Elucidating the role of the host genome in shaping microbiome composition

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ABSTRACT
A major goal of microbiome research is to identify the factors that determine bacterial composition within and upon a host. Environmental factors are thought to play a large role, such as diet in determining gut microbiome composition and moisture in determining skin microbiome composition. The role of host genetics, however, has been a source of debate in the literature. Recently, we examined the association of host genetics with human gut microbiome composition in the Hutterites, a population that lives and eats communally. We identified heritable bacterial taxa and host genetic loci associated with their abundances. In this addendum, I put these results into a broader context along with other recent studies of microbiome heritability, and synthesize common themes that appear across organisms and tissues, such as the relatively small extent genetics plays compared to environment and the role of host genetic variation in immune response and barrier integrity.

Introduction
It is generally accepted that many environmental factors influence the microbiomes of both animals (e.g., diet, antibiotic usage, and humidity) and plants (e.g., microbes in the surrounding soil and pH). However, the extent to which host genetic variation may play a role in determining microbiome composition is debated. Although several candidate gene studies have found evidence that the microbiomes of humans and mice are associated with host genetic variation (see review by Spor et al.) and one study demonstrated that the overall similarity of the human gut microbiome increased with closer degrees of relatedness in families, other studies have not observed strong evidence for a host genetic effect. Specifically, two studies examining general measures of microbiome similarity (UniFrac distances) found that monozygotic (MZ) twins on average did not have more similar gut microbiomes than dizygotic twins (DZ), leading to the conclusion that the microbiome is not highly heritable. Both of these studies, however, had fairly low sample sizes (~20–60 twin pairs total) and only considered broad measures of microbiome composition rather than the heritability of individual taxa.

In the several years since the two twin study reports were published, multiple other groups have examined the role of host genetics in a variety of different organisms and sampling sites in order to estimate the heritability of the microbiome and also to identify host genomic loci associated with microbial abundance. These studies collectively demonstrate that at least a subset of the organisms comprising the microbiome appear to be heritable, calling into question the previous assertion that host genetics does not influence microbiome composition.

Recently, we published one of the first studies to examine human genetic variation on a genome-wide scale in relation to fecal microbiome composition in a founder population: the Hutterites. Unlike many Western populations studied to date, the Hutterites live and eat communally, which limits the extent that inter-individual variation in diet can influence the composition of the gut microbiome. We examined the fecal microbiome in two seasons, winter and summer, an additionally considered a composite microbiome (consisting of the average abundance of the common
taxa from winter and summer). Between 10–14 common bacterial taxa were identified as heritable within each season based on the calculation of “chip heritability” - or the proportion of variation explained by ~200,000 host SNP genotypes measured across individuals. Additionally, we identified at least 8 taxa within each season that were associated with host genetic variation at a genome-wide significance level. Finally, we identified candidate tissues in which host genetic variation may act to influence gut microbial composition, including endothelium, intestine, and stomach, by intersecting the results of our genome-wide association studies (GWAS) with DNase hypersensitivity sites (DHS) from 349 different cell types.

This addendum aims to place our work on the Hutterite microbiomes alongside other recent studies in this field in order to update our understanding of the ways host genotypic variation shapes the microbiome. Specifically, I review the evidence that supports the notion of a heritable component to the microbiome that comes from work with diverse organisms - including mouse, human, *Arabidopsis*, and maize - and diverse microbiome sources - including stool, skin, rhizosphere, and endophytic microbiomes. Additionally, I synthesize a set of common themes observed across organisms and sample sources, including highlighting the types of host genes that have repeatedly been associated with microbial abundance. Finally, I explore some open questions relating to the role of host genetic variation and propose future directions to address these gaps.

**Heritability of the microbiome**

Heritability is the extent to which the total phenotypic variation for a trait is attributable to genetic rather than environmental factors. Several recent studies have sought to examine heritability of the microbiome using a variety of methods (Table 1). One approach has been to examine microbial differences between inbred lines of model organisms for which the genetic background of all individuals within a line is identical. This method allows for strict control of environmental variables via experimental blocking. One such study examined the rhizosphere of 27 maize lines grown in different field environments and found that ~19% of the inter-line variation of operational taxonomic unit (OTU) richness and ~5% of variation in β diversity could be attributed to host genotype.14 Similarly, another study examined stool from 113 inbred mouse lines and was able to identify 16 genera that were heritable.15 While study designs of this type are effective at measuring the extent to which both environmental and genetic factors contribute to microbiome variation, one major limitation is that the extent of genetic variation examined is reduced compared to variation segregating in outbred populations.

In addition to examining inbred model organisms, others have utilized classic heritability measurement techniques in naturally occurring populations, for example by comparing concordance among pairs of MZ and DZ twins. Goodrich *et al.*16 examined overall community similarity (via β-diversity metrics) as well as the heritability of individual taxa in stool from 416 pairs of MZ and DZ twins from the TwinsUK cohort. In contrast to the earlier twin studies,11,12 the relatively large sample size of this study proved powerful enough to demonstrate that the overall microbiome composition was significantly more similar between pairs of MZ twins than DZ twins, and that many individual taxa were heritable, in particular taxa in the Firmicutes phylum. In addition, the authors reexamined twin data from the Turnbaugh *et al.*11 and Yatsunenko *et al.*12 studies, finding that many of the taxa identified as heritable in the TwinsUK samples were also heritable in other populations.

In the Hutterites, we identified ~15 taxa in stool as heritable in winter, summer, or when both sampling periods were combined.13 Although differences in analysis methods do not allow for direct comparison, we observed similar trends along the bacterial phylogeny in the Hutterites as seen in the TwinsUK. Most of the heritable bacteria in the Hutterites were from either the Proteobacteria or Firmicutes phyla, including the family Lachnospiraceae, which contained some of the most highly heritable taxa in the TwinsUK study. Taken together, these results demonstrate that certain taxa in stool, in particular within Firmicutes and Proteobacteria, are consistently heritable, regardless of environmental and cultural differences between human populations.

One major concern with host genetic studies of the microbiome is that vertical transmission of bacteria from parent to offspring can be confounded with measures of heritability. This is not an issue for twin studies, as similar amounts of vertical microbiome transmission from the mother to MZ and DZ twins are expected. Otherwise, a study of stool microbiome
heritability in chickens that had been selectively bred for weight over 54 generations was able to at least partially control for vertical transmission. Although some microbiome drift likely occurred over the course of the breeding regimen, the two diverged populations originally shared the same microbiota, minimizing the extent to which vertical transmission could interfere with measures of heritability. Thus, while these studies appear to have established that at least some component of the microbiome is indeed heritable, the potential for vertical transmission should be kept in mind when interpreting heritability results from other studies, including the estimates of chip heritability from our Hutterite study.

### Association of host genetic variation with the microbiome

Once the heritability of a trait is established, a natural next step is to identify the variants and genes in the genome responsible for contributing to inter-individual variation in the phenotype. Several groups have now performed genome-wide association studies (GWAS) to identify host genetic variants associated with microbial abundance. The first to do this was Benson et al.,¹⁸ who identified 18 quantitative trait loci (QTL) that were associated with the abundances of individual bacteria taxa in stool across 645 advanced intercross mouse lines (4<sup>th</sup> generation – G<sub>4</sub>). In a follow up study, four of these hits were replicated in later generations of intercross mice (G<sub>10</sub>), along with the identification of an additional ~40 QTLs.¹⁹ Another study in mice was able to identify 7 loci associated with microbial abundance in stool using a panel of 113 inbred mouse strains.¹⁵ Notably, the taxa for which genome-wide significant hits were observed are largely members of taxonomic groups that were also identified as being heritable in the above-discussed studies of human gut microbiota,¹³,¹⁶ including

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**Table 1. Summary of recent studies that examined microbiome heritability or identified QTL.**

| Analysis            | Methodology         | Organism       | Sample type                | Sample size  | Loci tested | Significance threshold | Results | Reference               |
|---------------------|---------------------|----------------|----------------------------|--------------|-------------|------------------------|---------|-------------------------|
| heritability        | linear mixed model/partial constrained PCoA | maize          | root/soil                  | ~500         | N/A         | N/A                    | N/A     | Peiffer et al.¹⁴        |
| heritability        | wOmbit              | chicken        | stool                      | 60           | N/A         | N/A                    | 0 species | Zhao et al.¹⁷           |
| heritability        | ACE model           | human          | stool                      | 833²        | N/A         | N/A                    | 290 taxa | Goodrich et al.¹⁶       |
| heritability        | SNP based           | mouse          | cecum/stool                | 599²        | N/A         | N/A                    | 16 genera | Org et al.¹⁷            |
| heritability        | SNP based           | human          | stool                      | 127         | N/A         | N/A                    | >10 taxa  | Davenport et al.¹³      |
| heritability        | SOLAR               | human          | skin                       | 45          | N/A         | N/A                    | 8 taxa    | Si et al.²²             |
| heritability        | ICC                 | human          | nasal                      | 178         | N/A         | N/A                    | 1 measure  | Liu et al.¹³            |
| QTL R/qtl with GRAIP| mouse               | stool          | 645                       | 530         | P < 0.1¹⁷   | 18 loci                 | Benson et al.²¹ |
| QTL R/qtl Reaper    | mouse               | stool          | 30                       | 3.785       | P < 0.05     | 5 regions               | McKnite et al.³² |
| QTL mixomogam       | Arabidopsis         | leaf           | 196                       | N/A         | FDR < 0.25   | 48 genes                | Horton et al.²⁰ |
| QTL                 | human               | intestinal     | biopsy                     | 474         | 154         | FDR < 0.25              | 40 loci   | Leamy et al.¹⁹         |
| QTL R/qtl with GRAIP| mouse               | stool          | 472                       | 2,058       | P < 0.1⁵    | 42 loci                 | Leamy et al.¹⁹ |
| QTL FaST-LMM         | mouse               | cecum/stool    | 599²                      | ~200k        | P < 4 × 10⁻⁶ | 7 loci                  | 83 SNPs   | Blekhman et al.²²       |
| QTL PLINK            | human               | HMP sites      | 93                        | 33,814      | q < 0.1     | 233 SNPs                | Davenport et al.²¹ |
| QTL GEMMA           | human               | stool          | 127                       | ~210k        | q < 0.2      | 233 SNPs                | Davenport et al.²¹ |
| QTL microbiomeGWAS  | human               | lung           | 147                       | ~382k        | P < 5 × 10⁻⁶ | 0 SNPs                  | Hua et al.³¹ |
| QTL PLINK            | human               | skin           | 45                        | 275         | P < 0.000182 | 1 SNP                   | Si et al.²² |

A From 27 inbred maize lines planted in 5 different field locations.
B Genotype explained ~19% of the variance in OTU richness and 5–7% in β-diversity.
C 15 males and 15 females from 2 lines.
D Heritability was calculated using 171 monozygotic and 245 dizygotic twin pairs.
E From 113 mouse strains.
F 14 taxa in winter sampling, 10 taxa in summer sampling, and 13 taxa when considering samples from both seasons.
G Intraclass Correlation Coefficient (ICC).
H 46 monozygotic twin pairs and 43 dizygotic twin pairs.
I The authors designate P < 0.05 (significant) and P < 0.1 (suggestive), however, results in the abstract and discussion generally consider all associations that met the suggestive p-value threshold.
J 30 mouse strains.
K 196 accessions.
L 5 loci were significantly associated with multiple bacterial taxa.
M Human Microbiome Project (HMP) sites include: stool, saliva, tongue dorsum, hard palate, buccal mucosa, attached keratinized gingiva, palatine tonsils, throat, anterior nares, supragingival plaque, subgingival plaque, left antecubital fossa, right antecubital fossa, left retroauricular crease, and right retroauricular crease.
Lachnospiraceae, Ruminococcaceae, and Bacilli (all members of the Firmicutes phylum).

In addition to mouse studies, GWAS have also been performed in plants and humans. In plants, both bacteria and fungi that compose the leaf endophyte microbiome were examined across 196 accessions of Arabidopsis thaliana. QTLs for both species richness and the abundances of individual taxa were identified. Additionally, a subset of the identified QTLs were associated with the abundances of multiple bacterial and fungal taxa. In humans, the first study to move beyond interrogating single candidate genes examined associations of 154 single nucleotide polymorphisms (SNPs) previously associated with irritable bowel disease (IBD) with common gut bacteria in three cohorts of individuals. SNPs in NOD2 and other immune-related genes showed consistent signals of correlation with microbial traits across cohorts. Recently, a study examining the skin microbiome identified one QTL in FLG, a gene important for skin barrier function, by focusing on 275 SNPs located in a panel of genes related to sebum production, pigmentation, skin humidity, skin barrier function, and hair follicle development.

The first study to perform a true microbiome GWAS in humans identified associations of the microbiota from 15 different body sites sampled in the Human Microbiome Project (HMP). Genic SNPs identified as significantly associated with microbial abundance are enriched in genes with known immune and signaling functions. In the Hutterites, we also performed GWAS for stool microbial abundance and identified SNPs near genes associated with immune and olfactory functions. In combination, the results from these studies suggest that many cellular mechanisms, such as immune response and cell-to-cell signaling, may play a role in the heritability of bacterial abundances.

Synthesizing common themes across host species and microbiome sources

From both the heritability calculation and genome-wide association studies across organisms and sampling sites, several consistent and important themes emerge. First, for many of the microbiomes examined to date, it seems clear that environmental factors play a larger role in determining the composition than host genetics. This observation has been made in studies of inbred organisms, where the contribution of both environmental and genetic factors can be directly measured. For example, the study in maize was able to measure the effect of the field of growth (five different locations) as well as genotypic effects by line. Field accounted for 13–18% of the variation in \( \beta \)-diversity across all samples, while genotype only accounted for 5% once the effects of field and soil type were accounted for. Results from our study of a naturally occurring population, the Hutterites, were similar. Specifically, we observed much larger environmental influences compared to host genetic effects, as there were large, consistent gut microbiome compositional changes observed longitudinally between the same individuals sampled in winter and then again in the following summer. Together, these examples point to the major role that environment and exposure play in determining microbiome composition across a wide range of organisms. However, it is also clear from these same studies that host genetic variation does explain a portion of the variation between individuals.

Another major theme across organisms is that host defense and immunity genes tend to be implicated in microbiome GWAS. In the Arabidopsis GWAS, the top gene ontology (GO) categories for both the fungal and bacterial hits were for host defense, and the top GO enrichment category for species richness was regulation of viral reproduction. Additionally, a pleiotropic QTL associated with multiple taxa in the G4 intercross mouse QTL mapping study was next to several genes with known immune functions such as Il22, Il12, and Il18. In the human GWAS of the 15 HMP sites, the top GO enrichments were in immune categories such as melatonin signaling, JAK/Stat signaling, chemokine signaling, CXCR4 signaling, and role of pattern recognition receptors in bacteria and viruses. In the Hutterites, there were enrichments of immune processes for the top GWAS hits for genus Sporacetigenium as well as for multi-organism process and communication for genus Anaerostipes. Overall, the results from both plants and animals demonstrate the role that natural variation in host immune genes can play in shaping microbial composition.

Finally, it is also apparent that host genetic variation controlling cellular and tissue barrier integrity likely acts to influence microbiome composition. For the human skin microbiome, the one significant QTL identified was for the gene FLG, which encodes a protein important for barrier function in the
skin. In *Arabidopsis*, cell wall components (cellulose, callose, and pectin) were implicated in the GWAS. Additionally, the GO terms for cell wall modification and cell-cell junction assembly were significantly enriched among the GWAS hits for bacterial abundance. Finally, the top GWAS hits for genus *Akkermansia* in our Hutterite study were significantly overrepresented in putative regulatory regions (DNase hypersensitive sites (DHS)) in endothelial tissues. Interestingly, *Akkermansia* has been shown to be protective against weight gain in mice, while endothelial tissue barrier integrity breaks down in obesity. Given that strong barriers are often thought of as the first line of defense organisms have against invading pathogens, it is unsurprising that genetic variation in regions containing genes involved in barrier integrity and cell-to-cell adhesion also consistently appear among top microbiome GWAS hits across a variety of organisms, along with other immune-related genes.

**Future directions**

The recent studies of the heritability of the microbiota across a number of different organisms have definitively demonstrated that there is some degree to which the host genome influences microbiome composition. However, a number of open questions remain about the role of host genetics.

First, although many studies have started to perform GWAS to identify variants in the host genome that may be important for determining microbiome composition, all of these studies are very underpowered compared to most GWAS for quantitative traits. Sample sizes at least an order of magnitude larger will likely be necessary to achieve signals that meet study-wide significance thresholds. Additionally, replication across studies and with independent cohorts will be necessary to confidently determine which signals are biologically meaningful and not false discoveries.

Second, the genetic studies conducted to date have focused on examining taxonomic abundance measures and composition as the phenotypic unit. While shared phylogeny implies shared function among closely related organisms, the extensive horizontal gene transfer between bacteria in the microbiome likely means that many organisms sharing the same 16S rRNA marker sequence have different gene content. As metagenomic experimental and computational analyses improve, it will be necessary to examine the same types of questions using bacterial genes and function as the phenotypes of interest.

Third, studies that explicitly model gene by environment interactions may prove powerful, as it is likely that host genotype is only relevant in certain environmental contexts. As one illustration of this concept, the advanced intercross QTL mapping study (G10 mice) performed GWAS on a subset of their lines after incorporating a high fat diet. Eight of the QTLs they identified showed significant interactions with diet, demonstrating the importance of taking into account environmental variation in genetic studies. While diet is an obvious variable to consider for gut studies, other environmental factors to consider include temperature, humidity, and pH.

Finally, the role of host genetics in determining microbiome composition from many different organisms or body niches has yet to be examined. The most extensively studied human microbiome by far is the gut, where diet likely drives much of the phenotypic differences between individuals. Other tissues may harbor microbiota that are more highly heritable. For instance, 8 QTL were identified that were associated with abundances of stool bacteria, while 17 QTL were found for supragingival plaque in the HMP. Expanding future studies to include additional organisms or sampling sites may reveal trends in the types of environments where host genetic variation plays a more substantial role than those that have been studied to date.

**Abbreviations**

- DHS: DNase hypersensitive site
- DZ: dizygotic
- FDR: false discovery rate
- GO: gene ontology
- GWAS: genome-wide association study
- HMP: Human Microbiome Project
- IBD: irritable bowel disease
- MZ: monozygotic
- OTU: operational taxonomic unit
- PCoA: principal coordinate analysis
- QTL: quantitative trait locus
- SNP: single-nucleotide polymorphism

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.
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