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ORIGINAL ARTICLE

Discovering the missense variant allele in rs7041 of GC gene among individuals with low serum vitamin D

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ABSTRACT

Background: *Vitamin D deficiency is a global health concern affecting more than a billion people and is increasingly recognized in tropical countries like Bangladesh despite adequate sunlight. Genetic variations, particularly in the Group-specific component (GC) gene encoding vitamin D binding protein (DBP), may influence serum vitamin D levels. The present study aimed to investigate the association of rs7041 polymorphism of the GC gene with serum vitamin D status among healthy Bangladeshi adults.* ***Methods:*** *This cross-sectional study was conducted at the Department of Physiology, Dhaka Medical College, from July 2019 to June 2020. A total of 59 healthy adults were screened for serum vitamin D, of whom 32 with low levels (<30 ng/ml) were included as the study population and 10 with normal levels as controls. Socio-demographic, anthropometric, and biochemical data were collected. Genotyping of rs7041 of the GC gene was performed at the Center for Medical Biotechnology (CMBT), Mohakhali, using PCR, agarose gel electrophoresis, purification, and sequencing. Statistical analysis was carried out with chi-square testing, with p<0.05 considered significant.* ***Results:*** *The mean serum vitamin D level of the study population was 18.91 ± 4.86 ng/ml compared to 49.23±16.29 ng/ml in controls. The allele frequency distribution of rs7041 among the study population revealed major allele T (59.4%) and minor allele G (40.6%) with a minor allele frequency of 0.406. In controls, allele T was 45% and allele G was 55%. The chi-square test showed no statistically significant difference in allele distribution between study and control groups (p=0.258). However, low serum vitamin D was observed more frequently in carriers of the T allele.* ***Conclusions:*** *The findings suggest a possible association of the rs7041 T allele of the GC gene with low serum vitamin D levels in Bangladeshi adults, despite adequate sun exposure. This highlights the importance of genetic determinants in vitamin D status and suggests the need for further large-scale studies to better define population-specific reference ranges and risk groups.*

Keywords: *Vitamin D deficiency, GC gene, rs7041 polymorphism, Vitamin D binding protein, Bangladesh, Genetic association*

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INTRODUCTION

Vitamin D deficiency is a global public health issue affecting more than one billion people worldwide. Deficiency of vitamin D leads to a wide range of complications like osteoporosis, fractures, childhood rickets, osteomalacia, cardiovascular diseases, obesity, diabetes mellitus, asthma, multiple sclerosis and even certain types of carcinomas. Researchers are considering it to be a potential risk factor for impaired immunity as well. Finding the cause is no less important than treating this upcoming pandemic.[1,2,3] Vitamin D acts as a hormone concerned with calcium homeostasis, bone metabolism, body growth and development. It increases the intestinal absorption of calcium and phosphate and boosts up the immune system. Being fat-soluble and hydrophobic, it cannot circulate freely in blood. So, vitamin D is transported within the blood, bound to a carrier protein called vitamin D binding protein or DBP. Vitamin D binding protein exerts its highest affinity for serum levels of 25-hydroxyvitamin D or 25(OH) D. Due to the rigid binding affinity and high plasma concentration (0.3 to 0.5 mg/ml) of all 25(OH) D in the circulation is combined with vitamin D binding protein. DBP also is complexed to megalin protein to limit the excretion of 25(OH) D through proximal convoluted tubule in the kidneys.[3,4,5] The richest source of vitamin D is sunlight exposure. When the sun light containing UVB falls on skin the pre-vitamin D3 is activated. After activation in the skin,

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vitamin D is carried in the blood to the liver by a circulating protein called vitamin D binding protein (DBP).[6] Vitamin D Binding protein (DBP) binds to ergocalciferol (vitamin D2), cholecalciferol (vitamin D3), 25-hydroxylated form (calcifediol) and the active product 1,25-dihydroxyvitamin D (calcitriol). It transports vitamin D between skin, liver and kidney and then on target tissues.[7] It is the primary carrier protein for vitamin D. It binds to 85% to 90% of the total circulating 25-hydroxyvitamin D. The rest is non-vitamin D-binding protein fraction (bioavailable 25- hydroxyvitamin D), around 10% to 15% which binds to albumin, and less than 1% 25-hydroxyvitamin D remain in the free form. Some of the actions of vitamin D might be inhibited by vitamin D binding protein as the bound form is not available to act on the target cell.[8] Vitamin D binding protein (DBP) is decreased in sepsis, cutaneous malignant melanoma, hepatocellular carcinoma, primary non-metastatic breast cancer.[9,10,11,12] Hypovitaminosis D is an alarming problem affecting all continents, ethnicities, and age groups. Apart from different cultural behavior, latitude and sun exposure, skin pigmentation, clothing, sunscreen use and nutritional gain, the genetic traits are important contributing factors for the low vitamin D status of healthy individuals.[13,14] The dietary source serves very little in comparison to the cutaneous synthesis for maintenance of a sufficient vitamin D level in the circulation.[15] The best indicator of vitamin D status is the serum 25-hydroxyvitamin D or 25 (OH) D. The serum 25(OH) D has a 1000 fold greater circulating level than 1, 25 (OH) D. It has a half- life of 3-4 weeks whereas 1, 25 (OH) D has 3-4 hours. The concentration of serum 25(OH) D in blood reflects the endogenous generation via UVB exposure. Genetic variation exerts a great impact on the circulating 25(OH) D levels. It is important to identify the people at risk to develop hypovitaminosis D. This will eventually help to expand our knowledge about the association between vitamin D and the diseases related to this condition[2,17] Bangladesh being a tropical country receives a good source of sunlight round the year. Despite abundant sun exposure, different studies have revealed the evidence of low serum vitamin D status among different age groups, gender, occupation, and several disease conditions.[18,19,20] In Bangladesh a laboratory investigation-based study revealed that, out of 793 vitamin D reports 61.4% are deficient, 24.1% are insufficient and 13.1% are sufficient[21].

METHODS & MATERIALS

Study Procedure & Study design:

It was a cross-sectional type of study conducted at the Department of Physiology, Dhaka Medical College, Dhaka, Bangladesh, from July 2019 to June 2020, in this study, a total of 59 apparently healthy adults participated from different areas of Dhaka city. Among them, 32 subjects with low serum vitamin D were enrolled as study population (N=32). From the rest of the subjects with normal serum vitamin D 10 subjects were enrolled as control for comparison. Healthy Bangladeshi adults were the study population. Data were collected with face-to-face interviews. A semi-structured questionnaire was developed to collect data according to the objectives of the study. After explaining the purpose of the study, written and verbal consent was obtained from the respondents.

Among the study population, the age range was 18-53 years, 26 were males and 6 were females and with a Body Mass Index (BMI) range 18.62–24.90 kg/m^2 were included. All of them belonged to middle class socioeconomic background and from different occupations such as outdoor players, health workers and traffic police. The duration of sun exposure was 2-9 hours. Other biochemical parameters like, serum calcium, serum albumin, serum creatinine, fasting blood sugar, prothrombin time were done to fulfill the sample size according to inclusion and exclusion criteria. Individuals with a use of sunscreen and umbrella, veiled women and people with any supplements were excluded. Same criteria were taken for the control group also.

Blood sample collection & Biochemical tests:

Collection of blood samples was done until accomplishment of the sample size. A total number of 59 blood samples were collected. Among them 32 samples were found to have low serum vitamin D and considered as study population (N=32). Rest of the subjects had normal serum vitamin D. Among them, 10 samples with normal serum vitamin D were selected as controls for comparison.

Genetic study:

Genetic study involves very sensitive and delicate procedures. The whole procedure was performed in Center for Medical Biotechnology (CMBT), Mohakhali, Dhaka. Genotyping of target region of GC gene rs7041 was done into following steps: Primer designing and Validation, DNA Extraction and Quantification, PCR (Polymerase Chain Reaction), Agarose Gel Electrophoresis, PCR Purification and Sequencing.

RESULTS

Table 1 shows the sociodemographic and physiological characteristics of both groups. Age ranged 18–53 years (mean 30.91±11.31) in the study group and 20–48 years (mean 32.90±7.89) in controls. Mean BMI was 20.94±1.94 kg/m^2 in the study group versus 22.89±1.63 kg/m^2 in controls. Systolic BP ranged 100–120 mmHg (mean 113.28±6.91) in the study group and 110.00±8.16 in controls; diastolic BP ranged 60–85 mmHg and 60–80 mmHg, respectively. Serum calcium levels were within the normal range, with mean values showing no remarkable variation. Similarly, serum albumin, serum creatinine, fasting blood sugar, and prothrombin time were all recorded within normal limits across the participants, confirming that no metabolic or renal dysfunction influenced the study outcome (Table 2). Table 3 summarizes the molecular and genomic features of the rs7041 single nucleotide variation (SNV) in the GC gene. The variation occurs in *Homo sapiens* at chromosomal position chr4:71752617 (GRCh38.p12), with alleles A>G>T, and represents a missense variant affecting the GC gene. The gene is located on chromosome 4 at cytogenetic band 4q13.3, with a variant length of 1 base pair. Additional identifiers include Gene ID 2638 and Allele ID 31026, as referenced in GRCh38 and UCSC genome assemblies. In the study population, the T

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allele (59.4%) was more common than G (40.6%), while in the control group, the G allele (55%) was more frequent than T (45%). The chi-square test revealed a value of 5.7828 with a p-value of 0.016, suggesting significant deviation from Hardy-Weinberg equilibrium (Table 4). In the proportion of T and G alleles among the study group, T allele predominated with 61.00% compared to G at 39.00% (Figure 1). Figure 2 demonstrated the distribution of alleles among controls, showing G allele predominance (55%) compared to T allele (45%). Table 5 presented the distribution of rs7041 alleles (T and G) among individuals with low serum vitamin D levels (study population, N=32, total alleles n×2=64) and healthy controls with normal serum vitamin D levels (Nc=10, total alleles Nc×2=20). In the study population, the T allele was observed in 38 alleles (59.4%) and the G allele in 26 alleles (40.6%). Among controls, the T and G alleles were observed in 9 (45%) and 11 (55%) alleles, respectively. This bar graph illustrated the number of T and G alleles of the GC gene among individuals with low serum vitamin D levels (study population, N=32) and healthy controls with normal serum vitamin D levels (Nc=10). The study population shows 38 T alleles and 26 G alleles, while controls show 9 T alleles and 11 G alleles (Figure 3).

Table – I: Socio-demographic characteristics of study population and controls

Parameters	Study population (N=32)	Controls (Nc=10)
Age (in years)	18-53	20-48
Gender:		
Male	26 (81.3%)	05 (50%)
Female	06 (18.8%)	05 (50%)
BMI (Kg/m^2)	18.62-24.90	20.55-24.65
Systolic Blood Pressure (in mmHg)	100-120	100-120
Diastolic Blood Pressure (in mmHg)	60-85	60-80
Occupation:		
Outdoor Players	14 (43.8%)	03 (30%)
Health Workers	06 (18.8%)	03 (30%)
Traffic Police	12 (37.5%)	04 (40%)
Duration of sun exposure (in hours)	2-9	2-5
Skin complexion (Light brown)	32 (100%)	10 (100%)
Socio-economic status Middle Class)	32 (100%)	10 (100%)

Table – II: Biochemical parameters of the study population (*n*=32) and controls (*n*=10)

Parameter	Study population (N=32)	Controls (Nc=10)
Serum vitamin D (ng/ml)	12.45-29.03	32.03-78.19
Serum Calcium (mg/dl)	08.58-10.00	08.56-9.91
Serum Albumin (gm/dl)	03.51-05.02	03.77-5.00
Fasting blood glucose (mmol/L)	03.98-06.01	03.89-5.55
Serum Creatinine (mg/dl)	0.41-01.21	0.67-0.98
Prothrombin time (seconds)	11-15	11-14

Table – III: General characteristics of rs7041 of GC gene

Organism	Position	Alleles	Variation Type	Gene Consequence
Homo sapiens	chr4:71752617 (GRCh38.p12)	A>G>T	SNV (Single Nucleotide variation)	GC Missense Variant
Gene ID	**Allele ID**	**Variant length[b]**	**Cytogenetic location[a]**	**Genomic location**
2638	31026	1 bp	4q13.3	4:71752617 (GRCh38) GRCh38 UCSC

[a] *SNP identifier based on NCBI dbSNP.*

[b] *Chromosomal location based on NCBI Human Genome Build 35 coordinates.*

Table – IV: Alleles frequency among study population (*n*=32)

Alleles (NA=N×2=64)	Frequency	Percentages
Major Allele: T (38)	0.595	59.4%
Minor Allele: G (26)	0.405	40.6%
Alleles (NcA=Nc×2=20)		
Major Allele: T (09)	0.45	45%
Minor Allele: G (11)	0.55	55%

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Minor Allele Frequency (MAF)	0.406
Hardy Weinberg Equilibrium (HWE)	
chi- squared value	5.7828
chi-squared test p-value	0.016184

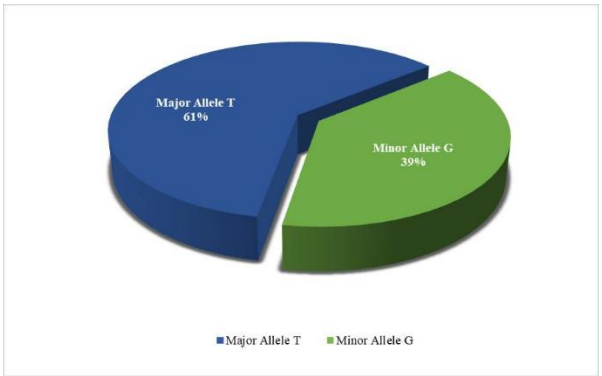


Figure – 1: Distribution of the major and minor alleles of rs7041 of GC gene among the study population (*n*=32)

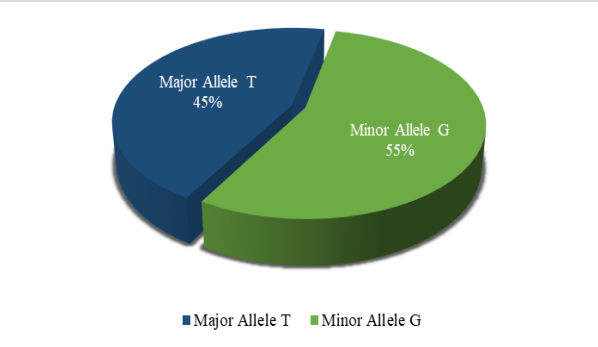


Figure – 2: Distribution of the major and minor alleles of rs7041 of GC gene among the control (NC=10)

Table – V: Comparison of alleles among the study population (*n*=32) and control (NC=10).

Serum vitamin D	Alleles		p- value
Study population with	**T (NT=47)**	**G (NG=37)**	
low serum vitamin D	38	26	0.258^{ns}
(n×2=64)	(59.4%)	(40.6%)	
Controls with normal	09	11	
serum vitamin D (N_c×2=20)	(45%)	(55%)	

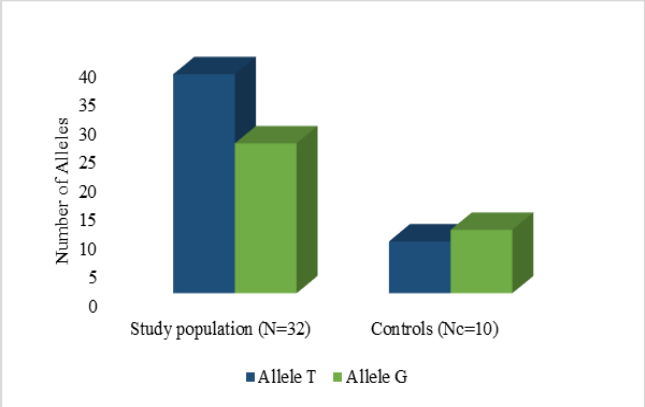


Figure – 3: Distribution of alleles among study population (*n*=32) and controls (Nc=10)

DISCUSSION

The present study was undertaken to observe the relationship between variants in rs7041 of Group specific component (GC) gene with low serum vitamin D level among Bangladeshi adults. For this cross-sectional study, a total number of 32 adults with low serum vitamin D level and 10 adults with normal serum vitamin D level were enlisted on the basis of inclusion and exclusion criteria. The genotype of rs7041 of Group specific component (GC) gene was the study parameter. A total number of 59 individuals were investigated for serum vitamin D. Finally, a number of 32 two subjects were found to have low serum vitamin D and enrolled as the study population (N=32). Their age ranged from 18-53 years. The Body Mass Index (BMI) ranged from 18.62-24.90 kg/m2. Among them, 26 were males and 06 were females. All belonged to middle class socioeconomic background and from different occupations like outdoor players 14 (43.8%), community health workers 6 (18.8%) and traffic police 12 (37.5%) who were adequately exposed to sunlight. The duration of sun exposure ranged from 2-9 hours with a mean (± SD) of 6.5 ±1.85 hours. Among the controls, age ranged from 20-48 years with a mean (± SD) age of 32.90 ± 7.89 years. There were 5 males and 5 females. The Body Mass Index (BMI) of the controls ranged from 20.55–24.65 kg/m^2 with mean (± SD) of 22.89 ± 1.63 kg/m^2. All of them belonged to middle class socioeconomic background and from different occupations like 3 outdoor players, 4 health workers and 3 traffic police.

In this study, out of all (NT=59), 32 subjects with a serum vitamin D level below 30 ng/ml (54%) were included as study population (N=32). The serum vitamin D of the study population (N=32) ranged from 12.45-29.03 ng/ml with mean (± SD) of 18.91± 4.86 ng/ml. The mean serum vitamin D of the controls were 49.23 ± 16.29 ng/ml and ranged from 32.03-78.19 ng/ml.[22] Prevalence of low serum vitamin D of other studies are similar to this study (55.6%). This percentage was higher among Jordanians.[23,24,25] Jordan and Pakistan are countries with adequate sun exposure, but the effect of clothing style of the people covering nearly the whole body and unavailability of food fortification with vitamin D might be factors contributing to the high prevalence of vitamin D deficiency.

The current study was concerned with assessment of the genotype of a single nucleotide variant (SNV) of Group specific component (GC) gene with the reference sequence accession number rs7041. Out of total 64 allele 'T' was the major allele with a total number of 38 (59.4%) and 'G' was the minor allele with a total number of 26 (40.6%). The minor allelic frequency (MAF) was found to be 0.406. So, 40% of the population has G allele versus the most common allele or major allele T, which was 60% of the population. The Hardy Weinberg formula Chi squared test p value was 0.016. The major allele was T, found in 09 subjects (45%) and the minor allele was G, found in 11 subjects (55%). A comparative study was performed between the distribution of alleles among the study population and controls were not statistically significant.

The observations of this study were analogous to other researchers round the world.[22] A significant association between low serum vitamin D status of heathy subjects with heterozygous and homozygous genotypes containing nonsynonymous polymorphism rs7041 carrying variant allele T among Jordanians.[25] The geographical location, latitude, ethnicity, food habit, cultural and religious behaviour, clothing style of Bangladeshi population are similar to the people of South Asian population as well as to some extent to the countries of Middle East like Jordan. Therefore, these might be potential causal factors for sharing similar pattern of genotypic variants among the population of Bangladesh, rest of South Asian and Middle East countries.

The presence of allele G might contribute to the normal function of vitamin D binding protein (DBP) thus leading to a normal serum vitamin D level.[26]

This study reports an association of low serum vitamin D with genotype TG and TT carrying major allele T which exists in a larger proportion (60%) among the population. Similarly, significant associations between T allele in rs7041 and low serum vitamin D has been reported in several studies around the world. The T allele was associated with low serum vitamin D.[27] Similar results were reported in studies conducted among Americans,[28,29,30,31] Brazilians, Chinese Singaporean and Chinese pregnant women. A study performed among black and white Americans has also found the association of T allele with low serum vitamin D.[32] Genome wide association studies (GWAS) conducted on different ethnicities and races have also exhibited strong associations between rs7041 GC gene and low serum vitamin D level in Finnish population[33] and a large population from European ancestry in five different cohorts.[34]

The possible mechanism to explain the effect of variants in the single nucleotide variant (SNV) rs7041 in exon 11 of Group specific component (GC) gene is suggested by many researchers round the world. The single nucleotide variant (SNV) occurs due to substitution of a single nucleotide T in the genetic codon 416, resulting in production of an amino acid glutamic acid that is different from the usual amino acid aspartic acid at that position. This substitution does not result into any pathogenic variant that is it does not produce any disease, rather might refer to evolution of a variant allele from the ancestral allele and exhibits variation in the same SNV among different ethnicities and population.[29,35,34,4]

The relationship of low levels of serum vitamin D among Bangladeshi adults with the SNV rs7041 Group specific component gene can likely be explained by the functional alteration of the binding protein encoded by this variant SNV rs7041 due to variation with the presence of major allele T. This leads to either decreased synthesis or faulty function of vitamin D binding protein (DBP), ultimately forming functionally lower concentrations or a decreased binding capacity of vitamin D binding protein (DBP) in serum. This might lead to a low count of serum vitamin D.

On the contrary, a Genome Wide Association study (GWAS) conducted among five different cohorts from European ancestry including 4051 individuals did not find any significant association with rs7041 and low vitamin D

status[17]. Difference in ethnicity, race, latitude, sociodemographic factors, variations in methodology of different studies contribute to the dissimilarity also could not show significant association of low serum vitamin D with rs7041 of Group specific component gene.[36]

The circulating vitamin D level is affected by various environmental and behavioural factors which were avoided during setting up the exclusion and inclusion criteria in this study. For example, a minimum of 45 min exposure to sunlight, a healthy diet and nutritional factors were ensured, clothing style like hijab wearer and veiled participants were excluded, sunscreen and umbrella users were not included in this study, individuals with vitamin D supplementation were excluded. It was a strength of this study that all these contributing factors were taken care of which might had influenced the natural synthetic pathway of serum vitamin D. This ensured avoidance of any interruption in vitamin D synthesis other than genetic conformation of the population. The current study included apparently heathy Bangladeshi population with the increased prevalence of low serum vitamin D status and the genotype evaluation exhibited observations different from other races and ethnicities. This might be an effect of natural adaptive changes from ancestral genetic configuration which ensures better survival from various environmental stress factors.

LIMITATIONS

1) The allele and genotype analysis of other variant single nucleotide polymorphisms on the same Group specific component gene could have helped to obtain more detailed knowledge to the etiology of low-level vitamin D of Bangladeshi people, which was not possible due to financial constraints.

2) The sample size was small. Due to financial constraints the study could not include a large number of populations.

CONCLUSIONS

The present study has reported presence of a single nucleotide variant allele T at rs7041 of Group specific component (GC) gene with low serum vitamin D level among Bangladeshi adults which might be a determining factor for low serum vitamin D level of Bangladeshi population. Therefore, it might be important to consider the impact of Group specific component gene in respect of redefining the reference range of serum vitamin D level in adults of Bangladesh.

DECLARATIONS

Funding: *No funding sources*

Conflict of interest: *None declared*

Ethical approval: *The study was approved by the Institutional Ethics Committee.*

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