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New Insight in Etiology of Vitiligo, Association of lncRNA and some Immunological Parameters with Expression of Melanin Concentration Hormone and Sirtuin 1 Genes in Generalized and Segmented Vitiligo

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Abstract

Background: Long non-coding RNAs (LncRNAs) represent a subset of genetic material exceeding 200 base pairs that lack protein-coding capacity, yet possess the unique capability to modulate gene expression. This study was conducted with the purpose of identifying the expression levels of LncRNA SIRT-1, LncRNA MCH, as well as the serum levels of IL-17, IL-33, and IFNγ in individuals with vitiligo. Furthermore, the investigation aimed to explore the potential correlation between long non-coding RNA and the parameters of study.

Methods: The investigation was carried out on a cohort consisting of 30 patients with Generalized Vitiligo (GV) - both treated and untreated, 30 patients with Segmented Vitiligo (SV) - also both treated and untreated, and 25 Healthy Controls (HC). Using ELISA, the serum levels of IL-17, IL-33, IFNγ, SIRT 1, and PMCH were measured. Additionally, a gene expression analysis of long non-coding RNA (LncRNA) SIRT-1 and LncRNA PMCH was conducted in patients with GV and SV in order to shed light on their potential implications in the pathogenesis of vitiligo.

Results: LncRNA SIRT-1 expression was significantly higher in GV compared to SV (p=0.030, Mann-Whitney test), with mean expression levels of 2.851 (SE: 1.052) and 0.507 (SE: 0.134), respectively. In contrast, no significant difference in LncRNA MCH expression was observed between the two vitiligo types.

Conclusion: After investigation of the association between lncRNA expression of the SIRT1 and MCH genes and their corresponding serum concentrations in vitiligo patients, this research elucidated the dysregulated manifestations of LncRNA SIRT-1 and LncRNA MCH in individuals diagnosed with vitiligo, indicating their potential contributions to the etiology of vitiligo. This mechanism could involve the down regulation of serum SIRT-1 and MCH, as well as the elevation of cytokines. `

Keywords: *Vitiligo , Long non-coding RNAs, sirtuin 1 gene ,* melanin-concentrating hormone*, interleukins*

Abbreviations: LncRNAs: Long non- coding RNAs, SIRT-1 gene: Sirtuin – 1 gene , MCH; melanin-concentrating hormone , GV: GV , SV: Segmented Vitiligo , HCs: Healthy controls, IL-17, interleukin-17; IFN-γ, interferon-gamma; IL-33, interleukin-33; CI, confidence interval; IQR, interquartile range**,**

INTRODUCTION

Vitiligo is a dermatological condition characterized by depigmentation of the skin, resulting in areas of hypopigmented skin. This happens because the melanocytes, which are responsible for producing melanin, become exhausted in certain areas of the skin. A noticeable sign of vitiligo is the presence of white patches with well-defined borders that are not scaly or dry[1]**.**

The comprehension of the etiology of vitiligo has progressed significantly in recent years. It is now known definitively that it is an autoimmune disorder related with oxidative stress and metabolism, in addition to environmental and genetic factors [1]**.** Vitiligo, also known as GV, can appear on any part of the body, but it often shows up on the hands, face, and fingers. This condition usually affects both sides of the body and presents as matching spots and patches [2]. Segmental vitiligo, also known as **(SV),** makes up about 5-16% of all cases of vitiligo, and interestingly enough, it affects both men and women in almost equal numbers, though some studies suggest that there may be a slight tendency for more cases in females. One of the unique aspects of segmental vitiligo is that it typically only appears on one specific area of the body and creates a distinct division along the midline [3]**.** LncRNAs are non-coding transcripts having more than 200 nucleotides (200 nt), nonprotein coding transcripts that don't have any significant open reading frames [4]**. LncRNAs are** also described as 'mRNA-like' because it is polyadenylated and spliced, on the other hand not all lncRNAs have 7 methylguanosine capped or poly adenylated [5]. According to where they locations on chromosomes, lncRNAs are divided into many classifications: overlapping lncRNAs, intergenic, antisense, bidirectional and intron , antisense lncRNAs transcription from the opposite direction of the coding gene of their sense protein or a sense strand-derived RNA [6]. lncRNA molecules have the incredible ability to regulate gene expression by forming specific interactions with target genes to bring in enzymes that can modify chromatin structure or activating enhancer RNA and sponging miRNA [7]**.** MCH peptide consist of 19 amino acid expressed in the brain lateral hypothalamic area, and have multiple physiological functions such as food intake, memory formation, sleep-wake arousal, reproduction and nutrient sensing [8]. Thus, it is evident that the equilibrium of the MCH and melanocortin system functions is probably essential for the regulation of skin pigmentation, while the disruption of these mechanisms might be associated with negative effects on human skin conditions. The application of MCH peptides from an external source stimulates the aggregation of melanosomes, which in turn has the potential to modulate skin pigmentation [9]. Human Sirtuin 1 gene (SIRT1) is found on chromosome 10q22.1. It is made up of nine exons and eight introns that come together to form a protein consisting of 747 amino acid residues. This protein includes C-terminal and N-terminal domains, as well as a catalytic region [10]**.** Cytokines, which are critical in the development of autoimmune disorders, may also contribute to the loss of skin pigmentation. Interleukin (IL)-17, a cytokine, is progressively being linked to the etiology of numerous immune-mediated disorders.

In vitiligo patients, keratinocytes have been shown to secrete IL33, which is observed to be transferred from the nucleus to the cytoplasm of the keratinocyte, Furthermore, IL-33 act on keratinocytes

modification through basic fibroblast growth factor (bFGF) and stem cell factor (SCF) expression, which are essential for melanocyte development , suppress by IL-33, while IL-6 and tumour necrosis factor α (TNF-α) expression can be increased. [11]. INFγ plays a crucial part in the worsening of inflammation and in the collaboration between keratinocytes and lymphocytes. IFNγ enhances the movement of melanocyte-specific CD8 cytotoxic T lymphocytes (CTLs) towards the skin, stimulating keratinocytes to produce various chemokines, primarily CXCL10. The relationship between CXCL10 and its autoreactive T cell receptor, CXCR3, plays a role in sustaining skin depigmentation in vitiligo [12]. Thus, the aim of the current work was to explore the possible correlation between the LncRNA and some immunological parameters with expression of MCH and SIRT-1and their role in vitiligo pathogenesis.

MATERIALS AND METHODS

Ethical Approval

This study was approved by the Council of the AL- Anbar University. Signed informed consent was obtained from every participant involved in the research. The demographic data for each subject and control group was collected through a structured questionnaire overseen by the principal investigator, following the necessary permissions for sample collection. The research protocols adhered to the guidelines set forth by the Ethics Committee for Human Research of the Ministry of Health in Iraq.

The study was conducted on 30 (GV) , 30 (SV), and 25 age- and gender-matched (HCs) during the time interval between December 2021 to July 2022. HCs didnot have vitiligo or any other disease, furthermore, there was no record of tobacco or alcohol consumption among the individuals, and they were not experiencing any acute illnesses or infections during the sampling period. The healthy controls did not take any particular prescribed medications or have dietary limitations, and they were free of other excluded illnesses. The participants included in this research were all between the ages of 11 and 40 years old.

In this study, the verbal consent of the volunteer patients were taken, and following a thorough clinical assessment conducted by the attending physicians and subsequent written consent obtained from the individuals, specimens were gathered. The patients' medical history and lifestyle choices were duly noted. Additionally, a survey was administered post clinical evaluation by the consulting medical practitioners, with patient identities anonymized to protect their privacy.

Patients

From each patient 3 ml of blood was obtain by venipuncture.The blood was used for the analysis required to complete the research. **and was divided into two parts**.two parts:

The first part of the blood sample was placed in a gel tube, serum was isolated to use in the estimation of serum concentration each of IL- 17, IL-33, IFN-γ, MCH, and SIRT-1 by ELISA technique. The second part of sample used (300 µl) to RNA Isolation With Trizol. All samples were transported for storage in a freezer at -80ºC until use.

The protocol supplied by Bioneer company was used for RNA isolation using specific kit genomic RNA purification, Quantitative real-time polymerase chain reaction (qRT-PCR) was employed for the evaluation of gene expression levels among distinct patient cohorts and a control group,

focusing on LncRNA molecules of SIRT-1 and MCH. Specifically designed qRT-PCR primers were utilized for the purpose of measuring the relative change in expression levels for each target. The primer sequences corresponding to the genes under investigation can be found in Table 1.

Statistical analysis:

Data analysis and presentation were done by using GraphPad Prism 8 (GraphPad Software, California, USA) for graphical representations, Jamovi 2.3.28 (The Jamovi Project 2023, Sydney, Australia) for correlation analyses, and MedCalc (MedCalc Software Ltd, Ostend, Belgium) for receiver operating characteristic (ROC) curve analysis. Normality of the data was assessed using the Shapiro-Wilk test. Generally, continuous variables were presented as mean ± standard deviation (SD) for normally distributed data or median and interquartile range (IQR) for non-normally distributed data. Categorical variables were presented as frequencies and percentages. Comparisons among three or more groups were conducted using one-way analysis of variance (ANOVA) for normally distributed data or the Kruskal-Wallis test for non-normally distributed data. The ROC curve analysis was used to evaluate the diagnostic accuracy of serum biomarkers in distinguishing vitiligo patients from healthy controls. Gene expression data obtained from RT-PCR were analyzed using the 2-ΔΔCt method.

Table 1: Primers used for gene Expression Prepared in the present work

Primer Name	Description	Sequence	Amplicon size (bp)	Annealing
lncSIRT1	Forward	GAGCAAAGGAGGCACAAAAC	159	
	Reverse	GCCCAGTGTCAATCTGGAAT		
lncMCH	Forward	GGGGATGAAGAAAACTCAGC	214	
	Reverse	AACGGAACTGCACTGATAACG		
GAPDH	Forward	TGCCACCCAGAAGACTGTGG	129	58
	Reverse	TTCAGCTCAGGGATGACCTT		

Results:

Clinicopathologic features

The demographic and clinical attributes of the individuals involved in the study are detailed in **Table 2.**

The median age of the control group (n=25) and the vitiligo group (n=63) was 25 years, with no significant difference between the groups (p>0.05). The sex distribution was similar in both groups, with 48% males and 52% females in the control group, and 52.38% males and 47.62% females in the vitiligo group (p>0.05). Among the vitiligo patients, 49.2% had GV, while 50.8% had SV vitiligo. The majority of the vitiligo patients (≈54%) had the disease for 1-5 years, while 22% had it for less than a year and 24% for more than 5 years. Family history of vitiligo was present in 6.35% of the vitiligo patients and none of the controls, but this difference was not statistically significant (p>0.05). Approximately 46% of the vitiligo patients were undergoing treatment at the time of the study.

Table 2. Demographic and clinical attributes of the individuals involved in the study

	Control group (n= 25)	Vitiligo group (n= 50)	*P*-value
Age (years)	25 (15.5, 33)	25 (16, 33)	0.721
Sex **Male** **Female**	 12 (48) 13 (52)	 33 (52.38) 30 (47.62)	0.797
Vitiligo types **Generalized** **Segmental**	 – –	 31 (49.2) 32 (50.8)	NA
Period of disease **<1 year** **1 – 5 years** **>5 years**	 – – –	 14 (22.2) 34 (54) 15 (23.8)	NA
Family history **Yes** **No**	 0 (0) 25 (100)	 4 (6.35) 59 (93.65)	0.574
Treatment **Yes** **No**	 – –	 29 (46.03) 34 (53.97)	NA

Data presented as median (interquartile range) for age and frequency (percentage) for other parameters. *P*-values from Mann-Whitney U test for age and Fisher's exact test for other parameters. NA: Non-applicable

Circulating biomarkers

The circulatory levels of various biomarkers (SIRT-1, MCH, IL-17, IFN-γ, and IL-33) and their ratios were also investigated in individuals with vitiligo compared to HC (**Table 3**). The ratios of these biomarkers were also calculated to provide a comprehensive understanding of their interrelationships in the context of vitiligo. The plasma levels of SIRT-1 and MCH were significantly lower in the vitiligo group compared to the control group ($p<0.05$). In contrast, the levels of IL-17, IFN-γ, and IL-33 were significantly higher in the vitiligo group ($p<0.05$ for all).

According to vitiligo type , the circulatory levels of biomarkers SIRT-1, MCH, IL-17, IFN-γ, and IL-33 were further analyzed to investigate potential differences based on the type of vitiligo, namely GV and SV, compared to the HCs group (Figure 1). SIRT-1 levels were significantly lower in the SV group (IQR: 0.4-0.69) compared to the HC group (IQR: 0.46-2.98) ($p<0.05$, Figure 1A). However, there was no significant difference in SIRT-1 levels between the GV group (IQR: 0.51-0.73) and the HC group. In addition, MCH levels were significantly lower in both the GV (IQR: 2.42-3.51) and SV (IQR: 2.35-3.51) groups compared to the HC (IQR: 3.04-7.00) ($p<0.05$, Figure 1B). Also, IL-17 levels were significantly higher in both the GV (IQR: 5.91-9.99) and SV (IQR: 6.22-8.42) groups compared to the HC group (IQR: 0.85-1.31) ($p<0.05$, Figure 1C). Likewise, IFN-γ levels were significantly elevated in both the GV (IQR: 3.02-4.23) and SV (IQR: 2.73-4.37) groups compared to the HCs group (IQR: 0.93-1.87) ($p<0.05$, Figure 1D). Lastly, IL-33 levels were significantly higher

in both the GV (IQR: 6.41-9.32) and SV (IQR: 5.44-8.58) groups compared to the HC group (IQR: 1.45-4.74) (p<0.05, Figure 1E).

Table 3. Circulatory levels of biomarkers and their ratios in the control and vitiligo groups.

	Control group (n= 25)	Vitiligo group (n= 63)	*P*-value
	Median (IQR)	Median (IQR)	
SIRT-1 (pg/mL)	1.19 (2.52)	0.56 (0.26)	0.001
MCH (pg/mL)	4.92 (3.95)	3.04 (1.08)	<0.001
IL-17 (pg/mL)	0.99 (0.39)	7.58 (2.97)	<0.001
IFN-γ (pg/mL)	1.34 (0.78)	3.53 (1.2)	<0.001
IL-33 (pg/mL)	2.34 (2.95)	7.61 (3.24)	<0.001

Data are presented as mean (95% confidence interval) and median (interquartile range) because the data is non-normally distributed. P-values were calculated using the Mann-Whitney U test for comparing the control and vitiligo groups.

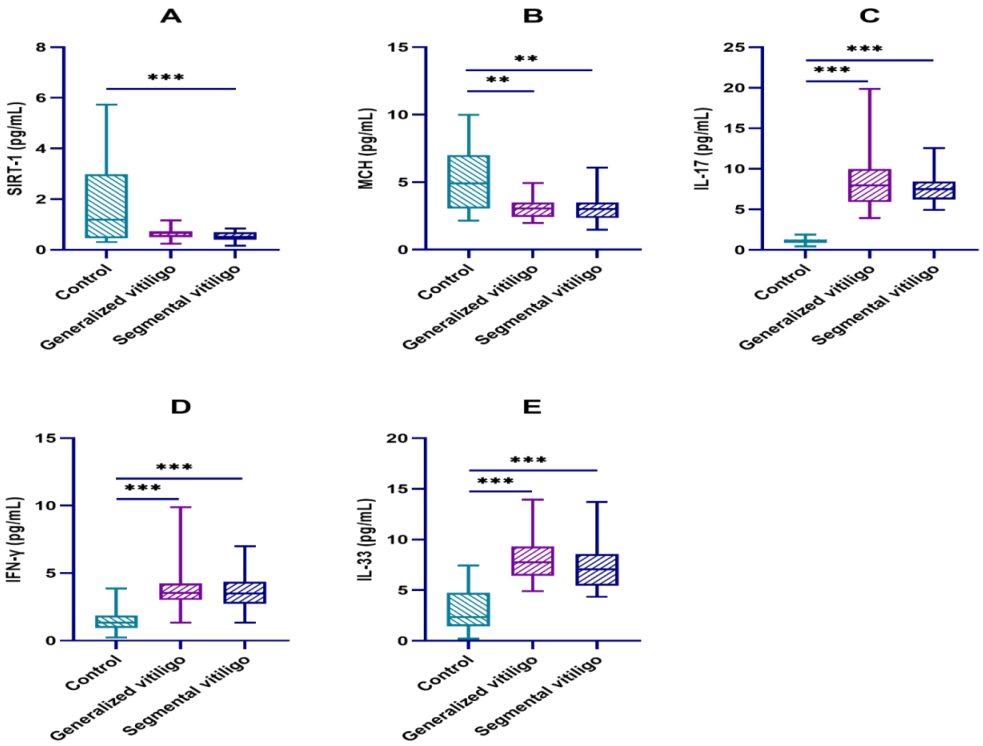

Figure 1. Comparison of serum levels of SIRT-1, MCH, IL-17, IFN-γ, and IL-33 among healthy controls, generalized and segmental vitiligo patients. (A) SIRT-1 levels, (B) MCH levels, (C) IL-17 levels, (D) IFN-γ levels, and (E) IL-33 levels. Data in the box plots are presented as median, IQR (with minimum and maximum values). Statistical significance was determined using Dunn's multiple comparisons test (* p<0.05, ** p<0.01, ***p< 0.001, ns: non-significant).

Receiver operating characteristic (ROC) analysis was conducted in order to assess the diagnostic precision of the examined biomarkers (SIRT-1, MCH, IL-17, IFN-γ, and IL-33) for discriminating between vitiligo patients and individuals in HC. Figure 2 illustrates the results of our ROC analysis. The SIRT-1 demonstrated a high sensitivity of 98.4% (95% CI: 91.5 - 100.0) and a moderate specificity of 64% (95% CI: 42.5 - 82.0) at a cut-off value of ≤0.986 (Figure 2A). The area under the curve (AUC) was 0.721 (p=0.006), indicating fair diagnostic accuracy. The positive and negative likelihood ratios (LR+ and LR-) were 2.73 and 0.025, respectively. In addition, MCH exhibited a sensitivity of 95.2% (95% CI: 86.7 - 99.0) and a specificity of 56% (95% CI: 34.9 - 75.6) at a cut-off value of ≤4.663 (Figure 2B). The AUC was 0.77 (p<0.001), suggesting fair diagnostic performance. The LR+ and LR- were 2.16 and 0.085, respectively.

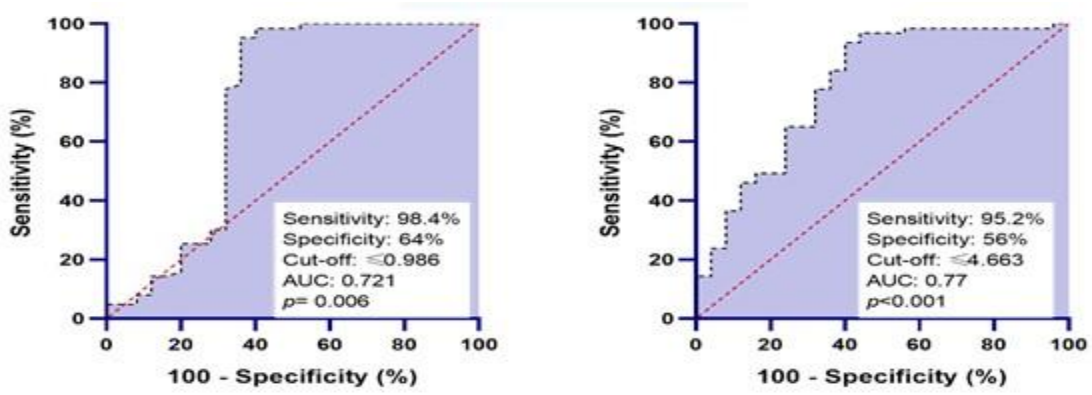

Figure 2. Receiver operating characteristic (ROC) curves for biomarkers in vitiligo and healthy controls. (A) SIRT-1, (B) MCH. The area under the curve (AUC), sensitivity, specificity, cut-off values, and *p*-values are shown for each biomarker.

Gene expression Analysis

Gene expression analysis of SIRT-1 and PMCH was performed in GV and SV patients to elucidate their potential roles in the pathogenesis of vitiligo. LncRNA SIRT-1 expression was significantly higher in GV compared to SV (p=0.030, Mann-Whitney test), with mean expression levels of 2.851 (SE: 1.052) and 0.507 (SE: 0.134), respectively (Figure 3A). In contrast, no significant difference in LncRNA PMCH expression was observed between the two vitiligo types (p=0.695, Mann-Whitney test), with mean expression levels of 1.750 (SE: 0.870) in GV and 1.883 (SE: 0.962) in SV patients (Figure 3B) . However, to further elucidate the potential impact of treatment on gene expression in different vitiligo types, we stratified the data based on treatment status (treated or untreated) within each vitiligo type (generalized or segmental).

Interestingly, no significant differences in LncRNA SIRT-1 or PMCH expression were found among the four subgroups (untreated GV, treated GV, untreated SV, and treated SV) (p=0.142 and p=0.178, respectively, Kruskal-Wallis test). For SIRT-1, the mean expression levels were3.838 (SE: 1.770) in untreated SV, 1.700 (SE: 0.936) in treated SV , 0.508 (SE: 0.208) in untreated GV, and 0.507 (SE: 0.196) in treated GV. Also, for PMCH, the mean expression levels were

0.319 (SE: 0.136) in untreated SV , 3.419 (SE: 1.695) in treated SV, 0.702 (SE: 0.399) in untreated GV, and 2.828 (SE: 1.654) in treated GV.

Table 4. Spearman's rank correlation coefficient between parameter of thus work.

		SIRT-1	MCH	IL-17	IFN-γ	IL-33
Overall (all participants)	SIRT-1	—				
	MCH	0.224	—			
	IL-17	-0.324**	-0.211	—		
	IFN-γ	-0.133	-0.305**	0.379**	—	
	IL-33	-0.163	-0.236*	0.253*	0.425***	—
Patients	SIRT-1	—				
	MCH	-0.121	—			
	IL-17	-0.201	0.097	—		
	IFN-γ	-0.205	-0.008	-0.171	—	
	IL-33	-0.270*	-0.161	-0.230	0.425	—

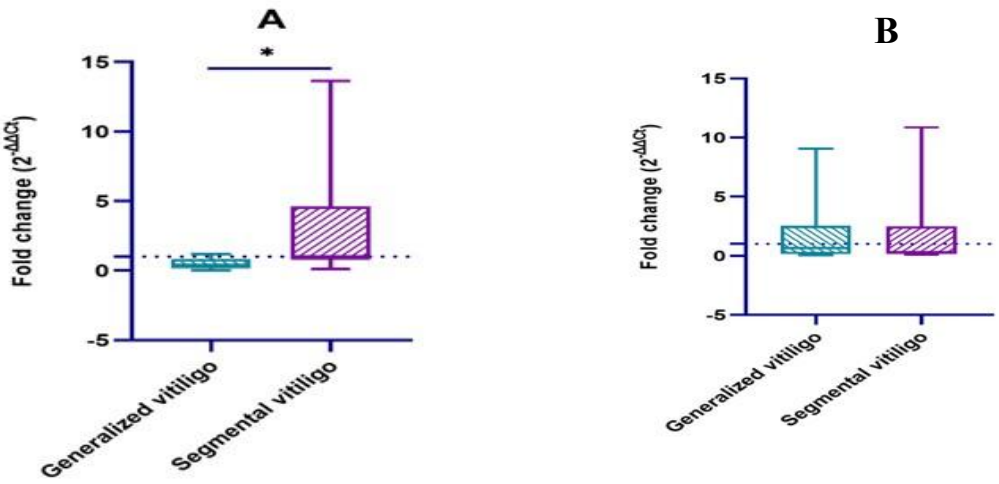

Figure 3. Gene expression levels of (A) LncRNA SIRT-1 and (B) LncRNA PMCH in GV and SV Patients .

Correlation Analysis

The correlations between immunological cytokine and the circulatory levels of SIRT-1, MCH were investigated using Spearman's rank correlation coefficient. the relationships between SIRT-1 and MCH (r = 0.224 , p < 0.01), In the overall sample, significant correlations were observed between IL-17 and SIRT-1 (r= -0.324, p < 0.01), IL-17 and MCH (r= -0.211, p < 0.05), IL-17 and IFN-γ (r= 0.379, p< 0.01), IL-17 and IL-33 (r= 0.253, p < 0.05). Among patients a significant negative correlation was observed between IFN-γ and SIRT-1 (r = -0.205 , p< 0.05), IFN-γ and MCH (r = -0.121, p< 0.05), as well as significant positive correlation observed between IFN-γ and IL-33 (r = 0.425 , p< 0.05). Weakly negative correlation was observed between SIRT-1 and MCH with IL-33 as shown in **table 4.**

We also investigated the association between lncRNA expression of the *SIRT1*

and *MCH* genes and their corresponding plasma concentrations in vitiligo patients. The results, presented in Figures 4, demonstrate varying degrees of correlation between lncRNA expression and protein levels, depending on the patient subgroups analy**is,** when dividing patients into subgroups based on treatment status, a moderate, statistically significant negative correlation (r= -0.396, *p*= 0.04) was observed in treated patients, while non-treated patients exhibited a weak significant negative correlation (r= -0.154, *p*= 0.444).

Figure 4 presents the association between lncRNA expression of *SIRT1* and SIRT1 concentration in segmental and generalized vitiligo patients. In segmental vitiligo patients, a weak, significant negative correlation was observed in the overall group (Figure 4A; r= -0.149, *p*= 0.529), treated patients (Figure 4B; r= -0.151, *p*= 0.682), and non-treated patients (Figure 4C; r= -0.236, *p*= 0.513). Conversely, in generalized vitiligo patients, a weak, significant negative correlation was found in the overall group (Figure 4D; r= -0.268, *p*= 0.125), while treated patients displayed a strong, statistically significant negative correlation (Figure 4E; r= -0.54, *p*= 0.027). Intriguingly, non-treated generalized vitiligo patients exhibited a weak, non-significant positive correlation (Figure 4F; r= 0.213, *p*= 0.410).

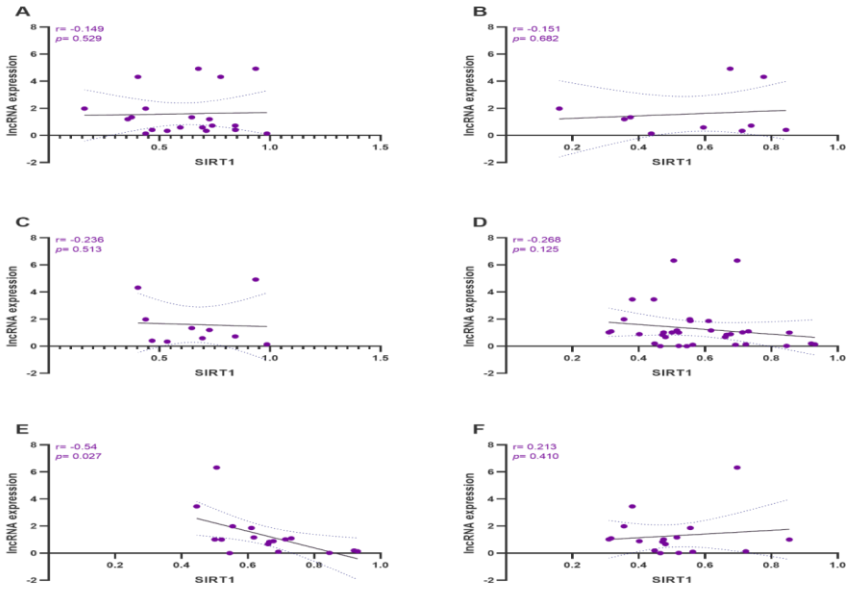

Figure 4. Scatter plots illustrating the association between lncRNA expression of SIRT1 and SIRT1 plasma concentration in segmental and generalized vitiligo patients. (A-C) Correlation analysis in segmental vitiligo patients: (A) all patients (n=30), (B) treated patients (n=20), and (C) non-treated patients (n=10). (D-F) Correlation analysis in generalized vitiligo patients: (D) all patients (n=30), (E) treated patients (n=18), and (F) non-treated patients (n=12). The x-axis represents SIRT1 plasma concentration (pg/ml), while the y-axis represents lncRNA expression of *SIRT1* (fold change). Each data point corresponds to an individual patient, with the solid line indicating the line of best fit and the shaded area representing the 95% confidence interval.

Expanding on these findings, Figure 5 presents the association between lncRNA expression of MCH and MCH concentration in segmental and generalized vitiligo patients. In segmental vitiligo patients, a weak, non-significant negative correlation was observed in the overall group (Figure 5A; r= -0.075, *p*= 0.548), while treated patients displayed a strong, statistically significant negative correlation (Figure 5B; r= -0.83, *p*= 0.005). Non-treated segmental vitiligo patients exhibited a weak, significant negative correlation (Figure 5C; r= -0.139, *p*= 0.707). In contrast, generalized vitiligo patients showed very weak, non-significant negative correlations in the overall group (Figure 4D; r= -0.04, p= 0.747) and non-treated patients (Figure 5F; r= -0.066, *p*= 0.802), while treated patients demonstrated a very weak, non-significant positive correlation (Figure 5E; r= 0.102, *p*= 0.694).

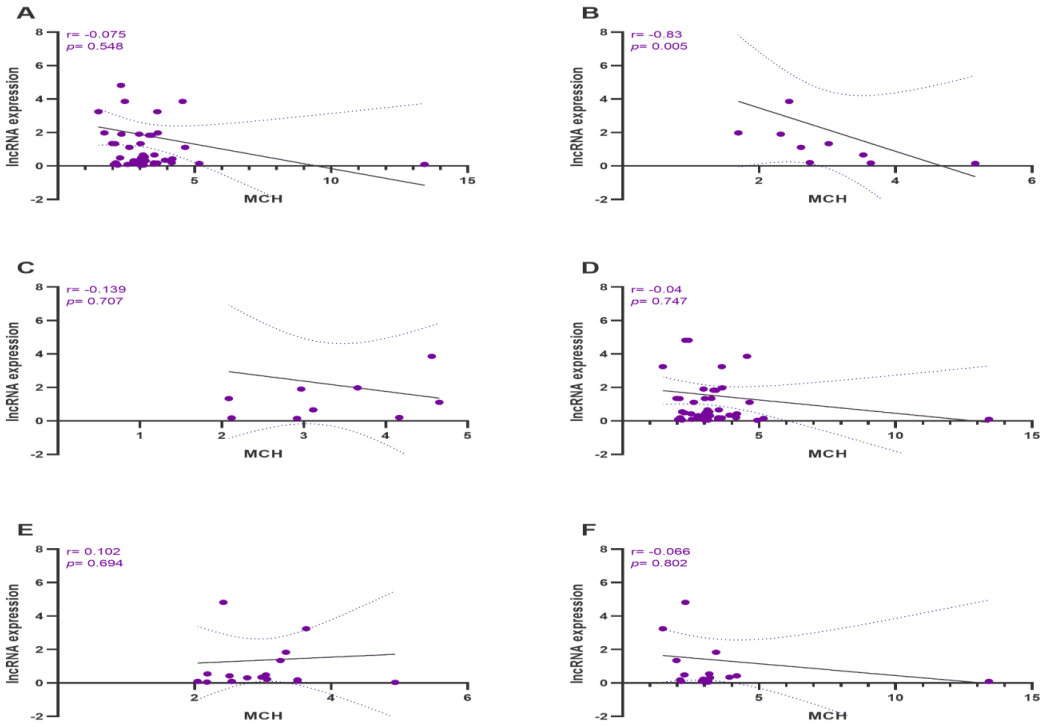

Figure 5. Scatter plots illustrating the association between lncRNA expression of *MCH* and MCH plasma concentration in segmental and generalized vitiligo patients. (A-C) Correlation analysis in segmental vitiligo patients: (A) all patients (n=30), (B) treated patients (n=20), and (C) non-treated patients (n=10), showing a weak, significant negative correlation, a strong, statistically significant negative correlation, and a weak, significant negative correlation, respectively. (D-F) Correlation analysis in generalized vitiligo patients: (D) all patients (n=30), (E) treated patients (n=18), and (F) non-treated patients (n=12).The x-axis represents MCH plasma concentration (pg/ml), while the y-axis represents lncRNA expression of *MCH* (fold change). Each data point corresponds to an individual patient, with the solid line indicating the line of best fit and the shaded area representing the 95% confidence interval.

DISCUSSION

The etiology of vitiligo remains largely unclear; nevertheless, alterations in cytokine patterns, autoimmune response, and genetic elements may play a role in the onset of the condition [13]. The current investigation evaluated the serum levels of IL-17, IL-33, IFNγ, SIRT-1, and MCH in individuals with vitiligo and healthy controls, along with the expressions of lncRNA-SIRT-1 and lncRNA-MCH. This was done in an effort to elucidate their respective roles in the pathogenesis of vitiligo, explore their potential as therapeutic targets, and investigate potential statistical correlations between variables and lncRNA. The present study was conducted on 30 (GV), 30 (SV), in addition to 25 HCs, matched for age and gender, the current study indicates that among lncRNAs, the expression of LncRNA SIRT-1 and LncRNA MCH were elevated in vitiligo patients and participated in the immunopathogenesis of vitiligo via decline serum level of SIRT -1, MCH and elevated immunological cytokine. The study highlighted the crucial role of IL-17 ,IL-33 and IFNγ in progression of the disease. IL-17, classified as pro-inflammatory cytokines, plays a crucial role in the pathogenesis of autoimmune conditions [14]. Previous studies indicated that IL-17 increases in vitiligo patients, also the association with the participation area of the disease and were important in the development of vitiligo[15] [16]. IL-17 molecule exhibits a synergistic effect with the inflammatory factors present in the local environment, this interaction could potentially lead to additional suppression of the proliferation of melanocytes, IL-17 is overexpressed in a variety of other chronic autoimmune inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, multiple sclerosis, systemic sclerosis, and chronic inflammatory bowel disease [17]

IL-33 have an important role in vitiligo. Its effective role lies in its secretion from apoptotic keratinocytes as well as inhibition expression of bFGF and SCF [18]. Results of this study showed elevated levels of IFNγ in vitiligo patients, which enhances the movement of melanocyte-specific CD8 cytotoxic T lymphocytes (CTLs) towards the skin, stimulating keratinocytes to produce various chemokines, primarily CXCL10. The relationship between CXCL10 and its autoreactive T cell receptor, CXCR3, plays a role in sustaining skin depigmentation in vitiligo [12].

SIRT1, a protein in our bodies, regulates the MAPK pathway by communicating with other proteins like Akt-apoptosis signal-regulating kinase-1. This communication helps to reduce the levels of molecules that promote cell death, ultimately reducing oxidative stress and stopping cells from dying in areas of perilesional vitiligo keratinocytes [19]. SIRT1 is considered to increase the level of differentiated keratinocytes and protect them from UVB-induced DNA damage, which may explain the intriguing fact that patients with skin cancer are insusceptible to vitiligo [20].

Furthermore, recent research has pointed towards the potential involvement of LncRNAs in the regulation of vitiligo. Interestingly, one study revealed that the expression of LncRNA TUG1 was notably reduced in the serum of individuals with vitiligo. On the other hand, different investigations have suggested that lncRNA MALAT1 is increased in the skin lesions of vitiligo patients and may provide protection against DNA damage caused by UV radiation through its role as a miR-211 inhibitor. Another study reported no significant

alterations in the levels of LncRNA TUG1 and lncRNA MALAT1 in the peripheral blood mononuclear cells (PBMC) of individuals with vitiligo [21].

The results of the current study showed a decrease in expression of serum MCH, SIRT-1 and an increase in gene expression of lncRNA in GV group compared to HCs. This indicates a regulatory role for lncRNA in vitiligo patients, according to what this study indicated, the increased expression of LncRNA may be implicated in the depletion of melanocytes through the reduction of the activity of essential genes involved in the proliferation and viability of these cells.

Recently people with vitiligo produce autoantibodies against their own melanocyte proteins, including melanogenic enzymes and a receptor called MCH-R1[22]. Researchers suggested that the melanocortin system and MCH have opposing effects on pigmentation, with MCH expression promoting lighter pigmentation and melanocortin activity promoting darker pigmentation [9].

LncRNAs possess the capacity to modulate the transcription of nearby protein-coding genes, thus affecting the global abundance of messenger RNA and proteins in a cellular context. The increased expression of lncRNA may be associated with the development of vitiligo, as evidenced by a research investigation carried out by Doss [23], which indicates that excessive expression of lncRNA H19 is associated with the pathogenesis of vitiligo through dysregulation of genes regulating immune response. SIRT1 related interaction and its possible contribution and involvement in dermatological diseases are not investigated enough so far [24]. It is worth noting that there is no study to our knowledge that explains the role of these genes in vitiligo. LncRNAs and circular RNAs (circRNAs) which influence melanogenesis in a variety of ways, whereas miRNAs can directly target a large number of genes relevant to melanogenesis [25]. We propose the utilization of laboratory animals to investigate therapeutic non-coding RNA targeting lncRNAs that disrupt certain genes associated with the development of vitiligo.

CONCLUSION:

Sirtuin – 1 (SIRT-1) type of Sirtuins family (deacetylase enzyme family SIRT 1-7 activity) with NAD+ dependent activity, SIRT-1 gene located on chromosome 10q22.1. melanin-concentrating hormone (MCH): pipted was first discovered in the pituitary of chum salmon, the name comes from its ability to control pigmentation in skin. There are insufficient studies supporting the functions of MCH in mammalian skin physiology including skin pigmentation. Cytokine is implicated in several immunological diseases, and cytokine is involved in pathogenesis of vitiligo. This study demonstrated the deregulated expressions of LncRNA SIRT-1 and LncRNA PMCH in patients with vitiligo suggesting that both contributed to the pathogenesis of vitiligo that might be through serum SIRT-1, MCH down regulation and cytokines up regulation.

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نظرة جديدة في اسباب نشوء مرض البهاق، ارتباط جزيئات RNA الطويلة وبعض المعايير المناعية مع تعبير جينات هرمون المركز للميلانين والسيروتوين 1 في البهاق العام والمجزأ

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الملخص

حلفية الدراسة والأهداف : يمثل الحمض النووي الريبوزي الطويل غير المشفر (LncRNAs) مجموعة فرعية من المواد الوراثية تتجاوز 200 زوج قاعدي تفتقر إلى القدرة على ترميز البروتين، ولكنها تمتلك القدرة الفريدة على تعديل التعبير الجيني.

منهجية الدراسة : أجريت هذه الدراسة لغرض تحديد مستويات التعبير عن LncRNA SIRT-1 وLncRNA MCH، بالإضافة إلى المستويات المصلية IL-17وIL-33 وIFNγ لدى الأفراد المصابين بالبهاق. كما هدف هذا البحث إلى استكشاف الارتباط المحتمل بين الحمض النووي الريبوزي الطويل غير المشفر والمعايير المدروسة. تم إجراء الدراسة على مجموعة مكونة من 30 مريضًا مصابًا بالبهاق العام (GV) و30 مريضًا مصابًا بالبهاق المجزأ (SV) بغض النظر عن الحالة العلاجية، و25 من الاشخاص الاصحاء (HC). باستخدام تقنية ELISA، تم قياس مستويات IL-17 وIL-33 وIFNγ و1 SIRT وPMCH في المصل. بالإضافة إلى ذلك، تم إجراء تحليل التعبير الجيني لـ SIRT-1 وLncRNA PMCH في مرضى GV وSV من أجل تسليط الضوء على آثارهم المحتملة في التسبب في البهاق. كان التعبير عن LncRNA SIRT-1 أعلى بشكل ملحوظ في GV مقارنة بـ SV (p = 0.030، اختبار مان ويتني)، مع متوسط مستويات التعبير 2.851 (SE: 1.052) و0.507 (SE: 0.134)، على التوالي. في المقابل،

النتائج : لم يُلاحظ أي فرق كبير في التعبير عن LncRNA MCH بين نوعي البهاق. وكخلاصة عامة بعد التحقيق في الارتباط بين التعبير عن lncRNA لجينات SIRT1 وMCH وتراكيزها في المصل لدى مرضى البهاق, أوضح هذا البحث المظاهر غير المنظمة لـ LncRNA SIRT-1 و LncRNA MCH في الأفراد الذين تم تشخيصهم بالبهاق، مما يشير إلى مساهماتهم المحتملة في نشوء

الكلمات الدالة: البهاق، RNAs الطويلة غير المشفرة، جين السيرتوين 1، الهرمون المركز للميلانين، الإنترلوكينات