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Distribution of *VDR* Gene Polymorphisms in Northern Eurasia Populations

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ABSTRACT

Maintaining bone health involves a complex balance of factors, including the intake and absorption of minerals such as calcium and phosphorus. These processes are influenced by the presence of vitamin D and its receptor (VDR). The *VDR* gene is essential for regulating these processes, and variations in the gene can impact bone density and susceptibility to diseases.

This study aimed to analyze the frequencies of potentially "risky" alleles C*ApaI (rs7975232), G*BsmI (rs1544410), A*TaqI (rs731236) and G*FokI (rs2228570) in ethnic groups of Northeastern Europe, Central and Northern Asia, taking into account their origin and local environmental features (latitude and UV-B radiation). The analysis included 3,464 DNA samples from 96 geographic locations, representing 70 populations.

The study revealed distinct differences in the distribution of *VDR* polymorphisms between European and Asian populations. In European populations, the frequencies of the G*BsmI and C*ApaI alleles increased with higher latitudes and lower UV-B radiation levels during winter months (R_{sp}=0.356 and R_{sp}=0.327, respectively, $p<0.05$). Conversely, the frequency of the G*FokI allele decreased with higher latitudes and lower UV-B radiation levels (R_{sp}=-0.537, $p<0.001$). No significant correlations were observed in Asian populations.

These interpopulational differences in *VDR* polymorphism frequencies can be attributed to selection pressure to eliminate maladaptive variants. The study concludes that populations in Northeastern Europe, Central Asia, and Northern Asia exhibit significant variation in the frequencies of these potentially "risky" *VDR* gene alleles.

The results highlight the importance of environmental factor, such as UV-B radiation, in maintaining bone tissue health. Further research is necessary to elucidate the roles of diet and other factors in the metabolic chain ensuring bone health, particularly in understanding the observed ethnic and regional differences.

Keywords: vitamin D receptor; mineral metabolism in bone; genetic diversity; ultraviolet radiation; European populations; Asian populations.

Introduction

The body's requirements for mineral elements to maintain bone health are fulfilled through a dynamic balance of several factors.

First, the mineral substrate (most importantly calcium and phosphorus) must be ingested and absorbed by the organism. The body's ability to absorb these minerals depends on the presence of two elements that have identical physiological effects but differ in their evolutionary history and routes of entry: cholecalciferol (D3) synthesized in the skin and ergocalciferol (D2) consumed in food[1]. The levels of D2 and D3 metabolites, particularly 25(OH)D (25-hydroxyvitamin D), are commonly interpreted as an indicators of a patient's vitamin D status[2,3]. However, high blood serum 25(OH)D concentrations do not guarantee that tissues will receive sufficient amounts of vitamin D: the metabolite can be transported to target organs only when bound to vitamin D-binding protein (DBP)[4]. Yet even high concentrations of the bound metabolite may be functionally ineffective if a vitamin D receptor (VDR) in the target tissue has low sensitivity to the vitamin. On the other hand, increased VDR activity can compensate for the deficiency of other factors[5].

The activity of this intracellular receptor is controlled by the vitamin D receptor gene (*VDR*). *VDR* is located on chromosome 12g13.1; the gene is quite large (over 100 kb in size) and has an extensive promoter region. Single nucleotide polymorphisms (SNPs) in the functional regions of this gene affect the absorption of minerals, including calcium, and consequently the density of bone tissue[6]. VDR allelic variants are distinguished according to their respective endonuclease (restrictase) recognition sites. The three following SNPs (among those variants) are of most interest: ApaI (rs7975232), BsmI (rs1544410), and TaqI (rs731236). They are located between exons 8 and 9 and are in non-equilibrium linkage with each other. FokI, another important SNP (rs2228570 previously known as rs10735810), was found within exon[2 7,8].

The ApaI polymorphism is located in the 3´regulatory region within intron 8 and it is essentially a C→A substitution; C*ApaI is its reference allele. This polymorphism does not have a functional impact because it does not cause a change in the amino acid sequence of the VDR protein[9]. However, there are reports that it may affect messenger RNA (mRNA) stability[10]. In addition, research has shown that *AC* heterozygotes and ***CC*** homozygotes have reduced mineral bone density in comparison with ***AA*** homozygotes[11].

The BsmI polymorphism is also located in the 3´regulatory region and is a G→A substitution (its reference allele is G*BsmI)[9]. It changes the splice sites for mRNA transcription or the intron regulatory elements of *VDR*[12]. According to some studies, the G allele is associated with reduced bone density, increasing the risk of osteoporosis in both men and women, and response to antiresorptive therapy[12,13].

The TaqI polymorphism occurs within exon 9. It affects mRNA stability and biological functions of vitamin D. Its reference allele A*TaqI is associated with age-independent reduced mineral bone density[11] and may affect mRNA stability[9].

The FokI polymorphism is located in exon 2 of the *VDR* gene and involves a G-to-A point mutation (rs2228570). This mutation affects the start codon of the *VDR* gene, leading to the translation of two VDR proteins. The A→G substitution results in a shorter VDRA protein with 424 amino acids, whereas the presence of the A nucleotide results in a full-sized protein (427 amino acids) and has higher transcription activity[14]. The G*FokI variant is associated with reduced bone density and is more common in Europeans and Asians than in Africans[7,13]. Some authors have reported that FokI polymorphism is also linked to an increased risk of postmenopausal osteoporosis in Asian (but not European) populations[15].

Based on these findings, we make a working conclusion that carriage of C*ApaI (rs7975232), G*BsmI (rs1544410), A*TaqI (rs731236), and G*FokI (rs2228570) alleles is associated with a decrease in bone mineral density and conditionally consider these alleles as "risky" in relation to the development of osteoporosis and other pathologies of the bone system. From the perspective of evolutionary medicine, interpopulational differences in the presence of these polymorphisms can be regarded as a result of selection pressure to eliminate maladaptive variants. Revealing trends in the prevalence of these alleles in different habitats will provide information for identifying limiting environmental factors and for specifying risk groups in modern populations.

Our study sought to analyze the frequencies of potentially "risky" alleles C*ApaI (rs7975232), G*BsmI (rs1544410), A*TaqI (rs731236) and G*FokI (rs2228570) in ethnic groups of Northeastern Europe, Central and Northern Asia, taking into account their origin and local environmental features (latitude and UV-B radiation).

Materials and Methods

A total of 3,464 samples contributed by the Biobank of North Eurasia were included in the analysis.

The samples were collected from unrelated indigenous individuals whose ancestors from two previous generations, including grandparents, were members of a studied ethnic group and were descended from the same population. The study was approved by the Ethics Committee of the Research Center for Medical Genetics (protocol No. 1 dated June 29, 2020). The study was conducted in accordance with the principles of human experimentation as defined in the Declaration of Helsinki. Informed consent was obtained from each donor.

The samples were collected at 96 geographic localities, mainly covering the genetic diversity of Northeastern Europe, Central Asia, and Northern Asia (or Northern Eurasia). Most of the samples represent peoples living in the area of the Caucasus Mountains and adjacent territories but whose genesis involved not only the population of Europe, but also some of West and Central Asia. To avoid confusion, we did not use the term "Caucasians" but identified them as populations of European or Asian descent. Ethnic groups related to the studied populations but living in different latitudes and/or under different insolation conditions were considered different populations. Only 70 populations, represented by more than 20 samples, were included in the analysis. Among them we discern two groups of populations – of European or Asian descent, hereinafter European or Asian groups.

All populations considered in that study are shown and listed in Figure 1. The ordering and numbering of the populations reflect their longitudinal distribution (degrees East, °E).

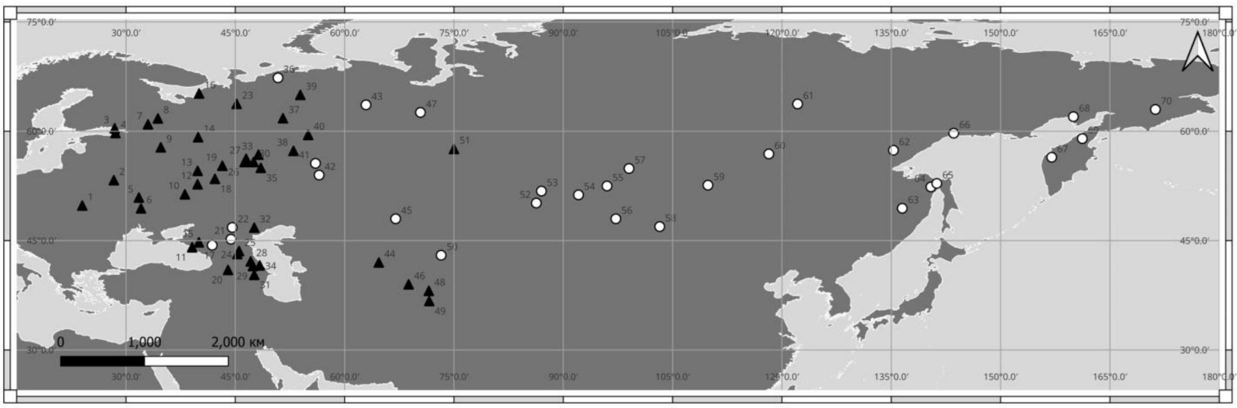

Figure 1. Localization of the surveyed populations. Note: ▲ – populations of European descent; ○ - populations of Asian descent.

1, 5, 6 – Ukrainians; 2 – Belarusians; 3 – Finns; 4 – Izhora; 7 – Karelians; 8 – Veps; 9, 10, 12, 13, 14, 16, 23 – Russians; 11, 15 – Adyghe; 17, 21 – Nogais; 18, 19 – Mordvins; 20 – Armenians; 22 – Kalmyk; 24 – Chechens; 25 – Trukhmen; 26, 30 – Chuvash; 27, 33 – Mari; 28, 29 – peoples of Dagestan; 31 – Azeri; 32, 35, 51 – Tatars; 34 – Lezgin; 36 – Nenets; 37 – Komi; 38, 39 – Udmurts; 40 – Komi-Permyaks; 41, 42 – Bashkirs; 43 – Mansi; 44 – Uzbeks; 45 – Kazakhs; 46 – Tajiks; 47 – Khanty; 48, 49 – Peoples of Pamir; 50 – Kyrgyz; 52, 53 – Altaians; 54, 55 – Tuvans; 56, 58 – Mongols; 57 – Tofalar; 59 – Buryats; 60, 62 – Evenks; 61 – Yakuts; 63 - peoples of Amur; 64 – Ulchi; 65 – Nivkh; 66, 68 – Evens; 67 – Itelmens; 69 – Koryaks; 70 – Chukchi.

Medium-wavelength UV radiation (280-315 nm), or UV-B, have the most prominent effect on cholecalciferol (D3) synthesis in human skin. Given that the half-life of 25(OH)D is 2-3 weeks[16], three consecutive months during which UV-B radiation levels are the lowest were considered critical in terms of cholecalciferol availability. The mean daily UV-B radiation values during winter months (UV-B_{mean}; J/m²/day) were obtained from the global UV-B radiation dataset (glUV)[17]. The data were processed in ArcGIS Pro, and the obtained values were assigned to the corresponding points using the Extract Values to Points (Spatial Analyst) tool.

DNA genotyping was performed using an Infinium iSelect HD Custom BeadChip (Illumina, USA) and an iScan microarray scanner (Illumina, USA). Our custom biochip included an additional marker of VDR activity. Some data were generated by genotyping genome-wide Illumina panels that were fully comparable to our custom panel. The allele frequencies of the analyzed SNPs were calculated using Python 3 and PLINK 1.9.

All computations and data analysis were carried out in Statistica 10.0. The significance threshold was set at the level p = 0.05. Intergroup differences in the frequencies of *VDR* alleles and genotypes were analyzed using the maximum likelihood chi-square test. Confidence intervals (95% CI) were calculated using the exact Clopper-Pearson method. The Mann–Whitney U test was used to compare allele frequencies between groups.

Results

On the scatterplots of C*ApaI, G*BsmI, G*FokI, and A*TaqI frequencies at different latitudes, populations of European and Asian descent visibly deviate from each other (Figure 2). Therefore, we analyzed the distribution patterns of *VDR* alleles in European and Asian groups separately.

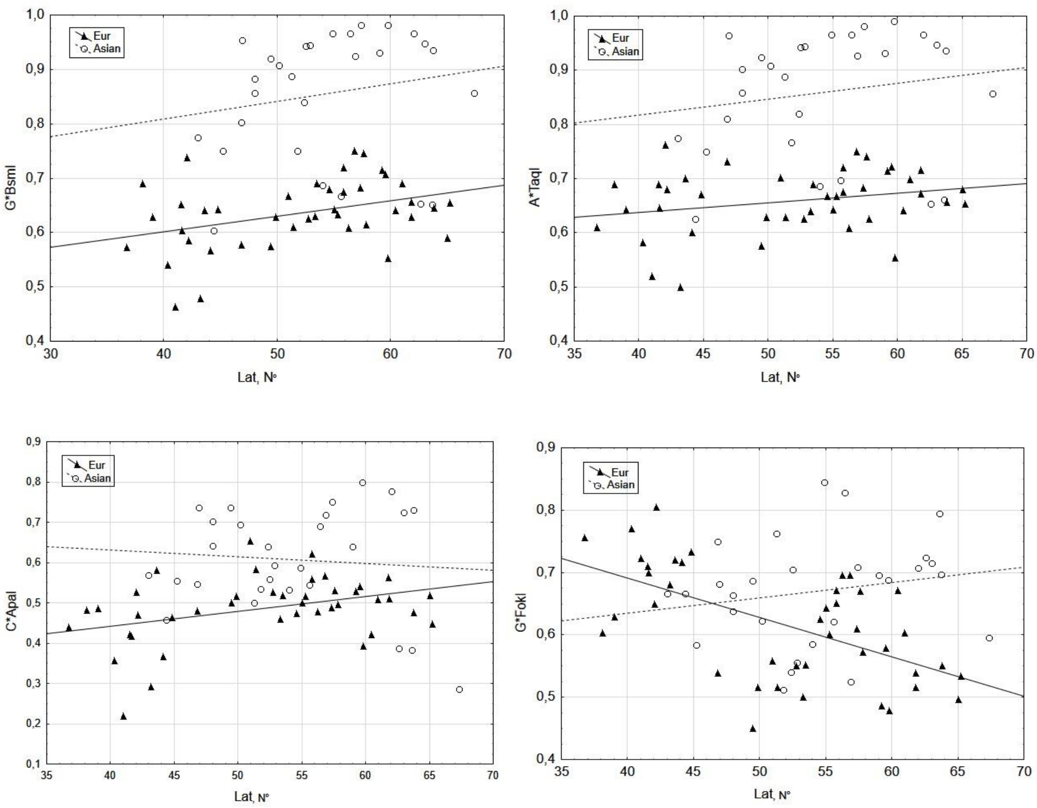

Figure 2. Scatterplots of C*ApaI, G*BsmI, G*FokI, and A*TaqI allele frequencies at different geographical latitudes of populations

The frequencies of *VDR* polymorphisms in the European and Asian groups are presented in Table 1. The Mann–Whitney U test revealed that A*TaqI and G*BsmI were less common in European (n=41) than Asian (n=29) groups; this difference was significant for both alleles (p<0.00001).

Table 1. Prevalence of *VDR* polymorphisms in European (n=41) and Asian (n=29) groups of populations and p-values of Mann–Whitney comparison U test

Median values of polymorphysm prevalence	*VDR* polymorphism			
	A*TaqI	G*BsmI	C*ApaI	G*FokI
in European group of populations	0.667	0.640	0.496	0.610
in Asian group of populations	0.902	0.888	0.639	0.687
Significance levels of U test	**0.0001**	**0.0001**	**0.0001**	**0.0267**

Note: significant differences (p<0.05) are indicated in **bold**

However, the correlation between latitude and frequencies of the G*BsmI allele (Table 2) was statistically significant only in European populations (Rsp=0.356, p<0.05). The frequencies of the C*ApaI allele were also lower (p<0.00001) in European group and increased at higher latitudes (Rsp=0.327, p<0.05). No significant correlation was detected between latitude and C*ApaI frequencies in the Asian group of populations.

Table 2. Spearman rank order correlation between frequencies of *VDR* polymorphisms and latitude (°N)

Polymorphism *VDR*	European groups (n=41)		Asian groups (n=29)	
	Rsp	p	Rsp	p
A*TaqI	0.225	0.157	0.290	0.134
G*BsmI	**0.356**	**0.022**	0.300	0.121
C*ApaI	**0.327**	**0.037**	0.076	0.700
G*FokI	**-0.537**	**0.001**	0.283	0.145

Note: significant correlations (p<0.05) are indicated in **bold**; Rsp – Spearman rank-order correlation; p – significance level

The difference in G*FokI frequencies between the European and Asian groups was not so notable, though, this allele was less common in the populations of European descent (p=0.027), similar to A*TaqI, G*BsmI, and C*ApaI. However, in contrast to these SNPs, G*FokI frequencies increased at higher latitudes in European populations (Rsp=-0.537, p<0.05), i.e., the trend was opposite (Table 2). In the Asian group, the correlation between G*FokI frequencies and latitude was statistically insignificant.

Drawing on the statistically significant results (p<0.05), we conclude that the frequencies of G*BsmI and C*ApaI alleles increase from south to north in the populations of European descent, whereas G*FokI, by contrast, occurs at higher frequencies in southern regions (the geographic trends of A*TaqI frequencies are statistically insignificant). Therefore, the Spearman rank-order correlation values reflect the geographic variation in VDR allele frequencies determined by the latitude of the European region where the population originated. For Asian group of populations, no reliable correlation between the frequency of VDR alleles and latitude was detected.

UV radiation is strongly associated with geographic latitude. The rank correlation for all 96 geographic sites of sample collection was Rsp=-0.98 (p<0.001; n=96), i.e., the higher the latitude, the weaker the radiation. Consequently, the correlations between VDR allele frequencies and mean daily values of UV-B radiation over three months with the least amount of sunlight (Table 3) have the same strength as the correlations between VDR allele frequencies and latitude, but their direction is opposite. A positive correlation between UV-B_{mean} and G*FokI frequency was observed in the European group of populations (Rsp=0.537, p=0.001; n=41), but it dropped to zero in the Asian group. Similar to latitude, only the European group showed significant negative correlations between the mean daily UV-B radiation values during winter months and the frequencies of G*BsmI and C*ApaI polymorphisms (Table 3).

Table 3. Spearman rank order correlation between frequencies of *VDR* polymorphisms and mean daily of UV-B radiation levels during winter months

VDR polymorphisms	European group (n=41)		Asian group (n=29)	
	Rsp	p	Rsp	p
A*TaqI	-0.206	0.196	-0.286	0.140
G*BsmI	**-0.338**	**0.030**	-0.293	0.130
C*ApaI	**-0.320**	**0.042**	-0.095	0.631
G*FokI	**0.537**	**0.001**	-0.368	0.054

Note: significant correlations ($p<0.05$) are indicated in **bold**; Rsp – Spearman rank order correlation; p –significance level

Discussion

Figure 2 and Tables 2, 3 show a weak yet significant increase in the frequency of risk alleles G*BsmI and C*ApaI to the north and in regions with low levels of UV-B radiation during winter months (in all cases Rsp=0.3; $p<0.05$). By contrast, G*FokI frequencies exhibit the opposite trend, decreasing to the north and in regions with low UV radiation levels. The rank correlations of G*FokI frequencies with geography and climate (Rsp=-0.537, $p<0.001$ for both parameters) were substantially higher than those of G*BsmI and C*ApaI.

The differences in the strength of associations between the frequencies of *VDR* polymorphisms and geography and climate are consistent with currently available data. Numerous publications have demonstrated that the FokI polymorphism is an independent *VDR* gene marker unrelated to BsmI, ApaI or TaqI (review: [7]). From this perspective, interpopulational differences in the prevalence of *VDR* allelic variants may be interpreted as a result of selective pressure of different intensities and/or directions.

The absence of significant correlations in Asian group of populations and their presence in European group does not contradict this point of view. Reviews and meta-analyses confirm the lack of similarity in VDR allele frequencies between populations of European, Asian and African origin[7,18-20]. The variation in the distribution of *VDR* polymorphisms and the strength of associations between VDR alleles and bone tissue development, the risk of osteoporosis and other bone pathologies raises the need for further analyses that may benefit from an ecological approach.

Previously, we demonstrated that the results of case-control studies may vary among populations living under different environmental conditions. For example, the association of G*FokI and G*BsmI polymorphisms with height, body mass, and the amount of bone and muscle tissue in young Komi (far regions of European Northeast)[21] is consistent with or does not contradict the data obtained for the populations of Sweden[22], the Netherlands[23], England[24] and Northern France[25] but is in discord with the results for the populations of Southern Italy[26], Turkey[27] and India[28] who live in environments with higher UV-B radiation levels and have different dietary habits.

We completely agree with Uitterlinden et al.[7(p.148)], who proposed that "VDR allele frequency differences between ethnic groups most likely result from evolutionary processes and population genetic behavior". This is also evidenced by paleogenetic data, according to which Eurasian populations of temperate and northern latitudes in the last 8-10 thousand years experienced selective pressure in favor of genotypes determining the increase in sensitivity to UV-B irradiation and the ability to stably assimilate milk as a source of calcium[29].

Studies of vitamin D status and serum 25(OH)D concentrations in present-day populations in

Eastern Europe and Northern Asia corroborate the importance of investigating various adaptation pathways that maintain bone tissue homeorhesis. In the Eastern European populations of the temperate climate zone (45-60°N) and high-latitude regions (60-68°N), 25(OH)D concentrations are weakly associated with latitude but strongly associated with the duration of daylight hours (Rsp=0.396, p<0.00001; n=245). Vitamin D levels decline during three winter months, hitting their minimum in February[30,31]. Consequently, as in the case of VDR, the leading factor is not the "northerness" of the population itself but the level of UV radiation that affects the autosynthesis of cholecalciferol D3. Another important determinant of vitamin D status in northern and high-latitude regions is the availability of food-provided vitamin D2, which depends on dietary habits[32,33].

Therefore, the results of studies on D-vitamin status and 25(OH)D content in the groups geographically and ethnically close to those included in the present study are consistent with population genetic data and indicate an important role of environmental factors and nutrition in the metabolic chain providing maintenance of bone tissue status.

Limitations and Prospects

The fact that we were able to cover a large number of Northern Eurasian populations with the study allowed us to see the specificity of the distribution of potentially "risky" alleles of the VDR gene in groups of European or Asian descent. At the same time, it should be kept in mind that the revealed differences may be mediated by the influence of some other underlying factors, which became apparent when distinguishing European and Asian groups. The search for these factors should be the goal of the future studies.

Conclusion

The populations of Northeastern Europe, Central and Northern Asia exhibit significant variation in the frequencies of the potentially 'risky' C*ApaI, G*BsmI, A*TaqI, and G*FokI alleles of *VDR* gene.

In the European populations, the frequencies of the G*BsmI and C*ApaI alleles increased to the north and in regions with low levels of UV-B radiation during winter months (Rsp=0.3).

The prevalence of the G*FokI allele shows the opposite trend, decreasing to the north and in regions with low UV-B radiation (Rsp=-0.537). Supposedly, under northern conditions, carriage of the G*FokI allele resulted in significant bone status disorders and was being eliminated in the course of selection. According to literature data, it can be concluded that in modern populations of European origin, carriage of the G*FokI allele should be regarded as a factor increasing a risk of bone metabolism disorders.

In contrast to European populations, no significant correlations were observed between the frequencies of *VDR* gene polymorphisms, the geographic latitude of population locality, and the winter level of UV-B radiation in Asian group. Further research is needed to understand the underlying causes of these ethnic and regional differences and test the hypothesis regarding their association with the dietary habits of indigenous populations.

The results of the population genetic study are consistent with clinical and laboratory data and confirm the important role of environmental factors in shaping the metabolic chain that ensures bone health.

Further research is needed to elucidate the roles of diet and other factors in the metabolic chain that provide the maintenance of bone health, particularly in understanding the ethnic and regional differences observed.

Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

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