



Adaptive evolution of gut bacteria during dietary transitions

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Summary

Diet exerts selection on bacterial species within the mammalian gut microbiota [1-5], but the extent, repeatability, modes, and genomic bases of gut bacterial adaptive evolution in response to dietary variation within hosts are poorly understood. Here, we show that within-host dietary transitions drive ubiquitous and reproducible adaptive evolution of gut bacterial species.

Experimental evolution of mouse gut microbiota

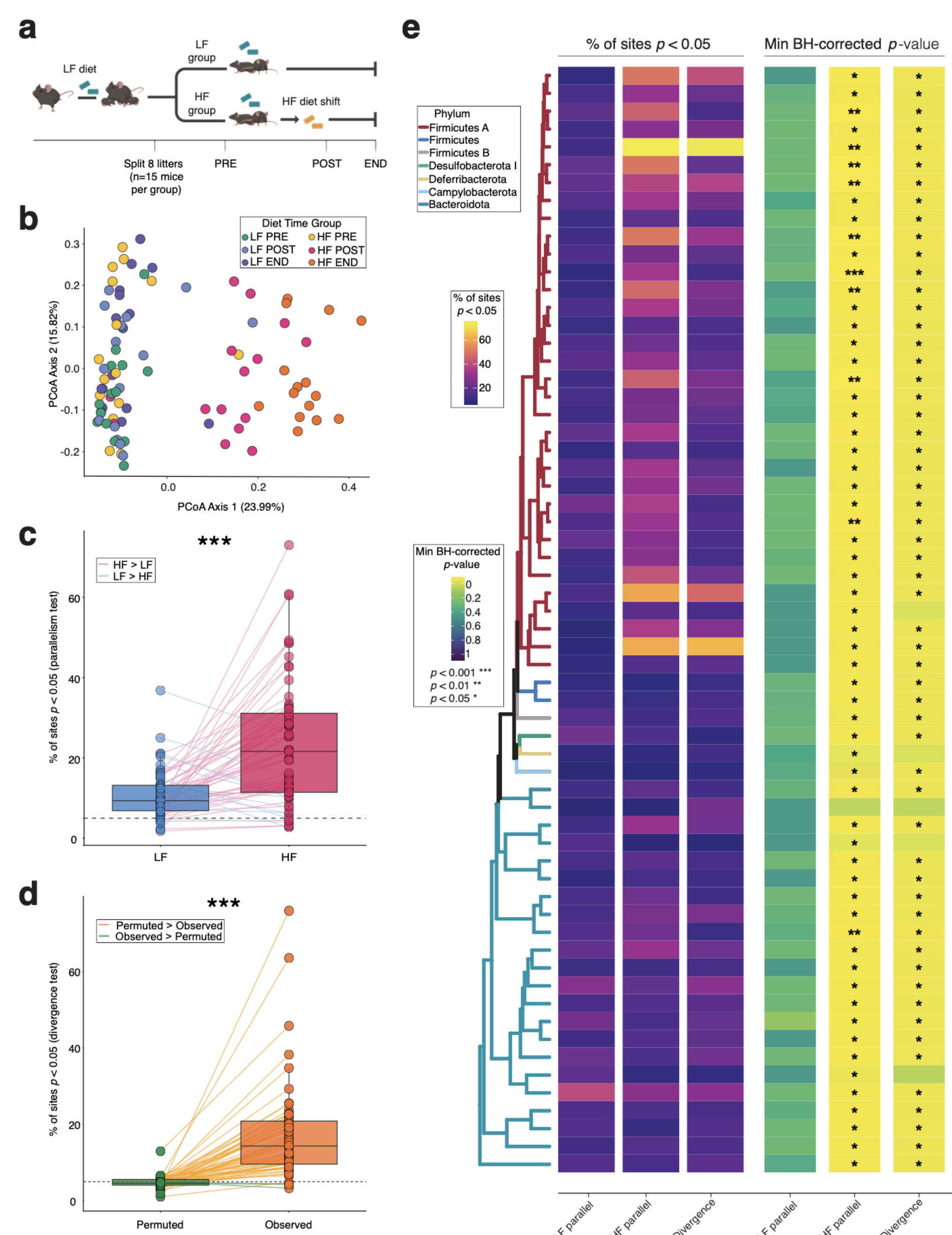


Figure 1: **a**, Litter-matched mice were transitioned to a high-fat/low-carbohydrate (HF) diet or maintained on their ancestral low-fat/high-carbohydrate (LF) diet. **b**, the Bray-Curtis dissimilarities of species composition from HF- and LF-fed mice metagenomes. **c**, The percentage of variable sites in bacterial species displaying parallel allele frequency shifts across replicates. **d**, The percentage of variable sites in bacterial species displaying divergent allele frequency shifts between LF and HF groups. **e**, Phylogeny shows relationships among 62 core gut bacterial species tested for parallel and divergent allele frequency changes mediated by HF diets.

High-fat/low-carbohydrate diets reproducibly drove bacteria strain-replacements

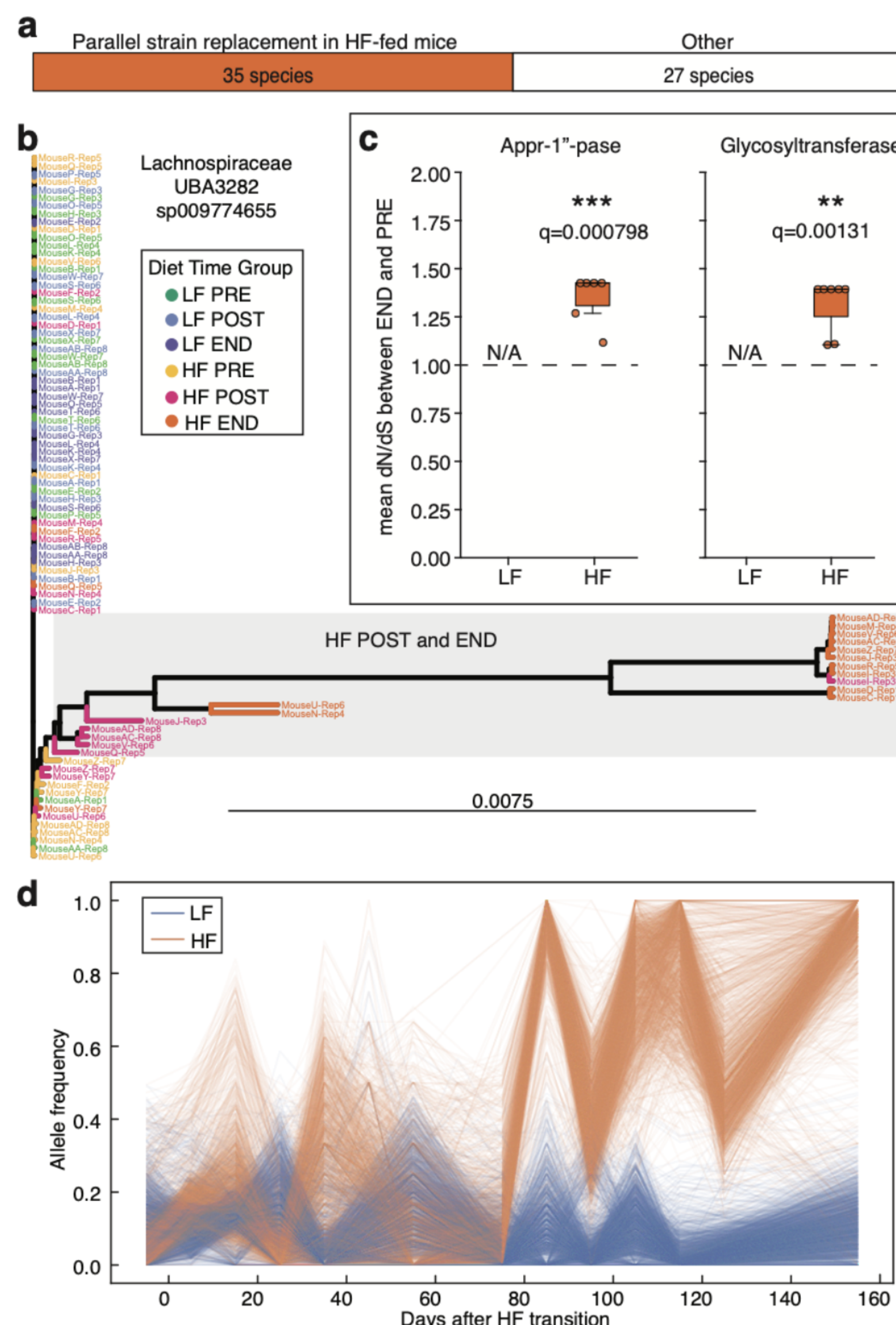


Figure 2: **a**, Stacked bar chart shows number of species displaying evidence of diet-mediated strain replacement. **b**, Dendrogram shows genomic similarity (popANI) among strains of *Lachnospiraceae* UBA3282 sp009774655, the species which showed the strongest evidence of diet-mediated strain replacement. Each tip represents sp009774655 in a metagenomic sample, and branches are colored by treatment group and timepoint, as indicated by the key. **c**, Boxplots show mean per-replicate dN/dS in LF- and HF-fed mice of the two genes that showed significantly elevated (> 1) dN/dS across replicates in sp009774655. **d**, Line plot shows allele frequency trajectories of each variable site in sp009774655. **e**, Phylogeny showing BH-corrected significant evidence of allele-frequency divergence between HF and LF groups.

Genomic signatures of adaptation shared among species

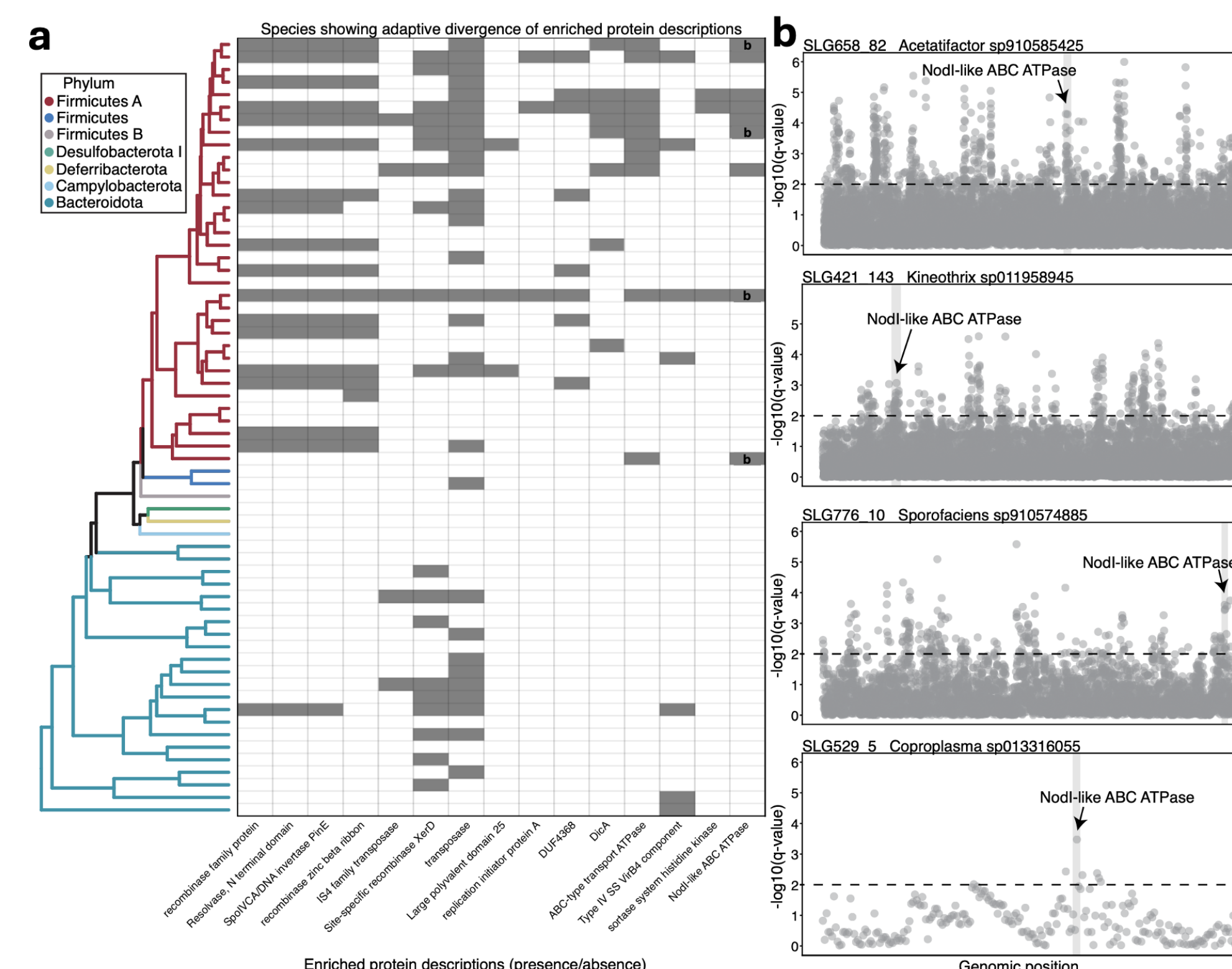


Figure 3: **a**, Phylogeny shows relationships among the 62 species tested for parallel and divergent allele frequency changes mediated by HF diets. **b**, Manhattan plots show degree of significance of allele-frequency divergence at each variable site in four representative gut bacterial species that showed parallel significant allele-frequency divergence in NodI-like ABC ATPase.

Adaptive phase variation

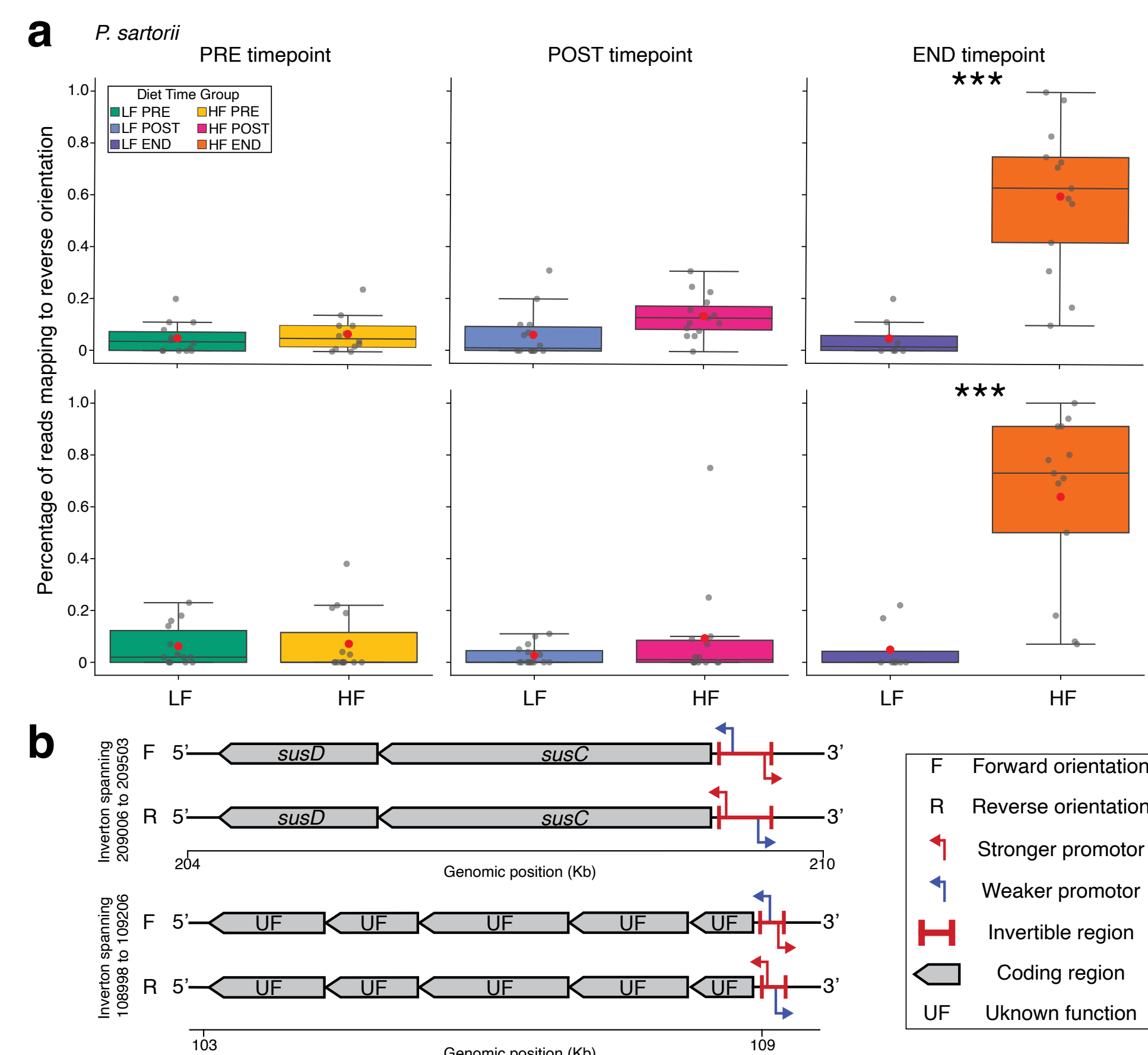


Figure 4: **a**, Invertions in *Phocaeicola sartorii* respond reproducibly to HF diets. **b**, Cartoons show nearby genes and promoters within the invertible region in a

Conclusions

- Investigating population genomic responses of complex gut microbiota within an isogenic, native host genetic background allowed us to quantify how gut bacterial species adapt to dietary transitions within individual hosts.
- Adaptive evolutionary responses were nearly ubiquitous, detected in nearly every core gut bacterial species. Within species, responses to selection were highly reproducible across experimental replicates and included both strain replacement events and gene-specific allele-frequency changes (Figures 1 and 2).
- In species that did not exhibit genome-wide allele-frequency responses, signatures of HF diet-mediated selection were enriched in specific functional categories and protein families (Figure 3), indicating parallel responses to selection across gut bacterial species within hosts.
- A subset of gene-specific allele-frequency changes could be attributed to inducible structural variation, which we demonstrated by combining analyses of genome-resolved metagenomes and isolate genomes (Figure 4). In the Bacteroidaceae species *P. sartorii* we identified invertible DNA segments (invertons) whose orientations reversed reproducibly across replicates in response to HF diets. These included a genetic switch activating a promoter of cell-surface glycan foraging proteins *susC/susD* under low-carbohydrate conditions.
- Cumulatively, these results elucidate the prevalence, modes, and genomic bases of diet-mediated within-host bacterial adaptive evolution in mammalian gut microbiota.

References

- David, L. A. *et al.* (2014) *Nature*.
- Carmody, R. N. *et al.* (2015) *Cell Host Microbe*.
- Nicholson, J. K. *et al.* (2012) *Science*.
- Dapa, T., *et al.* (2018). *Cell Host Microbe*.
- Yilmaz, B. *et al.* (2021). *Cell Host Microbe*.

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