How to Cite:
Rradeef, S. T., & Mahdi, I. A. (2022). Recognition of interferon–induced helicase-1 gene polymorphism (rs1990760G/A) in patients with Hashimoto's thyroiditis. *International Journal of Health Sciences*, *6*(S4), 10506–10517.
https://doi.org/10.53730/ijhs.v6nS4.12217

Recognition of interferon–induced helicase-1 gene polymorphism (rs1990760G/A) in patients with Hashimoto's thyroiditis

Shahad Tareq Rradeef
Master Student, Faculty of Education for Girls, Department of chemistry, University of Kufa, An-Najaf, Iraq
Corresponding author email: ilhama.aljuburi@uokufa.edu.iq

Ilham Abed Mahdi
Faculty of Education for Girls, Department of chemistry, University of Kufa, An-Najaf, Iraq
Email: ilhama.aljuburi@uokufa.edu.iq

***Abstract*---**A case-control study was conducted on 100 females who diagnosed as Hashimoto's thyroiditis patients aged 32-62 years and 100 healthy volunteers who matched in age and gender with patients. Patients were attended to Al-Sader medical city in Al-Najaf Governorate, Iraq. All participants underwent medical examinations to make sure they were suffering from Hashimoto's thyroiditis. The TaqMan real-time- PCR method was applied to investigate the genotyping of The IFIH1 gene in addition to the levels of T3, T4, TSH, Anti TPO, and Anti-TG were determined by applying ELISA method by certain kit in all study groups individuals. Current study recorded that allelic and genotypic distributions of IFIH1 polymorphism at position rs1990760 G/A were not significantly different between control subjects and HT patients for the GA genotype (OR = 1.2, %95 CI: 0.57-2.30, P = 0.68), for the GA genotype. While for AA genotype (OR = 1.76, %95 CI: 0.78-3.9, P = 0.16). The same result was obtained when comparing healthy control and HT patients in the dominant, recessive, and additive models. Additionally, significant association of the IFIH1 polymorphism in codominant and dominant models with TPO and Anti-TG, and non-significant correlation with other biochemical features, Age, BMI, T3, T4, TSH, fT3, fT4. present research suggests that IFIH1 may has an endogenous role as a viral receptor, nonrelated to any specific immunoregulatory effect.

***Keywords*---**IFIH1, polymorphisms, Hashimoto's thyroiditis, autoimmune, thyroid disease.

Introduction

Hashimoto's thyroiditis (HT) is a thyroid autoimmune illness, that can cause hypothyroidism in which the immune system turns against thyroid glands, in another meaning, the immune system makes antibodies that attack the thyroid follicles, which resynthesize and store thyroid hormones in a large protein called thyroglobulin these antibodies included, anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO), which act as biochemical markers of HT illness(1)(2). TPO autoantibodies are discovered in more than 90% of HT patients, while (anti-TG) antibodies are found in around 80% of HT patients, with approximately 18% of them being older women. (3). In addition to anti-TPO are found in about 10% of females, while in other study indicate that disease incidence eight times higher in female than males especially in elderly women (4). Patients with Gravis disease, rheumatoid arthritis, pernicious anemia, gluten enteropathy, lupus illness are all examples of primary adrenal hypofunction, and type 1 diabetes are more susceptible to develop Hashimoto's thyroiditis.(5). Furthermore, many pathogenesis are linked to the interaction of hereditary and environmental variables(6) Additionally most prevalent cause of hypothyroidism is iodine deficiency; however, in areas where iodine usage is adequate,The most prevalent cause of hypothyroidism is HT. (7). T lymphocytes that are specific for thyroglobulin are created and sent to the thyroid glands, where they release cytokines such Interferon (IFN), which aids in the death of thyrocytes(8). At the early stages of Hashimoto's thyroiditis, the immune system attacks and destroys thyroid follicles, resulting in elevated or normal levels of triiodothyronine (T3) and thyroxine (T4) produced in peripheral blood as a result of destroyed thyroid gland cells, simulating a transient hyperthyroid state(9). Hashimoto's thyroiditis is inherited and can occur alone or in combination with Human leukocyte antigen-DR3 (HLA-DR3), HLA-DR5, and Cytotoxic T lymphocyte antigen-4 (CTLA-4) genes (10)(11). Thyroid autoimmunity has been related to a polymorphism in the , thyroglobulin gene, which codes for TG forms with various immunological activities(12). Genetic susceptibility to autoimmune thyroid disease had been well investigated and verified in twin and family investigations. The formation, progression, and severity of autoimmune thyroid disease have all been related to some genes(10). HLA, CTLA-4, PTPN type-22, VDR gene,TG gene, and cytokines such as interferon - induced helicase1 gene IFIH1, are all believed to have a role in the HT disease(13).

The interferon induced helicase1 (IFIH1) gene belongs to the Interferon (IFNs) family, it has a genetic immune responsive and is a ribonucleic acid (RNA) helicase gene. It plays a function in the immune system's innate response by identifying viral nucleic acid in the cytoplasm and targeting immunological mediator secretion of cells known as interferon's(14).The most recent evidence of genome-wide interaction that IFIH1 T gene is an important factor. combining of the environmental with genetic effectors in the development of multiple autoimmune illnesses have including, psoriasis, systemic lupus erythematous , Hashimoto’disese, type I diabetes mellitus, , and vitiligo(15).

Patients and Methods

Present study was applied on 100 females who were suffered from HT disease aged 32-67 years and 100 healthy volunteers matched in age and gender with patients. Patients were attended to Al-Sader medical city in Al-Najaf Governorate, Iraq. Participants from patients underwent medical examinations to make sure they were complaining from Hashimotos thyroiditis. The subjects who recorded were included in this investigated Inclusion requirements included, firstly all patients who had been previously or recently diagnosed by a physician as having autoimmune hypothyroidism (Hashimoto's thyroiditis, in addition to these patients, have all clinical signs and symptoms of Hashimoto's thyroiditis, secondly all patients have a high level of thyroid antigen tests (thyroid peroxidase and thyroglobulin).

Exclusion criteria included, thyroidectomy or under radioactive iodine treatment, non-thyroidal systemic disorders include acute and chronic hepatic, renal, cardiovascular, and cerebrovascular diseases, as well as benign and malignant tumor and patients with other autoimmune illnesses include rheumatoid arthritis, diabetes, systemic lupus erythematous (SLE), and celiac disease.

Method

A venous whole blood sample of five milliliters was taken from each of the participants in this study. The blood was separated into two parts and labeled as follows: 3 mL of blood was placed in a gel activator tube, then subjected to centrifuge for ten minutes at 3000 Xg and divide into small aliquots (0.5 mL) for measuring thyroid activity tests, anti-TPO and anti-TG antibodies. In K3-EDTA tubes, the remaining two milliliters of whole blood were collected for DNA extraction then, it was maintained frozen at 80 °C for IFIH1 (rs1990760) by applying RT PCR then the allelic discrimination assay was done by utilizing a TaqMan probe, Applied Alpha DNA (Canada). Promega also provided the primers, probes, and Master Mix (80). (USA). TaqMan chemistry employs a fluorogenic probe to detect a specific PCR product as it accumulates throughout PCR cycles. TaqMan® probes (quencher dye) and TaqMan® MGB probes. 0.2 µl Eppendorf tube in terms of overall volume of 25mL using 2µg of genomic g DNA and a qPCR Master Mix GoTaq® Probe. The tubes were then placed in a thermal cycler, and heated at 95 °C for 10 minutes, followed by 40 cycles of 95 °C for 15 seconds and 60 °C for 1 minute.

Statistical Analysis

The data was statistically handled and analyzed with MICROSOFT EXCEL 2010 and SPSS v. 26. (SPSS Inc., Chicago, IL, USA). Results were expressed as mean and standard deviation. Significant variations was estimated by using Chi-Squared (x2), t-test, R0 studio software was performed to assess the PCA. A P value less than 0.05 was taken into account lowest limit of significant.

Results

The current case-control study was applied on 200 females, 100 patients and 100 healthy female as a control group matched with patients in age and gender. The patients' ages ranged from 18 to 67 years old, with a mean of 38.40 ± 11.18) years. Control subjects ages ranged from 18 to 68 years old, with a mean age of of 39.25 ± 12.20 years, and illustrated a non-significant differences in age as shown Table 1. The p-values of body mass index (BMI) were calculated in patients with Hashimoto's thyroiditis and control groups, it was non-significant variation between both groups in the present study (P<0.45) and the mean ± SD was (30.21±5.32, and 29.75±5.70) respectively

Hashimoto's thyroiditis patients from two groups presenting with an aggressive form of hypothyroidism disease had significantly lower levels of T3, and T4, in addition to FT3 and FT4 (p<0.000) each other when compared with control who had normal values of these hormones. The outcomes showed a significant increase in TSH, Anti TPO, and AntiTG levels in Hashimoto's thyroiditis patients compared with healthy control as shown in Table (1).

In (figure 1)the frequency of the alleles of IFIH1 SNP re1990760 has mildly different, As it shows that the G allele is)0.455%) in groups of patients while it is ((0.515%) This means that the G allele is more prevalent in the control group than in the afflicted group. On the other hand, the A allele is (0.555%) in the patient group and (0.485%) within the control group That is, the A allele is more prevalent in the sick than in the controls.

Table 1. (Mean ± SD) of some characteristics and functional thyroid tests in Sera of Studied Groups

Item	Group No.	Mean ± SD	P Value
Age	Control (100) Patient (100)	38.4 ± 11.18 39.25 ± 12.20	0.313
BMI	Control (100) Patient (100)	30.21 ± 5.32 29.75 ± 5.70	0.45
T3	Control (100) Patient (100)	2.19 ± 0.41 1.47 ± 0.55	<0.0001
T4	Control (100) Patient (100)	103.16 ± 20.75 62.96 ± 27.70	<0.0001
TSH	Control (100) Patient (100)	2.66 ± 1 .15 35.96 ± 36.65	<0.0001
fT3	Control (100) Patient (100)	4.98 ±0 .62 3.48 ± 1.18	<0.0001
fT4	Control (100) Patient (100)	16.01 ± 7.58 9.94 ± 3.98	<0.0001
Anti TPO	Control (100) Patient (100)	13.13 ± 8.03 337.81 ± 172.94	<0.0001
Anti TG	Control (100) Patient (100)	29.96 ± 17 .53 1364.47 ± 1463.53	<0.0001

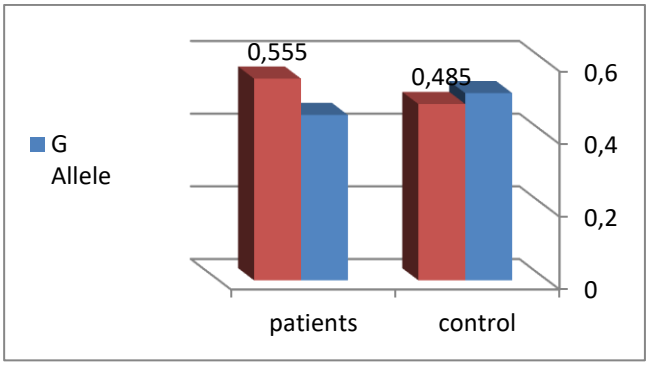

Figure 2. The percent frequency of G&A alleles in two groups according to the HWE of IFIH1 SNP rs1990760

Table 1. IFIH1 SNP rs1990760 (Ala946Thr) analysis of genotype of control according to the HWE

Genotype of Control	Observed	Expected	Difference	X^2	P Value
GG Reference	25	26.50	1.50%	0.337	0.45
GA Heterozygote	53	49.96	4.96%		
AA Recessive	22	23.54	1.54%		

The genotype frequencies of IFIH1 gene SNP rs1990760 (Ala946Thr) were came consistent with Hardy–Weinberg equilibrium in control subjectss as seen in (Table 2).

Table 3. IFIH1 SNP rs1990760 (Ala946Thr) analysis of genotype of HT patients according to the HWE

Genotype of Control	Observed	Expected	Difference	X^2	P Value
GG Reference	20	19.80	1.80%	0.006	0.94
GA Heterozygote	49	49.40	0.40%		
AA Recessive	31	30.80	1.80%		

Table 4. Genotype of IFIH1 SNP rs1990760 (Ala946Thr) in the studied groups of both control and HT patients

SNP IFIH1	Control N=100	Patients N=100	Crude OR (CI95%) P Value	Adjusted OR (CI95%) P Value
Codominant				
GG (Wild Type)	25	20	1	
GA	53	49	1.2 (0.57-2.30) 0.68	1.5 (0.95-1.01) 0.6

AA	22	31	1.76 (0.78-3.9) 0.16	1.7 (0.76-3.89) 0.19
Dominant				
GA+AA	75	80	1.3 (0.68-2.59) 0.39	1.4 (0.69-2.72) 0.36
Recessive GG+GA (Wild Type)	78	69	1	
AA	22	31	1.59 (0.84-3.00) 0.15	1.5 (0.78-2.88) 0.22
Additive 2GG+GA	103	89	----	
2AA+AG	97	111	1.3 (0.8937-1.9625) 0.162	

In the current study, the allelic and genotypic distributions of IFIH1 polymorphism at position rs1990760 G/A were not significantly different between control subjects and HT patients for the GA genotype (OR=1.2, %95 CI: 0.57-2.30, P=0.68) ; so there were not huge different in (OR=1.5, %95 CI: 0.95-1.01, P=0.6) after adjustment in age, sex and BMI. While for AA (OR=1.76, %95 CI: 0.78-3.9, P=0.16) and there were not find sense change in (OR= 1.7, %95 CI: 0.76-3.89, P=0.19) after adjustment in age, sex and BMI. The same result obtained when compared healthy control and HT patients in dominant, recessive and additive models which examined by multinomial logistic regression analysis show (Table 4) that appear no significant variations of all genotypes in all groups.

Finally (Table 5) shows the biochemical characteristics of subjects with HT which studied according to the IFIH1 gene rs1990760 G/A genotype. The biochemical features of (Age, BMI, T3, T4, TSH, fT3, fT4, TPO, Anti-TG) of relative to Codominant model of IFIH1gene SNP (rs1990760) which were studied by ANOVA test (table 5), while (Table 6) demonstrate that dominant model were examined by t- test. Results in (Table 5) demonstrate a significant association of Codominant model of IFIH1gene SNP (rs1990760) only with TPO and Anti-TG ($p< 0.01$, $p < 0.05$) respectively, the same result obtained in dominant model of IFIH1gene SNP (rs1990760) shows non-significant association with biochemical features that studied, Age, BMI, T3, T4, TSH, fT3, fT4 except TPO and Anti-TG which recorded significant P value ($p< 0.01$, $p < 0.02$) show (Table 6).

Table 5. Clinical distinctive of patient groups in proportion IFIH1 gene polymorphism SNP rs1990760 genotype (Codominant model)

Clinical parameter	GG N=20	GA N=49	AA N=31	P value
Age	39.55 ± 13.11	37.1 ± 10.7	41.6 ± 13.1	<0.25
BMI	30.3 ± 2.69	28.7 ± 6.88	30.9 ± 4.89	<0.22
T3	1.2 ± 0.43	1.5 ± 0.56	1.5 ± 0.61	<0.18
T4	59.5 ± 29.88	63.2 ± 26.2	64.7 ± 29.4	<0.81

TSH	42.5 ± 9.5	36.74 ± 5.22	30.5 ± 5.96	<0.5
fT3	3.0 ± 1.3	3.5 ± 1.2	3.6 ± 1.1	<0.17
fT4	9.4 ± 4.93	9.8 ± 3.86	10.4 ± 3.58	<0.7
TPO	257.36 ± 169.7	310.5 ± 171.9	366.34 ± 166.3	<0.01
Anti-TG	2033.65 ± 359.7	1291.3 ± 210.79	1048 ± 229.51	<0.05

Table 6. Clinical distinctive of patient groups in proportion IFIH1 gene polymorphism SNP rs1990760 genotype in (dominant model)

Clinical parameter	GG N=20	GA+AA N=80	P value
Age	39.55 ± 13.11	38.88 ±1 1.8	<0.81
BMI	30.31 ± 2.669	29.62 ±6.24	<0.69
T3	1.27 ± 0.09	1.52 ± 0.06	<0.70
T4	59.55 ± 29.87	63.82 ± 27.27	<0.54
TSH	42.51 ± 10.5	34.32 ± 6.4	<0.37
fT3	3.04 ± 1.32	3.59 ± 1.13	<0.06
fT4	9.45 ± 4.9	10.07 ± 3.7	<0.53
TPO	257.36 ± 169.96	357.92 ± 168.84	<0.01
Anti-TG	2033.65 ± 1599.86	1197.18±1302.1	<0.02

Figure (2) Anthropometric and clinical factors are represented as arrows, with longer ones indicating a greater impact on separation.

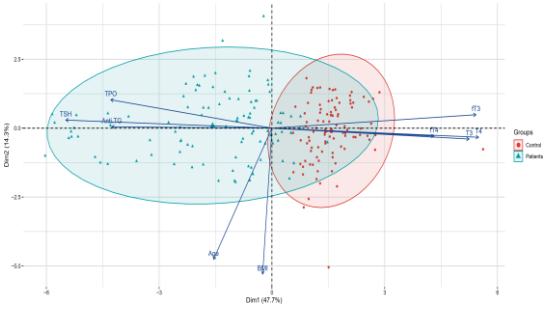

Figure 2. Principal component assay (PCA) is used to evaluate the data. Multivariate examination revealed study clustering population is divided into two groups: The blue zone dimension (controls) and the red zone dimension (patients) Dimensions 1 (Dim1) and 2 (Dim2) accounted for 47.7% and 14.3% of the

variance, respectively, in PCA, the clinical and anthropometric characteristics are written as arrows. Abbreviations: BM: Body mass index; Age ;T3; T4; TSH; fT3; fT4; Anti TG; and Anti TPO.

Discussions

Interferon induced with helicase C domain 1 (IFIH1), also known as Helicard or melanoma differentiation-associated gene 5 (MDA-5), is a protein that helps the body's immune system fight viruses, IFIH1 could trigger IFN-/ and interferon-inducible genes to regulate the production of type I IFN and different proinflammatory cytokines by activating transcription factors such as IRF3, IRF7, and NF-B(Erna Domsgen1,*, Katharina Lind1,*, Lingjia Kong2, Michael H. Hühn1,†, Omid Rasool2, Frank van Kuppeveld3, Olle Korsgren4, Riitta Lahesmaa2 & Malin Flodström-Tullberg1, 2016). IFIH1 is a member of the RNA helicase family that binds viral RNA (Alejandra RODRÍGUEZ et al., 2014)(Looney et al., 2015). Recent research suggests that a number of genes implicated in inflammation reactions may be able to change their function and expression. (Loza et al., 2007). Previous investigations found The development of autoimmune disorders and viral infection may have a biological foundation, which genetic variants of IFIH1 support(Knip, 2005). IFIH1 genotyping could result in aberrant activation of antiviral defense signaling pathways, resulting to the emergence of autoimmune illness. such as in HT body substance and cell-mediated thyroid injury end up in the destruction of thyroid cells and hypothyroidism as a consequence.

Previous GWAS on IFIH1 found a link between a few SNPs in this gene and the likelihood of developing autoimmune disorders such as type 1 diabetes (T1DM), multiple sclerosis, psoriasis, selective IgA deficiency, dilated cardiomyopathy, and SLE(21)(20), and auto immune thyroid disease (AITD). previous studies according to our knowledge for connection between the IFIH1 rs1990760 polymorphism and the HT disease so in this direction there were very few researches for citation, also the evidence for a connection between this SNP and a variety of autoimmune diseases is conflicting and indeterminate so that a meta-analysis was performed to better assessment the relationship between the IFIH1 rs1990760 polymorphism and other autoimmune disease prevalence. PubMed, Web of Science, and a study of the references were used to check for studies that looked at the IFIH1 rs1990760 polymorphism's connection to other autoimmune diseases. This meta-analysis included 19 studies with 26 associations, including 8 type 1 diabetes mellitus (T1DM), 5 systemic lupus erythematous (SLE), 5 Graves' disease (GD), 2 multiple sclerosis (MS), 2 rheumatoid arthritis (RA), and 2 autoimmune addison's disease (AAD). So The variation in the gene relates to changes in IFIH1 expression between individuals and may affect the research of illness causes with an increased risk of numerous autoimmune diseases(22).

In the current study, the outcomes did not give significant differences in allele or genotype frequencies for the rs1990760 SNP between Hashimotos thyroiditis patients and control subjects. In addition, there was no significant difference between cases and controls concerning IFIH1 genotype distribution with a predominance of GA and AA genotypes in studied cases. Indeed, there was a mild difference between cases and controls regarding IFIH1 alleles 51.5% had a G

allele while 48.5% had an A allele .While, in controls, 45.5% had a G allele while 55.5% of cases had an A allele. As well as, IFIH1 rs1990760 AA genotype carriers had higher serum levels of Anti-TPO ($P < 0.01$) and Anti-TG ($P < 0.05$) than GG and GA genotype carriers.

Present data are in agreement with other studies conducted by Ban. Y (23)this result revealed no significant alteration in IFIH1 polymorphism autoimmune thyroid disease patients, so in the case of HT, patients rs1990760 A alleles were more frequent in patients compared to healthy subjects (65% vs. 42%). P-value=0.086 with OR=2.47 and 95% CI for OR: 0.9–7.5, which means that the risk for development of HT is nearly two and a half times higher for the A allele in comparison to the G allele(24). In contrast other study carried out on systemic Lupus Erythroditis (SLE) disease, which identified a Significant associations were observed between alleles of IFIH1 (rs1990760 G > A, P = 0.005, OR = 1.36, 95%CI = 1.10–1.69; rs3747517 A> G, P = 0.004, OR = 1.31, 95%CI = 1.09–1.58, respectively) and SLE disease susceptibility(25).

The differences could be related to a decrease in the number of observations in some categories, or they could represent actual sensitive subgroups. In addition, Boca's, et al(26) . The relationship of the common missense polymorphisms, rs1990760 (G/A), has been confirmed with type 1 diabetes mellitus. Magdalena Żuraweket al.(27) Established that IFIH1 is an autoimmunity locus, increasing its role in type 1 diabetes mellitus susceptibility to Graves' and HT illness, and discovered that the Ala946Thr IFIH1 polymorphism of SNP rs1990760 is strongly linked to organ-specific autoimmune disorders including Graves' and HT disease.
Although the mechanisms through which IFIH1 polymorphisms contribute to HT pathogenesis are unknown, the IFIH1 gene locus clearly plays a role in susceptibility to all autoimmune thyroid diseases, including HT. Although additional research is needed, a single point mutation at the IFIH1 gene, rs1990760, may be a risk factor for HT susceptibility. In addition, IFIH1 is a promising gene candidate for autoimmune thyroid illness. Several research conducted in different populations reveal that more than one IFIH1 polymorphism is associated to this condition, which means that not only does the rs1990760 polymorphism affect HT susceptibility, but there are many additional polymorphisms that are more effective on HT susceptibility. Future research is needed to explain the molecular mechanisms underlying the link between these SNPs and HT and other autoimmune disorders. As a result, understanding the factors that contribute to the development of autoimmune thyroid diseases may aid in the research of their etiology and may lead to more effective methods of treating and preventing autoimmune thyroid illnesses, including the condition. The finding of the strong association of IFIH1 alleles with GD, a condition with no established link to viral infection, suggests that IFIH1 might have an specific role as a viral receptor, unrelated to any endogenous immunoregulatory effect.

In conclusion, current findings identified that fact, there is no association between rs1990760 SNP of the IFIH1 gene and the development of HT disease in the present study population, with the limitation of the present small sample size, the additionally present research suggests that IFIH1 may have an endogenous immunoregulatory effect, nonrelated to any specific role as a viral receptor.

Finally, more new and powerful research is needed to explain the role of IFIH1gene in AITD including HT disease.

Conclusion

In conclusion, despite the small sample size, IFIH1 polymorphisms rs1990760 were not associated with HT illness susceptibility in the current study patients, additionally present research suggests that IFIH1 maybe have an endogenous role as a viral receptor, nonrelated to any specific immunoregulatory effect .

Abbreviations

IFN : Interferon, TSH : Thyroid stimulating hormone ,TSHR:TSH receptor, HT : Hashimoto thyroiditis, AITD: Auto immune disease, IFIH1: Interferon-induced helicase-1, T3: Triiodothyronine, T4:Thyroxine , Anti TPO: Thyroid peroxidase anti gene ,Anti TG: Thyroglobulin anti gene ,fT3: Free T3, fT4:Free T4 , HT: Hashimoto's thyroiditis, (CTLA-4) genes: Cytotoxic T lymphocyte antigen-4, HLA : Human leukocyte antigens, PTPN type-22: protein tyrosine phosphatase non-receptor type22, VDR : Vitamin D receptor, TG gene: Thyroglobulin gene, SLE Systemic lupus erythematous, BMI: Body mass index , IRF3 :Interferon Regulatory Factor 3,IRF7: Interferon Regulatory Factor7, NF-κB :Nuclear factor kappa B, GWAS: Genome-wide association studies ,AITD: Auto immune thyroid disease, T1DM :Type 1 diabetes mellitus, SLE :Systemic lupus erythematous, GD: Graves' disease , MS: Multiple sclerosis, RA :Rheumatoid arthritis, AAD: Autoimmune Addison's disease, PCA: Principal component assay.

Consent to Participate
Everyone who took part completed a written informed consent document.

Conflict of Interest
The authors have no conflicts of interest regarding this investigation.

References

Alejandra RODRÍGUEZ, 1, Juan Manuel ALFARO, 1, 2 Vital BALTHAZAR1, 2 and, & Nicolás PINEDA TRUJILLO1 1. (2014). Association analysis of PTPN22, CTLA4 and IFIH1 genes with type 1 diabetes in Colombian families Alejandra.

Bouças, A P; Brondani, L A; Souza, B. M. et. al. (2013). The A allele of the rs1990760 Polymorphism in the IFIH1 gene is associated with protection for arterial hypertension in type 1 diabetic patients and with expression of this gene in human mononuclear cells. PLoS ONE, 8(12).

Delamater, A. M., de Wit, M., McDarby, V., Malik, J. A., Hilliard, M. E., Northam, E., & Acerini, C. L. (2018). ISPAD Clinical Practice Consensus Guidelines 2018: Psychological care of children and adolescents with type 1 diabetes. Pediatric Diabetes, 19, 237–249.

Erna Domsgen1,*, Katharina Lind1,*, Lingjia Kong2, Michael H. Hühn1,†, Omid Rasool2, Frank van Kuppeveld3, Olle Korsgren4, Riitta Lahesmaa2 & Malin Flodström-Tullberg1, 5. (2016). An IFIH1 gene polymorphism associated with risk for autoimmunity regulates canonical antiviral defence pathways in Coxsackievirus infected human pancreatic islets.

Fathima, N., Narne, P., & Ishaq, M. (2019). Association and gene–gene interaction analyses for polymorphic variants in CTLA-4 and FOXP3 genes: role in susceptibility to autoimmune thyroid disease. Endocrine, 64(3), 591–604.

Frommer, L., & Kahaly, G. J. (2021). Type 1 Diabetes and Autoimmune Thyroid Disease—The Genetic Link. Frontiers in Endocrinology, 12(March), 1–15.

Harding1, J. L., & Meda E. Pavkov1 & Dianna J. Magliano2, 3 & Jonathan E. Shaw2 & Edward W. Gregg1, & Received: (2018). Global trends in diabetes complications: a review of current evidence Jessica.

Hasham, A., & Tomer, Y. (2012). Genetic and epigenetic mechanisms in thyroid autoimmunity. Immunologic Research, 54(1–3), 204–213.

Inaba, H., Ariyasu, H., Takeshima, K., Iwakura, H., & Akamizu, T. (2019). Comprehensive research on thyroid diseases associated with autoimmunity: Autoimmune thyroid diseases, thyroid diseases during immune-checkpoint inhibitors therapy, and immunoglobulin-G4-associated thyroid diseases. Endocrine Journal, 66(10), 843–852.

Junlong Zhang, Xinle Liu, Yanming Meng, Hengxu Wu, Yongkang Wu, B. Y. & L. W. (2018). Autoimmune disease associated IFIH1 single nucleotide polymorphism related with IL-18 serum levels in Chinese systemic lupus erythematosus patientsf.

Knezevic, J., Starchl, C., Berisha, A. T., & Amrein, K. (2020). Thyroid-gut-axis: How does the microbiota influence thyroid function? Nutrients, 12(6), 1–16.

Knip, M. M. V. F. R. V. H. (2005). Environmental_Triggers_and_Determinants_of_Type_1_.pdf.

Looney, B. M., Xia, C. Q., Concannon, P., Ostrov, D. A., & Clare-Salzler, M. J. (2015). Effects of Type 1 Diabetes-Associated IFIH1 Polymorphisms on MDA5 Function and Expression. Current Diabetes Reports, 15(11), 1–11.

Loza, M. J., McCall, C. E., Li, L., Isaacs, W. B., Xu, J., & Chang, B. L. (2007). Assembly of inflammation-related genes for pathway-focused genetic analysis. In PLoS ONE (Vol. 2, Issue 10).

Ma, W. T., Chang, C., Gershwin, M. E., & Lian, Z. X. (2017). Development of autoantibodies precedes clinical manifestations of autoimmune diseases: A comprehensive review. Journal of Autoimmunity, 83, 95–112.

Malikov, D. M. (2017). Traditional Chinese Medicine Approach to Hypothyroidism. International Journal of Complementary & Alternative Medicine, 5(1).

Ostrózka-Cieślik, A., & Dolińska, B. (2020). The role of hormones and trophic factors as components of preservation solutions in protection of renal function before transplantation: A review of the literature. Molecules, 25(9). https://doi.org/10.3390/molecules25092185

Parmin, P., Suarayasa, K., & Wandira, B. A. (2020). Relationship between quality of service with patient loyality at general polyclinic of kamonji public health center. *International Journal of Health & Medical Sciences*, *3*(1), 86-91. https://doi.org/10.31295/ijhms.v3n1.157

Pyzik, A., Grywalska, E., Matyjaszek-Matuszek, B., & Roliński, J. (2015). Immune disorders in Hashimoto's thyroiditis: What do we know so far? Journal of Immunology Research, 2015.

Ragusa, F., Fallahi, P., Elia, G., Gonnella, D., Paparo, S. R., Giusti, C., Churilov, L. P., Ferrari, S. M., & Antonelli, A. (2019). Hashimotos' thyroiditis: Epidemiology, pathogenesis, clinic and therapy. Best Practice and Research: Clinical Endocrinology and Metabolism, 33(6), 101367.

Rydzewska, M., Góralczyk, A., Gościk, J., Wawrusiewicz-Kurylonek, N., Bossowska, A., Krętowski, A., & Bossowski, A. (2018). Analysis of chosen polymorphisms rs2476601 a/G–PTPN22, rs1990760 C/T–IFIH1, rs179247 a/G–TSHR in pathogenesis of autoimmune thyroid diseases in children. In Autoimmunity (Vol. 51, Issue 4, pp. 183–190).

Sibarani, R. P. (2009). Genetics of Graves' disease: the lost concept. Acta Medica Indonesiana, 41(1), 37–40.

Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2022). Post-pandemic health and its sustainability: Educational situation. *International Journal of Health Sciences*, *6*(1), i-v. https://doi.org/10.53730/ijhs.v6n1.5949

Wegiel, M., Antosz, A., Gieburowska, J., Szeliga, K., Hankus, M., Grzybowska-Chlebowczyk, U., Wiecek, S., Malecka-Tendera, E., & Gawlik, A. (2019). Autoimmunity predisposition in girls with turner syndrome. Frontiers in Endocrinology, 10(July), 1–6.

Y. Ban 1 , T. Tozaki 2 , M. Taniyama 3 , Y. Nakano 2 , Y. Ban 4, T. H. (2009). Genomic Polymorphism in the Interferon-induced Helicase (IFIH1) Gene does not Confer Susceptibility to Autoimmune Thyroid Disease in the Japanese Population.

Ye, B. S., Leung, A. O. W., & Wong, M. H. (2017). The association of environmental toxicants and autism spectrum disorders in children. Environmental Pollution, 227, 234–242.

Żurawek1, M., , Marta Fichna1, 2, Danuta Januszkiewicz1, 3, P. F., & Jerzy Nowak. (2012). Polymorphisms in the Interferon-Induced Helicase (IFIH1) locus and susceptibility to Addison`s disease.