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Authors: Rietveld CA, Medland SE, Derringer J, Yang J, Esko T, Martin NW, Westra HJ, Shakhbazov K, Abdellaoui A, Agrawal A, Albrecht E, Alizadeh BZ, Amin N, Barnard J, Baumeister SE, Benke KS, Bielak LF, Boatman JA, Boyle PA, Davies G, de Leeuw C, Eklund N, Evans DS, Ferhmann R, Fischer K, Gieger C, Gjessing HK, Hägg S, Harris JR, Hayward C, Holzapfel C, Ibrahim-Verbaas CA, Ingelsson E, Jacobsson B, Joshi PK, Jugessur A, Kaakinen M, Kanoni S, Karjalainen J, Kolcic I, Kristiansson K, Kutalik Z, Lahti J, Lee SH, Lin P, Lind PA, Liu Y, Lohman K, Loitfelder M, McMahon G, Vidal PM, Meirelles O, Milani L, Myhre R, Nuotio ML, Oldmeadow CJ, Petrovic KE, Peyrot WJ, Polasek O, Quaye L, Reinmaa E, Rice JP, Rizzi TS, Schmidt H, Schmidt R, Smith AV, Smith JA, Tanaka T, Terracciano A, van der Loos MJ, Vitart V, Völzke H, Wellmann J, Yu L, Zhao W, Allik J, Attia JR, Bandinelli S, Bastardot F,

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GWAS of 126,559 Individuals Identifies Genetic Variants Associated with Educational Attainment

Cornelius A. Rietveld[1,2], Sarah E. Medland[3], Jaime Derringer[4], Jian Yang[5], Tõnu Esko[6], Nicolas W. Martin[3,7], Harm-Jan Westra[8], Konstantin Shakhbazov[5,9], Abdel Abdellaoui[10], Arpana Agrawal[11], Eva Albrecht[12], Behrooz Z. Alizadeh[13], Najaf Amin[14], John Barnard[15], Sebastian E. Baumeister[16], Kelly S. Benke[17], Lawrence F. Bielak[18], Jeffrey A. Boatman[19], Patricia A. Boyle[20], Gail Davies[21], Christiaan de Leeuw[22], Niina Eklund[24,25], Daniel S. Evans[26], Rudolf Ferhmann[8], Krista Fischer[6], Christian Gieger[12], Håkon K. Gjessing[27], Sara Hägg[28,29,30], Jennifer R. Harris[27], Caroline Hayward[31], Christina Holzapfel[32,33], Carla A. Ibrahim-Verbaas[14,34], Erik Ingelsson[28,29,30], Bo Jacobsson[27,35], Peter K. Joshi[36], Astanand Jugessur[27], Marika Kaakinen[37,38], Stavroula Kanoni[39], Juha Karjalainen[8], Ivana Kolcic[40], Kati Kristiansson[24,25], Zoltán Kutalik[41,42], Jari Lahti[43], Sang H. Lee[3], Peng Lin[11], Penelope A. Lind[3], Yongmei Liu[44], Kurt Lohman[45], Marisa Loitfelder[46], George McMahon[47], Pedro Marques Vidal[48], Osorio Meirelles[49], Lili Milani[6], Ronny Myhre[27], Marja-Liisa Nuotio[24,25], Christopher J. Oldmeadow[50], Katja E. Petrovic[51], Wouter J. Peyrot[52], Ozren Polašek[40], Lydia Quaye[53], Eva Reinmaa[6], John P. Rice[11], Thais S. Rizzi[22], Helena Schmidt[54], Reinhold Schmidt[46], Albert V. Smith[55,56], Jennifer A. Smith[18], Toshiko Tanaka[49], Antonio Terracciano[49,57], Matthijs J.H.M. van der Loos[1,2], Veronique Vitart[31], Henry Völzke[16], Jürgen Wellmann[58], Lei Yu[20], Wei Zhao[18], Jüri Allik[59], John R. Attia[50], Stefania Bandinelli[60], François Bastardot[61], Jonathan Beauchamp[62], David A. Bennett[20], Klaus Berger[58], Laura J. Bierut[11], Dorret I. Boomsma[10], Ute Bültmann[63], Harry Campbell[36], Christopher F. Chabris[64], Lynn Cherkas[53], Mina K. Chung[15], Francesco Cucca[65,66], Mariza de Andrade[67], Philip L. De Jager[68], Jan-Emmanuel De Neve[69,70], Ian J. Deary[21,71], George V. Dedoussis[72], Panos Deloukas[39], Maria Dimitriou[72], Gudny Eiriksdottir[55], Martin F. Elderson[73], Johan G. Eriksson[74,75,76,77], David M. Evans[78], Jessica D. Faul[79], Luigi Ferrucci[49], Melissa E. Garcia[49], Henrik Grönberg[30], Vilmundur Gudnason[55,56], Per Hall[30], Juliette M. Harris[53], Tamara B. Harris[49], Nicholas D. Hastie[31], Andrew C. Heath[80], Dena G. Hernandez[49], Wolfgang Hoffmann[16], Adriaan Hofman[81], Rolf Holle[83], Elizabeth G. Holliday[50], Jouke-Jan Hottenga[10], William G. Iacono[82], Thomas Illig[33,84], Marjo-Riitta Järvelin[37,38,85,86,87], Mika Kähönen[88], Jaakko Kaprio[24,89,90], Robert M. Kirkpatrick[82], Matthew Kowgier[91], Antti Latvala[89,90], Lenore J. Launer[49], Debbie A. Lawlor[78], Terho Lehtimäki[92], Jingmei Li[93], Paul Lichtenstein[30], Peter Lichtner[94], David C. Liewald[21], Pamela A. Madden[11], Patrik K. E. Magnusson[30], Tomi E. Mäkinen[95], Marco Masala[65], Matt McGue[82], Andres Metspalu[6], Andreas Mielck[83], Michael B. Miller[82], Grant W. Montgomery[3], Sutapa Mukherjee[96,97,98], Dale R. Nyholt[3], Ben A. Oostra[14], Lyle J. Palmer[91], Aarno Palotie[24,39,99], Brenda Penninx[52], Markus Perola[24,25,6], Patricia A. Peyser[18], Martin Preisig[61], Katri Räikkönen[43], Olli T. Raitakari[100,101], Anu Realo[59], Susan M. Ring[47], Samuli

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[1]Department of Applied Economics, Erasmus School of Economics, Erasmus University Rotterdam, 3000 DR Rotterdam, The Netherlands [2]Department of Epidemiology, Erasmus Medical Center, Rotterdam 3000 CA, The Netherlands [3]Queensland Institute of Medical Research, 300 Herston Road, Brisbane, Queensland 4006, Australia [4]Institute for Behavioral Genetics, University of Colorado Boulder, Boulder, CO 80309–0447, USA [5]University of Queensland Diamantina Institute, The University of Queensland, Princess Alexandra Hospital, Brisbane, Queensland 4102, Australia [6]Estonian Genome Center, University of Tartu, Tartu 51010, Estonia [7]School of Psychology, University of Queensland, Brisbane, Queensland 4072, Australia [8]Department of Genetics, University Medical Center Groningen, University of Groningen, 9713 GZ Groningen, The Netherlands [9]Queensland Brain Institute, The University of Queensland, Brisbane, Queensland 4072, Australia [10]Department of Biological Psychology, VU University Amsterdam, 1081 BT Amsterdam, The Netherlands [11]Department of Psychiatry, Washington University School of Medicine, St. Louis, MO 63110, USA [12]Institute of Genetic Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, 85764 Neuherberg, Germany [13]Department of Epidemiology, University Medical Center Groningen, University of Groningen, 9700 RB Groningen, The Netherlands [14]Genetic Epidemiology Unit, Department of Epidemiology, Erasmus Medical Center, Rotterdam 3000 CA, the Netherlands [15]Heart and Vascular and Lerner Research Institutes, Cleveland Clinic, Cleveland, OH 44195, USA [16]Institute for Community Medicine, University Medicine Greifswald, Greifswald 17489, Germany [17]Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Ontario M5G 1X5, Canada [18]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI 48109–2029, USA [19]Division of Biostatistics, University of Minnesota, Minneapolis, MN 55455, USA [20]Rush University Medical Center, Rush Alzheimer's Disease Center, Chicago, IL 60612, USA [21]Centre for Cognitive Aging and Cognitive Epidemiology, The University of Edinburgh, Edinburgh EH8 9JZ, Scotland, UK [22]Department of Functional Genomics, VU University Amsterdam and VU Medical Center, 1081 HV Amsterdam, The Netherlands [23]Machine Learning Group, Intelligent Systems, Institute for Computing and Information Sciences, Faculty of Science, Radboud University Nijmegen, 6500 GL Nijmegen, The Netherlands [24]Institute for Molecular Medicine Finland, University of Helsinki, Helsinki 00014, Finland [25]Public Health Genomics Unit, Department of Chronic Disease Prevention, The National Institute for Health and Welfare, Helsinki 00014, Finland [26]California Pacific Medical Center Research Institute, San Francisco, CA 94107–1728, USA [27]Department of Genes and Environment, Division of Epidemiology, Norwegian Institute of Public Health, Nydalen, N-0403 Oslo, Norway [28]Molecular Epidemiology, Department of Medical Sciences, Uppsala University, 751 85 Uppsala, Sweden [29]Science for Life Laboratory, Department of Medical Biochemistry and Microbiology, Uppsala University, 751 23 Uppsala, Sweden [30]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, 171 77 Stockholm, Sweden [31]Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh EH4 2XU, UK

[32]Else Kroener-Fresenius-Centre for Nutritional Medicine, Technische Universität München, 81675 Munich, Germany [33]Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, 85764 Neuherberg, Germany [34]Department of Neurology, Erasmus Medical Center, Rotterdam 3000 CA, The Netherlands [35]Department of Obstetrics and Gynecology, Institute of Public Health, Sahlgrenska Academy, Sahgrenska University Hospital, Gothenburg, 413 45, Sweden [36]Centre for Population Health Sciences, The University of Edinburgh, Edinburgh EH8 9AG, UK [37]Institute of Health Sciences, University of Oulu, Oulu 90014, Finland [38]Biocenter Oulu, University of Oulu, Oulu 90014, Finland [39]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton CB10 1SA, UK [40]Faculty of Medicine, University of Split, 21000 Split, Croatia [41]Department of Medical Genetics, University of Lausanne, 1005 Lausanne, Switzerland [42]Swiss Institute of Bioinformatics, 1015 Lausanne, Switzerland [43]Institute of Behavioral Sciences, University of Helsinki, Helsinki 00014, Finland [44]Department of Epidemiology & Prevention, Division of Public Health Sciences, Wake Forest University Health Sciences, Winston-Salem, NC 27157–1063, USA [45]Department of Biostatistical Sciences, Division of Public Health Sciences, Wake Forest University Health Sciences, Winston-Salem, NC 27157–1063, USA [46]Division for Neurogeriatrics, Department of Neurology, Medical University of Graz, Graz 8036, Austria [47]School of Social and Community Medicine, University of Bristol, Bristol BS8 2PR, UK [48]Institute of Social and Preventive Medicine, Lausanne University Hospital, 1005 Lausanne, Switzerland [49]National Institute on Aging, National Institutes of Health, Baltimore, MD 20892, USA [50]Hunter Medical Research Institute and Faculty of Health, University of Newcastle, Newcastle, NSW 2308, Australia [51]Division of General Neurology, Department of Neurology, General Hospital and Medical University of Graz, Graz 8036, Austria [52]Department of Psychiatry, VU University Medical Center, 1081 HL Amsterdam, The Netherlands [53]Department of Twin Research and Genetic Epidemiology, King's College London, London SE1 7EH, UK [54]Institute of Molecular Biology and Biochemistry, Medical University of Graz, Graz 8036, Austria [55]Icelandic Heart Association, Kopavogur 201, Iceland [56]Department of Medicine, University of Iceland, Reykjavik 101, Iceland [57]College of Medicine, Florida State University, Tallahassee, FL 32306–4300, USA [58]Institute of Epidemiology and Social Medicine, University of Muenster, 48129 Muenster, Germany [59]Department of Psychology, University of Tartu, Tartu 50410, Estonia [60]Geriatric Unit, Azienda Sanitaria Firenze, 50125 Florence, Italy [61]Department of Internal Medicine, University Hospital, 1011 Lausanne, Switzerland [62]Department of Economics, Harvard University, Cambridge, MA 02138, USA [63]Department of Health Sciences, Community & Occupational Medicine, University Medical Center Groningen, 9700 AD Groningen, The Netherlands [64]Department of Psychology, Union College, Schenectady, NY 12308, USA [65]Istituto di Ricerca Genetica e Biomedica, CNR, Monserrato, 09042, Cagliari, Italy [66]Dipartimento di Scienze Biomediche, Università di Sassari, 07100 SS, Italy [67]Department of Health Sciences Research, Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN 55905, USA [68]Program in Translational Neuropsychiatric Genomics, Department of Neurology, Brigham and Women's Hospital, Boston, MA 02115, USA [69]School of Public Policy, University College London, London WC1H 9QU, UK [70]Centre for Economic Performance, London School of Economics, London WC2A 2AE, UK [71]Department of Psychology, The University of Edinburgh, Edinburgh EH8 9JZ, Scotland, UK [72]Department of Nutrition and Dietetics, Harokopio University of Athens, Athens 17671, Greece [73]LifeLines Cohort Study, University of Groningen, University Medical Center Groningen, 9700 RB Groningen, The Netherlands [74]Department of General Practice and Primary Health Care, University of Helsinki, Helsinki 00014, Finland [75]Unit of General Practice, Helsinki University Central Hospital, Helsinki 00280, Finland [76]Folkhälsan Research Center, Helsinki 00250, Finland [77]Vaasa Central Hospital, Vaasa 65130, Finland [78]MRC Centre for Causal Analyses in Translational Epidemiology, School of Social and Community Medicine, University of Bristol, Bristol BS8 2PR, UK [79]Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI 48106, USA [80]Division of Biology and Biomedical Sciences, Washington University, St. Louis, MO 63110–

1093, USA [81]Faculty of Behavioral and Social Sciences, University of Groningen, 9747 AD Groningen, The Netherlands [82]Department of Psychology, University of Minnesota, Minneapolis, MN 55455–0344, USA [83]Institute of Health Economics and Health Care Management, Helmholtz Zentrum München, German Research Center for Environmental Health, 85764 Neuherberg, Germany [84]Hannover Unified Biobank, Hannover Medical School, 30625 Hannover, Germany [85]Department of Epidemiology and Biostatistics, MRC-HPA Centre for Environment and Health, Imperial College London, London W2 1PG, UK [86]Unit of Primary Care, Oulu University Hospital, Oulu 90220, Finland [87]Department of Children and Young People and Families, National Institute for Health and Welfare, Oulu 90101, Finland [88]Department of Clinical Physiology, Tampere University Hospital and University of Tampere School of Medicine, Tampere 33520, Finland [89]Department of Public Health, University of Helsinki, 00014 Helsinki, Finland [90]Department of Mental Health and Substance Abuse Services, National Institute for Health and Welfare, 00300 Helsinki, Finland [91]Ontario Institute for Cancer Research, Toronto, Ontario M5G 0A3, Canada [92]Department of Clinical Chemistry, Fimlab Laboratories, Tampere University Hospital, Tampere 33520, Finland [93]Human Genetics, Genome Institute of Singapore, Singapore 138672, Singapore [94]Institute of Human Genetics, Helmholtz Centre Munich, German Research Center for Environmental Health, 85764 Neuherberg, Germany [95]Department of Health, Functional Capacity and Welfare, National Institute for Health and Welfare, Helsinki 00271, Finland [96]Western Australia Sleep Disorders Research Institute, Sir Charles Gairdner Hospital, Perth, Western Australia 6009, Australia [97]Department of Medicine, University of Toronto, Toronto, Ontario M5S 1A8, Canada [98]Women's College Research Institute, University of Toronto, Toronto, Ontario M5G 1N8, Canada [99]Department of Medical Genetics, University of Helsinki, 00014 Helsinki, Finland [100]Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku 20520, Finland [101]Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku 20520, Finland [102]Department of Internal Medicine, Erasmus Medical Center, Rotterdam 3000 CA, The Netherlands [103]Department of Economics, University of Minnesota, Minneapolis, MN 55455–0462, USA [104]Chronic Disease Epidemiology Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki 00271, Finland [105]School of Oral and Dental Sciences, University of Bristol, Bristol BS1 2LY, UK [106]Alzheimer Scotland Dementia Research Centre, The University of Edinburgh, Edinburgh EH8 9JZ, Scotland, UK [107]Department of Computer Science, University of California, Los Angeles, CA 90095, USA [108]Department of Economics, Oulu Business School, University of Oulu, Oulu 90014, Finland [109]Interfaculty Institute for Genetics and Functional Genomics, Department of Functional Genomics, University Medicine Greifswald, Greifswald 17487, Germany [110]Department of Child and Adolescent Psychiatry, Erasmus Medical Center, 3000 CB Rotterdam, The Netherlands [111]Division of Welfare and Health Promotion, National Institute for Health and Welfare, Helsinki 00271, Finland [112]Department of Medicine, Turku University Hospital, Turku 20520, Finland [113]Institute of Medical Informatics, Biometry and Epidemiology, Chair of Epidemiology, Ludwig-Maximilians-Universität, 81377 Munich, Germany [114]Klinikum Grosshadern, 81377 Munich, Germany [115]Institute of Epidemiology I, Helmholtz Zentrum München, German Research Centre for Environmental Health, 85764 Neuherberg, Germany [116]Department of Sociology, New York University, New York, NY 10012, USA [117]Department of Economics, Harvard University, Cambridge, MA 02138, USA [118]Petrie-Flom Center for Health Law Policy, Biotechnology, & Bioethics, Harvard Law School, Cambridge, MA 02138, USA [119]Nelson A. Rockefeller Institute of Government, State University of New York, Albany, NY 12203–1003, USA [120]Department of Clinical Genetics, VU University Medical Centrer, 1081 BT Amsterdam, The Netherlands [121]Econometric Institute, Erasmus School of Economics, Erasmus University Rotterdam, Rotterdam 3000 DR, The Netherlands [122]Department of Economics, Stockholm School of Economics, Stockholm 113 83, Sweden [123]Panteia, Zoetermeer 2701 AA, Netherlands [124]GSCM-Montpellier Business School, Montpellier 34185, France [125]Centre for Medical Systems Biology, Leiden University Medical Center, 2300 RC Leiden, The Netherlands [126]Department of

Economics, Cornell University, Ithaca, NY 14853, USA [127]Center for Experimental Social Science, Department of Economics, New York University, New York, NY 10012, USA [128]Division of Social Science, New York University Abu Dhabi, PO Box 129188, Abu Dhabi, UAE [129]Research Institute of Industrial Economics, Stockholm 102 15, Sweden

Abstract

A genome-wide association study of educational attainment was conducted in a discovery sample of 101,069 individuals and a replication sample of 25,490. Three independent SNPs are genome-wide significant (rs9320913, rs11584700, rs4851266), and all three replicate. Estimated effects sizes are small ($R^2 \approx 0.02\%$), approximately 1 month of schooling per allele. A linear polygenic score from all measured SNPs accounts for $\approx 2\%$ of the variance in both educational attainment and cognitive function. Genes in the region of the loci have previously been associated with health, cognitive, and central nervous system phenotypes, and bioinformatics analyses suggest the involvement of the anterior caudate nucleus. These findings provide promising candidate SNPs for follow-up work, and our effect size estimates can anchor power analyses in social-science genetics.

Twin and family studies suggest that a broad range of psychological traits (1), economic preferences (2–4), and social and economic outcomes (5) are moderately heritable. Discovery of genetic variants associated with such traits leads to insights regarding the biological pathways underlying human behavior. If the predictive power of a set of genetic variants considered jointly is sufficiently large, then a "risk score" that aggregates their effects could be useful to control for genetic factors that are otherwise unobserved, or to identify populations with certain genetic propensities, for example in the context of medical intervention (6).

To date, however, few if any robust associations between specific genetic variants and social-scientific outcomes have been identified likely because existing work [for review see (7)] has relied on samples that are too small [for discussion, see (4, 6, 8, 9)]. In this paper, we apply to a complex behavioral trait—educational attainment—an approach to gene discovery that has been successfully applied to medical and physical phenotypes (10), namely meta-analyzing data from multiple samples. The phenotype of educational attainment is available in many samples with genotyped subjects (5). Educational attainment is influenced by many known environmental factors, including public policies. Educational attainment is strongly associated with social outcomes, and there is a well-documented health-education gradient (5, 11). Estimates suggest that around 40% of the variance in educational attainment is explained by genetic factors (5). Furthermore, educational attainment is moderately correlated with other heritable characteristics (1), including cognitive function (12) and personality traits related to persistence and self-discipline (13).

To create a harmonized measure of educational attainment, we coded study-specific measures using the International Standard Classification of Education (ISCED 1997) scale (14). We analyzed a quantitative variable defined as an individual's years of schooling (*EduYears*) and a binary variable for college completion (*College*). *College* may be more comparable across countries, whereas *EduYears* contains more information about individual differences within countries.

A genome-wide association study (GWAS) meta-analysis was performed across 42 cohorts in the discovery phase. The overall discovery sample comprises 101,069 individuals for *EduYears* and 95,427 for *College*. Analyses were performed at the cohort level according to a pre-specified analysis plan, which restricted the sample to Caucasians (to help reduce

stratification concerns). Educational attainment was measured at an age at which subjects were very likely to have completed their education [over 95% of the sample was at least 30; (5)]. On average, subjects have 13.3 years of schooling, and 23.1% have a college degree. To enable pooling of GWAS results, all studies conducted analyses with data imputed to the HapMap 2 CEU (r22.b36) reference set. To guard against population stratification, the first four principal components of the genotypic data were included as controls in all the cohort-level analyses. All study-specific GWAS results were quality controlled, cross-checked, and meta-analyzed using single genomic control and a sample-size weighting scheme at three independent analysis centers.

At the cohort level, there is little evidence of general inflation of p-values. As in previous GWA studies of complex traits (15), the Q-Q plot of the meta-analysis exhibits strong inflation. This inflation is not driven by specific cohorts and is expected for a highly polygenic phenotype even in the absence of population stratification (16).

From the discovery phase, we identified one genome-wide significant locus (rs9320913, $p = 4.2 \times 10^{-9}$) and three suggestive loci (defined as $p < 10^{-6}$) for *EduYears*. For *College*, we identified two genome-wide significant loci (rs11584700, $p = 2.1 \times 10^{-9}$, and rs4851266, $p = 2.2 \times 10^{-9}$) and an additional four suggestive loci (Table 1). We conducted replication analyses in 12 additional, independent cohorts that became available after the completion of the discovery meta-analysis, using the same pre-specified analysis plan. For both *EduYears* and *College*, the replication sample comprises 25,490 individuals.

For each of the ten loci that reached at least suggestive significance, we brought forward for replication the SNP with the lowest p-value. The three genome-wide significant SNPs replicate at the Bonferroni-adjusted 5% level, with point estimates of the same sign and similar magnitude (Fig. 1 and Table 1). The seven loci that did not reach genome-wide significance did not replicate (the effect went in the anticipated direction in 5 out of 7 cases). The meta-analytic findings are not driven by extreme results in a small number of cohorts (see p_{het} in Table 1), by cohorts from a specific geographic region (figs. S7 to S15), or by a single sex (figs. S3 to S6). Given the high correlation between *EduYears* and *College* (5), it is unsurprising that the set of SNPs with low p-values exhibit considerable overlap in the two analyses (tables S8 and S9).

The observed effect sizes of the three replicated individual SNPs are small [see (5) for discussion]. For *EduYears*, the strongest effect identified (rs9320913) explains 0.022% of phenotypic variance in the replication sample. This R^2 corresponds to a difference of ~1 months of schooling per allele. For college completion, the SNP with the strongest estimated effect (rs11584700) has an odds ratio of 0.912 in the replication sample, equivalent to a 1.8 percentage-point difference per allele in the frequency of completing college.

We subsequently conducted a "combined stage" meta-analysis, including both the discovery and replication samples. This analysis revealed additional genome-wide significant SNPs: four for *EduYears* and three for *College*. Three of these newly genome-wide significant SNPs (rs1487441, rs11584700, rs4851264) are in linkage disequilibrium with the replicated SNPs. The remaining four are located in different loci and warrant replication attempts in future research: rs7309, a 3′UTR variant in *TANK*; rs11687170, close to *GBX2*; rs1056667, a 3′UTR variant in *BTN1A1*; and rs13401104 in *ASB18*.

Using the results of the combined meta-analyses of discovery and replication cohorts, we conducted a series of complementary and exploratory supplemental analyses to aid in interpreting and contextualizing the results: gene-based association tests; eQTL analyses of brain and blood tissue data; pathway analysis; functional annotation searches; enrichment analysis for cell-type-specific overlap with H3K4me3 chromatin marks; and predictions of

likely gene function using gene-expression data. Table S20 summarizes promising candidate loci identified through follow-up analyses (5). Two regions in particular showed convergent evidence from functional annotation, blood cis-eQTL analyses, and gene-based tests: chromosome 1q32 (including *LRRN2*, *MDM4*, and *PIK3C2B*) and chromosome 6 near the Major Histocompatibility Complex (MHC). We also find evidence that in anterior caudate cells, there is enrichment of H3K4me3 chromatin marks (believed to be more common in active regulatory regions) in the genomic regions implicated by our analyses (fig. S20). Many of the implicated genes have previously been associated with health, central nervous system, or cognitive-process phenotypes in either human-GWAS or model-animal studies (table S22). Gene co-expression analysis revealed that several implicated genes (including *BSN*, *GBX2*, *LRRN2*, and *PIK3C2B*) are likely involved in pathways related to cognitive processes (such as learning and long-term memory) and neuronal development or function (table S21).

Although the effects of individual SNPs on educational attainment are small, many of their potential uses in social science depend on their combined explanatory power. To evaluate the combined explanatory power, we constructed a linear polygenic score (5) for each of our two education measures using the meta-analysis results (combining discovery and replication), excluding one cohort. We tested these scores for association with educational attainment in the excluded cohort. We constructed the scores using SNPs whose nominal *p*-values fall below a certain threshold, ranging from 5×10^{-8} (only the genome-wide significant SNPs were included) to 1 (all SNPs were included).

We replicated this procedure with two of the largest cohorts in the study, both of which are family-based samples (QIMR and STR). The results suggest that educational attainment is a highly polygenic trait (Fig. 2 and table S23): the amount of variance accounted for increases as the *p*-value threshold becomes less conservative (i.e., includes more SNPs). The linear polygenic score from all measured SNPs accounts for $\approx 2\%$ ($p = 1.0 \times 10^{-29}$) of the variance in *EduYears* in the STR sample and $\approx 3\%$ ($p = 7.1 \times 10^{-24}$) in the QIMR sample.

To explore one of the many potential mediating endophenotypes, we examined how much the same polygenic scores (constructed to explain *EduYears* or *College*) could explain individual differences in cognitive function. While it would have been preferable to explore a richer set of mediators, this variable was available in STR, a dataset where we had access to the individual-level genotypic data. Cognitive function had been measured in a subset of males using the Swedish Enlistment Battery (used for conscription) (5, 17). The estimated $R^2 \approx 2.5\%$ ($p < 1.0 \times 10^{-8}$) for cognitive function is actually slightly larger than the fraction of variance in educational attainment captured by the score in the STR sample. One possible interpretation is that some of the SNPs used to construct the score matter for education through their stronger, more direct effects on cognitive function (5). A mediation analysis (table S24) provides tentative evidence consistent with this interpretation.

The polygenic score remains associated with educational attainment and cognitive function in within-family analyses (table S25). Thus, these results appear robust to possible population stratification.

If the size of the training sample used to estimate the linear polygenic score increased, the explanatory power of the score in the prediction sample would be larger because the coefficients used for constructing the score would be estimated with less error. In (5), we report projections of this increase. We also assess, at various levels of explanatory power, the benefits from using the score as a control variable in a randomized educational intervention (5). An asymptotic upper bound for the explanatory power of a linear polygenic score is the additive genetic variance across individuals captured by current SNP

microarrays. Using combined data from STR and QIMR, we estimate that this upper bound is 22.4% (*S.E.* = 4.2%) in these samples (5) (table S12).

Placed in the context of the GWAS literature (10), our largest estimated SNP effect size of 0.02% is over an order of magnitude smaller than those observed for height and BMI: 0.4% (15) and 0.3% (18) respectively. While our linear polygenic score for education achieves an R^2 of 2% estimated from a sample of 120,000, a score for height reached 10% estimated from a sample of 180,000 (15), and a score for BMI using only the top 32 SNPs reached 1.4% (18). Taken together, our findings suggest that the genetic architecture of complex behavioral traits is far more diffuse than that of complex physical traits.

Existing claims of "candidate gene" associations with complex social-science traits have reported widely varying effect sizes—many with R^2 values more than one hundred times larger than those we find (4, 6). For complex social-science phenotypes that are likely to have a genetic architecture similar to educational attainment, our estimate of 0.02% can serve as a benchmark for conducting power analyses and evaluating the plausibility of existing findings in the literature.

The few GWAS studies conducted to date in social-science genetics have not found genome-wide significant SNPs that replicate consistently (19, 20). One commonly proposed solution is to gather better measures of the phenotypes in more environmentally homogenous samples. Our findings demonstrate the feasibility of a complementary approach: identify a phenotype that, although more distal from genetic influences, is available in a much larger sample [see (5) for a simple theoretical framework and power analysis]. The genetic variants uncovered by this "proxy-phenotype" methodology can then serve as a set of empirically-based candidate genes in follow-up work, such as tests for associations with well-measured endophenotypes (e.g., personality, cognitive function), research on gene-environment interactions, or explorations of biological pathways.

In social-science genetics, researchers must be especially vigilant to avoid misinterpretations. One of the many concerns is that a genetic association will be mischaracterized as "the gene for X," encouraging misperceptions that genetically influenced phenotypes are immune to environmental intervention [for rebuttals, see (21, 22)] and misperceptions that individual SNPs have large effects (which our evidence contradicts). If properly interpreted, identifying SNPs and constructing polygenic scores are steps toward usefully incorporating genetic data into social-science research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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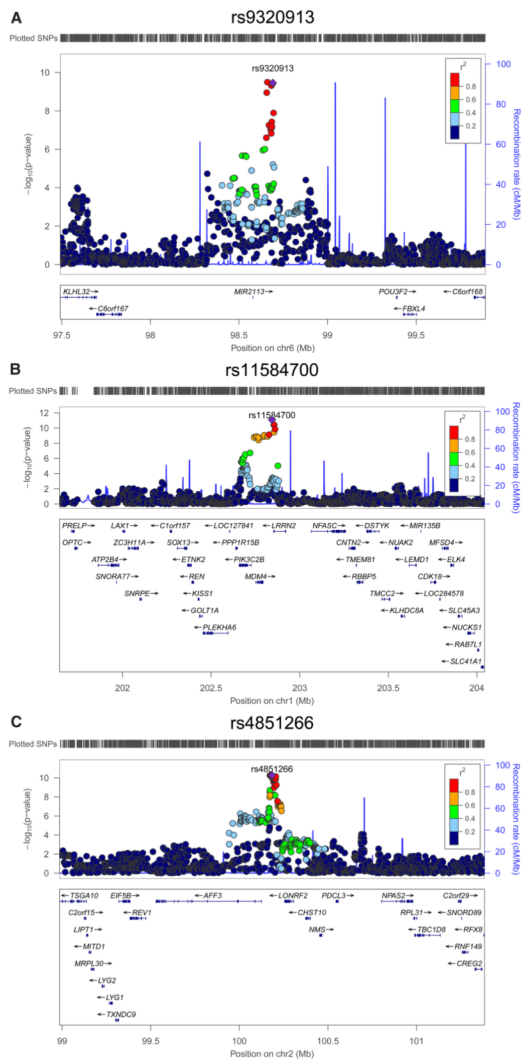
Fig. 1.
Regional association plots of replicated loci associated with educational attainment [(**A**): rs9320913, (**B**): rs11584700, (**C**): rs4851266]. The plots are centered on the SNPs with the lowest p-values in the discovery stage (purple diamond). The R^2 values are from the CEU HapMap 2 samples. The CEU HapMap 2 recombination rates are indicated with a blue line on the right-hand y-axis. The figures were created with LocusZoom (http://csg.sph.umich.edu/locuszoom/).

Fig. 2.
Solid lines show results from regressions of *EduYears* on linear polygenic scores in a set of unrelated individuals from the QIMR ($N = 3526$) and STR ($N = 6770$) cohorts. Dashed lines show results from regressions of *Cognitive function* on linear polygenic scores in a sample from STR ($N = 1419$). The scores are constructed from the meta-analysis for either *EduYears* or *College*, excluding the QIMR and STR cohorts.
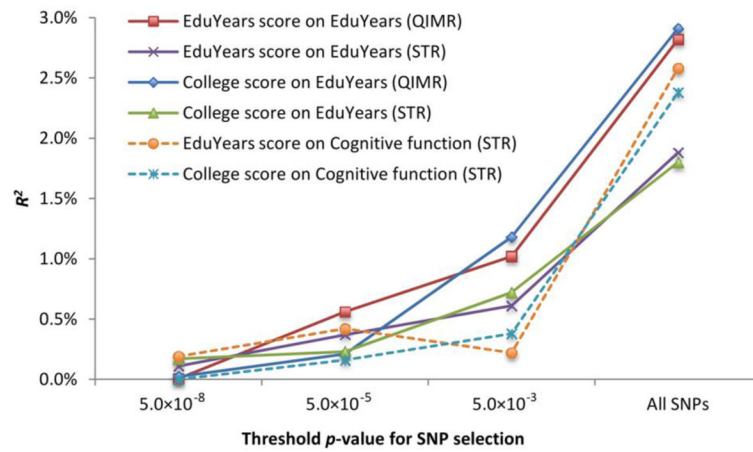
Table 1

The results of the GWAS meta-analysis for the independent signals reaching $p < 10^{-6}$ in the discovery stage.

SNP	Chr	Position (bp)	Nearest gene	Effective allele	Frequency	Discovery stage				Replication stage		Combined stage			Combined stage – sex-specific			
						Beta/OR	P-value	I^2	P_{het}	Beta/OR	P-value	Beta/OR	P-value	P_{het}	Beta/OR (Males)	P-value (Males)	Beta/OR (Females)	P-value (Females)
						EduYears												
rs9320913	**6**	**98691454**	**LOC100129158**	A	**0.483**	**0.106**	**4.19×10^{-9}**	**18.3**	**0.097**	**0.077**	**0.012**	**0.101**	**3.50×10^{-10}**	**0.350**	**0.095**	**1.87×10^{-4}**	**0.100**	**1.43×10^{-6}**
rs3783006	13	97909210	STK24	C	0.454	0.096	2.29×10^{-7}	0	0.982	0.056	0.055	0.088	8.45×10^{-8}	0.959	0.064	1.44×10^{-2}	0.108	3.35×10^{-7}
rs8049439	16	28745016	ATXN2L	T	0.581	0.090	7.12×10^{-7}	10.7	0.229	0.065	0.026	0.086	1.15×10^{-7}	0.205	0.097	1.43×10^{-4}	0.078	1.90×10^{-4}
rs1318378	5	101958587	SLCO6A1	A	0.878	−0.136	7.49×10^{-7}	0	0.791	0.091	0.914	−0.097	1.37×10^{-4}	0.646	−0.134	8.21×10^{-3}	−0.080	5.92×10^{-3}
						College												
rs11584700	**1**	**202843606**	**LRRN2**	A	**0.780**	**0.921**	**2.07×10^{-9}**	**13.8**	**0.179**	**0.912**	**4.86×10^{-4}**	**0.919**	**8.24×10^{-12}**	**0.221**	**0.934**	**6.11×10^{-4}**	**0.911**	**2.12×10^{-9}**
rs4851266	**2**	**100184911**	**LOC150577**	T	**0.396**	**1.050**	**2.20×10^{-9}**	**23.7**	**0.049**	**1.049**	**0.003**	**1.050**	**5.33×10^{-11}**	**0.072**	**1.054**	**1.55×10^{-5}**	**1.052**	**6.74×10^{-8}**
rs2054125	2	19909366	PLCL1	T	0.064	1.468	5.55×10^{-8}	7	0.325	1.098	0.225	1.376	2.12×10^{-7}	0.268	1.264	1.74×10^{-2}	1.503	1.95×10^{-7}
rs3227	6	3370273	ITPR3	C	0.498	1.043	6.02×10^{-8}	5	0.363	1.010	0.280	1.037	3.24×10^{-7}	0.415	1.046	9.44×10^{-5}	1.029	1.37×10^{-3}
rs4073894	7	104254200	LHFPL3	A	0.207	1.076	4.41×10^{-7}	0	0.765	1.003	0.467	1.062	5.55×10^{-6}	0.513	1.050	2.18×10^{-2}	1.073	1.74×10^{-5}
rs12640626	4	176863266	GPM6A	A	0.580	1.041	4.94×10^{-7}	10.9	0.234	1.000	0.495	1.034	7.48×10^{-6}	0.420	1.038	1.59×10^{-3}	1.031	7.61×10^{-4}

The rows in bold are the independent signals reaching $p < 5 \times 10^{-8}$ in the discovery stage. "Frequency" refers to allele-frequency in the discovery stage. "Beta/OR" refers to the effect size in the *EduYears* analysis and to the Odds Ratio in the *College* analysis. All p-values are from the sample-size-weighted meta-analysis (fixed effects). The p-value in the replication stage meta-analysis was calculated from a one-sided test. I^2 represents the % heterogeneity of effect size between the discovery stage studies. P_{het} is the heterogeneity p-value.