Childhood intelligence is heritable, highly polygenic and associated with *FNBP1L*

Beben Benyamin[1,2,26], Beate St Pourcain[3,26], Oliver SP Davis[4,26], Gail Davies[5,26], Narelle K Hansell[2], Marie-Jo A Brion[3,6], Robert M Kirkpatrick[7], Rolieke AM Cents[8,9], Sanja Franić[10], Mike B Miller[7], Claire MA Haworth[4], Emma Meaburn[11], Thomas S Price[4], David M Evans[3], Nicholas Timpson[3], John Kemp[3], Sue Ring[3], Wendy McArdle[3], Sarah E Medland[2], Jian Yang[12], Sarah E Harris[13,14], David C Liewald[5,14], Paul Scheet[10], Xiangjun Xiao[15], James J Hudziak[16], Eco JC de Geus[10], Wellcome Trust Case Control Consortium 2 (WTCCC2), Vincent WV Jaddoe[8,17,18], John M Starr[14,19], Frank C Verhulst[9], Craig Pennell[6], Henning Tiemeier[9,17,20], William G Iacono[7], Lyle J Palmer[21,22], Grant W Montgomery[2], Nicholas G Martin[2], Dorret I Boomsma[10], Danielle Posthuma[9,23,24], Matt McGue[7,25], Margie J Wright[2], George Davey Smith[3,27], Ian J Deary[5,14,27], Robert Plomin[4,27] & Peter M Visscher[1,2,12,14,27]

[1]The University of Queensland, Queensland Brain Institute, Qld 4072, Australia

[2]Queensland Institute of Medical Research, Brisbane, Australia

[3]Medical Research Council Centre for Causal Analyses in Translational Epidemiology, University of Bristol, Bristol, UK

[4]Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College, London, UK

[5]Department of Psychology, University of Edinburgh, Edinburgh, Scotland, UK

[6]School of Women's and Infants' Health, The University of Western Australia, Perth, Australia

[7]Department of Psychology, University of Minnesota, US

[8]The Generation R Study Group, Erasmus MC-University Medical Centre Rotterdam, Rotterdam, The Netherlands

[9]Department of Child and Adolescent Psychiatry, Erasmus MC-University Medical Centre Rotterdam, Rotterdam, The Netherlands

[10]Netherlands Twin Register, Department of Biological Psychology, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.

[11]Department of Psychology, Birkbeck University of London, London, UK

[12]The University of Queensland Diamantina Institute, Princess Alexandra Hospital, Brisbane, Australia

[13]Molecular Medicine Centre, Institute for Genetics and Molecular Medicine Centre, University of Edinburgh, Edinburgh, UK
[14]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK
[15]Department of Epidemiology, University of Texas M. D. Anderson Cancer Center, Houston, Texas, US
[16]Department of Psychiatry, College of Medicine, University of Vermont, Burlington
[17]Department of Epidemiology, Erasmus MC-University Medical Centre Rotterdam, Rotterdam, The Netherlands
[18]Department of Pediatrics, Erasmus Medical Center Rotterdam, The Netherlands
[19]Alzheimer Scotland Dementia Research Centre, Department of Psychology, University of Edinburgh, Edinburgh, Scotland, UK
[20]Department of Psychiatry, Erasmus MC-University Medical Centre Rotterdam, Rotterdam, The Netherlands
[21]Genetic Epidemiology and Biostatistics Platform, Ontario Institute for Cancer Research, University of Toronto, Toronto, Canada
[22]Samuel Lunenfeld Research Institute, University of Toronto, Toronto, Canada
[23]Department of Functional Genomics, Center for Neurogenomics and Cognitive Research (CNCR), Neuroscience Campus Amsterdam (NCA), VU University Amsterdam and VU Medical Centre
[24]Department of Clinical Genetics, section Medical Genomics, VU Medical Centre, Amsterdam, The Netherlands
[25]Department of Epidemiology, University of Southern Denmark, Denmark
[26]These authors contributed equally to this work
[27]These authors jointly directed this work

Correspondence: Dr Peter M. Visscher

Queensland Brain Institute, University of Queensland

QBI Building (#79), St Lucia, QLD 4072, Australia

Email: peter.visscher@uq.edu.au

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SUPPLEMENTARY NOTE

The calculation of the average effective sample size from each cohort

As part of the quality controls (QC) procedure, we calculated the average effective sample size (*N*) per cohort as a function of the allele frequency (*p*) and the standard error of the effect size (*se*) from the association test as $N = \frac{1}{m}\sum_{i=1}^{m}\frac{1}{(2p(1-p)se^2 Rsq)}$, where m is the number of SNPs and *Rsq* is the imputation quality score.

This formula was derived from linear regression theory, where the sampling variance of an estimate of a regression coefficient from a model y = m + b*x + e is var(b) = $se^2(b) = \sigma^2 / \Sigma(x^2)$. If y is standardised to unit variance (as in our study), b is small and x a random variable then the sampling variance is approximately 1 / [N*var(x)]. From quantitative genetics theory, the variance of x is 2*p*(1-p), assuming Hardy-Weinberg equilibrium. With imputed data, this variance is reduced by a fraction of Rsq, where Rsq is the imputation accuracy. Hence, in total we get $se^2(b) \sim 1/ [N * Rsq * 2 * p * (1-p)]$. The effective sample size (N) calculated accordingly.

Study Cohort Information

Avon Longitudinal Study of Parents and Children (ALSPAC)

Cohort description: ALSPAC is a population based longitudinal pregnancy-ascertained birth-cohort in the Bristol area of the UK. Specifically, recruitment sought to enrol all pregnant women with an estimated delivery date between 1st April 1991 and 31st December 1992[1], who where residents within three Health Districts of the former administrative county of Avon[2]. The initial cohort included 14,541 pregnancies and additional children eligible using the original enrolment definition were recruited up to the age of 18 years, increasing the total number of pregnancies to 15,247 (4.1% Non-White mothers). Information on the children from these pregnancies is available from questionnaires, clinical assessments, linkage to health and administrative records as well as biological samples including genetic and epigenetic information. Ethical approval was obtained from the ALSPAC Law and Ethics Committee (IRB00003312) and the Local Research Ethics Committees, and written informed consent was provided by all parents.

Intelligence measure: Intelligence in ALSPAC children at the age of 8 years was measured with the Wechsler Intelligence Scale for Children (WISC-III). A short version of the test consisting of alternate items only (except the Coding task) was applied by trained psychologists. Verbal (information, similarities, arithmetic, vocabulary, comprehension) and performance (picture completion, coding, picture arrangement, block design, object assembly) subscales were administered, each subtest was age-scaled according to population norms and a summary score for total IQ derived. Pertinent to this analysis, we generated sex and principal component (i.e. the two most significant principal components from Eigenstrat analysis, see below) adjusted Z-standardised intelligence quotient (IQ) scores for independent ALSPAC children with information on total IQ and genome-wide data. For this, IQ scores within a range of ±4SD relative to the total ALSPAC sample were regressed on sex (coded as 1 = male and 2 = female) and the principal components. The residuals were Z-transformed and subjected to genome-wide analysis.

Quality Controls (QCs): ALSPAC children were genotyped using the Illumina HumanHap550 quad chip genotyping platforms by 23andme subcontracting the Wellcome Trust Sanger Institute, Cambridge, UK and the Laboratory Corporation of America, Burlington, NC, US. The resulting raw genome-wide data were subjected to standard quality control methods. Individuals were excluded on the basis of gender mismatches; minimal or excessive heterozygosity; disproportionate levels of individual missingness (>3%), cryptic relatedness measured as proportion of identity by descent (IBD > 0.1) and insufficient sample replication (IBD < 0.8). The remaining individuals were assessed for evidence of population stratification by multidimensional scaling analysis and compared with Hapmap II (release 22) European descent (CEU), Han Chinese, Japanese and Yoruba reference populations; all individuals with non-European ancestry were removed. Hidden population stratification was thereafter controlled for by using EIGENSTRAT[3] derived ancestry informative principal components scores. SNPs with a minor allele frequency of < 1%, a call rate of < 95% or evidence for violations of Hardy-Weinberg equilibrium (P < 5E-7) were removed.

Statistical analysis/additional information: Genotypic data were subsequently imputed using Markov Chain Haplotyping software (MACH v.1.0.16)[4] and phased haplotype data from CEU individuals (Hapmap release 22, Phase II NCBI B36, dbSNP 126) based on a cleaned dataset of 9545 individuals and 464,311 autosomal SNPs. For the current analysis, the sample was restricted to a subset of 8365 independent individuals with imputed genotypes, 5517 of which also had phenotype data. Assuming an additive genetic disease

model, association analysis was performed on imputed SNP data markers using Mach2QTL (v.108) software.

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Lothian Birth Cohort 1921 (LBC1921)

Cohort description: The LBC1921 is a longitudinal study of healthy ageing, with a focus on cognitive ageing. The sample comprises 550 relatively healthy, community-dwelling individuals and was recruited between 1999 and 2001. Recruitment and testing are fully described elsewhere[5], and a recent cohort profile article[6] describes the data that have been collected to date. They were all born in 1921. Most took part in the Scottish Mental Survey 1932 (SMS1932) which took place on 1st June 1932 and applied the Moray House Test No. 12 (MHT) to almost everyone born in 1921 (95% of the population; N = 87,498)[7, 8]. The SMS1932 was conducted by the Scottish Council for Research in Education, who permitted access to the childhood intelligence data. For the present study, only the childhood MHT scores are used. These were available for 464 subjects, whose mean (SD) age was 10.9 years (0.28) when they sat the test.

Intelligence measure: The measure of general intelligence was the Moray House Test No. 12. This is one of a series of tests of general intelligence devised by Godfrey Thomson at the Moray House College, University of Edinburgh, from the late 1920s onwards. The MHT is a group test of intelligence. It has 71 items and a maximum possible score of 76. It has a time limit of 45 minutes. It was also known as the 'Verbal Test' because the items have a predominance of verbal reasoning. The test has a variety of items, as follows: following directions (14 items), same–opposites (11), word classification (10), analogies (8), practical

items (6), reasoning (5), proverbs (4), arithmetic (4), spatial items (4), mixed sentences (3), cypher decoding (2), and other items (4). Following the SMS1932, 500 boys and 500 girls were tested on the Stanford Revision of the Binet Test, to provide concurrent validity. The MHT-Binet correlations were 0.81 for the boys and 0.78 for the girls[7].

Quality controls: Genotyping was performed with the Illumina Human610_Quadv1 chip at the Wellcome Trust Clinical Research Facility, Edinburgh, UK. The data were then subjected to the following quality control measures, which have been described previously[9]. Individuals were excluded based on unresolved gender discrepancy, relatedness, call rate (≤ 0.95), and evidence of non-Caucasian descent. SNPs were included if they met the following conditions: call rate ≥ 0.98, minor allele frequency ≥ 0.01, and Hardy-Weinberg equilibrium test with $P \geq 0.001$.

Statistical analysis/additional information: Imputation was performed using the MACH software[3] and the CEU reference panel (HAPMAP II rel.23, build 36). Association between the imputed SNPs and childhood intelligence was analysed using dosage scores in an additive model using the MACH2QTL software (V1.0.4)[3].

Acknowledgments for LBC1921 and LBC1936: We thank the cohort participants who contributed to these studies and the team members who assisted with recruitment, testing and data collation and validation. We thank the Scottish Council for Research in Education for allowing access to the Moray House Test data. Genotyping of the ABC1936, LBC1921, and LBC1936 cohorts and the analyses conducted here were supported by the UK's Biotechnology and Biological Sciences Research Council (BBSRC BB/F019394/1). Phenotype collection in the Lothian Birth Cohort 1921 was supported by the BBSRC, The Royal Society, and The Chief Scientist Office of the Scottish Government. Phenotype collection in the Lothian Birth Cohort 1936 was supported by Research Into Ageing (continues as part of Age UK's The Disconnected Mind project). The work was undertaken in The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (G0700704/84698), for which funding from the BBSRC, EPSRC, ESRC and MRC is gratefully acknowledged.

Lothian Birth Cohort 1936 (LBC1936)

Cohort description: The LBC1936 is a longitudinal study of healthy ageing, with a focus on cognitive ageing. The sample of 1091 relatively healthy, community-dwelling individuals was recruited between 2004 and 2007. Recruitment and testing are fully described elsewhere,[5] and a recent cohort profile article[6] describes the data that have been collected to date. They were

all born in 1936. Most took part in the Scottish Mental Survey 1947 (SMS1947) which took place on 4th June 1947 and applied the Moray House Test No. 12 (MHT) to almost everyone born in 1936 (~95% of the population; N = 70,805)[7, 8]. The SMS1947 was conducted by the Scottish Council for Research in Education, who permitted access to the childhood intelligence data. For the present study, only the childhood MHT scores are used. These were available for 947 subjects, whose mean (SD) age was 10.9 years (0.28) when they sat the test.The same MHT was applied to this sample as was described for the LBC1932/SMS1932. Concurrent validity was confirmed by testing over 1000 children on the Terman-Merrill Revision (Form L) of the Binet Test[10]. The MHT-Binet correlation was 0.81 for both the boys and the girls.

Quality controls: Genotyping was performed with the Illumina Human610_Quadv1 chip at the Wellcome Trust Clinical Research Facility, Edinburgh, UK. The data were then subjected to the following quality control measures, which have been described previously[9]. Individuals were excluded based on unresolved gender discrepancy, relatedness, call rate (≤ 0.95), and evidence of non-Caucasian descent. SNPs were included if they met the following conditions: call rate ≥ 0.98, minor allele frequency ≥ 0.01, and Hardy-Weinberg equilibrium test with $P \geq 0.001$.

Statistical analysis/additional information: Imputation was performed using the MACH software[3] and the CEU reference panel (HAPMAP II rel.23, build 36). Association between the imputed SNPs and childhood intelligence was analysed using dosage scores in an additive model using the MACH2QTL software (V1.0.4)[3].

Acknowledgments: See LBC1921.

Brisbane Adolescent Twins Study, Queensland Institute of Medical Research (QIMR) cohort

Cohort description: The Brisbane Adolescent Twin Study cohort[11] is a population sample that supports ongoing studies conducted at the Genetic Epidemiology Laboratory, Queensland Institute of Medical Research (QIMR), Brisbane, on a wide range of traits. IQ data were collected as part of the cognition project[12], which targets twins aged 16 years and their siblings and were available for 1752 individuals (778 families), with a mean age of 16.5 years (±1.0 years, range 15.4-28.9 years). Exclusion criteria were parental or self-report of head injury, neurological or psychiatric illness, substance abuse/dependence, or current use of psychoactive medication in either twin. Written, informed consent was obtained from all participants and from a parent or guardian for those aged under 18 years. Ethics approval was obtained from the Human Research Ethics Committee at QIMR.

Intelligence measure: Full-scale IQ in the QIMR cohort was measured using a shortened version of the computerised Multi-dimensional Aptitude Battery (MAB)[13], a general intelligence test similar to Wechsler Adult Intelligence Scale-Revised. The shortened MAB includes three verbal subtests (information, arithmetic, vocabulary) and two performance subtests (spatial, object assembly). Scaled scores for full-scale IQ were computed in accordance with the manual.

Quality controls: We applied stringent quality controls as described in Medland et al (2009)[14]. In particular we removed SNPs based on missingness (Call Rate < 0.95), minor allele frequency (MAF < 1%), Hardy-Weinberg test (HWE P-value < 10^{-6}), Mendelian errors and the mean value of BeadStudio GeneCall score for Illumina array (GeneCall < 70%). We also excluded subjects of Non-European Ancestry based on principal component analysis.

Statistical analysis/additional information: We imputed unobserved genotypes from the HAPMAP II CEU panel (Release 22, NCBI Build36, dbSNP 126) data using MACH[4] software. We performed association analysis between SNPs and childhood intelligence under an additive model using a family-based test in MERLIN[15].

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Western Australian Pregnancy Cohort (Raine) Study

Cohort description: The Raine study is a prospective pregnancy cohort study of 2,868 live births. Women were recruited between May 1989 and November 1991 (N=2,900) through the public antenatal clinic at King Edward Memorial Hospital (KEMH) and nearby private clinics in Perth, Western Australia. Comprehensive data regarding social and demographic characteristics were collected at 18 and at 34 weeks gestation. Data were collected at birth, including physiological and clinical information, and the study children and their families provided sociodemographic and behavioural data at one, two, three, five, eight, ten, 14 and 17 years of age. Complete details of enrolment methods have been published elsewhere[16]. The Human Ethics Committees at KEMH and/or Princess Margaret Hospital for Children approved the protocols for the study

Intelligence measure: General cognitive ability ('g factor') was estimated based on four cognitive measures carried out at approximately 10 years of age (Peabody Picture Vocabulary Test[17], Raven's Colored Progressive Matrices[18], Symbol Digits Modalities Test (SDMT)[19] written score and SDMT oral score. Principal component analysis was performed using each of the four cognitive measures and the first principal component was used for analyses.

Quality controls: Genotyping was carried out using the Illumina Human660W Quad Array in 1593 children. Individuals were excluded on the basis of gender mismatches (N=7), relatedness (for pairs of individuals with $\pi > 0.1875$ the individual with the higher proportion of missing data was excluded; N=63), low genotyping success (>3% missingness; N=16), and heterozygosity (<0.30; N=4). SNPs with minor allele frequency of <1%, a call rate of <95% or Hardy-Weinberg equilibrium violations (p-values $<5.7 \times 10^{-7}$) were excluded.

Statistical analysis/additional information: Imputation of genotypes was carried out using the CEU samples from Hapmap (Phase 2, Build 36, Release 22) and MACH software (v1.0.16). Association analysis was performed under an additive model using Mach2QTL software.

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Twins of Early Development Study (TEDS)

Cohort description: The Twins Early Development Study (TEDS) is a study of twins born in England and Wales between 1994 and 1996[20]. TEDS twins have participated in a dozen projects over 15 years. The TEDS families are representative of the general population in terms of parental education, ethnicity and employment status[21]. The project has received ethical approval from the appropriate institutional review boards. Parental consent was

obtained for each subject before the testing commenced. Twins with severe medical problems or severe birth complications or whose zygosity could not be determined were excluded from the sample. To help ensure homogeneity of ancestry, the sample was restricted to families who identified themselves as white and whose first language was English. After exclusions the sample with at least one cognitive test available at age 12 was 10,459 individuals (mean age = 11.6, SD = 0.7).

Intelligence measure: Individuals were tested at 12 years using two verbal and two nonverbal measures[22]. Test scores were adjusted for age within each testing period, and first principal component *g* scores were derived using principal component analysis implemented in R. This *g* score was standardized to a mean of 0 and unit variance, and used for the GWAS analysis.

Quality controls (QCs): 3747 DNA samples from unrelated children (one member of a twin pair) were sent for genotyping at the Wellcome Trust Sanger Institute, Hinxton, UK. 3665 samples were successfully hybridized to Affymetrix GeneChip 6.0 SNP genotyping microarrays using standard experimental protocols. Of the individuals genotyped, samples were excluded because of low call rate or heterozygosity outliers, intensity outliers, ancestry outliers, relatedness/duplicates or gender mismatches. Samples were re-genotyped on a panel of 30 SNPs using Sequenom and were excluded because of low concordance (<90%). The remaining samples were consistent with previous genotyping. 2825 of the remaining individuals had *g* phenotype data. SNPs were excluded based on minor allele frequency (MAF < 1%) and Hardy–Weinberg (HWE p-value < 10-6). SNPs with greater probability of a null call were down-weighted in the analysis, thresholding at 0.9.

Statistical analysis/additional information: Imputation was carried out using the IMPUTE2 software on QCed data by a two-stage approach with both a haploid reference panel and a diploid reference panel. For the haploid reference panel we used HapMap2 and HapMap3 SNP data on the 120 unrelated CEU trios. 5175 WTCCC2 controls were genotyped on both Affymetrix 6.0 and Illumina Human1.2M-Duo arrays, and these were used for the diploid reference panel. Association analysis was performed on the dosage score using an additive model in SNPTEST 2.1.1. Covariates were sex and eight principal components from an Eigenstrat analysis.

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The Membership of Wellcome Trust Case Control Consortium 2 Management Committee includes Peter Donnelly (Chair)[1,2], Ines Barroso (Deputy Chair)[3], Jenefer M Blackwell[4, 5], Elvira Bramon[6] , Matthew A Brown[7] , Juan P Casas[8] , Aiden Corvin[9],Panos Deloukas[3], Audrey Duncanson[10], Janusz Jankowski[11], Hugh S Markus[12], Christopher G Mathew[13], Colin NA Palmer[14], Robert Plomin[15], Anna Rautanen[1], Stephen J Sawcer[16], Richard C Trembath[13], Ananth C Viswanathan[17], Nicholas W Wood[18] ; the Data and Analysis Group includes Chris C A Spencer[1], Gavin Band[1], Céline Bellenguez[1], Colin Freeman[1], Garrett Hellenthal[1], Eleni Giannoulatou[1], Matti Pirinen[1], Richard Pearson[1], Amy Strange[1], Zhan Su[1], Damjan Vukcevic[1], Peter Donnelly[1,2]; the DNA, Genotyping, Data QC and Informatics Group includes Cordelia Langford[3], Sarah E Hunt[3], Sarah Edkins[3], Rhian Gwilliam[3], Hannah Blackburn[3], Suzannah J Bumpstead[3], Serge Dronov[3], Matthew Gillman[3], Emma Gray[3], Naomi Hammond[3], Alagurevathi Jayakumar[3], Owen T McCann[3], Jennifer Liddle[3], Simon C Potter[3], Radhi Ravindrarajah[3], Michelle Ricketts[3], Matthew Waller[3], Paul Weston[3], Sara Widaa[3], Pamela Whittaker[3], Ines Barroso[3], Panos Deloukas[3]**;** and the Publications Committee includes Christopher G Mathew (Chair)[13], Jenefer M Blackwell[4,5], Matthew A Brown[7], Aiden Corvin[9], Chris C A Spencer[1]. [1]Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK; [2]Dept Statistics, University of Oxford, Oxford OX1 3TG, UK; [3]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK; [4]Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, 100 Roberts Road, Subiaco, Western Australia 6008; [5]Cambridge Institute for Medical Research, University of Cambridge School of Clinical Medicine, Cambridge CB2 0XY, UK; [6]Department of Psychosis Studies, NIHR Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King's College London and The South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AF, UK; [7]University of Queensland Diamantina Institute, Brisbane, Queensland, Australia; [8]Dept Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London WC1E 7HT and Dept Epidemiology and Public Health, University College London WC1E 6BT, UK; [9]Neuropsychiatric Genetics Research Group, Institute of Molecular Medicine, Trinity College Dublin, Dublin 2, Eire; [10]Molecular and Physiological Sciences, The Wellcome Trust, London NW1 2BE; [11]Department of Oncology, Old Road Campus, University of Oxford, Oxford OX3 7DQ, UK, Digestive

Diseases Centre, Leicester Royal Infirmary, Leicester LE7 7HH, UK and Centre for Digestive Diseases, Queen Mary University of London, London E1 2AD, UK; [12]Clinical Neurosciences, St George's University of London, London SW17 0RE; [13]King's College London Dept Medical and Molecular Genetics, King's Health Partners, Guy's Hospital, London SE1 9RT, UK; [14]Biomedical Research Centre, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK; [15]King's College London Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Denmark Hill, London SE5 8AF, UK; [16]University of Cambridge Dept Clinical Neurosciences, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK; [17]NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London EC1V 2PD, UK; [18]Dept Molecular Neuroscience, Institute of Neurology, Queen Square, London WC1N 3BG, UK.

Generation Rotterdam Study (GenR)

Cohort description: Total n=1458 children with GWAS and IQ data. Total n=16 children with IQ < 70, excluded => n=1442 children with GWAS and IQ data.

Quality controls: Genotyping was performed with the Illumina 610K array. Individuals were removed based on Illumina call rate <97.5%, excess autosomal heterozygosity, mismatch between genotypic and phenotypic gender, outliers identified by the identity-by-state (IBS) clustering analysis and with familial relationships (monozygotic twins or samples done twice). SNPs were excluded when the minor allele frequency was 1% or less, the HWE-pvalue was smaller than 1 x 10(-5), or the SNP call rate was 90% or less.

Intelligence measure: Test = SON-R 2,5-7 (Snijders-Oomen Non-verbal Intelligence Test). The overall IQ score was calculated based on two subtests: Mosaics (performance) and Categories (reasoning). Correlation SON-R with WISC; total IQ 0.62, verbal scale 0.47, performance scale 0.76 (SON manual).

Statistical analysis/additional information: Imputation was performed using the MACH software using HAPMAP II CEU Panel (release 21/22)

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Netherlands Twin Register (NTR)

Cohort description: The YNTR (Young Netherlands Twin Register) is a population-based register of Dutch twins born after 1986, recruited at birth and measured longitudinally at ages 1 through 18[23, 24]. Subsamples of twins are invited to participate in a number of studies, including those on IQ. Studies were approved by the Medical Ethical Committee of the VU Medical Centre, Amsterdam, the Netherlands (IRB00002991).

Quality controls: Blood and/or buccal samples for DNA extraction were collected in the IQ projects. Genotyping was performed on the Affymetrix Human SNP Array 6.0 by the Avera Institute, Sioux Falls, South Dakota (USA). Genotypes were called using the BIRDSEED V2 algorithm from the Affymetrix CEL files. We filtered SNPs based on the following criteria: concordance rate >95%, missing data rate < 95%, minor allele frequency (MAF) < 0.01, Hardy-Weinberg equilibrium (HWE) < 0.00001, and Mendelian incompatibilities (MIs), N>26 or >1.6%. SNPs that passed all 4 criteria were propagated to the imputation stage. Of the 872,242 SNPs before the QC process, 761,750 passed all criteria. Imputation was conducted using the software BEAGLE with the HapMap II release 22 as reference. Post-imputation, SNPs were removed based on minor allele frequency (MAF < 1%) and HWE (p-value < 10-6). Individuals were removed based on heterozygosity, relatedness, Mendelian errors, and population and ethnic outliers (38 individuals in total). Of the remaining individuals, 739 had phenotype and genotype measures available. The gene prediction analysis was performed on unrelated individuals (N=303) only. For the remaining analyses, the entire sample (N=739) was used.

Intelligence measure: Age-appropriate measures were used to longitudinally assess cognitive abilities. These include the Revised Amsterdam Children Intelligence Test (RAKIT), Wechsler Intelligence Scale for Children (WISC), and Wechsler Adult Intelligence Scale (WAIS). Participants were assessed at ages 5, 7, 9, 10, 12, and/or 18 years. For the association analysis, the phenotype was defined as the mean IQ over the different ages. We consider this to be justifiable, given that we had previously analyzed the genetic and environmental

temporal stability of IQ measures in a larger YNTR sample, and found the genetic stability to be high (above .9 at most ages).

Statistical analysis/additional information: The association analysis was performed on dosage scores, using the --offline option in the Merlin software to account for the family structure in the data. Sex was included as a covariate.

Acknowledgments: Genotyping was supported by the NIMH Genomics of Developmental Trajectories in Twins grant (1RC2MH089995-01). The NTR studies were supported by grants from the European Research Council (ERC-230374); NWO: the Netherlands Organization for Scientific Research; ZonMw: the Netherlands Organisation for Health Research and Development and the Neuroscience Campus Amsterdam (NCA). The DETECT (DEvelopmental TrajECtories Twins) consortium consists of JJ Hudziak, R Althoff, D Rettew, E Crehan, (Vermont), P Scheet, X Xiao (Houston), G Davies, E Ehli (South Dakota), DI Boomsma, EJC de Geus, G Willemsen, JJ Hottenga, M Bartels, CEM van Beijsterveldt and M Groen-Blokhuis (Amsterdam).

University of Minnesota Study (UMN)

Cohort description: The Minnesota sample is derived from offspring participants in three separate longitudinal studies undertaken under the auspices of the Minnesota Center for Twin and Family Research (MCTFR): 1) the Minnesota Twin Family Study (MTFS) [25], which consists of two cohorts of twins, age-11 or age-17 at initial assessment, and their parents; 2) the Sibling Interaction and Behavior Study (SIBS)[26], which consists of adolescent adopted and non-adopted offspring and their rearing parents; and 3) the Enrichment Study (ES) [27], which consists of a single cohort of age-11 twins at initial assessment and their parents. Only Caucasian offspring from these three studies were included in the present analysis. Ethnicity was established using a combination of self-report and birth records and confirmed through Eigenstrat analysis[3] as described by Miller et al[28]. IQs were available for 3376 offspring, 2909 of whom were twins (1765 in the younger and 1144 in the older cohort) and the remaining 458 were either adopted or non-adopted offspring from SIBS. The percentage of females in the Minnesota sample was 53.3%, which varied little across the separate samples. The mean (SD) age for the various samples was 11.8 (0.4) for the younger cohort of twins, 17.5 (0.5) for the older cohort of twins, and 15.3 (1.8) for the non-twin sample. The comparable mean (SD) IQ for these three samples was 104.8 (13.6), 99.7 (14.1), and 108.1 (13.6), respectively)

Quality controls: The Minnesota samples were genotyped using the Illumina Hman660W-Quad Array (Illumina, Inc. San Diego, CA) following standard protocols. The genotype data

has undergone rigorous quality control screens as described by Miller et al[28]. Briefly, autosomal markers were eliminated if they: 1) had been identified by Illumina as bad markers, 2) had a call rate < 99%, 3) had a minor allele frequency < 1%, 4) had more than one mismatch in duplicate samples or more than two mendelian inconsistencies across families, 5) deviated from Hardy-Weinberg equilibrium at p < 1e-7, or 6) were significantly associated with plate or participant sex. Samples were eliminated if: 1) they had a call rate < 99%, 2) had Illumina Gen_Call scores suggestive of problems, 3) showed extreme homozygosity or heterozygosity, or 4) we could not confirm familial relationships or sex, suggesting a possible sample mixup. Imputation of untyped markers was undertaken using HapMap2 as the reference sample. Samples were first phased using Beagle[29] taking into account the familial relationships; and then phased using Minimac, an efficient version of MACH[4]. Imputed markers used in the current analysis all had r^2 of .50 or greater.

Intelligence measure: Participants' cognitive ability was measured at their intake assessment, using a short form of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) for participants age 16 or older, or the Wechsler Intelligence Scale for Children-Revised (WISC-R) for those younger than 16. The short-form consisted of two Verbal subtests (information and vocabulary) and two Performance subtests (block design and picture arrangement), selected because performance on these subtests correlates .90 with overall IQ[30]. An estimate of full-scale IQ was determined by prorating the scaled scores for these four subtests.

Statistical analysis/additional information: Individual SNP analysis and the analysis of the aggregate genetic score was undertaken using a Rapid Feasible Generalized Least Squares (RFGLS) algorithm[31], which was developed to efficiently account for the familial clustering in the Minnesota data. In all analysis, covariates included age, sex and the first 10 principal components from an Eigenstrat analysis[3] of the genetic data from the Minnesota Caucasian sample.

Acknowledgments: The collection of the Minnesota data was supported in part by United States Public Health Service grants U01 DA024417, R01 DA005147, R01 DA013240, R01 AA009367, R01 AA011886, and R01 MH066140.

SUPPLEMENTARY TABLES

Supplementary Table 1. Quality controls of the discovery cohorts

Cohort	N	Estimated N (mean±SD)	Total SNPs	Rsq < 0.3	PHWE < 10^{-6}	MAF < .01	Call <0.95	Clean SNPs
ALSPAC	5517	5532±175	2543887	36458	11	75292	0	2450289
LBC21	464	463±25	2543887	44202	N/A	39661	104	2445931
LBC36	947	942±34	2543887	40857	N/A	39221	0	2447226
QIMR	1752(778 families)	1421±91	2383238	0	0	3061	4	2380173
RAINE	936	937±42	2543887	34779	579	52274	478656	2001177
TEDS*	2825	2833±70	2648535	N/A	0	0	0	1721343
Total	12441							

*In addition to the standard quality controls, for the TEDS cohort we removed SNPs if the info statistic (IMPUTE2 imputation package) in TEDS and WTCC2 controls < 0.98 (for SNPs that were imputed from HapMap) and < 0.90 (for SNPs that were imputed from HapMap and WTCC2 controls). We removed 927,192 SNPs following this exclusion.

Supplementary Table 2. The effect size of the top 100 SNPs (discovery + replication cohorts) sorted based on the association P-value. The direction was ordered as QIMR, ALSPAC, LBC21, LBC36, RAINE, TEDS, NTR, GenR, and UMN. 0 indicates that the effect size is zero.

SNP	A1	A2	FREQ_A1	BETA	SE	PMETA	DIRECTION	PHETERO
rs2981205	T	C	0.226	-0.060	0.013	4.5E-06	--+------	0.701
rs6536413	A	C	0.130	-0.075	0.017	6.3E-06	---------	0.301
rs6042314	C	G	0.748	0.058	0.013	6.8E-06	+++++++++	0.541
rs16932667	T	G	0.660	0.052	0.012	7.7E-06	++++-++++	0.160
rs6540731	A	G	0.415	-0.050	0.011	8.6E-06	----+--+-	0.353
rs13387221	A	G	0.187	0.064	0.015	9.3E-06	++++-+-++	0.787
rs716580	A	G	0.566	0.050	0.012	1.3E-05	++++++++-	0.479
rs979201	T	C	0.173	0.062	0.015	1.7E-05	+++++++-+	0.328
rs10785513	T	C	0.380	-0.050	0.012	1.8E-05	---------	0.509
rs17086144	A	T	0.023	0.160	0.037	1.8E-05	++++-+++-	0.237
rs10744753	T	G	0.843	0.068	0.016	2.2E-05	+++++++++	0.396
rs3777376	T	C	0.786	-0.057	0.014	3.0E-05	-------+-	0.851
rs2076540	T	C	0.625	0.049	0.012	3.1E-05	++--++-+-	0.054
rs1257934	A	G	0.324	-0.051	0.012	3.3E-05	------+--	0.596
rs6768702	T	C	0.030	0.136	0.033	3.8E-05	++-+-++++	0.205
rs10803142	A	G	0.537	0.048	0.012	3.8E-05	++++-++++	0.281
rs1880863	A	G	0.476	0.046	0.011	4.5E-05	+++--++++	0.084
rs17646249	A	G	0.119	-0.070	0.017	4.7E-05	------+--	0.956
rs11723566	A	C	0.346	0.047	0.012	5.8E-05	+++-+++++	0.367
rs264737	A	T	0.219	-0.054	0.014	5.9E-05	---+--+0-	0.004
rs9297534	T	C	0.675	0.047	0.012	6.2E-05	-++++++++	0.035
rs13260283	T	G	0.175	0.058	0.015	6.2E-05	++++++-++	0.918
rs4883777	T	C	0.602	-0.045	0.011	7.5E-05	--------+	0.080
rs6098099	A	C	0.926	0.084	0.021	7.9E-05	++++++-++	0.760
rs8039515	T	G	0.446	-0.046	0.012	8.1E-05	--+----+-	0.164
rs12946892	A	G	0.730	0.048	0.012	8.5E-05	++-++++++	0.884
rs860526	T	C	0.558	-0.044	0.011	9.4E-05	------+--	0.877
rs9323783	T	C	0.157	0.060	0.015	9.6E-05	++++++++-	0.639
rs1434095	T	C	0.124	-0.066	0.017	1.0E-04	------+-+	0.631
rs10924380	A	G	0.164	-0.059	0.015	1.1E-04	------+--	0.785
rs7675034	A	G	0.563	0.043	0.011	1.2E-04	++-++++++	0.929
rs6461851	T	C	0.130	-0.063	0.017	1.2E-04	--+-----+	0.183
rs17640975	T	C	0.459	0.043	0.011	1.4E-04	+++++++++	0.637
rs10972628	A	G	0.260	0.049	0.013	1.4E-04	++++++++-	0.037
rs10212266	T	C	0.525	0.042	0.011	1.6E-04	++-+++-++	0.782
rs2805446	T	C	0.189	0.055	0.014	1.6E-04	++++++-+-	0.268
rs672033	T	G	0.121	-0.064	0.017	1.8E-04	--+-+-+--	0.142

rs458275	A	G	0.480	0.042	0.011	1.9E-04	++-+++-+-	0.686
rs4322755	A	G	0.486	-0.043	0.012	2.1E-04	--+-----+	0.424
rs17066681	A	G	0.090	0.073	0.020	2.2E-04	++-+++-+-	0.537
rs1403725	A	G	0.046	-0.101	0.027	2.2E-04	----+---+	0.231
rs922177	T	C	0.208	0.050	0.014	2.5E-04	+++++++++	0.875
rs7104475	T	C	0.470	0.041	0.011	2.5E-04	+++-++-++	0.645
rs1999574	A	G	0.336	0.043	0.012	2.6E-04	+++-++++-	0.454
rs1994497	A	G	0.870	0.060	0.017	2.8E-04	++-+++-++	0.262
rs8015306	A	G	0.541	0.041	0.011	2.9E-04	+++++++++	0.564
rs1093016	T	C	0.674	-0.043	0.012	3.1E-04	+-----+-+	0.155
rs1107154	A	G	0.372	0.042	0.012	3.1E-04	++-++++++	0.088
rs7111329	A	G	0.933	-0.081	0.023	3.2E-04	------++-	0.221
rs11679849	A	G	0.789	-0.052	0.015	3.4E-04	-------+-	0.723
rs8049125	T	C	0.683	-0.045	0.012	3.5E-04	--+---+++	0.081
rs12607920	T	G	0.690	0.044	0.012	3.6E-04	++++-+--+	0.585
rs12645056	T	G	0.785	0.048	0.014	3.9E-04	+++-+++++	0.354
rs7572753	T	C	0.676	0.044	0.012	4.2E-04	++-++++-+	0.741
rs663378	A	G	0.833	-0.052	0.015	4.4E-04	------++-	0.338
rs4833619	T	C	0.338	-0.042	0.012	4.4E-04	------++-	0.331
rs6574598	T	C	0.871	0.058	0.017	4.8E-04	++++++++-	0.222
rs1442398	A	G	0.423	-0.039	0.011	4.8E-04	+-+---++-	0.332
rs6427160	T	C	0.578	0.039	0.011	4.8E-04	+++-++-+-	0.268
rs236330	T	C	0.246	-0.043	0.013	5.4E-04	----+-+-+	0.198
rs3752172	A	G	0.205	-0.050	0.015	6.0E-04	------++-	0.144
rs4723807	A	G	0.295	0.041	0.012	6.4E-04	+++-+++-+	0.311
rs1875067	T	C	0.597	-0.038	0.011	7.4E-04	+-------+	0.414
rs4732154	T	C	0.226	-0.044	0.013	7.6E-04	------+--	0.029
rs4478803	T	C	0.025	0.104	0.031	7.7E-04	++-++++++	0.146
rs9546063	A	G	0.855	-0.056	0.017	8.0E-04	--------+	0.349
rs925037	T	C	0.434	0.038	0.011	8.2E-04	++++++-+-	0.227
rs16974087	T	C	0.901	0.061	0.019	9.6E-04	++++-++--	0.015
rs8045739	T	G	0.919	0.065	0.020	9.9E-04	++-+++-+-	0.048
rs12456203	T	C	0.117	0.057	0.017	1.0E-03	++++++---	0.073
rs17526697	A	G	0.107	-0.054	0.016	1.1E-03	--+---++-	0.353
rs10066520	A	G	0.056	0.079	0.024	1.1E-03	+++++++--	0.135
rs1516194	T	G	0.179	0.048	0.015	1.1E-03	++-+++---	0.204
rs1444067	T	G	0.442	-0.037	0.012	1.2E-03	------++-	0.148
rs922971	T	G	0.240	0.042	0.013	1.3E-03	-++++++-+	0.239
rs13430277	T	C	0.154	0.050	0.016	1.3E-03	+++++---+	0.020
rs12326878	T	G	0.557	-0.036	0.011	1.3E-03	--------+	0.211
rs1421594	A	G	0.349	0.037	0.012	1.5E-03	++++++---	0.485
rs7291469	A	G	0.228	0.043	0.014	1.6E-03	++++-++--	0.299
rs7295162	C	G	0.883	-0.052	0.017	1.8E-03	+------++	0.111
rs10850544	A	G	0.464	-0.036	0.012	1.9E-03	-------++	0.162
rs6663109	A	G	0.135	-0.049	0.016	2.3E-03	------+-+	0.555

rs2392820	A	G	0.279	-0.038	0.012	2.4E-03	--+---++-	0.159
rs17174897	A	C	0.137	0.048	0.016	2.6E-03	+++-0++-+	0.079
rs7462991	T	C	0.921	-0.064	0.021	2.7E-03	--+----+-	0.284
rs6021597	T	C	0.552	0.034	0.012	2.8E-03	++-+++++-	0.001
rs4568137	T	C	0.118	0.051	0.017	3.0E-03	+++-++++-	0.052
rs2839458	A	G	0.035	-0.087	0.030	3.8E-03	---++--++	0.063
rs11040396	C	G	0.075	-0.055	0.019	3.9E-03	--+-+---+	0.035
rs9644921	T	C	0.255	-0.037	0.013	3.9E-03	--+-----+	0.002
rs17600963	A	G	0.191	0.041	0.014	4.7E-03	+++--+---	0.013
rs7678448	T	C	0.797	0.039	0.014	5.7E-03	+++-++++-	0.133
rs5761423	A	G	0.791	-0.038	0.014	6.4E-03	+--+--+++	0.033
rs715827	A	G	0.855	-0.042	0.016	8.1E-03	--+---+-+	0.016
rs1936741	A	C	0.817	0.038	0.014	8.8E-03	+++-++---	0.014
rs7137475	A	G	0.906	-0.050	0.020	1.1E-02	-------++	0.074
rs11005597	T	C	0.953	0.052	0.021	1.2E-02	+++++++-+	0.114
rs2414699	A	G	0.075	-0.050	0.020	1.2E-02	---+--+++	0.024
rs6909266	A	G	0.337	-0.029	0.012	1.3E-02	------+++	0.009
rs7174914	T	C	0.970	-0.065	0.031	3.5E-02	--+---+++	0.135

Supplementary Table 3. Top 20 genes sorted based on P-value from the gene-based analysis in the discovery cohorts (N=12,441) and the corresponding P-values in the replication cohorts

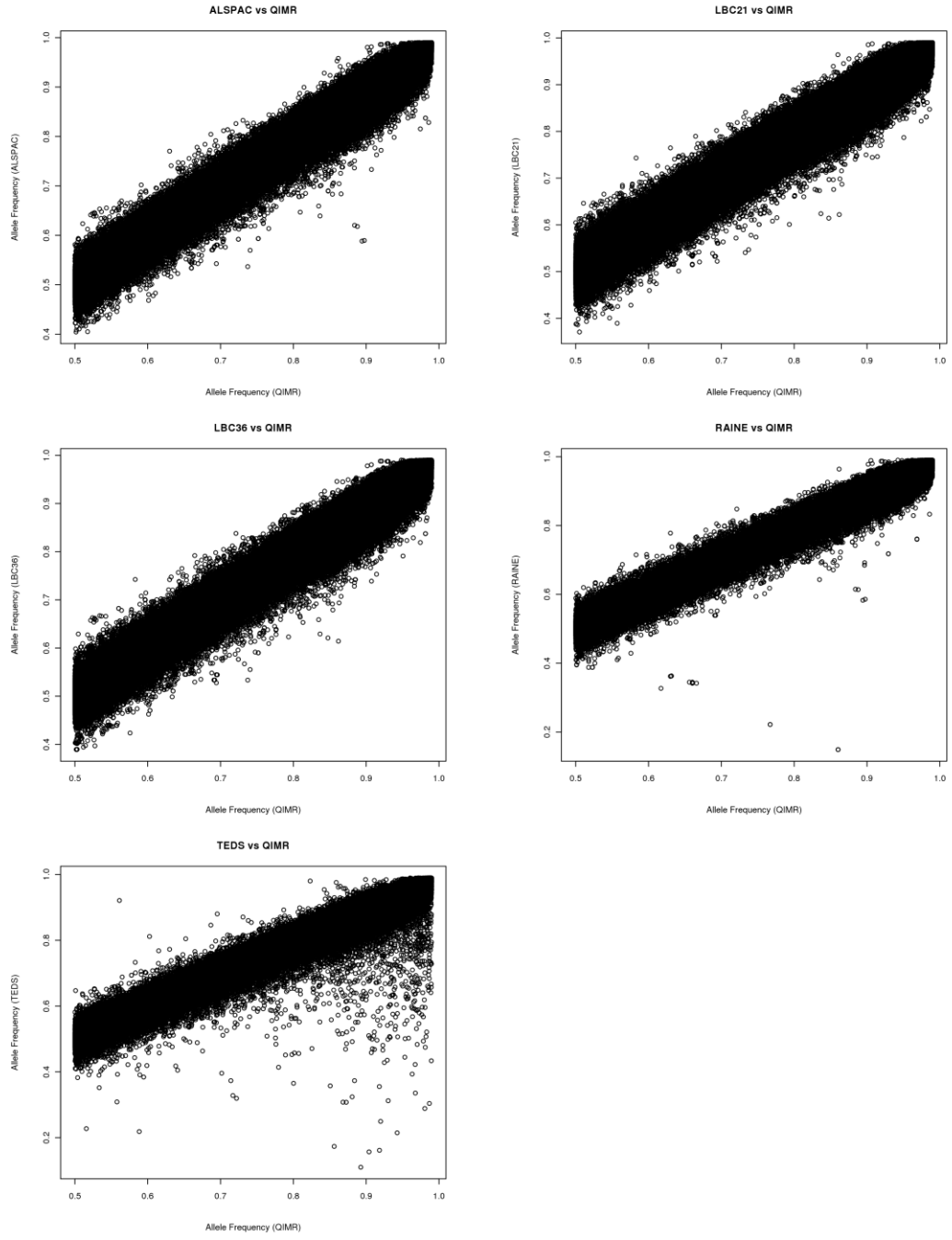
Chr	Gene	Gene-Based P-value			
		Discovery	**GenR (N=1442)**	**NTR (739)**	**UMN (3367)**
1	*FNBP1L*	0.00004	0.073	0.882	0.335
6	*C6orf10*	0.00009	0.006	0.968	0.401
6	*C6orf48*	0.00009	0.018	0.593	0.301
6	*NEU1*	0.00009	0.013	0.561	0.327
6	*SLC44A4*	0.0001	0.021	0.219	0.36
5	*GFRA3*	0.00013	0.755	0.2	0.726
6	*HSPA1B*	0.00015	0.03	0.628	0.259
6	*ZBTB12*	0.00015	0.022	0.041	0.521
6	*EHMT2*	0.00017	0.029	0.053	0.42
15	*GABPB2*	0.00018	0.5	0.169	0.409
6	*HLA-DRB1*	0.0002	0.085	0.621	0.255
1	*TRIT1*	0.00022	0.898	0.186	0.695
4	*YTHDC1*	0.00025	0.835	0.557	0.473
18	*MAPK4*	0.00033	0.579	0.923	0.186
4	*ANAPC4*	0.00034	0.178	0.876	0.129
6	*BTNL2*	0.00039	0.016	0.945	0.487
2	*CALM2*	0.00043	0.71	0.55	0.189
2	*PDIA6*	0.00043	0.565	0.021	0.028
2	*ATP6V1C2*	0.00045	0.485	0.021	0.05
7	*PIP*	0.00045	0.903	0.737	0.85

Supplementary Table 4. Genetic prediction analysis results in three independent replication samples, i.e. GenR, NTR and UMN. R^2 is the proportion of the phenotypic variance in childhood intelligence that was explained by genetic predictors that are derived from selecting SNPs in the meta-analysis at different P-value thresholds.

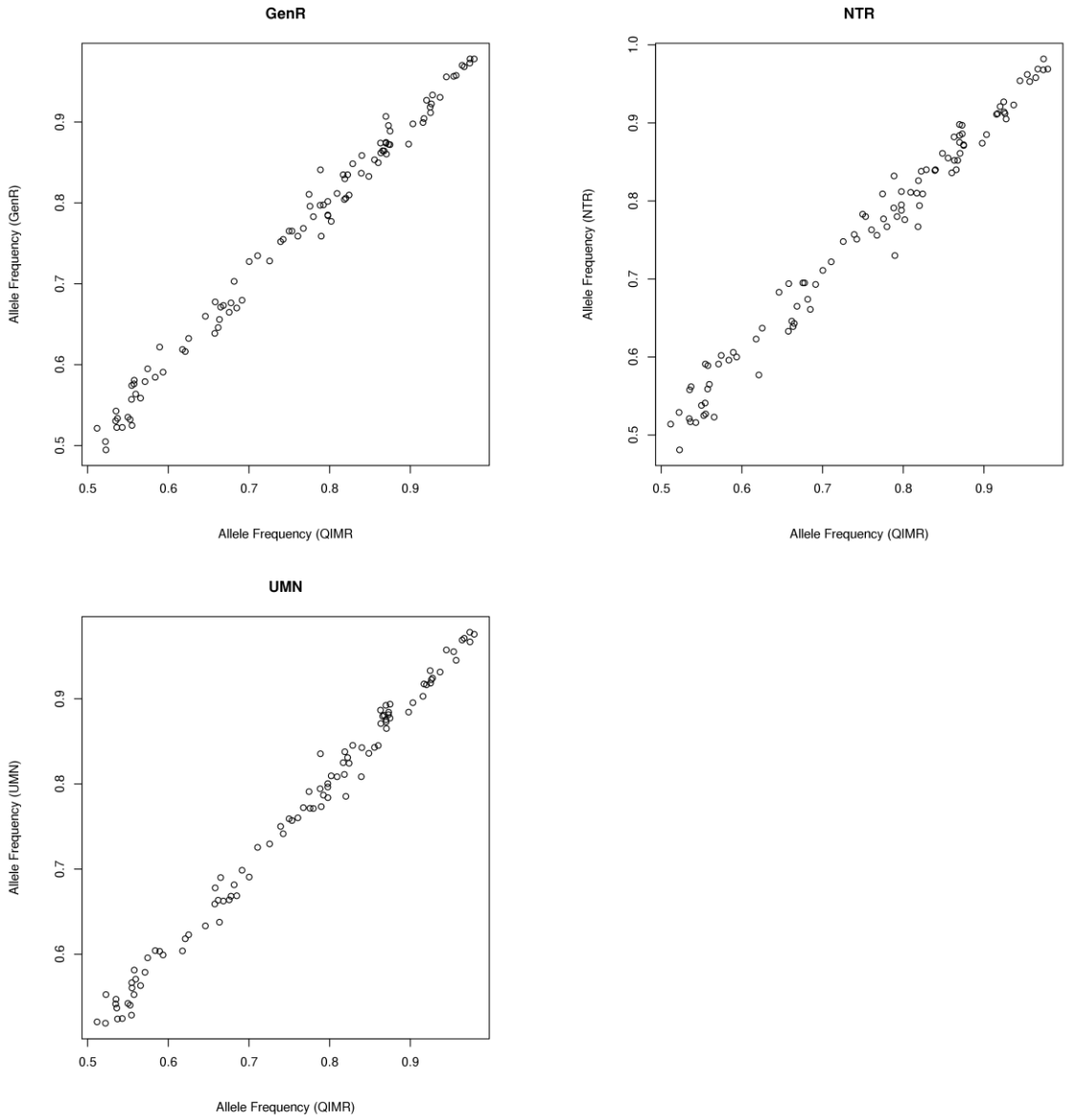
P-value Cut-Off	Number of SNPs	GenR (N = 1,355)		NTR (N = 303)		UMN (N = 3,367)	
		R^2	P-value	R^2	P-value	R^2	P-value
0.001	465	0.003	0.04700	0.022	0.010	0.000	0.96769
0.005	1,842	0.002	0.08600	0.015	0.031	0.001	0.11373
0.01	3,389	0.003	0.03800	0.023	0.008	0.003	0.00196
0.05	13,232	0.010	0.00030	0.033	0.002	0.005	0.00006
0.1	23,637	0.012	0.00006	0.035	0.001	0.004	0.00032
0.25	49,803	0.007	0.00200	0.027	0.004	0.003	0.00066
0.5	84,301	0.008	0.00100	0.020	0.015	0.003	0.00139
1	124,481	0.009	0.00050	0.019	0.016	0.003	0.00164

SUPPLEMENTARY FIGURES

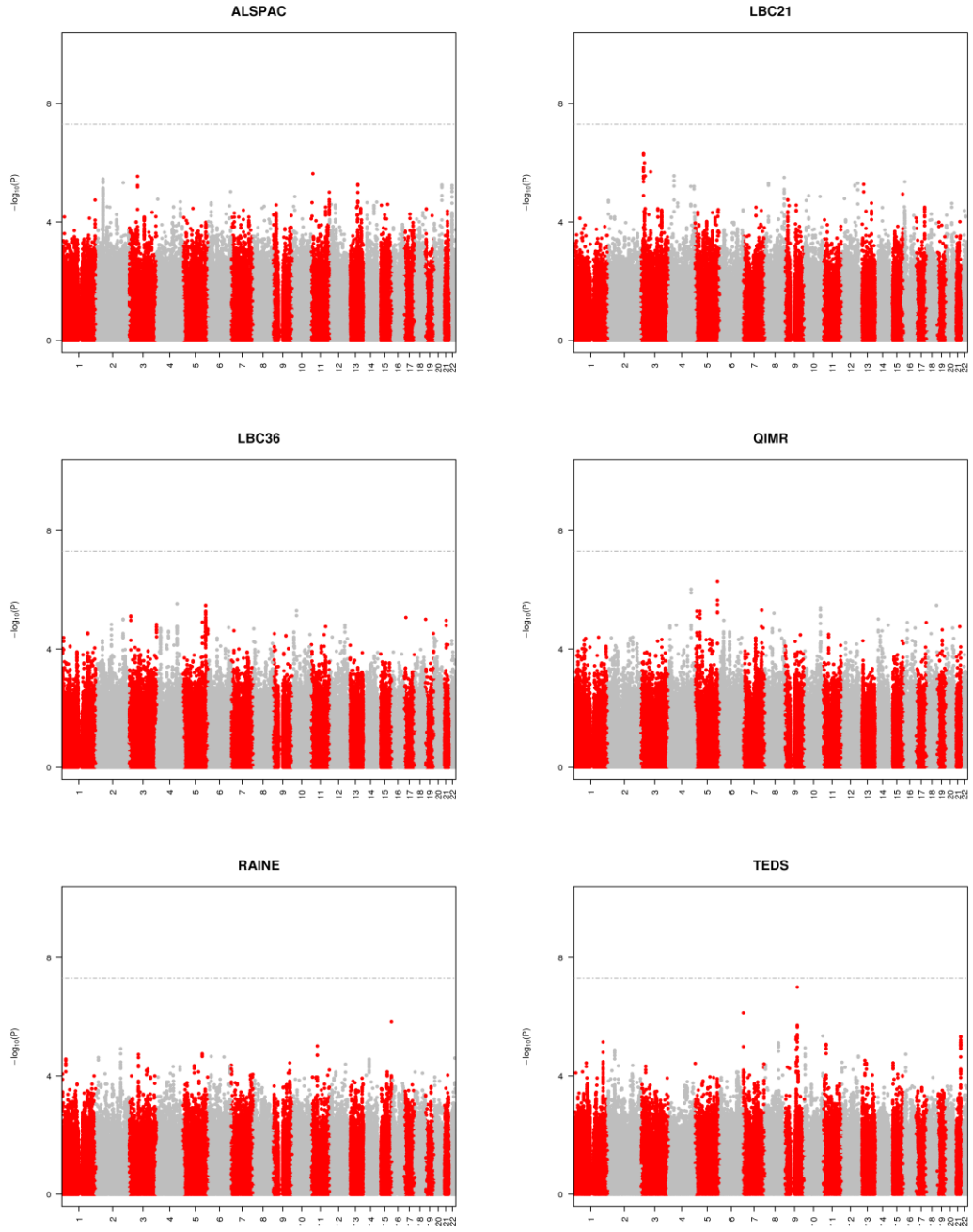
Supplementary Figure 1. Allele frequency between each of the discovery cohorts and the frequency of QIMR cohort. The apparent discrepancy in a small proportion of SNPs in TEDS cohort may be due to TEDS being the only sample using Affymetrix chip rather than Illumina chip.



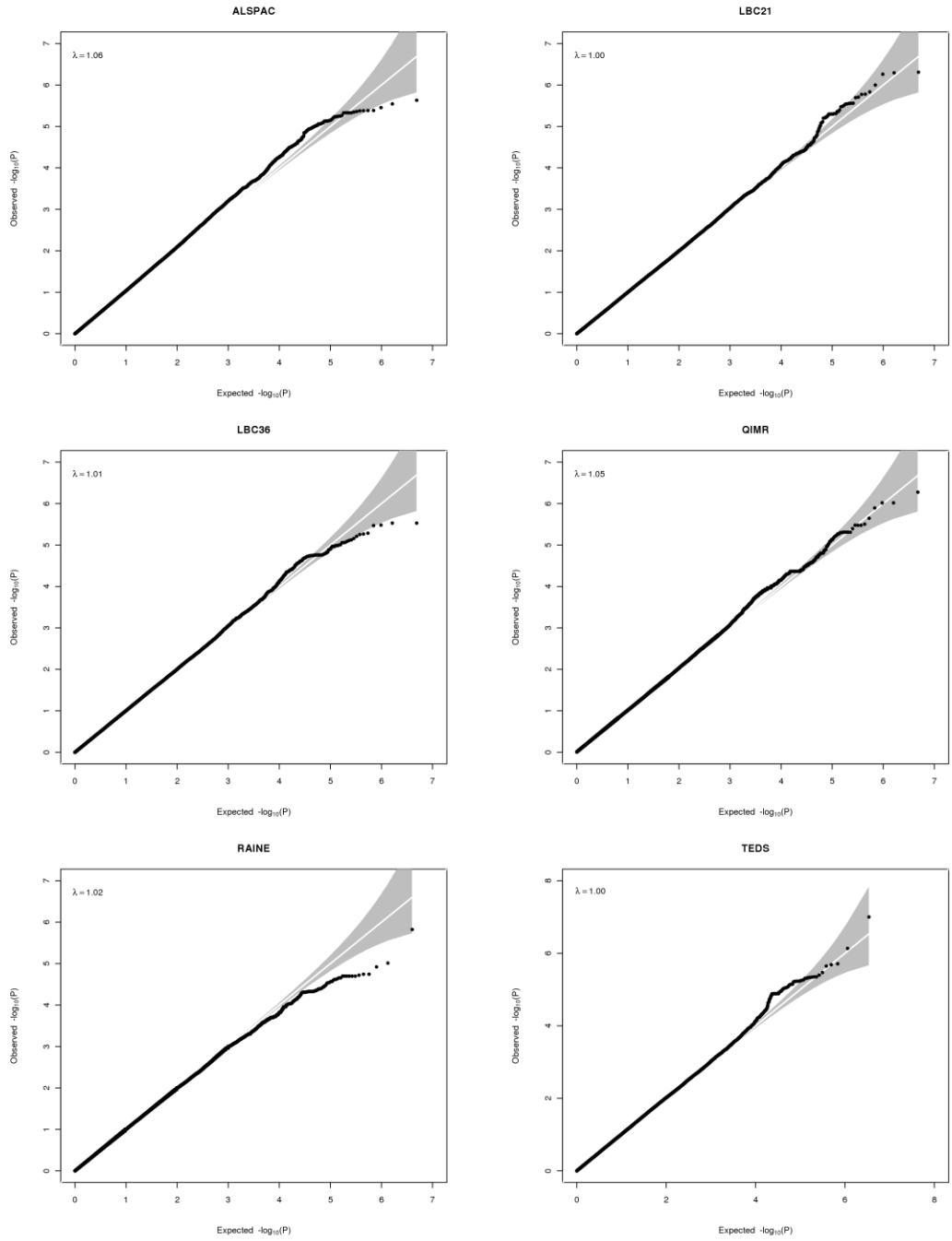
Supplementary Figure 2. Allele frequency between each of the replication cohorts and the frequency of QIMR cohort.



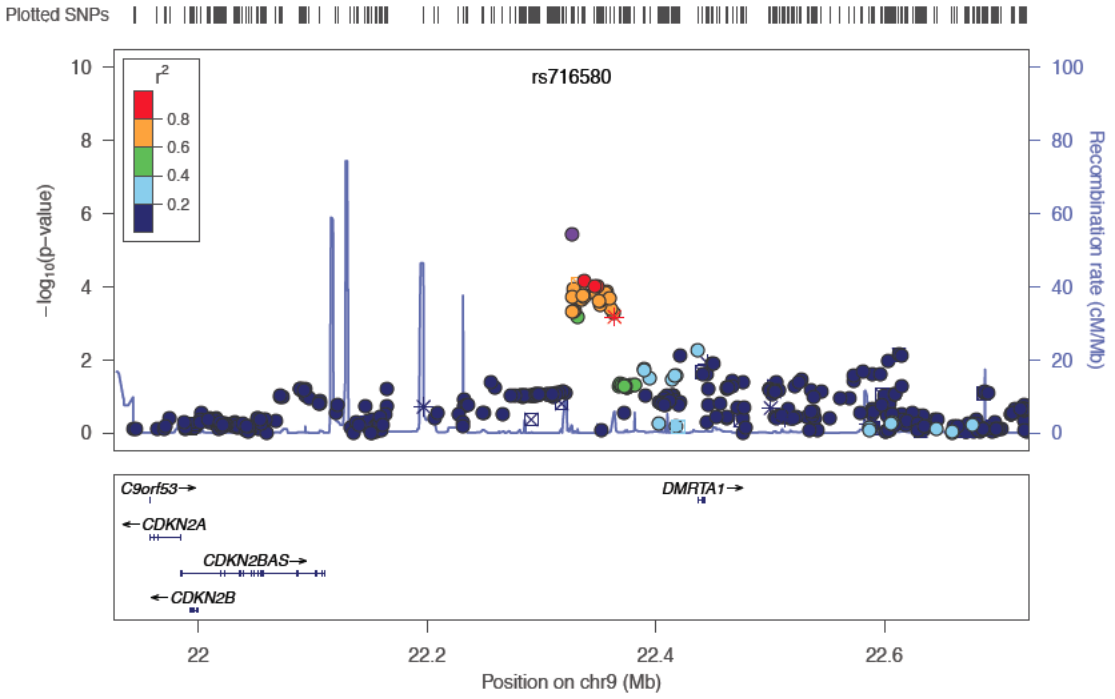
Supplementary Figure 3. Manhattan plots of the discovery cohorts



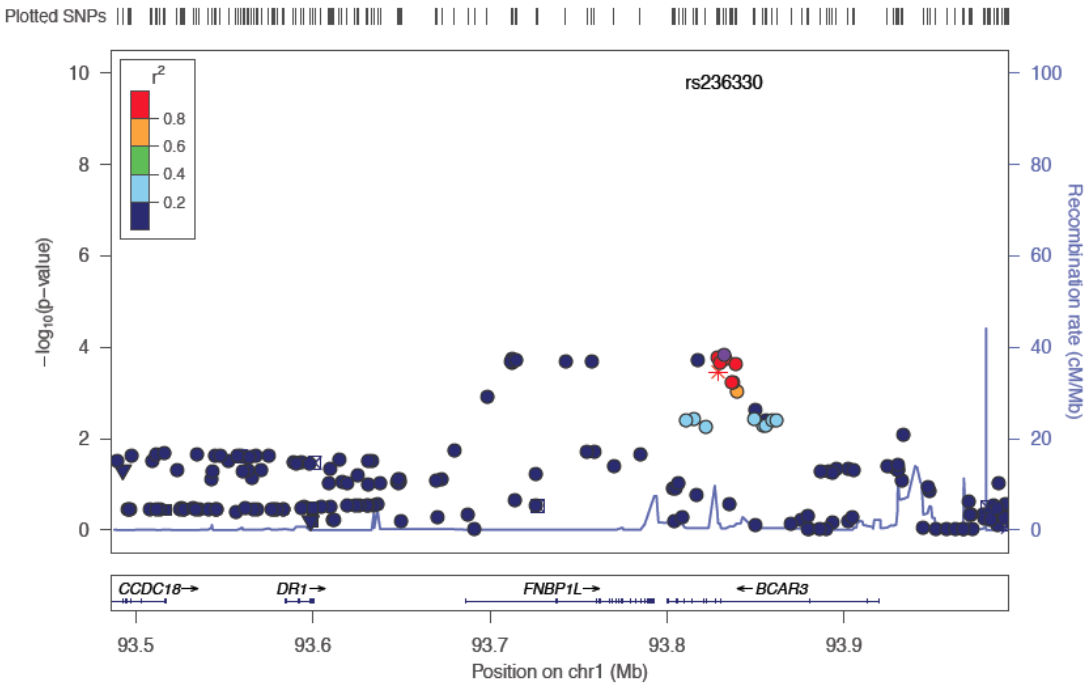
Supplementary Figure 4. QQ plots of the discovery cohorts



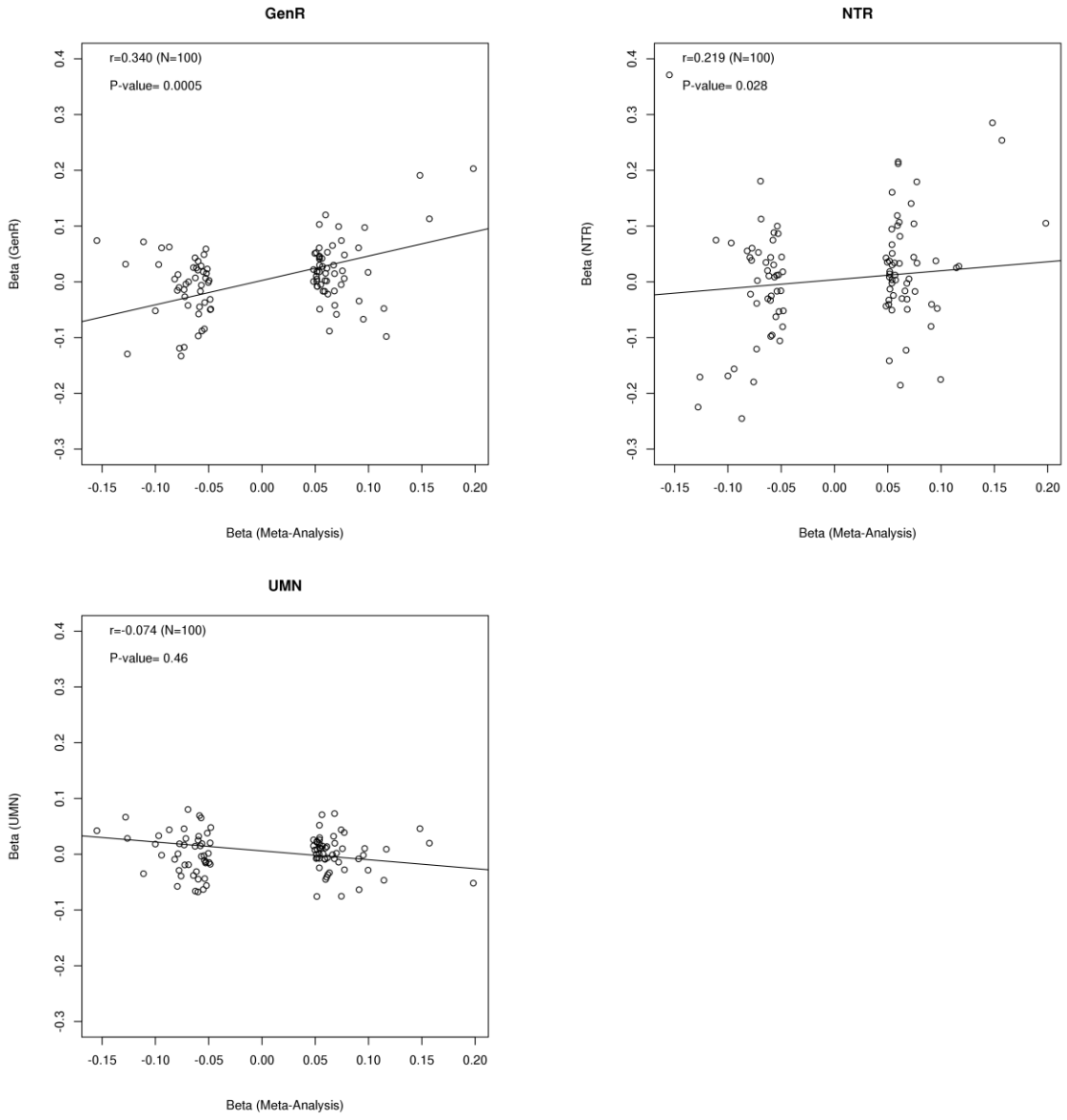
Supplementary Figure 5. Association P-values around the most significantly associated SNP in the meta-analysis of the discovery cohorts



Supplementary Figure 6. Association P-values around *FNBP1L*, the most significantly associated gene from gene-based analysis



Supplementary Figure 7. Effect size from the meta-analysis of the discovery cohorts vs the replication cohorts



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