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Association of genetic variations of interleukin-6 polymorphism (*rs1800795*) with susceptibility to Hashimoto's thyroiditis in West Algerian population

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Abstract

Aim: Hashimoto's thyroiditis is a polygenic auto-immune disease with a complex etiopathogenesis. It is more common in females. An imbalance between pro-inflammatory and anti-inflammatory cytokines may play an important role in the disease pathogenesis. Numerous studies have been conducted to find an association between genetic polymorphisms and the development of Hashimoto's thyroiditis. In this context, we proposed to study the impact of the interleukin-6 (*IL-6*) gene polymorphism (*rs1800795*) on the genetic susceptibility to Hashimoto's thyroiditis.

Methods: Polymorphism in *IL-6* gene (*rs1800795*) was assessed in a case-control study involving a population of Western Algeria with 81 Hashimoto's thyroiditis patients and 211 unrelated healthy subjects, matched in age and sex. The DNA was extracted by a magnetic bead-based technique. The genetic study was performed by molecular biology: real-time PCR using TaqMan single nucleotide polymorphism (SNP) genotyping assay with Applied Biosystems 7500 device.

Results: Results showed that the GG and GC genotypic distribution is similar between patient and control groups with a higher frequency of the GG genotype (80.25% in patients and 78.67% in controls vs. 19.75% of patients and 20.38% of controls with the GC genotype). The CC genotype is absent in patients and present in only 02/211 healthy subjects. The frequency of the polymorphic G allele was similar in the two groups, with 90.1% and 88.8% in patients and controls respectively ($P > 0.05$).

Conclusions: This study reports no significant difference in *IL-6* (*-174 G/C*) gene polymorphism at the allelic or the genotypic level between Hashimoto's patients and the control group ($P > 0.05$). No association between the SNP *IL-6 rs1800795* and susceptibility to Hashimoto's thyroiditis in Western Algerian population.

Keywords

Hashimoto's thyroiditis, IL-6, SNP, polymorphism, West Algeria

Introduction

Hashimoto's thyroiditis (HT) is the first and most common organ-specific autoimmune disease described and its high prevalence varies according to the populations. An incidence of about 0.3 to 1.5 cases per 1,000 people per year is reported and is gradually increasing. Chabchoub et al. [1], estimate a prevalence of 22.8% in Africa. HT mainly occurs in young and middle-aged women. However, it can be diagnosed in patients of any age, including children [2–4].

Also known as chronic lymphocytic thyroiditis, HT was first described by Hashimoto H in 1912 as struma lymphomatosa. It is characterized by a lymphocyte infiltration of the thyroid parenchyma and the presence of anti-thyroid autoantibodies [5].

Currently, HT is believed being linked to multiple factors, including genetic susceptibility and environment. Among genetical factors, so far, several loci have been associated with HT, such as *HLADR*, immunoregulatory genes (*CTLA-4*, *FoxP3*, *CD25*, and *PTPN22*) and thyroid-specific genes [thyroglobulin (Tg)]. In addition, interferon-γ and inflammatory pathways [TNF-α and interleukin-6 (IL-6)] may also promote disease onset and development [3, 6, 7]. Indeed, IL-6, a pleiotropic cytokine with a wide range of biological activities, recognized in particular for its pro-inflammatory effects, is considered being a very important cytokine in the pathogenesis of thyroid autoimmunity, in part by its ability to induce Th17 cell differentiation, antibody production, cell activation, and modulation of thyroid cells function [8–10]. Furthermore, thyroid follicles constitutively produce IL-6. Its expression in thyroid cells correlated positively with the degree of lymphocyte infiltration in HT. This may contribute to the localization of the autoimmune response to the thyroid gland [8, 11, 12]. Therefore, SNPs (single nucleotide polymorphisms) of the *IL-6* gene that can lead to an altered level of cytokine expression are considered as important candidates for susceptibility to Hashimoto's disease.

Studies investigating the relationship between *IL-6* gene polymorphism (*rs1800795*) and HT are inconclusive and few data are available in the literature. The aim of the present study is to investigate the association of *IL-6* gene polymorphism (*rs1800795*) with the risk of developing HT in the population of Western Algeria.

Materials and methods

Population

This work is a case-control study, performed at the Immunology Laboratory of Pasteur Institute, Annex of Oran, Algeria. Patients were enrolled in the study from February 2022 to September 2022.

Controls

Two hundred and eleven (n = 211) healthy individuals were included in the study. The mean age was 45.25 ± 13.29 years. Sex ratio F:M = 20:1. These data are matched with those of patients group.

HT patients

Eighty-one (n = 81) individuals diagnosed with Hashimoto's disease were included in the study with a mean age of 47.03 ± 15.43 years (between 18–87 years). Sex ratio F:M = 19:1.

Inclusion criteria

Were included in the study, patients newly (diagnosis reports) and formerly (follow-up reports) diagnosed with Hashimoto's disease. The inclusion criteria for the diagnosis of HT were at least two of the followings:

- Hypothyroidism with high thyroid-stimulating hormone (TSH) serum levels.

- Positive serum antibodies to thyroid peroxidase antibodies (TPOAb) and/or Tg antibodies (TgAb).

- Lymphocyte infiltration in the thyroid gland confirmed by cytology and/or evidence of a hypoechoic pattern and non-homogeneous texture on ultrasound examination.

Exclusion criteria

Were excluded from the study, patients with a single HT criterion and patients with secondary hypothyroidism. Patients' clinicopathological details are described in Table 1.

Table 1. Demographic data and clinical characteristics of patients with Hashimoto's thyroiditis

Sex ratio (F:M)	TSH (µIU/mL)	FT4 (ng/dL)	Positive TPOAb (UI/mL)	Positive TgAb (UI/mL)
19:1	11.59 ± 25.38	0.82 ± 0.4	*N* = 76 (74/76)	*N* = 73 (64/73)
			97%	88%

F: female; M: male; FT4: free T4; TSH: thyroid-stimulating hormone; TPOAb: thyroid peroxidase antibodies. Reference values: TSH (0.35–4.94 µIU/mL); FT4 (0.70–1.48 ng/dL); anti-Tg (< 4.11 UI/mL); anti-TPO (< 5 UI/mL) (ABBOTT LABS ARCHITECT)

DNA extraction

Patients and controls genomic DNA were isolated from blood using a magnetic bead-based extraction (MagNA Pure LC Total Nucleic Acid Isolation Kit). The quantity and quality of the extracted DNA were evaluated by spectrophotometry (NANO MAESTROGEN).

Genotyping

Using TaqMan® Pre-designed SNP Genotyping Assay, all the primers and probes used for the *IL-6* SNP *rs1800795* in this study are shown in Table 2. PCR amplification and allelic discrimination were performed using the ABI 7500 Fast Real Time PCR System (Applied Biosystems).

Table 2. *IL-6* SNP *rs1800795* primers and probes

SNP *rs1800795*	
Primers	Forward: 5'-CGACCTAAGCTGCACTTTTCC-3'
	Reverse: 5'-GGGCTGATTGGAAACCTTATTAAGATTG-3'
Probes	5'-CCTTTAGCATGGCAAGAC-3' labelled with VIC
	5'-CCTTTAGCATCGCAAGAC-3' labelled with FAM

The PCR program used for amplification: 1 cycle, 2 min at 50°C; 1 cycle, 10 min at 95°C (initial denaturation); 40 cycles, 15 sec at 95°C (denaturation), 1 min at 60°C (extension). IL-6: interleukin-6; SNP: single nucleotide polymorphism

Qualitative analysis "Allelic discrimination plot"

Our study is based on a qualitative analysis to verify the association of variants (G>C) of the *IL-6* gene polymorphism in the population. The first probe, labeled with the fluorescent dye FAM, is designed to detect the wild-type allele sequence (G), while the second probe, labeled with the fluorescent dye VIC, detects the mutant type allele sequence (C).

- If the sample is homozygous for the G allele, the fluorescence reading or "Allelic discrimination plot" mainly shows VIC fluorescence, while for a sample homozygous for the C allele, the plot mainly shows the FAM dye signal.

- If the sample is heterozygous, however, there should be approximately equal signal for each dye.

Allele and genotype frequencies were estimated by direct counting and then divided by the number of subjects (to produce genotype frequency) or chromosomes (to produce allele frequency). The polymorphism was tested for Hardy-Weinberg equilibrium.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics v.26 (Free trial). Differences in allelic and genotypic distributions between patients and controls were assessed for statistical significance using Chi-square (χ^2) test. Pearson's χ^2 test is valid under the null hypothesis of no association between the disease status and genotype (case and controls have the same distribution of genotype frequencies). Any departure from this null hypothesis is regarded as evidence for association. *P* values ≤ 0.05 were accepted as statistically significant and the marker may be considered being associated with the disease.

Results

In control group, the frequencies of all SNPs did not deviate significantly from those expected under Hardy-Weinberg equilibrium (*P* value = 0.66).

Genotype frequency

The GG and GC genotypic distribution (Table 3) was similar between patients and controls with a highest frequency of the GG genotype (80.25% in patients and 78.67% in controls vs. 19.75% of patients and 20.38% of controls with GC genotype). Statistically significant differences were not observed in the genotypic frequencies of *rs1800795* SNP between HT patients and controls (*P* > 0.05).

Table 3. Genotypic distribution of *IL-6* SNP *rs1800795* in HT patients and controls

Genotype	Patients		Controls		OR (95% CI)	*P* value
	N = 81	%	*N* = 211	%		
GG	65	80.25	166	78.67	1.02 (0.89–1.16)	0.76
CC	0	-	2	0.95	-	*F = 1
GC	16	19.75	43	20.38	0.96 (0.58–1.62)	0.90

*F: according to Fisher's exact test; IL-6: interleukin-6; SNP: single nucleotide polymorphism; HT: Hashimoto's thyroiditis

Allelic frequency

As detailed in Table 4, the frequency of the G allele is the highest in both HT patients (90.1%) and controls (88.8%). While the C allele frequency is low, with 9.8% and 11.1% in patients and controls, respectively. According to the *P* value, no statistically significant differences were determined between the two groups (HT patients vs. controls) in the frequency of gene alleles (*P* > 0.05).

Table 4. Allelic distribution of *IL-6* SNP *rs1800795* in HT patients and controls

Allele	Patients		Controls		OR (95% CI)	*P* value
	N = 81	%	*N* = 211	%		
G carriers	81	100	209	99	1.01 (0.09–1.02)	*F = 1
C carriers	16	19.8	43	20.4	0.92 (0.5–1.54)	0.76
G	146	90.1	375	88.8	-	0.66
C	16	9.8	47	11.1		

*F: according to Fisher's exact test; IL-6: interleukin-6; SNP: single nucleotide polymorphism; HT: Hashimoto's thyroiditis

In short, our results report that *IL-6* (*-174 G/C*) polymorphism is not significantly different (at the allelic and genotypic level between patients with Hashimoto's disease and controls (*P* values > 0.05).

Discussion

IL-6 is a pleiotropic cytokine with a wide range of biological activities. It is produced by monocytes and macrophages, fibroblasts, keratinocytes, astrocytes, and endothelial cells. IL-6 plays an important role in regulating the adaptive immune response by stimulating antibody production and the development of effector T cells. IL-6, in combination with TGF-β, is essential for Th17 differentiation. It also impairs TGF-β-

induced Treg differentiation. Thus, the upregulation of the Th17/Treg balance is considered being responsible for the disturbance of immunological tolerance, and is therefore pathologically implicated in the development of autoimmune diseases, including thyroid autoimmunity. Furthermore, thyroid follicles constitutively produce IL-6. Its expression in thyroid cells correlated positively with the degree of lymphocyte infiltration in HT. Additionally, IL-6 can act in a paracrine manner to modulate thyroid cell function. This may contribute to the localization of the autoimmune response to the thyroid gland [8, 11, 12].

The gene encoding for IL-6 is located on chromosome 7 at position 21 (Chr 7p21). It contains 5 exons separated by 4 introns. Genetic variants in the *IL-6* gene promoter can have the potential to alter the regulation of the transcript production and expression of the cytokine. Considering the role of proinflammatory cytokines in the pathogenesis of the autoimmune response involved in HT, a change in the function or the quantity of IL-6 serum levels may lead to the initiation or perpetuation of the inflammatory process and then influencing an individual's susceptibility to Hashimoto's disease. For the *IL-6 rs1800795* polymorphism, a functional SNP located at position -174 is linked to the constitutive transcription rate of IL-6, which could control its blood levels. A single nucleotide change from G to C at this position corresponds to a negative regulatory domain and results in downregulation of IL-6 transcription. Indeed, the presence of the G allele at position -174 has been found to be associated with high production of IL-6 and with an increased inflammatory response (GG/GC genotype carriers), whereas low production is observed with the C allele (homozygous CC genotype carriers) [13–15]. Thus, this polymorphism can be used as a functional variant to explore the causative role of elevated levels of IL-6 in many common diseases and can further explain the susceptibility of certain populations to different inflammatory and autoimmune diseases.

Our results report no significant associations of *IL-6* (*-174 G/C*) genetic variants (at the allelic and genotypic level) between patients with Hashimoto's disease and controls ($P > 0.05$). Nevertheless, conflicting data were reported in the literature concerning the genotypic and allelic frequencies of the *IL-6* (*-174 G/C*) polymorphism in HT (Tables 5 and 6). In fact, in disagreement with our findings, Erdogan et al. [16] report that the *rs1800795* polymorphism of the *IL-6* gene promoter may represent a potential "candidate" genetic marker to predict the susceptibility of an individual to HT with a significantly different genotypic distribution between control group and HT patients ($P < 0.001$). This could be explained by an ethnic bias because the control group had a different distribution of genotypes (predominance of the CG genotype vs. GG genotype in our study). Moreover, certain polymorphisms have population-specific effects, and the Algerian population may lack other interacting genetic or environmental factors that would make *IL-6* (*-174 G/C*) relevant to HT susceptibility. However, the results of the allelic distribution are similar to ours with no significant association ($P > 0.05$) with the susceptibility to HT [16].

Table 5. Genotypic results of *IL-6* (*-174G/C*) polymorphism in the literature

Genotype	Controls			HT patients		
IL-6 -174 G>C	**GG**	**GC**	**CC**	**GG**	**GC**	**CC**
Our study (West Algeria)	166/211 (78.67%)	43/211 (20.38%)	02/211 (0.95%)	65/81 (80.25%)	16/81 (19.75%)	0
Erdogan et al. [16] (Turkey)	5/110 (4.5%)	86/110 (78.2%)	19/110 (17.3%)	27/110 (24.5%*)	51/110 (46.4%*)	32/110 (29.1%*)
Baki et al. [17] (Turkey)	126/231 (54.6%)	90/231 (39%)	15/231 (6.5%)	117/190 (61.6%)	63/190 (33.2%)	10/190 (5.2%)
Durães et al. [18] (Portugal)	319/735 (43.4%)	324/735 (44.1%)	92/735 (12.5%)	156/418 (37.3%)	189/418 (45.2%)	73/418 (17.5%*)
Aberkan [19] (Blida, center of Algeria)	26/35 (74.29)	8/35 (22.86)	1/35 (2.86)	21/27 (80.77)	1/27 (3.70)	5/27 (18.52)

* Results statistically significant (*P* value < 0.05). HT: Hashimoto's thyroiditis; IL-6: interleukin-6

Table 6. Allelic results of *IL-6* (*-174 G/C*) polymorphism in the literature

Allelic studies of *IL-6* (*-174 G>C*)		Allele	Frequency
Our study (West Algeria)	Controls	G	375/422 (88.8%)
	N = 211	C	47/422 (11.1%)
		G carriers	209/211 (99%)
		C carriers	43/211 (20.4%)
	Patients	G	146/162 (90.1%)
	N = 81	C	16/162 (9.8%)
		G carriers	81/81 (100%)
		C carriers	16/81 (19.8%)
Erdogan et al. [16] (Turkey)	Controls	G	96 (43.6%)
	N = 110	C	124 (56.4%)
	Patients	G	105 (47.7%)
	N = 110	C	115 (52.3%)
Durães et al. [18] (Portugal)	Controls	log-additive (G/C)	962 (65.4%)/508 (35.6%)
	N = 735	C carriers vs. GG	416 (56.6%)/319 (43.4%)
	Patients	Log-additive (G/C)	501 (59.9%)/335 (40.1%)*
	N = 418	C carriers vs. GG	262 (62.7%)/156 (37.3%)
Baki et al. [17] (Turkey)	Controls	G	74%
	N = 231	C	26%
	Patients	G	88%
	N = 190	C	22%
Aberkan [19] (Blida, center of Algeria)	Controls	G	60 (85.71%)
	N = 35	C	10 (14.29%)
	Patients	G	43 (79.63%)
	N = 27	C	11 (20.37%)

* Results statistically significant (*P* value < 0.05). IL-6: interleukin-6

Baki et al. [17] on their side investigated whether polymorphisms of cytokine genes *TNF-α -308*, *IL-6 -174* and *IL-10 -1082* are associated with HT. They concluded that there is no significant risk to HT afflicted by these polymorphisms alone (including *IL-6 -174 G/C*), again in agreement with our genetic results. Interestingly, their results rather suggest that the combined effects of the variant *TNF-α -308*, *IL-6 -174* and *IL-10 -1082* alleles may be more decisive in inducing functional differences and changing the risk of HT. Thus, the concomitant presence of mutant alleles *IL-10 -1082A* and *IL-6 -174C* multiplies by three the risk of HT [17]. Durães et al. [18] report in their study a significant association of the C allele in *IL-6* (*-174 G/C*) with the risk of developing HT in a log-additive model (OR = 1.28; 95% CI = 1.06–1.54; *P* value = 8.96×10^{-3}). Their results also indicate that a combination of TNF-α (*-308 G/A*) and IL-6 (*-174 G/C*) genotypes reveals an increased risk for individuals harboring more than one high-risk allele/genotype for HT [18]. Thus, the association of *IL-6* (*-174 G/C*) variants with HT susceptibility might not be due to polymorphism within the gene alone, but to a cumulative effect of cytokines genes variants.

In discussing the differences between local studies, it is important to highlight both the geographic and potential sociocultural distinctions. Our study focuses on a West Algerian population, while the one conducted by Aberkan [19] in 2016, focuses on a Central Algerian (Blida) population. While significant ethnic differences between the two regions may not exist, differences in environmental exposures and socio-cultural practices—such as dietary habits and lifestyle—could potentially influence the expression of genetic markers (i.e., an epigenetic effect), which could justify expecting some differences in results between these populations. Central Algeria, with its urban and diverse cultural interactions due to its capital status, contrasts with Western Algeria, where more specific regional or tribal customs may persist.

The consistency in genotypic and allelic frequencies of *IL-6* gene polymorphism observed between the two studies (Tables 5 and 6) points to significant genetic homogeneity across Algerian populations, suggesting that *IL-6* (*-174 G/C*) polymorphism frequencies may be relatively stable across Algerian regions.

Additionally, neither study found a significant association between the *IL-6* (*-174 G/C*) polymorphism and HT ($P > 0.05$) indicating that this polymorphism may not be a major genetic risk factor for HT in the broader Algerian population.

Current data suggest that the C allele at position -174 is responsible for lower expression of IL-6, leading to decreased serum levels. However, studies have shown that patients with HT have higher IL-6 serum levels inversely correlated with the thyroid function and hormone secretion [6, 20, 21].

Some studies have been performed to assess the association of another SNP in the *IL-6* promoter region at position -572 C/G (*rs1800796*) with susceptibility to HT. No significant association was identified in HT patients, according to Mestiri et al. [22] in Tunisia. However, Inoue et al. [23] demonstrated an association between CG and GG genotypes and Hashimoto's disease and its prognosis. Similar reports in a Chinese population suggest that *IL-6* (*-572 C/G*) may be a potential genetic marker (heterozygous genotype CG) for susceptibility to Hashimoto's disease [24].

In conclusion, there is no conclusive evidence that the *IL-6* (*-174 G/C*) polymorphism is a causal variant of HT. Although, several factors are thought to interfere in the susceptibility and initiation of the disease while others are responsible for the perpetuation and enhancement of the autoimmune process. Since HT is a multifactorial disease, a combination of several elements can be at the origin of the susceptibility to the disease and/or its prognosis.

Abbreviations

HT: Hashimoto's thyroiditis

IL-6: interleukin-6

SNP: single nucleotide polymorphism

Tg: thyroglobulin

TgAb: thyroglobulin antibodies

TPOAb: thyroid peroxidase antibodies

TSH: thyroid-stimulating hormone

Declarations

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Author contributions

NL: Conceptualization, Data curation, Writing—original draft. MM: Conceptualization, Data curation, Writing—review & editing. YBY: Data curation, Writing—review & editing. HK: Writing—review & editing, Supervision. NO: Writing—review & editing, Supervision.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

This study was approved by the Ethics and Professional Conduct Committee of the Faculty of Medicine of ORAN/Decision 001/2023.

Consent to participate

Informed consent to participate in the study was obtained from all participants.

Consent to publication

Not applicable.

Availability of data and materials

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

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