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Educational attainment-related loci identified by GWAS are associated with select personality traits and mathematics and language abilities

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ABSTRACT

A recent genome-wide association study of educational attainment identified three significant single nucleotide polymorphisms (SNPs) (rs9320913, rs11584700, and rs4851266). In this study, we expanded this previous work by investigating behavioral correlates of these SNPs in a Han Chinese sample (rs9320913 was not available in our data and was thus replaced by rs12202969, which is in high linkage disequilibrium [i.e., correlations of alleles] with the former, $r^2 = 0.96$ in Han Chinese population based on the 1000 Genomes Project). Association analysis for individual SNPs showed significant associations between rs4851266 and a measure of language ability (Chinese word recognition), and between rs12202969 and a personality trait (fear of negative evaluation) and a measure of mathematical ability (number paired-associates learning). A polygenic score based on these three SNPs was also significantly associated with the measures of mathematical and language abilities. Specifically, educationally advantaged alleles identified in the previous study were associated with less fear of negative evaluation and higher mathematical and language abilities in the current study. This exploratory study provides evidence of psychological mechanisms for the association between genes and educational attainment.

1. Introduction

Educational attainment usually refers to the highest degree of education that an individual has completed. Twin studies showed that educational attainment had moderate heritability, ranging from 18% to 77% across different studies (Branigan, McCallum, & Freese, 2013).

A recent genome-wide association study, using a large Caucasian sample, showed that three independent single nucleotide polymorphisms (SNPs, rs9320913, rs11584700, and rs4851266) were associated with educational attainment (Rietveld et al., 2013). They found positive associations between years of schooling and allele A of rs9320913 (located on Chromosome 6 at position 98,691,454 bp near the gene *LOC*100129158), and positive associations between college completion and allele A of rs11584700 (located on Chromosome 1 at position 202,843,606 bp near the gene *LRRN2* [leucine rich repeat neuronal 2]) and allele T of rs4851266 (located on Chromosome 2 at position 100,184,911 bp near the gene *LOC*150577). These researchers suggested that follow-up studies should use the candidate gene approach to explore the potential associations between these genetic variants and well-measured endophenotypes, such as personality and cognition (Flint & Munafò, 2013; Rietveld et al., 2013).

Indeed, Ward et al. (2014) recently reported a significant association between the composite score of the three educational attainment-related SNPs (i.e., rs9320913, rs11584700, and rs4851266) and children's school performance as measured by the Standard Assessment Tests (SATS) at age 13–14 years. More specifically, rs9320913 was found to be associated with both the English ($p = 0.002$) and mathematics scores ($p = 0.015$), but there were no significant associations between the other two SNPs (i.e., rs11584700 and rs4851266) and the test scores (p's > 0.05).

The current study aimed to expand on the work by Ward et al. (2014) by examining possible associations between genetic variants linked to educational attainments and various endophenotypes, including an extensive set of measures of personality, mental health, cognition, and mathematical and language abilities (see Methods for a brief description and see Chen et al., 2013 Table S2 for details). Using data from an existing project (e.g.,

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Chen et al., 2013), we analyzed the associations between these behavioral measures and three SNPs (i.e., rs12202969, rs11584700, and rs4851266). SNP rs12202969 was used instead of rs9320913 because the latter is not available in our data and these two SNPs are 8.5 kb apart and have extremely high linkage disequilibrium (LD), $r^2 = .98$ and .96 in European and Han Chinese populations, respectively, based on the data of the 1000 Genomes Project (http://browser.1000genomes.org). Allele A of rs9320913 corresponds to allele A of rs12202969. Results should help elucidate the underlying mechanisms for the genetic basis of educational attainment.

2. Material and methods

2.1. Participants

Of the original sample of 480 subjects (Chen et al., 2013), genetic data for the three SNPs were available for 342, who were the subjects of the current study. All subjects were healthy Han Chinese undergraduates (sophomores, mean age = 20.42 years, SD = .89, range 18–22 years old; 55% female) from Beijing Normal University in China. All subjects had normal or corrected-to-normal vision and had no neurological or psychiatric history based on their self-report. They all signed written informed consent. This study was approved by the Institutional Review Board (IRB) of Beijing Normal University, China.

Individuals in this sample were all unrelated to one another. To ensure that there was no stratification effect in our sample, we conducted the following analyses using PLINK software (Purcell et al., 2007). First, we used PLINK to calculate the genomic inflation factor (lambda values) based on the genome-wide data of our subjects. In the current study, lambda values were all near 1 indicating no stratification effect on the association results. Second, we assessed the stratification effects by PLINK via clustering individuals into homogenous subsets based the genome-wide average proportion of alleles shared identity by state (IBS) between any two individuals. At the first level, we constrained the cluster solution to two classes, and the results showed that only one subject belonged to the second cluster, suggesting little systematic stratification. Deleting one subject made little difference to the results, so data for all 342 subjects were analyzed.

2.2. Behavioral assessment

To explore the potential behavioral correlates of educational attainment-related SNPs, we analyzed the data from a battery of behavioral measures including 17 personality and mental health self-reported measures, 18 cognitive tasks, 9 mathematical tasks, and 5 language tasks (see Chen et al. (2013) Table S2, for details). These measures have been widely used in previous research and proved to have good psychometric properties. Preliminary analyses resulted in three measures with significant ($p < 0.01$) associations with the targeted SNPs (see Table S1 for complete results on all measures). Therefore, we describe the three measures in greater detail below.

2.2.1. Personality: Fear of negative evaluation

Fear of negative evaluation was measured by a personality questionnaire called Brief Fear of Negative Evaluation (BFNE). It includes 12 items measuring the degree to which people experience apprehension at the prospect of being evaluated negatively (Leary, 1983). For example, a sample item is "I often worry that I will say or do the wrong things." Each item is answered using a five-point Likert scale, ranging from 1 (not at all characteristic of me) to 5 (extremely characteristic of me). Previous research has shown that the scale has satisfactory reliability and construct validity (Leary, 1983). Similar to previous studies, the Cronbach alpha value was 0.90 in the current study.

2.2.2. Mathematical ability: Number paired-associates learning

This test was based on a study by Delazer et al. (2005) and a previous study for measuring mathematical ability among Chinese college students (Wei, Yuan, Chen, & Zhou, 2012). An artificial operation '§' was defined as '12b − 9a + 70'. That is, $a \S b = 12b - 9a + 70$. For example, $5 \S 3 = 61$ (because $5 \S 1 = 12 \times 3 - 9 \times 5 + 70$). Two other examples of the equations were $2 \S 1 = 64$, $4 \S 2 = 58$. Fifteen equations were created based on the artificial operation. The participants, however, were not given the above definition of the operation. Instead, they were briefly presented an expanded form of the operation (i.e., '$a \S b' = (10 - a) \times b - (b - a) \times (b - a) - (a - 3) \times (b - 1) + a \times a + b \times b + (100 - 10 \times a - b) - 27$'). Because of its complexity, the participants were not able to memorize the definition of the artificial operation. Instead, they were asked to memorize the associations between pairs of operands and their answer for the 15 equations. During the learning stage, an equation was presented in the middle of the screen for 10 s. After subjects memorized all equations, they were tested. During the test stage, participants needed to judge whether a given equation (e.g., '$5 \S 3 = 61$', '$5 \S 3 = 64$') was correct or not. Half of the trials in the test stage were correct equations, and the other half were incorrect equations. Each trial was presented for 9 s. After the test stage, participants learned the equations again and were tested again. The percentage of correct answers on the second test was analyzed. The split-half reliability of this test was 0.69.

2.2.3. Language ability: Chinese word recognition

Participants were asked to read aloud very low-frequency Chinese characters (50 characters in total). These characters were selected from a Chinese character psycholinguistic norm (Liu, Shu, & Li, 2007). This task was used in a previous study that measured Chinese reading ability (Mei et al., 2013). The subjects were told that they would see some Chinese characters and have 5 s to read each character aloud before they were prompted to move on to the next character. The experimenter pointed to each Chinese character one by one from left to right, asked the subject to read each character aloud within 5 s, and recorded the performance of the subject on the answer sheet. The number of characters recognized correctly was used as the index for this task.

2.3. Genotyping

A 4 ml venous blood sample was collected from each subject. Genomic DNA was extracted according to the standard method within 2 weeks after the blood sample was collected. All samples were genotyped using the standard Affymetrix genotyping protocol (Affymetrix, Inc.). As described in Table 1, the allele frequencies of genotyped SNPs (rs11584700, rs4851266, and rs12202969) in our sample were very similar to those of the Asians (e.g., Chinese and Japanese) in the HapMap dataset (www.hapmap.org [phase 3]). All SNPs met the criteria of a call rate of >95%, Minor Allele Frequency (MAF) of >0.05, and Hardy–Weinberg equilibrium (HWE) of $p > 0.05$ in the current study.

2.4. Polygenic score

Following the procedure used by Rietveld et al. (2013), we created a polygenic score based on the selected SNPs for each individual. The polygenic score for the ith individual was calculated as