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Association of HLA class II gene polymorphisms and expression levels of *ORAI1/STIM1* genes in HIV-1–positive patients with HIV-related dermatoses in Latvia

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Abstract

Introduction: This study explores the immunogenetic associations of human leukocyte antigens (HLA) and the calcium release-activated calcium modulator 1 (*ORAI1*) and stromal interaction molecule 1 (*STIM1*) genes in HIV-1–positive patients with HIV-related skin disorders.

Methods: This study assessed the distribution of variants of HLA class II alleles and expression levels of *ORAI1* and *STIM1* genes in the blood between HIV-1–positive patients with HIV-related skin disorders and the control group with no HIV within the Latvian population.

Results: The research group comprised 115 HIV-1–positive patients with HIV-related skin disorders, and the control group included 80 healthy individuals. Risk alleles (HLA-DQB1*02:01-0301 and HLA-DQA1*01:01-0501) and protective alleles (HLA-DRB1*07-13, DRB1*01-13, DRB1*04-11, and HLA-DQA1*05:01-0501) showed statistical significance in the groups. In 38 out of 115 patients, higher expression levels of *ORAI1* and *STIM1* genes were detected in the blood at the beginning of treatment. A significantly higher level of the microribonucleic acid (mRNA) *ORAI1* gene was also found in the control group.

Conclusions: The results demonstrate that HLA class II alleles are associated with a trend toward risk/protection concerning HIV-related skin disorders in HIV-1–positive patients. It was also shown that a low level of *ORAI1* mRNA and the risk allele HLA-DQB1*0201-0301 were simultaneously present in the research group.

Keywords: HLA, polymorphisms, *ORAI1*, *STIM1*, HIV-related dermatoses

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Introduction

The global HIV epidemic remains a significant concern, with more than 39 million people worldwide living with HIV infection in 2022, according to the Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO) estimates (1). Skin disorders are frequently observed in individuals with HIV, often serving as the initial sign of the disease. Up to 90% of people with HIV experience skin conditions during their illness (2). Cutaneous disorders linked to HIV-1 can have a negative impact on self-esteem, leading to depression and an increased risk of suicide among patients. Many of these skin disorders associated with HIV-1 are now recognized as markers of disease progression and may offer valuable clinical insights into the individual's immune status (3, 4).

Dermatological conditions associated with HIV encompass a range of disorders such as pruritus papular eruptions (PPE), xerosis with secondary staphylococcal and superficial mycotic infections, seborrheic dermatitis, atopic dermatitis (AD), atopic-like dermatitis, eosinophilic folliculitis, psoriasis, prurigo nodularis, and manifestations induced by antiretroviral therapy (ART) therapy (3, 5, 6).

In HIV-positive adults, a condition often resembling AD, referred to as "atopic-like dermatitis," is common. It can be accompanied by generalized xerosis, extensive excoriation with secondary staphylococcal infection, and prurigo nodularis (7).

Mohseni Afshar et al. (8) explore various opportunistic infections in their research, including bacillary angiomatosis, histoplasmosis, herpetic and mycobacterial infections, molluscum contagiosum, cryptococcosis, systemic fungal infections such as *Talaromyces marneffei*, sporotrichosis, cutaneous tuberculosis (TB), herpes zoster, and cutaneous leishmaniasis.

HLA antigens

The immunogenetic associations of human leukocyte antigens (HLA) in HIV-related skin disorders remain a relatively understudied area. However, studying the influence of immunogenetic biomarkers is a concept of personalized medicine and one method to predict clinical outcomes.

Certain HLA antigens have been found to be more frequent than others among HIV-positive patients. Furthermore, different HLA antigens seem to influence the variability of disease progression (4).

HLA-B35 has been associated with rapid HIV disease progression, whereas HLA-B27 and HLA-B*57 have been linked to delayed HIV progression (9). Observational studies indicate that individuals with HIV that develop opportunistic infections typically exhibit a normal frequency of HLA-DR2 and HLA-DR5 antigens, but a notably higher frequency of HLA-DR3. The progression of HIV infection, especially in individuals with unexplained lymphadenopathy, might be influenced by genetic factors associated with these specific HLA-DR types (4).

HLA antigens play a critical role in presenting antigens to T cells

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and shaping their diversity. These genes encode proteins that control immune reactions and distinguish between foreign and self-antigens. Variations in HLA molecules across individuals due to genetic differences can result in changes in how antigens bind and alter the immune response to pathogens (4, 10).

According to a study by Khan et al. (11), HLA class II gene polymorphism may play a role in HIV-related skin disorders. The authors suggest that the diverse alleles of HLA class II genes could play a role in preserving humoral immunity against infectious illnesses. They propose that polymorphisms in HLA class II genes provide specific humoral immunity against prevalent pathogens (11).

It is well known that individuals with cell-mediated immunodeficiencies are susceptible to human papillomavirus (HPV) infections and often show resistance to treatment. Increased frequencies of the HLA-DQA103:01, HLA-DQB103:01, HLA-DRB107, and HLA-DRB109 genes have been observed, whereas decreased frequencies of the HLA-DQA105:01, HLA-DQB106:03, HLA-DRB101, and HLA-DRB103 genes have been found in patients with prolonged skin warts due to HPV2, HPV27, and HPV57 infections (10).

Studies have shown that seborrheic dermatitis (SD) patients exhibit cells expressing class II antigens, suggesting potential T-cell function impairment and defective cellular immune responses. Specific alleles, such as A30, A31, and B12 (HLA-B44 or HLA-B45), have been associated with SD. Furthermore, alleles such as A32, DQB105, and DRB1*01 have been linked to a higher risk of developing SD (12).

An increased frequency of the HLA-DR5 antigen has been reported in patients with HIV-related thrombocytopenic purpura, suggesting that DR5 may indicate a predisposition to developing clinical symptoms of purpura in HIV-infected individuals (13).

Studies investigating the persistence of HPV infection among HIV-infected individuals have revealed that HLA-B44 is more prevalent among HIV-positive patients with warts, and that protective genes such as HLA-DQB106 might also play a role. HLA-DRB113:01/02 and HLA-DQB106:03 have been linked to protection against HPV-related diseases, whereas HLA-DQB106:02 has shown varied associations (protective, neutral, or deleterious). In addition, alleles such as HLA-DRB103:01 and HLA-DQB103:01/02/03, as well as the haplotype HLA-DRB115:01, HLA-DQB1*06:02, have been associated with increased susceptibility (9).

The HLA-Cw0602 allele has been found to correlate with type 1 psoriasis, with a stronger association observed in HIV-associated cases. It is suggested that HIV-associated immune dysregulation may trigger psoriasis in patients genetically predisposed by the Cw0602 allele. The presence of HLA-Cw6 (serologically defined) is associated with a relative risk ranging from 10% to 25% for developing psoriasis (14).

Recent research has uncovered associations between HLA-Cw1 and specific Asian populations in the context of psoriasis. HLA-Cw6 has been correlated with type I early-onset psoriasis, Koebner phenomenon, guttate psoriasis, and a more favorable response to medications targeting interleukin (IL)-17, IL-12/23, IL-23, and methotrexate. Conversely, the presence of HLA-Cw1 has been linked to pustular psoriasis, erythrodermic psoriasis, and the axial form of psoriatic arthritis. In addition, HLA-Cw1 positivity has been more commonly observed in patients requiring intensive treatments that showed inadequate responses to conventional therapies (15).

HLA alleles are also implicated in the absence of response to ART in HIV infection. The genetic profile of locus B was found to be significantly associated with treatment nonresponse, particularly with the B13, B35, and B*39 alleles having the most substantial probabilistic impact. Among these alleles, B13 posed the highest risk of treatment nonresponse because carriers of this allele exhibited a detectable viral load and a CD4+ T lymphocyte count of less than 400 cells/μl within 2 years of initiating therapy (16).

ORAI1 and *STIM1* genes

The calcium release-activated calcium modulator 1 (ORAI1) protein functions as a pore subunit of a store-operated Ca^{2+} channel, which plays a crucial role in facilitating Ca^{2+} influx in nonexcitable cells.

To establish and maintain the structure and homeostasis of the skin, keratinocytes must carefully regulate growth, differentiation, and directed movement, all of which are influenced by calcium (17).

The influx of Ca^{2+} into cells triggers various signaling pathways that impact vital cellular functions such as gene expression, cellular apoptosis and proliferation, secretion, and transcription of genes (18).

The ORAI1 protein is predominantly found in the basal layer of the skin and decreases as cells differentiate. The ORAI1 channel and stromal interaction molecule 1 (STIM1) proteins play central roles in the store-operated calcium current in human keratinocytes. The ORAI1 channel is implicated in the proliferation and movement of undifferentiated primary human keratinocytes (hPK). *ORAI1* and *STIM1* genes oversee the turnover of focal adhesions and the directional movement of undifferentiated hPK (19).

Calcium release-activated calcium (CRAC) channels facilitate a particular type of calcium influx known as store-operated calcium entry (SOCE), which is crucial for the functioning of various cell types. ORAI1 proteins within the plasma membrane form the ion-conducting pore of CRAC channels. These channels are activated by stromal interaction molecule (STIM1 and STIM2) proteins located in the endoplasmic reticulum. In human patients, mutations resulting in loss or gain of function in *ORAI1* and *STIM1* genes lead to distinct disease syndromes. These syndromes manifest as severe combined immunodeficiency (SCID)-like conditions, muscular weakness, ectodermal dysplasia, autoimmune disorders and dental enamel defects (19).

ORAI1 polymorphism is also linked to AD susceptibility. The results of research by Chang et al. (20) indicate that a non-synonymous single nucleotide polymorphism (SNP) (rs3741596, Ser218Gly) is linked to vulnerability to AD in the Japanese population.

A SNP of the *ORAI1* gene (rs3741595) was also found to be associated with the risk of AD in the Taiwanese population (20). These findings suggest that the genetic polymorphisms of the *ORAI1* gene likely play a role in AD susceptibility.

In a study by Stanisz et al. investigating the role of ORAI-STIM calcium channels in melanocytes, it was discovered that SOCE regulates various processes, including proliferation, migration, invasion, and melanin synthesis in both melanocytes and melanoma cells (21).

Methods

This study sought to identify and detect markers of genetic predisposition and expression levels of *ORAI1* and *STIM1* genes in HIV-related skin disorders among HIV-1–positive patients in Latvia.

A retrospective and prospective study was conducted at Riga East University Hospital, the Latvian Center for Infectious Diseas-

es, and the Joint Laboratory of Clinical Immunology and Immunogenetics of Riga Stradiņš University (RSU/JLCII) between 2021 and 2023.

The study protocol was approved by the Latvian Central Medical Ethics Committee, Riga, Latvia (approval code no. 01-29.1.2/1670) and the Genetic Council (approval code no. A-3/22-05-09) for the genetic analysis. Before enrollment, all study participants or their legal representatives provided written informed consent.

Our study focused exclusively on patients with HIV-related skin disorders, including PPE, xerosis with secondary staphylococcal and superficial mycotic infections, SD, AD, atopic-like dermatitis, eosinophilic folliculitis, psoriasis, prurigo nodularis, and ART-induced drug manifestations. We excluded HIV-positive patients with infectious and neoplastic opportunistic pathologies from our analysis with the exception of TB.

The research group comprised the Latvian target sample of 115 HIV-1–positive patients with HIV-related skin disorders from 43 to 54 years old, with a mean age of 48 years. Among them, 31% were women and 69% were men. The control group comprised a sample of 80 healthy individuals between 43 and 61 years old, with a mean age of 52 years. All the individuals in this group were without HIV-1 infection, active TB, or any skin pathologies.

In 38 out of 115 HIV-1–positive patients with HIV-related skin disorders, we detected expression levels of *ORAI1* and *STIM1* genes in the blood at the beginning of treatment, as well as expression levels of *ORAI1* and *STIM1* genes after 1 month of follow-up. The therapies administered primarily consisted of topical corticosteroids, antibacterials, antimycotics, antiparasitics, calcineurin inhibitors, and skin emollients. In some cases, therapy was supplemented with systemic antibiotics and antifungal drugs in standard doses. The control group consisted of 80 healthy people, varying in age and sex, without HIV-1 infection.

The HLA class II genotype investigation for each patient was conducted at the Joint Laboratory of Clinical Immunology and Immunogenetics of Riga Stradiņš University. Peripheral blood samples (5 ml) were collected in tubes containing EDTA and stored at –20 °C. Human DNA extraction was performed using the QIAamp® DNA Blood Kit (QIAGEN, Hilden, Germany) following the manufacturer's instructions. DNA amplification was carried out via polymerase chain reaction (PCR) using low-resolution sequence-specific primers (DNA-Technology, Moscow, Russia) as per the manufacturer's protocol. Each kit included an internal control to assess PCR quality and a positive control. HLA typing involved identifying HLA-DRB1* alleles (01 to 18), HLA-DQA1* alleles (01:01, 01:02; 01:03; 01:04, 02:01; 03:01; 04:01, 05:01, 06:01), and HLA-DQB1* alleles (02:01-02:02; 03:01-04; 04:01-04:02; 05:01-04; 05:02-03; 06:01; 06:02-08). The Real-Time PCR Thermal Cycler "DT-Lite" with four channels and 48 wells (DNA-Technology) was used for amplification. The reaction mixture underwent 35 amplification cycles, each consisting of denaturation at 94 °C (60 s), followed by one cycle of annealing at 94 °C (20 s), 67 °C (2 s) for seven cycles, and extension at 93 °C (5 s) and 65 °C (4 s), with a final extension step after 35 cycles.

To examine the expression of *ORAI1* and *STIM1* genes, 1 ml of peripheral blood containing EDTA was collected and preserved at –20 °C until analysis. Ribonucleic acid (RNA) extraction from the preserved blood samples was carried out using the innuPREP Blood RNA Life Science Kits & Assays (Analytik Jena Company, Jena, Germany) following the manufacturer's instructions. The quality and quantity of the extracted RNA were assessed using spectrophotometry with the Nanofotometr NF80 (Implen GmbH, Munich, Germany), with a concentration of RNA at 40 µg/ml per reaction. For reverse transcription-PCR (RT-qPCR), the Revert First-Strand cDNA synthesis system utilizing an oligo dT primer (QuantiTect Reverse Transcription, oligo dT primer Invitrogen, Hilden, Germany) was employed according to the manufacturer's protocol. The first-strand cDNA was diluted 1:20 with distilled water and utilized as a template ($K1^+$) in RT-qPCR analysis. Human *STIM1* (Hs STIM1 FAM_1, QF00208159) and *ORAI1* (Hs ORAI 1 FAM_1, QF00163611) specific primers were detected by one-step qRT-PCR using sequence-specific probes for gene expression analysis (QuantiFast Probe Assay, Invitrogen, Hilden, Germany). RT-qPCR was conducted in a DTlite Cycler (DNA-Technology) utilizing fast real-time PCR System under the following amplification conditions: initial denaturation at 95 °C for 5 minutes, followed by 45 cycles of 95 °C for 30 seconds and 60 °C for 30 seconds. The specificity of RT-qPCR products was validated by analyzing the melting curve. Absolute quantification of *STIM1* and *ORAI1* gene expression was determined relative to a standard curve, automatically generated by serial dilution of the reference gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH). The following primers (Invitrogen by Thermo Fischer Scientific, Waltham, Massachusetts, USA) and reference gene (Bioneer Corporation, Daejeon, Korea) were used for amplification: *ORAI1*, forward: 5'-CGTATCTAGAATGCATCCGGAGCC-3', reverse: 5'-CAGCCACTATGCCTAGGTCGACTAGC-3'; *STIM1*, forward: 5'-CCTCGGTACCATCCATGTTGTAGCA-3', reverse: 5'-GCGAAAGCTTACGCTAAAATGGTGTCT-3'; GAPDH, forward: 5'-CCACTCCTCCACCTTTGAC-3', reverse: 5'-ACCCTGTTGCTGTAGCCA-3'; probe, 5'-TTGCCCTCAACGACCACTTTGTC-3'.

Statistical data analysis

The evaluation of data distribution was conducted using the Shapiro–Wilk test and examination of normal Q–Q plots. Homogeneity of variance was assessed through Levene's test. The Wilcoxon signed rank test was used to compare mRNA *STIM1* and mRNA *ORAI1* before and after treatment. To compare the mRNA *STIM1* gene and mRNA *ORAI1* gene between the research and control group, the Mann–Whitney *U* test was used. The association between quantitative variables (mRNA *STIM1*, mRNA *ORAI1*, years to skin, CD4+, HIV-1 RNA load) and dichotomous variables (protective/risk alleles) was tested with the rank biserial correlation test. The correlation between mRNA *STIM1* gene expression, mRNA *ORAI1* gene expression, time (years) to the manifestation of HIV-related dermatoses, CD4+ cell count, and HIV-1 RNA load was assessed with Spearman's correlation test. To test the association between alleles, the chi-squared test of association was used. The statistical data analysis was conducted with Jamovi software (v.2.3). The results were considered statistically significant when the p-value < 0.05.

Results

Among the participants in our research group, 70 out of 115 patients were diagnosed with TB. Diagnosis of pulmonary TB was confirmed by chest radiography and positive bacteriological culture from sputum (GeneXpert MTB/RIF, Cepheid, France). In the research group, HIV-related skin pathologies were diagnosed within a range of 3 to 11 years after detection of HIV-1 infection, with a mean interval of 6 years. The median CD4+ cell count at the time of HIV-1 infection detection was 448 cells/ml³. The diagnosis of HIV-related skin disorders was confirmed by dermatologists of

the Latvian Center for Infectious Diseases.

The characteristics of patients in both the research and control groups are presented in Table 1. All subjects enrolled in the study met specific eligibility criteria: permanent residence in Latvia, absence of relatives in the group, exclusion of children under age 18, and, for the control group, healthy individuals that were third-generation residents of Latvia.

Expression levels of *ORAI1/STIM1* genes

A statistically significant difference in mRNA *ORAI1* gene expression was observed between the control and research groups, exhibiting a moderate effect size ($p < 0.05$). No significant difference in mRNA *STIM1* gene expression was observed between the two groups ($p > 0.05$; Table 2).

In addition, we examined the mRNA expression levels of *ORAI1* and *STIM1* genes in HIV-1–positive patients with HIV-related dermatoses before commencing dermatological treatment and after 1 month of follow-up. Our findings revealed significantly reduced levels of *ORAI1* mRNA and *STIM1* mRNA after 1 month of treatment within our study group, with a p-value of less than 0.05 (Table 3). The effect size suggests a substantial practical significance of this observed difference.

Relationships between factors in the research group with HIV-related skin disorders

The correlation analysis between CD4+ cell count and other markers in our research revealed several significant associations. CD4+ cell count at the beginning of HIV-1 infection exhibited a significant negative correlation with HIV-1 RNA load at the time of HIV-1 infection detection ($r = -0.29$, $n = 115$, $p < 0.05$) and a significant positive correlation with the time to manifestation of HIV-related skin pathologies ($r = 0.30$, $n = 115$, $p < 0.001$). In addition, HIV-1 RNA load at the time of HIV-1 infection detection showed a significant negative correlation with the time to HIV-related skin disorders ($r = -0.26$, $n = 115$, $p < 0.05$).

Among all identified protective and risk alleles, only the HLA-DQB1*0201-0301 (risk) allele was significantly related to HIV-1 RNA load ($r = 0.26$, $n = 115$, $p < 0.05$). Patients with this allele exhibited a higher viral load than patients without it. Furthermore, the HLA-DRB1 07-13 allele (protective) was related to the time to HIV-related skin disorders ($r = 0.20$, $n = 115$, $p < 0.05$).

Our data also revealed a moderate association between the HLA-DQB10201-0301 (risk) allele and mRNA ORAI1 gene expression ($r = 0.48$, $n = 38$, $p < 0.001$), as well as a weak association between this risk allele HLA-DQB10201-0301 and HIV-1 RNA load at the time of HIV-1 infection detection ($r = 0.26$, $n = 115$, $p < 0.05$).

Polymorphisms of HLA class II

We assessed the polymorphism of HLA class II by comparing observed frequencies of alleles in two study groups (research and control), and by identifying protective and risk alleles in loci HLA-DRB1, HLA-DQA1, and HLA-DQB1 (Table 4).

Among HLA-DRB1 alleles, HLA-DRB107-13, DRB101-13, and

Table 1 | Clinical and demographic information on research and control groups.

Parameter	Group	
	Research	Control
Number of patients, *n* (%)	115 (59%)	80 (41%)
Mean age (years), median (IQR)	48 (43–54)	52 (43–61)
Sex, *n* (%)		
Male	79 (69%)	48 (60%)
Female	36 (31%)	32 (40%)
All TB, *n* (%)	70 (61%)	NA
Time to skin*, median (IQR)	6 (3–11)	NA
CD4+ cell count (cells/μl), median (IQR)	448 (288–631)	NA
HIV-1 RNA load (copies/ml), median (IQR)	17,000 (1,315–109,500)	NA

IQR = interquartile range (presented as Q1–Q3,) TB = tuberculosis, NA = not applicable.
*Time to manifestation of HIV-related dermatoses (years).

Table 2 | Comparison of mRNA *ORAI1* and *STIM1* expression levels between research and control groups.

Markers, copies/ml	Group, median (IQR)		*p*	*r*
	Research	Control		
ORAI1 mRNA	461 (42–859)	1,973 (53 – 3.10×10^{11})	0.006	0.32
STIM1 mRNA	1,100 (12–1,690)	130 (7–13,608)	0.489	NA

IQR = interquartile range (presented as Q1–Q3), *r* = effect size, NA = not applicable.

Table 3 | Expression levels of *ORAI1* and *STIM1* in the research group at the beginning of therapy and after 1 month of follow-up.

Parameter, copies/ml	Median (Q1–Q3)		*p*	*r*
	Before	After		
ORAI1 mRNA	784 (44 – 1.10×10^{8})	82 (44–82)	0.004	0.56
STIM1 mRNA	978 (8–3,230)	16 (8–31)	0.003	0.58

IQR = interquartile range (presented as Q1–Q3), *r* = effect size.

Table 4 | Distribution of protective and risk alleles of HLA class II in the research ($n = 115$) and control ($n = 80$) groups.

Alleles	Relative frequency		OR (95% CI)	*p*
	Research	Control		
DRB1 07-13	0.02	0.09	0.19 (0.04–0.91)	0.022
DRB1 01-13	0.01	0.09	0.09 (0.01–0.76)	0.006
DRB1 04-11	0.00	0.05	0.07 (0.001–1.39)	0.015
DQA1 0101-0501	0.22	0.06	4.20 (1.5–11.4)	0.003
DQA1 0501-0501	0.03	0.10	0.24 (0.06–0.94)	0.028
DQB1 0201-0301	0.10	0.00	19.40 (1.1–333)	0.003

OR = odds ratio, CI = confidence interval.

DRB104-11 alleles were less frequently detected in the research group compared to the control group. The comparison of frequencies of HLA-DQA1 alleles revealed varying effects. HLA-DQA10101-0501 was identified as a risk factor with a similarly high risk for HIV-related dermatoses in patients with HIV-1. Conversely, patients with HLA-DQA1*0501-0501 alleles were more commonly found in the control group than in our research group.

Protective and risk effects were also observed in the HLA-DQB1 locus. The HLA-DQB1*0201-0301 allele was detected more frequently in the research group (Table 4).

Discussion

HLA

This study observed a higher frequency of the HLA-DQB1*02:01-0301 allele in the HIV-related group. Interestingly, contrary to findings from other investigations, the study revealed a correlation between the presence of the HLA class II allele DQB103:02 and immune defense against HIV infection. Conversely, the presence of the HLA class I allele A02:01 was associated with HIV infection (22). Other studies have also indicated a correlation between the DQB1*0301 allele and ongoing hepatitis B virus infection (23).

Regarding other skin disorders, significant increases in HLA DQA10301, DQB10302, and HLA-DQB1*0502 were observed in pemphigus vulgaris patients (24). Furthermore, our study identified a relationship between the HLA-DQB1 0201-0301 (risk) allele and HIV-1 RNA load. In a study of pulmonary TB in HIV patients, homozygosity in HLA-DQB1 loci was found to be an unfavorable factor, accelerating complications and death in co-infected patients (25).

In addition, other studies have found that the protective allele HLA-DQB106:02 is associated with a lower viral load and a longer interval between the beginning of HIV-1 infection and TB manifestation. This suggests that the HLA-DQB106:02 allele delays the development of HIV-1 infection (28).

ORAI1

Our study revealed a significantly higher level of mRNA *ORAI1* gene expression in the control group. This finding suggests that lower levels of *ORAI1* gene expression may pose a risk for impaired keratinization, potentially leading to dermatoses such as hyperkeratosis, psoriasis, xerosis, AD, and HIV-related dermatoses. Wang et al. (26) elucidate the diverse roles of calcium channels in the pathogenesis of dermatological conditions, underscoring their significance as potential therapeutic targets. For instance, the transient receptor potential gene (*TRPC6*) is associated with AD and non-melanoma cancer development, *TRPC1* with psoriasis and Darier's disease, and *TRPV1* with prurigo nodularis, skin aging, burn injuries, and AD. In addition, upregulation of the *STIM1* gene in psoriasis induces chemotactic factors and neutrophil chemotaxis (26).

In our study, we observed that the levels of mRNA *ORAI1* and mRNA *STIM1* gene expression were lower 1 month after treatment in our research group, validating the established roles of the *ORAI1* gene in immune response and inflammation (27).

Other studies have highlighted that individuals with TB exhibit reduced expression levels of the *ORAI1* gene in their blood compared to those without TB. This suggests a disruption in the SOCE mechanism of immune cells, which is associated with TB. In addition, TB patients often demonstrate concurrent low *ORAI1* gene expression and elevated levels of inflammation markers in their blood. The reduced expression of the *ORAI1* gene in TB patients may be attributed to mycobacterial infection. Previous research has indicated that mycobacteria alter calcium signaling and promote survival in macrophages by regulating the expression of microRNAs, endogenous regulators of gene expression in TB patients. MicroRNAs may inhibit the expression of the *ORAI1* gene (28).

This study also identified relationships among all parameters. We observed a moderate association between the HLA-DQB1*0201-0301 (risk) allele and mRNA *ORAI1* gene expression. Thus, our findings highlight the mutual influence of all the markers studied: ORAI1 protein, HLA, CD4+ cell count, and HIV-1 RNA load. These insights provide an avenue for further investigation into gene polymorphism associated with dermatological manifestations, disease course, severity, and the potential for targeted therapy studies.

Conclusions

In summary, this study revealed significant associations between a patient's HLA class II profile and various factors, including CD4+ cell count, HIV-1 RNA load, mRNA expression of *ORAI1/STIM1* genes, and the duration between HIV-1 onset and the occurrence of HIV-related skin disorders. These findings support the notion that HLA class II alleles not only confer genetic susceptibility to HIV-1 infection but also influence the progression and manifestation of HIV-related skin conditions. The results underscore the potential contribution of HLA class II genes to the genetic risk of HIV-related dermatoses in HIV-1–positive patients.

Patients with HIV-related skin disorders exhibited lower levels of *ORAI1* gene expression compared to individuals without HIV-1 and skin dermatoses. Following treatment, mRNA levels of both *ORAI1* and *STIM1* were reduced in HIV-1 patients with skin manifestations, suggesting impairment in the SOCE mechanism of immune cells associated with HIV-1 and dermatoses. Although no significant associations were observed between *ORAI1/STIM1* gene expression and HLA class II alleles, a concurrent presence of low mRNA *ORAI1* levels and the risk allele HLA-DQB1*0201-0301 was demonstrated.

Nonetheless, further investigations, including repetitive, multicenter, and large-sample studies, are warranted to provide more robust insights. Such studies would aid in confirming the relationship between HIV-1 infection, susceptibility to HIV-related skin manifestations, and gene polymorphisms, and elucidating the immunopathological mechanisms underlying these dermatological conditions. These endeavors are crucial for establishing a solid theoretical basis for the prevention and treatment of dermatoses in the context of HIV-1 infection.

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