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Review article

VITAMIN D LEVELS AND VDR rs2228570 GENETIC VARIANT IN AUTOIMMUNE THYROIDITIS

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Abstract

Autoimmune Thyroiditis (AIT) is a prevalent autoimmune disorder characterized by an immune response targeting the thyroid gland. Genetic factors play a significant role in AIT susceptibility, with immune-related genes, especially the vitamin D receptor (VDR) gene, potentially influencing AIT development. This comprehensive review delves into the intricate association between VDR gene polymorphisms, particularly rs2228570 (FokI), and AIT susceptibility, exploring various populations. Research has unveiled contrasting outcomes regarding the link between the VDR rs2228570 polymorphism and AIT risk across diverse ethnic groups. Certain populations have exhibited a noteworthy correlation, suggesting that population-specific genetic factors contribute to AIT risk. A recurring observation of vitamin D deficiency in AIT patients has correlated with elevated anti-thyroid antibodies, abnormal thyroid function, and thyroid volume. The results emphasize the possible role of vitamin D in the development of AIT, suggesting the importance of vitamin D supplementation to address deficiencies associated with AIT. In addition to VDR rs2228570, other genetic variants have also shown associations with AIT susceptibility, displaying varying results across different populations. Ethnicity emerges as a pivotal factor influencing these associations, underscoring the need to consider genetic variations in diverse populations. We emphasize the intricate interplay between VDR gene polymorphisms, vitamin D, and AIT susceptibility. Extensive research is essential to unveil the clinical significance of these genetic variations, offering prospects for enhanced diagnostic and therapeutic strategies for individuals with AIT.

Keywords: VDR Gene, SNP, Vitamin D, Autoimmune Thyroiditis

INTRODUCTION

Autoimmune thyroiditis (AIT) is a widespread pathological condition characterized by an autoimmune response targeting the thyroid gland (1,2). Genetics is a key factor contributing to the development and progression of AIT (3). Research suggests that various immune-related genes play a role in the genetic predisposition to Autoimmune Thyroiditis (AIT) (4). The vital involvement of the vitamin D receptor (VDR) and its system is integral to the inflammatory response mechanism that leads to autoimmunity. Among autoimmune thyroid diseases (AITDs), Hashimoto's Thyroiditis (HT), or Autoimmune Thyroiditis (AIT), stands out as the most widespread manifestation. The origins of AIT are multifaceted and not entirely understood. However, it is widely believed that there is an interplay between environmental factors and genetic predisposition in its development (5).

Environmental factors, including the use of certain medications, iodine intake, exposure (6) to radiation (7), viral infections (8), and hormonal influences (9), can directly impact the function of thyrocytes. These factors may have detrimental effects on the immune system and can disrupt its normal functioning, leading to the development of AIT. Overall, the pathogenesis of AIT involves a complex interplay between genetic factors, particularly immune-related genes, and environmental influences. Additional investigation is required to clarify the complex mechanisms underlying the development and progression of AIT, which could potentially lead to improved diagnostic and therapeutic approaches for individuals affected by this autoimmune thyroid disorder. Genetic factors play a significant role, accounting for approximately 70-80% of the disease development in autoimmune disorders. Like many other autoimmune diseases, certain conditions, such as autoimmune thyroiditis (AIT), affect females more frequently. Vitamin D is now recognized for its pleiotropic effects, meaning it has multiple functions and impacts various aspects of health. The literature confirms the potential link between vitamin D and the incidence of thyroid diseases, specifically autoimmune thyroid diseases (AITD) (10).

Moreover, the correlation between vitamin D receptor (VDR) polymorphism and various autoimmune disorders has been extensively studied. VDR polymorphisms have also been implicated in autoimmune thyroiditis. However, the impact of VDR single nucleotide polymorphisms (SNPs) on susceptibility to autoimmunity can vary among different populations and ethnicities. VDR gene SNPs have a significant contribution to numerous diseases (11). It is important to note that further research is needed to fully understand the specific mechanisms by which VDR SNPs influence autoimmunity and their potential implications for individuals with autoimmune thyroiditis. The interplay between genetic factors, vitamin D, and their association with autoimmune disorders is a complex and evolving field of study. The Vitamin D receptor (VDR) is a receptor located within the cell nucleus. The VDR gene is on chromosome 12q13.1 and comprises 11 exons (12). Researchers have focused their investigations on genetic variations in the regulatory regions of the VDR gene,

collectively known as VDR polymorphisms. These polymorphisms involve changes in a single nucleotide and have been extensively studied in relation to various diseases, including AITDs. Approximately sixty VDR SNPs have been identified thus far. Some notable SNPs associated with an increased risk of AITD include FokI rs2228570, ApaI rs7975232, TaqI rs731236, and BsmI rs1544410. In addition, these genetic variants have been linked to a higher susceptibility to developing AITD. In this review, we summarize the association between Vitamin D and VDR gene genotypes.

VITAMIN D LEVELS IN AUTOIMMUNE THYROIDITIS

Vitamin D contributes significantly to numerous diseases (13,14). Vitamin D, through its active form 1,25(OH)2D, exerts regulatory influence over a wide range of biological functions, extending beyond maintaining bone mineral balance. These roles include overseeing hormone secretion, adjusting the immune response, and coordinating cellular proliferation and differentiation. Recently, there has been increasing recognition of the diverse functions of vitamin D and its active metabolites across various bodily tissues. This finding has led to the recognition that most tissues throughout the body possess receptors known as vitamin D receptors (VDRs), referring to the active form of vitamin D as 1,25 dihydroxy vitamin D [1,25(OH)2D] or calcitriol. These VDR-containing tissues are considered potential target areas, highlighting the multifaceted impact of vitamin D on the body's overall function (15).

Particularly, vitamin D suppresses proliferation and immunoglobulin production while inhibiting the differentiation of B cell precursors into plasma cells. This ability of 1,25(OH)2D to dampen the adaptive immune response offers advantages in situations where the immune system mistakenly targets the body's tissues, as seen in autoimmune disorders (16).

An analysis of a study conducted in the Hungarian population revealed markedly higher vitamin D deficiency among individuals diagnosed with autoimmune thyroid diseases (AITDs) compared to healthy individuals. Specifically, deficiency was found in 72% of AITD patients, while only 30.6% of healthy individuals exhibited the same condition ($P<0.001$). Within the AITD group, patients with Hashimoto's thyroiditis displayed a higher prevalence of vitamin D deficiency than those with non-AITDs. Among Hashimoto's thyroiditis patients, 79% had a deficiency, whereas only 52% of non-AITD patients had the same deficiency ($P<0.05$). This analysis also revealed a correlation between vitamin D deficiency and the presence of antithyroid antibodies, indicating an association between these factors ($P=0.01$). Additionally, abnormal thyroid function tests were linked to vitamin D deficiency, although the correlation was slightly weaker ($P=0.059$). The analysis provided evidence of significantly low levels of vitamin D among patients with AITDs, particularly those with antithyroid antibodies and abnormal thyroid function tests. Recent research suggests vitamin D's

involvement in AITD development and indicates potential benefits of vitamin D supplementation for managing these conditions (17).

In an investigation of the relationship between 25OHD levels and Hashimoto's thyroiditis (HT) in three groups - HT patients on L-thyroxine (LT), newly diagnosed HT patients, and healthy volunteers - the results demonstrated that HT patients on levothyroxine (LT) had significantly diminished levels of 25-hydroxyvitamin D (25OHD) compared to both recently diagnosed HT patients and healthy controls. Higher 25OHD levels were associated with larger thyroid volume and lower levels of anti-TPO and anti-TG antibodies. Severe 25OHD deficiency was observed in a significant proportion of HT patients as well as in a smaller percentage of the control group. Furthermore, the study identified gender differences, with female HT patients having the lowest 25OHD levels and male controls having the highest levels. The findings demonstrate that individuals with HT exhibit a higher occurrence and severity of vitamin D insufficiency than healthy controls. Additionally, the extent of 25OHD deficiency is associated with the duration of Hashimoto's Thyroiditis (HT), thyroid volume, and antibody levels. These findings imply a possible involvement of 25OHD in the onset of HT and its progression towards hypothyroidism (18).

The level of 25(OH)D3 independently influences the presence of TPOAb in individuals with AITDs. A study in the Korean population revealed that patients with increased anti-thyroid antibodies had lower levels of serum 25(OH)D3 compared to those without elevated antibodies ($p<0.001$). Interestingly, there was a negativecorrelation between 25(OH)D3 and anti-thyroid antibody (TPOAb) levels in the group with autoimmune thyroid diseases (AITDs) ($r=-0.252$, $p<0.001$), but no such correlation was observed in the group without AITDs ($r=0.117$, $p=0.127$), after accounting for age, sex, and body mass index. Furthermore, the concentration of 25(OH)D3 was considered an independent causative factor linked to the presence of TPOAb in the AITDs group, even after considering other factors that could impact the presence of TPOAb.

In conclusion, this suggests that vitamin D deficiency is more closely associated with the level of anti-thyroid antibodies rather than the thyroid function itself. The study proposes vitamin D as an immunomodulatory agent in autoimmune thyroiditis, and further research is required to understand the mechanisms and establish clarity. Notably, a significant association between anti-thyroid antibody levels and 25(OH)D3 was observed only in the group with AITDs. This finding may be attributed to the Korean population's generally low vitamin D levels. Interestingly, the correlation between 25(OH)D3 levels and anti-thyroid antibodies is also observed within the range of vitamin D deficiency (19).

VITAMIN D LEVELS AND FOKI (rs2228570) SNP

Studies suggest that genes' SNPs, including the VDR gene SNP, are associated with numerous conditions (20-23). Research has revealed a correlation between serum vitamin D levels and the manifestation of AITDs. Studies have shown that individuals with lower serum vitamin D levels are more likely to exhibit symptoms of AITDs (24). As an immunomodulator, vitamin D plays a crucial role in initiating and progressing AITD. Patients with AITD often exhibit deficiencies in vitamin D levels. Additionally, a correlation exists between vitamin D deficiency and elevated levels of antithyroid antibodies and increased thyroid volume, influencing the duration and severity of HT, a common form of AITD (25).

The immunomodulatory properties of vitamin D and its impact on various disease manifestations, including AITD, underscore the need for further research. Understanding precisely how vitamin D deficiency influences AITD development and progression can aid in developing targeted interventions and personalized treatment strategies for individuals affected by these autoimmune thyroid disorders.

A study conducted in western Ukraine, including 153 patients with various thyroid disorders, revealed that patients diagnosed with hypothyroidism and possessing the AA genotype had notably lower levels of Vitamin D, decreased by 18.8%, irrespective of the underlying cause of their condition, whether postoperative or autoimmune. This finding suggests that low levels of Vitamin D contribute to the exacerbation of thyroid insufficiency in these individuals. Additionally, the study demonstrated that different thyroid pathologies exhibited variations in Vitamin D levels.

Comparing patient groups to a control group, individuals with postoperative hypothyroidism displayed significantly decreased Vitamin D levels, approximately 1.89 times lower. Similarly, patients with hypothyroidism induced by Hashimoto thyroiditis showed a significant reduction in Vitamin D levels, approximately 2.05 times lower than the control group (26).

These findings underscore the significance of Vitamin D in thyroid health and suggest that insufficient levels of this vitamin may contribute to the onset and development of autoimmune thyroid disorders, especially Hashimoto's thyroiditis. The study highlights differences in Vitamin D levels among various thyroid pathologies, indicating the need for tailored approaches to managing and treating these conditions.

In the Serbian population, a study involving 44 female patients diagnosed with Hashimoto's thyroiditis and exhibiting reduced or deficient Vitamin D levels showed a significant difference in the VDR-FokI polymorphisms compared to control subjects (p-value < 0.05). This finding suggests a notable correlation between the VDR-FokI polymorphisms and the development of Hashimoto thyroiditis. Moreover, individuals with the VDR-FokI polymorphism were at a higher risk of developing the disease, with an odds ratio of 4.472 (27).

Similarly, in the Asian population, particularly among the Japanese, investigating the CC genotype and C allele frequencies for the VDR rs2228570 polymorphism revealed interesting results. The researchers found a higher prevalence of these polymorphisms in Hashimoto thyroiditis patients with low serum Vitamin D levels compared to the healthy group (p-values = 0.0174 and 0.0458, respectively). The CC genotype was found to contribute to autoimmune thyroid destruction directly, while the C allele was associated with increased interleukin 12 (IL-12) production, leading to cytotoxic T cell and Th1 cell-mediated thyroid destruction (28).

This information sheds light on the underlying mechanisms and pathogenesis of the disease, suggesting that immune regulation mediated by VDR is suppressed in patients with Hashimoto thyroiditis.

Interestingly, a similar distribution of the VDR-FokI genotype was noticed in the Chinese and Japanese populations. Lin et al. illustrated that 36.7% of HT patients in the Chinese population had CC genotypes compared to only 23.3% in the control group. Furthermore, they also highlighted a notable disparity in the distribution of VDR SNP genotypes (p-value: 0.0458) (29).

In summary, these studies conducted on the Serbian, Japanese, and Chinese populations provide valuable insights into the role of VDR-FokI polymorphisms and VDR rs2228570 polymorphisms in the development and pathogenesis of Hashimoto thyroiditis. They establish a significant association between these genetic variations and the disease, highlighting the importance of immune regulation mediated by VDR in the occurrence and progression of Hashimoto thyroiditis.

Additionally, other SNPs in the VDR gene, including rs1544410 (BsmI), rs7975232 (ApaI), and rs731236 (TaqI), have shown associations with AITD. In particular, a study in the Southwest Chinese Han population indicated that the AA genotype and A allele of VDR/ApaI significantly correlate with an increased risk of developing Graves' disease (GD). However, no significant associations were found between GD and other polymorphisms, including FokI, TaqI, and BsmI. These findings suggest that VDR mRNA expression and levels of secreted cytokines may play a role in GD development (24).

A subsequent meta-analysis exploring the relationship between ethnicity and VDR polymorphisms revealed that the rs1544410 polymorphism is linked to an increased risk of AITD in Asian populations, while African and European populations demonstrated a decreased risk. Moreover, the rs731236 polymorphism was associated with an increased risk of AITD, encompassing Hashimoto’s thyroiditis and Graves, in both Asian and African populations, while no significant relationship was detected in European populations. These findings emphasize the influence of VDR polymorphisms on AITD risk, varying based on ethnicity, highlighting the importance of considering genetic variations across different populations (30-35).

In conclusion, the altered Vitamin D levels and VDR SNP rs2228570 (FokI) may be considered potential risk factors for AITD susceptibility, though their association varies among different populations. The precise pathogenesis explaining this association remains unclear, emphasizing the need for further studies to determine the clinical significance of these genetic variations across diverse populations.

Abbreviation

AIT-Autoimmune thyroiditis; **VDR**-Vitamin D receptor; **AITDs**-Autoimmune thyroid diseases; **HT**-Hashimoto Thyroiditis; **SNPs-**Single Nucleotide Polymorphisms;**1,25(OH)2D** - 1,25 dihydroxy Vitamin D; **LT**- L-thyroxine; **25OHD**- 25-hydroxyvitamin D; **Anti-TPO**-Anti-thyroid peroxidase; **Anti-TG**-Antithyroglobulin antibodies; **IL-12**-Interleukin 12; **GD** - Graves disease; **PCR** - polymerase chain reaction; **mRNA**-messenger ribonucleic acid.

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Sažetak

NIVOI VITAMINA D I GENETSKI VARIANT VDR rs2228570 U AUTOIMUNOM TIREODITISU

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Autoimuni tireoiditis (AIT) je rasprostranjeno autoimuno oboljenje koje karakteriše imunološki odgovor usmeren protiv tireoidne žlezde. Genetski faktori imaju značajnu ulogu u podložnosti za AIT, pri čemu geni povezani s imunološkim sistemom, posebno gen za receptor vitamina D (VDR), potencijalno utiču na razvoj AIT-a. Ova sveobuhvatna analiza istražuje kompleksnu povezanost između polimorfizama gena VDR, posebno rs2228570 (FokI), i podložnosti za AIT, istražujući različite populacije. Istraživanja su otkrila kontrastne rezultate u vezi sa povezanošću polimorfizma VDR rs2228570 i rizikom od AIT-a u različitim etničkim grupama. Određene populacije su pokazale značajnu korelaciju, sugerišući da specifični genetski faktori unutar populacija doprinose riziku od AIT-a. Ponavljano zapažanje nedostatka vitamina D kod pacijenata s AIT-om povezano je s

povišenim antitireoidnim antitelima, poremećajem funkcije tireoidne žlezde i zapreminom žlezde. Rezultati naglašavaju moguću ulogu vitamina D u razvoju AIT-a, sugerišući važnost suplementacije vitamina D radi rešavanja nedostataka povezanih s AIT-om. Osim VDR rs2228570, i druge genetske varijante su pokazale povezanost s predispozicijom za AIT, prikazujući varirajuće rezultate u različitim populacijama. Etnicitet se ističe kao ključni faktor koji utiče na ove veze, ističući potrebu za razmatranjem genetskih varijacija u različitim populacijama. Naglašavamo kompleksnu međuigru između polimorfizama gena VDR, vitamina D i podložnosti za AIT. Obimna istraživanja su neophodna kako bi se otkrila klinička značajnost ovih genetskih varijacija, pružajući mogućnosti za unapređene dijagnostičke i terapijske strategije za osobe s AIT-om.

Ključne reči: Gen VDR, SNP, Vitamin D, Autoimuni Tireoiditis

REFERENCES

1. Santoro D, Vadalà C, Siligato R, Buemi M, Benvenga S. Autoimmune thyroiditis and glomerulopathies. Front Endocrinol. 2017;8:119. doi: 10.3389/fendo.2017.00119.

2. Fallahi P, Ferrari SM, Antonelli A. Autoimmune thyroiditis. In: Gu D, Dupre ME, editors. Encyclopedia of gerontology and population aging. Cham: Springer International Publishing; 2021. p. 563–72. Available from: https://doi.org/10.1007/978-3-030-22009-9_63.

3. Wang B, Shao X, Song R, Xu D, Zhang JA. The emerging role of epigenetics in autoimmune thyroid diseases. Front Immunol. 2017;8:396. doi: 10.3389/fimmu.2017.00396.

4. Zhang C, Qin L, Sun B, Wu Y, Zhong F, Wu L, et al. Transcriptome analysis of the effect of diosgenin on autoimmune thyroiditis in a rat model. Sci Rep. 2021;11(1):6401. doi:10.1038/s41598-021-85822-1.

5. Balázs C. Örökletes és környezeti tényezők szerepe autoimmun pajzsmirigybetegségekben [The role of hereditary and environmental factors in autoimmune thyroid diseases]. Orv Hetil. 2012;153(26):1013-22. Hungarian. doi: 10.1556/OH.2012.29370.

6. Ferrari SM, Fallahi P, Antonelli A, Benvenga S. Environmental issues in thyroid diseases. Front Endocrinol (Lausanne). 2017;8:50. doi: 10.3389/fendo.2017.00050.

7. Brent GA. Environmental exposures and autoimmune thyroid disease. Thyroid. 2010 ;20(7):755–61. doi: 10.1089/thy.2010.1636.

8. Weider T, Genoni A, Broccolo F, Paulsen TH, Dahl-Jørgensen K, Toniolo A, et al. High prevalence of common human viruses in thyroid tissue. Front Endocrinol. 2022;13:938633. doi:10.3389/fendo.2022.938633.

9. Kravchenko V, Zakharchenko T. Thyroid hormones and minerals in immunocorrection of disorders in autoimmune thyroid diseases. Front Endocrinol. 2023;14:1225494. doi:

10.3389/fendo.2023.1225494.

10. Maciejewski A, Kowalczyk MJ, Herman W, Czyżyk A, Kowalska M, Żaba R, et al. Vitamin D receptor gene polymorphisms and autoimmune thyroiditis: are they associated with disease occurrence and its features? Bio Med Res Int. 2019;2019:8197580. doi: 10.1155/2019/8197580

11. Shaikh AP, Shaikh NP, Irina N. VDR Gene SNPs in Gastrointestinal Tumors. JSM Gastroenterol Hepatol.2022; 9(2): 1111.

12. Apaydın M, Beysel S, Eyerci N, Pinarli FA, Ulubay M, Kizilgul M, et al. The VDR gene FokI polymorphism is associated with gestational diabetes mellitus in Turkish women. BMC Med Genet. 2019;20(1):82. doi: 10.1186/s12881-019-0820-0.

13. Albi E, Borrelli A, Cataldi S, Ceccarini M, Nakashidze I, Codini M et al. Protective effect of rMnSOD in mice exposed to cosmonaut simulation radiation:involvement of vitamin D receptor. J Biotechnol. 2019;305:S64. doi: 10.1016/j.jbiotec.2019.05.226.

14. Zhang R, Naughton DP. Vitamin D in health and disease: current perspectives. Nutr J. 2010;9:1-3. doi: 10.1186/1475-2891-9-65.

15. Bikle D. Nonclassic actions of vitamin D. J Clin Endocrinol Metab. 2009;94(1):26-34. doi: 10.1210/jc.2008-1454.

16. Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. J Immunol. 2007;179(3):1634–47. doi:10.4049/jimmunol.179.3.1634.

17. Kivity S, Agmon-Levin N, Zisappl M, Shapira Y, Nagy EV, Dankó K, et al. Vitamin D and autoimmune thyroid diseases. Cell Mol Immunol. 2011;8(3):243–7. doi:10.1038/cmi.2010.73.

18. Bozkurt NC, Karbek B, Ucan B, Sahin M, Cakal E, Ozbek M, et al. The association between severity of vitamin D deficiency and Hashimoto's thyroiditis. Endocr Pract. 2013;19(3):479–84. doi:10.4158/EP12376.OR.

19. Shin DY, Kim KJ, Kim D, Hwang S, Lee EJ. Low serum vitamin D is associated with anti-thyroid peroxidase antibody in autoimmune thyroiditis. Yonsei Med J. 2014;55(2):476–81. doi: 10.3349/ymj.2014.55.2.476.

20. Nakashidze I, Ahmad S. Genetic predisposition for pancreatic cancer. In: Ganji PN, Sarfraz A, editors.Theranostic approach for pancreatic cancer. Elsevier; 2019. p. 153–69. doi: 10.1016/B978-0-12-819457-7.00008-6

21. Shaikh AP, Khurana R, Shaikh NP, Barua JD, Ali A, Murvanidze I, et al. Peculiarities of some candidate gene polymorphisms in Parkinson's disease. Pomeranian J Life Sci. 2023;69(2):22-7. doi: 10.21164/pomjlifesci.893.

22. Nakashidze I, Dariya B, Peshkova T, Beridze S. The genetic polymorphisms in colon

cancer. Crit Rev Oncog. 2020;25(4):405–15. doi: 10.1615/CritRevOncog.2020035957.

23. Nakashidze I, Petrović N, Kedelidze N, Dariya B. Clinical significance of genetic variants in colon cancer. In: Shukla D, Vishvakarma NK, Nagaraju GP, editors. Colon cancer diagnosis and therapy Vol 3. Cham: Springer International Publishing; 2022. p. 69–91. Available from: https://link.springer.com/10.1007/978-3-030- 72702-4_4.

24. Ahi S, Dehdar MR, Hatami N. Vitamin D deficiency in non-autoimmune hypothyroidism: a case-control study. BMC Endocr Disord. 2020;20(1):41. doi:10.1186/s12902-020-0522-9.

25. Bizzaro G, Shoenfeld Y. Vitamin D and autoimmune thyroid diseases: facts and unresolved questions. Immunol Res. 2015 ;61(1–2):46–52. doi: 10.1007/s12026-014-8579-z

26. Kamyshna II, Pavlovych LB, Malyk IV, Kamyshnyi AM. 25-OH Vitamin D blood serum linkage with VDR gene polymorphism (rs2228570) in thyroid pathology patients in the West-Ukrainian population. J Med Life. 2021;14(4):549–56. doi: 10.25122/jml-2021-0101.

27. Djurovic J, Stojkovic O, Ozdemir O, Silan F, Akurut C, Todorovic J, et al. Association between FokI , ApaI, and TaqI RFLP polymorphisms in VDR gene and Hashimoto's thyroiditis: preliminary data from female patients in Serbia. Int J Immunogenet. 2015;42(3):190–4. doi: 10.1111/iji.12199.

28. Inoue N, Watanabe M, Ishido N, Katsumata Y, Kagawa T, Hidaka Y, et al. The functional polymorphisms of VDR, GC, and CYP2R1 are involved in the pathogenesis of autoimmune thyroid diseases. Clin Exp Immunol. 2014;178(2):262–9. doi: 10.1111/cei.12420.

29. Lin WY, Wan L, Tsai CH, Chen RH, Lee CC, Tsai FJ. Vitamin D receptor gene polymorphisms are associated with risk of Hashimoto's thyroiditis in Chinese patients in Taiwan. J Clin Lab Anal. 2006;20(3):109–12. doi: 10.1002/jcla.20110.

30. Zarrin R, Bagheri M, Mehdizadeh A, Ayremlou P, Faghfouri AH. The association of FokI and ApaI polymorphisms in vitamin D receptor gene with autoimmune thyroid diseases in the northwest of Iran. Med J Islam Repub Iran. 2018;32:4. doi:10.14196/mjiri.32.4.

31. Yazici D, Yavuz D, Tarcin O, Sancak S, Deyneli O, Akalin S. Vitamin D receptor gene ApaI, TaqI, FokI and BsmI polymorphisms in a group of Turkish patients with Hashimoto's thyroiditis. Minerva Endocrinol. 2013;38(2):195–201.

32. Hanna HWZ, Rizzo C, Abdel Halim RM, El Haddad HE, Salam R, El-Sayed Abou-Youssef H. Vitamin D status in Hashimoto's thyroiditis and its association with vitamin D receptor genetic variants. J Steroid Biochem Mol Biol. 2021;212:105922. doi: 10.1016/j.jsbmb.2021.105922

33 Majid WJ, Abulrazzaq AB, Al-Koofee DAF, Algenabi AHA, Omara AM. The possible role of vitamin D receptor gene polymorphisms and the risk of Hashimoto's thyroiditis: An Iraqi case-control

study. Hum Gene. 2024;39:201239. doi:10.1016/j.humgen.2023.201239 Available online 22 November 2023.

34. Gao XR, Yu YG. Meta-analysis of the association between vitamin D receptor polymorphisms and the risk of autoimmune thyroid disease. Int J Endocrinol. 2018;2018: 2846943. doi: 10.1155/2018/2846943.

35. Shaikh AP, Khurana R, Inaishvili M, Shaikh NP, Glonti S, Kedelidze N, et al. VDR FokI rs2228570 SNP in autoimmune thyroiditis. Transl Clin Med - Georgian Med J. 2022;7(4):10–3.

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