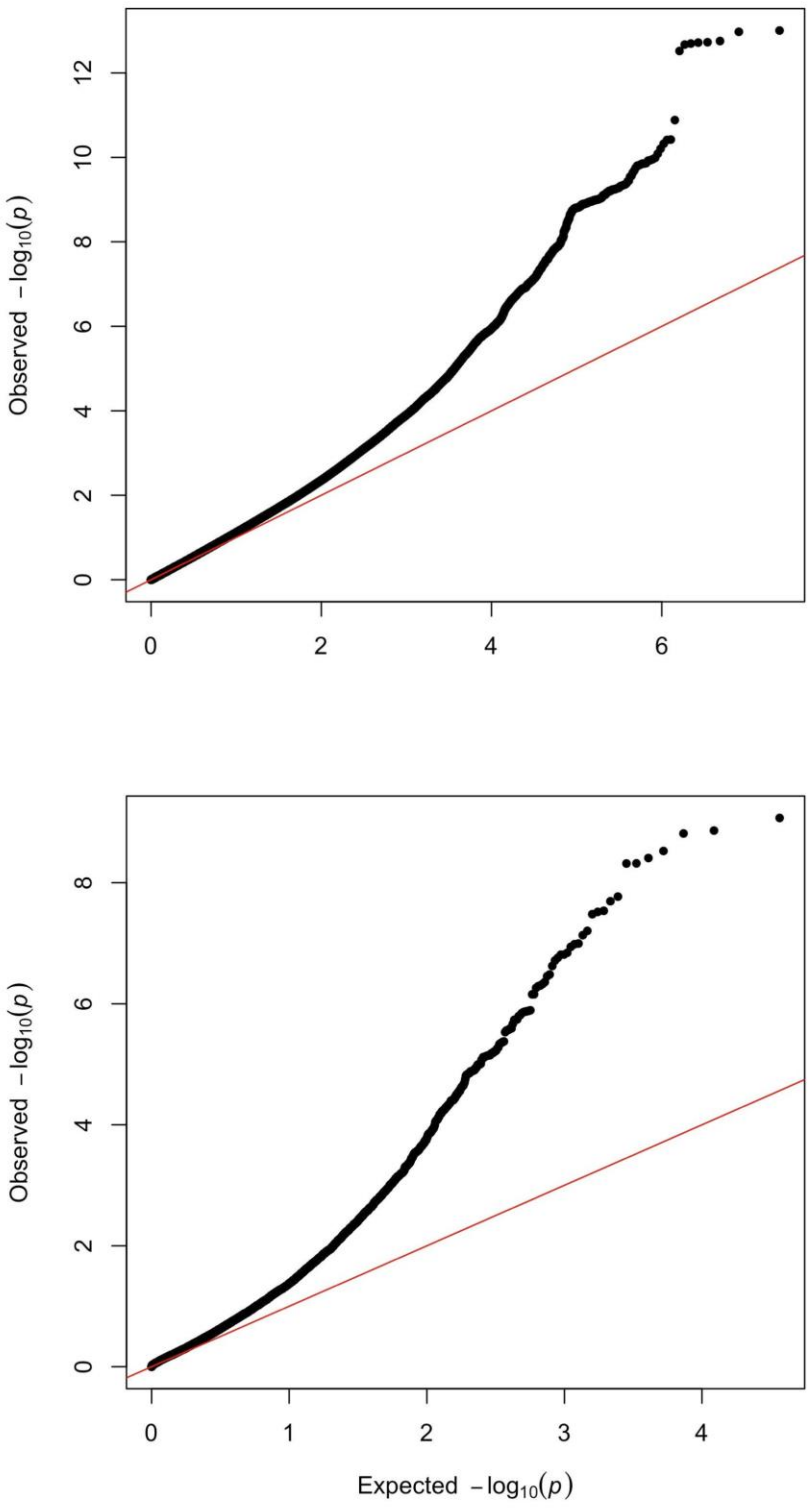
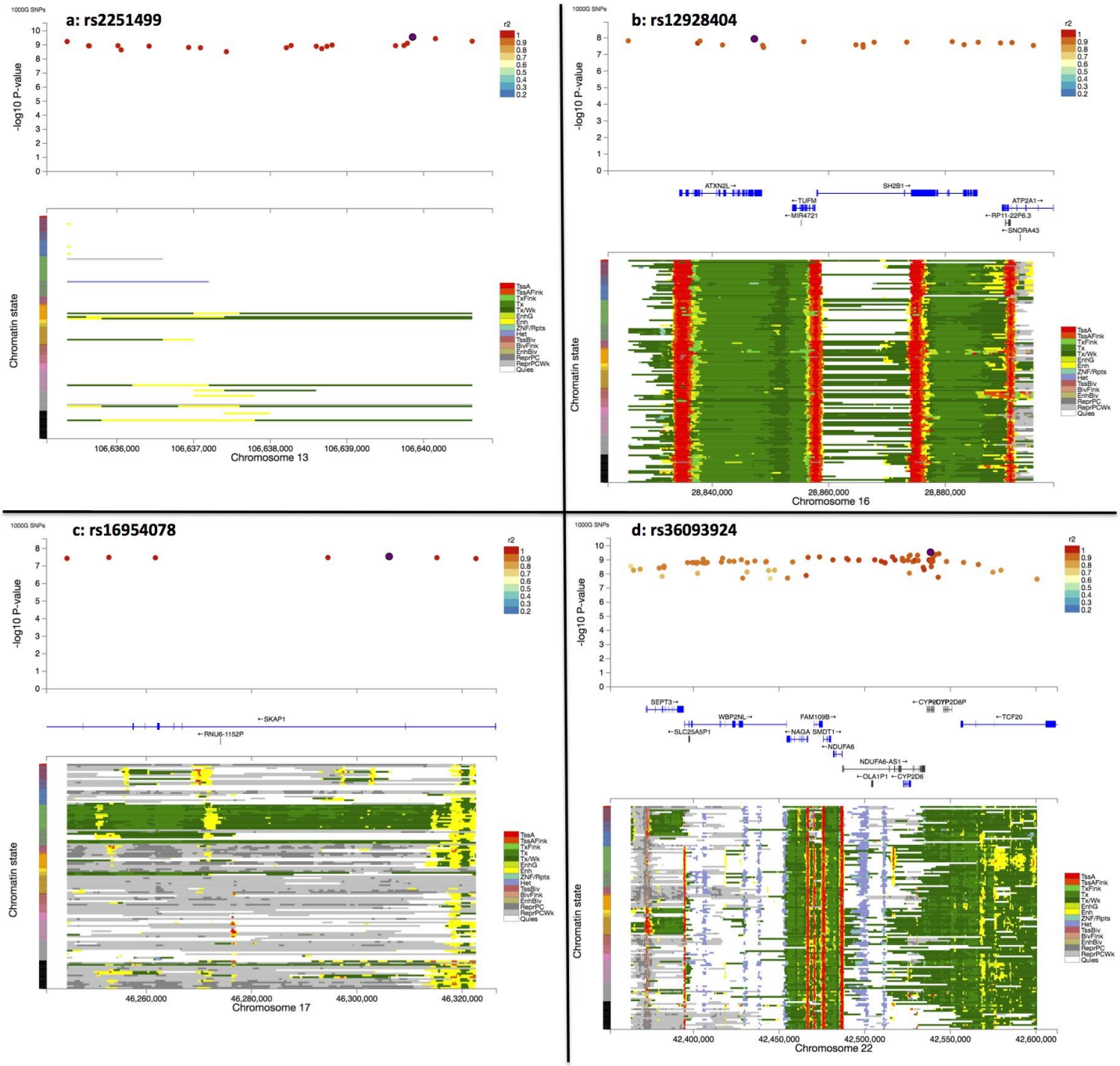


Supplementary Figure 1

Quantile–quantile plots.

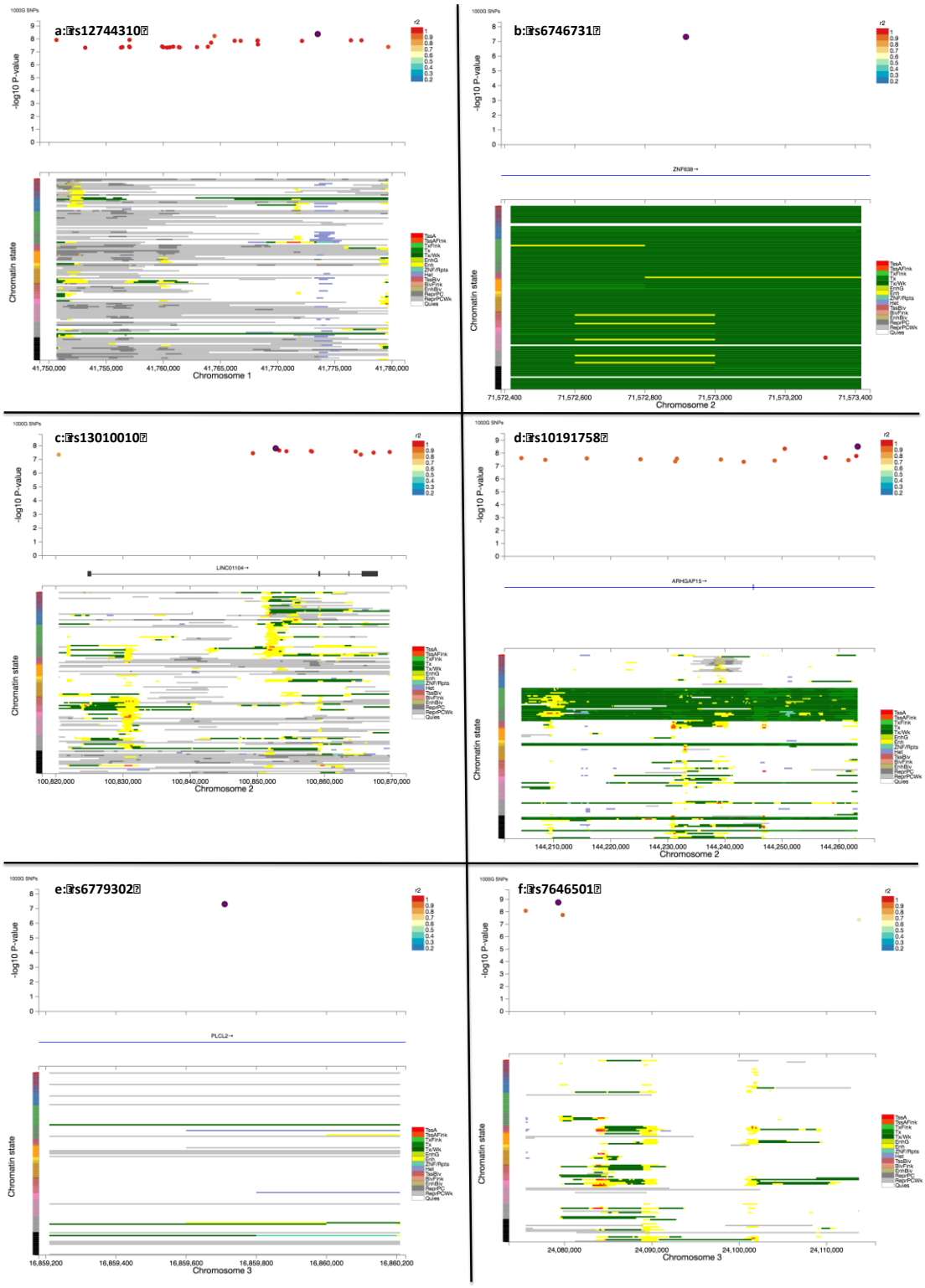
Quantile–quantile plot for SNP-based *P* values (top) and gene-based *P* values (bottom).



Supplementary Figure 2

Regional chromatin state plots for SNPs with $P < 5 \times 10^{-8}$ in four genomic loci.

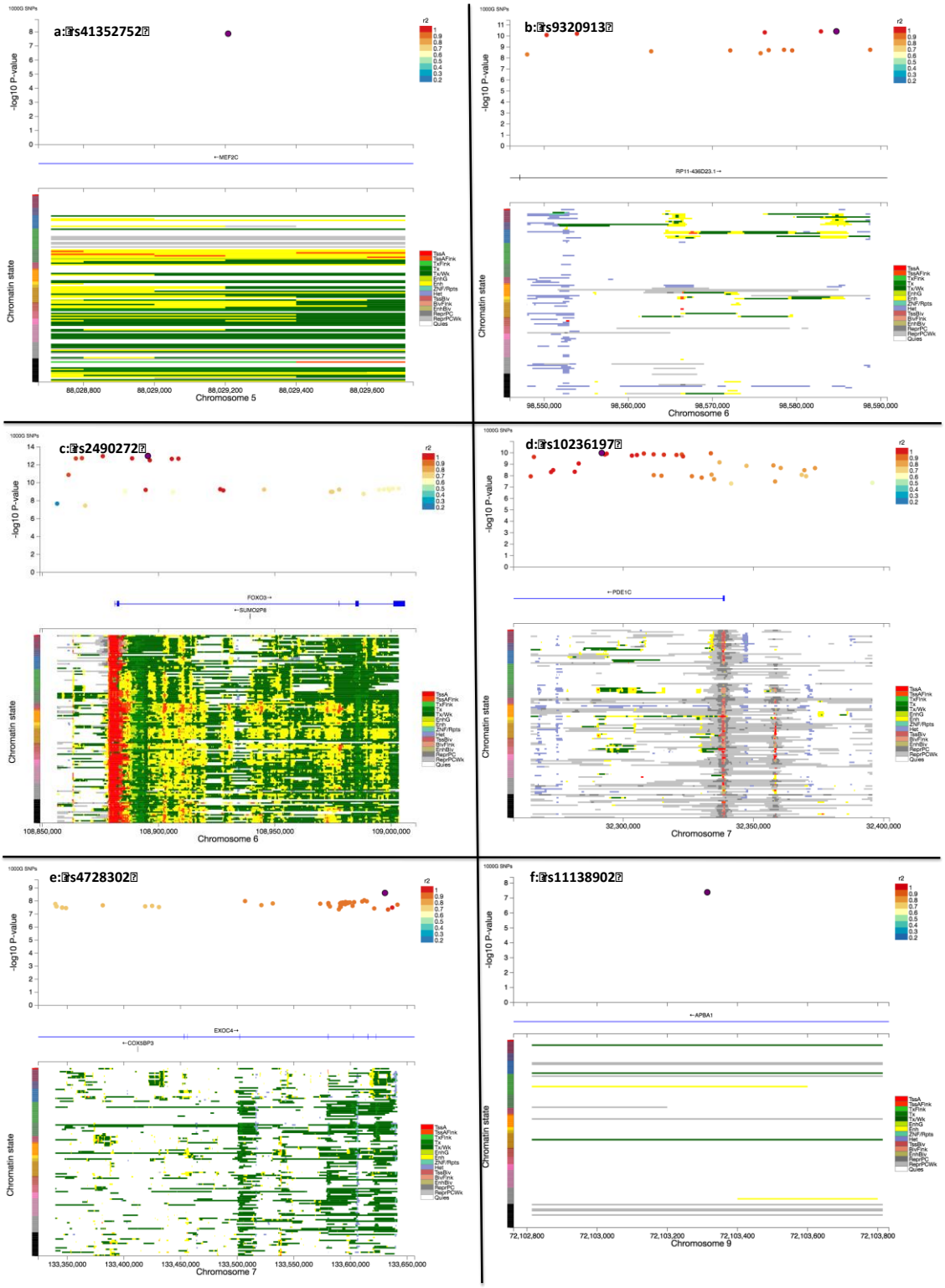
(**a**–**d**) Chromatin state plots are included for 4 of the 18 genome-wide significant loci. The 1p31.1 and 20q13.13 loci are not included because the lead SNPs in these regions (rs66495454 and rs113315451) are indels. In each picture, the top panel shows the lead SNP (purple) and all other SNPs reaching genome-wide significance in the region. The colors represent r^2 with the lead SNP. The bottom panel shows chromatin states for 127 tissue types (*y* axis) across the whole region. Different colors represent the different states, varying from “active TSS” (state 1) to “quiescent/low” (state 15). This information can be used to determine which SNPs to study in a functional follow-up.



Supplementary Figure 3

Regional chromatin state plots for SNPs with $P < 5 \times 10^{-8}$ in six genomic loci.

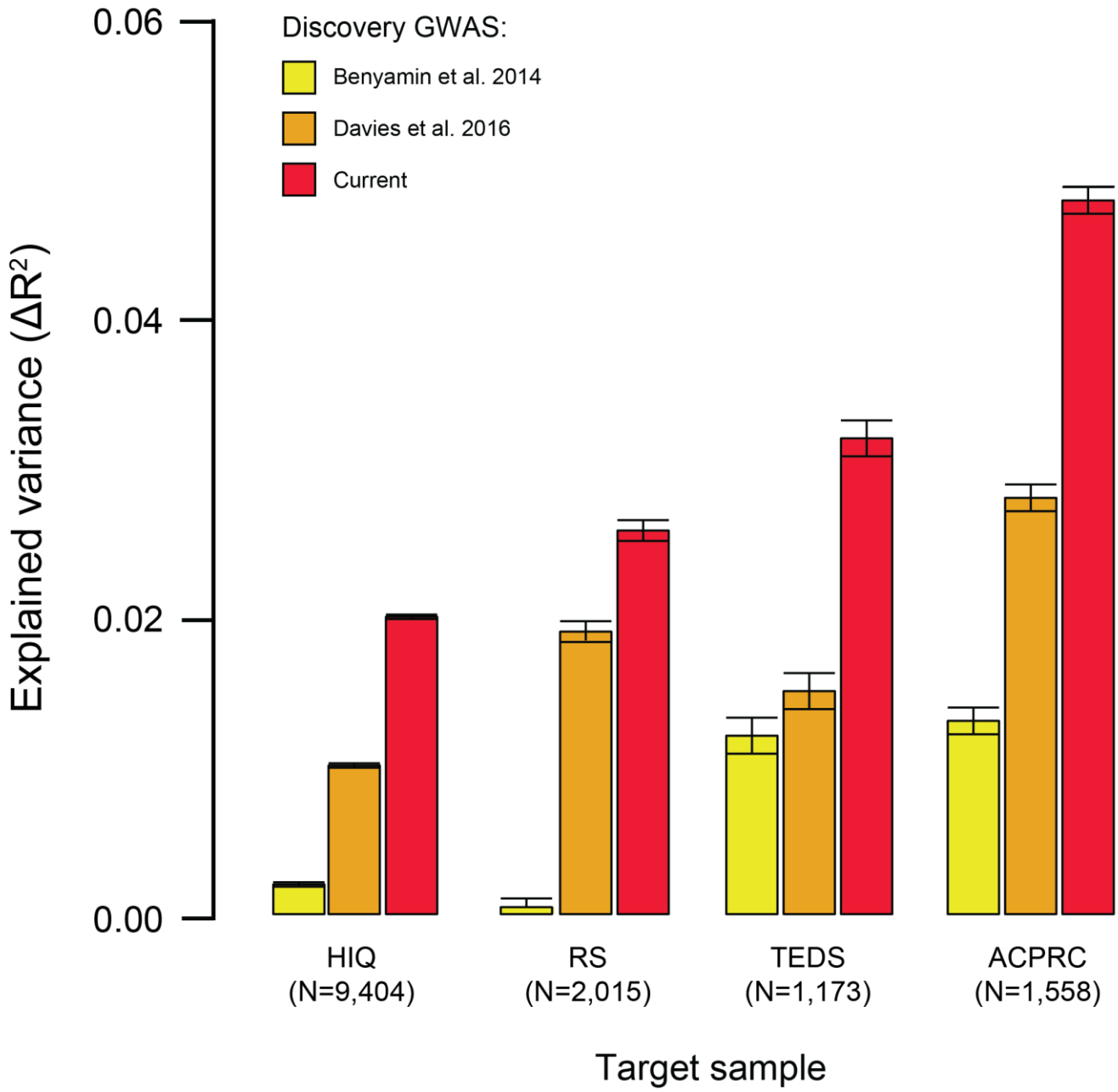
(**a**–**f**) Chromatin state plots are included for 6 of the 18 genome-wide significant loci.



Supplementary Figure 4

Regional chromatin state plots for SNPs with $P < 5 \times 10^{-8}$ in six genomic loci.

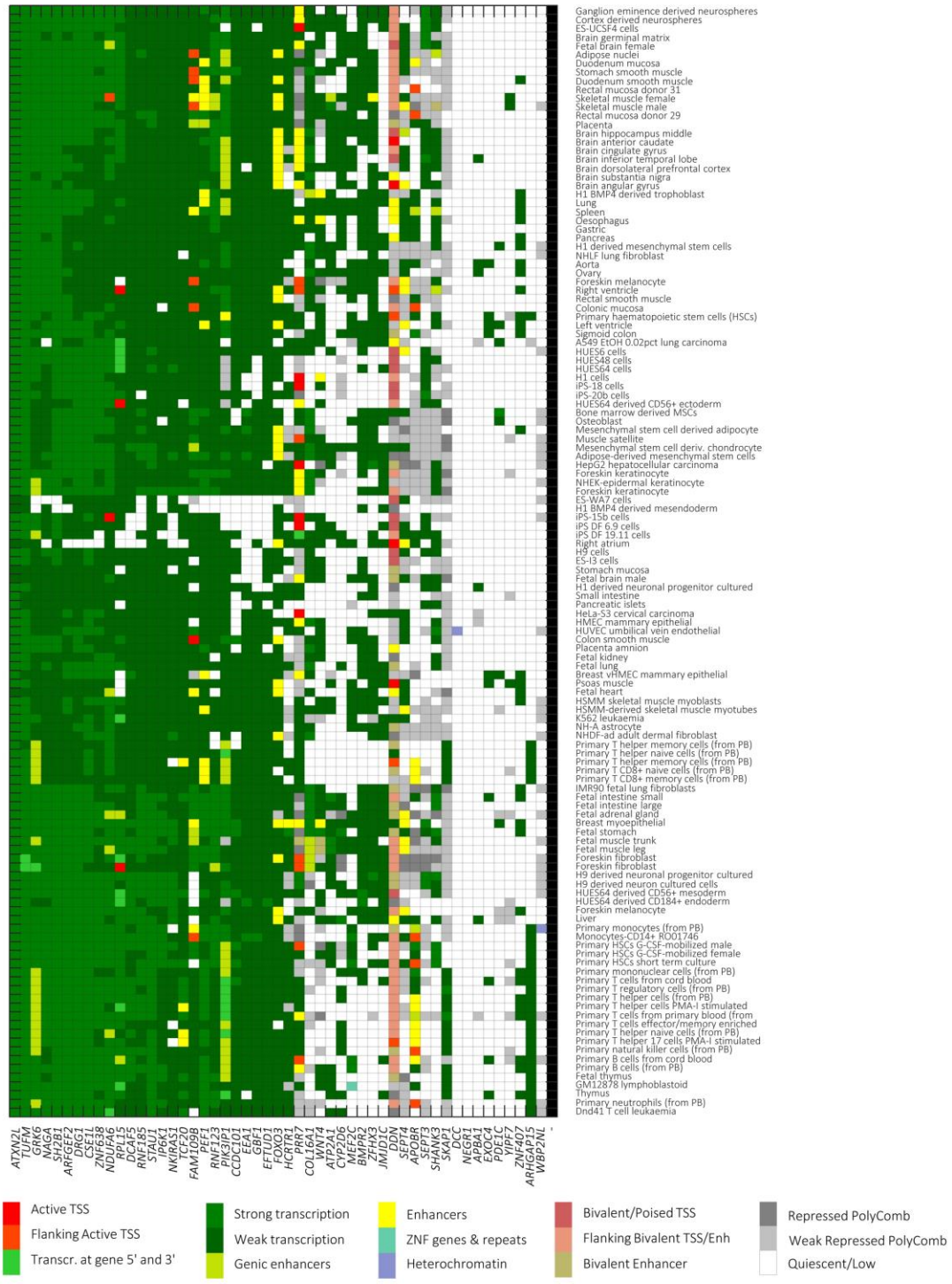
(**a**–**f**) Chromatin state plots are included for 6 of the 18 genome-wide significant loci.



Supplementary Figure 5

Predictive power (R^2) of the polygenic score based on different intelligence discovery GWAS studies in four independent hold-out samples.

Comparisons of the explained variance *(R^2)* in cognitive ability between polygenic scores based on the current meta-analysis and previous GWAS studies. The error bars represent the standard error. Cohorts: HIQ: High IQ sample; RS: Rotterdam Study; TEDS: Twins Early Development Study; ACPRC: Age and Cognitive Performance Research Centre; Discovery GWAS: Benyamin et al. 2014: childhood IQ; Davies et al. 2016: UK Biobank cognitive test (touchscreen). The R^2 for HIQ is reported on the liability scale (assuming a population prevalence of $3x10^{-4}$).



Supplementary Figure 6

Epigenetic states of genes.

Nature Genetics: doi:10.1038/ng.3869

Supplementary Note for

Genome-wide association meta-analysis of 78,308 individuals identifies new loci and genes influencing human intelligence

Suzanne Sniekers[1], Sven Stringer[1], Kyoko Watanabe[1], Philip R Jansen[1,2], Jonathan RI Coleman[3,4], Eva Krapohl[3], Erdogan Taskesen[1,5], Anke R Hammerschlag[1], Aysu Okbay[1,6], Delilah Zabaneh[3], Najaf Amin[7], Gerome Breen[3,4], David Cesarini[8], Christopher F Chabris[9], William G Iacono[10], M. Arfan Ikram[11], Magnus Johannesson[12], Philipp Koellinger[1,6], James J Lee[13], Patrik K. E. Magnusson[14], Matt McGue[10], Mike B. Miller[10], William ER Ollier[15], Antony Payton[15], Neil Pendleton[16], Robert Plomin[3], Cornelius A Rietveld[6,17], Henning Tiemeier[2,11,18], Cornelia M van Duijn[7,19], Danielle Posthuma[1,20*]

Affiliations:

1 Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, VU University Amsterdam, The Netherlands.
2 Department of Child and Adolescent Psychiatry, Erasmus Medical Center, 3000 CB, Rotterdam, The Netherlands.
3 MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK.
4 NIHR Biomedical Research Centre for Mental Health, South London and Maudsley NHS Trust, London, UK.
5 Alzheimer Centrum, Amsterdam Neuroscience, VU University Medical Center, Amsterdam, The Netherlands.
6 Erasmus University Rotterdam Institute for Behavior and Biology, 3062 PA Rotterdam, The Netherlands.
7 Genetic Epidemiology Unit, Department of Epidemiology, Erasmus Medical Center, 3000 CA Rotterdam, The Netherlands.
8 Center for Experimental Social Science, Department of Economics, New York University, New York, NY 10012.
9 Department of Psychology, Union College, Schenectady, NY 12308 (currently at: Geisinger Health System, Danville, PA 17822).
10 Department of Psychology, University of Minnesota, Minneapolis, MN 55455-0344.
11 Department of Epidemiology, Erasmus Medical Center, 3000 CB, Rotterdam, The Netherlands.
12 Department of Economics, Stockholm School of Economics, 113 83 Stockholm, Sweden.
13 Department of Psychology, Harvard University, Cambridge, MA 02138; Department of Psychology, University of Minnesota, Minneapolis, MN 55455-0344.
14 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, 171 77 Stockholm, Sweden.
15 Centre for Epidemiology, Division of Population Health, Health Services Research & Primary Care, The University of Manchester.
16 Division of Neuroscience and Experimental Psychology, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester M13 9PL.

Nature Genetics: doi:10.1038/ng.3869

[17] Department of Applied Economics, Erasmus School of Economics, Erasmus University Rotterdam, 3062 PA Rotterdam, The Netherlands.
[18] Department of Psychiatry, Erasmus Medical Center, 3000 CB, Rotterdam, The Netherlands.
[19] Translational Epidemiology, Faculty Science, Leiden University, The Netherlands.
[20] Department of Clinical Genetics, Amsterdam Neuroscience, VU University Medical Center, Amsterdam, The Netherlands.

*Correspondence to: Danielle Posthuma: Department of Complex Trait Genetics, VU University, De Boelelaan 1085, 1081 HV, Amsterdam, The Netherlands. Phone: +31 20 598 2823, Fax: +31 20 5986926, d.posthuma@vu.nl

This PDF file includes:

Supplementary Text
Additional Acknowledgements

Nature Genetics: doi:10.1038/ng.3869

Supplementary Text

Results of chromatin state mapping for 16 lead SNPs

The loci 1p31.1 and 20q13.13 were not included, because the lead SNPs in these regions (rs66495454 and rs113315451) are indels. For rs2251499 the consensus state is quiescent/low and the minimum state is weak transcription (**Supplementary Fig. 2a**). For rs12928404 the consensus state is strong transcription and the minimum state is transcr. at gene 5' and 3' (**Supplementary Fig. 2b**). For rs16954078 the consensus state is weak repressed PolyComb and the minimum state is strong transcription (**Supplementary Fig. 2c**). For rs36093924 the consensus state is weak transcription and the minimum state is strong transcription (**Supplementary Fig. 2d**). For rs12744310 the consensus state is quiescent/low and the minimum state is weak transcription (**Supplementary Fig. 3a**). For rs6746731 the consensus state is weak transcription and the minimum state is strong transcription (**Supplementary Fig. 3b**). For rs13010010 the consensus state is quiescent/low and the minimum state is weak transcription (**Supplementary Fig. 3c).** For rs10191758 the consensus state is quiescent/low and the minimum state is strong transcription (**Supplementary Fig. 3d**). For rs6779302 the consensus state is quiescent/low and the minimum state is weak transcription (**Supplementary Fig. 3e**). For rs7646501 the consensus state is quiescent/low and the minimum state is enhancers (**Supplementary Fig. 3f**). For rs41352752 the consensus state is quiescent/low and the minimum state is transcribed (**Supplementary Fig. 4a**). For rs9320913 the consensus state is quiescent/low and the minimum state is weak transcription **(Supplementary Fig. 4b**). For rs2490272 the consensus state is weak transcription and the minimum state is strong transcription (**Supplementary Fig. 4c**). For rs10236197 the consensus state is quiescent/low and the minimum state is weak transcription (**Supplementary Fig. 4d**). For rs4728302 the consensus state is weak transcription and the minimum state is weak transcription (**Supplementary Fig. 4e**). For rs11138902 the consensus state is quiescent/low and the minimum state is weak transcription. (**Supplementary Fig. 4f**).

Gene Summaries for implicated genes

We included the gene summaries from GeneCards (http://www.genecards.org) for all genes that were significant in the GWGAS (ordered by *P*-value) or implicated by single SNP GWAS (the last five in this list):

CSE1L

Proteins that carry a nuclear localization signal (NLS) are transported into the nucleus by the importin-alpha/beta heterodimer. Importin-alpha binds the NLS, while importin-beta mediates translocation through the nuclear pore complex. After translocation, RanGTP binds importin-beta and displaces importin-alpha. Importin-alpha must then be returned to the cytoplasm, leaving the NLS protein behind. The protein encoded by this gene binds strongly to NLS-free importin-alpha, and this binding is released in the cytoplasm by the combined action of RANBP1 and RANGAP1. In addition, the encoded protein may play a role both in apoptosis and in cell proliferation. Alternatively spliced transcript variants have been found for this gene. [provided by RefSeq, Jan 2012]

EXOC4

Nature Genetics: doi:10.1038/ng.3869

The protein encoded by this gene is a component of the exocyst complex, a multiple protein complex essential for targeting exocytic vesicles to specific docking sites on the plasma membrane. Though best characterized in yeast, the component proteins and functions of exocyst complex have been demonstrated to be highly conserved in higher eukaryotes. At least eight components of the exocyst complex, including this protein, are found to interact with the actin cytoskeletal remodeling and vesicle transport machinery. The complex is also essential for the biogenesis of epithelial cell surface polarity. Alternate transcriptional splice variants, encoding different isoforms, have been characterized. [provided by RefSeq, Jul 2008]

CYP2D6
This gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. This protein localizes to the endoplasmic reticulum and is known to metabolize as many as 25% of commonly prescribed drugs. Its substrates include antidepressants, antipsychotics, analgesics and antitussives, beta adrenergic blocking agents, antiarrythmics and antiemetics. The gene is highly polymorphic in the human population; certain alleles result in the poor metabolizer phenotype, characterized by a decreased ability to metabolize the enzyme's substrates. Some individuals with the poor metabolizer phenotype have no functional protein since they carry 2 null alleles whereas in other individuals the gene is absent. This gene can vary in copy number and individuals with the ultrarapid metabolizer phenotype can have 3 or more active copies of the gene. Alternatively spliced transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Jul 2014]

WBP2NL
WBP2NL is a sperm-specific WW domain-binding protein that promotes meiotic resumption and pronuclear development during oocyte fertilization (Wu et al., 2007 [PubMed 17289678]).[supplied by OMIM, Mar 2008]

FOXO3
This gene belongs to the forkhead family of transcription factors which are characterized by a distinct forkhead domain. This gene likely functions as a trigger for apoptosis through expression of genes necessary for cell death. Translocation of this gene with the MLL gene is associated with secondary acute leukemia. Alternatively spliced transcript variants encoding the same protein have been observed. [provided by RefSeq, Jul 2008]

APBA1
The protein encoded by this gene is a member of the X11 protein family. It is a neuronal adapter protein that interacts with the Alzheimer's disease amyloid precursor protein (APP). It stabilizes APP and inhibits production of proteolytic APP fragments including the A beta peptide that is deposited in the brains of Alzheimer's disease patients. This gene product is believed to be involved in signal transduction processes. It is also regarded as a putative vesicular trafficking protein in the brain that can form a complex with the potential to couple synaptic vesicle exocytosis to neuronal cell adhesion. [provided by RefSeq, Jul 2008]

SEPT3

Nature Genetics: doi:10.1038/ng.3869

This gene belongs to the septin family of GTPases. Members of this family are required for cytokinesis. Expression is upregulated by retinoic acid in a human teratocarcinoma cell line. The specific function of this gene has not been determined. Alternative splicing of this gene results in two transcript variants encoding different isoforms. [provided by RefSeq, Jul 2008]

NAGA
NAGA encodes the lysosomal enzyme alpha-N-acetylgalactosaminidase, which cleaves alpha-N-acetylgalactosaminyl moieties from glycoconjugates. Mutations in NAGA have been identified as the cause of Schindler disease types I and II (type II also known as Kanzaki disease). [provided by RefSeq, Jul 2008]

STAU1
Staufen is a member of the family of double-stranded RNA (dsRNA)-binding proteins involved in the transport and/or localization of mRNAs to different subcellular compartments and/or organelles. These proteins are characterized by the presence of multiple dsRNA-binding domains which are required to bind RNAs having double-stranded secondary structures. The human homologue of staufen encoded by STAU, in addition contains a microtubule- binding domain similar to that of microtubule-associated protein 1B, and binds tubulin. The STAU gene product has been shown to be present in the cytoplasm in association with the rough endoplasmic reticulum (RER), implicating this protein in the transport of mRNA via the microtubule network to the RER, the site of translation. Five transcript variants resulting from alternative splicing of STAU gene and encoding three isoforms have been described. Three of these variants encode the same isoform, however, differ in their 5'UTR. [provided by RefSeq, Jul 2008]

NDUFA6
No Entrez Gene Summary. GeneCards Summary:
NDUFA6 (NADH:Ubiquinone Oxidoreductase Subunit A6) is a Protein Coding gene. Diseases associated with NDUFA6 include Korean Hemorrhagic Fever and Bird Fancier's Lung. Among its related pathways are Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins. and Metabolism. GO annotations related to this gene include NADH dehydrogenase (ubiquinone) activity.

DCAF5
No Entrez Gene Summary. GeneCards Summary:
DCAF5 (DDB1 And CUL4 Associated Factor 5) is a Protein Coding gene. Diseases associated with DCAF5 include Leiomyoma. An important paralog of this gene is DCAF6.

EFTUD1
No Entrez Gene Summary. GeneCards Summary:
EFL1 (Elongation Factor Like GTPase 1) is a Protein Coding gene. Diseases associated with EFL1 include Shwachman-Diamond Syndrome. Among its related pathways are Ribosome biogenesis in eukaryotes.

DDN
No Entrez Gene Summary. GeneCards Summary:

Nature Genetics: doi:10.1038/ng.3869

DDN (Dendrin) is a Protein Coding gene. GO annotations related to this gene include RNA polymerase II core promoter proximal region sequence-specific DNA binding and transcription factor activity, RNA polymerase II core promoter proximal region sequence-specific binding.

ZNF407
This gene encodes a zinc finger protein whose exact function is not known. It may be involved in transcriptional regulation. Several alternatively spliced transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Sep 2009]

ZNF638
The protein encoded by this gene is a nucleoplasmic protein. It binds cytidine-rich sequences in double-stranded DNA. This protein has three types of domains: MH1, MH2 (repeated three times) and MH3. It is associated with packaging, transferring, or processing transcripts. Multiple alternatively spliced transcript variants have been found for this gene, but the biological validity of some variants has not been determined. [provided by RefSeq, Jul 2008]

PDE1C
This gene encodes an enzyme that belongs to the 3'5'-cyclic nucleotide phosphodiesterase family. Members of this family catalyze hydrolysis of the cyclic nucleotides, cyclic adenosine monophosphate and cyclic guanosine monophosphate, to the corresponding nucleoside 5'-monophosphates. The enzyme encoded by this gene regulates proliferation and migration of vascular smooth muscle cells, and neointimal hyperplasia. This enzyme also plays a role in pathological vascular remodeling by regulating the stability of growth factor receptors, such as PDGF-receptor-beta. [provided by RefSeq, Jul 2016]

RPL15
Ribosomes, the organelles that catalyze protein synthesis, consist of a small 40S subunit and a large 60S subunit. Together these subunits are composed of 4 RNA species and approximately 80 structurally distinct proteins. This gene encodes a ribosomal protein that is a component of the 60S subunit. The protein belongs to the L15E family of ribosomal proteins. It is located in the cytoplasm. This gene shares sequence similarity with the yeast ribosomal protein YL10 gene. Although this gene has been referred to as RPL10, its official symbol is RPL15. This gene has been shown to be overexpressed in some esophageal tumors compared to normal matched tissues. Alternate splicing results in multiple transcript variants. As is typical for genes encoding ribosomal proteins, there are multiple processed pseudogenes of this gene dispersed through the genome. [provided by RefSeq, Nov 2011]

ATXN2L
This gene encodes an ataxin type 2 related protein of unknown function. This protein is a member of the spinocerebellar ataxia (SCAs) family, which is associated with a complex group of neurodegenerative disorders. Several alternatively spliced transcripts encoding different isoforms have been found for this gene. [provided by RefSeq, Jul 2008]

SH2B1
This gene encodes a member of the SH2-domain containing mediators family. The encoded protein mediates activation of various kinases and may function in cytokine and growth factor

Nature Genetics: doi:10.1038/ng.3869

receptor signaling and cellular transformation. Alternatively spliced transcript variants have been described. [provided by RefSeq, Mar 2009]

NKIRAS1
No Entrez Gene Summary. GeneCards Summary:
NKIRAS1 (NFKB Inhibitor Interacting Ras Like 1) is a Protein Coding gene. Among its related pathways are NF-KappaB Family Pathway and TNF-alpha/NF-kB Signaling Pathway. GO annotations related to this gene include GTP binding and GTPase activity. An important paralog of this gene is NKIRAS2.

TUFM
This gene encodes a protein which participates in protein translation in mitochondria. Mutations in this gene have been associated with combined oxidative phosphorylation deficiency resulting in lactic acidosis and fatal encephalopathy. A pseudogene has been identified on chromosome 17. [provided by RefSeq, Jul 2008]

BMPR2
This gene encodes a member of the bone morphogenetic protein (BMP) receptor family of transmembrane serine/threonine kinases. The ligands of this receptor are BMPs, which are members of the TGF-beta superfamily. BMPs are involved in endochondral bone formation and embryogenesis. These proteins transduce their signals through the formation of heteromeric complexes of two different types of serine (threonine) kinase receptors: type I receptors of about 50-55 kD and type II receptors of about 70-80 kD. Type II receptors bind ligands in the absence of type I receptors, but they require their respective type I receptors for signaling, whereas type I receptors require their respective type II receptors for ligand binding. Mutations in this gene have been associated with primary pulmonary hypertension, both familial and fenfluramine-associated, and with pulmonary venoocclusive disease. [provided by RefSeq, Jul 2008]

ATP2A1
This gene encodes one of the SERCA Ca(2+)-ATPases, which are intracellular pumps located in the sarcoplasmic or endoplasmic reticula of muscle cells. This enzyme catalyzes the hydrolysis of ATP coupled with the translocation of calcium from the cytosol to the sarcoplasmic reticulum lumen, and is involved in muscular excitation and contraction. Mutations in this gene cause some autosomal recessive forms of Brody disease, characterized by increasing impairment of muscular relaxation during exercise. Alternative splicing results in three transcript variants encoding different isoforms. [provided by RefSeq, Oct 2013]

JMJD1C
The protein encoded by this gene interacts with thyroid hormone receptors and contains a jumonji domain. It is a candidate histone demethylase and is thought to be a coactivator for key transcription factors. It plays a role in the DNA-damage response pathway by demethylating the mediator of DNA damage checkpoint 1 (MDC1) protein, and is required for the survival of acute myeloid leukemia. Mutations in this gene are associated with Rett syndrome and intellectual disability. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Dec 2015]

Nature Genetics: doi:10.1038/ng.3869

SHANK3
This gene is a member of the Shank gene family. Shank proteins are multidomain scaffold proteins of the postsynaptic density that connect neurotransmitter receptors, ion channels, and other membrane proteins to the actin cytoskeleton and G-protein-coupled signaling pathways. Shank proteins also play a role in synapse formation and dendritic spine maturation. Mutations in this gene are a cause of autism spectrum disorder (ASD), which is characterized by impairments in social interaction and communication, and restricted behavioral patterns and interests. Mutations in this gene also cause schizophrenia type 15, and are a major causative factor in the neurological symptoms of 22q13.3 deletion syndrome, which is also known as Phelan-McDermid syndrome. Additional isoforms have been described for this gene but they have not yet been experimentally verified. [provided by RefSeq, Mar 2012]

ARFGEF2
ADP-ribosylation factors (ARFs) play an important role in intracellular vesicular trafficking. The protein encoded by this gene is involved in the activation of ARFs by accelerating replacement of bound GDP with GTP and is involved in Golgi transport. It contains a Sec7 domain, which may be responsible for its guanine-nucleotide exchange activity and also brefeldin A inhibition. [provided by RefSeq, Jul 2008]

GRK6
This gene encodes a member of the guanine nucleotide-binding protein (G protein)-coupled receptor kinase subfamily of the Ser/Thr protein kinase family. The protein phosphorylates the activated forms of G protein-coupled receptors thus initiating their deactivation. Several transcript variants encoding different isoforms have been described for this gene. [provided by RefSeq, Jul 2008]

RNF123
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. [provided by RefSeq, Feb 2016]

RNF185
No Entrez Gene Summary. GeneCards Summary:
RNF185 (Ring Finger Protein 185) is a Protein Coding gene. Among its related pathways are Protein processing in endoplasmic reticulum. GO annotations related to this gene include ligase activity. An important paralog of this gene is RNF5.

YIPF7
No Entrez Gene Summary. GeneCards Summary:
YIPF7 (Yip1 Domain Family Member 7) is a Protein Coding gene. An important paralog of this gene is YIPF5.

GBF1

Nature Genetics: doi:10.1038/ng.3869

This gene encodes a member of the Sec7 domain family. The encoded protein is a guanine nucleotide exchange factor that regulates the recruitment of proteins to membranes by mediating GDP to GTP exchange. The encoded protein is localized to the Golgi apparatus and plays a role in vesicular trafficking by activating ADP ribosylation factor 1. The encoded protein has also been identified as an important host factor for viral replication. Multiple transcript variants have been observed for this gene. [provided by RefSeq, Dec 2010]

PEF1
This gene encodes a calcium-binding protein belonging to the penta-EF-hand protein family. The encoded protein has been shown to form a heterodimer with the programmed cell death 6 gene product and may modulate its function in Ca(2+) signaling. Alternative splicing results in multiple transcript variants and a pseudogene has been identified on chromosome 1.[provided by RefSeq, May 2010]

COL16A1
This gene encodes the alpha chain of type XVI collagen, a member of the FACIT collagen family (fibril-associated collagens with interrupted helices). Members of this collagen family are found in association with fibril-forming collagens such as type I and II, and serve to maintain the integrity of the extracellular matrix. High levels of type XVI collagen have been found in fibroblasts and keratinocytes, and in smooth muscle and amnion. [provided by RefSeq, Jul 2008]

DCC
This gene encodes a netrin 1 receptor. The transmembrane protein is a member of the immunoglobulin superfamily of cell adhesion molecules, and mediates axon guidance of neuronal growth cones towards sources of netrin 1 ligand. The cytoplasmic tail interacts with the tyrosine kinases Src and focal adhesion kinase (FAK, also known as PTK2) to mediate axon attraction. The protein partially localizes to lipid rafts, and induces apoptosis in the absence of ligand. The protein functions as a tumor suppressor, and is frequently mutated or downregulated in colorectal cancer and esophageal carcinoma. [provided by RefSeq, Oct 2009]

PRR7
No Entrez Gene Summary. GeneCards Summary:
PRR7 (Proline Rich 7 (Synaptic)) is a Protein Coding gene.

CCDC101
CCDC101 is a subunit of 2 histone acetyltransferase complexes: the ADA2A (TADA2A; MIM 602276)-containing (ATAC) complex and the SPT3 (SUPT3H; MIM 602947)-TAF9 (MIM 600822)-GCN5 (KAT2A; MIM 602301)/PCAF (KAT2B; MIM 602303) acetylase (STAGA) complex. Both of these complexes contain either GCN5 or PCAF, which are paralogous acetyltransferases[1]. [supplied by OMIM, Apr 2010]

ARHGAP15
RHO GTPases (see ARHA; MIM 165390) regulate diverse biologic processes, and their activity is regulated by RHO GTPase-activating proteins (GAPs), such as ARHGAP15[2]. [supplied by OMIM, Mar 2008]

Nature Genetics: doi:10.1038/ng.3869

SEPT4
This gene is a member of the septin family of nucleotide binding proteins, originally described in yeast as cell division cycle regulatory proteins. Septins are highly conserved in yeast, Drosophila, and mouse, and appear to regulate cytoskeletal organization. Disruption of septin function disturbs cytokinesis and results in large multinucleate or polyploid cells. This gene is highly expressed in brain and heart. Alternatively spliced transcript variants encoding different isoforms have been described for this gene. One of the isoforms (known as ARTS) is distinct; it is localized to the mitochondria, and has a role in apoptosis and cancer. [provided by RefSeq, Nov 2010]

ZFHX3
This gene encodes a transcription factor with multiple homeodomains and zinc finger motifs, and regulates myogenic and neuronal differentiation. The encoded protein suppresses expression of the alpha-fetoprotein gene by binding to an AT-rich enhancer motif. The protein has also been shown to negatively regulate c-Myb, and transactivate the cell cycle inhibitor cyclin-dependent kinase inhibitor 1A (also known as p21CIP1). This gene is reported to function as a tumor suppressor in several cancers, and sequence variants of this gene are also associated with atrial fibrillation. Multiple transcript variants expressed from alternate promoters and encoding different isoforms have been found for this gene. [provided by RefSeq, Sep 2009]

EEA1
No Entrez Gene Summary. GeneCards Summary:
EEA1 (Early Endosome Antigen 1) is a Protein Coding gene. Diseases associated with EEA1 include Subacute Cutaneous Lupus Erythematosus and Cat-Scratch Disease. Among its related pathways are Tuberculosis and Cytoskeletal Signaling. GO annotations related to this gene include protein homodimerization activity and 1-phosphatidylinositol binding. An important paralog of this gene is FYCO1.

WNT4
The WNT gene family consists of structurally related genes which encode secreted signaling proteins. These proteins have been implicated in oncogenesis and in several developmental processes, including regulation of cell fate and patterning during embryogenesis. This gene is a member of the WNT gene family, and is the first signaling molecule shown to influence the sex-determination cascade. It encodes a protein which shows 98% amino acid identity to the Wnt4 protein of mouse and rat. This gene and a nuclear receptor known to antagonize the testis-determining factor play a concerted role in both the control of female development and the prevention of testes formation. This gene and another two family members, WNT2 and WNT7B, may be associated with abnormal proliferation in breast tissue. Mutations in this gene can result in Rokitansky-Kuster-Hauser syndrome and in SERKAL syndrome. [provided by RefSeq, Jul 2008]

DRG1
No Entrez Gene Summary. GeneCards Summary:
DRG1 (Developmentally Regulated GTP Binding Protein 1) is a Protein Coding gene. GO annotations related to this gene include identical protein binding and transcription factor binding.

Nature Genetics: doi:10.1038/ng.3869

IP6K1
This gene encodes a member of the inositol phosphokinase family. The encoded protein may be responsible for the conversion of inositol hexakisphosphate (InsP6) to diphosphoinositol pentakisphosphate (InsP7/PP-InsP5). It may also convert 1,3,4,5,6-pentakisphosphate (InsP5) to PP-InsP4. Alternatively spliced transcript variants have been described. [provided by RefSeq, Jun 2011]

APOBR
Apolipoprotein B48 receptor is a macrophage receptor that binds to the apolipoprotein B48 of dietary triglyceride (TG)-rich lipoproteins. This receptor may provide essential lipids, lipid-soluble vitamins and other nutrients to reticuloendothelial cells. If overwhelmed with elevated plasma triglyceride, the apolipoprotein B48 receptor may contribute to foam cell formation, endothelial dysfunction, and atherothrombogenesis. [provided by RefSeq, Jul 2008]

HCRTR1
The protein encoded by this gene is a G-protein coupled receptor involved in the regulation of feeding behavior. The encoded protein selectively binds the hypothalamic neuropeptide orexin A. A related gene (HCRTR2) encodes a G-protein coupled receptor that binds orexin A and orexin B. [provided by RefSeq, Jan 2009]

PIK3IP1
No Entrez Gene Summary. GeneCards Summary:
PIK3IP1 (Phosphoinositide-3-Kinase Interacting Protein 1) is a Protein Coding gene. GO annotations related to this gene include phosphatidylinositol 3-kinase catalytic subunit binding.

TCF20
This gene encodes a transcription factor that recognizes the platelet-derived growth factor-responsive element in the matrix metalloproteinase 3 promoter. The encoded protein is thought to be a transcriptional coactivator, enhancing the activity of transcription factors such as JUN and SP1. Mutations in this gene are associated with autism spectrum disorders. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Sep 2015]

SKAP1
This gene encodes a T cell adaptor protein, a class of intracellular molecules with modular domains capable of recruiting additional proteins but that exhibit no intrinsic enzymatic activity. The encoded protein contains a unique N-terminal region followed by a PH domain and C-terminal SH3 domain. Along with the adhesion and degranulation-promoting adaptor protein, the encoded protein plays a critical role in inside-out signaling by coupling T-cell antigen receptor stimulation to the activation of integrins. [provided by RefSeq, Jul 2008]

FAM109B
No Entrez Gene Summary. GeneCards Summary:
FAM109B (Family With Sequence Similarity 109 Member B) is a Protein Coding gene. GO annotations related to this gene include protein homodimerization activity. An important paralog of this gene is FAM109A.

Nature Genetics: doi:10.1038/ng.3869

MEF2C
This locus encodes a member of the MADS box transcription enhancer factor 2 (MEF2) family of proteins, which play a role in myogenesis. The encoded protein, MEF2 polypeptide C, has both trans-activating and DNA binding activities. This protein may play a role in maintaining the differentiated state of muscle cells. Mutations and deletions at this locus have been associated with severe mental retardation, stereotypic movements, epilepsy, and cerebral malformation. Alternatively spliced transcript variants have been described. [provided by RefSeq, Jul 2010]

NEGR1
No Entrez Gene Summary. GeneCards Summary:
NEGR1 (Neuronal Growth Regulator 1) is a Protein Coding gene. Diseases associated with NEGR1 include Podoconiosis and Obesity. Among its related pathways are Cell adhesion molecules (CAMs). An important paralog of this gene is LSAMP.

ATP2A1-AS1
No Entrez Gene Summary. GeneCards Summary:
ATP2A1-AS1 (ATP2A1 Antisense RNA 1) is an RNA Gene, and is affiliated with the non-coding RNA class.

Genetic correlation with Alzheimer's disease for different age groups
Since Alzheimer's variants could be affecting cognitive abilities through cognitive decline in older subjects, we calculated the genetic correlation between intelligence and Alzheimer's disease for three different age groups:

1. UKB group (aged 40-77.5): r_g=-0.33, SE=0.10, P=$1.7x10^{-3}$
2. Adults (aged 18-78): r_g=-0.35, SE=0.11, P=$1.1x10^{-3}$
3. Children (aged < 18): r_g=-0.30, SE=0.11, P=$6.2x10^{-3}$.

As can be seen, the r_g's are very similar across age (which we would expect given the high genetic correlation between intelligence in children and adults that we found), suggesting that the observed genetic correlation between Alzheimer's disease and intelligence based on the full sample is not influenced by one particular age group.

Independent datasets available for PRS
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[3]. 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 Tests, the Cattell and Cattell Culture Fair intelligence tests, and the Wechsler Adult Intelligence Scale Vocabulary test. Detailed task descriptions were provided

Nature Genetics: doi:10.1038/ng.3869

previously[3]. 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 A and B Tests 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[5–7]. The project received approval from the Institute of Psychiatry ethics committee (05/Q0706/228) and parental consent was obtained before data collection. For the current study, we selected individuals that were not included in ref. 8, which resulted in a sample of N=1,173 available for PRS analyses. DNA 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

Nature Genetics: doi:10.1038/ng.3869

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[9], after stringent pruning to remove markers in linkage disequilibrium ($r^2 > 0.1$) and excluding high linkage disequilibrium genomic regions so as to ensure that only genome-wide effects were detected. Thirty PCs were used in the present analyses.

Individuals were tested on two verbal tests at the age of 12, the WISC-III-PI Multiple Choice Information (General Knowledge) and Vocabulary Multiple Choice subtests[10], and on two nonverbal reasoning tests, the WISC-III-UK Picture Completion[10] and Raven's Standard and Advanced Progressive Matrices[11,12], which were all administered online[13,14]. g-scores were derived as the arithmetic mean of the four standardized test scores. The residuals after regressing the measure on sex and age at assessment were used. These were obtained using the rstandard function of the lm package in R (version 3.2.2), which produces standardized residuals via normalization to unit variance using the overall error variance of the residuals.

3. High IQ Sample

Individuals with extremely high intelligence were recruited from the top 1% of the Duke University Talent Identification Program[15] (TIP), which recruits from the top 3% of the intelligence distribution. DNA was collected using buccal swabs. Illumina Omni Express genotypes were available for 1,236 white European Caucasian individuals following quality control. A population comparison cohort was obtained from The University of Michigan Health and Retirement Study (HRS). Details about the HRS can be found on (http://hrsonline.isr.umich.edu/). DNA was extracted from saliva. Genotypes were available from the Illumina Human Omni-2.5 Quad Beadchip, with a coverage of 2.5 million SNPs. Genotype 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[16] 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

Nature Genetics: doi:10.1038/ng.3869

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[17]. 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.

Additional Acknowledgements
The authors of this article are grateful to the Social Science Genetic Association Consortium (http://www.ssgac.org) for providing the meta-analysis results for educational attainment. We are also grateful to the CHIC consortium for providing the meta-analysis results for childhood intelligence.

HU (Harvard/Union Study) – This study was supported by the authors' research funds and a grant from the National Institute on Aging to the National Bureau of Economic Research (T32-AG00186).

MCTFR (Minnesota Center for Twin and Family Research) – The Minnesota Center for Twin and Family Research (MCTFR) is supported by USPHS Grants from the National Institute on Alcohol Abuse and Alcoholism (AA09367 and AA11886), the National Institute on Drug Abuse (DA036216, DA05147, DA13240, and DA024417) and the National Institute on Mental Health (MH066140). Jaime Derringer was supported by NIH grants DA029377 and MH016880.

STR (Swedish Twin Registry) – The Jan Wallander and Tom Hedelius Foundation, the Ragnar So□derberg Foundation (E9/11), the Swedish Council for Working Life and Social Research, the Ministry for Higher Education, Karolinska Institutet, the Swedish Research Council (421-2013-1061; M-2005-1112), GenomEUtwin (EU/QLRT- 2001-01254; QLG2-CT-2002-01254), NIH DK U01-066134, The Swedish Foundation for Strategic Research (SSF).

ERF (Erasmus Rucphen Family Study) – The ERF study as a part of EUROSPAN (European Special Populations Research Network) was supported by European Commission FP6 STRP

grant number 018947 (LSHG-CT-2006-01947) and also received funding from the European Community's Seventh Framework Programme (FP7/2007-2013)/grant agreement HEALTH-F4-2007-201413 by the European Commission under the programme "Quality of Life and Management of the Living Resources" of 5th Framework Programme (no. QLG2-CT-2002-01254). The ERF study was further supported by ENGAGE consortium and CMSB. High-throughput analysis of the ERF data was supported by joint grant from Netherlands Organisation for Scientific Research and the Russian Foundation for Basic Research (NWO-RFBR 047.017.043). We are grateful to all study participants and their relatives, general practitioners and neurologists for their contributions and to P. Veraart for her help in genealogy, J. Vergeer for the supervision of the laboratory work and P. Snijders for his help in data collection.

GenR (Generation R) – The Generation R Study is conducted by the Erasmus Medical Center, Rotterdam in close collaboration with the Erasmus University Rotterdam, the Municipal Health Service Rotterdam area, the Rotterdam Homecare Foundation and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR), Rotterdam. The authors wish to thank the parents and children that participate in the Generation R Study. The Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam and the Netherlands Organization for Health Research and Development (ZonMw grant numbers 10.000.1003); the present study was supported by an additional grant from the Sophia Foundation for Scientific Research (SSWO; grant 547, 2008) and a VIDI grant to HT from the Netherlands Organization for Scientific Research (NWO; grant number 017.106.370). DP gratefully acknowledges financial support from the Netherlands Organization for Scientific Research (NWO/MaGW VIDI 016-065-318, NWO/NIHC 433-09-228, and NWO Complexity project 645.000.003).

Philipp Koellinger gratefully acknowledges funding from the ERC Consolidator Grant (647648 EdGe).

Niels Rietveld gratefully acknowledges funding from the Netherlands Organization for Scientific Research (NWO Veni grant 016.165.004).

We acknowledge the Biotechnology and Biological Sciences Research Council UK supporting the Manchester and Newcastle Age and Cognitive Performance Research Cohorts genome wide genotyping (Grant BB/F022441.1).

The research on the high IQ sample was supported by a European Research Council Advanced Investigator award (295366) to RP. Collecting DNA from the highest-scoring TIP individuals was supported by an award from the John Templeton Foundation (13575) to RP. The Twins Early Development Study (TEDS), which was used to test the extent to which the extremely high intelligence case-control GWA yields a polygenic score that also accounts for genetic influence throughout the normal distribution, is supported by the UK Medical Research Council (MR/M021475/1 and previously G0901245), with additional support from the US National Institutes of Health (HD044454; HD059215). EK is supported by the MRC/IoPPN Excellence Award. RP is supported by a Medical Research Council Research Professorship and a European Research Council Advanced Investigator award (295366). GB and the laboratory work were supported in part by the NIHR Biomedical Research Centre ('BRC') and NIHR Dementia

Biomedical Research Unit ('BRU') hosted at King's College London and South London and Maudsley NHS Foundation Trust and funded by the National Institute for Health Research under its Biomedical Research Centre's funding initiative. The views expressed are those of the authors and not necessarily those of the BRC or the BRU, the NHS, the NIHR or the Department of Health or King's College London. We gratefully acknowledge capital equipment funding from the Maudsley Charity (Grant Ref. 980) and Guy's and St Thomas's Charity (Grant Ref. STR130505).

Data on coronary artery disease have been contributed by CARDIoGRAMplusC4D investigators and have been downloaded from www.CARDIOGRAMPLUSC4D.ORG.

Data on the infant head circumference trait, the childhood body mass index trait, the childhood obesity trait and the birth weight trait have been contributed by the EGG Consortium and have been downloaded from www.egg-consortium.org.

We thank the International Genomics of Alzheimer's Project (IGAP) for providing summary results data for these analyses. The investigators within IGAP contributed to the design and implementation of IGAP and/or provided data but did not participate in analysis or writing of this report. IGAP was made possible by the generous participation of the control subjects, the patients, and their families. The i–Select chips was funded by the French National Foundation on Alzheimer's disease and related disorders. EADI was supported by the LABEX (laboratory of excellence program investment for the future) DISTALZ grant, Inserm, Institut Pasteur de Lille, Université de Lille 2 and the Lille University Hospital. GERAD was supported by the Medical Research Council (Grant n° 503480), Alzheimer's Research UK (Grant n° 503176), the Wellcome Trust (Grant n° 082604/2/07/Z) and German Federal Ministry of Education and Research (BMBF): Competence Network Dementia (CND) grant n° 01GI0102, 01GI0711, 01GI0420. CHARGE was partly supported by the NIH/NIA grant R01 AG033193 and the NIA AG081220 and AGES contract N01–AG–12100, the NHLBI grant R01 HL105756, the Icelandic Heart Association, and the Erasmus Medical Center and Erasmus University. ADGC was supported by the NIH/NIA grants: U01 AG032984, U24 AG021886, U01 AG016976, and the Alzheimer's Association grant ADGC–10–196728.

Data on anorexia nervosa, autism spectrum disorder, schizophrenia, attention-deficit/ hyperactivity disorder, bipolar disorder and major depressive disorder have been contributed by the Psychiatric Genomics Consortium (PGC) and have been downloaded from http://www.med.unc.edu/pgc/results-and-downloads.

Data on subjective well-being, neuroticism and depressive symptoms have been contributed by the Social Science Genetic Association Consortium (SSGAC) and have been downloaded from http://www.thessgac.org/data.

Data on childhood intelligence have been contributed by the Childhood Intelligence Consortium (CHIC) and have been downloaded from http://www.thessgac.org/data.

Data on smoking traits have been contributed by the Tobacco and Genetics Consortium (TaG) and have been downloaded from http://www.med.unc.edu/pgc/results-and-downloads.

Data on height, hip circumference, waist-hip ratio and waist circumference have been contributed by the Genetic Investigation of ANthropometric Traits (GIANT) and have been downloaded from http://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files.

Data on asthma have been contributed by the GABRIEL Consortium and have been downloaded from https://www.cng.fr/gabriel/results.html.

Data on type 2 diabetes have been contributed by DIAGRAM and have been downloaded from http://diagram-consortium.org/downloads.html.

Data on anxiety disorders have been contributed by the Anxiety Neuro Genetics STudy (ANGST) and have been downloaded from http://www.med.unc.edu/pgc/results-and-downloads.

Data on intracranial volume have been contributed by ENIGMA and have been downloaded from http://enigma.ini.usc.edu.

Data on longevity have been downloaded from http://hmg.oxfordjournals.org/content/suppl/2014/03/27/ddu139.DC1.

Data on Parkinson's disease have been contributed by the National Institute of Neurological Disorders and Stroke (NINDS) and have been downloaded from https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000089.v4.p2, dbGaP analysis accession pha002868.

The Genotype-Tissue Expression (GTEx) Project was supported by the Common Fund of the Office of the Director of the National Institutes of Health. Additional funds were provided by the NCI, NHGRI, NHLBI, NIDA, NIMH, and NINDS. Donors were enrolled at Biospecimen Source Sites funded by NCI\SAIC-Frederick, Inc. (SAIC-F) subcontracts to the National Disease Research Interchange (10XS170), Roswell Park Cancer Institute (10XS171), and Science Care, Inc. (X10S172). The Laboratory, Data Analysis, and Coordinating Center (LDACC) was funded through a contract (HHSN268201000029C) to The Broad Institute, Inc. Biorepository operations were funded through an SAIC-F subcontract to Van Andel Institute (10ST1035). Additional data repository and project management were provided by SAIC-F (HHSN261200800001E). The Brain Bank was supported by a supplements to University of Miami grants DA006227 & DA033684 and to contract N01MH000028. Statistical Methods development grants were made to the University of Geneva (MH090941 & MH101814), the University of Chicago (MH090951, MH090937, MH101820, MH101825), the University of North Carolina - Chapel Hill (MH090936 & MH101819), Harvard University (MH090948), Stanford University (MH101782), Washington University St Louis (MH101810), and the University of Pennsylvania (MH101822). The data used for the analyses described in this manuscript were obtained from the GTEx Portal on 11/24/2016.

Supplementary Tables 1-18 (separate file)

Supplementary Table 1: **Cohorts included in the meta-analysis based on N=78,308.**
Supplementary Table 2: **Genetic correlations between the individual cohorts.**
Supplementary Table 3: **Genomic inflation factors for the individual cohorts.**
Supplementary Table 4: **Top SNPs associated with intelligence in the meta-analysis based on N=78,308.**
Supplementary Table 5: **Look-up of all top SNPs in previous genome-wide association studies of intelligence.**
Supplementary Table 6: **Genome-wide significant SNPs that are eQTLs with corresponding genes and tissue types.**
Supplementary Table 7: **Variance explained in cognitive ability by three cognition GWAS studies in four independent hold-out samples**.
Supplementary Table 8: **Genes associated with intelligence in the gene-based MAGMA analysis based on N=78,308.**
Supplementary Table 9: **Twelve genes out of the 52 genes associated with intelligence that were previously found to be associated with intelligence in gene-based genome-wide tests.**
Supplementary Table 10: **GO pathways with *P*-value from the MAGMA gene-set analysis.**
Supplementary Table 11: **Reactome pathways with *P*-value from the MAGMA gene-set analysis.**
Supplementary Table 12: **Genes in the GO regulation of cell development pathway with gene-based MAGMA *P*-value.**
Supplementary Table 13: **Genetic correlations between intelligence and 32 other traits.**
Supplementary Table 14: **Look-up of all top SNPs in a genome-wide association study of educational attainment based on N=196,931.**
Supplementary Table 15: **Look-up of all top genes in a genome-wide association study of educational attainment based on N=196,931.**
Supplementary Table 16: **Genes implicated either by GWAS or GWGAS reported in GWAS catalog.**
Supplementary Table 17: **Top SNPs reported in GWAS catalog.**
Supplementary Table 18: **GTEx tissue types.**

Nature Genetics: doi:10.1038/ng.3869

References:

1. Wang, Y. L., Faiola, F., Xu, M., Pan, S. & Martinez, E. Human ATAC is a GCN5/PCAF-containing acetylase complex with a novel NC2-like histone fold module that interacts with the TATA-binding protein. *J. Biol. Chem.* **283,** 33808–33815 (2008).
2. Seoh, M. L., Ng, C. H., Yong, J., Lim, L. & Leung, T. ArhGAP15, a novel human RacGAP protein with GTPase binding property. in *FEBS Letters* **539,** 131–137 (2003).
3. Rabbitt, P. M. a *et al.* The University of Manchester longitudinal study of cognition in normal healthy old age, 1983 through 2003. *Aging Neuropsychol. Cogn.* **11,** 245–279 (2004).
4. Davies, G. *et al.* Genome-wide association studies establish that human intelligence is highly heritable and polygenic. *Mol. Psychiatry* **16,** 996–1005 (2011).
5. Krapohl, E. & Plomin, R. Genetic link between family socioeconomic status and children's educational achievement estimated from genome-wide SNPs. *Mol. Psychiatry* **21,** 1–7 (2015).
6. Selzam, S. *et al.* Predicting educational achievement from DNA. *Mol. Psychiatry* **doi,** 1–6 (2016).
7. Kovas, Y., Haworth, C. M. A., Dale, P. S. & Plomin, R. The Genetic and Environmental Origins of Learning Abilities and Disabilities in the Early School Years. *Monogr. Soc. Res.* **72,** vii-160 (2007).
8. Benyamin, B. *et al.* Childhood intelligence is heritable, highly polygenic and associated with FNBP1L. *Mol. Psychiatry* **19,** 253–8 (2014).
9. Altshuler, D. M. *et al.* Integrating common and rare genetic variation in diverse human populations. *Nature* **467,** 52–58 (2010).
10. Wechsler, D. Wechsler intelligence scale for children–Third Edition. *San Antonio, TX Psychol. Corp.* (1991).
11. Raven, J. C., Raven, J. & Court, J. H. *The Mill Hill vocabulary scale. Manual for Raven's progressive matrices and vocabulary scales* (1988).
12. Raven, J., Raven, J. C. & Court, J. *Manual for Raven's progressive matrices and vocabulary scales. Raven manual* (1998).
13. Haworth, C. M. A. *et al.* Internet cognitive testing of large samples needed in genetic research. *Twin Res. Hum. Genet.* **10,** 554–63 (2007).
14. Davis, O. S. P., Haworth, C. M. A. & Plomin, R. Learning abilities and disabilities: Generalist genes in early adolescence. *Cogn. Neuropsychiatry* **14,** 312–331 (2009).
15. Lubinski, D., Webb, R. M., Morelock, M. J. & Benbow, C. P. Top 1 in 10,000: A 10-year follow-up of the profoundly gifted. *J. Appl. Psychol.* **86,** 718–729 (2001).
16. Durbin, R. Efficient haplotype matching and storage using the positional Burrows-Wheeler transform (PBWT). *Bioinformatics* **30,** 1266–1272 (2014).
17. Hofman, A. *et al.* The Rotterdam Study: 2016 objectives and design update. *Eur. J. Epidemiol.* **30,** 661–708 (2015).