Can DRD2 Gene Affect Mathematical Ability? The Impact of a Working Memory-Associated Gene on Mathematical Ability

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Research Article

Keywords: DRD2 gene, Haplotype, Mathematical ability, gene-environment interaction

Posted Date: April 3rd, 2024

DOI: https://doi.org/10.21203/rs.3.rs-4179999/v1

Additional Declarations: No competing interests reported.

Abstract

Mathematical ability is influenced by various factors, particularly environment and genetics. This study focused on the effect of DRD2, a candidate gene for working memory, on mathematical ability. Our analysis of the DRD2 gene and mathematical ability performance in child participants revealed associations between the DRD2 gene and mathematical ability. It was found that individual's mathematical abilities are influenced by single nucleotide polymorphisms (SNPs) in DRD2, both in the form of haplotypes and in the way the gene interacts with parental education. The results also showed that mathematical ability is influenced by multiple genes. These findings suggest that dopaminergic genes may be linked to mathematical ability. Additionally, dopaminergic genes affect the development of children's mathematical ability by regulating working memory and related brain functions and structures. This study provides important insights into the genetic basis of mathematical ability and offers guidance for individual learning and education.

Introduction

Mathematical ability is heritable(Geary, 1993). Individuals vary more and more in their math performance as they get older, even if they are in the similar levels of environment. Previous studies have conducted genome-wide association studies for math-related abilities and found that mathematical ability appears to be influenced by multiple genes(Docherty et al., 2010; Zhang et al., 2023). However, only candidate genes related to reading abilities have been investigated for their influence on mathematical ability(Mascheretti et al., 2014). Interventions on the neural mechanisms and cognitive functions responsive to target genes are important measures for subsequent intervention and training for mathematical ability.

Working Memory (WM) allows for the control, maintenance, and manipulation of stored information in order to complete present tasks(D'Esposito & Postle, 2015). In mathematical problems (e.g., arithmetic, algebra, and geometry), solving them involves retaining partial information and processing new information to obtain a relevant solution. This often requires the utilization of WM resources(Raghubar et al., 2010). A series of projects have supported the influence of WM on mathematical abilities, including training(Judd & Klingberg, 2021), intervention(Fuchs et al., 2014), and association studies(Peng et al., 2016). From a WM perspective, a hypothesis was derived, namely, whether candidate genes associated with WM could also be identified as candidate genes for mathematical ability. DRD2 gene encodes the subtype of Dopamine (DA) receptor known as DRD2 receptor and affects the transmission of DA by inhibiting the activity of adenylyl cyclase and the production of cAMP(Störmer et al., 2012). Within the cortex, DRD2 receptors are specifically found in the temporal, parietal, frontal, occipital, and anterior cingulate cortices (Quintana & Beaulieu, 2019). It has been demonstrated that the DRD2 gene can influence cognitive processes(Reuter et al., 2005) and WM(Colzato et al., 2016; Xu et al., 2007). DRD2 gene has been associated with variations in DRD2 receptor density, thereby influencing WM performance in mice(Kellendonk et al., 2006). (Zhang et al., 2007) indicated that the splicing variations of DRD2 receptors, driven by genes (SNPs: rs1076560 and rs2283265), have a significant impact on the neural

network involved in executive function, particularly when these receptors are expressed in different neurons receiving dopamine innervation. These variations can consequently affect WM activities.

In addition, mathematical abilities appear to be influenced by parental genetics and the environment provided by parents(Docherty et al., 2011; Petrill et al., 2009). There is no doubt that gene-environment interactions play a role in shaping children's mathematical performance. The dopaminergic system, an important neurotransmitter system, is closely linked to the environment. Dopaminergic system is susceptible to environmental influences, whether it is exposed to chronic or acute stress, which can alter the concentration of dopamine release and thereby have adverse effects on cognitive and neurological disorders(Pani et al., 2000). Similarly, under environmental enrichment, the number of dopamine neurons in the midbrain increases and modifies the brain's plasticity projected by Dopaminergic system(Aumann et al., 2013). These individual differences, resulting from genetic factors, are also confirmed in gene-environment interactions. In a study about dopaminergic polygenic composite×parental behavior interactions, dopaminergic genes associated with increased reward sensitivity showed an association with poorer executive function in children when negative parental behavior was present(Andrews Espy et al., 2023; Vrantsidis et al., 2022). Based on the aforementioned findings, we propose a second hypothesis that the DRD2 gene might also be susceptible to peripheral stimuli, thereby potentially affecting an individual's mathematical ability.

Parental education (PE), as a variable on the parental end of the spectrum, influences both parental behavior and child behavior(Davis-Kean, 2005). Higher-educated parents tend to provide richer environments or stimuli that can influence the neural development and functional connectivity of children's brains(Tooley et al., 2021). Children with low PE have limited access to resources and environments compared to children with high PE, resulting in poorer cognitive and academic performance. Previous studies have revealed an interplay between genetics and PE(Friend et al., 2008; Keltikangas-Järvinen et al., 2010). Based on this evidence, we propose a third hypothesis suggesting that the interaction between the DRD2 gene and PE can significantly influence children's mathematical ability, when PE is considered as an environmental factor.

Material and Methods

Participants

A cohort of primary school students from two provinces in the northwestern part of China, including Shaanxi province and Gansu province, was recruited as participants for this study. Nonverbal intelligence of these children was assessed using Raven's Standard Progressive Matrices. all children had normal IQ levels. A total of 1097

participants were eligible for subsequent genotyping and association analysis. This study received approval from the ethics committee of Shaanxi Normal University, and written informed consent was obtained from the parents of all participants.

Parental Education (PE) Levels

A total of 798 participants in this study had information about their parents' educational levels, with 1 representing the lowest educational level and 8 representing the highest educational level: 1 = primary school education, 2 = junior high school education, 3 = senior high school education, 4 = junior college education, 5 = undergraduate degree, 6 = master's degree, 7 = doctoral degree, and 8 = postdoc. The average score of mother's and father's educational levels was used as a child's parental educational level.

SNP selection and genotyping

First, 28 SNPs related to WM and language ability were selected. These SNPs were then included in the genotyping and imputation phases for the individuals under study (see Table S1). Among them, three variants were imputed using Michigan Imputation Server(Minimac4).The parameters were minor allele frequency (MAF) over 1%. SNPs were eliminated if they showed a variant call rate < 0.95, a missing genotype data (mind) < 0.90, or a hardy-weinberg equilibrium (HWE) < 10^{-5} with each dataset. We also impute DRD2 by using the Genome Asia Pilot-GasP (GRCh37/hg19) reference panel on the Michigan Imputation Server (Minimac4). For quality control of all SNPs, please refer to the corresponding article (Zhang et al., 2023).

Phenotypic measure

A Chinese version of Heidelberg mathematics test was used to test the mathematical ability. The test includes 11 subtests corresponding to 11 categories of mathematical abilities, which are divided into three areas: arithmetic operations, mathematical reasoning and visuospatial skills. The arithmetic operations area assesses performance in six tasks, including addition, subtraction, multiplication, division, equation, and magnitude perception tasks. The mathematical reasoning evaluates that children comlplete the next three numbers of the sequence according to the potential rules. The visuospatial skills includ visual size estimation, spatial conception, quantity counting, and visuomotor tasks.

Data analysis

Linear associations were performed to investigate the DRD2 genetic risk (28 SNPs) and phenotypes through PLINK. The interactions between PE and individual SNPs were analyzed by using PLINK and the GLM model in R. Haplotypes were designated based on r^2 indicating linkage disequilibrium (LD) (Gabriel et al., 2002). Haplotype main effects analyses were performed using the PLINK haplotype linear association test. Haplotype×PE interaction analyses were also conducted using the GLM model in R (version 3.1.2). Rare haplotypes (frequency < 0.02) were excluded from the linear association and interaction analysis (Table S1).

In all statistical assessments, Bonferonni's correction for multiple testing was applied to set appropriate significance thresholds. Adjusted p-value thresholds were set at $p \leq 0.0018$ (0.05/28) for single SNP analysis, and $p \leq 0.0018$ SNP×PE interaction analyses. Bonferonni- adjusted p-values for haplotypes and

haplotype×PE interaction are $p \leq 0.0019$ (3SNPs, 26 haplotypes), $p \leq 0.0020$ (4SNPs, 25 haplotypes) and $p \leq 0.0021$(5SNPs, 24 haplotypes) respectively.

Results

Preliminary description

The kurtosis and skewness values of each phenotype was computed and all phenotypes followed normal distribution. Most of the skewness and kurtosis values are between − 2 and 2. These traits also showed moderate to high correlations (Table S1). To exclude the gene-environment correlations, the correlation analysis was conducted (Table S1). The relation between SNPs and PE was not significant ($r = - .04\text{-}.05$, $r_p = .15\text{-}.91$), thus PE can be used as an environmental variable in our study.

Single SNP analysis

None of the investigated polymorphisms yielded statistically significant associations with every phenotypes (Table S2). However, when SNP×PE interactions were investigated, the interactions reached statistical significance on division and equation solving (Table 1 and Table S3). Through simple slope analysis, we found that the homozygotes of the first allele of these 4 SNPs (rs4648317, rs4350392, rs4938019 and rs10891556)have a negative effect on the phenotype under the influence of environmental factors (PE). This suggests that differences in environmental conditions from the middle to upper levels may affect gene expression, and the variation effect of the homozygotes of the first allele is increased. Conversely, the minor allele, in response to the environment, reverses the negative effect, causing individuals to have better performances (Figure S1 and Figure S2). Meanwhile, we verified, again, the interaction between these 4 SNPs and PE through R language.

Table 1
Significant SNP x PE interaction analyses on phenotypes.

SNP	A1	Phenotype	BETA	P
rs4648317×PE	A	Division	-0.9128	0.0016
rs4350392×PE	A	Division	-0.931	0.0012
		Equation	-0.7301	0.002
rs4938019×PE	C	Division	-1.043	0.0003
		Equation	-0.8132	0.0005
rs10891556×PE	T	Division	-1.051	0.0003
		Equation	-0.7661	0.0010

Haplotype analysis

Haplotype analyses identified two haplotype blocks for polymorphisms reaching statistically significant(rs2734831-rs1125394-rs7103679 (TCC) and rs1125394-rs7103679-rs7125415 (CCC)) (Table 2 and Table S2). These two haplotype blocks affected mainly as 3 SNPs for magnitude perception and quantity counting. When we analysed 25 haplotypes consisting of four adjacent SNPs, rs2734836-rs2734831-rs1125394-rs7103679 (TTCC), rs2734831-rs1125394-rs7103679-rs7125415 (TCCC) and rs1125394-rs7103679-rs7125415-rs4648318 (CCCC) were related to magnitude perception and quantity counting. Further analyses with haplotype combinations of 5 neighbouring SNPs showed that 2 haploype blocks ware correlated with subtraction. 4 SNPs (rs2734831, rs1125394, rs71679 and rs7125415) are present in more haplotype blocks and have an effect on mathematical ability in a combined form.

Table 2
Haplotype association analyses and predicted betas for MA.

SNPs	Haplotype	Phenotype	BETA	p
rs2734831-rs1125394-rs7103679	TCC	Magnitude perception	1.64	0.001
		Quantity counting	1.15	0.001
rs1125394-rs7103679-rs7125415	CCC	Magnitude perception	1.64	0.001
		Quantity counting	1.16	0.001
rs2734836-rs2734831-rs1125394-rs7103679	TTCC	Magnitude perception	1.744	0.0005
		Quantity counting	1.193	0.0008
rs2734831-rs1125394-rs7103679-rs7125415	TCCC	Magnitude perception	1.625	0.0011
		Quantity counting	1.117	0.0017
rs1125394-rs7103679-rs7125415-rs4648318	CCCC	Magnitude perception	1.698	0.0007
		Quantity counting	1.153	0.0013
rs1125394-rs7103679-rs7125415-rs4648318-rs12574471	CCCCT	Subtraction	1.68	0.0005
		Magnitude perception	1.807	0.0004
rs7103679-rs7125415-rs4648318-rs12574471-rs4274224	CCCTA	Subtraction	1.354	0.0012
rs2075654-rs2734836-rs2734831-rs1125394-rs7103679	TTTCC	Magnitude perception	1.744	0.0005
		Quantity counting	1.193	0.0008
rs2734836-rs2734831-rs1125394-rs7103679-rs7125415	TTCCC	Magnitude perception	1.734	0.0005
		Quantity counting	1.161	0.0012
rs2734831-rs1125394-rs7103679-rs7125415-rs4648318	TCCCC	Magnitude perception	1.657	0.0009

In Haplotype×PE interaction analyses (Table 3 and Table S4), we mainly performed interaction analyses between 3 haplotype blocks and 4 haplotype blocks and PE. The results showed that the environment factor mostly moderated the effect of haplotypes on quantity counting. rs1076560 (rs6275-rs1076560-rs2511521 (ACG and GAA), p = 0.001) influenced mathematical reasoning, as risk haplotypes, through haplotype×environment interactions, while rs2283265 and Taq 1A nominallyaffected quantity counting and spatial conception abilities through similar haplotype×environment interactions.

Table 3
Haplotype×PE interaction analyses, p-values and betas.

Phenotype	SNPs	Haplotype×PE	Beta	p
Magnitude perception	rs4648318-rs12574471-rs4274224	CTA×PE	1.54532	**0.0009**
	rs7103679-rs7125415-rs4648318	TCC×PE	1.83133	0.0023
	rs7103679-rs7125415-rs4648318-rs12574471	TCCT×PE	3.62023	0.0076
Subtraction	rs12574471-rs4274224-rs4581480-rs7131056	CGTC×PE	-5.561375	**0.0011**
	rs12574471-rs4274224-rs4581480	ATC×PE	3.110731	0.0093
Equation	rs4648318-rs12574471-rs4274224	CTA×PE	1.40115	0.0078
		CTG×PE	2.22024	0.0062
Division	rs4648317-rs4350392-rs4938019-rs1799978	GCTT×PE	1.31617	0.0076
Mathematical reasoning	rs6275-rs1076560-rs2511521	ACG×PE	-24.02675	**0.0010**
		GAA×PE	-23.9267	**0.0010**
	rs7103679-rs7125415-rs4648318	TCC×PE	-2.292862	0.0059
Quantity counting	rs7103679-rs7125415-rs4648318	TCC×PE	1.5394	**0.0006**
		TCT×PE	1.24921	**0.0005**
	rs2734849-rs1800497-rs10891549-rs6278	AGTC×PE	-0.84662	**0.0017**
	rs1800497-rs10891549-rs6278-rs6279	GTCG×PE	-0.85659	**0.0018**
	rs7125415-rs4648318-rs12574471	CTC×PE	1.31382	0.0083
	rs4648318-rs12574471-rs4274224	CTG×PE	-1.94551	0.0042
	rs7131056-rs4648317-rs4350392	GTC×PE	-0.65991	0.0098
	rs10891549-rs6278-rs6279	CGG×PE	-0.8382	0.0020
	rs1800497-rs10891549-rs6278	GTC×PE	-0.65991	0.0098
	rs2511521-rs2283265-rs12363125-rs2075654	GCCC×PE	-0.76791	0.0061
	rs12363125-rs2075654-rs2734836-rs2734831	CTTT×PE	0.76726	0.0056
	rs1125394-rs7103679-rs7125415-rs4648318	CTCT×PE	-1.55994	0.0084

Phenotype	SNPs	Haplotype×PE	Beta	p
	rs7103679-rs7125415-rs4648318-rs12574471	TCTC×PE	1.59475	0.0094
	rs4648318-rs12574471-rs4274224-rs4581480	CTGC×PE	-1.64561	0.0071
	rs12574471-rs4274224-rs4581480-rs7131056	TATC×PE	-2.34369	0.0095
Visual size estimation	rs4648318-rs12574471-rs4274224	CTA×PE	-2.72252	0.0038
Spatial conception	rs4350392-rs4938019-rs1799978-rs10891556	CTTG×PE	0.94203	**0.0017**
	rs4350392-rs4938019-rs1799978	CTT×PE	0.83099	0.0043
	rs4938019-rs1799978-rs10891556	TTG×PE	0.90643	0.0036
	rs2511521-rs2283265-rs12363125	GCC×PE	-0.76791	0.0061
	rs4648317-rs4350392-rs4938019-rs1799978	GCTT×PE	0.86894	0.0031

Our results show that in the two tasks of subtraction calculation and magnitude perception, the SNPs obtained from the haplotype analysis alone and the interaction analysis are almost identical, differing only in the way haplotypes blocks are combined (rs7103679-rs7125415, CC and TC). Differently, we also found another interactions on magnitude perception, which means that PE regulates gene expression. As for mathematical reasoning, the effects of all interactions were negative (β = -24.02675 and − 23.9267), suggesting that the genetic variance increases with increasing PE. In contrast, we noted that the effects of rs703679-rs7125415-rs4648318 (TCC) showed positive effects at different levels of environment, particularly in magnitude perception and quantity counting, reflecting different patterns of inheritance. It is noteworthy that, although there were differences in the way SNPs were combined in individual haplotype analyses and in interaction analyses, rs7125415-rs4648318 not only had a separate genetic effect, but was also affected by modulation by PE level.

Discussion

This study confirmed the “Generalist Gene” hypothesis, which states that genes affecting various aspects of learning ability also have an impact on other aspects of learning ability(Kovas & Plomin, 2006). In the sample of Chinese children, DRD2 gene demonstrated a significant effect on mathematical ability. These findings suggest that DRD2 can be considered as a generalist gene, as it not only influences attention deficit and WM but also affects mathematical ability. Particularly, when children engage in more complex mathematical tasks, the genetic effects of DRD2 become even more pronounced.

For the studies of complex diseases or quantitative traits, haplotype-based association analyses often provide more robust evidence when the individual SNPs

exhibit low statistical power (Botstein & Risch, 2003). In the context of mathematical ability, a complex trait characterized by genetic variations arising from interactions between multiple variants (Docherty et al., 2010; Stranger et al., 2011). Consistently, our research findings did not reveal significant effects at the level of individual SNPs but instead highlighted the remarkable influence of haplotypes on mathematical ability. Notably, our study identified rs2734831-rs1125394-rs7103679 and rs1125394-rs7103679-rs7125415 as haplotype combinations demonstrating higher significance in the test of association analysis, even when involving three or more haplotypes in the candidate gene study. In haplotype analysis, we observed a moderate effect of haplotypes on basic mathematical abilities in children. According to these findings, we propose DRD2 as a potential candidate gene implicated in mathematical ability.

The present study supports the hypothesis that the dopamine system is susceptible to modulation by the surrounding environment. Parental characteristics are important for the expression of genes in the dopamine system, especially when it comes to cognitive abilities (Lewis et al., 2019). Our findings indicate that the genotypes of intron rs1076560 and rs2283265, when considered individually, did not exert a significant influence on mathematical ability. However, when moderated by parental education, both variants exhibited an impact on children's mathematical reasoning and mathematical spatial ability as haplotypes.

Based on the results of the study, the Gene×PE interaction was mainly in terms of children's more advanced mathematical abilities, such as division, equations, quantity counting, and mathematical reasoning. These results emphasise a gene-environment interaction, in other words, the DRD2 gene is influenced by PE and its expression influences the children's more advanced mathematical abilities. In these mathematical abilities, more complex cognitive processes are involved, requiring in particular the support of cognitive abilities such as WM (Peng et al., 2016), semantic long-term memory (Zhou et al., 2018) and processing speed (Lambert & Spinath, 2017). And these cognitive functions are often influenced by genes and brain structure. Thus, the gene show significant effects on inter-individual differences in response to parental and environmental influences. This founding seems to be in line with the bioecological model that genetic factors have a stronger effect on individuals in better environments (Bronfenbrenner & Ceci, 1994; Harden et al., 2007). Furthermore, in terms of the basic mathematical calculations, SNPs(e.g. rs7103679, rs7125415, rs4648318) play a role in both Gene and Gene×PE interactions in the form of haplotypes. Environmental factors play a greater moderating role, and more generally, basic arithmetic ability is more dependent on environmental and educational influences when compared with more complex maths, although genes may also have some influence on it (de Zeeuw et al., 2016).

The cohort size utilised in this study can be considered exploratory and should be substantiated by larger studies and validated in independent replication cohorts. It is challenging to view PE as solely an

environmental factor, despite the absence of a correlation between PE and DRD2. This study shows that children's mathematical ability can be influenced by children’s parents. Further analysis is needed to determine whether PE is an intergenerational or environmental influence. Although the DRD2 gene cannot fully account for all aspects of mathematical ability, the development of mathematical skills is influenced by the interaction of multiple genes. Therefore, the findings of this study are still valuable. Since we used Gaussian distributions to fit the model results for haplotypes and environmental interactions during the calculations, there may be numerical instability in the matrix inversion or iterative algorithms, resulting in some haplotype results that do not exist. Therefore, rigorous and robust models will need to be fitted for haplotypes and environmental interactions in the future.

Conclusion

In this study, we explored the effects of the DRD2 gene and environmental interactions on children's mathematical ability. The DRD2 gene affects children's maths ability more as a haplotype. This implies that we can target the positive expression of the DRD2 gene in children by intervening and training the neural mechanisms that DRD2 responds to as well as working memory, thereby enhancing their level of mathematical ability. In addition, parental behaviour seems to have a greater influence on basic mathematical skills and therefore shows more positive results. Similarly, good parental behaviour can mitigate the negative effects of the DRD2 gene. Particularly for children who carry the DRD2 gene, supportive and positive behavioural patterns can help children to develop their mathematical skills.

Declarations

Ethics approval and consent to participate

All experimental procedures have been authorized by the Shaanxi Normal University and written informed consent was obtained from all participants’ parents.

Funding

This study was supported by National Natural Science Foundation of China (61807023), Fund for Humanities and Social Sciences Research of the Ministry of Education of China (23XJC740010 and 17XJC190010), Fund for Natural Science Basic Research Program of Shaanxi Province (2018JQ8015 and 2023-JC-YB-703) and Fundamental Research Funds for the Central Universities of China (GK201702011) to Jingjing Zhao.

Conflict of interest

The authors have no conflicts of interest to disclose.

Author contributions

Jingjing Zhao conceived of the presented idea. Qing Yang and Ximiao Zhang performed data analysis and assisted in writing the manuscript. Chen Cheng and Liming Zhang collected the behavioral and genetic data. Jingjing Zhao, Qing Yang designed the study and wrote the manuscript. All authors read and approved the final manuscript.

Transparency and Openness

The beta values of the SNPs in this paper can be found in previous studies (Zhang et al., 2023). The statistical methods and statistical data available from the corresponding author upon reasonable request. The raw data are not publicly available due to legal or ethical restrictions. Data were analyzed using R version 4.0.0 (R Core Team, 2020) and Plink 1.90.

Consent for publication

Not applicable.

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