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The Involvement of miRNA-375, miRNA-451, and IL-6 in the Immunopathogenesis of Hashimoto's Thyroiditis and Its Implications

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Abstract. *Hashimoto's thyroiditis (HT) is an autoimmune disorder that leads to thyroid dysfunction and chronic inflammation, often resulting in hypothyroidism. The exact mechanisms driving HT are not fully understood, but recent research has highlighted the potential role of various molecular markers in the disease's pathogenesis. This study investigated the roles of miRNA-375, miRNA-451, and interleukin-6 (IL-6) in HT. Serum samples were collected from 100 HT patients and 100 healthy controls, and their expression levels were analyzed using quantitative polymerase chain reaction (qPCR) and enzyme-linked immunosorbent assay (ELISA). The results revealed significant alterations in the levels of these molecules. miRNA-375 was significantly elevated in HT patients (5.85 ± 1.30 vs. 1.0, $p < 0.001$), while miRNA-451 was markedly reduced (1.43 ± 0.22 vs. 10.91 ± 2.44, $p < 0.001$). Additionally, IL-6 levels were found to be significantly higher in HT patients (115.79 ± 12.62 vs. 21.34 ± 4.03 pg/ml, $p < 0.001$). These findings suggest that these molecules play critical roles in the immunopathogenesis of HT. Receiver operating characteristic (ROC) analysis further confirmed that miRNA-375, miRNA-451, and IL-6 are excellent diagnostic markers, with area under the curve (AUC) values ranging from 0.956 to 1.000. miRNA-375 showed 96% sensitivity and specificity at a cutoff >1.66-fold, while miRNA-451 demonstrated 100% sensitivity and specificity at a cutoff <3.48-fold. IL-6 also exhibited perfect diagnostic accuracy with 100% sensitivity and specificity at a cutoff >53.73 pg/ml. No significant variations were observed across demographic or treatment subgroups, supporting the stability of these biomarkers in clinical applications. These findings suggest that miRNA-375, miRNA-451, and IL-6 are dysregulated in HT and could serve as reliable biomarkers for diagnosis and potential therapeutic targets, offering new strategies for the management of Hashimoto's thyroiditis.*

Keywords: *Biomarkers, Hashimoto's thyroiditis, IL-6, miRNA-375, miRNA-451*

1. INTRODUCTION

Hashimoto's thyroiditis (HT) is a common autoimmune disorder characterized by chronic lymphocytic infiltration and progressive destruction of the thyroid gland, leading to hypothyroidism [1]. The pathogenesis involves dysregulated immune responses, including abnormal cytokine production and altered microRNA (miRNA) expression [2]. Among these, miRNA-375 and miRNA-451 have emerged as key regulators of immune and thyroid function, modulating apoptosis, inflammatio and autoantibody production [3,4]. Additionally, interleukin-6 (IL-6), a pro-inflammatory cytokine, is elevated in HT and contributes to thyroid follicular cell damage and autoimmune activation [5].

Recent studies suggest that miRNA-375 influences thyrocyte survival, while miRNA-451 modulates immune cell activity, potentially exacerbating thyroid autoimmunity [6,7]. Concurrently, IL-6 promotes B-cell differentiation and autoantibody production, further perpetuating thyroid injury [8]. Understanding the interplay between these miRNAs and IL-6 may provide insights into HT's immunopathogenesis and identify novel therapeutic targets.

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This review explores the roles of miRNA-375, miRNA-451, and IL-6 in HT, highlighting their contributions to thyroid dysfunction and autoimmune responses. Recent evidence underscores their potential as biomarkers or therapeutic candidates, offering new avenues for managing HT [9,10].

2. MATERIALS AND METHODS

Sample collection: The present case-control research included 100 female patients with a definitive diagnosis of Hashimoto's thyroiditis (HT group) and 100 age- and gender-matched healthy females (the control group).

MiRNA Primers: The qPCR primers for miR-375 and miR-451 were created in-house utilizing the Sanger Center miRNA information Registries and the miRNA Primer Creation Tools.

Housekeeping Gene Primer: The qPCR primer for the housekeeping gene GAPDH (NM_001256799.3) was designed in-house using the NCBI database and the Primer3 Plus design tool. The primers are shown were provided by (Macrogen company, Korea) as in the following table (1):

Table 1. Housekeeping Gene Primer

PRIMER		**SEQUENCE (5'-3')**
miRNA universal RT primers		GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGG ATACGACTTTTTTTTTTTVN
miR-375 qPCR primer	F	AACAAGTTTGTTCGTTCGGCT
	R	GTCGTATCCAGTGCAGGGT
miR-451 qPCR primer	F	AACAAGAAACCGTTACCATTACTGA
	R	GTCGTATCCAGTGCAGGGT
GAPDH qPCR primer	F	AATTCCATGGCACCGTCAAG
	R	ATCGCCCCACTTGATTTTGG

Total RNA extraction: The total RNA extraction were extracted from serum samples from Hashimoto's thyroiditis (HT) patients and healthy controls used (Accuzol.RNA extraction kit. Bioneer. Korea).

Statistical Analysis: The data was given as mean ± SD or median (interquartile range), as applicable. The Student's t-test or Mann-Whitney U test were used to compare the HT group to the control group, if appropriate. A p-value < 0.05 indicated statistical significance [11].

3. RESULTS

MiR-375 gene expression in patients with HT and healthy control. The comparison of miR-375 gene expression between patients with HT and healthy control subjects has been carried out and the results were demonstrated in table (3-23) and figure (3-20). Mean of miR-375 gene expression were 5.85 ± 1.30 and 1.0, in patients with HT and healthy control respectively; mean of gene expression was highly significant increase in patients with HT in comparison with healthy control (P< 0.001).

Table 2. miR-375 gene expression in patients with HT and healthy control.

	Cases –control comparison		
	Patients with HT *n* = 100	Healthy control *n* = 100	*P*
miR-375 gene expression			
Mean± SD	5.85 ± 1.30	1.0	< 0.001 † S
Range	0.34 – 14.33	0.70-1.72	

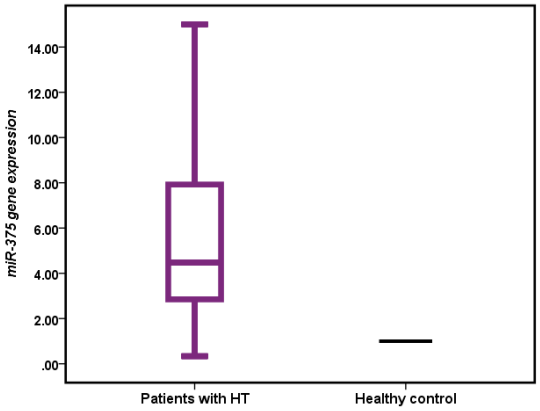

Figure 1. miR-375 gene expression in patients with HT and healthy controls

Evaluation of miR-375 gene expression.

To evaluate the miR-375 gene cutoff value as well as to predict the Hashimoto Thyroiditis as diagnostic tests or adjuvant diagnostic tests, receiver operator characteristic (ROC) curve analysis was carried out and the results are shown in (3-24), and figure (3-21). The miR-375 gene cutoff value was > 1.66-fold with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under curve of 96.0%, 96.0%, 96.0%, 96.0% and 0.956 (0.921- 0.991). The present results indicates miR-375 gene is considered as excellent diagnostic marker.

Table 3. Sensitivity and specificity of miR-375 gene (> 1.66-fold) in HT disease

miR-375 gene	**HT patients *n* = 100**	**Healthy control *n* = 100**
> 1.66	96	4
< 1.66	4	96
Sensitivity %	96.0 %	
Specificity %	96.0 %	
Accuracy	96.0%	
PPV %	96.0 %	
NPV %	96.0%	
AUC (95% CI)	0.956 (0.921- 0.991)	

CI: Confidence interval, AUC: Area under curve; PPV : positive predictive value;NPV : negative predictive value

Frequency distribution of miR-375 gene expression according to some characteristics.

The comparison of miR-375 gene expression according to some characteristics has been carried out and the results were demonstrated in table (3-25). The present results show non-significant difference of miR-375 gene expression according to all studied characteristic (P> 0.05).

Table 4. Distribution of miR-375 gene expression according to some characteristic

Characteristics		N	*miR-375 expression* Mean ± SD	*P*
Family History	Positive	4	5.66 ± 1.78	0.917 † NS
	Negative	96	5.86 ± 1.81	
Duration of treatment	< 1 years, *n* (%)	54	5.71 ± 1.62	0.519 K NS
	≥ 1 years , *n* (%)	36	5.70 ± 1.33	
	Without treatment , *n* (%)	10	7.15 ± 1.84	
Treatment type	Thyroxin 25, *n* (%)	10	5.23 ± 1.46	0.091 K NS
	Thyroxin 50, *n* (%)	22	5.33 ± 1.23	
	Thyroxin 75, n (%)	8	6.04 ± 1.61	
	Thyroxin 100, *n* (%)	28	5.58 ± 1.32	
	Thyroxin 125, *n* (%)	10	6.86 ± 1.42	
	Thyroxin 150, *n* (%)	4	5.12 ± 1.41	
	Neo Merrcazole, *n* (%)	8	7.08 ± 1.47	
	Without treatment, n (%)	10	6.05 ± 1.38	

n: number of cases; SD: standard deviation; †: Mann Whitney test; K: Kruskal–Wallis test; NS: not significant at P > 0.05

miR-451 gene expression in patients with HT and healthy control.

The comparison of miR-451 gene expression between patients with HT and healthy control subjects has been carried out and the results were demonstrated in table (3-26) and figure (3-22). Mean of miR-451 gene expression were 1.43 ± 0.22 and 10.91 ± 2.44, in patients with HT and healthy control respectively; mean of gene expression was highly significant decrease in patients with HT in comparison with healthy control (P< 0.001).

Table 5. miR-451 gene expression in patients with HT and healthy control

	Cases –control comparison		
	Patients with HT *n* = 100	Healthy control *n* = 100	*P*
miR-451 gene expression			
Mean± SD	1.43 ± 0.22	10.91 ± 2.44	< 0.001 † S
Range	0.29 – 2.97	4.00-19.98	

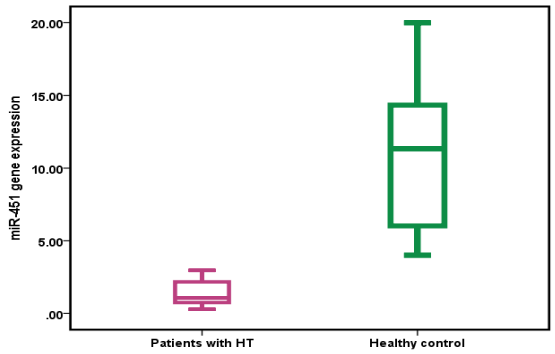

Figure 2. miR-451 gene expression in patients with HT and healthy controls

Evaluation of miR-451 gene expression.

To evaluate the miR-451 gene cutoff value as well as to predict the Hashimoto Thyroiditis as diagnostic tests or adjuvant diagnostic tests, receiver operator characteristic (ROC) curve analysis was carried out and the results are shown in (3-27), and figure (3-23). The miR-451 gene cutoff value was < 3.48-fold with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under curve of 100.0%, 100.0%, 100.0%, 100.0% and 1.000 (1.000- 1.000). The present results indicates miR-451 gene is considered as excellent diagnostic marker

Table 6. Sensitivity and specificity of miR-451 gene (< 3.48-fold) in HT disease

miR-451 gene	**HT patients *n* = 100**	**Healthy control *n* = 100**
< 3.48	100	0
> 3.48	0	100
Sensitivity %	100.0 %	
Specificity %	100.0 %	
Accuracy	100.0%	
PPV %	100.0 %	
NPV %	100.0%	
AUC (95% CI)	1.000 (1.000- 1.000)	

I: Confidence interval, AUC: Area under curve; PPV : positive predictive value;NPV : negative predictive value

Frequency distribution of miR-451 gene expression according to some characteristics.

The comparison of miR-451 gene expression according to some characteristics has been carried out and the results were demonstrated in table (3-28). The present results show non-significant difference of miR-451 gene expression according to all studied characteristic (P> 0.05).

Table 7. Distribution of miR-451 gene expression according to some characteristic

Characteristics		N	*miR-451 expression* Mean ± SD	*P*
Family History	Positive	4	1.63 ± 0.21	0.623 † NS
	Negative	96	1.42 ± 0.20	
Duration of treatment	< 1 years, *n* (%)	54	1.38 ± 0.22	0.771 K NS
	≥ 1 years , *n* (%)	36	1.51 ± 0.23	
	Without treatment , *n* (%)	10	1.39 ± 0.32	
Treatment type	Thyroxin 25, *n* (%)	10	1.50 ± 0.24	0.505 K NS
	Thyroxin 50, *n* (%)	22	1.33 ± 0.20	
	Thyroxin 75, n (%)	8	1.37 ± 0.21	
	Thyroxin 100, *n* (%)	28	1.29 ± 0.24	
	Thyroxin 125, *n* (%)	10	1.42 ± 0.27	
	Thyroxin 150, *n* (%)	4	1.19 ± 0.15	
	Neo Merrcazole, *n* (%)	8	1.66 ± 0.34	
	Without treatment, n (%)	10	1.39 ± 0.32	

n: number of cases; SD: standard deviation; †: Mann Whitney test; K: Kruskal–Wallis test;NS: not significant at P > 0.05.

Interleukin-6 (IL-6) level in patients with HT and healthy control.

The comparison of Interleukin-6 (IL-6) levels between patients with HT and healthy control subjects has been carried out and the results were demonstrated in table (3-10) and figure (3-11). Mean levels of IL-6 were 120.32 ± 12.62 and 21.34 ± 4.03, in patients with HT and healthy control respectively; the mean level was highly significant higher than in patients with HT in comparison with healthy control (P< 0.001).

Table 8. Interleukin-6 level in patients with HT and healthy control

	Cases –control comparison		
	Patients with HT ***n*** **= 100**	**Healthy control** ***n*** **= 100**	***P***
Interleukin-6 (IL-6) levels (pg/ml)			
Mean± SD	**115.79 ± 12.62**	**21.34 ± 4.03**	**< 0.001 † S**
Range	**73.51 – 182.42**	**6.53-33.96**	

n: number of cases; SD: standard deviation; †: independent samples t-test; S: significant at P ≤ 0.05.

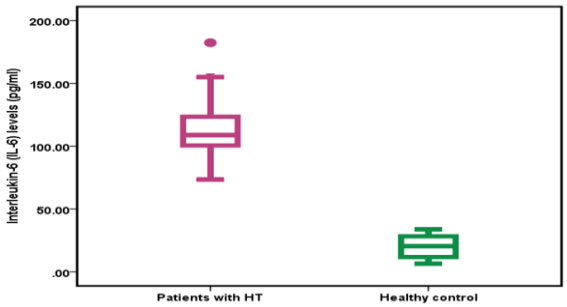

Figure 3. Mean Interleukin-6 (IL-6) levels of patients and healthy controls

Evaluation of Interleukin-6 levels.

To evaluate the Interleukin-6 levels cutoff value as well as to predict HT disease as diagnostic tests or adjuvant diagnostic tests, receiver operator characteristic (ROC) curve analysis was carried out and the results are shown in table (3-11), and figure (3-12). The Interleukin-6 cutoff value was >53.73-fold with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under curve of 100.0%, 100.0%, 100.0%, 100.0% and 1.000 (1.000- 1.000) . The present results indicates Interleukin-6 is considered as excellent diagnostic marker.

Table 9. Sensitivity and specificity of IL-6 (> 53.73-fold) in HT disease

IL-6 levels	**HT patients** ***n*** **= 100**	**Healthy control** ***n*** **= 100**
> 53.73	100	0
< 53.73	0	53
Sensitivity %	100.0 %	
Specificity %	100.0 %	
Accuracy	100.0 %	
PPV %	100.0 %	
NPV %	100.0%	
AUC (95% CI)	1.000 (1.000- 1.000)	

CI: Confidence interval, AUC: Area under curve; PPV : positive predictive value;NPV : negative predictive value

Frequency distribution of IL-6 levels according to some characteristics.

The comparison of IL-6 levels according to some characteristics has been carried out and the results were demonstrated in table (3-12). The present results show non-significant difference of IL-6 levels according to all studied characteristic (P> 0.05

Table 10. Distribution of serum IL-6 level according to some characteristic

Characteristics		N	IL-6 Mean ± SD	*P*
Family History	Positive	4	118.78 ± 13.92	0.831 † NS
	Negative	96	115.68 ± 14.21	
Duration of treatment	< 1 years, *n* (%)	54	112.51 ± 16.34	0.102 K NS
	≥ 1 years , *n* (%)	36	116.00 ± 10.38	
	Without treatment , *n* (%)	10	132.76 ± 11.72	
Treatment type	Thyroxin 25, *n* (%)	10	128.64 ± 12.90	0.067 K NS
	Thyroxin 50, *n* (%)	22	110.21 ± 11.66	
	Thyroxin 75, n (%)	8	96.90 ± 12.60	
	Thyroxin 100, *n* (%)	28	104.58 ± 11.95	
	Thyroxin 125, *n* (%)	10	119.15 ± 14.35	
	Thyroxin 150, *n* (%)	4	131.38 ± 11.43	
	Neo Merrcazole, *n* (%)	8	134.95 ± 13.28	
	Without treatment, n (%)	10	132.76 ± 11.72	

n: number of cases; SD: standard deviation; †: Mann Whitney test; K: Kruskal–Wallis test; NS: not significant at P > 0.05.

4. DISCUSSION

its increase has a clear effect on immunity and immune cells and increased programmed death by regulating target genes, as it affects and weakens innate immunity through its effect on the histone protein, because H2B is considered the main stimulator for activating the innate (Chandan et al., 2020)[13] found that miR-375 plays an effective and crucial role in controlling cell proliferation, spread, and programmed cell death via its action on Yes-associated protein 1 (YAP1), a protein that regulates cell proliferation and programmed cell death. miR-375 also has an effect on the SEC23A gene, which encodes the main protein in the formation of the secondary coat protein complex (COPII), which plays a critical role in transporting proteins from the endoplasmic reticulum to the Golgi apparatus via the formation of protein-carrying vesicles[14]. This, in turn, influences immune cells and their function by changing the gene pathways responsible for the cell's internal signals, represented by the movement of proteins from the endoplasmic reticulum to the Golgi apparatus inside cells[15]. This suggests that miR-375 expression levels are consistently elevated in HT patients regardless of these factors, reinforcing its potential role as a stable biomarker for HT. Recent studies have highlighted the involvement of miR-375 in autoimmune thyroid diseases, where it modulates inflammatory pathways and thyroid function[16] . The lack of variation in miR-375 expression across subgroups may indicate its central role in HT pathogenesis, independent of external clinical variables, as confirmed by findings that miR-375 is dysregulated in autoimmune conditions due to its influence on immune cell activity and cytokine production[17]. miR-451 downregulation The pituitary gland's gene encoding miR-451 is located on chromosome 17, specifically in the 17q11.2 region. When secreted, it regulates a number of immune cells, including B and T cells, neutrophils, and macrophages, which in turn affects the development of the disease. This change in gene expression of immune cells during the disease is the reason for the decreased expression[18]. T cells differentiate into subsets like CD4 and CD8 as a result of the interaction between T cell antigens and antigens presented to T cell antigens. Through a feedback mechanism, this process can both influence and be influenced by miRNA[19]. This result is consistent with recent research showing that some microRNAs, such as miR-451, may function as reliable biomarkers for autoimmune thyroid disorders since their expression is less affected by outside factors[20]. The absence of substantial fluctuation highlights *miR-451's potential dependability as an HT diagnostic marker, in line with studies showing its significance in immune modulation and thyroid dysfunction[21]. Toll-like receptor stimulation triggers myeloid cells to release IL-6, as well as the cytokines TNFα and IL-1β. Through a feed-forward loop, this causes an increase in IL-6 production during inflammatory conditions.

No other protein in the human body is likely capable of experiencing a six-fold increase in levels. This suggests that the human body uses IL-6 as its main warning signal in response to inflammation, infection, and most likely cancer[22]. IL-6 is considered a key factor in autoimmune diseases, as the IL-6 gene contains several elements for binding transcription factors, and IL-6 transcription is stimulated by reactive oxygen species. Since IL-6 controls the differentiation pathway of CD4 + T cells to Th17, these cells have an impact on the development of the disease, the secretion of pro-inflammatory cytokines, and the inhibition of the differentiation of regulatory T cells (Treg), which have an important role in immune balance and preventing the autoimmune response[23]. In addition to providing complete protection against rheumatoid arthritis and multiple sclerosis, turning off the IL-6 gene highlights the critical function that IL-6 plays in autoimmune diseases[22]. There were no discernible variations in the frequency distribution of IL-6 levels among patients with Hashimoto's thyroiditis (HT) according to a number of clinical and demographic factors, such as treatment type, length of treatment, and family history (Table 10). This implies that, independent of these variables, HT's elevated IL-6 may be a systemic inflammatory marker. According to recent research, IL-6 is a crucial cytokine in autoimmune thyroiditis that contributes to thyroid damage and persistent inflammation[24]. The absence of differences in IL-6 levels between subgroups is consistent with research by[25] . who stated that regardless of the length of the disease or the course of treatment, HT always has high IL-6. Although more investigation is required to examine its predictive significance in the course of the disease, this consistency highlights IL-6's potential as a stable biomarker for HT-related inflammation[26].

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