Meta-Analysis of 78,308 Individuals Identifies 15 Novel Loci and 40 Novel Genes for Intelligence

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Intelligence is associated with important economic and health-related life outcomes[1]. Despite substantial heritability[2] (0.54) and confirmed polygenic nature, initial genetic studies were mostly underpowered[3–5]. Recent larger genome-wide association studies (GWAS) yielded six genomic loci, of which only one replicated[6,7]. Therefore, the molecular basis of intelligence is still largely unknown. Here we report a meta-analysis for intelligence of 78,308 individuals. We identify 336 single nucleotide polymorphisms (SNPs) ($P<5x10^{-8}$) in 18 genomic loci, of which 15 are novel. Of the 336 SNPs, 61% are likely to have a regulatory function. Roughly half are located inside a gene, implicating 22 genes, of which 11 are novel findings. Gene-based analyses identified an additional 30 genes ($P<2.73\times10^{-6}$), of which all but one have not been implicated previously. We show that identified genes are predominantly expressed in brain tissue, and pathway analysis indicates the involvement of genes regulating cell development (competitive $P=3.5x10^{-6}$). Despite the well-known difference in twin-based heritability for intelligence in childhood (0.45) and adulthood[2] (0.80), we find highly similar SNP-based heritabilities (0.20 in childhood versus 0.21 in adulthood), and show substantial genetic correlation ($r_g=0.89$, $P=5.4x10^{-29}$). We show genetic overlap with educational attainment ($r_g=0.70$, $P=2.5x10^{-287}$), smoking cessation ($r_g=0.32$, $P=8.7x10^{-6}$) and intracranial volume ($r_g=0.29$, $P=3.4x10^{-4}$) and inverse genetic overlap with several neuropsychiatric and metabolic traits. These findings provide novel insight into the genetic architecture of intelligence.

We combined GWAS data for intelligence in 78,308 unrelated individuals from 13 cohorts (**Methods**). Of these, full GWAS results for intelligence on N=48,698 have been published in two different studies[5,7] (N=12,441 and N=36,257 respectively), while GWAS results on the remaining 29,610 individuals have not been published previously. Across the different cohorts,

various tests to measure intelligence were used. Therefore – following previous publications on combining intelligence phenotypes across different cohorts[5,8] – the cohorts either calculated Spearman's g or used a primary measure of fluid intelligence (**Extended data Table 1)**, which is known to correlate highly with g[9]. Previous research has shown that many different aspects of intelligence are highly correlated to each other, and that Spearman's g captures the latent general intelligence trait, irrespective of the specific tests used to construct it[10,11].

All association studies were performed on individuals of European descent; standard quality-control procedures included correcting for population stratification and filtering on minor allele frequency and imputation quality (**Methods**). As eight out of the 13 cohorts consisted of children (aged < 18; total N=19,509) and five of adults (N=58,799, aged 18-78), we first meta-analyzed the children- and adult-based cohorts separately using METAL software[12], and subsequently calculated the r_g using LD Score regression[13]. The estimated r_g was 0.89 (SE=0.08, P=5.4x10^{-29}), indicating substantial overlap between the genetic variants influencing intelligence in childhood and adulthood, and warranting a combined meta-analysis. The genetic correlations between all individual cohorts were generally larger than 0.80 except for those involving some of the smaller sized cohorts (N<4,000), which, given the large standard errors of the r_g's, is likely due to the relatively low sample sizes in some of the individual cohorts (**Extended Data Table 2).** The full meta-analysis of all 13 cohorts (maximum N=78,308) included 12,104,294 SNPs. The quantile-quantile (Q-Q) plot of all SNPs exhibited some inflation (λ_{ALL}=1.21; **Extended Data Fig. 1; Extended Data Table 3**), which is within the expected range for a polygenic trait at the current sample size and heritability[14]. We performed LD Score regression to quantify the proportion of inflation in the mean χ^2 that was due to confounding biases. An intercept of 1.01 and mean χ^2 of 1.30 were obtained, suggesting that more than 95% of the inflation was caused by true polygenic

signal. SNP-based heritability was estimated at 0.20 (SE=0.01) in the total sample, and this was comparable in adults (0.21, SE=0.01) and children (0.20; SE=0.03). These estimates were obtained using LD Score regression and are likely to be biased downwards.

The meta-analysis identified 18 independent genome-wide significant loci (**Fig. 1; Fig. 2A; Table 1**), including 336 top SNPs (i.e. below the genome-wide threshold of significance; **Supplementary Table 1)**. Of the 18 identified loci, three have been implicated in intelligence previously: 6q16.1[6], 7p14.3 and 22q13.2[7] (**Supplementary Table 2**). The top SNPs implicated 22 genes of which 11 were novel. Functional annotation of the 336 genome-wide significant SNPs showed that a large proportion was intronic (162/336) (**Fig. 2B**). Of the 18 lead SNPs, 10 were intronic (**Fig 2B**), all were in an active chromatin state (**Fig. 2C; Extended Data Fig. 2A-P)** and 8 SNPs were expression quantitative trait loci (eQTLs; **Fig. 2D; Supplementary Table 1; Supplementary Table 3**). Lead SNPs *rs12928404* (located in the intronic region of *ATXN2L*) had the highest probability of being a regulatory SNP based on the Regulome database score[15] and of the eight lead SNPs that were eQTLs, this SNP was associated with differential expression of the largest number of genes (i.e.14). Focusing on brain tissue, the T allele of this SNP, which was associated with higher intelligence scores, was associated with lower expression of the *TUFM* gene (**Supplementary Table 3**).

We calculated the variance explained (R^2) in intelligence by the GWAS results in four independent samples, using LDpred[16] (**Methods** and **Extended Data Table 4** and **Extended Data Fig. 3).** Our results show that the current results explain up to 4.8% of the variance in intelligence and that on average across the four samples there is a 1.9-fold increase in explained variance compared to the most recent GWAS on intelligence[7].

Apart from a SNP-by-SNP GWAS we conducted a genome-wide gene association analysis (GWGAS) as implemented in MAGMA[17] (**Methods**). GWGAS relies on converging evidence from multiple genetic variants in the same gene and can yield novel genome-wide significant signals on a gene-based level that are not necessarily picked up by a standard GWAS. The GWGAS identified 47 genes (**Fig. 3A, Supplementary Table 4**). The GWGAS and GWAS identified 17 overlapping genes, thus the total number of implicated genes either by a SNP hit or by GWGAS was 22+47-17=52. Twelve out of 52 genes have been associated with intelligence previously (**Extended Data Table 5**). Tissue expression analyses (**Methods)** of the 52 genes using the GTEx data resource showed that 14 out of 44 genes for which GTEx data was available were more strongly expressed in the brain than in other tissues (**Fig. 3B**). Epigenetic states were calculated for 51 out of 52 implicated genes (**Methods)** and showed that 57% of genes were at least weakly transcribed in at least 50% of tissues (**Fig. 3C; Extended Data Fig. 4).** Pathway analysis for 6,166 gene ontology (GO[18]) and 674 Reactome[19] gene-sets (obtained from MSigDB[20]) resulted in one associated gene-set (GO: regulation of cell development, which is defined as any process that modulates the rate, frequency or extent of the progression of the cell over time, from its formation to the mature structure.) (MAGMA competitive P=3.5x10^{-6}; corrected P=0.03, **Supplementary Tables 5, 6**). This gene-set contains four genes that were genome-wide significant: *BMPR2, SHANK3, DCC* and *ZFHX3*, and many other genes that showed weaker association (**Supplementary Table 7)**. Three of the genome-wide significant genes are involved in neuronal function: *SHANK3* is involved in synapse formation, *DCC* encodes a netrin receptor involved in axon guidance and is associated with putamen volume, and *ZFHX3* is known to regulate myogenic and neuronal differentiation. The fourth gene, *BMPR2*, plays a role in embryogenesis and endochondral bone formation and has been linked to

pulmonary arterial hypertension. The four GO pathways with the subsequent smallest *P*-values are not independent from the top associated gene-set and provide insight in more specific functions of the genes driving the observed gene-set association. These four gene-sets are: regulation of nervous system development (P=3.0x10^{-5}; 87% of genes overlapping with the regulation of cell development pathway, including the four genome-wide significant genes), negative regulation of dendrite development (P=7.9x10^{-5}; 100% overlapping, thus a complete subset), myelin sheath (P=8.5x10^{-5}; 14% overlapping) and neuron spine (P=1.5x10^{-4}; 34% overlapping).

Intelligence has been associated with many socio-economic and health-related outcomes. We used whole-genome LD Score Regression[13] to calculate the genetic correlation with 32 traits from these domains for which GWAS summary statistics were available for download. Significant genetic correlations were observed with 14 traits. The strongest, positive genetic correlation was with Educational attainment (r_g=0.70, SE=0.02, P=2.5x10^{-287}). Moderate, positive genetic correlations were observed with smoking cessation, intracranial volume, head circumference in infancy, Autism spectrum disorder and height. Moderate negative genetic correlations were observed with Alzheimer's disease, depressive symptoms, having ever smoked, schizophrenia, neuroticism, waist-to-hip ratio, body mass index, and waist circumference (**Fig. 3D; Extended Data Table 6**).

To examine the robustness of the 336 SNPs and 47 genes that reached genome-wide significance in the primary analyses, we sought replication. Since there are no reasonably large GWAS for intelligence available and given the high genetic correlation with educational attainment, which has been used previously as a proxy for intelligence[8], we used the summary statistics from the latest GWAS for educational attainment (EA[21]) for proxy-replication (**Methods**). We first

deleted overlapping samples, resulting in a sample of 196,931 individuals for EA. Out of the 336 top SNPs for intelligence, 306 were available for look-up in EA, and 16 out of 18 independent lead SNPs. We found that the effects of 305 out of 306 available SNPs in EA were sign concordant between EA and intelligence, and the effects of all 16 independent lead SNPs ($P<10^{-16}$; **Supplementary Table 8**). This approach resulted in nine proxy-replicated loci ($P<0.05/16$): seven for which the lead SNP was significant (16p11.2, 1p34.2, 2q11.2, 2q22.3, 3p24.3, 6q16.1 and 7q33) and two for which another correlated top SNP in the same locus was significant (3p24.2 and 7p14.3). Of the 47 genes that were significantly associated with intelligence in the GWGAS, 15 were also significantly associated with EA ($P<0.05/47$, **Supplementary Table 9**). Given the high (0.70) but not perfect genetic correlation between EA and intelligence, these results strongly support the involvement of the proxy-replicated SNPs and genes in intelligence.

The strongest emerging association with intelligence is with *rs2490272* (6q21) in the intronic region and its surrounding SNPs in the promotor of the *FOXO3* gene. This gene is part of the insulin/insulin-like growth factor 1 signaling pathway and is believed to trigger apoptosis, including neuronal cell death as a result of oxidative stress[22]. Moreover, it has been shown to be associated with longevity[23,24]. The gene with the strongest association in the GWGAS is *CSE1L*, which also plays a role in apoptosis and cell proliferation[25]. Of all 52 genes that were implicated, 35 were reported in the GWAS catalog for a previous association with at least one of 67 distinct traits. Nine genes (*ATP2A1, NEGR1, SKAP1, FOXO3, COL16A1, YIPF7, DCC, SH2B1* and *TUFM*) were previously implicated with body mass index[26–29], seven (*CYP2D6, NAGA, NDUFA6, TCF20* and *SEPT3, FAM109B* and *MEF2C)* with schizophrenia[30] and four (*NEGR1, SH2B1, DCC* and *WNT4*) with obesity[31–33]. *EXOC4* and *MEF2C* have been associated previously with Alzheimer's disease (**Supplementary Tables 10, 11**). Many of the implicated

genes are involved in neuronal function: *DCC, APBA1, PRR7, ZFHX3, HCRTR1, NEGR1, MEF2C, SHANK3* and *ATXN2*L (**see Supplementary Information for the GeneCards summaries**).

In conclusion, we conducted a meta-analysis GWAS and GWGAS for intelligence, including 13 cohorts and 78,308 individuals. We confirmed three loci and 12 genes, and identified 15 novel genomic loci and 40 novel genes for intelligence. Pathway analysis demonstrated the involvement of genes regulating cell development. We showed genetic overlap with several neuropsychiatric and metabolic disorders. These findings provide starting points for understanding the molecular neurobiological mechanisms underlying intelligence, one of the most investigated traits in humans.

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Supplementary Materials:

Supplementary Information

Extended Data Figs. 1 to 4

Extended Data Tables 1 to 7

Supplementary Tables 1-11 (separate file)

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Summary statistics will be made available for download from http://ctglab.vu.nl.

Author Contributions: S.Sn. performed the analyses. D.P. conceived the study. S.St. QC-ed the UKB data. K.W. and E.T. conducted in silico follow-up analyses. P.R.J., E.K. and J.C. conducted PRS analyses. H.T, C.v.D, N.A., P.M., D.C., M.J., M.McG, M.B.M., W.G.I., J.J.L.,

G.B., R.P., N.P., A.P. ,W.O., A.I. and C.F.C contributed data. S.Sn. and D.P. wrote the paper. All authors discussed the results and commented on the paper.

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Table 1. Genomic loci and lead SNPs associated with intelligence in the meta-analysis based on N=78,308.

rsID	Annotation	Locus[a]	EffA	NEffA	EffAF	*Z*	*P*-value	Direction[b]	N	N_{GWS}
rs2490272	FOXO3 intronic	6q21	t	c	0.63	7.44	9.96E-14	++++-+++	78307	28
rs9320913	intergenic	6q16.1	a	c	0.48	6.61	3.79E-11	++++-+++	78307	13
rs10236197	PDE1C intronic	7p14.3	t	c	0.63	6.46	1.03E-10	+++++-++	78286	35
rs2251499	intergenic	13q33.2	t	c	0.26	6.31	2.74E-10	++++++++	78307	22
rs36093924	CYP2D7 ncRNA_intr	22q13.2	t	c	0.46	-6.31	2.87E-10	?--?????	54119	100
rs7646501	intergenic	3p24.2	a	g	0.74	6.02	1.79E-09	?++-++++	65866	5
rs4728302	EXOC4 intronic	7q33	t	c	0.60	-5.97	2.42E-09	---+--+-	78307	45
rs10191758	ARHGAP15 intronic	2q22.3	a	g	0.61	-5.93	3.06E-09	?--?????	54119	17
rs12744310	intergenic	1p34.2	t	c	0.22	-5.88	4.20E-09	?-------	65866	28
rs66495454	NEGR1 upstream	1p31.1	g	gtcct	0.62	-5.75	9.08E-09	?--?????	54119	1
rs113315451	CSE1L intronic	20q13.13	a	attat	0.43	5.71	1.15E-08	?++?????	54119	1
rs12928404	ATXN2L intronic	16p11.2	t	c	0.59	5.71	1.15E-08	++++++++	78307	19
rs41352752	MEF2C intronic	5q14.3	t	c	0.97	-5.68	1.35E-08	?--?????	54119	1
rs13010010	LINC01104 ncRNA_intr	2q11.2	t	c	0.38	5.65	1.56E-08	++++++++	78308	11
rs16954078	SKAP1 intronic	17q21.32	a	t	0.21	-5.55	2.84E-08	?----+--	65866	7
rs11138902	APBA1 intronic	9q21.11	a	g	0.54	5.49	4.12E-08	+++++-++	78307	1
rs6746731	ZNF638 intronic	2p13.2	t	g	0.43	-5.46	4.88E-08	-----+--	78307	1
rs6779302	intergenic	3p24.3	t	g	0.37	-5.45	4.99E-08	?--?????	54119	1

SNP *P*-values and *Z*-scores were computed in METAL by a weighted *Z*-score method. A total of 336 SNPs reached genome-wide significance ($P<5x10^{-8}$); 18 independent signals were obtained by LD-based clumping, using an r^2 threshold of 0.1 and a window of 300 kb. EffA, effect allele; NEffA, non-effect allele; EffAF, effect allele frequency in UK Biobank, based on individuals of Caucasian ancestry; *Z, Z*-score from METAL; Direction, Direction of the effect in each of the cohorts; N, sample size; N GWS; number of genome-wide significant SNPs in the locus.

[a]Cytogenetic band, build hg19.

[b]Order: CHIC, UKB-wb, UKB-ts, ERF, GENR, HU, MCTFR, STR.

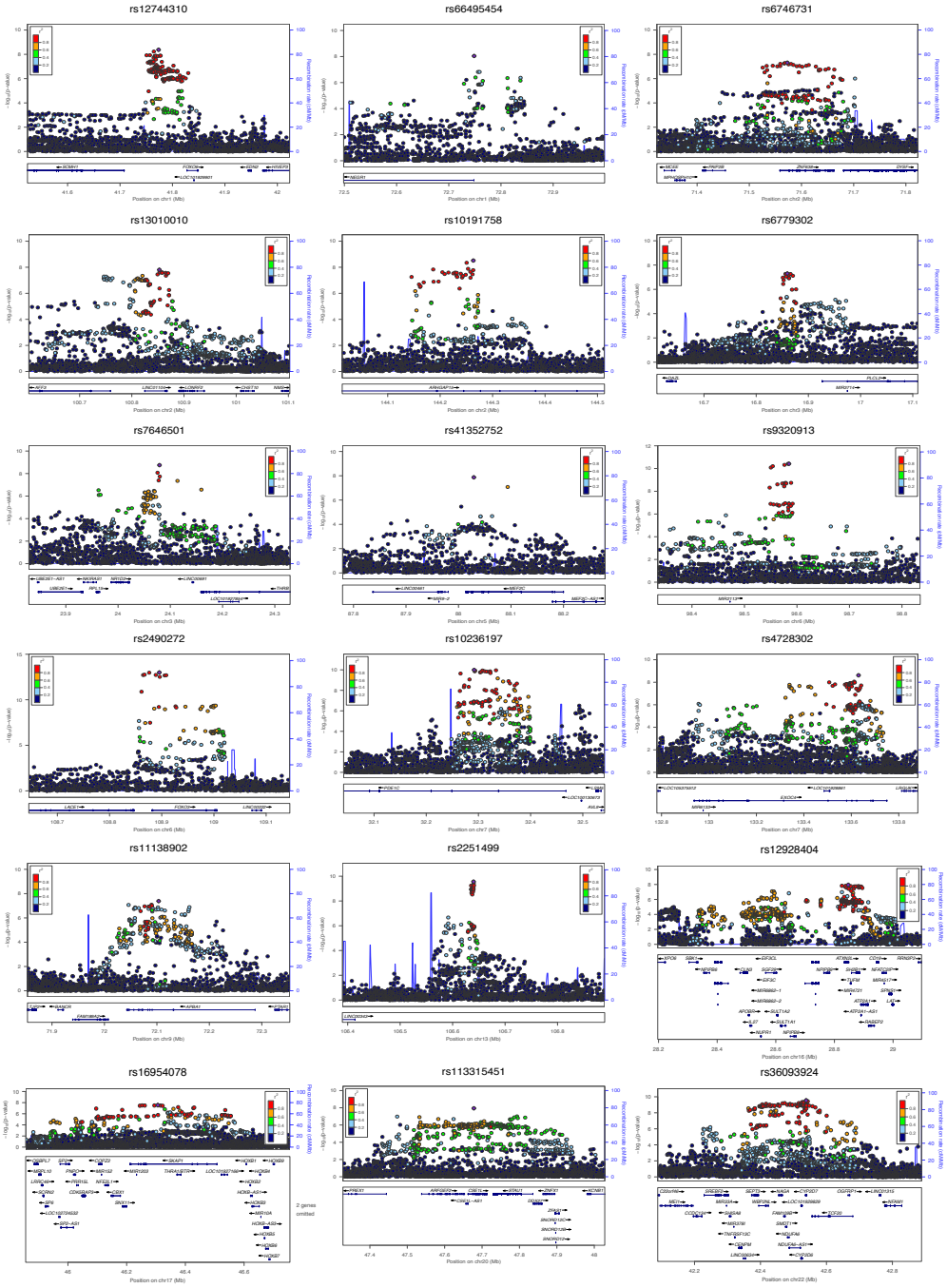


Fig. 1. **Regional association and linkage disequilibrium plots for 18 genome-wide significant loci.** The *y*-axis represents the negative logarithm (base 10) of the SNP *P*-value and the *x*-axis the position on the chromosome, with the name and location of genes in the UCSC Genome Browser in the bottom panel. The SNP with the lowest *P*-value in the region is marked by a purple diamond. The colors of the other SNPs indicate the r^2 of these SNPs with the lead SNP. Plots are generated with LocusZoom[34].

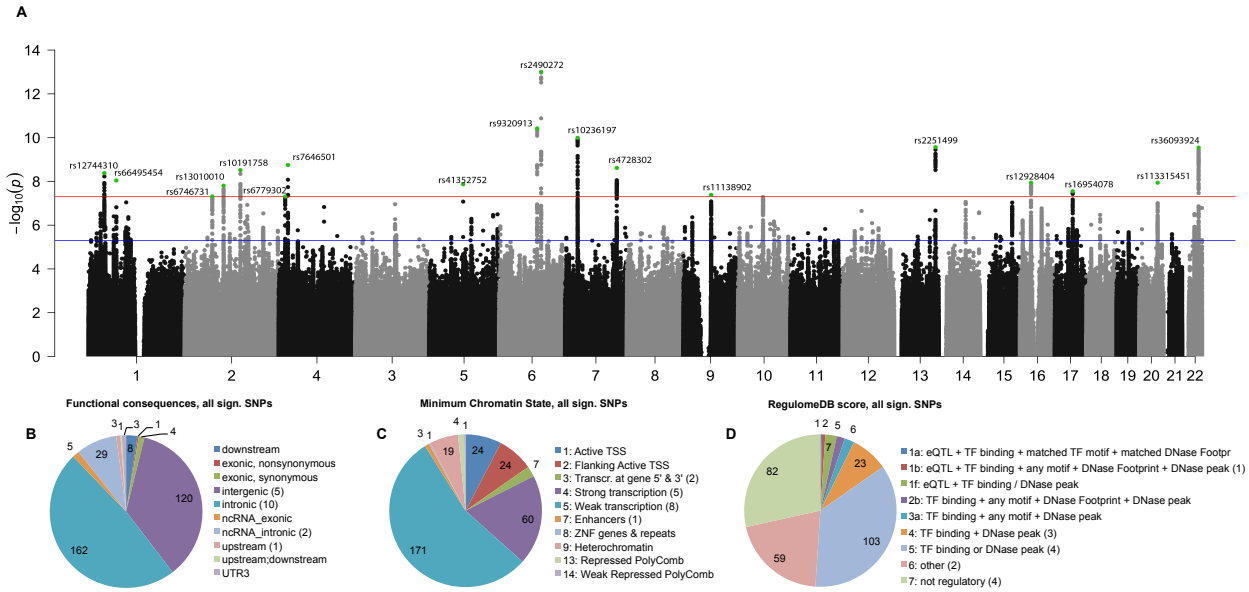
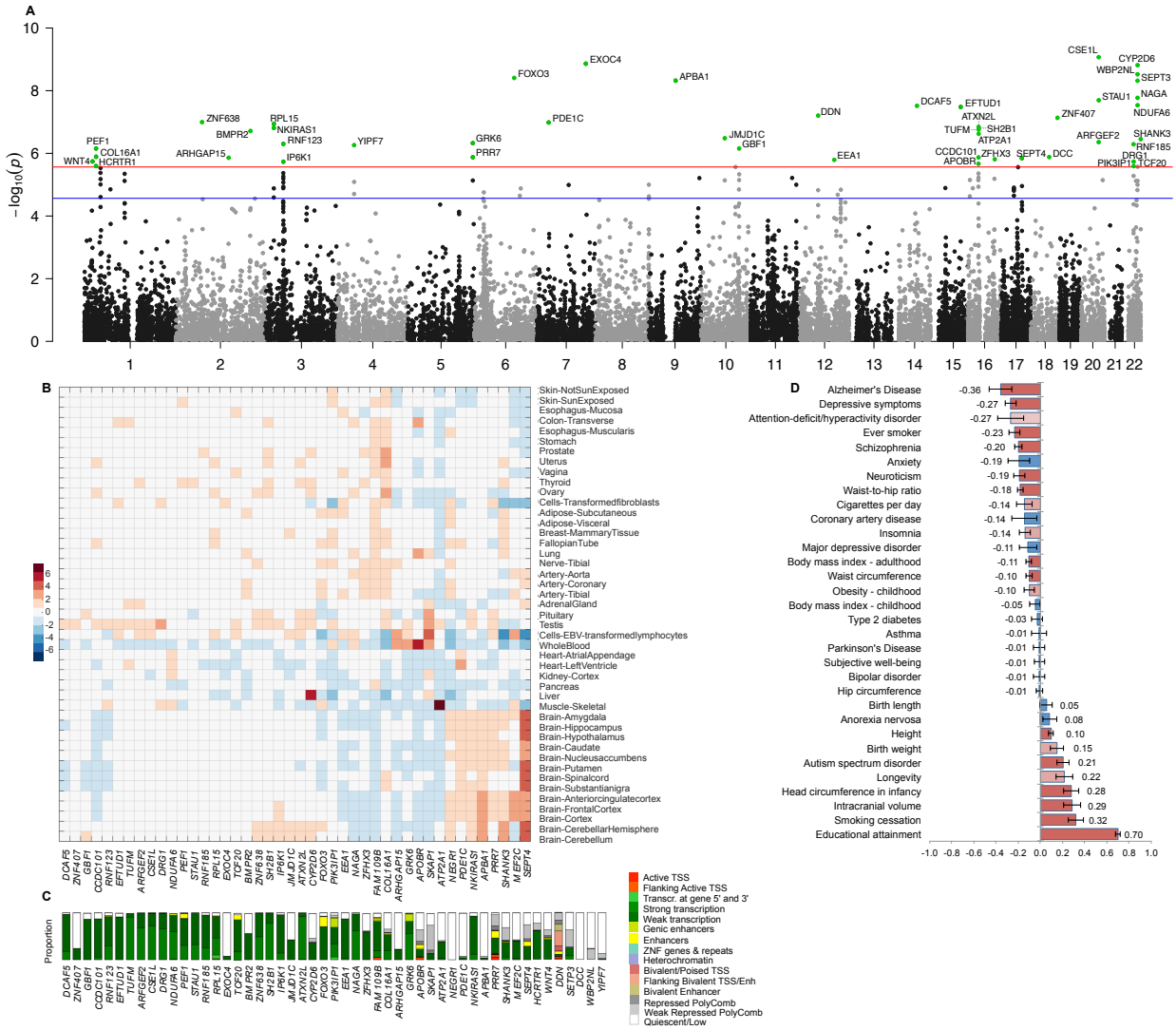


Fig. 2. Results of SNP-based meta-analysis for intelligence based on 78,308 individuals. Association results from the GWAS meta-analysis pertaining to individuals of European descent. (**A**) Negative $\log_{10}$-transformed *P*-values for each SNP (*y*-axis) are plotted by chromosomal position (*x*-axis). The red and blue lines represent the thresholds for genome-wide statistical significant associations ($P=5\times10^{-8}$) and suggestive associations ($P=1\times10^{-5}$) respectively. Green dots represent the independent hits. (**B**) Functional categories for 336 genome-wide significant SNPs. (**C**) The minimum (most active) chromatine state across 127 tissues for 336 genome-wide significant SNPs. (**D**) The Regulome database score for 336 genome-wide significant SNPs. The lower the score the more likely it is that a SNP has a regulatory function. For **B-D** the numbers in brackets in the legends refer to the number of lead SNPs for that category.



284
285 **Fig. 3. Gene-based genome wide analysis for intelligence and genetic overlap with other**
286 **traits.** (**A**). Negative $\log_{10}$-transformed *P*-values for each gene are plotted. Green dots represent
287 significantly associated genes from GWGAS. The threshold for gene-wide statistical significant
288 associations was set at the Bonferroni threshold of $P=2.73\times10^{-6}$, the suggestive threshold was set
289 at $P=2.73\times10^{-5}$. (**B**) Heatmap of gene-expression levels of genes for intelligence in 45 tissue
290 types (see **Extended Data Table 7** for N per tissue). A value above zero (red) depicts a
291 relatively high expression level with respect to the mean expression level of the gene over all
292 tissues, whereas a value below zero (blue) depicts a relatively low expression level. (**C**)
293 Epigenetic states of genes. The bars denote the proportions of epigenetic states across 127 tissue
294 types. (**D**) Genetic correlations between intelligence and 32 health-related outcomes. Error bars
295 show 95% confidence intervals for estimates of r_g. Red bars represent the traits that showed a
296 significant genetic correlation after correction for multiple testing ($P<1.56\times10^{-3}$), pink bars the
297 traits that showed a nominal significant correlation ($P<0.05$), and blue bars the traits that did not
298 show a genetic correlation significantly different from zero.
299

Methods

Discovery sample

The current study was based on 78,308 individuals. The origin of the samples is as follows:

1. UK Biobank web-based measure (UKB-wb; N=17,862), GWAS results have not yet been published previously, raw genotypic data is available for the present study.
2. UK Biobank touchscreen measure (UKB-ts; N=36,257, non-overlapping with UKB-wb) has been published before[7], raw genotypic data is available for the present study.
3. CHIC consortium[5] (N=12,441) has been published before, meta-analysis summary statistics are available for the present study.
4. Five additional cohorts (N=11,748), of which 69 SNP associations with IQ have previously been published as part of a lookup effort[8], but full GWAS results have not been published previously. Per cohort full GWAS summary statistics are available for the present study.

We describe these datasets in more detail below.

UK Biobank samples (UKB-wb, UKB-ts)

We used the data provided by the UK Biobank Study[35] (www.ukbiobank.ac.uk) resource, which is a major national health resource including >500,000 participants. All participants provided written informed consent; the UK Biobank received ethical approval from the National Research Ethics Service Committee North West–Haydock (reference 11/NW/0382), and all study procedures were performed in accordance with the World Medical Association Declaration of Helsinki ethical principles for medical research. The current study was conducted under the UK Biobank application number 16406.

The study design of the UK Biobank has been described in detail elsewhere[35,36]. Briefly, invitation letters were sent out in 2006-2010 to ~9.2 million individuals including all people aged 40-69 years who were registered with the National Health Service and living up to ~25 miles from one of the 22 study assessment centers. A total of 503,325 participants were subsequently recruited into the study[35]. Apart from registry based phenotypic information, extensive self-reported baseline data have been collected by questionnaire, in addition to anthropometric assessments and DNA collection. For the present study we used imputed data obtained from UK Biobank (May 2015 release) including ~73 million genetic variants in 152,249 individuals. Details on the data are provided elsewhere (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155580). In summary, the first ~50,000 samples were genotyped on the UK BiLEVE Axiom array, and the remaining ~100,000 samples were genotyped on the UK Biobank Axiom array. After standard quality control of the SNPs and samples, which was centrally performed by UK Biobank, the dataset comprised 641,018 autosomal SNPs in 152,256 samples for phasing and imputation. Imputation was performed with a reference panel that included the UK10K haplotype panel and the 1000 Genomes Project Phase 3 reference panel.

We used two fluid intelligence phenotypes from the Biobank data set. These are based on questionnaires that were taken either in the assessment center at the initial intake ('touchscreen', field 20016) or at a later moment at home ('web-based', field 20191). The measures indicate the number of correct answers out of 13 fluid intelligence questions. The data distribution roughly approximates a normal distribution.

For the analyses in our study, we only included individuals of Caucasian descent. After removal of related individuals, discordant sex, withdrawn consent, and missing phenotype data, 36,257

individuals remained for analysis for the fluid intelligence touchscreen measure and 28,846 for the web-based version. As 10,984 individuals had taken both the touchscreen and the web-based test, we only included the data from the touchscreen test for these individuals. This resulted in 54,119 individuals with a score on either the fluid intelligence web-based (UKB-wb) or touchscreen (UKB-ts) version (**Extended Data Table 1**). At the time of taking the test, participants' ages ranged between 40 and 78. Half of the participants were between 40 and 60 years old, 44% between 60 and 70 and 6% were older than 70. The mean age was 58.98 with a standard deviation of 8.19.

Summary statistics from CHIC consortium.

We downloaded the publicly available combined GWAS results from the meta-analyses as reported by CHIC[5] from http://ssgac.org/documents/CHIC_Summary_Benyamin2014.txt.gz. Details on the included cohorts and performed analyses are reported in the original publication [5]. Briefly, CHIC includes 6 cohorts totaling 12,441 individuals: the Avon Longitudinal Study of Parents and Children (ALSPAC, N = 5,517), the Lothian Birth Cohorts of 1921 and 1936 (LBC1921, N = 464; LBC1936, N = 947), the Brisbane Adolescent Twin Study subsample of Queensland Institute of Medical Research (QIMR, N = 1,752), the Western Australian Pregnancy Cohort Study (Raine, N = 936), and the Twins Early Development Study (TEDS, N = 2,825). All individuals are children aged between 6-18 years. Within each cohort the cognitive performance measure was adjusted for sex and age and principal components were included to adjust for population stratification. See also **Extended Data Table 1**.

Full GWAS data from additional cohorts

We used the same additional (non-CHIC) cohorts as described in detail in ref. 8, which included 11,748 individuals from 5 cohorts. In ref. 8, results were only reported for 69 SNPs, as these served as a secondary analysis for a look-up effort. In the current study we use the full genome-wide results from these cohorts. GWAS were conducted in 2013 and summary statistics were obtained from the PIs of the 5 cohorts. The quality control protocol entailed excluding SNPs with MAF < 0.01, imputation quality score < 0.4, Hardy-Weinberg *P*-value < 10^{-6} and call rate < 0.95[8]. The five cohorts included the Erasmus Rucphen Family Study (ERF, N = 1,076), the Generation R Study (GenR, N = 3,701), the Harvard/Union Study (HU, N = 389), the Minnesota Center for Twin and Family Research Study (MCTFR, N = 3,367) and the Swedish Twin Registry Study (STR, N = 3,215). Detailed descriptions of these cohorts are provided in ref. 8, and summarized in **Extended Data Table 1**. Within each cohort the cognitive performance measure was adjusted for sex and age and principal components were included to adjust for population stratification.

SNP analysis in UK Biobank sample

Association tests were performed in SNPTEST [37] (https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html), using linear regression. Both phenotypes were corrected for a number of covariates, including age, sex and a minimum of five genetically determined principal components, depending on how many were associated with the phenotype (i.e. 5 for the web-based test and 15 for the touchscreen version, tested by linear regression). Additionally we included the Townsend deprivation index as a covariate, which is based on postal code and measures material deprivation. The touchscreen version of the phenotype was also corrected for assessment center and genotyping array. SNPs with imputation

quality < 0.8 and MAF < 0.001 (based on all Caucasians present in the total sample) were excluded after the association analysis, resulting in 12,573,858 and 12,595,966 SNPs for the touchscreen and web-based test respectively.

Gene analysis.

The SNP based *P*-values from the meta-analysis were used as input for the gene-based analysis. We used all 19,427 protein-coding genes from the NCBI 37.3 gene definitions as basis for a genome-wide gene association analysis (GWGAS) in MAGMA (http://ctg.cncr.nl/software/magma). After SNP annotation there were 18,338 genes that were covered by at least one SNP. Gene-association tests were performed taking LD between SNPs into account. We applied a stringent Bonferroni correction to account for multiple testing, setting the genome-wide threshold for significance at 2.73×10^{-6}.

Pathway analysis.

We used MAGMA to test for association of predefined gene-sets with intelligence. A total of 6166 Gene Ontology and 674 Reactome gene-sets were obtained from http://software.broadinstitute.org/gsea/msigdb/collections.jsp. We computed competitive *P*-values, which are less likely to be below the threshold of significance compared to self-contained *P*-values. Competitive *P*-values are the outcomes of the test that the combined effect of genes in a gene-set is significantly larger than the combined effect of all other genes, whereas self-contained *P*-values are informative when testing against the null hypothesis of no association. Self-contained *P*-values are not interpreted and not reported by us. Competitive *P*-values were

corrected for multiple testing using MAGMA's built in empirical multiple testing correction with 10,000 permutations.

Meta-analysis.

Meta-analysis of the results of the 13 cohorts was performed in METAL[12] (http://genome.sph.umich.edu/wiki/METAL_Program). We did not include SNPs that were not present in the UK Biobank sample. The analysis was based on *P*-values, taking sample size and direction of effect into account using the samplesize scheme.

Genetic correlations.

Genetic correlations (r_g) were calculated between intelligence and 32 other traits for which summary statistics from GWAS were publicly available, using LD Score regression (https://github.com/bulik/ldsc). This method corrects for sample overlap, by estimating the intercept of the bivariate regression. A conservative Bonferroni-corrected threshold of 1.56×10^{-3} was used to determine significant correlations.

Functional annotation.

We identified all SNPs that had an r^2 of 0.1 or higher with the 18 independent lead SNPs and were included in the METAL output. We used the 1000G phase 3 reference panel to calculate r^2. We further filtered on SNPs with a *P*-value < 0.05. In addition, we only annotated SNPs with MAF > 0.01.

Positional annotations for all lead SNPs and SNPs in LD with the lead SNPs were obtained by performing ANNOVAR gene-based annotation using refSeq genes. In addition, CADD scores[38], and RegulomeDB[15] scores were annotated to SNPs by matching chromosome, position,

reference and alternative alleles. For each SNP eQTLs were extracted from GTEx (44 tissue types)[39], Blood eQTL browser[40] and BIOS gene-level eQTLs[41]. The eQTLs obtained from GTEx were filtered on gene *P*-value < 0.05 and eQTLs obtained from the other two databases were filtered on FDR < 0.05. The FDR values were provided by GTEx, BIOS and Blood eQTL browser. For GTEx eQTLs, there is one FDR value available per gene-tissue pair. As such, the FDR is identical for all eQTLs belonging to the same gene-tissue pair. For BIOS and Blood eQTL browser, an FDR value was computed per SNP.

To test whether the SNPs were functionally active by means of histone modifications, we obtained epigenetic data from the NIH Roadmap Epigenomics Mapping Consortium[42] and ENCODE[43]. For every 200bp of the genome a 15-core chromatin state was predicted by a Hidden Markov Model based on 5 histone marks (i.e. H3K4me3, H3K4me1, H3K27me3, H3K9me3, and H3K36me3) for 127 tissue/cell types [44]. We annotated chromatin states (15 states in total) to SNPs by matching chromosome and position for every tissue/cell type. We computed the minimum state (1: the most active state) and the consensus state (majority of states) across 127 tissue/cell types for each SNP.

Chromatin states were also determined for the 52 genes (47 from the gene-based test + 5 additional genes implicated by single SNP GWAS). For each gene and tissue, the chromatin state was obtained per 200 bp interval in the gene. We then annotated the genes by means of a consensus decision when multiple states were present for a single gene; i.e. the state of the gene was defined as the modus of all states present in the gene.

Tissue expression of genes.

RNA sequencing data of 1,641 tissue samples with 45 unique tissue labels was derived from the GTEx consortium[39]. This set includes 313 brain samples over 13 unique brain regions (see **Extended Data Table 6** for sample size per tissue). Of the 52 genes implicated by either the GWAS or the GWGWAS, 44 were included in the GTEx data. Normalization of the data was performed as described previously[45]. Briefly, genes with RPKM (Reads Per Kilobase Million) value smaller than 0.1 in at least 80% of the samples were removed. The remaining genes were $\log_2$ transformed (after using a pseudocount of 1), and finally a zero-mean normalization was applied.

Proxy-replication in educational attainment

For the replication analysis we used a subset of the data from ref. [21]. In particular, we excluded the Erasmus Rucphen Family, the Minnesota Center for Twin and Family Research Study, the Swedish Twin Registry Study, the 23andMe data and all individuals from UK Biobank, to make sure there was no sample overlap with our IQ dataset. Genetic correlation between intelligence and EA in this non-overlapping subsample was r_g=0.73, SE=0.03, P=1.4x10^{-163}. The replication analysis was based on the phenotype *EduYears*, which measures the number of years of schooling completed. A total of 306 out of our 336 top SNPs (and 16 out of 18 independent lead SNPs) was available in the educational attainment sample. We performed a sign concordance analysis for the 16 independent lead SNPs, using the exact binomial test. For each independent signal we determined whether either the lead SNP had a *P*-value smaller than 0.05/16 in the educational attainment analysis, or another (correlated) top SNP in the same locus if this was not the case. All 47 genes implicated in the GWGAS for intelligence were available for look-up in the EA sample. For each gene we determined whether it had a *P*-value smaller than 0.05/47 in the EA analysis.

Polygenic Risk Score analysis

We used LDpred to calculate the variance explained in intelligence in independent samples by a polygenic risk score based on our discovery analysis, as well as based on two previous GWAS studies for intelligence[5,7]. LDpred adjusts GWAS summary statistics for the effects of linkage disequilibrium (LD) by using an approximate Gibbs sampler that calculates posterior means of effects, conditional on LD information, when calculating polygenic risk scores. We used varying priors for the fraction of SNPs with non-zero effects (prior: 0.01, 0.05, 0.1, 0.5, 1, and an infinitesimal prior).

Independent datasets available for PRS analyses:

1. Manchester and Newcastle Longitudinal Studies of Cognitive Ageing Cohorts

The University of Manchester Age and Cognitive Performance Research Centre (ACPRC) programme was established in 1983 and this study has documented longitudinal trajectories in cognitive function in a large sample of older adults in the North of England, UK[46]. Recruitment took place in Newcastle and Greater Manchester between 1983 and 1992. At the outset of the study, 6063 volunteers were available (1825 men and 4238 women), with a median age of 65 years (range 44 to 93 years). Over the period 1983 to 2003, two alternating batteries of cognitive tasks applied biennially were designed to measure fluid and crystallized aspects of intelligence. These included: the Alice Heim 4 (AH4) parts 1 and 2 tests of general intelligence, Mill Hill Vocabulary A and B vocabulary tests, the Cattell and Cattell Culture Fair intelligence tests, and the Wechsler Adult Intelligence Scale Vocabulary test. Detailed task descriptions were provided previously[46]. Following informed consent, venesected whole blood was collected for DNA

extraction in approximately 1600 volunteers who had continued to participate in the longitudinal study in 1999-2004 which constitutes the Dyne-Steel DNA bank for the genetics of ageing and cognition. Ethical approval for all projects was obtained from the University of Manchester.

To represent crystallized intelligence (g_c), we used the Mill Hill Vocabulary Test in the Manchester and Newcastle samples. For fluid-type intelligence (g_f) in the Manchester and Newcastle samples empirical Bayes estimates for each individual were obtained from a random effects model fitted by maximum likelihood (ML) to the standardized age-regressed residuals obtained for each sex from the Alice Heim 4 test and the Cattell Culture Fair test scores. The phenotypes for g_c were corrected for age and gender and the phenotypes for g_f were corrected for age and derived separately for males and females. The standardized residuals were used for all subsequent analyses.

Participants had DNA extracted and were genotyped for 599,011 common single nucleotide polymorphisms (SNPs) using the Illumina610-Quadv1 chip. Stringent quality control analyses of the genotype data were applied, after which 549,692 of the 599,011 SNPs on the Illumina 610 chip in 1,558 individuals were retained. Individuals were excluded from this study based on unresolved gender discrepancy, relatedness, call rate (≤ 0.95), and evidence of non-Caucasian descent. SNPs were included in the analyses if they met the following conditions: call rate $\geq$ 0.98, minor allele frequency ≥ 0.01, and Hardy-Weinberg equilibrium test with $P \geq 10^{-3}$. Each cohort was tested for population stratification and any outliers were excluded. More details can be found in ref. 4.

2. **Twins Early Development Study**

The Twins Early Development Study (TEDS) is a multivariate longitudinal study that recruited over 11,000 twin pairs born in England and Wales in 1994, 1995 and 1996. Both the overall TEDS sample and the genotyped subsample have been shown to be representative of the UK population[47–49]. The project received approval from the Institute of Psychiatry ethics committee (05/Q0706/228) and parental consent was obtained before data collection. DNA for 4,649 individuals was extracted from saliva and buccal cheek swab samples and hybridized to HumanOmniExpressExome-8v1.2 genotyping arrays at the Institute of Psychiatry, Psychology and Neuroscience Genomics & Biomarker Core Facility. The raw image data from the array were normalized, pre-processed, and filtered in GenomeStudio according to Illumina Exome Chip SOP v1.4. (http://confluence.brc.iop.kcl.ac.uk:8090/display/PUB/Production+Version%3A+Illumina+Exome+Chip+SOP+v1.4). In addition, prior to genotype calling, 869 multi-mapping SNPs and 353 samples with call rate < 0.95 were removed. The ZCALL program was used to augment the genotype calling for samples and SNPs that passed the initial QC.

Samples were removed from subsequent analyses on the basis of call rate (< 0.99), suspected non-European ancestry, heterozygosity, array signal intensity, and relatedness. SNPs were excluded if the minor allele frequency was < 5%, if more than 1% of genotype data were missing, or if the Hardy Weinberg *P*-value was lower than 10^{-5}. Non-autosomal markers and indels were removed. Association between the SNP and the platform, batch, or plate on which samples were genotyped was calculated and SNPs with an effect *P*-value smaller than 10^{-3} were excluded. After alignment to the 1000 Genomes (phase 3) reference data, 3,617 individuals and 515,536 SNPs remained. A principal component analysis was performed on a subset of 42,859 common (MAF > 5%) autosomal HapMap3 SNPs[50], after stringent pruning to remove markers in

553 linkage disequilibrium ($r^2 > 0.1$) and excluding high linkage disequilibrium genomic regions so
554 as to ensure that only genome-wide effects were detected. Thirty PCs were used in the present
555 analyses.
556 Individuals were tested on two verbal tests at the age of 12, the WISC-III-PI Multiple Choice
557 Information (General Knowledge) and Vocabulary Multiple Choice subtests[51], and on two
558 nonverbal reasoning tests, the WISC-III-UK Picture Completion[51] and Raven's Standard and
559 Advanced Progressive Matrices[52,53], which were all administered online[54,55]. g-scores were
560 derived as the arithmetic mean of the four standardized test scores. The residuals after regressing
561 the measure on sex and age at assessment were used. These were obtained using the
562 rstandard function of the lm package in R (version 3.2.2), which produces standardized residuals
563 via normalization to unit variance using the overall error variance of the residuals.
564 For the current study, we selected individuals that were not included in ref. 5, which resulted in a
565 sample of N=1,173 available for PRS analyses.
566
567 **3. High IQ Sample**
568 Individuals with extremely high intelligence were recruited from the top 1% of the Duke
569 University Talent Identification Program (TIP), which recruits from the top 3% of the
570 intelligence distribution. DNA was collected using buccal swabs. Illumina Omni Express
571 genotypes were available for 1,236 white European Caucasian individuals following quality
572 control. A population comparison cohort was obtained from The University of Michigan Health
573 and Retirement Study (HRS). DNA was extracted from saliva. Genotypes were available from
574 the Illumina Human Omni-2.5 Quad Beadchip, with a coverage of 2.5 million SNPs. Genotype
575 data were obtained through dbGaP (accession: phs000428.v2.p2). After quality control and

ancestry-matching to the TIP participants, genotypes were available for 8,168 white Caucasian individuals. All individuals were imputed to the Haplotype Reference Consortium reference panel (rv1.1), using PBWT 32 as implemented in the Sanger Imputation Server (imputation.sanger.ac.uk). SNPs taken forward to analyses had INFO > 0.9, MAF ≥ 0.01, call rate > 99.9% and Hardy-Weinberg $P<10^{-8}$. Samples had call rate > 98%, heterozygosity < 4 standard deviations from the mean, and one of each pair of related samples was removed (r > 0.025). For the analyses performed in LDpred high IQ individuals were treated as "cases" and population comparisons as controls. All analyses were controlled for gender and 10 principal components.

4. Rotterdam Study

The Rotterdam Study is a large population-based cohort study in the Netherlands among individuals aged ≥ 45 years and residing in the Ommoord area, a suburb of Rotterdam[56]. The current study includes all participants under 60 years of age for whom genotypic information was available, who underwent cognitive testing at the study centre from 2002 onwards, and have 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. Written informed consent was obtained from all participants. Genotype data were collected on Illumina 550, Illumina 550duo and Illumina 610 quad SNP arrays. Variants were filtered on MAF < 0.01, call rate < 95% and Hardy-Weinberg $P<10^{-6}$. Individuals were filtered based on genotype missingness rate > 0.05, gender mismatch and relatedness (one of each pair of individuals with IBD > 0.185). Analyses were restricted to individuals from Northern European ancestry, resulting in a sample size of 2,015.

Participants underwent detailed cognitive assessment with a neuropsychological test 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). To obtain a measure of global cognitive function, a compound score (g-factor) was computed based on the aforementioned tests using principal component analysis. The g-factor explained 56.0% of the variance in cognitive test scores in the population.

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