Prevotella diversity, niches and interactions with the human host

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Abstract | The genus *Prevotella* includes more than 50 characterized species that occur in varied natural habitats, although most *Prevotella* spp. are associated with humans. In the human microbiome, *Prevotella* spp. are highly abundant in various body sites, where they are key players in the balance between health and disease. Host factors related to diet, lifestyle and geography are fundamental in affecting the diversity and prevalence of *Prevotella* species and strains in the human microbiome. These factors, along with the ecological relationship of *Prevotella* with other members of the microbiome, likely determine the extent of the contribution of *Prevotella* to human metabolism and health. Here we review the diversity, prevalence and potential connection of *Prevotella* spp. in the human host, highlighting how genomic methods and analysis have improved and should further help in framing their ecological role. We also provide suggestions for future research to improve understanding of the possible functions of *Prevotella* spp. and the effects of the Western lifestyle and diet on the host–*Prevotella* symbiotic relationship in the context of maintaining human health.

Prevotella is a diverse genus of Gram-negative anaerobic bacteria that was first described in 1990 by Shar and Collins to include some oral species with specific phenotypic traits (moderately saccharolytic capabilities and bile salt sensitivity) that were formerly placed in the genus *Bacteroides*. *Prevotella* was named after the pioneering anaerobic microbiologist A. R. Prévot[1]. The type strain for the genus is from *Prevotella melaninogenica*, which was isolated by Oliver and Wherry in 1921 from various human body sites and was named for the black pigmentation of its colonies[1,2]. *Prevotella* spp. are non-spore-forming, non-motile short rods that are saccharolytic or moderately saccharolytic[3,4]. The genus *Prevotella* is part of the family Prevotellaceae, which also contains the three closely related genera *Paraprevotella*, *Alloprevotella* and *Hallella*.

Prevotella spp. have been isolated from various animal hosts and even occur free living in the environment. In comparison with other genera, which contain members with clear associations with disease or that are easily cultured, *Prevotella* has received less attention, maybe due to limitations in culturing these bacteria and confusion in phenotype-based taxonomic classification of isolates[5,6]. Nevertheless, the advent of cultivation-free microbial profiling showed that *Prevotella* spp. are common, abundant, consistent features of mammal-associated microbial communities (microbiomes) and in humans have been found to inhabit multiple body sites, including the skin, oral cavity, vagina and gastrointestinal tract. *Prevotella* spp. are not rare in human microbiomes, and they are members of one of the most dominant genera in the oral cavity[7]. In rural populations that follow a more pre-industrial, 'traditional' lifestyle and diet — so-called 'non-Westernized populations' — *Prevotella* spp. tend to dominate the gut microbiome[8–15]. Westernization is the consequence of industrialization over the past 200 years. While separating populations into Westernized and non-Westernized categories demarcates what is best seen as a continuum and is not without its difficulties (as discussed elsewhere[14–16]), multiple reports have consistently highlighted a decreased prevalence of *Prevotella* spp. in Westernized populations, which is generally compensated by the domination of *Bacteroides* species[8–15]. Our understanding of the human microbiome is skewed towards Western populations, and therefore *Bacteroides* spp. have received more attention than *Prevotella* spp., although as the number of non-Westernized populations sampled expands, the diversity, prevalence, abundance and importance of *Prevotella* is becoming increasingly evident. This is particularly true for intestinal *Prevotella* spp., which have been shown to be long-standing key members of our co-evolved microbiome, supporting the hypothesis that the modern Western lifestyle is causal in the loss of *Prevotella* diversity and further raising the question of what are the consequences of this loss from a health perspective[16].

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Box 1 | **Metagenomic approaches to uncover the diversity of *Prevotella* spp.**

The study of human-associated *Prevotella* spp. has been hampered by the intrinsic difficulty in cultivating in vitro some taxa, especially anaerobic strains in the gut. By surveying the genetic content of complex microbial samples by high-throughput sequencing (that is, metagenomics[60]), it is possible not only to identify and quantify known species but also to discover previously uncharacterized 'novel' species. This approach is becoming increasingly effective by metagenomic assembly, which first reconstructs relatively long fragments of the genomes (called 'contigs')[181,182] and then groups contigs into draft genomes termed 'metagenome-assembled genomes' (MAGs) by exploiting read coverage and intrinsic genetic features (such as tetranucleotide frequency distribution) across contigs[183]. After quality control of the resulting MAGs[184], high-quality sequences can be phylogenetically and taxonomically contextualized[185], revealing in many cases that MAGs do not belong to any previously named or catalogued species. As metagenomic assembly reaches maturity, large collections of MAGs are being built and analysed[15,49,50]. Currently, more than 200,000 MAGs have been deposited in catalogues that are based on many large human metagenomic studies; thousands of these MAGs have expanded the strain-level genetic diversity of known species, while many others define new species-level genome bins, which are interpreted as yet-to-be cultivated new candidate species. Applied to the genus *Prevotella*, such approaches confirmed the existence of at least four genetically and functionally distinct clades of *Prevotella copri* that form a species complex[4,16], and a total of 4,886 human-associated MAGs that are assigned to the family Prevotellaceae but do not belong to any known *Prevotella* spp.[15]. (FIG. 3). While in vitro cultivation remains indispensable to understand the physiology of bacterial species and their possible involvement in host diseases, metagenomic assembly is emerging as a key tool to characterize previously overlooked bacterial diversity, drive targeted cultivation efforts and formulate hypotheses on the biomedical relevance of some taxa.

Despite the abundance and prevalence of *Prevotella* spp. associated with humans, their involvement in health and disease, their role within the microbiome and their contribution to host–microbiome crosstalk are unclear. *Prevotella* contains no known obligate pathogenic species, yet members have been implicated in multiple diseases, including inflammatory autoimmune diseases[17], opportunistic infections[18–21], bacterial vaginosis[22] and oral biofilm formation and diseases[23,24], although direct causation of disease is uncertain. Similarly, in the intestine, there are conflicting reports regarding whether *Prevotella* spp. are beneficial or detrimental to health, particularly in glucose homeostasis[25–27]. Establishing general associations and specific causal links between *Prevotella* and disease is likely further confounded by the recent discovery that this genus may be more diverse than previously appreciated[4,16]. In the view of the human microbiome as an integral part of human biology, *Prevotella* is an exemplar case of a genus that is likely involved in intricate ecological interactions and crosstalk with the host, with indirect but potentially substantial effects on human health.

In light of the open questions regarding these enigmatic bacteria, it is timely to discuss the genus *Prevotella* and its association and distribution on and within the human host, across ages, lifestyles and diseases. Using available genomes from cultivated strains and those recovered directly from thousands of metagenomic samples (BOX 1), we explore and summarize the overall diversity and current knowledge of the genus *Prevotella*, as well as the role of *Prevotella* spp. in human health and disease.

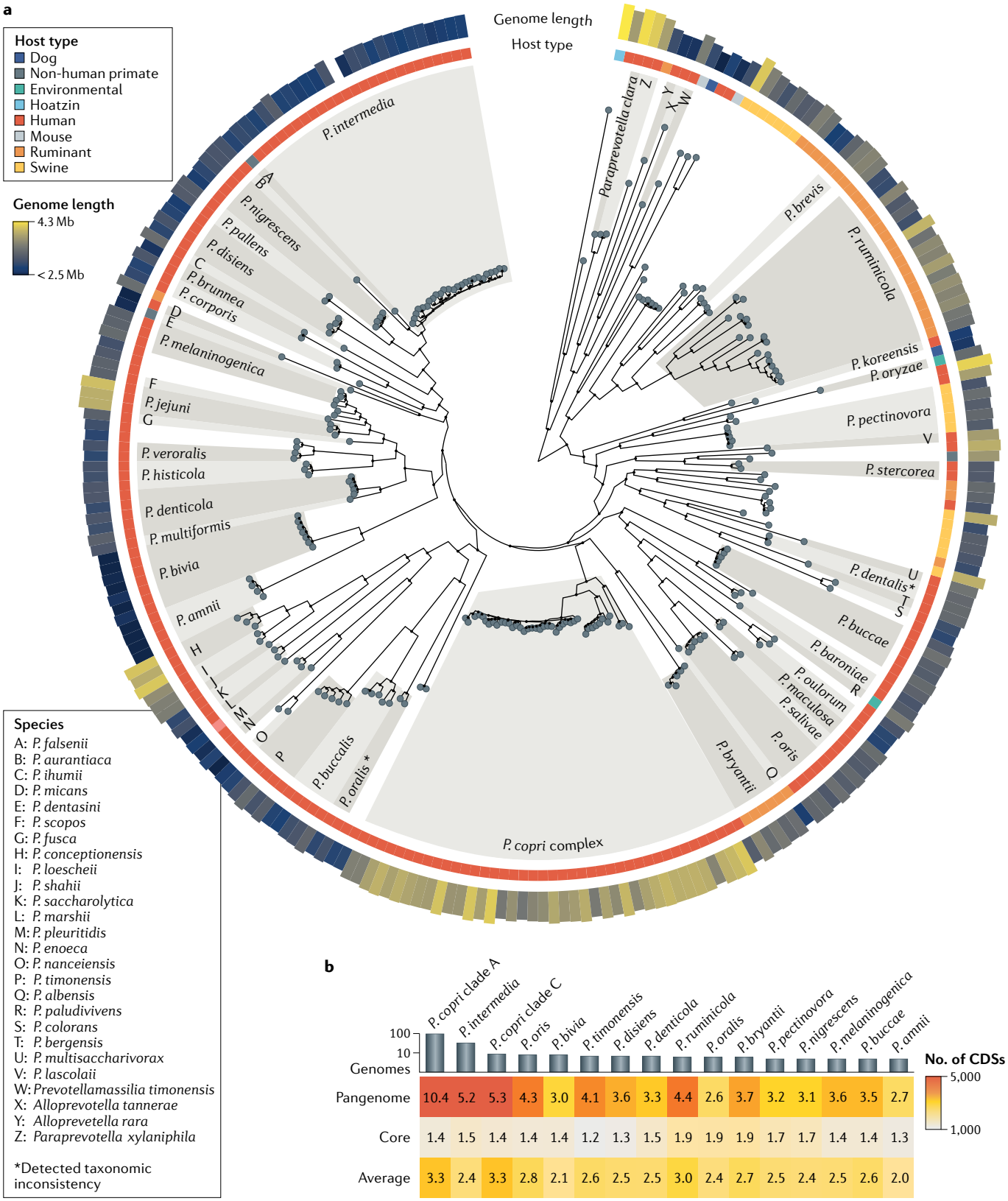
Phylogenetic and ecological diversity

Since the initial isolation of *Prevotella* spp. from the human oral cavity and respiratory tract, they have been shown to occupy ecologically diverse habitats. Currently, 57 species of *Prevotella* for which isolates are publicly available (FIG. 1; TABLE 1; Supplementary Table 1) have been characterized. By far the largest number of isolates and known species are associated with human hosts, but *Prevotella* spp. can also be found associated with other mammalian hosts. For example, *Prevotella* spp. are a common and predominant feature of the gut microbiota of ruminants; in particular, *Prevotella bryantii*, *Prevotella ruminicola*, *Prevotella brevis* and *Prevotella albensis* are well-known members[28,29]. *Prevotella* spp. are integral in carbohydrate utilization in the rumen[30] and are a particularly common feature of the swine gut microbiome[31,32]. Genomes of other members of the Prevotellaceae have been recovered from non-human primates, dogs and mice[33,34] (Supplementary Table 1) and non-mammalian hosts, including from the fermentative crop of the tropical bird *Opisthocomus hoazin* (the hoatzin) and have been found free living in natural habitats, including soil[35].

The distinguishing feature between human and non-human isolates of *Prevotella* is their species-level evolutionary history, as inferred from whole-genome phylogenetics (FIG. 1; Supplementary Box 1). There is clustering of large subtrees, in which human-associated species are mostly separated from those of non-human origin (FIG. 1), and a large multispecies clade is present, which comprises *P. ruminicola* and *P. brevis* and numerous unnamed species that are specific to swine and ruminants. The genome size of the isolates differs: the largest genome (4.26 Mb) is from a member of the *Prevotella copri* complex, and *Prevotella amnii* has the smallest genome (2.37 Mb) (FIG. 1; TABLE 1). In comparison, the average genome size for *Bacteroides* spp. (5.46 Mb from

Fig. 1 | **Genomic overview of the genus *Prevotella*.** **a** | Phylogenetic tree of reference genomes of strains or species of *Prevotella* and other Prevotellaceae species, with an indication of their ecological niches. The largest number of genomes are associated with human hosts, although *Prevotella* genomes are also identified in several other host types. *Prevotella* spp. exhibit variable genome length, ranging from 4.26 Mb for *Prevotella copri* to 2.37 Mb for *Prevotella amnii*. Only named species are reported in the tree, which was built using a maximum likelihood approach applied on marker genes. **b** | Genome characteristics for *Prevotella* spp. with at least five available genomes. The average number of coding sequences (CDSs) ranges between 2,000 and 3,300. The core size (that is, the number of CDSs that are present in almost all genomes) ranges from 1,200 to 1,900 genes. The pangenome size ranges between 2,600 and 10,400 genes; however, this is partially affected by the number of available genomes (Spearman correlation between genome number and pangenome size of 0.64). Data were generated by whole-genome analysis of currently available *Prevotella* genomes in public repositories. TABLE 1 and Supplementary Table 1 contain the genomic characteristics of *Prevotella* spp. considered in this figure and the list of available reference genomes. Numbers in the heat map are in thousands.

1,116 isolate genomes) is larger. There is also a considerable spread in G+C content across the genus, ranging from 36.4% in *P. amnii* to 56.1% in *Prevotella dentalis* (TABLE 1), which is further evidence of the remarkable diversity of *Prevotella*. A comparison of the core genome for species for which there are multiple independent isolates reveals that *Prevotella* spp. have a core of ~1,200–1,900 genes (accounting for ~50–75% of the genome), which is consistent for species from different host types (FIG. 1). *Prevotella* is a diverse microbial genus,



yet like most isolate collections, it likely suffers from sampling bias; increased isolation efforts from animal species and undersampled environments will surely expand the number of hosts and diversity of *Prevotella* spp.

The ecological importance of bacteriophages (phages) in shaping the complex host-associated microbiome has been established; nevertheless, investigation of these phage communities is still in its infancy[36]. Consequently, little is known about *Prevotella*-specific phages, with only a few reports describing phages associated with *Prevotella* spp. in ruminants[37,38]. Recently, metagenomics-based discovery has identified large 'megaphages' termed 'Lak phages,' which are associated with *Prevotella* spp. in humans, non-human primates, other mammalian hosts and reptiles[39,40]. These phages use an alternative genetic code and, with a genome size of up to ~660 kb, they are the largest intestinal phages discovered to date[40]. The identification of these diverse phages raises intriguing questions about their ability to modulate *Prevotella* populations in the intestine and the implications of this modulation on the whole microbiome and ultimately on its influence on the host.

Prevotella in humans across body sites

Even within a specific host, different *Prevotella* spp. are present in multiple different body locations. In humans, and similarly to other bacterial genera[41], distinct *Prevotella* spp. have been identified and isolated from the oral cavity, respiratory tract, vagina, skin and intestine. Surveying the prevalence and abundance of the known characterized *Prevotella* spp. in more than 9,500 individuals from multiple integrated datasets[15] reveals that, with the exception of vaginal *Prevotella* spp., most species are body-site-specific (FIG. 2a,b; Supplementary Box 2). A genome-based analysis of human *Prevotella* isolates identified differing functional potential at different body

Table 1 | **Genomic characteristics of *Prevotella* species**

Prevotella species[a]	Number of sequenced genomes	Genome length[b] (Mb)	G+C content[b] (%)	Host	Host sites
P copri complex	106	3.65 ± 0.21	44.93 ± 0.23	Human	Gut
P. intermedia	33	2.79 ± 0.13	43.45 ± 0.15	Human	Oral cavity, empyema
P. ruminicola	9	3.53 ± 0.30	47.69 ± 0.71	Ruminant	Rumen
P. bivia	8	2.49 ± 0.08	39.79 ± 0.17	Human	Vagina
P. denticola	7	3.06 ± 0.11	50.04 ± 0.18	Human	Vagina, oral cavity
P. disiens	7	2.86 ± 0.13	39.93 ± 0.21	Human	Vagina, gut, Bartholin abscess
P. timonensis	7	3.09 ± 0.16	42.41 ± 0.16	Human	Vagina, breast abscess
P. bryantii	6	3.41 ± 0.14	38.8 ± 0.19	Ruminant	Rumen
P. amnii	5	2.4 ± 0.03	36.52 ± 0.08	Human	Vagina, amniotic fluid
P. melaninogenica	5	3.14 ± 0.12	41.02 ± 0.23	Human	Vagina, oral cavity, sputum
P. nigrescens	5	2.85 ± 0.16	42.64 ± 0.11	Human	Oral cavity
P. oralis	5	2.87 ± 0.07	44.54 ± 0.09	Human	Vagina, gut, oral cavity
P. oris	5	3.18 ± 0.12	43.86 ± 0.09	Human	Oral cavity, airways
P. pectinovora	5	3.17 ± 0.12	47.74 ± 0.25	Swine	Gut
P. buccae	4	3.22 ± 0.12	51.15 ± 0.19	Human	Oral cavity
P. buccalis	4	2.99 ± 0.20	45.5 ± 0.18	Human	Vagina
P. baroniae	3	3.09 ± 0.06	53.1 ± 0.17	Human	Oral cavity
P. corporis	3	2.81 ± 0.04	44.1 ± 0.10	Human	Vagina
P. histicola	3	3.0 ± 0.06	41.2 ± 0.01	Human	Vagina, oral cavity
P. loescheii	3	3.49 ± 0.02	46.6 ± 0.01	Human	Oral cavity
P. maculosa	3	3.25 ± 0.09	47.5 ± 0.17	Human	Oral cavity
P. micans	3	2.45 ± 0.03	45.5 ± 0.01	Human	Oral cavity
P. oulorum	3	2.82 ± 0.02	46.8 ± 0.01	Human	Oral cavity
P. pallens	3	3.1 ± 0.04	37.47 ± 0.06	Human	Oral cavity
P. salivae	3	3.22 ± 0.10	41.5 ± 0.17	Human	Gut, oral cavity
P. scopos	3	3.23 ± 0.06	40.7 ± 0.01	Human	Oral cavity
P. stercorea	3	3.11 ± 0.01	48.93 ± 0.06	Human	Gut
P. veroralis	3	2.89 ± 0.09	41.83 ± 0.06	Human	Oral cavity

Supplementary Table 1 contains the complete species and genome lists. [a]Only species with at least three sequenced genomes are included. [b]Values are reported as averages and the standard deviations.

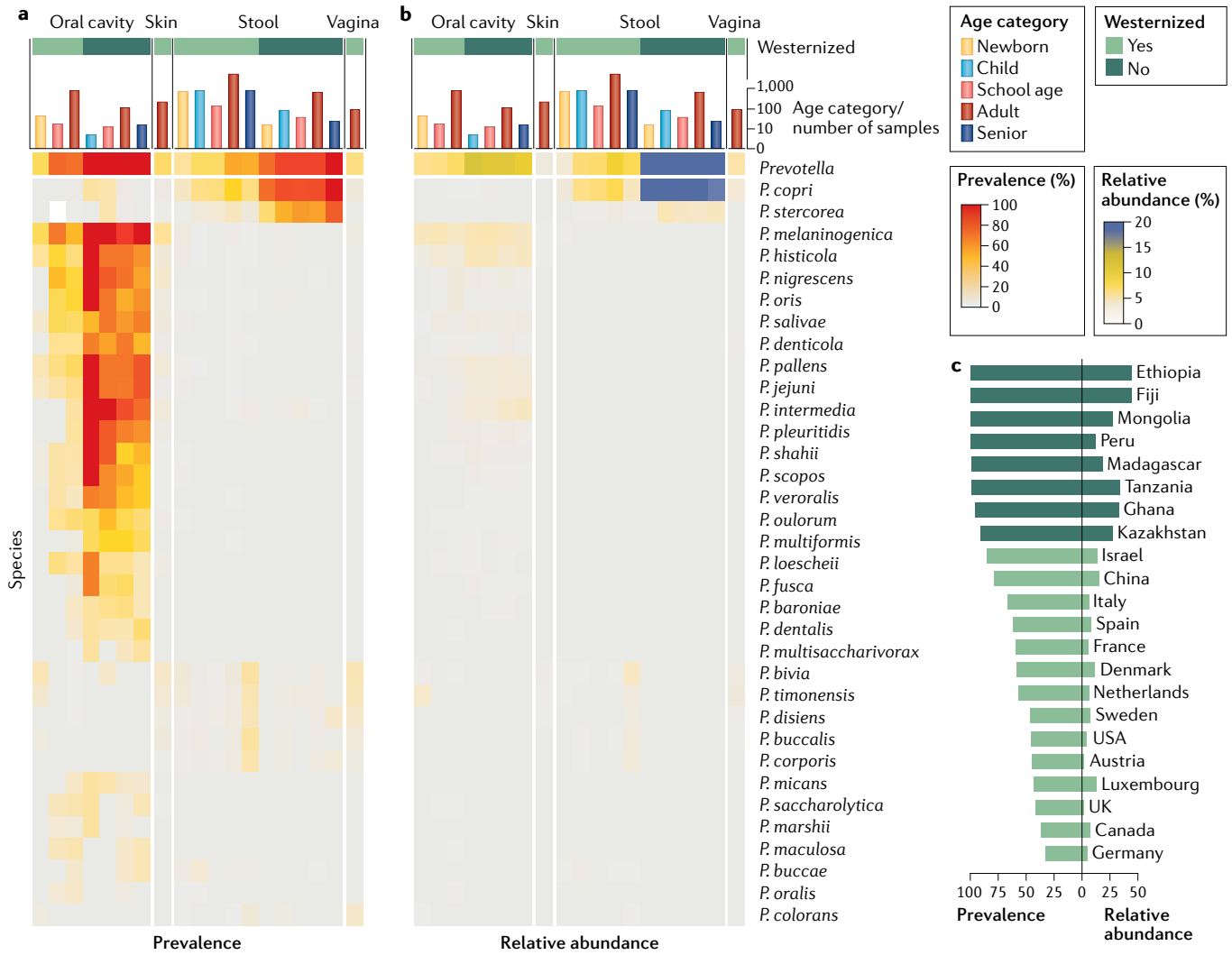


Fig. 2 | **Distribution and stratification of *Prevotella* spp. across human populations and body sites.** Prevalence (part **a**) and relative abundance (part **b**) of known *Prevotella* spp. across four main body sites (that is, the oral cavity (saliva or oral swabs), the skin (cutaneous swabs), the gut (stool samples) and the vagina (vaginal swabs)), five age categories (that is, newborn, child, school-age child, adult and senior) and two main lifestyles (that is, Westernized and non-Westernized). These data were obtained from public repositories of more than 9,500 profiled human metagenomes (curated metadata information is available elsewhere[109]). Quantitative taxonomic profiles were generated with MetaPhlAn 3.0 (REF.[180]). Only named species with a prevalence greater than 0.1% in at least one category are reported. Most species are body-site-specific, and further differences are observed across age categories. The prevalence and relative abundance of *Prevotella* in the gut (part **c**) are largely influenced by lifestyle. Non-Westernized populations, which follow a more traditional diet and lifestyle, are enriched in *Prevotella* spp., and this is consistently observed across countries. Extended heat maps are available in Supplementary Fig. 1.

sites, suggesting the existence of niche-specific differentiation and specialization[42]. Further stratification is also observed across lifestyles; non-Westernized populations, which follow a more traditional lifestyle and diet, tend to have a higher prevalence of several distinct *Prevotella* spp.[8–13] in both the gut and the oral cavity (FIG. 2c). The distribution of *Prevotella* spp. is also influenced by age; in the gut, both *P. copri* and *Prevotella stercorea* show an age-dependent increase in prevalence regardless of Westernization, although their relative abundance drops from adulthood to old age (more than 65 years) (FIG. 2a,b). However, some species (*Prevotella bivia*, *Prevotella timonensis*, *Prevotella buccalis*, *Prevotella disiens* and *Prevotella corporis*) seem to have the highest prevalence in the gut of elderly individuals in Westernized populations and, intriguingly, they have a correspondingly similar prevalence pattern in the vagina (FIG. 2a,b). Sex effects have also been observed, with *Prevotella* being more prevalent in men than women[43,44]. However, female hormone metabolism seems to be linked to the regulation of *Prevotella* spp. in the human body. Steroidal hormones can favour the growth of *Prevotella intermedia* and *P. melaninogenica* in the oral cavity[45,46] and affect oral microbial ecology and the occurrence of gingivitis in hormone-driven diseases[47]. It is evident that the distribution and prevalence of *Prevotella* spp. in the human host are driven by multiple factors, including body site, lifestyle, sex and age, and this is an area of continued research.

While strain isolation has been, and continues to be, the predominant approach in microbiological research, culture-independent methods offer a new complementary approach in microbial discovery. For example, recovering and identifying genomes directly from mixed environmental samples (metagenomes) has begun to transform our understanding of the true microbial diversity in natural systems[4,15,16,48–51] (BOX 1) and gives an unprecedented opportunity to characterize the role and ecology of *Prevotella* by exploiting the increasingly available large metagenomic datasets. To assess *Prevotella* diversity in the human host, we examined 7,480 *Prevotella*-assigned metagenome-assembled genomes (MAGs) from more than 9,500 human-associated metagenomes covering multiple geographic populations, lifestyles and body sites in combination with the isolate genomes from multiple sources in public repositories[15]. Fifty-six *Prevotella* species-level genome bins (SGBs; using a 5% nucleotide whole-genome distance threshold to define the bins) were identified with at least 20 genomes reconstructed from human sources. Of these, only 32 SGBs were populated with at least one isolate genome with assigned taxonomy (FIG. 3a, Supplementary Box 3), demonstrating that human-associated *Prevotella* spp. are far more diverse than appreciable from the current catalogue of *Prevotella* isolates. These unnamed and uncharacterized *Prevotella* SGBs are not all rare metagenomic occurrences, as in some cases hundreds of genomes were recovered from independent metagenomic samples (FIG. 3a,b). Of note, nine uncharacterized SGBs are at the boundary of the *Prevotella* genus (FIG. 3a; subtree at the root) and contain only two isolate genomes, labelled as 'Prevotellaceae bacterium'.

Prevotella in the oral cavity. The oral cavity is the body site that hosts by far the largest diversity of known human *Prevotella* spp. (FIG. 2; FIG. 3). While the human gut may still harbour many undiscovered *Prevotella* spp. that are particularly recalcitrant to cultivation (FIG. 3b), the oral *Prevotella* taxa were studied long before the advent of cultivation-free surveys[52] owing to their less complex cultivation conditions and their potential (sometimes confirmed) role in oral diseases[53] and systemic infections[54]. According to the first comprehensive 16S rRNA gene sequencing investigation, the total abundance of the genus *Prevotella* in the oral cavity of healthy individuals exceeds, on average, 10% of the whole microbiome of the saliva (13.0%), tongue (10.3%), tonsils (11.4%) and throat (11.6%)[7]. Recent microbiome studies confirmed even higher average abundances in the saliva (from 12% to 17%) in multiple socio-economic and age categories[55,56], making *Prevotella* the most abundant oral genus after *Streptococcus*. Slightly lower *Prevotella* abundance is estimated in oral locations that have more divergent structural and biochemical conditions, such as the dental plaque, the gingiva and the buccal mucosa[7]. Our analysis (FIG. 2) gives an overall *Prevotella* prevalence of 85% in Westernized populations when all oral sites are combined and 100% in non-Westernized populations, with an average abundance of 7.4% and 11.5% respectively. Our oral metagenomic data for non-Westernized populations are based on a single cohort from Fiji[57], but reanalysis of another dataset of Filipino individuals[58] confirmed the intriguing observation of higher prevalence and abundance of *Prevotella* in the oral cavity of individuals from non-Westernized populations. Interestingly, the levels of *P. intermedia* in the saliva microbiome decrease when a Mediterranean diet nutritional intervention is initiated in individuals with obesity[59], suggesting a dependence of oral *Prevotella* on lifestyle factors that may include those connected with the Westernization process.

Genus-level quantification clearly conceals extensive species-level and interindividual diversity that is now readily detectable by shotgun metagenomics[60]. Available metagenomic analyses[61–65] point to the presence of at least 15 known *Prevotella* spp. in the oral cavity (and a couple of taxa that are still to be characterized; FIG. 3); however, the oral microbiome in individuals is usually dominated by *P. melaninogenica* and, to a slightly lesser extent, *Prevotella histicola* and *P. intermedia* in adult non-Westernized populations (FIG. 2). Recent analyses for other oral genera in the context of the healthy oral microbiome, such as *Neisseria*[41], *Streptococcus*[66] and other genera[67,68], revealed extensive strain-level variation hidden at the species level, and that strains within a species are individual-specific except for related individuals such as mother–infant couples in which direct transmission can occur[63,69,70]. Currently, such strain-level analyses are not available for oral *Prevotella* spp., and while the extent of within-species genetic and genomic variability is species-specific, it is likely that similar strain-level variation and individual specificity will also be observed for *Prevotella* spp.

As for other members of the oral microbiome, oral *Prevotella* spp. have the potential to colonize the lower gastrointestinal tract. Indeed, a systematic metagenomic investigation of oral to gut microbial transmission[71] found that all oral *Prevotella* spp. can occasionally be found in the stool microbiome (FIG. 2b) and, in most cases, the oral and gut strains were the same within a host, suggesting a direct oral–faecal route in healthy individuals. Interestingly, high enrichment of oral species in the gut has been observed in patients with newly diagnosed colorectal cancer[72,73], although only *P. intermedia* and, to a lesser extent, *Prevotella nigrescens* are biomarkers of this cancer. Oral *Prevotella* seeding of the gut environment seems to be a physiological mechanism, despite oral *Prevotella* species occasionally being implicated in systemic infections[74].

In the oral cavity, *Prevotella* is also involved in the complex process of biofilm formation, which is potentially connected with poor oral hygiene[24] and involved in the cause of oral diseases, such as prevalent gingivitis and periodontitis[23]. In particular, *P. nigrescens* and *P. intermedia* are associated with the plaque microbiome in periodontitis, an association that was already established in the presequencing era[75], and these two species may promote tissue inflammation by driving T helper 17 cell (T_H17 cell)-mediated immune responses[23,76]. Intriguingly, complementary fluorescence in situ hybridization-based investigations of dental plaque[77,78] identified *Prevotella* spp. as one of the early colonizers that are necessary for stable biofilm formation. Several *Prevotella* spp., including *Prevotella loescheii*,

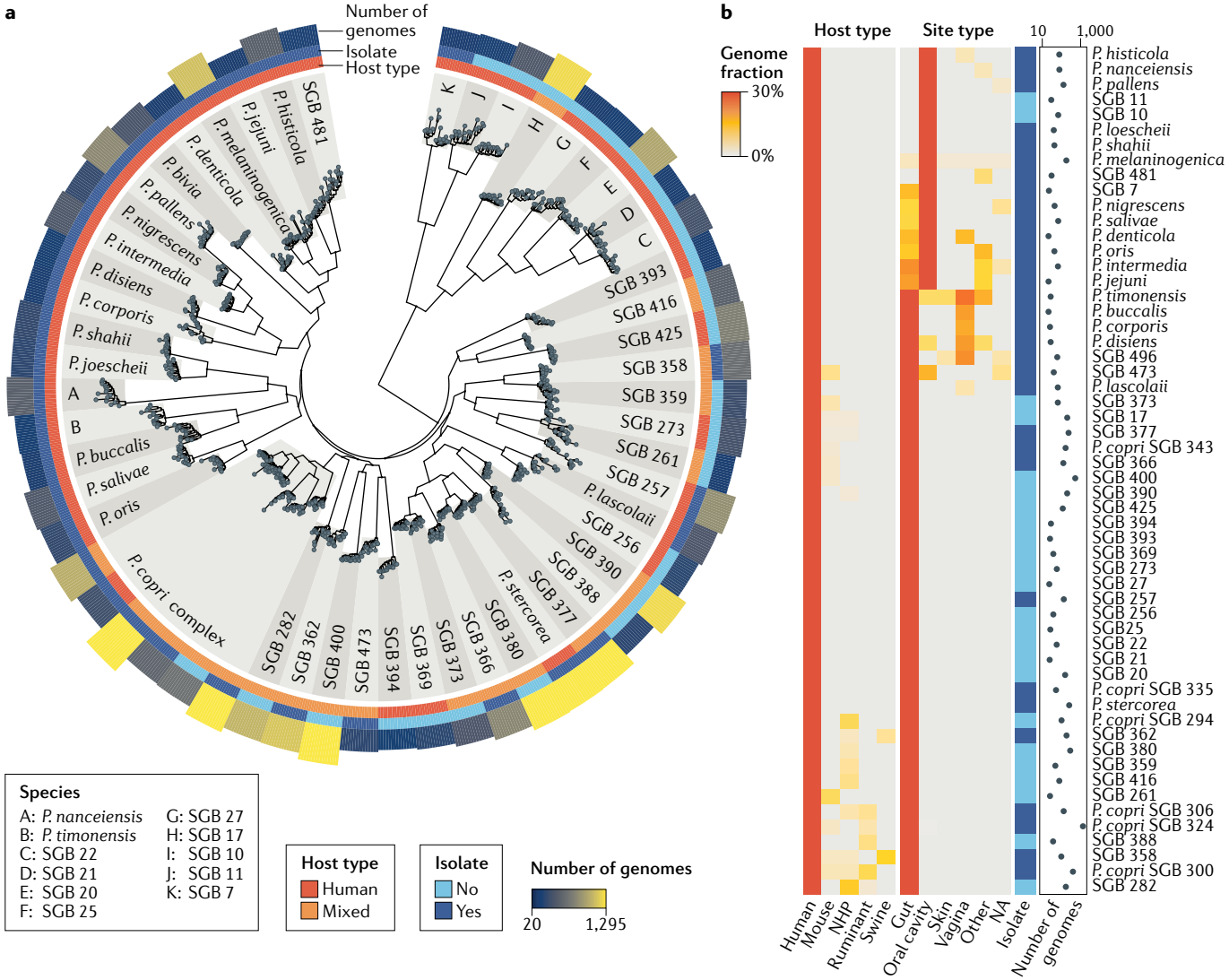


Fig. 3 | **Current diversity of *Prevotella* spp. in the human microbiome.** **a** | A large phylogenetic tree spanning the 56 most prevalent *Prevotella* species (with at least 20 genomes retrieved from human microbiomes). Isolate sequences were integrated with metagenome-assembled genomes (MAGs) retrieved from more than 10,000 metagenomes and more than 50 human populations. For each species, 15 randomly selected genomes are reported along with the information on the host type (that is, human or mixed sources), the public availability of isolate sequences and the number of retrieved genomes. The tree highlights the gap in strain isolation, with 24 human-associated species that completely lack isolate genomes, the within-species strain diversity and the remarkably well-defined taxonomic species based on the interspecies versus the intraspecies diversity. **b** | The fraction of *Prevotella* genomes retrieved from human and non-human hosts (both from isolation and assignment to MAGs) and different human site types suggest multiple ecological patterns. In addition to human-specific species, other species are present in two or more host types. Of note, a few species are ecologically adapted to multiple human body sites, which might also be due to the influx of oral species into the lower gastrointestinal tract[71]. Supplementary Table 1 provides a list of available reference genomes and reconstructed MAGs with their genomic characteristics for the species considered in this figure. NA, not assigned; NHP, non-human primate; SGB, species-level genome bin.

P. intermedia and *Prevotella denticola*, may have a role in the early and middle stages of biofilm formation by promoting cell–cell adhesion and creating the physical and biochemical conditions that favour later colonizers[79,80]. The microbial consortia in oral biofilms can be very diverse; for example, in biofilm models in the absence of *Streptococcus* species, the abundance of *P. intermedia* increases and filamented chains that resemble those of streptococci are formed[81]. *Prevotella* spp. can also synergistically support *Aggregatibacter actinomycetemcomitans*, a species that is strongly associated with aggressive periodontitis[82], by molecular interspecies regulation[83]. Although an area of continuous research for many years, the complexity of oral biofilm formation and the intricate interactions of the biofilm community with host tissues and immunity remain only partially understood. Furthermore, the hypothetical role of low-abundance taxa and of synergistic bacterial interactions[84] further underlines the relevance of biofilm formation as a model for microbial ecology and as a potential therapeutic target. *Prevotella* is likely one of the most relevant genera in this context, as physical proximity analysis revealed that, together with *Actinomyces*, this genus had the highest intergenus interactions[77].

Despite their abundance and role in oral biofilm formation, oral *Prevotella* spp. are still understudied compared with other oral bacteria. In particular, comparative analysis of oral *Prevotella* spp. is limited[85], and clearly more studies are required to better understand their characteristics and ecological role in the oral microbiome[86,87].

Vaginal Prevotella spp. The human vaginal microbiome has been comprehensively surveyed, and *Prevotella* stands out as one of the dominant genera[88]. The most prevalent vaginal species are *P. bivia*, *P. timonensis*, *P. buccalis*, *P. disiens* and *P. corporis*. Interestingly, these species belong to separate phylogenetic clusters and none occurs uniquely in the urogenital tract, as they are also found in the oral and/or gut microbiome (FIG. 2). However, it is possible that for these species, genomic adaptation to the different body sites may occur at the subspecies level and is therefore undetectable at the species level. *Prevotella* spp. have a recognized role in bacterial vaginosis, which occurs when the protective guilds of the normally dominant *Lactobacillus* species are lost and strictly anaerobic microorganisms become established[22]. *Prevotella* spp. are the most heritable vaginal bacteria and are also associated with increased body mass index[22,89]. *P. bivia* is an important source of ammonia, lipopolysaccharide and sialidase activity in vaginal mucus and is linked to epithelial cytokine production, which occurs in infected uterine and placental tissues and amniotic fluid during pregnancy complications[90–92]. *P. bivia* often co-occurs with *Gardnerella vaginalis*, and this is recognized as a clear example of how microbial species can interact synergistically in certain environments. These two bacteria are co-abundant in the vagina and both are increased in abundance in cases of bacterial vaginosis[93], although neither induces a robust inflammatory response[94]. Their co-inoculation has no major effect on their growth in mouse models of bacterial vaginosis, although co-colonization seemed to increase the chances of *P. bivia* ascension to the uterus[90], which is relevant for the recognized association of *Prevotella* spp. with increased risk of preterm birth[95–97]. Interestingly, a network of other *Prevotella* spp., including *P. amnii*, *P. buccalis* and *P. timonensis*, can co-occur in other infections, such as those caused by *Chlamydia trachomatis*[98], and have a role in bacterial vaginosis and increased predisposition to viral infections such as HIV infection[99,100]. *P. timonensis* interacts with vaginal dendritic cells, which are involved in mucosal inflammation[101], and has also recently been associated with persistence and slower regression of cervical intraepithelial neoplasia[102].

In the absence of further data to clarify the role of *Prevotella* spp. and strains in the development of bacterial vaginosis and related diseases, *Prevotella* simply appears as an inhabitant of the female urogenital tract that opportunistically increases in abundance when the abundance of protective vaginal lactobacilli is reduced.

Gut Prevotella spp. and P. copri. The human gut is home to many microbial species, belonging predominantly to the phylum Firmicutes or Bacteroidetes[61,103]. Of the Bacteroidetes, two genera tend to dominate, *Bacteroides* and *Prevotella*, while the dominant Firmicutes genera include *Ruminococcus*, *Blautia*, *Eubacterium* and *Faecalibacterium*. The observation that these groups of taxa drive a subject-specific microbiome type led to the concept of human gut enterotypes[104]. Since its introduction almost 10 years ago, this concept has fed further studies and fuelled debate within the field[105], which resulted in a revisited formulation of the enterotypes as non-discrete microbiome types[106]. It is clear that *Prevotella* spp. (particularly members of the *P. copri* complex) seem to be a discrete and well-defined feature of the gut microbiome, and their relative abundance is inversely correlated with that of the *Bacteroides*; that is, the presence of one seems to result in exclusion of the other[61,104,107]. Nevertheless, quantitative profiling based on absolute abundance suggests that this inverse correlation may simply be an artefact of microbiome profiling approaches based on relative abundance[108]. In the human gut, the average prevalence of *Prevotella* spp. ranges from 20% to 100% depending on the population surveyed[109]. Of the characterized *Prevotella* spp., *P. stercorea* and the *P. copri* complex are the two most common. Of note, despite both species being present in the gut, they are more phylogenetically distant from each other compared with other *Prevotella* spp. that occupy other body sites (FIGS 1,2). However, analysis of MAGs suggests that the number of *Prevotella* spp. in the gut is underestimated, with 22 additional SGBs (containing at least 20 MAGs) being identified that are not represented by a genome from an isolate (FIG. 3).

Of the human intestinal *Prevotella* spp., the most recognized and relevant member is *P. copri*. Although *P. copri* is not universally present, when identified it tends to be highly abundant[15]. *P. copri* has increasingly come under the spotlight owing to conflicting reports about whether its effect on human health is positive or detrimental[25–27]. Detrimental effects include inflammatory conditions, such as rheumatoid arthritis[17,110,111], increased mucosal and systemic immune activation in patients with HIV infection[112] or ankylosing spondylitis[113], and exacerbating *Listeria monocytogenes* intestinal infection[114]. The association of *Prevotella* and *P. copri* with rheumatoid arthritis[115] was reported on the basis of their abundance in the faecal microbiome[17,116,117] and presence in the synovial fluid[110,118] (Supplementary Table 2). An increased *Prevotella* abundance has been associated not only with patients with symptomatic rheumatoid arthritis but also with individuals at high risk of developing the disease, including those with rheumatoid arthritis-predisposing genotypes[111,119]. In preclinical models, faecal transplantation from patients with early-stage rheumatoid arthritis who have increased abundance of *P. copri* induced a proinflammatory T_H17 cell response and rheumatoid arthritis phenotype in mice prone to rheumatoid arthritis[120]. Proinflammatory T_H17 and T_H1 cell immune responses mediated by *P. copri*-specific antibodies have also been reported in patients with rheumatoid arthritis[17,110,111]. Beyond associations with disease, studies have also suggested contrasting diet-dependent effects of *P. copri* on insulin resistance (discussed later). Of note, studies of *Prevotella* and particularly *P. copri* associations with diet or disease

have relied mostly on the type strain DSM18205 (REF.[121]), despite *P. copri* displaying considerable subspecies strain-level variation[67,122,123]. Therefore, future mechanistic and intervention studies should better factor in such strain-level diversity, as some of the observed host phenotypes could be subspecies-dependent.

Two studies in 2019 expanded the concept of *P. copri* genetic and functional diversity, combining a large-scale meta-analysis of publicly available metagenomes (more than 6,800) with a targeted isolation and sequencing of human *P. copri* isolates[4,16]. These studies revealed that, in contrast to what had been previously assumed, *P. copri* is not monotypic (that is, it is not a single species-level lineage) but is a complex comprising four genetically distinct clades designated A–D[16] (FIG. 1). The average nucleotide identity (13–21.4%) shared between clades is greater than would be expected within a single species lineage (less than 5–6%)[124–126]. *Prevotella* spp. have long been associated with non-Westernized populations, where they tend to be the dominant bacteria in the gut[8–13]. Analysis of the prevalence of the *P. copri* complex in these populations confirmed that it is very common (95.4% in non-Westernized populations versus 29.6% in Westernized populations)[16] and is a long-standing constituent of the human microbiome, having been identified in ancient faecal and intestinal contents (BOX 2), but is rapidly being lost, most likely owing to the process of Westernization. Another revelation was the presence of multiple cohabiting *P. copri* clades within an individual. The presence of multiple *P. copri* clades was more likely than the presence of a single clade in non-Westernized individuals (more than two clades present in 93.5% of non-Westernized individuals versus 32.1% in Westernized individuals)[16]. This result suggests that the members of the *P. copri* complex are niche separated and potentially complementary, as the same result has also been obtained in mice studies[127].

Gut Prevotella, diet and health. Intestinal *Prevotella* spp. and the *P. copri* complex in particular are commonly associated with non-Western diets and nutritional patterns rich in carbohydrates, resistant starch and fibre[8,128–132]. In Western-style diets, members of the class Clostridia (Ruminococcaceae and Lachnospiraceae) often contribute as degraders of dietary fibre[133], although nutritional interventions with fibre-rich foods usually result in an increase in *Prevotella* abundance[131,134–137]. In addition, a loss of members of the order Bacteroidales (including *Prevotella*) was observed in humanized mice fed a diet with low amounts of microbiota-accessible carbohydrates from dietary fibre[138]. The first attempts to develop a microbiome-oriented personalized nutrition demonstrated that stratifying individuals on the basis of microbiome composition may be a way to maximize clinical responses to dietary treatments. Indeed, having a *Prevotella*-rich gut microbiome potentiates weight loss[139–142], decreases cholesterol levels[143] and limits the bifidogenic effect[144] in individuals consuming a fibre-rich diet. Improved glucose metabolism from fibre consumption has also been attributed to a higher *Prevotella*-to-*Bacteroides* ratio and succinate metabolism[145,146]. A study examining the association between gut bacteria and postprandial responses in more than 1,000 individuals identified *P. copri* as potentially beneficial in glucose homeostasis and host metabolism[147]. By contrast, another study found that *P. copri* was associated with insulin resistance[148], and lower baseline levels of *P. copri* were linked to a reduction in insulin resistance in overweight individuals following a Mediterranean diet intervention[149].

These effects might be explained by the potential of *Prevotella* spp. to degrade the complex polysaccharides in individuals with a mixed, high-fibre diet. This is relevant to human metabolism because the human genome encodes enzymes for the degradation of only a limited number of carbohydrates, including sucrose, lactose and starch[150]. Consequently, the ability of gut microorganisms to ferment polysaccharides is crucial in human nutrition. *Prevotella* spp. are proficient producers of the short-chain fatty acid propionate from arabinoxylans and fructo-oligosaccharides in vitro[151], and the efficiency of specific strains in degrading these polysaccharides is linked with dominance patterns of *Prevotella* in mice[127]. In addition, the *P. copri* complex is capable of breaking down plant polysaccharides and host-derived mucin but not dietary-derived animal polysaccharides[4,152]. This fact might explain the decreased gut *Prevotella* diversity in

Box 2 | **Ancient and evolutionary *Prevotella* genomic fossils**

The human microbiome is the result of a continuous interplay and co-evolution of microbial communities with the human host. Understandably, our knowledge of the microbiome relating to human health has been gleaned almost exclusively from biological samples collected from modern contemporary populations; more specifically, populations that have undergone Westernization, a process driven by industrialization and culminating in dietary and lifestyle changes. Recently, comparison of the microbiome of Westernized populations with that of contemporary non-Westernized populations (that is, those that follow a more traditional lifestyle and diet) revealed stark differences[8–15]. This raises interesting questions: how similar is the microbiome in Westernized populations to the long established, co-evolved 'ancestral' human microbiome, and are non-Westernized populations a better representation of this ancestral microbiome? Ancient samples have started to give a historical snapshot of the microorganisms that were present in our ancestors and how they have evolved, with the help of accurate dating of samples using molecular clocks[186]. These studies have focused primarily on the evolution of human pathogens and were made possible from samples where microbial DNA has been preserved, such as dental calculus or pulp and other skeletal remains. Examples include the unravelling of the evolutionary and adaptive trajectories of *Yersinia pestis*, the cause of the Black Death[187], and *Mycobacterium tuberculosis*[188] (reviewed elsewhere[189]).

Although small in number, ancient microbiomes from stool or intestinal samples have become available, including those from coprolites (fossilized faeces) and the Iceman (Ötzi)[16], a natural ice mummy[190]. These studies have provided an initial awareness of how the ancestral human microbiome compares with that of contemporary populations. For example, analysis of the Iceman offered an insight into the historical global spread and evolutionary history of the stomach parasite *Helicobacter pylori*[191]. Ancient samples also revealed that the divergence of *Prevotella copri* into four distinct clades may possibly predate modern humans, and *P. copri* was almost certainly a core species in the microbiome of populations before the waves of human migration out of Africa[16]. As a consequence, the decreased prevalence of *P. copri* in the microbiome of Westernized populations compared with non-Westernized populations suggests that the non-Westernized microbiome is more representative of the co-evolved microbiome. However, to definitively answer this question, efforts are needed to increase the number of ancient samples from different human populations. Nevertheless, the increasing evidence that Westernized microbiomes are not accurate representations of our ancestral microbiome raises the question of whether this perturbation is ultimately detrimental to overall health, and warrants further investigation.

industrialized, Westernized populations[153], in which a high intake of diverse plant-based foods is rarely maintained. A highly specialized enzymatic potential, with remarkable strain-level variation, has been demonstrated in vitro and is responsible for complex polysaccharide degradation by different strains of the *P. copri* complex[4]. The diversity and mechanism of complex polysaccharide digestion is driven by the starch utilization system (Sus) comprising different transmembrane proteins (such as SusC) that transport polysaccharides into the periplasm. The genes encoding these transport proteins are usually located in polysaccharide utilization loci (together with degradation enzyme genes) and are selectively overexpressed on exposure of *P. copri* strains to different plant polysaccharides, with such exposure influencing growth capability[4]. Consequently, it might be plausible that the higher the *P. copri* diversity in the gut, the greater the number of types of complex polysaccharides that can be potentially utilized. Indeed, strain-level variation in *P. copri* genomes seems to be dependent on different dietary habits[123,154], and such diversity may simply be driven by selective exposure of individuals to different types and amounts of plant polysaccharides. Remarkably, diet-driven selection can have unexpected health implications, as *P. copri* strains associated with an omnivorous diet have a higher prevalence of the *leuB* gene, which is involved in branched-chain amino acid biosynthesis, a risk factor for glucose intolerance and type 2 diabetes mellitus[123].

Overall, the literature supporting a key role for *Prevotella*, and especially the *P. copri* complex, in driving individual clinical and metabolic responses to diet variation and to health status is substantial. However, the mechanisms of microbial contributions to these responses are far from clear, and this uncertainty is likely the cause of debate about whether *Prevotella* and *P. copri* are beneficial or detrimental in human health[26,27,155]. Factors that prevent clarity on the role of *Prevotella* spp. in gut health include the species-level and strain-level variability of gut *Prevotella*, in particular how many clades of the *P. copri* complex are present, which can hugely affect the response to different diets; and the variability of the dietary patterns studied, which all have a different supply of fibre and/or fibre-rich foods. The *Prevotella* arsenal of enzymes for digestion of polysaccharides represents an invaluable resource for optimal digestion dynamics and gut homeostasis. Thus, the current most likely interpretation is that the higher the diversity of *Prevotella* spp. (and other fibre degraders), the more advantageous the fermenting ability of the microbiome will be for the benefit of the human gut.

Prevotella spp. as potential pathogens

Prevotella spp. have been implicated in local and systemic infections, so to determine the extent of their involvement, we analysed the available literature by using a systematic approach (see Supplementary Box 4). Studies linking *Prevotella* spp. with human infections are mostly observational (43%), but there are also case reports and retrospective and prospective studies (Supplementary Table 2; Supplementary Fig. 2a). *Prevotella* spp. are most commonly associated with infections in the oral cavity, with periodontal infections ($n = 31$) and endodontic infections ($n = 35$) being the most frequently reported. Of the non-oral infections, musculoskeletal, head and neck, lower respiratory tract and skin infections have been reported (Supplementary Fig. 2b). Interestingly, oral infections may cause secondary systemic or organ-related infections[156]. For example, cases of *Prevotella*-related bacteraemia after dental extraction[157] or periodontal probing[158] have been documented, as well as a case of liver pyogenic abscess related to dental disease[159]. Furthermore, a relationship between oral infections and cardiac diseases has also been proposed[160]. In other cases, *Prevotella*-related infections have occurred as a result of major diseases, such as heart failure[161], in individuals with a compromised immune system[162] or as a complication of surgery[162–166].

P. intermedia, *P. bivia*, *P. nigrescens* and *P. melaninogenica* are the species most frequently associated with infections in humans (FIG. 4a; Supplementary Fig. 2d). However, the methods that are routinely used to identify *Prevotella* taxa have ranged from standard clinical microbiology methods to low-throughput or high-throughput molecular approaches, and species-level identification was reliably achieved in only a fraction of these clinical cases. Bacterial isolation and cultivation were the most prevalent methods (FIG. 4b; Supplementary Fig. 2c), especially in clinical case reports. Particular attention must be paid to the 'causation' link in clinical cases, as the mere presence of *Prevotella* spp. does not indicate causality, whereas isolation of *Prevotella* spp. from blood or from infection fluids provides some evidence that they are the cause of infection, especially if the infection involves a single bacterial species. However, for oral infections, *Prevotella* can be present in the infection site as a consequence of its presence in the (healthy) oral microbiome. A causative role for *Prevotella* spp. in infections has rarely been confirmed by reproducing the human disease phenotype in animal models. In a bacterial vaginosis mouse model, co-inoculation of *P. bivia* with *Gardnerella vaginalis* reproduced some features of human bacterial vaginosis, including uterus ascension, epithelial exfoliation and sialidase activity[90]. Overall, only a small percentage of studies have addressed the causative role of *Prevotella* spp. (FIG. 4b), and for only a few infections (for example, genitourinary infections) or in autoimmunity (for example, multiple sclerosis and rheumatoid arthritis) has the pathogenic potential of *Prevotella* strains been further questioned. Furthermore, in most cases (60%; Supplementary Fig. 2b) *Prevotella* spp. tend to co-infect humans with other microorganisms[167,168], suggesting that, while not obligate pathogens, *Prevotella* spp. may be opportunistic pathogens, alone or synergistically with other microorganisms, when the ecological conditions allow.

Anaerobic bacterial infections, such those involving *Prevotella* spp., are usually treated with broad-spectrum antibiotics. However, the increased incidence of antibiotic resistance may constitute a major limitation to resolving infections and poses a major issue for global health care. Despite this, the available information on antibiotic resistance in *Prevotella* spp. is scarce.

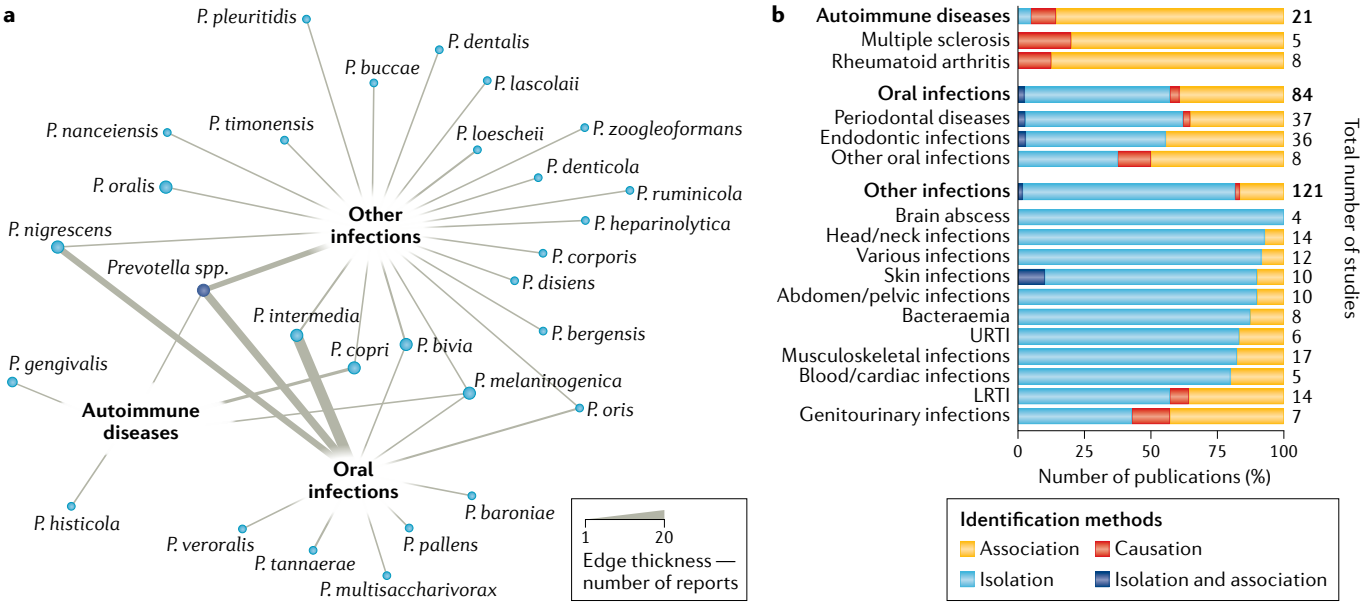


Fig. 4 | **Evidence for a role of *Prevotella* spp. in human infections and autoimmunity. a** | Network analysis showing the association of each *Prevotella* species with one or more diseases (grouped into three broad categories: autoimmune diseases, oral infections or other infections) based on a total of 226 studies (see Supplementary Box 4 for the search and inclusion criteria for the systematic literature review; Supplementary Table 2 includes all the data extracted from the articles included in this work). The thickness of the edges is proportional to the number of articles reporting the involvement of *Prevotella* spp. in diseases. While some species were specifically associated with one disease group, a few were shared among the three categories. Cases for which species identification was not available are labelled as '*Prevotella* spp.'. The number of the four most abundant *Prevotella* spp. associated with each detailed disease is shown in Supplementary Fig. 4d. **b** | Proposed role of *Prevotella* spp. in human diseases. The percentage of studies for each disease (with at least four studies linking them with *Prevotella* spp.) are categorized on the basis of the identification method, namely 'isolation' (standard microbiology approaches of isolation and cultivation without mechanistic or causative investigation), 'association' (low-input or high-input molecular approaches, such as species-specific PCR or 16S rRNA gene sequencing that surveys the presence of bacteria in a sample) and 'causation' (studies in which the causative role of *Prevotella* spp. in the infection was demonstrated in animal models). Most of the studies providing evidence of a link between *Prevotella* and disease are isolation-based or merely associative. Diseases are ordered on the basis of a descending 'isolation' order, and the total number of studies considered per disease is indicated. Supplementary Fig. 2c provides further details of the method used to identify the *Prevotella* spp. in each disease and extends the results presented here. LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.

Indeed, of the 226 studies we considered here, only 80 (35.4%) investigated the antibiotic resistance of *Prevotella* spp. through either biochemical or genetic methods. Resistance to β-lactam antibiotics, in particular penicillin and ampicillin, was reported in *Prevotella* isolates from head and neck infections[169]. Metronidazole resistance is also possible and has been reported in the clinic[170], more specifically for *Prevotella buccae*[171] and *P. bivia*[172]. While *Prevotella* does not seem to be one of the major resistant infectious threats, antibiotic resistance should be tested whenever possible, especially in patients with critical conditions, such as cystic fibrosis[173–177].

Conclusions and outlook

Prevotella is the second most abundant genus in the human oral cavity, and when present, it is frequently the most abundant in the gut microbiome. Therefore, it is surprising how little is known about this genus and it is puzzling why other oral and intestinal genera have received much more attention. This discrepancy can be explained only partially by the substantially non-pathogenic nature of *Prevotella* spp. and the difficulty in cultivating intestinal *Prevotella* taxa. However, two main aspects are stimulating the study of this genus: the increased availability of (untargeted) metagenomic datasets (BOX 1) of the human microbiome that can reveal the hidden *Prevotella* diversity across worldwide populations, and the recognition that intestinal *Prevotella* spp. are key players in host–microbiome interactions, especially in relation to nutrition and metabolism.

A number of important questions and research directions could have a considerable impact on the current understanding of *Prevotella* genomics and ecology. First, there is now overwhelming evidence that the abundance of *Prevotella* spp. in oral and intestinal microbiomes is higher in non-Westernized populations than in Westernized populations[8–13,15,57,58]. Analysis of ancient microbiome samples supports the theory, at least for the *P. copri* complex, that the loss of *Prevotella* diversity is associated with, and is likely driven by, the process of Westernization and is not just a common feature of modern non-industrialized communities[16]. Other gut bacteria may be subject to the same forces, but the link with a Western lifestyle is stronger for *Prevotella* on the basis of the observed differential prevalence and within-subject genus-level diversity. Because *Prevotella* spp. in the intestine also tend to be highly abundant, some of the differences observed for other bacterial species across populations with different lifestyles could partially be

a statistical artefact owing to the use of microbiome profiling methods based on relative abundance as well as a consequence of *Prevotella*-induced ecological effects. Further investigation to understand the genetic and ecological features driving the distinct host–*Prevotella* equilibrium is thus urgently needed. Unravelling such features will be particularly crucial in combination with a good study design when assessing which of the multiple lifestyle aspects (including diet, availability of antimicrobial drugs and hygiene practices) that differentiate Westernized and non-Westernized populations are most clearly related to differences in *Prevotella* prevalence and diversity. Ultimately, the major outstanding question is whether the decreased *Prevotella* prevalence and diversity observed at the population level in modern industrialized society is a reversible process and whether reversing this trend is indeed desirable from a health perspective. If it is desirable, then studies will be necessary to understand whether individual dietary-induced and lifestyle-induced microbiome alterations are sufficient to restore gut homeostasis or whether direct supplementation of *Prevotella* diversity would be required.

Second, it is crucial that future research be directed at unravelling the biomedical relevance of *Prevotella* spp. Indeed, while their pathogenic potential has proved to be limited and mostly connected with opportunistic infections, the role of *Prevotella* spp. in the onset and development of immune-mediated diseases remains unclear. Initial reports of a link with diseases such as rheumatoid arthritis[17] were only partially confirmed by follow-up studies[110,111,116]. The complexity of *Prevotella* spp. interactions with mucosal immunity[23,178] could explain the involvement of this genus in both autoimmunity and increased protection against pathobionts, and strain-level differences are likely responsible for the variability in immunological phenotypes between individuals, especially in light of the expanded genomic diversity of the *P. copri* complex[16]. Therefore, studies involving larger cohorts, with longitudinal sampling and accounting for host population differences, immunological aspects and strain-level *Prevotella* diversity, are needed to clarify this link, which could have a broad translational impact.

Third, the relationship between intestinal *Prevotella* spp. and nutrition should receive more research focus. Multiple convincing studies have demonstrated an association between *Prevotella* spp. and dietary patterns and cardiometabolic health, but such studies often report conflicting results[128,130,139–143,145,146,148,149]. Again, subspecies and strain diversity may obscure the consistency of experimental outcomes, which argues for improved study designs and larger clinical and preclinical cohorts. Because of the potential to manipulate the gut microbiome, a clear understanding of the role of *Prevotella* in human metabolism and nutrition might have tremendous clinical applications, such as the development of advanced probiotics and prebiotics, similar to those that are starting to be implemented for other bacteria, such as *Akkermansia muciniphila*[179]. For this application, efforts to isolate *Prevotella* strains will be pivotal in the coming years. The possibility to characterize strains, particularly from individuals with different diets and lifestyles, and observe their behaviour in vitro or in animal models will be of utmost importance to clarify the role of *Prevotella* spp. in health and how effective lifestyle features are in selecting strains with defined attributes.

Intriguingly, these three open questions could be interconnected in one hypothetical scenario. Considering the clear dietary implications of the Westernization process, the link between *Prevotella* and diet might be driving its decreasing presence in Westernized populations with their fat-rich and fibre-poor diet. Such a changing equilibrium potentially affects the host–*Prevotella* symbiotic relationship that was established over hundreds of thousands of years of co-evolution, leading in turn to impaired host–microorganism interactions that could make the host more prone to disease. This scenario remains for now an unproven hypothesis, but *Prevotella* seems to be the most promising genus to test this hypothesis.

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This is one of the first studies showing that reconstruction of genomes from ancient samples is possible, which is particularly relevant to study the evolutionary history of *Prevotella* spp.

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D.E. and N.S. conceived the article. All authors researched data for the article. N.S., D.E. and A.T. contributed substantially to discussion of the content. E.P. performed the analyses. N.S., D.E. and A.T. wrote the article. All authors reviewed and/or edited the manuscript before submission.

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