

Taxonomic and functional profiling of skin microbiome in psoriasis

Dear Editor, Maintaining the delicate balance between microorganisms and the host is essential for immune homeostasis and microbial community resilience in healthy skin. In disease states such as psoriasis, this critical balance can be disrupted, leading to alterations in both the skin microbiome and local immunity. Many psoriasis studies, using mainly the amplicon-sequencing approach, have reported highly variable skin microbial profiles associated with the disease, making it challenging to establish a clear link between skin microbial community composition and psoriasis.^{1,2} In this study, we explore this intricate relationship by thoroughly mapping the microbiome derived from a comprehensive study involving patients with psoriasis (PwP) and healthy volunteers (controls, HCs) from three European countries.³ By employing whole metagenomic shotgun sequencing (WMS) our findings give novel insight into bacterial and viral presence and function related to psoriatic skin inflammation.

Samples for skin microbiota were obtained from 109 HCs and 90 PwP (Psoriasis Area and Severity Index score > 7), taken from the lower back of both groups. Lesional samples were collected from psoriasis plaques and nonlesional samples were taken 2 cm away from an active plaque. The mean age was 29 years (range 18–79) for HCs and 47 years (range 20–77) for PwP. Among the HCs, 22 were smokers, compared with 15 of the PwP. Additionally, 21 PwP had been using immunosuppressive therapies. After removing rare taxa and samples with fewer species than the median, 125 subjects provided the data used for taxonomical analyses (56 females and 69 males; 65 HCs and 60 PwP).

A clear distinction in the composition of skin microbiome between PwP and HCs was found (Figure 1a), corroborating the observations of earlier studies.^{4,5} Pairwise comparisons highlighted a strikingly significant difference in cutaneous microbial communities between healthy skin and both nonlesional and lesional psoriatic skin (Figure 1a). A domain-specific analysis further revealed that mainly bacteria and virus differentiated between lesional and nonlesional psoriatic skin, and healthy skin (data on file). Interestingly, the viral families (including *Papillomaviridae*, *Herpesviridae*, *Polyomaviridae* and *Poxviridae*) differentiated lesional samples from nonlesional psoriasis samples, suggesting that viral elements might play a more prominent role in skin health and disease than previously described.^{6,7} We further identified that several bacterial species were consistently more abundant in healthy skin compared with psoriatic skin. Particularly, *Cutibacterium acnes* and *Propionibacterium namnetense* from the *Propionibacteriaceae* family were less abundant in nonlesional psoriatic skin and least abundant in

psoriatic lesions. This aligns with Chang *et al.*,⁸ who noted decreased *Propionibacteriaceae* abundance in skin inflammatory disorders.

Co-occurrence networks revealed disruption of cutaneous microbial communities in inflamed psoriatic skin (Figure 1b). In HCs, typical skin colonizers, such as *Staphylococcus epidermidis*, *S. hominis* and *C. acnes*, as well as *Corynebacterium*, *Micrococcus* and *Acinetobacter*, formed their own co-occurrence networks, respectively. These findings align with recent studies that underscore the cooperative interactions among the skin microbiota, contributing to a balanced microbial ecosystem and promoting skin health.⁹ The species composition and network topology between the skin of HCs and nonlesional skin in PwP showed notable similarities. However, *Staphylococci* and *Corynebacteria* formed stronger associations in nonlesional psoriatic skin than in healthy skin (Figure 1b). *S. capitis* and *S. epidermidis* appeared to be important hub species, forming several associations with other species (Figure 1b). In stark contrast, in psoriatic skin lesions, the co-occurrence networks were disrupted, including substantially reduced interactions between microbial species. This observation could carry important implications for our understanding of microbial dysbiosis in psoriasis pathogenesis and suggests that disruption of microbial communities could be a hallmark of the disease.

The microbial functional capacity, based on UniRef 90 gene families, varied significantly among lesional ($n=74$) and nonlesional ($n=68$) psoriatic skin, and HCs ($n=74$), as shown in Figure 1c. The variation in gene families (8.9%) explained by the clinical groups was notably higher than that in microbial species composition (Figure 1a). To identify robust gene categories and pathways that characterize the clinical groups, we performed Random Forest (RF) classification. The abundance profiles of MetaCyc gene categories (EC-numbered) for HCs and nonlesional psoriasis samples appeared to be quite similar. In the RF classification, RNA-directed DNA polymerase was particularly notable, showing the highest mean decrease in accuracy and differentiating psoriatic skin lesions from nonlesional samples (Figure 1d). Both ubiquitinyl hydrolase 1 and enzyme 7.1.1.2 were more prevalent in psoriatic skin lesions (Figure 1d), distinguishing healthy skin and nonlesional samples from lesional psoriasis samples. Moreover, among RF-selected MetaCyc-numbered metabolic pathways, 'aerobic respiration I' was more abundant in psoriatic lesions compared with nonlesional skin or HCs (Figure 1d). However, generally, gene categories and metabolic pathways were less abundant in psoriasis lesions, indicating an overall reduction in microbial activity. Our findings may pave the way for new psoriasis treatments focused on specific microbial functions.

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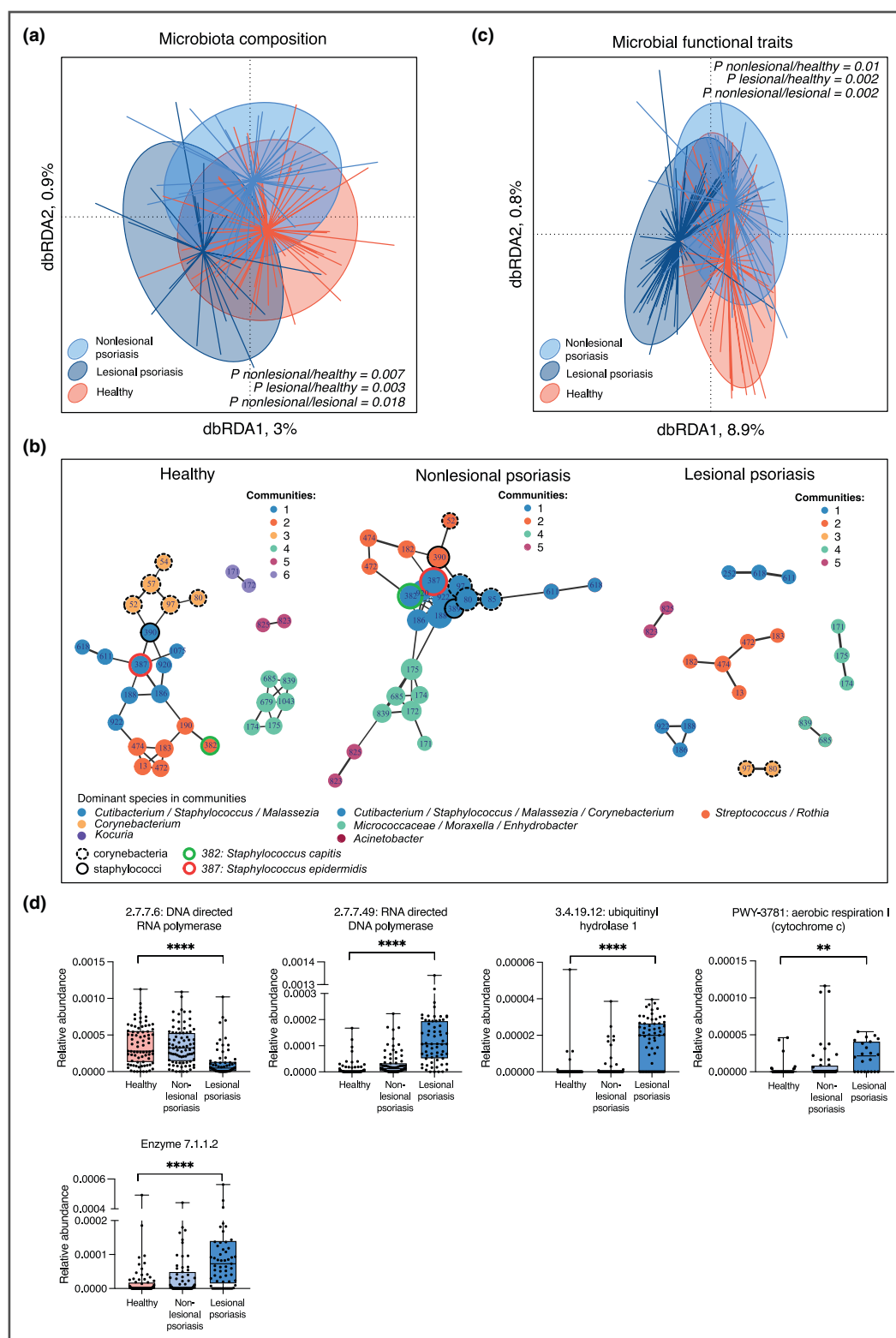


Figure 1 (a) Skin microbiota compositional differences between healthy and psoriatic skin analysed by distance-based redundancy analysis (dbRDA). dbRDA1 and dbRDA2 represent the first and second constrained axes from dbRDA, showing data variation explained by experimental variables. Variation in geographic location and confounding factors were removed in the analysis. (b) Positive Spearman rho-based (> 0.4 , $P < 0.05$) networks of co-occurring metagenomic species. Microbial communities were detected using the walktrap method, with corynebacteria labelled as dotted circles and staphylococci as solid circles. Microbial species have been numbered for clarification. *Staphylococcus capitis* is marked with a green circle, and *S. epidermidis* with a red circle. (c) Compositional differences in functional genes of microbiomes between healthy and psoriatic skin analysed by dbRDA. Variation in geographic location and confounding factors were removed in the analysis. (d) Selected Random Forest-classified microbial functional traits characterizing psoriatic and healthy skin.

In conclusion, our study presents a comprehensive examination of the skin microbiota based on WMS data, revealing distinct microbial signatures and functional profiles in PwP compared with HCs. These differences, spanning from species composition and microbial networks to functional features, underscore the intricate role of skin microbiota in both health and disease. Our work highlights the potential significance of microbial functions in psoriatic skin, suggesting that knowledge of specific genes and pathways may play a more crucial role in understanding the impact of microbiota in psoriatic skin inflammation than microbial taxonomic composition alone. Overall, our study opens new avenues for understanding the role of skin microbiota in psoriasis and lays the groundwork for developing novel microbiota-targeted strategies for managing this chronic skin condition.

Hanna Sinkko,^{1,2} Peter Olah,^{3,4} Ying Yang,¹ Guilherme Maia,⁵ Mauricio Barrientos-Somarrivas,⁵ Zoltan Rádai,^{3,6} Kuunsäde Mäenpää,² Tatiany Soratto,⁵ Alexander Salava,⁷ Antti Lauerma,⁷ Jonathan Barker,⁸ Annamari Ranki,⁷ Bernhard Homey,³ Björn Andersson,⁵ Nanna Fyhrquist¹ and Harri Alenius^{1,2} the MAARS consortium⁹

¹Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; ²Human Microbiome Research Program (HUMI), Medical Faculty, University of Helsinki, Helsinki, Finland;

³Department of Dermatology, University Hospital Düsseldorf, Medical Faculty, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany; ⁴Department of Dermatology, Venereology and Oncodermatology, Medical Faculty, University of Pécs, Pécs, Hungary; ⁵Department of Cell and Molecular Biology, Karolinska Institutet, Stockholm, Sweden; ⁶One Health Institute, Faculty of Health Sciences, University of Debrecen, Debrecen, Hungary;

⁷Department of Dermatology, Allergology and Venereology, University of Helsinki and Helsinki University Hospital, Inflammation Centre, Helsinki, Finland; ⁸St John's Institute of Dermatology, King's College London, London, UK; and ⁹See Appendix 1 for the full list of MAARS consortium collaborators

Correspondence: Harri Alenius. Email: harri.alenius@ki.se

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Data availability: The data supporting the findings of this study are available in the National Library of Medicine database at <http://www.ncbi.nlm.nih.gov/bioproject/1000281>.

Ethics statement: All clinical procedures were approved by the appropriate local Institutional Review Boards (University of Helsinki, Dnro 91/13/03/00/2011; Heinrich-Heine-University,

3647/2011; King's College London, 11/H0802/6). All subjects provided written informed consent before participation.

Patient consent: Written patient consent for publication was obtained.

References

- 1 Liang X, Ou C, Zhuang J *et al*. Interplay between skin microbiota dysbiosis and the host immune system in psoriasis: potential pathogenesis. *Front Immunol* 2021; **12**:764384.
- 2 Hsu DK, Fung MA, Chen H-L. Role of skin and gut microbiota in the pathogenesis of psoriasis, an inflammatory skin disease. *Med Microecol* 2020; **4**:100016.
- 3 Fyhrquist N, Muirhead G, Prast-Nielsen S *et al*. Microbe–host interplay in atopic dermatitis and psoriasis. *Nat Commun* 2019; **10**:4703.
- 4 Alekseyenko AV, Perez-Perez GI, De Souza A *et al*. Community differentiation of the cutaneous microbiota in psoriasis. *Microbiome* 2013; **1**:31.
- 5 Kapoor B, Gulati M, Rani P *et al*. Psoriasis: interplay between dysbiosis and host immune system. *Autoimmun Rev* 2022; **21**:103169.
- 6 Yan D, Issa N, Afifi L *et al*. The role of the skin and gut microbiome in psoriatic disease. *Curr Dermatol Rep* 2017; **6**:94–103.
- 7 Wang H, Chan HH, Ni MY, *et al*. Bacteriophage of the skin microbiome in patients with psoriasis and healthy family controls. *J Invest Dermatol* 2020; **140**:182–90.e5.
- 8 Chang HW, Yan D, Singh R *et al*. Alteration of the cutaneous microbiome in psoriasis and potential role in Th17 polarization. *Microbiome* 2018; **6**:154.
- 9 Flowers L, Grice EA. The skin microbiota: balancing risk and reward. *Cell Host Microbe* 2020; **28**:190–200.

Appendix 1: MAARS consortium collaborators

Juha Kere, Tiina Skoog, Francesca Levi-Schaffer, Dario Greco, Stefanie Prast-Nielsen, Vassili Soumelis, Sophia Tsoka, Jens M. Schröder, Frank O. Nestle and Philippe Hupé