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ORIGINAL ARTICLE

Biomarkers for disease progression identified in psoriasis patients: A pilot study

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Abstract

Background: Psoriasis is an immune-mediated polygenic skin disorder. It is influenced by multiple genes as well as environmental factors including infection and trauma. Psoriasis is associated with molecular biomarkers such as HLA-C*06:02 and associated single-nucleotide variants (SNVs). Furthermore, the circulatory cytokines, interleukin (IL)-17 and IL-23 are elevated in psoriasis patients.

Objectives: To investigate the incidence of biomarkers namely, HLA-C*06:02, SNV's (rs30187, rs27044, rs2248374), and IL17 and IL23 as possible diagnostic/prognostic biomarkers of value, individually or in combination in psoriasis patients.

Methods: These biomarkers, HLA-C*06:02, SNV's (rs3018, rs27044, rs2248374), and IL17 and IL23 (and their ratio) were tested in a cohort of 40 psoriasis patients attending a dermatology clinic situated in a tertiary academic hospital as well as 40 healthy controls by: HLA typing using sequence-specific primers (PCR SSP), real time PCR, and Luminex technology, respectively.

Results: HLA-C*06:02 was significantly elevated in our patient cohort with 53% ($n = 21$) of psoriasis patients expressing the HLA-C*06:02 allele versus 15% ($n = 6$), $p = 0.001$ in the healthy controls. Both IL-17 and IL-23 were significantly elevated in the psoriasis patients compared to the normal controls ($p = 0.0001$ and $p = 0.0005$, respectively). The SNV rs2248374 showed an association with both IL-17 and HLA-C*06:02 in patients with psoriasis.

Conclusions: Overall, these novel findings are the first to be published for South African and African populations in the public health sector. The finding of the current study corroborates international studies. Further validation through geographic and population expansion may assist in identifying individuals at risk of disease progression in psoriasis. These biomarkers may

be used as potential prognosticators which will offer the opportunity for early medical intervention to reduce the burden of disease.

KEYWORDS
immunology, psoriasis, psoriatic arthritis

INTRODUCTION

Psoriasis is an immune-mediated polygenic skin disorder characterised by chronic skin inflammation related to innate and adaptive immune responses. It is influenced by multiple genes, as well as environmental factors, including infections and trauma.[1] Plaque psoriasis (psoriasis vulgaris), is the most common form, representing nearly 90% of psoriasis patients. Clinically, the lesions are characterised by thick, erythematous dry, sharply demarcated plaques with a silvery white scale.[1–3]

According to the World Health Organisation's global report (2016), approximately 2% of people worldwide suffer from psoriasis. It is classified as a non-communicable disease associated with reduced quality of life and to date, still has no cure.[4] Males and females are equally affected.[5–7] The prevalence of psoriasis in children ranges from 0.0% to 1.4% and in adults from 0.5% to 11.4%, which makes it a common disease that occurs more frequently with advancing age.[3,6] However, as far as can be discerned, prevalence statistics are not available for individuals affected with psoriasis in South Africa.

Psoriasis Area and Severity Index (PASI) scoring is used to clinically evaluate and quantitate the extent and severity of psoriasis.[8,9] The PASI scoring is used to record the erythema, thickness and scaling of a patient's lesion and to measure response to treatment.[9] Body surface area (BSA) can also be used to assess the severity of psoriasis—mild psoriasis: 0%–3% BSA, moderate psoriasis: 3%–10% BSA and severe psoriasis: >10% BSA.[7,10,11]

Studies conducted on the pathogenic factors and immune mediators involved in the disease have improved the understanding of psoriasis pathogenesis. These studies have highlighted several biomarkers to assist in the diagnosis of psoriasis, as well as being indicators of disease severity. Psoriasis occurrence has been positively associated with interleukins (IL)-23 and IL-17 and these biomarkers have been shown to underpin the disorder.[2,12–15] The IL-23/IL-17 ratio is also reported to play a critical role in the development of clinical manifestations associated with psoriasis. According to Cataldi et al.,[15] cytokines are present in psoriasis lesions and their serum levels correlate with the severity of the illness. The focus of the present study is on circulating IL-17 and IL-23 levels. The rationale behind investigating these biomarkers was based on studies showing that levels of IL-17 and IL-23 and the IL-23/IL-17 ratio play a critical role in the development of the clinical manifestations of psoriasis.[16–19]

It is well documented that development of psoriasis is associated with the predisposing human leukocyte antigen (HLA) gene variant, HLA-C*06:02.[20–24] The major genetic determinant of psoriasis resides in the locus of susceptibility PSORS1, which encodes the gene variant, HLA-C*06:02, which is present in up to 60% of patients with psoriasis.[2,25] The presence of the HLA-C*06:02 allele in psoriasis patients is associated with disease progression and treatment response.[20,26]

Endoplasmic reticulum aminopeptidases (ERAP) play a key role in the maturation of proteins involved in multiple biological processes. ERAP1 and ERAP2 trim peptides in the endoplasmic reticulum, which facilitates the processing of these peptides for major histocompatibility complex (MHC) class I presentation. Single nucleotide variants (SNVs) in ERAP1 and ERAP2 may lead to dysfunction, causing alterations in the presentation of peptides to the MHC class I, which affects the recognition of cluster of differentiation (CD)8+ T lymphocytes.[27,28] In addition, about 25% of individuals in all human populations tested are found to be homozygous for an ERAP2 variant, which results in the lack of ERAP2 proteins.[27]

Although molecular biomarkers are well documented in reference to psoriasis, to the best of our knowledge, there is a paucity of studies and data investigating the South African population inflicted with psoriasis. The diagnosis and severity of psoriasis are based on characteristic skin examination findings as observed by a skilled clinician or dermatologist. To this effect, there is a lack of scientific and laboratory findings in the form of biomarkers with regard to disease progression of psoriasis in the South African population as assessment of severity relies solely on clinical detection.[29]

METHODS

Study population

Forty consenting participants with psoriasis were recruited from the Dermatology Outpatient Department at Steve Biko Academic Hospital, Pretoria, South Africa and 40 healthy volunteers were recruited from the students and staff of the Department of Immunology, University of Pretoria between September 2020 to November 2021. Each participant signed informed consent. Participants with a clinical diagnosis of psoriasis and above the age of 18 years were included in the study. Ethical approval (reference 355/2020) was obtained for the current study from the Research Ethics Committee of the Faculty of Health Sciences of the University of Pretoria.

Sample collection, processing and storage

A total of 5 mL of venous blood was drawn in ethylenediaminetetraacetic acid containing vacutainer tubes from each participant. The samples were processed and aliquoted within 2 h of collection for storage at −80°C until use.

Measurement of cytokines

The circulating levels of IL-17 and IL-23 were determined simultaneously in the stored plasma samples. All samples were thawed at 22°C before use. Analysis of the samples was performed using a Human Th17 Magnetic Bead Panel (Milliplex® MAP Kit, Merck KGaA). The assay was conducted according to the manufacturer's instructions and assayed on a Bio-Plex Suspension Array platform (Bio-Rad Laboratories Inc.). Bio-Plex Manager Software 6.0 was used for bead acquisition and analysis of median fluorescence intensity. The results are reported as picograms (pg)/millilitre (mL).

HLA-C*06:02 molecular typing

All psoriasis patients and healthy controls were typed for the HLA-C*6:02 allele using the primers as indicated in Table 1. Maxwell®16 DNA Purification kits were used with the Maxwell®16 Instrument (Promega Corporation). The PCR reaction was carried out using the SSP sequence-specific primer (SSP) method as described by Bunce et al.[30] using AccuStart II PCR Supermix (Quantabio, LLC). The PCR product was visualised on gel agarose.

Single nucleotide variation detection

Single nucleotide variations in ERAP1 (rs30187 and rs27044), as well as ERAP2 (rs2248374), were determined using the TaqMan genotyping assay (ABI) and performed according to the manufacturer's instructions. The standard qPCR cycling was performed using a QuantStudio™ 6 Flex, Real-Time PCR System. The results were analysed using QuantStudio™ allelic discrimination software.

Statistical analysis

Descriptive (medians with interquartile ranges and 95% confidence intervals [CIs]) and inferential statistical techniques were utilised in the data analyses. Tests for an association of contingency tables were performed using two-tailed χ^2 or Fisher's exact tests. One-way analysis of variance was performed using Dunn's test using multiple comparisons using rank sums or the Kruskal-Wallis test for non-parametric data for more than two groups, or the Mann–Whitney test when two groups were compared. Multinomial logistic regression reporting relative risk ratios (RRR) was performed with the dependent variable being the controls as the base outcome and the patient's BSA score classification with biomarker outcomes.

The Hardy–Weinberg (HW) equilibrium was verified for all single-nucleotide polymorphism (SNPs) by the Pearson χ^2 test and linear regression analysis to

TABLE 1 The sequence of primer mixes used for high-resolution HLA C typing.

SP	Sequence	ASP	Sequence	Alleles
367	TACTACAACCAGAGCGAGGA	127	GGTCGCAGCCATACATCCA	C*06:02
122	AGTCCAAGAGGGGAGCCC	214	CTTGCCGTCGTAGGCGG	C*06:02, 13:02
144	ACAAGCGCCAGGCACAGG	377	CCTCCAGGTAGGCTCTCCA	C*06:02, 12:01, 12:02, 12:03, 13:01

Abbreviations: ASP, anti-sense primer; HLA, human leukocyte antigen; SP, sense primer.

evaluate the SNPs for possible association with quantitative traits and covariates (p values were scored *≤0.1, **≤0.05, ***≤0.001).

Statistical significance was set at a $p \leq 0.05$. The analyses was done using STATA 17.0 (Statacorp LLC, TX, USA) and the SNV analysis using PLINK (v1.07, ©2009 Shaun Purcell).[31]

RESULTS

The demographics of psoriasis patients versus healthy control individuals are shown in Table 2 with almost no significant difference found between the groups' gender and ethnicity, however, a significant age difference, both overall, as well as stratified according to gender was observed. The male:female ratio was 16 (40%) males to 24 (60%) females in both cohorts.

According to the BSA scores allocated to psoriasis cases 22% ($n = 9$) had mild disease, 28% ($n = 11$) had moderate disease and the remaining 50% ($n = 20$) had severe disease with more than 10% of their body surface area affected.

The systemic concentrations of both cytokines, IL-17 and IL-23, were significantly elevated ($p = 0.0006$ and $p = 0.005$, respectively) in the psoriasis cohort when compared to the healthy controls as shown in Figure 1. Dunn's test analysis revealed that psoriasis patients with moderate and severe BSA scores were the main drivers of the differences between the healthy controls and psoriasis patients IL-17 values ($p = 0.006$ and $p = 0.002$, respectively); the same trend was also observed for IL-23 ($p = 0.02$ and $p = 0.008$ for moderate and severe groups, respectively). There was no significant difference between patients and healthy controls when the IL-23/IL-17 ratio was compared, or between the different psoriasis classification groups.

Only 15% ($n = 6$) of healthy controls expressed the HLA-C*06:02 allele whereas 53% ($n = 21$) of psoriasis patients tested positive for the HLA-C*06:02 allele (Fisher's exact test $p = 0.001$). Furthermore, the majority (70%, $n = 14$) of patients with severe psoriasis expressed the HLA-C*06:02 allele (Pearson's $\chi^2 = 18.077$, $p \leq 0.0001$). Notably, 68% ($n = 13$) of combined mild and moderate cases did not express the HLA-C*06:02 allele, with only 32% ($n = 7$) expressing the associated HLA allele.

Multinomial logistic regression was performed to determine if the dependent variable (controls [base outcome], mild, moderate and severe psoriasis patients) showed any significance with IL-17, IL-23 and the presence of the HLA-C*06:02 allele as outcomes. Overall, the model showed a likelihood ratio $\chi^2(9) = 38.25$ and $p \leq 0.0001$, log-likelihood = −77.815. The patients with mild or moderate disease only showed an association with IL-17 ($z = 2.05$, $p = 0.041$, relative risk reduction [RRR] = 1.05, 95% CI = 1.00–1.09 and $z = 2.04$, $p = 0.041$, RRR = 1.04, 95% CI = 1.00–1.08, respectively). Patients with severe disease showed significance with respect to ($I = 2.52$–79.3 and $z = 3.80$, $p \leq 0.0001$, RRR = 23.05, 95% CI = 4.57–116.32, respectively).

The HW equilibrium was established for the psoriasis patients and healthy control participants and is presented in Table 3. Concerning the patients, rs30187 indicates that only 75% are due to change, rs27044 indicates 100% are due to change and rs2248374 shows that 30% are not due to change.

Four models of test associations are shown in Table 4. Only rs2248374 shows a statistically significant association with two of the models (i.e., genotypic and recessive).

The screening of all three SNVs for possible associations with quantitative traits for IL-17, IL-23 and the HLA-C*06:02 locus as a covariate showed that rs2248374 (ERAP2) has a significant dominant effect on IL-17 ($F = 4.71$, $p = 0.039$) and IL-23 ($F = 3.2$, $p = 0.078$) using a dominant genetic model. No other SNVs showed any significance. Only IL-17 with HLA-C*06:02 as a covariate was found to be significant in psoriasis patients ($F = 2.83$, $p = 0.073$).

TABLE 2 Patient and control demographics.

	Psoriasis patients ($n = 40$)						Healthy controls ($n = 40$)						
	n	**p25**	**p50**	**p75**	**min**	**max**	***n***	**p25**	**p50**	**p75**	**min**	**max**	***p***
Age	40	39	53	64	31	79	40	24	27	33	21	56	**<0.000**
Age (female)	24	38	52	61	33	79	24	24	27	32	21	56	**<0.000**
Age (male)	16	39	60	67	31	72	16	24	26	34	22	52	**<0.000**

Note: Bold values are statistically significant.

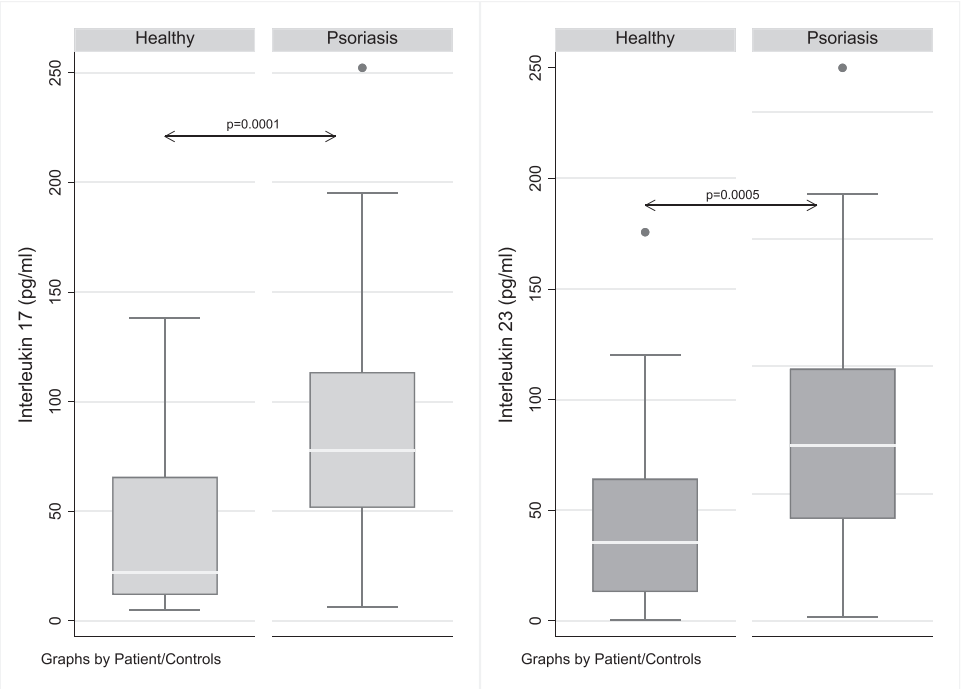

FIGURE 1 Box and Whisker plots showing the differences in levels of IL-17 (left graph) and IL-23 (right graph) between the psoriasis patients and healthy controls. IL, interleukin.

TABLE 3 Hardy–Weinberg equilibrium.

SNV	Test	A1	A2	Geno	O (Het)	E (Het)	*P*
	All	T	C	11/39/27	0.507	0.478	0.811
rs30187	Patients	T	C	8/18/13	0.462	0.492	0.748
	Controls	T	C	3/21/14	0.553	0.458	0.298
	All	G	C	6/38/36	0.475	0.430	0.441
rs27044	Patients	G	C	5/19/16	0.475	0.462	1.000
	Controls	G	C	1/19/20	0.475	0.387	0.237
	All	G	A	15/35/28	0.449	0.486	0.491
rs2248374	Cases	G	A	3/21/15	0.539	0.453	0.311
	Controls	G	A	12/14/13	0.359	0.500	0.107

Note: A1 = minor allele; A2 = major allele; Geno = genotype counts; O (Het) = observed heterozygosity; E (Het) = expected heterozygosity; P = Hardy–Weinberg *p* value.

Abbreviation: SNV, single-nucleotide variants.

DISCUSSION

The current study describes the molecular biomarker SNV: ERAP1 (rs30187, rs27044), ERAP2 (rs2248374) and HLA-C*06:02 in conjunction with circulating levels of the cytokines: IL-17 and IL-23, as well as the IL-23/IL-17 ratio in psoriasis patients in South Africa. To date, no studies have been conducted on a South African cohort investigating these biomarkers in psoriasis patients. Overall, this study has shown that our cohort of patients, largely of African descent, conforms to the findings of other studies regarding the raised levels of IL-17 and IL-23[18,19] and the predominance of the HLA-C*06:02 allele,[20] as well as the ERAP2-associated SNVs as shown in other populations.[27,32]

According to the available evidence, the HLA class I allele (HLA-C*06) on PSORS1 at 6p21.3 is the major genetic determinant of psoriasis, which is mostly associated with type I early onset, severity and familial clustering of psoriasis.[33,34] The current study found that a

TABLE 4 Modelling of several tests for association.

SNV	A1	A2	Test	Cases	Controls	*p*
	T	C	Geno	8/18/13	3/21/14	0.327
	T	C	Trend	34/44	27/49	0.292
rs30187	T	C	Allelic	34/44	27/49	0.327
	T	C	Dom	26/13	24/14	0.814
	T	C	Rec	8/31	3/35	0.192
	G	C	Geno	5/19/16	1/19/20	0.250
	G	C	Trend	29/51	21/59	0.149
rs27044	G	C	Allelic	29/51	21/59	0.232
	G	C	Dom	24/16	20/20	0.501
	G	C	Rec	5/35	1/39	0.201
	G	A	Geno	3/21/15	12/14/13	**0.033**
	G	A	Trend	27/51	38/40	0.085
rs2248374	G	A	Allelic	27/51	38/40	0.104
	G	A	Dom	24/15	26/13	0.814
	G	A	Rec	3/36	12/27	**0.019**

Note: A1 = minor allele; A2 = major allele; Geno = genotypic (2df) test; Allelic = Cochran-Armitage trend test; Dom = dominant gene action (1df) test; Rec = recessive gene action (1df) test. Bold values are statistically significant.

Abbreviation: SNV, single-nucleotide variants.

small number of healthy controls expressed the HLA-C*06:02 allele compared to more than half of the participants with psoriasis, which is highly significant. Furthermore, the majority of participants that expressed the HLA-C*06:02 allele, had severe psoriasis. These results concur with those observed by Griffiths et al.[35] In addition, Chen et al.[24] and Wiśniewsk et al.[27] also reported a strong association between psoriasis and the presence of the HLA-C*06:02 allele.[24,27,35]

It has been well-documented that, psoriasis is an IL-17 and/or IL-23-mediated disorder.[2,12,25] Previously published work has shown that IL-17, IL-23 and the IL-23/IL-17 ratio play a critical role in the development of clinical manifestations associated with psoriasis.[16–19] This was also found to be the case in this study cohort with IL-17 and IL-23 found to be significantly elevated in psoriasis participants when compared to healthy controls. However, there was no significant difference between healthy controls and participants with psoriasis when the IL-23/IL-17 ratio was compared or between the different psoriasis classification groups.

Multinomial logistic regression was performed to determine if the dependent variable (controls and severity of psoriasis) showed any significance with IL-17, IL-23 and the presence of the HLA-C*06:02 allele as outcomes. The participants with mild or moderate disease were found to have only an association with IL-17, whereas the participants with severe disease showed significance for both IL-17, as well as the presence of the HLA-C*06:02 allele, which concurs with the findings of Ramessur et al.[26]

Notwithstanding a small study group, statistically, significant differences were observed for individuals inflicted with psoriasis compared with the healthy control participants. The current study presents data previously unexplored in the South African and indeed the African context and contributes significantly to establishing a reference framework in the diagnosis of severity of disease in psoriasis patients. In addition, these findings may assist clinicians in the administration of biologicals in treating patients with psoriasis as recently reviewed by Ogawa et al.[21] and Vecellio et al.[36]

Limitations of the present study include the small number of patients and controls, as well as the scope of SNVs utilised, as there are several publications with numerous SNVs showing associations with psoriasis. Despite this, the current study has established credible evidence that the susceptibility of the patients in this setting is influenced by these biomarkers. Furthermore, these biomarkers are strongly associated with the severity of disease as measured using the BSA scoring index.

CONCLUSION

Overall, the results of the study displayed significant elevations in the plasma levels of IL-17 and IL-23, as well as in the expression levels of the HLA C*06.02 allele in the participants with psoriasis, particularly those with severe disease. Due to the paucity of data in South Africa and the African settings, the use of HLA-C*06:02 as a marker of disease progression in combination with systemic levels of IL-17 and IL-23 needs to be further investigated in a larger cohort of psoriasis patients.

AUTHOR CONTRIBUTIONS

Nomzamo Mkhize: first author and her contribution was concept and design, experimental analysis, data interpretation, and preparation and drafting of article. **Mahlatse Kgokolo**: co-author, her contribution was concept and design, experimental analysis, and preparation and drafting of article. **Pieter WA Meyer**: co-author, his contribution was concept and design, experimental analysis, and preparation and drafting of article. **Helen Steel**: co-author and her contribution was concept and design, experimental analysis, data interpretation, and preparation and drafting of article. **Luyand Kwofie**: senior author and her contribution was concept

and design, experimental analysis, data interpretation, and preparation and drafting of article.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ETHICS STATEMENT

Ethical approval (reference 355/2020) was obtained from the Research Ethics Committee of the Faculty of Health Sciences of the University of Pretoria.

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REFERENCES

1. Boehncke WH, Schön MP. Psoriasis. The Lancet. 2015; 386(9997):983–94. https://doi.org/10.1016/S0140-6736(14)61909-7
2. Diani M, Altomare G, Reali E. T cell responses in psoriasis and psoriatic arthritis. Autoimmun Rev. 2015;14(4):286–92. https://doi.org/10.1016/j.autrev.2014.11.012
3. Parisi R, Iskandar IYK, Kontopantelis E, Augustin M, Griffiths CEM, Ashcroft DM. National, regional, and world-wide epidemiology of psoriasis: systematic analysis and modelling study. BMJ. 2020;369:m1590. https://doi.org/10.1136/bmj.m1590
4. Organization WH [Internet]. Global report on psoriasis. 2016 [cited 2022 22/08/2022]. Available from: https://apps.who.int/iris/handle/10665/204417
5. Raboobee N, Aboobaker J, Jordaan HF, Sinclair W, Smith JM, Todd G, et al. Guideline on the management of psoriasis in South Africa. S Afr Med J. 2010;100(4 Pt 2):257–82.
6. Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol Venereol. 2017;31(2):205–12. https://doi.org/10.1111/jdv.13854
7. Christophers E, Kerkhof PCM. Severity, heterogeneity and systemic inflammation in psoriasis. J Eur Acad Dermatol Venereol. 2019;33(4):643–7. https://doi.org/10.1111/jdv.15339
8. Fredriksson T, Pettersson U. Severe psoriasis—oral therapy with a new retinoid. Dermatology. 1978;157(4):238–44. https://doi.org/10.1159/000250839
9. Goon PKC, Farooqui UA, Koopmans I, Skellett AM, Levell NJ. Assessment of a 3-dimensional computerised psoriasis area and severity index (pasi) tool for calculating and documenting pasi scores. J Eur Acad Dermatol Venereol. 2017;31(8):e352–3. https://doi.org/10.1111/jdv.14154
10. Johnson MAN, Armstrong AW. Clinical and histologic diagnostic guidelines for psoriasis: a critical review. Clin Rev Allergy Immunol. 2013;44(2):166–72. https://doi.org/10.1007/s12016-012-8305-3
11. Ogdie A, Shin DB, Love TJ, Gelfand JM. Body surface area affected by psoriasis and the risk for psoriatic arthritis: A prospective population-based cohort study. Rheumatology. 2021;61(5):1877–84. https://doi.org/10.1093/rheumatology/keab622
12. Deng Y, Chang C, Lu Q. The inflammatory response in psoriasis: a comprehensive review. Clin Rev Allergy Immunol. 2016;50(3):377–89. https://doi.org/10.1007/s12016-016-8535-x
13. Liu L, Wang J, Li H, Zhang S, Jin M, Chen S, et al. Sphingosine-1-phosphate and its signal modulators alleviate psoriasis-like dermatitis: preclinical and clinical evidence and possible mechanisms. Front Immunol. 2021;12:759276. https://doi.org/10.3389/fimmu.2021.759276
14. Chiricozzi A, Romanelli P, Volpe E, Borsellino G, Romanelli M. Scanning the immunopathogenesis of psoriasis. Int J Mol Sci. 2018;19(1):179. https://doi.org/10.3390/ijms19010179
15. Cataldi C, Mari NL, Lozovoy MAB, Martins LMM, Reiche EMV, Maes M, et al. Proinflammatory and anti-inflammatory cytokine profiles in psoriasis: use as laboratory biomarkers and disease predictors. Inflamm Res. 2019;68(7):557–67. https://doi.org/10.1007/s00011-019-01238-8
16. Christophers E, Metzler G, Röcken M. Bimodal immune activation in psoriasis. Br J Dermatol. 2014;170(1):59–65. https://doi.org/10.1111/bjd.12631
17. Mease PJ. Inhibition of interleukin-17, interleukin-23 and the th17 cell pathway in the treatment of psoriatic arthritis and psoriasis. Curr Opin Rheumatol. 2015;27(2):127–33. https://doi.org/10.1097/BOR.0000000000000147
18. Hawkes JE, Yan BY, Chan TC, Krueger JG. Discovery of the il-23/il-17 signaling pathway and the treatment of psoriasis. The Journal of Immunology. 2018;201(6):1605–13. https://doi.org/10.4049/jimmunol.1800013
19. Lockshin B, Balagula Y, Merola JF. Interleukin 17, inflammation, and cardiovascular risk in patients with psoriasis. J Am Acad Dermatol. 2018;79(2):345–52. https://doi.org/10.1016/j.jaad.2018.02.040
20. Dand N, Duckworth M, Baudry D, Russell A, Curtis CJ, Lee SH, et al. Hla-c*06:02 genotype is a predictive biomarker of biologic treatment response in psoriasis. J Allergy Clin Immunol. 2019;143(6):2120–30. https://doi.org/10.1016/j.jaci.2018.11.038
21. Ogawa K, Okada Y. The current landscape of psoriasis genetics in 2020. J Dermatol Sci. 2020;99(1):2–8. https://doi.org/10.1016/j.jdermsci.2020.05.008
22. Morelli M, Galluzzo M, Madonna S, Scarponi C, Scaglione GL, Galluccio T, et al. Hla-cw6 and other hla-c alleles, as well as micb-dt, ddx58, and tyk2 genetic variants associate with optimal response to anti-il-17a treatment in patients with

psoriasis. Expert Opin Biol Ther. 2021;21(2):259–70. https://doi.org/10.1080/14712598.2021.1862082
23. Douroudis K, Ramessur R, Barbosa IA, Baudry D, Duckworth M, Angit C, et al. Differences in clinical features and comorbid burden between HLA-C*06:02 carrier groups in >9,000 people with psoriasis. J Invest Dermatol. 2022;142(6):1617–1628.e10. https://doi.org/10.1016/j.jid.2021.08.446
24. Chen L, Tsai TF. Hla-cw6 and psoriasis. Br J Dermatol. 2018;178(4):854–62. https://doi.org/10.1111/bjd.16083
25. Furue K, Ito T, Tsuji G, Kadono T, Nakahara T, Furue M. Autoimmunity and autoimmune co-morbidities in psoriasis. Immunology. 2018;154(1):21–7. https://doi.org/10.1111/imm.12891
26. Ramessur R, Corbett M, Marshall D, Acencio ML, Barbosa IA, Dand N, et al. Biomarkers of disease progression in people with psoriasis: a scoping review*. Br J Dermatol. 2022;187(4):481–93. https://doi.org/10.1111/bjd.21627
27. Wiśniewski A, Matusiak Ł, Szczerkowska-Dobosz A, Nowak I, Łuszczek W, Kuśnierczyk P. The association of erap1 and erap2 single nucleotide polymorphisms and their haplotypes with psoriasis vulgaris is dependent on the presence or absence of the hla-c*06:02 allele and age at disease onset. Hum Immunol. 2018;79(2):109–16. https://doi.org/10.1016/j.humimm.2017.11.010
28. Cifaldi L, Romania P, Lorenzi S, Locatelli F, Fruci D. Role of endoplasmic reticulum aminopeptidases in health and disease: from infection to cancer. Int J Mol Sci. 2012;13(7):8338–52. https://doi.org/10.3390/ijms13078338
29. Augustin M, Langenbruch A, Gutknecht M, Reich K, Körber A, Maaßen D, et al. Definition of psoriasis severity in routine clinical care: current guidelines fail to capture the complexity of long-term psoriasis management. Br J Dermatol. 2018;179(6):1385–91. https://doi.org/10.1111/bjd.17128
30. Bunce M, Barnardo MCNM, Procter J, Marsh SGE, Vilches C, Welsh KI. High resolution hla-c typing by pcr-ssp: identification of allelic frequencies and linkage disequilibria in 604 unrelated random uk caucasoids and a comparison with serology. Tissue Antigens. 1996;48(6):680–91. https://doi.org/10.1111/j.1399-0039.1996.tb02692.x
31. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, et al. Plink: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007;81(3):559–75. https://doi.org/10.1086/519795
32. Popa OM, Cherciu M, Cherciu LI, Dutescu MI, Bojinca M, Bojinca V, et al. Erap1 and erap2 gene variations influence the risk of psoriatic arthritis in Romanian population. Arch Immunol Ther Exp. 2016;64(Suppl 1):123–9. https://doi.org/10.1007/s00005-016-0444-4
33. Prinz JC. Human leukocyte antigen-class I alleles and the autoreactive t cell response in psoriasis pathogenesis. Front Immunol. 2018;9:9. https://doi.org/10.3389/fimmu.2018.00954
34. Langley RGB. Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis. 2005;64(SUPP/2):ii18–23.
35. Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker JNWN. Psoriasis. The Lancet. 2021;397(10281):1301–15. https://doi.org/10.1016/S0140-6736(20)32549-6
36. Vecellio M, Hake VX, Davidson C, Carena MC, Wordsworth BP, Selmi C. The il-17/il-23 axis and its genetic contribution to psoriatic arthritis. Front Immunol. 2021;11:596086. https://doi.org/10.3389/fimmu.2020.596086

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