Independent Evidence for an Association between General Cognitive Ability and a Genetic Locus for Educational Attainment

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Cognitive deficits and reduced educational achievement are common in psychiatric illness; understanding the genetic basis of cognitive and educational deficits may be informative about the etiology of psychiatric disorders. A recent, large genome-wide association study (GWAS) reported a genome-wide significant locus for years of education, which subsequently demonstrated association to general cognitive ability ("g") in overlapping cohorts. The current study was designed to test whether GWAS hits for educational attainment are involved in general cognitive ability in an independent, large-scale collection of cohorts. Using cohorts in the Cognitive Genomics Consortium (COGENT; up to 20,495 healthy individuals), we examined the relationship between g and variants associated with educational attainment. We next conducted meta-analyses with 24,189 individuals with neurocognitive data from the educational attainment studies, and then with 53,188 largely independent individuals from a recent GWAS of cognition. A SNP (rs1906252) located at chromosome 6q16.1, previously associated with years of schooling, was significantly associated with g ($P = 1.47 \times 10^{-4}$) in COGENT. The first joint analysis of 43,381 non-overlapping individuals for this *a priori*-designated locus was strongly significant ($P = 4.94 \times 10^{-7}$), and the second joint analysis of 68,159 non-overlapping individuals was even more robust ($P = 1.65 \times 10^{-9}$). These results provide independent replication, in a large-scale dataset, of a genetic locus

associated with cognitive function and education. As sample sizes grow, cognitive GWAS will identify increasing numbers of associated loci, as has been accomplished in other polygenic quantitative traits, which may be relevant to psychiatric illness.

INTRODUCTION

A general cognitive ability factor (also termed g) typically captures just under half of the overall variance in performance on diverse laboratory measures of neurocognitive functioning [Johnson et al., 2008]. General performance on neurocognitive tests has remarkable predictive value across a diverse range of social, health and behavioral outcomes, more so than any other psychological trait [Gottfredson, 1997; Deary et al., 2011; Deary, 2012]. As examples, low g performance is associated with lower educational attainment and income [Johnson et al., 2009], is a better predictor of mortality from cardiovascular disease than smoking, blood glucose and cholesterol [Deary, 2008], and predicts longevity [Batty et al., 2008]. Deficits in general neurocognitive performance are pervasive in most psychiatric and neurologic disorders, yet are often the most difficult component to treat [Millan et al., 2012]. As such, understanding the neurobiology of human cognition is potentially critical to improving physical and mental health outcomes in society [Deary et al., 2010].

While both genetic background and environmental experience interact to shape cognitive development [Deary et al., 2012], twin and family studies have consistently demonstrated heritability of more than 50% for general cognitive ability measured in adulthood [Deary et al., 2009]. Allelic variation can have a direct influence on brain biology by modifying the molecular structure and/or function of brain-expressed transcripts and proteins such as neurotransmitter receptors and neurodevelopmental growth factors [Chen et al., 2004]. However, attempts to pinpoint loci associated with human cognition across diverse population samples have proven challenging due to the difficulty of assembling the large cohorts required to detect small expected effects of individual variants in a highly polygenic trait [Need et al., 2009; Davies et al., 2011, 2015; Luciano et al., 2011; Martin et al., 2011; Chabris et al., 2012; Lencz et al., 2014; Benyamin et al., 2014].

By contrast, educational history is easily obtainable demographic information collected in any field of medical research, and can therefore be collected in more readily across large cohorts as compared to cognition. Educational attainment, as measured by self-reported years of schooling, has been proposed as a 'proxy phenotype' for cognitive ability for GWAS since much larger samples can be utilized compared to neurocognitive studies [Martin et al., 2011; Rietveld et al., 2013, 2014a,b]. The Social Science Genetic Association Consortium (SSGAC) reported on a 126,559 person GWAS that detected three genome-wide significant SNPs associated with completion of college (rs11584700 and rs4851266)

and years of schooling (rs9320913) [Rietveld et al., 2013]. In a post hoc analysis, these SNPs had a stronger and more direct effect on cognitive function than on education [Rietveld et al., 2013]. Further, a polygenic risk score of educational attainment SNPs accounted for 2–3% of the variance in general cognitive ability an in independent sample, and a mediation analysis suggested that g mediated more than half of the effect these SNPs had on education [Rietveld et al., 2013]. Here, we analyzed the three SNPs obtained in the SSGAC educational attainment GWAS in ≈20,000 independent subjects in the Cognitive Genomics Consortium (COGENT) [Donohoe et al., 2013; Lencz et al., 2014], and found converging evidence across multiple large cohorts that common variation at genomic region 6q16.1, previously associated with years of schooling, reliably predicts variation in g.

Methods and Materials

COGENT is an international GWAS collaboration formed to conduct genetic analyses of g and related neurocognitive processes in healthy individuals [Donohoe et al., 2013]. Though common GWAS markers have been proposed to account for ~30% or more of the variance in general intelligence in adults, individual SNPs only contribute a small fraction of the variance to the heritability of g due to extreme polygenicity [Davies et al., 2011; Marioni et al., 2014]. Detecting SNP associations of such small magnitudes via GWAS requires large samples many times the size an individual lab can ascertain, leading to consortia such as COGENT. The decision to study g in COGENT stemmed from longstanding evidence that a g factor can be derived consistently, captures almost half the variance in overall test performance, and is relatively invariant to the neurocognitive test battery used and specific abilities assessed [Johnson et al., 2008; Panizzon et al., 2014].

The first phase of COGENT ('COGENT1') resulted in a GWAS of general cognitive ability in ≈5,000 individuals from the general population [Lencz et al., 2014]. The next (and ongoing) wave of data collection in COGENT ('COGENT2') has resulted in the acquisition of ≈15,000 independent subjects with neurocognitive and GWAS data for analysis (see Table 1 for cohort details). To be included as a participant in COGENT, data from at least one neuropsychological measure across at least three domains of cognitive performance (e.g., digit span for working memory; logical memory for verbal declarative memory; and digit symbol coding for processing speed), or the use of a validated g-sensitive measure was required. Tests missing for more than 5% of the sample in an individual study were excluded. Each COGENT study administered an average of 10.3 neurocognitive tests, and the internal consistency of performance within each study was strong (mean Cronbach's $\alpha = 75\%$; supplementary table S1). The first unrotated principal component accounted for just under half of the variance across the 21 studies on average, as expected based on an extensive prior literature [Carroll, 1993]. As Figure 1 shows, g had normal distributional properties within all 21 studies, a feature critical to enhancing statistical power in quantitative trait analysis.

All COGENT samples were genotyped on commercial Illumina or Affymetrix genome-wide SNP microarrays (supplementary table S1). Standard GWAS quality control (QC) methods were

TABLE I. Sites and Basic Demographics of Samples Included in the Cognitive Genomics Consortium (COGENT; Ordered Alphabetically)

| Study	Study Name	N	Age (mean)	Age range	% Male
ADNI1	Alzheimer's Disease Neuroimaging Initiative, Phase 1	127	75.7	62–90	55.9
CHS	Cardiovascular Health Study	2,114	77.9	69–99	37.1
DNS	Duke Neurogenetics Study	357	19.7	18–22	47.6
FHS	Framingham Heart Study, Second Generation Cohort	1,650	65.3	38–90	45.6
GCAP	NIMH Genes, Cognition and Psychosis Program	655	31.5	18–60	46.9
GenADA	Genotype-Phenotype Associations in Alzheimer's Disease	782	73.4	48–94	35.7
HBCS	Helsinki Birth Cohort Study	332	67.7	64–75	100.0
IBG	Institute for Behavioral Genetics	299	15.9	12–19	78.6
LBC1936	Lothian Birth Cohort 1936	1,005	69.6	68–71	50.6
LLFS	Long Life Family Study	3,606	64.6	24–89	45.2
LOAD	Late Onset Alzheimer's Disease Family Study	1,141	75.1	53–98	36.6
LOGOS	Learning on Genetics of Schizophrenia Spectrum	864	22.5	18–44	100.0
MAN	Manchester Longitudinal Studies of Cognitive Aging	805	67.2	45–87	28.9
MUC1	Munich, Germany Sample 1	588	50.5	19–79	50.0
MUC2	Munich, Germany Sample 2	538	45.1	19–72	45.7
NCNG	Norwegian Cognitive NeuroGenetics	670	47.6	18–79	31.9
NEW	Newcastle Longitudinal Studies of Cognitive Aging	753	67.0	54–87	29.0
PING	Pediatric Imaging, Neurocognition and Genetics Study	637	11.6	3–18	52.4
PNC	Philadelphia Neurodevelopmental Cohort	4,412	13.8	8–21	50.2
TOP	Thematic Organized Psychosis Research Study	394	34.6	17–55	49.2
ZHH	Zucker Hillside Hospital	219	35.3	8–78	49.3
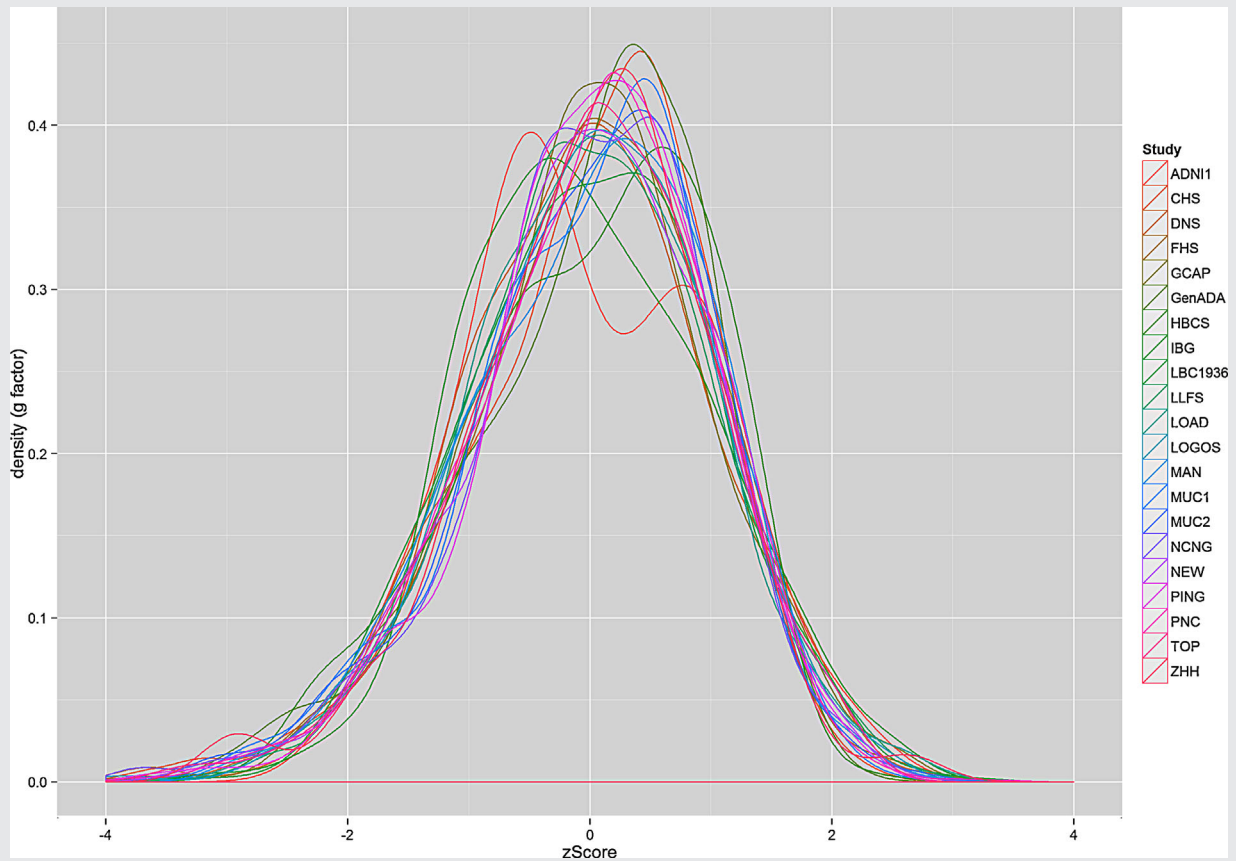
FIG. 1. Kernel density plot (KDP) of the g factor across 21 COGENT studies. Each g score is smoothed for each individual using a strongly peaked kernel function in order to evaluate every point along the x-axis. The y-axis represents density. As can be seen, the shape of the distribution tightly fits a Gaussian curve across all studies.

applied to the genetic data (described in detail in the supplementary information). Subjects in the study were Caucasian of European ancestry, which we confirmed by analysis of genotype data using multidimensional scaling (MDS). Genetic outliers were removed in each study based on MDS axis plotting versus HapMap3 ethnic subgroups. Note that none of the three SNPs previously associated with education were variants included on commercially available microarrays, and thus were imputed into their datasets [Rietveld et al., 2013]. In the COGENT1 studies, SNPs were imputed using HapMap3 reference panels as previously described [Lencz et al., 2014]. COGENT2 samples that did not have genotypes for the SNPs of interest were imputed using IMPUTE2 [Howie et al., 2009] and 1000 Genomes Project reference panels (downloaded June 2014).

SNP analysis of g was completed separately within each COGENT study using Plink [Purcell et al., 2007] or Genome-wide Complex Trait Analysis (GCTA) [YanG et al., 2011]. Plink was used to analyze datasets comprising unrelated individuals, and GCTA used to analyze five datasets in which multiple family members were known to be included a priori. GCTA has implemented a mixed-linear-model association (MLMA) analytic function that corrects for population or relatedness structure through a correction that is specific to the structure of interest [Yang et al., 2014]. Regression coefficients and standard error estimates were generated within each study and then carried forward for meta-analysis using Metasoft [Han and Eskin, 2011] and the R MetABEL package [Aulchenko et al., 2007] for plotting of results. Although we expected that allelic effects for cognitive ability would mirror the direction observed for educational attainment, all analyses were conservatively carried out using two-tailed tests.

A multi-stage approach was utilized to determine if GWAS hits associated with educational attainment were also associated with general cognitive ability in COGENT. First, we examined the p-values of the three educational attainment SNPs (and their close proxies) in the database housing the results of the COGENT1 GWAS [Lencz et al., 2014]. SNPs with P-values $<.05$ identified in this first stage were then meta-analyzed for association to g in $\approx$16,000 independent subjects in the subsequent replication stage.

RESULTS
COGENT Analysis

Using the approach described above, the two SNPs previously associated with the dichotomous variable of completing college (rs11584700 and rs4851266) in [Rietveld et al., 2013] were not significantly associated with g in COGENT1 (P's $>.05$). The third SNP (rs9320913) associated with years of schooling was neither genotyped nor imputed in COGENT1; however, a close proxy SNP (rs1906252, $R^2 = 1.0$ in HapMap2 CEU, $R^2 = .905$ in 1000 Genomes CEU) was available for analysis in the COGENT1 GWAS data. rs1906252 was either typed or imputed in all nine COGENT1 studies, and was significantly associated with general cognitive ability in the expected direction, such that the minor (A) allele was associated with higher g scores ($\beta = .050$,

TABLE II. Results of the Association Between rs1906252 and General Cognitive Ability in COGENT

Data set	Studies (N)	Subjects (N)	Fixed effects			Random effects			Heterogeneity estimates			
			β	S.E.	P	β	S.E.	P	I^2	Q	P_Q	Tau^2
COGENT1	9	4,962	.050	.020	1.20E-02	.050	.022	2.08E-02	11.411	9.030	.340	0
COGENT2	12	15,533	.027	.009	2.34E-03	.027	.009	2.34E-03	0	8.472	.671	0
COGENT, all cohorts	21	20,495	.031	.008	1.47E-04	.031	.008	1.47E-04	0	18.668	.543	0
COGENT, excluding HBCS and LBC1936[a]	19	19,192	.026	.008	1.60E-03	.026	.008	1.60E-03	0	11.126	.889	0
COGENT, excluding HBCS, LBC1936, CHS, FHS and NCNG[b]	16	14,971	.022	.010	2.81E-02	.022	.010	2.81E-02	0	10.467	.789	0

COGENT, Cognitive Genomics Consortium; COGENT1, nine sites included in COGENT Phase 1 [Lencz et al., 2014]; COGENT2, 12 sites added to Phase 2 of COGENT; HBCS, Helsinki Birth Cohort Study; LBC1936, Lothian Birth Cohort 1936; CHS, Cardiovascular Health Study; FHS, Framingham Heart Study; NCNG, Norwegian Cognitive NeuroGenetics Study.

[a]HBCS and LBC1936 removed since both studies were part of the Social Science Genetic Association Consortium (SSGAC) educational attainment GWAS study (Rietveld et al., 2013) and/or SSGAC cognition study (Rietveld et al., 2014).

[b]HBCS and LBC1936 removed since both studies were part of the SSGAC educational attainment GWAS study (Rietveld et al., 2013) and/or SSGAC cognition study (Rietveld et al., 2014), and CHS, FHS and NCNG removed since these studies were part of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium cognition study (Davies et al., 2015).

$P = .012$; $P_Q = .340$). This SNP was therefore carried forward for analysis in COGENT2.

To date, GWAS and neurocognitive data have been acquired for more than 15,000 participants from 12 independent cohorts in COGENT2. The average sample size of individual COGENT2 studies was 1,398 and ranged from 127 to 4,412 Caucasian subjects of European ancestry. rs1906252 was genotyped or imputed in all 12 COGENT2 samples (N = 16,544 genotypes), of which 15,533 had g factor data. As shown in Table 2, the association between allelic variation at SNP rs1906252 and g in COGENT2 was statistically significant and not biased by heterogeneity ($\beta = .027$, $P = 2.34 \times 10^{-3}$, two-tailed; $P_Q = .671$). The direction of the minor allele effect was positive in 10 out of 12 COGENT2 studies, which was consistent with the educational attainment GWAS studies and COGENT1, and statistically different from chance (binomial test, $P = .02$). Finally, all 21 COGENT datasets were merged to analyze the association between rs1906252 and g in the combined sample of 20,495 individuals. A significant association was again detected in the combined analysis that was not confounded by heterogeneity ($\beta = .031$, $P = 1.47 \times 10^{-4}$, two-tailed; $P_Q = .543$). Figure 2 presents the combined results in a forest plot, and as shown in Figure 3, a linear increase in general cognitive ability was related positively to minor A allele load.

We tested the robustness of the association between rs1906252 and g in a series of sensitivity analyses. First, a potential confound worthy of consideration was the fact that two COGENT1 studies (Helsinki Birth Cohort Study [HBCS; n = 332] and the 1936 Lothian Birth Cohort Study [LBC1936; n = 1,005]) [Lencz et al., 2014] were also included in SSGAC [Rietveld et al., 2014b; 2013]. The non-independence of our collective studies and the high correlation between educational attainment and cognition necessitated a sensitivity analysis requiring HBCS and LBC1936 be excluded and the
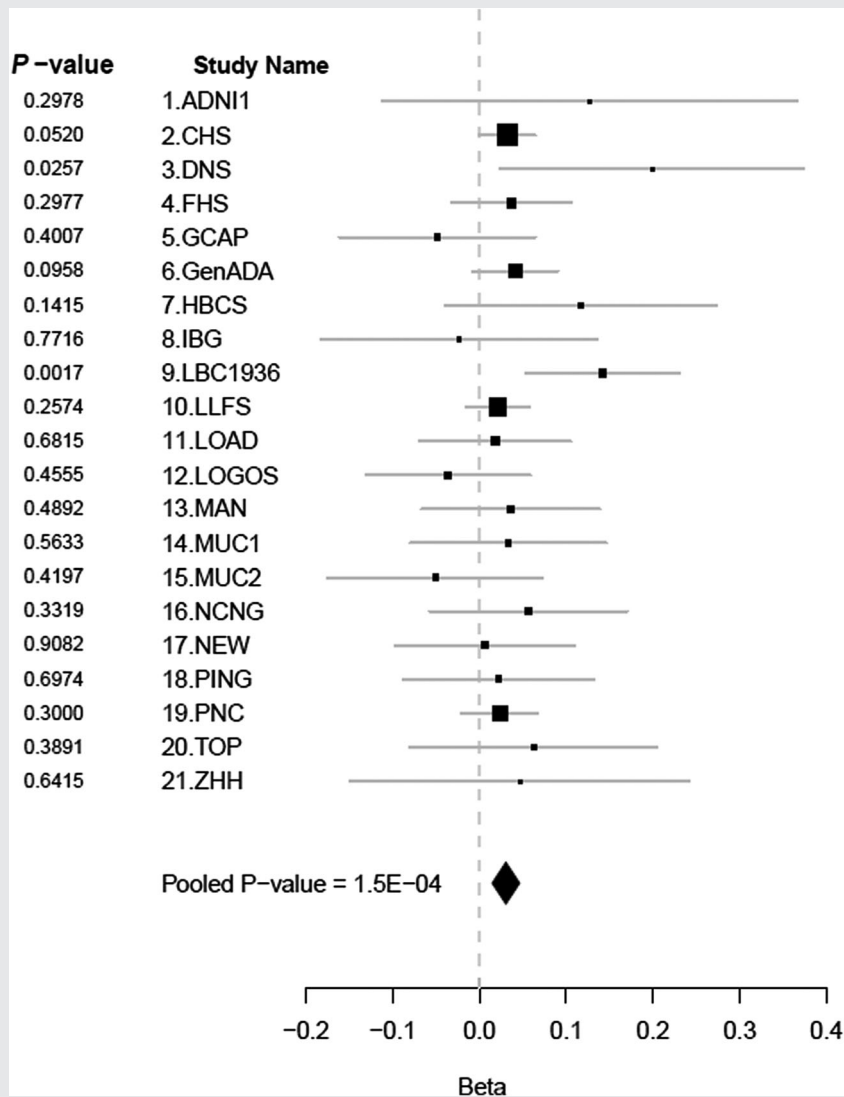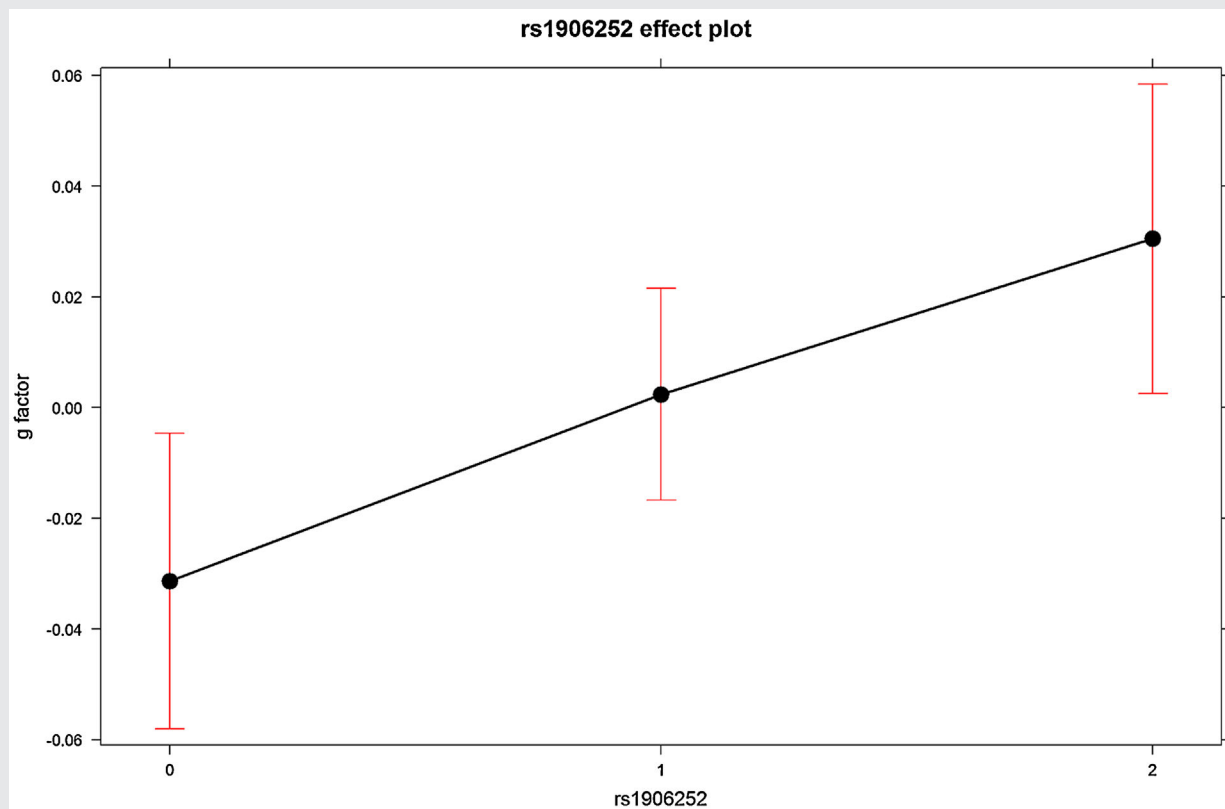

FIG. 2. Results (in forest-plot format) of the meta-analysis between rs1906252 and general cognitive ability in all 21 COGENT studies. A positive effect was detected in 17 out of 21 studies.

FIG. 3. Effect plot of the association between rs1906252 and general cognitive ability. A linear increase in general cognitive ability was related positively to minor A allele load. In the combined sample, 5,254 subjects had no copies of the minor allele, 10,329 subjects were heterozygous, and 4,912 subjects had two copies of the minor A allele.

remaining COGENT studies reanalyzed. This analysis also yielded a significant result between variation in rs1906252 and g ($\beta = .026$, $P = 1.60 \times 10^{-3}$, two-tailed; $P_Q = .889$; see Table 2).

Next, age had a bimodal distribution across the 21 COGENT studies. The first peak was at approximately 18 years of age, and the second peak at approximately 70 years (supplemental figure S1). To explore the effect of age on the association between rs1906252 and g across the lifespan, we examined the interaction between rs1906252 and age on g, which was not significant ($\beta = .0004$, $P = .302$). We then split the sample at the 'valley' of the distribution at age 40. This resulted in a group of 7,208 individuals under 40 years of age and a group of 13,287 individuals 40 years of age or older. The interaction between rs1906252 and this dichotomous age split was not significant ($\beta = .007$, $P = .728$). Thus, age did not moderate the association between rs1906252 and general cognitive function across the lifespan in COGENT.

SSGAC Meta-Analysis

The SSGAC reanalyzed their GWAS data utilizing a two-stage design in order to examine whether educational attainment is a valid proxy phenotype for cognitive ability [Rietveld et al., 2014b]. Subjects with available neurocognitive data (n = 24,189) were removed from the larger cohort, and a GWAS of years of education was then conducted in the remaining ~106K participants (Stage 1). The top 69 SNPs associated with educational attainment were then carried forward for analysis in relation to cognitive performance in the ~24K subsample (Stage 2). In Stage 1, the chromosome 6q16.1 locus previously associated with years of schooling was again genome-wide significant for educational attainment, although the top SNP at this locus was slightly different (rs9320913 in the original GWAS and rs1487441 in the second GWAS; $R^2 > .9$ between the two SNPs). In Stage 2, rs1487441 was the SNP most strongly associated with cognitive performance ($P = 1.24 \times 10^{-4}$).

Notably, rs1487441 is a perfect proxy for our SNP, rs1906252 ($R^2 = 1$ in both HapMap and 1000 Genomes). Thus, we sought to integrate our current results with the most recent SSGAC findings. As shown in Table III, we performed a meta-analysis of the SSGAC cognitive subcohort with our fully independent COGENT cohorts. LBC1936 and HBCS were part of the SSGAC studies, so they were excluded for this particular analysis. However, this was a conservative approach since (i) LBC1936 was included in the cognitive performance sample as part of the Childhood Intelligence Consor-

TABLE III. Meta-Analytic Results of the Association Between General Cognitive Ability and Genetic Variants in Chromosome 6q16.1 Associated With Educational Attainment in COGENT (SNP rs1906252), SSGAC (SNP rs1487441) and CHARGE (SNP rs1906252)

Consortium	N studies	N subjects	β	S.E.	P
COGENT, excluding HBCS and LBC1936	19	19,192	.026	.008	1.60E-03
SSGAC	11	24,189	.036	.009	1.24E-04
COGENT and SSGAC	30	43,381	.031	.006	4.94E-07
COGENT, excluding HBCS, LBC1936, CHS, FHS and NCNG	16	14,971	.022	.010	2.81E-02
CHARGE	26	53,188	.031	.006	1.55E-08
COGENT and CHARGE	42	68,159	.029	.005	1.65E-09

COGENT, Cognitive Genomics Consortium; SSGAC, Social Science Genetic Association Consortium; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium. *Note*: COGENT studies that overlapped with SSGAC (HBCS and LBC1936) and/or CHARGE (HBCS, LBC1936, CHS, FHS, and NCNG) were removed prior to conducting joint analyses. The Lothian Birth Cohort Studies of 1921 and 1936 and the Helsinki Birth Cohort Study (HBCS) overlapped between SSGAC and CHARGE.

tium, which used age 11 cognitive phenotypes for LBC1936, whereas LBC1936 adult phenotypes were included in COGENT; and (ii) HBCS was not included in the SSGAC cognitive analysis, only the educational attainment GWAS [Rietveld et al., 2014b]. With a total sample size of 43,381 non-duplicated individuals across SSGAC and COGENT, the association between this locus and *g* had an estimated effect size of β = .031 ($P = 4.94 \times 10^{-7}$).

CHARGE Meta-Analysis

A GWAS of general cognitive function that included ≈53,000 individuals from 31 population-based cohorts was recently published by the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium [Davies et al., 2015]. The study reported genome-wide significant SNP associations with general cognitive ability in three genomic regions, including rs1906252 ($P = 1.55 \times 10^{-8}$). We sought to integrate the COGENT findings with the CHARGE findings as well, and conducted a second meta-analysis of rs1906252 and *g*. In this analytic series, the COGENT samples were fully independent from both the SSGAC and the CHARGE samples. In other words, we excluded HBCS and LBC1936 as above, and excluded additional data from our Framingham Heart Study, Second Generation Cohort (FHS) sample, the Cardiovascular Health Study (CHS) sample, and the Norwegian Cognitive NeuroGenetics (NCNG) sample, all of which overlapped with CHARGE to some extent. In the reduced CO-GENT sample of 16 sites and ≈15,000 subjects fully independent from SSGAC and CHARGE, rs1906252 retained a significant association to *g* (β = .022, $P = 2.81 \times 10^{-2}$). Further, the joint analysis of the 42 independent COGENT and CHARGE cohorts (N ≈ 68,000) was robust (β = .029, $P = 1.65 \times 10^{-9}$).

CONCLUSIONS

The current study identified a significant association of a SNP at chromosome 6q16.1 with general cognitive ability across 21 well-characterized international samples of European-ancestry individuals from the general population. Sensitivity analysis suggested that the association between rs1906252 and *g* was significant, independent of the previously published cohorts from the educational

attainment GWAS; moreover, the strength of the association was not affected by age of the subjects. In COGENT, the direction of association with *g* was consistent with the association to self-reported educational attainment in the SSGAC, with more copies of the minor A allele linked to better performance on objectively-measured sub-traits that comprise general cognitive ability.

Based on the commonly used formula [Thorleifsson et al., 2009], $R^2 = 2f(1-f) a^2$, where *f* is the allele frequency (0.47 in this instance) and *a* is the additive effect as measured by standardized beta, the independent COGENT cohort produces an estimated effect size of $R^2 = .0382\%$ (Table 3). This effect size estimate is slightly more than half the value obtained in the SSGAC cognitive subcohort. This is probably due, at least in part, to the 'winner's curse' phenomenon in which initial observations produce inflated effects by chance [Zollner and Pritchard, 2007]. The present report provides the first estimate of the effect size that is fully independent of the initial discovery cohort. This effect size is approximately an order of magnitude smaller than the largest allelic effect sizes observed for other complex polygenic traits such as height or weight [Visscher et al., 2012; Wood et al., 2014], possibly due to the inherent noise and heterogeneity in the construction of the *g* phenotype. However, the success of GWAS for height and weight provide optimism that future, larger GWAS of cognitive ability will prove increasingly successful at identifying significant associations.

For example, the first study reporting a genome-wide significant QTL for height [Weedon et al., 2007] had power of only 3.2% to detect the *HMGA2* locus, based on the effect size estimate later derived from an independent cohort that was an order of magnitude larger [Lango Allen et al., 2010]. Similarly, subsequent height GWAS [Weedon et al., 2008] remained underpowered by conventional criteria (1-β = .80) to detect even the strongest loci, yet were still able to obtain genome-wide significance for multiple loci, including those for which power was <1%. This pattern applies to all polygenic complex traits, due to the very large number of loci that are available to be detected, especially given that the number of associated loci tends to increase very rapidly as effect sizes drop [Park et al., 2010].

Functionally, rs1906252 is about 700 kilobases from the nearest annotated gene, but it is in an intron of a long intergenic non-coding RNA (lincRNA; transcript ID: *RP11-436D23.1*; Gene ID:

LOC101927335; Ensembl Gene ID: *ENSG00000271860*) that is expressed in human brain tissue based on searches in BrainSpan (http://www.brainspan.org/) and GeneProf [Halbritter et al., 2012] (http://www.geneprof.org/). In order to identify potential regulatory elements at this genomic locus, we interrogated rs1906252 using HaploReg v3 [Ward and Kellis, 2012]. While rs1906252 is unannotated, it is in nearly perfect LD ($R^2 = .99$) with rs77910749, which is highly conserved (by both GERP and SiPhy computations), is a DNase hypersensitivity site in fetal brain, and serves as a weak enhancer or transcription start site across multiple brain tissues. Notably, rs1906252 was recently reported to be a genome-wide significant variant associated with bipolar disorder [Mühleisen et al., 2014], again providing evidence of the important overlap of general cognitive ability and psychiatric illness; the primary finding of our previous COGENT study was a significant polygenic overlap between SNPs for general cognitive ability and schizophrenia [Lencz et al., 2014]. Additionally, rs1906252 was among the top findings (though not significant after correction for multiple comparisons) in an earlier GWAS of processing speed based on performance on the symbol search test conducted in part in the LBC1936 cohort [Luciano et al., 2011]. Most recently, rs1906252 and 10 other SNPs in this region were associated with general cognitive function in a GWAS of ≈53,000 subjects at a threshold considered to reach genome-wide significance [Davies et al., 2015].

In summary, the current study provides an independent replication of a link between genetic variation at rs1906252 and neurocognitive ability. Results also provide evidence that the proxy phenotype approach of using educational attainment as an indirect measure of cognitive ability for GWAS has external validity.

DESCRIPTION OF SUPPLEMENTAL DATA

Supplemental Data include detailed descriptions of the 21 COGENT cohorts including neurocognitive and genetic assays employed across sites. In addition, detailed statistical methodology, imputation methods, and quality control procedures of phenotypes and genotypes are described in detail, and three supplemental figures along with two supplemental tables and supplemental references are included.

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