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

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Includes **Supplementary Information, Extended Data Tables 1-7, Extended Data Figs. 1-4, Supplementary Tables 1-11**

1 Intelligence is associated with important economic and health-related life outcomes¹. Despite
2 substantial heritability² (0.54) and confirmed polygenic nature, initial genetic studies were
3 mostly underpowered³⁻⁵. Recent larger genome-wide association studies (GWAS) yielded six
4 genomic loci, of which only one replicated^{6,7}. Therefore, the molecular basis of intelligence is
5 still largely unknown. Here we report a meta-analysis for intelligence of 78,308 individuals. We
6 identify 336 single nucleotide polymorphisms (SNPs) ($P < 5 \times 10^{-8}$) in 18 genomic loci, of which
7 15 are novel. Of the 336 SNPs, 61% are likely to have a regulatory function. Roughly half are
8 located inside a gene, implicating 22 genes, of which 11 are novel findings. **Gene-based analyses**
9 **identified an additional 30 genes ($P < 2.73 \times 10^{-6}$), of which all but one have not been implicated**
10 **previously.** We show that identified genes are predominantly expressed in brain tissue, and
11 pathway analysis indicates the involvement of genes regulating cell development (competitive
12 $P = 3.5 \times 10^{-6}$). Despite the well-known difference in twin-based heritability for intelligence in
13 childhood (0.45) and adulthood² (0.80), we find highly similar SNP-based heritabilities (0.20 in
14 childhood versus 0.21 in adulthood), and show substantial genetic correlation ($r_g = 0.89$,
15 $P = 5.4 \times 10^{-29}$). We show genetic overlap with educational attainment ($r_g = 0.70$, $P = 2.5 \times 10^{-287}$),
16 smoking cessation ($r_g = 0.32$, $P = 8.7 \times 10^{-6}$) and intracranial volume ($r_g = 0.29$, $P = 3.4 \times 10^{-4}$) and
17 inverse genetic overlap with several neuropsychiatric and metabolic traits. These findings
18 provide novel insight into the genetic architecture of intelligence.

19

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

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

30 All association studies were performed on individuals of European descent; standard quality-
31 control procedures included correcting for population stratification and filtering on minor allele
32 frequency and imputation quality (**Methods**). As eight out of the 13 cohorts consisted of children
33 (aged < 18; total N=19,509) and five of adults (N=58,799, aged 18-78), we first meta-analyzed
34 the children- and adult-based cohorts separately using METAL software¹², and subsequently
35 calculated the r_g using LD Score regression¹³. The estimated r_g was 0.89 (SE=0.08, $P=5.4 \times 10^{-29}$),
36 indicating substantial overlap between the genetic variants influencing intelligence in childhood
37 and adulthood, and warranting a combined meta-analysis. The genetic correlations between all
38 individual cohorts were generally larger than 0.80 except for those involving some of the smaller
39 sized cohorts (N<4,000), which, given the large standard errors of the r_g ’s, is likely due to the
40 relatively low sample sizes in some of the individual cohorts (**Extended Data Table 2**). The full
41 meta-analysis of all 13 cohorts (maximum N=78,308) included 12,104,294 SNPs. The quantile-
42 quantile (Q-Q) plot of all SNPs exhibited some inflation ($\lambda_{ALL}=1.21$; **Extended Data Fig. 1**;
43 **Extended Data Table 3**), which is within the expected range for a polygenic trait at the current
44 sample size and heritability¹⁴. We performed LD Score regression to quantify the proportion of
45 inflation in the mean χ^2 that was due to confounding biases. An intercept of 1.01 and mean χ^2 of
46 1.30 were obtained, suggesting that more than 95% of the inflation was caused by true polygenic

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

50 The meta-analysis identified 18 independent genome-wide significant loci (**Fig. 1; Fig. 2A;**
51 **Table 1**), including 336 top SNPs (i.e. below the genome-wide threshold of significance;
52 **Supplementary Table 1**). Of the 18 identified loci, three have been implicated in intelligence
53 previously: 6q16.1⁶, 7p14.3 and 22q13.2⁷ (**Supplementary Table 2**). The top SNPs implicated
54 22 genes of which 11 were novel. Functional annotation of the 336 genome-wide significant
55 SNPs showed that a large proportion was intronic (162/336) (**Fig. 2B**). Of the 18 lead SNPs, 10
56 were intronic (**Fig 2B**), all were in an active chromatin state (**Fig. 2C; Extended Data Fig. 2A-**
57 **P**) and 8 SNPs were expression quantitative trait loci (eQTLs; **Fig. 2D; Supplementary Table**
58 **1; Supplementary Table 3**). Lead SNPs *rs12928404* (located in the intronic region of *ATXN2L*)
59 had the highest probability of being a regulatory SNP based on the Regulome database score¹⁵
60 and of the eight lead SNPs that were eQTLs, this SNP was associated with differential
61 expression of the largest number of genes (i.e.14). Focusing on brain tissue, the T allele of this
62 SNP, [which was associated with higher intelligence scores](#), was associated with lower expression
63 of the *TUFM* gene (**Supplementary Table 3**).

64 We calculated the variance explained (R^2) in intelligence by the GWAS results in four
65 independent samples, using LDpred¹⁶ (**Methods and Extended Data Table 4 and Extended**
66 **Data Fig. 3**). Our results show that the current results explain up to 4.8% of the variance in
67 intelligence and that on average across the four samples there is a 1.9-fold increase in explained
68 variance compared to the most recent GWAS on intelligence⁷.

69 Apart from a SNP-by-SNP GWAS we conducted a genome-wide gene association analysis
70 (GWGAS) as implemented in MAGMA¹⁷ (**Methods**). GWGAS relies on converging evidence
71 from multiple genetic variants in the same gene and can yield novel genome-wide significant
72 signals on a gene-based level that are not necessarily picked up by a standard GWAS. The
73 GWGAS identified 47 genes (**Fig. 3A, Supplementary Table 4**). The GWGAS and GWAS
74 identified 17 overlapping genes, thus the total number of implicated genes either by a SNP hit or
75 by GWGAS was 22+47-17=52. Twelve out of 52 genes have been associated with intelligence
76 previously (**Extended Data Table 5**). Tissue expression analyses (**Methods**) of the 52 genes
77 using the GTEx data resource showed that 14 out of 44 genes for which GTEx data was available
78 were more strongly expressed in the brain than in other tissues (**Fig. 3B**). Epigenetic states were
79 calculated for 51 out of 52 implicated genes (**Methods**) and showed that 57% of genes were at
80 least weakly transcribed in at least 50% of tissues (**Fig. 3C; Extended Data Fig. 4**). Pathway
81 analysis for 6,166 gene ontology (GO¹⁸) and 674 Reactome¹⁹ gene-sets (obtained from
82 MSigDB²⁰) resulted in one associated gene-set (GO: regulation of cell development, [which is](#)
83 [defined as any process that modulates the rate, frequency or extent of the progression of the cell](#)
84 [over time, from its formation to the mature structure.](#)) (MAGMA competitive $P=3.5 \times 10^{-6}$;
85 corrected $P=0.03$, **Supplementary Tables 5, 6**). This gene-set contains four genes that were
86 genome-wide significant: *BMP2*, *SHANK3*, *DCC* and *ZFHX3*, and many other genes that
87 showed weaker association (**Supplementary Table 7**). [Three of the genome-wide significant](#)
88 [genes are involved in neuronal function: *SHANK3* is involved in synapse formation, *DCC*](#)
89 [encodes a netrin receptor involved in axon guidance and is associated with putamen volume, and](#)
90 [ZFHX3 is known to regulate myogenic and neuronal differentiation. The fourth gene, *BMP2*,](#)
91 [plays a role in embryogenesis and endochondral bone formation and has been linked to](#)

92 pulmonary arterial hypertension. The four GO pathways with the subsequent smallest P -values
93 are not independent from the top associated gene-set and provide insight in more specific
94 functions of the genes driving the observed gene-set association. These four gene-sets are:
95 regulation of nervous system development ($P=3.0 \times 10^{-5}$; 87% of genes overlapping with the
96 regulation of cell development pathway, including the four genome-wide significant genes),
97 negative regulation of dendrite development ($P=7.9 \times 10^{-5}$; 100% overlapping, thus a complete
98 subset), myelin sheath ($P=8.5 \times 10^{-5}$; 14% overlapping) and neuron spine ($P=1.5 \times 10^{-4}$; 34%
99 overlapping).

100 Intelligence has been associated with many socio-economic and health-related outcomes. We
101 used whole-genome LD Score Regression¹³ to calculate the genetic correlation with 32 traits
102 from these domains for which GWAS summary statistics were available for download.
103 Significant genetic correlations were observed with 14 traits. The strongest, positive genetic
104 correlation was with Educational attainment ($r_g=0.70$, $SE=0.02$, $P=2.5 \times 10^{-287}$). Moderate,
105 positive genetic correlations were observed with smoking cessation, intracranial volume, head
106 circumference in infancy, Autism spectrum disorder and height. Moderate negative genetic
107 correlations were observed with Alzheimer's disease, depressive symptoms, having ever
108 smoked, schizophrenia, neuroticism, waist-to-hip ratio, body mass index, and waist
109 circumference (**Fig. 3D; Extended Data Table 6**).

110 To examine the robustness of the 336 SNPs and 47 genes that reached genome-wide significance
111 in the primary analyses, we sought replication. Since there are no reasonably large GWAS for
112 intelligence available and given the high genetic correlation with educational attainment, which
113 has been used previously as a proxy for intelligence⁸, we used the summary statistics from the
114 latest GWAS for educational attainment (EA²¹) for proxy-replication (**Methods**). We first

115 deleted overlapping samples, resulting in a sample of 196,931 individuals for EA. Out of the 336
116 top SNPs for intelligence, 306 were available for look-up in EA, and 16 out of 18 independent
117 lead SNPs. We found that the effects of 305 out of 306 available SNPs in EA were sign
118 concordant between EA and intelligence, and the effects of all 16 independent lead SNPs ($P < 10^{-16}$;
119 **Supplementary Table 8**). This approach resulted in nine proxy-replicated loci ($P < 0.05/16$):
120 seven for which the lead SNP was significant (16p11.2, 1p34.2, 2q11.2, 2q22.3, 3p24.3, 6q16.1
121 and 7q33) and two for which another correlated top SNP in the same locus was significant
122 (3p24.2 and 7p14.3). Of the 47 genes that were significantly associated with intelligence in the
123 GWAS, 15 were also significantly associated with EA ($P < 0.05/47$, **Supplementary Table 9**).
124 Given the high (0.70) but not perfect genetic correlation between EA and intelligence, these
125 results strongly support the involvement of the proxy-replicated SNPs and genes in intelligence.
126 The strongest emerging association with intelligence is with *rs2490272* (6q21) in the intronic
127 region and its surrounding SNPs in the promotor of the *FOXO3* gene. This gene is part of the
128 insulin/insulin-like growth factor 1 signaling pathway and is believed to trigger apoptosis,
129 including neuronal cell death as a result of oxidative stress²². Moreover, it has been shown to be
130 associated with longevity^{23,24}. The gene with the strongest association in the GWAS is *CSEIL*,
131 which also plays a role in apoptosis and cell proliferation²⁵. Of all 52 genes that were
132 implicated, 35 were reported in the GWAS catalog for a previous association with at least one of
133 67 distinct traits. Nine genes (*ATP2A1*, *NEGRI*, *SKAP1*, *FOXO3*, *COL16A1*, *YIPF7*, *DCC*,
134 *SH2B1* and *TUFM*) were previously implicated with body mass index²⁶⁻²⁹, seven (*CYP2D6*,
135 *NAGA*, *NDUFA6*, *TCF20* and *SEPT3*, *FAM109B* and *MEF2C*) with schizophrenia³⁰ and four
136 (*NEGRI*, *SH2B1*, *DCC* and *WNT4*) with obesity³¹⁻³³. *EXO4* and *MEF2C* have been associated
137 previously with Alzheimer's disease (**Supplementary Tables 10, 11**). Many of the implicated

138 genes are involved in neuronal function: *DCC*, *APBA1*, *PRR7*, *ZFHX3*, *HCRTR1*, *NEGR1*,
139 *MEF2C*, *SHANK3* and *ATXN2L* (see **Supplementary Information for the GeneCards**
140 **summaries**).

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

148

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222

223

224 **Supplementary Materials:**

225 Supplementary Information

226 Extended Data Figs. 1 to 4

227 Extended Data Tables 1 to 7

228 Supplementary Tables 1-11 (separate file)

229

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

238

239 **Author Contributions:** S.Sn. performed the analyses. D.P. conceived the study. S.St. QC-ed the
240 UKB data. K.W. and E.T. conducted in silico follow-up analyses. P.R.J., E.K. and J.C.
241 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.,

242 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.

243 All authors discussed the results and commented on the paper.

244

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246 www.nature.com/reprints. The other authors declare no competing financial interests.

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248

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

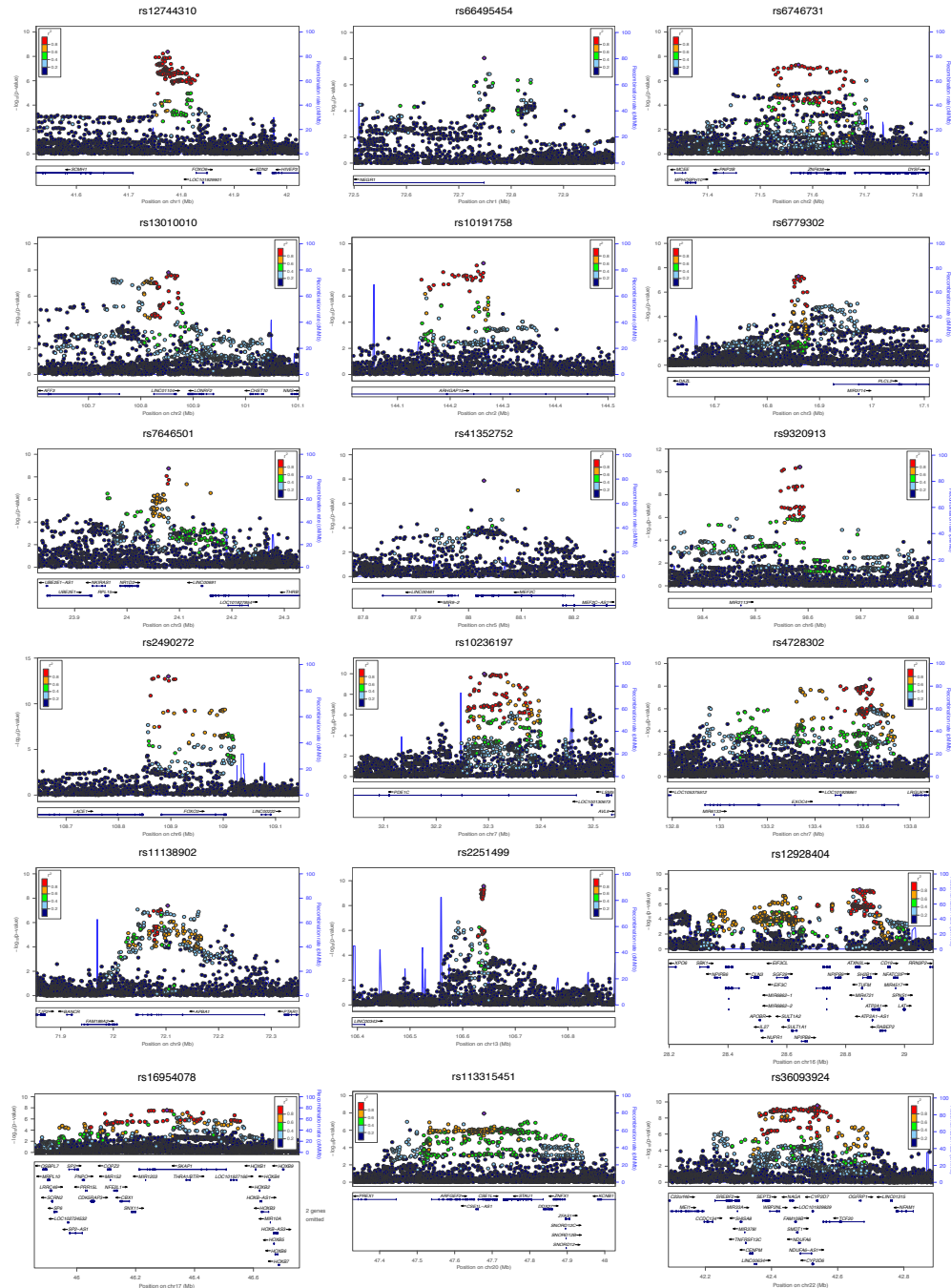
rsID	Annotation	Locus ^a	EffA	NEffA	EffAF	Z	P-value	Direction ^b	N	N _{GWS}
rs2490272	FOXO3 intronic	6q21	t	c	0.63	7.44	9.96E-14	++++-+++	78307	28
rs9320913	intergenic	6q16.1	a	c	0.48	6.61	3.79E-11	++++-+++	78307	13
rs10236197	PDE1C intronic	7p14.3	t	c	0.63	6.46	1.03E-10	++++-+++	78286	35
rs2251499	intergenic	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	gtct	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

251 SNP *P*-values and *Z*-scores were computed in METAL by a weighted *Z*-score method. A
 252 total of 336 SNPs reached genome-wide significance ($P < 5 \times 10^{-8}$); 18 independent signals
 253 were obtained by LD-based clumping, using an r^2 threshold of 0.1 and a window of 300 kb.
 254 EffA, effect allele; NEffA, non-effect allele; EffAF, effect allele frequency in UK Biobank,
 255 based on individuals of Caucasian ancestry; *Z*, *Z*-score from METAL; Direction, Direction of
 256 the effect in each of the cohorts; N, sample size; N_{GWS}; number of genome-wide significant
 257 SNPs in the locus.

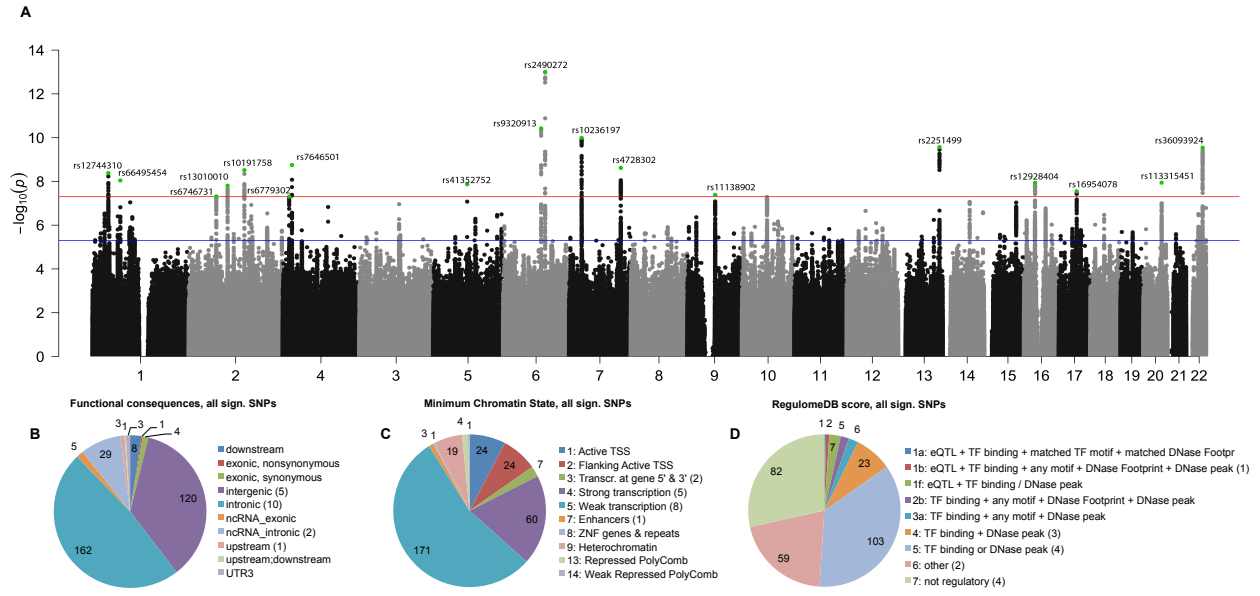
258 ^aCytogenetic band, build hg19.

259 ^bOrder: CHIC, UKB-wb, UKB-ts, ERF, GENR, HU, MCTFR, STR.

260
 261



262
 263 **Fig. 1. Regional association and linkage disequilibrium plots for 18 genome-wide significant**
 264 **loci.** The y-axis represents the negative logarithm (base 10) of the SNP P -value and the x-axis the
 265 position on the chromosome, with the name and location of genes in the UCSC Genome Browser
 266 in the bottom panel. The SNP with the lowest P -value in the region is marked by a purple
 267 diamond. The colors of the other SNPs indicate the r^2 of these SNPs with the lead SNP. Plots are
 268 generated with LocusZoom³⁴.
 269
 270



271
 272 **Fig. 2. Results of SNP-based meta-analysis for intelligence based on 78,308 individuals.**
 273 Association results from the GWAS meta-analysis pertaining to individuals of European descent.
 274 (A) Negative \log_{10} -transformed P -values for each SNP (y -axis) are plotted by chromosomal
 275 position (x -axis). The red and blue lines represent the thresholds for genome-wide statistical
 276 significant associations ($P=5 \times 10^{-8}$) and suggestive associations ($P=1 \times 10^{-5}$) respectively. Green
 277 dots represent the independent hits. (B) Functional categories for 336 genome-wide significant
 278 SNPs. (C) The minimum (most active) chromatin state across 127 tissues for 336 genome-wide
 279 significant SNPs. (D) The Regulome database score for 336 genome-wide significant SNPs. The
 280 lower the score the more likely it is that a SNP has a regulatory function. For B-D the numbers in
 281 brackets in the legends refer to the number of lead SNPs for that category.
 282
 283

300 **Methods**

301 Discovery sample

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

- 303 1. UK Biobank web-based measure (UKB-wb; N=17,862), GWAS results have not yet been
304 published previously, raw genotypic data is available for the present study.
- 305 2. UK Biobank touchscreen measure (UKB-ts; N=36,257, non-overlapping with UKB-wb)
306 has been published before⁷, raw genotypic data is available for the present study.
- 307 3. CHIC consortium⁵ (N=12,441) has been published before, meta-analysis summary
308 statistics are available for the present study.
- 309 4. Five additional cohorts (N=11,748), of which 69 SNP associations with IQ have
310 previously been published as part of a lookup effort⁸, but full GWAS results have not
311 been published previously. Per cohort full GWAS summary statistics are available for the
312 present study.

313 We describe these datasets in more detail below.

314

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

316 We used the data provided by the UK Biobank Study³⁵ (www.ukbiobank.ac.uk) resource, which
317 is a major national health resource including >500,000 participants. All participants provided
318 written informed consent; the UK Biobank received ethical approval from the National Research
319 Ethics Service Committee North West–Haydock (reference 11/NW/0382), and all study
320 procedures were performed in accordance with the World Medical Association Declaration of
321 Helsinki ethical principles for medical research. The current study was conducted under the UK
322 Biobank application number 16406.

323 The study design of the UK Biobank has been described in detail elsewhere^{35,36}. Briefly,
324 invitation letters were sent out in 2006-2010 to ~9.2 million individuals including all people aged
325 40-69 years who were registered with the National Health Service and living up to ~25 miles
326 from one of the 22 study assessment centers. A total of 503,325 participants were subsequently
327 recruited into the study³⁵. Apart from registry based phenotypic information, extensive self-
328 reported baseline data have been collected by questionnaire, in addition to anthropometric
329 assessments and DNA collection. For the present study we used imputed data obtained from UK
330 Biobank (May 2015 release) including ~73 million genetic variants in 152,249 individuals.
331 Details on the data are provided elsewhere
332 (<http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155580>). In summary, the first ~50,000
333 samples were genotyped on the UK BiLEVE Axiom array, and the remaining ~100,000 samples
334 were genotyped on the UK Biobank Axiom array. After standard quality control of the SNPs and
335 samples, which was centrally performed by UK Biobank, the dataset comprised 641,018
336 autosomal SNPs in 152,256 samples for phasing and imputation. Imputation was performed with
337 a reference panel that included the UK10K haplotype panel and the 1000 Genomes Project Phase
338 3 reference panel.

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

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

346 individuals remained for analysis for the fluid intelligence touchscreen measure and 28,846 for
347 the web-based version. As 10,984 individuals had taken both the touchscreen and the web-based
348 test, we only included the data from the touchscreen test for these individuals. This resulted in
349 54,119 individuals with a score on either the fluid intelligence web-based (UKB-wb) or
350 touchscreen (UKB-ts) version (**Extended Data Table 1**). *At the time of taking the test,*
351 *participants' ages ranged between 40 and 78. Half of the participants were between 40 and 60*
352 *years old, 44% between 60 and 70 and 6% were older than 70. The mean age was 58.98 with a*
353 *standard deviation of 8.19.*

354

355 Summary statistics from CHIC consortium.

356 We downloaded the publicly available combined GWAS results from the meta-analyses as
357 reported by CHIC⁵ from http://ssgac.org/documents/CHIC_Summary_Benjamin2014.txt.gz.
358 Details on the included cohorts and performed analyses are reported in the original publication⁵.
359 Briefly, CHIC includes 6 cohorts totaling 12,441 individuals: the Avon Longitudinal Study of
360 Parents and Children (ALSPAC, N = 5,517), the Lothian Birth Cohorts of 1921 and 1936
361 (LBC1921, N = 464; LBC1936, N = 947), the Brisbane Adolescent Twin Study subsample of
362 Queensland Institute of Medical Research (QIMR, N = 1,752), the Western Australian
363 Pregnancy Cohort Study (Raine, N = 936), and the Twins Early Development Study (TEDS, N =
364 2,825). All individuals are children aged between 6-18 years. Within each cohort the cognitive
365 performance measure was adjusted for sex and age and principal components were included to
366 adjust for population stratification. See also **Extended Data Table 1**.

367

368 Full GWAS data from additional cohorts

369 We used the same additional (non-CHIC) cohorts as described in detail in ref. 8, which included
370 11,748 individuals from 5 cohorts. In ref. 8, results were only reported for 69 SNPs, as these
371 served as a secondary analysis for a look-up effort. In the current study we use the full genome-
372 wide results from these cohorts. GWAS were conducted in 2013 and summary statistics were
373 obtained from the PIs of the 5 cohorts. The quality control protocol entailed excluding SNPs with
374 MAF < 0.01, imputation quality score < 0.4, Hardy-Weinberg P -value < 10^{-6} and call rate <
375 0.95⁸. The five cohorts included the Erasmus Rucphen Family Study (ERF, N = 1,076), the
376 Generation R Study (GenR, N = 3,701), the Harvard/Union Study (HU, N = 389), the Minnesota
377 Center for Twin and Family Research Study (MCTFR, N = 3,367) and the Swedish Twin
378 Registry Study (STR, N = 3,215). Detailed descriptions of these cohorts are provided in ref. 8,
379 and summarized in **Extended Data Table 1**. Within each cohort the cognitive performance
380 measure was adjusted for sex and age and principal components were included to adjust for
381 population stratification.

382

383 SNP analysis in UK Biobank sample

384 Association tests were performed in SNPTTEST³⁷
385 (https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html), using linear regression.
386 Both phenotypes were corrected for a number of covariates, including age, sex and a minimum
387 of five genetically determined principal components, depending on how many were associated
388 with the phenotype (i.e. 5 for the web-based test and 15 for the touchscreen version, tested by
389 linear regression). Additionally we included the Townsend deprivation index as a covariate,
390 which is based on postal code and measures material deprivation. The touchscreen version of the
391 phenotype was also corrected for assessment center and genotyping array. SNPs with imputation

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

395

396 Gene analysis.

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

404

405 Pathway analysis.

406 We used MAGMA to test for association of predefined gene-sets with intelligence. A total of
407 6166 Gene Ontology and 674 Reactome gene-sets were obtained from
408 <http://software.broadinstitute.org/gsea/msigdb/collections.jsp>. We computed competitive *P*-
409 values, which are less likely to be below the threshold of significance compared to self-contained
410 *P*-values. Competitive *P*-values are the outcomes of the test that the combined effect of genes in
411 a gene-set is significantly larger than the combined effect of all other genes, whereas self-
412 contained *P*-values are informative when testing against the null hypothesis of no association.
413 Self-contained *P*-values are not interpreted and not reported by us. Competitive *P*-values were

414 corrected for multiple testing using MAGMA's built in empirical multiple testing correction with
415 10,000 permutations.

416

417 Meta-analysis.

418 Meta-analysis of the results of the 13 cohorts was performed in METAL¹²
419 (http://genome.sph.umich.edu/wiki/METAL_Program). We did not include SNPs that were not
420 present in the UK Biobank sample. The analysis was based on *P*-values, taking sample size and
421 direction of effect into account using the samplesize scheme.

422

423 Genetic correlations.

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

429

430 Functional annotation.

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

435 Positional annotations for all lead SNPs and SNPs in LD with the lead SNPs were obtained by
436 performing ANNOVAR gene-based annotation using refSeq genes. In addition, CADD scores³⁸,
437 and RegulomeDB¹⁵ scores were annotated to SNPs by matching chromosome, position,

438 reference and alternative alleles. For each SNP eQTLs were extracted from GTEx (44 tissue
439 types)³⁹, Blood eQTL browser⁴⁰ and BIOS gene-level eQTLs⁴¹. The eQTLs obtained from GTEx
440 were filtered on gene *P*-value < 0.05 and eQTLs obtained from the other two databases were
441 filtered on FDR < 0.05. The FDR values were provided by GTEx, BIOS and Blood eQTL
442 browser. For GTEx eQTLs, there is one FDR value available per gene-tissue pair. As such, the
443 FDR is identical for all eQTLs belonging to the same gene-tissue pair. For BIOS and Blood
444 eQTL browser, an FDR value was computed per SNP.

445 To test whether the SNPs were functionally active by means of histone modifications, we
446 obtained epigenetic data from the NIH Roadmap Epigenomics Mapping Consortium⁴² and
447 ENCODE⁴³. For every 200bp of the genome a 15-core chromatin state was predicted by a
448 Hidden Markov Model based on 5 histone marks (i.e. H3K4me3, H3K4me1, H3K27me3,
449 H3K9me3, and H3K36me3) for 127 tissue/cell types⁴⁴. We annotated chromatin states (15 states
450 in total) to SNPs by matching chromosome and position for every tissue/cell type. We computed
451 the minimum state (1: the most active state) and the consensus state (majority of states) across
452 127 tissue/cell types for each SNP.

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

458

459 Tissue expression of genes.

460 RNA sequencing data of 1,641 tissue samples with 45 unique tissue labels was derived from the
461 GTEx consortium³⁹. This set includes 313 brain samples over 13 unique brain regions (see
462 **Extended Data Table 6** for sample size per tissue). Of the 52 genes implicated by either the
463 GWAS or the GWGWAS, 44 were included in the GTEx data. Normalization of the data was
464 performed as described previously⁴⁵. Briefly, genes with RPKM (Reads Per Kilobase Million)
465 value smaller than 0.1 in at least 80% of the samples were removed. The remaining genes were
466 \log_2 transformed (after using a pseudocount of 1), and finally a zero-mean normalization was
467 applied.

468

469 Proxy-replication in educational attainment

470 For the replication analysis we used a subset of the data from ref. ²¹. In particular, we excluded
471 the Erasmus Rucphen Family, the Minnesota Center for Twin and Family Research Study, the
472 Swedish Twin Registry Study, the 23andMe data and all individuals from UK Biobank, to make
473 sure there was no sample overlap with our IQ dataset. [Genetic correlation between intelligence
474 and EA in this non-overlapping subsample was \$r_g=0.73\$, \$SE=0.03\$, \$P=1.4 \times 10^{-163}\$](#) . The replication
475 analysis was based on the phenotype *EduYears*, which measures the number of years of
476 schooling completed. A total of 306 out of our 336 top SNPs (and 16 out of 18 independent lead
477 SNPs) was available in the educational attainment sample. We performed a sign concordance
478 analysis for the 16 independent lead SNPs, using the exact binomial test. For each independent
479 signal we determined whether either the lead SNP had a *P*-value smaller than 0.05/16 in the
480 educational attainment analysis, or another (correlated) top SNP in the same locus if this was not
481 the case. All 47 genes implicated in the GWGAS for intelligence were available for look-up in
482 the EA sample. For each gene we determined whether it had a *P*-value smaller than 0.05/47 in
483 the EA analysis.

484

485 Polygenic Risk Score analysis

486

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

494

495 Independent datasets available for PRS analyses:

496 **1. Manchester and Newcastle Longitudinal Studies of Cognitive Ageing Cohorts**

497 The University of Manchester Age and Cognitive Performance Research Centre (ACPRC)
498 programme was established in 1983 and this study has documented longitudinal trajectories in
499 cognitive function in a large sample of older adults in the North of England, UK⁴⁶. Recruitment
500 took place in Newcastle and Greater Manchester between 1983 and 1992. At the outset of the
501 study, 6063 volunteers were available (1825 men and 4238 women), with a median age of 65
502 years (range 44 to 93 years). Over the period 1983 to 2003, two alternating batteries of cognitive
503 tasks applied biennially were designed to measure fluid and crystallized aspects of intelligence.
504 These included: the Alice Heim 4 (AH4) parts 1 and 2 tests of general intelligence, Mill Hill
505 Vocabulary A and B vocabulary tests, the Cattell and Cattell Culture Fair intelligence tests, and
506 the Wechsler Adult Intelligence Scale Vocabulary test. Detailed task descriptions were provided
507 previously⁴⁶. Following informed consent, venesected whole blood was collected for DNA

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

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

519 Participants had DNA extracted and were genotyped for 599,011 common single nucleotide
520 polymorphisms (SNPs) using the Illumina610-Quadv1 chip. Stringent quality control analyses of
521 the genotype data were applied, after which 549,692 of the 599,011 SNPs on the Illumina 610
522 chip in 1,558 individuals were retained. Individuals were excluded from this study based on
523 unresolved gender discrepancy, relatedness, call rate (≤ 0.95), and evidence of non-Caucasian
524 descent. SNPs were included in the analyses if they met the following conditions: call rate \geq
525 0.98, minor allele frequency ≥ 0.01 , and Hardy-Weinberg equilibrium test with $P \geq 10^{-3}$. Each
526 cohort was tested for population stratification and any outliers were excluded. More details can
527 be found in ref. 4.

528

529 **2. Twins Early Development Study**

530 The Twins Early Development Study (TEDS) is a multivariate longitudinal study that recruited
531 over 11,000 twin pairs born in England and Wales in 1994, 1995 and 1996. Both the overall
532 TEDS sample and the genotyped subsample have been shown to be representative of the UK
533 population⁴⁷⁻⁴⁹. The project received approval from the Institute of Psychiatry ethics committee
534 (05/Q0706/228) and parental consent was obtained before data collection. DNA for 4,649
535 individuals was extracted from saliva and buccal cheek swab samples and hybridized to
536 HumanOmniExpressExome-8v1.2 genotyping arrays at the Institute of Psychiatry, Psychology
537 and Neuroscience Genomics & Biomarker Core Facility. The raw image data from the array
538 were normalized, pre-processed, and filtered in GenomeStudio according to Illumina Exome
539 Chip SOP v1.4.
540 ([http://confluence.brc.iop.kcl.ac.uk:8090/display/PUB/Production+Version%3A+Illumina+Exo](http://confluence.brc.iop.kcl.ac.uk:8090/display/PUB/Production+Version%3A+Illumina+Exome+Chip+SOP+v1.4)
541 [me+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
542 samples with call rate < 0.95 were removed. The ZCALL program was used to augment the
543 genotype calling for samples and SNPs that passed the initial QC.
544 Samples were removed from subsequent analyses on the basis of call rate (< 0.99), suspected
545 non-European ancestry, heterozygosity, array signal intensity, and relatedness. SNPs were
546 excluded if the minor allele frequency was < 5%, if more than 1% of genotype data were
547 missing, or if the Hardy Weinberg *P*-value was lower than 10⁻⁵. Non-autosomal markers and
548 indels were removed. Association between the SNP and the platform, batch, or plate on which
549 samples were genotyped was calculated and SNPs with an effect *P*-value smaller than 10⁻³ were
550 excluded. After alignment to the 1000 Genomes (phase 3) reference data, 3,617 individuals and
551 515,536 SNPs remained. A principal component analysis was performed on a subset of 42,859
552 common (MAF > 5%) autosomal HapMap3 SNPs⁵⁰, 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 subtests⁵¹, and on two
558 nonverbal reasoning tests, the WISC-III-UK Picture Completion⁵¹ 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

576 ancestry-matching to the TIP participants, genotypes were available for 8,168 white Caucasian
577 individuals. All individuals were imputed to the Haplotype Reference Consortium reference
578 panel (rv1.1), using PBWT 32 as implemented in the Sanger Imputation Server
579 (imputation.sanger.ac.uk). SNPs taken forward to analyses had INFO > 0.9, MAF \geq 0.01, call
580 rate > 99.9% and Hardy-Weinberg $P < 10^{-8}$. Samples had call rate > 98%, heterozygosity < 4
581 standard deviations from the mean, and one of each pair of related samples was removed ($r >$
582 0.025). For the analyses performed in LDpred high IQ individuals were treated as "cases" and
583 population comparisons as controls. All analyses were controlled for gender and 10 principal
584 components.

585

586 **4. Rotterdam Study**

587 The Rotterdam Study is a large population-based cohort study in the Netherlands among
588 individuals aged \geq 45 years and residing in the Ommoord area, a suburb of Rotterdam⁵⁶. The
589 current study includes all participants under 60 years of age for whom genotypic information was
590 available, who underwent cognitive testing at the study centre from 2002 onwards, and have
591 been approved by the medical ethics committee according to the Population Study Act
592 Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands.
593 Written informed consent was obtained from all participants. Genotype data were collected on
594 Illumina 550, Illumina 550duo and Illumina 610 quad SNP arrays. Variants were filtered on
595 MAF < 0.01, call rate < 95% and Hardy-Weinberg $P < 10^{-6}$. Individuals were filtered based on
596 genotype missingness rate > 0.05, gender mismatch and relatedness (one of each pair of
597 individuals with IBD > 0.185). Analyses were restricted to individuals from Northern European
598 ancestry, resulting in a sample size of 2,015.

599 Participants underwent detailed cognitive assessment with a neuropsychological test battery
600 comprising of the letter-digit substitution task (number of correct digits in one minute), the
601 verbal fluency test (animal categories), the Stroop test (error-adjusted time in seconds for Stroop
602 reading and interference tasks), and a 15-word learning test (delayed recall). To obtain a measure
603 of global cognitive function, a compound score (g-factor) was computed based on the
604 aforementioned tests using principal component analysis. The g-factor explained 56.0% of the
605 variance in cognitive test scores in the population.

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