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Impact of Interleukin-18 Genetic Polymorphisms on the Susceptibility to Hashimoto's Thyroiditis in Iraqi Patients

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ABSTRACT

Background & Objective: Hashimoto's Thyroiditis (HT) is one of the prevalent autoimmune thyroid disorders. This disease is characterized by chronic lymphocytic infiltration and progressive thyroid tissue destruction. The development of HT is influenced by the complex interplay between immunological and genetic factors. This study aimed to investigate the association between gene polymorphisms of Interleukin-18 (IL-18), a pro-inflammatory cytokines, and susceptibility to HT in Iraqi population. In particular, three single nucleotide polymorphisms (SNPs): (rs1946518, rs187238, and rs1946519) were examined and analyzed to enhance the understanding of the genetic contribution of IL-18 polymorphisms to HT pathogenesis, thereby supporting the improvement of early diagnosis, treatment, and prevention strategies.

Materials & Methods: The total number of participants included in this study was 100. The patients who were diagnosed with HT were 50 and the healthy were 50 representing the control group. The study was conducted using standard molecular biology methods including genotyping of the samples via sequencing techniques. Statistical methods were subsequently applied to analyze the results of the distribution of alleles and genotypes.

Results: We observed no significant difference in the genotype or allele frequency of rs1946518 between HT patients and healthy controls. The results of rs187238 demonstrate no genetic variation in the study population: all samples exhibited the homozygous wild-type genotype, suggesting that this SNP may not be polymorphic in the Iraqi population. Similarly, rs1946519 displayed no significant differences among the patient and control groups.

Conclusion: In conclusion, the examined IL-18 gene polymorphisms showed a non-significant correlation with HT in the observed Iraqi samples. It is recommended to continue the research on this topic with larger sample sizes and include more diverse groups.

Keywords: Interleukin-18, Hashimoto's Thyroiditis, Autoimmune Disease, Thyroid Gland, Gene Polymorphism

1. Introduction

Hashimoto's thyroiditis (HT) is a chronic autoimmune disorder with heredity predisposition and recognized globally as a leading cause of hypothyroidism (1, 2). It is also known as chronic autoimmune thyroiditis or lymphocytic thyroiditis (3). HT is an endocrine disorder that affect 1–2% of the global population (4). The condition's incidence increases with age, predominantly occurring among the middle-aged people between 30 and 60 years old, furthermore, and females exhibit a 8- to 15-fold higher rate of HT compared to males (5).

Since HT is an autoimmune disease (6), it's defined as medical condition in which the antibodies that are naturally produced by the body to function as protectors against foreign substances as part of the immune system, it starts targeting the thyroid cells, this attack causes inflammation and disruption in the thyroid. Consequently, the thyroid gland is unable to fulfill its function which leads to decreasing in the amount of secreted hormones production over time (7).

These hormones play a vital roles in the body's metabolic processes and its deficiency due to HT can

result clinical symptoms, including; increased body weight, coldness, pale skin, fertility issues, birth defect and in rare cases of uncontrolled hypothyroidism it might lead to death (8, 9). This autoimmune destruction in the thyroid, is correlated between HT and the presence of abnormal levels of antithyroid antibodies (anti-TAbs), specifically antibodies against thyroid peroxidase (TPOAbs) and thyroglobulin antibodies (TgAbs) (10). Serological tests showed that approximately 90% of patients with autoimmune thyroiditis test positive for TPOAbs and TgAbs (11, 12). These specific autoantibodies alongside the circulating T cell population abnormalities and a goiter with lymphocytic infiltration, represent the hallmarks of HT (13).

The cytokines play a significant role in the regulation of the immune system, thus, in autoimmune conditions, such as HT, the dysfunction of certain cytokines, specifically the pro inflammatory one can activate the immune system to target and attack the thyroid gland (14).

Interleukin-18 (IL-18) is one of these pro-inflammatory cytokines, which play an effective role in the host defense mechanisms against infections, also, regulates the innate and adaptive immune responses. Thus, IL-18 could potentially perform a potent role in the developing of autoimmune diseases since it has the ability to induce inflammatory responses and cytotoxic activities of immune cells (15).

In the consideration of the IL-18 importance in immune responses, IL-18 might play a key role in the pathology of HT. IL-18 expression in thyroid follicular cells which is associated with lymphocytic infiltration has been shown in thyroid gland in HT patients, suggesting that IL-18 could act as secreted immune-modulator in HT (16).

Cytokines and cytokine receptor genes have long been considered potential contributors to autoimmune diseases (17). The purpose of this study is to investigate the correlation between the main interleukin-18 gene polymorphisms and the risk of developing HT disease in Iraqi population. The findings might help to clarify the protentional role of IL-18 in the disease's pathogenesis and to identify any genetic markers that might have a role in early diagnosis, treatment, patient's management or prevention of the disease.

2. Materials and Methods

2.1 Blood collection

The study included 100 subjects (50 samples represent the patients and 50 samples represent the controls) with the age range between 20-75 years old. Venous blood samples were collected from each one of the patients and the controls under aseptic conditions. The collected blood was divided into two portions: One part of the blood was placed into a gel tube for serum collection which was separated through the centrifugation at 5000 rpm for 10 minutes for the estimation of the hormonal and immunological assays. While the remaining of blood was placed in EDTA tube to be used in DNA extraction for molecular tests (18).

2.2 DNA Extraction

For the extraction of genomic DNA from whole blood, the gSYNC™ DNA Extraction Kit (Taiwan, Geneaid) is an optimized method. According to the manufacturer's instructions, the protocol involves the usage of Proteinase K and chaotropic salts for cell lysis and degradation of proteins. Next, the DNA is binding to the glass fiber matrix of the GS spin column, all the contaminants are removed by the addition of Wash Buffers. Finally, The Elution step of purified genomic DNA via Elution Buffer. The yield of purified genomic DNA via this extraction method is suitable for the following downstream applications (19).

For the measurement of the concentration and purity of the extracted genomic DNA, NanoDrop spectro-photometer 2000 (USA, Thermo) was used at 260-280 nm. The Concentrations and purity of DNA is automatically calculated from its measured absorbance values at the desired wavelength. The DNA purity ranges between 1.7 and 1.8 while the concentration ranges between 10 and 75 ng/µ (20).

2.3 Polymerase Chain Reaction (PCR)

PCR is a molecular technique used to amplify a specific sequence of DNA by producing several copies of a DNA template. This process is based on repeated heating and cooling cycles of the DNA samples, known as thermal cycling, it was performed using Gradient thermal cycler (China, Bio-Gener). PCR consists of three main phases: Denaturation, Annealing and Extension. These phases were repeated 30-40 times to amplify the targeted DNA sequence. In Table 1, the used primers for IL-18 gene receptor in this study are listed. In the PCR tube, 12.5 µl of Master Mix, 1 µl of each primer, 6 µl of DNA sample and 4.5 µl of nuclease-free water were added to the reaction mixture (25 µl). Table 2 provides an overview of the PCR protocol. The PCR findings were detected by 1.5% agarose gel electrophoresis technique, then placed under UV light to visualize the DNA bands (21).

2.4 Sequencing

After the visualizing of DNA bands under the UV light, it was excised from the agarose gel and purified using the GenepHlow™ Gel/PCR Kit (Tiawan, Geneaid). The sequencing technique was conducted based on Sanger chain termination method via capillary electrophoresis using the genetic analyzer Classic116 (China, Superyears) and after the recording and analyzing of the signals, the sequence of DNA is determined (22).

2.5 Statistical Analysis

The Statistical Packages of Social Sciences -SPSS (2019) program was applied on the results of the samples to analyze which included the use of T-test to significantly compare between means. Chi-square test was used to significantly compare between percentage (0.05 and 0.01

probability) in this study to calculate the distribution of genotypes and allele frequency.

Table 1. Primer sequence used for PCR.

	Sequence (5'-3')	Product Size
Forward Primer	GCCACCTTGCTAATTCCCTT	1082 pb
Reverse Primer	TTTAGCAGCCAGAGTTGGCA	

Table 2. Protocol used in PCR amplification.

Step	Temp (°C)	Time	No. of cycle
Initial Denaturation	95	5:00 min	1 Cycle
Denaturation	95	0:30 sec	
Annealing	65	0:30 sec	35 Cycles
Extension	72	1:00 min	
Final Extension	72	3:00 min	1 Cycle

3. Result

3.1 PCR Product

The result of the detection of the PCR product via gel electrophoresis which contained clear DNA bands under the UV light as shown in figure 1. Based on the size of PCR product, which was 1082 bp, the band was detected contains the SNPs for IL-18, rs1946518, rs1946519 and rs187238.

3.2 Statistical Tests of Sequencing

As for the results of the sequencing of the samples, after it was analyzed with statistical tests, it was established in the Table 3, it included the T-test, Chi-square test and the calculation of the distribution of genotypes and allele frequency.

Table 3. The Genotype distribution and allele frequency of rs1946518 and rs1946519 in patients and control.

rs1946518					
Genotype/ rs1946518	**Patients No. (%)**	**Control No. (%)**	**Chi-Square**	**P-value**	**O.R. (C.I)**
TT	2 (6.67%)	4 (13.33%)	0.333 NS	0.563	Ref.=1
TG	18 (60.00%)	12 (40.00%)	0.600 NS	0.438	0.407 (0.28-0.91)
GG	10 (33.33%)	14 (46.67%)	0.333 NS	0.563	0.294 (0.16-0.67)
Total	30	30		---	
Allele	**Frequency**			---	
T	22 (0.37)	20 (0.33)		P-value= 0.827 NS	
G	38 (0.63)	40 (0.66)		P-value= 0.873 NS	

NS: Non-Significant.

rs1946519					
Genotype/ rs1946519	**Patients No. (%)**	**Control No. (%)**	**Chi-Square**	**P-value**	**O.R. (C.I)**
AA	0 (0.00%)	4 (13.33%)	0.873 NS	0.169	Ref.=1
AC	24 (80.00%)	18 (60.00%)	0.428 NS	0.512	0.502 (0.27-0.84)
CC	6 (20.00%)	8 (26.67%)	0.142 NS	0.705	0.366 (0.21-0.72)
Total	30	30		---	
Allele	**Frequency**			---	
A	24 (0.40)	26 (0.43)		P-value= 0.841 NS	
C	36 (0.60)	34 (0.57)		P-value= 0.865 NS	

NS: Non-Significant.

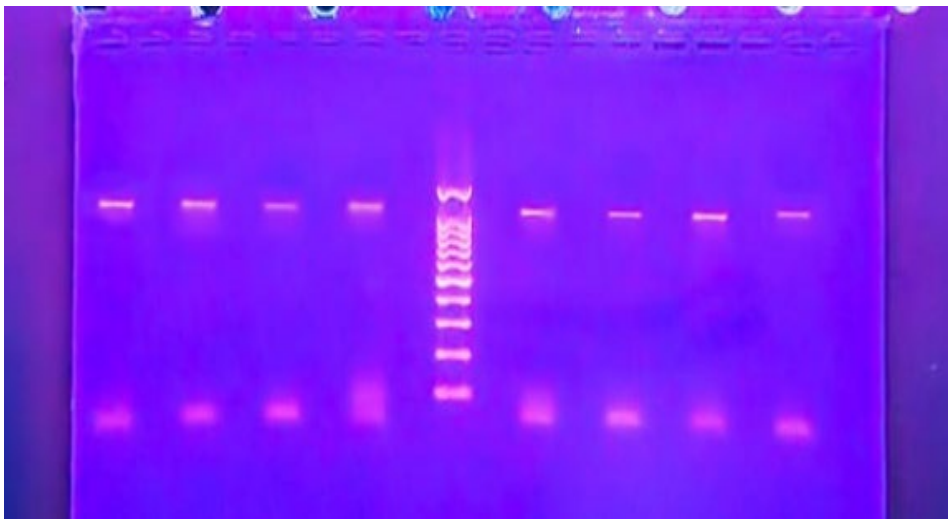

Figure 1. Amplified DNA fragment of the interleukin-18 receptor gene for rs1946518, rs1946519 and rs187238 on 1.5% concentration of agarose gel with DNA ladder 100bp (**Prepared by Authors, 2025**).

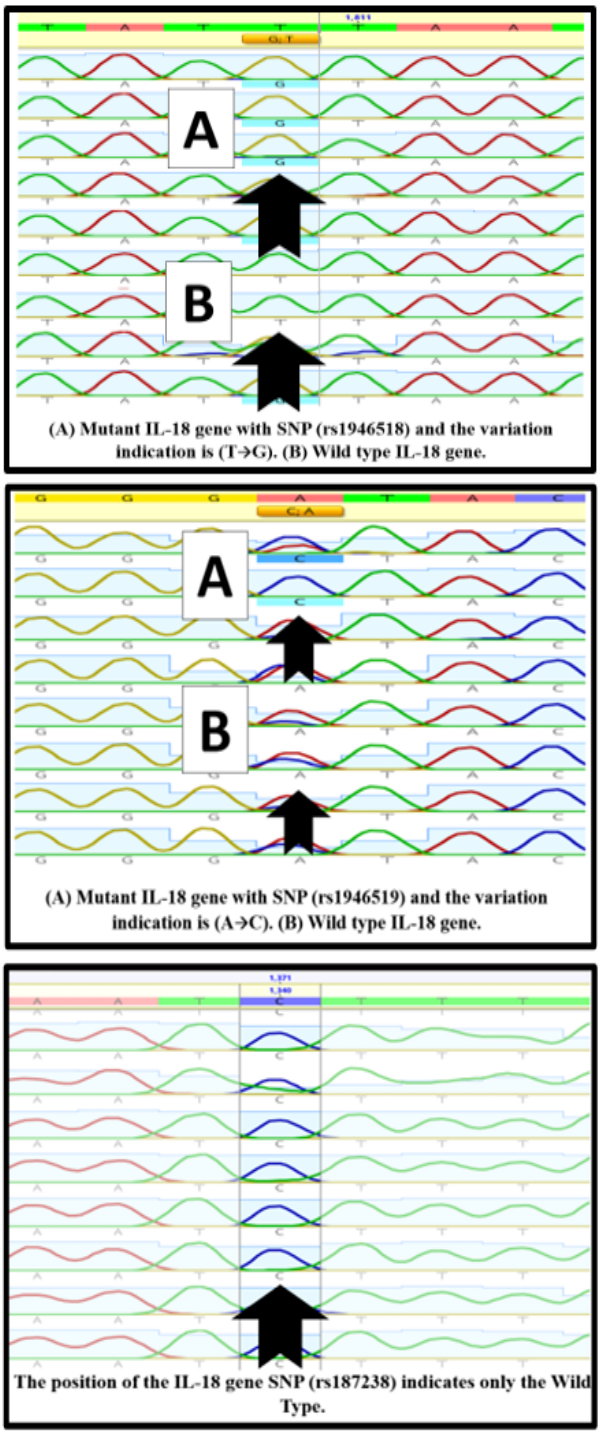

Figure 1. Sequencing of IL-18 gene polymorphisms (rs1946518, rs187238 and rs1946519) compared with wild type of IL-18 gene in the patients of Hashimoto's Thyroiditis. (**Prepared by Authors, 2025**).

4. Discussions

The present study examined the associations between IL-18 gene polymorphism and susceptibility to HT in an Iraqi population. The analysis was done by comparing the frequency of distribution of the genotypes between the patients with HT and healthy individuals. Statistical tests were applied using chi-square test to calculate P-value for each of the genotypes. The findings of this study were documented in table 3, which revealed that the distribution of the examined IL-18 polymorphisms' genotypic and allelic frequencies did not show a significant difference.

For the rs1946518, the homozygous genotype (TT) was 6.67% in HT and 13.33% in controls while the statistical values of this genotype were ($\chi 2$= 0.333, P value=0.563) and it was used as reference genotype (TT Ref.=1). For

the results of the mutant homozygous (GG) and the mutant heterozygous (TG) in HT patients, it was 33.33% and 60% respectively while the control results were 46.67% and 40% respectively while the statistical values of (GG) were ($\chi2$= 0.333, P value=0.563, O.R=0.407 at 95% C.I = 0.28-0.91) and the statistical values of (TG) were ($\chi2$= 0.600, P value=0.438, , O.R=0.294 at 95% C.I = 0.16-0.67). For the allele frequency in both groups there was no significant difference reported ($P_{\text{allele T}}$ = 0.827, $P_{\text{allele G}}$= 0.873). Notably all the P-values were higher than 0.05, which implies that none of the genotypes express a significant association with the risk of developing HT in the samples.

While rs187238 did not show any noticeable variation in the investigated samples, both the HT patients and the healthy subjects were homozygous (CC) which is the wild genotype, neither one of the mutant genotypes were found in any of the samples, based on this, all the statistical tests including chi-square, odds ratio and allele frequency cannot be determined to this SNP, since there was no polymorphism to examine. The absence of rs187238 variation may suggest that this SNP is not polymorphic in the Iraqi population which was examined in this study, or the variant is occurring at low frequency that was not detectable in this sample size, which may indicate that this SNP is not likely to be associated with the susceptibility of HT disease in this study.

Originally, this study was designed to examine the polymorphism of the SNPs rs1946518 and rs187238 and their susceptibility to HT. However, an additional SNP was detected, rs1946519, this gave the opportunity to explore more of the genetic susceptibility of HT. The findings of rs1946519 indicated that the homozygous genotype (AA) was not observed in HT patients 0% and 13.33% in controls while the statistical values of this genotype were ($\chi2$= 0.873, P value=0.169) and it was used as reference genotype (AA Ref.=1). The mutant homozygous (CC) and the mutant heterozygous (AC) in HT patients, 20% and 80% respectively while the controls results were 26.67% and 60% respectively while the statistical values of (CC) were ($\chi2$= 0.142, P value=0.705, O.R=0.366 at 95% C.I = 0.21-0.72) and the statistical values of (AC) were ($\chi2$= 0.428, P value=0.512, O.R=0.502 at 95% C.I= 0.27-0.84). However, for the allele frequency, both of the groups did not show a significant difference as the results were ($P_{\text{allele A}}$= 0.841, $P_{\text{allele C}}$= 0.865). Since all the P-values are greater than 0.05 which determines that all genotypes express a non-significant association with the risk of developing HT in the samples of this study.

The results of this study suggest that the IL-18 polymorphisms may not have a direct association with the susceptibility of HT in the Iraqi population. A recent study in Al-Najaf, Iraq, done by *Noor Al-Huda* in 2025 suggests a potential association between the G allele of rs1946518 and the susceptibility of HT (23). However, our results align with the study was done by IDE et al (24) that found no association between the Interleukin-18 polymorphisms of the promoter and autoimmune thyroid diseases in the Japanese population (24). Furthermore, a study done by Huang et al (25) their findings concluded that rs1946518 has no association with the risk of the development of HT while rs187238 is associated with the risk of developing it in children (25). As for a study done by Karakaya et al (26) their results concluded that rs187238 genotype CG might represent a risk factor for HT (26). Meta-analysis research by Pan et al (27) in 2011 stated that there is no association between IL-18 gene promoter rs1946518 polymorphism and the development of autoimmune diseases which align with the findings of this study (27). On the other hand, a study by Inoue et al (28) suggested that rs1946518 polymorphism may increase the severity of HT although their findings of rs187238 suggest that there may play a minor role in the risk of developing HT (28).

Finally, several factors might explain lack of significant association between the IL-18 gene polymorphism and HT. First, since the sample size is relatively limited, which affects the statistical analysis, making the detection of small meaningful variation in the genotype distribution more difficult. Second, HT exhibits a complex pathogenicity involving the interaction of multiple genes and other factors that collectively can contribute to the susceptibility of the disease. In addition, the differences in genetic predisposition among populations may also contribute to the discrepancies across studies, as a polymorphism that is significant and associated with disease in one ethnic group can be neutral or even protective in another leading to variations in the results of different studies.

5. Conclusion

In conclusion, this study investigated the association between IL-18 gene polymorphisms (rs1946518, rs187238, and rs1946519) and risk of developing HT in an Iraqi population. The results indicated non-significant association between any of the examined genotypes in the selected samples and the susceptibility to HT. Remarkably, the rs187238 variant exhibited no variation in all the samples, proposing that it may not be polymorphic in this population. These findings reveal that IL-18 polymorphisms may not have an essential part in HT susceptibility in Iraqi patients. However, more studies with genetically diverse populations in larger sample sizes are recommended to help in better understanding of the genetic factors involved in HT pathogenesis.

6. Declarations

6.1 Acknowledgments

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6.2 Ethical Considerations

This study was approved by the local ethical committee at Al-Nahrain University/College of Biotechnology, it ensured the author's adherence to the ethical standards and the protection of participants' rights. The manuscript of this study has not been sent to other journals at the same time. It has not been published elsewhere in any form or language.

6.3 Authors' Contributions

Author A.A was responsible for the methodology and conducted the experiments required for this research, in addition to the interpretation of the results and writing the manuscript. While Author R.A had a role in conceptualization and supervising this research, providing guidance, and designing the study. In addition, Author S.S provided technical support during some of the laboratory work and handling procedures. All authors reviewed, edited, and approved the final version of the manuscript.

6.4 Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

6.5 Fund or Financial Support

This study did not have external funding, the costs of the sample collection, the laboratory procedures, the data analysis, and the manuscript preparation were covered by the authors.

6.6 Using Artificial Intelligence Tools (AI Tools)

AI tools were not applied in this study.

7. Publisher's Note

This article is part of the Special Issue arising from the Second International Conference for Pharmaceutical Sciences (SICPS 2025), College of Pharmacy, University of Misan, Iraq (29 Nov – 1 Dec 2025, see https://uomisan.edu.iq/pharmacy/conference/). All manuscripts in this issue were peer-reviewed and accepted for publication in *Journal of Advances in Medical and Biomedical Research (J Adv Med Biomed Res)*.

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