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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	-The preparation of genomic sequencing library of strains was conducted in accordance with the Nextera XT DNA Library Prep Guide (Illumina) or NEBNext Ultra library prep Kit for Illumina (New England Biolabs) . The shearing of the DNA to fragments was on a Bioruptor Pico instrument (Diagenode). The libraries were sequenced on a MiSeq platform (Illumina) using a MiSeq Reagent Kit v2 or on a NextSeq Platform or using a NextSeq 500/550 v2 kit. Velvet or SPAdes was used to generate de-novo assemblies. S. epidermidis E73 was also sequenced at the Norwegian Sequencing Centre using the PacBio Sequel platform. DNA was sheared using g-TUBEs (Covaris). SMRTbell libraries were constructed using standard procedures (Pacific Biosciences). The genome was de-novo assembled using the Hierarchical Genome Assembly Process (HGAP4) workflow in SMRT Link version 5.1.0.26411 (Pacific Biosciences). The circular chromosome was annotated using the NCBI Prokaryotic Genome Annotation Pipeline. -NMR spectra were recorded with a Bruker AvanceII 700 MHz spectrometer using Bruker TopSpin version 3.1 or 3.2 software for WTA elucidation. -Identification of WTA polymer type was performed using an Ultimate 3000RS HPLC system (Dionex) coupled to a micrOTOFII electrospray-ionization time-of-flight mass spectrometer (Bruker).
Data analysis	- For phylogenetic analyses, mapping of sequence reads and SNP calling were carried out using the Northern Arizona SNP Pipeline (NASP). Sequence reads were mapped against the S. epidermidis ST2 reference isolate BPH0662 (GenBank accession no. NC_017673) using the Burrows-Wheeler Alignment tool. SNP calling was achieved using the GATK Unified Genotyper. Phages in BPH0662 were identified with PHASTER. Gubbins was used to remove recombination tracts. The MUSCLE algorithm was used to construct multiple sequence alignments for each of the tarIJLM genes and calculate pairwise nucleotide identities. A subset of tarIJLM genes representing the diversity observed within S. epidermidis was used as queries in BLASTN searches against non-S. epidermidis genomes present in the NCBI Reference Sequence Database (accessed October 29 2018). Phylogenetic reconstruction was carried out using the maximum-likelihood program PhyML with a GTR model of nucleotide substitution. Support for the nodes was assessed using aBayes. - The tarIJLM2 genes in E73 (accession no. CP035643) were used as queries in BLASTN searches against S. epidermidis genomes obtained from the NCBI Reference Sequence Database (accessed July 3 2018). MLST typing was performed by comparing contigs with the S. epidermidis MLST database using an in-house script. SCCmec typing was carried out with the SCCmecFinder tool. IS elements were classified according to transposase gene similarity by using BLAST analysis with the ISfinder database.

- Statistical analysis was performed by using GraphPad Prism (GraphPad 419 Software, Inc.) Version 8.
- qPCR results were analyzed in LightCycler 480 SW 1.5.1. and GenEx software (multiD).
- Exact masses in positive ion mode for GroP and Rbop were presented as extracted ion chromatograms with Data Analysis (Bruker).
- NMR spectra of WTA were analyzed by using Bruker TopSpin 4.0.7 Processing Only for MacOS.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The whole-genome sequences data from this study of S. epidermidis isolates were deposited in the NCBI Sequence Read Archivedeposited at GenBank; the accession numbers can be found in in Supplementary Information Table 1 and Source Data Extended Fig. 5b. All source data are provided with this paper. Additional information can be obtained from the corresponding author upon reasonable request.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample sizes of in vitro and in vivo experiments were chosen to obtain significant results. The prospective power analysis was performed with appropriate statistical methods.
Data exclusions	No data points from our in vitro or in vivo experiments were excluded.
Replication	Each major experiment was repeated at least three times as stated in the manuscript except the qRT-PCR and growth curve of strain with plasmid pT181. These experiments were only repeated for two times as the repeats gave highly congruent results.
Randomization	There was no need for randomization as the donors of bacterial isolates were not alloated to specific groups.
Blinding	There was no need for blinding as the donors of bacterial isolates were not allocated to specific groups.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	A549 human bronchial epithelial cells (American Type Culture Collection (ATCC CCL-185)) were purchased from ATCC. Human umbilical vein endothelial cells (HUVECs) (C-12203) cryopreserved from pooled donors and primary human nasal epithelial cells (HNEpC) (C-12620) cryopreserved from normal human nasal mucosa of pooled donors were purchased from PromoCell.

Authentication	Cell morphology was checked under the microscope. Mycoplasma detection was done to exclude contamination.
Mycoplasma contamination	Mycoplasma detection was performed. No contamination was found.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines were used.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Female four to six-weeks old BALB/c mice were used. The housing conditions for the mice in all animal models are: ambient temperature: 20-25℃, relative humidity (%): 40-70%, light/dark alternation time (h): 12-14/12-10.
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve field-collected animals or organisms.
Ethics oversight	All mouse work was performed in China, which was approved by the Ethics Committee of Renji Hospital, School of Medicine, Shanghai Jiaotong University.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Human research participants

Policy information about studies involving human research participants

Population characteristics	Individual donors of skin and nose S. epidermidis strains were healthy volunteers selected randomly irrespective of sex and age. Donors of nasal S. epidermidis strains did not suffer from a documented infectious disease. Invasive S. epidermidis strains were isolate from anonymized diagnostic samples.
Recruitment	Donors of skin and nasal S. epidermidis strains were healthy volunteers selected randomly irrespective of sex.
Ethics oversight	Bacterial samples from human volunteers were collected upon written informed consent and approval by the institutional review boards of the Universities of Tübingen (577/2015A) and Shanghai Jiaotong University (protocol 2017001). Isolates from Hamburg were obtained in accordance with §12 of the Hamburg hospital law (HmbKHG).

Note that full information on the approval of the study protocol must also be provided in the manuscript.