Experimed 2019; 9(3): 93-8

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

DOI: 10.26650/experimed.2019.19017

Investigation of The Vitamin D Receptor (VDR) Gene Polymorphisms in Lumbar Disc Herniation in Turkish Patients

Lomber Disk Hernisi Tanısı Konan Türk Hastalarda Vitamin D Reseptör (VDR) Gen Polimorfizmlerinin Araştırılması

Bahar Toptaş Hekimoğlu[1], Hakan Eraltan[2], Hidayet Sarı[2], Mehmet Tolgahan Hakan[3], Dilara Sönmez[1], Cem Horozoğlu[4], Ümit Zeybek[1], Arzu Ergen[1], İlhan Yaylım[1], Turgay İsbir[5]

[1]Department of Molecular Medicine, İstanbul University Institute of Experimental Medicine, İstanbul Turkey
[2]Department of Physical Therapy and Rehabilitation, İstanbul University Cerrahpasa, Cerrahpasa School of Medicine, İstanbul, Turkey
[3]Department of Biology, Science and Art Faculty, Hitit University, Çorum Turkey
[4]Department of Technical and Medical Services, İstanbul Gelişim University, Medical Laboratory Techniques Program, İstanbul, Turkey
[5]Department of Medical Biology, Yeditepe University School of Medicine, İstanbul, Turkey

Cite this article as: Toptaş Hekimoğlu B, Eraltan H, Sarı H, Hakan MT, Sönmez D, Horozoğlu C, et al. Investigation of The Vitamin D Receptor (VDR) Gene Polymorphisms in Lumbar Disc Herniation in Turkish Patients. Experimed 2019; 9(3): 93-8.

ABSTRACT

Objective: Lumbar disc herniation (LDH) is a common degenerative disease. It is still not clear if there is a possible association between the vitamin D pathway and the etiopathogenesis of the disease. In this study, we investigated certain VDR polymorphisms which are known to affect vitamin D levels in patients with lumbar disc herniation.

Material and Method: TaqI (rs731236) and Fok-I (rs2228570) polymorphisms were studied by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) in 72 LDH patients and 81 healthy controls.

Results: After evaluation of our results, the frequency of LDH patients who have VDR Taq-I Tt genotype was significantly higher than the controls and carriers of Taq-I Tt genotype and t allele who had an increased risk for lumbar disc hernia cases, respectively p=0.002, OR:1.688, 95%CI:1.206-2.360; p=0.006, OR:1.420, 95%CI:1.104-1.825. VDR Fok-I genotypes did not differ significantly between lumbar disc herniation and control cases. (p=0.079). But, Ff genotype and f allele carriers had a higher risk for lumbar disk hernia than those with other genotypes, respectively p=0.025, OR:1.594, 95%CI:1.052-2.414; p=0.037, OR:1.514, 95%CI:1.019-2.250.

Conclusion: Our study contributes to the identification of genetic risk factors for specific subgroups of patients with LDH, and emphasizes the contribution of these biomarkers to the detailed clinical evaluation of patients with genetic biomarkers.

Keywords: Vitamin D receptor, polymorphism, lumbar disc herniation

ÖZ

Amaç: Lomber disk hernisi (LDH) yaygın bir dejeneratif hastalıktır. D vitamini yolu ile hastalığın etyopatogenezi arasında olası bir ilişkinin varlığı çalışmalarda tam olarak gösterilememiştir. Bu çalışmada LDH hastalarında D vitamini düzeyini etkilediği bilinen VDR polimorfizmlerini araştırdık.

Gereç ve Yöntem: TaqI (rs731236) ve Fok-I (rs2228570) polimorfizmleri 72 LDH hasta ve 81 sağlıklı kontrol örneğinde polimeraz zincir reaksiyonu- restriksiyon fragman uzunluk polimorfizmi (PCR-RFLP) yöntemi kullanılarak incelendi.

Bulgular: Elde edilen bulguların değerlendirilmesi sonrası VDR Taq-I Tt genotipine LDH hastalarında görülme sıklığı kontrollerden anlamlı olarak yüksek olduğu ve Taq-I Tt genotip ve t alel taşıyıcılarının LDH vakaları için yüksek risk taşıyıcısı olduğu tespit edildi, sırasıyla; p=0,002, OR: 1,688,% 95CI: 1,206-2,360; p=0,006, OR: 1,420,% 95CI: 1,104-1,825. VDR Fok-I genotipleri LDH ve kontrol vakaları arasında değerledirildiğinde anlamlı farklılık gözlemlenmemiştir (p=0,079). Ancak, Ff genotipi ve f allel taşıyıcıları LDH hastaları için diğer genotiplere göre daha yüksek bir risk taşımaktadır. Sırasıyla; p=0,025, OR: 1,594, %95 CI: 1,052-2,414; p=0,037, OR: 1,514, %95 CI: 1,019-2,250.

Sonuç: Çalışmamız, LDH'li hastaların belirli alt grupları için genetik risk faktörlerinin tanımlanmasına katkıda bulunmaktadır ve genetik biyobelirteçlerin hastaların ayrıntılı klinik değerlendirmesine katkısının önemini vurgulamaktadır.

Anahtar Kelimeler: D vitamini reseptörü, polimorfizm, lomber disk hernisi

Corresponding Author/Sorumlu Yazar: İlhan Yaylım **E-mail:** ilhanyaylim@gmail.com
Received Date/Geliş Tarihi: 09.10.2019 **Revision Date/Revizyon Tarihi:** 26.10.2019 **Accepted Date/Kabul Tarihi:** 12.11.2019

INTRODUCTION

The intervertebral disc, a bond between two adjacent vertebrae, contributes to the flexibility of the spine (1, 2). An intervertebral disc disorder involves several pathological conditions such as, deterioration, herniation, or other defects of intervertebral discs. Degenerative changes of a disc lead to several symptoms. Generally, these disorders are usually characterized by low back pain (LBP). (1). More than 80% of people suffer from LBP during their life time (3). LBP has been defined as one of the most common musculoskeletal disorders in the world, especially in the working population (4, 5) and affects up to 50-80 % of people at least once during their lifetime (4). Studies have shown that lumbar disc degeneration (LDD) is associated with LBP. The etiology of LDD has complex features (4, 5). According to the general opinion, there are several potential risk factors for a lumbar disc herniation, such as, age, weight, gender, occupation and smoking, and probably contribute to the genesis or to the acceleration of spinal degeneration (1, 4). The etiology of disc degeneration is based on environmental factors as well, as recent studies have shown that the physiological, molecular and genetic characteristics of herniated intervertebral disc tissues play a very important role in explaining the pathogenesis of human diseases (6, 7). Recent studies have demonstrated that, the effect of genetic factors was found to be more important in the progression of the lumbar disc hernias (1). Moreover, it is also proposed that intervertebral disc disease is very similar to complex disorders with multiple genetic forms. In the studies conducted so far, some genes were analyzed in the pathogenesis of lumber disc disease. Previous studies implied that, many genes are connected with lumbar disc disease, such as collagen IX (*COL9A2*), matrix metalloprotease-3 (*MMP-3*), vitamin-D receptor (*VDR*), estrogen receptor (*ER*) genes. These genetic factors have been reported to influence the regeneration and degeneration degree of the spine (1, 8).

Vitamin D is one of the critical determinants involved in bone metabolism and development (6, 9). The *VDR* gene, one of the top members of the nuclear receptor family, is encoded by chromosome 12 (8, 10). VDR are expressed in the growth plate of the bone and cartilage cells osteoblastic cells (11). Several studies determined that VDR play an important function in healthy bone structure. Therefore, VDR gene variants were thought to be related with various bone diseases, such as osteoporosis, osteoarthritis and degenerative disc disease (1, 11). The *VDR* gene has been investigated as a genetic factor according to development of spine pathologies since 1998 (12). Recent studies have shown that VDR gene polymorphisms have an effect on the development of various degenerative disc diseases (8). The Fok-I (rs10735810, merged into rs2228570) polymorphism, one of the most important variants in the *VDR*, is located on exon 2, and known as the main responsible agent for creating an alternative transcription initiation region that leads to alterations in the activity of the VDR protein. Because of the replacement of cytosine (C) by thymine (T), the Fok-I polymorphism causes different translation initiation sites to occur. These variations are associated with a different capacity to induce transcription of the VDR gene and VDR related genes (12). The VDR Fok-I polymorphism prompts a change translation promoter site, prompting the formation of a longer than wild VDR isoform. As predicted, this caused it to be less active (7, 13). In the end of the studies that have examined the relationship between LDD and the Fok-1 polymorphism have presented conflicting data. For this reason, studies to be carried out in different populations are important (7, 14, 15). Another significant SNP of the VDR gene, the the Taq-I (rs731236T / C) polymorphism is caused by a *switch* from ATT to ATC, which leads to a synonym change in codon 352 (isoleucine) (12, 16, 17). In a recent study by Toktaş et al., the intensity level of disk degeneration has been shown to be enhanced by Taq-I. This study suggests that the Taq-I SNP variant is associated with the severity and development of intervertebral disc degeneration (IVDD) (18).

The aim of this study was to determine any relationship tween the Taq-I and Fok-I polymorphisms of the VDR gene in lumbar disc hernias.

MATERIAL AND METHOD

Subject selection: In our study, in 72 patients with lumbar disc herniation, we analyzed the Taq-I and Fok-I gene polymorphisms in the VDR gene, and in 81 healthy individuals who applied to the Department of Neurosurgery of İstanbul University Cerrahpaşa School of Medicine. The mean age between the groups of the patients and the control group was 44.75±15.63 and 47.22±10.63 years, respectively. Samples from both groups were taken after the informed consent form was signed, and the study was conducted prospectively. İstanbul Medical Faculty Clinical Research Ethics Committee approved our study. The protocol followed during the study is consistent with the Declaration of Helsinki World Medical Association (Ethical Principles for Medical Research Involving Human Subjects).

Polymorphism Analysis

All blood samples were collected in tubes containing EDTA, and DNA was taken from whole blood using the salting-out method (19). Genotyping by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) was performed using these methods (Table 1).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 21.0 (IBM Corp.; Armonk, NY, USA) revision software package. Clinical laboratory data, which are expressed as mean ± SD, were compared between the patients and the control group by the unpaired Student's t test. The differences in the distribution of VDR genotypes or alleles between the patient and the controls were tested using chi-square statistics. VDR alleles frequencies were calculated by gene counting methods. $p<0.05$ was considered statistically significant.

Table 1. Taq-I / Fok-I RFLP methods

Gene	Primers	PCR reaction mixture	Restriction Enzym	Genotype	PCR conditions
Taq-I polymorphism	Forward:5' CAGAGCATGGACAGGGAGCAAG 3'; Reverse:5' GCAACTCCTCATGGGCTGAGGTCTCA 3'	3mM $MgCl_2$, 0,2mM dNTP, 0.2mM primers 0.2mM Taq polymerase (in a 50 µl reaction volume for 1x polymerase chain reaction)	TaqI (65 °C)	TT (490, 245 bp) Tt (490, 290, 245, 205 bp) tt (290, 245, 205 bp)	Initial denaturation step of 94°C for 4 min followed by 5 cycles of 94°C for 45 sec, 64°C for 60 sec and 72°C for 2 min; and a further, 25 cycles of 94°C for 30 sec, 64°C for 30 sec and 72°C for 45 sec.
Fok-I polymorphism	Forward :5' GATGCCAGCTGGCCCTGGCACTG 3'; Reverse: 5'ATGGAAACACCTTGCTTCTTCTCCCTC 3'	3mM $MgCl_2$ 0.2mM dNTP 0.25 mM primer 0.25mM Taq polymerase (in a 50 µl reaction volume for 1x polymerase chain reaction)	Fok-I (37°C)	FF (272) Ff (272, 198, 74) Ff (198, 74)	Initial denaturation step of 94°C for 4 min followed by 5 cycles of 94°C for 45 sec, 64°C for 60 sec and 72°C for 2 min; and a further, 25 cycles of 94°C for 30 sec, 64°C for 30 sec and 72°C for 45 sec. For Fok-I; initial denaturation of 4 min at 94°C , followed by 30 cycles of 94°C for 1 min, annealing at 60°C for 1 min and extension at 720C for 1 min. A final elongation step occurs at 72°C for 4 minutes.

RESULTS

The analysis included 72 lumbar disc hernia patients (32 female and 40 male) and 81 healthy controls (47 female and 34 male). The patient and control groups had similar distributions for age and sex differences. The genotype and allele frequencies of the VDR polymorphisms (Fok-I and Taq-I) of lumbar disc herniation patients and controls are demonstrated in Table 2. After evaluation of our results, a significant difference was found in Taq I genotype distribution of *VDR* between patients and the control group (p=0.006) (Table 2). The VDR Taq-I Tt genotype was significantly higher in lumbar disc hernia patients (60.9%) compared with controls (39.2%), and carriers of the Taq-I Tt genotype and the t allele had an increased risk for lumbar disc hernia cases, respectively, as shown in the clinical features of the study groups (p=0.002, OR:1.688, 95%CI:1.206-2.360; p=0.006, OR:1.420, 95%CI:1.104-1.825). VDR Fok-I genotype frequencies did not differ significantly between lumbar disc herniation and control cases. (p=0.079). But, Ff genotype and f allele carriers

Table 2. Allele and genotype frequencies of lumbar disc hernia cases and controls

SNP	Controls (n=81) n (%)	Lumbar disc hernia (n=72) n(%)	p
Fok-I Genotype			
FF	55 (67.9)	37 (51.4)	0.079
Ff	24 (29.6)	34 (47.2)	
ff	2 (2.5)	1 (1.4)	
Taq-I Genotype			
TT	39 (48.1)	19 (26.4)	0.006
Tt	30 (37)	45 (62.5)	
tt	12 (14.8)	8 (11.1)	

Table 3. Lumbar function assessment test results in patient group

	Mean	Std. Deviation
VAS (Visual Analog Scale)	6.4559	1.59695
SLR - Right (Straight Leg Raise)	59.4444	20.13320
SLR - Left (Straight Leg Raise)	60.1786	17.55418
LFA (Lumbar Flexion Angle)	50.5147	19.41571
LFA-ROM (Lumbar Flexion-Range of Motion)	4.6812	1.42066

Table 4. Comparison of homozygous genotypes according to VDR Taq-I Polymorphism with lumbar function tests

	Taq-1	Mean	Std. Deviation	p
VAS	TT Genotype	6.1111	1.32349	0.617
	tt Genotype	6.4286	1.61835	
LFA-ROM	TT Genotype	2.1765	0.72761	0.534
	tt Genotype	2.3750	0.74402	
SLR - Right	TT Genotype	63.9286	20.20839	0.125
	tt Genotype	47.0000	19.87461	
SLR – Left	TT Genotype	67.1875	18.43626	0.025*
	tt Genotype	46.6667	15.05545	
LFA	TT Genotype	51.7647	22.28657	0.824
	tt Genotype	50.0000	17.32051	

*:p<0.05

had a higher risk for lumbar disk hernia than those with other genotypes (p=0.025, OR:1.594, 95%CI:1.052-2.414; p=0.037, OR:1.514, 95%CI:1.019-2.250, respectively). In our study, according to gender, there is not any statistical significance of the genotypes distribution. In addition, according to lumbar flexion degrees in lumbar disc herniation patients compared to the distribution of VDR Taq-I and Fok-I polymorphisms genotypes, the Fok-I polymorphisms genotypes for the ff genotype in individuals (73.3±16.9) were determined to be statistically significantly higher than the Fok-I Ff genotype in individuals (48.4±15.3); (p=0.018). Functional lumbar evaluation tests (Table 3) applied in the diagnosis and evaluation process of our patient group were evaluated for VDR Taq-I and VDR Fok-I polymorphisms. SLR-Left who have TaqI TT genotype was found to be 1.44 times than patients with tt genotype (Table 4; p=0.025). For the Fok-I polymorphism, the VAS value was found to be 1.14 times statistically higher in patients with the f allele than in patients carrying the FF genotype (Table 5; p=0.04). The lumbar functional evaluation data of the patient group are presented in Table 4.

Table 5. Comparison of f allele carriage or FF genotype carriage with lumbar function tests in VDR Fok-I polymorphism

	Fok-I	Mean	Std. Deviation	p
VAS	f allele	6.8485	1.62252	0.048*
	FF genotype	6.0857	1.50238	
LFA-ROM	f allele	5.9412	2.51857	0.386
	FF genotype	3.4571	1.37528	
SLR - Right (Straight Leg Raise)	f allele	63.3333	20.39833	0.113
	FF genotype	54.5833	19.10592	
SLR – Left	f allele	60.9259	15.13002	0.762
	FF genotype	59.4828	19.79109	
LFA	f allele	48.1818	16.94745	0.340
	FF genotype	52.7143	21.50044	

*:p<0.05

DISCUSSION

Some of the polymorphisms in the *VDR* gene encoding vitamin D, which is an important factor in the regulation of cell division and differentiation, were investigated for their functional significance and potential effects on disease sensitivity (20). Several studies have shown that cellular effects of *VDR* may be associated with cell proliferation of disc cells. In addition, expression rates of matrix genes are related to specific cytokines and protein production (21, 22). Despite the recent research on lumbar disc disease, knowing that genetic factors play a critical role as the VDR gene, these genes have not yet been fully described (23). Researchers have rapidly turned to polymorphisms of these genes to determine the expression and effects of the full functions of these genes (23). In our study, although there was no statistically significant difference in terms of genotype distribution according to sex, we found a positive correlation between Taq-I genetic variant of *VDR* gene and lumbar disc herniation. We also determined that the VDR Taq-I Tt genotype might affect the development of lumbar disc hernia. These results are correlated with the work of Toktaş et al. (18). At the same time, this work constitutes evidence for the suggestion of TaqI SNP, which Taq-I SNP of VDR could be associated with both escalated developing IVDD and violent IVDD, in the compilations of Martrosyan et al. (3) in 2016.

Another gene associated with the VDR in our study, Fok-I polymorphism FF genotype, could be a less active variant, therefore, this alternation may lead to a more aggressive disease prognosis (24, 25). In several studies, the association of the Fok-I polymorphism in the VDR with the hernia, disc degeneration in different ethnic groups or lumbar spinal stenosis was analyzed (12). Colombini et al. According to the data obtained from the study, VDR Fok-I polymorphism in Italian population reported that there is no correlation with the risk of lumbar spine disease (12). In addition, several studies have determined similar results according to various types of disc pathologies (26). On the other hand, several previous studies have reported a relationship between the Fok-I polymorphism in VDR and the specific signs of disc degeneration in different populations such as Turkish (14), Brazilian (13) and Finnish (27). But some studies with Italian (12) and Mexican Mestizo patients (28), and a study of Norway case/control found an association with Fok-I genotypes (7). According to the findings of our studies, the individuals who have the genotype Ff and ff are associated with a worse prognosis than the individuals having the genotype FF.

The results of VDR Fok-I polymorphism in Italian athletes showed that f allele carrying was associated with LBP (29). However, it has been shown in the Italian population that the F allele is associated with a two-fold increase in risk for lumbar spine pathologies. In addition, the protective effect of f allele was emphasized (12). In our results, f allele carriage and Ff genotype carriage were associated with lumbar disc hernia. At the same time, the f allele was found to be associated with pain scores (VAS). This may be due to allele frequency differences between populations. In terms of VDR Taq-I polymorphism, SLR-Left was found to be higher in TT genotype than tt genotype in our study. The fact that this data have not been reported in different populations and similar spectrum of diseases is unique in terms of its contribution to the literature.

We observed a positive correlation between the levels of Vitamin D in lumbar disk degeneration patients. But these genetic polymorphisms play two important roles in regional disparities of race and ethnicity. Some polymorphisms tend to be more potent or less effective in some races, and there are two important genetic polymorphism aspects that occur in variations originating from race and ethnic origin. Fok-I SNP, for example, has been associated with more intervertebral disk degeneration risk in Hispanics than in Asian populations, but no association with intervertebral disk degeneration has been found in Caucasians (3, 30).

Our limitation is small size of the sample. A stronger statistical result and our findings are needed to verify the number of patients with more advanced studies.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Research Ethics Committee of İstanbul University School of Medicine (2009/1861).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.İ., İ.Y.; Supervision - T.İ., İ.Y.; Materials - H.E., H.S.; Data Collection and/or Processing - B.T.H., M.T.H., C.H.; Analysis and/or Interpretation - C.H., İ.Y., A.E., Ü.Z.; Literature Search - B.T.H., D.S. M.T.H.; Writing - B.T.H., C.H.; Critical Reviews - H.S., İ.Y., B.T.H.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: This study was funded by Scientific Research Projects Coordination Unit of İstanbul University (Project number: 4364).

Etik Komite Onayı: Bu çalışma için etik komite onayı İstanbul Üniversitesi Tıp Fakültesi Klinik Araştırmalar (2009/1861) alınmıştır.

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - T.İ., İ.Y.; Denetleme - T.İ., İ.Y.; Gereçler - H.E., H.S.; Veri Toplanması ve/veya İşlemesi - B.T.H., M.T.H., C.H.; Analiz ve/veya Yorum - C.H., İ.Y., A.E., Ü.Z.; Literatür Taraması - B.T.H., D.S. M.T.H.; Yazan - B.T.H., C.H.; Eleştirel İnceleme - H.S., İ.Y., B.T.H.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Bu çalışma İstanbul Üniversitesi Bilimsel Araştırma Projeleri Koordinasyon Birimi tarafından desteklenmiştir (Proje No:4364).

REFERENCES

1. Zhang Y, Sun Z, Liu J, Guo X. Advances in susceptibility genetics of intervertebral degenerative disc disease. Int J Biol Sci 2008; 4: 283-90. [CrossRef]
2. Paesold G, Nerlich AG, Boos N. Biological treatment strategies for disc degeneration: potentials and shortcomings. Eur Spine J 2007; 16: 447-68. [CrossRef]
3. Martirosyan NL, Patel AA, Carotenuto A, Kalani MYS, Belykh E, Walker CT, et al. Genetic Alterations in Intervertebral Disc Disease. Front Surg 2016; 3: 59. eCollection 2016. [CrossRef]
4. Colombini A, Cauci S, Lombardi G, Lanteri P, Croiset S, Brayda-Bruno M, et al. Relationship between vitamin D receptor gene (VDR) polymorphisms, vitamin D status, osteoarthritis and intervertebral disc degeneration. J Steroid Biochem Mol Biol 2013; 138: 24-40. [CrossRef]
5. Eskola PJ, Lemmelä S, Kjaer P, Solovieva S, Männikkö M, Tommerup N, et al. Genetic association studies in lumbar disc degeneration: a systematic review. PLoS One 2012; 7: e49995. doi: 10.1371/journal.pone.0049995. [CrossRef]
6. Zawilla NH, Darweesh H, Mansour N, Helal S, Taha FM, Awadallah M, et al. Matrix metalloproteinase-3, vitamin D receptor gene polymorphisms, and occupational risk factors in lumbar disc degeneration. J Occup Rehabil 2014; 24: 370-81. [CrossRef]
7. Taha MM, Sabbah NA, Rezk NA, Mansour H. Vitamin D Receptor Expression in Lumbar Disc Degeneration Patients. Open J Mod Neurosurg 2017; 7: 19-33. [CrossRef]

8. Kalichman L, Hunter DJ. The genetics of intervertebral disc degeneration.Familial predisposition and heritability estimation. Joint Bone Spine 2008; 75: 383-7. [CrossRef]
9. Vuolo L, Di Somma C, Faggiano A, Colao A. Vitamin D and cancer. Front Endocrinol (Lausanne) 2012; 3: doi: 10.3389/fendo.2012.00058. eCollection 2012. [CrossRef]
10. Mittal RD, Manchanda PK, Bhat S, Bid HK. Association of vitamin-D receptor (Fok-I) gene polymorphism with bladder cancer in an Indian population. BJU Int 2007; 99: 933-7. [CrossRef]
11. Amizuka N, Kwan MY, Goltzman D, Ozawa H, White JH. Vitamin D3 differentially regulates parathyroid hormone/parathyroid hormone-related peptide receptor expression in bone and cartilage. J Clin Invest 1999; 103: 373-81. [CrossRef]
12. Colombini A, Brayda-Bruno M, Lombardi G, Croiset SJ, Vrech V, Maione V, et al. FokI polymorphism in the vitamin D receptor gene (VDR) and its association with lumbar spine pathologies in the Italian population: a case-control study. PLoS One 2014; 9: e97027. doi: 10.1371/journal.pone.0097027. eCollection 2014. [CrossRef]
13. Vieira LA, De Marchi PL, dos Santos AA, Christofolini DM, Barbosa CP, Fonseca FLA, et al. Analysis of FokI polymorphism of vitamin D receptor gene in intervertebral disc degeneration. Genet Test Mol Biomarkers 2014; 18: 625-9. [CrossRef]
14. Eser B, Cora T, Eser O, Kalkan E, Haktanır A, Erdogan MO, et al. Association of the polymorphisms of vitamin D receptor and aggrecan genes with degenerative disc disease. Genet Test Mol Biomarkers 2010; 14: 313-7. [CrossRef]
15. Eskola PJ, Kjaer P, Daavittila IM, Solovieva S, Okuloff A, Sorensen JS, et al. Genetic risk factors of disc degeneration among 12-14-year-old Danish children: a population study. Int J Mol Epidemiol Genet 2010; 1: 158-65.
16. Bhanushali AA1, Lajpal N, Kulkarni SS, Chavan SS, Bagadi SS, Das BR. Frequency of fokI and taqI polymorphism of vitamin D receptor gene in Indian population and its association with 25-hydroxyvitamin D levels. Indian J Hum Genet 2009; 15: 108-13. [CrossRef]
17. Xu G, Mei Q, Zhou D, Wu J, Han L. Vitamin D receptor gene and aggrecan gene polymorphisms and the risk of intervertebral disc degeneration - a meta-analysis. PLoS One 2012; 7: e50243. doi: 10.1371/journal.pone.0050243. [CrossRef]
18. Toktaş ZO, Ekşi MŞ, Yılmaz B, Demir MK, Özgen S, Kılıç T, et al. Association of collagen I, IX and vitamin D receptor gene polymorphisms with radiological severity of intervertebral disc degeneration in Southern European Ancestor. Eur Spine J 2015; 24: 2432-41. [CrossRef]
19. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 1988; 16: 1215. [CrossRef]
20. Toptaş B, Kafadar AM, Cacina C, Turan S, Yurdum LM, Yiğitbaşı N, et al. The vitamin D receptor (VDR) gene polymorphisms in Turkish brain cancer patients. Biomed Res Int 2013; 2013: 295791. doi: 10.1155/2013/295791. [CrossRef]
21. Colombini A, Brayda-Bruno M, Lombardi G, Croiset SJ, Vrech V, Maione V, et al. FokI polymorphism in the vitamin D receptor gene (VDR) and its association with lumbar spine pathologies in the Italian population: a case-control study. PLoS One 2014; 9: e97027. doi: 10.1371/journal.pone.0097027. eCollection 2014. [CrossRef]
22. Colombini A, Lanteri P, Lombardi G, Grasso D, Recordati C, Lovi A, et al. Metabolic effects of vitamin D active metabolites in monolayer and micromass cultures of nucleus pulposus and annulus fibrosus cells isolated from human intervertebral disc. Int J Biochem Cell Biol 2012; 44: 1019-30. [CrossRef]
23. Rajasekaran S, Kanna RM, Senthil N, Raveendran M, Ranjani V, Cheung KMC, et al. Genetic susceptibility of lumbar degenerative disc disease in young Indian adults. Eur Spine J 2015; 24:1969-75. [CrossRef]
24. Yaylım-Eraltan İ, Arzu Ergen H, Arıkan S, Okay E, Öztürk O, Bayrak S, et al. Investigation of the VDR gene polymorphisms association with susceptibility to colorectal cancer. Cell Biochem Funct 2007; 25: 731-7. [CrossRef]
25. Neyestani TR, Djazayery A, Shab-Bidar S, Eshraghian MR, Kalayi A, Shariatzadeh N, et al. Vitamin D Receptor Fok-I polymorphism modulates diabetic host response to vitamin D intake: need for a nutrigenetic approach. Diabetes Care 2013; 36: 550-6. [CrossRef]
26. Omair A, Lie BA, Reikeras O, Brox JI. An Association Study of Interleukin 18 Receptor Genes (IL18R1 and IL18RAP) in Lumbar Disc Degeneration. Open Orthop J 2012; 6: 164-71. [CrossRef]
27. Videman T, Leppävuori J, Kaprio J, Battié MC, Gibbons LE, Peltonen L, et al. Intragenic polymorphisms of the vitamin D receptor gene associated with intervertebral disc degeneration. Spine (Phila Pa 1976) 1998; 23: 2477-85. [CrossRef]
28. Cervin Serrano S, González Villareal D, Aguilar-Medina M, Romero-Navarro JG, Romero Quintana JG, Arámbula Meraz E, et al. Genetic polymorphisms of interleukin-1 alpha and the vitamin d receptor in mexican mestizo patients with intervertebral disc degeneration. Int J Genomics 2014; 2014: 302568. doi: 10.1155/2014/302568. [CrossRef]
29. Cauci S, Migliozzi F, Trombetta CS, Venuto I, Saccheri P, Travan L, et al. Low back pain and FokI (rs2228570) polymorphism of vitamin D receptor in athletes. BMC Sports Sci Med Rehabil 2017 9: 4. doi: 10.1186/s13102-017-0069-x. eCollection 2017. [CrossRef]
30. Zhao J, Yang M, Shao J, Bai Y, Li M. Association Between VDR FokI Polymorphism and Intervertebral Disk Degeneration. Genomics Proteomics Bioinformatics 2015; 13: 371-6. [CrossRef]