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Taq1 Polymorphism (rs731236) of VDR Gene in depressive patients in Babylon Governorate

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Abstract

Depression is a prevalent and complex condition that carries a serious risk to public health due to its severe effect on mental health. Modern research on depression treatment has focused on creating new therapeutic options because major depressive disorder therapy has its limitations. A variety of pathways in the brain show vitamin D could have a role in the pathophysiology of depression. Our study sought to assess the relationship among VDR gene polymorphism and depression. Furthermore, we evaluated blood levels of 25-hydroxy vitamin D in depressive individuals.

Methods: Whole blood was collected from 60 depressive patients. Genomic DNA was extracted, and genetic variation was detected by means of polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) with the TaqI restriction enzyme. furthermore, serum was collected for Vitamin D measurement

Results: In a large cohort of depressed and healthy, we discovered that, after accounting for a variety of potential confounding factors, a low serum level of 25(OH) D was related with the occurrence and severity of depressive disorders.

Conclusion: Vitamin D levels were substantially lower in patients with depression than in control group. Furthermore, allele polymorphism in the current study revealed modest relevance between TT and Tt polymorphisms with illness development

Keywords: Depression; Vitamin D; 25-hydroxyvitamin D; VDR

1. Introduction

Depression is one of the most prevalent and complex mental conditions that can lead to disability. Loss of interest in once enjoyable activities, melancholy, impatience, hopelessness, feelings of worthlessness, worries about dying, and suicidal thoughts are typical signs of depression (1). Despite the fact that depression is a frequent mental health issue affecting millions of people. Relapse or recurrence of symptoms is prevalent among those who recover, and a large proportion of them are unable to reach treatment-induced remission (2). Vitamin D is an essential steroid hormone that can be produced in the skin or obtained from diet (3). Medium-wave ultraviolet UVB transforms 7-dehydrocholesterol in skin on the way to pre-vitamin D3, which is then converted to vitamin D3 by a non-enzymatic photolysis route. Vitamin D3 circulates in the blood, interacts with vitamin D binding protein, and then is transported to the liver. Vitamin D's traditional function is to maintain constant calcium levels (4). Furthermore, substantial research has been conducted on the role of in brain development and function (5).

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Vitamin D receptor (VDR) expression has been revealed to be high in numerous brain regions., including the cingulate cortex and hippocampus (6). As a result, it was suggested that 1,25(OH)2D3 was associated with the pathophysiology of schizophrenia, Alzheimer's disease, and depression (7). The link between depression and vitamin D levels has often been a source of concern and confusion. Some observational studies have found that serum 25(OH)D levels are in reverse related to mental health and life stress, particularly among those with low blood 25(OH)D levels (8). Some meta-analyses have suggested that vitamin D has no effect on depressive symptoms (9), but others have demonstrated that vitamin D helps lessen depressive symptoms (10).

VDR gene is situated on chromosome 12 and have approximately 900 allelic variants. most widely studied VDR gene polymorphisms are ApaI (rs7973232), BsmI (rs1544410), TaqI (rs731236), and FokI (rs10735810), which are silent genetic variants and increase mRNA stability (11). These genetic differences have been related to an increased risk of chronic illnesses such as type 2 diabetes, cardiovascular alterations, rheumatic arthritis cancer, autoimmune disorders, and metabolic bone diseases (12).

More than 60 single nucleotide polymorphisms of the VDR gene were located in the promoter area in exons (2–9). These include (TaqI, ApaI, BsmI) which located in the intron among exons 8 and 9 and (FokI) that located in exon 2 (13).

Hereditary and environmental variables influence VDR regulation, including diet, UV exposure, diseases, and pollution. It has been suggested that these environmental factors alter vitamin D levels, which modify the receptor (14). Genetic factors may influence the effect of environmental stimuli on VDR regulation. Individual reactions to vitamin D supplementation vary widely, and one theory holds that genetic variations in the VDR gene play an important role in this response. Polymorphisms in the VDR gene may affect VDR function, explaining why people respond differently to vitamin D supplementation (15).

To that end, we wanted to explore one single nucleotide polymorphism (SNP)—TaqI—of the VDR gene within patients with depression, to evaluate its connection with depression development and progression.

2. Materials and methods

2.1. Samples collections

Three ml of blood was acquired from each participant by vein puncture. Blood samples were collected in EDTA tubes, and two ml of blood in a gel tube for serum separation. This study included 20 patients with depression, and the samples were collected from Imam AL-Sadiq hospital in AL-Hillah city. The participants' ages ranged from 20 to 60 years old. Questionnaires were used to obtain related information on the participants' socioeconomic status and health history. Physicians reviewed the clinical assessments of individuals with depression. The study excluded contributors with chronic conditions such as liver or renal disorders, malabsorption and other diseases that potentially impair vitamin D levels.

2.2. Genomic DNA Extraction

About 3.0 mL of peripheral blood from participants was collect into a tube containing EDTA anticoagulants, and DNA was take out from the blood samples using Genomic DNA extraction kit (Promega), as directed by the manufacturer. A bio photometer (Eppendorf, Germany) was used to qualify and quantify DNA using conventional A260/A280 and A260/A230 ratios. After extraction, The DNA samples were kept at -20°C for use later on.

2.3. PCR Protocol for VDR Gene Polymorphism PCR

The reactions were carried out with AmpliTaq Gold 360 Master Mix, sequence-specific primers as in the table 1, and template DNA. The typical three-step PCR profile, namely denaturation, annealing, and extension, was used table 2.

Table 1 A set of VDR primers

Primers	Sequence	Products	Reference
Forward Primer	5′- CAG AGC ATG GAC AGG GAG CAA -3′	740 bp	[16]
Reverse Primers	5′- GCA ACT CCT CAT GGC TGA GGT CTC-3′		

Table 2 Amplification conditions of VDR gene

Stage		Temp(C)		Cycle
1	Initial denaturation	95	2min	1
2	DNA Denaturation	95	20min	25
	Primer Annealing	55	20min	
	Extension	72	50min	
3	Final extension	72	7	1

The PCR conditions and annealing temperature were established according to Ippokratis Messaritakis et al. (2020). Amplified DNA fragments were electrophoresed in 1% agarose (0.5x) TBE buffer for 40 minutes at 75 volts, and the bands were visible under UV light after being stained with ethidium bromide. A 100 base-pair ladder was employed as a size marker to estimate the fragment sizes..

2.4. Handling and Safety Protocols

During gel electrophoresis, hazardous substances like ethidium bromide were handled with extreme caution. Gloves were used during safety measures, and tainted objects were disposed away carefully.

2.5. PCR-RFLP Procedure

The VDR gene polymorphism has been determined using RFLP approach, which involves amplifying a 740 bp fragment of the VDR gene using PCR and then digesting it for four hours at 37 °C using Taq1 restriction enzyme. After two hours of incubation at 37°C, the samples were electrophoresis on (1%) agarose gel to examine digestion patterns. Taq1 enzyme was used to digest PCR results, and agarose gel electrophoresis was used to visualize the fragments and identify the genotype. After being separated by electrophoresis on a 1% agarose gel, the restriction fragments (495 bp, 245 bp or 290 bp, 245 bp, 205 bp) were stained with Sybr Safe DNA Gel Stain and observed. In its own special buffer, the TaqI restriction enzyme optimally cuts at 37°C and identifies T-CGA sites.

2.6. Serum Vitamin-D Estimation

Electrochemiluminescence immunoassay (ECLIA) Catalog number 07464215190 was used to detect serum vitamin D levels and evaluate changes in electrochemiluminescence signals following antigen-antibody immunoreaction.

2.7. Ethical concentration

College of Applied Biotechnology at Al-qasim green university in Babylon provided ethical permission (CON-HE-005) prior to the start of the study. Before proceeding of the surveys, all participants read the study introduction and clicked the accept button to indicate their willingness to participate in the research.

2.8. Statistical Analysis

The data were statistically evaluated using GraphPad Prism7 software. Chi-square was performed to determine the P-value.

3. Results

The results of demographic study recorded that the percentage of depressed patients of age ≤32 years old was (36.2%), (31-45) years was (35.2%), (46-65) years was (27.5%) .in comparison with control group was 35.2%),(40.0%),(22.0%) respectively.

Table 3 Features of the case and control groups' demographics

	Control	**Patients**
Total Number	30	60
Age (years)		
(≤30) years	11 (35.2%)	20(36.2%)
(31-45) years	12 (40.0%)	22 (35.2%)
(46-65) years	7 (22.0%)	18(27.5%)
Gender		
Male	15 (50.0%)	25(41.6%)
Female	15(50.0%)	35 (58.3%)

3.1. DNA Extraction

Blood samples were subjected to DNA isolation procedures. Band integrity and DNA concentration were discovered to be varied according to the produced amount of genomic DNA, and purity was determined by the number of white blood cells in the blood samples.

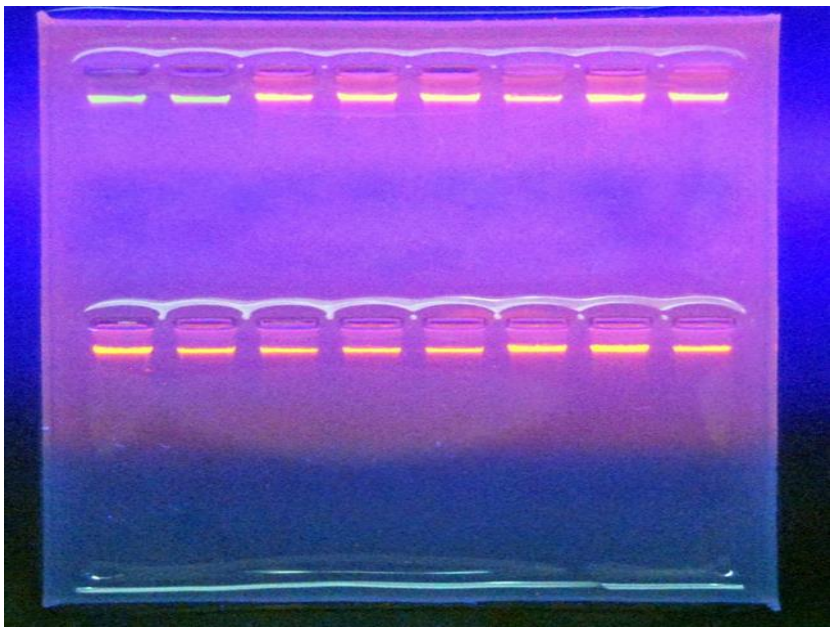

Figure 1 The electrophoresis pattern of chromosomal DNA bands extracted from human blood samples on 1% agarose gel

3.2. Amplification of VDR gene

The present study's goal was to assess the potential link between the VDR gene and the risk of depression by examining VDR polymorphisms in patients and otherwise healthy persons in a control group. The process of amplification of the VDR gene by using specific primers by PCR resulted in a product with a molecular size of approximately 740 bp, as demonstrated in Figure (2): 740 pb

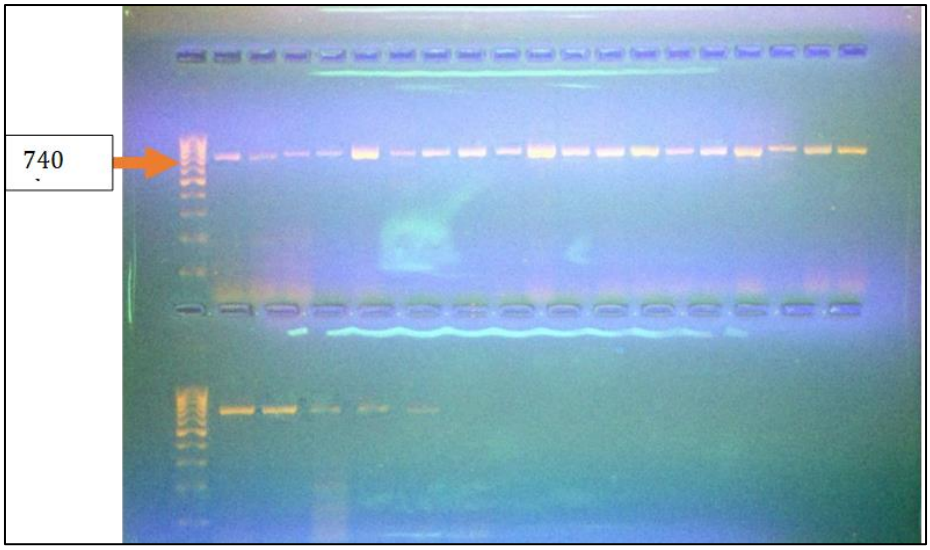

Figure 2 Electrophoresis pattern of PCR product of VDR gene, the optimum annealing temperature was 59 oC

3.3. The Genotype of VDR gene polymorphism using PCR RFLP

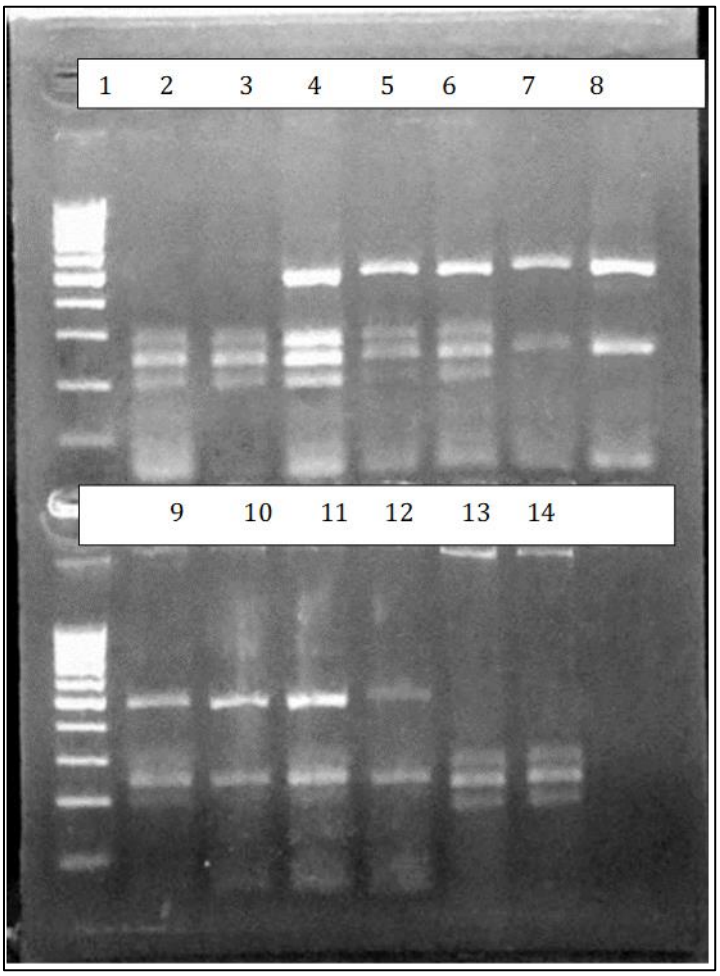

Figure 3 Electrophoresis layout of RFLP-PCR for PCR product (740 bp) with restriction enzyme Taq1, 1% agarose, 5 V/cm, for 120 minutes. (10 µl per well) Lane 1 represents a 100-bp DNA ladder. Lanes 7, 9, 10, 11, and 12 represent the wild-type (TT) genotype. Lane 4 and 6 reveal the heterozygote (Tt) genotype. Lanes 2, 3, 13, 14 reveal the homozygote (tt) genotype.

The Genotype of VDR gene polymorphism between the two-group control and patient group were detected using the PCR-RFLP technique. Results from the figure (3) show the genotype of the VDR gene in the two study groups control and patients, TT Wild type represented (740 bp), Tt heterogenotype represented (740 bp, 495bp, 245 bp and 205 bp) and tt homogenotype represented (495bp, 245 bp and 205 bp)

The genotype frequency of TT, Tt, and tt of VDR gene polymorphism was 36 (60%), 15 (25%) and 9 (15 %) in the patient group, while 7 (70%), 0(0%) and 3 (30%) in the control group was showed in table (4.1).

Table 4 Genotype of VDR gene polymorphism with Allele frequency

Genotype VDR	Control	Patient	$\chi 2$	Sig.	Odds
TT	21(70%)	36(60%)	7.038	0.029	1.5
Tt	1(1%)	15(25%)			
Tt	9(29%)	9(15%)			
Total number	30(100%)	60 (100%)			
Allele frequency					
Alleles	Control	Patient			
T	0.7	0.73			
T	0.3	0.27			

Table 4 shows the risk relations related with gene polymorphisms in the study of depression. The Tt genotype was found in 25% of the 60 cases studied, but in one sample of the 30 controls. The variations in genotype distributions were statistically significant.

(p=0.02), showing a higher risk of depression with the Tt genotype compared to controls.

3.4. Vitamin D level

Vit D level in patients and control was shows in the table (4)

Table 5 Vitamin D level in the serum od patient and control as (mean ±Sdv)

Parameter	Patients	Control	P-value
Vit D	12.3± 0.89****	37.86±2.83	0.0001

*Significant at (0.05)

4. Discussion

Major depressive disorder (MDD) is a prevalent mental condition that can develop at any age. However, the peak risk period for onset is from mid to late teens to the early 40s (17). Middle-aged individuals who have a physical disorder are more likely to have a mental problem (18). Anxiety problems in middle-aged and older persons are linked to physical health, socioeconomic level, immigrant status, and dietary variables (19). Increased depression in 40-year-olds is common, and it is often linked to midlife stressors such as financial concerns, hormonal shifts (especially for women), evolving responsibilities, physical health changes, and a reassessment of life goals. For many, depression reaches a climax around the age of 40-44, with specific symptoms varying by gender. Family history, childhood trauma, lower income, smoking, and inactivity are all risk factors. Treatment consists of therapy, lifestyle adjustments, and occasionally medication, with urgent professional intervention suggested in extreme situations (20).

Vitamin D is a steroid hormone that plays several important roles in the body, including psychological roles (21). In Iraq, individuals have not gotten enough sunlight, and they tend to avoid indoor activities. Many Iraqis are ignorant of the importance of naturally occurring vitamin D in sunshine and regular dietary consumption. These aspects should be considered (22). The primary objective of Vitamin D was to regulate levels of calcium and phosphor in the bones, which

supported ossification, neuromuscular, and cellular processes (23). Furthermore, its deficiency can induce rickets in children, osteomalacia in adults, osteoporosis, cancer, diabetes, and autism (24). Supplementation of vitamin D can treat several disorders, including cancer, multiple sclerosis, and cardiovascular disease (25). Canadian recommendations for optimal vitamin D dietary intake advise six hundred International Units for persons of age (1 – 70) years and 800 IU for those aged seventy-one and up (26). Hoogendijk et al. hypothesized that vitamin D is a secosteroid hormone that may cross the blood-brain barrier. Its receptors are found in several brain areas, which include the cortex, cerebellum, and limbic system (27). Other studies demonstrate that low vitamin D levels may increase parathyroid hormone, a hormone linked to depression. So, addressing hyperthyroidism can help with depression (28).

There has been an increasing number of studies suggesting a link between vitamin D and depression (29, 30, 31), as well as established links between adequate blood vitamin D concentrations and improved scores on mental health indicators (29)

In this study we want to investigate if *the Taq1* SNP in the VDR gene was connected with depressed symptoms. The SNP was linked and had substantial associations with depression, which was accepted by other studies (35). We also looked at how *the Taq1* SNP in the VDR gene can affect the vitamin D level in serum (tables 4, 5), and the results showed a normal range in healthy subjects, while a deficiency was observed in depressed subjects (Table 4).

So far, research on vitamin D's significance in the human brain has mostly focused on its effects on mood disorders. Furthermore, research has connected low vitamin D levels to mood problems and impaired cognitive capacities (32, 33, 34). Different tissues contain the active metabolite $1,25(OH)_2D$, which is produced from 25(OH)D (35). After being produced, $1,25(OH)_2D$ binds directly to vitamin D receptors (VDRs) in target organs, controlling gene transcription and cellular membrane structures to mediate a range of non-genomic responses. The majority of bodily tissues and cells have VDRs, but in the brain, they are more prevalent in the substantia nigra, thalamus, hypothalamus, cingulate gyrus, hippocampus, and prefrontal cortex. Many of these areas have been linked to the pathophysiology of depression (36). Most of these brain regions also revealed significant immunoreactivity for the enzyme 1-alpha-hydroxylase, which may metabolize 25(OH)D into $1,25(OH)_2D$, implying that $1,25(OH)_2D$ likely has autocrine and paracrine function in these areas (37). One function of vitamin D is to regulate the production of serotonin, a neurotransmitter closely linked to social behavior and sadness. Tryptophan hydroxylase-2 gene expression converts tryptophan into cerebral serotonin. In this setting, vitamin D plays a vital role in the activation of tryptophan hydroxylase-2, raising the possibility that it may prevent depression while maintaining appropriate amounts of serotonin (38).

5. Conclusion

According to the current data, vitamin D levels were considerably lower in depressed people compared to the control group. Furthermore, allele polymorphism revealed a moderate correlation between TT and Tt polymorphisms and sickness development, highlighting the role of VDR polymorphisms in depression and disease progression. Our findings demonstrate that TaqI influences cognitive performance and depressive symptoms in adults, indicating that VDR polymorphisms may influence depression through interactions with blood vitamin D levels.

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