regions^{67,71}, as indicated by a minimum chromatin state of 1-7 (**Figure 1e**).

From the full GWAS results, the strongest signal ($P=7.48^{-31}$) was on chromosome 6 (risk locus 104), with the most associated lead SNP rs1906252. There were two other independent lead SNPs in the same locus (rs77418166 and rs6928545), indicative of multiple strong signals co-localized in this region of the genome (**Supplementary Tables 5 and 6; Supplementary Figure 4**). rs1906252 is located in a non-coding gene (*RP11-436D23.1*), which is specifically expressed in brain⁷². This specific SNP showed a GWS association with intelligence in two previous studies^{20,73}, and has also been linked to educational attainment⁶² and bipolar disorder⁷⁴.

The second most associated locus (locus 50, **Supplementary Table 6**) on chromosome 3 includes 4 lead SNPs. The top lead SNP is rs2352974 ($P=3.69 \times 10^{-29}$), which is in an intronic region of the *TRAIP* gene. The other three lead SNPs are rs73078367 ($P=1.81 \times 10^{-9}$), in an intronic

region of *NCKIPSD*), rs13096357 ($P=4.52\times 10^{-8}$, in an intronic region of *CELSR3*), and rs1540293 ($P=2.46\times 10^{-9}$, in an intronic region of *CACNA2D2*). However, in this locus, there are also 5 exonic SNPs with CADD scores >20 (**Supplementary Table 11**). The highest CADD score is for rs13324142 (CADD score 25.6, GWAS $P=1.98\times 10^{-87}$, $r^2 = 0.98$ with lead SNP rs13096357 in this locus), which is a missense mutation in *SLC26A6*; the ancestral C allele (allele frequency = 0.90 in HRC) is associated with lower intelligence scores. rs3197999 (CADD score = 25.5; GWAS $P=1.47\times 10^{-22}$; $r^2 = 0.48$ with lead SNP rs73078367), is a missense mutation in the *MST1* gene, where the ancestral allele (G) is associated with lower intelligence scores and has an allele frequency of 0.71 (in HRC). rs11552724 (CADD score 25.4; GWAS $P=4.63\times 10^{-11}$; $r^2 = 0.80$ with lead SNP rs13096357) is a missense mutation in *USP19*, and the ancestral allele (G, allele frequency of 0.11 in HRC) is associated with higher intelligence scores. rs34759087 (CADD 23.1; GWAS $P=3.22\times 10^{-8}$; $r^2 = 0.73$ with lead SNP rs73078367) is a missense mutation in *LAMB2* with the ancestral allele associated with lower intelligence scores (C, allele frequency = 0.89 in HRC). And finally, rs3821875 (CADD score = 21.9; GWAS $P=1.12\times 10^{-7}$; $r^2 = 0.91$ with lead SNP rs13096357) is a missense mutation in *CELSR3* where the ancestral allele G (allele frequency 0.11 in HRC) is associated with lower intelligence scores. Full details of all genomic risk loci and their putative functional implications are listed in **Supplementary Tables 5 and 6**.

2.3.6 Gene mapping of GWS SNPs in genomic risk loci

We used three gene-mapping strategies implemented in FUMA⁷⁵ to select genes of interest based on SNPs in the significantly associated risk loci. For positional mapping, we mapped SNPs in the risk loci to genes using a window of 10 Kb, resulting in 522 mapped genes. eQTL mapping

resulted in 684 genes, of which 315 were located outside of the positional boundaries of the genomic risk loci, and chromatin interaction mapping resulted in 227 genes, of which 41 were located outside of the genomic risk loci. These 859 genes were mapped by FUMA based on the parameter settings as described in the methods and annotating all SNPs that are in LD ($r^2 \geq 0.6$) with an independent significant SNP. All of these genes include GWS SNPs within their genic boundaries and/or are influenced by GWS SNPs via eQTL and/or chromatin interactions. We note that they are not necessarily all relevant to intelligence: this is something that still needs to be validated in functional experiments. However, these 859 genes are starting points for generating hypotheses that can be functionally tested, because for annotated SNPs we now know the direction of effect (e.g. an allele that is associated with higher intelligence is also associated with higher expression of gene X; or an allele associated with higher intelligence leads to an altered protein structure). From this gene list, we can use the FUMA results to further select the genes that are most interesting for functional follow-up. For example, of the 859 unique genes mapped by FUMA, 189 had a probability of loss-of-function intolerance⁷⁶ (pLI) >0.90, indicating that these were extremely sensitive to mutations within the gene that result in truncation or loss of function of the protein product (**Supplementary Table 12**). In addition, for some genes we obtained converging evidence from multiple sources, such as two independent loci that point to the same gene, or that both eQTL associations outside a gene and GWS SNPs within the gene were present. Information like this may guide the order of priority for functional follow-up of these numerous reported genes.

As described in the main text, fifteen genes are particularly interesting because they are linked via chromatin interactions in one or more tissue types between two independent genomic risk

loci (**Figure 2**): *SATB2* in locus 45, *MEF2C* in locus 83, *FBXL17* and *MAN2A1* in locus 87/88, 8 genes (*ZNF184*, *ZNF311*, *ZNF322*, *HIST1H2AG*, *HIST1H2AH*, *HIST1H2BJ*, *HIST1H2BK*, and *HIST1H4I*) in locus 101/102, *ELAVL2* in locus 129, *PTCH1* in locus 130, and *ATF4* in locus 212. These interactions involved 7 pairs of independent genomic regions in linkage equilibrium and separated by >250kb. Given the prevalence of chromatin interactions found between similarly independent loci defined by our gene-mapping parameters (25,924 out of 73,499 regions as mapped in the HiC database), the probability of finding 7 or more pairs of interacting loci in our set of genomic risk loci (213 regions, or 22,578 possible pairs) was significantly higher than expected by chance (binomial test $P=3.16 \times 10^{-11}$). Additional evidence supports several of these genes: all except *SATB2* and *FBXL17* also demonstrated multiple intra-locus chromatin interactions, and *FBXL17*, *MAN2A1*, *ZNF322*, *PTCH1*, and *ATF4* were mapped via eQTL associations in multiple tissues (**Supplementary Table 12**).

Despite the strong enrichment for GWAS association signal in genes specifically expressed in the brain (see below), these cross-locus chromatin interactions were mostly found in non-brain tissue types. Of the 55 total cross-locus interactions involving these 15 genes (the same interaction regions were frequently linked in multiple tissues), 31 were in the heart (aorta or ventricle), 11 were in the liver, and only 2 were in the brain (hippocampus); an additional 6 involved the spleen, and 5 the pancreas. While Sniekers et al.²⁰ found that genes significantly associated with intelligence in a previous study were most strongly enriched for expression in brain tissues, there was also some enrichment of certain genes in whole blood, lymphocytes, liver, and skeletal muscle. It is possible that this reflects the high oxygen and metabolic demands of cognitive processes, and that disruption in genetic functions that affect such

processes are consequently linked to individual differences in intelligence. However, we also note that currently available HiC data is still limited and may not be equally representative of all different tissues. For example, there are over ten-fold more interactions observed in some tissues (like ventricle and liver) than there are in brain tissues in the HiC interaction database⁷⁷. The extent to which this is a result of true biological differences in the frequency of chromatin interactions between tissues or simply a methodological artefact due to differences in sample size, methods, and accuracy in generating this data for different tissues is currently uncertain. We further investigated the FUMA-mapped genes for enrichment using hypergeometric tests on 7,246 pre-defined gene-sets derived from MSigDB⁷⁸ and gene expression profiles in 53 tissue types obtained from the GTEx Project⁷⁹ (**Online Methods**). We found significant differential expression of these genes in multiple brain tissues (cerebellar hemisphere, cerebellum, cortex, frontal cortex) (**Supplementary Figure 9**). These genes were also overrepresented among 15 sets of microRNA targets, 4 transcription factor binding targets, and cell adhesion and synaptic regulation pathways, among other curated gene-sets (**Supplementary Table 14**).

2.4 Gene-based (GWGAS) and Gene-set Association

2.4.1 Genome-wide gene-based association (GWGAS)

We tested 18,128 protein-coding genes for association with intelligence using MAGMA's gene-based test and detected 507 genes significantly associated at the Bonferroni corrected ($P < 2.76 \times 10^{-6}$) threshold. Of these, 452 were novel genes which have not been previously implicated by either GWAS or GWGAS (**Supplementary Table 25**), and 157 genes were located outside the SNP-based genomic risk loci (**Supplementary Table 15**). The top gene *RNF123*

($P=1.63 \times 10^{-33}$) on chromosome 3 in locus 50 was also mapped by positional and eQTL mapping and has a pLI score of 0.97 (**Supplementary Table 12**), which is an extremely high probability of being intolerant to loss of function mutations. The protein encoded by this gene contains a C-terminal RING finger domain, a motif present in a variety of functionally distinct proteins and known to be involved in protein-protein and protein-DNA interactions, and an N-terminal SPRY domain. This protein displays E3 ubiquitin ligase activity toward the cyclin-dependent kinase inhibitor 1B which is also known as p27 or KIP1. Alternative splicing results in multiple transcript variants (description from <http://www.genecards.org>, provided by RefSeq, Feb 2016).

2.4.2 Gene-set association

We conducted gene-set analysis on a total of 7,323 gene-sets: 7,246 sets derived from the MSigDB, 53 tissue specific gene-sets and 24 cell specific gene-sets. The threshold for significance of gene-sets was thus set at $0.05/7,323=6.83 \times 10^{-6}$, and competitive testing was used throughout (**Online Methods**).

Analysis of gene-sets from MSigDB resulted in six significantly associated gene-sets: *neurogenesis*, *neuron differentiation*, *central nervous system neuron differentiation*, *regulation of nervous system development*, *positive regulation of nervous system development*, and *regulation of synapse structure or activity* (**Supplementary Table 17**). These gene-sets are all involved in neuronal/nervous system processes and include many overlapping genes. Of 3,861 total genes in these 6 sets, only 1,509 are unique, and three sets are wholly encompassed by other sets: *central nervous system neuron differentiation* is a subset of *neuron differentiation*, which is in turn a subset of *neurogenesis*, and *positive regulation of nervous system*

development is a subset of *regulation of nervous system development*. Conditional gene-set testing was therefore used to test which of these sets was most responsible for the association signal (**Online Methods**). The strongest signal came from the *neurogenesis* gene-set, but *regulation of nervous system development* accounted for more of the variance in the other significant gene-sets than did *neurogenesis* (i.e. their association signal declined more when conditioning on this gene-set). Together, the *regulation of nervous system development*, *central nervous system neuron differentiation*, and *regulation of synapse structure or activity*, gene-sets accounted for the observed association signal of the other three sets (**Supplementary Table 17**).

Of the 750 genes in the *regulation of nervous system development* gene-set, 41 genes had a significant GWAS *P*-value and 6 of these (*CPNE1*, *IST1*, *MAN2A1*, *MTMR2*, *NEGR1*, and *RHOA*) were implicated by positional, eQTL, and chromatin interaction mapping in addition to GWAS (**Supplementary Table 18**). Of the 166 genes in the *central nervous system neuron differentiation* set, 8 genes had a significant GWAS *P*-value (*DCC*, *FGF8*, *PLXNA4*, *PTCH1*, *RORA*, *SHANK3*, *SZT2*, *TAL1*) and *PTCH1* was implicated by all four gene-mapping strategies. Of the 232 genes in the *regulation of synapse structure or activity* set, 16 genes had a significant GWAS *P*-value (*STAU1*, *DBN1*, *NCAM1*, *SYNGR1*, *FLRT1*, *LRRC24*, *MEF2C*, *GRIN2A*, *NTRK3*, *SHISA9*, *BAIAP2*, *CTNNA2*, *EFNA5*, *SHANK3*, *SLC8A3*, *SORCS3*), and one of these (*STAU1*) was also implicated by all three other gene mapping strategies (**Supplementary Table 18**).

We additionally conducted gene-set analysis on gene-expression values from 53 GTEx tissues (**Online Methods**). We found Bonferroni-corrected significant associations for 11 tissue specific gene-sets, all of which were brain tissues, with the strongest association in cortical and

cerebellar regions (**Supplementary Table 19**). Conditional gene-set analysis indicated that these associations were driven by a single source, either the cortex or specifically the frontal cortex (Brodmann's area 9), as the effect of all other regions disappeared when conditioning on either of these two tissues (**Supplementary Table 19**).

Cell-type specific gene-set analysis showed significant association with three cell types: medium spiny neurons, pyramidal CA1 neurons, pyramidal SS neurons, (**Supplementary Table 20**). The association with the pyramidal neurons from the somatosensory cortex likely explains the tissue specific association with the cortical areas as these neurons are enriched in cortical tissue. Conditional gene-set analysis showed that the association signal from the single-cell sets tested were driven by three independent cell types: medium spiny neurons, neuroblasts, and pyramidal CA1 neurons (**Supplementary Table 20**). Neuroblasts were not individually significant ($P=4.73 \times 10^{-4}$) after applying a Bonferroni threshold, but they did account for the signal seen in other cell types such as dopaminergic neuroblasts.

The results in this section are parallel to the gene-set enrichment tests (i.e. 2x2 tests) based on FUMA-mapped genes described briefly in **Supplementary Results 2.3.6**. Both analyses concurrently indicated the strongest gene-set enrichment for genes expressed in the brain, but implicated different curated gene-sets. However, the FUMA annotated results are based on genes that are selected by their mapping from individually significant GWAS SNPs (which may be few or many SNPs linking a particular gene), while the MAGMA gene-set results are based on the aggregate gene-level association signal of all SNPs within a gene. We focus on the MAGMA gene-set results as they provide a more formal test of the association of gene-sets whose definition is based on the genes they comprise rather than specific SNPs.

2.5 Associations Between Intelligence and Other Phenotypes

2.5.1 Genetic correlations

We calculated genetic correlations (r_g) with 38 traits and found an r_g significantly different from 0 for 17 (using a corrected significance level of $0.05/38=.0013$). Ten traits showed a significant negative r_g with intelligence, while seven traits showed a significant positive genetic correlation. For example, the r_g of intelligence with attention deficit hyperactivity disorder (ADHD) was -0.360 (**Supplementary Table 21; Supplementary Figure 10**), which should be interpreted as that on average, $-0.360^2=13\%$ of genetic effects associated with a higher intelligence score are also associated with a lower risk for ADHD. This thus does not suggest that *all* genetic variants associated with higher intelligence are necessarily associated with lower risk for ADHD or are necessarily relevant for ADHD. The genetic variants associated with our measure of intelligence were negatively correlated with the genetic variants involved in a number of diseases and negative health-related outcomes (ADHD, depressive symptoms, Alzheimer's disease, schizophrenia, neuroticism, coronary artery disease, waist-hip ratio, body mass index [BMI], and waist circumference), and positively correlated with indicators of better health (longevity, former [vs. current] smoker status). Unlike the other neurocognitive and neurodevelopmental disorders examined, autism and intelligence had a positive rather than negative genetic correlation, which has been observed previously²⁰ and is consistent with some theories that autism involves a dysregulation of the systems governing cognitive development⁸⁰. The genetic variants associated with intelligence were also positively correlated with those linked to the anthropometric traits of infant head circumference and intracranial volume. As has been

commonly observed, genetic variants associated with higher intelligence were also related to genetic influences on socioeconomic outcomes, being correlated strongly with higher educational attainment and with delayed reproductive age (higher age of first birth) and having fewer children.

2.5.2 Overlap of intelligence risk loci with risk loci implicated in other phenotypes

Comparing the GWS loci identified by this study with those in the previously reported literature using the NHGRI-EBI catalog (**Online Methods**), we found that loci significantly associated with intelligence in the SNP meta-analysis have also been linked to psychiatric phenotypes including schizophrenia (20 loci), mood disorders (5 loci), and neuroticism (5 loci), as well as educational attainment (24 loci), brain volume (2 loci), Alzheimer's disease (1 locus) and a number of physiological traits and diseases (**Supplementary Table 22**). Genes implicated by GWS SNP mapping in FUMA were most strongly enriched for sets of genes linked to schizophrenia ($P=1.35\times 10^{-53}$), educational attainment ($P=9.91\times 10^{-37}$), and cognitive function ($P=1.78\times 10^{-24}$) (**Supplementary Table 23**). These results indicate a common biological pathway implicating both normal variation in cognitive functioning and neurocognitive dysfunction.

2.5.3 Mendelian randomization with correlated traits

We performed Mendelian Randomization (MR) using Generalized Summary-data-based Mendelian Randomization⁸¹ (GSMR, see **URLs; Online Methods**) to test for credible causal associations between intelligence and traits that were significantly genetically correlated with intelligence (described in **Supplementary Results 2.5.1; Supplementary Table 21;**

Supplementary Figure 10). We excluded traits for which there was significant sample overlap with the current intelligence meta-analysis, as known or as indicated by the intercept of the bivariate LD score regression. This was the case for age of first child, coronary artery disease, longevity, infant head circumference, number of children, neuroticism and depressive symptoms. For educational attainment, Mendelian randomization was performed on GWAS summary statistics based on the non-overlapping sample used in the proxy replication analyses (**Supplementary Results 2.3.2**). In the reverse causation analysis (i.e. testing the opposite hypothesis that the other trait causes intelligence), there were 3 traits with less than 10 independent lead SNPs. Relaxing this threshold to $P < 1 \times 10^{-5}$ allowed for a sufficient number of SNPs to include autism, former smoker status, and intracranial volume.

We performed analyses in two ways in order to test bidirectionality: forward GSMR was performed using GWS SNPs associated with intelligence as the instrumental variables (exposure) and correlated traits from non-overlapping samples as the outcome, while reverse GSMR was performed using GWS SNPs from the other traits as instrumental variables and intelligence as the outcome. All analyses were run before and after removing SNPs detected by the HEIDI outlier tool as showing pleiotropic effects. Results are shown in **Supplementary Table 26** and **Supplementary Figures 11-12**. A large drop in significance of the estimated b after removing SNPs with pleiotropic effects indicates that a substantial part of the observed association between two traits is due to pleiotropic SNPs.

The GSMR bidirectional analyses for intelligence and educational attainment showed weak evidence for pleiotropy: HEIDI detected 12 suspected pleiotropic SNPs (out of 239) in the intelligence -> educational attainment analysis and a somewhat larger proportion (7 SNPs out

of 47) in the reverse analysis. Also, the P -value of the estimated associations were similar before and after removal of pleiotropic SNPs. Both directions of causation were highly significant, and the causal effect of intelligence on educational attainment ($\hat{b}_{xy} = 0.549$, $P < 1 \times 10^{-320}$) was similar in magnitude to the effect of educational attainment on intelligence ($\hat{b}_{yx} = 0.480$, $P = 6.85 \times 10^{-82}$), suggesting a bidirectional effect. Similarly, a bidirectional effect was observed with intracranial volume, with a somewhat stronger positive effect of intelligence on intracranial volume ($\hat{b}_{xy} = 0.246$, $P = 2.97 \times 10^{-13}$) than the reverse ($\hat{b}_{yx} = 0.068$, $P = 8.44 \times 10^{-20}$).

We also observed a protective effect of intelligence on several neurological and psychiatric disorders. Intelligence was associated with lower risk for ADHD (OR=0.48, $\hat{b}_{xy} = -0.734$, $P = 2.57 \times 10^{-46}$), with little evidence for pleiotropic effects. The OR of 0.48 can be interpreted such that individuals whose intelligence scores are 1 SD above the population mean have 52% lower risk of ADHD compared to the population prevalence. The reverse test (that the presence of ADHD causes lower intelligence) was also statistically significant, but with a smaller effect size ($\hat{b}_{yx} = -0.084$, $P = 4.41 \times 10^{-19}$). A modest association was also observed between higher intelligence and higher risk for autism (OR=1.38, $b_{xy} = 0.321$, $P = 1.12 \times 10^{-3}$), with no effect in the opposite direction (although it should be noted that there were few instrumental SNPs available to index genetic influences on autism).

Intelligence also had a protective effect on Alzheimer's disease (OR=0.65, $\hat{b}_{xy} = -0.435$, $P = 3.59 \times 10^{-14}$), with only two SNPs (out of 233) showing pleiotropic effects, and no evidence for reverse causation. This association is potentially complicated by the fact that the sample for intelligence included older adults whose cognitive test scores may be influenced by genetic effects on cognitive decline (rather than ability), even after screening procedures to exclude

observable instances of dementia or Alzheimer's. We therefore re-ran the meta-analysis and corresponding GSMR analysis using a subset of participants from UKB aged <50 and the other cohorts under this age (GenR, IMAGEN, BLTS-C, BLTS-A, S4S, STR, and TEDS), with a total $N = 59,590$. The genetic correlations for this subset, calculated with LD score regression, were 0.99 with the full meta-analysis sample and 0.71 with the older adult ($M_{age} > 60$) subset. Although the pattern of results appeared similar to the full meta-analysis, only 6 independent GWS lead SNPs were found for intelligence in this smaller subset, therefore we reduced the significance threshold to $P < 1 \times 10^{-5}$ for the purposes of GSMR. The GSMR results remained similar, with intelligence demonstrating a somewhat attenuated protective effect on Alzheimer's ($OR=0.83$, $\hat{b}_{xy}=-0.191$, $P=2.35 \times 10^{-5}$) and zero out of 189 variants showing pleiotropic effects. These results are indicative of a phenotypic causal effect of intelligence on Alzheimer's that is most likely independent of any pleiotropic SNPs affecting both traits through impacts on cognitive decline. The association between intelligence and schizophrenia was more complex. GSMR detected a strong protective effect of intelligence on schizophrenia ($OR=0.50$, $b_{xy}=-0.685$, $P=2.02 \times 10^{-57}$) and reverse GSMR analysis showed evidence of a bidirectional association, indicating that schizophrenia may cause impaired cognitive functioning, although this effect was relatively weaker ($b_{xy}= -0.214$, $P=4.19 \times 10^{-52}$). There was also strong evidence for pleiotropic effects of 31 SNPs (out of 240) identified in the intelligence $\rightarrow$ schizophrenia analysis and 18 SNPs (out of 111) in the reverse, with a substantial decrease in the effect of intelligence on schizophrenia after filtering these pleiotropic SNPs.

We further found potentially causal relationships with several anthropomorphic and health-related outcomes. Waist circumference had a modest effect on lower intelligence, while

conversely it was found that intelligence had a modest impact on lower waist-hip ratio and body mass index. The opposite causal directions were not significantly supported for any of these three phenotypes. Finally, an association was observed between higher intelligence and higher likelihood of being a former (vs. current) smoker, with no significant reverse effect, indicating that individuals with higher intelligence are more likely to successfully quit smoking.

The precise mechanisms underlying the putative causal relationships suggested here cannot be determined from the available data. Higher intelligence is prospectively predictive of better socioeconomic outcomes⁸² and lower mortality/morbidity later in life⁸³ so it is possible that the protective effects observed for some outcomes are mediated through better social/economic resources such as access to preventative care and healthier environments, or engagement in lifestyle choices (diet, exercise, social activities, substance use) that prevent cognitive and/or physical decline. Alternatively, these associations may be a function of direct biological effects by which genetic variants that increase intelligence simultaneously lower risk for psychiatric illness, perhaps due to their effects on brain structure/function or overall health.

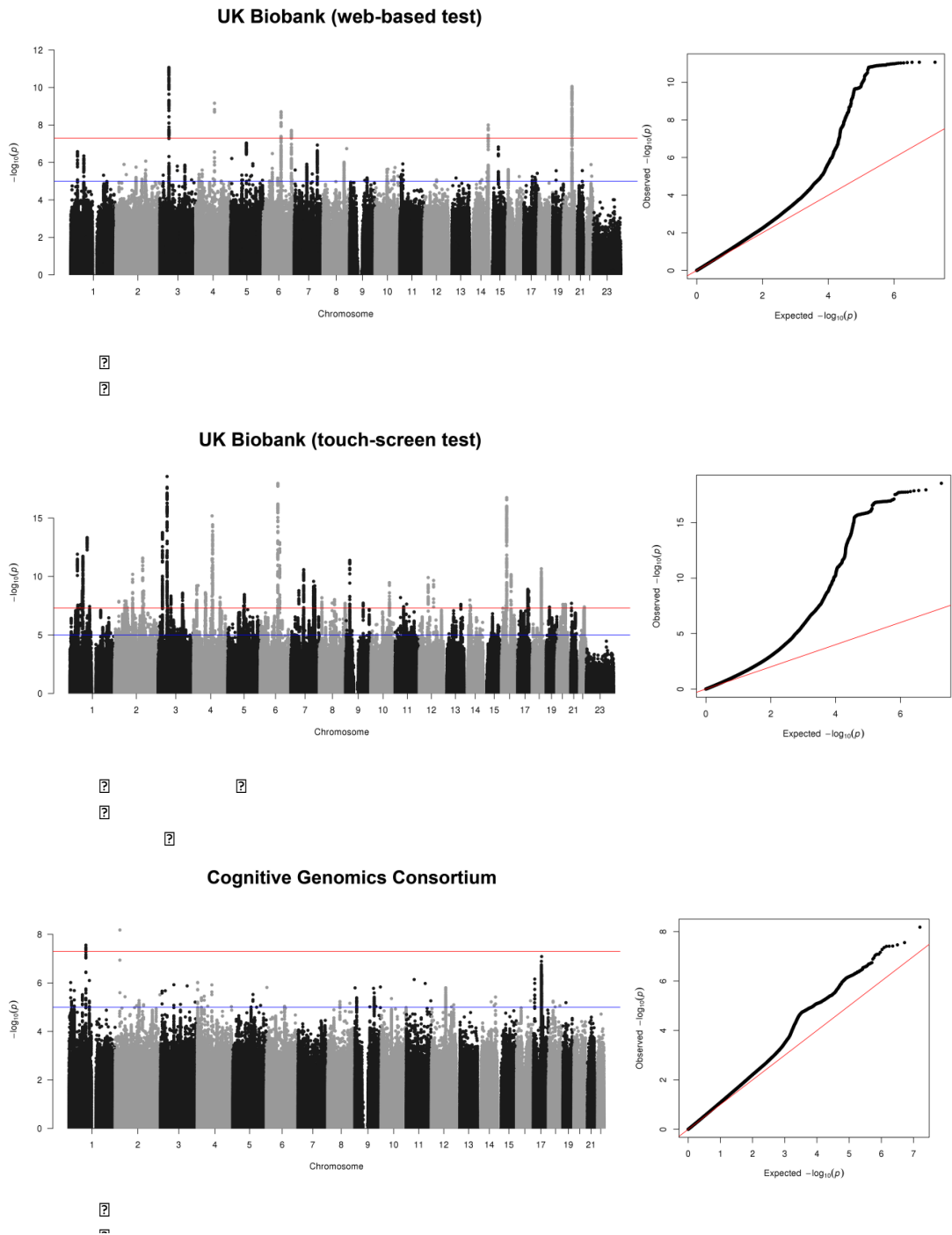
It is also possible that these associations (particularly for Alzheimer's disease) were observed because the variants identified in our meta-analysis contained a mixture of genetic effects impacting intelligence as well as cognitive decline since our meta-analyzed sample covered a wide age range. However, the high genetic correlation across age groups and the consistency of the GSNR results in the younger age subset suggests that this is not likely the case. Further, we saw no evidence of GWAS association with the *APOE* gene, which massively impacts Alzheimer's disease risk and general cognitive decline⁸⁴ and would be evident in the association results if the phenotypes indexed cognitive decline rather than general intelligence. The *APOE*

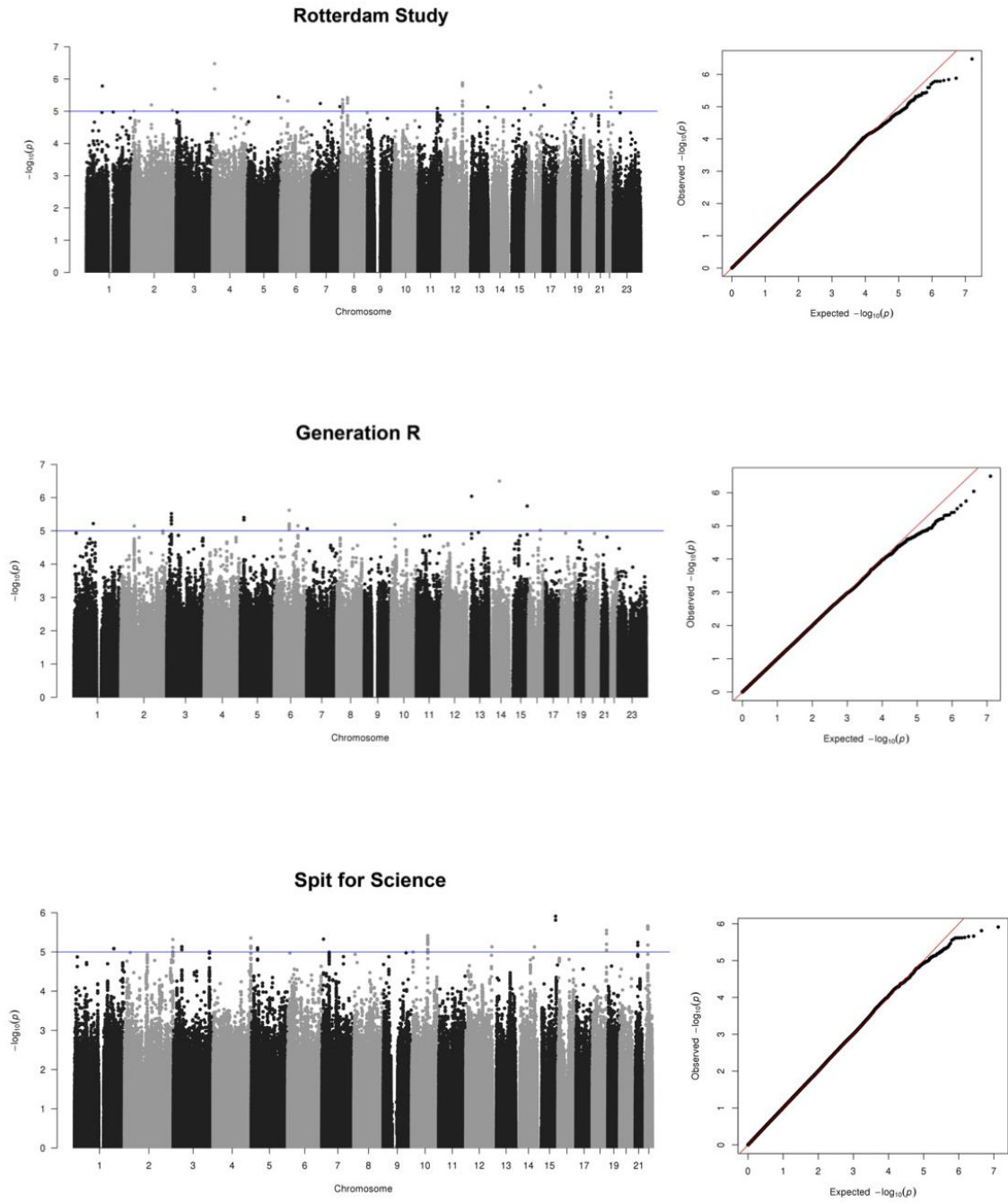
gene was not identified by any of our gene mapping strategies or gene/gene-set analyses, and none of the GWS SNPs identified in the most recent Alzheimer's GWAS⁸⁵ were among the GWS SNPs for intelligence. Although one identified genomic locus overlapped a region previously linked to Alzheimer's (**Supplementary Table 22**), there was not a significant enrichment for genes associated with both phenotypes (**Supplementary Table 23**). This suggests that the causal pathway between intelligence and Alzheimer's may be more likely to emerge through protective lifestyle factors correlated with higher intelligence than through direct biological pathways between the phenotypes. We speculate that other observed causal relationships implied by the GSMR results (e.g., height, BMI, smoking) are also likely to come about through lifestyle factors associated with higher intelligence or its associated higher socioeconomic status, but these mechanisms remain to be tested.

Our results are in line with evidence from other epidemiological, longitudinal, and co-twin control study designs which support these putative causal relationships, although true experimental research is necessarily lacking for these phenotypes due to ethical and practical constraints. For example, evidence exists for both a bidirectional relationship and a shared genetic etiology between intelligence and educational attainment^{60,86-90}, with numerous studies finding genetic overlap between them but also prospective evidence that intelligence predicts later educational outcomes and vice versa. Empirical research also supports the existence of a shared genetic etiology between better cognitive function and lower risk for schizophrenia, in addition to direct causal links between lower intelligence and schizophrenia (though not the bidirectional causal effects observed here)⁹¹⁻⁹⁵. There is less literature to support the other findings, but they are consistent with the well-replicated link between higher intelligence and

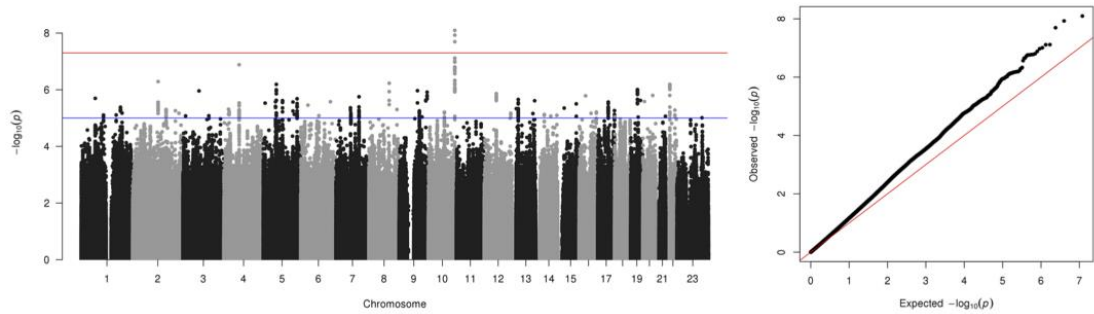
better health-related outcomes across multiple domains⁸³. While our results are limited by the availability of GWS SNPs for various phenotypes used to conduct the GSMR analyses, they provide incremental molecular genetic support to the existing literature and point to potential causal mechanisms for the commonly observed correlational relationships that merit in-depth investigation.

3. Supplementary Figures

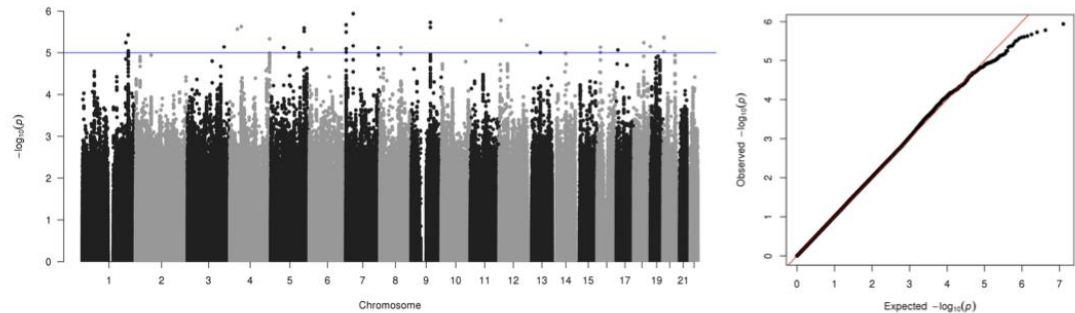




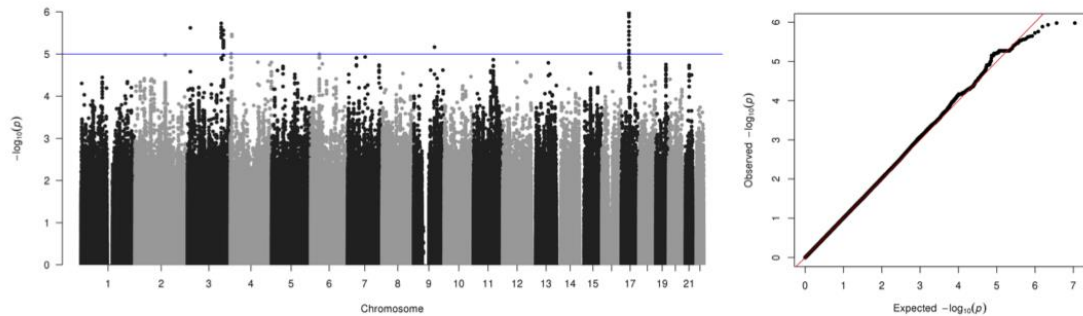
High IQ / Health and Retirement Study

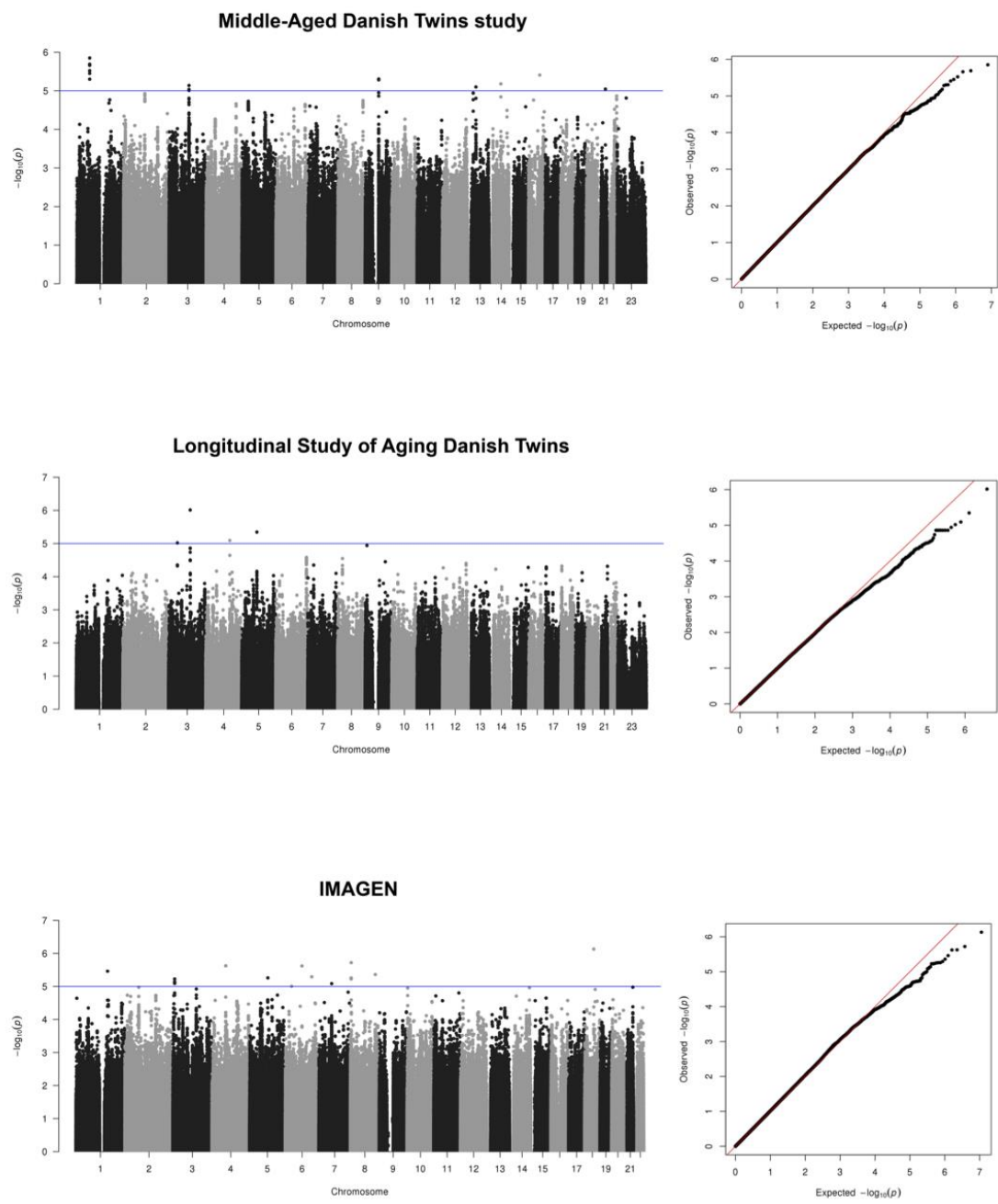


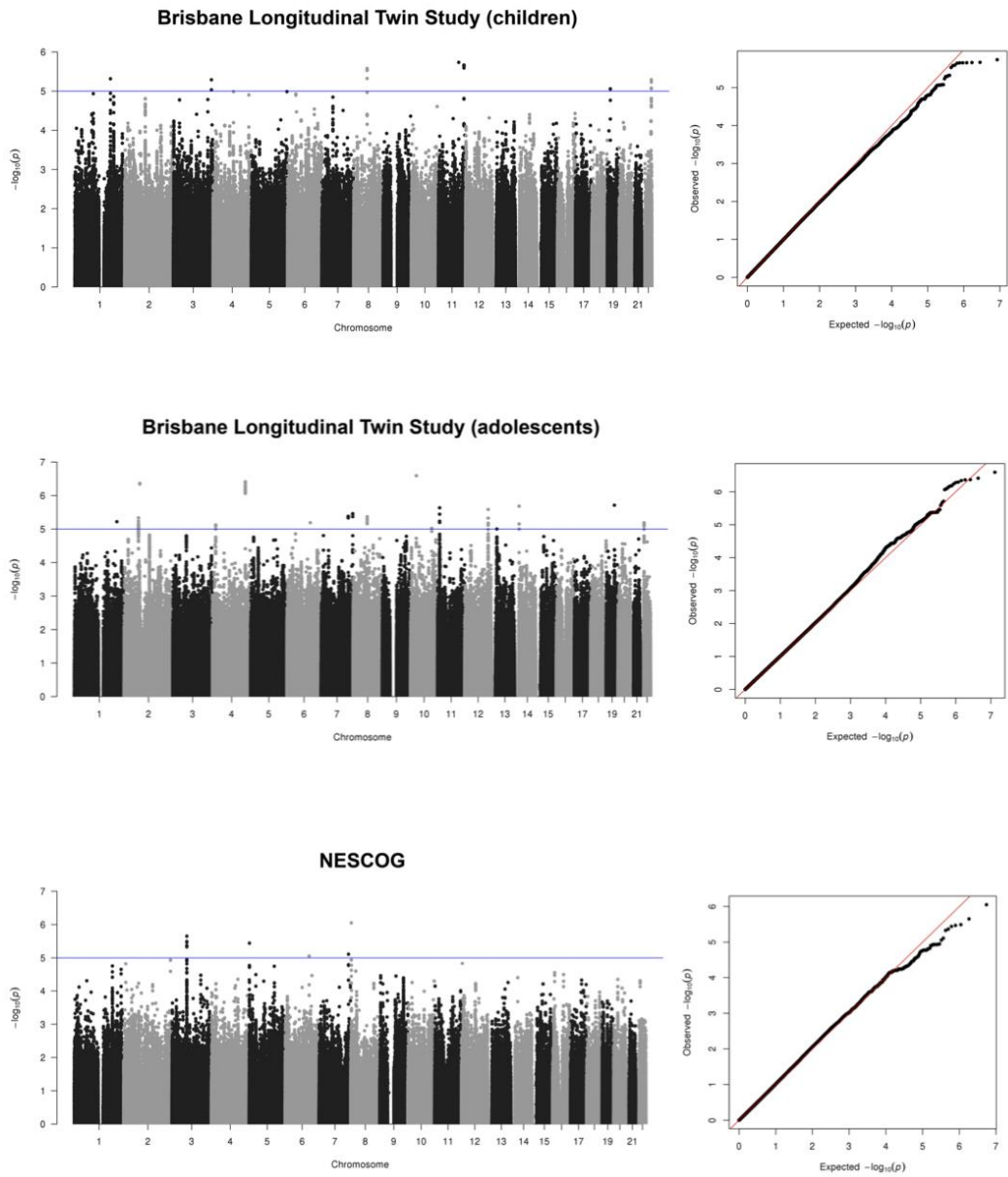
Twins Early Development Study 1

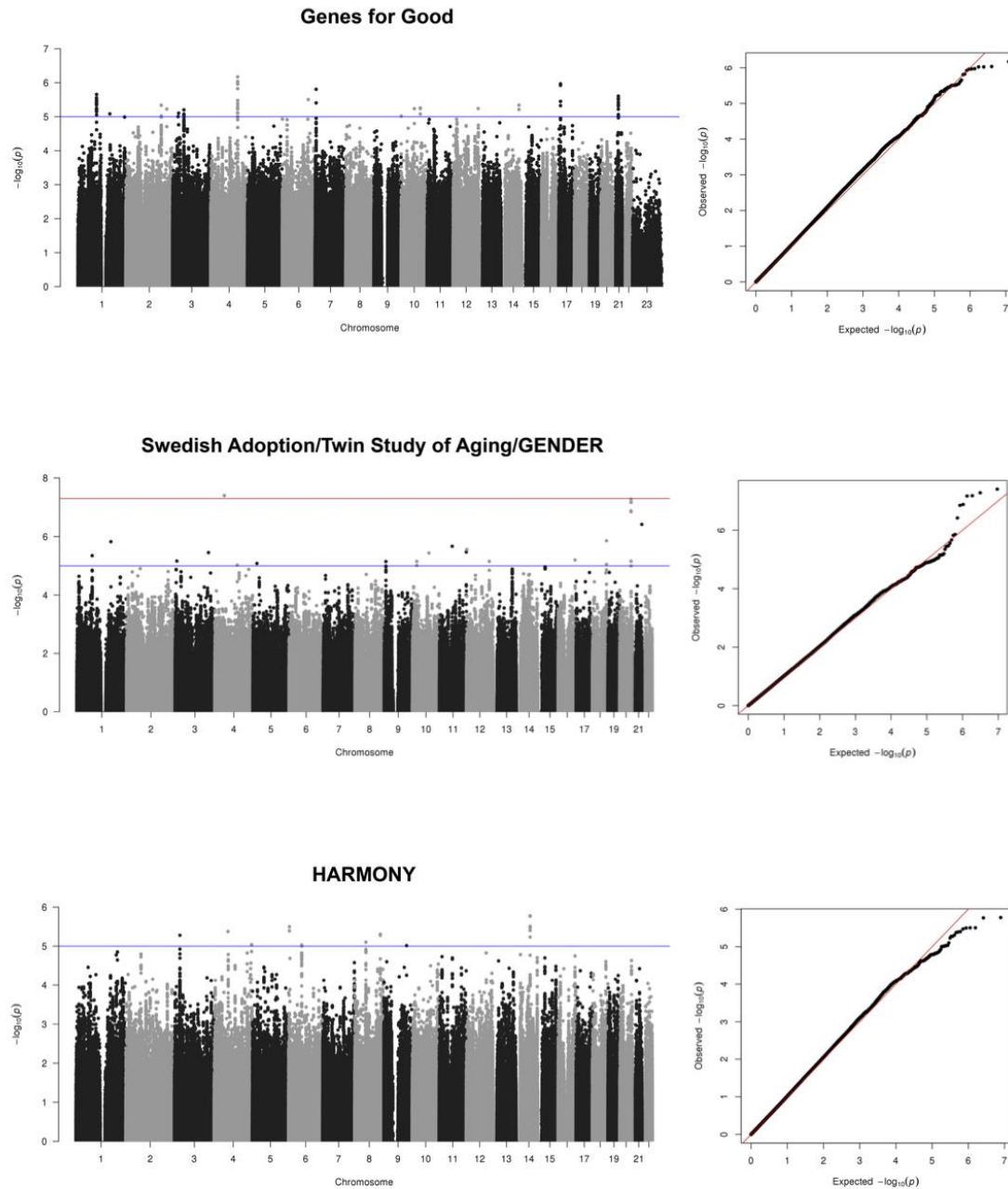


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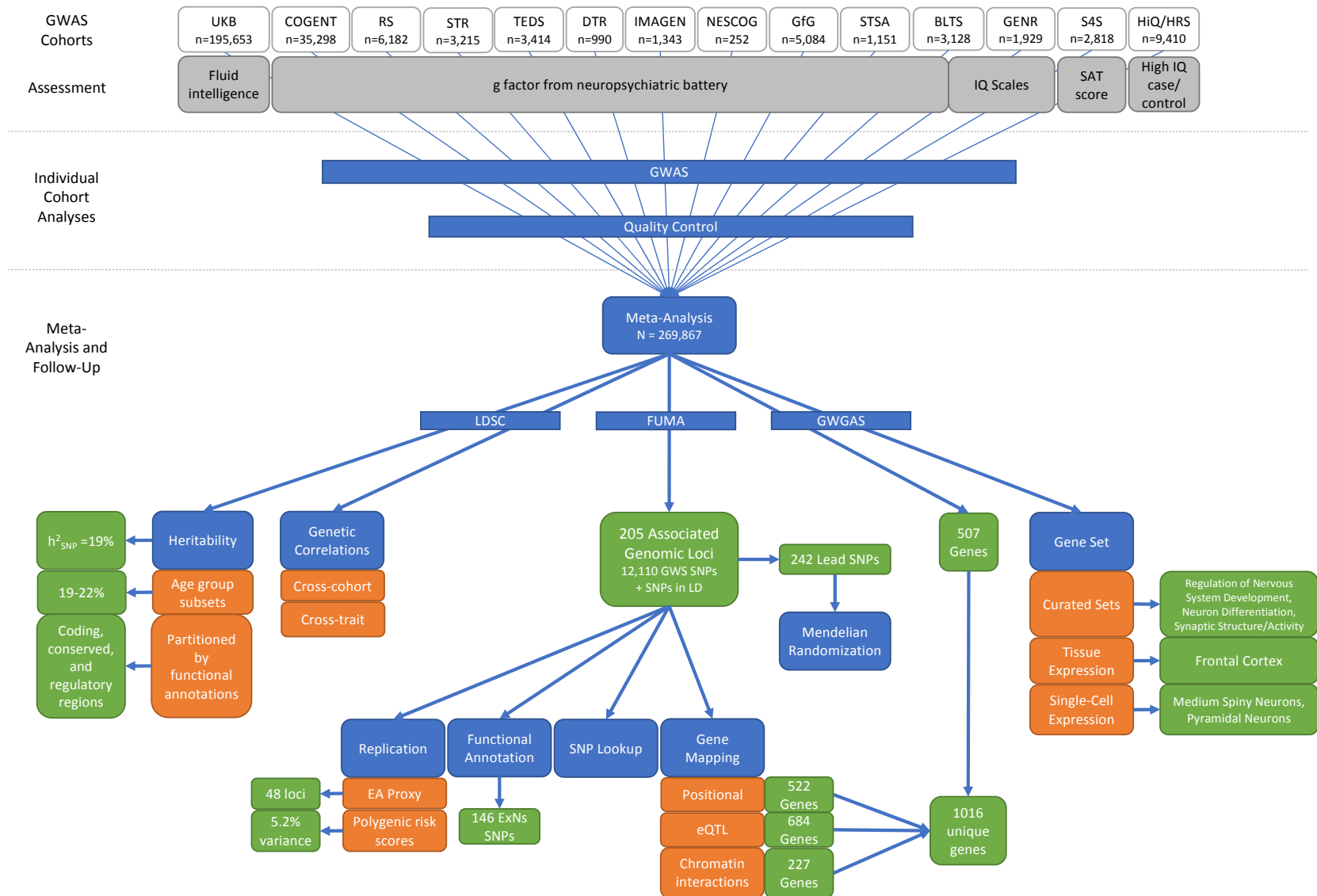






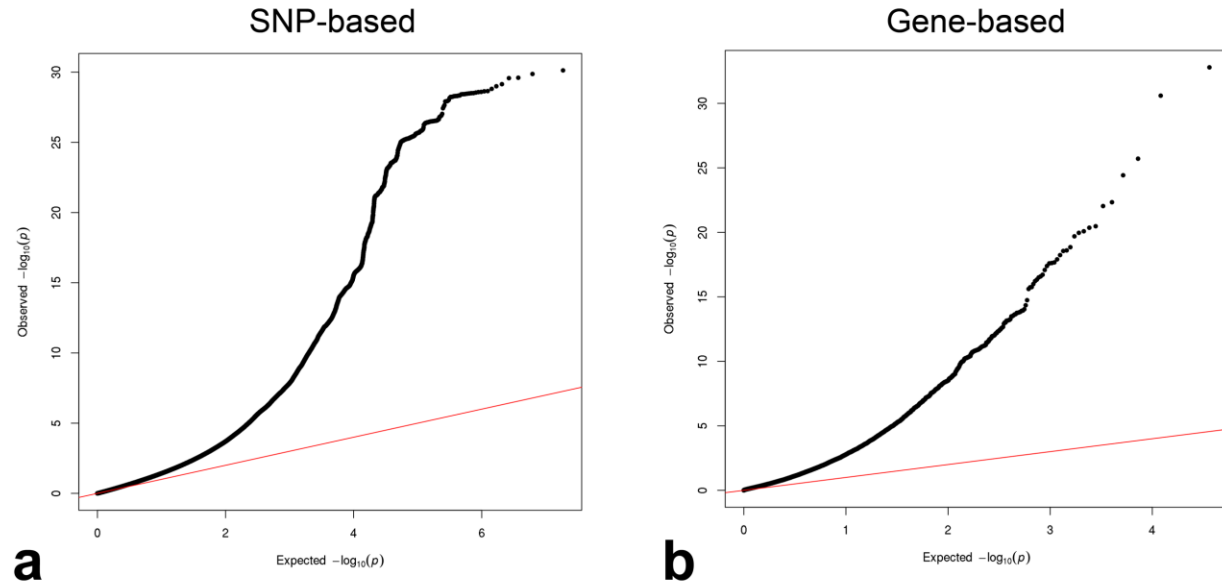


Supplementary Figure 1. Manhattan and QQ plots of the individual cohort GWAS results included in a meta-analysis of intelligence in 269,867 independent individuals. For each of 14 cohorts included in the GWAS meta-analysis, $-\log_{10}$ transformed two-tailed P -values of SNP associations with intelligence measures in a linear or logistic regression model are presented against their chromosomal position in a Manhattan plot (left) and against expected null P -values in a QQ plot (right). Sample sizes and details of the statistical analyses for each cohort are presented in Supplementary Information 1.1. The dotted red line indicates Bonferroni-corrected genome-wide significance ($P < 5 \times 10^{-8}$), the blue line the threshold for suggestive associations ($P < 1 \times 10^{-5}$).

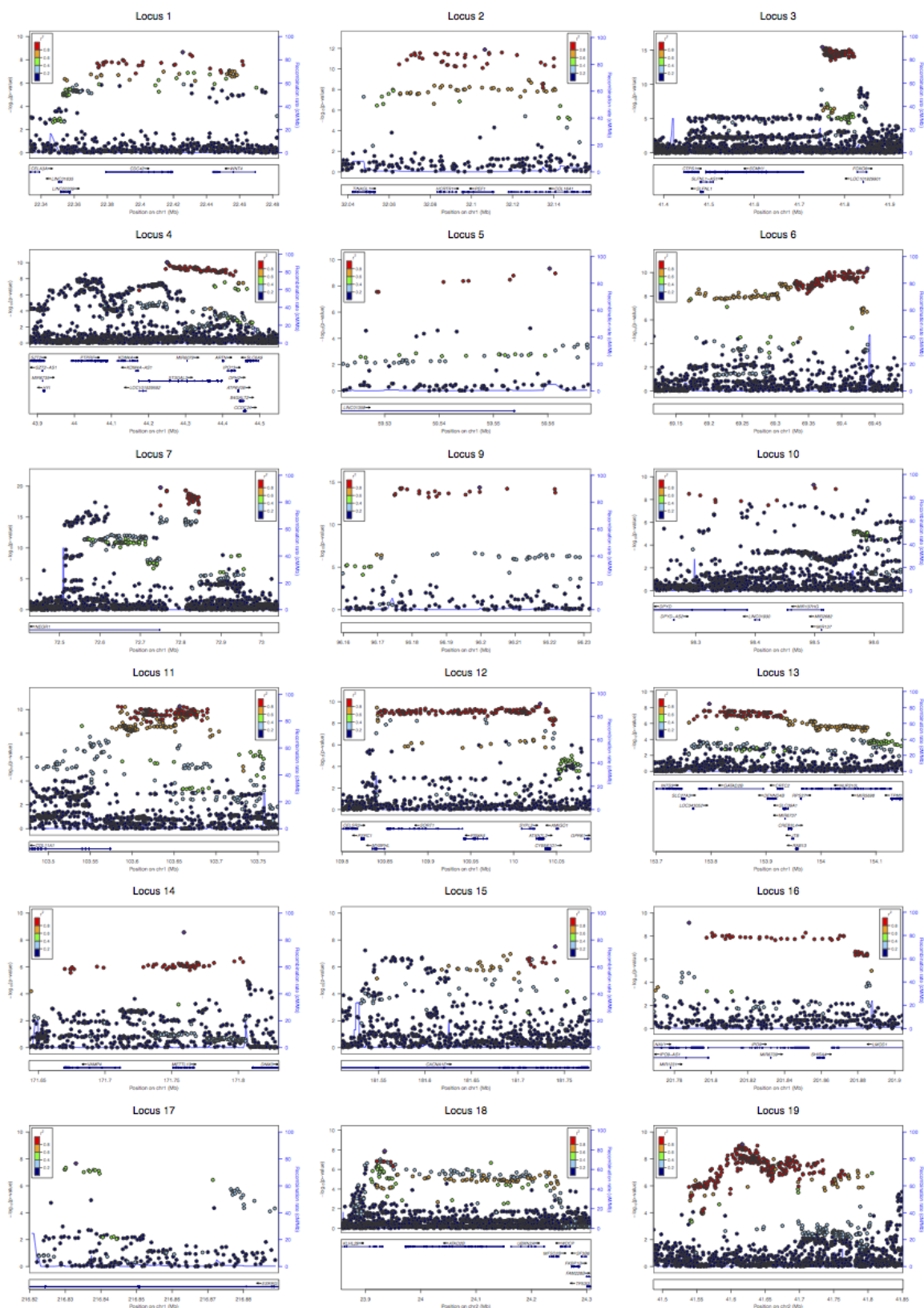


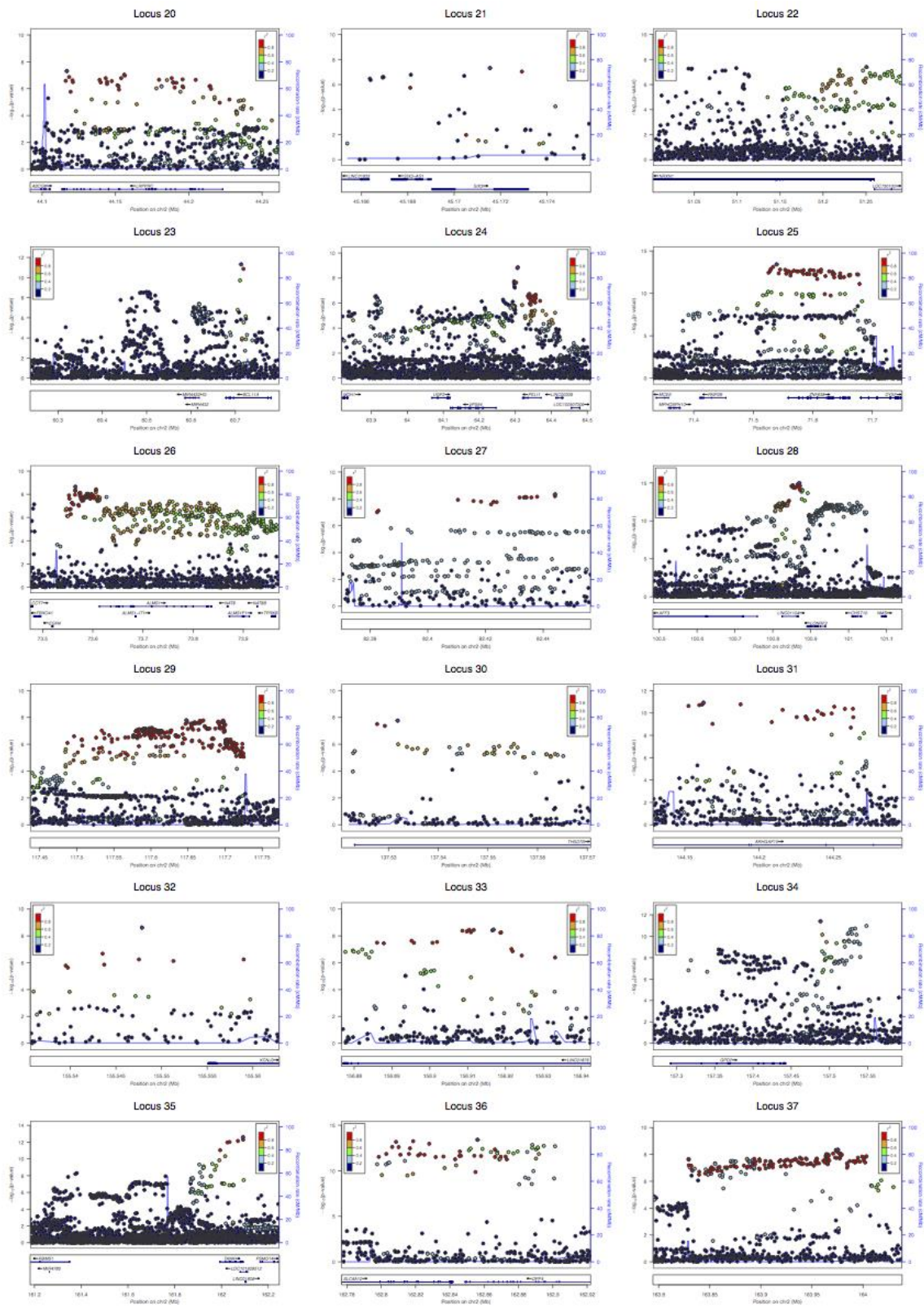
Supplementary Figure 2. Flowchart of study methodology and results of a GWAS meta-analysis of intelligence in 269,867

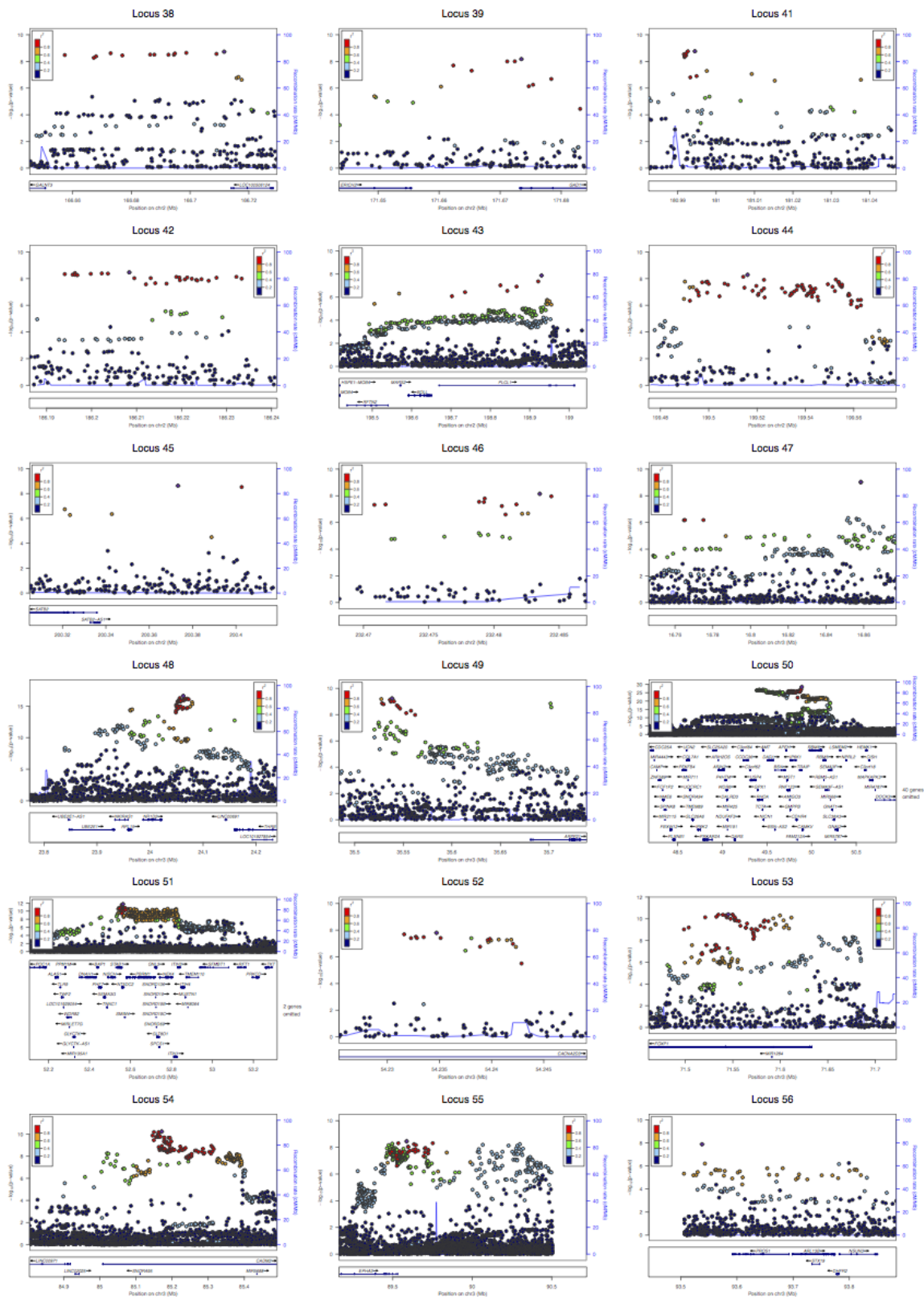
independent individuals. White boxes indicate study cohorts, grey boxes indicate assessment measures, blue boxes indicate groups of analytic procedures, orange boxes indicate sub-analyses, green boxes indicate results. GWAS = genome-wide association; LDSC = linkage disequilibrium (LD) score regression; FUMA = functional mapping and annotation; GWGAS = genome-wide gene-based association; SNP = single nucleotide polymorphism; EA = educational attainment; ExNS = exonic non-synonymous; eQTL = expression quantitative trait locus.

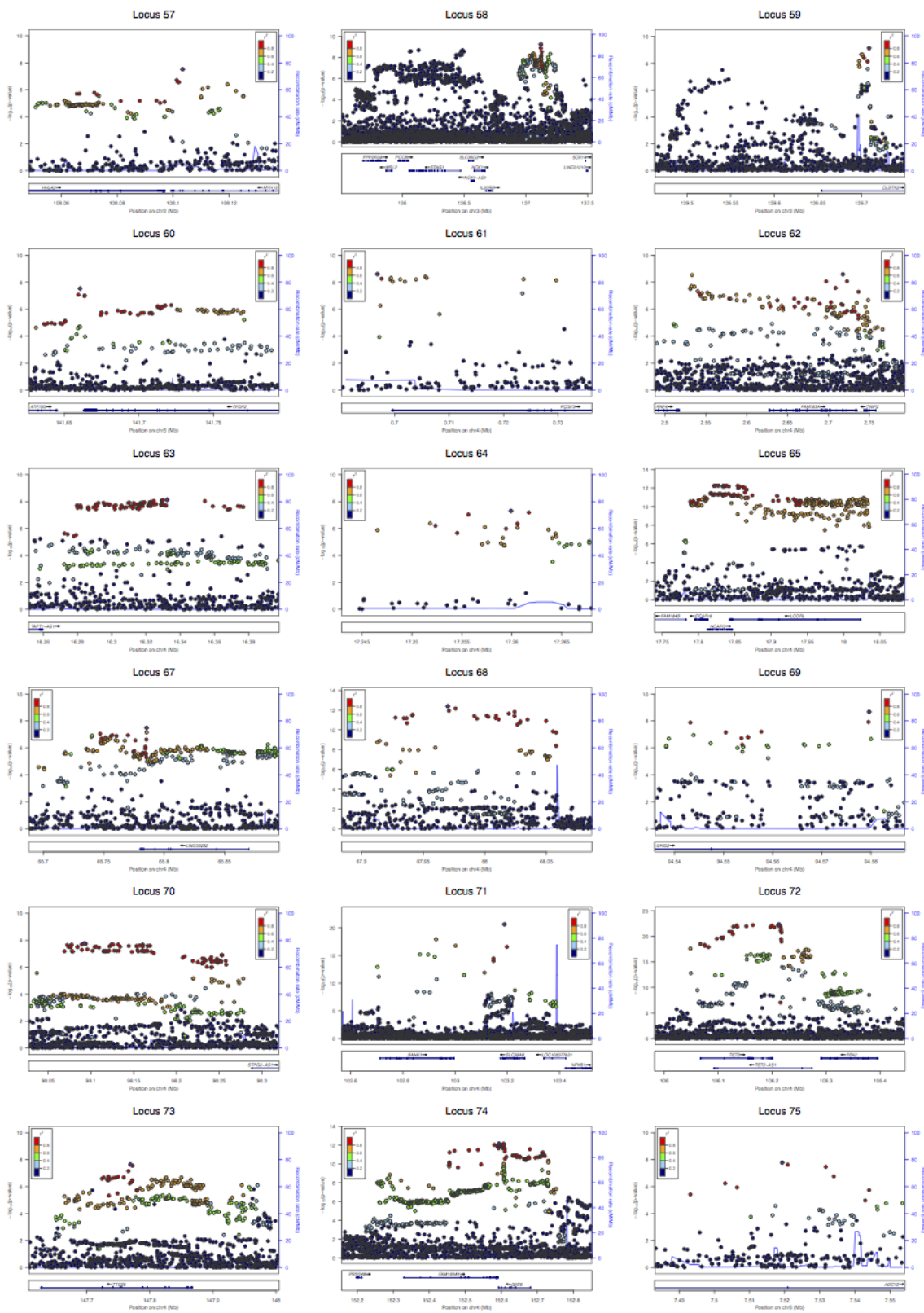


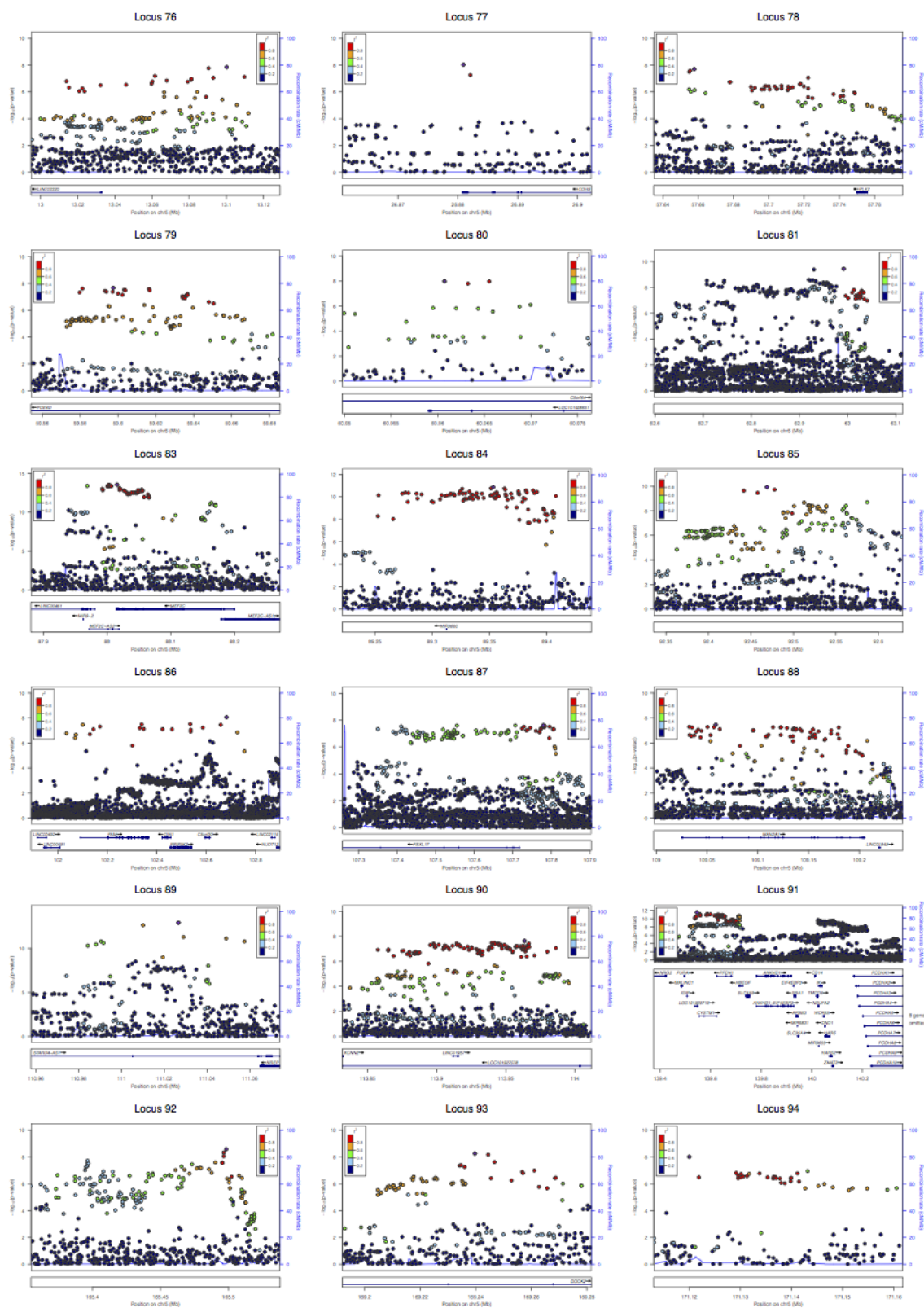
Supplementary Figure 3. QQ-plots of SNP and gene association results in a meta-analysis of intelligence in 269,867 independent individuals. Observed $-\log_{10}$ transformed two-tailed P -values of associations with intelligence measures are plotted against expected null P -values for **a)** all SNPs in the GWAS meta-analysis, and **b)** all genes in the gene-based meta-analysis.

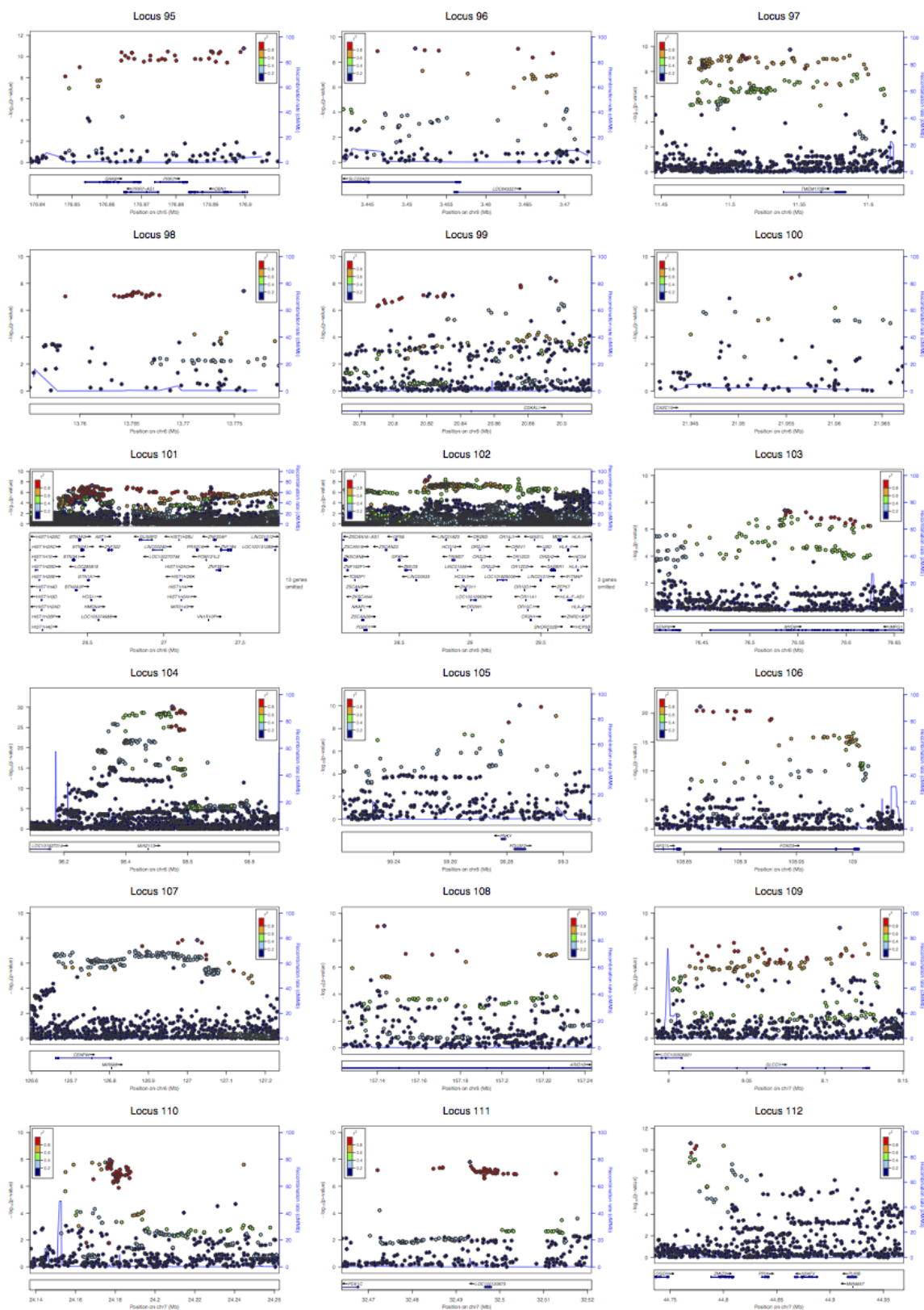


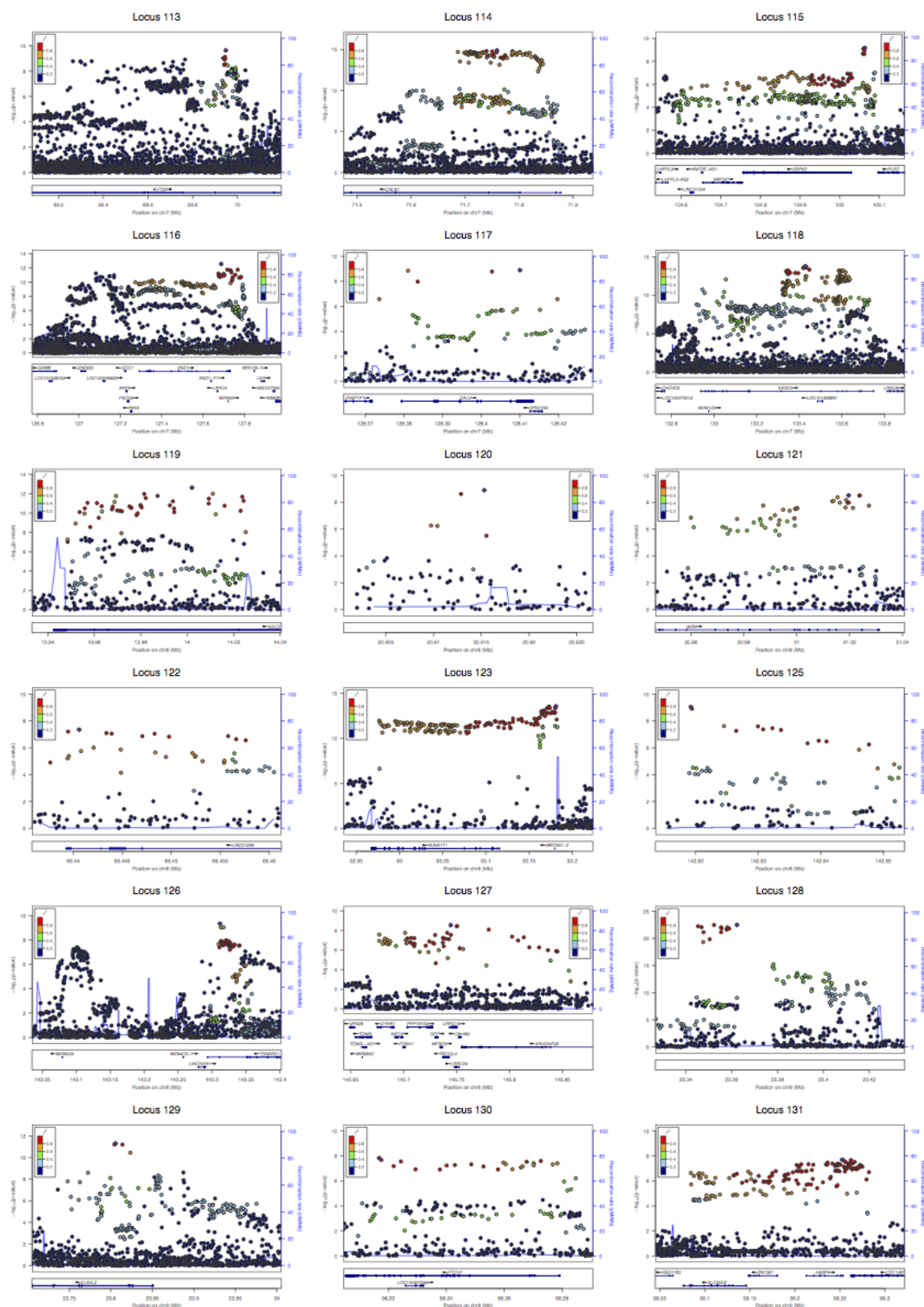


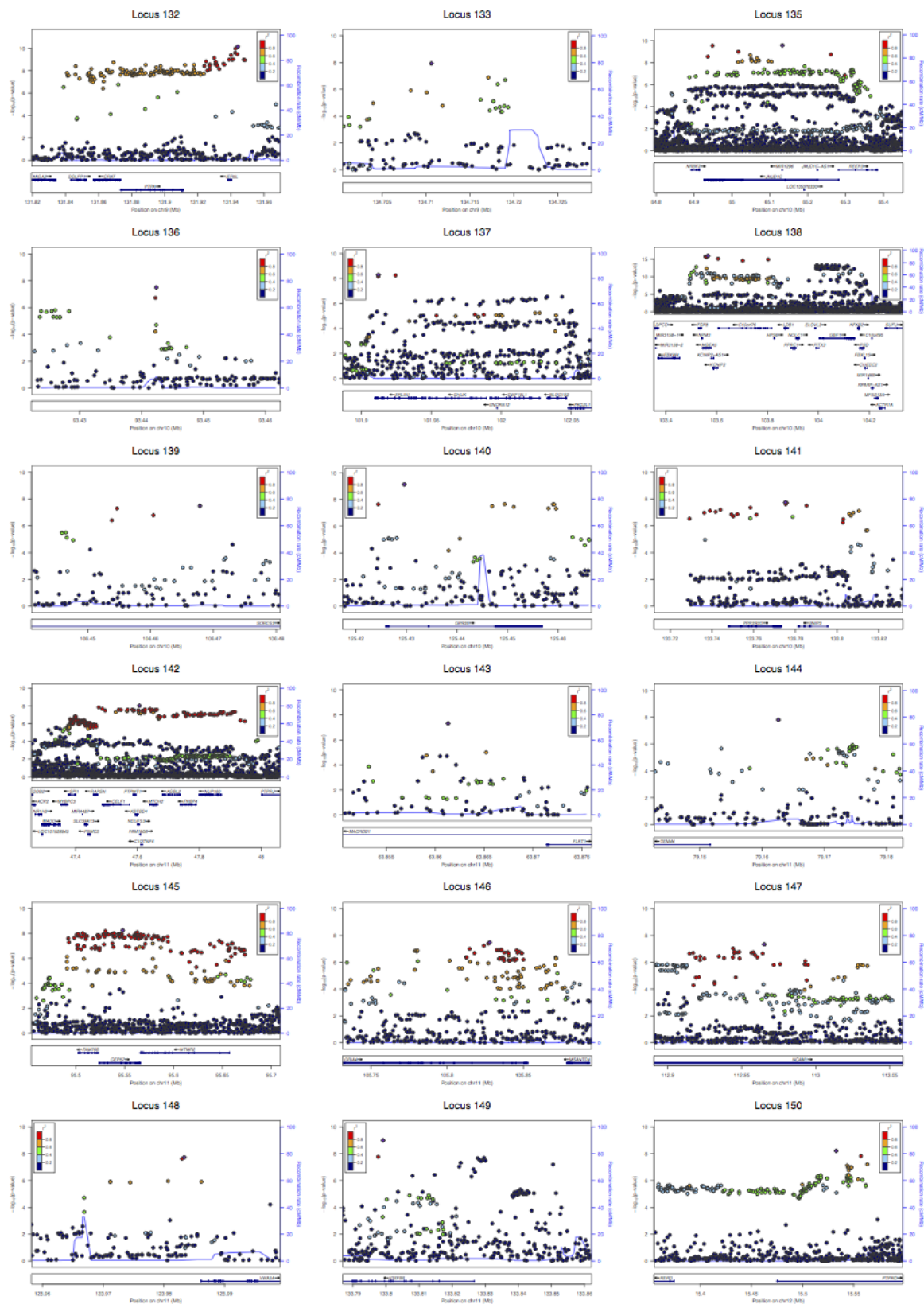


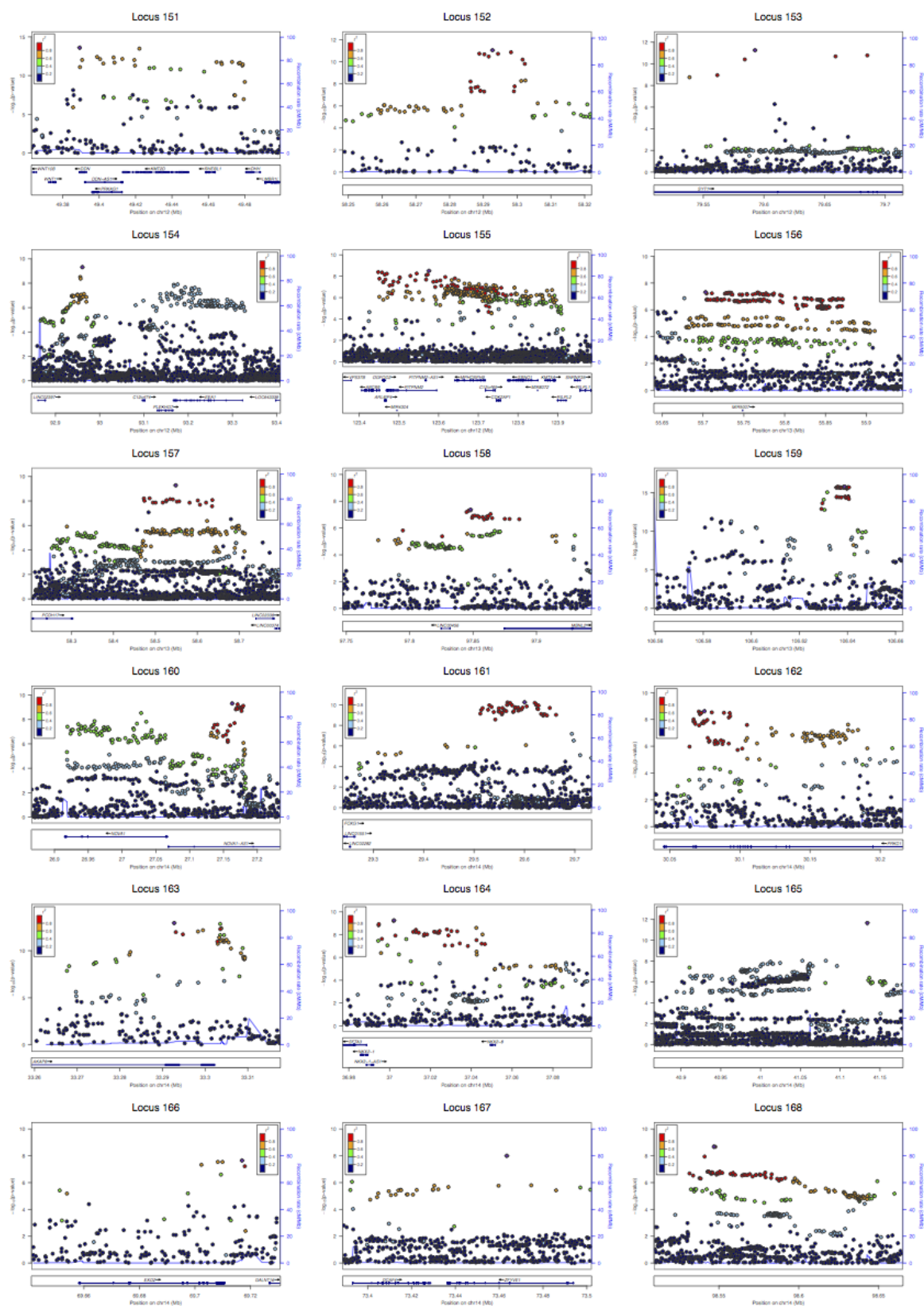


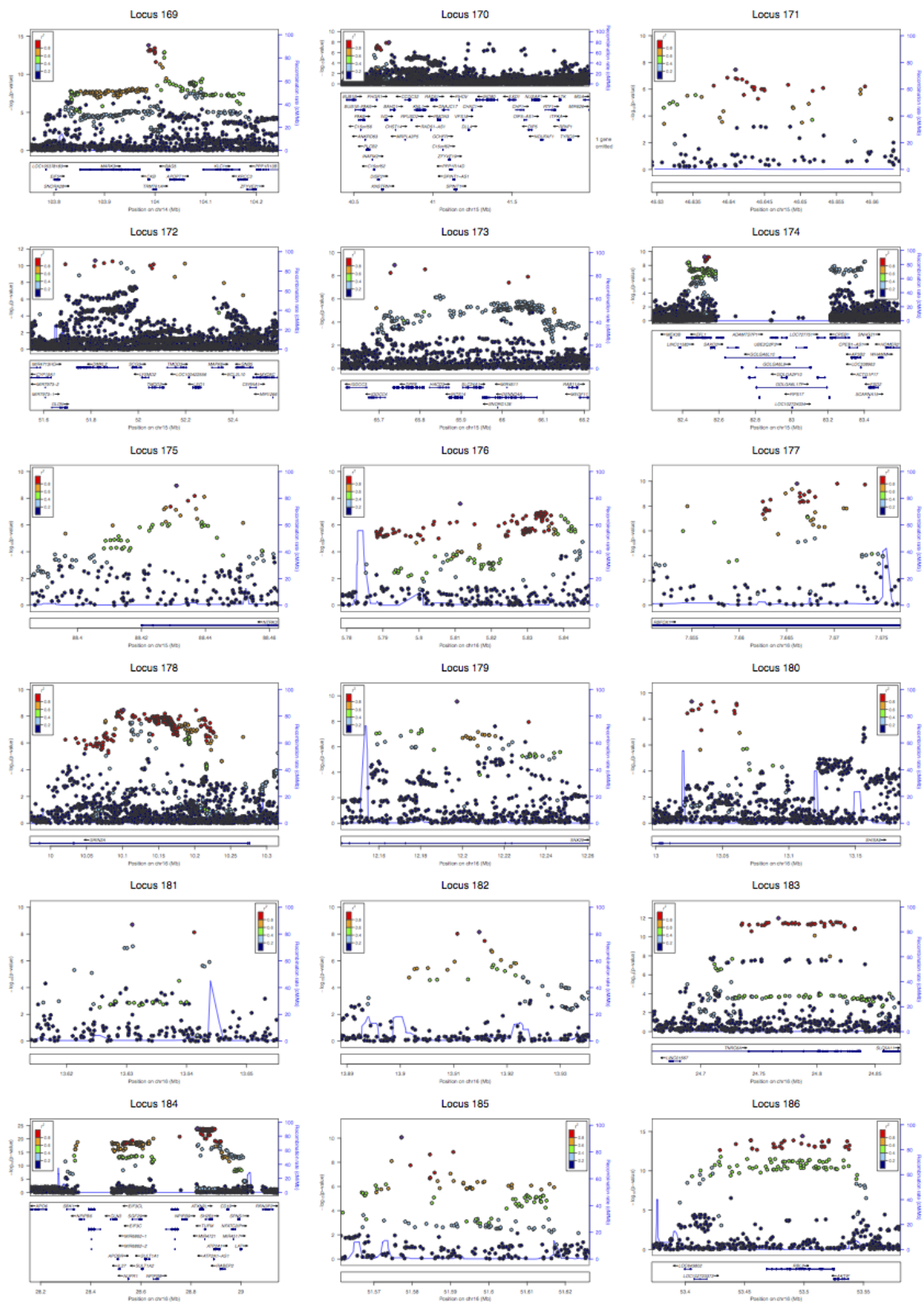


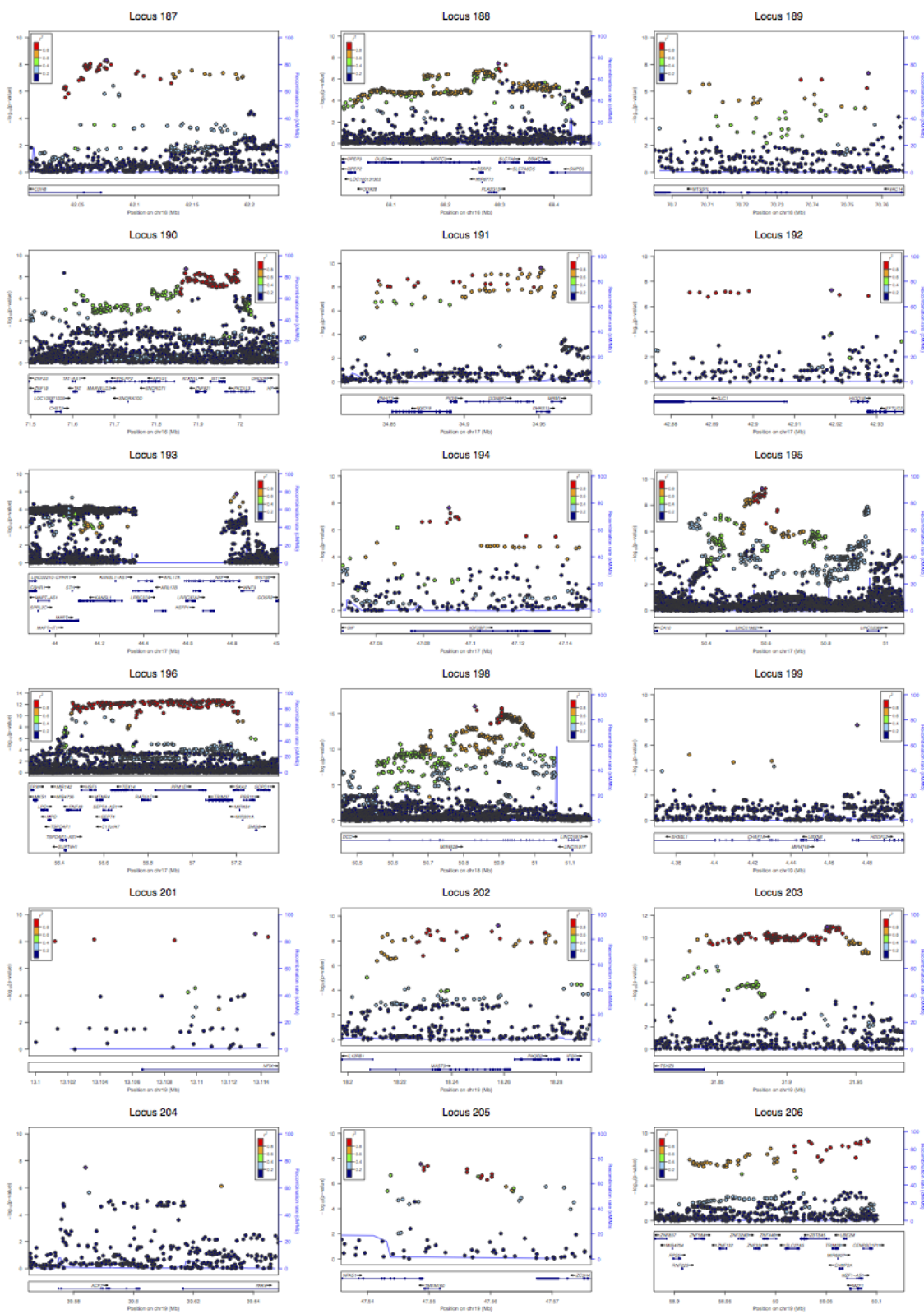


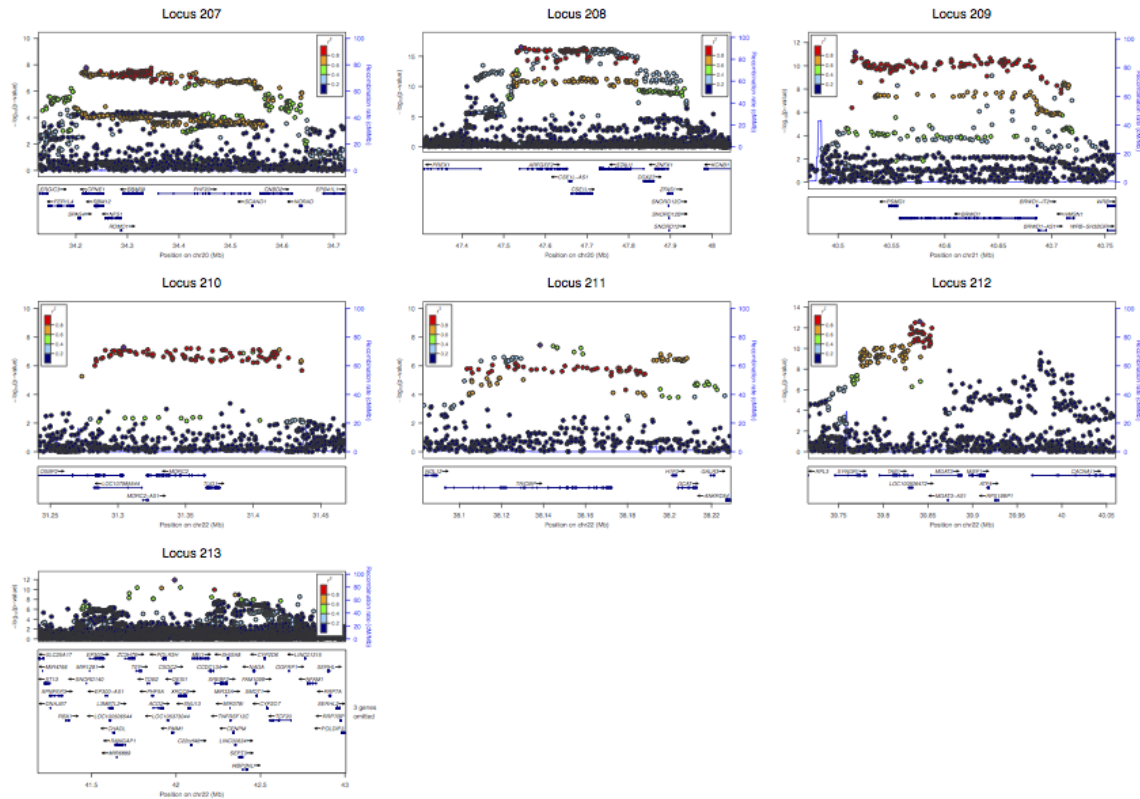




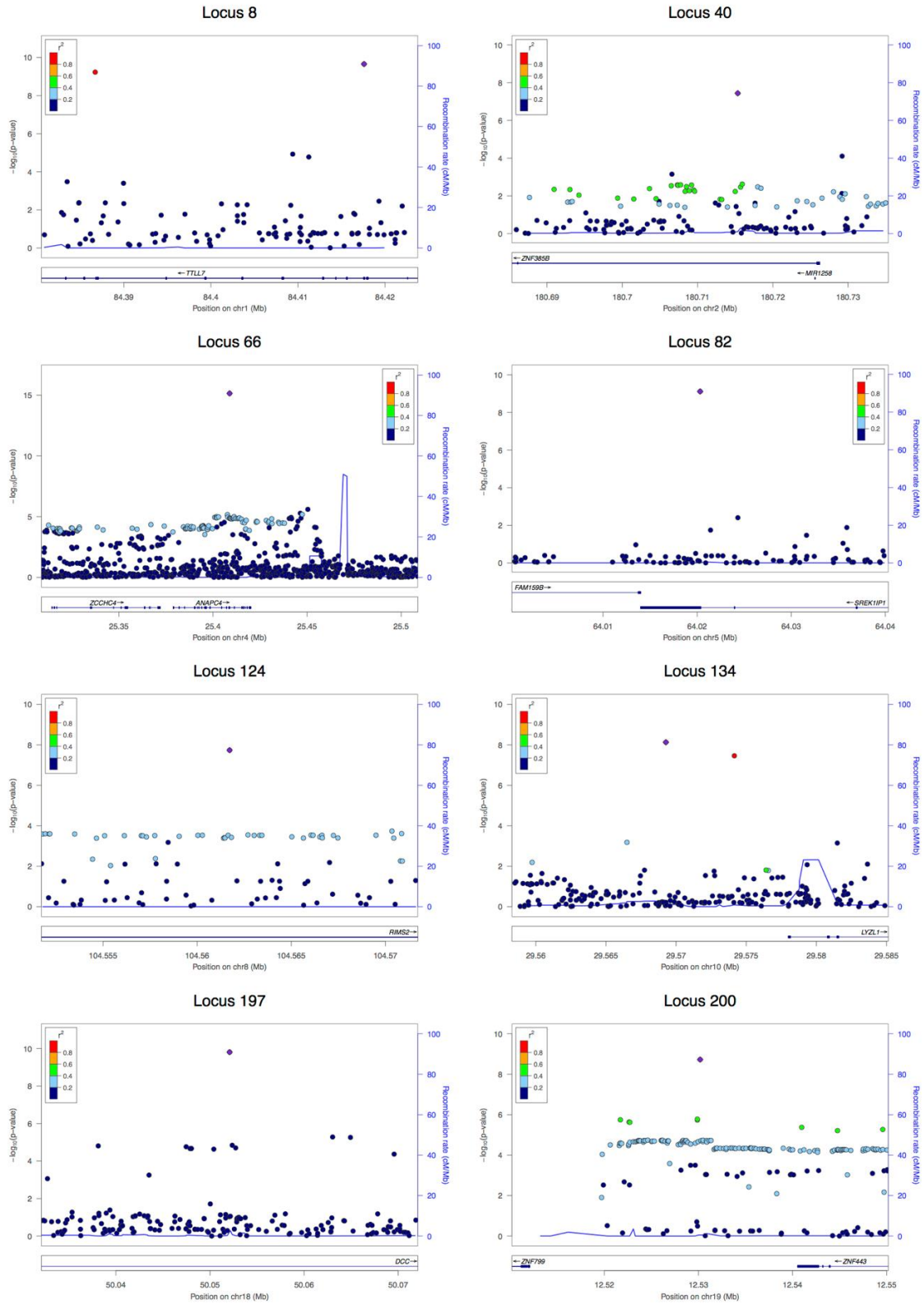






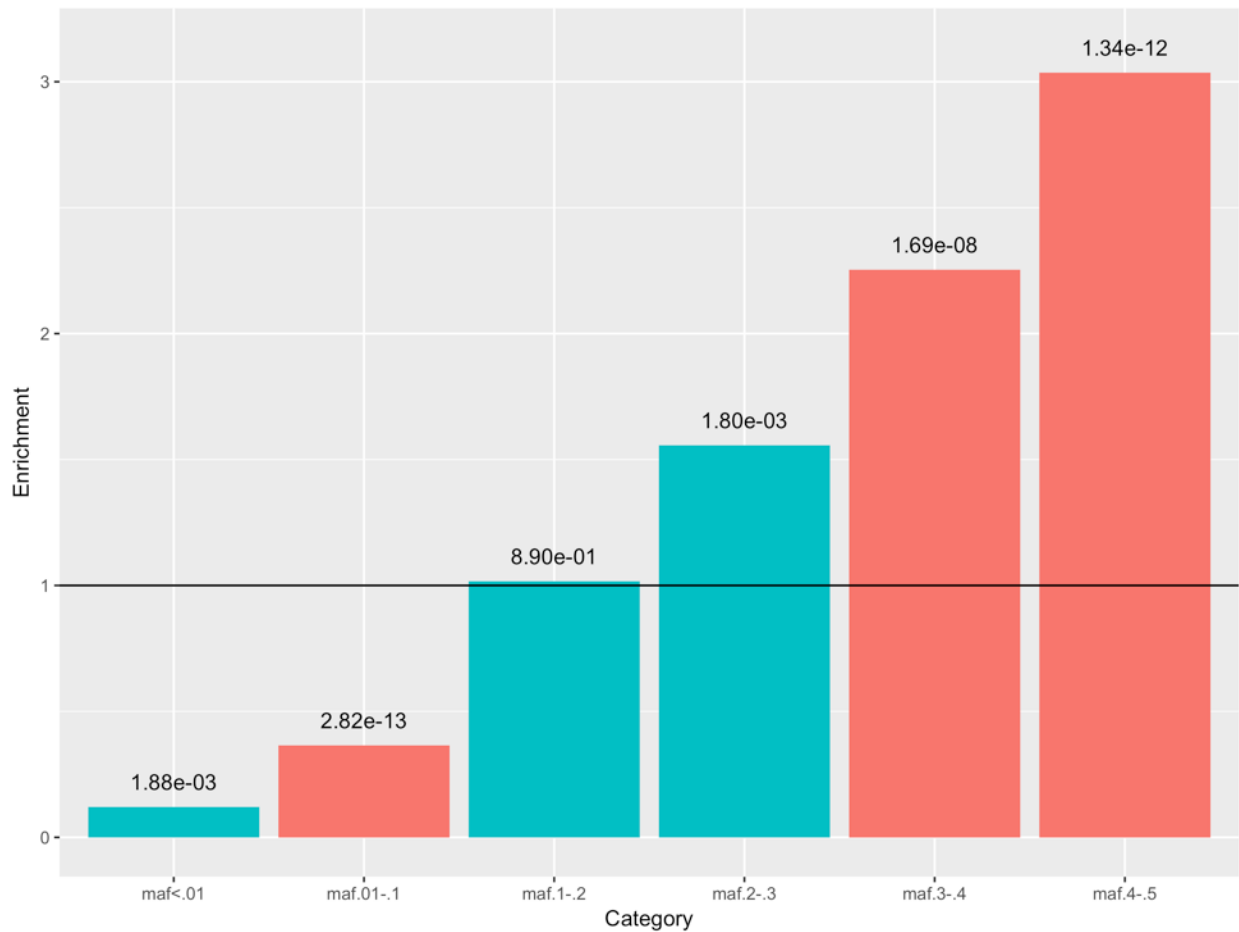


Supplementary Figure 4. Regional association plots of genomic risk loci identified in a GWAS meta-analysis of intelligence in 269,867 independent individuals. Distinct genomic risk loci were defined as LD-independent regions ($r^2 < 0.1$) separated by 250 kb and containing one or more SNPs with a Bonferroni-corrected genome-wide significant association (two-tailed $P < 5 \times 10^{-8}$) with intelligence in a meta-analysis of linear and logistic regression statistics. For each locus, the regional association plot shows the $-\log_{10}$ transformed two-tailed P -value of each SNP from the meta-analysis on the y-axis and base pair positions along the chromosomes on the x-axis. Genes overlapping the locus are displayed below the plot. Independent lead SNPs are indicated by a purple diamond, and each SNP is colored by its LD value with the lead SNP in the region.

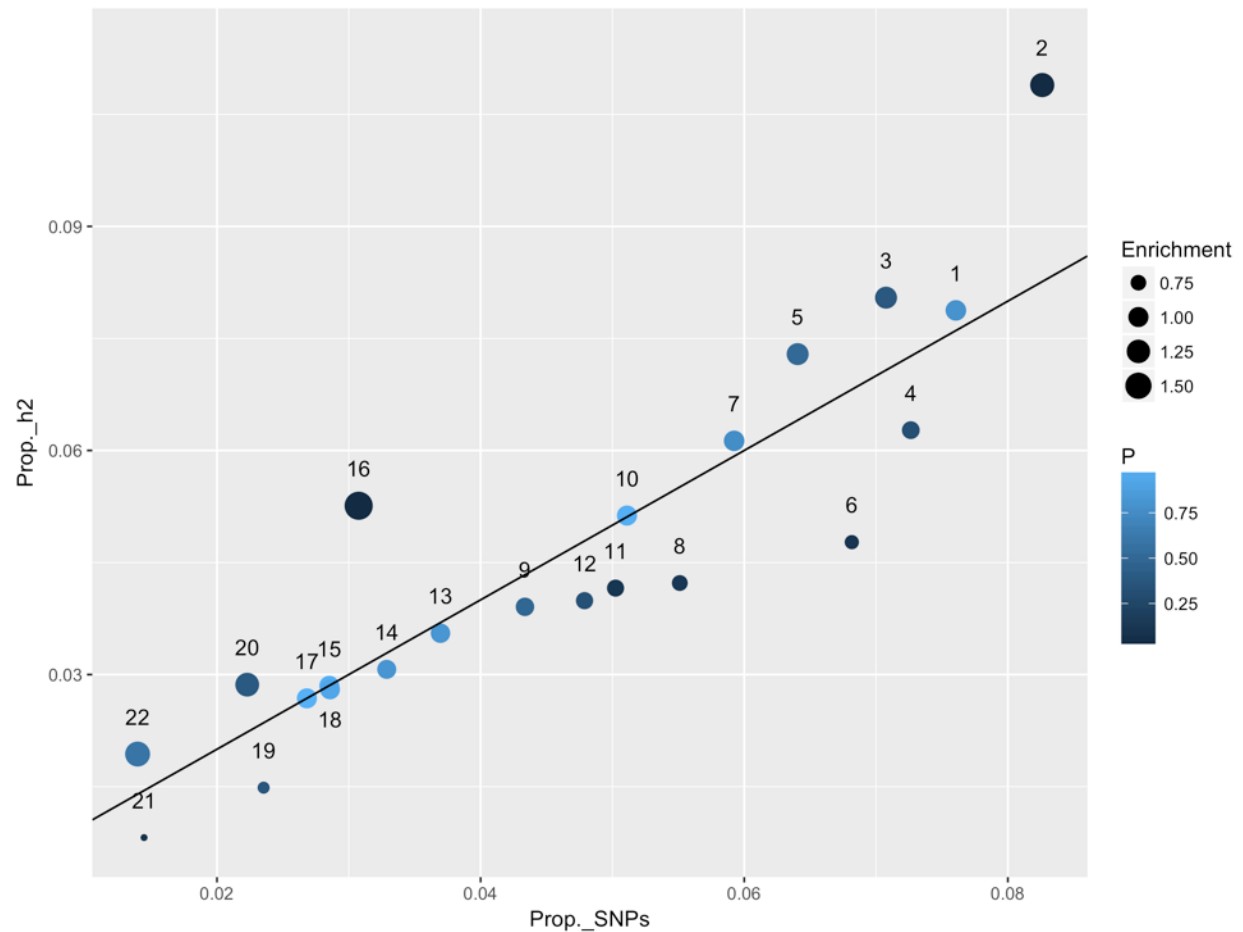


Supplementary Figure 5. Regional association plots for eight genome-wide significant loci with suspicious patterns of linkage disequilibrium in a GWAS meta-analysis of intelligence in

269,867 independent individuals. Distinct genomic risk loci were defined as LD-independent regions ($r^2 < 0.1$) separated by 250 kb and containing one or more SNPs with a Bonferroni-corrected genome-wide significant association (two-tailed $P < 5 \times 10^{-8}$) with intelligence in a meta-analysis of linear and logistic regression statistics. For each locus, the regional association plot shows the $-\log_{10}$ transformed two-tailed P -value of each SNP from the meta-analysis on the y-axis and base pair positions along the chromosomes on the x-axis. Genes overlapping the locus are displayed below the plot. Independent lead SNPs are indicated by a purple diamond, and each SNP is colored by its LD value with the lead SNP in the region. Lead SNPs were isolated GWS signals in a region; these did not show obvious quality issues but were excluded from the number of reported risk loci (**Supplementary Results 2.3.1**).

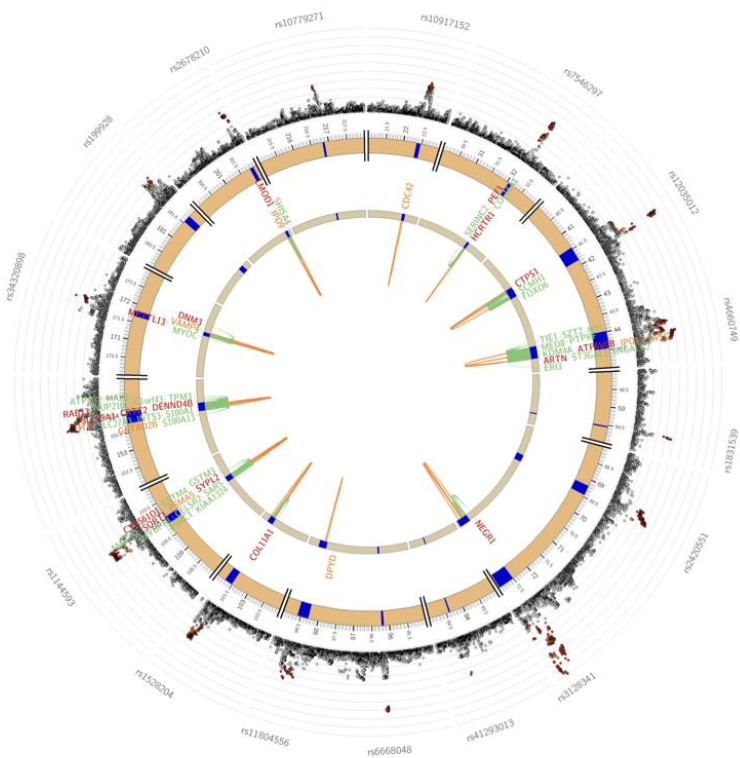


Supplementary Figure 6. Heritability of intelligence in a GWAS meta-analysis of 269,867 independent individuals, stratified by minor allele frequency (MAF) bins. Tests of enrichment/depletion of SNP heritability within a bin relative to the proportion of SNPs in the bin were conducted with LD score regression. Two-tailed *P*-values are presented above the bins; red bins are significant after Bonferroni correction for 56 total strata. Horizontal line ($=1.0$) indicates no enrichment.

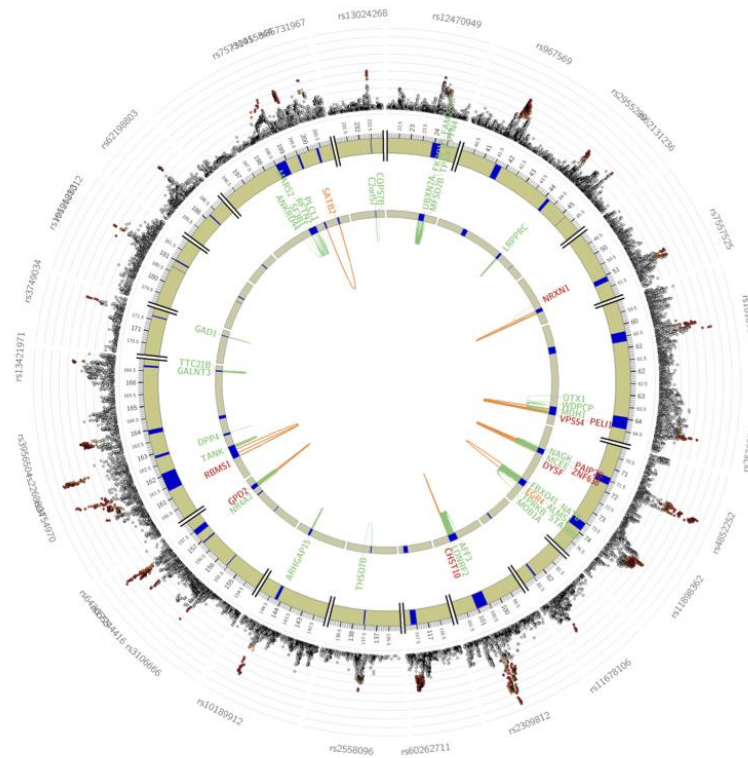


Supplementary Figure 7. Heritability of intelligence in a GWAS meta-analysis of 269,867 independent individuals, stratified by chromosome. Tests of enrichment/depletion of SNP heritability within a chromosome relative to the proportion of SNPs on the chromosome were conducted with LD score regression. The chromosome size (proportion of total SNPs) is on the x-axis and the proportion of total heritability (h^2) attributable to each chromosome is on the y-axis. The X chromosome was not available in the reference panel for LD scores. Chromosomes are colored by two-tailed P -values; none were significant after Bonferroni correction for 56 total strata. Diagonal line indicates no enrichment.

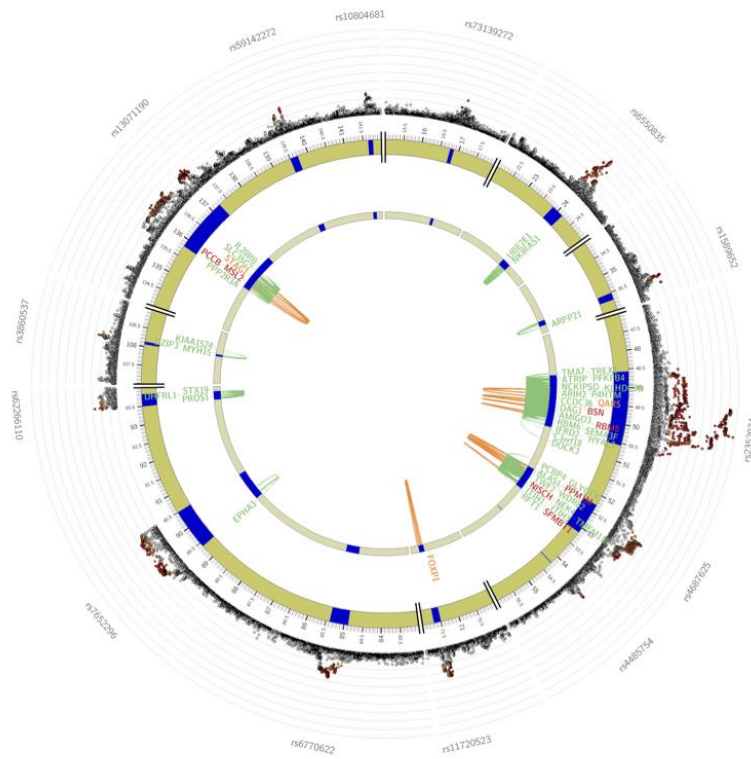
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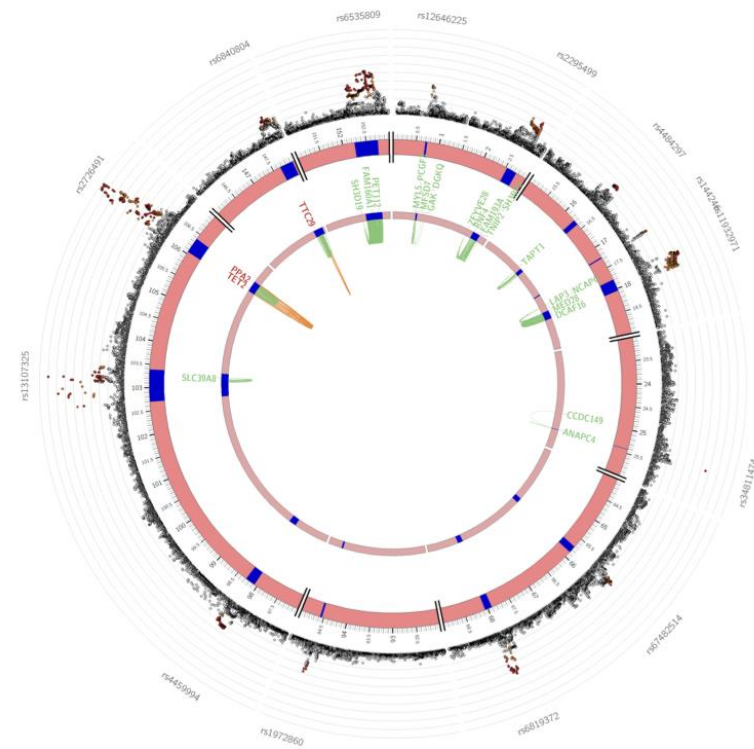
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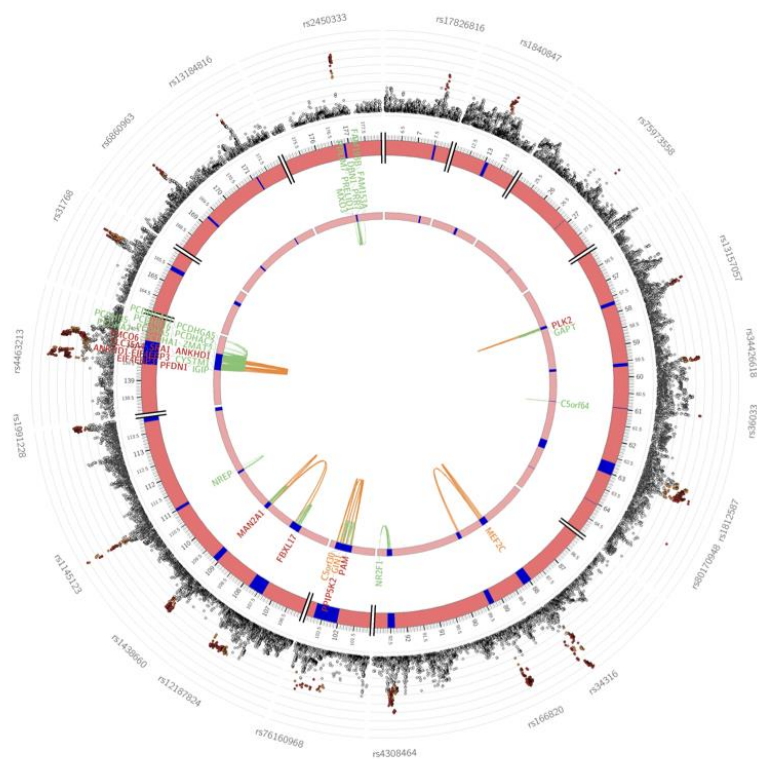
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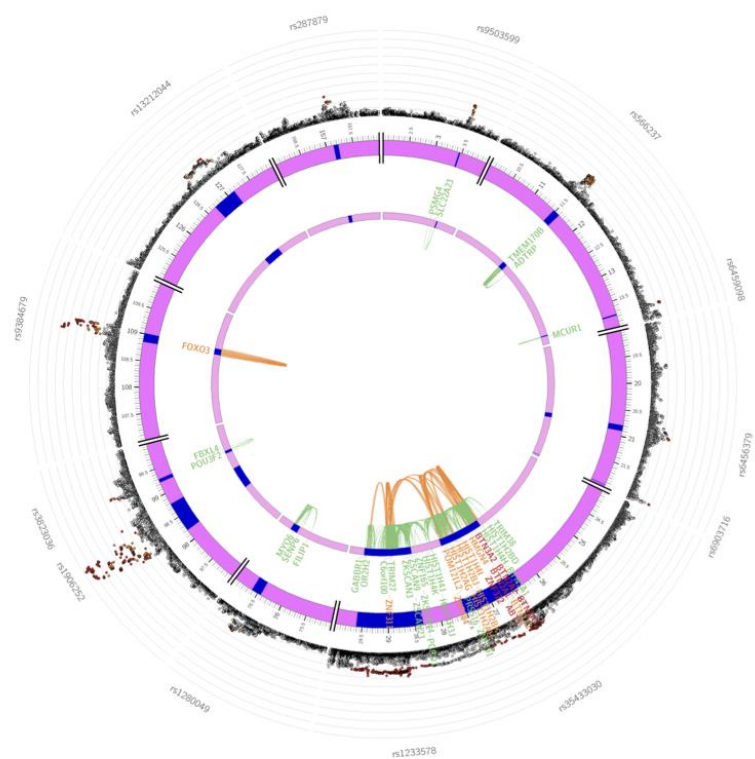
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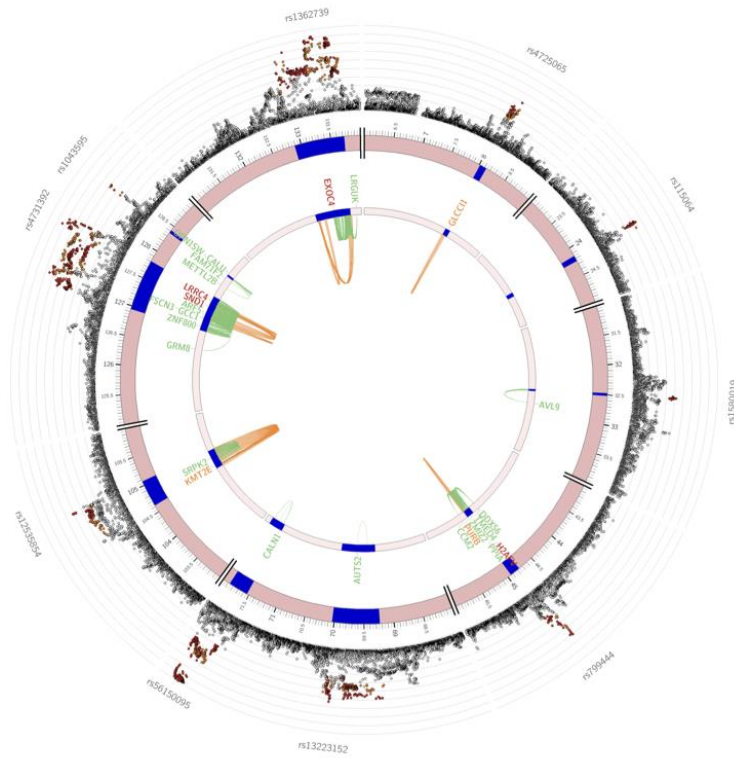
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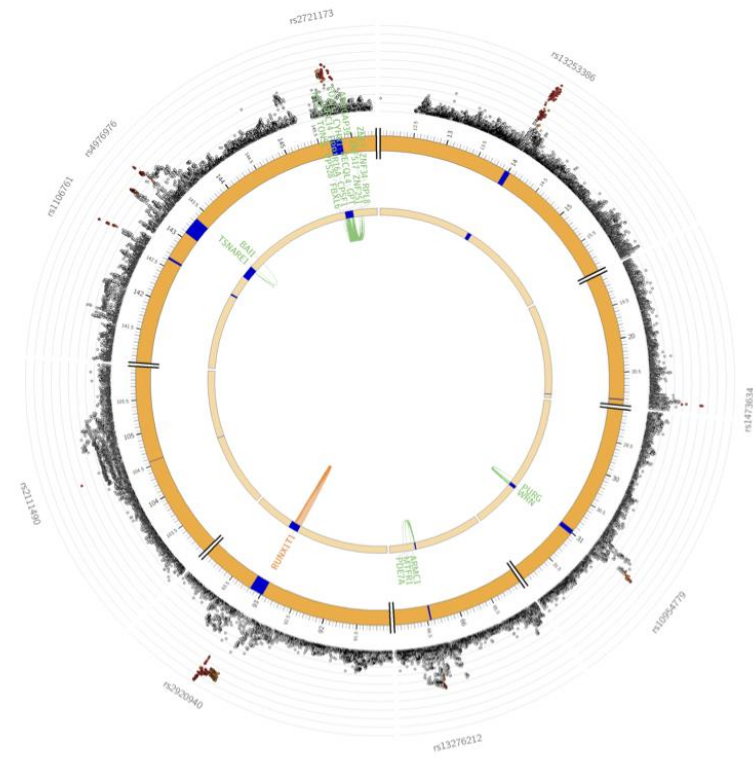
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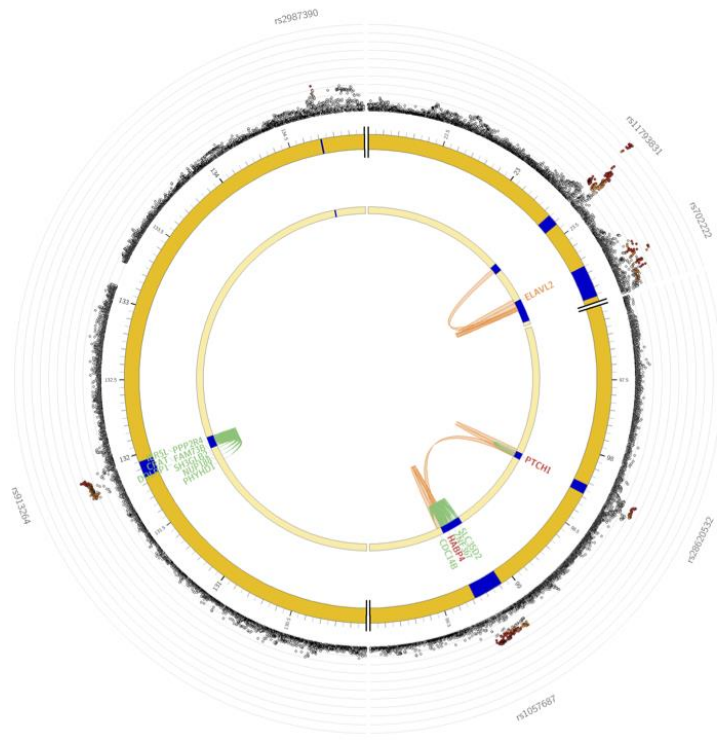
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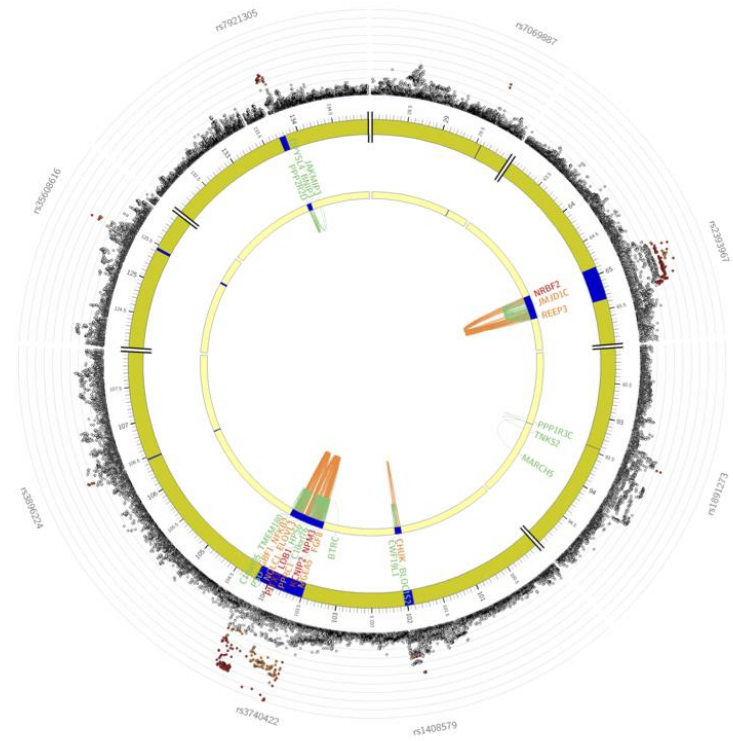
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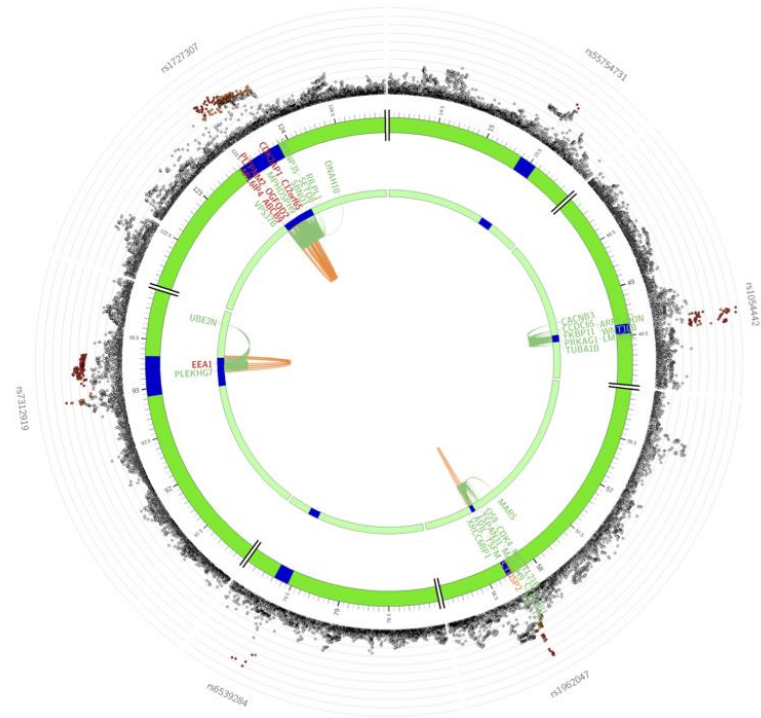
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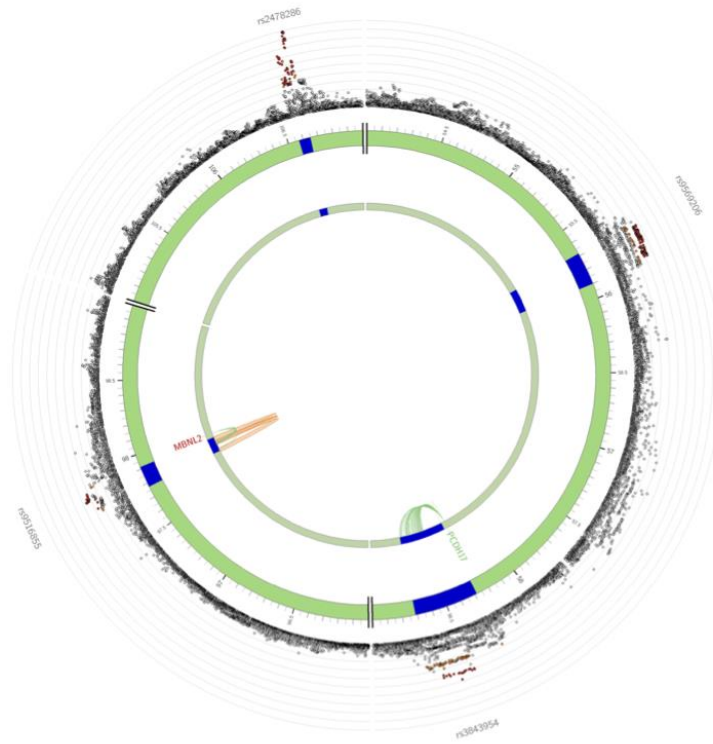
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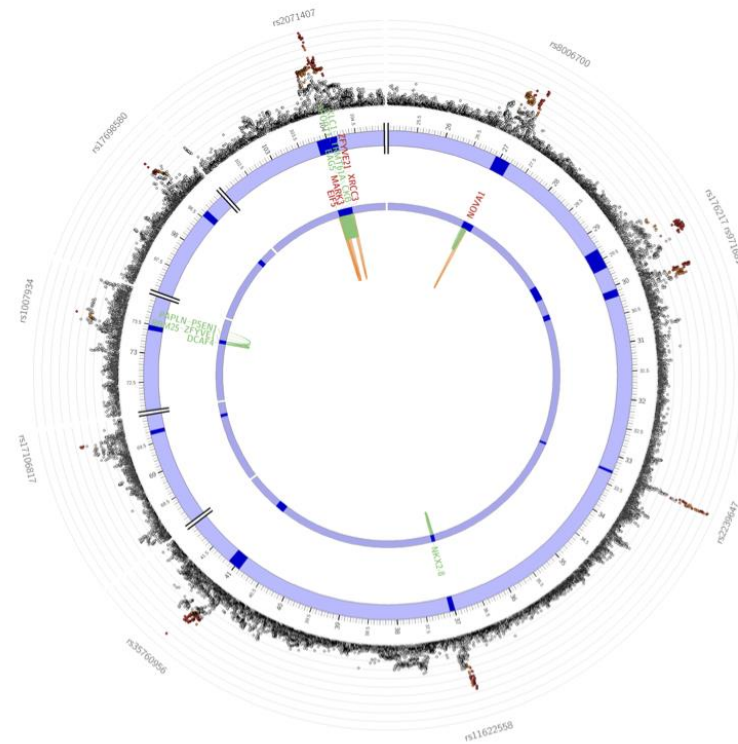
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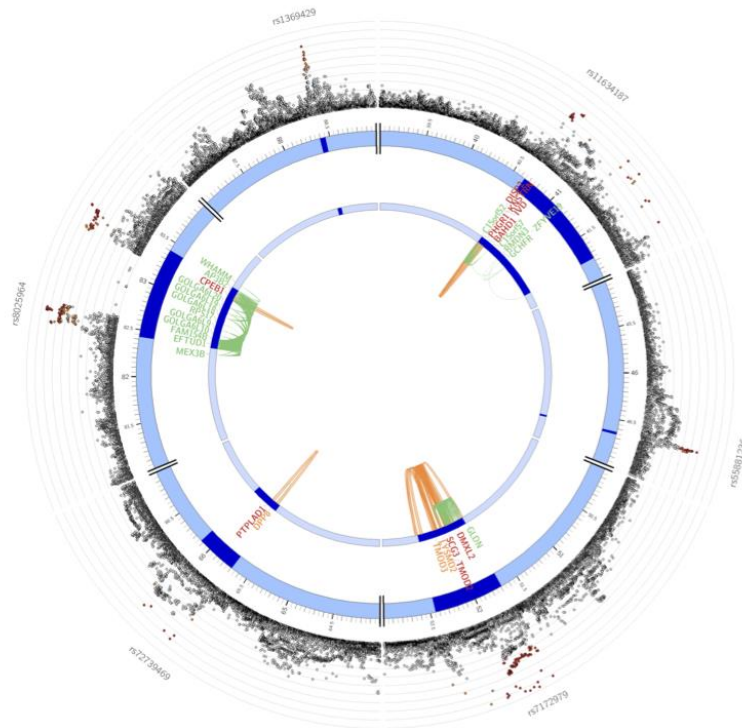
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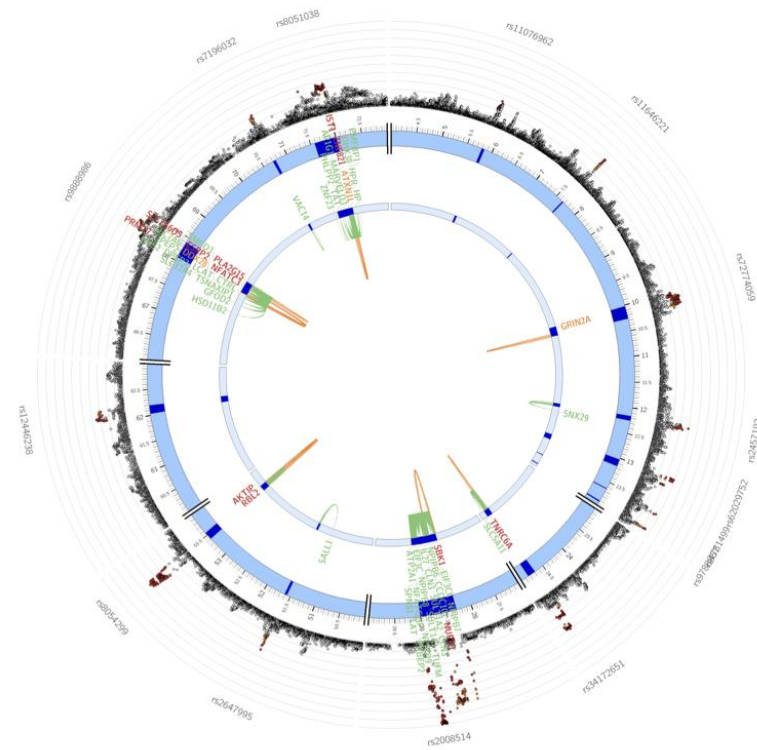
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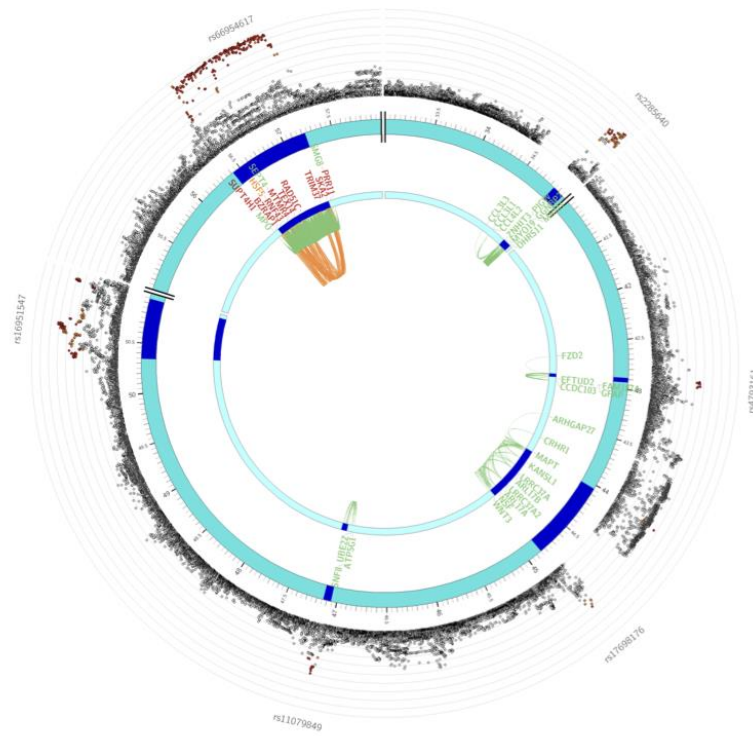
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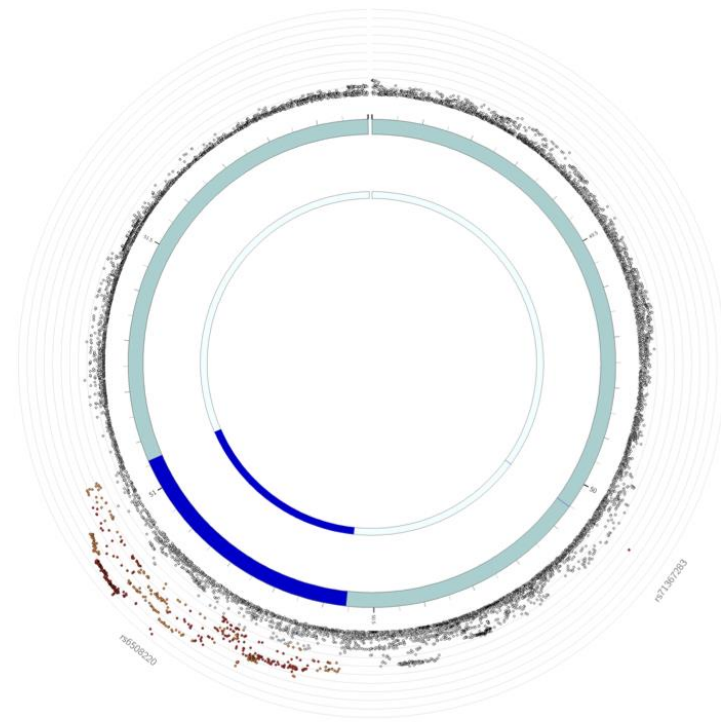
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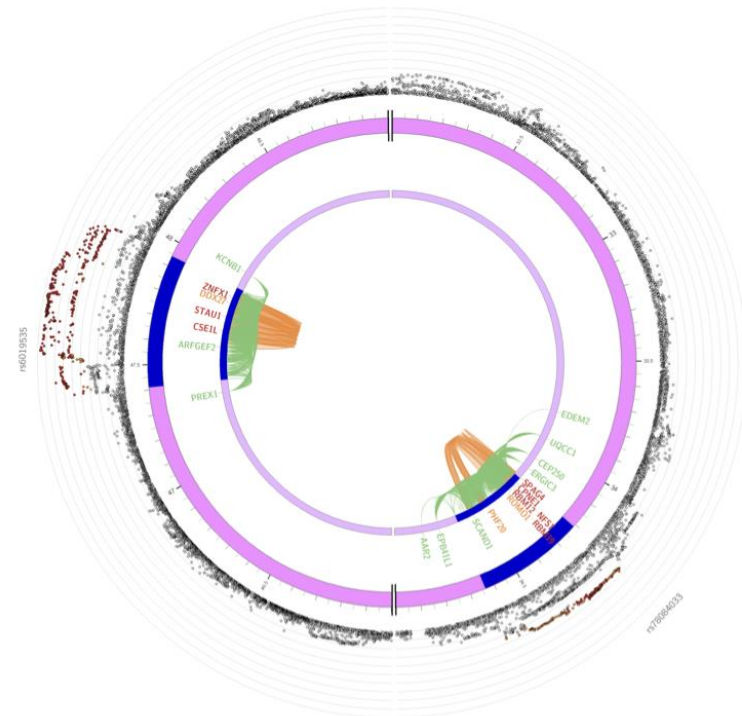
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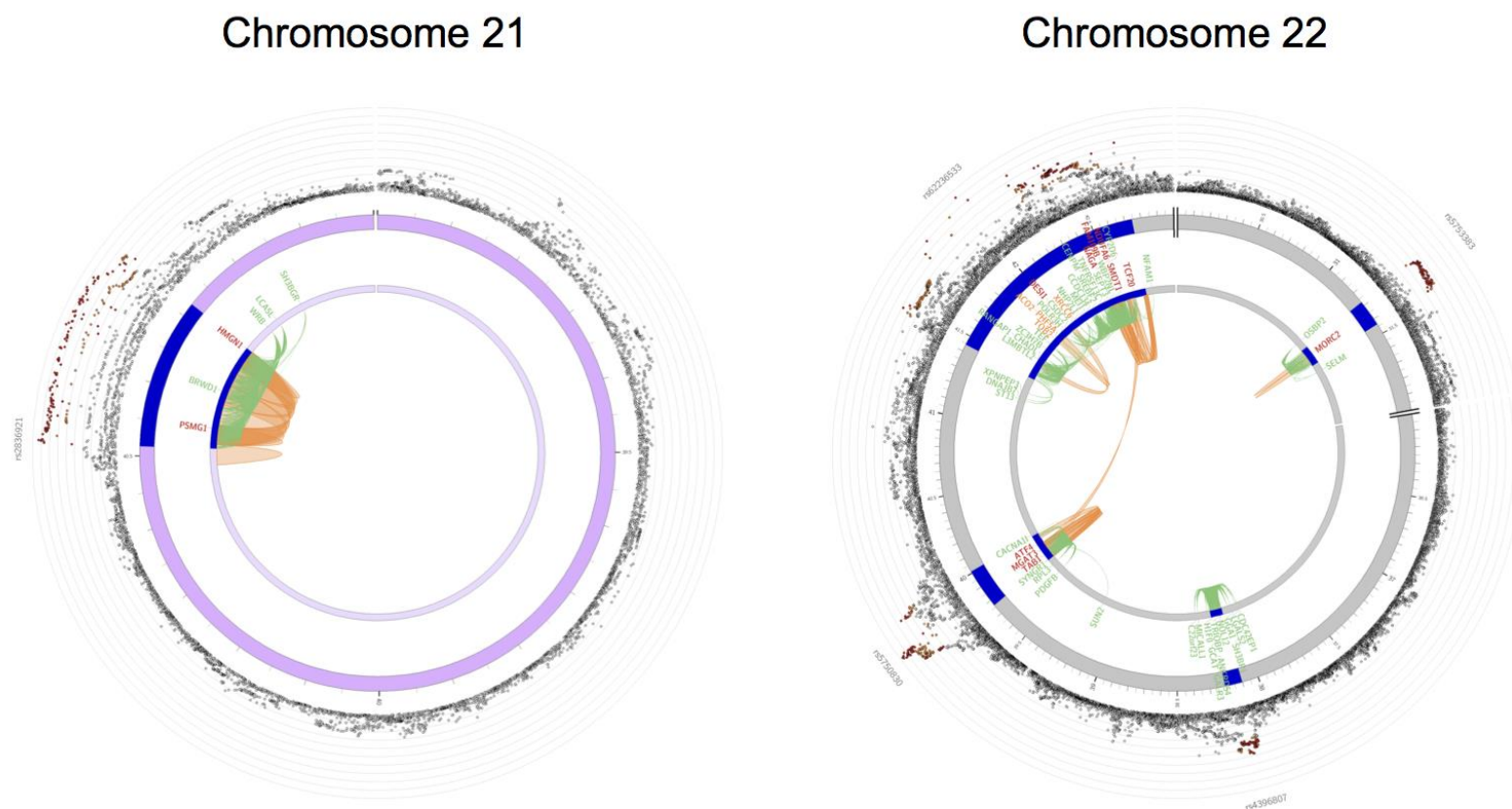


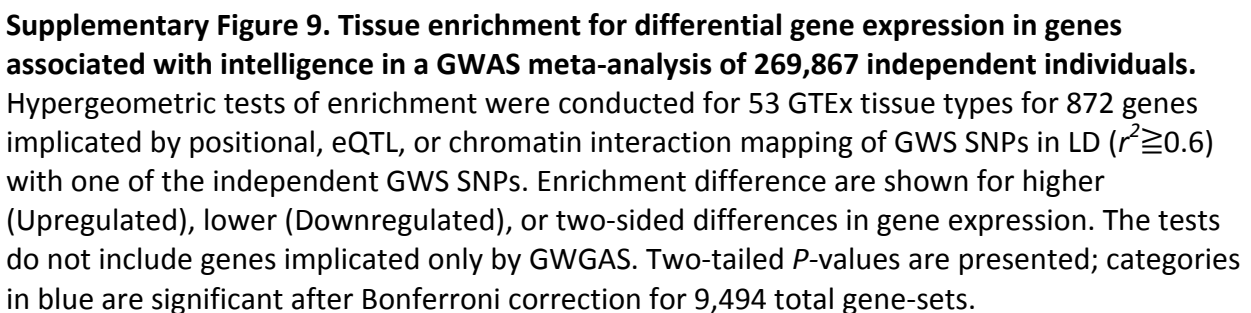
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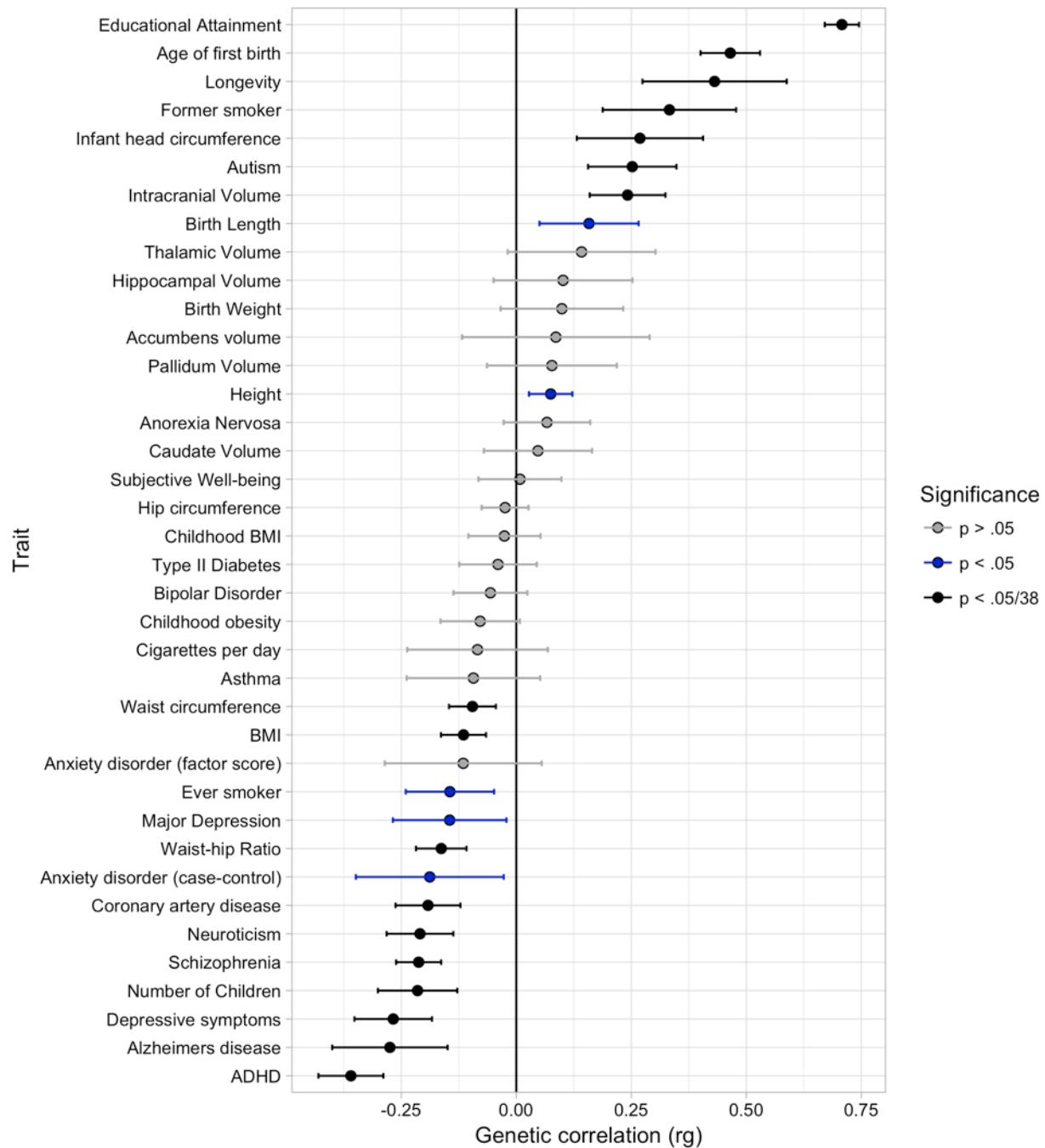


Chromosome 20

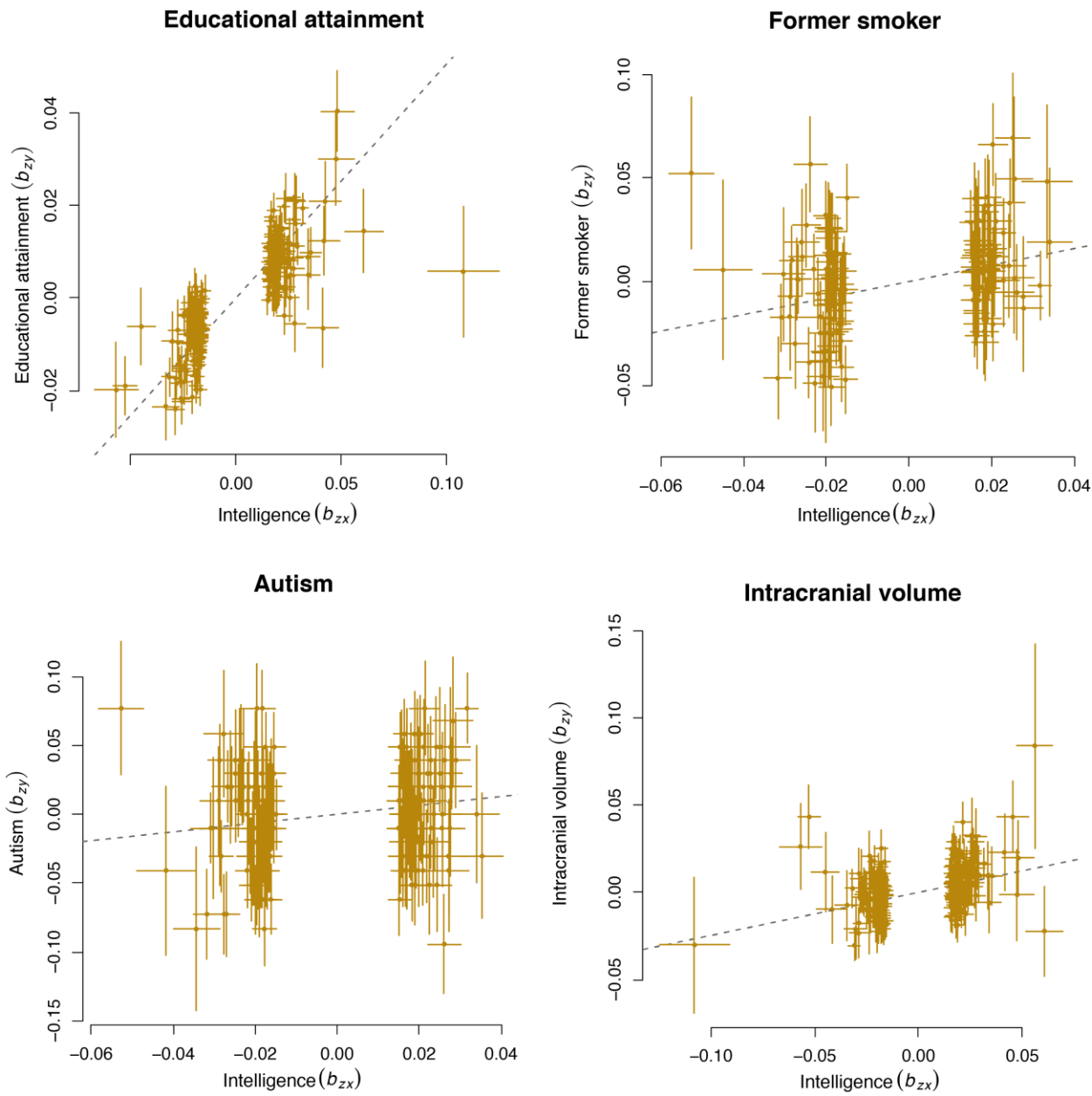


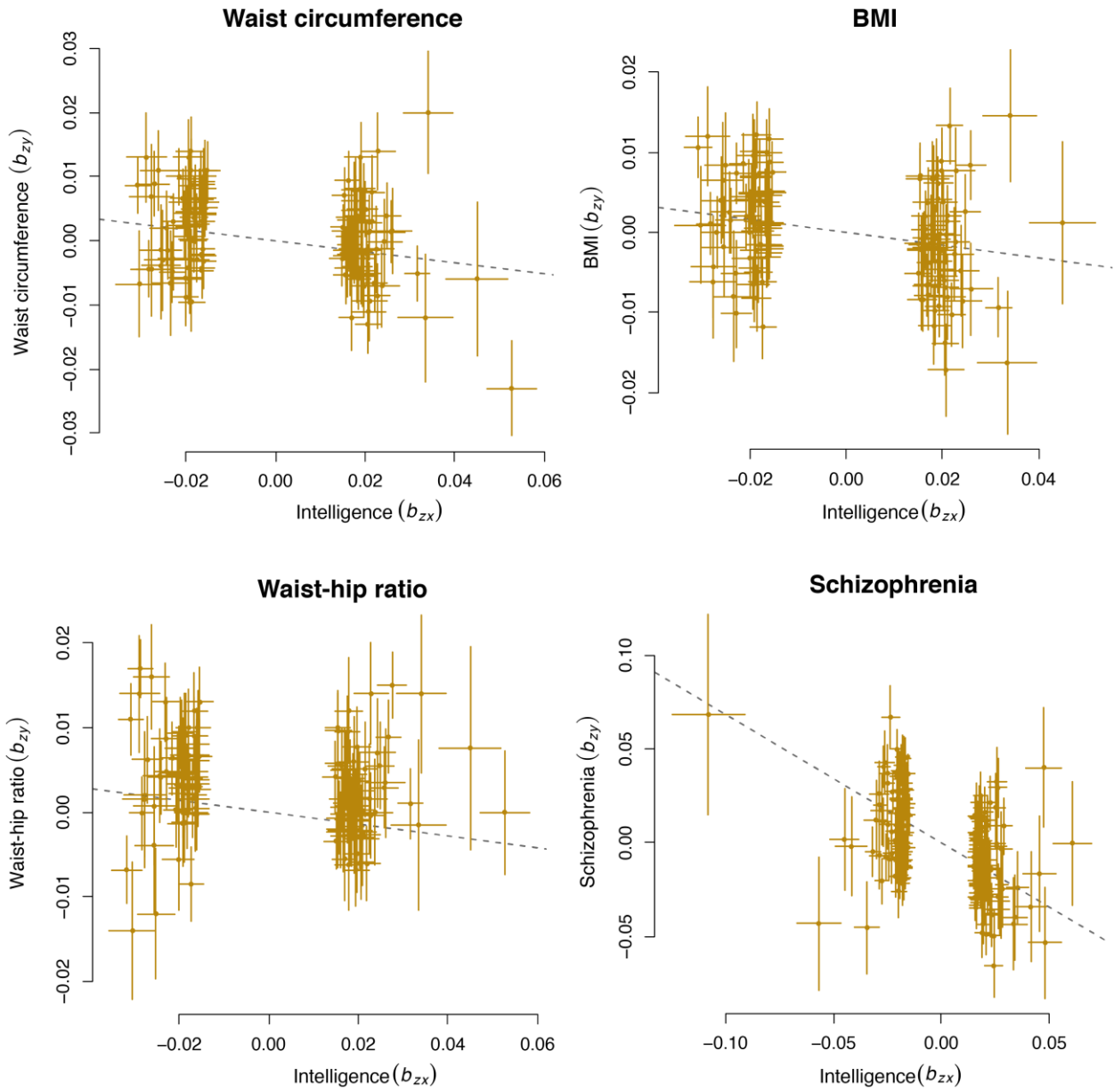


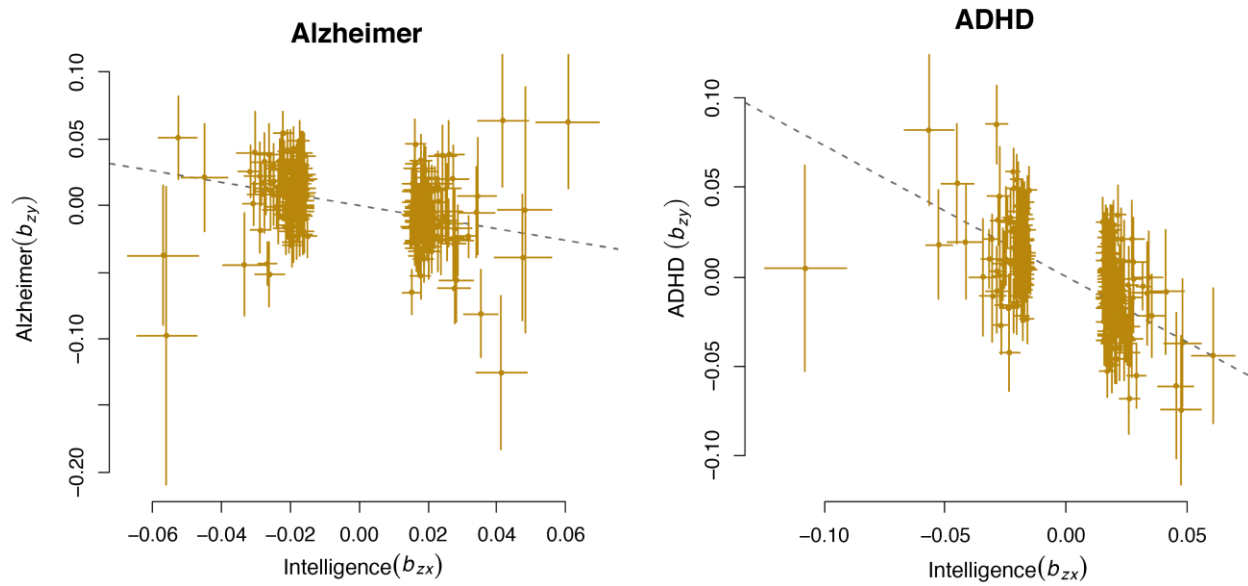




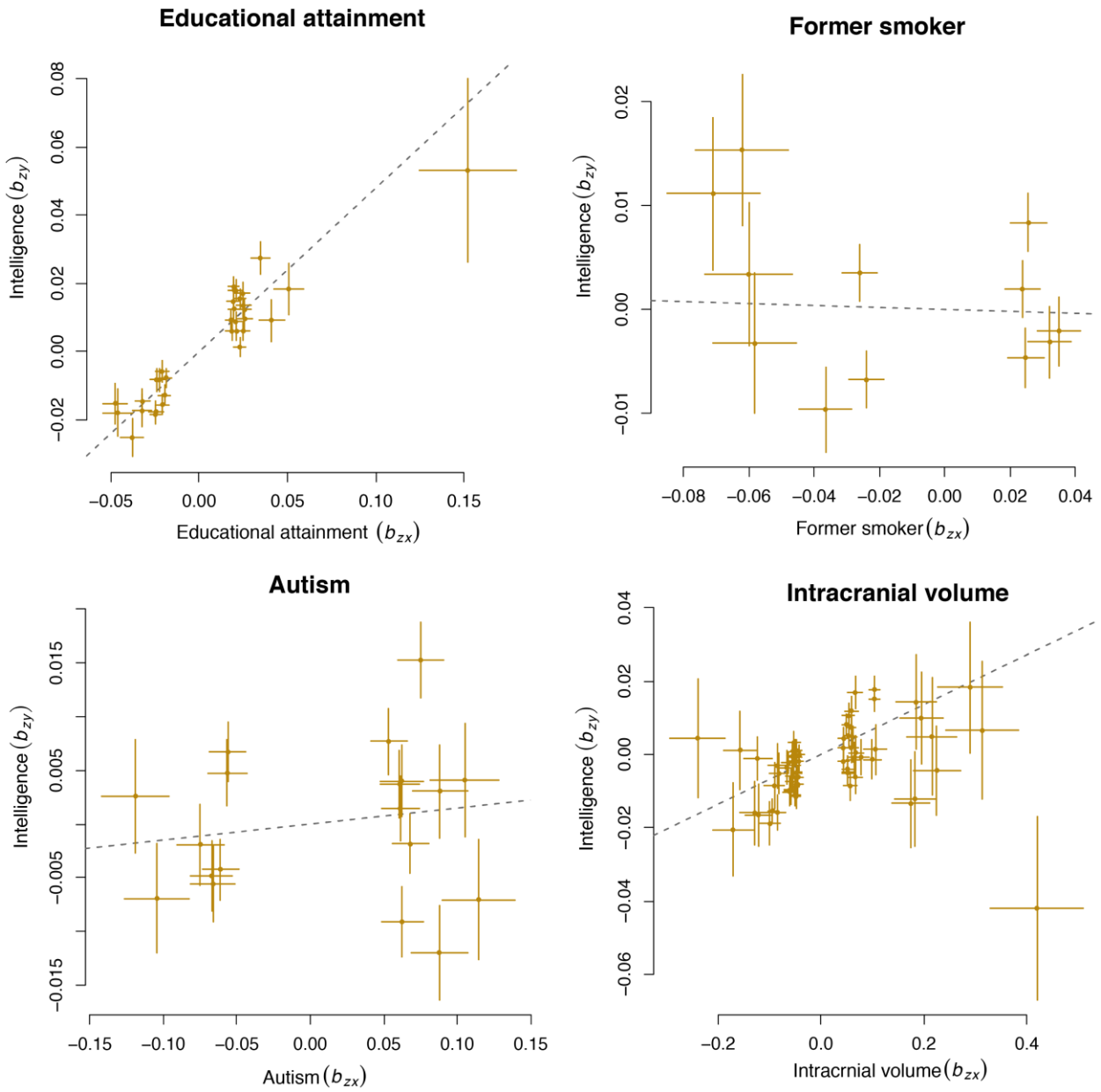
Supplementary Figure 10. Genetic correlations between intelligence and other traits previously investigated with GWAS. Correlations were calculated with LD score regression using SNP summary statistics from the GWAS meta-analysis of intelligence in 269,867 individuals and publically available summary statistics for other traits (**Supplementary Table 21**). Point estimates for correlations and 95% confidence intervals are shown; black dots indicate significant two-tailed P -values after Bonferroni correction for 38 pairs of traits.

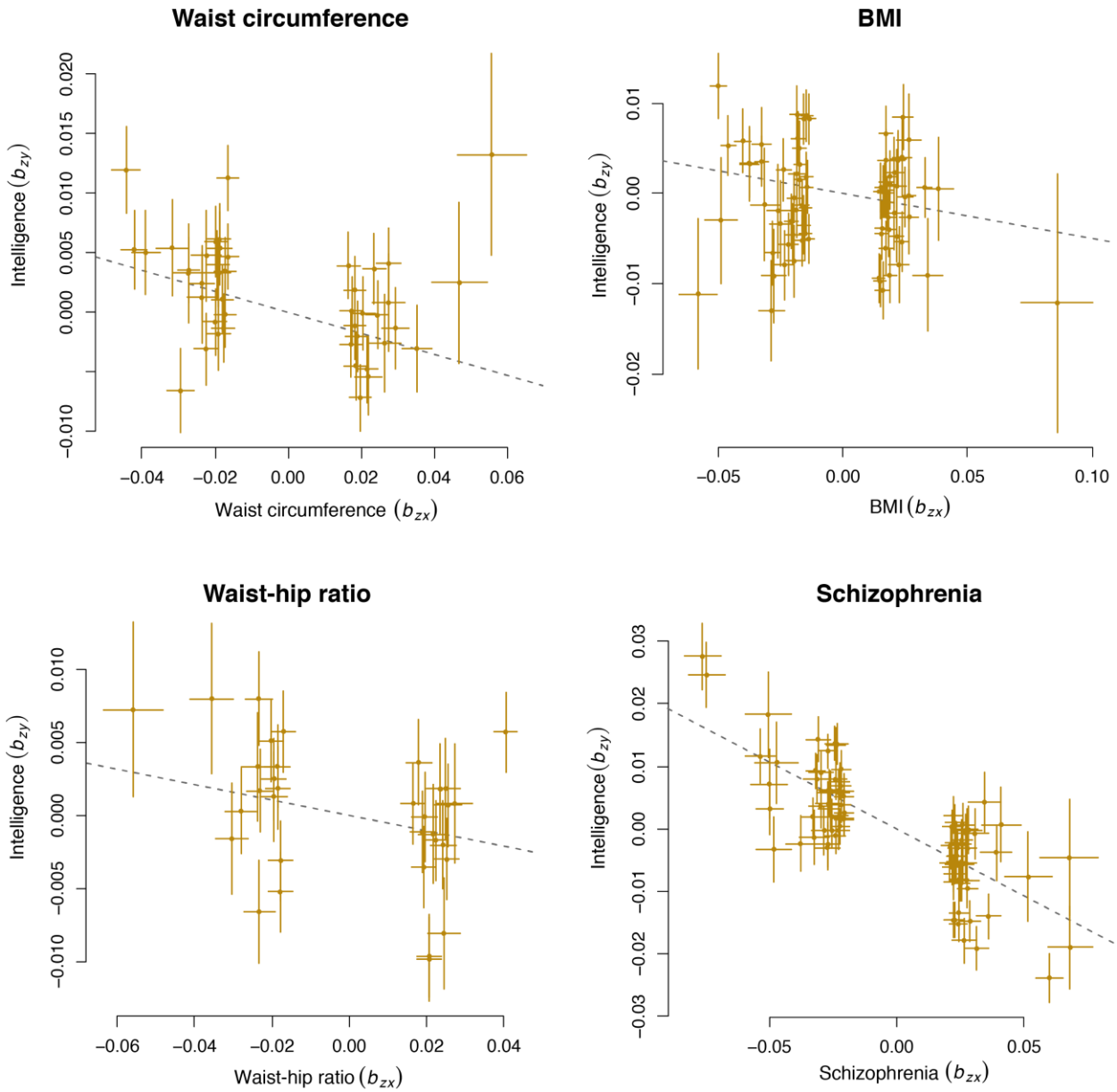


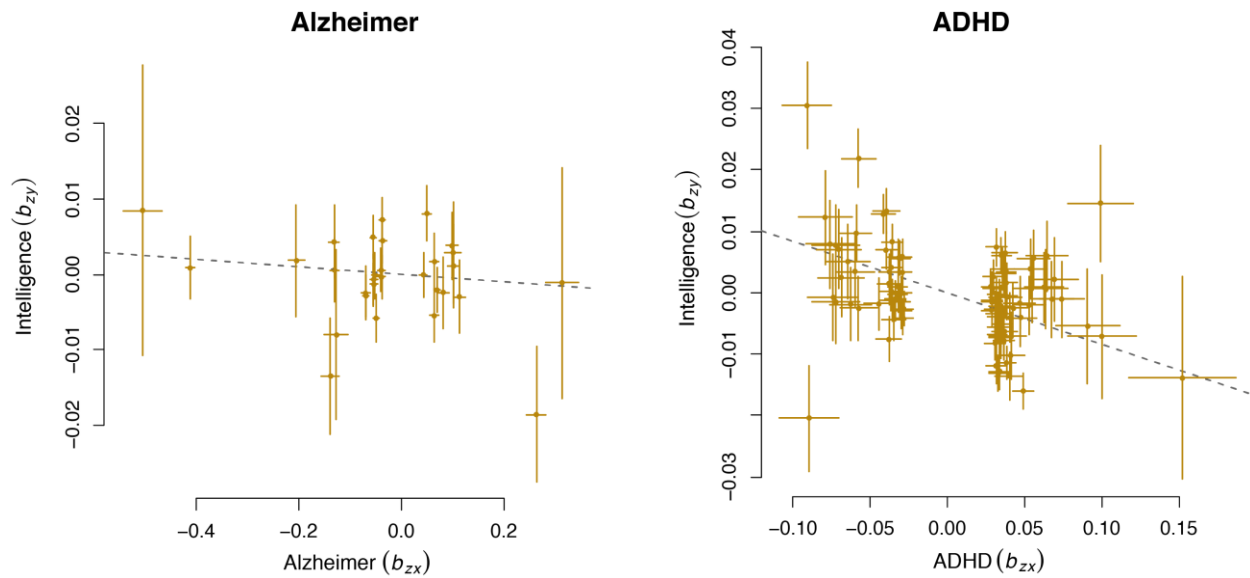




Supplementary Figure 11. Mendelian Randomization tests for the effect of intelligence on other correlated traits. Plots of effect sizes of independent lead SNPs from a GWAS meta-analysis of intelligence in 269,867 independent individuals (b_{zx}) on the x-axis and SNP GWAS effect sizes for correlated traits on the y-axis (b_{zy}). The dotted line represents a line with slope of (b_{xy}) and an intercept of 0. Error bars show 95% confidence intervals for the effect sizes for each trait.







Supplementary Figure 12. Mendelian Randomization reverse tests for the effect of other correlated traits on intelligence. Plots of effect sizes of independent lead SNPs from a GWAS meta-analysis of intelligence in 269,867 independent individuals (b_{zy}) on the y-axis and SNP GWAS effect sizes for correlated traits on the x-axis (b_{zx}). The dotted line represents a line with slope of (b_{xy}) and an intercept of 0. Error bars show 95% confidence intervals for the effect sizes for each trait.

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