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Existence of the rs7041 Polymorphism in the Vitamin D Binding Protein Gene Among Bangladeshis with Low Serum Vitamin D: A Pilot Study

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INTRODUCTION

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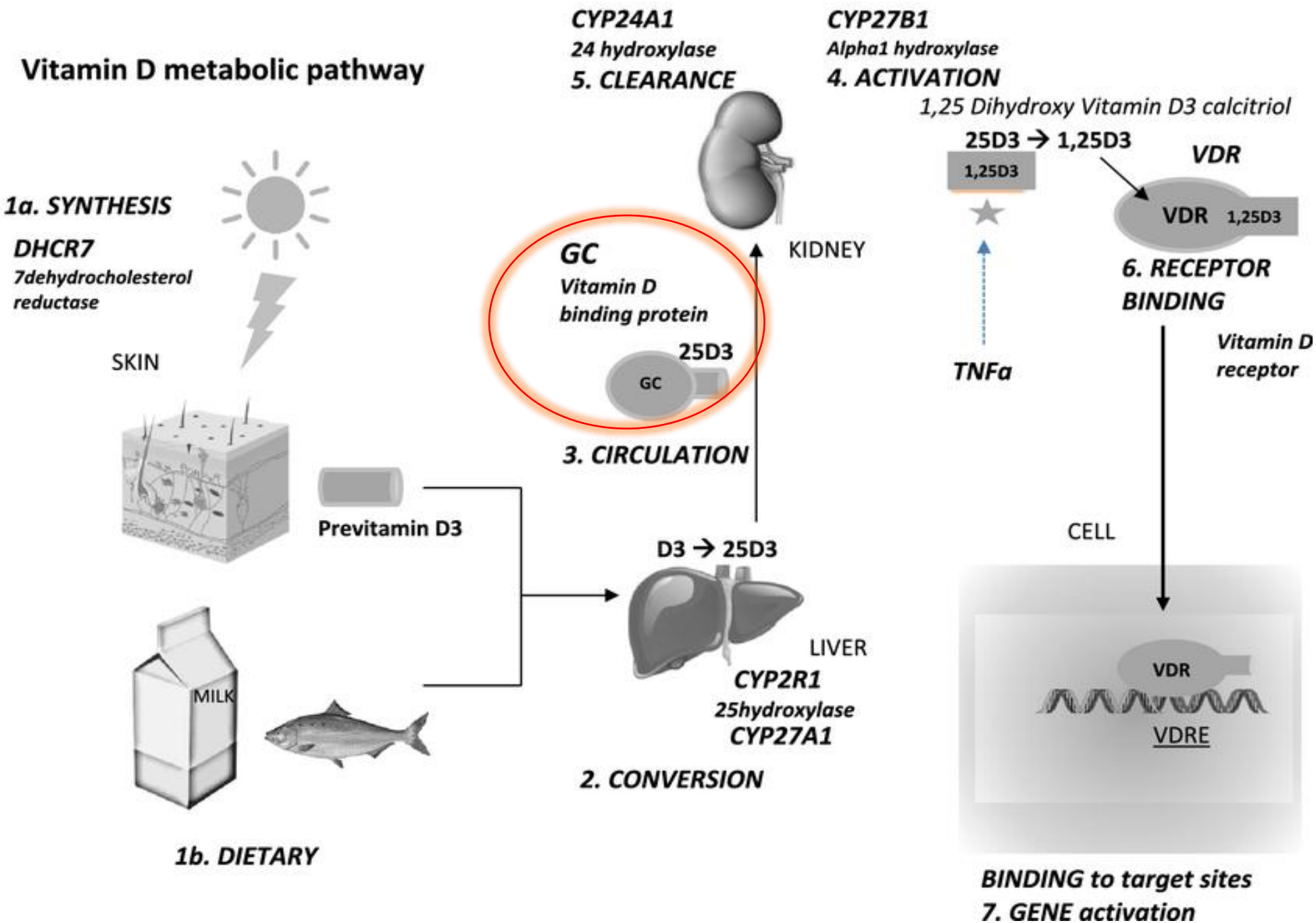
- Vitamin D deficiency is a major health issue affecting more than one billion people globally with a wide range of complications [1].
- Genetic variations among healthy people may arise from aberrations in vitamin D metabolism [4].

- Elderly people, females, higher latitude, winter season, darker skin pigmentation, inadequate sunlight exposure, dietary habits, and lack of vitamin D fortification are the factors that are significantly associated with low serum vitamin D levels [3].

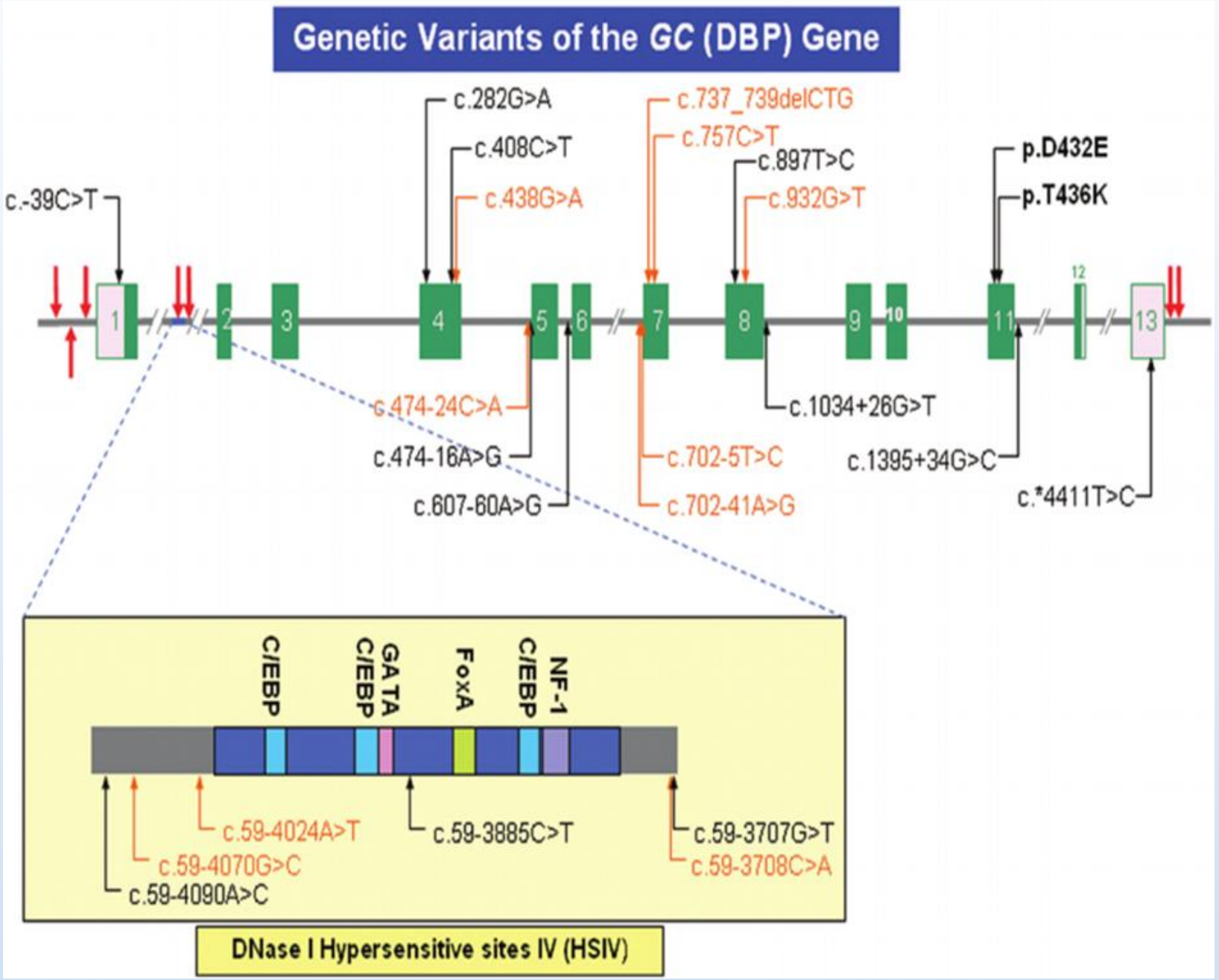
- Vitamin D consists of a group of **fat-soluble seco-sterols** also called calciferols (Vit D2 and D3).
- Vitamin D synthesis is initiated by:
  - ➢activation of pre-vitamin D3 by UVB light in the skin
  - ➢carried to the liver by vitamin D binding protein (DBP)
  - ➢where it is initially converted to 25-hydroxyvitamin D [25(OH)D][5]
  - ➢From liver to kidney for final hydroxylation


Vitamin D metabolic pathway
CYP24A1
24 hydroxylase
5. CLEARANCE
CYP27B1
Alpha1 hydroxylase
4. ACTIVATION
1,25 Dihydroxy Vitamin D3 calcitriol
25D3 → 1,25D3
1,25D3
VDR
VDR 1,25D3
6. RECEPTOR BINDING
Vitamin D receptor
1a. SYNTHESIS
DHCR7
7dehydrocholesterol reductase
SKIN
GC
Vitamin D binding protein
25D3
GC
KIDNEY
3. CIRCULATION
TNFa
Previtamin D3
D3 → 25D3
LIVER
CYP2R1
25hydroxylase
CYP27A1
2. CONVERSION
CELL
MILK
VDR
VDRE
1b. DIETARY
BINDING to target sites
7. GENE activation

Vitamin D binding protein (DBP) is a glycosylated alpha globulin with a strong affinity for 25(OH)D and is encoded by the group-specific component (GC) gene in humans [6,7].

The Group specific component gene is–

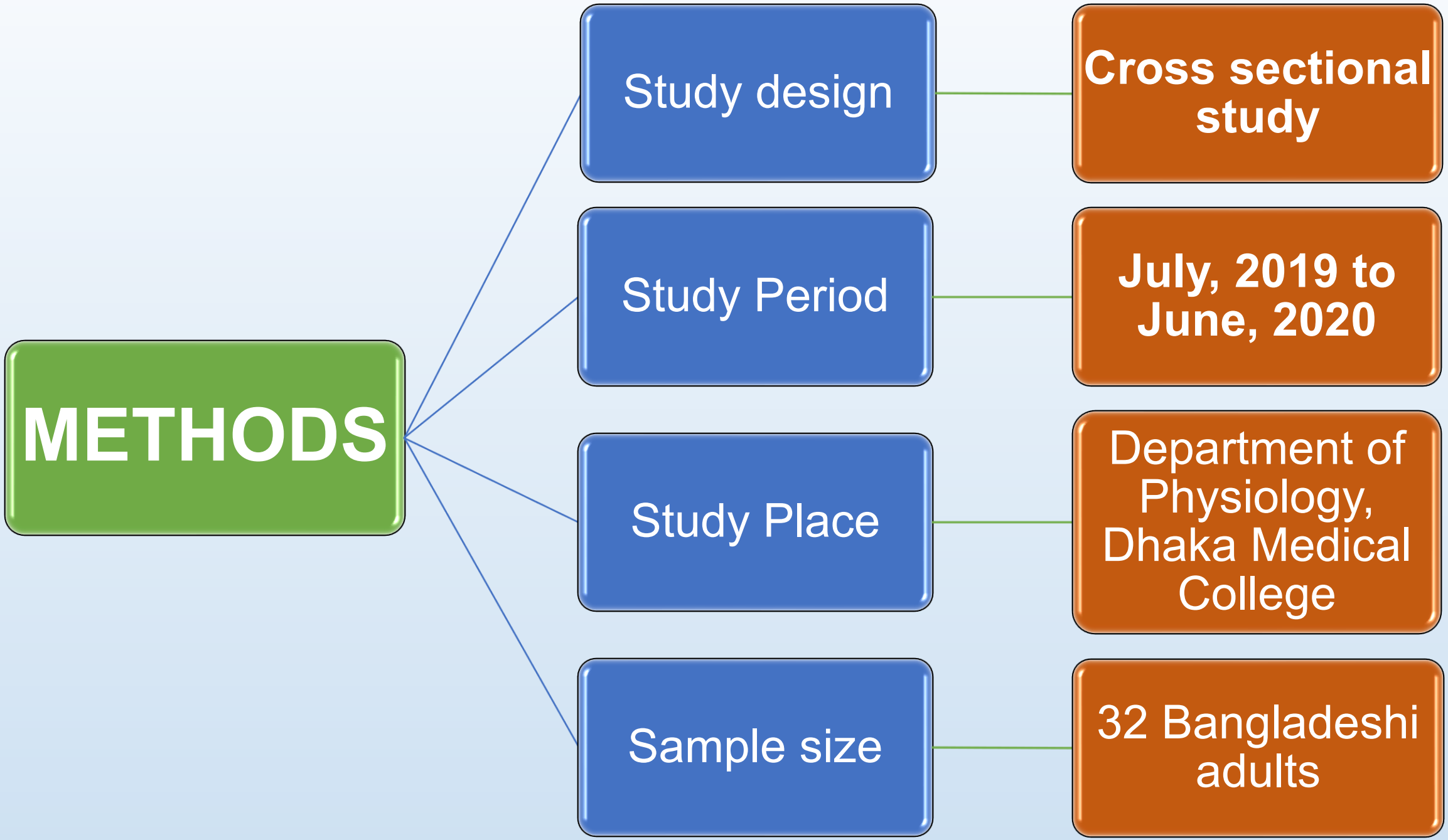
- Size: 58 kDa
- Genomic sequence: 35kb
- Exon number:13
- Amino acid: 458 coded by
- Nucleotides:1690
- Chromosome: 4 (4q12-q13).


Genetic Variants of the GC (DBP) Gene
c.-39C>T
c.282G>A
c.408C>T
c.438G>A
c.737_739delCTG
c.757C>T
c.897T>C
c.932G>T
p.D432E
p.T436K
c.474-24C>A
c.474-16A>G
c.607-60A>G
c.702-5T>C
c.702-41A>G
c.1034+26G>T
c.1395+34G>C
c.*4411T>C
C/EBP
GATA C/EBP
FoxA
C/EBP
NF-1
c.59-4090A>C
c.59-4070G>C
c.59-4024A>T
c.59-3885C>T
c.59-3707G>T
c.59-3708C>A
DNase I Hypersensitive sites IV (HSIV)

- Several SNPs (single nucleotide polymorphism) of Group specific component (GC) gene have been studied by researchers of different countries. Among others, rs7041 is one of the commonly studied polymorphisms of Group specific component (GC) gene.

- This gene encodes vitamin D binding protein which carries vitamin D in the circulation.
- Any **variation** in the Group specific component (GC) gene may lead to **structural or functional alteration** of the binding protein as well as may affect the serum concentrations of vitamin D.

METHODS


METHODS
Study design
Cross sectional study
Study Period
July, 2019 to June, 2020
Study Place
Department of Physiology, Dhaka Medical College
Sample size
32 Bangladeshi adults

Grouping of the subjects

Study Population

32 individuals with serum vitamin D level < 30ng/ml

Controls

10 individuals with serum vitamin D level > 30 ng/ml.

Selection Criteria of Study Population

Inclusion criteria

- Age: 18-60 years
- Sex: Male and Female
- Ethnicity: Bengali
- Middle class socio-economic group
- Skin complexion: Light Brown
- BMI: 18.4-24.9Kg/m^2
- Sun Exposure: minimum 45 minutes (from 11 a.m. to 2 p.m.) for at least 1 month
- Serum vitamin D level: < 30ng/ml

Exclusion Criteria

- Pathological conditions: Chronic liver, pulmonary, cardiovascular and renal disease, thyroid disease, acute infection, malignancy, trauma
- Systemic disease: Hypertension, Diabetes mellitus
- Replacement or supplement therapy with vitamin D, steroid, oestrogen, progesterone, calcium, anticonvulsant, thiazide diuretics.
- Smokers, veiled women, sunblock users, pregnant and lactating mothers.

Selection criteria of the controls

All the inclusion and exclusion criteria are same as the study population except for the serum vitamin D level, which was >30 ng/ml.

STUDY PROCEDURE

Primer designing and validation

History taking, Anthropometric measurements, documentation of all data

Blood collection

Contd.

A part of blood samples were sent for biochemical tests in DMCH and rest were stored at -70°c for genotype analysis

Identification of study population and controls as per selection criteria on the basis of biochemical test results

Genotype analysis of the blood samples of population and controls as per following steps:

Genotype analysis

DNA Extraction and Quantification of DNA

Polymerase Chain Reaction (PCR)

Gel electrophoresis

Purification of PCR products

Sanger sequencing

DNA Extraction

Fig. Micropippete

Fig. Blue tip

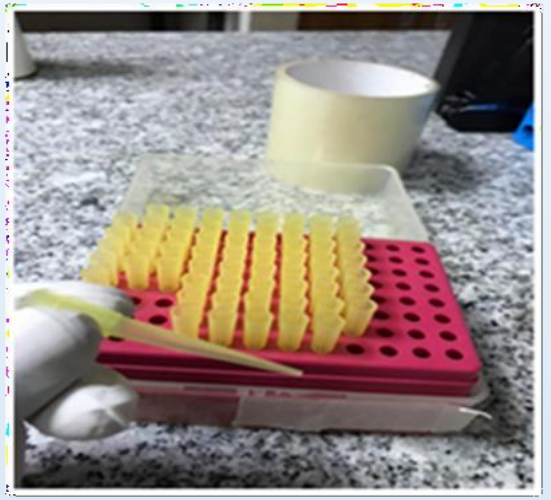


Fig. Yellow tips

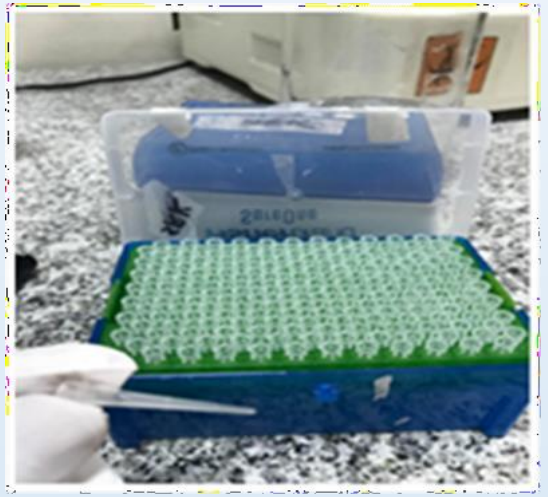


Fig. Nano tips

Fig. ReliaPrep Blood gDNA Miniprep System kit (USA)

Fig. Proteinase K

DNA Extraction

Fig. Column wash solution (CWD)

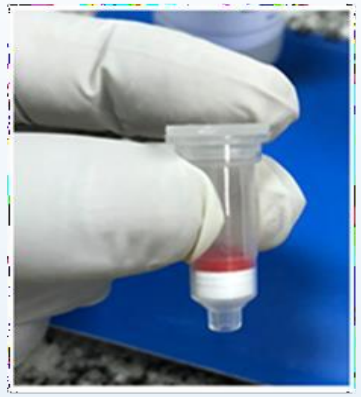


Fig. Column

Fig. Promega Kit apparatus

Fig. Q- Solution

Fig. Nuclease Free Water

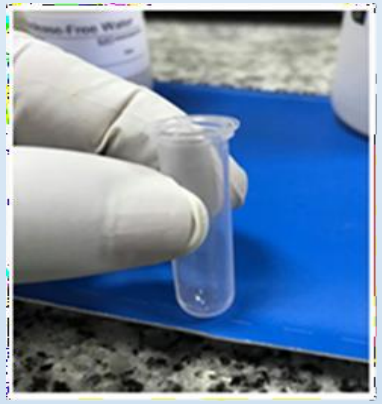


Fig. Collection tube

PCR Machine and gel setting tray

Fig. Thermal cycler

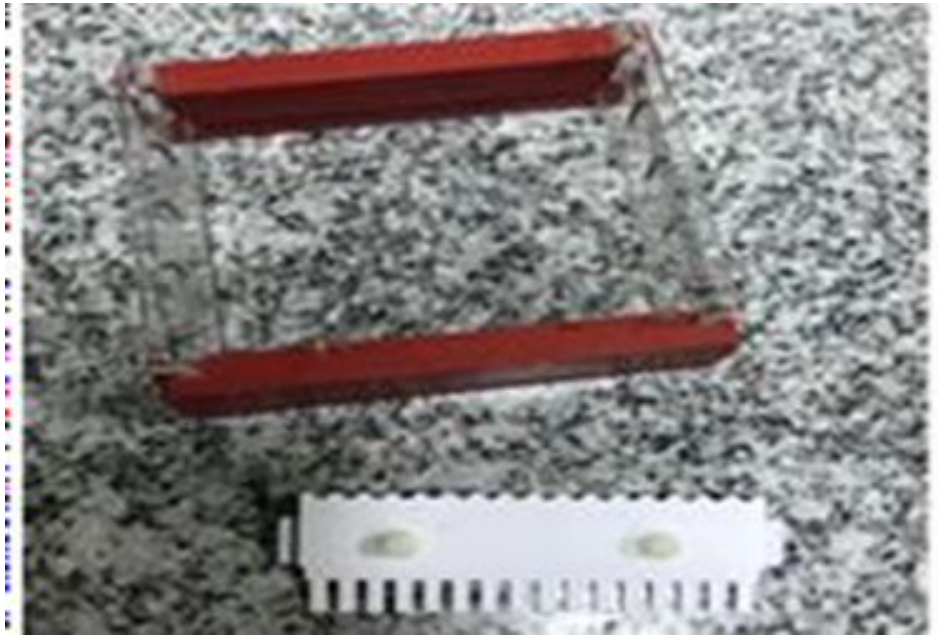
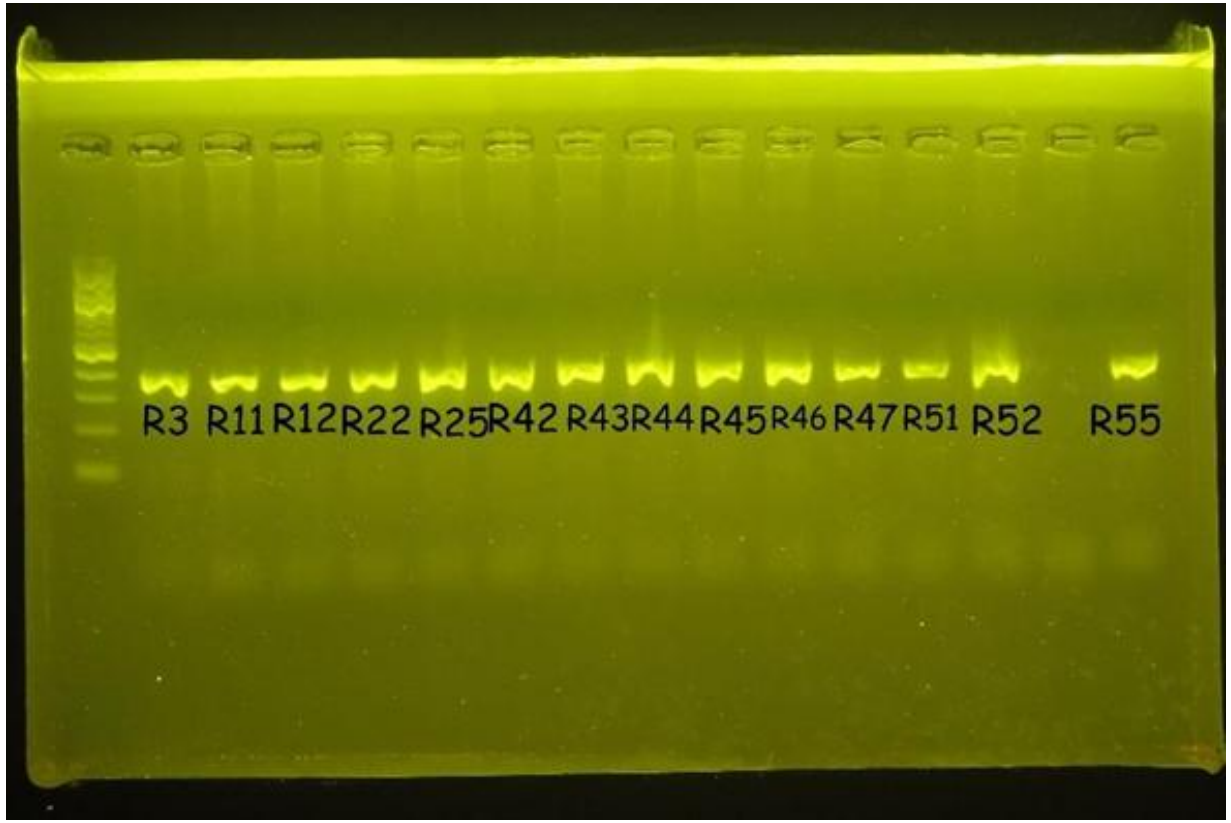


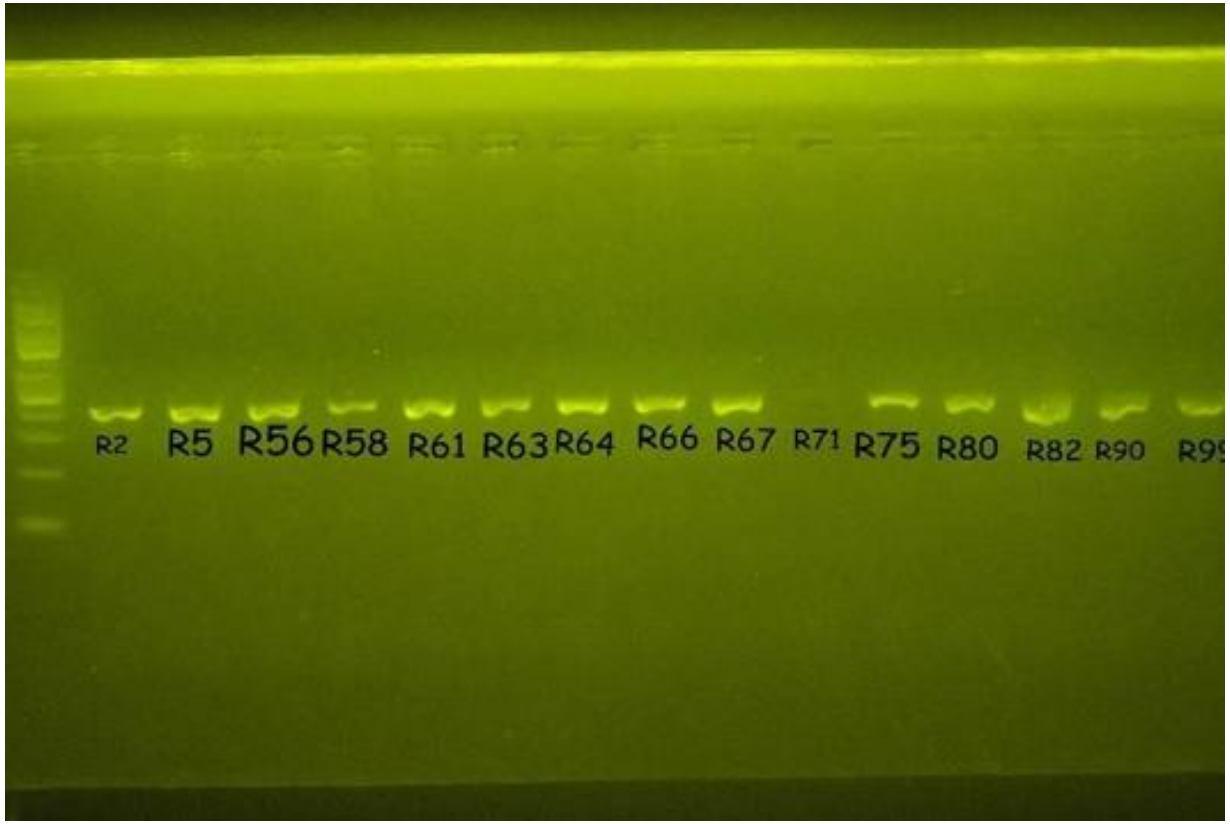
Fig. Gel setting tray with rubbery edges and comb

Standard Operating procedure (SOP) of PCR

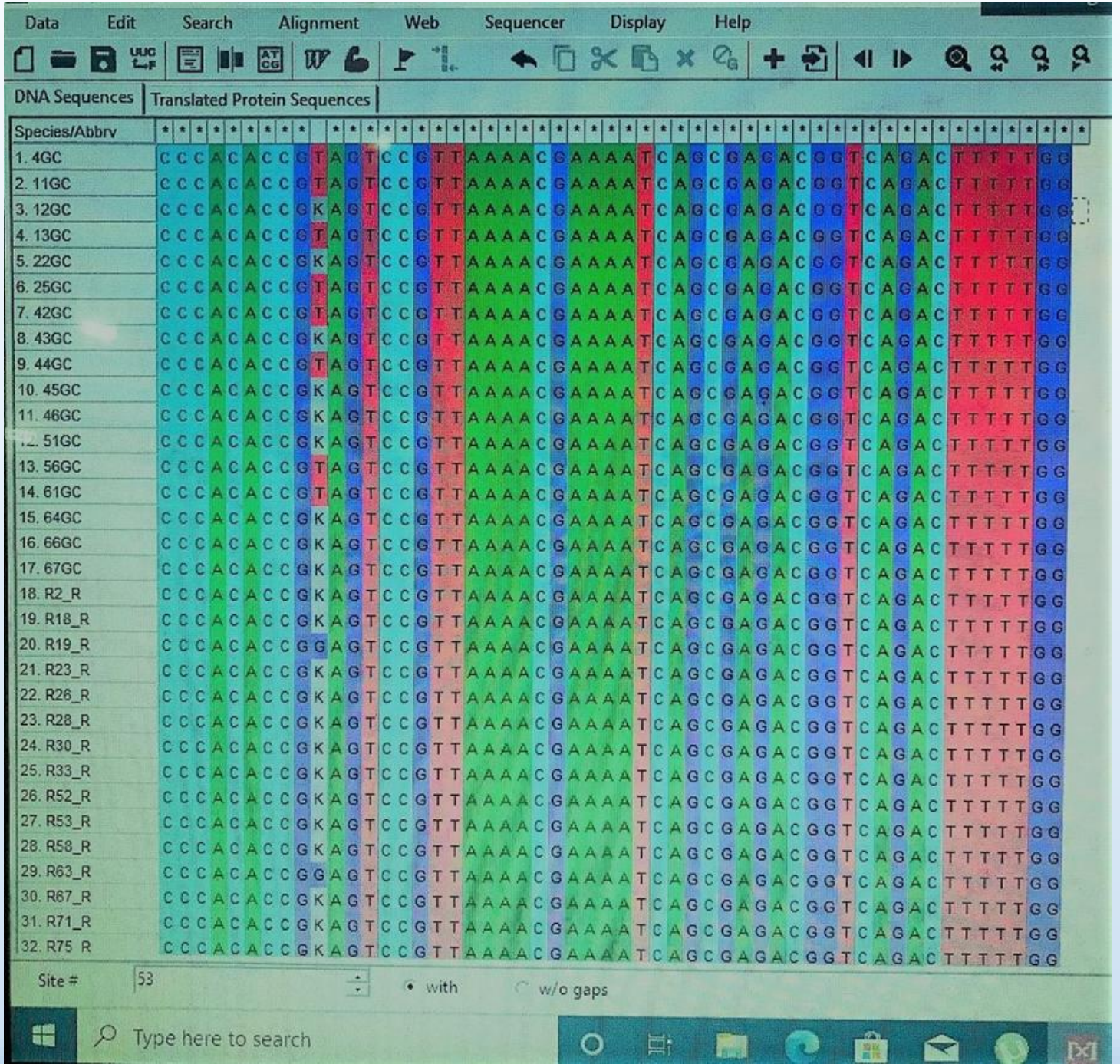
STEP	TEMPERATURE (Degree Celsius)	TIME	NO. OF CYCLES
Initial denaturation	95	3 min.	1
Denaturation	95	30 sec.	32
Annealing	57.4	30 sec.	32
Extension	72	1 min.	32
Final extension	72	15 min.	1
Holding	4	Till removal of the Amplicon	

Pictures of Gel Electrophoresis

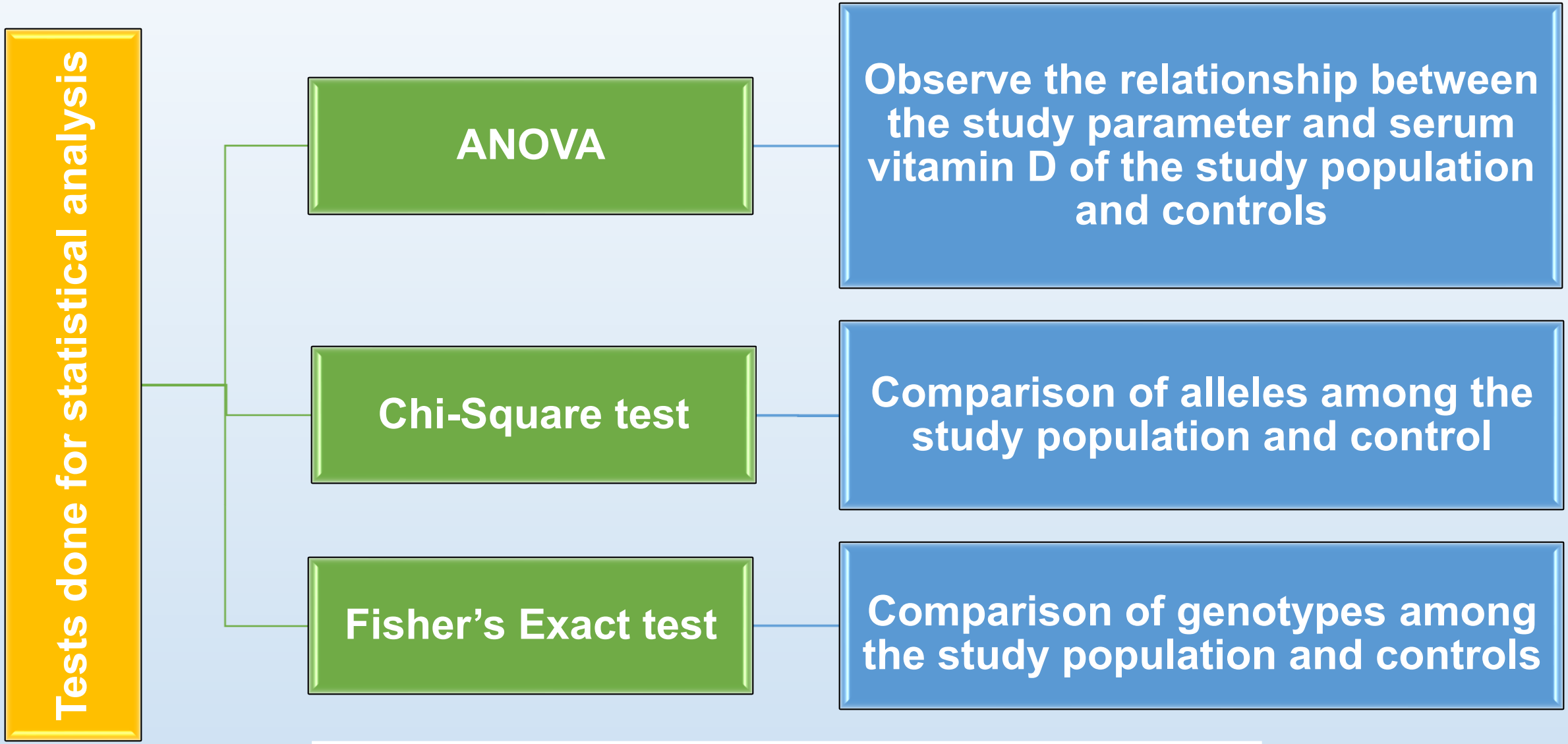




Alignment of Sequencing data of the study subjects in Mega software



STATISTICAL ANALYSIS



***$p < 0.05$ was taken as the level of significance**

RESULTS

Table 1 General characteristics of study population and controls. Results presented as mean ± s.d. A statistically significant difference (by independent samples *t*-test) was taken as $p < 0.05$

Characteristic	Case	Control	P-value
Age (y)	30.91 ± 11.31	32.90 ± 7.89	0.6084
BMI (kg/m^2)	20.94 ± 1.94	21.29 ± 0.79	0.5826
Systolic BP (mmHg)	113.28 ± 6.91	110.00 ± 8.16	0.2165
Diastolic BP (mmHg)	75.28 ± 5.38	74.00 ± 6.99	0.5446
Duration of sun exposure (h)	6.50 ± 1.85	5.90 ± 1.37	0.3506

Table 2 Biochemical characteristics of study population and controls. Results presented as mean ± s.d. A statistically significant difference (case *vs*. control using independent samples *t*-test) was taken as $p < 0.05$

Characteristic	Case	Control	p-value
Vitamin D (ng/mL)	**18.91 ± 4.86**	49.23 ± 16.29	**0.0001**
Calcium (mg/dL)	09.08 ± 0.38	09.22 ± 0.49	0.3485
Albumin (g/dL)	03.83 ± 0.83	04.10 ± 0.69	0.3575
Fasting glucose (mmol/L)	05.01 ± 0.55	04.75 ± 0.52	0.1941
Creatinine (mg/dL)	0.79 ± 0.18	0.83 ± 0.10	0.5083
Prothrombin time (s)	12.53 ± 1.32	12.30 ± 1.59	0.6492

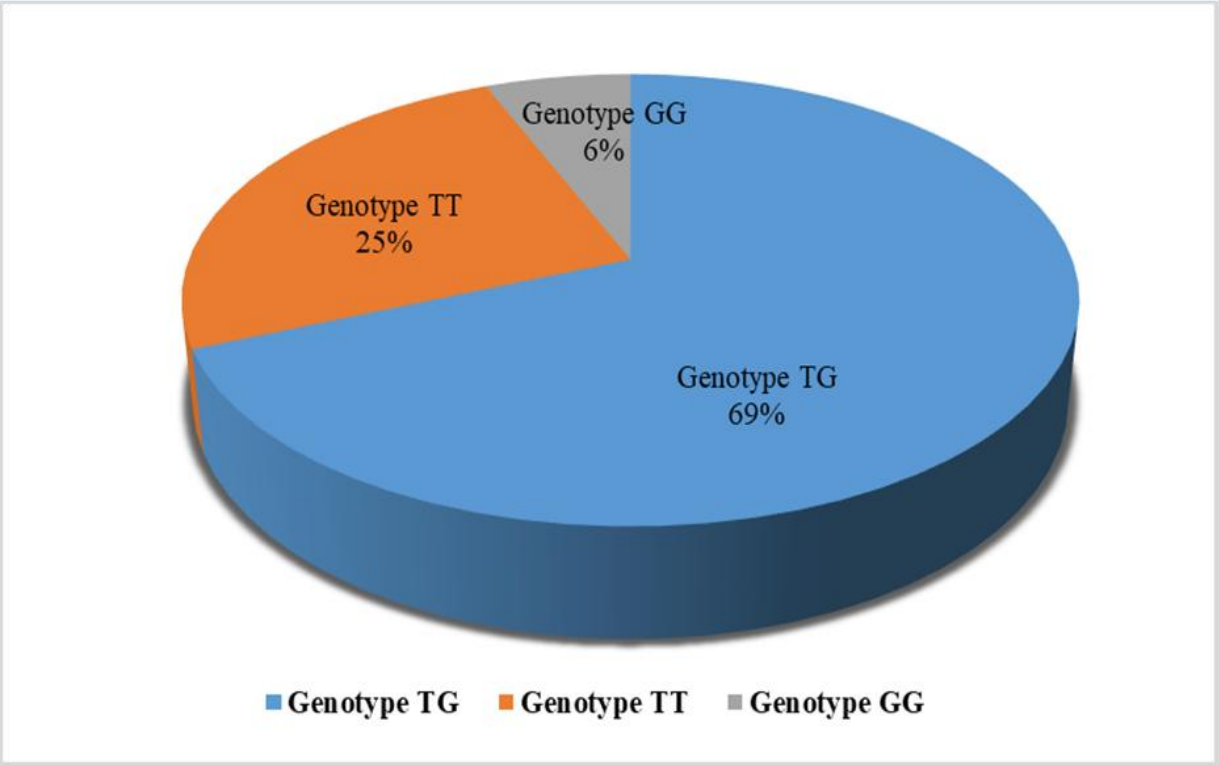
Table 3 Allele and Genotype Frequencies. Results presented as frequency (number of instances) and as a percentage of the total

	Case		**Control**		
	Frequency	Percentage	Frequency	Percentage	P-Value
Major Allele: T	0.595(38)	**59.4%**	0.45 (09)	45%	0.383
Minor Allele: G	0.405(26)	40.6%	0.55 (11)	**55%**	
Genotype: TG	0.69 (22)	**68.8%**	0.30 (03)	30%	0.062
Genotype: TT	0.25 (08)	25.0%	0.30 (03)	30%	1.000
Genotype: GG	0.06 (02)	06.3%	0.40 (04)	40%	0.021

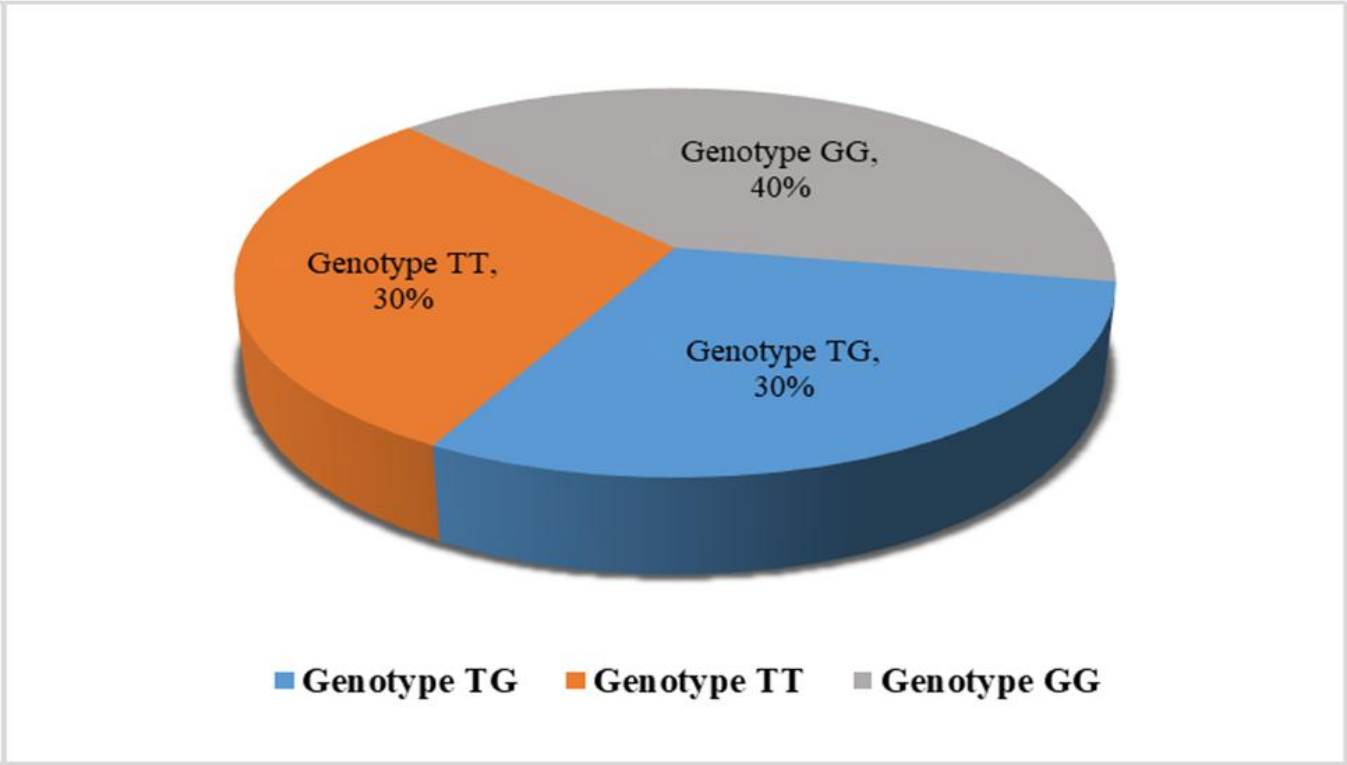
Table 4: Relationship between genotypes at rs7041 of Group specific component gene and serum vitamin D level among the study population and control.

Groups	Genotype Frequency	Genotype vs Genotype	Serum vitamin D (ng/ml)	p value
Study population (N=32)		**TG vs TT vs GG**	**20.08 ± 4.86 vs 15.08 ± 02.66 vs 16.50 ± 01.88**	**0.031***
	TG (22)	**TG vs TT**	20.08 ± 4.86 vs 15.08 ± 02.66	**0.012***
	TT (08)	TG vs GG	20.08 ± 4.86 vs 16.50 ± 01.88	0.725
	GG (02)	TT vs GG	15.08 ± 02.66 vs 16.50 ± 01.88	0.092
Control (Nc=10)		TG vs TT vs GG	37.36 ± 1.13 vs 55.17 ± 23.08 vs 53.66 ± 15.43	0.358
	TG (3)	TG vs TT	37.36 ± 1.13 vs 55.17 ± 23.08	0.214
	TT (3)	TG vs GG	37.36 ± 1.13 vs 53.66 ± 15.43	0.223
	GG (4)	TT vs GG	55.17 ± 23.08 vs 53.66 ± 15.43	0.905

Figure 1: Distribution of the genotypes of rs7041 of Group specific component gene among the study population and controls

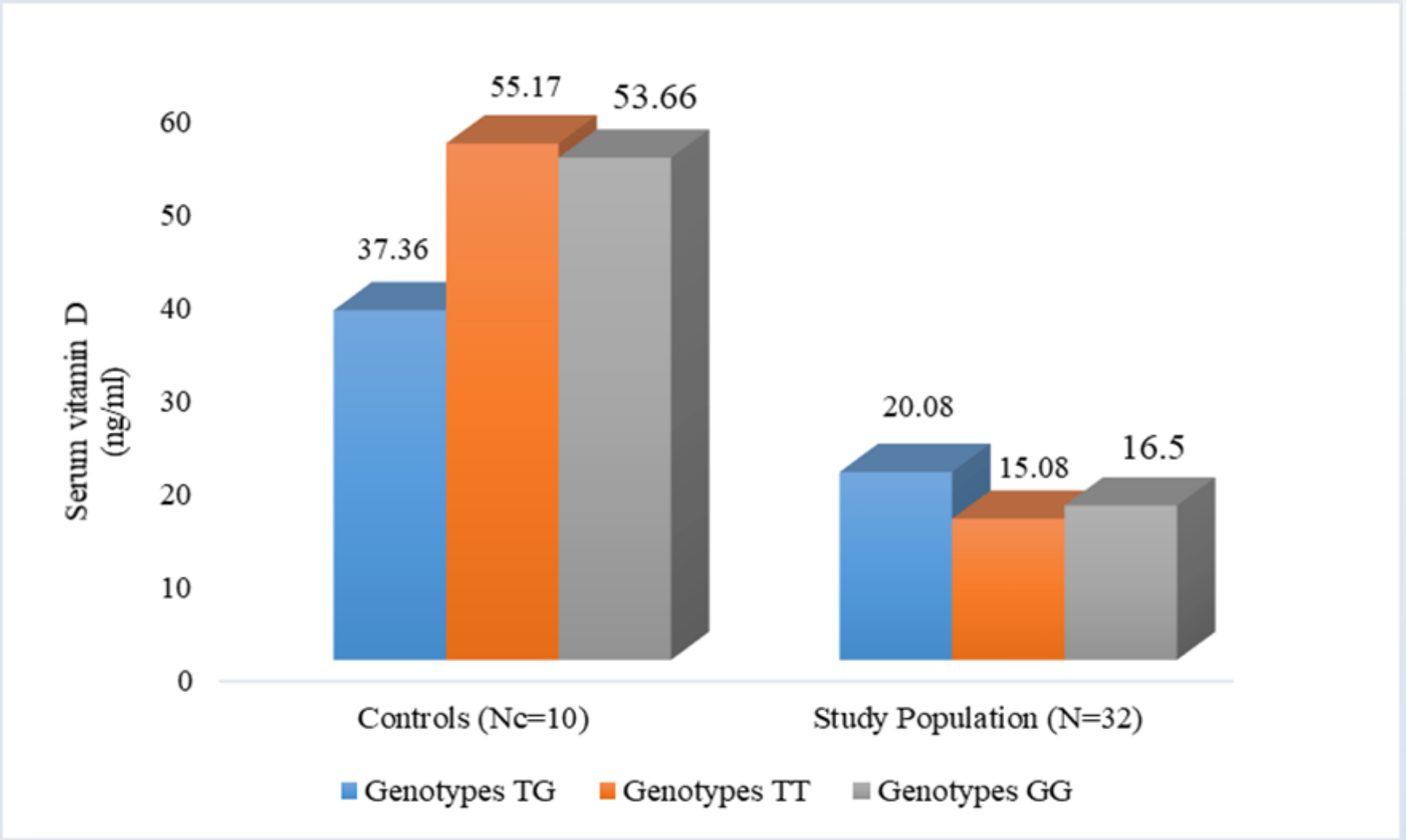


Study population (N=32)



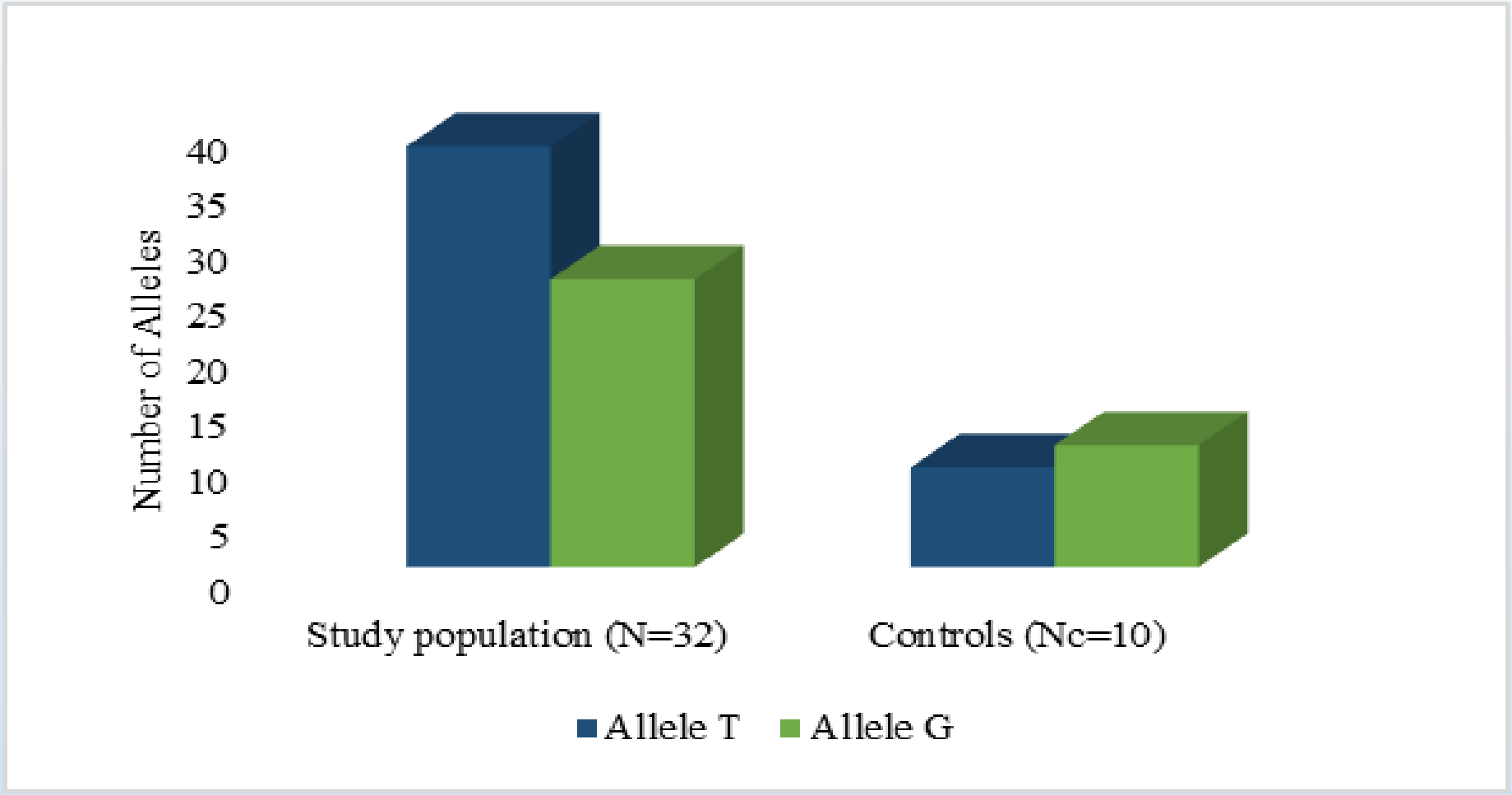
Controls (N_C=10)

Figure 2
Distribution of genotypes and serum vitamin D among study subjects



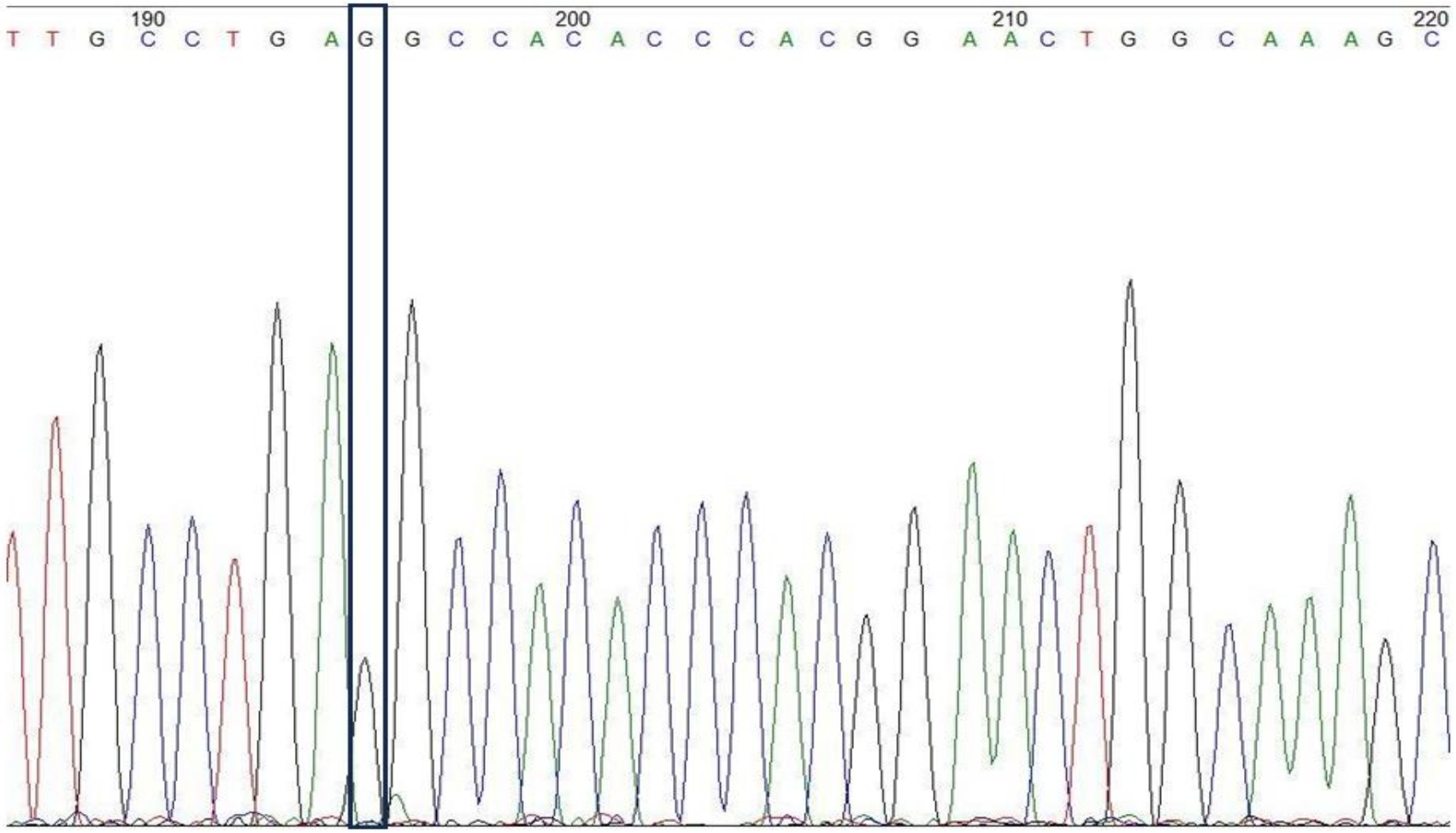
N= Number of study population with low serum vitamin D level; N_c= Number of controls with normal serum vitamin D level

Figure 3
Distribution of alleles among study population (N=32) and controls (N_c=10)



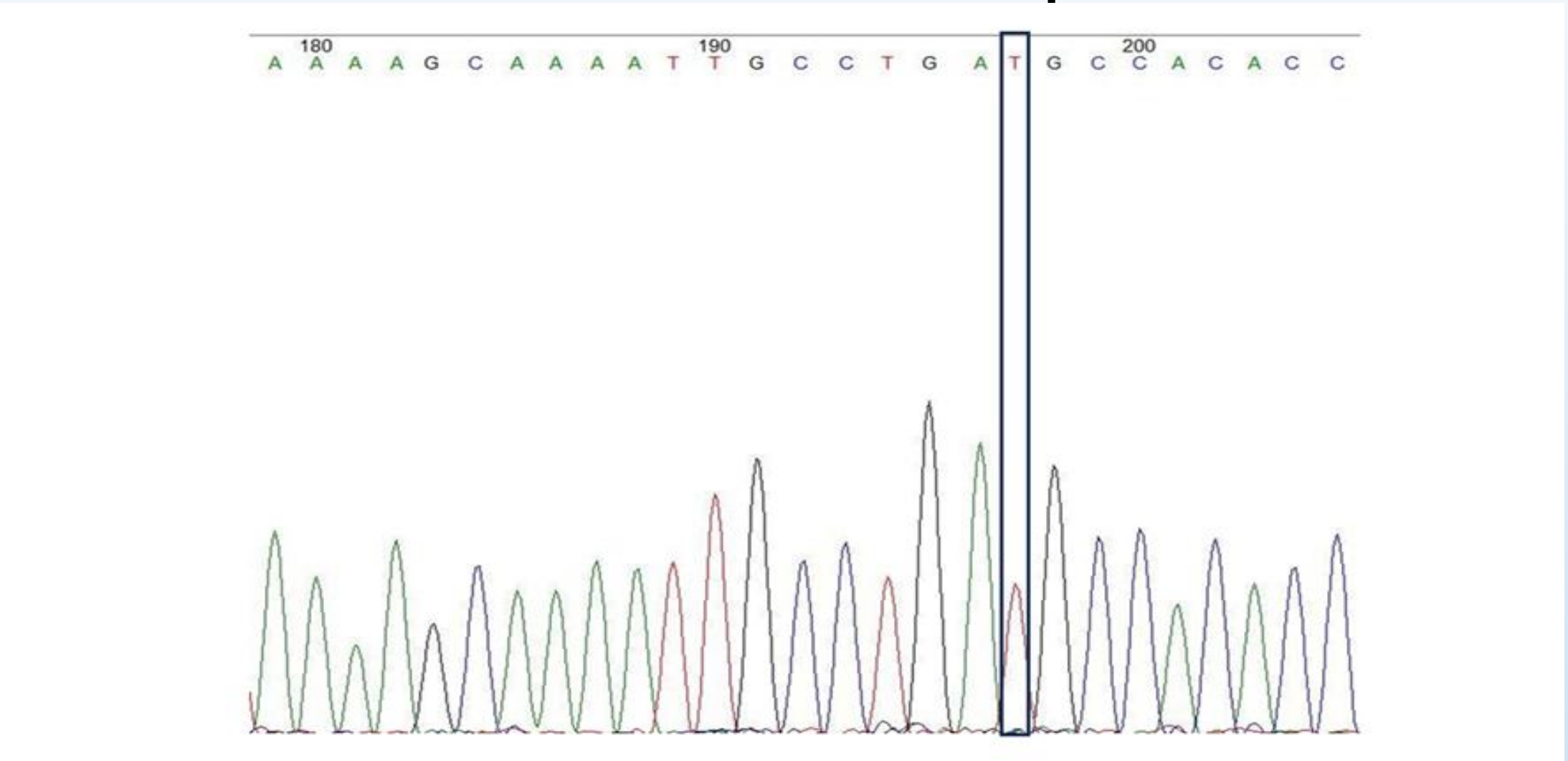
N= Number of study population with low serum vitamin D level, N_c= Number of controls with normal serum vitamin D level

Sample of DNA Sequencing Chromatogram data showing allele G in rs7041 in location 195 bp



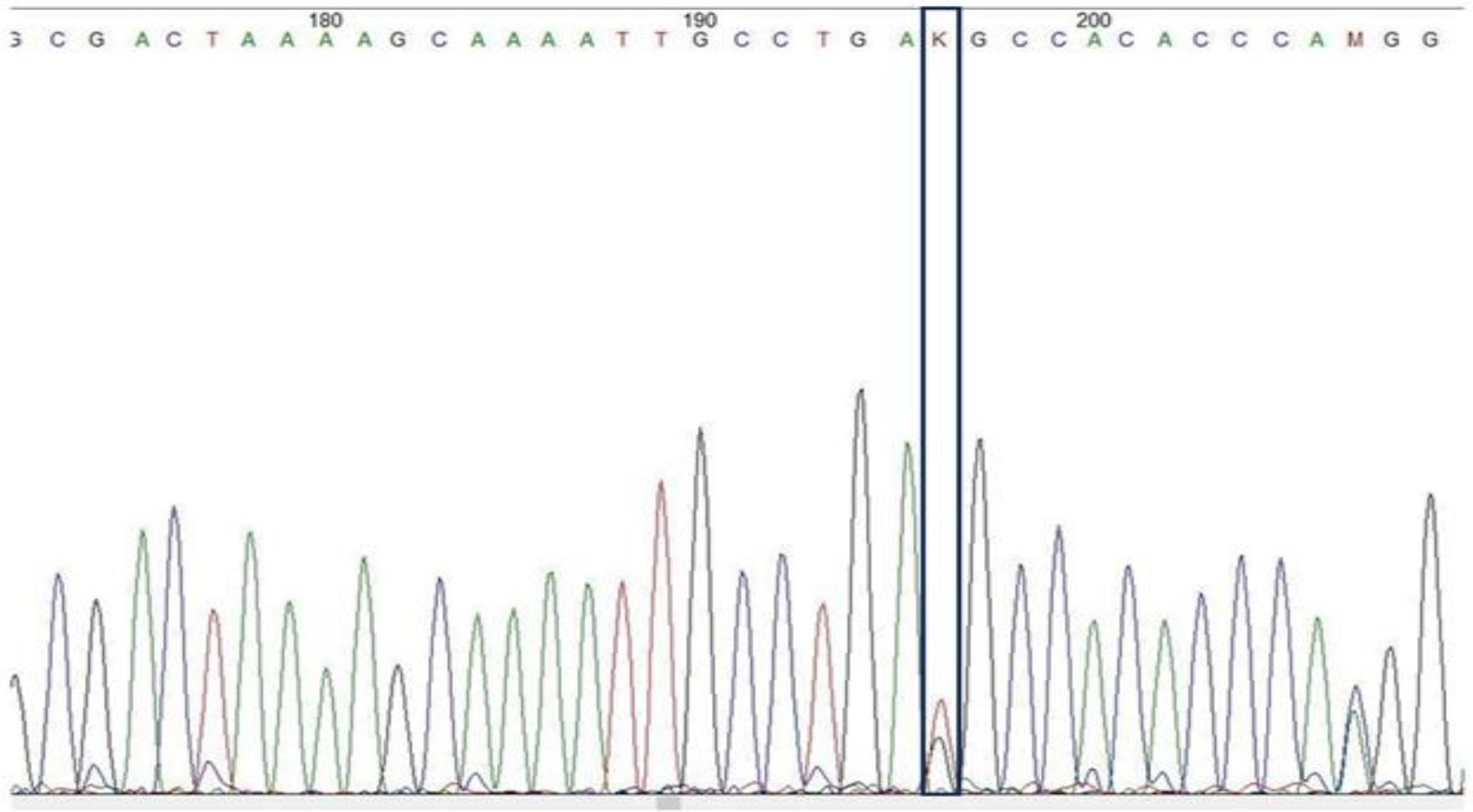
Raw data derived from Sanger sequencer. Data showing nucleotide G (Guanine) of rs7041 of Group specific component gene at location 195 bp. Sample was edited by Chromas software.

Sample of a DNA Sequencing Chromatogram data showing allele T in rs7041 in location 197 bp



Raw data derived from Sanger sequencer. Data showing nucleotide T (Thymine) of rs7041 of Group specific component gene at location 197 bp. The data was edited by Chromas software.

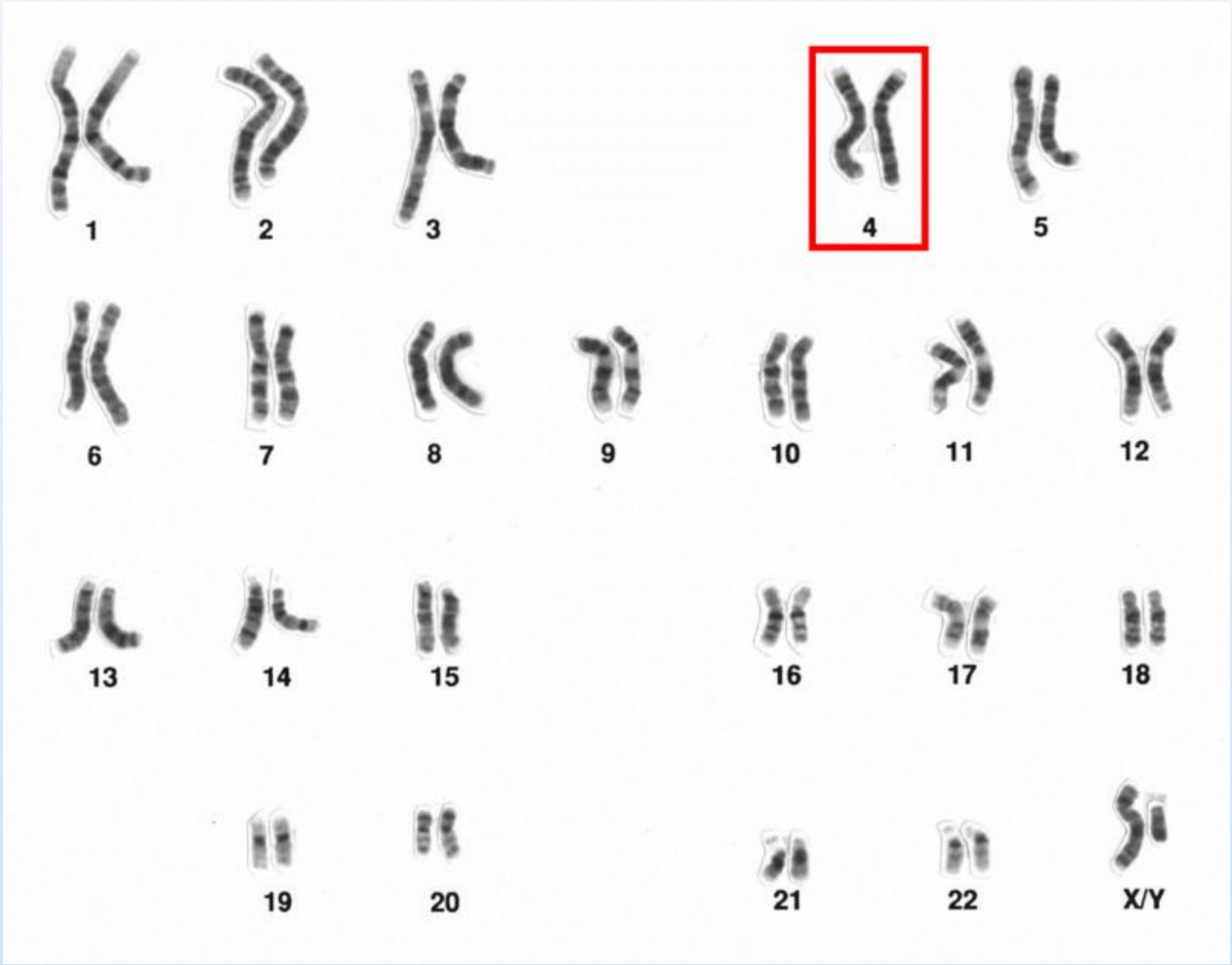
Sample of DNA Sequencing Chromatogram data showing allele K (T, G) in rs7041 in location 197 bp

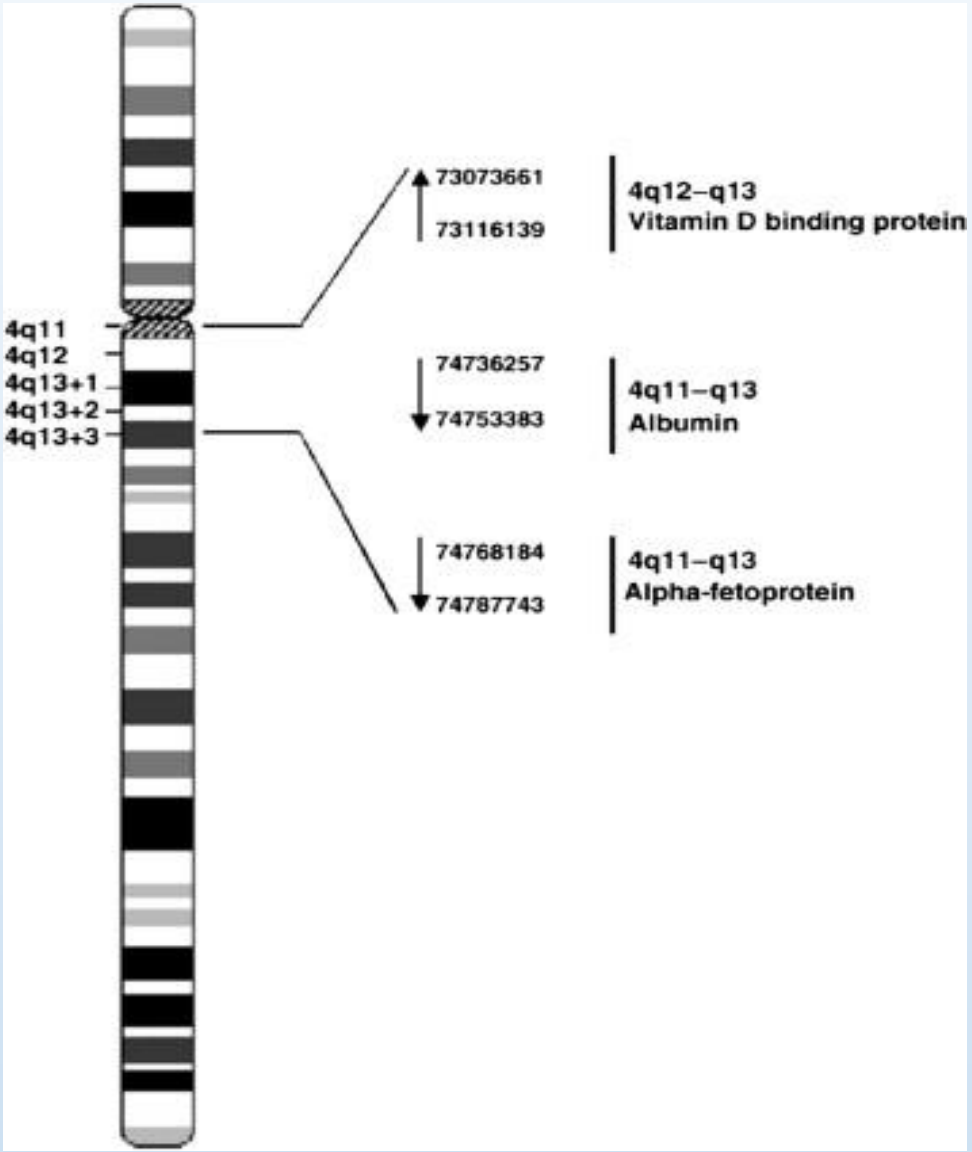


Raw data derived from Sanger sequencer. Data showing nucleotide K (T=Thymine, G= Guanine) of rs7041 of Group specific component gene at location 197 bp. Sample was edited by Chromas software.

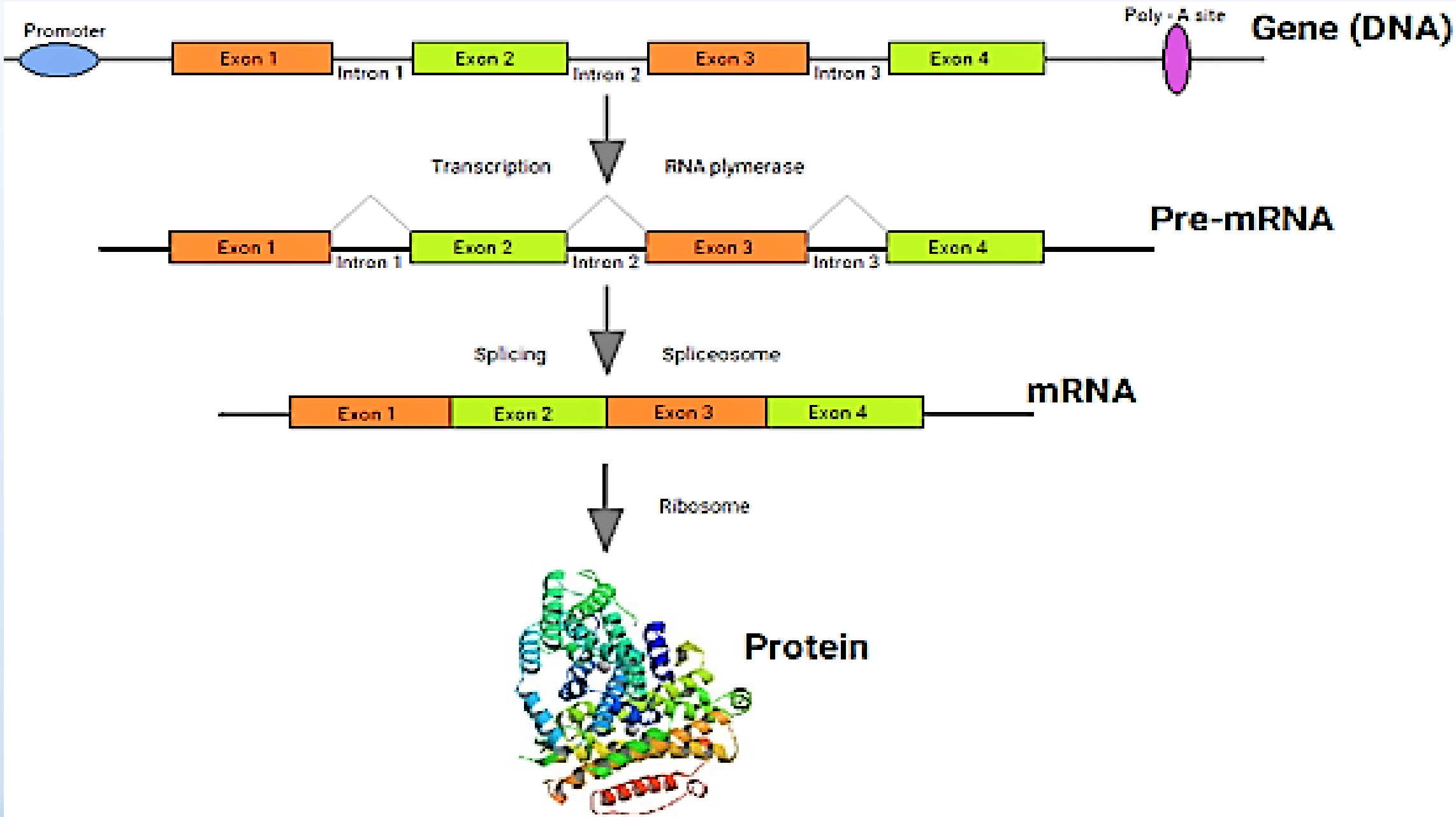
POSSIBLE MECHANISMS

Image of Human Chromosome 4

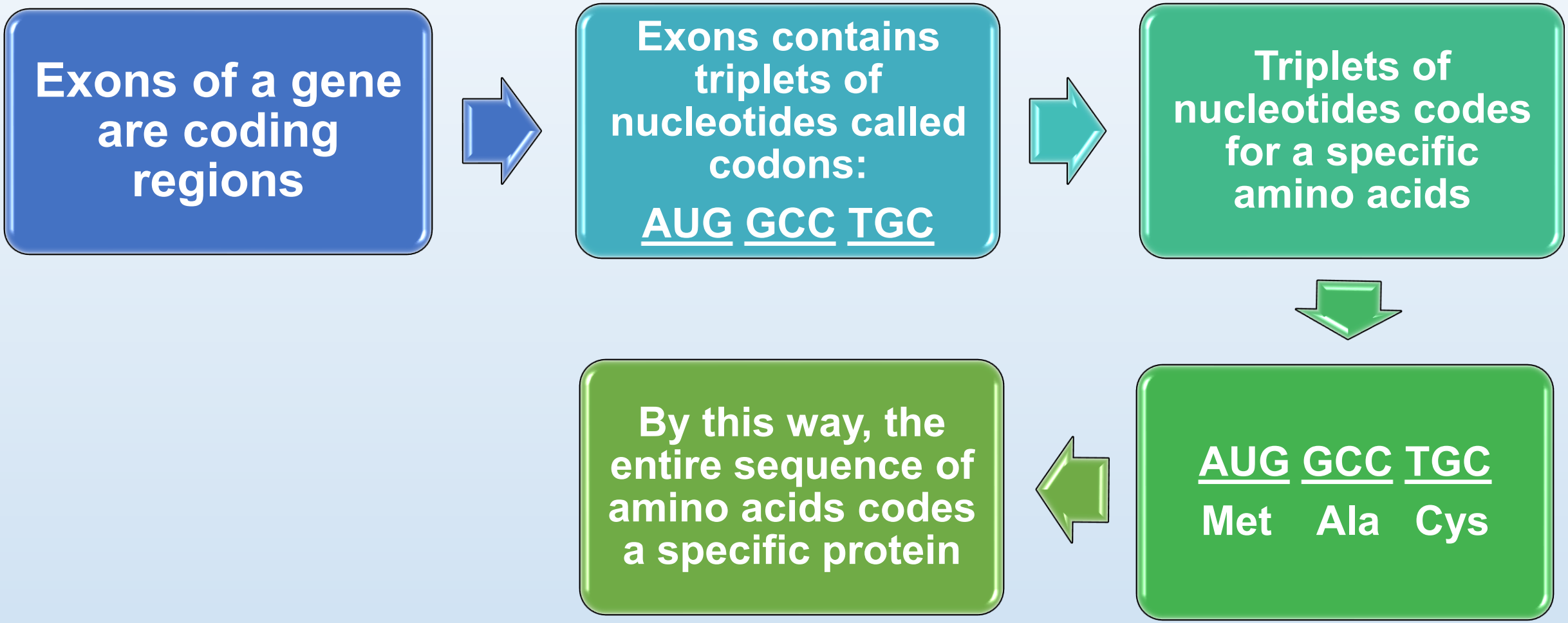




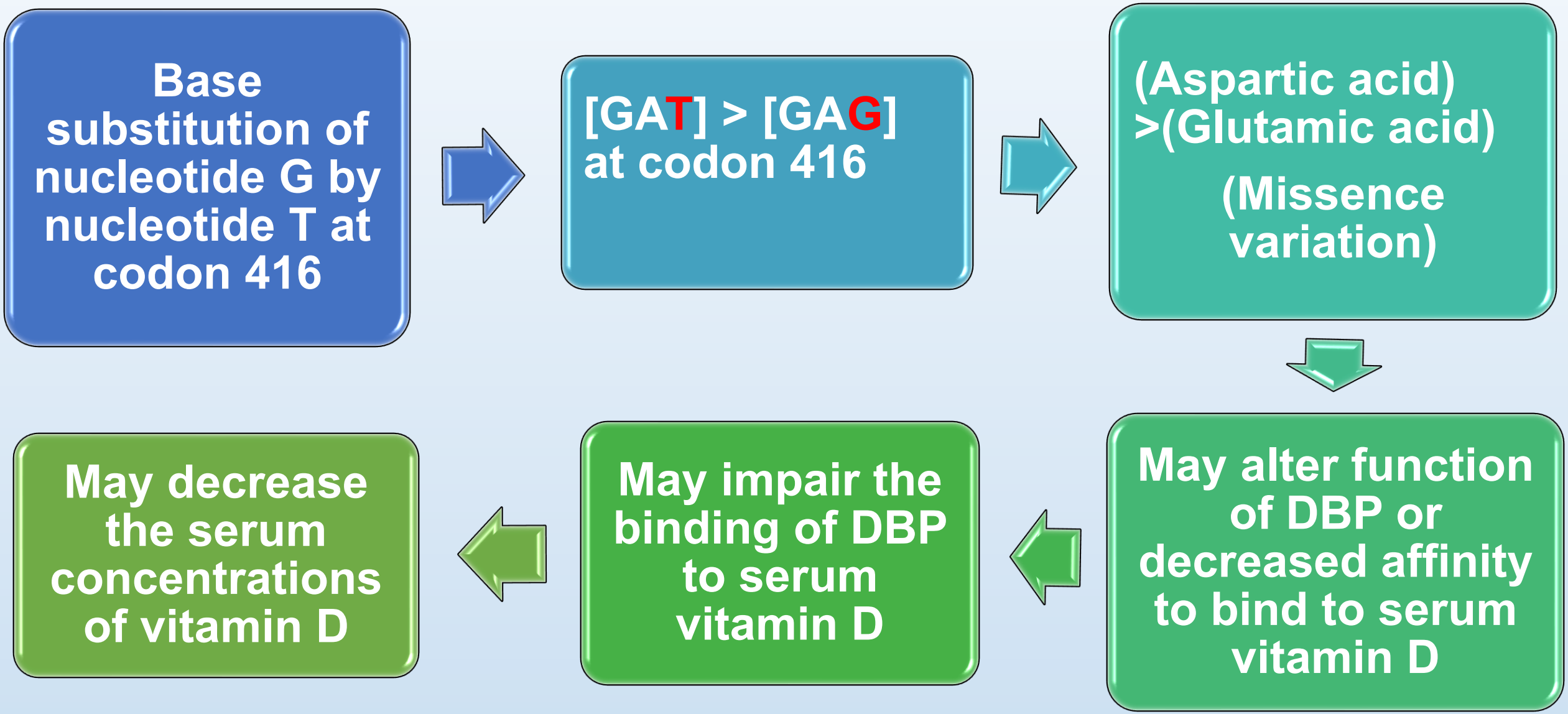
Structure of a gene showing different regions including exons



How exons of a gene code for proteins?



How rs7041 polymorphism affect DBP synthesis?



CONCLUSIONS

- The present study has reported a statistically significant relationship between TG and TT genotypes at rs7041 of Group specific component (GC) gene with low serum vitamin D levels among Bangladeshi adults.
- The heterozygous TG and homozygous TT genotypes of rs7041 of Group specific component gene might be a determining factor for low serum vitamin D levels in the 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 levels in adults of Bangladesh.
- However, as this is a pilot study with a small number of participants, the results should be taken carefully and confirmed by studies with larger sample sizes.

LIMITATIONS

LIMITATIONS

- It is a pilot study with a small sample size, which limits the ability to generalize the findings. The study was conducted with limited laboratory facilities in Bangladesh, and financial constraints also restricted its scope. Despite these challenges, the analyses were conducted carefully.

RECOMMENDATIONS

- The study can be done in a large sample size, which will help to obtain a better picture of genetic constitution of Bangladeshi people.
- Similar study can be done in different centers or institutions of the country which will help out to obtain more reliable outcomes.

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Existence of the *rs7041* polymorphism in the vitamin D binding protein gene among Bangladeshis with low serum vitamin D: A pilot study

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ABSTRACT

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