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SHORT COMMUNICATION

Characterization of distinct microbiota associated with androgenetic alopecia patients treated and untreated with platelet-rich plasma (PRP)

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Abstract

Background: Androgenic alopecia (AGA) is the most common type of hair loss in men, and there are many studies on the treatment of hair loss by platelet-rich plasma (PRP). The human scalp contains a huge microbiome, but its role in the process of hair loss remains unclear, and the relationship between PRP and the microbiome needs further study. Therefore, the purpose of this study was to investigate the effect of PRP treatment on scalp microbiota composition.

Methods: We performed PRP treatment on 14 patients with AGA, observed their clinical efficacy, and collected scalp swab samples before and after treatment. The scalp microflora of AGA patients before and after treatment was characterized by amplifying the V3-V4 region of the 16 s RNA gene and sequencing for bacterial identification.

Results: The results showed that PRP was effective in the treatment of AGA patients, and the hair growth increased significantly. The results of relative abundance analysis of microbiota showed that after treatment, g_*Cutibacterium* increased and g_*Staphylococcus* decreased, which played a stable role in scalp microbiota. In addition, g_*Lawsonella* decreased, indicating that the scalp oil production decreased after treatment.

Conclusions: The findings suggest that PRP may play a role in treating AGA through scalp microbiome rebalancing.

Qian Zhang, Yanan Wang and Cheng Ran contributed equally to this manuscript.

KEYWORDS
androgenic alopecia, microbiome, platelet-rich plasma, scalp

1 | INTRODUCTION

Androgenic alopecia (AGA) is the most common type of hair loss, affecting 80% of men and 50% of women.[1] It can occur at any age, and the incidence rate will usually increase with age. The characteristic of AGA is the gradual miniaturization of hair follicles and a decrease in the number of hairs. The typical pattern for males is hair loss in the temporal, frontal, and fixed areas of the scalp, while females typically exhibit diffuse sparsity of hair on the top of the head.[2] AGA may affect a patient's quality of life, leading to loss of confidence, depression, and social withdrawal. The purpose of treating AGA is to suppress hair follicle shrinkage, stabilize hair loss, and promote hair follicle regeneration.[3]

AGA is an inherited genetic disease. However, its etiology is multifactorial, including changes in micronutrients, stress, and hormone secretion.[4] Research has shown the presence of a large number of microbiota in hair follicles, and the strongest evidence of microbial quantification related to the scalp has been found in cases of seborrheic dermatitis and dandruff.[5] These microbiota help regulate host immune mechanisms through interactions between microorganisms and immune cells, affecting body balance and inflammation. Bacteria affect immune responses by controlling the local inflammatory environment, and the destruction of the inflammatory environment can lead to chronic inflammatory diseases.[6] The most abundant bacteria found in scalp swabs of healthy individuals are *Cutibacterium* spp. and *Staphylococcus* spp., accounting for approximately 90% of the total gene sequence. *Corynebacterium* spp., *Streptococcus* spp., *Acinetobacter* spp. and *Prevotella* spp. are listed among other significantly less numerous species.[7] Filaire et al. found that compared with healthy volunteers, the abundance of *Cutibacterim acnes* ($p < 0.05$) and *Stenotrophomonas geniculata* ($p < 0.01$) in the scalp of AGA patients significantly increased. A lower proportion of *Malassezia* genus in samples corresponding to AGA scalps and an increase of other bacterial genera (*Wallemia*, *Eurotium*) were also noted.[8] Therefore, it is speculated that an imbalance of scalp microbiota is also one of the causes of AGA.

Currently, the US Food and Drug Administration has only approved two drugs for treating AGA, namely oral finasteride[9] and topical minoxidil.[10] But these two drugs are not only ineffective for many patients, but also have serious side effects, including decreased libido, erectile dysfunction, liver function damage, and so on.[11] PRP is a novel method for treating AGA, which has achieved excellent results in basic research and clinical trials in the past decade.[1] It has shown promise for treating AGA, but its therapeutic mechanism is still unclear.

This project conducted PRP treatment on 14 AGA volunteers for six months. High throughput DNA sequencing technology was used to analyze the characteristics of scalp microbiota before and after treatment, providing a theoretical basis for further understanding the impact of scalp microbiota on the occurrence and development of AGA and elucidating the mechanism of PRP treatment for AGA.

2 | METHODS

2.1 | AGA volunteer treatment plan

One week before treatment, 36 mL of peripheral blood was extracted from each AGA volunteer (male, aged 32.5 ± 4.98 years, stage II-III alopecia based on the Norwood Hamilton classification). PRP was isolated, divided into three parts, pre-frozen at −80°C for 24 h, and then freeze-dried using a freeze-drying machine for 48 h. After freeze-drying, PRP was stored at −20°C.[3,12,13] Subjects were treated once a month and then blood was collected again after three months to isolated PRP. The total treatment course was 6 months. Informed consent was obtained from all patients for examination and treatment, and the project was been approved by the Ethics Committee of Huazhong University of Science and Technology Union Shenzhen Hospital.

2.2 | Observation of clinical efficacy of PRP in AGA

AGA patients were photographed in the same position before each PRP treatment. Afterwards, dermatoscopy (FlexScan EV2450, Japan) was used for detection.

2.3 | Swab sample collection

Using the methods reported in the literature[14] with slight modifications, swab sampling was performed on the scalp of the AGA patients. The samples were taken before the first and sixth treatment, and the patient's hair was washed two days before sampling. Before sampling, 20 sampling swabs were soaked in physiological saline for 30 s, and the samples were collected in a hair loss area of approximately 16 cm^2 on the head. Afterwards, each swab was placed in a 50 mL centrifuge tube and stored at −80°C until DNA was extracted.

2.4 | DNA extraction

Genomic DNA was extracted using the PowerSoil DNA Isolation Kit (MoBio Laboratories, Carlsbad, CA, USA) following manufacturer's

instructions. Purity and quality of the genomic DNA were checked on 1% agarose gels.

2.5 | PCR amplification

Microbiota composition analysis of samples was performed by amplifying the hypervariable regions V3-V4 of the 16S RNA gene. For each scalp sample, an 8-digit barcode sequence was added to the 5′ end of the forward and reverse primers (provided by Allwegene Company, Beijing). The first PCR was carried out on a Mastercycler Gradient (Eppendorf, Germany) using 25 μL reaction volumes, containing 12.5 μL 2× Taq PCR MasterMix, 3 μL BS (2 ng/μL), 1 μL Forward Primer (ACTCCTACGGGAGGCAGCAG) (5 μM), 1 μL Reverse Primer (GGACTACHVGGGTWTCTAAT) (5 μM), 2 μL template DNA, and 5.5 μL ddH_2O, with the following cycling conditions: 94°C for 5 min, followed by 30 cycles of 94°C for 60 s, 52°C for 60 s and 72°C for 60 s with a final extension at 72°C for 7 min. The second PCR conditions were the same as those of the first PCR, but with the following cycles: 94°C for 5 min, followed by 20 cycles of 94°C for 30 s, 50°C for 30 s and 72°C for 60 s with a final extension at 72°C for 7 min. The PCR products were purified using a Agencourt AMPure XP Kit.

2.6 | High throughput sequencing

Deep sequencing was performed on the Miseq platform at Allwegene Company (Beijing). After the run, image analysis, base calling and error estimation were performed using Illumina Analysis Pipeline Version 2.6.

2.7 | Statistical analysis

Statistically significant differences in clinical efficacy and bacterial community between PRP treatment before and after treatment and the bacterial communities, were detected by *t* test. The level of significance was set at 5%. Qualified reads were clustered into operational taxonomic units (OTUs) at a similarity level of 97% using the Uparse algorithm of Vsearch (v2.7.1) software.[15] QIIME (v1.8.0) was used to generate rarefaction curves and to calculate the richness and diversity indices based on the OTU information. To compare the membership and structure of communities in different samples, heatmaps were generated with the top 20 OTUs using Mothur.[16] Based on the results of taxonomic annotation and relative abundance, R (v3.6.0) software was used for bar-plot diagram analysis. To examine the similarity between different samples, clustering analyses and PCA were analyzed by R (v3.6.0) based on the OTU information from each sample.[17]

3 | RESULTS

3.1 | Macroscopic and dermatoscopic effects after PRP treatment

After 6 treatments with PRP, AGA patients showed a macroscopic increase in the number of hairs (Figure 1A). Observation using a dermatoscope showed significant changes in various parameters of hair growth (Figure 1B). From the pictures, it can be seen that the hair density of AGA patients has significantly increased, and the above research results indicate that PRP is effective in the treatment of AGA.

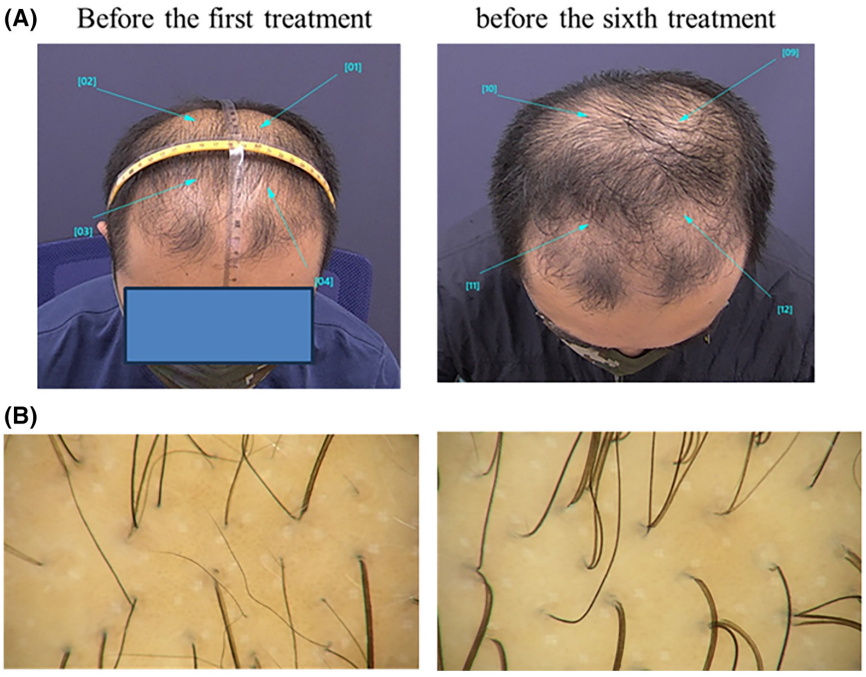

FIGURE 1 Clinical effect of PRP on AGA. (A) Clinical hair condition after 0 and 5 injections of PRP. (B) Clinical trichodermoscopy after 0 and 5 injections of PRP.

3.2 | Scalp microbiome diversity in AGA patients treated and untreated with PRP

We performed 16 s DNA sequencing on scalp samples from 14 AGA patients before treatment (TB, 14 samples) and after treatment (TA, 8 samples). We obtaining about 2 521 319 high quality reads for the total V3-V4 sequences from before treatment (TB) and after treatment (TA) (Table S1). A total number of 1346 OTUs was identified. The rarefaction curve (Figure S1A) and rank-abundance curve (Figure S1B) indicate that the sequencing data of the sample is reasonable and can reflect the vast majority of microbial information in the sample. And from the species accumulation curve (Figure S1C), it can be seen that the curve becomes a slowly rising asymptote after an initial sharp rise, indicating that the sampling size is sufficient for data analysis. To identify the alpha diversity of each sample, Chao1, observed_species, PD_whole_tree, and Shannon were used. The results for bacterial population were slightly higher in the TA group than in the TB group, but there was all no statistically significant difference between the two groups (Figure S2).

To display the microbiome space between samples, beta diversity was calculated through partial least squares discrimination analysis (PLS-DA). This method uses PLS-DA to establish a relationship model between microbial content and sample category, in order to achieve prediction of sample category. Although there were differences between the TA group and TB group, no significant differences were observed ($p = 0.203$) (Figure 2A). In addition, 824 of the

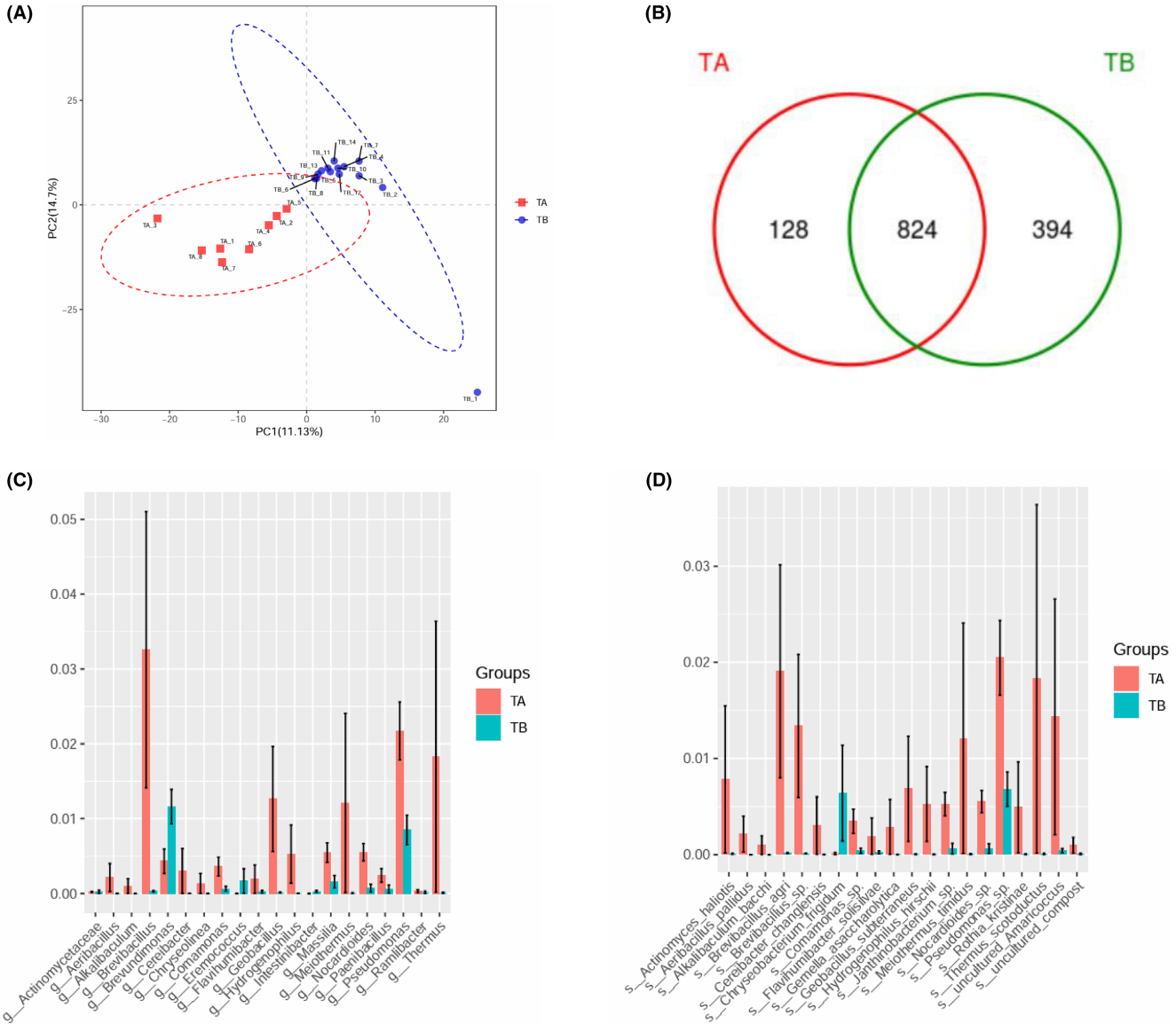

FIGURE 2 Diversity and difference analysis of microbiota. (A) Results of β diversity analysis based on PLS-DA. (B) Venn diagram, the unique and common conditions of OTUs in the two groups before and after treatment. (C) At the generic level, 26 OTUs were different between the two groups before and after treatment. (D) At the species level, 27 OTUs were different between the pre- and post-treatment groups.

1346 OTUs were shared between the TB group and the TA group as shown in a Venn diagram (Figure 2B). Notably, 394 of 1346 OTUs were unique to the TB group.

3.3 | Shift of the scalp surface microbiome between TB and TA

We examined the taxonomical composition of the scalp microbiome in the TB group and TA group, and analyzed the abundance of specific bacterial groups at various taxonomic levels.

At the phylum level, about 39.4% of sequences from the TB group were assigned to *Firmicutes*, 23.4% of sequences were assigned to *Proteobacteria*, and 21.5% were assigned to *Actinobacteriota* (Table 1). Thirty phyla were identified, but were not statistically significant between the two groups (Table S2).

At the genus level, among those present, *Staphylococcus* (28.3% in TB and 21.7% in TA), *Lawsonella* (10% in TB and 6.7% in TA), *Cutibacterium* (8.5% in TB and 13.9% in TA), *Bacteroides* (5.1% in TB and 4.1% in TA) were the most abundant bacterial genera in the two groups (Table 1). A total of 528 genera were identified, and 26 OTUs were significantly different between the groups (Table S3 and Figure 2C).

At the species level, *uncultured_bacterium* (39.1% in TB and 41.5% in TA), *uncultured_Staphylococcus* (12.2% in TB and 7.4% in TA), *Staphylococcus_warneri* (7.4% in TB and 2.4% in TA) were the most abundant bacterial genera in the two groups (Table 1), but there is no significant statistical difference between them ($p > 0.05$). A total of 528 species were identified, and 27 OTUs were significantly different between the groups (Table S4 and Figure 2D). The above results indicated that there are discernible differences in the scalp microbial composition of the scalp before and after treatment at the species and genus levels.

TABLE 1 Mean relative abundance at the phylum, genus, and species levels in the TB and TA groups.

	Relative abundance in TB group	Relative abundance in TA group
Phylum		
Firmicutes	39.4	37.9
Proteobacteria	23.4	20.5
Actinobacteriota	21.5	26.6
Genus		
Staphylococcus	28.3	21.7
Lawsonella	10	6.7
Cutibacterium	8.5	13.9
Bacteroides	5.1	4.1
Pseudomonas	0.85	2.2
Species		
Uncultured_bacterium	39.1	41.5
Uncultured_Staphylococcus	12.2	7.4
Staphylococcus_warneri	7.4	2.4

3.4 | Taxonomic biomarkers of TB and TA groups

According to LEfSe analysis (ANOVA and Wilcoxon rank-sum tests were used for analysis). The threshold was set at 0.05. Finally, linear discriminant analysis (LDA) was used to reduce the data and assess the impact of species with significant differences (LDA score), and the threshold was set at 3. Based on OTUs characterizing microbiota between TB and TA, 8 families, 17 genera, 4 orders, and 19 species varied statistically between the two groups (Figure 3A). Among the identified genera, 3 bacterial genera (*Brevundimonas*, *uncultured*, *and Eremococcus*) were abundant in the TB group, while 14 genera (*Paenibacillus*, *Aeribacillus*, *Spirosoma*, *Comamonas*, *Cereibacter*, *Massilia*, *Nocardioides*, *Hydrogenophilus*, *Granulicatella*, *Geobacillus*, *Meiothermus*, *Pseudomonas*, *Thermus*, *and Brevibacillus*) were enriched in the TA group. The LEfSe cladogram displayed the differential abundance of taxa in scalp microbiota between the two groups (Figure 3B). Analysis of dominant species with an average relative abundance greater than 0.1% revealed that *Pseudomonas_sp.* was more abundant in the TA group (2.05%) than in the TA group (0.68%) (Figure 3C).

4 | DISCUSSION

The skin hosts a diverse and abundant microbial community,[18] maintaining a delicate balance in a healthy state. Research has shown that microbial ecological imbalance plays a distinct role in scalp diseases.[19] However, there is currently relatively little research on the relationship between the microbiota on the scalp and hair growth related hair diseases.[20] In this study, we conducted PRP treatment on 14 patients with AGA and observed significant hair growth. We collected scalp samples from AGA patients before and after treatment for 16s RNA sequencing and analyzed changes in microbial composition.

To our knowledge, there have been no studies on changes in the microbiota composition of the scalp after receiving PRP treatment for AGA. At the genus level, the health scalp microbiome of the participants mostly consisted of *Cutibacterium* and *Staphylococcus*.[21] Filarire et al.'s study showed that compared to healthy scalp microbiota, the proportion of g_*Cutibacterium* in the scalp of AGA patients increased (79%: 76.5%), while the proportion of g_*Staphylococcus* decreased (12%: 14%).[8] The balance of g_*Cutibacterium*: g_*Staphylococcus* plays an important role in AGA, and the bacteria maintain skin health by regulating the immune response.[22] The latest research shows that *Cutibacterium* is a sentinel in the microbiome of healthy human skin, with a role in skin homeostasis and important roles in lipid regulation, follicular niche competition, immune regulation, and oxidative stress mitigation.[23] Alteration of its structure is related to many skin diseases, such

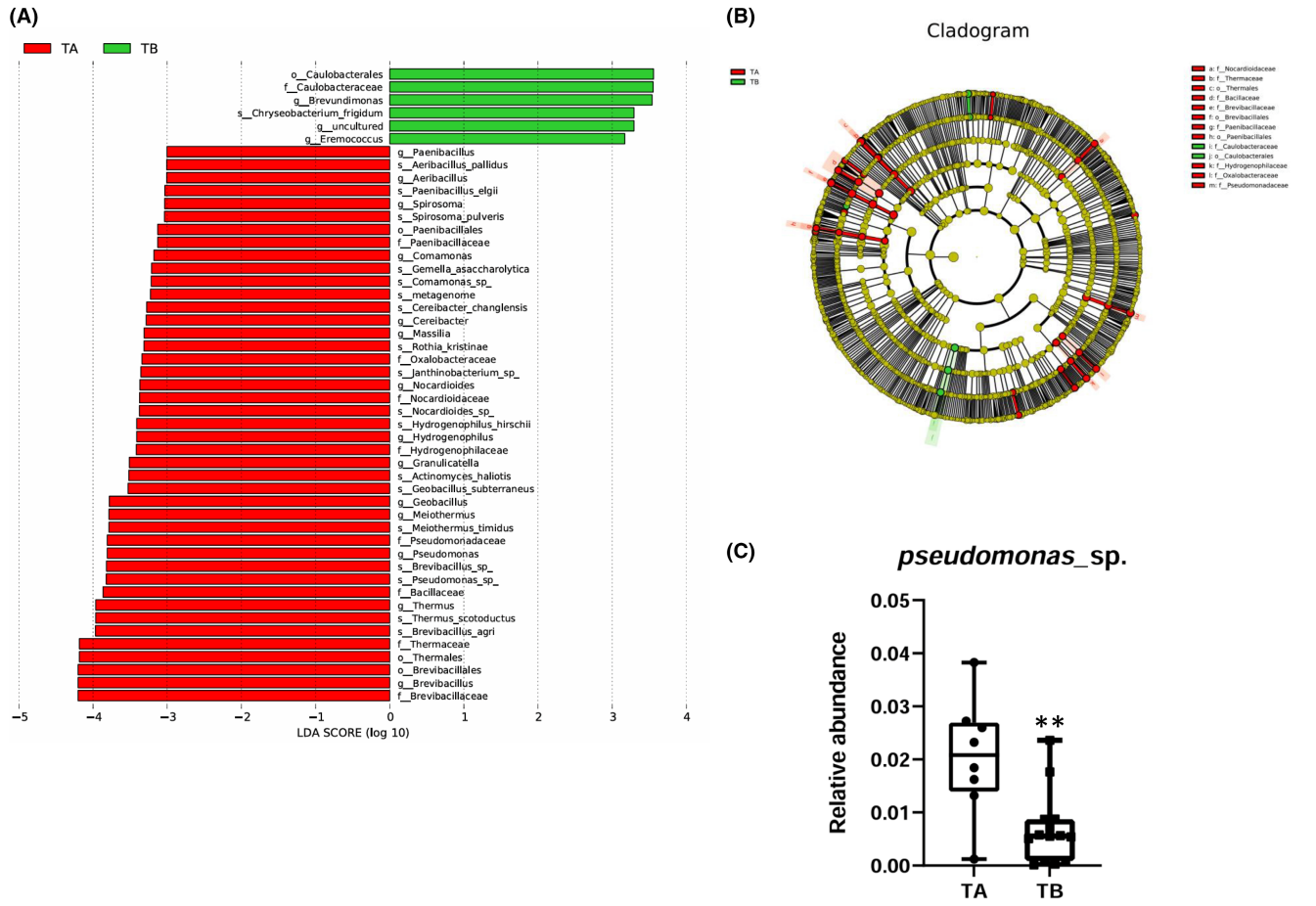

FIGURE 3 OTU based LEfSe and LDA analyses characterized the microbiome between the TB group and TA group. (A) The histogram of LDA score showed that the difference in the scalp microbiome between the two groups was statistically significant. The higher the LDA score, the higher the importance of microbial biomarkers. (B) Phylogenetic tree maps of the LEfSe method show the phylogenetic distribution of the scalp microbiome in both TA group and TB group. Circles radiating from inside out represent taxonomic levels from phylum to genus. The circle of each level indicates the classification of that level, and the diameter of the circle indicates its relative abundance. The species with no significant difference are colored yellow, and the biomarker of different species is colored according to the group. The red nodes represent the important microbial groups in the red group, and the green nodes represent the important microbial groups in the green group. (C) Relative abundance of *Pseudomonas*_sp. in TA group and TB group. A default LDA score greater than 3 and a *p* value less than 0.05 are considered to indicate species differences. TA group versus TB group, $^{**}p < 0.01$.

as atopic dermatitis (AD), psoriasis, rosacea, and acne.[24,25] The reason may be a decrease in *Cutibacterium*, leading to opportunistic infection of competitive species such as *Staphylococcus* in hair cysts.[26] Our results showed that compared to the TA group, the proportion of g_*Cutibacterium* decreased (13.9%:8.5%) and the proportion of g_*Staphylococcus* (21.7%: 28.3%) increased in the TB group. The proportion of g_*Cutibacterium* and g_*Staphylococcus* in the TA group tended to be higher in the microbiota of healthy scalp. We speculated that PRP treatment of AGA increases the proportion of g_*Cutibacterium*: g_*Staphylococcus* in the skin microbiota, which is more conducive to hair growth. This result can be interpreted as showing that g_*Cutibacterium* can secrete bacteriocin, one g_*Staphylococcus* growth, two g_*Staphylococcus* can mediate glycerol fermentation, and the excessive growth of g_*Cutibacterium* leads to the imbalance of scalp flora,[27] which is also a cause of hair loss. After the treatment of AGA, hair density increased significantly, the composition of scalp flora was improved, and the ratio of g_*Cutibacterium* and g_*Staphylococcus* also tended to be normal.

In our study, *Lawsonella* was found to be higher in the TB group than in the TA group, the first time this has been found in the scalp microbiota. Studies have shown a negative correlation between *Lawsonella* and skin moisture content. The human scalp is an androgen sensitive and sebum rich area[28]; the daily delivery of sebum to the scalp and hair surface is within the range of grams. Sebum is a nutritional component of scalp biopathology, and studies have shown a significant increase in sebum excretion rate in patients with androgenic alopecia. So we speculate that AGA patients have increased sebum and decreased water content before treatment. After treatment, the scalp condition has improved, the sebum excretion rate decreases and water content increases, resulting in an increase in *Lawsonella* content.

Notably, based on LEfSe analysis, we found differences in the abundance of bacterial microbiota on the scalp of AGA patients

before and after treatment. LEfSe analysis showed that 3 bacterial genera (*Brevundimonas*, *uncultured*, *and Eremococcus*) were abundant in the TB group, while 14 genera (*Paenibacillus*, *Aeribacillus*, *Spirosoma*, *Comamonas*, *Cereibacter*, *Massilia*, *Nocardioides*, *Hydrogenophilus*, *Granulicatella*, *Geobacillus*, *Meiothermus*, *Pseudomonas*, *Thermus*, *and Brevibacillus*) were enriched in the TA group. The genus *Brevundimonas*, which can cause human infection,[29] belongs to the family *Caulobacteraceae*, first described by Segers et al.[30] in 1994, and consists of a group of bacteria with basic microbiological characteristics: gram-negative, motile, rods 0.5μm~1 to 4μm, non-ferment, oxidase positive, as well as aerobic or facultative anaerobic.

In summary, the results of this study suggest that the composition of the scalp microbiota in AGA patients after PRP treatment may be different from that in AGA patients before treatment. For example, in healthy people, the proportion of g_*Cutibacterium*: g_*Staphylococcus* on the scalp was high, while in AGA patients, the proportion of g_*Cutibacterium*: g_*Staphylococcus* decreased, and after treatment, the proportion of g_Cutibacterium: g_Staphylococcus increased, indicating that PRP treatment may have a positive impact on the composition of scalp microbiota. However, further research is needed on the impact of microbial communities on AGA, and further exploration is needed to determine whether PRP plays a therapeutic role by altering the composition of the scalp microbiota in AGA patients.

AUTHOR CONTRIBUTIONS

Yuan Lu and Tianhua Xu designed the experiment. Qian Zhang and Yingmei Zhou performed the experiment. Hongwei Hou, Yanan Wang, Cheng Ran and Zigang Zhao carried out data analysis. Hongwei Hou and Qian Zhang prepared the manuscript. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

ETHICS STATEMENT

Informed consent was obtained from all patients for examination and treatment, and the project was been approved by the Ethics Committee of Huazhong University of Science and Technology Union Shenzhen Hospital.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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