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Last updated by author(s): Feb 6, 2026

Reporting Summary

Nature Portfolio 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 Portfolio policies, see our Editorial Policies 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	Commercial, open-source, and online software were used for data acquisition, processing, statistical analysis, and visualization. Statistical analyses and plotting were performed using GraphPad Prism v10 and R v4.4.1, with relevant R packages including DESeq2 v1.44.0, ggplot2 v3.5.2, pheatmap v1.0.12, ropls v1.36.0, rstatix v0.7.2, and ggpubr v0.6.0. Genome assembly and annotation were carried out using Canu v2.2, Minimap2 v2.22, Racon v1.4.13, Prokka v1.14.6, BLAST+ v2.16.0, BEDTools v2.18, inStrain v1.0.0, BCFtools v1.21, MetaPhlAn v4.0.6, and HUMAnN v3.9. RNA-seq data processing and quantification were performed using fastp v0.23.2 and Salmon v1.9.0. Targeted metabolomics data acquisition and quantification were conducted using Analyst v1.6.3 and MultiQuant v3.0.3. Molecular structure prediction and docking analyses were performed using the AlphaFold server, Open Babel v3.1.1, AutoDockTools v1.5.7, AutoDock Vina v1.5.7, and PyMOL v2.5.4. Venn diagram analyses were performed using the Evenn online tool. No custom-written code was used in this study.
Data analysis	Statistical analyses were performed using GraphPad Prism v10 and R software (v4.4.1). Data are presented as mean ± standard deviation (SD) or mean ± standard error of the mean (SEM), as indicated in the figure legends. Data distribution was assessed for normality. Comparisons between two groups were conducted using unpaired two-tailed Student's t-tests or Mann–Whitney U tests. For comparisons among more than two groups, one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test or Kruskal–Wallis tests followed by Dunn's multiple comparisons test were applied. To correct for multiple testing in large-scale datasets (e.g., metabolomics and transcriptomics), the False Discovery Rate (FDR) was controlled using the Benjamini–Krieger–Yekutieli two-stage step-up method (or the Benjamini–Hochberg method for RNA-seq).

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 and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio 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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

All the data that support the findings of this study are available within the paper and its Supplementary Data. All third-generation long-read, whole-genome resequencing, transcriptomic (RNA-seq), and metagenomic sequencing data generated in this study have been deposited in the NCBI database under the following BioProject accession numbers: PRJNA1281804 (https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1281804), PRJNA1281807 (https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1281807), PRJNA1380636 (https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1380636), PRJNA1281849 (https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1281849), and PRJNA1283298 (https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1283298). Metagenomic data for sample H22B656-6 is not available due to DNA extraction failure. The predicted structures of the wild-type protein and the N192D mutant have been deposited in Figshare (https://doi.org/10.6084/m9.figshare.31272826). Targeted metabolomics data for bile acids are available in the MetaboLights database under identifier MTBLS13718(https://www.ebi.ac.uk/metabolights/MTBLS13718). Source data are provided with this paper.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	*Use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Indicate if findings apply to only one sex or gender; describe whether sex and gender were considered in study design; whether sex and/or gender was determined based on self-reporting or assigned and methods used. Provide in the source data disaggregated sex and gender data, where this information has been collected, and if consent has been obtained for sharing of individual-level data; provide overall numbers in this Reporting Summary. Please state if this information has not been collected. Report sex- and gender-based analyses where performed, justify reasons for lack of sex- and gender-based analysis.*
Reporting on race, ethnicity, or other socially relevant groupings	*Please specify the socially constructed or socially relevant categorization variable(s) used in your manuscript and explain why they were used. Please note that such variables should not be used as proxies for other socially constructed/relevant variables (for example, race or ethnicity should not be used as a proxy for socioeconomic status). Provide clear definitions of the relevant terms used, how they were provided (by the participants/respondents, the researchers, or third parties), and the method(s) used to classify people into the different categories (e.g. self-report, census or administrative data, social media data, etc.) Please provide details about how you controlled for confounding variables in your analyses.*
Population characteristics	*Describe the covariate-relevant population characteristics of the human research participants (e.g. age, genotypic information, past and current diagnosis and treatment categories). If you filled out the behavioural & social sciences study design questions and have nothing to add here, write "See above."*
Recruitment	*Describe how participants were recruited. Outline any potential self-selection bias or other biases that may be present and how these are likely to impact results.*
Ethics oversight	*Identify the organization(s) that approved the study protocol.*

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

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	This study consisted of two distinct animal experiments: Experiment 1:In vivo, host-mediated induction of the probiotic Bifidobacterium animalis subsp. lactis in germ-free mice. Animals: Male C57BL/6 mice (GF grade,7 weeks old; n = 4) were procured from Shenzhen Jingtai Biotech (Guangdong, China). Prior to the experiments, the mice were allowed to adapt to the laboratory conditions for one week. The animals were housed in an environment

	regulated for temperature (23 ± 1°C) and humidity (60 ± 5%) and subjected to a fixed 12-hour cycle of light and darkness. During this period, the mice had unrestricted access to purified drinking water and standard rodent feed. Experiment 2: Functional and safety validation of the adapted strain. Animals: 24 7-week-old male SPF-grade C57BL/6 mice were acclimatized for 1 week and then randomly divided into 4 groups (n=6 per group).
Data exclusions	No data were excluded from the analysis.
Replication	Most of the in vitro experiments were repeated independently at least three times.
Randomization	The mice were allocated randomly to each treatment group.
Blinding	All experiments were performed in a non-blinded manner, because the researchers were limited, and blinding feasibility was poor.

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 and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

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

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	This study consisted of two distinct animal experiments: Experiment 1:In vivo, host-mediated induction of the probiotic Bifidobacterium animalis subsp. lactis in germ-free mice. Animals: Male C57BL/6 mice (GF grade,7 weeks old; n = 4) were procured from Shenzhen Jingtai Biotech (Guangdong, China). Prior to the experiments, the mice were allowed to adapt to the laboratory conditions for one week. The animals were housed in an environment regulated for temperature (23 ± 1°C) and humidity (60 ± 5%) and subjected to a fixed 12-hour cycle of light and darkness. During this period, the mice had unrestricted access to purified drinking water and standard rodent feed. Experiment 2: Functional and safety validation of the adapted strain. Animals: 24 7-week-old male SPF-grade C57BL/6 mice were acclimatized for 1 week and then randomly divided into 4 groups (n=6 per group).
Wild animals	The study did not involve wild animals.
Reporting on sex	For our experiments, only male mice were used, as extensive studies have shown significant differences between male and female mice in metabolism, hormone levels, and immune responses (Nat Metab. 2022. 4(5):507-523; Gut Microbes. 2016.7(4):313-322; Annu Rev Immunol. 2022. 40:75–94). These differences can impact the gut microbiome, potentially influencing the interpretation of experimental results.
Field-collected samples	This study did not involve samples collected from field.
Ethics oversight	All animal experiments were approved by the Animal Ethics Committee of Hainan University (Approval No. HNUAUCC-2023-00190) and were conducted in strict accordance with the Guidelines for the Care and Use of Experimental Animals of Hainan University.

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

Plants

Seed stocks

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.