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POLYMORPHISM OF *GC* GENE, ENCODING VITAMIN D BINDING PROTEIN, IN ABORIGINAL POPULATIONS OF SIBERIA

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❀ The analysis of the nucleotide sequences of exons and adjacent non-coding regions of the *GC* gene in 108 representatives of various ethnic groups of aboriginal population of Siberia was carried out. Polymorphism was found in four nucleotide positions: non-synonymous substitutions at the rs4588 and rs7041 loci, a synonymous substitution at the rs4752 locus, and a replacement in the non-coding region at the rs3733359 locus. Seven haplotypes of the *GC* gene were identified. Of these, 4 haplotypes encode the Gc1F isoform, 2 haplotypes encode the Gc1S isoform, and 1 haplotype encodes the Gc2 isoform. Between-regional differences were found in the distribution of variants of the *GC* gene: in the northeast and in the central part of Siberia, the highest prevalence of the Gc1F and Gc1F/Gc1F variants is observed, and in the south and west of Siberia, the Gc2, Gc1S/Gc2 and Gc2/Gc2 variants are most common. In the case of the *GC* gene, gene-environment interactions are apparently aimed at creating a balance between the activity of vitamin D-binding protein and the level of 25-hydroxyvitamin D in the blood serum.

❀ **Keywords:** genetic polymorphism; vitamin D binding protein; gene *GC*; human populations; Siberia.

ПОЛИМОРФИЗМ ГЕНА *GC*, КОДИРУЮЩЕГО ВИТАМИН D-СВЯЗЫВАЮЩИЙ БЕЛОК, У КОРЕННОГО НАСЕЛЕНИЯ СИБИРИ

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❀ Проведен анализ нуклеотидных последовательностей экзонов и прилегающих к ним некодирующих участков гена *GC* у 108 представителей различных этнических групп коренного населения Сибири. Полиморфизм обнаружен в четырех нуклеотидных позициях: несинонимичные замены в локусах rs4588 и rs7041, синонимичная замена в локусе rs4752 и замена в некодирующей области в локусе rs3733359. Выявлено семь гаплотипов гена *GC*. Из них 4 гаплотипа кодируют изоформу Gc1F, 2 гаплотипа — изоформу Gc1S и 1 гаплотип — изоформу Gc2. Обнаружены межрегиональные различия по распределению вариантов гена *GC*: на северо-востоке и в центральной части Сибири наблюдается самая высокая распространенность вариантов Gc1F и Gc1F/Gc1F, а на юге и западе Сибири чаще всего распространены варианты Gc2, Gc1S/Gc2 и Gc2/Gc2. По всей видимости, в случае гена *GC* ген-средовые взаимодействия направлены на формирование баланса между активностью витамин D-связывающего белка и уровнем 25-гидроксивитамина D в сыворотке крови.

❀ **Ключевые слова:** генетический полиморфизм; витамин D-связывающий белок; ген *GC*; популяции человека; Сибирь.

INTRODUCTION

Vitamin D is essential in the functioning of the body as it participates in the metabolism of calcium and phosphorus, transport of calcium to bone tissue, immunomodulation, and regulation of cell energy metabolism. Vitamin D enters the body in two forms: i) cholecalciferol (D_3) is synthesized in the skin under the influence of ultraviolet radiation, and ii) ergocalciferol (D_2) enters the body through food. On the territory of Northern

Eurasia (north of 35 °N), the level of ultraviolet radiation is insufficient for the year-round synthesis of cholecalciferol (D_3) in the skin; hence, the exogenous consumption of vitamin D by humans is of great importance there [1]. The transport form of vitamin D (25(OH)D, calcidiol) is synthesized in the liver, and then it is converted into the active hormonal form of vitamin D ($1.25(OH)_2D$), calcitriol) in the kidneys. Calcitriol is further involved in the activation of vitamin D receptors, which, in turn, are involved in the regulation of transcription of various genes [2].

The main carrier of vitamin D_3 and its derivatives is vitamin D-binding protein (DBP), which belongs to blood Gc-globulins (Groups specific component) [3]. This polyfunctional glycoprotein consists of three structural domains that are responsible for binding to vitamin D, fatty acids, actin, and the cell membrane of neutrophils [4]. DBP is encoded by *GC*, which is located on chromosome 4 and is represented by 13 exons [5]. Furthermore, DBP has been revealed to be a mixture of modified polypeptides, and its degree of glycosylation is determined by the genotype [5]. Three main DBP isoforms have been described (Gc1F, Gc1S, and Gc2). Protein variants Gc1F and Gc1S, characterized by the D432E amino acid substitution, can be converted into the active protein GcMAF, a macrophage activating factor that is significant in the development of an anticancer response in some viral and neurodegenerative diseases [6, 7]. Meanwhile, the Gc2 variant cannot be converted to GcMAF because it lacks the main site of O-bound glycosylation of saccharides due to the amino acid substitution of T436K. In this regard, the Gc2/Gc2 genotypes are associated with an increased risk of certain diseases [6, 7].

Studies have revealed that there are regional aspects in the distribution of Gc variants in human populations, which are most likely due to differences in the ability of Gc variants to bind to 25(OH)D. Several studies have shown that the blood plasma Gc level is determined genotypically, as the highest Gc concentrations are noted in the carriers of the Gc1F allele, and the lowest are observed in the carriers of the Gc2 allele [8, 9]. Accordingly, the carriers of the Gc1F and Gc1S variants have the highest affinity for 25(OH)D, and those of the Gc2 variants have the lowest affinity for 25(OH)D. The frequency distribution of Gc variants correlates with ecological, climate, and geographic factors (intensity of solar radiation, altitude, type of nutrition, etc.) [10–12]. The highest frequencies of the Gc1F variant were found in the most dark-pigmented population groups, and the highest Gc2 frequencies were found in the populations of regions with relatively low solar illumination [10, 13, 14]. V.A. Spitsin also established a positive correlation between the frequency of the Gc2 allele and geographic latitude, and a negative correlation between that frequency and the level of mean annual temperature [11].

It should be noted that after years of studies on immunobiochemical polymorphism (using the methods of electrophoresis and isoelectric focusing of proteins), large amounts of data have been accumulated on the frequencies of Gc1 and Gc2 variants in populations of Northern Eurasia, including the populations of the former Soviet Union [15]. In recent years, the databases of genetic polymorphism have been updated with the results of genome-wide and exome-wide studies, so that the researchers have the opportunity to assess the prevalence of genetic variants of loci rs4588 and rs7041, which determine the main Gc variants, in human populations. Meanwhile, in international databases, there is very little information on the allelic and haplotype diversity of *GC* in Russian populations. This work presents the results of the analysis of *GC* polymorphism in the indigenous population of Siberia, based on data on exome-wide polymorphism [16–18].

MATERIALS AND METHODS

The previously published data on full exome polymorphism in the populations of the indigenous population of North-Eastern Siberia (Eskimos, Chukchi, Koryaks; $n = 28$), Central Siberia (Evens, Evenks, Yakuts; $n = 32$), Southern Siberia (Tuvinians, Shorts, Altaians, Buryats; $n = 28$), and Western Siberia (Kets, Khanty, Mansi, Selkups, Nenets, Nganasans; $n = 20$) was analyzed with the participation of the author of this work [16–18]. The polymorphism of all exons and adjacent regions of introns of *GC* located on chro-

mosome 4 between positions 72607410 and 72669758 was analyzed. Nucleotides were numbered according to the reference sequence of the human genome GRCh37.p13 (hg19).

To identify haplotypes from the genotypes of *GC* with an unknown gamete phase, the ELB algorithm of the Arlequin 3.01 software package was used [19]. The statistical significance of the differences in the allele and genotype frequencies of the *GC* loci analyzed in the compared groups was determined using Fisher's exact test. The degree of interpopulation differentiation in terms of the frequencies of *GC* variants was assessed using *FST* values (Arlequin 3.01).

For a comparative analysis, we used information on the frequencies of variants of the population polymorphism of *GC* from the dbSNP databases (https://www.ncbi.nlm.nih.gov/snp/), 1000 Genomes (https://www.internationalgenome.org/), gnomAD and ExAC (https://gnomad.broadinstitute.org), and ALFRED (https://alfred.med.yale.edu).

RESULTS AND DISCUSSION

The analysis of the nucleotide sequences of exons and adjacent noncoding regions of *GC* in 108 representatives of various ethnic groups of the indigenous population of Siberia revealed the presence of a polymorphism at four nucleotide positions (Table 1). Three substitutions were found in exons (nonsynonymous substitutions at the rs4588 and rs7041 loci and a synonymous substitution at the rs4752 locus), and one substitution was found in the noncoding region (rs3733359). As can be seen from the distribution of *GC* allele frequencies in regional samples of Siberia (Table 2), the rs4588-T variant is significantly less common in the northeast and central Siberia

Table 1

GC polymorphism in the indigenous population of Siberia

Position No.	Nucleotide position of chromosome 4	Polymorphism identifier	Substitution location	Type of nucleotide and amino acid substitutions
1	72618323	rs4588	Exon	G → T, Thr436Lys
2	72618334	rs7041	Exon	A → C, Asp432Glu
3	72622566	rs4752	Exon	A → G, Cys318Cys
4	72649774	rs3733359	5′-utr	G → A

Note. Substitution type is presented in the direction of ancestral to derived variant. 5′-utr – 5′-non-translated section.

Table 2

Frequency of *GC* alleles in populations

Allele	Allele frequency, %					
	North-Eastern Siberia (n = 28)	Central Siberia (n = 32)	Southern Siberia (n = 28)	Western Siberia (n = 20)	Eastern Asia (n = 1008)*	Africa (n = 1322)*
rs4588-T	5.4	3.1	28.6	27.5	26.1	6.7
rs7041-C	28.6	39.1	30.4	52.5	30.0	9.4
rs4752-G	32.1	46.9	16.1	12.5	7.9	29.7
rs3733359-A	32.1	17.2	25.0	7.5	40.0	27.4

Note. n: sample size. The frequencies of the derived alleles are given according to Table 1. * dbSNP database (www.ncbi.nlm.nih.gov/projects/SNP).

than in the south and west of Siberia ($p < 0.003$, Fisher's exact test) and in other East Asian populations, and is as rare as in African populations. The rs4752-G allele was found to have the highest frequency in the central Siberian sample (among the Evens, Evenks, and Yakuts), while its frequency was significantly lower ($p < 0.0004$) in the south and west of Siberia. According to the ALFRED database, in East Asia, the highest frequency of the rs4752-G allele is the characteristic of the Yakuts (32% and 47.6% in different samples). The rs3733359-A allele was most often detected in North-Eastern Siberia (32.1%) and less frequently in the West Siberian sample (7.5%) (Table 2). According to the ALFRED database, the frequency of this variant in Tuvinians and Yakuts was 17% and 19.5%, respectively, which is in the range of frequencies recorded in Siberian samples based on the results of this work.

Analysis of the nucleotide sequences of *GC* enabled us to identify seven haplotypes characterized by different combinations of alleles at loci rs4588, rs7041, rs4752, and rs3733359 (Table 3). It is known that combinations of polymorphism variants at loci rs4588 and rs7041 determine the main variants of DBP isoforms, that is, the rs4588-G/rs7041-A diplotype corresponds to the Gc1F variant, rs4588-G/rs7041-C corresponds to the Gc1S variant, and rs4588-T/rs7041-A corresponds to the Gc2 variant. Therefore, based on genotypic data, the distribution of Gc alleles and genotypes in the Siberian samples under study has been reconstructed as presented in Table 4. As can be seen, the samples differ significantly in the frequencies of Gc2, Gc1S/Gc2, and Gc2/Gc2, and the highest frequencies of these variants were revealed to be in the south and west of Siberia. Conversely, the highest prevalence of the Gc1F and Gc1F/Gc1F variants was noted in the northeast and central part of Siberia. These results, in general, are consistent with the data obtained previously that minimum Gc2 frequencies are typical for the population of the northeastern part of Siberia [12].

The analysis of genetic differentiation in the studied samples of Siberian population according to the frequencies of the *GC* haplotypes (Table 3) showed that the samples were differentiated into two groups (Table 5). In terms of F_{ST} values, the northeastern and central Siberian samples differ significantly from the samples of the south and west Siberia ($p < 0.05$). Not only the rs4588 and rs7041 loci, but also two other loci (rs4752 and rs3733359) contribute to differentiation (Table 3). Thus, the Gc1F isoform is encoded by four haplotypes, of which two haplotypes are more common and they are characterized by derived alleles at loci rs4752 and rs3733359 (haplotypes 1 and 4). It is noteworthy that the combination of the derived alleles rs4752-G and rs3733359-A was noted only once in haplotype 6. For the Gc1S isoform, in Siberian samples, two haplotypes are registered, differing in substitutions at the rs3733359 locus (haplotypes 2 and 7), and Gc2 is encoded by a single haplotype (Table 3).

The polymorphism of the rs4588 and rs7041 loci is of functional importance as the Gc isoforms determined by them are characterized by different affinities for 25(OH)D. Meanwhile, there is little information regarding the loci rs4752 and rs3733359, but both loci are known to contain substitutions that increase the risk of arthritis of peripheral joints and uveitis in Korean patients with ankylosing spondylitis, a group of joint and spinal diseases [20]. Thus, carriers of the rs3733359-A variant exhibit a decreased risk for peripheral arthritis, while carriers of the rs4752-G variant exhibit an increased risk for uveitis. These data may be related to Siberian populations as a fairly high prevalence of spondyloarthropathy has been revealed among the indigenous population of North-Eastern Siberia (in the Eskimos, Chukchi and Koryaks) [21].

Thus, the study demonstrated that the distribution of *GC* alleles and genotypes in the indigenous population of Siberia has a regional nature, which, most likely, is associated with the peculiarities of the metabolism of vitamin D and its derivatives in certain population groups. The sizes of the studied samples are not large, and therefore the continuation of the studies of *GC* polymorphism at the population level has great prospects in terms of studying the gene-environment interactions by taking into account the vitamin D status of the indigenous population, ethnicity, influence of environmental conditions (the level of natural

Table 3

Frequency of *GC* haplotypes in the indigenous population of Siberia

Haplotype No.*	Haplotype	Encoded isoform of Gc protein	Haplotype frequency in the population, %			
			North-Eastern Siberia (n = 28)	Central Siberia (n = 32)	Southern Siberia (n = 28)	Western Siberia (n = 20)
1	GAGG	Gc1F	32.0	45.4	16.0	12.5
2	GCAG	Gc1S	28.6	35.9	28.6	52.5
3	GAAG	Gc1F	3.6	0	1.8	2.5
4	GAAA	Gc1F	30.4	10.9	23.2	5.0
5	TAAG	Gc2	5.4	3.1	28.6	25.0
6	GAGA	Gc1F	0	1.6	0	0
7	GCAA	Gc1S	0	3.1	1.8	2.5

Note. n: sample size. * Number of haplotypes formed by allelic variants of loci, indicated in the same order as in Table 1.

Table 4

Frequency of isoforms and genotypes of Gc protein in the indigenous population of Siberia

Isoforms and genotypes of Gc	Frequency in the population, %			
	North-Eastern Siberia (n = 28)	Central Siberia (n = 32)	Southern Siberia (n = 28)	Western Siberia (n = 20)
Gc1F	66.0	57.8	41.0	20.0
Gc1S	28.6	39.1	30.4	55.0
Gc2	5.4	3.1	28.6	25.0
Gc1F/Gc1F	42.9	28.1	10.7	0
Gc1F/Gc1S	35.7	53.1	21.4	30.0
Gc1S/Gc1S	10.7	12.5	14.3	25.0
Gc1F/Gc2	10.7	6.3	39.3	10.0
Gc1S/Gc2	0	0	10.7	25.0
Gc2/Gc2	0	0	3.6	10.0

Table 5

Pairwise differences in F_{ST} in the distribution of *GC* gene haplotypes in Siberian populations

Population	1	2	3	4
1. North-Eastern Siberia	0	–	–	–
2. Central Siberia	0.023	0	–	–
3. Southern Siberia	0.038*	0.098**	0	–
4. Western Siberia	0.111**	0.119**	0.035	0

Note. Significance levels: * $p < 0{,}05$, ** $p < 0{,}01$.

ambient light and seasonal patterns), and specifics of nutrition [22]. The influence of such factors on the distribution of *GC* polymorphism variants is evidenced by the data obtained in this work on the high prevalence of haplotypes encoding the Gc1F isoform in northeast Asia under condition of low intensity of solar radiation. In addition, an important factor contributing to vitamin D deficiency may be a relatively high level of melanin in the skin of representatives of the Arctic peoples, which prevents the penetration of ultraviolet rays into the skin and thereby hinders the synthesis of vitamin D_3 [23]. The deficiency of vitamin D in the aborigines of the North could be compensated to some extent by the peculiarities of the traditional diet, which includes vitamin D-rich products of sea-hunting industry, fish, and venison. However, the contribution of the food factor to the formation of vitamin D in the indigenous peoples of Siberia has been little studied so far. It is also very important to expand studies on the haplotype diversity of *GC* based on the results of sequencing of both coding and noncoding regions of the gene. This is due to the fact that the selection of the most optimal variants of *GC* (not only for the main loci rs4588 and rs7041, but also for additional loci located in introns and regulatory regions) in various regional human groups is the result of a balance between the activity of DBP and the blood level of 25(OH)D [24]. The data obtained in this work also indicate that the distribution of haplotypes at four loci of *GC* in Siberian populations may have a functional meaning.

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