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ORIGINAL RESEARCH

# Antimicrobial Resistance Profiles and *mupA* Gene Characterization of *Staphylococcus epidermidis* Recovered from Facial Skin of Healthy Females in Shanghai, China

Bingqing Chen[1], Lingyun Yao[2], Rongjuan Cai[2], Wei Chen[3], Yue Wang[2,4]

[1]Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China; [2]School of Perfume and Aroma Technology, Shanghai Institute of Technology, Shanghai, People's Republic of China; [3]Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China; [4]Institute of Shanghai Oriental Beauty Valley, Shanghai Institute of Technology, Shanghai, People's Republic of China

Correspondence: Yue Wang, Institute of Shanghai Oriental Beauty Valley, Shanghai Institute of Technology, Fengxiani District, Shanghai, 201418, People's Republic of China, Email yue_wong@sit.edu.cn

**Purpose:** To explore antimicrobial resistance profiles and *mupA* gene characterization of *Staphylococcus epidermidis* recovered from facial skin of healthy females in Shanghai, China.

**Patients and Methods:** In this study, we collected facial skin samples from 107 healthy females in Shanghai, China, and *S. epidermidis* isolation was performed. The minimal inhibitory concentrations of 10 antibiotics were determined for the *S. epidermidis* isolates using the agar dilution method. High-level mupirocin-resistant isolates were subjected to whole-genome sequencing and bioinformatics analysis. A total of 94 un-duplicated *S. epidermidis* isolates were obtained from 107 facial skin samples.

**Results:** Antimicrobial susceptibility tests revealed that 23.4% of the 94 *S. epidermidis* isolates were resistant to oxacillin and positive for the *mecA* gene, which could be cauterized as methicillin-resistant *S. epidermidis* (MRSE). Resistance rates for erythromycin, clindamycin, tetracycline, ciprofloxacin, and gentamicin were 8.5%, 11.7%, 10.6%, 12.8%, and 1.1%, respectively. For mupirocin, the rates of low- and high-level resistance were 3.2% (3/94) and 11.7% (11/94), respectively. Resistance to vancomycin or linezolid was not observed. High-level mupirocin resistance in facial skin isolates is mediated by *mupA*. WGS and SNP-based phylogenetic analyses revealed diverse phylogenies among the 11 *mupA*-positive *S. epidermidis* isolates. Additionally, various resistance and virulence genes were identified in *mupA*-positive isolates. A new hybrid plasmid carrying *mupA* genes was found in two *S. epidermidis* isolates.

**Conclusion:** We observed a considerable level of antimicrobial resistance to several antibiotics and the prevalence of abundant and diverse resistance and virulence genes in the facial skin-origin *S. epidermidis* isolates. This may pose a potential risk for both public health and *S. epidermidis* infection.

**Keywords:** *Staphylococcus epidermidis*, skin, resistance, mupirocin

## Introduction

*Staphylococcus epidermidis*, a coagulase-negative *Staphylococcus*, is one of the most abundant bacterial colonizers of the human skin.[1,2] Numerous studies have demonstrated that *S. epidermidis* is a beneficial member of the skin microbiot that plays an important role in the maintenance of skin integrity and homeostasis by promoting cutaneous immune priming, interacting with other resident bacteria, and controlling opportunistic pathogens.[3–5] It is also very important for skin barrier function and repair.[6] Nonetheless, *S. epidermidis* can also act as a so-called "accidental pathogen" because many reports have shown that some *S. epidermidis* infections were from skin-origin strains.[7–9] In addition to its role as a skin colonizer, *S. epidermidis* is an opportunistic pathogen implicated in hospital-acquired infections. It is the most common cause of infections associated with indwelling medical devices, including implant-associated bloodstream infections.[2,10]

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Antimicrobial resistance in *S. epidermidis* primarily targets strains associated with clinical infections.[11–14] Currently, the common antimicrobials used for treatment of *S. epidermidis* infections include isoxazolyl penicillin, vancomycin, rifampicin, clindamycin, and linezolid.[14] However, a growing number of reports indicate the emergence and spread of resistance to these drugs, complicating the treatment of *S. epidermidis* infections.[15–17] For instance, MRSE is increasingly prevalent in hospital environments. It is estimated that approximately 75–90% of *S. epidermidis* strains present in hospitals are MRSE, which is higher than that of methicillin-resistant *S. aureus* (MRSA).[18]

Additionally, resistance or decreased susceptibility to vancomycin has been frequently reported in *S. epidermidis* isolates.[19,20] Furthermore, resistance to linezolid, another last-resort antimicrobial used for the treatment of *S. epidermidis* infections, is emerging and spreading globally in healthcare settings.[21–23]

Mupirocin, also known as pseudomonic acid A, is a topical antimicrobial agent commonly used for treating staphylococcal and streptococcal infections (such as impetigo).[24] It has been used for the eradication of nasal and cutaneous colonization of *S. aureus* and *S. epidermidis* to reduce the infections caused by these bacteria in clinical settings, such as blood and prosthetic joint infections.[25–28] Mupirocin resistance can be divided into two types: low-level and high-level resistance.[28] Low-level mupirocin resistance (MIC=8–256 mg/mL) is mediated by mutations in the mupirocin target isoleucyl-tRNA synthetase (IleRS).[29] High-level mupirocin resistance (MIC≥512 μg/mL) is mainly mediated by *mupA*, and occasionally by *mupB*, both of which encode alternate IleRS with low affinity to mupirocin.[29,30]

In contrast to strains from hospital infections, there is limited information concerning the antimicrobial resistance of *S. epidermidis* derived from the skin of healthy individuals, despite the fact that the human skin serves as a highly significant habitat for *S. epidermidis* colonization. Although skin-derived *S. epidermidis* infections are infrequent, occasional cases have been documented.[7–9] Moreover, a few large-scale genomic analyses have shown that *S. epidermidis* derived from the skin carries a variety of resistance genes and virulence factors.[31] The persistent presence of commensal *S. epidermidis* may act as a reservoir for antimicrobial resistance genes and virulence factors, which can be disseminated by horizontal transfer,[32] thereby posing potential public health risks.

In this study, we aimed to determine the antimicrobial resistance profiles of *S. epidermidis* from the facial skin of healthy females in Shanghai, China. Furthermore, we investigated the genomic characterization of *S. epidermidis* strains carrying *the mupA* gene, which confer resistance to mupirocin.

# Materials and Methods

## Sample Collection and Bacteria Isolation

Between October 2022 and January 2023, facial skin samples were collected from 107 healthy female volunteers in Shanghai, China (aged 18–45 years) with "one sample per person" principles. These volunteers were non-smokers, had no visible signs of lesion at sampling sites, were free from any cutaneous diseases, and had not topically or systematically used any antibiotics for at least one year prior to sampling. For sampling, a sterile cotton swab was rigorously rubbed onto the cheek surface (approximately 30 times for at least 20 s) and then placed in 500 μL of Tryptic Soy Broth (TSB) medium (OXOID, Basingstoke, Hampshire, England). Orientation non-selective chromogenic culture medium (CHROMagar, Paris, France) was used for *S. epidermidis* isolation. After streaking the plate and incubating at 37°C for 24 h, three small and creamy colonies were randomly picked from each sample and subjected to species identification using MALDI-TOF MS (VITEK MS, bioMérieux, Marcy-l'Étoile, France). Only one confirmed *S. epidermidis* colony from one sample was subcultured for preservation and further testing.

### Antimicrobial Susceptibility Testing

The minimum inhibitory concentrations (MICs) of 10 antibiotics — penicillin, oxacillin, vancomycin, gentamicin, erythromycin, tetracycline, ciprofloxacin, linezolid, clindamycin, and mupirocin — were determined by the agar dilution method, in accordance with the recommendations of the Clinical Laboratory Standard Institute (CLSI).[33] The antibiotics were purchased from Shanghai Yuanye Bio-Technology Co., Ltd (Shanghai, China). The resistance breakpoints of all antibiotics were interpreted according to the CLSI-M100-S32 document (https://clsi.org/standards/products/microbiology/documents/m100/), except for mupirocin, for which MIC=8–256 μg/mL and MIC≥512 μg/mL were categorized as low- and high-level resistance, respectively.[34] *S. aureus* ATCC 29213 served as quality control strains.

### DNA Extraction and PCR Assays for Screening of Resistant Genes

DNA extraction from *S. epidermidis* isolates was performed using the TIANamp Bacteria DNA Kit (Tiangen Biotech Co. Ltd., Beijing, China), according to the manufacturer's instructions. PCR screening of *mecA* and *mecC* genes was performed for the oxacillin-resistant isolates to further confirm methicillin resistance, as previously described.[35] In addition, the mupirocin resistance genes *mupA* and *mupB* were detected in isolates with MIC≥512 μg/mL.[36] The amplicons were purified and sequenced to confirm the PCR results.

### Whole-Genome Sequencing (WGS) and Bioinformatic Analysis

The 11 *mupA*-positive *S. epidermidis* isolates were subjected to WGS using the Illumina HiSeq 2000 platform, and the raw data were assembled using SPAdes v.3.13.0. The draft genomes were subjected to ResFinder (http://genepi.food.dtu.dk/resfinder) to obtain the profiles of resistance genes and locate the *mupA*-carrying contigs. Moreover, the flanking sequences of the *mupA*-carrying contigs were obtained using a combination of BLAST comparison and PCR-based gap-filling approaches.[37] Annotations were automatically generated using RAST (https://rast.nmpdr.org/) and manually checked using BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi).[38] The whole genome sequences of the 11 *mupA*-positive *S. epidermidis* isolates were further subjected to phylogenetic analysis based on the concatenated alignment of SNPs using CSI Phylogeny (https://cge.food.dtu.dk/services/CSIPhylogeny/). The virulence factors were analyzed with VirulenceFinder (https://cge.food.dtu.dk/services/VirulenceFinder/).

## Results and Discussion

### Isolation of S. epidermidis

*S. epidermidis* is the most common colonizer of human skin.[2] However, information about the resistance status of skin-origin *S. epidermidis* is very scarce, especially for facial skin-origin isolates. In this study, we collected facial skin samples from 107 healthy females in Shanghai, China and isolated *S. epidermidis*. In total, 94 unduplicated *S. epidermidis* isolates were identified from 107 samples. The agar dilution method was used to test the susceptibility of all *S. epidermidis* isolates ($n$ = 94) to the 10 antibiotics (Table 1). Surprisingly, although these *S. epidermidis* isolates were obtained from healthy females who had not used topical or systemic antibiotics for at least a year, considerable high resistance rates for several antibiotics were observed. Of the 94 *S. epidermidis* isolates, 23.4% showed resistance to oxacillin and were positive for *mecA*, which could be cauterized as MRSE. MRSE is a public health-associated bacterium that shows methicillin (oxacillin) resistance mediated by *mecA* gene encoding penicillin-binding protein 2a, which has a low affinity for β-lactam antibiotics.[39] There have been many reports on the prevalence and carriage rate of MRSE; however, most have focused on strains derived from hospital infections and nasal colonizers.[12,13,40,41] A recent report showed that 43.5% of clinical isolates from various sterile specimens of inpatients in a hospital in Wenzhou, eastern China, were identified as MRSE.[13] For hospital workers, extremely high carriage rates were observed in different hospitals[12,41] in China and Sweden. Moreover, it has been reported that 11% of *S. epidermidis* isolates from the hands of volunteers and different non-healthcare/general public settings were identified as MRSE in London, UK.[42] The 23.4% MRSE isolate rate observed in the present study indicates that the facial skin of healthy personnel is also an important reservoir of MRSE.

### Antimicrobial Susceptibility of the S. epidermidis Isolates

Thirty-seven of the 94 *S. epidermidis* isolates (39.4%) were resistant to penicillin, and only one isolate (1.1%) was resistant to gentamicin. The resistance rates to erythromycin and clindamycin were 8.5% (8/94) and 11.7% (11/94), respectively. Tetracycline resistance was detected in 10 isolates (10.6%), and 12.8% (12/94) of the isolates displayed resistance to ciprofloxacin. For mupirocin, the rates of low- and high-level resistance were 3.2% (3/94) and 11.7% (11/94), respectively. No resistance was observed to the last-resort antibiotics vancomycin and linezolid (Table 1). Most investigations into antimicrobial susceptibility in *S. epidermidis* have focused on isolates of hospital origin. A previous study collected 223 clinical *S. epidermidis* isolates from a hospital in China. These isolates showed resistance rates of 95.5%, 34.1%, 29.6%, 32.3%, 49.3%, and 82.5% to penicillin, tetracycline, ciprofloxacin, gentamicin, clindamycin, and erythromycin, respectively. And the resistance rates for colonized isolates in the same hospital were 82.1%, 17.9%, 34.9%, 19.8%, 34.0%, and 62.3% to penicillin, tetracycline, ciprofloxacin, gentamicin, clindamycin, and erythromycin, respectively.[13] No linezolid- and

**Table 1** MIC Distribution and Resistance Profiles of 10 Antibiotics for 94 *Staphylococcus epidermidis* Isolates

| Antibiotic | MIC (μg/mL) | | | | | | | | | | | | | | | | | $MIC_{50}$ | $MIC_{90}$ | Resistance % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <0.032 | 0.032 (<0.063) | 0.063 (<0.125) | 0.125 (<0.25) | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 (>8) | 32 | 64 (>32) | 128 | 256 | 512 | >512 | | | |
| Penicillin | 15 | 1 | 3 | 38 | 9 | 4 | 13 | 8 | 1 | 0 | 2 | – | – | – | – | – | – | 0.125 | 2 | 39.4% |
| Oxacillin | – | 8 | 0 | 50 | 14 | 1 | 3 | 13 | 5 | 0 | 0 | 0 | – | – | – | – | – | 0.125 | 2 | 23.4% |
| Vancomycin | – | – | – | 1 | 0 | 1 | 1 | 65 | 26 | 0 | 0 | 0 | 0 | 0 | – | – | – | 2 | 4 | 0% |
| Gentamicin | – | 84 | 0 | 1 | 0 | 0 | 1 | 2 | 1 | 4 | 1 | 0 | 0 | 0 | – | – | – | <0.063 | 0.125 | 1.1% |
| Erythromycin | – | – | 38 | 0 | 11 | 0 | 2 | 2 | 33 | 7 | 1 | 0 | 0 | 0 | – | – | – | 0.25 | 4 | 8.5% |
| Tetracycline | – | – | 0 | 0 | 3 | 20 | 17 | 17 | 25 | 2 | 2 | 3 | 5 | 0 | – | – | – | 2 | 16 | 10.6% |
| Ciprofloxacin | – | – | – | 17 | 19 | 31 | 6 | 9 | 2 | 8 | 0 | 2 | 0 | 0 | – | – | – | 0.5 | 8 | 12.8% |
| Linezolid | – | – | – | – | 0 | 2 | 84 | 8 | 0 | 0 | 0 | 0 | 0 | – | – | – | – | 1 | 1 | 0% |
| Clindamycin | 12 | 0 | 36 | 22 | 0 | 2 | 8 | 3 | 0 | 1 | 0 | 0 | 10 | – | – | – | – | 0.063 | >32 | 11.7% |
| Mupirocin | – | – | 7 | 22 | 25 | 9 | 10 | 4 | 3 | 0 | 2 | 0 | 0 | 1 | 0 | 2 | 9 | 0.25 | 512 | 14.9% |

**Notes**: The thin vertical lines denote the breakpoints between susceptible and intermediate values. The thick vertical lines indicate breakpoints between the intermediate and resistant values. For mupirocin, the thick vertical line represents the breakpoints between susceptible and resistant values. White areas indicate the range of dilutions tested for each antibiotic, and The $MIC_{50}$ and $MIC_{90}$ values are the concentrations at which ≥50% and ≥90% of isolates were inhibited, respectively.

vancomycin-resistant isolates were detected. Another study in different hospitals in China demonstrated that resistance rates of 86% for penicillin, 5% for tetracycline, 8% for gentamicin, 42% for erythromycin, 38% for teicoplanin, 42% for clindamycin, and 7% for linezolid were observed in isolates from the hands and nasal cavities of hospital personnel.[12] It is reasonable to expect that antimicrobial resistance to clinical *S. epidermidis* isolates is significantly higher than that for facial skin-origin isolates observed in this study, because clinical settings, such as hospitals, have more frequent antibiotic exposure, which provides bacteria with consistent selective pressure.[43] There are no systematic studies into the antimicrobial susceptibility profile of *S. epidermidis* isolates from the facial skin of healthy people. A previous genomic analysis revealed that a considerable proportion of *S. epidermidis* isolates in healthy human skin carried various resistance genes, and frequent horizontal transfer of resistance genes was observed within individuals.[44] Although the resistance rates of facial skin-origin *S. epidermidis* isolates were generally lower than those from clinical settings, together with previous studies our results indicated that facial skin of healthy people may be an important reservoir for resistant *S. epidermidis* isolates. It should be noted that the volunteers for sampling in this study had not taken any antibiotics for at least a year. The persistent existence of resistant *S. epidermidis* isolates suggests that resistance determinants do not pose a risk of significant fitness costs for their hosts. Another possible explanation is that resistant *S. epidermidis* isolates have a strong colonization ability, which prevents them from being weeded out during microbial competition. Further studies to investigate antimicrobial resistance on a larger scale, the transmission mechanisms of resistance genes, and the pathogenicity of skin-colonized *S. epidermidis* are warranted.

## MupA-Mediated High-Level Mupirocin Resistance

In this study, we identified 11 high-level mupirocin-resistant *S. epidermidis* strains in the facial skin of healthy females. PCR showed that they were all positive for the *mupA* gene. The genomic relationships between *mupA*-carrying isolates and the genetic environments associated with *mupA* transmission were investigated using WGS. First, an SNP-based phylogenetic tree was constructed for the genomes of the 11 *S. epidermidis* isolates (Figure 1). Overall, diverse phylogeny of *mupA*-carrying *S. epidermidis* isolates was observed; however, some isolates showed very close relatedness, such as S24-1 and S40-3 (299 SNPs), S23-2 and S42-2 (163 SNPs), S65-1 and S65-3 (51 SNPs), and S50-2, S52-1, and S52-3 (4–8 SNPs). It should be noted that each of these *S. epidermidis* isolates was from a different individual; some of these individuals, however, worked in the same factory and lived in the same dormitories. For example, the volunteer hosts of isolates S65-1 and S65-3 shared a room, and similar conditions were observed for isolates S52-1 and S52-3.

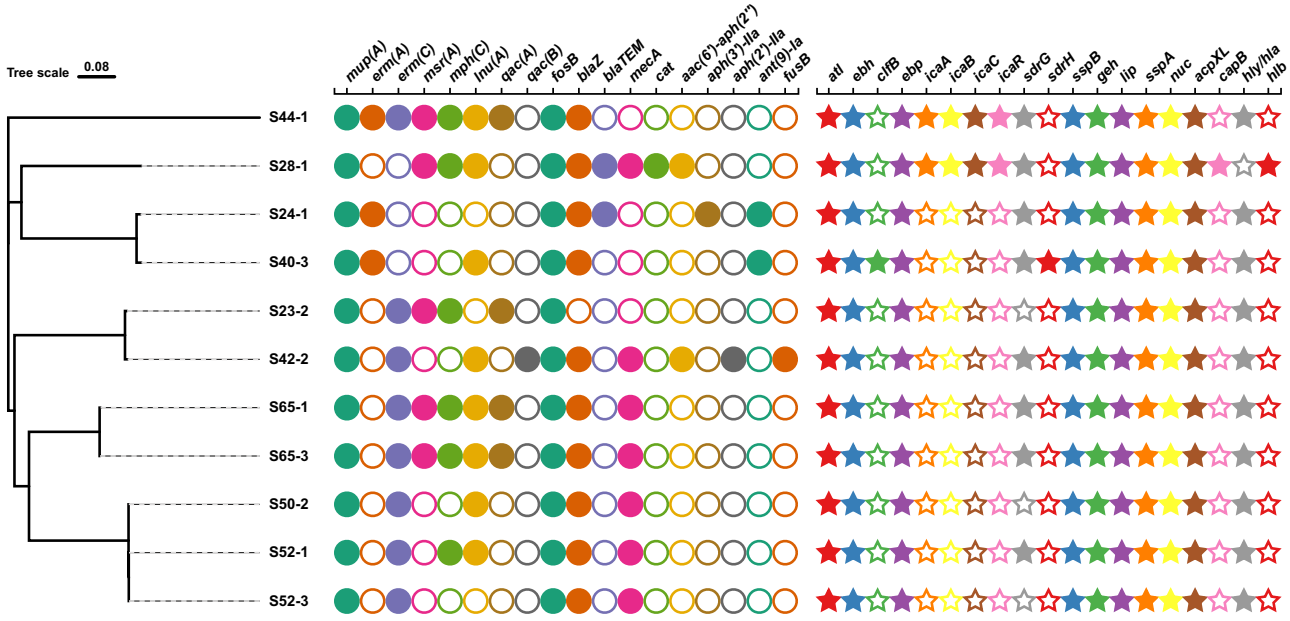


**Figure 1** SNP-based phylogenetic tree of the *mupA*-carrying *S. epidermidis* isolates subjected to WGS in this study.
**Notes**: The presence or absence of AMR genes (circles) and virulence genes (stars) is denoted by filled and empty shapes, respectively.

Genomic analysis in this study suggested that *mupA*-carrying *S. epidermidis* isolates could be clonally transferred among people in close contact.

The *mupA* gene in staphylococci is generally plasmid-borne.[29,45,46] In this study, a novel *mupA*-carrying plasmid, pMUPA4024, was identified in two *S. epidermidis* isolates, S24-1 and S40-3. The plasmid pMUPA4024 was 31, 850 bp in size, had an average G/C content of 27.5%, and comprised 36 predicted ORFs (Figure 2). pMUPA4024 contained three replication initiation genes and one resistance gene, *mupA*, around which no mobile genetic elements such as transposase or insertion sequences (ISs) were observed. BLAST searches and structural comparisons revealed that the *tnp-repA-res /int-mupA-pglE* fragment of pMUPA4024 exhibited >99% sequence homology with the corresponding region of an unnamed plasmid 2 from *S. epidermidis* strain FDAARGOS_1361 isolated in the USA (GenBank accession no. CP070061), and the corresponding region of another unnamed plasmid 3 from *S. epidermidis* strain Z0118SE0269 isolated from South Korea (GenBank accession no. CP069217). The *res/int-mupA-pglE* cluster showed a high nucleotide sequence identity with the corresponding parts of the plasmid pC100MK1 from *S. epidermidis* strain C100 isolated from Australia (GenBank accession no. CP094866). The remaining plasmid, pMUPA4024, did not show great similarity to the sequences deposited in the GenBank database. The ORFs in this region encode enzymes associated with sugar biosynthesis pathways, such as UDP-glucose 4-epimerase, D-glycero-D-manno-heptose 1-phosphate guanosyltransferase, glucose-1-phosphate thymidylyltransferase, and dTDP-4-dehydrorhamnose 3.5-epimerase. In addition to S24-1 and S40-3, *mupA* in the remaining nine isolates was located on small contigs, indicating that the *mupA* genes in these isolates were flanked by mobile genetic elements such as transposase and IS sequences.

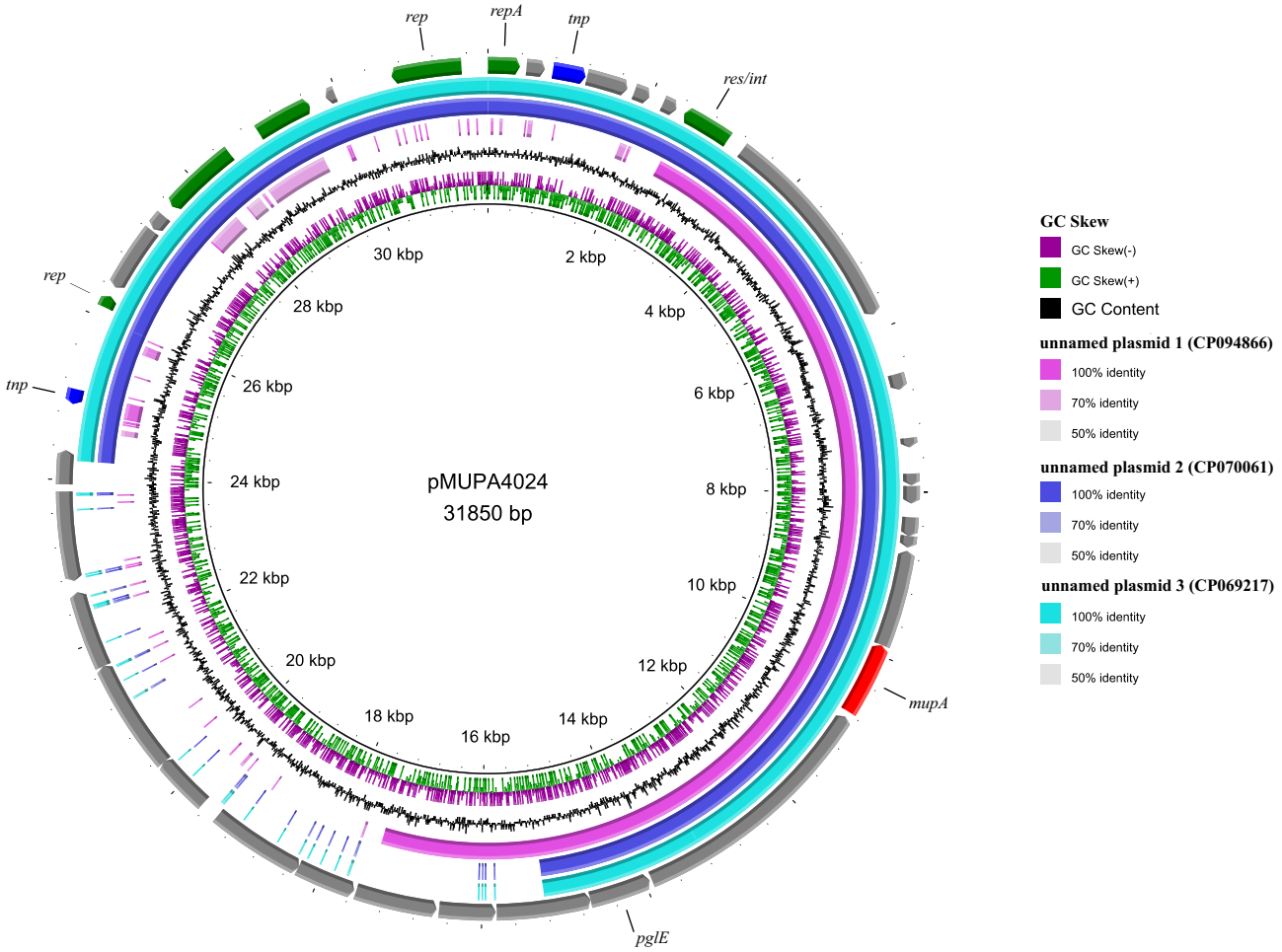


**Figure 2** Comparison between the *mupA*-carrying plasmid pMUPA4024 and other closely related plasmids deposited in GenBank.
**Notes**: The positions and orientations of the genes of the plasmids pMUPA4024 are indicated by arrows on the outermost circle.

## Resistance Genes and Virulence Factors (VFs) in the mupA-Carrying S. epidermidis Isolates

In addition to the mupirocin resistance gene *mupA*, various genes associated with resistance to different antibiotics were detected in the 11 *mupA*-carrying *S. epidermidis* isolates (Figure 1): 27.2% (3/11), 72.7% (8/11), 45.5% (5/11), and 54.5% (6/11) of isolates harbored the macrolide resistance genes *erm*(A), *erm*(C), *msr*(A), and *mph*(C), respectively; 72.7% (8/11) of isolates contained lincosamide resistance gene *lnu*(A). Four and one of the 11 isolates were positive for *qac*(A) and *qac*(B), respectively, both of which confer resistance on a series of structurally different organic cations via proton-motive force-dependent multidrug efflux.[47–49] The prevalence of the two *qac* genes in facial skin-origin *S. epidermidis* isolates may be due to widespread and massive use of personal care products for facial cleaning and nourishment, which contain organic cations in their composition.[50] All isolates harbored the fosfomycin resistance gene *fos*(B), while 10 and 2 of the 11 isolates carried the *blaZ* and $bla_{\mathrm{TEM}}$ for β-lactam resistance, respectively. The *mupA*-carrying *S. epidermidis* isolates are identifiable as MRSE due to the presence of the *mecA* gene. One isolate was positive for the chloramphenicol resistance gene *cat*, and one or two isolates carried different aminoglycoside resistance genes, including *aac*(6')-*aph*(2"), *aph*(3')-*IIa*, *aph*(2')-*IIa*, and *ant*(9)-*Ia*. Only one isolate, S42-2, harbored the fusidic acid resistance gene *fus*(B). A close look at the genome sequence data of isolate S42-2 demonstrated that the *fus*(B) gene is located on a phage-related island, which shows structural and sequence homology to other *fus*(B)-carrying islands previously reported in *S. epidermidis* isolates.[51]

Virulence factors of *S. epidermidis* play a vital role in providing selective advantages and pathogenicity. We listed the known VFs, including genes associated with adherence, enzymes, immune evasion, secretion systems, and toxins (Figure 1). Diverse VFs were detected in these facial skin-origin *S. epidermidis* isolates, and a considerable portion of them were associated with adherence, such as *atl*, *ebh*, *clfB*, *ebp*, *icaA*, *icaB*, *icaC*, *icaR*, *sdrG*, and *sdrH*. The 11 *S. epidermidis* isolates are all positive for virulence-related enzymes, including *sspB*, *geh*, *lip*, *sspA*, *nuc*,and *acpXL*. *CapB* gene, involved in immune evasion, was positive in one isolate, S28-1. Two toxin genes, *hly/hla* and *hlb*, were detected in 10 and 1 isolates, respectively. The diversity and high prevalence of different types of VFs may be involved in *S. epidermidis* colonization of the facial skin, and more attention should be paid to their potential pathogenicity and the risk of clinical infections.

## Conclusion

In this study, we observed a considerable level of antimicrobial resistance to several antibiotics and the prevalence of abundant and diverse resistance and virulence genes in *S. epidermidis* isolates originating from facial skin. This may pose a potential risk for both public health and *S. epidermidis* infection, particularly in immunocompromised and skin-injured patients. To the best of our knowledge, this is the first comprehensive report on the antimicrobial resistance profiles of *S. epidermidis* isolates from the facial skin of healthy individuals. The mupirocin resistance and the transmission of the *mupA* in the facial skin-origin *S. epidermidis* isolates were also investigated. The high prevalence of mupirocin resistance and the plasmid-borne *mupA* observed in this study may pose a potential threat to public health, as it could lead to reduced effectiveness of mupirocin in treating *S. epidermidis* infections and contribute to the spread of antibiotic resistance.

## Data Sharing Statement

The WGS data of the 11 *mupA*-carrying *S. epidermidis* isolates were deposited in the NCBI database under BioProject accession no. PRJNA1097679.

## Ethical Approval

The study complied with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Ethics Committee of the Shanghai Jiao Tong University Affiliated Sixth People's Hospital South Campus (approval no. 2022-KY-07-01). The research protocols were approved by each center's institutional review board or ethics committee. All volunteers provided written informed consent.

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## Disclosure

The authors declare no conflicts of interest related to the publication of this work.

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