

# Investigation of Vitamin D Receptor Gene Polymorphism in Pediatric Patients with Brain Cancer

## Abstract

**Aim:** In recent years, it is believed that Vitamin D may play a protective role in some cancer types. Certain regions of the Vitamin D receptor (VDR) gene may show a genetic difference in structure. The most frequent polymorphisms in this gene are in Taq-1, Fok-1, and Bsm-1 regions. Some adult cancer types are associated with VDR gene polymorphism such as; colorectal carcinoma, breast carcinoma, and prostate carcinoma. Reviewing the medical literature, no such study had been done on children so far. **Materials and Methods:** We investigated the association of the three most common gene polymorphisms (Taq-1, Fok-1, and Bsm-1 regions) in VDR gene in 32 children with brain tumors and forty control healthy volunteers. **Results:** We could not find any relationship between childhood brain tumors and VDR gene polymorphism in these three regions. **Conclusion:** The present results suggest that the Taq-1, Fok-1, and Bsm-1 polymorphism in the VDR gene and pediatric brain cancers have no association.

**Keywords:** Brain cancers, childhood, polymorphism, Vitamin D receptor

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## Introduction

Vitamin D is a steroid in structure. It binds to special receptors and plays an important role in cell proliferation and inflammation.<sup>[1]</sup> Certain regions of the Vitamin D receptor (VDR) gene may show a genetic difference in structure. The most frequent polymorphisms in this gene are in Bsm-1 [Figure 1], Fok-1 [Figure 2], and Taq-1 [Figure 3] regions.

In recent years, the relevance of VDR gene restriction fragment length polymorphisms for various types of cancer has been investigated by a great number of studies.<sup>[2]</sup> It has been hypothesized that VDR polymorphisms may influence both the risk of cancer occurrence and prognosis. After careful evaluation of the actual literature, it can be summarized that data indicating an association of VDR polymorphisms and cancer risk are strongest for breast cancer (Bsm1, Fok1), prostate cancer (Fok1), and malignant melanoma (MM) (Fok1). Data indicating an association of VDR polymorphisms and cancer prognosis are strongest for prostate cancer (Fok1), breast cancer (Bsm1, Taq1), MM (Bsm1), and renal cell carcinoma (Taq1).<sup>[2-13]</sup>

When we reviewed the medical literature, we could not find any studies,

investigating the relationship between VDR polymorphism and pediatric cancers. For this reason, we planned to investigate the association of VDR polymorphism and childhood brain malignant tumors.

## Materials and Methods

This study was performed on 32 volunteer patients between ages 0 and 18 who were diagnosed with brain tumor by radiological or pathological modalities. All of them were being followed up by Marmara University Paediatric Hematology and Oncology Department. As a control group, forty volunteer patients between ages 0 and 18 who had admitted to Marmara University Pediatric Polyclinics for other reasons than a chronic illness were chosen.

All patients and/or guardians participating in this study confirmed informed consent following institutional guidelines in accordance with the Declaration of Helsinki. The study was approved by Marmara University Ethics Committee.

## DNA isolations

Five milliliters whole blood samples were taken into 0.5 M ethylenediaminetetraacetic acid (EDTA) tube (Sigma, USA) from the individuals. All samples were mixed up with red blood cell (RBC) lysis solutions

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(155 mM ammonium chloride [AppliChem, Germany]), 10 mM sodium bicarbonate (Merck, Germany), and 0.5 mM EDTA (AppliChem, Germany) and incubated at 20° for 20 min.

Moreover, this solution was centrifuged for 20 min at +4°C, 4000 rpm (Hettich, Germany). Then, supernatant was removed, and residual liquid was mixed with RBC lysis solution. This procedure was repeated until all erythrocytes lysed and removed. Residual leukocytes were mixed with 1000 µl RBC lysis solution; 800 µl of it was kept in the Eppendorf tube. 20 µl/ml proteinase K (MBI Fermentas, Lithuania), sodium dodecyl sulfate 10% (Merck, Germany) in final concentration %0.5, nuclease solution (10 mM Trichloride [Amresco, USA]) pH: 8, 100 mM sodium chloride (Merck, Germany) in an amount that two and a half times the volume of leukocytes, 1 mM EDTA (AppliChem, Germany) added into the residual 200 µl solution, and incubated over a night in +56°C hot water (Kottermann Labortechnik, Germany). On the 2<sup>nd</sup> day, 1:1 phenol/chloroform (Merck, Germany) and isoamyl alcohol (isopentyl alcohol) were added and shaken for 10 min. The sample was held in the ice for 20 min and centrifuged at +4°C, 4000 rpm for 20 min. The solution was splitted up into two parts. The upper portion was taken into an another Eppendorf tube. 3 M sodium acetate (Sigma, USA) as much as 1/10 volume of solution and in an amount that is two times the volume of solution 95% alcohol (Tekel, Turkey) was added. After the tube upturned, DNA became visible and incubated at 20°C over the night. Centrifuged DNA at +4°C and 4000 rpm for 20 min precipitated. Supernatant part throwed away. 500 µl 70% alcohol was added and centrifuged +4°C 4000 rpm for 20 min. At the end of centrifugation, alcohol was poured and let the tube dry. After drying, tris-EDTA (10 mM Tris-HCl, 1 mM EDTA) was added and incubated over the night at 37°C to let the DNA dissolve.

### Screening for Vitamin D receptor gene FokI (rs10735810), BsmI (rs1544410), and TaqI (rs731236) polymorphism

For the analysis of VDR gene, polymorphism polymerase chain reaction (PCR) - restriction fragment length polymorphism method was used. Other PCR components are 10 mM tris-HCl (25°C pH: 8.8), 50 mM KCl, arranged last concentrations 0.2 mM deoxynucleoside triphosphates deoxyadenosine triphosphate (dATP), deoxyguanosine triphosphate (dGTP), deoxycytidine triphosphate (dCTP), deoxythymidine triphosphate (dTTP) (Fermentas, Lithuania), and 15 mM MgCl<sub>2</sub>. PCR is implemented by completing total volume to 25 µl with deionized H<sub>2</sub>O.

VDR gene BsmI polymorphism region;

5'-CAA CCA AGA CTA CAA GTA CCG CGT CAG TGA-3'

5'-AAC CAG CGG GAA GAG GTC AAG GG-3'

FokI polymorphism region;

5'-AGC TGG CCC TGG CAC TGA CTC TGC TCT-3'

5'-ATG GAA ACA CCT TGC TTC TTC TCC CTC-3'

TaqI polymorphism region;

5'-CAG AGC ATGGAC AGG GAG CAA-3'

5'-GCA ACT CCT CAT GGC TGA GGT C CTC-3'

By using those primers, gene region multiplied through PCR. After amplification with PCR method, BsmI polymorphism was found 825 base pairs (bp), FokI polymorphism was found 265 bp, TaqI polymorphism was found 740 bp.

Temperature conditions for PCR are 5 min denaturation at 95°C, 1 min forty cycles denaturation at 95°C, 1 min hybridization at 60°C, elongation at 72°C, and 7 min last elongation was implemented (T100, Bio-Rad).

After PCR experiment, products of PCR are loaded to 2% agarose gel electrophoresis and controlled; if the correct gene region amplification is seen, cutting process was performed by using restriction endonuclease enzyme.

### Agarose gel electrophoresis

Cutting results of endonuclease restriction enzyme are evaluated in 3% agarose gel electrophoresis. Products, which were cut with matching enzyme, treated with orange G, load to the gel and patterns moved at 90–100 V (Biogen, USA) for 30–50 min and results evaluated under ultraviolet light.

The statistical package, SPSS 17.0 (SPSS Inc, Chicago, USA), was used to analyze the data. The allele groups were compared to chi-square test and  $P < 0.05$  level was significant. We were used to odds ratio and 95% confidence interval for the VDR alleles risk be possibility for central nervous system (CNS) tumors.

### Results

A total of 32 patients between ages 0 and 18 with a diagnosis of brain tumor chosen for the study group. Control group consisted of forty healthy volunteers without any chronic illness [Table 1].

There was no statistically significant difference in gender distribution between two groups ( $P = 0.96$ ).

The median patient age was  $8.35 \pm 4.77$  years old; for the control group, it was  $8.72 \pm 4.67$  years old. There was no statistically significant difference in age distribution between two groups ( $P = 0.74$ ).

**Table 1: Gender distribution of the study and control groups**

Gender	Female	Male	Total
Patient	19	13	32
Control	24	16	40
Total	43	29	72

$P=0.96$

Calcium (Ca), phosphorus (P), and alkaline phosphatase (ALP) levels are indicators of Ca metabolism in serum. Ca level was  $9.6 \pm 0.67$  mg/dl in patient group and  $9.7 \pm 0.56$  mg/dl in control group ( $P = 0.4$ ). P level was  $4.3 \pm 0.9$  mg/dl in patient group and  $4.6 \pm 0.8$  mg/dl in control group ( $P = 0.063$ ). ALP level was  $163 \pm 72$  U/L in patient group and  $168 \pm 67$  U/L in control group ( $P = 0.76$ ). There was no statistically significant difference in Ca, P, ALP levels between two groups [Tables 2 and 3].

### Evaluation of Vitamin D receptor gene polymorphisms

#### *Vitamin D receptor; Bsm1 polymorphism*

When evaluation was made in terms of Bsm1 gene polymorphism, bb allele was 8/32 in patient group and 11/40 in control group. The distribution of bb allele was similar between two groups ( $P = 0.97$ ) [Table 4].

#### *Vitamin D receptor; Fok1 polymorphism*

No one was carrying ff allele among patients. One person was found with ff allele in control group [Table 5].

There was no significant difference between the patient and control groups in terms of Fok1 polymorphism.

#### *Vitamin D receptor; Tak1 polymorphism*

For Tak1 polymorphism, CC was positive in 6/32 of the patients and 10/40 of the control group. There was no significant difference statistically between the patient and control groups in terms of VDR Tak1 polymorphism ( $P = 0.81$ ) [Table 6].

As a result, we could not find any relationship between childhood brain tumors and VDR gene polymorphism in these three regions.

## Discussion

Vitamin D is an important factor in the regulation of cell division and differentiation. The VDR gene is a member of nuclear receptor superfamily, and it is located on chromosome 12.

For a long time, several polymorphisms in VDR gene have been investigated for functional significance and potential effects on disease susceptibility.<sup>[14]</sup> Many studies reported that Vitamin D has an antiproliferative effect on many cancer types, which is promoting apoptosis in a variety of malignant cells, such as glioma, neuroblastoma, leukemia, lymphoma cells, breast cancer, and colon cancer,<sup>[3,15,16]</sup> and numerous Vitamin D analogs have been produced for the treatment of several cancer types. Alternations of Vitamin D levels may be related to the changing in the expression of several transcription factors, cell cycle arrested proteins, growth factor, and other genes.<sup>[17]</sup> Several studies implicated that the ff and Ff genotypes of the VDR gene are associated with a decreased transcriptional activity. VDR Fok-I polymorphism changes the size of the VDR

**Table 2: Age, calcium, phosphorus, alkaline phosphatase levels of patient and control groups**

	Mean±SD	P
Age (year)		
Patient	8.35±4.77	0.74
Control	8.72±4.67	
Calcium (mg/dl)		
Patient	9.6±0.67	0.4
Control	9.7±0.56	
Phosphorus (mg/dl)		
Patient	4.3±0.9	0.063
Control	4.6±0.8	
ALP (U/L)		
Patient	163±72	0.76
Control	168±67	

SD – Standard deviation; ALP – Alkaline phosphatase

**Table 3: Histological dispersion of brain tumors**

	Frequency (%)
LGG	14 (43.8)
Medulloblastoma	10 (31.3)
SPNET	3 (9.4)
Ependymoma	2 (6.3)
HGG	2 (6.3)
Craniopharyngioma	1 (3.1)
Total	32 (100.0)

LGG – Low-grade glioma; SPNET – Supratentorial primitive neuroectodermal tumor; HGG – High-grade glioma

**Table 4: Bsm1 gene polymorphism, distribution of patient and control groups**

Bsm1	BB	Bb	bb	Total
Patient	8	16	8	32
Control	10	19	11	40
Total	18	35	19	72

$P=0.97$

**Table 5: Fok1 gene polymorphism, distribution of the study and control groups**

Fok1	FF	Ff	ff	Total
Patient	15	17	0	32
Control	14	25	1	40
Total	29	42	1	72

$P=0.43$

**Table 6: Tak1 gene polymorphism, distribution of the study and control groups**

Tak1	TT	TC	CC	Total
Patient	10	16	6	32
Control	11	19	10	40
Total	21	35	16	72

$P=0.81$

protein.<sup>[18-21]</sup> The shorter VDR variant could be less active; therefore, this variation may lead to more aggressive

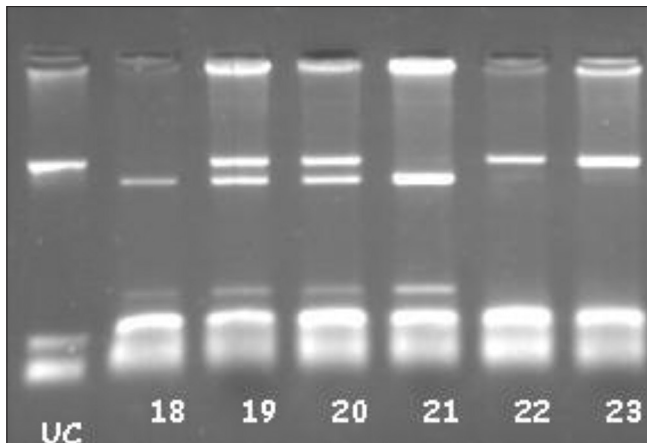


Figure 1: Vitamin D receptor BsmI polymorphism samples: UC: Un Cut. 18 and 21 bb, 19 and 20 Bb, 22–23 BB

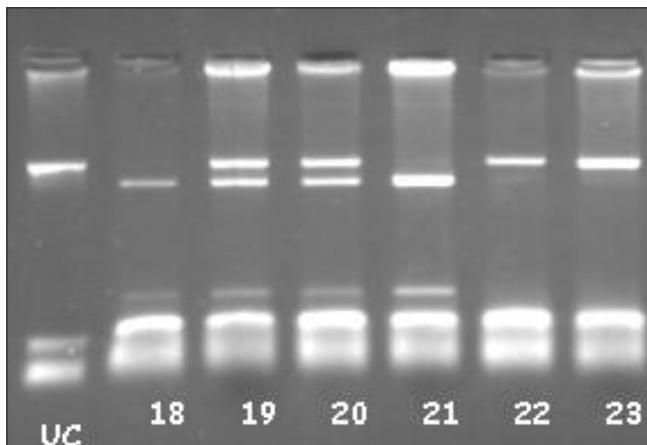


Figure 2: Vitamin D receptor FokI polymorphism rif-lip genotyping. UC: Un Cut FF: 30, Ff; 26, 27, 28, 29 and 31 (Samples)

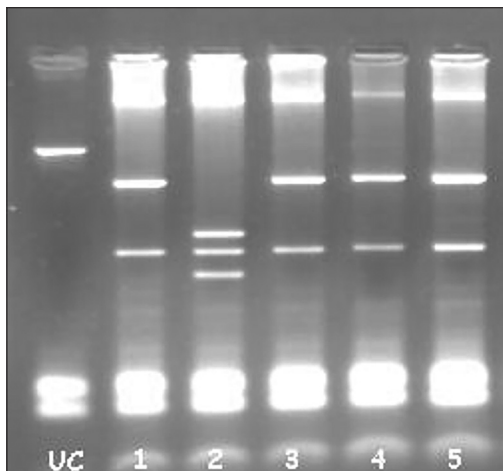


Figure 3: VDR TaqI polymorphism. UC: Un cut. CC: 2. Sample TT: except 2 (all samples)

disease prognosis.<sup>[15]</sup> There are some studies showing that Vitamin D deficiency affected the brain morphology and cellular proliferation and growth factor signaling in other tissue.<sup>[22-25]</sup>

VDR expression rates were associated with KRAS mutation in several cancer types. Several studies suggest that cellular effects of VDR may be associated with MAPK signaling pathways, especially KRAS mutation in several cancer types such as breast and colorectal cancers.<sup>[26,27]</sup> Sutton *et al.* demonstrated that protein levels of MN1 were significantly in a relationship with Vitamin D-mediated transcription mechanism in osteoblastic cells.<sup>[17]</sup>

It has been reported that VDRs localized in neuronal and glial cells affect the metabolism of brain cells and change the expression of VDR. Synthetic Vitamin D analogs are among the preferred options in the treatment of CNS tumors. In addition, phase II clinical studies have correlated with positive effects of Vitamin D therapy on glioblastoma cells.<sup>[23,29-34]</sup>

In their study, Toptas *et al.* found that there was statistically significant difference between the control and meningioma patients for Fok-I ff genotypes. The individuals who had VDR Fok-I ff genotype had an increased risk for meningioma.<sup>[35]</sup>

We think that there is not enough study about relationship between childhood cancers and VDR gene polymorphism, when the medical literature is reviewed. In our study, we investigated the association of the three most common gene polymorphisms (Taq-1, Fok-1, and Bsm-1 regions) in VDR gene in 32 children with brain malignant tumors.

We could not find any relationship between childhood brain tumors and VDR gene polymorphism in these three regions.

## Conclusion

The present results suggested that the Taq-1, Fok-1, and Bsm-1 polymorphism in the VDR gene and pediatric brain cancers have no association. However, further studies with large number of individuals are needed in that subject.

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This study was supported by Marmara University Scientific Research Fund, and this study was approved by Marmara University Ethics Committee.

## Conflicts of interest

There are no conflicts of interest.

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