## Conflict of interest

The authors have no conflict of interest to declare.

## Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (C) no. 18K08261 to H. N. from the Ministry of Education, Culture, Sports Science and Technology of Japan.

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Received 9 October 2018
Received in revised form 6 November 2018
Accepted 12 November 2018

http://dx.doi.org/10.1016/j.jdermsci.2018.11.004

# Letter to the Editor

## Dysbiosis of oral microbiota in palmoplantar pustulosis patients

Palmoplantar pustulosis (PPP), a chronic inflammatory skin disease, is characterized by sterile pustular eruptions and erythematous scaling on the palms and soles [1]. Nearly 10% of patients suffer from joint manifestation, pustulotic arthro-osteosis (PAO) [1]. Both skin and joint symptoms are triggered or worsened by focal infections including tonsillitis and dental infection [1]. Recently, we retrospectively evaluated the efficacy of dental infection control and tonsillectomy on the clinical outcomes of 85 PPP patients, and demonstrated that oral focal infections were closely associated with disease severity [2]. These findings led us to hypothesize that changes in oral microbioata based on focal infections may correlate to disease severity and clinical characteristics of PPP. Here, oral microbiota of PPP patients and healthy controls were comparatively analyzed by next generation sequencing (NGS) of the V3-V4 region of the bacterial 16S ribosomal RNA (rRNA) gene.

We surveyed the microbiota of unstimulated saliva collected from 12 PPP patients (pts) and 10 healthy controls (HCs), who were all Japanese and residents in central Japan. General and clinical characteristics of the subjects are shown in Table 1. Prevalence of major worsening factors for PPP, smoking habit and periodontitis were higher in the pts. The methods of sequencing and statistical analysis are described in Supplementary materials and methods. First, we compared the bacterial community composition of the pts and HCs using UniFrac, a phylogenic tree-based measurement ranging from 0 (identical communities) to 1 (completely different communities). The UniFrac distance between HCs-pts (0.37) was significantly higher than that between HCs-HCs (0.31) and between pts-pts (0.31) ($P < 0.05$), indicating a significant difference in oral microbiota between pts and HCs (Fig. 1B). According to the principle coordinate analysis (PCoA) plot based on UniFrac distances, a clearly different distribution between pts and HCs (Fig. 1A) was shown. These results indicated that oral microbiota of the pts significantly differed from that of the HCs, and suggested oral dysbiosis in PPP patients. Second, we evaluated the difference in the oral microbiota among the pts regarding the following characteristics: joint manifestation (PAO) (n = 7), periodontitis (n = 6), smoking habit (n = 9) and higher disease severity according to Palmoplantar Pustulosis Area and Severity Index (PPPASI) score (n = 6). From these results, subjects in the pts with these characteristics showed a different oral bacterial community (Fig. 1C). Third, we analyzed the relative bacterial abundance in all subjects in the pts, subjects in the pts with PAO, periodontitis, smoking habit and higher PPPASI score, and subjects without these characteristics. Six major phyla: Actinobactera, Bacteroidetes, Firmicutes, Fusobacteria, Proteobacteria and TM7, and 13 genera selected as the majority of 16S readings were analyzed (Fig. 1D and Table S1). Results of comparison between the pts and HCs demonstrated that the pts had less Proteobacteria (pts = 24%, HCs = 37%, $P < 0.05$) at the phyla level, and less *Haemophilus* (pts = 10%, HCs = 17%, $P < 0.05$) and more Prevotella (pts = 17%, HCs = 10%, $P < 0.05$) at the genus level. Interestingly, all of these features were shared only in subjects in the pts with PAO (Proteobacteria: pts with PAO = 21%, HCs = 37%; *Haemophilus*: pts with PAO = 8%, HCs = 17%; Prevotella: pts with PAO = 20%, HCs = 10%; $P < 0.05$). According to previous oral microbiome studies in other autoinflammatory diseases by two Japanese groups, these changes in bacterial abundance (less Proteobacteria, less *Haemophilus* and more Prevotella) were also observed. The

**Table 1**
Characteristics of patients with Palmoplantar Pustulosis (pts) and healthy controls (HCs).

| | pts (n = 12), n(%) | HCs (n = 10), n(%) |
|---|---|---|
| Sex | | |
| Female | 8 (67%) | 3 (30%) |
| Male | 4 (33%) | 7 (70%) |
| Age (yrs), mean ± SD | 53.7 ± 14.6 | 29.5 ± 2.87 |
| Smoking habit | 9 (75%) | 3 (30%) |
| Periodontitis [a] | 6 (50%) | 0 (0%) |
| Tonsillitis | 0 (0%) | 0 (0%) |
| Joint manifestation | 7 (58%) | NA [b] |
| PPPASI [c] | | |
| Range | 0.4–19.2 | NA [b] |
| Low score group (range) | 6 (0.4–4.9) | NA [b] |
| High score group (range) | 6 (5.4–19.2) | NA [b] |

[a] Periodontitis was diagnosed using CDC-AAP.
[b] NA: not applicable.
[c] PPPASI : Palmoplantar Pustulosis Area and Severity Index.

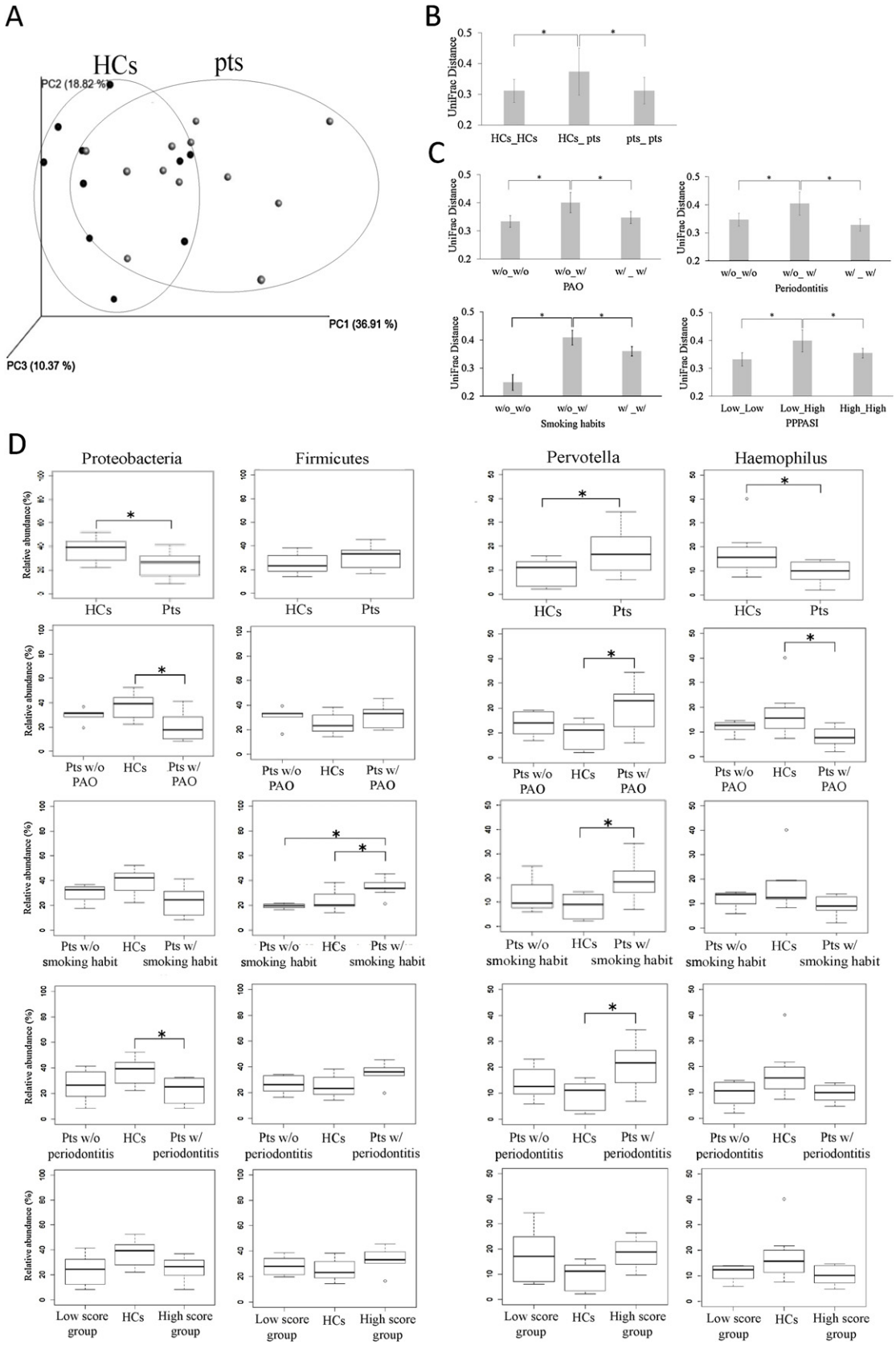


**Fig. 1.** Results of analysis of oral microbiota in PPP patients. (A) PCoA plot of PPP patients (grey dots) and healthy controls (black dots). (B) UniFrac distance between the pts and HCs. (C) UniFrac distance between PPP patients with (w/) and without (w/o) the following characteristics: joint manifestation (PAO), periodontitis, smoking habit and higher disease severity as evaluated by PPPASI score. The results are expressed as mean +/- SD. *$P < 0.05$, Student's t-test. (D) Mean bacterial abundance in all patients, healthy controls and patients with joint manifestation (PAO), periodontitis, smoking habit and higher PPPASI score at the phylum levels (left panels) and genus levels (right panels). Data are expressed as box plot with median, 25th-75th percentiles (box), and minimum and maximum (whiskers). Mann-Whitney U test for two groups comparisons and Kruskal-Wallis test followed by Steel–Dwass post hoc test for three groups comparisons, *$P < 0.05$.

analysis of the oral microbiota of 35 inflammatory bowel disease patients showed fewer phylum Proteobacteria and genus *Haemophilus*, and more genus Prevotella. Moreover, this study also identified a correlation between an increase in the amount of Prevotella and a higher level of IL-1β in patient saliva [3]. The analysis of the microbiome of tonsillar crypts in 48 IgA nephropathy patients showed less *Haemophilus* and more Prevotella in comparison with 21reccurent tosillits patients and 30 children with tonsillar hyperplasia [4]. Taken together, these changes in oral bacterial abundance common in these auto-inflammatory diseases and PPP may indicate a shared underlying pathophysiology associated with oral dysbiosis.

In our study, pts who smoke showed more Firmicutes (Fig. 1D). In a study of the oral microbiota in 1204 adults in the US, current smokers also had more Firmicutes compared with non-smokers (past and never) [5]. Habitual smoking is closely associated with PPP, and cessation of smoking improved in many cases [1]. Thus, the changes in oral microbiota due to smoking may be associated with PPP.

Finally, although it was beyond the scope of this paper, we preliminary analyzed the temporal changes of the microbiota of two patients with different clinical courses after dental focal infection treatment. One patient remitted after the treatment, while another patient did not improve (Fig. S1A). Although PCoA plot showed microbiota shift after periodontal therapy in both patients, the degree of temporal changes of microbiota of "not-improved" patient was larger than that of "remitted" patient (Fig. S1B). Previously, high microbial diversity was shown to lead to higher resilience within microbiological ecosystems [6], and was hypothesized to have a protective effect on humans [7]. In line with this notion, Shannon index analysis indicated that the diversity of the microbiota of "remitted" patient was higher than that of "not-improved" patient (Fig. S1C). Thus, these results suggested that the microbiota of "remitted" patient had higher diversity and stability leading to less disease severity. Although these preliminary data were not enough for conclusive evidence, we speculated that oral microbiota might affect the clinical course of PPP.

Previous human microbiome studies have described divergence in human microbiota depending on differences in geography and ethnicity [8]. One study on oral microbiomes reported ethnicity-specific clustering of microbial communities in saliva and subgingival biofilms [8]. The prevalence of PPP in Japan is known to be generally higher than that in Western countries [9]. Therefore, there may be a possible link between the Japanese-specific oral microbiome and PPP susceptibility in the Japanese population. Our preliminary study suggests oral dysbiosis exists in Japanese PPP patients. As future data is collected by a nationwide study, the relationship between geography- and ethnicity-specific oral microbiome and susceptibility to PPP by Japanese population is expected to be further understood.

**Funding sources**

None.

**Conflict of interest**

The authors have no conflict of interest to declare.

**Authorship note**

Michiyoshi Kouno and Yurie Akiyama contributed equally to this work.

**Appendix A. Supplementary data**

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jdermsci.2018.12.003.

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Received 26 August 2018
Received in revised form 25 December 2018
Accepted 25 December 2018

http://dx.doi.org/10.1016/j.jdermsci.2018.12.003

## Letter to the Editor

### The key question of irradiance when it comes to the effects of visible light in the skin

*Dear Editor,*

We read with great interest the article from Rascalou et al. [1]. In this study, the authors assessed the impact of a device using 36 light emitting diodes (LEDs) that simultaneously produce blue, green and red light (wavelengths of 450 nm, 525 nm and 625 nm, respectively) to reproduce the main wavelengths emitted by electronic devices. After one single irradiation with a dose of 99 J/cm2 they performed cell proliferation and ATP assays, followed by