Title: Genome-wide association study identifies 74 loci associated with educational attainment

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Summary: Educational attainment (EA) is strongly influenced by social and other environmental factors, but genetic factors are also estimated to account for at least 20% of the variation across individuals\(^1\). We report the results of a genome-wide association study (GWAS) for EA that extends our earlier discovery sample\(^1,2\) of 101,069 individuals to 293,723 individuals, and a replication in an independent sample of 111,349 individuals from the UK Biobank. We now identify 74 genome-wide significant loci associated with number of years of schooling completed. Single-nucleotide polymorphisms (SNPs) associated with educational attainment are disproportionately found in genomic regions regulating gene expression in the fetal brain. Candidate genes are preferentially expressed in neural tissue, especially during the prenatal period, and enriched for biological pathways involved in neural development. Our findings demonstrate that, even for a behavioral phenotype that is mostly environmentally determined, a well-powered GWAS identifies replicable associated genetic variants that suggest biologically relevant pathways. Because EA is measured in large numbers of individuals, it will continue to be useful as a proxy phenotype in efforts to characterize the genetic influences of related phenotypes, including cognition and neuropsychiatric disease.

Main Text:

We study educational attainment (EA), which is measured in all main analyses as the number of years of schooling completed (\(EduYears\), \(N = 293,723\), mean = 14.33, SD = 3.61; Supplementary Information sections 1.1-1.2). All genome-wide association studies (GWAS) were performed at the cohort level in samples restricted to individuals of European descent whose EA was assessed at or above age 30. A uniform set of quality-control (QC) procedures
was applied to the cohort-level summary statistics. In our GWAS meta-analysis of ~9.3M SNPs from the 1000 Genomes Project, we used sample-size weighting and applied a single round of genomic control at the cohort level.

Our meta-analysis identified 74 approximately independent genome-wide significant loci. For each locus, we define the “lead SNP” as the SNP in the genomic region that has the smallest $P$-value (Supplementary Information section 1.6.1). Fig. 1 shows a Manhattan plot with the lead SNPs highlighted. The three SNPs that reached genome-wide significance in the discovery stage of our previous GWAS meta-analysis of EA$^1$ are also highlighted. The quantile-quantile (Q-Q) plot of the meta-analysis (Extended Data Fig. 1) exhibits inflation ($\lambda_{GC} = 1.28$), as expected under polygenicity$^3$.

Extended Data Fig. 2 shows the estimated effect sizes of the lead SNPs. The estimates range from 0.014 to 0.048 standard deviations per allele (2.7 to 9.0 weeks of schooling), with incremental $R^2$ in the range 0.01% to 0.035%.

To quantify the amount of population stratification in the GWAS estimates that remains even after the stringent controls used by the cohorts (Supplementary Information section 1.4), we used LD Score regression$^4$. The regression results indicate that ~8% of the observed inflation in the mean $\chi^2$ is due to bias rather than polygenic signal (Extended Data Fig. 3a), suggesting that stratification effects are small in magnitude. We also found evidence that the genetic association signals taken as a whole replicate reliably in several within-family analyses (Supplementary Information section 2 and Extended Data Fig. 3b).

To further test the robustness of our findings, we examined the within-sample and out-of-sample replicability of SNPs reaching genome-wide significance (Supplementary Information sections 1.7-1.8). We found that SNPs identified in the previous EA meta-analysis replicated in the new cohorts included here, and conversely, that SNPs reaching genome-wide
significance in the new cohorts replicated in the old cohorts. For the out-of-sample replication analyses of our 74 lead SNPs, we used the interim release of the U.K. Biobank $^5$ (UKB) ($N = 111,349$). As shown in Extended Data Fig. 4, 72 out of the 74 lead SNPs have a consistent sign ($P = 1.47 \times 10^{-19}$), 52 are significant at the 5% level ($P = 2.68 \times 10^{-50}$), and 7 reach genome-wide significance in the U.K. Biobank dataset ($P = 1.41 \times 10^{-42}$). For comparison, the corresponding expected numbers, assuming each SNP’s true effect size is its estimated effect adjusted for the winner’s curse, are 71.4, 40.3, and 0.6. (Supplementary Information section 1.8.2). We also find out-of-sample replicability of our overall GWAS results; the genetic correlation between $EduYears$ in our meta-analysis sample and in the UKB data is 0.95 (s.e. = 0.021; Supplementary Table 1.14).

It is known that EA, cognitive performance, and many neuropsychiatric phenotypes are phenotypically correlated, and several studies of twins find that the phenotypic correlations partly reflect genetic overlap$^6$–$^8$ (Supplementary Information section 3.3.4). Here, we investigate genetic correlation using our GWAS results for $EduYears$ and published GWAS results for 14 other phenotypes, using bivariate Linkage-Disequilibrium (LD) Score regression$^9$. First, we estimated genetic correlations with $EduYears$. As shown in Fig. 2, on average, alleles associated with greater EA are also associated with increased cognitive performance ($P = 9.9 \times 10^{-50}$) and intracranial volume ($P = 1.2 \times 10^{-6}$), increased risk of bipolar disorder ($P = 7 \times 10^{-13}$), decreased risk of Alzheimer’s ($P = 4 \times 10^{-4}$), and lower neuroticism ($P = 2.8 \times 10^{-8}$). We also found positive, statistically significant, but very small, genetic correlations with height ($P = 5.2 \times 10^{-15}$) and risk of schizophrenia ($P = 3.2 \times 10^{-4}$).

Second, we examined whether our 74 lead SNPs are jointly associated with each phenotype (Extended Data Fig. 5 and Supplementary Information section 3.3.1). We reject the null hypothesis of no enrichment at $P < 0.05$ for 10 of the 14 phenotypes (all the exceptions are subcortical brain structures).
Third, for each phenotype, we tested (in the published GWAS results) each of our 74 lead SNPs or proxy for association at a significance threshold of 0.05/74. We found a total of 25 SNPs meeting this threshold for any of these phenotypes (but only one reaching genome-wide significance). While these results provide suggestive evidence that some of these SNPs may be associated with other phenotypes, further testing of these associations in independent cohorts is required (Supplementary Tables 3.2-3.4, Extended Data Fig. 6).

To consider potential biological pathways, we first tested whether SNPs in particular regions of the genome are implicated by our GWAS results. Unlike what has been found for other phenotypes, SNPs in regions that are DNase I hypersensitive in the fetal brain are more likely to be associated with EduYears by a factor of ~5 (95% confidence interval 2.89–7.07; Extended Data Fig. 7). Moreover, the 15% of SNPs residing in regions associated with histones marked in the central nervous system (CNS) explain 44% of the heritable variation (Extended Data Fig. 8a and Supplementary Table 4.4.2). This enrichment factor of ~3 for CNS ($P = 2.48 \times 10^{-16}$) is greater than that of any of the other nine tissue categories in this analysis.

Given that our findings disproportionately implicate SNPs in regions regulating brain-specific gene expression, we examined whether genes located near EduYears-associated SNPs show elevated expression in neural tissue. We tested this hypothesis using data on mRNA transcript levels in the 37 adult tissues assayed by the Genotype-Tissue Expression Project (GTEx). Remarkably, the 13 GTEx tissues that are components of the CNS—and only those 13 tissues—show significantly elevated expression levels of genes near EduYears-associated SNPs (FDR < 0.05; Extended Data Fig. 8b and Supplementary Table 4.5.2).

To investigate possible functions of the candidate genes from the GWAS associated loci, we examined the extent of their overlap with groups of genes (“gene sets”) whose products are known or predicted to participate in a common biological process. We found 283 gene sets significantly enriched by the candidate genes identified in our GWAS (FDR < 0.05;
Supplementary Table 4.5.1). To facilitate interpretation, we used a standard procedure to group the 283 gene sets into “clusters” defined by degree of gene overlap. The resulting 34 clusters, shown in Fig. 3, paint a coherent picture, with many clusters corresponding to stages of neural development: the proliferation of neural progenitor cells and their specialization (the cluster npBAF complex), the migration of new neurons to the different layers of the cortex (forebrain development, abnormal cerebral cortex morphology), the projection of axons from neurons to their signaling targets (axonogenesis, signaling by Robo receptor), the sprouting of dendrites and their spines (dendrite, dendritic spine organization), and neuronal signaling and synaptic plasticity throughout the lifespan (voltage-gated calcium channel complex, synapse part, synapse organization).

Many of our results implicate candidate genes and biological pathways that are active during distinct stages of prenatal brain development. To directly examine how the expression levels of candidate genes identified in our GWAS vary over the course of development, we used gene expression data from the BrainSpan Developmental Transcriptome. As shown in Extended Data Fig. 9, these candidate genes exhibit above-baseline expression in the brain throughout life but especially higher expression levels in the brain during prenatal development (1.36 times higher prenatally than postnatally, $P = 6.02 \times 10^{-8}$).

A summary overview of some promising candidate genes for follow-up work is provided in Table 1.

We constructed polygenic scores to assess the joint predictive power afforded by the GWAS results (Supplementary Information section 5.2). Across our two holdout samples, the mean predictive power of a polygenic score constructed from all measured SNPs is 3.2% ($P = 1.18 \times 10^{-39}$; Supplementary Table 5.2 and Supplementary Information section 5).

Studies of genetic analyses of behavioral phenotypes have been prone to misinterpretation, such as characterizing identified associated variants as “genes for education.” Such
characterization is not correct for many reasons: EA is primarily determined by environmental factors, the explanatory power of the individual SNPs is small, the candidate genes may not be causal, and the genetic associations with EA are mediated by multiple intermediate phenotypes. To illustrate this last point, we studied mediation of the association between the all-SNPs polygenic score and *EduYears* in two of our cohorts. We found that cognitive performance can statistically account for 23–42% of the association (*P* < 0.001) and the personality trait “openness to experience” for approximately 7% (*P* < 0.001; Supplementary Information section 6).

It would also be a mistake to infer from our findings that the genetic effects operate independently of environmental factors. Indeed, a recent meta-analysis of twin studies found that genetic influences on EA are heterogeneous across countries and birth cohorts. We conducted exploratory analyses in the Swedish Twin Registry to illustrate how environmental factors may amplify or dampen the impact of genetic influences (Supplementary Information section 7). We found that the predictive power of the all-SNPs polygenic score is heterogeneous by birth cohort, with smaller explanatory power in younger cohorts (Extended Data Fig. 10; see also Supplementary Information section 7.4 for discussion of the contrast between these results and findings from a seminal twin study that estimated EA heritability by birth cohort).

**Methods:** All methods are described in the Supplementary Information.

**References:**


**Supplementary Information** is linked to the online version of the paper at www.nature.com/nature.
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contributing components of the meta-analysis. For a full list of author contributions, see Supplementary Information section 8.

Author Information Results can be downloaded from the SSGAC website (http://ssgac.org/Data.php). Data for our analyses come from many studies and organizations, some of which are subject to a MTA, and are listed in the Supplementary Information. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Correspondence and requests for materials should be addressed to D.J.B. (daniel.benjamin@gmail.com), D.C. (dac12@nyu.edu), P.D.K. (p.d.koellinger@vu.nl), or P.M.V. (peter.visscher@uq.edu.au).
Table 1 | Selected candidate genes implicated by bioinformatics analyses. Fifteen candidate genes implicated most consistently across various analyses. To assemble this list, each gene in a DEPICT-defined locus (Supplementary Information section 4.5) was assigned a score equal to the number of criteria it satisfies out of ten (see Supplementary Table 4.1 for details). The DEPICT prioritization $P$-value was used as the tiebreaker. “SNP”: the SNP in the gene’s locus with the lowest $P$-value in the EduYears meta-analysis. “Syndromic”: which, if any, of three neuropsychiatric disorders have been linked to de novo mutations in the gene (Supplementary Information section 4.6). “Top-ranking gene sets”: DEPICT reconstituted gene sets of which the gene is a top-20 member (Supplementary Table 4.5.1). The three most significant gene sets are shown if more than three are available. ID, intellectual disability; ASD, autism spectrum disorder; SCZ, schizophrenia.
<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Syndromic Score</th>
<th>Score</th>
<th>Top-ranking gene sets</th>
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<tr>
<td>TBR1</td>
<td>rs4500960</td>
<td>ID, ASD</td>
<td>6</td>
<td>Developmental biology, decreased brain size, abnormal cerebral cortex morphology</td>
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<tr>
<td>MEF2C</td>
<td>rs7277187</td>
<td>ID, ASD</td>
<td>5</td>
<td>ErbB signaling pathway, abnormal sternum ossification, regulation of muscle cell differentiation</td>
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<td>ZSWIM6</td>
<td>rs61160187</td>
<td>–</td>
<td>5</td>
<td>Transcription factor binding, negative regulation of signal transduction, PI3K events in ErbB4 signaling</td>
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<tr>
<td>BCL11A</td>
<td>rs2457660</td>
<td>ASD</td>
<td>5</td>
<td>Dendritic spine organization, abnormal hippocampal mossy fiber morphology, SWI/SNF-type complex</td>
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<tr>
<td>CELSR3</td>
<td>rs11712056</td>
<td>SCZ</td>
<td>5</td>
<td>Dendrite morphogenesis, dendrite development, abnormal hippocampal mossy fiber morphology</td>
</tr>
<tr>
<td>MAPT</td>
<td>rs192818565</td>
<td>ID</td>
<td>5</td>
<td>Dendrite morphogenesis, abnormal hippocampal mossy fiber morphology, abnormal axon guidance</td>
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<tr>
<td>SNO1</td>
<td>rs7306755</td>
<td>SCZ</td>
<td>5</td>
<td>Protein serine/threonine phosphatase complex</td>
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<td>NBAS</td>
<td>rs12987662</td>
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<td>–</td>
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<td>NBEA</td>
<td>rs9544418</td>
<td>SCZ</td>
<td>4</td>
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<td>SMARCA2</td>
<td>rs1871109</td>
<td>ID</td>
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<td>–</td>
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<tr>
<td>MAP4</td>
<td>rs11712056</td>
<td>ASD</td>
<td>4</td>
<td>Developmental biology, signaling by Robo receptor, SWI/SNF-type complex</td>
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<td>LINC00461</td>
<td>rs10061788</td>
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<td>4</td>
<td>Decreased brain size, abnormal cerebral cortex morphology, abnormal hippocampal mossy fiber morphology</td>
</tr>
<tr>
<td>POU3F2</td>
<td>rs9320913</td>
<td>–</td>
<td>4</td>
<td>Dendrite morphogenesis, developmental biology, decreased brain size</td>
</tr>
<tr>
<td>RAD54L2</td>
<td>rs11712056</td>
<td>SCZ</td>
<td>4</td>
<td>Decreased brain size, SWI/SNF-type complex, nBAF complex</td>
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<tr>
<td>PLK2</td>
<td>rs2964197</td>
<td>–</td>
<td>4</td>
<td>Negative regulation of signal transduction, PI3K events in ErbB4 signaling</td>
</tr>
</tbody>
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