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Common Polymorphisms in Genes Related to Vitamin D Metabolism Affect the Response of Cognitive Abilities to Vitamin D Supplementation

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Abstract

It is possible that vitamin D acts as a neurosteroid and that vitamin D deficiency may have an adverse impact on brain function and cognitive function. There are a few reports that have demonstrated an association between polymorphisms of genes involved in vitamin D metabolism and neurodegenerative disease. We aimed to evaluate the relationship between common, functional vitamin D–associated gene variants and cognitive abilities and to investigate the effect size of this polymorphism on cognitive capabilities associated with high-dose vitamin D supplementation. A total of 319 healthy adolescents received a high dose of vitamin D (50,000 IU)/week for 9 weeks. A questionnaire was used to assess cognitive abilities at baseline and after treatment. The genotypes of the CYP2R1-rs10766197 and GC-rs4588 variants were determined using TaqMan genotyping techniques. At baseline, total cognitive ability scores were higher in the AA group who were homozygous for the uncommon allele, compared with the other (AG and GG) genotypes of the *CYP2R1*-rs10766197 polymorphism (104.9 ± 27.8 vs. 79.1 ± 38.8 vs. 73.1 ± 25.6; $p < 0.001$, respectively). During the supplementation period, cognitive ability scores increased in individuals with the AG and GG genotypes, while individuals with a AA genotype did not show significant change in total score after intervention ($p = 0.17$). For GC SNP (rs4588), no major differences at baseline and trial-net change of cognitive tasks score were observed between the genotypes under three genetic models ($p_{SNP} = 0.67$). Vitamin D supplements have trait-dependent effects on cognitive performance that suggests a causal role for vitamin D in cognitive performance. The rs10766197 variant, near the CYP2R1 gene locus, significantly modified the efficacy of high-dose vitamin D3 supplementation for its effects on improving cognitive abilities indicate that some subjects might require a higher dose to benefit from in terms of cognitive performance.

Keywords Memory · Planning · Variation · Cytochrome P450 family · Group-specific component

Introduction

There is growing evidence that an inadequate dietary intake of essential micronutrients such as vitamins and minerals may have an adverse impact on brain function and cognitive ability (Prado and Dewey 2014; McCann et al. 2006).

Vitamin D is a fat-soluble vitamin, with some of the properties of a steroid hormone. It is primarily produced in the skin from 7 dehydrocholesterol (previtamin D) through solar UV-B exposure and also obtained to a lesser degree from dietary intake. Both circulating serum levels and polymorphisms in genes related to vitamin D metabolism are correlated with

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several conditions/disorders such as metabolic and inflammatory diseases, common cancers, as well as dementias and cognitive impairments (Holick and Chen 2008; Shah et al. 2012; Grant et al. 2017).

The molecular basis underlying the roles of vitamin D on human brain development is diverse. The ubiquitous distribution of vitamin D receptor (VDR) and two enzymes involved in terminal activation of calcitriol (25-hydroxylase and 1, α-hydroxylase) throughout the brain as well as presence of vitamin D target genes in the central nervous system (CNS) which induced neurogenesis highlighted the importance of vitamin D for normal cognitive function (McCann and Ames 2008).

Multiple calcium-binding proteins are found in the brain (Zhang et al. 2014) and vitamin D–enhanced calcium homeostasis can also protect against cognitive decline. It has been shown that one vitamin D–related protein, calbindin-D, which modulate intra-cellular calcium amounts in neurons was significantly decreased in the hippocampus tissue from Alzheimer's disease (AD) (Sutherland et al. 1992). In vitro experiments have supported potential anti-inflammatory, neurotrophic, and neuroprotective potential of calcitriols (Ślusarczyk et al. 2016; Kajta et al. 2009), as vitamin D supplementation could delay hippocampal aging in experimental animal studies (Brewer et al. 2006). In VDR knockout mice, vitamin D deficiency may be possibly linked with aging, hearing loss, and communicative, motor, and sensory deficits (Keisala et al. 2009; Zou et al. 2008).

Neuroepidemiologic studies have reported associations between hypovitaminosis D and age-related cognitive difficulties, impaired neurocognitive performance, dementia, and schizophrenia risk (Breitling et al. 2012; Feart et al. 2017; Miller et al. 2015; Noublanche and Annweiler 2016; Itzhaky et al. 2012) although, other studies have not supported this association (Norelli et al. 2010; Tolppanen et al. 2011; Slonin et al. 2010; McGrath et al. 2007). Indeed, results from interventional studies that have assessed the effects of vitamin D supplementation on cognitive performance have not been positive (Rossom et al. 2012; Dean et al. 2011; Stein et al. 2011). Taken together, the association between vitamin D and cognitive function is not yet completely established.

SNPs in the vitamin D–binding protein or group-specific component (*DBP/GC*), which transports vitamin D metabolites, and the Cytochrome P450, family 2, subfamily R, polypeptide 1 (*CYP2R1*) as a 25-hydroxylase, which catalyzes the transformation of vitamin D3 to its main circulating metabolite 25(OH) D3, have previously been shown to affect serum vitamin D levels in different populations. Moreover, healthy individuals with various CYP2R1 or DBP genotypes have different magnitude responses to the similar vitamin D dose (Fu et al. 2009; Bahrami et al. 2018b). Genetic variability may therefore explain differences in vulnerability to cognitive dysfunction and incidence of cognitive impairments. There are few studies that have demonstrated associations between polymorphism of vitamin D–associated genes (i.e., VDR, megalin, GC, CYP27B1, and CYP2R1) and neurodegenerative condition (Keyimu et al. 2014; Alfred et al. 2013; Beydoun et al. 2012; Lehmann et al. 2011), and none so far have examined the effects of vitamin D supplements on cognitive function.

Taking into account these conflicting findings, we aimed to evaluate the relationship between the common, functional vitamin D–associated gene variants and cognitive abilities and to investigate the effect of this polymorphism on cognitive capabilities scores in response to vitamin D supplementation.

Material and Method

Study Design

Three hundred and nineteen adolescent girls aged between 12 and 18 years were recruited between January and April 2015 in Mashhad City, using a randomized cluster sampling method. Informed consent was signed by all participants and their parents and study protocols approved by the Ethics Committee of the Mashhad University of Medical Sciences (MUMS). Participants with any history of chronic diseases, metabolic disorders, cancer, or who were taking any types of anti-depressant or psychotropic agents were excluded from study. Participants received high-dose vitamin D (capsule containing 50,000 IU vitamin D per week) for 9 weeks.

Cognitive Ability Assessment

A cognitive ability questionnaire (CAQ) was used to assess a number of cognitive functions that included memory, inhibitory control, selective and sustained attention, decision making, planning, and social and flexibility of cogitation (Nejati 2013). CAQ encompasses 30 independent items which are rated on a 5-point Likert scale (1–5) and provided a total score of 30–150. Higher scores indicate superior cognitive function. This questionnaire was fulfilled by study subjects at baseline and after 9 weeks of supplementation.

Genotyping

Two candidate gene loci were investigated in the present study: the CYP2R1 (rs10766197) and GC (rs4588) have been shown to be involved in the synthesised and transport vitamin D as well related with neurological diseases in previous studies (Bahrami et al. 2018c). Blood specimens were collected from all of the participants after overnight fasting. DNA was isolated from the peripheral blood using a QIAamp-DNA Mini-Kit (Qiagen, San Diego, CA) in accordance with the manufacturer's instructions. The DNA concentration and

purity were measured using a NanoDrop-1000-Detector (Nano-Drop-Technologies, Wilmington, USA). Genotyping was performed using a TaqMan allelic discrimination assay with ~ 20 ng of DNA in the total 12.5-ml volume PCR reaction (Applied Biosystems Foster City, CA). Allelic content of each sample was determined by an ABIPRISM-7500 machine with the SDS analysis software.

Statistics Analysis

Data were analyzed using SPSS version 16 (SPSS Inc., IL, USA) and GraphPad Prism version 3 softwares. Variables are reported as mean ± standard deviation (SD). The normality of variables was examined by the Kolmogorov–Smirnov test. Independent sample *t* test or ANOVA was used to compare changes in task scores after supplementation in different genotype groups. Chi-square tests checked agreement of genotypic frequencies to those of Hardy-Weinberg equilibrium. An ANCOVA test was conducted to investigate the effect of the genotypes on cognition score in response to supplementation. Logistic regression analysis clarifies the probability of change in cognition scores across various genetic models. A p value less than 0.05 considered statistically significant.

Results

Baseline characteristics of participants included in this interventional study, as well as effect of high-dose vitamin D supplementation on different biochemical and metabolic parameters, have been reported previously (Bahrami et al. 2018a). As we have shown, serum vitamin D concentrations were significantly increased after the vitamin D supplements (9.4 ± 8.8 ng/ml vs. 36.4 ± 15.4 ng/ml, $p < 0.001$) (Bahrami et al. 2018a). Allele frequencies of variation were in Hardy-Weinberg equilibrium ($p = 0.35$).

To evaluate the association between the CYP2R1 (rs rs10766197) and GC (rs4588) variants on cognitive ability tasks score after supplementation, participants were grouped based on their genotype (Table 1).

Cytochrome P450 Gene Variant

Regarding *CYP2R1*-rs10766197, at baseline, total cognitive abilities score was higher in the AA group (homozygous for uncommon allele) compared with AG and GG genotypes (104.9 ± 27.8 vs. 79.1 ± 38.8 vs. 73.1 ± 25.6; $p < 0.001$, respectively). During the supplementation period, cognitive ability scores increased in the girls with an AG or GG genotype, although the AA genotype did not show a significant change in their total score after the intervention ($p = 0.17$). The rs10766197 SNP of the *CYP2R1* gene appeared to modulated cognitive task scores in response to intervention ($p_{\text{intervention}} < 0.001$ and $p_{\text{SNP}} = 0.05$) (Fig. 1a). Further subanalysis showed that memory, inhibitory control and selective attention, decision making, planning, and sustained attention scores increased after 9 week supplementation in all participants but subjects with the GG genotype revealed a greater increment (Table 1). Interestingly, social cognition was reduced in the AG and GG carriers, while in the subjects with the AA genotypes, there was a small increase after vitamin D supplements, but this change was not statistically significant using three genetic models (dominant, additive, and recessive models). Also, cognitive flexibility only increased in the GG and AG genotype groups (Table 1).

Regression analysis also showed that the probability of change in the scores of tasks including memory, inhibitory control and selective attention, decision making, planning, and total cognitive abilities after intervention, in persons who had homozygous major allele GG, was higher than those who had the homozygous for uncommon A allele after adjustment for confounding variables that included age, BMI percentile, and serum vitamin D at baseline ($p < 0.05$). The regression analysis also showed a significant effect using both dominant and recessive models after adjustment for potential confounders ($p < 0.05$) (Table 2).

GC/DBP Variant

For GC SNP (rs4588), no major differences at baseline and trial-net change of cognitive tasks score were observed between genotypes under the three genetic models ($p_{\text{SNP}} = 0.67$) (Fig. 1b). Hence, these changes were not attributable to the GC polymorphisms, since during follow-up, no differences in measures of cognitive abilities were seen for carriers of this polymorphism (Table 1).

Discussion

To the best of our knowledge, this is the first study to explore the relationship between variations at vitamin D–associated genes with cognitive ability and demonstrated that *CYP2R1*-rs10766197 variation was significantly related with the baseline score and change in cognitive abilities score after 9 weeks of vitamin D administration. Our analyses indicate that, on average, subjects with a dominant G allele responded favorably to vitamin D, with enhanced cognitive ability score.

Another SNP (in *GC*) was not associated with baseline cognitive abilities score and did not show a significant impact on the response to supplementation. The reason for this is unknown. It may be due to the small sample size and thereupon limited power.

The multiple positive but weak associations are a frequent finding in complex diseases. For vitamin D status, more than 20 genes have now been reported to be modifiers but no single gene has been found to rigorously involve risk in all populations evaluated (Bahrami et al. 2018c). Clearly, there are small genetic effects with large heterogeneity; occasionally, there is unrecognized

Table 1 Comparisons of the score of cognitive ability task scores before and after 9 weeks of vitamin D supplementation in different genetic models

Cognitive ability task scores		CYP2R1–10766197				GC-rs4588			
		GG ($n = 88$)	AG ($n = 148$)	AA ($n = 83$)	p	CC ($n = 209$)	AC ($n = 93$)	AA ($n = 17$)	p
Memory	Baseline	12.0 ± 7.6	17.6 ± 8.4	25.3 ± 2.4	$< 0.001^{\alpha, \beta, \gamma}$	16.0 ± 8.1	16.0 ± 8.3	14.2 ± 7.3	Ns
	Follow-up	26.5 ± 4.1	25.2 ± 4.6	25.9 ± 4.2		25.3 ± 4.1	25.7 ± 4.2	24.3 ± 4.3	
	Change	14.2 ± 8.7	7.9 ± 10.2	0.6 ± 4.4		9.6 ± 9.5	9.9 ± 9.6	9.5 ± 8.5	
Inhibitory control and selective attention	Baseline	13.6 ± 6.1	18.4 ± 7.0	22.5 ± 4.7	$< 0.05^{\alpha,\beta,\gamma}$	17.1 ± 5.9	17.0 ± 6.5	14.9 ± 5.6	Ns
	Follow-up	19.7 ± 4.3	19.3 ± 4.1	21.5 ± 4.9		19.5 ± 3.9	19.8 ± 4.2	18.9 ± 5.5	
	Change	5.9 ± 7.6	1.2 ± 7.8	0.01 ± 6.3		2.5 ± 7.4	2.9 ± 7.8	4.1 ± 8.5	
Decision making	Baseline	11.8 ± 6.2	15.0 ± 5.6	18.3 ± 4.4	$0.001^{\alpha,\beta,\gamma}$	14.1 ± 5.5	14.5 ± 5.5	13.5 ± 5.7	Ns
	Follow-up	19.7 ± 4.7	18.7 ± 3.9	18.5 ± 2.2		18.3 ± 4.3	19.2 ± 4.3	16.2 ± 5.8	
	Change	7.7 ± 7.7	3.7 ± 6.8	0.4 ± 5.7		4.4 ± 7.0	4.9 ± 7.0	2.5 ± 9.0	
Planning	Baseline	7.0 ± 3.7	9.5 ± 3.8	11.3 ± 2.7	$< 0.01^{\alpha,\beta,\gamma}$	8.6 ± 3.5	8.6 ± 3.7	8.5 ± 3.9	Ns
	Follow-up	11.9 ± 3.1	11.1 ± 3.0	11.4 ± 3.0		11.2 ± 3.0	11.1 ± 3.2	11.5 ± 2.7	
	Change	4.4 ± 4.8	1.4 ± 4.7	0.3 ± 4.7		2.6 ± 4.6	2.5 ± 5.1	2.9 ± 5.5	
Sustain attention	Baseline	8.1 ± 3.4	9.2 ± 3.2	10.1 ± 2.9	$< 0.05^{\alpha,\beta}$	8.6 ± 3.1	8.3 ± 3.1	8.5 ± 3.7	Ns
	Follow-up	10.4 ± 3.4	9.6 ± 2.9	9.8 ± 3.0		9.7 ± 3.3	9.9 ± 3.4	10.0 ± 3.8	
	Change	1.8 ± 5.1	0.32 ± 4.3	0.001 ± 0.01		1.1 ± 4.8	1.6 ± 4.6	1.5 ± 5.2	
Social cognition	Baseline	9.6 ± 3.2	9.6 ± 5.0	9.8 ± 3.2	Ns	9.4 ± 3.2	9.8 ± 4.3	9.9 ± 2.9	Ns
	Follow-up	8.7 ± 3.5	8.6 ± 3.3	10.2 ± 2.7		8.5 ± 3.3	8.9 ± 3.3	8.3 ± 3.3	
	Change	− 1.1 ± 4.8	− 1.2 ± 6.2	0.43 ± 3.6		− 0.8 ± 4.5	− 0.9 ± 5.0	− 1.5 ± 4.5	
Cognitive flexibility	Baseline	9.9 ± 3.4	10.6 ± 4.4	13.5 ± 3.7	$< 0.005^{\alpha,\beta,\gamma}$	11.5 ± 3.1	11.8 ± 3.3	10.5 ± 3.2	Ns
	Follow-up	14.3 ± 3.0	13.3 ± 3.6	10.8 ± 5.2		13.3 ± 3.4	13.6 ± 3.6	13.5 ± 3.1	
	Change	4.1 ± 4.8	2.8 ± 5.7	− 1.7 ± 4.4		1.8 ± 4.7	1.8 ± 5.1	2.7 ± 4.4	
Total cognitive ability	Baseline	73.1 ± 25	79.1 ± 38	108.9 ± 27	$< 0.001^{\alpha,\beta,\gamma}$	85.8 ± 24.5	86.4 ± 26.8	80.7 ± 23	Ns
	Follow-up	110.8 ± 17	102.1 ± 25	99.7 ± 46		101.0 ± 24	104.3 ± 24	101.2 ± 20	
	Change	37.2 ± 33	23.2 ± 47	− 8.3 ± 33		15.2 ± 37.3	18.3 ± 37.3	18.9 ± 37	

p value obtained using ANOVA or independent sample t test for net change score (Follow-up_baseline)

$^{\alpha}$ Significant for additive genetic model (GG genotype vs. AA genotype)

$^{\beta}$ Significant for dominant genetic model (GG genotype vs. AG + AA genotypes)

$^{\gamma}$ Significant for recessive genetic model (GG + AG genotypes vs. AA genotype)

Ns non-significant under any genetic model

population stratification and there is plausible occurence of phenotyping and genotyping mistakes.

We investigated variants that have been consistently related with circulating vitamin D levels (Bahrami et al. 2018c). CYP2R1 is a member of the CYP2 family that encodes cytochrome P450 proteins. This enzyme specifically hydroxylates cholecalciferol at the 25-C position to generate 25-hydroxyvitamin D in the liver (Bahrami et al. 2018c). The SNP-rs10766197 is located in the promoter region of the *CYP2R1* gene. GC as a member of the albumin family codifies DBP which is the principal transporter for vitamin D metabolites in the circulation. SNP-rs4588 is in exon 11 of GC and maybe causes defects in function of GC (Bahrami et al. 2018c). Data from 1207 subjects in the Baltimore Longitudinal Study of Aging with mean 10.4-year follow-up showed that vitamin D influences brain performance trait—dependently during aging. *GC* gene polymorphisms are associated with poorer performance in executive function, visuospatial, and verbal abilities although, we did not observe any relationships between GC composite SNP score and memory performance (Kueider et al. 2016). Similarly, in a case-control study performed by Schmidt et al. child *CYP2R1* (rs10741657) and *GC* (rs4588) variants showed no association with risk of autism spectrum disorder in the logistic regression model (Schmidt et al. 2015). Pooled analysis of 16,527 individuals aged > 44 years from the UK demonstrated among different items of cognitive capability including word recall, semantic fluency, phonemic fluency, and search speed, the T allele of rs2282679 (GC) was only related with fewer word recall scores ($\beta = 20.0$, 95% CI 20.05, 20.003; $p = 0.03$) (Alfred et al. 2013).

The effects of genetic variation in vitamin D–related SNPs on specific cognitive abilities become more comprehensive than the effects of serum/plasma vitamin D levels alone. Notably, we observed an association between the rs-107661697 polymorphism on cognitive function at baseline,

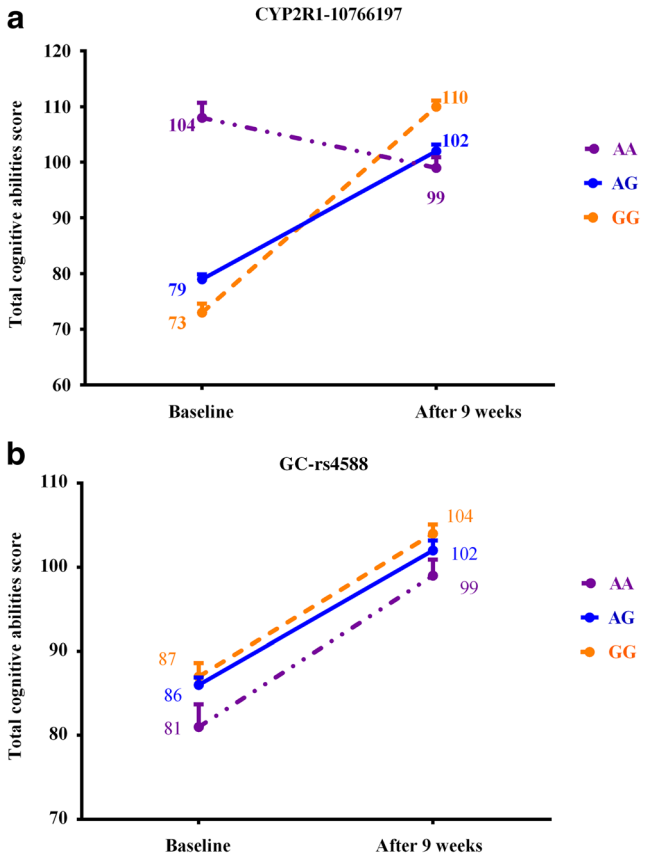

Fig. 1 Cognitive abilities score stratified by a polymorphisms in **a** CYP2R1-rs10766197 and **b** GC-rs4588 gene. Values are means ± SD. Two-way ANCOVA-repeated measures adjusted for multiple comparisons by the Bonferroni test. Covariates used were age, BMI percentile, and serum vitamin D at baseline

Table 2 Association of CPY2R1 variant-rs10766197 with the changes in cognitive ability scores 9 weeks of supplementation (under different genetic models)

	Additive model		Dominant model		Recessive model	
Cognitive ability task scores	Genotype	OR (95% CI), *p*	Genotype	OR (95% CI), *p*	Genotype	OR (95% CI), *p*
Memory	AA	Reference (risk group)	AA/AG	Reference (risk group)	AA	Reference (risk group)
	GG	1.2 (1.1–1.3), < *0.001*	GG	1.1 (1.05–1.2), < *0.001*	AG/GG	1.1 (1.06–1.2), < *0.001*
Inhibitory control and selective attention	AA	Reference (risk group)	AA/AG	Reference (risk group)	AA	Reference (risk group)
	GG	1.1 (1.04–1.2), *0.001*	GG	1.1 (1.05–1.2), < *0.001*	AG/GG	1.06 (1.01–1.2), *0.044*
Decision making	AA	Reference (risk group)	AA/AG	Reference (Risk group)	AA	Reference (Risk group)
	GG	1.2 (1.01–1.3), < *0.001*	GG	1.1 (1.05–1.2), < *0.001*	AG/GG	1.1 (1.04–1.2), *0.001*
Planning	AA	Reference (risk group)	AA/AG	Reference (risk group)	AA	Reference (risk group)
	GG	1.2 (1.1–1.3), < *0.001*	GG	1.2 (1.1–1.2), < *0.001*	AG/GG	1.1 (1.02–1.2), *0.021*
Sustain attention	AA	Reference (risk group)	AA/AG	Reference (risk group)	AA	Reference (risk group)
	GG	1.1 (1.0–1.2), 0.055	GG	1.02 (1.1–1.2), *0.017*	AG/GG	1.06 (0.96–1. 2), 0.24
Cognitive flexibility	AA	Reference (risk group)	AA/AG	Reference (risk group)	AA	Reference (risk group)
	GG	1.3 (1.1–1.4), 0.055	GG	1.1 (1.03–1.2); *0.004*	AG/GG	1.2 (1.1–1.3), < *0.001*
Total cognitive abilities	AA	Reference (risk group)	AA/AG	Reference (risk group)	AA	Reference (risk group)
	GG	1.03 (1.02–1.04),< *0.001*	GG	1.01 (1.005–1.02), *0.001*	AG/GG	1.02 (1.01–1.03), *0.001*

Additive genetic model (GG genotype vs. AA genotype); Dominant genetic model (GG genotype vs. AG + AA genotypes); Recessive genetic model (GG + AG genotypes vs. AA genotype)

Significance of italicized values are $p < 0.05$

suggesting that genetic predisposition is associated with lower cognitive abilities; these individuals show enhanced increments in cognition during the trial.

Interpretation of relationship between vitamin D and cognitive function is complicated. In a Mendelian randomization study, Maddock et al. found no associations between *DHCR7* and *CYP2R1*SNPs/synthesis score with global and memory cognition even after stratifying by gender, age, and vitamin D tertiles (Maddock et al. 2017). In other Mendelian randomization analysis, SNPs contributed in metabolism of vitamin D including GC (rs2282679) and CYP24A1 (rs6013897) to be potent predictors of AD risk by increasing the 46% odds of AD (CI 1.03–2.07; $p = 0.032$). In contrast, a null effect that was found for SNPs contributed in the synthesis of vitamin D including DHCR7 (rs12785878) and CYP2R1 (rs10741657) on AD ($OR_{synthesis} = 1.17$, 95% CI 0.9–1.5) (Mokry et al. 2016).

Gezen and colleagues examined whether there is a link between the *VDR* gene and late-onset AD. Regarding ApaI genotypes, the frequency of the AA genotype was considerably significantly higher in AD patients compared with healthy individuals ($p = 0.008$, $\chi^2 = 9.577$, OR = 2.30), but the TaqI genotype distribution was not different between the two groups. Thus, this study supported the potential association between AD and vitamin D. Indeed, "AT" haplotype was more common in controls, suggesting a protective role for AD (Gezen-ak et al. 2007).

Adolescence is associated with an elevated need to regulate impact and behavior. Since maturation and the developing brain during adolescence, mental, behavioral, and cognitive networks occur with different speed, this time is usually one of the higher vulnerability and modification. Therefore, normative progression in adolescence can beneficially be followed with respect to the coordination of emotional, intelligence, subconscious and behavioral tendencies, and abilities, and psychopathology in adolescence may be a representative challenge in this coordination trend (Steinberg 2005).

The current study has several strengths: first, by performing this study on healthy subjects, the analysis of the genetic effect on the cognitive ability score is not confounded by the plausible effect of other diseases; second, selected rigorous genetic marker previously demonstrated in GWASs implied vitamin D metabolism; and third, all of the trial were taken during the winter to make effect of sun exposure least. The main limitation of the study was the lack of a placebo group due to the ethical considerations.

Conclusion

Taken together, we observed that vitamin D has trait-dependent effects on cognitive performance which provides evidence to support a causal role for vitamin D in cognitive performance. In novel analyses, we found one SNP that significantly modified the efficacy of mega-dose vitamin D3 supplementation for improving cognitive abilities: rs10766197 near *CYP2R1*, indicating that some subjects might require a higher dose to benefit from better cognitive performance. Since we did not find any previous investigations on the association between genetic polymorphisms of gene-related vitamin D and cognitive abilities in response to supplementation, this result may need confirmation to elucidate the physiological context for the genetic associations.

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