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Decoding skin mysteries

Unveiling the link between microbiota and keloid scars through a Mendelian randomization study

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Abstract

The cause of keloids remains unclear, but studies suggest a link between skin microbiota and keloid formation. However, the causal relationship has not been confirmed. This study utilized Genome-Wide Association Studies (GWAS) data from 2 population-based German cohorts, comprising a total of 1656 skin samples. To bolster the reliability of our results, we incorporated GWAS data from 3 keloid cohorts, encompassing 2555 patients and 870,556 controls (GWAS ID: keloid$_1$, ebi-a-GCST90018874; keloid$_2$, bbj-a-131; keloid$_3$, ebi-a-GCST90018654). Subsequently, we employed bidirectional 2-sample Mendelian randomization (MR) analysis to probe the causal relationship between the variables. The primary method employed was the inverse-variance weighted (IVW) method, supported by heterogeneity analysis, horizontal pleiotropy testing, outlier detection, and "leave-one-out" sensitivity analysis. By synthesizing the results from 3 groups of MR analyses, we discovered a negative causal association between a.ASV063 [*Finegoldia* (unc.)] located on the volar forearm and keloid disease (IVW (keloid$_1$) odds ratio (OR): 0.939, 95% confidence interval (CI): 0.886–0.994, $P = .032$; IVW (keloid$_2$) OR: 0.897, 95% CI: 0.813–0.990, $P = .031$; IVW (keloid$_3$) OR: 0.900, 95% CI: 0.825–0.981, $P = .017$). Similarly, a negative causal relationship may also exist between the genus: *Bacteroides* from the antecubital fossa and keloid disease (IVW (keloid$_1$) OR: 0.928, 95% CI: 0.884–0.973, $P = .002$; IVW (keloid$_2$) OR: 0.891, 95% CI: 0.820–0.968, $P = .007$; IVW (keloid$_3$) OR: 0.918, 95% CI: 0.849–0.992, $P = .030$). Additionally, no reverse causation was found, with all analyses showing no signs of horizontal pleiotropy or heterogeneity. This study offers new insights for the prevention and treatment of keloids.

Abbreviations: ASVs = amplicon sequence variants, BWMR = Bayesian weighted Mendelian randomization, CI = confidence interval, GWAS = Genome-Wide Association Studies, IVs = instrumental variables, IVW = inverse-variance weighted, MR = Mendelian randomization, SNPs = single nucleotide polymorphisms, STROBE = strengthening the reporting of observational studies in epidemiology.

Keywords: causal relationship, dermatology, genetically predicted, GWAS, single nucleotide polymorphism

1. Introduction

Keloids are defined as fibroproliferative disorders of the skin,[1] resulting from abnormal healing processes following injury or irritation, leading to pathological or inflammatory scars. These scars are characterized by redness, elevation above the skin surface, expansion beyond the original wound margins, and an unsightly appearance, significantly impacting patients' psychological well-being and quality of life.[2–4] Due to the obscure underlying mechanisms, the lack of effective medical treatments, and the high recurrence rate after surgical intervention, keloids represent a significant challenge for plastic surgeons.[5]

Research indicates that keloid tissues have more inflammatory cells and fibroblasts, along with new blood vessels and collagen deposits.[6] Fibroblasts cause keloids by depositing too much extracellular matrix, driven by growth factors like Transforming Growth Factor-β, Platelet-Derived Growth Factor, Fibroblast Growth Factor β, and Insulin-like Growth Factor I, as well as other signaling cascades involved in fibrosis.[7,8] Changes in the microenvironment and inflammatory responses following microbial infections are believed to play a crucial role in the formation of keloids.[9] Recent studies suggest a potential causal relationship between the gut microbiome and the development of hypertrophic scar.[10] Given that human skin microbiota is

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The datasets generated during and/or analyzed during the current study are publicly available.

This study was based on publicly available summary data and required no ethics approval or participant consent.

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associated with inflammation in various skin diseases such as seborrheic dermatitis, acne, and psoriasis,[11] focusing research on the interaction between keloids and the skin microbiota could unveil deeper pathological mechanisms and therapeutic potentials.

To our knowledge, current research on the relationship between human skin microbiota and keloids is remarkably limited, with only a recent study of note. Shan et al, utilizing a multi-omics approach, identified notable differences in the bacterial communities between keloids and the surrounding healthy skin, particularly a higher prevalence of hydrogen peroxide-negative bacteria in the keloid areas.[9] However, it is important to highlight that this study, while conducting bacterial 16S rRNA gene sequencing, only preserved the dermal layer and removed the epidermal layer.[9] This approach overlooks the fact that skin's microbial communities are not limited to the dermis but also proliferate within the epidermis.[12] These epidermal microbes play a crucial role in defending against pathogen invasion and regulating immune responses.[13] Therefore, analyzing only the dermal microbiota might overlook the key role of epidermal microbes in skin health and disease. Furthermore, microbial communities exhibit variations across different skin regions,[14,15] suggesting that a 1-size-fits-all approach may undermine the accuracy of the findings. Finally, it is imperative to recognize that the foundation of current knowledge is observational studies, which come with inherent limitations such as potential unmeasured or inaccurately measured confounding variables, the risk of reverse causality, and other biases.

To circumvent these limitations, leveraging Mendelian randomization (MR) analysis alongside data from Genome-Wide Association Studies (GWAS) has emerged as a compelling approach for exploring causal relationships within presumed exposure-outcome pathways.[16] MR capitalizes on the principle of the random allocation of genetic variants at conception, effectively mirroring a natural experiment. This technique enables the investigation of potential causal connections between risk factors (such as skin microbiota) and disease outcomes (such as keloids), with the added advantage of minimizing the impact of confounding variables through their randomized distribution.[17] In our study, we meticulously collected several recent GWAS summary datasets and conducted independent analyses on the microbial communities of different skin regions. To our knowledge, this represents the first attempt to use 2-sample MR analysis to delve into the complex interactions between the microbial communities on various parts of the skin surface and the development of keloids, with further validation analyses conducted using multiple datasets. This research is crucial for uncovering the role of skin microbiota in the formation of keloids and identifying targets for future therapeutic strategies.

2. Methods

2.1. Study design

In conducting this study, we exclusively utilized data from publicly available databases, which had already received approval from the relevant institutional review boards, thereby negating the need for further ethical review. Our research adhered to the core principles outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, as well as the specific recommendations of the STROBE-MR guidelines for MR studies.

Our investigation employed single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) in a comprehensive 2-sample bidirectional MR analysis to explore the causal relationship between the human skin microbiota and keloid disease.[18] The validity of our MR analysis rests on 3 critical assumptions: a clear association exists between the SNPs and the exposure; the SNPs are not associated with any confounders that might influence the exposure-outcome relationship; and the SNPs affect the outcome solely through their impact on the exposure, ensuring a direct causal pathway.[19]

2.2. GWAS summary data sources

2.2.1. Data for human skin microbiota. The GWAS data on human skin microbiota analyzed in this study were derived from 2 population-based, cross-sectional German cohorts: KORA FF4, with 324 participants, and PopGen, with 273 participants, yielding a total of 1656 skin samples.[20] These samples represented a variety of skin environments: dry [dorsal and volar forearm (PopGen)], moist [antecubital fossa (KORA FF4 and PopGen)], and sebaceous areas [retroauricular fold (KORA FF4) and forehead (PopGen)] (Table S1, Supplemental Digital Content, http://links.lww.com/MD/N689). Genome-wide association analyses were conducted on univariate relative abundances of individual bacteria (amplicon sequence variants; ASVs) and nonredundant taxonomic groups ranging from genus to phylum levels. The microbial community characteristics within these skin samples were determined through sequencing the V1-V2 region of the 16S ribosomal RNA gene. The GWAS summary statistics for the 150 human skin microbiota are available in the GWAS catalog under the codes GCST90133164 to GCST90133313 (Table S1, Supplemental Digital Content, http://links.lww.com/MD/N689).

2.2.2. Data for keloid disease. To enhance the credibility of the results of this study, we incorporated 3 sets of GWAS summary statistics for keloid disease. These data were sourced from the Medical Research Council Integrative Epidemiology Unit's OpenGWAS project database (https://gwas.mrcieu.ac.uk). Specifically, the GWAS data with the ID ebi-a-GCST90018874 represents a European cohort, encompassing 668 keloid patients and 481,244 control individuals.[21] The GWAS data identified by the ID bbj-a-131 pertains to an East Asian population, including 812 patients and 211,641 control individuals. Lastly, the GWAS data with the ID ebi-a-GCST90018654 also concerns an East Asian demographic, comprising 1055 patients and 177,671 control individuals.[21] Detailed information on the aforementioned data will be provided in Table 1.

2.3. IVs selection and data harmonization

In our study, we implemented stringent selection criteria for SNPs to enhance the reliability of our results. Following the protocol established in the foundational study,[10] we selected SNPs that achieved genome-wide significance ($P < 1 \times 10^{-5}$) for detailed scrutiny. To preserve the purity of our IVs, we meticulously excluded palindromic and ambiguous SNPs from our analysis.[22] SNPs were then clustered according to linkage disequilibrium, using a 10,000 kb window and setting an r^2 threshold below 0.001. The *F*-statistic, calculated via the formula $[(N - K - 1)/K]/[R^2/(1 - R^2)]$, was employed as a metric to quantify the proportion of variance accounted for by each SNP, where K represents the number of genetic instruments and N the sample size. IVs with an *F*-statistic lower than 10 were considered too weak and subsequently excluded to maintain analytical precision.[23] Furthermore, our comprehensive literature review was diligently conducted to evaluate all phenotypes linked to the genetic instruments used in our analysis. This allowed us to carefully eliminate SNPs that could be associated with confounding factors, thereby ensuring the integrity of our causal deductions.

2.4. Primary analysis

To investigate the potential causal relationship between the human skin microbiota and keloid disease, we initially utilized

Table 1

Details of the genome-wide association studies and datasets used in our analyses.

Phenotypes	Cases/controls	Consortium/author	Population	PubMed ID	Data download link
Human skin microbiota	KORA FF4 (n = 324) PopGen (n = 273)	Lucas Moitinho-Silva et al	German	36261456	https://www.ebi.ac.uk/gwas/; Accession numbers GCST90133164 to GCST90133313
$Keloid_1$	688/481,244	Sakaue et al	European	34594039	https://gwas.mrcieu.ac.uk; GWAS ID: ebi-a-GCST90018874
$Keloid_2$	812/211,641	Ishigaki et al	East Asian	-	https://gwas.mrcieu.ac.uk; GWAS ID: bbj-a-131
$Keloid_3$	1055/177,671	Sakaue et al	East Asian	34594039	https://gwas.mrcieu.ac.uk; GWAS ID: ebi-a-GCST90018654

Note: $Keloid_1$, GWAS ID ebi-a-GCST90018874; $Keloid_2$, GWAS ID bbj-a-131; $Keloid_3$, GWAS ID ebi-a-GCST90018654.

GWAS data for 150 human skin microbiota as the exposure and sequentially analyzed the 3 sets of keloid GWAS data as outcomes. The cornerstone of our analytical strategy in this study is the inverse-variance weighted (IVW) method, which synergizes meta-analysis techniques with Wald estimates for each individual SNP. Assuming the absence of horizontal pleiotropy, IVW offers unbiased results,[24] with significance thresholds set at $P < .05$. To complement this approach, we also applied additional methods such as Bayesian weighted MR (BWMR)[25] and the weighted median method.[26] The BWMR technique, in particular, is tailored for causal inference, adept at navigating the uncertainties introduced by weak effects in polygenic traits. By employing Bayesian weighting, it effectively identifies outliers and mitigates the impact of pleiotropic IV assumption breaches. The weighted median method, offering a tighter standard deviation compared to the MR-Egger approach, enhances precision. Remarkably, it can provide reliable estimates even amidst horizontal pleiotropy, accommodating up to 50% of the genetic variation from potentially invalid instruments.[27] To enhance the reliability of our conclusions, we conducted an integrated analysis of the results, retaining information on skin microbiota that reached a significant level of association in all 3 MR analyses.

2.5. Reverse MR analysis

To explore whether there is a potential reverse causal relationship between human skin microbiota and keloid disease, we conducted a reverse MR analysis with keloid disease as the exposure variable and skin microbiota as the outcome variable. The methods and standards for the reverse MR analysis were consistent with those described above.

2.6. Sensitivity analysis

To bolster the credibility of our findings, we implemented several strategies. Initially, our 2-sample MR analysis accounted for potential heterogeneity arising from variations in experimental setups, study demographics, and SNPs, which could skew the estimation of causal relationships. To tackle this, we utilized both the IVW and MR-Egger methods to evaluate heterogeneity. The heterogeneity among our genetic instruments was quantified using Cochrane Q statistic, with a P-value > 0.05 indicating an absence of significant heterogeneity.[28] Furthermore, a critical premise of MR analysis is the exclusive influence of the IV on the outcome via the exposure, necessitating the investigation of possible horizontal pleiotropy that could confound the exposure-outcome dynamic.[29] The MR-Egger intercept method was employed to detect the presence of pleiotropy, where a P-value > 0.05 implied minimal or no significant pleiotropic effects, thus affirming the integrity of our causal inference. Additionally, we identified and excluded outliers in the IVW analysis using the MR-PRESSO test.[30] Finally, we conducted a "leave-one-out" analysis to determine the genetic causal effect of individual SNPs on the exposure-outcome relationship.[31]

2.7. Statistical analysis

We conducted MR analysis using R software (version 4.2.0, http://www.r-project.org) in conjunction with the "Two-Sample MR" package (version 0.5.6) for precise and comprehensive analysis.

3. Results

Refer to Figure 1 for a detailed schematic diagram of the study design.

3.1. Association of human skin microbiota and keloid disease

To delve into the causal relationship between human skin microbiota and keloid disease, this study initially utilized GWAS data of the skin microbiota as the exposure variable, conducting MR analyses with keloid disease as the outcome. Furthermore, to bolster the robustness of our conclusions, we employed 3 sets of GWAS data on keloid disease for a combined analysis. In the analysis of keloid data identified by GWAS ID ebi-a-GCST90018874, we identified 12 skin microbial communities potentially having a causal relationship with keloid disease. From the dataset with GWAS ID bbj-a-131, we found 8 skin microbial communities likely linked causally to keloid disease. In the analysis associated with GWAS ID ebi-a-GCST90018654, we pinpointed 5 skin microbial communities potentially causally related to keloid disease. The detailed data for the above analysis are provided in Table 2.

Upon integrated analysis, we discovered that the univariate microbial feature (a.ASV063 [*Finegoldia* (unc.)]) on the volar forearm (dry skin) and the univariate microbial feature (genus: *Bacteroides*) at the antecubital fossa (moist skin) both reached a significant level in all 3 MR analyses. Moreover, their relationships with keloid disease were consistently negative, indicating a uniform direction of effect (Fig. 2).

It is worth noting that the harmonized data for the MR analysis (Table S2, Supplemental Digital Content, http://links.lww.com/MD/N689) and the complete analysis results (Table S3, Supplemental Digital Content, http://links.lww.com/MD/N689) are available in the supplementary files. Additionally, none of the MR analyses showed evidence of heterogeneity or horizontal pleiotropy (Table S4, Supplemental Digital Content, http://links.lww.com/MD/N689). The MR-PRESSO test also did not detect any outliers. Finally, using the "leave-one-out" sensitivity analysis method, we found that systematically excluding each SNP did not substantially alter the effect estimates or the qualitative conclusions of the model (Figure S1, Supplemental Digital Content, http://links.lww.com/MD/N688).

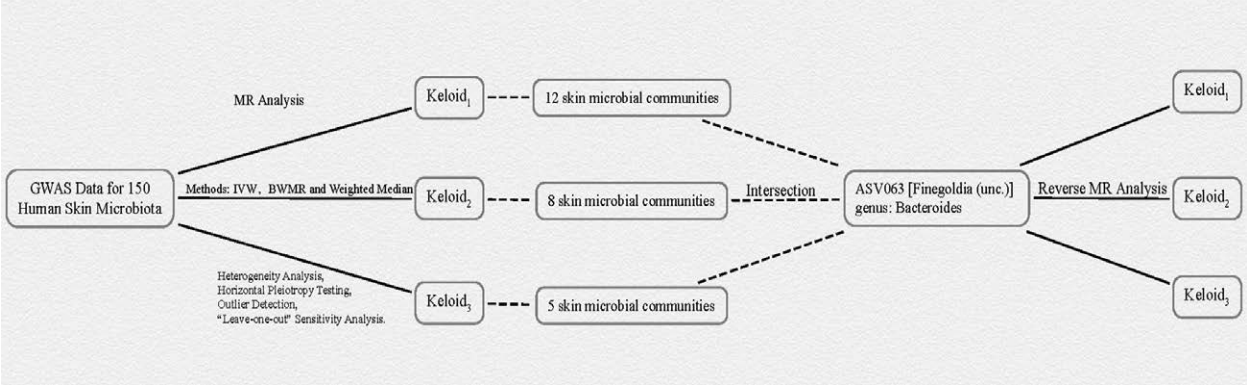

Figure 1. The schematic representation of the study design. Note: $Keloid_1$, GWAS ID ebi-a-GCST90018874; $Keloid_2$, GWAS ID bbj-a-131; $Keloid_3$, GWAS ID ebi-a-GCST90018654; MR, Mendelian randomization; GWAS, genome-wide association study; IVW, inverse-variance weighted; BWMR, Bayesian Weighted Mendelian Randomization.

Table 2

Detailed data for the MR analysis between human skin microbiota and GWAS data for 3 groups of keloid disease.

ID	Site	Microbial feature level	Microbial feature	Outcome	*P*-value (IVW)
GCST90133192	Forehead	Order	Actinomycetales	$Keloid_1$	.019
GCST90133219	Dorsal forearm	Genus	Haemophilus	$Keloid_1$	.044
GCST90133259	Dorsal forearm	ASV	ASV021	$Keloid_1$	.041
GCST90133300	Antecubital fossa	ASV	ASV001	$Keloid_1$	.039
GCST90133194	Retroauricular fold	Phylum	Proteobacteria	$Keloid_1$	.048
GCST90133272	Volar forearm	ASV	ASV063[Finegoldia (unc.)]	$Keloid_1$	.032
GCST90133248	Volar forearm	ASV	ASV072	$Keloid_1$	.006
GCST90133253	Volar forearm	ASV	ASV008	$Keloid_1$	.028
GCST90133291	Antecubital fossa	Genus	Bacteroides	$Keloid_1$	.002
GCST90133295	Antecubital fossa	Order	Pseudomonadales	$Keloid_1$	.001
GCST90133304	Antecubital fossa	Family	Moraxellaceae	$Keloid_1$	.001
GCST90133310	Volar forearm	Family	Flavobacteriaceae	$Keloid_1$	.016
GCST90133200	Forehead	Family	Neisseriaceae	$Keloid_2$	.033
GCST90133252	Dorsal forearm	ASV	ASV006	$Keloid_2$	.027
GCST90133262	Dorsal forearm	ASV	ASV035	$Keloid_2$	.042
GCST90133218	Volar forearm	Order	Lactobacillales	$Keloid_2$	.028
GCST90133272	Volar forearm	ASV	ASV063[Finegoldia (unc.)]	$Keloid_2$	.031
GCST90133275	Volar forearm	ASV	ASV076	$Keloid_2$	.049
GCST90133291	Antecubital fossa	Genus	Bacteroides	$Keloid_2$	.007
GCST90133310	Volar forearm	Family	Flavobacteriaceae	$Keloid_2$	.015
GCST90133200	Forehead	Family	Neisseriaceae	$Keloid_3$	.014
GCST90133191	Antecubital fossa	ASV	ASV057	$Keloid_3$	.043
GCST90133272	Volar forearm	ASV	ASV063[Finegoldia (unc.)]	$Keloid_3$	.017
GCST90133255	Volar forearm	Phylum	Bacteroidetes	$Keloid_3$	.013
GCST90133291	Antecubital fossa	Genus	Bacteroides	$Keloid_3$	.030

Yellow and green respectively represent the MR results of ASV063 (Finegoldia [unc.]) and Bacteroides in the three groups of keloid disease.

Note: $Keloid_1$, GWAS ID ebi-a-GCST90018874; $Keloid_2$, GWAS ID bbj-a-131; $Keloid_3$, GWAS ID ebi-a-GCST90018654;

ASV = amplicon sequence variant, GWAS = Genome-Wide Association Study, IVW = inverse-variance weighted, MR = Mendelian randomization, unc. = unclassified.

3.2. Reverse MR analysis

To further investigate the potential bidirectional causal relationship between the aforementioned 2 skin microbial communities and keloid disease, we conducted reverse MR analyses using 3 sets of GWAS data for keloid disease as exposures, with the 2 skin microbial communities as outcomes. The results indicated that there was no evidence of a reverse causal relationship between the 2 entities across all MR analyses conducted (Fig. 3). Concurrently, the harmonized data utilized for the MR analysis (Table S5, Supplemental Digital Content, http://links.lww.com/MD/N689) and the comprehensive analysis results (Table S6, Supplemental Digital Content, http://links.lww.com/MD/N689) are accessible in the supplementary files. Moreover, subsequent tests for heterogeneity (Table S4, Supplemental Digital Content, http://links.lww.com/MD/N689), horizontal pleiotropy (Table S4, Supplemental Digital Content, http://links.lww.com/MD/N689), outlier detection, and "leave-one-out" sensitivity analysis (Figure S2, Supplemental Digital Content, http://links.lww.com/MD/N688) all yielded negative results, further solidifying the robustness of our study findings.

4. Discussion

To delve into the causal relationship between the skin microbiome and keloid disease, we consolidated GWAS summary data on the skin microbiome with 3 sets of GWAS data related to keloids. Through a bidirectional 2-sample MR analysis, we found, after integrating the data, that a univariate microbial feature (a.ASV063 [*Finegoldia* (unc.)]) on the volar forearm (dry skin) and a univariate microbial feature (genus: *Bacteroides*) at the antecubital fossa (moist skin) both achieved significant levels across all 3 MR analyses. Crucially, their associations with

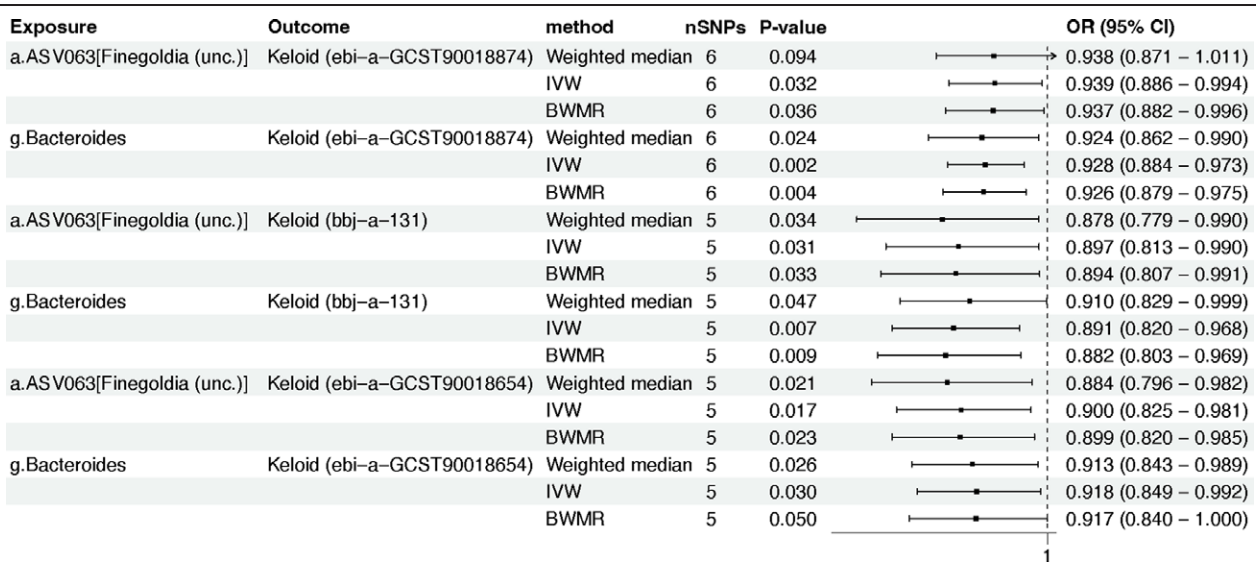

Figure 2. The MR analysis between skin microbiota and keloid disease. Note: MR, Mendelian randomization; nSNPs, Number of Single Nucleotide Polymorphisms; OR, odds ratio; CI, Confidence Interval; IVW, inverse-variance weighted; BWMR, Bayesian Weighted Mendelian Randomization; g. *Bacteroides*, genus: *Bacteroides.*

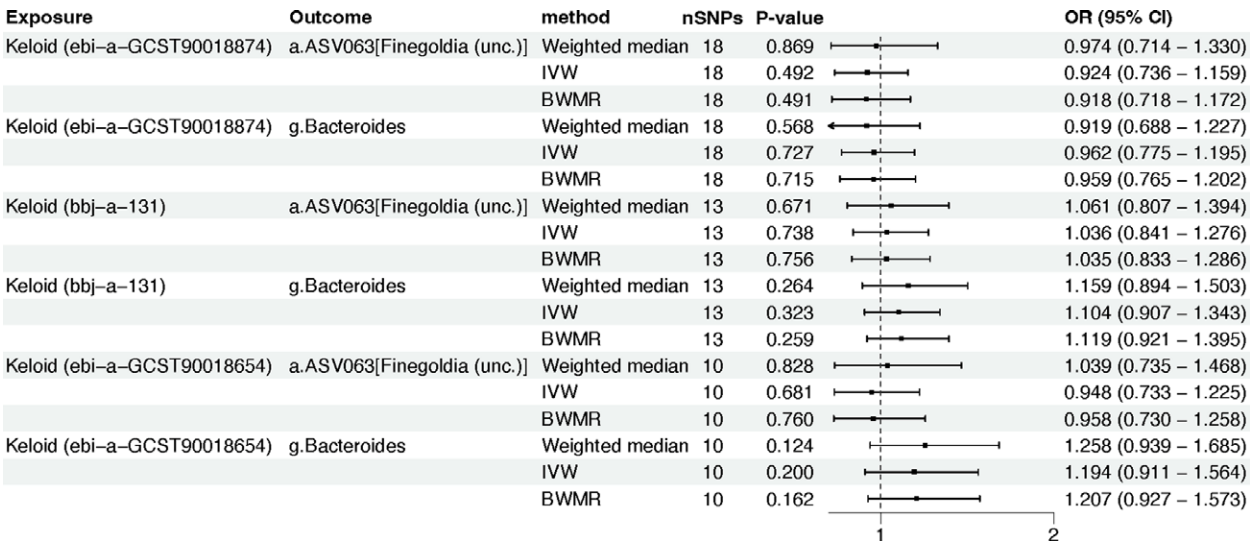

Figure 3. The reverse MR analysis between skin microbiota and keloid disease. Note: MR, Mendelian randomization; nSNPs, Number of Single Nucleotide Polymorphisms; OR, odds ratio; CI, confidence interval; IVW, inverse-variance weighted; BWMR, Bayesian Weighted Mendelian Randomization; g. *Bacteroides*, genus: *Bacteroides.*

keloid disease consistently exhibited a negative correlation, suggesting a uniform direction of effect. Furthermore, these findings were corroborated by validation through BWMR and the Weighted Median methods, enhancing the robustness and credibility of our results.

The skin microbiota, which resides on the skin and interacts with it, plays a crucial role in influencing its barrier function. Moreover, similar to the microbiomes of most organ systems, the skin microbiome is essential for the normal functioning of the immune system.[12,32] Genus: *Bacteroides* are Gram-negative, anaerobic, rod-shaped bacteria that neither produce spores nor pigments, belonging to the family: *Bacteroidaceae* within the phylum: *Bacteroidetes*. This study has identified that genus: *Bacteroides* located in the antecubital fossa serve as a protective factor against keloids. Despite the oxygen-rich environment of the skin surface, its specific microenvironments can also support the survival of anaerobic bacteria. Furthermore, the distribution of bacteria within the stratum corneum is uneven, with the highest bacterial density observed in the superficial layers, decreasing near the granular layer, and even detectable within the dermis.[9,33] While studies exploring the connection between genus: *Bacteroides* and skin conditions are still relatively scarce, the research conducted by Shan et al could potentially corroborate our findings. They observed that the dermal layer in healthy individuals exhibits a greater presence of phylum: *Bacteroidetes* when compared to those afflicted with keloids.[9] Nevertheless, given the minimal fold change, they refrained from elaborating on this observation. Moreover, there has been extensive research on genus: *Bacteroides* within the gut microbiome, with numerous studies indicating that genus: *Bacteroides* can secrete propionate.[34,35] This not only inhibits the growth of Gram-negative facultative and obligate anaerobes[36] but also reduces the transcription of pro-inflammatory cytokines/chemokines by inhibiting histone deacetylase, thereby alleviating the progression of psoriasis.[37] Additionally, research has found that genus: *Bacteroides*

in the gut microbiome play a significant role in alleviating atopic dermatitis.[38] However, the mechanisms through which genus: *Bacteroides* on the skin surface mitigate the formation of keloids require further exploration. Additionally, we identified an ASV marked as ASV063, which belongs to an unclassified member of the genus: *Finegoldia* (a.ASV063 [*Finegoldia* (unc.)]). Compared to the healthy control group, the relative abundance of this skin microbiota was significantly reduced in the keloid disease. This result suggests that a.ASV063 [*Finegoldia* (unc.)] may play a protective role in the formation of keloids. The specific details and potential mechanisms of action of this skin microbiota remain to be elucidated through extensive future research.

Our study showcases both strengths and limitations. To our knowledge, this study is the first to utilize skin microbiome and keloid GWAS summary data, employing MR analysis to investigate the causal relationships between microbiota from different skin sites and keloids, with validation across various datasets. Furthermore, our findings have been validated in both European and Asian populations, demonstrating a high degree of result stability. However, there are several limitations to our study. Firstly, our analysis of the skin microbiome was limited to the genus to phylum levels, without reaching the granularity of species-level analysis, which complicates further validation efforts. Secondly, due to variations in microbial communities across different skin sites, the source of skin microbiome samples in our study was relatively limited, primarily including the dorsal and palmar sides of the forearm, antecubital fossa, postauricular crease, and forehead, thereby restricting the comprehensiveness of our analysis results. Lastly, the adoption of a lower significance threshold for SNP selection may impact the reliability of our findings.

5. Conclusion

We conducted a 2-sample bidirectional MR analysis using GWAS data for the skin microbiome and GWAS data from 3 keloid groups. Ultimately, we discovered a negative causal relationship between a.ASV063 [*Finegoldia* (unc.)] from the volar forearm and the genus: *Bacteroides* from the antecubital fossa with keloids. This research is crucial for uncovering the role of skin microbiota in the formation of keloids and for identifying targets for future therapeutic strategies.

Author contributions

Conceptualization: Jie Zhou.
Data curation: Jie Zhou, Chao Chen.
Formal analysis: Jie Zhou.
Funding acquisition: Yixin Xu.
Investigation: Yixin Xu.
Methodology: Jie Zhou, Haitao Wang, Chao Chen, Kun Wang.
Resources: Jie Zhou, Haitao Wang.
Software: Jie Zhou, Haitao Wang, Kun Wang.
Supervision: Yixin Xu.
Validation: Jie Zhou, Yixin Xu.
Writing – original draft: Jie Zhou.
Writing – review & editing: Yixin Xu.

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