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Long Non-coding RNA HOTAIR as Diagnostic Marker in Dermatological Autoimmune Diseases: A Systematic Review

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Abstract:

Damage to different organs is caused by aberrant responses from the innate and adaptive immune systems in autoimmune disorders, which encompass a variety of issues. The cause of autoimmune diseases is a very complex and poorly understood phenomenon. The search results contained original research from PubMed, Medline, and EMBASE. There were no review papers included. Studies must have published at least one lncRNA that they discovered through experimentation. Psoriasis, alopecia areata, systemic sclerosis, and melanoma were among the autoimmune dermatological conditions that were mentioned. Except for alopecia areata, where expression was downregulated relative to control, HOTAIR expression was significantly higher in cases of autoimmune dermatological diseases than in the control group in all cases. We can conclude that the long non-coding RNA known as HOTAIR functions as a diagnostic marker for skin autoimmune diseases.

Keywords: autoimmune diseases; HOTAIR; long non-coding RNA.

1. Introduction

Psoriatic arthritis (PsA) is a persistent, immune-mediated, unevenly distributed inflammatory condition affecting the joints. It is typified by inflammation of the synovial membrane and the areas where tendons or ligaments attach to the bone (enthesis), which can ultimately lead to joint erosion and the creation of new bone [1]. Approximately 30% of individuals with skin psoriasis may experience the development

of PsA, with a prevalence rate estimated at 1% in the overall population. Psoriatic arthritis shares clinical and genetic traits with other seronegative spondyloarthritis types [2, 3]. The 2006 Classification Criteria for Psoriatic Arthritis [CASPAR criteria] define PsA, and use it to enroll patients in clinical trials, and support physicians; however, the Psoriatic arthritis diagnostic criteria have not been confirmed [4, 5]. As a result, after ruling out the possibility of other seronegative arthritis, the diagnosis of PsA is primarily based on clinical symptoms. Moreover, no useful diagnostic tests are available at this time.

Although much remains to be understood, autoimmunity and autoinflammation are thought to play major roles in the pathogenesis of PsA. Synovial tissue in PsA is characterized by marked angiogenesis, T-cell infiltration, and synovial hyperplasia along with increased protease and cytokine production. These results might intensify the local inflammatory process, which would lead to joint destruction in the end [6]. One important inflammatory mediator that has been connected to the advancement of joint degeneration in PsA patients is tumor necrosis factor-alpha (TNF-α) [6]. Currently, TNF-α inhibitors are used to treat psoriatic arthritis. However, a considerable fraction of people with PsA show insufficient reaction to TNF-α antagonists [1, 7]. As a result, additional cytokines, such as IL-12, IL-17, and interleukin-23 [IL-23], have become key players for biological agents [1, 7]. IL-17 plays a critical role in the development and course of the illness [8].

LncRNAs are significant molecules involved in inflammatory and immunological processes; they affect gene expression in a variety of ways [11]. There is little evidence that psoriasis causes the deregulation of specific lncRNAs, and no studies have looked at the expression patterns of these lncRNAs in patients with psoriatic arthritis [12, 13].

2. Methods

2.1.Selection criteria for studies

Inclusion criteria

RCT studies, controlled clinical trials, retrospective cohort studies, and studies published in English.

Exclusion criteria

Languages other than English, duplicates, non-clinical outcome studies, case report studies, case series studies, review articles, cross-sectional studies, abstract only, not full text, cadaver or Model Studies, and data sets that are considered as duplicated or overlapping.

2.2.Statistical considerations

The results of all relevant research were merged using systematic review management software, ensuring that each study met the established inclusion criteria. A PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] flow chart was built to demonstrate the process of selecting papers for review (**Figure 1**). This chart shows how many studies were included in the review, screened, and appraised for eligibility. Each trial included in the study had its potential for bias assessed using the Cochrane Collaboration's risk-assessment technique. They included elements like as blinding, randomization, and the thoroughness with which outcome reporting was conducted. The relative risk of each primary outcome measure, including the frequency of thromboembolic events and bleeding complications, was calculated. This necessitated merging data from multiple research and using statistical techniques appropriate for meta-analysis, such as random-effects models or fixed-effects models, based on the heterogeneity observed in the studies. I^2 statistics were used to analyze heterogeneity in study results. Sensitivity analyses were conducted to examine how different methodologies and participant characteristics affected the overall results. To determine the impact of unpublished studies on the review's conclusions, publication bias was assessed using techniques such as funnel plots and Egger's regression test.

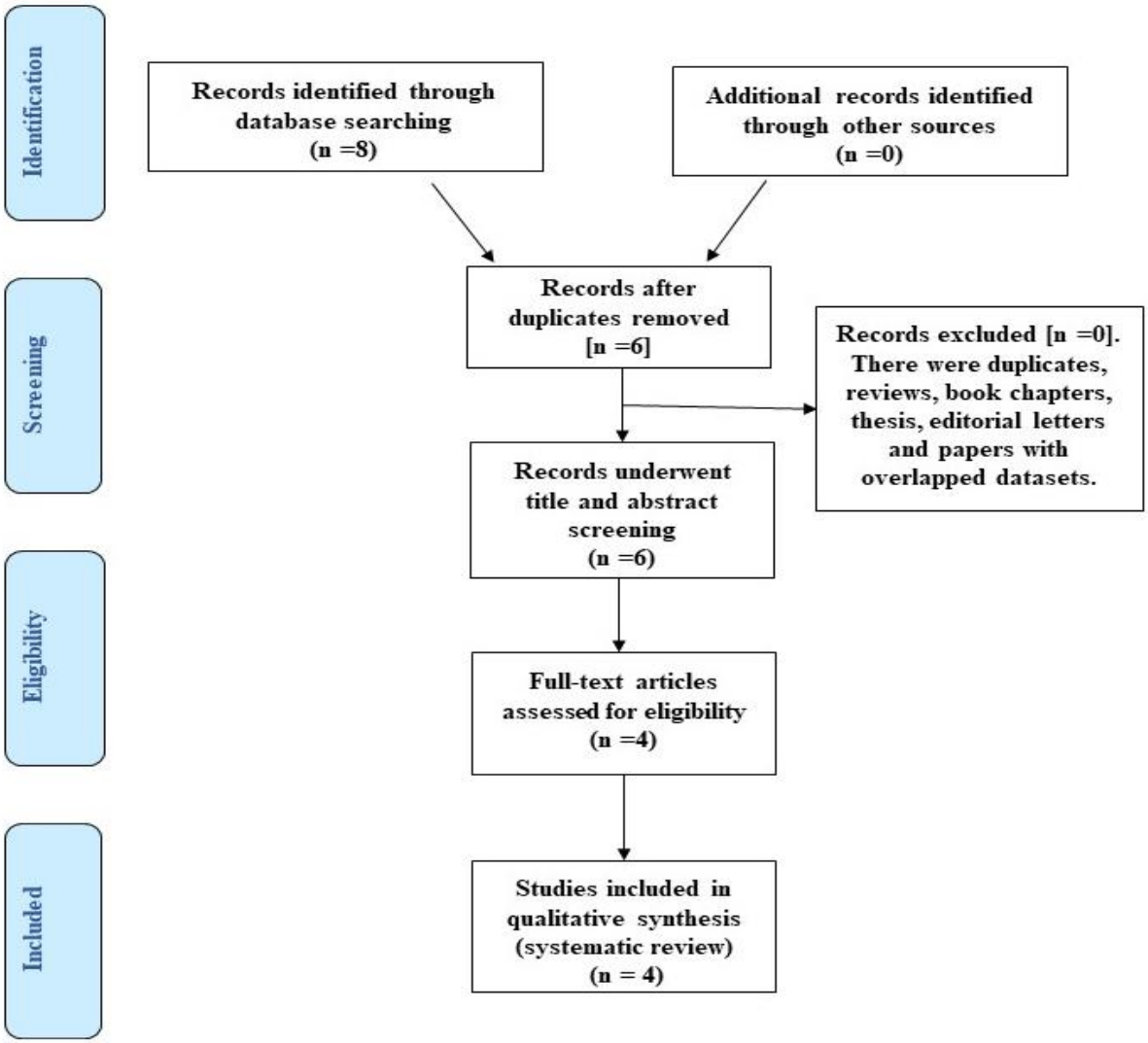

Figure 1: PRISMA flow diagram showing the process of study selection.

3. Results

Four studies were included three as Case-control studies and one retrospective. A total of 200 participants were included and divided into case and control groups with a mean age was 43.06 years as shown in **Table 1.**

Table1. Studies characteristics**.**

The study	Year	Type	Group	Age	Male/ Female
Mohamad et al. [14]	2023	Case-control	Control (50) Cases (50)		
Zahra et al. [15]	2023	Case-control	Control (20), Cases (40)	Cases (37.8) Control (41.4)	50/50in case group, 50/50 in control group.
Wasson et al. [16]	2020	Case-control	Cases (3)		
Cantile et al. [17]	2017	Retrospective	Cases (37)	50	16/21

Autoimmune dermatological disease and HOTAIR expression. Autoimmune dermatological diseases included were psoriasis, alopecia areata, systemic sclerosis and melanoma in all diseases HOTAIR expression was significantly higher in cases with autoimmune dermatological disease than in control except in alopecia areata expression was down-regulated than control as shown in **Table 2**.

Table2. Autoimmune dermatological disease and HOTAIR expression.

The study	Year	Types of autoimmune dermatological disease	HOTAIR expression
Mohamad et al. [14]	2023	Alopecia areata	• Significantly, AA individuals had a downregulated serum expression of lncRNA HOTAIR ($p < 0.001$).
Zahra et al. [15]	2023	Psoriasis	• Expression of the HOTAIR in 40 psoriatic patients' serum was assessed in comparison with its level in the serum of 20 matched control subjects. It showed a highly significant statistical result of upregulation in the expression of the

			HOTAIR in the serum of psoriatic cases compared to the control participants ($p \leq 0.001$).
Wasson et al. [16]	2020	Systemic sclerosis	• Dermal fibroblasts overexpressing HOTAIR induced the Hedgehog pathway's transcription factor GLI2 production. The epigenetic suppression of miRNA-34a expression results in the activation of Notch signalling, which facilitates the process. Reduced GLI2 expression was observed in fibroblasts that express HOTAIR and in fibroblasts from patients with systemic sclerosis (SSc) due to suppression of H3K27 methylation and Notch signalling. Crucially, the pro-fibrotic phenotype caused by HOTAIR may be alleviated by inhibiting the action of GLI2 by GANT61 or siRNA.
Cantile et al. [17]	2017	Melanoma	• In all of the benign melanocytic lesions, HOTAIR was not found. The HOTAIR staining showed a significantly high intensity in all primary tissues and the corresponding metastases, but a significantly low intensity in the primary pT1 lesions. Surprisingly, they found that HOTAIR was present in certain cells inside the tumour, though the amount of positive decreased in lymphocytes located farther away from the tumour. Additionally, HOTAIR was found in the serum of some patients who had metastatic illnesses.

4. Discussion

Autoimmune disorders encompass a diverse range of illnesses that arise from abnormal immune responses to antigens inside the body. These immune reactions result in attacks on healthy molecules, cells, and tissues, leading to damage in many systems and organs of the human body [18].

The term "autoimmune diseases" refers to a broad category of complicated illnesses, the most common of which are RA, SSc, SLE, idiopathic inflammatory myopathy [IIM], and Sjögren's syndrome (pSS). These illnesses can manifest clinically as anything from minor skin rashes to severe organ dysfunction. Most autoimmune conditions are difficult for doctors to diagnose and treat quickly because the pathogenic process involved in these illnesses is complex and still poorly understood. Therefore, it's imperative to identify the key regulators in autoimmune diseases and learn more about the underlying molecular mechanisms [19, 20]. According to Cao et al. (2020), there is a decrease in lncRNA TUG1 in SLE patients' PBMCs, compared to healthy controls [21]. TUG1 levels were even lower in SLE patients with lupus nephritis, according to these authors' findings. Additionally, they found a negative correlation between TUG1 levels and 24-hour urine protein, SLEDAI, ESR, and length of illness. Because of this, this lncRNA may serve as a particular diagnostic marker for people who have systemic lupus erythematosus [SLE] or SLE combined with lupus nephritis. Circulating lncRNAs may be a promising biomarker for SLE, according to mounting evidence. Moreover, it has been discovered that the serum exosomes of RA patients contain lncRNAs. These include TUG1, NEAT1, and MALAT1.

Mohamad et al. (2023) sought to evaluate the relationship between the onset, course, and severity of AA and the levels of miRNA-205, HOTAIR, lncRNA, and TGF-β1 [14]. There were two participant groups, according to the case-control study: fifty people with AA diagnoses and fifty matched healthy controls. Using quantitative RT-PCR, the expression levels of long noncoding RNA HOTAIR and miRNA-205 were determined. Conversely, ELISA methods were employed to ascertain the blood's TGF-β1 levels. It was discovered that AA individuals had considerably lower blood levels of the long noncoding RNA HOTAIR, with a P value of less than 0.001. Moreover, it was demonstrated that these people had noticeably higher blood levels of TGF-β1 and miRNA-205. Karimi et al. (2022) sought to evaluate the role of lncRNAs in both innate and adaptive immune responses,

as well as their irregularity in the development of autoimmune disorders [22]. Their study highlighted the potential involvement of low lncRNA HOTAIR serum expression and high TGF-β1 and miRNA-205 serum expression in the development of AA.

Conclusion

Long non-coding RNA HOTAIR can be used as a diagnostic marker for dermatological autoimmune diseases.

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References

1. Wang Y, Yu H, He J. Role of dyslipidemia in accelerating inflammation, autoimmunity, and atherosclerosis in systemic lupus erythematosus and other autoimmune diseases. Discov Med. 2020;30(159):49-56.
2. Huang Y, Chen Z, Wang Y, Han L, Qin K, Huang W, Huang Y, Wang H, Shen P, Ba X, Lin W, Dong H, Zhang M, Tu S. Clinical characteristics of 17 patients with COVID-19 and systemic autoimmune diseases: a retrospective study. Ann Rheum Dis. 2020;79(9):1163-1169. doi: 10.1136/annrheumdis-2020-217425.
3. Muntyanu A, Le M, Ridha Z, O'Brien E, Litvinov IV, Lefrançois P, Netchiporouk E. Novel role of long non-coding RNAs in autoimmune cutaneous disease. J Cell Commun Signal. 2022;16(4):487-504. doi: 10.1007/s12079-021-00639-x.
4. Muntyanu A, Le M, Ridha Z, O'Brien E, Litvinov IV, Lefrançois P, Netchiporouk E. Novel role of long non-coding RNAs in autoimmune cutaneous disease. J Cell Commun Signal. 2022;16(4):487-504. doi: 10.1007/s12079-021-00639-x.
5. Zou Y, Xu H. Involvement of long noncoding RNAs in the pathogenesis of autoimmune diseases. J Transl Autoimmun. 2020;3:100044. doi: 10.1016/j.jtauto.2020.100044.
6. Gao Y, Li S, Zhang Z, Yu X, Zheng J. The Role of Long Non-coding RNAs in the Pathogenesis of RA, SLE, and SS. Front Med (Lausanne). 2018;5:193. doi: 10.3389/fmed.2018.00193.
7. Geng L, Xu X, Zhang H, Chen C, Hou Y, Yao G, Wang S, Wang D, Feng X, Sun L, Liang J. Comprehensive expression profile of long non-coding RNAs in Peripheral blood mononuclear cells from patients with neuropsychiatric systemic lupus erythematosus. Ann Transl Med. 2020;8(6):349. doi: 10.21037/atm.2020.03.25.
8. Wu GC, Pan HF, Leng RX, Wang DG, Li XP, Li XM, Ye DQ. Emerging role of long noncoding RNAs in autoimmune diseases. Autoimmun Rev. 2015;14(9):798-805. doi: 10.1016/j.autrev.2015.05.004.
9. Sandhya P, Joshi K, Scaria V. Long noncoding RNAs could be potential key players in the pathophysiology of Sjögren's syndrome. Int J Rheum Dis. 2015;18(8):898-905. doi: 10.1111/1756-185X.12752.

10. Fang Y, Tu J, Han D, Guo Y, Hong W, Wei W. The effects of long non-coding ribonucleic acids on various cellular components in rheumatoid arthritis. Rheumatology (Oxford). 2020;59(1):46-56. doi: 10.1093/rheumatology/kez472.
11. Tang Y, Zhou T, Yu X, Xue Z, Shen N. The role of long non-coding RNAs in rheumatic diseases. Nat Rev Rheumatol. 2017;13(11):657-669. doi: 10.1038/nrrheum.2017.162.
12. Gao X, Liu L, Min X, Jia S, Zhao M. Non-Coding RNAs in CD4+ T Cells: New Insights Into the Pathogenesis of Systemic Lupus Erythematosus. Front Immunol. 2020;11:568. doi: 10.3389/fimmu.2020.00568.
13. Chen J, Ao L, Yang J. Long non-coding RNAs in diseases related to inflammation and immunity. Ann Transl Med. 2019;7(18):494. doi: 10.21037/atm.2019.08.37.
14. Mohamad N, Khedr AMB, Shaker OG, Hassan M. Expression of Long Noncoding RNA, HOTAIR, and MicroRNA-205 and Their Relation to Transforming Growth Factor β1 in Patients with Alopecia Areata. Skin Appendage Disord. 2023;9(2):111-120. doi: 10.1159/000527851.
15. Zahra A, Elamir A, Mohammed B, Elsayed H. LncRNA HOTAIR as a novel biomarker in Psoriasis. Fayoum University Medical Journal. 2023;12[3]:53-62. Doi: 10.21608/FUMJ.2023.336853
16. Wasson CW, Abignano G, Hermes H, Malaab M, Ross RL, Jimenez SA, Chang HY, Feghali-Bostwick CA, Del Galdo F. Long non-coding RNA HOTAIR drives EZH2-dependent myofibroblast activation in systemic sclerosis through miRNA 34a-dependent activation of NOTCH. Ann Rheum Dis. 2020;79(4):507-517. doi: 10.1136/annrheumdis-2019-216542.
17. Cantile M, Scognamiglio G, Marra L, Aquino G, Botti C, Falcone MR, Malzone MG, Liguori G, Di Bonito M, Franco R, Ascierto PA, Botti G. HOTAIR role in melanoma progression and its identification in the blood of patients with advanced disease. J Cell Physiol. 2017;232(12):3422-3432. doi: 10.1002/jcp.25789.
18. Mehmandar-Oskuie A, Jahankhani K, Rostamlou A, Mardafkan N, Karamali N, Razavi ZS, Mardi A. Molecular mechanism of lncRNAs in pathogenesis and diagnosis of auto-immune diseases, with a special focus on lncRNA-based therapeutic approaches. Life Sci. 2024;336:122322. doi: 10.1016/j.lfs.2023.122322.
19. Zou Y, Xu H. Involvement of long noncoding RNAs in the pathogenesis of autoimmune diseases. J Transl Autoimmun. 2020;3:100044. doi: 10.1016/j.jtauto.2020.100044.
20. Khan AQ, Ahmad F, Raza SS, Zarif L, Siveen KS, Sher G, Agha MV, Rashid K, Kulinski M, Buddenkotte J, Uddin S, Steinhoff M. Role of non-coding RNAs in the progression and resistance of cutaneous malignancies and autoimmune diseases. Semin Cancer Biol. 2022;83:208-226. doi: 10.1016/j.semcancer.2020.07.003.
21. Cao HY, Li D, Wang YP, Lu HX, Sun J, Li HB. Clinical significance of reduced expression of lncRNA TUG1 in the peripheral blood of systemic lupus erythematosus patients. Int J Rheum Dis. 2020;23(3):428-434. doi: 10.1111/1756-185X.13786.
22. Karimi B, Dehghani Firoozabadi A, Peymani M, Ghaedi K. Circulating long noncoding RNAs as novel bio-tools: Focus on autoimmune diseases. Hum Immunol. 2022;83(8-9):618-627. doi: 10.1016/j.humimm.2022.06.001.