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Genome-wide association studies establish that human intelligence is highly heritable and polygenic

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Abstract

General intelligence is an important human quantitative trait that accounts for much of the variation in diverse cognitive abilities. Individual differences in intelligence are strongly associated with many important life outcomes, including educational and occupational attainments, income, health and lifespan[1,2]. Data from twin and family studies are consistent with a high heritability of intelligence[3], but this inference has been controversial. We conducted a genome-wide analysis of 3511 unrelated adults with data on 549 692 SNPs and detailed phenotypes on cognitive traits. We estimate that 40% of the variation in crystallized-type intelligence and 51% of the variation in fluid-type intelligence between individuals is accounted for by linkage disequilibrium between genotyped common SNP markers and unknown causal variants. These estimates provide lower bounds for the narrow-sense heritability of the traits. We partitioned genetic variation on individual chromosomes and found that, on average, longer chromosomes explain more variation. Finally, using just SNP data we predicted approximately 1% of the variance of crystallized and fluid cognitive phenotypes in an independent sample ($P = 0.009$ and 0.028, respectively). Our results unequivocally confirm that a substantial proportion of individual differences in human intelligence is due to genetic variation, and are consistent with many genes of small effects underlying the additive genetic influences on intelligence.

Keywords

Intelligence; genetics; GWAS; quantitative trait

Introduction

People differ in their cognitive abilities, and the origins and impacts of these differences are sought after and much debated. The quantitative trait of general intelligence reflects the fact that diverse cognitive abilities show universally positive covariation; that is, no matter the cognitive task being undertaken, much of the human variation in any cognitive task will be caused by people's differences in general intelligence[4]. The latent trait of general intelligence ranks people very similarly, irrespective of the group of cognitive tests used to extract it[5]. Human intelligence is highly stable through the lifecourse and the resemblance between relatives suggests it is highly heritable throughout adulthood[3]. Intelligence is strongly associated with many important outcomes in life. People with higher intelligence tend to have more education, more professional occupations, higher incomes, and longer lives[1,2]. The foundations of intelligence differences in brain structure and function are becoming increasingly clear[6-8]. Especially in later adulthood, an important distinction is

made between general fluid and crystallized intelligences, with the former showing earlier and more rapid age-related decline[9,10].

Intelligence is highly familial, yet the extent and nature of the genetic contribution to intelligence differences has been controversial[11]. Twin and adoption studies suggest that additive genetic effects contribute over half of the population variance in intelligence in adulthood[3,6]. However, no single genes or gene variants have been identified that are robustly associated with intelligence-related phenotypes[3]. Moreover, it has been suggested that the apparent high heritability for intelligence is the result of a correlation (confounding) between genetic and environmental factors and that breaking up this correlation would result in the trait being much less heritable[12,13].

We present here the results of a genome-wide association study (GWAS) which examines cognitive ability phenotype-genotype associations in the five cohorts which constitute the CAGES (Cognitive Ageing Genetics in England and Scotland) project: the Lothian Birth Cohorts of 1921 and 1936 (LBC1921, LBC1936), the Aberdeen Birth Cohort 1936 (ABC1936), and the Manchester and Newcastle Longitudinal Studies of Cognitive Aging (Supplementary Table 1). All five cohorts comprise non-clinical samples of relatively healthy people from middle to older adulthood with detailed, though not identical, cognitive phenotypes.

Materials and Methods

Participants: discovery cohorts

The five cohorts within the CAGES project are the Lothian Birth Cohorts of 1921[14,15] and 1936[16] (LBC1921, LBC1936), the Aberdeen Birth Cohort 1936 (ABC1936) [14,15], and the Manchester and Newcastle Longitudinal Studies of Cognitive Aging cohorts[17] (Supplementary Table 1). Together these cohorts comprise 3511 healthy individuals with detailed cognitive abilities measured in middle to older adulthood.

Lothian Birth Cohort 1921—The LBC1921 is a longitudinal study of cognitive ageing. All participants were born in 1921 and completed the Moray House Test (MHT) No. 12 assessment of general intelligence in the Scottish Mental Survey 1932 at a mean age of 11 years[14,18]. Their recruitment and re-testing in old age has been described previously[14,15]. Relatively healthy surviving participants of the Scottish Mental Survey 1932 were identified within Edinburgh and its surrounding area, the Lothians. A total of 550 individuals (234 men and 316 women) were recruited and tested at a mean age of 79.1 years (SD = 0.6)[15]. The LBC1921 participants were tested individually and completed a battery of cognitive tests: The Moray House Test No. 12 (MHT)[18], Raven's Standard Progressive Matrices[19], Verbal Fluency[20], and Logical Memory[21]. Participants also completed the National Adult Reading Test (NART)[22]. Following informed consent, venesected whole blood was collected for DNA extraction. Ethical approval for all projects was obtained from the Lothian Research Ethics Committee.

Lothian Birth Cohort 1936—The Lothian Birth Cohort 1936 (LBC1936) is a longitudinal study of cognitive ageing. All participants were born in 1936 and had completed the MHT in the Scottish Mental Survey 1947 at a mean age of 11 years[14,23]. Their recruitment and re-testing in old age has been described previously[16]. Relatively healthy surviving participants of the Scottish Mental Survey 1947 were identified within Edinburgh and its surrounding area, the Lothians. A total of 1091 participants (548 men and 543 women) were recruited and tested individually at a mean age of 69.5 years (SD = 0.8). The LBC1936 participants completed a large battery of cognitive tests[16]. For the purposes of the present study, only those tests relevant to the phenotypes analysed here are described.

These are: the MHT, and a battery of cognitive tests consisting of 6 tests from the Wechsler Adult Intelligence Scale-III UK (WAIS-III^{UK} [Ref. 24]): Digit Symbol Coding, Block Design, Matrix Reasoning, Digit Span Backwards, Symbol Search, and Letter-number Sequencing. Participants also completed the NART[22]. Following informed consent, venesected whole blood was collected for DNA extraction. Ethical approval for all projects was obtained from Scotland's Multicentre Research Ethics Committee and the Lothian Research Ethics Committee.

Aberdeen Birth Cohort 1936—The Aberdeen Birth Cohort 1936 (ABC1936) is a longitudinal study of cognitive ageing. All participants were born in 1936 and had completed a version of the MHT test of general intelligence in the Scottish Mental Survey 1947 at mean age 11 years[14,23]. Their recruitment and re-testing in old age has been described previously[14,15]. A total of 498 relatively healthy participants (243 men, 255 women) was traced and tested at mean age 64.6 years (SD = 0.9). The cognitive tests carried out were: the NART[22], Raven's Standard Progressive Matrices[19], the Rey Auditory Verbal Learning Test[20], Digit Symbol and Block Design sub-tests of the Wechsler Adult Intelligence Scale-Revised[25], and the Uses of Common Objects Test[22]. Following informed consent, venesected whole blood was collected for DNA extraction. Ethical approval for all projects was obtained from the Grampian Research Ethics Committee.

Manchester and Newcastle Longitudinal Studies of Cognitive Ageing Cohorts —The University of Manchester Age and Cognitive Performance Research Centre (ACPRC) programme began in 1983 and this study has documented longitudinal trajectories in cognitive function in a large sample of older adults in the North of England, UK[17]. Recruitment took place in Newcastle and Greater Manchester between 1983 and 1992. At the outset of the study, 6063 volunteers were available, (1825 men, 4238 women), with a median age of 65 years (range 44 to 93 years). Over the period 1983 to 2003, two alternating batteries of cognitive tasks applied biennially were designed to measure fluid and crystallized aspects of intelligence. These included: the Alice Heim 4 (AH4) parts 1 and 2 tests of general intelligence; Mill Hill Vocabulary A and B vocabulary tests; the Cattell and Cattell Culture Fair intelligence tests; and the Wechsler Adult Intelligence Scale Vocabulary test. Detailed task descriptions were provided previously[17]. Following informed consent, venesected whole blood was collected for DNA extraction. Ethical approval for all projects was obtained from the University of Manchester.

Participants: replication cohort

The Norwegian Cognitive NeuroGenetics cohort (NCNG) consists of 670 participants, ranging from 18 to 79 years of age (mean = 47.6; SD = 18.3) (Supplementary Table 1). The participants completed a battery of psychometric tests, assessing general cognition, memory, attention, and speed of processing faculties. Informed consent was approved by the relevant regional ethical committee for medical research (Project ID: S-03116). Permission to obtain and store blood samples for genotyping together with cognitive and MRI data in a bio-bank and to establish a registry with relevant information for a time period of 10 years was granted by the Norwegian Department of Health.

Cognitive phenotypes

For each of the cohorts we constructed cognitive phenotypes of fluid-type and crystallized-type intelligence. Crystallized-type intelligence is typically assessed using tests of acquired knowledge, and most often through tests of vocabulary. Fluid-type intelligence tends to involve unfamiliar, sometimes abstract, materials, to involve on-the-spot thinking, to be completed under time pressure, and to rely relatively little on prior knowledge. Here, to

represent crystallized intelligence (g_c), we used: the National Adult Reading Test in the Lothian Birth Cohorts of 1921 and 1936, and the Aberdeen Birth Cohort 1936; the Mill Hill Vocabulary Test in the Manchester and Newcastle samples; and the Wechsler Adult Intelligence Scale Vocabulary subtest in the Norwegian Cognitive NeuroGenetics sample. For fluid-type intelligence, principal components analyses (PCA) were used in the following cohorts to derive a general intelligence factor (g_f): the Lothian Birth Cohorts 1921 and 1936, the Aberdeen Birth Cohort 1936, and the Norwegian Cognitive NeuroGenetics sample. In each case, the scores on a number of fluid-type cognitive tests were subjected to PCA. The tests used to form the g_f factor in the LBC1921 were the Moray House Test, Raven's Matrices, Logical Memory, and Verbal Fluency. For the LBC1936 the six tests from the WAIS-III^{UK} were used. The ABC1936 g_f factor included Raven's Progressive Matrices, Digit Symbol, Uses of Common Objects, and AVLT. For the NCNG sample, a hierarchy of PCA analyses was used (see Supplementary Methods for further details). In all cases a single component was indicated and was extracted. Thus, individuals' scores on the first unrotated principal component were used as the indicator of general fluid-type intelligence (g_f). For g_f in the Manchester and Newcastle samples empirical Bayes's estimates for each individual were obtained from a random effects model fitted by maximum likelihood (ML) to the standardized age-regressed residuals obtained for each sex from the Alice Heim 4 test and the Cattell Culture Fair test scores. All of the phenotypes were corrected for age and sex (with the exception of Manchester and Newcastle g_f which was derived separately for males and females) and the standardized residuals were used for all subsequent analyses.

Genotyping and Quality Control

Discovery cohort

A total of 3511 CAGES participants had DNA extracted and were genotyped for 599 011 common single nucleotide polymorphisms (SNPs) using the Illumina610-Quadv1 chip (Supplementary Table 1). We applied stringent quality control analyses of the genotype data and retained 549 692 of the 599 011 SNPs on the Illumina 610 chip in 3511 individuals (2115 females) (Supplementary Figure 1). Individuals were excluded from this study based on unresolved gender discrepancy, relatedness, call rate (≤ 0.95), and evidence of non-Caucasian descent. SNPs were included in the analyses if they met the following conditions: call rate ≥ 0.98, minor allele frequency ≥ 0.01, and Hardy-Weinberg equilibrium test with P ≥ 0.001. Differences in allele frequencies between the discovery and replication samples were investigated, and no sizeable deviations were observed (Supplementary Figure 1). We tested for population stratification within each cohort and excluded any outliers. The first four components from a multidimensional scaling (MDS) analysis of the SNP data, based on the remaining individuals, were included as covariates in subsequent analyses (Supplementary Figure 2). A total of 3400 and 3482 samples with both phenotypic and SNP data were available for g_f and g_c, respectively.

Replication cohort

NCNG DNA samples were newly extracted from blood using the Qiagen Gentra Autopure LS system. They were genotyped on the Illumina Human610-Quad Beadchip. A strict quality control protocol was applied which resulted in a final dataset of 554 225 SNPs genotyped in a homogenous Norwegian sample of 670 individuals (See Supplementary Methods for further details).

Statistical Analysis

Genotype-phenotype analyses were performed within each cohort[26]. Meta-analysis was implemented using an inverse variance weighted model (www.sph.umich.edu/csg/abecasis/

Metal). Gene-based tests for association were carried out using results from the meta-analyses[27].

Statistical analyses to estimate the proportion of variation explained by all SNPs were performed as in Yang *et al.*[28]. This method captures the variance in the trait that is due to linkage disequilibrium between genotyped SNPs and unknown causal variants[28,30]. The interpretation of the estimate of variance accounted for is different from that estimated from traditional family or twin studies, because these latter designs capture the variation due to all causal variants in the genome and, possibly, variation due to environmental factors, for example when the effect of shared environment is larger in monozygotic twin pairs than in dizygotic pairs [30]. We firstly estimated pairwise genetic relationships between 3511 individuals from CAGES from 549 692 autosomal SNPs. We excluded one individual from any pair that had an estimated coefficient of relatedness of > 0.025 and retained 3291 individuals for analysis: 1800 from Scotland and 1491 from Northern England. The reason for excluding close relatives is that: (i) their phenotypic covariance will have a large impact on the estimate of variance explained; (ii) the phenotypic covariance of close relatives captures the effects of all causal variants in the genome and not just those in close LD with the genotyped SNPs; and (iii) phenotypic covariance of close relatives can include effects due to shared environment[30]. We fitted a linear mixed model $y = \mu + g + e$, where y is phenotype, μ is the mean term, g is the aggregate additive genetic effect of all the SNPs, and e is the residual effect. We have previously demonstrated that this model is mathematically equivalent to the model of fitting all the SNPs[28]; i.e., $y = \mu + \sum x_i b_i + e$, where x_i is the number of copies of the reference allele for a SNP i with its additive effect of b_i. The covariance structure fitted in the data was the relationship estimated from all SNPs; i.e., $\mathrm{cov}(y_j, y_k) = A_{jk}\sigma_g^2 + \sigma_e^2$, where A_{jk} is SNP-derived genetic relationship between individuals j and k, σ_g^2 is the additive genetic variance and σ_e^2 is the residual variance. We used restricted maximum likelihood (REML) to estimate additive genetic variance. To maintain consistency with the single SNP analyses, four principal components were fitted as covariates in the model. Genome-partitioning of genetic variation was done similarly, by fitting chromosomal relationships estimated from all SNPs on a particular chromosome. The cross-validation prediction analyses were done by including the genotypes of all individuals but setting the phenotype of individuals in the validation cohort to unknown, and then performing a regression of the phenotype on the best linear unbiased predictor[28]. For the Norwegian sample, SNP effects were estimated from the entire CAGES sample by exploiting the mathematical equivalence of a model based upon genome-wide genetic effects and individual SNP effects[29].

Results

Analyses of individual SNPs and genes did not result in any replicable genome-wide significant association (Fig. 1a,c, Supplementary Figures 3-6, and Supplementary Tables 3,4). A gene-based test for association[27] showed one genome-wide significant association ($P = 9.2 \times 10^{-7}$), with *formin-binding protein 1-like* (*FNBP1L*) on g_f (Supplementary Figure 7). This single genome-wide association result for *FNBP1L* did not replicate in the independent NCNG sample ($P = 0.211$, gene-based test).

We observed that the test statistic for association from the meta-analysis, but not the individual cohort analyses, was inflated for both g_f and g_c (Figures 1 b,d and Supplementary Figures 4,6). Inflated test statistics are indicative of either population stratification or polygenic variation. There was no strong evidence of population stratification within each of the five discovery cohorts (Supplementary Figure 2). Moreover, four multi-dimensional scaling (MDS) components were fitted in each individual cohort analysis to account for the

effects of possible subtle population stratification. Therefore, we reasoned that the inflation of the test statistic across the genome was indicative of polygenic variation.

We quantified the proportion of phenotypic variation accounted for by all genotyped SNPs, using an analysis method we recently developed[28] (See Supplementary Method for further details and Supplementary Figure 8). This model is mathematically equivalent to fitting all SNPs in the model, provided that the SNP effects are treated as random[28]. Therefore, our estimate of additive genetic variance is that explained from considering all SNPs simultaneously. Because there are many more ungenotyped genetic variants in the genome than there are genotyped SNPs, this is likely to be due to LD between genotyped SNPs and unknown causal variants. Further details on and explanation of this method can be found in a recent detailed commentary on the method provided by Visscher and collegaues[30]. We estimated that a proportion of 0.40 (SE = 0.11, $P = 5.7 \times 10^{-5}$, likelihood-ratio test) and 0.51 (SE = 0.11, $P = 1.2 \times 10^{-7}$, likelihood-ratio test) of the phenotypic variance can be explained by all SNPs for g_c and g_f, respectively (Table 1). Analysing the English and Scottish samples separately or fitting 20 principal components as covariates in the model of analysis did not change the results markedly, nor did the inclusion of pairs of individuals whose estimated relatedness was > 0.025 (Supplementary Table 2). We subsequently partitioned additive genetic variation to individual chromosomes using the software package GCTA[31], fitting all chromosomes simultaneously, and found that, on average, longer chromosomes explain more variation (Figure 2).

To further corroborate evidence of polygenic variation, we tested whether phenotypes for intelligence could be predicted solely from SNP data[32,33]. We performed cross-validation analyses in which four of the five CAGES cohorts were used to estimate SNP effects while the remaining cohort was used to estimate the correlation between the phenotype and the predictor created from all autosomal SNPs (Table 2 and see Supplementary Method for further detail). For g_f, four of the five prediction analyses showed significant ($P < 0.05$) results. The correlations for the five analyses fell consistently in a narrow band of values between 0.067 and 0.148 (mean $R = 0.11$). For g_c, three of the five prediction analyses showed significant results, and the correlations for the five analyses ranged between 0.049 and 0.133 (mean $R = 0.081$). Non-significance of some of the associations in Table 2 should not be taken to mean that there are different results in different cohorts. The standard errors of the estimates of correlation in Table 2 vary from ~0.03 (LBC1936) to ~0.05 (LBC1921), and none is significantly different from the other, either by trait or by validation cohort.

We next used the entire set of five CAGES samples to estimate SNP effects and predicted cognitive phenotypes in the independent NCNG (Norwegian NeuroGognitive Genetics) sample. For g_f and g_c, the correlations between phenotype and predictor were, respectively, 0.076 ($P = 0.028$, one-sided t-test) and 0.092 ($P = 0.009$, one-sided t-test). Individuals with a higher predicted score had, on average, a higher phenotype. Thus, SNP effects estimated in the discovery cohort are significantly predictive of cognitive phenotype outcomes in a fully independent cohort.

Discussion

Here we report results from a GWAS of intelligence in middle to older adulthood. Despite the fact that no specific genetic variants have been robustly associated with human intelligence, apart perhaps for *APOE* at older ages[34,35], our results show for the first time that a substantial proportion (approximately 40 to 50%) of variation in human intelligence is associated with common SNPs (Minor allele frequency (MAF) > 0.01) that are in LD with causal variants. These results are consistent with a highly polygenic model because we detect variation across the entire genome. If the narrow-sense heritability for intelligence is

approximately 0.6 in the age groups studied in the CAGES samples[3,36], then not all additive variation is accounted for by our analyses. One reason for this difference could be that causal variants for intelligence have, on average, a lower MAF than the SNPs on the chip used. Such a frequency difference causes imperfect LD between the genotyped SNPs and unobserved causal variants. Traditional pedigree analysis is not affected by such imperfect LD because it is based on the correct expected identity-by-descent coefficients at loci (including loci with causal variants) of relatives. It is also possible that causal variants are present in regions of the genome not well covered by the commercial SNP arrays. Nevertheless, our results suggest that common SNPs that are in LD with unknown causal variants account for more than half of all additive genetic variation for human intelligence. The method we have used here does not attempt to test the effects of single SNPs; rather, it tests their accumulated effects. It estimates the joint effect of genotyped SNPs and that effect reflects their linkage disequilibrium (LD) with unknown causal variants. These variants are not necessarily common SNPs or, indeed, even SNPs; however, causal variants are in sufficient LD with the genotyped SNPs to be captured[30].

One genome-wide significant association, *FNBP1L*, was reported with fluid intelligence from a gene-based test for association[27]. *FNBP1L* (previously known as Toca-1) binds to both CDC42 and WASL, promoting CDC42-induced actin polymerization by activating the N-WASP-WIP complex (*15*), and is thus implicated in a pathway that links cell surface signals to the actin cytoskeleton, a system that allows the movement of cells and cellular processes. *FNBP1L* is strongly expressed in neurons, including hippocampal neurons, in developing brains and regulates neuronal morphology. The genome-wide significance threshold for the gene-based test is different to that for the SNP-based test because fewer hypotheses were tested (~17,800). This result did not replicate in the NCNG sample; however, the sample size of the validation cohort was much smaller than the discovery set and it will be necessary to attempt replication of this finding in larger samples before pursuing it further.

Only 1% (approximately) of the variance was explained in the prediction analysis due to the individual SNP effects being very small and therefore estimated with much error, which detracts to a great extent from the accuracy (8-11%) of the prediction equation[30]. Our finding that 40-50% of phenotypic variation is explained by all SNPs is fully consistent with the low precision of a predictor based upon a discovery sample of ~3,500 individuals; estimation of the SNPs' effects is different from prediction accuracy[30,37]. The difference lies in the precision with which individual SNP effects are estimated. Although we can obtain an unbiased estimate of a SNP effect (using, for example, a least squares estimator), a prediction of a phenotype using the estimated SNP effect suffers from the sampling variance with which the effect is estimated. In the case of intelligence, the individual effect sizes are very small so that they are estimated with much error. One explanation of this apparent paradox is to consider the extreme case of a single variant when it is known that this variant is associated with the trait but the effect size is not known and needs to be estimated. Estimating its effect size will be unbiased across repeated samples from the same population and the standard error of estimation informs about the precision (standard error) of the estimate of effect size. This is the scenario analogous to our estimate of the variance explained by all SNPs. Now consider that, for each (unbiased) estimate of effect size, we make a prediction of phenotypes in an independent sample based upon the estimated effect size of the variant in the discovery sample. The correlation between predicted value and actual phenotype will depend on how well the variant has been estimated—the worse the estimate of the effect size of the variant in the discovery sample, the worse will be the variance explained by the predictor in the validation sample. This is the scenario analogous to our prediction analysis.

There are other possible reasons for being unable to predict phenotypes with greater precision. First, different cognitive phenotypes were used in each cohort. However, this should not be over-emphasised as it has been shown clearly that the general factors derived from different mental test batteries tend to rank people almost identically[5]. In the case of crystallized intelligence—where single tests were used—different vocabulary tests are very highly correlated. Second, there may be genetic differences between the UK and Norwegian populations which could result in dissimilar patterns of LD[38] (Supplementary Figure 1). However, this is unlikely to be important because LD is very similar across European populations[38].

The reason why this and other GWAS analyses of complex diseases and traits are unable to detect strong individual signals—and why there has been much concern about the "missing heritability" [39]—is probably because the individual effects of common SNPs are too small to pass the stringent genome-wide significance level. This suggests that human intelligence and perhaps other complex traits are highly polygenic, and that very large sample sizes are required to detect such small individual effects, if the same experimental design is used which relies on LD between common SNPs and causal variants. These findings are consistent with the recently reported results for other complex traits, including schizophrenia[33] and human height[28]. If genetic variation that is not captured through LD with common SNPs is due to rare variants with large effect sizes, then other experimental designs such as those employing exome or whole genome resequencing may facilitate the identification of genes and/or gene variants that are associated with human intelligence.

Can the results reported here be explained by population stratification or a correlation between environmental and genetic similarity? A number of reasons suggest strongly that these explanations are unlikely. The results were consistent when we estimated genetic variance within sub-populations and when we adjusted for up to 20 principal components (Supplementary Table 2). The observation that individual cohorts do not show an inflation of the test statistic, but the combined sample does, would require undetected spurious phenotype-genotype associations due to stratification in all cohorts to be in the same direction, which seems very unlikely. We recently showed that when investigating a trait under polygenic inheritance, increasing the sample size would indeed be expected to increase the inflation factor[40]. A correlation between environmental and genetic similarity might occur if similarity due to environmental factors between relatives segregates with the degree of separation. For example, cousins five times removed might be more similar than cousins six times removed because they have a more similar environment. This argument applies to single SNP associations with any complex trait, and there is no evidence that the robustly associated variants from GWAS are spurious in this respect. Moreover, we estimated the actual amount of genome-sharing between very distant relatives, which is different from the expected amount of sharing if we knew the entire pedigree of all individuals. In fact, the more distantly related a pair of individuals is from the pedigree, the larger the amount of variation in actual genome-wide sharing around this expectation (see Supplementary Method for further detail)[28,41]. Finally, we partitioned genetic variation to individual chromosomes by fitting the relationship matrices from all autosomes simultaneously in the model. For very distant relatives, as we have in our study, this method is robust to stratification[30].

What do our results imply about the heritability of intelligence? If our estimated relationships had been based on all causal variants instead of being derived from SNPs that may be in LD with such variants, then we would have had an unbiased estimate of the full narrow-sense heritability. Therefore, our estimates provide a lower bound for the narrow-sense heritability, due to imperfect LD between the genotyped SNPs and unknown causal variants. Our estimates are based upon realized relationships between very distant relatives

and not on pedigree relationships between close relatives. This breaks up a possible correlation (confounding) between genetic and environmental factors, since the variation in realized relationships given pedigree relations is large for distant relatives. Our estimates of the phenotypic variance explained by all SNPs are ~0.4-0.5, and we therefore conclude that the narrow-sense heritability for human intelligence is large and consistent with the inference from twin and family studies.

The estimates of the total proportion of variance explained for g_f and g_c are not significantly different from each other. Nor are the prediction accuracies for g_f and g_c in the Norwegian replication sample. However, a larger sample size is required to differentiate between any genetic architecture of these two traits.

In summary, we report the first study to show that a large proportion of the heritability estimate of intelligence in middle to older adulthood can be traced to biological variation using SNP data. It is the first to show biologically and unequivocally that human intelligence is highly polygenic and that purely genetic (SNP) information can be used to predict intelligence. Our findings imply that very large sample sizes will be needed to detect individual loci with genome-wide significance and that the majority of additive genetic variation for human intelligence is not explained by rare variants that are not in LD with common SNPs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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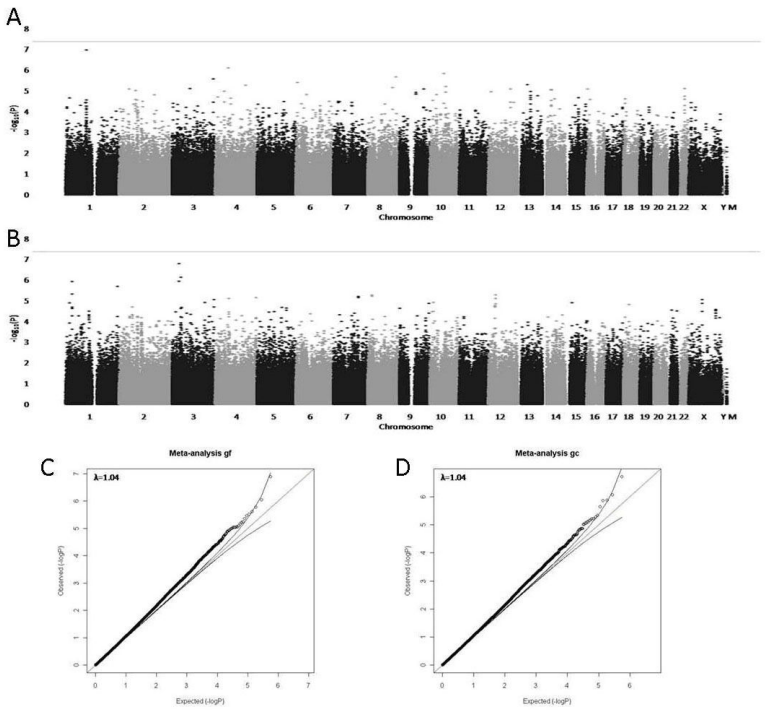

Figure 1. Meta-analytic genome-wide association results for all five samples in the Cognitive Ageing Genetics in England and Scotland study

Manhattan plot showing meta-analysis results for g_f. The $-\log_{10} P$ values (y axis) of 549,692 SNPs in 3,400 individuals are presented based on their choromosomal position (x axis). The red line is the genome-wide significance threshold 5×10^{-8}(**a**). Manhattan plot showing meta-analysis results for g_c. The $-\log_{10} P$ values (y axis) of 549,692 SNPs in 3,482 individuals are presented based on their chromosomal position (x axis). The red line is the genome-wide significance threshold 5×10^{-8} (**b**). Quantile-quantile plots of the meta-analysis P-values for g_f. The black circles represent the observed data, the red line is the expectation under the null hypothesis of no association, and the black curves are the boundaries of the 95% confidence interval. A clear deviation from the expected values is evident (**c**). Quantile-quantile plots of the meta-analysis P values for g_c. The black circles represent the observed data, the red line is the expectation under the null hypothesis of no association, and the black curves are the boundaries of the 95% confidence interval. A clear deviation from the expected values is evident (**d**).

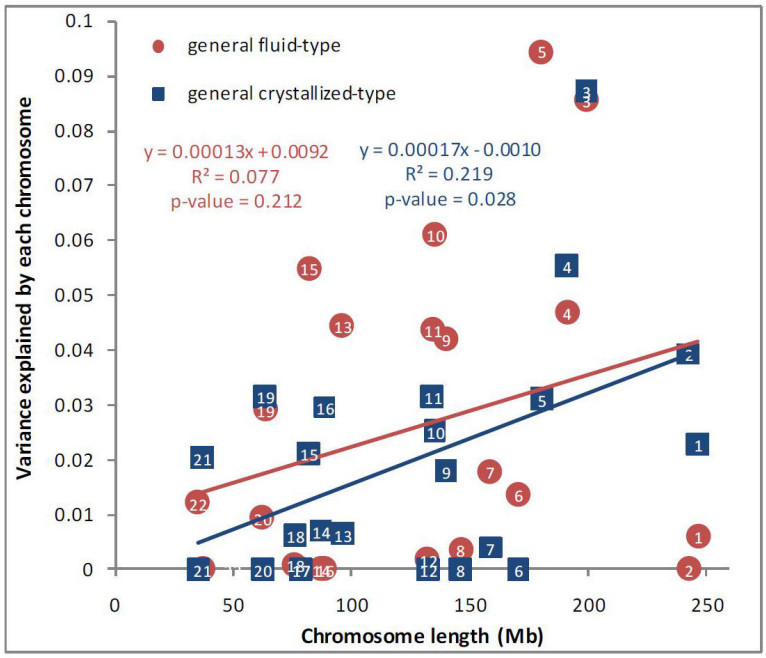

Figure 2. Estimate of the proportion of variance explained by each chromosome for g_f and g_c in the combined dataset against chromosome length

The numbers in the circles and squares are the chromosome numbers.

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Table 1
Estimates of variance explained by all SNPs

	g_c	g_f
N	3254	3181
h^2 (se)	0.40 (0.11)	0.51 (0.11)
P value	5.7×10^{-5}	1.2×10^{-7}

Estimates of the proportion of phenotypic variance explained by all SNPs for the traits g_f and g_C from the combined CAGES samples. h^2 = proportion of phenotypic variance accounted for by fitting all SNPs

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Table 2

Results of prediction analyses

Validation cohort	Rg_f	Pg_f	Rg_c	Pg_c
Lothian Birth Cohort 1921	0.098	0.014	0.133	1.3×10^{-3}
Lothian Birth Cohort 1936	0.094	1.5×10^{-3}	0.082	4.9×10^{-3}
Aberdeen Birth Cohort 1936	0.067	0.11	0.049	0.16
Newcastle	0.137	7.5×10^{-5}	0.057	0.06
Manchester	0.148	1.3×10^{-5}	0.086	7.5×10^{-3}
Mean	*0.11*		*0.081*	
NCNG	0.076	0.028	0.092	0.009

For the CAGES samples each cohort, in turn, was used as the validation cohort and the predictor was generated from a joint analysis of the four remaining cohorts. A joint analysis of the five UK cohorts was used to create the predictor for the NCNG cohort. *R* is the correlation coefficient between the observed phenotype and the predicted value for each individual based on genetic information. *P* indicates the statistical significance (one-sided t-test, since the alternative hypothesis is that the predictor is positively correlated with outcome) of the correlation coefficient *R*.