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THE STUDY OF VDR FOKI rs2228570 SNP IN AUTOIMMUNE THYROIDITIS

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Abstract.

Aim: Autoimmune thyroid disease (AITD) is a common organ-specific autoimmune disease. A strong influence of genetic and epigenetic modifications has been demonstrated to take part in the development and progression of autoimmune thyroid diseases. The linkage between the Vitamin D receptor (VDR) polymorphism and several autoimmune disorders, including the AITD. In this article, we aim to investigate the Frequency of VDR Fokl (rs2228570) genotypes (CC, CT, TT) and alleles (C, T) in autoimmune thyroiditis.

Materials and methods: The investigation of VDR Fokl (rs2228570) was conducted on 150 samples (control (75 healthy women) and diseased women (75 diseased with autoimmune thyroiditis)) patients from the Adjara (Georgia) Population. It also examined some clinical and laboratory characteristics of the study population. Autoimmune thyroiditis’s disease was diagnosed by measuring blood antibodies, determining the level of hypothroperoxidase, and conducting an ultrasound examination. Anti-TPO and TSH were studied using the ELISA method. The genomic DNA was extracted from the peripheral blood. The polymerase chain reaction was evaluated to examine the VDR Fokl rs2228570 SNP polymorphism.

Results: According to VDR Fokl (rs2228570) genotypes (CC; CT, TT) frequency, in the control group, the Frequency of CC-genotype is 48%, CT-heterozygous genotype is 29.33%, and TT-genotype is 22.67%; in the diseased population, the Frequency of CC-genotype is 57.33%, CT-genotype is 34.67%, and TT-genotype is 8%. According to VDR Fokl (rs2228570) alleles (C, T), the Frequency of the C-allele is high, and the Frequency of the T-allele is low in both populations.

Conclusion: The Frequency of the CC and CT genotypes of VDR Fokl (rs2228570) is high in the population with autoimmune thyroiditis compared to the control group; the TT genotype is relatively low in the population suffering from autoimmune thyroiditis; According to VDR Fokl (rs2228570) alleles (C, T), the Frequency of C-allele is high both population.

Key words. Autoimmune thyroiditis, Vitamin D Receptor, single nucleotide polymorphism.

Introduction.

Autoimmune thyroid disease (AITD) is a common organ-specific autoimmune disease. A strong influence of genetic and epigenetic modifications has been demonstrated to take part in the development and progression of autoimmune thyroid diseases. Environmental factors like drugs, iodine, hormone, multivitamin levels, radiation, and viral infections have been shown to have immunomodulatory and toxic effects. Some genes have been identified that contribute to the phenotype of the diseases. The genes involved can be classified as 1) Thyroid specific, e.g., the genes regulating the TSH receptor and Thyroglobulin, and 2) Immunomodulatory- the genes that regulate the immune system, e.g., HLA, CTLA4, IL2, Vitamin D Receptor (VDR- FOXP3) etc. Over centuries, it has been observed that first-degree relatives are more common to suffer from autoimmune diseases if someone in the family has one. The association between AITD and Human Leukocyte Antigens (HLAs) was the pioneer study that provided a mechanism for the genetic basis of AITD. These associations have been studied and demonstrated in twin studies [1]. The HLA genes form the major histocompatibility complex (MHC), which contains many genes related to immune system functions. These include a) HLA class I (A, B, and C), b) HLA class II (DP, DM, DOA, DOB, DQ, and DR), and c) HLA class III (coding for other immune proteins). The major GD-associated HLA is HLA-DR3 as a predisposing factor, while HLA DR7 was shown to have a protective role [2]. It plays a vital role in the normal immune response by binding peptide antigens in its pocket and presenting them to T-cell receptors. HLA genes aren't well established in the case of HT. A few studies have demonstrated HLA DR and DQ to be linked to Hashimoto's thyroiditis (HT) development and progression. The cytotoxic T-lymphocyte-associated protein 4 (CTLA4) gene is an immune regulatory molecule and negatively regulates Helper T cell activation. DeGroot and Colleagues first demonstrated the association between CTLA4 and autoimmunity. CTLA-4 was shown to confer susceptibility to producing thyroid antibodies (Tab) alone without the clinical disease [3]. Numerous research has been done, but the mechanisms by which the CTLA4 variant makes susceptibility to AITD have not been ascertained. The Protein Tyrosine Phosphatasease-22 (PTPN22) produces a protein called LYP- lymphoid tyrosine phosphatase, which like CTLA4, negatively regulates T-cell activation. A tryptophan/arginine substitution at the codon 620 (R620W) of PTPN22 was found to be associated with AITD, including both Graves' disease (GD) [4] and HT [5] as well as with other autoimmune diseases. Genetic polymorphisms in the FOXP3 gene may promote autoimmune thyroid disease by weakening the inhibitory function of Tregs. Vitamin D receptor (VDR) polymorphisms have been receiving attention recently. VDR is an intranuclear receptor that has been shown to regulate immunoregulation by altering the expression of T-regulatory (Tregs) cells. Several SNPs have been known to be involved in VDR polymorphisms. Significant associations have been seen between SNP rs2228570 and AITD risk. The association is seen significantly more in HT than GD. Thyroglobulin is a homodimer protein that serves as a substrate and storehouse for the synthesis of thyroid hormones. It is one of the main targets of immune responses and the antibodies against it are also used as a marker for disease development and progression. HT
is characterized by chronic inflammation of the thyroid gland and the synthesis of thyroid peroxidase antibodies (TPO Ab) and/or thyroglobulin antibodies (TG Ab) [6]. Numerous VDR Single nucleotide polymorphisms (SNPs) have been identified, although the most studied is VDR SNP rs2228570 (FokI) in developing AITD. FokI is located in the start codon of the VDR gene, resulting in alternative splicing and production of two VDR isoforms, namely, VDR L and VDR S [7]. Long isoform (VDR L) contains the functional domain of the receptor. In contrast, the short isoform (VDR S) has reduced transcriptional activity [8]. The T allele in rs2228570 results in VDR L isoform production while the C allele leads to VDR S isoform production. [9] It has been postulated that the mechanism that influences FokI polymorphism in the pathogenesis of AITD is due to VDR S reduced transcriptional activity, there is decreased expression of genes involved in inflammation, and various immunological functions. In addition, it is hypothesized that FokI polymorphism has altered interaction of various coactivators and corepressors with the VDR receptor leading to altered gene expression. The association between Vitamin D receptor (VDR) polymorphism and several autoimmune disorders, including but not limited to diabetes mellitus 1, Systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, and tuberculosis, has been extensively studied. Autoimmune thyroiditis is one of the disorders where this association is observed. However, the impact of VDR SNPs on autoimmunity susceptibility varies across different populations and ethnicities. In this article, we aim to investigate the Frequency of VDR Fokl (rs2228570) genotypes (CC, CT, TT) and alleles (C, T) in autoimmune thyroiditis.

Materials and methods.

The investigation of VDR Fokl (rs2228570) was conducted on 150 samples (control (75 healthy women) and diseased women (75 diseased with autoimmune thyroiditis)) patients from Adjara (Georgia) Population. The study also examined certain clinical and laboratory characteristics of the study population. The mean age of the control group was 43±16.84, and the mean age of the diseased group was 41.71±14.96 (p=0.5747). Autoimmune thyroiditis was diagnosed by measuring blood antibodies, determining the level of thyroperoxidase, and conducting an ultrasound examination. Anti-TPO, and TSH were studied using the ELISA method. The genomic DNA was extracted from the peripheral blood. The polymerase chain reaction (PCR) was performed to investigate the polymorphisms of the VDR rs2228570 gene. The PCR primers were: Forward, 5'-CTGGCAGCTGACTCTGGCTCT and Reverse, 5'-GGGCTCACCTGAAGAAGCCT. PCR was performed: 5 min at 94°C - the initial denaturation step; then 30 amplification cycles of: the denaturation: 95°C for 30 s; annealing: at 59°C for 30 s; the extension - at 72°C for 30 s; Final extension - 5 min at 72°C; FokI genotyping was evaluated by restriction fragment length polymorphism (RFLP). C allele was not cleaved and presented a unique 204 bp band, while the T allele yielded 156 and 48 bp products detected by electrophoresis on the 2% agarose gel. The statistical analyses were performed by Graphed Prism (Version 9.0).

Results.

The pituitary thyrotrophic TSH hormone concentration in a healthy population was elevated about ~1.39 times within autoimmune thyroiditis compared to the control group (Figure 1). Compared to the healthy population, the high concentrations of antibodies against thyroperoxidase (Anti-TPO) were revealed in autoimmune thyroiditis. In particular, the level of Anti-TPO antibodies was increased ~48 times (Figure 2).

![Figure 1. Study of TSH's Levels in autoimmune thyroiditis. A - control group; B - autoimmune thyroiditis group.](image1)

![Figure 2. Anti-TPO's levels in autoimmune thyroiditis. A - the control group; B - The autoimmune thyroiditis group.](image2)

According to frequencies of VDR Fokl (rs2228570) CC, CT, and TT genotypes (Table 1) and alleles (C,T) have revealed differences between the healthy and diseased populations. As already well known, the rs2228570 polymorphism produces two different protein lengths by the vitamin D receptor, depending on whether t is in the second exon of the start codon (contains ATG or ACG. Specifically, if the second nucleotide in the start codon of the second exon is cytosine instead of thymine, a protein containing 423 amino acids is produced instead of the normal protein containing 427 amino acids. The literature suggests that the short (423 amino acid length) and long (427 amino acid length) vitamin D protein molecules have different activity levels.

The study population was analysed for the CC-dominant homozygous (which represents the wild type), CT-heterozygous,
and TT-genotypes. As previously mentioned, our research showed a difference in the Frequency of genotypes between the health and diseased groups. In the control group, the CC genotype’s Frequency is 48%, the CT genotype is 29.33%, and the TT genotype is 22.67% (Table 1). In the autoimmune thyroiditis’s population, the distribution of the CC genotype was 57.33%, the CT genotype - 34.67%, and the TT genotype - 8% (Table 1). The distribution of the CC- homozygous and CT-heterozygous genotypes was relatively higher in the autoimmune thyroiditis population compared to the control group. It should be noted that the frequency distribution of the CC and CT genotypes was higher in the control (health population) group than the TT genotype. Overall, the TT genotype was relatively low in both populations compared to the CC and CT genotypes. However, its percentage was relatively higher in the healthy population than in the diseased population. Our study shows that the CC and CT genotypes may represent relatively more disease-susceptible than the TT genotype.

The study revealed a high percentage of CC genotype in both study populations. However, a relatively higher prevalence of the CT genotype was observed in the diseased population (29.33% in the control group and 34.67% in the diseased population). In the entire population, the genotype distribution was as follows: CC-52.67%, CT-32%, and TT-15%. Based on these results, a relatively high frequency of the CC genotype was observed, suggesting that the CC genotype may be associated with susceptibility or propensity to autoimmune thyroiditis in the population of Adjara.

According to the alleles, the C allele frequency is higher than the T allele in both populations. Notably, the Frequency of the C allele was 0.74667 (q=0.74667) in Autoimmune thyroiditis compared to the control group, where there is 0.62667 (q=0.62667). On the other hand, the T allele frequency was high ~ 1.5 times in the healthy population than in the diseased population. The prevalence of the C allele was ~ 1.7-times higher than the T allele in the control group (p=0.00541). In contrast, in the population with autoimmune thyroiditis, the frequency of C allele was ~ 2.9 -times higher than the T allele. Although the Frequency of the T allele was slightly higher in the diseased population compared to the control group (p=0.2533), OR=1.450; (95%CI (0.8185-2.608)), it was still lower than the prevalence of the C allele in both study populations (Table 2).

**Discussion.**

Zarrin et al.’s research in northwest Iran compared 121 adult patients with autoimmune Thyroiditis and Graves' disease (GD) and 117 healthy controls. The results indicated that individuals with Fokl CC and CT genotype had a higher risk of AITDs; specifically, the CC genotype showed a higher likelihood of developing Hashimoto thyroiditis (p= 0.04; OR= 3.38). The study also concluded not much difference was noticed between Fokl and Apal polymorphism in AITD patients and healthy controls [10]. In a study conducted by Hanna et al. in 2021, the focus was on the prevalence of the Fokl polymorphism in the Egyptian population, specifically in patients with Hashimoto's Thyroiditis (HT) and hypothyroidism as controls. The study analyzed a sample size of 112 HT patients and 48 hypothyroid patients as controls. The study's results consistently showed a higher occurrence of the Fokl polymorphism in HT patients (11.4%) as compared to controls, where there were zero occurrences. The findings indicate a potential correlation between the Fokl polymorphism and the occurrence of Hashimoto's Thyroiditis in the Egyptian population. Moreover, the study also explored the Frequency of the FF genotype in the general Egyptian population, which was found to be relatively low in non-HT individuals (2.6%) and hypothyroid control patients (6%). Also found that BsmI polymorphism had no significant association compared to Fokl. This suggests that the Fokl polymorphism is more likely associated with autoimmunity in the Egyptian population, specifically in patients with Hashimoto's Thyroiditis [11].

An individual's genetic makeup determines their risk of developing certain diseases. In the case of Hashimoto's Thyroiditis, dominant or recessive genes have been found to impact the risk assessment. A study conducted in the Iraqi population found that the presence of the homozygous genotype (FF) was higher in patients with Hashimoto's Thyroiditis, with a p-value of 0.0002 and an odds ratio (OR) of 2.22. This indicates that individuals carrying the dominant genotype have a two-fold higher risk of developing Hashimoto’s Thyroiditis. On the other hand, the study also found that individuals with the heterozygous

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**Table 1. Study of the Fokl (rs2228570) genotypes’s frequency in autoimmune thyroiditis.**

<table>
<thead>
<tr>
<th>Study object</th>
<th>Number of samples (n)</th>
<th>Age</th>
<th>CC Genotype n (%)</th>
<th>CT Genotype n (%)</th>
<th>TT Genotype n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>n=150</td>
<td>42.8±25.7</td>
<td>79 (52.67%)</td>
<td>48 (32.3%)</td>
<td>23 (15%)</td>
</tr>
<tr>
<td>Control group</td>
<td>n=75</td>
<td>43 ±16.84</td>
<td>36 (48%)</td>
<td>22 (29.33%)</td>
<td>17 (22.67%)</td>
</tr>
<tr>
<td>Autoimmune thyroiditis’s group</td>
<td>n=75</td>
<td>41,71±14,96</td>
<td>43 (57.33%)</td>
<td>26 (34.67%)</td>
<td>6 (8%)</td>
</tr>
</tbody>
</table>

**Table 2. To study of VDR Fokl (rs2228570) alleles' frequency (C, T) in autoimmune Thyroiditis.**

<table>
<thead>
<tr>
<th>Study object</th>
<th>Number of samples (n)</th>
<th>Age</th>
<th>The Frequency of the C-allele</th>
<th>The Frequency of the T-allele</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>n=150</td>
<td>42.8±25.7</td>
<td>0.6867</td>
<td>0.3133</td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>n=75</td>
<td>43 ±16.84</td>
<td>0.62667</td>
<td>0.37333</td>
<td>0.00541</td>
</tr>
<tr>
<td>Autoimmune thyroiditis’s group</td>
<td>n=75</td>
<td>41,71±14,96</td>
<td>0.74667</td>
<td>0.25333</td>
<td>0.76922</td>
</tr>
</tbody>
</table>
genotype (Ff) and homozygous recessive genotype (ff) had a lower risk of developing the disease, with an OR of 0.63 and 0.40, respectively. The p-values for these genotypes were 0.029 and 0.017, respectively. This suggests that individuals carrying the heterozygous or recessive genotypes have a lower risk of developing Hashimoto's Thyroiditis. In summary, dominant, or recessive genes play a crucial role in the risk assessment of Hashimoto's Thyroiditis. While the homozygous genotype (FF) increases the risk of the disease, the heterozygous (Ff) and homozygous recessive (ff) genotypes offer protection against the condition in the Iraqi population [12]. Despite the observed association between VDR polymorphisms and autoimmune thyroid disease (AITD), some populations have failed to show consistent results [13]. For instance, a study was conducted on 223 adult Caucasian Polish patients with AIT and 130 unrelated controls of the same origin. The study found no significant association between the rs2228570 FokI polymorphism and the risk of disease occurrence in the studied population [14]. These findings suggest that the association between VDR polymorphisms and AITD may be influenced by factors such as ethnicity, geographical region, and lifestyle factors like diet and sunlight exposure, leading to inconsistencies in the results. SNPs such as VDR rs1544410 (BsmI), rs7975232(ApaI), and rs731236 (TaqI) polymorphisms have shown susceptibility to AITD development. An association in the Apa I gene has been identified in the Southwest Chinese Han population. A case-control cohort study was conducted to investigate this association, comprising 650 Chinese individuals with Graves' disease (GD) and 1209 healthy controls. The study aimed to examine the role of various genetic polymorphisms, including VDR/Apa I, FokI, TaqI, and BsmI, in developing GD. The study results showed that the AA genotype and A allele of VDR/Apa I were significantly associated with the risk of developing GD. In contrast, no significant correlation was found between GD and other polymorphisms, such as FokI, TaqI, and BsmI. These findings suggest that VDR mRNA expression and levels of secreted cytokines may play a role in the development of GD [15].

After conducting a meta-analysis that looked at the relationship between ethnicity and VDR polymorphisms found that the rs1544410 polymorphism is associated with an increased risk of autoimmune thyroid disease (AITD) in Asian populations. In contrast, African and European populations showed a decreased risk of AITD. Additionally, the rs731236 polymorphism in both Asian and African populations is associated with an increased risk of AITD, including Hashimoto's thyroiditis and Graves. At the same time, no significant relationship was found in European populations. These findings suggest that the effect of VDR polymorphisms on AITD risk varies by ethnicity, highlighting the importance of considering genetic variations in different populations [16]. Although association varies among the population, VDR SNP rs2228570 (FokI) is proposed as a potential risk for AITD susceptibility. However, this association's pathogenesis is unclear and requires further studies to determine the significant clinical significance of such genetic variations among populations.

Conclusion.

According to VDR FokI (rs2228570) genotypes (CC; CT, TT) frequency, in the control group, the Frequency of the CC-genotype is 48%, CT-heterozygous genotype is 29.33%, and TT-genotype is 22.67%; in the diseased population, the Frequency of CC-genotype is 57.33%, CT-genotype is 34.67%, and TT-genotype is 8%. The CC and CT genotypes of VDR FokI (rs2228570) are high in the population with autoimmune thyroiditis compared to the control group; TT genotype is relatively low in the population suffering from autoimmune thyroiditis. According to VDR FokI (rs2228570) alleles (C, T), the Frequency of C-allele is high both population; And the Frequency of T-allele is low in both populations; The high Frequency of the C-allele (1.2-fold) was revealed in the autoimmune thyroiditis’s population compared to the control group. The Frequency of the T allele is low (1.5 times) in the autoimmune thyroiditis population.

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