

1 Running title: new genetic variants associated with mathematical ability in Chinese
2 children

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4 **A genome-wide association study identified new variants associated with**
5 **mathematical abilities in Chinese children**

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23

Abstract

24 Mathematical ability is moderately heritable, and it is a complex trait which can be
25 evaluated in several different categories. A few genetic studies have been published on
26 general mathematical ability. However, no genetic study focused on specific
27 mathematical ability categories. In this study, we separately performed genome-wide
28 association studies (GWASs) on 11 mathematical ability categories in 1 146 students
29 from Chinese elementary schools. We identified 7 genome-wide significant single
30 nucleotide polymorphisms (SNPs) with strong linkage disequilibrium (LD) among
31 each other (all $r^2 > 0.8$) associated with mathematical reasoning ability (top SNP:
32 rs34034296, $p = 2.01 \times 10^{-8}$, nearest gene: CUB and Sushi multiple domains 3, CSMD3).
33 We replicated one SNP (rs133885) from 585 SNPs previously reported to be
34 associated with general mathematical ability associated with division ability in our
35 data ($p = 1.053 \times 10^{-5}$). In the gene- and gene-set enrichment analysis by MAGMA, we
36 found three significant enrichments of associations with three mathematical ability
37 categories for three genes. We also observed four significant enrichments of
38 associations with four mathematical ability categories for three gene sets. Our results
39 suggest new candidate genetic loci for the genetics of mathematical ability.

40

41 KEYWORDS

42 Genome-wide association study, quantitative trait, mathematical ability, enrichment

43 INTRODUCTION

44 Mathematical ability is a complex trait which is the key to excellent performance
45 in study and work. Substantial heritability estimates (0.2-0.9) have been reported in
46 previous studies indicating that mathematical ability was influenced by genetic
47 factors[1-5]. In recent years, several GWASs have been applied to study genetic
48 components associated with mathematical ability [6-11]. Among these GWASs,
49 rs133885 was considered to be associated with mathematical ability ($n=699$,
50 $p=7.71\times 10^{-10}$) [11], but the finding was not replicated in another study [12]. Then,
51 researchers found four loci associated with Chinese students' curriculum scores of
52 mathematics by conducting a meta-analysis [7]. Later, Lee and colleagues performed
53 a GWAS on two phenotypes reflecting mathematical ability in large samples ($n_1=564$
54 698 , $n_2=430$ 445), they found a total of 983 loci at genome-wide significant level [10].

55 According to the Syllabus of Primary and Secondary Schools in China,
56 mathematical ability can be divided into specific categories such as calculation ability
57 (addition, subtraction, multiplication, division, etc.), logical reasoning ability, spatial
58 ability and applied mathematics ability. According to UK National Curriculum (NC)
59 Key Stage 2 criteria, the mathematical knowledge evaluated by the examination
60 include number (number and position value, addition, subtraction, multiplication,
61 division, etc.), measurement, geometry (properties of shapes, position and direction)
62 and statistics. These mathematical ability categories are usually measured by some
63 specific scales. The Heidelberg mathematics test is a well-established test with good
64 reliability and validity, which considered to be one of the most comprehensive tests to
65 measure different mathematical ability categories [13].

66 Previous GWASs mostly used composite scores as phenotypes (self-reported
67 math ability, NC-based teacher ratings, NC-based web-based testing, academic

68 achievement, etc.), except for one study, which used test measurement (numerosity
69 judgements), a composite score of two tests (addition and multiplication) and a
70 composite score of three tests (addition, multiplication and numerosity judgements) as
71 three phenotypes, respectively [11]. To our knowledge, no researchers have
72 systematically used a wide range of mathematical tests, the detailed subphenotypes
73 such as those in Heidelberg mathematics test, to screen for genetic associations. In
74 addition, none of past large scale genetic association studies of mathematical abilities
75 have used asian populations.

76 In the present study, we performed a GWAS in students of the Chinese
77 elementary school to discover the genetic basis of mathematical ability measured by
78 Heidelberg mathematics test [13]. We separately analyzed eleven mathematical ability
79 categories. Then, we also tested 585 SNPs that have been reported to be associated
80 with general mathematical ability in our data for the eleven categories. Finally, we
81 found some significant enrichment of associations with categories for specific genes
82 or gene sets.

83 **METHODS AND MATERIALS**

84 **Participants**

85 A cohort of primary school students from two provinces in the northwestern part
86 of China, including Shaanxi province and Gansu province, were recruited as
87 participants in this study. Nonverbal intelligences of these children were measured by
88 Raven's Standard Progressive Matrices individually [14]. According to Zhang's local
89 norms [15], all children had normal IQ. In total, 1 182 participants were eligible for
90 subsequent genotyping and association analysis. This study was approved by the
91 ethics committee of Shaanxi Normal University, and written informed consent was
92 obtained for all the participants' parents.

93 **Phenotypic measure**

94 A Chinese version of Heidelberg mathematics test was used to test the
95 mathematical ability for the Chinese cohort [13-16]. The test included 11 subtests
96 corresponding to 11 mathematical ability categories divided into two areas, namely
97 the arithmetic operations area and the numerical-logical and spatial-visual skills area.
98 Area of arithmetic operations assess performance in six tasks, including addition,
99 subtraction, multiplication, division, equation and magnitude perception tasks. Area of
100 numeric-logical and spatial-visual evaluate performances in five tasks, including
101 mathematical reasoning, visual size estimation, spatial conception, quantity counting
102 and visuomotor tasks. A brief description of this test is shown in Table S1.

103 The test-retest reliabilities of the whole test and the area tests were $r = .69-.89$
104 and $r = .87-.93$, respectively [13]. Later investigations revealed that correlations
105 between whole test score and mathematical curriculum scores were $r = .67$ and $r = .68$
106 respectively in two different samples [17]. The split-half reliability of the Chinese
107 version of Heidelberg mathematics test was 0.9 and the test score was also correlated
108 with Chinese students' curriculum scores of mathematics [16].

109 Students were tested in groups. Each subtest was required to complete in a given
110 amount of time. Testing process of this test is shown in the supplementary methods.
111 All analyses were based on the raw data.

112 Scores of subtests showed moderate to high degree of correlations with each
113 other (see Table S2).

114 **Genotype quality control and imputation**

115 Genomic DNAs were extracted from saliva samples by Hi-Swab DNA Kit
116 (Lot#R7220, Cat.#DP362-02) of Tiangen Biotechnology in Beijing, China.
117 Genome-wide genotyping experiments used Illumina Asian screening array (650K)

118 supplied by Compass Biotechnology in Beijing, China. There were 1 177 samples and
119 704 415 SNPs in the original data. Genotype quality control was conducted in PLINK
120 v1.90. SNPs were removed if they displayed a Hardy-Weinberg Equilibrium (HWE)
121 $<10^{-5}$, a minor allele frequency (MAF) <0.01 , or a variant call rate <0.95 . Individuals
122 were removed if they displayed a sex discrepancy between the records and the
123 genetically inferred data [18, 19], an unexpected duplicates or probable relatives
124 (PI-HAT >0.20), or a genotyping call rate <0.9 . After this step of quality control, 1 146
125 samples and 497 823 SNPs were left.

126 Imputation was conducted using the Genome Asia Pilot-GasP (GRCh37/hg19)
127 reference panel on the Michigan Imputation Server (Minimac4). After imputation,
128 there were 8 625 058 SNPs. Imputed SNPs were removed if they showed a $R^2 <0.6$.
129 After the imputation, we carried out a quality control again. SNPs were removed if
130 they displayed a HWE $<10^{-5}$, a MAF <0.05 , or a variant call rate <0.95 . Individuals
131 were removed if they displayed a genotyping call rate <0.9 . Finally, there were 5 406
132 859 SNPs and 1 146 samples left.

133 **Statistical analysis**

134 After imputation and quality control, 1 146 individuals had genotype data,
135 covariate data and phenotype data simultaneously (age: 115.25 ± 9.59 months; sex
136 ratio(M:F): 588:558) (Table S3 for sample size of each continuous trait analysed in
137 this study).

138 We conducted GWASs with genotype dosage using PLINK v1.90. Linear
139 regression analyses for 11 mathematical ability categories were carried out by an
140 additive model using quadratic term for age, sex, school and the first five principal
141 components of population structure as covariates [19]. Population structure analysis
142 was conducted by PLINK v1.90 and GCTA. To perform this analysis, we used options

143 of –autosome, make-grm, grm and pca in the GCTA. Quantile-quantile plots were
144 generated by package qq-man (R3.5) to reveal the consistency between the observed
145 and expected P value and the rationality of analysis model. Manhattan plots were
146 generated by package qq-man (R3.5) to present the result of GWAS. Genome-wide
147 significance was defined as common threshold ($p=5\times 10^{-8}$). Since the 11 phenotypes
148 are highly correlated, we did not correct for the number of phenotypes tested.
149 Regional association plots were generated by a web-based tool LocusZoom
150 (<http://locuszoom.org/>) to reveal regional visualizations around top SNPs. Analysis
151 was performed on autosomes and unrelated individuals only. We also examined the
152 impact of identified significant loci on other phenotypes.

153 **Assessment of SNPs previously associated with mathematical ability**

154 To date, a total of 988 genome-wide significant ($p<5\times 10^{-8}$) SNPs have been
155 reported by previous publications. One of these SNPs (rs133885) associated with a
156 composite score (addition, multiplication and numerosity judgements) was discovered
157 in German-Austrian dyslexia samples ($p=7.71\times 10^{-10}$, $n=699$) and replicated in a
158 sample representing the general population ($p=0.048$, $n=1\ 080$) [11]. Four of these
159 SNPs associated with Chinese students' curriculum scores of mathematics were
160 reported from a study of meta-analysis of results in three different cohorts, and these
161 four SNPs have strong linkage disequilibrium [7]. The other 983 SNPs, of which 618
162 SNPs associated with self-reported math ability ($n=564\ 698$) and 365 SNPs associated
163 with highest math class taken ($n=430\ 445$), were identified in samples from 23andMe,
164 and all these SNPs are independent [10]. We looked up these SNPs in our data,
165 mapped 585 SNPs, and checked whether they were associated with mathematical
166 ability categories measured in Chinese children. Here we used a loose criterion $p =$
167 $0.05/585$ for significant replication. Details of these SNPs can be found in Table S4.

168 **Gene- and gene set-based enrichment tests**

169 Gene- and gene-set-based enrichment analyses for the mathematical ability
170 categories were performed by MAGMA [20]. The gene analysis was based on our raw
171 GWAS data. First of all, SNPs were allocated on the protein-coding genes according
172 to their genomic location. These genes containing at least one SNP of our data were
173 then subjected to internal quality control. Finally, the filtered genes were tested in the
174 gene-based enrichment analysis. Given the number of genes (17 734) finally tested,
175 the Bonferroni-corrected significance level for this analysis was set to 2.82×10^{-6}
176 ($p=0.05/17\ 734$).

177 The gene-set analysis used a competitive gene-set analysis in MAGMA based on
178 the result of gene analysis [21]. Original gene sets are from C2 data set (including
179 Chemical and genetic perturbations, Canonical pathways) on the Gene Set
180 Enrichment Analysis. We tested a total of 5 497 gene sets containing genes defined in
181 the genotype data. Given the number of gene sets finally analyzed, the
182 Bonferroni-corrected significance level for this analysis was set to 9.10×10^{-6}
183 ($p=0.05/5\ 497$).

184 **RESULTS**

185 **Single-variant genome-wide associations**

186 We separately analyzed eleven mathematical ability categories in this study.
187 Mathematical reasoning ability showed genome-wide significant associations with
188 seven SNPs, the most significant SNP we identified is rs34034296 ($p=2.01 \times 10^{-8}$,
189 $MAF=0.185$). Because the seven SNPs were in high LD with each other (all $r^2 > 0.8$),
190 indeed we only had one independent hit associated with this trait (we report the most
191 significant one). All these SNPs mapped to an intergenic region with the nearest gene
192 CSMD3 about 400 kb away from them.

193 Spatial conception ability showed a nominally genome-wide significant
194 association with rs1369404 ($p=5.40\times 10^{-8}$, $MAF=0.062$).

195 Manhattan plots for mathematical reasoning and spatial conception abilities are
196 revealed in Figure 1 and 2. Regional association plots with these two categories are
197 revealed in Figure 3 and 4. More details for all significant SNPs are reported in Table
198 1. Quantile-quantile plots for all traits and Manhattan plots for other traits are reported
199 in Supplementary Figures S1-20. Results of genome-wide association analysis of all
200 phenotypes ($p<10^{-5}$) are presented in supplementary Table S5.

201 The most significant SNP (rs34034296) also showed an association with another
202 trait (magnitude perception) withstanding the Bonferroni correction ($p=2.638\times 10^{-3} <$
203 $0.05/10$). Detailed information of analyses of the relationship between the SNP and all
204 other traits are reported in Table 2.

205 **SNPs previously reported to be associated with general mathematical ability**

206 We replicated one genetic locus (rs133885) associated with division ability in our
207 data ($p=1.053\times 10^{-5}$) that survived Bonferroni-corrected significance level of 8.5×10^{-5}
208 ($p=0.05/585$). The risk allele is identical in these two studies.

209 **Gene- and gene-set-based associations**

210 We observed a significant association for a gene LINGO2 (leucine rich repeat
211 and lg domain containing 2) with subtraction ability ($Z=4.60$, $p=2.08\times 10^{-6}$), a
212 significant association for a gene OAS1 (2'-5'-oligoadenylate synthetase 1) with
213 spatial conception ability ($Z=4.62$, $p=1.90\times 10^{-6}$), a significant association for a gene
214 HECTD1 (HECT domain E3 ubiquitin protein ligase 1) with division ability ($Z=4.54$,
215 $p=2.80\times 10^{-6}$).

216 Similarly, in the gene-set-based analysis, we observed a significant association
217 for a gene set (REACTOME_ERYTHROPOIETIN_ACTIVATES_

218 PHOSPHOINOSITIDE_3_KINASE) with magnitude perception ability ($p=3.50\times 10^{-7}$,
219 $\beta=1.36$, $SE=0.27$), a significant association for a gene set
220 (DASU_IL6_SIGNALING_DN) with addition ability ($p=1.42\times 10^{-6}$, $\beta=1.31$,
221 $SE=0.28$), a significant association for a gene set (DASU_IL6_SIGNALING_DN)
222 with division ability ($p=3.97\times 10^{-8}$, $\beta=1.52$, $SE=0.28$) and a significant association for
223 a gene set (BIOCARTA_P53_PATHWAY) with spatial conception ($p=1.88\times 10^{-6}$,
224 $\beta=0.80$, $SE=0.17$). The genes in these three gene sets are listed in Table S6a-d.

225 **DISCUSSION**

226 This is the first time that Heidelberg mathematics test has been used to measure
227 phenotypes in GWAS of mathematical ability. We identified seven SNPs associated
228 with mathematical reasoning ability. We replicated one SNP (rs133885) from the 585
229 SNPs previously reported to be associated with general mathematical ability. We also
230 found genes or gene sets significantly associated with addition, subtraction, division,
231 magnitude perception and spatial conception ability in enrichment analysis.

232 The most significant variant associated with mathematical reasoning ability was
233 rs34034296. This SNP is located in the desert region of genome. The nearest gene to
234 this locus is CSMD3. Researchers have reported copy number variants (CNVs) of
235 CSMD3 in patients with schizophrenia and autism [22-24]. Autism and developmental
236 dyscalculia are neurodevelopmental disorders, and they have comorbidities [25]. We
237 for the first time show that these genes are directly associated with mathematical
238 ability.

239 We assessed SNPs previously associated with mathematical ability. One SNP
240 (rs133885) associated with a composite score (addition, multiplication and numerosity
241 judgements) was replicated in the phenotype of division ability in our data. In
242 multiplication task, children were asked to judge whether the presented equations (e.g.

243 “ $5 \times 6 = 30$ ”) were correct. Division is the inverse of multiplication, so children may use
244 division to test the correctness of multiplication equations. SNPs associated with
245 self-reported math ability and highest math class taken were not replicated in any
246 phenotype. Self-reported math ability and highest math class taken were assessed by
247 questions, which is very different from the way we evaluated mathematical ability.
248 Also, SNPs associated with a composite curriculum score (understanding numbers,
249 computing and knowledge, non-numerical processes) were not replicated. Therefore,
250 different ways and dimensions of evaluating mathematical ability may affect the
251 replications of significant loci. Other reasons that significant loci were not replicated
252 may be related to our relatively small sample size and ethnicity differences.

253 Among these identified genes and gene sets, there are two genes associated
254 with cognition. LINGO2 was identified as a gene significantly associated with
255 subtraction ability. It can regulate synapse assembly and was reported to be a risk
256 gene for autism spectrum disorders [26]. OAS1 was identified as a gene significantly
257 associated with spatial conception ability. It has ubiquitous expression in various
258 tissues and was reported to be a risk gene for Alzheimer's disease [27]. Similarly,
259 these genes and gene sets above have been identified for the first time to be associated
260 with mathematical ability.

261 In conclusion, we identified SNPs, genes and gene sets associated with
262 mathematical skills in a sample of Chinese children. Results of our research provide
263 evidence that different mathematical abilities may have different genetic basis. This
264 study not only refined the current GWAS of mathematical ability but also added some
265 population diversity to the literature. Future studies should expand the sample size to
266 verify our findings.

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277 parents and teachers for their time and cooperation.

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279 **Conflict of interest**

280 Authors declared that there was no conflict of interest.

281

282 **SUPPORTING INFORMATION**

283 Additional supporting information may be found in the Supporting Information
284 section at the end of this article at MP's website.

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Table 1. Seven significant genetic loci ($p < 5 \times 10^{-8}$) detected in the GWAS analyses using genotype dosage

<i>Trait</i>	<i>SNP</i>	<i>CHR:BP</i>	<i>G/I</i>	<i>MAF</i>	<i>FRQ</i>	<i>INFO</i>	<i>BETA</i>	<i>SE</i>	<i>P</i>
MR	rs34034296	8:114796023	I	0.1824	0.8174	0.9503	0.7391	0.1308	2.01e-08
	rs13273940	8:114795581	G	0.1832	0.8178	0.9585	0.7311	0.1303	2.53e-08
	rs13274174	8:114795629	I	0.1841	0.8164	0.9583	0.7229	0.13	3.32e-08
	rs34769141	8:114794087	I	0.1841	0.816	0.9642	0.7194	0.1295	3.43e-08
	rs13273350	8:114795407	I	0.1841	0.8158	0.9615	0.7194	0.1296	3.52e-08
	rs13264592	8:114794819	I	0.1841	0.8151	0.9566	0.717	0.1297	4.05e-08
	rs13263837	8:114794308	I	0.1841	0.8148	0.957	0.7164	0.1296	4.08e-08

Note: G/I: Genotyped/Imputed; MR means mathematical reasoning ability.

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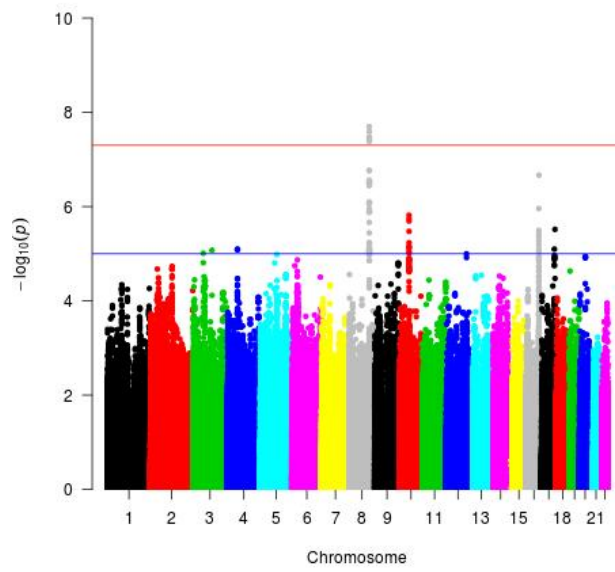
Table 2. Results of pleiotropy for the significant SNP.

SNP	TRAIT ²	FRQ	INFO	BETA	SE	P
TRAIT ¹						
rs34034296						
mathematical reasoning	magnitude perception	0.818	0.955	0.906	0.301	2.64e-03
	quantity counting	0.818	0.955	0.221	0.290	0.447
	division	0.818	0.955	0.921	0.375	1.42e-02
	visuomotor	0.818	0.958	-0.819	2.240	0.714
	multiplication	0.818	0.955	0.258	0.182	0.157
	visual size estimation	0.818	0.955	0.335	0.310	0.280
	quantity counting	0.818	0.954	0.069	0.209	0.741
	subtraction	0.818	0.956	0.604	0.271	2.62e-2
	addition	0.818	0.955	0.575	0.268	3.21e-2
	spatial conception	0.818	0.954	0.254	0.233	0.276

293 Note: ¹ means original traits of the SNP, ² means other traits tested in gene pleiotropy
 294 analysis. The effects of each significant SNP on the other 10 traits were examined, so
 295 the Bonferroni-corrected significance level for this analysis was set to 0.005
 296 (p=0.05/10).

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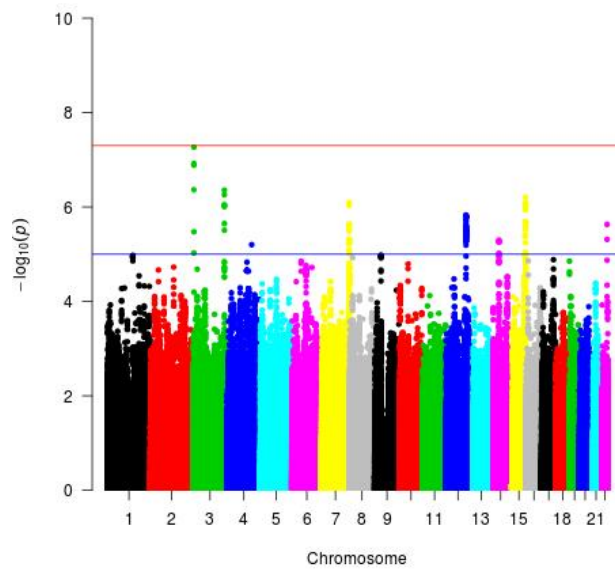


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Figure 1

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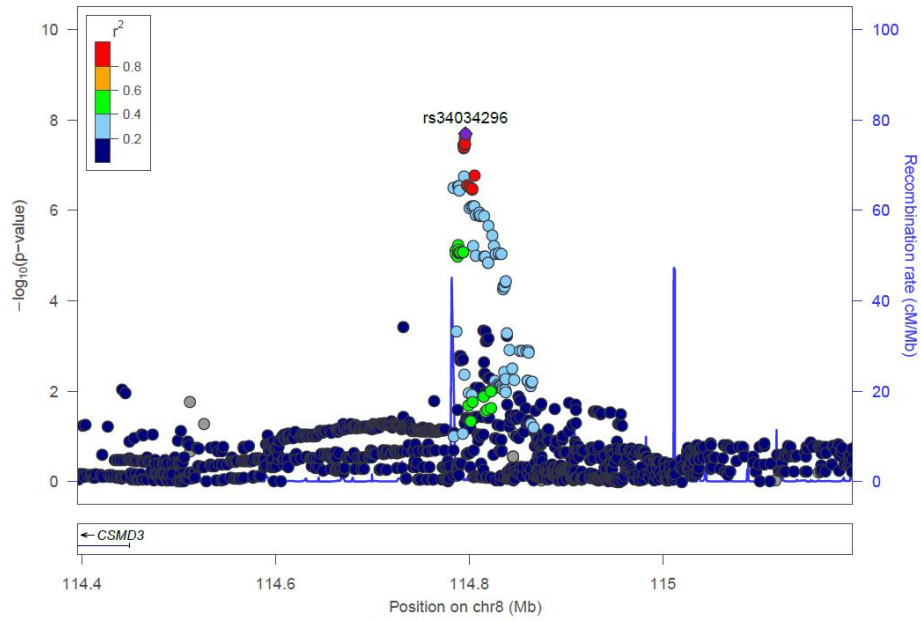


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Figure 2

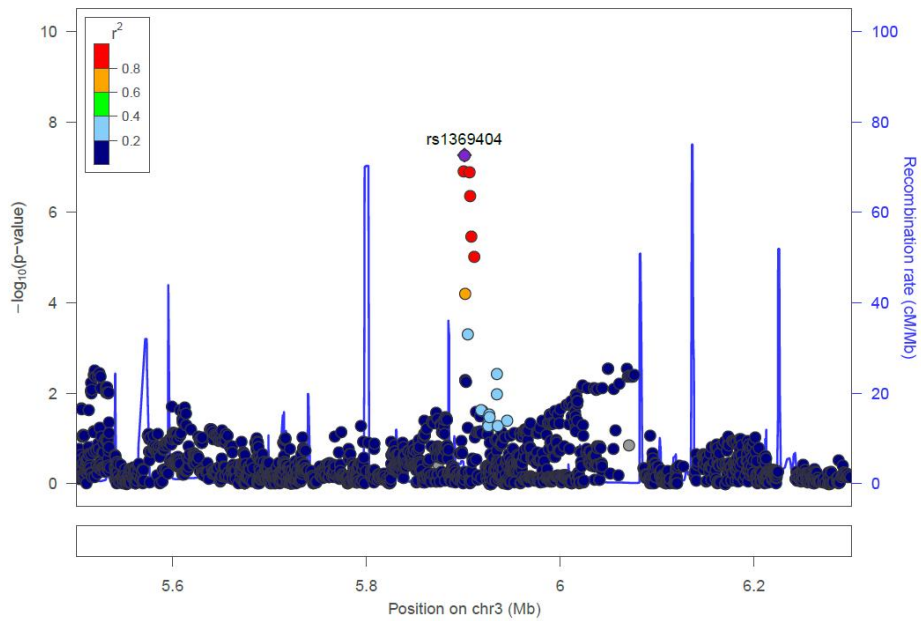
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Figure 3



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Figure 4

310 **Figure legends**

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312 Figure 1. Manhattan plots for mathematical reasoning ability. X-axis represents the
313 position of SNPs on each autosome, and y-axis represents the significance of
314 association with the phenotype. The horizontal blue line represents a threshold of
315 significance that we specified (1×10^{-6}). The horizontal red line represents the
316 threshold for genome-wide significance (5×10^{-8}).

317

318 Figure 2. Manhattan plots for spatial conception ability. X-axis represents the position
319 of SNPs on each autosome, and y-axis represents the significance of association with
320 the phenotype. The horizontal blue line represents a threshold of significance that we
321 specified (1×10^{-6}). The horizontal red line represents the threshold for genome-wide
322 significance (5×10^{-8}).

323

324 Figure 3. Regional association plots with mathematical reasoning ability. The most
325 significant genetic loci are highlighted in violet. r^2 are the LD values between other
326 loci and the most significant SNP.

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328 Figure 4. Regional association plots with spatial conception. The most significant
329 genetic loci are highlighted in violet. r^2 are the LD values between other loci and the
330 most significant SNP.

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