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Transmission mode and dispersal traits correlate with host specificity in mammalian gut microbes

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Abstract

Different host species associate with distinct gut microbes in mammals, a pattern sometimes referred to as phylosymbiosis. However, the processes shaping this host specificity are not well understood. One model proposes that barriers to microbial transmission promote specificity by limiting microbial dispersal between hosts. This model predicts that specificity levels measured across microbes is correlated to transmission mode (vertical vs. horizontal) and individual dispersal traits. Here, we leverage two large publicly available gut microbiota data sets (1490 samples from 195 host species) to test this prediction. We found that host specificity varies widely across bacteria (i.e., there are generalist and specialist bacteria) and depends on transmission mode and dispersal ability. Horizontally-like transmitted bacteria equipped with traits that facilitate switches between host (e.g., tolerance to oxygen) were found to be less specific (more generalist) than microbes without those traits, for example, vertically-like inherited bacteria that are intolerant to oxygen. Altogether, our findings are compatible with a model in which limited microbial dispersal abilities foster host specificity.

KEYWORDS
aerobe, anaerobe, generalist microbe, horizontal transmission, oxygen tolerance, phylosymbiosis, specialist microbe, spore, sporulation, vertical transmission

1 | INTRODUCTION

Mammals host a gut microbiota that plays a consistent role in their physiology by providing nutrients from food that is otherwise inaccessible, helping develop and maintain a homeostatic immune system and protecting against intestinal pathogens (Hammer et al., 2019; Sommer & Bäckhed, 2013). This microbial ecosystem is compositionally distinct from any other one found on Earth (Song et al., 2020; Thompson et al., 2017). The specificity of the whole microbial community (Figure 1) extends to within mammals: different species and clades host distinct microbiota (Amato et al., 2019; Brooks et al., 2016; Groussin et al., 2017; Knowles et al., 2019; Mazel et al., 2018; Youngblut et al., 2019), a pattern sometimes referred to as "phylosymbiosis" (Figure 1a). This is expected if individual gut microbes colonize a limited set of host lineages or species, that is, they are host specific (Figure 1a and hypothesis no. 1 in Figure 1b,c). For example different strains in the families Bacteroidaceae and Bifidobacteriaceae segregate across primate species (Moeller et al., 2016 but see Nishida & Ochman, 2021). A central question is whether beneficial effects conferred by the microbiota can be

provided by any consortium of microbes adapted to grow in the gut environment or if a microbiota specific and native to each host species is required to provide maximal benefits.

Experimental evidence suggests that the beneficial effects of the gut microbiota vary in a host species-specific manner. For example, germ-free rodent species that are inoculated with a non-native gut microbiota show abnormal development and maintenance of the immune system and decreased digestive abilities (Brooks et al., 2016; Chung et al., 2012; Moeller et al., 2019). These results suggest that there are intimate interactions that evolve between gut microbes and a specific host species that only benefit that species. On the microbial side, higher host specificity is expected to be selected for when there is a tradeoff between specialization and performance, that is, adaptation to a new host species imposes microbial fitness costs in the original host species (Lajoie & Parfrey, 2022; Poulin, 2011). In any case, the origin and maintenance of such a specific partnership requires that partners are reliably associated across generations, for example due to vertical (i.e., mother-to-juvenile) modes of transmission. Over long time-scales, one might expect this to translate into coevolutionary dynamics (Janzen, 1980), that is "an evolutionary change in a trait of the individuals in one population in response to a trait of the individuals of the second population, followed by an evolutionary response by the second population to the change in the first", resulting in a partnership that is both specific and mutually beneficial. From this framework, it could be tempting to interpret the widespread occurrence of microbiota specificity in mammals (Amato et al., 2019; Brooks et al., 2016; Groussin et al., 2017; Knowles et al., 2019; Mazel et al., 2018; Youngblut et al., 2019) as a result of widespread coevolutionary dynamics between mammals and their gut microbes.

Paradoxically, this reasoning contradicts recent theoretical results suggesting that coevolution is unlikely to happen between mammals and their gut microbes (Foster et al., 2017; Moran & Sloan, 2015; van Vliet & Doebeli, 2019). Specifically, even though mammals and their gut microbes might have been associated across generations, their respective fitness are unlikely to be aligned (low partner fidelity-feedback) because of (1) the orders of magnitude of difference between their generation times (van Vliet & Doebeli, 2019) and because (2) a lot of gut microbes are probably transmitted horizontally between unrelated individuals (but see Sharp & Foster, 2022). How can we then explain that experimental disruption of a specific microbiota impacts normal immune development or digestive abilities (Chung et al., 2012; Moeller et al., 2019)? One hypothesis posits that the difference in fitness benefits provided by the native versus non-native microbiota is not large enough to sustain long term coevolutionary dynamics

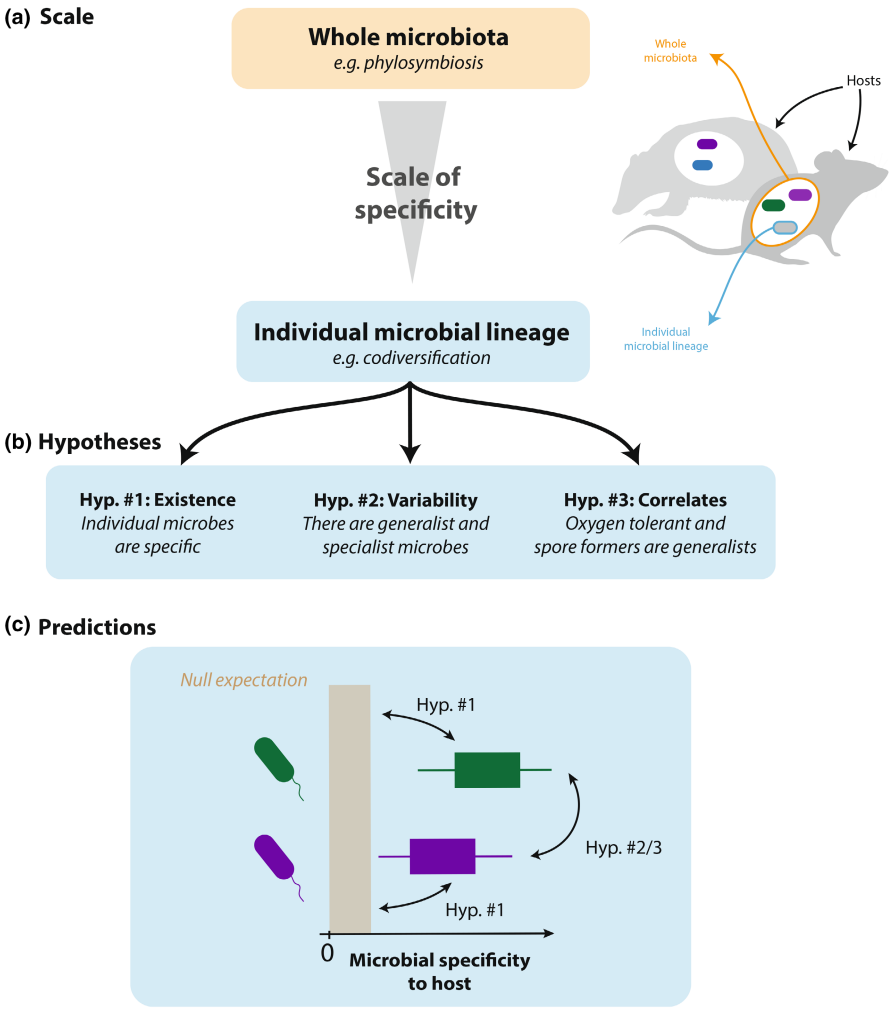

FIGURE 1 Conceptual framework of microbiota specificity to host species. (a) Microbial specificity to host species can be classified at two scales: specificity measured on the whole microbial community (light orange) and specificity measured on individual microbial lineages (light blue). (b) Three hypotheses related to individual microbial lineage specificity are proposed. (c) Examples of approaches to test these hypotheses. Individual microbial lineage specificity can be measured using, e.g., the inverse of the number of colonized host (x-axis, bottom graph). Some hypothetical value distribution (boxplots) are presented in the graphs. Random expectations for values of specificity of individual microbes are derived from null models using randomization of the data. Arrows between boxplots point out the specific comparisons that have to be made to test the hypotheses presented above. Animal silhouettes courtesy of Phylopics by Daniel Jaron and Ferran Sayol.

(Groussin et al., 2020). In any case, other models are needed to explain the widespread and strong specificity observed in the mammalian gut microbiota (Amato et al., 2019; Brooks et al., 2016; Groussin et al., 2017; Knowles et al., 2019; Mazel et al., 2018; Youngblut et al., 2019).

There are at least two nonmutually exclusive models that can explain host specificity without relying on complex coevolutionary dynamics (Hammer et al., 2019; Kohl, 2020; Moran et al., 2019). The first model posits that the guts of different host species represent different habitats that filter out distinct microbes from a larger pool of gut-adapted microbes (Douglas & Werren, 2016; Mazel et al., 2018). For example, diet and stomach pH vary widely between mammals (Beasley et al., 2015) and could act as an environmental barrier that prevents the colonization of certain microbes but facilitates others. While the ability of microbes to circumvent this barrier is likely the product of natural selection, it does not imply reciprocal natural selection between host and microbes (i.e., coevolution). This model, also known as "host filtering", represents a simple and parsimonious explanation for species specificity (Douglas & Werren, 2016; Mazel et al., 2018). The second model proposes that transmission barriers prevent microbial exchange between hosts and thus fosters specificity (Poulin, 2011). This hypothesis is based on growing empirical evidence (Moeller et al., 2013; Rothschild et al., 2018) and synthesis work (Miller et al., 2018; Robinson et al., 2019) suggesting that transmission (i.e., dispersal) of gut microbes between hosts is limited because it implies exposure to the outside environment and in particular to oxygen, which is harmful for many gut microbes (Madigan et al., 2017). Deciphering which of these alternative models –filtering or dispersal– is the most likely to explain specificity, or to what extent they act in concert, is a central and open question in the field (Kohl, 2020; Mallott & Amato, 2021).

Analysis of large comparative data sets can provide unique evolutionary insights and establish broad trends across clades (Mallott & Amato, 2021) and can complement experimental work in model organisms that can provide insights into the underlying mechanisms and fitness impacts of host specificity (Brooks et al., 2016; Moeller et al., 2019). The convergent evolution of high (and low) specificity in independent clades of microbes (Figure 1b,c, hypothesis no. 2) represent natural "experiments" that can be harnessed using comparative methods to unravel the mechanisms shaping microbiota specificity. The hypothesis that microbial dispersal limitation and transmission mode are key for the evolution of specificity informs predictions about specificity levels across microbial clades. We predict that microbes that are acquired from the environment (horizontal-like mode of transmission) will be less host-specific than microbes that are acquired from mother or close relatives (vertical-like mode of transmission). Indeed, we also expect horizontally transmitted microbes to be more easily exchanged between host species because successful transmission does not require close physical contact between individuals. Several bacterial dispersal traits could reflect these transmission mode effects. In particular, we predict that spore forming and oxygen tolerant gut microbes to be less specific than non-spore forming and oxygen intolerant microbes (Figure 1b,c, hypothesis no. 3). Oxygen tolerant gut microbes are likely to survive for longer amount of time outside of the gut environment and are thus more likely to be transmitted between individuals than oxygen intolerant gut microbes. Similarly, gut microbes that produce resistant structures (spores) can persist outside of the gut environment in a dormant state for extended period of time and act as a dispersal propagule facilitating transmission between individuals (Browne et al., 2020; Egan et al., 2021). For example, a recent study reported that spore formers found in the human gut are more prevalent across populations, maybe due to an increased rate of transmission between individuals (Browne et al., 2020). We hypothesize that because spore forming bacteria are expected to have a higher rate of intraspecies dispersal, they are also more likely to switch between host species and might thus have colonized more host species over evolutionary time scale. To the best of our knowledge, there are no large-scale studies that quantify host species specificity of microbes and whether this specificity is related to particular microbial transmission mode and traits (e.g., dispersal traits).

Here, we document how specificity varies across the bacterial tree of life. We use two recently published large data sets: the Song et al. (SEA hereafter) data set (Song et al., 2020) that encompasses 1373 samples representing 164 host species that we present in the main text and the Youngblut et al. (YEA hereafter) data set (Youngblut et al., 2019) with 117 samples representing 41 host species used to confirm our results and that we present in Supporting information materials. Specifically, we test the following predictions of the dispersal and gut habitat filtering model: vertically-like transmitted, oxygen intolerant and nonspore forming bacteria are more specific than horizontally-like transmitted, oxygen tolerant and spore forming gut bacteria.

2 | MATERIALS AND METHODS

2.1 | Reproducibility of the pipeline

All the bioinformatic pipeline described below has been written in BASH and R (R Development Core Team, 2015) with intensive use of the tidyverse (Wickham et al., 2019), vegan (Oksanen et al., 2016) and ggplot (Wickham, 2016) R packages. The associated R code is publicly available on github at https://github.com/FloMazel/Host_specificity_and_microbial_Traits.

2.2 | Raw microbiota data sets

We used two publicly available data sets of (V4) 16 S rRNA amplicon sequences that show complementary strengths (Song et al., 2020; Youngblut et al., 2019): the SEA data set contains a large number of samples with short sequences (90 pb) that come from different studies following the same protocol (Thompson et al., 2017). The YEA contains a smaller number of samples collected more consistently and with longer sequences (250 pb).

Fastq files used in SEA data set were downloaded from the ENA and MG-RAST websites (Table S1) and the associated metadata table was downloaded from the publisher's website. Following SEA, we removed samples from Delsuc et al. (2014) that showed signs of contaminations. In order to avoid pseudo-replication, we retained samples that originated from different individuals. We discarded samples from diseased or juvenile/newborn individuals as it is known that both disease and age affect the gut microbiota composition (Cho & Blaser, 2012; Yatsunenko et al., 2012). We also discarded samples that lacked information on the sample preservative used or the country of origin. To avoid computational burden, we randomly subsampled at most 20,000 reads from each sample. Fastq files from the YEA study were downloaded from the ENA website (BioProject PRJEB29403) and the associated metadata table was downloaded from the publisher website. The final data sets included 1373 samples and 164 species in the SEA data set (number of individuals per host species ranged from 2 to 139, median = 4, mean = 8.4) and 117 samples in 41 host species in the YEA data set (number of individuals per host species ranged from 2 to 11, median = 2, mean = 2.9) for a total of 1490 samples in 195 host species.

2.3 | Amplicon sequence variant (ASV) inference

Both data sets were processed similarly using the dada2 R package (Callahan et al., 2016). For the SEA data set, each study was processed independently due to potential differences in preparation and sequencing between studies. Reads were then quality filtered using the filterAndTrim dada2 R function (with parameters maxEE = 2, truncQ = 2, truncLen = 90). Chimera were removed using the removeBimeraDenovo dada2 R function. We assigned taxonomy for each ASV using the naïve Bayesian RDP classifier, as implemented in dada2 (function assignTaxonomy, parameter minBoot set to 50, that is, minimum bootstrap to 50) with the SILVA (version 132) database. Samples were rarefied to 5000 reads. A similar pipeline was used to process the reads from the YEA data set except that reads were truncated at 200 pb and merged.

2.4 | Host and microbial traits

Host diet and taxonomy were retrieved from the metadata of the initial studies. We used the mammal phylogeny available at https://megapast2future.github.io/PHYLACINE_1.2/ (Faurby & Svenning, 2015). For the microbes, we used the SILVA phylogeny (nonredundant 99 data set, version 132 available on the SILVA archive website https://www.arb-silva.de/download/archive/as an arb file). We gathered two microbial traits (oxygen tolerance and spore-forming ability) at the genus level using the Bergey manual of systematic bacteriology (Whitman, 2015) or, when the genus was not listed in the manual, the study describing the new genus. For oxygen tolerance, we derived two estimates. In the first more conservative estimate we split the Bergey Manual categories into strictly anaerobes (grouping genera categorized as "Obligate anaerobe", "obligately anaerobic", "Strictly anaerobic") and nonstrictly anaerobes (grouping genera qualified as "Microaerotolerant", "Obligately aerobic", "Microaerophilic", "Aerobic or facultatively anaerobic", "Aerotolerant", "Aerobe" and "Facultative anaerobes"). In a second, less conservative, estimate we also included as anaerobes genera listed as "Anaerobe" and considered all unknown genera in the family Rumonicoccacea as anaerobes. Both estimates yielded similar results (see Section 3). For both traits (oxygen tolerance and spore forming abilities) when the trait was documented as variable within genera, we assigned "NA" to the genus. We also gathered a quantitative measure of inferred transmission mode ("TM", horizontal-like vs. vertical-like) of gut bacteria from Moeller et al. (2018). This measure is derived from multigenerational tracking of gut bacteria transmission between two genetic lineages of mice (*Mus musculus*). It is quantified as "The ratio of between-line to within-line binary Sorensen-Dice dissimilarity for each genus [...] provided information about the degree of vertical versus horizontal transmission of ASVs belonging to the genus [...]". A TM score of >1 indicated that ASVs of the genus tended to be restricted to specific mouse lines (i.e., were vertically inherited), a score equal to 1 indicated that ASVs were distributed equally among mice irrespective of line, and a score of <1 indicated that ASVs were more often shared by mice from different lines than by mice from the same line (i.e., were horizontally transmitted). While it is true that this metric is likely to be variable within genus, we only used genus-level average to be able to match the taxonomic entities used here with the taxonomic entities used in the original study (Moeller et al., 2018).

2.5 | Statistical analysis

2.5.1 | Overall effect of host species on microbiota composition

To assess whether individuals within a host species harbour more similar microbiota than individuals between host species, we performed PERMANOVA (Anderson, 2001) (function adonis in R package vegan). Beta-diversity between samples was quantified using the Bray–Curtis dissimilarity index and the true turnover component of the Jaccard metric (Baselga, 2010). We also controlled for similarity in diet and phylogeny between host species using broad diet categories (herbivore, omnivore, carnivore and insectivore) or higher taxonomic rank (order) as permutation blocks in the PERMANOVA models. PERMANOVA results can be biased when there is significant dispersion in the data (which was the case here) and uneven sampling (i.e., different species have different number of sampled individuals). To avoid this bias, we reran our analysis only considering host species with five individuals in the SEA data set because PERMANOVA results have been shown to be robust to dispersion effects as long as the sampling is even (Anderson & Walsh, 2013).

2.5.2 | Specificity of individual gut microbes

To quantify specificity of each individual microbial lineage (here, ASVs) to their host, we used two classical measures: taxonomic and phylogenetic specificity. The first quantifies the host range by counting up the number of host species colonized by each ASV (also sometimes referred to as host range, note that other metrics such as Shannon index could also be used) (Poulin, 2011). The second quantifies phylogenetic specificity (Poulin, 2011) by measuring the phylogenetic diversity (PD) of the set of host species colonized by each ASV. We used the classical Faith PD metric (Faith, 1992) and an host phylogeny (Faurby & Svenning, 2015) to quantify phylogenetic diversity. Because both of these measures are sensitive to sampling effort (here reads counts), we standardized their values using null models (Gotelli, 2000). This implies computing a null distribution of the metrics and comparing the observed value of the metric to the null distribution using the following formula:

$$\text{Standardized specificity} = (\text{Observed Specificity} - \text{mean}(\text{null Specificity}))/\text{sd}(\text{null Specificity}).$$

We note that a careful choice of null models is of paramount importance to test specific hypothesis in community ecology (Gotelli, 2000; Münkemüller et al., 2020). For host range, we used a null model that randomizes, for each ASV, presence/absence across host samples by preserving the prevalence of each ASV (99 randomizations, function randomizeMatrix in picante R package (Kembel et al., 2010), null model argument set to "richness"). In other words, for each ASVs, presence/absence were shuffled across all samples (Gotelli, 2000). For phylogenetic specificity, we used a null model that shuffled the tip names of the host tree and kept ASV that were at least present in two host species, as implemented in the R package PhyloMeasures (Tsirogiannis & Sandel, 2016). We used the rarefied data sets (n = 5000 reads/sample) where each host species is represented by at least two samples (total: 1373 samples and 22,932 ASVs in the SEA data set; 117 samples and 17,464 ASVs in the YEA data set).

In order to focus on gut microbes that are abundant and prevalent in the gut and from which we can gather trait data via their taxonomic assignation, we restricted our analysis to ASVs that fulfil the three successive filters: (1) They are relatively abundant and prevalent, and are successfully assigned to a (2) known and (3) abundant and well-represented genus:

1. ASVs that were present in at least two samples and totalling more than 100 reads. SEA data set: 4787 ASVs totalling 93% of the initial read counts. YEA data set: 626 ASVs totalling 54% of the initial YEA read counts.
2. ASVs with a genus assignation. SEA data set: 2734 ASVs of the ASVs totalling 47% of the initial read counts. YEA data set: 510 ASVs totalling 28.4% of the initial read counts.
3. ASVs belonging to well-represented bacterial genera in the SEA data set only (to keep the list of genera similar between the two data sets). We kept only ASVs belonging to the 25% most abundant (in terms of total read counts) genera of the SEA, which corresponds to 102 genera with at least 5154 reads each in the SEA data set. SEA data set: 2084 ASVs totalling 48% of the initial read counts. YEA data set: 423 ASVs totalling 27.8% of the initial read counts.

We tested whether taxonomic and phylogenetic specificity measured at the ASV level differed between genera using a Kruskal-Wallis rank sum test. As genus identity had significant effect (i.e., there are specialist and generalist genera, see Section 3), we then computed a genus level estimate of ASV specificity by taking the median of specificity values of all ASVs within each genus (genus-aggregated taxonomic specificity and genus-aggregated phylogenetic specificity hereafter). Then, our aim was to relate these specificity measures to various microbial traits. A statistical relationship between genus-aggregated specificity measures and various genus level traits can not necessarily be inferred using standard (nonphylogenetic) methods because the units of analysis (here, microbial genera) are not phylogenetically independent (Felsenstein, 2004). Classic statistics can only be used if the residuals of the model do not harbour phylogenetic signal (Uyeda et al., 2018). Therefore, we used a phylogenetically generalized linear model (PGLS; as implemented in the caper R package) by jointly estimating model parameters along with phylogenetic signal in the model residuals with Pagel's lambda (Pagel, 1999). PGLS model were constructed using a genus-level phylogeny inferred from the SILVA phylogenetic tree (version 132): we randomly subsampled one SILVA sequence from each genus found in our data set and pruned the SILVA tree to these selected sequences (n = 102 sequences representing 102 genera). We repeated the random subsampling and model construction 50 times and took median values of Pagel lambda estimates, F statistics and associated p-values. We removed two outlier genera: *Ureoplasma* and *Fusobacterium* when testing the relationship between taxonomic specificity and TM metric in the SEA data set as these genera violated linear model assumptions.

3 | RESULTS

Overall, mammals harboured host species-specific microbiota (Figure 1; PERMANOVA: R^2 = .51, pseudo-F = 4.2, p < .001, Figure 2a). Two individuals from the same host species host a more similar microbiota (i.e., they have lower beta-diversity) than two individuals from different species (Figure 2b). This result was robust to various technical and biological factors such as host diet, host taxonomy, the metric of beta-diversity used to quantify similarity, the number of individuals sampled within host species and was also found using an independent data set (Table S2, Figure S1).

The specificity quantified so far was measured at the level of the whole microbiota and encompassed all microbial lineages present in the gut (Figure 1a). The next steps were to quantify whether specificity extend to individual microbial lineages (defined here at the

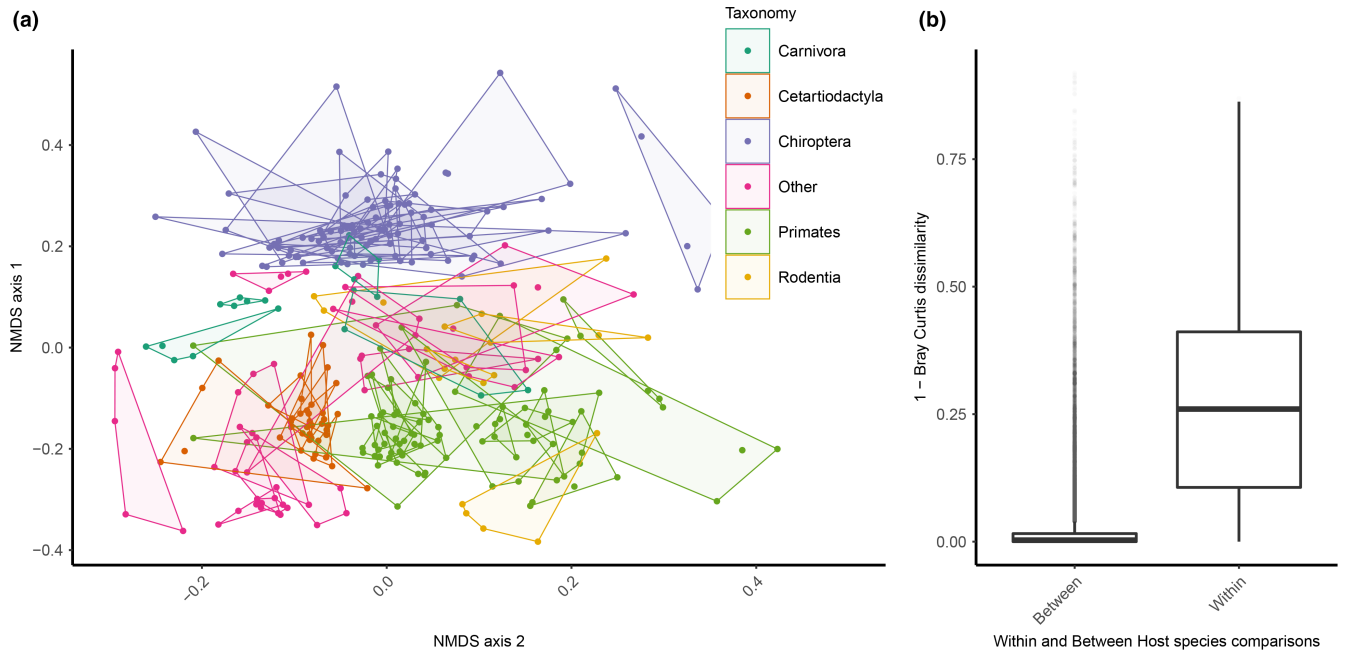

FIGURE 2 Mammals host a species-specific gut microbiota. (a) Shows an ordination (nonmetric multidimensional scaling [NMDS]) plot based on Bray–Curtis dissimilarity between samples. Lines link samples from the same host species and delineate host species composition in the ordination space (polygons). Colours refers to the taxonomic order of the host species. Clusters of species and orders are clearly visible. (b) Plots the raw Bray–Curtis similarity values (1 – Bray–Curtis dissimilarity) between samples, splitting within and between host species comparisons, showing greater similarity within than between hosts. For visualization purposes, only host species with more than five individuals are presented and for host species that were sampled more than five times, we randomly subsampled five individuals (67 species representing 335 individuals from the SEA data set, stress value = .19).

ASV level, Figure 1a,b, hypothesis 1) and if some microbial lineages contributed disproportionally to host species specificity (Figure 1b, hypothesis no. 2) by identifying generalist microbes that colonize multiple hosts and more specialized ASVs restricted to a reduced set of host species. Microbial specificity was measured for each ASV by (1) the standardized number of host species colonized (taxonomic specificity, also sometimes referred to as host range; standardization by randomizing the ASV table; see Methods and Figure 1c); and (2) the standardized phylogenetic diversity of the colonized host species (phylogenetic specificity; standardization by randomizing the host phylogeny; see Methods and Figure 1c). Because we were interested in microbes that are abundant and prevalent in mammalian guts and wanted to avoid transient microbes, we focused on ASVs assigned to the top 25% most abundant genera (2084 ASVs in 102 genera). We found that a large proportion of ASVs have higher specificity than random (i.e., supporting hypothesis 1 in Figure 1b), and that this effect is more pronounced for taxonomic specificity (i.e., ASVs colonize fewer host species than expected by chance, Figure 3a) than for phylogenetic specificity (i.e., ASVs colonize host species that are more closely related than expected by chance, Figure S2A). For both taxonomic and phylogenetic specificity, specificity values were more similar within than between genera (Kruskal-Wallis rank sum test, p-value < .001, Figures 3b and S2B) and varied across genera. For example, ASV from genera belonging to the families Lachnospiraceae (e.g., Lachnospiraceae UCG−004 and UCG−009) and Ruminococcaceae (e.g., Ruminococcaceae UCG−009) showed higher specificity than ASVs from *Enterococcus* or *Bacteroides* (Figure 3b). Those findings were confirmed with the YEA data set (Figures S3–S4).

Because ASVs belonging to the same genus showed similar specificity, we aggregated ASV specificity at the genus-level by calculating the median specificity across ASVs within each genus. We next analysed the correlates of aggregated genus-level specificity using generalized linear regression that controls for phylogenetic relationship between genera (phylogenetic generalized least squares [PGLS] model; see Methods and Figure S5 for details). Estimates of aggregated genus level specificity derived from the two independent data sets were significantly correlated to each other (PGLS model, p-value < .001, Figure S6). Genus-aggregated taxonomic and phylogenetic specificity were also significantly correlated to each other in both data sets (Figures 4a, S7A).

We then asked whether genus-aggregated specificity was related to bacterial traits and transmission mode as inferred from taxonomy. Taxonomic specificity was related to oxygen tolerance (Figures 4c, S7–S8, Table S3): strictly oxygen intolerant microbes were more likely to be specialists in both data sets (PGLS model, p-value < .01). Oxygen tolerance was significantly associated with phylogenetic specificity in the YEA data set but not in the SEA data set (Figures S9B–10B). The hypothesis that spores formers are less specialized was not supported (Figures 4d, S7D–S9C–S10C), although we did find a marginally significant effect towards lower specificity in spore-formers in the YEA data set (PGLS model, Figure S7D;

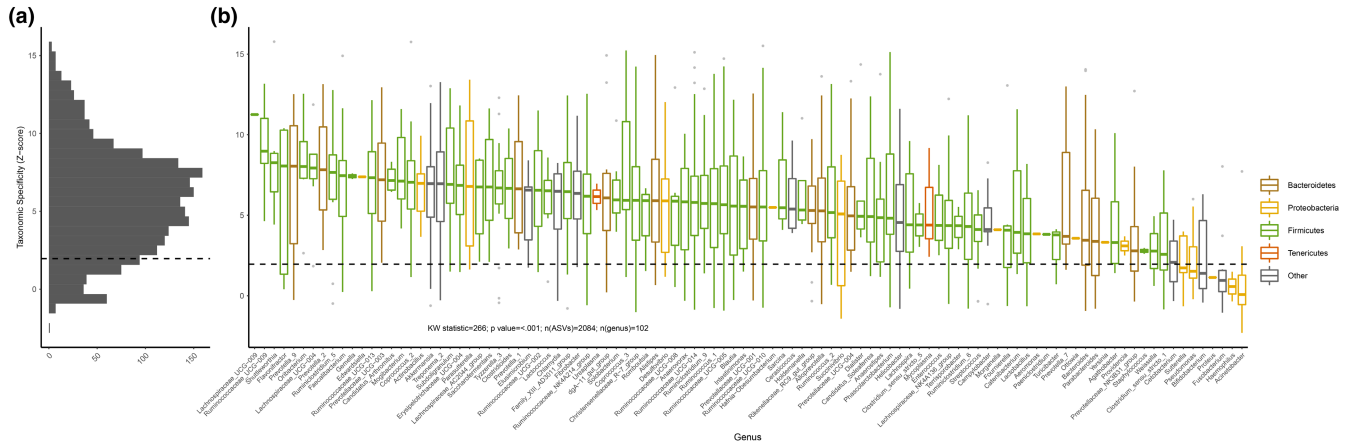

FIGURE 3 Individual microbe specificity for host species varies widely but is not uniform across microbial genera. The figure depicts how ASV specificity to host species (a, y-axis, measured as the standardized number of host species [Z-scores] in which a given ASV is observed) varies across bacterial genera (b). The dashed line corresponds to the value 1.96, the usual significance threshold (at 5%) for Z-scores. Bacterial genera are coloured according to their respective phylum (n = 2084 ASV in 102 genera).

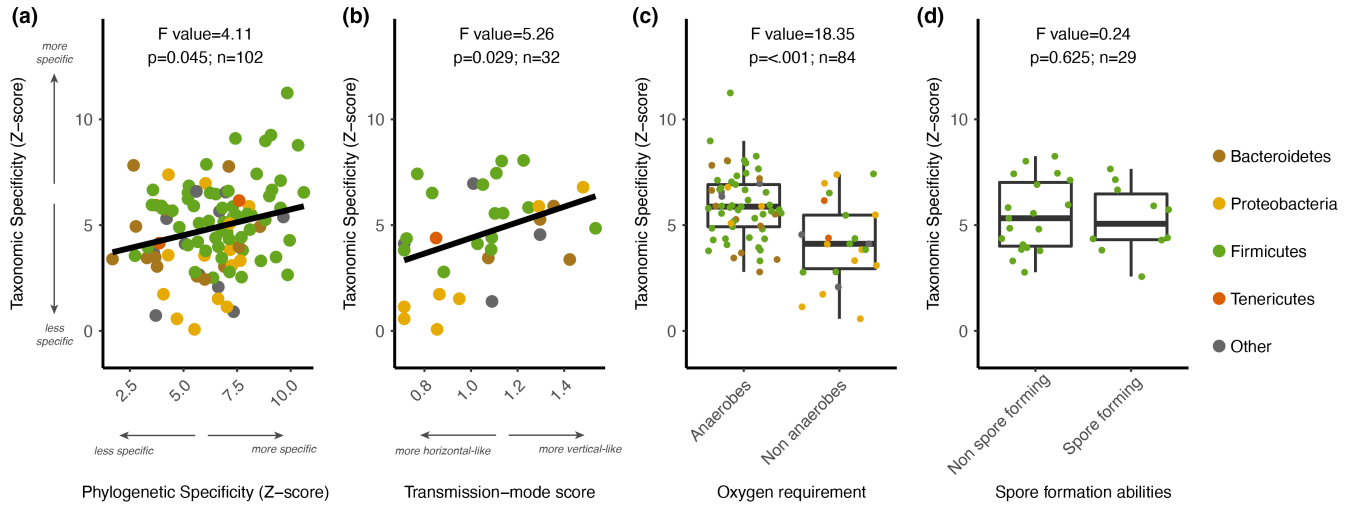

FIGURE 4 Genus-level microbe specificity relates to microbial functions. The figure shows how ASV specificity to host species (a–d, y-axis, measured as the standardized number of host species [Z-scores] in which a given ASV is observed) averaged at the genus level (median values) is correlated to phylogenetic specificity (a), bacterial mode of transmission (b) and bacterial functions (c–d). The transmission mode score (b) increases when the mode of transmission become more vertical-like (instead of horizontal like). Corresponding phylogenetic linear model statistics are given in the panels along with sample sizes.

F = 3.1, p = .09). Interestingly, we found that taxonomic specificity was related to a score of transmission mode measured for gut microbes across multiple generations of two genetic lineages of mice (Moeller et al., 2018). Microbial genera with a more vertical-like (see Section 4) mode of transmission had higher taxonomic specificity in both data sets (SEA data set: Figure 4b, p = .03; Figure S7B for the YEA data set, p < .001, both PGLS models). This trend was not observed for phylogenetic specificity (Figures S9A–10A).

4 | DISCUSSION

Using two large data sets (1490 samples in 195 host species), we confirm that the composition of the gut microbiota in mammals is correlated with host species identity. This host species identity effect on whole microbiota composition is strong (R^2 = .51), but high variability still exists between individuals within each host species. For example, average compositional similarity between individuals within a same species is around only 25%, which is probably due to local environmental (e.g., diet) and host factors not taken into account in this study. Our findings generalize similar conclusions made on focal host clades, such as rodents (Brooks et al., 2016; Grond et al., 2019; Knowles et al., 2019), bats (Lutz et al., 2019), primates (Amato et al., 2019) and cetaceans (Sanders et al., 2015). We further show that these whole-microbiota patterns scale down to the individual microbial taxa level: for example, individual bacterial ASVs show restricted host range compared to null expectations (Figure 1, hypothesis no. 1). Taken together, these findings demonstrate that

specificity at both the whole microbiota and individual taxa level is the rule rather than the exceptions in mammals.

Despite the widespread prevalence of host specificity, we still know little about the underlying mechanisms. Theory predicts that specificity can emerge due to host filtering or control and/or dispersal limitation, which includes vertical transmission (Kohl, 2020; Mallott & Amato, 2021). Elegant recent experimental work is starting to test both mechanisms in model organisms (Ellegaard et al., 2019; Sprockett et al., 2022). In this study, we used a comparative approach to harness the multiple and independent instances of convergent evolution of high and low specificity in different clades of microbes (Figure 1, hypothesis no. 2) to explore the mechanisms shaping microbiota specificity and establish broad trends across clades.

We found large variation of specificity across ASVs but relative consistency at the genus level: ASVs from the same genus generally had more similar specificity values than ASVs from different genera. This is probably because ASV from the same genus usually share a number of traits that contribute to the colonization and growth in the host gut habitat (e.g., dispersal traits such as spore formation and/or metabolic traits such as carbohydrate metabolism gene repertoire). Because dispersal traits are unknown for individual ASVs detected in this study and given the relative consistency within genera, we averaged host-specificity values at the genus level. We acknowledge that given the relative uncertainty of taxonomic assignation due to short 16S amplicons used here, it will be interesting for future studies to measure specificity at a finer taxonomic resolution, for example by using longer amplicon (e.g., full 16S) or even (metagenome assembled) genomes.

We then tested the hypothesis that microbial dispersal limitation is a key mechanism that promotes specificity by contrasting genus-aggregated specificity to genus-level transmission mode (abilities to disperse between genetic lineage of mice) and dispersal traits (spore formation, oxygen tolerance). We found that genus-level microbial specificity quantified across mammals correlates with genus-level transmission mode as measured between mice lineages in an experimental set up over multiple generations (Moeller et al., 2018). Microbial genera that tended to switch between mouse lineages over 10 host generations (horizontally-like transmitted) are also the ones that are found across a wide range of host species (i.e., have low specificity; Figure 4b). This suggest that microevolutionary processes such as transmission mode across host generations can potentially affect macroevolutionary dynamics of host specificity.

We then explored which microbial dispersal traits could mediate the observed effect of transmission mode on host specificity. We found that strictly anaerobic microbes tended to be more specific to their host species than aerotolerant or microaerophilic microbes that are more tolerant to oxygen in both data sets (Figures 4c, S7C), lending support to our hypothesis. Correspondingly, Moeller et al. (2018) also found that anaerobic microbes tended to be more vertically-like transmitted between mice lineages. Our results are thus compatible with a model where the reduced dispersal abilities of anaerobic gut microbes lead to a narrower host range, i.e. higher specificity, maybe because anaerobic microbes are less likely to be transmitted between individuals than oxygen tolerant gut microbes (Browne et al., 2020; Kohl, 2020). Our oxygen tolerance traits were inferred based on taxonomy at the level of entire genera and we acknowledge that intragenus variability in oxygen tolerance exits (Whitman, 2015). However, we minimized this potential bias by removing genera known to contain both oxygen tolerant and intolerant species. Further studies using metagenomic approaches or cultivation-based approaches could simultaneously estimate specificity and oxygen tolerance at a finer resolution (Levin et al., 2021). Correlation does not imply causation, and we acknowledge other traits not considered here that are correlated to oxygen tolerance across bacteria could be responsible for the pattern we report. In addition, the direction of causality between dispersal traits/transmission mode and specificity remains unclear: for example, the loss of oxygen tolerance could be a consequence (and not a cause) of the vertical-like mode of transmission and high host specificity. Indeed, if transmission is facilitated through repeated social contact or vertical inheritance, it is plausible that selective pressure to remain oxygen tolerant and facilitate transmission is reduced, thus potentially leading to function loss (e.g., the black queen hypothesis). Deciphering the directionality of causation would require reconstructing ancestral specificity and dispersal limitation trait (e.g., oxygen intolerance) on a microbial phylogeny and evaluate whether specificity or dispersal limitation evolved first. In any case, the intriguing correlation we report here could spur more in-depth comparative and experimental studies.

The hypothesis that spore formers are less specific than non-spore formers was not statistically supported, though there was a trend in the YEA data set. This is surprising as previous studies report that spore formers are more prevalent in the human gut, maybe due to their better dispersal abilities (Browne et al., 2020) so that we could expect that this would turn into lower specificity (broader host range) at macroevolutionary scale. One potential explanation could be that our genus-level resolution is too coarse and that there is variability of sporulation abilities within genera (Browne et al., 2020; Egan et al., 2021). As sporulation abilities can now be predicted based on metagenomes (Browne et al., 2020), it would be interesting to use this finer resolution to test our hypothesis (Levin et al., 2021).

In this study, we evaluated one of the predictions arising from the hypothesis that dispersal limitation impacts host specificity using a comparative approach and traits of gut bacterial lineages. It would be also interesting to investigate the hypothesis that microbial host-specificity correlates with mammalian traits like sociality. For example, it could be hypothesized that, in social mammals, increased contacts between individuals of the same host species will increase the transmission of gut microbes within host species rather than between host species, which could result in increased host specificity over evolutionary time, compared to nonsocial species (Raulo et al., 2021; Weinhold, 2022).

In conclusion, we found that host specificity is related to both oxygen tolerance and transmission mode across gut symbionts. It remains to be seen whether this trend holds at a finer genetic resolution, and whether codiversification rates also correlate to

oxygen tolerance across mammals (as observed within humans, Suzuki et al., 2022). Overall, our results suggest that dispersal limitation and a vertical-like mode of transmission are plausible causes of gut microbiota specificity, although we cannot rule out that they are consequences of specificity. To differentiate between these two alternative explanations, one potential approach is to test whether the evolution of a vertical-like transmission mode (or limited dispersal abilities) precede or follow the evolution of high host specificity. Comparative approaches such as ancestral state reconstruction coupled with the increasing availability of genomic data, that both resolve fine-scale relationships and allow bacterial traits to be better predicted, offer a unique opportunity to carry out this test.

AUTHOR CONTRIBUTIONS

F.M. designed the analysis, gathered the data and performed the analysis. F.M. and L.W.P. interpreted the results. F.M. wrote the first version of the manuscript and all authors contributed substantially to the revisions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

OPEN RESEARCH BADGES

This article has earned an Open Data badge for making publicly available the digitally-shareable data necessary to reproduce the reported results.

DATA AVAILABILITY STATEMENT

All the data used in this analysis is already publicly available. The DNA sequence data is hosted on ENA and MG-RAST website (the list of associated projects for the SEA data set is given in Table S1). Microbial and host phylogenies have been made available at https://megapast2future.github.io/PHYLACINE_1.2/ and on the SILVA archive webpage (Non redundant 99 data set, version 132 available on archive as an arb file, https://www.arb-silva.de/download/archive/). Microbial traits have been compiled from the Bergey manual and are available as Table S3. The associated R code is publicly published on github (https://github.com/FloMazel/Host_specificity_and_microbial_Traits).

BENEFIT-SHARING STATEMENT

This study only uses publicly available data sets.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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