Host genetics affect microbial ecosystems via host immunity

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Purpose of review
Genetic evolution of multicellular organisms has occurred in response to environmental challenges, including competition for nutrients, climate change, physical and chemical stressors, and pathogens. However, fitness of an organism is dependent not only on defense efficacy, but also on the ability to take advantage of symbiotic organisms. Indeed, microbes not only encompass pathogenicity, but also enable efficient nutrient uptake from diets nondegradable by the host itself. Moreover, microbes play important roles in the development of host immunity. Here we review associations between specific host genes and variance in microbiota composition and compare with interactions between microbes and host immunity.

Recent findings
Recent genome-wide association studies reveal that symbiosis between host and microbiota is the exquisite result of genetic coevolution. Moreover, a subset of microbes from human and mouse microbiota have been identified to interact with humoral and cellular immunity. Interestingly, microbes associated with both host genetics and host immunity are taxonomically related. Most involved are *Bifidobacterium*, *Lactobacillus,* and *Akkermansia*, which are dually associated with both host immunity and host genetics.

Summary
We conclude that future therapeutics targeting microbiota in the context of chronic inflammatory diseases need to consider both immune and genetic host features associated with microbiota homeostasis.

Keywords
chronic inflammatory diseases, commensals, immunogenetics, microbial pathogens, microbiome

INTRODUCTION

Multicellular organisms have evolved in complex environments charged with diverse microbial ecosystems. This coevolution has led to the development of symbiotic relationships between microbes and more advanced organisms tightly regulated by the latter. The host has developed antimicrobial (for instance through the promotion of tightly regulated barrier functions), but also promicrobial strategies (through secretion of nourishing substances, such as mucus). Host immunity itself is not only closely associated with host defense, but also with microbial symbiosis. Therefore, the immune system may exert antimicrobial and promicrobial pressures, simultaneously. Symbionts induce both innate and adaptive host immunity, which affects immunity not only to symbionts but also toward pathogens. Across species acquisition of immune complexity (e.g. acquisition of adaptive immunity) is positively associated with host-embedded microbiota diversity, suggesting that evolved immunity allows the containment of highly diverse microbial ecosystems, thus fully exploiting their metabolic potential [1]. Symbionts also protect their host from pathogens by competition for energy sources and by secreting antimicrobial substances.

It has been repeatedly demonstrated that environmental factors strongly influence microbiota composition. For example, change of diet [2], life style [3], and migration [4,5] have strong impact on gut microbiota composition. However, coevolution of host and its microbiota advocate

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KEY POINTS

- Host genes involved in metabolism and host defense are associated with gut microbiota composition.
- Host immune features are associated with gut microbiota composition.
- A subset of gut microbes are both affected by host gene polymorphisms and host immune features, suggesting a sequential mechanistic link between host genetics, host immunity, and gut microbiota composition.
- Genetic evolution is associated with regulation of gut microbial symbiosis via regulatory T cells and sIgA.
- Host genetics should be considered in the context of therapeutic approaches targeting the gut microbiota.

for a host genetic component regulating microbiota composition both cross and intraspecies. It is generally difficult to segregate environmental and genetic effects on biological traits. The best method to differentiate between environmental and genetic effects in humans is to study monozygotic and dizygotic twin pairs, which when brought up together can be considered to encounter approximately the same environmental factors. Indeed, the first study [6] to describe variation in human host genetics as a determinant for gut microbiota composition was conducted in a small twin cohort, suggesting that monozygotic twins have more similar gut microbiota composition than dizygotic twins. This observation was later tested in larger twin cohorts with state-of-the-art next generation sequencing analysis confirming that monozygotic twins have more similar gut microbiota composition compared with dizygotic twins [7,8▪]. At the population level, a range of chronic diseases, such as inflammatory bowel disease (IBD) [9], diabetes [10,11], and allergy [12▪], with well known genetic cause have recently been demonstrated to have dysbiotic gut microbiomes. If the dysbiosis observed in these pathologies are dependent or independent of host genetics remains unresolved.

HERITABILITY OF GUT MICROBIOTA IN ANIMAL MODELS

Benson *et al.* [13] were the first to identify quantitative trait loci (QTL) in an intercross outbred mouse line associated with major gut microbial taxa. They demonstrated that the abundance of *Helicobacter* [Proteobacteria;Epsilonproteobacteria], *Lactobacillus* [Firmicutes;Bacilli], *Proteobacteria*, *Coriobacteriacceae* [Actinobacteria;Actinobacteria], and *Lactococcus* [Firmicutes;Bacilli] are associated with QTLs primarily located on mouse chromosomes 6, 7, and 10 (Table 1) [13,14▪,15,16,17▪,18▪,19▪▪–21▪▪,22▪,23▪▪,24▪,25▪]. Indeed, *Coriobacteriacceae* [Actinobacteria;Actinobacteria] and *Lactococcus* [Firmicutes;Bacilli] abundances are associated with QTLs encompassing genes relevant for MyD88-mediated Toll-like receptor signaling and T-cell receptor signaling [IL-1 receptor-associated kinase-4 (*IRAK4*) and *IRAK3*, respectively] as well as antibacterial enzymes secreted in tears, saliva, and mucus (lysozyme genes *Lyz1* and *Lyz2*) and proinflammatory cytokines IL-22 and IFNγ. In an independent study [21▪▪], *IRAK4* was found to be associated with *Roseburia* spp. [Firmicutes;Clostridia]. MyD88 is situated upstream of IRAK4 in the signaling cascade. *MyD88* mutations, which reduce MyD88 activity has previously been linked with increased risk of bacterial infection [26] and *MyD88* knock-out mice display reduced secretory IgA (sIgA) levels and increases in multiple taxa containing mucolytic members, including *Desulfovibrionaceae* [Proteobacteria;Deltaproteobacteria], *Mucispirillum* [Deferribacteres;Deferribacteres], and *Ruminococcus* [Firmicutes;Clostridia] [22▪] (Table 1).

Org *et al.* [21▪▪] moreover identified two genes encoding for caspase activity and apoptosis inhibitor 1 (*Caap1*) and oxysterol-binding protein (*Osbp*), which were associated with the abundance of *Oscillospira* spp. [Firmicutes;Bacilli] and *Ruminococcus gnavus* [Firmicutes;Clostridia], respectively. Another member of the caspase pathway is the caspase recruitment domain family member 9 (*CARD9*). A *CARD9* homozygous mutation resulting in a premature termination codon was previously associated with susceptibility to fungal infection, likely caused by an impaired innate signaling from the antifungal pattern-recognition receptor dectin-1 [27], which is also crucial for sIgA-bound antigen uptake by M cells and downstream antigen presentation [28]. Moreover, *CARD9* is associated with IBD, likely as a result of reduced abundance of bacteria with capacity to metabolize tryptophan into aryl hydrocarbon receptor (AHR) agonists, such as *Lactobacillus* [Firmicutes;Bacilli] [23▪▪]. AHR-activity stimulates local intestinal IL-22 secretion, which has important influence on barrier function and bacterial defense mechanisms such as defensin secretion. Indeed, treatment with Lactobacillus strains rescues colitogenic mice. Moreover, *CARD9* knock-out mice show significantly reduced abundance of *Adlercreutzia* [Actinobacteria;Actinobacteria], which is a member of the coriobacteriacceae family [23▪▪]. As mentioned above, Coriobacteriacceae was previously associated with a QTL localized on mouse chromosome 10, which includes genes

Table 1. Host gene polymorphisms associated with microbiota composition

Study design	Gene	Gene function/disease risk	Microbiota association[a] (phylum;class)	Reference
Human studies				
655 MZ ($n=306$) and DZ ($n=74$) twins and their families ($n=275$) of which 121 individuals had metabolic syndrome (GWAS)	*APOA5* SNP rs651821	Association with triglyceride levels and metabolic syndrome	Each additional copy of the minor C allele at *APOA5* SNP rs651821 decrease the abundances of the Bifidobacteriaceae family [Actinobacteria;Actinobacteria]	[14▪]
Coeliac disease in 22 high-risk infants (HLA-DQ2 carriers)	HLA-DQ2	Strong genetic risk factor for coeliac disease	Higher proportions of Firmicutes and Proteobacteria and lower proportions of Actinobacteria in HLA-DQ2 carriers	[15]
Healthy MZ ($n=34$) and DZ ($n=38$) twins from Norwegian bone marrow donors	AH8.1	Associated with a large number of autoimmune disease	*Coprococcus* [Firmicutes;Clostridia] and *Enterorhabdus* [Actinobacteria;Actinobacteria] (lower abundances in AH8.1 carriers)	[16]
45 Korean individuals, including MZ and DZ twins aged 26–55 years and their mothers (GWAS)	FLG	Gene related to epidermal barrier function	*Corynebacterium jeikeium* [Actinobacteria;Actinomycetales] in skin	[17▪]
GWAS of Hutterites population ($n=91$ summer and $n=93$ winter of which 57 individuals were collected both seasons)	SNP lying within intronic and untranslated regions of the gene *PLD1*	Signal transduction and subcellular trafficking. Previously associated with BMI	*Akkermansia* [Verrucomicrobia;Verrucomicrobia] (taxon known to be associated with obesity)	[18▪]
93 individuals' microbiomes in 15 body sites (GWAS)	*LCT*	Lactase enzyme, which acts to hydrolyze lactose	*Bifidobacterium* [Actinobacteria;Actinobacteria]	[19▪▪,20▪▪]
	HLA-DRA	Gene related to immune and signaling functions	*Selenomonas* [Firmicutes;Negativicutes] in the throat	[19▪▪]
	TLR1	Gene related to immune and signaling functions	*Lautropia* in the tongue dorsum [Proteobacteria;Betaproteobacteria]	[19▪▪]
472 MZ twin pairs and 418 DZ twin pairs (GWAS)	*GNA12*	Gene Involved in the barrier and associated with ulcerative defense colitis	SMB53 genus [Firmicutes;Clostridia]	[20▪▪]
	CD36	Scavenger receptor promoting TLR4/6 signaling. Involved in innate immunity	*Blautia* [Firmicutes;Clostridia]	[20▪▪]
	RABGAP1	Blood lipid trait	*Bifidobacterium* [Actinobacteria;Actinobacteria]	[20▪▪]
	OR6A2	Olfactory receptor gene linked to cilantro soapy taste	*Erysipelotrichaceae Cc 115* [Firmicutes;Bacilli] (related to *lactobacillus*)	[20▪▪]
	ALDH1L1	One-carbon metabolism gene set	SHA-98 genus [Firmicutes;Clostridia] (a member of the Christensenellaceae family)	[20▪▪]
Mouse studies				
110 inbred mouse lines (GWAS)	Genes on chromosomes 15	Irak4, kif21a, Lrrk2	*Roseburia* ssp. [Firmicutes;Clostridia]	[13,21▪▪]
	Genes on chromosome 19	Osbp (oxysterol-binding protein)	*Ruminococcus gnavus* [Firmicutes;Clostridia]	[21▪▪]
	Genes on chromosomes 2 and 7	Peak SNP (rs33129247) associated with triglyceride levels	*Akkermansia muciniphila* [Verrucomicrobia;Verrucomicrobia]	[21▪▪]
	Genes on chromosome 4	Caap1 (caspase activity and apoptosis inhibitor)	*Oscillospira spp.* [Firmicutes;Clostridia] (from the family Ruminococcacea)	[21▪▪]
MyD88 deficient mice	T-cell intrinsic MyD88	MyD88 signaling in gut T cells coordinates germinal left response, including T_{FH} and IgA^+ B cell development	*Desulfovibrionaceae* [Proteobacteria;Deltaproteobacteria], *Mucispirillum* [Deferribacteres;Deferribacteres] and *Ruminococcus* [Firmicutes;Clostridia]	[22▪]
Card9$^{-/-}$ mice	*Card9*	Susceptibility gene for IBD. Promotes recovery from colitis through AHR-induced IL-22 production	*Adlercreutzia* [Coriobacteriacceae;Actinobacteria], *Lactobacillus reuteri.* [Firmicutes;Bacilli] and *Clostridium spp.* [Firmicutes;Clostridia]	[23▪▪]
Wild-type and *Bmal1* KO mice	*Bmal1* gene	Circadian rhythm	Shift in balance between Bacteroidetes and Firmicutes	[24▪]
Intercross outbred mouse line	Irak3, LysP/M, IL-22 and IFNγ	Host immunity and barrier integrity	*Coriobacteriacceae* [Actinobacteria;Actinobacteria] and *Lactococcus* [Firmicutes;Bacilli]	[13]
Fruit fly studies				
Drosophila lines (GWAS)	*pyd*	PDZ domain (homology = tight junction proteins)	*Acetobacter tropicalis* [Proteobacteria;Alphaproteobacteria] (of note, gut microbiota of the Drosophila lines comprises five bacterial species)	[25▪]
	para	Sodium channel Ca^{2+} binding	*Acetobacter tropicalis* [Proteobacteria;Alphaproteobacteria]	[25▪]
	def	Antimicrobial peptide	*Acetobacter tropicalis* [Proteobacteria;Alphaproteobacteria]	[25▪]
	htl	Fibroblast growth factor receptor	*Acetobacter tropicalis* [Proteobacteria;Alphaproteobacteria]	[25▪]

Table 1 (*Continued*)

Study design	Gene	Gene function/disease risk	Microbiota association[a] (phylum;class)	Reference
	dnc	cAMP phosphodiesterase (homolog associated with schizophrenia)	*Acetobacter tropicalis* [Proteobacteria;Alphaproteobacteria]	[25▪]
	Cnx14D	Ca^{2+} binding with neural function	*Acetobacter tropicalis* [Proteobacteria;Alphaproteobacteria]	[25▪]

ALDH1L1, aldehyde dehydrogenase 1 family member L1; AH8.1, 8.1 ancestral haplotype; *APOA5*, Apolipoprotein A-V gene; *Bmal1*, brain and muscle AHR nuclear translocator-like protein-1; cAMP, cyclic adenosine monophosphate; *Card9*, caspase recruitment domain family member 9; *Cnx14D*, calnexin 14D; *def*, defensin; *dnc*, dunce; DZ, dizygotic; FLG, Filaggrin; GWAS, genome-wide association studies; *HLA-DRA, human leukocyte antigen - DRA*; HLA-DQ2, OR6A2, olfactory receptor 6A2; *htl*, Heartless; Irak4, interleukin-1 receptor-associated kinase-4; JAK, janus kinase; kif21a, kinase family member 21a; KO, knock-out; LCT, lactase; Lrrk2, leucine-rich repeat kinase 2; MZ, monozygotic; *para, paralytic;* PDZ, post synaptic density protein, drosophila disc large timor suppressor and zonula occludes-1 protein; PLD1, phospholipase D1; *pyd*, Polychaetoid; SNP, single nucleotide polymorphism; *TLR1, toll-like receptor 1*; TFH, follicular helper T cell.

[a]Microbe abundances refer to gut microbiota unless indicated otherwise.

encoding IL-22 [13]. Since only *CARD9* is located on mouse chromosome 2 (but none of the QTLs identified in the previous study), it is possible that the association between Adlercreutzia [Actinobacteria;Actinobacteria] and *CARD9* is an indirect effect of the influence of CARD9 on AHR-mediated IL-22 secretion.

Brain and muscle AHR nuclear translocator-like protein-1 (*Bmal1*) is a transcription factor involved in the regulation of the circadian rhythm, which itself is transcriptionally regulated by a retinoic acid-related orphan receptor response element-binding site (RORE) located in the promotor of *Bmal1*. One of the ROR transcription factors binding RORE is RORγ, which is tightly linked with regulating Th17 cell differentiation and maintaining a balanced equilibrium between inducible regulatory T cells (iTreg) and Th17 cells. It was recently demonstrated that the equilibrium between gut microbes from the phyla Bacteroidetes and Firmicutes is associated with the circadian cycle with Bacteroidetes peaking several hours into the dark phase and Firmicutes peaking at the beginning of the light phase [24▪]. *Bmal1* knock-out mice lose this circadian change of their gut microbiota. Finally, two haplotypes of *Bmal1* in humans have been shown to be associated with type 2 diabetes [29], a disorder associated with gut microbiota dysbiosis [10,11].

The intestinal barrier physically separates gut microbiota from the host. As such it serves as the first line of defense. Second line of defense includes innate immune functions, such as antimicrobial peptides (e.g. defensins), which are secreted by cells in the barrier as a result of host sensing of microbes, which threaten to translocate across the barrier and thus invade the host. Evolutionarily, these defense mechanisms have developed very early. A number of genes regulating these defensive pathways show polymorphisms even in less complex organisms, such as Arabidopsis [30▪▪] and the fruit fly [25▪]. Indeed, polymorphisms of fruit fly genes, such as polychaetoid (*pyd*) and defensin (*def*), have been associated with gut microbiota dysbiosis manifested as variation in the abundance of *Acetobacter tropicalis* [Proteobacteria;Alphaproteobacteria] (Table 1). Of note, the *pyd* gene is homologous to human genes involved in the regulation of tight junctions, which control the permeability of the intestinal barrier.

Animal studies addressing the association between host gene polymorphisms and gut microbiota highlight the importance of host defense in the regulation of gut microbiota homeostasis. Animal studies are particularly well adapted for this type of analysis, because confounding factors, such as diet and environment may be harmonized, and because the effect of identified genes may be tested in knock-out models. Of note, animal models may encompass less host genetic diversity. Contrarily, confounding factors in human studies add a significant amount of variance to the microbiota composition to be associated with genetic variation. Classic genome-wide association studies (GWAS) with a limited amount of phenotypic traits compensate for such variation by increased cohort size. However, when the phenotypic traits are the abundance of hundreds of individual microbes, multiple comparisons seriously affect statistical power, thus requiring extremely large cohorts. In the next section we will discuss the associations between human genes and microbial abundances. In light of the statistical power of these analyses it is likely that we are still only observing the top of the iceberg. Slightly weaker but nevertheless meaningful disease-specific associations may be obtained from larger or targeted future studies.

HUMAN HERITABILITY OF MICROBIOTA

The first human GWAS using microbiota composition from various body sites as associative phenotypic trait included 93 individuals from the human microbiome project [19▪▪]. To gain statistical power they performed a principal component analysis of the microbiota composition data stratified by body

site and utilized the top-5 principal components of these analyses as phenotypic traits. A number of host defense-related pathways were identified using this approach, including leptin, JAK/Stat, chemokine, and pattern-recognition receptor signaling. These were all associated with microbiota composition of nose, throat, and skin. Similarly, two single nucleotide polymorphisms (SNPs) in *human leukocyte antigen - DRA* and *Toll-like receptor 1* were associated with the abundance of throat-derived *Selenomonas* and tongue dorsum-derived Lautropia, respectively (Table 1).

Gut-derived *Bifidobacterium* was associated with a SNP in the *lactase (LCT)* gene, which encodes lactase enzyme pivotal for the cleavage of diary-derived lactose. Of note, the *LCT* polymorphism is associated with lactose tolerance. Moreover, individuals with a functional *LCT* gene had lower levels of *Bifidobacterium*, likely because the host degrade lactose, thereby depriving *Bifidobacterium* for an important energy source. Importantly, the link between *LCT* and *Bifidobacterium* has also been observed in the Hutterites populations although without reaching statistical significance [18▪] and confirmed in the largest study [20▪▪] to date, including 2139 individuals among which 890 monozygotic and dizygotic twin pairs. The latter study, furthermore, identified *GNA12* and *CD36* genes, which are involved in barrier defense and innate immunity, respectively. *GNA12* and *CD36* polymorphisms are associated with gut abundances of SMB53 [Firmicutes;Clostridia] and *Blautia* [Firmicutes;Clostridia], respectively. In an independent study, Si *et al.* [17▪] identified a gene, filaggrin (FLG), related to epidermal barrier function, which is associated with *Corynebacterium jeikeium* [Actinobacteria;Actionbacteria] abundance. Finally, haplotypes of the 8.1 ancestral haplotype (AH8.1) gene associated with a large number of human autoimmune diseases as well as a polymorphism of the *HLA-DQ2* gene associated with strong genetic risk of coeliac disease were associated with gut microbial composition (Table 1).

Beyond host defense-related genes, a number of genes involved in host metabolism were discovered. Two genes implicated in blood lipid traits (apolipoprotein A-V and Rab GTPase-activating protein 1) were associated with the gut microbiota abundance of *Bifidobacterium* [Actinobacteria; Actinobacteria] [14▪,20▪▪]. Two additional genes involved in lipid taste and carbon metabolism (*OR6A2* and *ALDH1L1*) were equally identified to be associated with *Erysipelotrichaceae Cc 115* [Firmicutes;Bacilli] and SHA-98 [Firmicutes;Clostridia] gut microbiota abundance, respectively (Table 1).

CROSS TALK BETWEEN GUT MICROBIOTA AND CELLULAR IMMUNITY

Microbes play important roles for the development and maturation of host immunity. Indeed, germ-free mice display a severely impaired immune system affecting the development of Peyer's patches and germinal centers of the small intestine. In the absence of specialized sites for T and B-cell differentiation and maturation, the germ-free mice display reduced levels of $CD4^+$ and $CD8^+$ T cells, including iTregs. Th17 cells show a dichotomy with reduced levels in the small intestine and increased levels in the colon. Moreover, germ-free mice have drastically reduced levels of sIgA [31].

More specifically, Th17 cells may be induced by mucolytic members of the gut microbiota, such as segmented filamentous bacteria (SFB), *Citrobacter rodentium* and *Escherichia coli,* but also by a consortium of 20 bacteria displaying mucolytic characteristic isolated from an ulcerative colitis patient [32▪▪]. Equally, the induction and maturation of intestinal iTreg cells is affected by the presence of a large number of species from the Clostridium genus as well as species of the *Lactobacillus* genus [32▪▪,33]. Probiotic treatment of mice with these strains shows an effect on iTreg development and maturation. Moreover, polysaccharide A released by several species from the *Bacteroides* genus is able to induce IL-10 secretion by dendritic cells, which may drive iTreg differentiation [34,35].

CROSS TALK BETWEEN GUT MICROBIOTA AND HUMORAL IMMUNITY (SECRETORY IgA)

Although microbes colonize all accessible body habitats, including skin, oral, nose, vagina, and even the lung, almost all our knowledge with regard to the impact of natural microbial colonization on host immunity is restrained to the densest microbial community known to man, the gut microbiota. In recent years the development of flow cytometric analysis of sIgA-bound gut microbiota [36] and associated sorting procedures [37] have allowed an accurate evaluation of gut microbiota targeted by sIgA [9,38▪,39▪,40,41▪]. All these studies describe a heterogeneous sIgA immune response to gut microbiota with large variation between healthy individuals. However, all studies agree that the main targets of sIgA are found among the three phyla, Firmicutes, Proteobacteria, and Actinobacteria, which are also the more hereditable phyla. Previously reported sIgA/microbial interactions identified in literature are summarized in Fig. 1, highlighting *Bifidobacterium*, *Lactobacillus, Clostridium*, SFB, *Escherichia,* and *Akkermansia* as prominent sIgA targets. Of note,

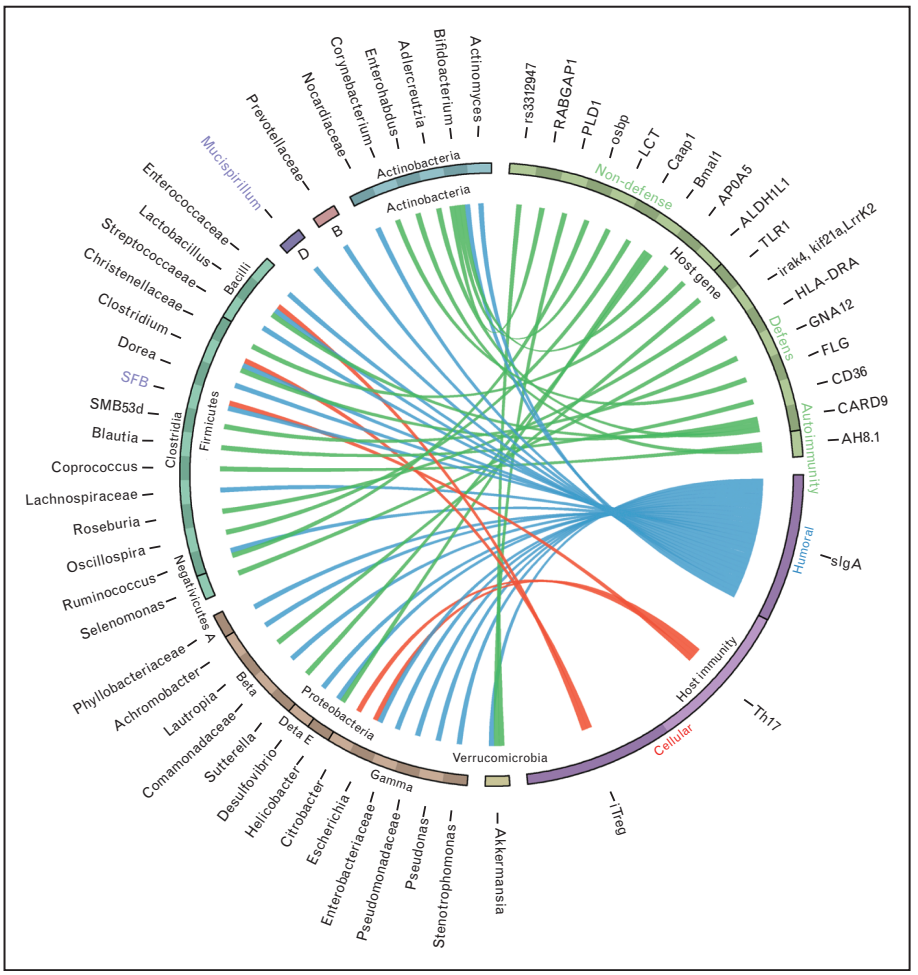

FIGURE 1. The plot illustrates associations between microbiota members and host features (genetics and immunity). Gut microbiota members are stratified according to phylum (inner circle labels) and class (outer circle labels). Of note, phyla B and D corresponds to Bacteroidetes and Deferribacteres, respectively. Each member is taxonomically identified at family or genus level (radial outer circle labels). Host genes are grouped according to their reported association with autoimmunity, host defense (defense) or other functions (nondefense). Host immune features comprise humoral (sIgA) and cellular (Th17 and iTreg) immunity. Associations between microbes and host genes, immune cells and/or sIgA are indicated with colored ribbons (green, red, and blue, respectively). Only microbes with known association with either host genes (Table 1) or immune features [9,32▪▪,33–35,37,38▪,39▪,40,41▪] are included in the plot. Associations are derived from both human and mouse studies. Two taxa found in rodent microbiota (but not in human microbiota) are marked in purple. iTreg, inducible regulatory T cell; sIgA, secretory IgA.

Lactobacillus, *Clostridium*, SFB, and *Escherichia* all impact cellular immunity, whereas *Bifidobacterium*, *Lactobacillus*, *Clostridium*, and *Akkermansia* have been associated with host gene polymorphisms (Fig. 1). *Bifidobacterium* are associated with host genes relevant for both host defense and nondefense pathways; *Lactobacillus* and *Clostridium* are uniquely associated with defense genes and *Akkermansia* is uniquely linked with nondefense genes. It is intriguing to notice that taxa (*Lactobacillus* and *Clostridium*) associated with regulatory T-cell biology are the only two taxa also associated with both sIgA and host defense gene polymorphisms (Fig. 1). Contrarily, Th17 cells are associated with pathobiont taxa (SFB, *E. coli*, and *Citrobacter*) bound by sIgA but nonassociated with host genetics. It is, therefore, tempting to speculate that host fitness through genetic evolution has prioritized regulating the symbiosis between host and microbiota above eliminating external danger through proinflammatory responses.

Interestingly, no bacteria from the Bacteriodetes phylum (approximately 50% of the human gut microbiome) are found to interact with sIgA under

nonpathological conditions nor do they associate with host gene polymorphisms. It is possible that extended evolutionary adaptation between host and Bacteroidetes-derived bacteria make associated host genes particularly conserved and thus undetectable in GWAS. Palm *et al*. observed that Bacteroidetes-derived bacteria from the Prevotellacaceae family were bound by sIgA in mice suffering from colitis, suggesting that deleterious associations between host genetics and immunity may be observed in patients' cohort studies [9]. They moreover demonstrated that sIgA-bound gut microbiota are colitogenic and evoke disorder in healthy mice upon transplantation. Finally, several immune genes are associated with microbe abundances merely in the throat and tongue dorsal rather than in the gut [19▪▪]. It is, therefore, likely that future studies focusing on these body sites may reveal many more interactions between host immunity and microbiota.

CONCLUSION

In recent years, fecal microbiota transplantation (FMT) has become a recognized therapeutic solution for *Clostridium difficile* infections and a promising therapeutic solution for chronic diseases associated with gut microbial dysbiosis, such as IBD, type 2 diabetes, rheumatoid arthritis, multiple sclerosis, and asthma [42,43]. Knowing how host genetic makeup impacts gut microbiota composition will be of major importance to understand if FMTs may have long-term beneficial impact on chronic diseases or if host genetics will enforce a dysbiotic equilibrium. Indeed, a recent kinetic study [44] post-FMT has shown that FMTs are unstable. In future, such instability should be ascribed not only to divergent life styles between donor and recipient but also genetic differences. Depending on the extent of the impact of host genetics on gut microbiota composition, FMTs in the context of chronic disease may possibly need a donor/recipient genetic match for at least a set of SNPs or better yet therapeutic compensation for lost or gained functionalities according to patient genotype.

So far no GWAS has been conducted on cohorts of individuals suffering from allergic diseases using gut microbiota composition as phenotypic trait. However, GWAS studies of allergic diseases have previously identified numerous polymorphisms in host genes associated with host defense in line with host genes identified to be associated with gut microbiota composition [45]. *Indeed, HLA-DQ* and *FLG* genes, which are associated with gut microbiota composition (Table 1), have also been associated with allergic asthma, atopic dermatitis (eczema), and seasonal allergic rhinitis. Moreover, allergic disease imprints a biased gut microbiota composition [12▪]. It is, therefore, likely that future studies will identify crucial links between gut microbiota composition and host genetics in allergic diseases. This could shed light on the underlying causes of disease and may guide the development of the pathway-specific therapeutics necessary to deal with the growing incidence of allergies.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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