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Frequency of rs731236 (TaqI), rs2228570 (Fok1) of Vitamin-D Receptor (VDR) gene in Emirati healthy population

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ABSTRACT

Vitamin D is getting more attention everyday due to its importance in maintaining bone and calcium homeostasis, cellular proliferation, differentiation and immune response. Vitamin D is derived from diet or elicited in the skin by the activation of 7-dehydrocholesterol, which is an inert molecule that must be activated by ultraviolet light to form pre-vitamin D3. Recent studies connected the gene encoding for vitamin D (*VDR*) to the genetic control of bone mass and other diseases. As *VDR* SNPs have been associated with several disorders and diseases, it's important to investigate the allelic and genotypic distribution among populations. The aim of this study is to determine the frequency of rs731236 (*Taq1*) and rs2228570 (*Fok1*) variants in healthy Emirati individuals and compare their genotype and allele distribution with other populations. In this study 282 (female, 187; male, 95) unrelated healthy UAE nationals were involved. Two hundreds and eight two DNA samples been collected to genotype rs731236 (*Taq1*) and rs2228570 (*Fok1*) *VDR* SNPs. Our results indicate that the distribution of the alleles and genotypes of rs731236 (*Taq1*) and rs2228570 (*Fok1*) vary considerably in different populations. In the Emirati population the distribution of rs731236 (*Taq1*) and rs2228570 (*Fok1*) were AA 38%, AG 42%, GG 20% and AA 27%, AG 42%, GG 31% respectively. The Emirati population genotype and allele distribution of rs731236 (*Taq1*) and rs2228570 (*Fok1*) had no difference with Caucasians from USA and France. However, there was significant difference with Asian populations.

1. Introduction

Vitamin D has gained a lot of interest in recent years; due to its importance in maintaining bone and calcium homeostasis, cellular proliferation, differentiation and immune response (Wang et al., 2012). Furthermore, it has been associated with prostate cancer, skin cancer, obesity, Metabolism syndrome, Type 2 Diabetes Mellitus (T2DM), and Cardiovascular diseases (CVD) (Rezende et al., 2007). Vitamin D is derived from diet or elicited in the skin by the activation of 7-dehydrocholesterol which is an inert molecule that must be activated by ultraviolet light to form pre-vitamin D3 (Holick et al., 1977). The nuclear Vitamin D Receptor (*VDR*) mediates most of the biological actions of Vitamin D (Tuoresmaki et al., 2014). *VDR* is a member of the steroid hormone receptor family which is located in chromosome 12q13.1 (Uitterlinden et al., 2004). It has eight exons and six alternatively spliced regions positioned in genetically active areas, containing the promoter region (Tuoresmaki et al., 2014).

Genetic polymorphism in *VDR* has been reported and more than 470 *VDR* single nucleotide polymorphisms (SNPs) have been identified. The two most common (SNPs) in *VDR* gene in Caucasian subjects are rs2228570 (*Fok-1*) and rs731236 (*Taq-1*) (Davis, 2008). These two RFLPs in the *VDR* gene were described by using *Fok-1* and *Taq-1* restriction enzymes. The *Taq*-1 RLFP is located between the 8 and 9 axon in an are of unknown function, while the *Fok-1* RFLP is located in the exon 2 and cause by T to C nucleotide substitution (Bhanushali et al., 2009).

The genetic control of bone mass as well as bone disease has been associated to genetic polymorphism in *VDR* (Bhanushali et al., 2009). Studies have shown that low vitamin D or *VDR* polymorphisms have been associated with autoimmune diseases and liver cancer (Zuniga et al., 2011). Moreover, it has been reported that vitamin D and *VDR* provide Reno-protection against diabetic nephropathy (Gross et al., 1996). Numerous reports have presented the frequency of *VDR* SNPs and their association to different diseases in different ethnic groups,

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nevertheless studies on this part of the world are scarce. Most of the *VDR* polymorphisms studies have been conducted on the Caucasian populations. In this study we present the genotype allele frequencies of rs731236 (*Taq-I*), rs2228570 (*Fok-1*) of Vitamin-D Receptor (*VDR*) gene in Emirati healthy population.

2. Materials and methods

2.1. Study population and design

For determining the sample size, we conducted the Power Calculator for Genetic Studies developed by Skol and his team from their website http://www.sph.umich.edu/csg/abecasis/CaTS/index.html. Using Vitamin deficiency prevalence of 20% in the adult population of United Arab Emirates as reported (Muhairi et al., 2013). We also predicted major allele frequencies of ≥ 0.50, and assumed a multiplicative disease model. From the power calculator: 100–250 controls were needed for this study to be able to reject the null hypothesis with an OR of ≥ 1.5 reaching at least 85% power.

This study involved a sample of 282 adult unrelated healthy UAE nationals (female, 187 and male, 95) aged between 18 and 88. Samples were collected from UAE national students who are studying at Khalifa University and UAE national patients during their clinical visit to a major hospital in Abu Dhabi. The study was approved and conducted in accordance with the guidelines of the Ethical Review Committee of Khalifa University and Burjeel/VPS healthcare hospital in Abu Dhabi. All subjects have participated after being verbally informed about the study and after signing a written informed consent form. There were several inclusion and exclusion criteria used in this study; Inclusion criteria: UAE National, healthy individuals, able to give consent and above 18 years old. Exclusion Criteria: Non-UAE national, pregnant female, not be able to consent and less than 18 years old.

One milliliter of saliva and two ml of blood was collected from each participant. Blood was collected using anti-coagulants tubes (BD Vacutainer®, Franklin Lakes, New Jersey, USA) and Saliva was obtained by using Oragene kit OGR-500 (DNA Genotek, Ottwa, Canada). DNA were extracted from all samples and kept on −80 °C for further use.

2.2. DNA extraction and quantification

The extraction of genomic DNA was done using QIAamp DNA Mini kit (Qiagen, Hilden, Germany), according to the manufacturer's instructions. The DNA samples were diluted with free nuclease water to 5–20 ng/μL at room temperature for the subsequent PCR reactions.

2.3. Genotyping of Taq-I (rs731236) and Fok-1 (rs2228570) polymorphisms

All molecular genetic studies were performed in the laboratory of Biotechnology Center at Khalifa University. Two SNPs (*Taq-I* (rs731236) and *Fok-1* (rs2228570)) in *VDR* been selected from Hap Map database phase III, to study the allelic and genotypic distribution of both *VDR* variants among Emirati population and compare it with other ethnic groups. The genotyping for the two *VDR* SNPs *Taq-I* (rs731236) and *Fok-1* (rs2228570) was performed using TaqMan SNP genotyping assay which consists of a predesigned mix of unlabeled polymerase chain reaction (PCR) primers and the TaqMan® minor groove binding group (MGB) probe (FAM™ and VIC® dye-labeled). All TaqMan SNP Genotyping Assays are designed to work with TaqMan® Universal PCR MasterMix which contains DNA polymerase, dNTPs and optimized mix components and uses the same thermal conditions. These assays were purchased from ABI (Applied Biosystems, USA), and they were applied using The ViiA™ 7 Real-Time PCR System (Applied Biosystems, USA). The real time PCR experiments were performed according to the manufacturer's instructions with a final reaction volume of 10 μl that contained 1 μl of genomic DNA (20 ng), 8.5 μl of TaqMan Genotyping Master Mix (2×) (Applied Biosystems, USA) and 0.5 μl of assay mix (20×). The Real Time PCR thermal conditions were as follows: Initial denaturing at 95 °C for 20 s; 40 cycles of 96 °C for 3 s (denaturing) and 60 °C for 30 s (annealing/extension). Results assessment was carried out using the ViiA™ 7 Software (Applied Biosystems, USA). Samples were run in duplicates, with positive, negative controls and blanks. SNPs call rate was 99.65%.

2.4. Data analysis

The Hardy–Weinberg equation was used for the assessment of the predicted genotype frequencies of the *VDR* gene polymorphism in healthy controls in UAE population. Two-tailed Fisher's exact test and chi square test was done to compare the allele and genotype frequencies of Emiraties to different population using NCSS 10.0 software program and data were analyzed by using the statistical program Stata (StataCorp. College Station, Texas, USA) (version 13). Haplotype analysis was performed using SNPstat from their website www.snpstats.net.

3. Results

The allele frequencies of *VDR* SNPs *Taq-I* (rs731236) and *Fok-1* (rs2228570) and genotype frequencies in the Emirati population are shown in Tables 1 and 2. Out of the 282 subjects analyzed for *Taq-I* (rs731236) and *Fok-1* (rs2228570), the following genotypic frequencies were obtained: AA 38%, AG 42%, GG 20% and AA 27%, AG 42%, GG 31% respectively.

The most frequently identified allele of *Taq-I* (rs731236) is A (333/562, 59.25%) while the most frequently identified allele of *Fok-1* (rs2228570) is G (292/562, 51.95%). Our data shows that the frequency of 'A' vs 'A' in *Taq-I* (rs731236) and *Fok-1* (rs2228570) were 59.25% vs 48.04% respectively. Comparison of the genotype and allele frequencies of *Taq-I* (rs731236) and *Fok-1* (rs2228570) between the Emirati population and other populations are illustrated in Tables 1 and 2, respectively.

In this study, no significant differences in the distribution of genotypes and alleles of *Taq-I* (rs731236) were found between Emirati individuals and the Caucasians of USA Minnesota and France and the African Americans of Pennsylvania (Bid et al., 2005; Zmuda et al., 1997). *Taq-I* (rs731236) genotypic and allelic distribution in Emiratis was statistically significant from those in Asians from Jordan (Karasneh et al., 2013), Japan (Tokita et al., 1996), India and North India (Bhanushali et al., 2009; Bid et al., 2005). The Emirati population *Taq-I* (rs731236) genotype distribution was significantly different from the Syrian population, however allelic frequency was not significantly different between the two populations. Likewise, *Fok-1* (rs2228570) allele and genotype frequencies in Emiratis were significantly different from the Asians populations of Jordan, Japan, India and North India. A significant difference in the genotype frequency of *Fok-1* (rs2228570) between Emiratis and Syrians was observed, while no significant difference was found in the allele frequencies of *Fok-1* (rs2228570) between these two populations.

Table 3 demonstrating the four haplotypes from the two SNPs (rs731236 and rs2228570) were analyzed among healthy Emirates. The haplotype having both alleles AA exhibited a frequency of 29% while the highest frequency of 31% was presented by the AG haplotype. However, the GA and GG haplotypes occurred at lower frequencies of 20% and 21% respectively.

4. Discussion

Ethnic differences in *VDR* polymorphism have been reported in literature by using Restriction Fragment Length Polymorphism (RFLP) assay (Smolders et al., 2009). The minor allele of *Fok-1* (rs2228570) has been shown to be present in a substantially lower frequency in Africans compared to Caucasians or Asians while the minor allele of *Taq-I* (rs731236) was found to be present in much lower frequency in Asians compared to Caucasians and African (Smolders et al., 2009).

Table 1
Comparing genotypes and allele frequency of VDR gene polymorphism (*Taql*) between Emirati and different populations.

Ethnicity	No.	Genotype (%)			*P*-value	Alleles (%)		*P*-value	Reference
		Taq-l (rs731236)				Major	Miner		
		AA	AG	GG		A	G		
Caucasian									
USA, white Minnesota	130	41	44	15	NS	63	37	NS	Bid et al. (2005)
French	189	33	49	18	NS	57	43	NS	Zmuda et al. (1997)
Asian									
Japan	488	77	22	1	***	88	12	***	Tokita et al., (1996)
North Indian	346	49	40	11	***	66	34	*	Bhanushali et al. (2009)
India	143	49	44	7	**	71	29	***	Bid et al. (2005)
African									
USA, Black Pennsylvania	101	32	53	15	NS	58	42	NS	Zmuda et al. (1997)
Middle East									
Jordan	126	32.5	47.7	19.8	**	56.4	43.6	**	Karasneh et al. (2013)
Syria	78	36	58	6	**	65	35	NS	Haddad (2014)
UAE	281	38	42.4	19.6		59.2	40.8		Current study

* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, NS = not significant.

In our study we have genotyped two *VDR* polymorphism SNPs *Taq-I* (rs731236) and *Fok-1* (rs2228570) using a high-throughput genotyping technology (Real-time PCR) to study the allele distribution in UAE population. Our results showed that the allele and genotype distribution of the *Taq-I* (rs731236) and *Fok-1* (rs2228570) in the Emirati population is similar to the Caucasians, since there was no significant difference in neither the allele nor the genotype frequencies of these two *VDR* SNPs *Taq-I* (rs731236) and *Fok-1* (rs2228570) between the two aforementioned cohorts. However, statistically significant differences in the genotype and allele frequencies of *Taq-I* (rs731236) between Emiratis and Asians from Jordan, Japan, India and North India were observed (Bhanushali et al., 2009; Haddad, 2014). Comparing with the results obtained from the Syrian study, *Taq-I* (rs731236) genotype distribution was significantly different, however allelic frequency was not (Haddad, 2014). Likewise, *Fok-1* (rs2228570) allele and genotype frequencies in Emiratis were significantly different from the Asians populations of Indians and North Indians (Bhanushali et al., 2009).

Many studies around the globe indicated associations between *VDR* SNPs and disorders as mentioned earlier. In the Chinese population the T allele of *Taq-I* (rs731236) in vitamin D receptor gene was significantly associated with degenerative disc disease, with an odds ratio (OR) of 2.61 (Cheung et al., 2006). In Greece, individuals with type 2 Diabetes presented less commonly with *Fok-1* (rs2228570) A allele ($p = 0.008$; OR 0.52, 95% CI 0.32 to 0.85) and *Taq-I* (rs731236) A allele ($p = 0.0001$; OR 2.24, 95% CI 1.49 to 3.36) (Panierakis et al., 2009). A study of 153 women with surgical and 260 with natural menopause showed a significant association between age at surgical menopause and two SNPs, and *Taq-I* (rs731236) ($p < 0.05$). For *Taq-I* (rs731236), the AA subjects had a greater chance of surgical menopause than the GG subjects (odds ratio = 2.01, 95% CI 1.07–3.78). Their results reveal the potential effect of the *VDR* gene on ovaries and uterus, and suggest that its SNPs can be used as predictors of genetic susceptibility for early surgical menopause and respective causal health problems (Dvornyk et al., 2006).

The importance of this study arises from elucidating the genotype, allele distribution any haplotype of the two most commonly studied SNPs of *VDR*, namely *Taq-I* (rs731236) and *Fok-1* (rs2228570) in Emiratis and understanding the differences from other ethnic groups. *VDR* haplotypes derived from *Taq-I* (rs731236) and *Fok-1* (rs2228570) polymorphisms were examined using combination of four genotypes. The distribution of haplotype frequencies in Emirati population is shown in Table 3. Results show that haplotype carrying A allele from *Taq-I* (rs731236) and G from *Fok-1* (rs2228570) are more frequent in Emirati population that's important for risk prediction and prognosis for a number of clinically significant diseases such as cancer and type 2 Diabetes in the Emirati population.

In conclusion, we have determined the frequency of *Taq-I* (rs731236) and *Fok-1* (rs2228570) polymorphism in the *VDR* gene in the Emirati population. In addition, the highest haplotype frequency of *Taq-I* (rs731236) and *Fok-1* (rs2228570) in Emirati population was presented by the AG haplotype. Further studies needs to be conducted to structure the haplotype between *VDR* variants and chronic disease.

Table 2
Comparing of genotypes and allele frequency of VDR gene polymorphism (*FokI*) between Emirati and different populations.

Ethnicity	No.	Genotype (%)			*P*-value	Alleles (%)		*P*-value	Reference
		Fok-1 (rs2228570)				Major	Minor		
		AA	AG	GG		A	G		
Caucasian									
UK	108	48	41	11	NS	68.50	31.50	NS	Bid et al. (2005)
French	100	43	47	10	NS	66.50	33.50	NS	Zmuda et al. (1997)
Asian									
Japan	249	37	51	12	NS	62.50	37.50	NS	Tokita et al. (1996)
North Indian	346	44	49	7	*	68.50	31.50	*	Bhanushali et al. (2009)
India	143	59	36	5	***	77.00	23.00	***	Bid et al. (2005)
Middle East									
UAE	282	27	42	31		48.04	51.96		Current study

* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, NS = not significant.

Table 3
Frequencies of haplotypes for two SNPs *Taq-I* (rs731236) and *Fok-1* (rs2228570) polymorphisms in Emirati population.

Haplotype	Frequency
A/G	0.31
A/A	0.29
G/A	0.20
G/G	0.21

Authors contribution

Drs. Alsafar, Al Anouti and Osman have designed the study, prepared the manuscript and performed all the data analyses with assistance from co-authors. Specifically, Ms. Enas has performed all laboratory work in Molecular Cell Biology laboratory at Khalifa University.

Conflict of interest

All the authors declare no conflict of interest.

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