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Studying of Vitamin D Receptor Gene Polymorphism in Somali Population Living in Türkiye

Türkiye'de Yaşayan Somali Popülasyonunda D Vitamini Reseptör Gen Polimorfizminin İncelenmesi

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ABSTRACT

Background: Differences in the vitamin D receptor (*VDR*) gene, which determines the vitamin D activity, have been associated with various diseases. In this study, determination, and comparison of *VDR* gene polymorphisms between Somali individuals who grew up in a different geography, have certain dietary habits and lifestyles, but have lived in Türkiye for at least 2 years and Turkish individuals born and raised in Türkiye was intended.

Materials and Methods: Fifty-five Somali individuals and 100 Turkish volunteers living in Türkiye were included in our study. 2 mL of peripheral blood samples were taken from the volunteers. Genomic DNA was isolated according to the kit protocol. Polymerase chain reaction (PCR) was performed with primers specially designed for the gene regions of interest. After PCR, restriction fragment length polymorphism was performed with appropriate enzymes to determine the genotypes. The results were statistically evaluated with the chi-square test and Student's t-test.

Results: The genotype frequencies for the *VDR* gene (ApaI rs7975232, G>T and TaqI rs731236, T> C) Somali group and Turkish group are listed. There was no significant difference between the two groups (p-value: >0.05).

Conclusion: The distribution of the *VDR* gene TaqI rs731236, T>C genotypes and alleles in the two groups was significantly different (*p-value: *0.006 and *p-value: 0.021).

Keywords: *VDR* gene polymorphism, TaqI, ApaI

ÖZ

Amaç: Bu çalışmada, farklı bir coğrafyada büyümüş, belirli beslenme alışkanlıkları ve yaşam tarzlarına sahip ancak en az iki yıldır Türkiye'de yaşayan Somalili bireyler ile Türkiye'de doğup büyümüş Türk bireyler arasında vitamin D reseptör (*VDR*) gen polimorfizmlerinin belirlenmesi ve karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Çalışmamıza Türkiye'de yaşayan 55 Somalili birey ve 100 Türk gönüllü dahil edildi. Gönüllülerden 2 mL periferik kan örneği alındı. Kit protokolüne uygun olarak alınan kan örneklerinden genomik DNA izole edildi. Polimeraz zincir reaksiyon (PCR), ilgili gen bölgeleri için özel olarak tasarlanmış primerler ile yapıldı. PCR işleminden sonra genotipleri belirlemek için uygun enzimlerle kısıtlama parçası uzunluk polimorfizmi yapıldı.

Bulgular: *VDR* geni (ApaI rs7975232, G> T ve TaqI rs731236, T> C) Somali grubu ve Türk grubu için genotip frekansları tablolarda listelenmiştir. İki grup arasında anlamlı fark bulunmadı (p-değeri: >0,05).

Sonuç: *VDR* geni TaqI rs731236, T>C genotipleri ve allellerinin iki gruptaki dağılımı anlamlı olarak farklı bulundu (*p-değeri: *0,006 ve *p-değeri: 0,021).

Anahtar Kelimeler: *VDR* gen polymorfizimi, TaqI, ApaI

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Introduction

Vitamin D, which is in the group of fat-soluble vitamins, has two forms that are metabolized in the same way, namely ergocalciferol (D2) and cholecalciferol (D3). Conversion to the active form takes place in the liver and kidney (1). The hormone form regulates the expression of related genes through its receptor. As a result, there is an increase in the level of calcium and phosphate in the serum. During the formation process of vitamin D, 25-hydroxyvitamin D form is synthesized in the liver, and 1α, 25-dihydroxyvitamin D form is synthesized in the kidney (2). There are factors that affect the production of vitamin D in the skin. To these factors, we can count the skin color of the person, the seasons, the choice of clothing, the geographical region where one lives, and even the exposure to the sun at changing times of the day. A certain vitamin D is needed to maintain bone health. Vitamin D deficiency or insufficiency is considered a global problem (3,4).

The vitamin D receptor (*VDR*) gene is located on the q arm of chromosome 12 (*12q13.1*), this gene contains nine exons and eight intron regions (5). It is known that vitamin D plays a role in activities that are not directly related to bone metabolism, such as regulating blood pressure, modulating immunological responses, regulating insulin production, and providing protection against some types of cancer. As a result of studies, it has been revealed that vitamin D is also effective on neurons during the brain development process (6). The VDR plays a role in the regulation of many genomic activities that occur in living things, and thus in the execution of metabolic events. Disruptions in vitamin D metabolism or genetic variations in its binding to the VDR pose a risk for the emergence of some diseases such as autism (6). There have been studies showing that autism rates are increasing among dark-skinned immigrants who migrated to countries located between northern latitudes (7).

Functional polymorphisms affecting gene expression have been reported in this gene (8). It has been proven rs7975232 (ApaI), rs2228570 (FokI) and 3' untranslated region (3'UTR) polymorphisms in the first codon cause epilepsy or schizophrenia, and conditions associated with neurodegenerative diseases (8,9). As a result of studies, the association of polymorphisms with various diseases draws attention to the effectiveness of these genomic changes, but the data is still very limited (10,11). In this study, our aim was to determine VDR polymorphisms in Somali individuals living in Türkiye and to compare them with the Turkish population.

Material and Methods

All procedures were followed in accordance with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was taken from all participants included to the study.

Study Groups

T.C. Ethics Committee permission was granted by Biruni University Clinical Research Ethics Committee with the date of 31.10.2018 and decision number 2015-KAEK-43-18-16. Fifty-five Somali individuals between the ages of 18-26 and 100 Turkish volunteers living in Türkiye for more than 2 years were included in the study. It was confirmed that the individuals participating in the study did not have any chronic health problems.

DNA Isolation

Blood samples were collected from Somali and Turkish participants in purple capped tubes containing EDTA. VDR (DNA) extraction was performed in accordance with the manufacturer's kit protocol (item no: 11796828001 Roche Applied Sciences, Germany). The concentration and purity of DNA obtained after isolation were measured with a spectrophotometer (Denovix DS-11 FX, USA) and DNA samples were placed in a -20 °C refrigerator for storage.

Genotyping

Genotyping processes were performed using restriction fragment length polymorphism as well as polymerase chain reaction (PCR). Two separate PCR reactions were used to detect the two polymorphisms in *VDR* gene (ApaI rs7975232, G> T and TaqI rs731236, T> C). The primers of the *VDR* gene used were as reported, ApaI: Forward 5′ CAGAGCATGGACAGGGAGCAA 3′ and Reverse 5′ GCAACTCCTCATGGCTGAGGTCTC 3′, TaqI: Forward 5′ GGGACGATGAGGGATGGATGGACAGAGC 3′ and Reverse 5′ GGAAAGGGGTTAGGTTGGACAGGA 3′. The ApaI polymorphism PCR cycle conditions were denaturation at 96 °C for 2 min, followed by 35 cycles at 94 °C for 1 min, 55 °C for 1 min, 72 °C for 1 min and one final cycle of extension at 72 °C for 1 min. PCR products were digested with ApaI restriction enzyme at 55 °C for 4 h. The TaqI polymorphism the PCR cycle conditions were denaturation at 96 °C for 2 min, followed by 35 cycles at 94 °C for 45 sec, 60 °C for 45 sec, 72 °C for 45 sec and one final cycle of extension at 72 °C for 10 min. PCR products were digested with Taq I restriction enzyme at 65 °C for 4 h. The digested products were analyzed after running on a 2% agarose gel stained with ethidium bromide and examined under transillumination

(Figure 1, 2). Each gel was evaluated by two observers who were unaware of the subject's condition. In the case of any conflict, the samples were repeated. The expected results after restriction for each gene are also given in Table 1.

Statistical Analysis

To analyze the data, obtained in our study; Fisher's Exact test was used to compare categorical variables and test the separation of genotype frequencies from Hardy Weinberg equilibrium. Comparison of variables between groups was performed using Student's t-test. All statistical analyzes were performed using SPSS V.20.0. (SPSS for Windows, version 20.0. Chicago, USA). A p-value of <0.05 was considered statistically significant.

Results

The gender distribution in Somalian group (60% male and 40% female) was comparable with that in Turkish group (62% male and 38% female, p-value: 0.802). Genotype frequencies for *VDR* gene (ApaI rs7975232, G> T and TaqI rs731236, T> C) Somalian group and Turkish group are listed in Table 2. The distribution of the *VDR* gene (ApaI rs7975232, G> T genotypes and alleles in two groups was not found to be significantly different (p-value: >0.05). The distribution of the *VDR* gene TaqI rs731236, T> C genotypes and alleles in two groups was found to be significantly different (*p-value: *0.006 and *p-value: 0.021).

Discussion

Vitamin D is involved in many biological processes such as bone development, metabolic functioning of the endocrine system, development of immune response, regulation of cell differentiation (12). Due to its complex role in biological processes, it has been the subject of many studies all over the world for a long time. Many variants of the *VDR* gene have been reported in association with different diseases, both due to its importance in the pathophysiology of diseases and its predisposition to many

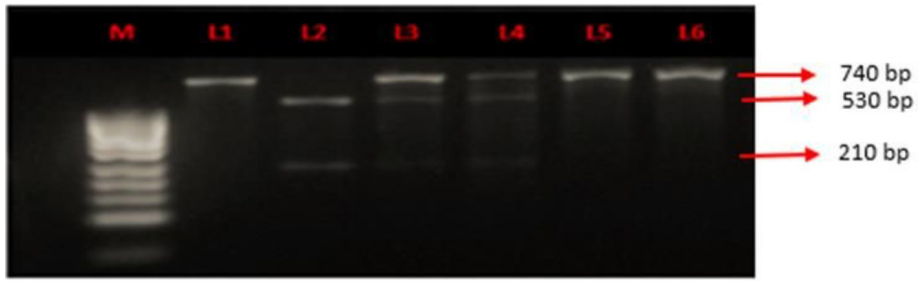

Figure 1. PCR-RFLP to detect (rs7975232, G> T) polymorphism of Apa I. Polymerase chain reaction products (740 bp) digested with restriction enzyme Apa I and analyzed by 2% agarose gel. M: Marker (Puc8X DNA ladder - MBI Fermentas); L1, L5, L6: Wild type homozygotic (GG); L3, L4: Heterozygotic (GT); L2: Homozygotic (TT)

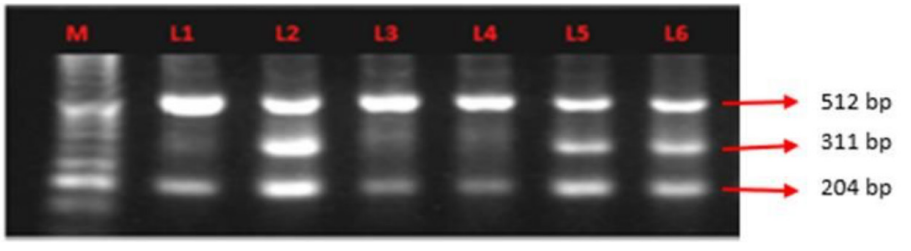

Figure 2. PCR-RFLP to detect (rs731236, T> C) polymorphism of Taq I. Polymerase chain reaction products (512 bp) digested with restriction enzyme Taq I and analyzed by 2% agarose gel. M: Marker (Puc8X DNA ladder - MBI Fermentas); L1, L3, L4: Wild type homozygotic (TT); L2, L5, L6: Heterozygotic (TC)
PCR: Polymerase chain reaction, RFLP: Restriction fragment length polymorphism

Table 1. Genotypes and PCR-RFLP product size

Genotypes and product size			
ApaI PCR product is 740 bp	**GG (wild type)**	**GT (heterozygous)**	**TT (homozygous)**
	740 bp	740 bp	740 bp
		530 bp	
	530 bp	210 bp	
TaqI PCR product is 716 bp	**TT (wild type)**	**TC (heterozygous)**	**CC (homozygous)**
	512 bp	512 bp	311 bp
		311 bp	
	204 bp	204 bp	204 bp

RFLP: Restriction fragment length polymorphism, PCR: Polymerase chain reaction

Table 2. Genotype frequencies for *VDR* gene (ApaI rs7975232, G> T and TaqI rs731236, T> C)

	Somalian group		Turkish group			
VDR ApaI	**n**	**%**	**n**	**%**	**X^2**	**p-value**
Genotyping						
GG	29	53.33	51	51	0.545	0.761
GT	25	45.00	45	45		
TT	1	1.67	4	4		
Allele					0.141	0.706
G	83	75.45	147	73.5		
T	27	24.55	53	26.5		
VDR TaqI						
Genotyping						
TT	14	25.45	58	58	9.929	***0.006**
TC	39	70.91	33	33		
CC	2	3.64	9	9		
Allele						
T	67	60.91	149	74,5	5.262	***0.021**
C	43	39.09	51	25.5		

VDR: Vitamin D receptor

diseases. The pathophysiological processes that are aimed to explained by matching epidemiological data with genetic findings make each of these variants important for different societies and diseases. In this study, the *VDR* gene ApaI rs7975232, G> T and TaqI rs731236, T> C genotypes and allele frequencies were reported in a population of healthy Somali and Turkish individuals living in Türkiye.

As indicated in Table 3 and Table 4, the *VDR* gene ApaI rs7975232 genotype and alleles are in the line with McClure et al. (26), Garnero et al. (14), Carling et al. (16), Fountas et al. (17), Riggs et al. (23), Zmuda et al. (24), Haddad (13) findings. Our findings of the TaqI rs731236 genotype and alleles are in line with the findings reported by Kung et al. (19) and Ongphiphadhanakul et al. (21) but not with the findings reported by McClure et al. (26), Garnero et al. (14), Carling et al. (16), Fountas et al. (17), Riggs et al. (23), Zmuda et al. (24), Haddad (13). Especially TaqI rs731236 genotype difference and frequency of T allele show statistically significant difference compared to frequency of C allele (*p-value: 0.000352 *p-value: 0.0127). VDR is known to regulate cell proliferation, intestinal calcium absorption and cell differentiation. The effect of VDR can be regulated not only by vitamin D, but also by protein kinase A, parathyroid hormone, and growth factors. Based on this information, it is predicted that SNP changes in the *VDR* gene may affect calcium metabolism and may predispose to many diseases such as beta thalassemia, diabetes mellitus type-II, breast cancer, osteoporosis, allergic diseases. In addition, some neurodegenerative diseases were found associated with *VDR* gene polymorphism in several studies. According to the

result of one of these studies, reported by Cieślińska et al. (28) in 2017, Taq-I polymorphism appears to be associated with childhood autism (28). In another study by Cieślińska et al. (29) in 2018, Taq-I polymorphism was associated with the development of acute pancreatitis (29). In a study conducted by Koroglu et al. (30) in 2014, it was reported that bronchopulmonary dysplasia was associated with Taq-I polymorphism. The role of *VDR* gene polymorphisms in different diseases have not been understood yet, and the results of the research about predispositions to diseases are variable. The importance of the research about polymorphisms is rely on the genotypic and allelic differences due to the ethnic origin of healthy individuals living in the same geography. This requires genotypic and allelic comparisons of healthy and sick individuals of the same population, and then comparing populations in different geographies. The gene polymorphisms we study on this research are related with many diseases in many populations in different research so far. But there is not any research compares healthy Turkish and Somalian population. As a result of the findings obtained in this study, we believe that conducting these studies with individuals who have diseases that are thought to be related to geography will be useful in understanding the pathogenesis of these diseases. It should be considered that the effect of polymorphisms may be related to differences in the stability of RNA or even changes in a completely different gene, rather than changes in protein structure. At this point miRNAs, which can inhibit the translation of RNA even though they are not coding, and to perform this function on many genes in the genome at the same time, are remarkable. Variables such as geographical differences, lifestyle, dietary habits, and duration of daylight benefit or vice versa, cannot fully explain the personal influences associated with susceptibility to diseases and low vitamin D levels in populations. Although polymorphic alterations are associated with various diseases, these disease susceptibility studies should be continued on large populations to fully understand the cellular and molecular processes. The results of data obtained from these studies should be examined with the meta-analysis method to determine the affection of geographical features on these processes. In addition, studying allelically different haplotypes instead of a single variant may be more decisive in understanding the disease pathophysiology of the

Table 3. Genotypes and allele frequency distribution of *VDR* gene (ApaI) polymorphism in various population and p-values of different allele and genotypes in different populations

Country/ethnicity	No	Age (years)	Genotype (%)				Allele (%)			Reference
			(AA)	(Aa)	(aa)	p	(A)	(a)	p	
Europe										
North India	150	20-74	36	44	20	NS	58	42	NS	13
France	189	31-57	30	50	20	NS	54	46	NS	14
Austria	163	44-78	29	45	26	NS	52	48	NS	15
Sweden	100	70±1	27	52	21	NS	53	47	NS	16
Greece	53	20-70	36	43	21	NS	58	42	NS	17
South Pacific										
Australia	518	NR	26	51	23	NS	51	49	NS	18
Asia										
Türkiye	102		39.2	42.2	18.6	NS	60	40	NS	13
Iran	100		17	56	27	***	45	55	**	13
Japan	488	8-78	9	48	43	***	33	67	**	18
China	144	30-40	10	36	54	***	29	71	***	19
Korea	104	NR	3	28	69	***	17	83	***	20
Thailand	84	40-79	11	50	39	***	36	64	**	21
South India	80	NR	38	46	16	NS	61	39	NS	22
Americas United States										
White, Minnesota	128	>30	30	46	24	NS	53	47	NS	23
Black Pennsylvania	101	≥65	44	46	10	NS	67	33	NS	24
Mexican, California	100	7-12	21	55	24	NS	48	52	NS	25

*p≤0.05, **p≤0.01, ***p≤0.001, at 5% level of significance, NS: Not significant (p>0.05)

Table 4. Genotypes and allele frequency distribution of *VDR* gene (Taq-I) polymorphism in various population and p-values of different allele and genotypes in different populations

Country/ethnicity	No	Age (years)	Genotype (%)				Allele (%)			Reference
			(TT)	(Tt)	(tt)	p	(T)	(t)	p	
Europe										
North India	346	20-74	49	40	11	*	66	34	NS	13
France	189	31-57	33	49	18	0.05	57	43	NS	14
Austria	163	44-78	12	49	39	***	36	64	***	15
Sweden	100	70±1	34	54	12	NS	61	39	NS	16
Greece	53	20-70	38	41	21	NS	59	41	NS	17
South Pacific										
Australia	518	NR	36	48	16	NS	60	40	NS	18
Asia										
Türkiye	102		47	35.2	6.9	*	70	30	NS	13
Iran	100		18	35.5	47	***	35.5	64.5	***	13
Japan	488	8-78	77	22	1	***	88	12	***	18
China	144	30-40	90	10	0	***	95	5	***	19
Thailand	84	40-79	83	17	0	***	92	8	***	21
Americas United States										
White, Minnesota	130	≥30	41	44	15	NS	63	37	NS	23
Black Pennsylvania	101	≥65	32	53	15	0.05	58	42	NS	24
Mexican, California	101	59-84	51	40	9	NS	71	29	NS	26
White, North Carolina	162	NR	33	45	22	*	55	45	NS	27

*p≤0.05, **p≤0.01, ***p≤0.001, at 5% level of significance, NS: Not significant (p>0.05)

possible association of polymorphic changes. Therefore, the data obtained from this study can form the basis for the development of future epidemiological and clinical databases. VDR involved studies of allelic association with various chronic inflammatory and degenerative diseases are ongoing. In the long term, these studies may help to understand genetic susceptibility to diseases and improve clinical management and treatment protocols.

Conclusion

The distribution of the *VDR* gene TaqI rs731236, T> C genotypes and alleles in two groups was found to be significantly different (*p-value: *0.006 and *p-value: 0.021).

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Ethics

Ethics Committee Approval: T.C. Ethics Committee permission was granted by Biruni University Clinical Research Ethics Committee with the date of 31.10.2018 and decision number 2015-KAEK-43-18-16.

Informed Consent: Informed consent was taken from all participants included to the study.

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Authorship Contributions

Surgical and Medical Practices: H.Y., S.M.M., Ş.Z.A., O.Ç., T.K., B.G., Concept: E.C., Design: E.C., Data Collection or Processing: S.M.M., Ş.Z.A., O.Ç., B.G., Analysis or Interpretation: E.C., Literature Search: H.Y., T.K., E.C., Writing: H.Y., S.M.M., Ş.Z.A., O.Ç., T.K., B.G., E.C.

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